Defining public attitudes and understanding of human gene therapy in Australia

Michel Elyse Watson

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Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university. To the best of the author's knowledge, it contains no material previously published or written by another person, except where due reference is made in the text.

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To start on a personal note, this PhD process has been one of the hardest challenges I have had to face in my life. What started off as an exciting journey, took many turns with many damages to my confidence.

My thesis evolved from medical genetics research into a review of public opinion surrounding a controversial genetic technology. This transition from a purely scientific discipline into the humanities was rough and not as straight forward as I would have liked.

During my PhD it took a year to relearn everything on how to communicate science. Life isn't as black and white as I initially thought. I came into this new field wanting to change minds on how the public perceive genetic technologies. This new-age science wasn't something that needed to be feared! Surely educating them with enthusiasm and passion would win them over? I was naïve and misguided. I soon learnt this was a trap that many scientists fall into. It took me a year to change my mind. Although I still miss my laboratory research, it was one of the best decisions I have ever made. I see the world differently, now.

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This challenging journey has made me the confident, strong women I am today. I come out of this experience completely changed, and I feel this is for the better.

Time for the next adventure!

Abstract

Since the mid-1900s, breakthroughs in the accuracy and efficiency of gene altering technologies have rapidly advanced the field of human gene therapy (HGT). HGT as a treatment modifies specific genes to eliminate common illnesses and improve the quality of life of many individuals, previously not thought possible. However, HGT does not come without risk. Medical risks range from an ineffective treatment to one that could either disable or kill the patient. There are also ethical and moral issues pertaining to informed consent and the effect of these modifications on future generations. With the advent of HGT, the implications are now extremely broad, ranging from personal to societal. The complexity of this technology is such that its mere existence brings into play complex ethical questions that are often reflected in public discourse. In order to answer key ethical and risk-assessment questions, representative data on public beliefs, attitudes and opinions towards HGT and gene editing is required.

This is the first Australian study that provides a snapshot of Australian's attitudes of HGT and their willingness to accept the wide variety of procedural applications and implications of this technology. To achieve this goal, two surveys using different collection methods were published. The first was a national online survey which used chain-sampling via major social media platforms in 2017, with 553 completed responses returned. The second survey was based on a mail-out of households in the Australian Capital Territory (ACT) in 2019, this received 170 completed responses. A central finding of this study was a general positivity in Australians' acceptance towards all human gene-editing applications, with a strong preference towards procedures to treat a severe medical condition, as opposed to procedures for personal enhancement or prevention of potential adverse conditions. This acceptability diminished with declining severity of the medical condition. In each case, enhancement and prevention procedures were viewed as less acceptable than therapeutic applications. Demographic associations were also identified in both surveys, with females in both surveys significantly less likely to find HGT acceptable across all Likert questions. Using two different sampling methods also allowed for a comparative assessment of the survey population demographic profile and response rates received using each data collection strategy. Little difference was observed between the two demographic profiles and response rates. These results build on and reflect findings of similar national and international public opinion studies and provide a more complete picture of current Australian sentiment.

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Acronyms and Abbreviations

ABS	Australian Bureau of Statistics
ACT	Australian Capital Territory
ADA-SCID	Adenosine Deaminase Deficiency Severe Combined Immunodeficiency Disorder
AHMAC	Australian Health Ministers' Advisory Council
ALL	Acute Lymphoblastic Leukemia
ANOVA	Analysis of Variance
ANU	Australian National University
ARRIGE	Association for Responsible Research and Innovation in Genome Editing
ATMP	Advanced Therapeutic Medicinal Product
BBC	British Broadcasting Corporation
B Cell	Bone Marrow Cell
CAT	Committee for Advanced Therapies
CAR	Chimeric Antigen Receptor
CBER	Center for Biologics Evaluation and Research
CCR5	C-C Chemokine Receptor Type 5
CDFA	China Food and Drug Administration
CHF	Swiss Franc
CHMP	Committee for Medicinal Products for Human Use
COAG	Council of Australian Governments
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CSIRO	Commonwealth Scientific and Industrial Research Organisation

DLBCL	Diffuse Large B-Cell Lymphoma
DNA	Deoxyribonucleic Acid
EFSA	European Food Safety Authority
ELSA	Ethical, Legal and Social Aspects
EMA	European Medicines Agency
EU	European Union
FDA	United States Food and Drug Administration
GM	Genetically Modified
GMO	Genetically Modified Organism
GTRAP	Gene and Related Therapies Research Advisory Panel
GTWP	Gene Therapy Working Party
HBB	Human β-globin
HFEA	Human Fertilisation and Embryology Authority
HGT	Human Gene Therapy
HHS	United States Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
HTA	Health Technology Assessment
IBM	International Business Machines Corporation
IRB	Institutional Review Board
IVF	In Vitro Fertilisation
LPLD	Lipoprotein Lipase Deficiency
MBS	Medical Benefits Schedule
MSAC	Medical Services Advisory Committee

NASEM	National Academies of Sciences, Engineering, and Medicine
NExTRAC	Novel and Exceptional Technology and Research Advisory Committee
NHMRC	Australian National Health and Medical Research Council
NIH	United States National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
OGTR	Australian Office of the Gene Technology Regulator
OHRP	United States Office for Human Research Protections
ORION	Open Responsible research and Innovation to further Outstanding kNowledge
OTC	Ornithine Transcarbamylase
RAC	Recombinant DNA Advisory Committee
RIS	Risk Impact Statement
RNA	Ribonucleic Acid
RRI	Responsible Research and Innovation
RSPH	Research School of Population Health
SPSS	Statistical Package for the Social Sciences
SV40	Simian Vacuolating Virus 40
T Cell	Thymus Cell
TGA	Therapeutic Goods Administration
TNF	Tumour Necrosis Factor
TRN	Transnational Regulatory Dialogue and Networks
UCLA	University of California, Los Angeles
UDHGHR	Universal Declaration on the Human Genome and Human Rights
UK	United Kingdom

UN	United Nations
UNESCO	United Nations Education, Scientific and Cultural Organization
US	United States
USDA	United States Department of Agriculture
WHO	World Health Organization
X-SCID	X-linked Severe Combined Immunodeficiency Disorder

Definitions

Allele	Variant forms of a gene occupying the same genetic locus.
Australian	For the purpose of this analysis, an Australian is a person who has self-identified as aged 18 years or over and as being current resident of Australia.
Autosomal	A chromosome that is not a sex chromosome. People normally have 22 pairs of autosomes (44 autosomes) in each cell.
Chromosome	DNA molecule coiled around histone proteins and further coiled into a compact structure visible under the microscope.
Deletion	Deletion of one or more nucleotides from a DNA sequence.
Differentiated Cell	A cell that has taken on individual characteristics and reached its mature (specialised) form and function.
Disease	A particular abnormal condition that negatively affects the structure or function of all or part of an organism, and that is not due to any immediate external injury. Often known to be medical conditions that are associated with specific symptoms and signs.
Disorder	An illness that disrupts normal physical or mental functions.

DNA	Genetic material of life on earth. Built from four nucleotides – adenosine (A), cytosine (C), guanine (G) and thymine (T) joined in strands by phosphodiester bonds. Exists as a double stranded molecule (double helix) of the complementary base pairs A-T and C-G.
DNA sequence	The order of the nucleotide bases in a DNA molecule.
Embryo	An early stage of development of a multicellular organism. In general, in organisms that reproduce sexually, embryonic development refers to the portion of the life cycle that begins just after fertilization and continues through the formation of body structures, such as tissues and organs.
Enhancement	Improving an already healthy person to confer an advantage.
Enzyme	A substance produced by a living organism which acts as a catalyst to bring about a specific biochemical reaction.
ex vivo	Refers to experimentation or measurements done in or on tissue from an organism in an external environment with minimal alteration of natural conditions.
Gene	A section of DNA that carries the code for a protein or RNA molecule.
Genome	All the genetic material of an organism; all the DNA, including all the genes. The human genome contains approximately 3 billion DNA nucleotides.

Genotype	The genetic makeup of an individual comprising all the alleles at all genetic loci.
Germline Cell	A reproductive cell of the body. Germ cells are egg cells in females and sperm cells in males.
Germline Variant	Genetic variants present in gametes and potentially inherited by offspring.
Human Gene Therapy	Describes the treatment or cure of a disease or disorder by genetic modification (i.e. human gene editing) of the affected cells to correct a cellular dysfunction or to provide a new cellular function.
Immunogenicity	The ability of a foreign substance, such as an antigen, to provoke an immune response in the body of a human or other animal.
in vitro	Performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.
in vivo	Performed or taking place in a living organism.
Insertion	Addition of one or more nucleotides to a DNA sequence.
Mitochondria	A membrane-bound organelle that generate most of the chemical energy needed to power the cell's biochemical reactions.

Monogenic	Condition or phenotype caused by a variant in one gene.
Murine	Relating to or affecting mice or related rodents.
Mutation	A change in DNA sequence; 'permanent' change in DNA sequence.
Nucleic acid	Biopolymers, or large biomolecules, essential to all known forms of life. The term nucleic acid is the overall name for DNA and RNA.
Nucleotide	A component of nucleic acid, comprised of sugar, phosphate, and nitrogenous base. The nitrogenous base components in DNA are adenine (A), cytosine (C), guanine (G) and thymine (T). In RNA, these are adenine (A), cytosine (C), guanine (G) and uracil (U)
Nucleus	A membrane-bound organelle that contains the cell's chromosomes. Pores in the nuclear membrane allow for the passage of molecules in and out of the nucleus.
Pathogenic	Disease-causing. A pathogenic variant affects cell function and causes disease.
Pathogenicity	The property of causing disease.
Phenotype	The physical appearance and physiology of an individual, resulting from expression of the genotype and influenced by environmental factors.

Plasmid	A small, extrachromosomal DNA molecule within a cell that is physically separated from chromosomal DNA and can replicate independently.
Prevention	Relating to techniques that potentially avoid a disease or disability.
Protein	Molecules encoded by genes, comprised of amino acids in a sequence specified by the gene sequence. Amino acid sequences determines protein folding and function.
Recessive	Relating to or denoting heritable characteristics controlled by genes which are expressed in offspring only when inherited from both parents.
Recombinant DNA	DNA molecules formed by laboratory methods (such as molecular cloning) to bring together genetic material from multiple sources, creating sequences that would not otherwise be found naturally in the genome.
RNA	A molecule essential in various biological roles in coding, decoding, regulation and expression of genes.
Somatic Cell	Any cell of a living organism other than the reproductive cell.
Somatic Variant	A change in DNA that occurs after fertilisation of egg and sperm and is not present in germline. Not inheritable.
Syndrome	A group of symptoms which consistently occur together, or a condition characterised by a set of associated symptoms.

Therapeutic	Relating to the healing of disease. A treatment, therapy, or drug.
Transduction	The process by which foreign DNA is introduced into a cell by a virus or viral vector.
Transfection	The process of introducing nucleic acids into cells by non-viral methods. For example, using various chemical or physical methods.
Quiescent	In a state or period of inactivity or dormancy.
Variant	A variation in DNA sequences as compared to a 'reference' sequence. Ranges from a single base change to large rearrangements of DNA. Can be benign or pathogenic.
X-linked	X-linked is a trait where a gene is located on the X chromosome. Humans and other mammals have two sex chromosomes, the X and the Y. In an X-linked or sex linked disease, it is usually males that are affected as they have a single copy of the X chromosome that carries the mutation.

Full Citations for Italicised Quotes

Sections of this dissertation contain short italicised quotes from various sources to complement the discussion. For brevity, we do not include the full citations in those quotes. Full citations for the sources of these quotes are given below.

Galton, Francis. 1905. In Charles Blacker's 1952 Eugenics: Galton and After, 94. Cambridge: Harvard University Press.

Lederberg, Joshua. 1963. "Molecular Biology, Eugenics and Euphenics." *Nature* 198 (4879):428–429.

Moore, Michael. 2009. "Venice Film Festival Press Conference." Venice.

Niccol, Andrew. 1997. *Gattaca*. United States.

Rayner, Steve. 2003. "Democracy in the Age of Assessment: Reflections on the Roles of Expertise and Democracy in Public-Sector Decision Making." *Science and Public Policy* 30 (3):163–70.

Shelley, Mary. 1869. "Chapter Three." In Frankenstein, or, The Modern Prometheus, 41. London: Sever, Francis, & Company.

Wade, Nicholas. 1980. "UCLA Gene Therapy Racked by Friendly Fire." *Science* 210:509–11.

1 Introduction

The 1950s saw a major turning point in medicine with Cambridge scientists James Watson and Francis Crick being the first to postulate the double-helix structure of deoxyribonucleic acid (DNA) (Watson and Crick 1953). Through this discovery, the physical mechanism for the gene and its replication started to be properly understood. This knowledge allowed scientists to explore the basic code for life, and with it, a genetics revolution was borne which transformed the way we understand disease. Prior to this time, genetic modification involved crude methods that altered the entire cell (Tüzmen et al. 2018). Unlocking and analysing the DNA code meant that scientists —for the first time in history— could accurately target their interventions to a specific gene, and even to individual nucleotides. Modern genetic modification now has the potential to cure devastating hereditary diseases by using a new procedure known as human gene therapy (HGT) (Friedmann 1992).

Since the 1950s, breakthroughs in the accuracy and efficacy of gene altering technologies have rapidly advanced this discipline. These new DNA editing tools have had a significant impact on this field, opening up opportunities for treatments for a range of medical conditions (Travis 2015; Ginn et al. 2018). Potential treatment of severe genetic-based diseases and disabilities could theoretically eliminate conditions such as cancers, muscular dystrophies, cardiac disease and many other ailments. Such treatments could not only improve the quality of life, but even save the lives of many individuals. However, gene therapy does not come without risk. Medical risks range from an ineffective treatment to one that could either disable or kill the patient. The latter could occur due to insertional mutagenesis (insertion of the new DNA in the wrong place) or an extreme immune response by the body caused by the techniques used (Couzin and Kaiser 2005; Fehse and Roeder 2008; Lundstrom 2018). There are also ethical and moral issues pertaining to informed consent and the effect of these modifications on future generations. With the advent of HGT, the implications are now extremely broad, ranging from personal to societal (Rabino 2003). The complexity of this technology is such that its mere existence brings into play complex ethical questions that are often reflected in public discourse.

This chapter begins with section 1.1, which provides a brief historical overview of HGT. Since its inception, key events have influenced public reaction and shaped attitudes towards this controversial technology. These events will be described and deliberated. Following, an outline

of the numerous human rights challenges evoked by HGT and enhancement procedures is presented. To guide this discussion, this section also aims to highlight the intricate and unique role ethics plays within this field. Public attitudes are heavily intertwined with arguments on the morality (or immorality) of HGT. Unlike other medical technologies that can reduce or cure individual suffering, HGT can also be used (and therefore abused) to alter the foundational code for human life. Studies eliciting the opinions, preferences and concerns are described and discussed in detail.

Section 1.2 provides a review of the current policy challenges within Australia, the European Union (EU), China and the United States (US). The latter have been selected due to their key roles in HGT regulatory formation. This section examines each selected regions current regulatory frameworks to highlight their strengths and limitations. This review also details the challenges affecting policy decisions involving public opinion and concludes with an overview on public participation strategies for controversial medical technologies. Previous regulatory strategies for controversial technologies have attempted —with varying degrees of success— to incorporate the beliefs and values of the public through consultative processes. The governments of the United Kingdom (UK) and France have recognised the value of investing in understanding the core values of citizens for controversial and risk-prone technologies when designing policy. Finally, section 1.3 and 1.4 provide a justification and objectives for this thesis, respectively.

1.1 A REVIEW OF THE HISTORY OF, AND PUBLIC ATTITUDES TOWARDS HUMAN GENE THERAPY

"The ultimate application of molecular biology would be the direct control of nucleotide sequences in human chromosomes, coupled with recognition, selection and integration of the desired genes"

(Lederberg, 1963)

To begin this journey, one must first understand the history of HGT, its tribulations and its triumphs. Subsequent to Watson and Crick's discovery, the 1960s saw the beginnings of experimental HGT trials (Friedmann 1992). From these initial experiments, this technique has

evolved into a technology that has the potential to save or enhance our lives. In its basic form, gene therapy describes the direct genetic modification of one or more target cells to correct a cellular dysfunction or to provide a new cellular function (Culver 1994).

There are two overarching categories of HGT which target different cell types: somatic and germline. Somatic cells are the 'adult' cells of the body which means the DNA that resides in this form of cell is not passed on to offspring (National Academies of Sciences, Engineering et al. 2017). In contrast, germline cells (either egg, sperm or embryos) will be passed to the next generation. As such, germline changes are inherited by subsequent offspring (Wivel and Walters 1993). This is a crucial distinction that has ethical implications described later in this section, owing to its effects on future generations.

Today, genetic modification can be achieved by many different methods; inactivating a pathogenic gene, replacing the abnormal gene with a normal copy, or the insertion of a new gene to aid the body in its fight against disease (Maeder and Gersbach 2016; Gaj et al. 2016). For example, chimeric antigen receptor (CAR) thymus cell (T cell) therapy, a targeted immunotherapy for cancer, is a form of human gene therapy that has generated a lot of media in recent years due to its success in clinical trials (Miliotou, Androulla, and Lefkothea 2018; Rizmal 2019; White and Mackenzie 2020). As of 2017, more than 2600 gene therapy clinical trials worldwide were approved, finished or were still ongoing (Ginn et al. 2018). The majority of these trials (60%) were for the treatment of cancer, followed by monogenic diseases (such as cystic fibrosis), cardiovascular diseases and infectious diseases (Wirth, Parker, and Ylä-Herttuala 2013; Ginn et al. 2013). Studies to see whether the various methods used are safe and efficacious are still underway and are helped by numerous scientific advances in other areas such as cell line production and recombinant DNA; these studies are discussed below.

1.1.1 A history of gene therapy

The second half of the 20th century saw a scientific innovation boom within the field of biology. A newly found ability to isolate, grow and maintain cells *ex vivo* (outside of an organism) led to an important first step in HGT (Alberts et al. 2002). In 1962, Elizabeth Szybalska and Waclaw Szybalski in Poland were the first to demonstrate *heritable* gene transfer in a human cell line (Szybalska and Szybalski 1962). A later investigation by Edward Tatum in America proved that viruses could be utilised to deliver genetic information into targeted somatic cells (Tatum 1966).

The life-cycle of a virus has several important characteristics that make it ideal for HGT. Foremost, any living organism has the potential to be infected by a virus (Thomas, Ehrhardt, and Kay 2003; Tomanin and Scarpa 2004; Lundstrom 2018). In order to achieve infection, the virus must first enter a cell. However, a virus is limited to which cells it can infect. A particular virus uses specialised proteins to bind to a host cell's surface and is therefore restricted to entering specific cell types based on the cell's surface proteins (Maginnis 2018). For example, the human rhinovirus (one of the main contributors to the 'common cold') tends to bind to cells of the upper and lower respiratory track causing nasal congestion and sneezing (Papadopoulos et al. 2000). Once bound to the cell's surface, the virus injects its nucleic acid (DNA or RNA i.e., ribonucleic acid) into the cell. In order to replicate, many viruses (all DNA viruses, and some RNA viruses) must use the host cell's machinery to create more viral particles that then infect other cells (Lodish et al. 2000). To achieve this, the viral nucleic acid enters the cell's nucleus and inserts itself into the host cell's own DNA (Fay and Panté 2015).

The first HGT trials were limited to viral vectors i.e., using the viral particles as vehicles to insert specific DNA sequences into a cell. Unfortunately, viral particles left un-attenuated and without patient pre-conditioning (treatment prior to the procedure that attempts to reduce adverse side-effects) have the potential to cause severe immune responses. Therefore, initial trials were often confined to severe diseases where no other options were available due to the immunogenicity of the procedure (Robbins and Ghivizzani 1998). Modern innovations have now allowed for non-viral vectors to be used to deliver genes to a target cell (Uchida et al. 2002).

1.1.1.1 The first direct human gene therapy trial

Early gene therapy trials tended to focus on correcting enzyme defects associated with metabolic diseases (i.e., diseases that affect the conversion of food to energy) (Chandler and Venditti 2016). The first known HGT trial was attempted by Stanfield Rogers and colleagues in America (Rogers et al. 1973). Wild-type (normal) Shope Papilloma viral particles were injected into two severely disabled young sisters suffering from hyperargininaemia, a rare autosomal recessive amino acid metabolism disorder which results in high levels of plasma arginine and ammonia due to a defect in the arginase I enzyme (Terheggen, Lowenthal, Lavinha, and Colombo 1975). Without treatment, this disorder can lead to poor growth, seizures and intellectual disability (Terheggen et al. 1969). This trial was unsuccessful (no effect on the

patients) due to the heavy reliance on the false belief that the viral genome included coding instructions for the arginase I enzyme protein (Rogers 1971). Later sequencing of the viral genome concluded that this gene is not naturally present (Giri, Danos, and Yaniv 1985). Furthermore, at the time of Rogers experiment, the genetic mechanisms behind hyperargininemia were not properly understood. The failure of this experiment was a result of the lack of biochemical and virological foundational knowledge at the time (Orth, Vielle, and Changeux 1967; Rogers et al. 1973; Terheggen, Lowenthal, Lavinha, Colombo, et al. 1975; Friedmann 1992).

Rogers' experiment took place just before the discovery of recombinant DNA. This technology appeared in the 1970s, substantially improving gene therapy research (Friedmann 1992; Cotrim and Baum 2008). In essence, recombinant DNA describes the joining together of DNA molecules from two different species, which can then be inserted into a host organism to produce new genetic combinations (Griffiths 2009). Theodore Friedmann and Richard Roblin, two American researchers, were the first to highlight this concept, suggesting that tumour viruses could be modified to carry genetic information. They proposed that the newly modified virus would be able to correct disease phenotypes in foreign cells (Friedmann and Roblin 1972). Simultaneously, Paul Berg, an American biochemist, confirmed this theory by creating a recombinant viral vector using the simian vacuolating virus 40 (SV40), able to transfer genetic information into monkey and human cells in a stable, heritable manner that maintains gene expression (Sambrook et al. 1968; Jackson, Symons, and Berg 1972; Topp, Lane, and Pollack 1981). This scientific feat won Berg the Nobel Prize in Chemistry in 1980 (Shampo and Kyle 2003). However, in the early stages of this discovery, scientists —including Berg— were still sceptical of this technology.

While the SV40 virus was thought to be harmless in humans, concerns led Berg to delay part of his research and publish a letter on the potential dangers of this technology and requested a moratorium on all related research (Berg et al. 1974). He stated in his letter that the technology could "result in the creation of novel types of infectious DNA elements whose biological properties cannot be completely predicted in advance". This letter was ultimately successful in

creating a temporary hold on research, until new guidelines produced by the Recombinant DNA Advisory Committee (RAC)[1] came into effect in 1976 (National Insitutes of Health 1976).

Despite initial setbacks, recombinant DNA technology improved HGT techniques and is now often included in its definition (Friedmann 1992; Cotrim and Baum 2008; Halioua-Haubold et al. 2017). For example, the European Commission states that HGT is a biological medicinal product which contains an active substance comprising of *recombinant* nucleic acid (European Commission 2013) where the product's therapeutic potential directly relates to the *recombinant* nucleic acid sequence or its genetic expression. This sequence is administered to humans to either repair, replace, add or delete a genetic sequence (Culver 1994; Wirth, Parker, and Ylä-Herttuala 2013).

1.1.1.2 The first human trial using recombinant DNA - The Cline experiment

> *"Cline has done this experiment in the mouse and, as I understand it, it didn't work. He has made a great conceptual leap from the failure in the model system to trying it in humans. He is saying, 'It didn't work in mice, so I'm going to try it in man'"*
>
> (Wade, 1980)

Early on, Human β-globin (HBB) was considered a prime candidate for HGT due to the molecule suiting two requirements: not only was HBB one of the first genes to be successfully characterised and cloned (Maniatis et al. 1976), but it was also associated directly with human disease of a genetic basis, β-thalassemia. A lack of β-globin protein due to a variation in the HBB gene results in limited mature red blood cells (Galanello and Origa 2010). Symptoms of this illness are severe, including life-threatening anaemia. The only available treatment at the time was frequent blood transfusions (Modell 1977). With new DNA vector methods becoming available, the HBB gene (as well as other cloned genes) was able to be efficiently introduced into mammalian cells, conferring normal functionality (Mulligan, Howard, and Berg 1979; M. Green, Treisman, and Maniatis 1983). Despite methodological challenges (such as initiating

[1] The RAC was established by the National Institutes of Health (NIH) in 1974 to provide recommendations on the scientific, safety, and ethical issues related to recombinant DNA technology (Lenzi, Altevogt, and Gostin 2014).

and maintaining a stable, safe and accurate DNA change) still to overcome, HGT experiments with human patients proceeded.

The first to attempt to use recombinant DNA in HGT trials was Martin Cline and colleagues at the University of California, Los Angeles (UCLA) in 1979 (Cline et al. 1980; Mercola et al. 1980). Initial experiments claimed the successful introduction of the HBB gene by calcium phosphate transfection into murine (mouse) bone marrow cells. These cells are responsible for the production of hematopoietic stem cells that develop into all blood cell types and are therefore implicated in producing the disease phenotype (Travlos 2006). In these murine cells, partial repopulation with the genetically modified bone marrow cells was observed (Cline et al. 1980; Mercola et al. 1982). Based on these preliminary investigations, Cline attempted human trials. In 1980, Cline's laboratory extracted bone marrow cells from two thalassaemia patients from Italy and Israel. The extracted cells were transfected *in vitro* (outside an organism) with plasmids containing the HBB gene. These 'modified' cells were then re-injected into the patients. Results were inconclusive and remain unpublished (Friedmann 1992).

The apparent failure of this human experiment caused intense focus on the ethics and governance of HGT (Fletcher 1983; Friedmann 1992). Later it was discovered that Cline had applied for ethics to the UCLA Institutional Review Board yet proceeded with human trials without approval (Beutler 2001). The UCLA board of ethics had voiced concerns about the efficacy of the method proposed. Following the experiment, criticism of the ethics, science and administration of Cline's procedure were publically raised by the UCLA, US National Institutes of Health (NIH) as well as the broader community (Wade 1981; Fletcher 1983). The acknowledged inefficiency of the technique used —which included the observed low frequency of bone marrow stem cells that expressed the corrected gene— made the preliminary results that this experiment was based on, questionable (Friedmann 1992; Beutler 2001). In 1981, Cline was found to be in breach of US federal regulation on human experimentations including the RAC guidelines and was consequently sanctioned by the NIH (Sun 1981; Dickson 1981; Sheridan 2011). In response, the RAC established the Gene Therapy Subcommittee designed specifically to regulate molecular genetic tools for human use (Friedmann 1992; National Insitutes of Health: Office of Science Policy 2020).

Human gene editing technologies have been associated with numerous individual risks. Even to this day, there is an identified deficiency in scientific knowledge of the potential physical and psychological risks (Baltimore et al. 2015). At the time this experiment took place, public

fear of the risks (both known and, more importantly, the unknown) posed by recombinant DNA technology were high (Beutler 2001). Cline posited that this may have, in part, contributed to the severe reactions directed at him, despite no harm coming to either patient (Cline 1985). Due to this heavily publicised experiment, the ethics of human research were also brought to the public's attention.

Even though this publicity was often framed in a negative light, by 1992, Friedmann, suggested there were few serious public reservations on the appropriateness of somatic HGT (Friedmann 1992). However, studies focusing on public support of genetic research had shown that the public thought of recombinant DNA as a 'moderate hazard', i.e., a technology to remain cautious about (Slovic 1987; Flynn, Slovic, and Mertz 1994). A 1997 study led by Lynn Frewer added insight to this finding by proposing that most negative attitudes were associated with genetic modification of animal or human DNA due to perceived 'unnaturalness' of these gene editing procedures (Frewer, Howard, and Shepherd 1997). Interestingly, public attitudes became more positive when animal and human genetic modifications were linked to medical applications or when they are directly related to a strong need for the technology (Frewer, Howard, and Shepherd 1997; Gaskell et al. 2017; van Eenennaam and Young 2018; Critchley et al. 2018). In other words, individuals tend to decide on the acceptability of HGT on a case-by-case basis. A review of public opinion is detailed below in section 1.1.3 (p.19).

1.1.1.3 The first officially approved clinical protocol and clinical trial

After the RAC's establishment, it was not until 1988 that the RAC approved a protocol to introduce foreign genes into humans (Wirth, Parker, and Ylä-Herttuala 2013). Previously in 1975, tumour necrosis factor α (TNFα) was isolated by Elizabeth Carswell and colleagues as a soluble protein produced naturally by host cells which caused necrosis of transplanted tumour cells (Carswell et al. 1975; Balkwill 2009). Based on this discovery, Steven Rosenberg was granted permission to treat two patients with advanced melanoma (skin cancer) with *ex vivo* immune cells modified to express a TNF (Rosenberg et al. 1990; Rosenberg 1992). Rosenberg's trial was a success, with the tumours targeted by this treatment not growing back (adjacent to the injection site) and with no evidence of tumours three weeks post-injection (Rosenberg et al. 1993).

Following, Ro Blaese received approval from both the US Food and Drug Administration (FDA) and the RAC in 1990 and was the first to attempt HGT using an *in vivo* technique (Blaese

et al. 1995; Wirth, Parker, and Ylä-Herttuala 2013). Two children suffering from adenosine deaminase deficiency severe combined immunodeficiency (ADA-SCID), a monogenic immune disorder, participated in this trial (Blaese et al. 1995). Those affected by ADA-SCID suffer from pneumonia, chronic diarrhoea, and widespread skin rashes, with most facing developmental delay (Flinn and Gennery 2018). ADA-SCID was anticipated to be the perfect target for gene therapy (Ferrua and Aiuti 2017). The disease was well defined, influenced by only one gene (the adenosine deaminase gene) and was demonstrated to be successfully modified in animal models (Lynch et al. 1992; Onodera and Sakiyama 2005). In addition, it was determined that even just low expression of the corrected gene conferred a survival advantage. However, despite these benefits, only one patient in Blaese's trial showed low expression of the corrected enzyme after treatment with a retroviral vector containing the ADA gene, and was receiving enzyme replacement therapy simultaneously (Kohn 2002). Even with uncertainty surrounding the trial, soon after, another ADA-SCID trial started in the European Union (EU) (Bordignon et al. 1995). While initial human trials were not as successful as initially expected, gene therapy trials were flourishing throughout the 90s: that is, until the death of 18 year old Jesse Gelsinger in 1999 (Stolberg 1999).

One major risk of utilising viral vectors is the capability of the virus to cause dangerous immune reactions. This was unfortunately the case in the highly publicised death of Gelsinger in the US which raised serious concerns about HGT (Stolberg 1999). Gelsinger suffered from a rare, X-linked metabolic disorder known as ornithine transcarbamylase (OTC) deficiency. If left untreated, a severe form of OTC deficiency in infants greatly increases their risk of neurological abnormalities such as intellectual disability, developmental delay, cerebral palsy or death (Brassier et al. 2015). As part of the HGT trial to correct this disease, recombinant adenovirus viral vectors were used to insert a new, 'normal' version of the gene in an attempt to cure Gelsinger's deficiency (Marshall 1999). Sadly, an extreme immune response caused by the viral vector used resulted in multiple organ failure, which precipitated in his death four days later. This arguably preventable death sparked outrage in the public and the scientific community alike (Beutler 2001; Wilson 2009).

Significantly, this was the first known case where a death could be directly linked to HGT. As a result, scientists reviewed the use of viral vectors like the adenovirus in all HGT trials (Marshall 1999; Thomas, Ehrhardt, and Kay 2003). In addition, further investigation into Gelsinger's case by the FDA and the US Department of Justice found the researchers guilty of research misconduct (Couzin and Kaiser 2005). A major concern highlighted by this process

was the lack of Gelsinger's informed consent. Not only were the risks of the procedure found not to be effectively communicated, hidden from patients who took part in this trial was the fact that, under similar treatment, laboratory monkeys had died. Fellow trial participants of Gelsinger's had also suffered from serious side effects as a consequence of the virus used (Savulescu 2001).

Less than one year later in 2000, Marina Cavazzana-Calvo and colleagues in France reported the first cure for X-linked severe combined immunodeficiency (X-SCID) disorder by gene therapy (Cavazzana-Calvo et al. 2000). Correction of the disease was observed in the two patients who took part in this initial trial. Tragically, in follow up trials, leukaemia was detected in several patients, triggered by insertional mutagenesis (Check 2002; Hacein-Bey-Abina et al. 2003). Similar mutations arose in other gene therapy trials, as a result of the viral vectors used (Fehse and Roeder 2008). As such, many studies were put on hold for a couple of years following these trials in light of safety concerns, with the withdrawal of many industry groups from preclinical studies (Hanna et al. 2017). This concern of unexpected complications when using delivery vectors is still an issue for researchers (Wirth, Parker, and Ylä-Herttuala 2013; Lundstrom 2018).

Despite the setbacks described above, China was the first country to approve a gene therapy based product for clinical use in 2003 (Wilson 2005). Gendicine™ is used to treat head and neck squamous cell carcinoma (Zhang, Lu, and Peng 2012). Controversially, this product was approved without data from phase III clinical trials (the assessment of an intervention's effectiveness in a large groups of participants, compared to the current standard intervention) which raised concerns about the efficacy of this treatment (Xin 2006). It wasn't until 2012 that the EU followed suit with Glybera receiving manufacturing approval. Glybera is a gene therapy designed for the treatment of the inherited metabolic disorder lipoprotein lipase deficiency (LPLD), a rare inherited disorder where fats struggle to be broken down in the body (Gaudet, Méthot, and Kastelein 2012; Wirth, Parker, and Ylä-Herttuala 2013).

1.1.1.4 Remaining challenges for human gene therapy

In HGT research, there have been two standard approaches for introducing genes into a cell: viral (transduction) and non-viral (transfection). Unfortunately no perfect vector system currently exists (Vorburger and Hunt 2002; Lundstrom 2018). For viral vectors in particular, past HGT trials have highlighted the limitations of their use (Thomas, Ehrhardt, and Kay 2003;

Kirubarajan, Lu, and Oliveria 2017; Lundstrom 2018). For example, viruses vary in how well they transfer genes into a host's cells, and once the viral nucleic acid is in the host's cell nucleus, the DNA changes may be permanent or temporary, and with varying levels of expression (Lundstrom 2018). This lack of permanent modification is due to a variety of factors including the target cell's cycle, especially if the cell is quiescent (dormant) (Thomas, Ehrhardt, and Kay 2003). In the case of dormant cells, viral vectors continue to be a problem as most viruses require dividing cells for successful transduction. Differentiated, quiescent cells —such as certain liver and white blood cells— are therefore less suitable therapy targets (Mali 2013). Viruses also contain the risk of insertional mutagenesis causing cancer and uncontrolled genetic changes, as seen in gene therapy trials in the early 2000s (Fehse and Roeder 2008). Furthermore, there is also a small chance that this foreign DNA could be introduced into the patient's reproductive cells (Monckton 2019). If this occurs, the new gene might be passed on to the individual's children, which raises ethical concerns over consent to the procedure (discussed in section 1.1.3.3-1.1.3.4, p. 25-31).

For patients, preparation for, and recovery from the procedure also remains challenging, with numerous side effects and a potential for toxic or pathogenic consequences (Lundstrom 2018). Adenoviruses are a popular viral vector due to their high infectivity rate in a range of different cell types (Vorburger and Hunt 2002). Unfortunately adenoviruses, like many other viruses, are considered to be highly immunogenic, although efforts have been made to correct this feature. A recent clinical trial for the treatment of ADA-SCID in a handful of affected patients employed a similarly highly infectious and immunogenic virus: the gammaretrovirus (Gaspar et al. 2006; Candotti et al. 2012). Despite its known immunogenicity, only mild conditioning (using chemotherapy to reduce the immune response) aimed to contain adverse side-effects was required for the patients, with a successful outcome. Further studies are still being made to perfect the safety and efficacy of the procedure (Ferrua and Aiuti 2017) and research addressing some of the safety obstacles that arise from the use of viral vectors require further evaluation (Lundstrom 2018).

To date, viral vectors have been used in approximately 70% of all clinical trials, although non-viral vectors are becoming increasingly popular as the technology expands (Uchida et al. 2002; Ginn et al. 2018). New non-viral vectors such as nanoparticles and chemical carriers are amongst a variety of other techniques being discovered (Ramamoorth and Narvekar 2015). Interestingly, the majority of cardiovascular and tumour targeted gene therapy clinical trials now utilise non-viral vectors (Li and Huang 2006; Ramamoorth and Narvekar 2015). While

these vectors are less immunogenic, low rates of specificity and efficiency are still being observed when used to insert a gene into the target cell, leading to a low and short-lived gene expression (Kirubarajan, Lu, and Oliveria 2017).

Vectors are not the only limiting factor of this procedure. Somatic gene therapy is currently restricted to monogenic diseases which affect specific, accessible tissues (Ginn et al. 2018). Suitable diseases for gene therapy must be well characterised and have a large amount of targetable cells due to low success rates (Chang 1994; Lundstrom 2018). Other challenges continue to hinder gene therapy advances including the high prices which must cover reimbursement of companies and infrastructure expenses which are all potential disincentives to pharmaceutical companies (Shukla et al. 2019). All these challenges described above are central reasons why HGT trials have had an uncertain beginning. Importantly, these combined challenges not only have an effect on the usefulness of the technology, but also begin to shed light on the numerous ways HGT has and will impact human rights. A review of the literature discussing the ethical issues of HGT raised several key issues regarding discrimination, equity of access and issues pertaining to consent, as discussed below.

1.1.2 Human rights violations

"I belonged to a new underclass, no longer determined by social status or the color of your skin. No, we now have discrimination down to a science."

(Gattaca, Andrew Niccol)

United Nation's (UN) Universal Declaration of Human Rights lists the obligations of governments to ensure citizens have the freedoms they are entitled to (United Nations 1948). This declaration therefore plays a crucial role in the formation of public policies, at a state, national, and on an international level. As discussed below, one of the major ethical dilemmas that arises from the use of HGT is the impact on our human rights. These impacts need to be addressed when developing regulatory frameworks that govern this technology. Currently, few human rights safe-guards are included in HGT policies, despite the fact that HGT products have been accessible to the public since 2003 (Wilson 2005; Montgomery 2018; van Beers 2020). However, this may be due to HGT research predominately focusing on therapeutic and not enhancive applications to date.

In 1997, genetic technologies —including HGT— had generated enough interest, and also sufficiently deviated from other mainstream technologies, that the United Nations Education, Scientific and Cultural Organization (UNESCO) adopted the Universal Declaration on the Human Genome and Human Rights (UDHGHR) (UNESCO 1997). In this Declaration, 25 Articles were presented as an addition to the 1948 Declaration. In 1998, on the 50th anniversary of the 1948 Declaration, the UN General Assembly also adopted the UDHGHR, highlighting the importance of the document (UN 1998). The adoption of the UDHGHR principles into Australian Commonwealth and jurisdictional law is yet to be studied and is therefore not commented on further in this thesis.

In the UDHGHR's opening summary, readers were asked to keep in mind that "… all research should fully respect human dignity, freedom and human rights, as well as the prohibition of all forms of discrimination based on genetic characteristics" (UNESCO 1997, p. 42). This statement strikes at the very core of HGT's controversial characteristics. As explored in the following section, fear of genetic discrimination born out of genetic modification procedures is a common theme identified in public opinion studies. This fear is partly due to concerns about the potential for HGT to create further societal divisions through unequal access to the technology and uses of the technology that would preference some, and reduce our diversity as a species (Simmons 2008; Sherman 2017). In response to this, Article 6 of the UDHGHR clearly prohibits this form of genetic discrimination by stating, "No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity." (p. 43) and, by Article 2 declaring that we have a responsibility "…not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity." (p. 42). Genetic discrimination can potentially manifest in several key areas as outlined below; this, however, is not an exhaustive list.

1.1.2.1 Gender discrimination

Despite major advancements being made by the gender equality revolution of the 20th century, sexism is still a global issue that needs to be continually addressed (Rinčić, Muzur, and Sodeke 2018). In particular, gender discrimination in the form of sex selection and gender categorisation (defining what is typically 'female' or 'male') will be an important issue impacting policy on human gene editing technologies (Macpherson, Roqué, and Segarra 2019).

A current example that portrays the problems arising from sex selection can be found in other medical technologies such as in vitro fertilisation (IVF). Since the arrival of IVF treatment, disputes over allowing parents to choose the gender of their child has been a topic of contention due to the potential for favouritism of one gender over another on a population level (Arnold, Kishor, and Roy 2002; Winckler 2002). This has been illustrated by countries like China in the implementation of a strict one child policy (abolished in 2015), a regulation intended to stem the exponential growth of the population (Peng 1991). An unintended outcome of this policy was gender favouritism, leading to a population skewed towards males (Ebenstein 2010; Radcliffe 2016). This revealed a society that, like many countries, recognised the inherent advantages that men, even to this day, receive. Loss of welfare due to menstruation, pregnancy, child rearing and menopause, as well as a propensity to be the target of sexual abuse can impact on a decision to select a specific gender (Casal 2013). This favouritism in turn fuels the entrenchment of a male-dominated society, as demonstrated by the male/female birth ratios in China (Sudbeck 2012). While not realised yet, selection and modification of gender and gender-traits will be an issue for governments to grapple with as HGT progresses.

Another issue of HGT is the defining, or redefining of sexual characteristics. A recent study by Moran Gershoni and Shmuel Pietrokovski suggested that, while males and females share almost the same set of genes, up to a third of the genome may have different levels of expression between the sexes (Gershoni and Pietrokovski 2017). This area of research has led governments, like the US, to propose the establishment of a legal definition for each sex based on their genetic makeup that could be confirmed by genetic testing at birth, or in the case of HGT, before birth when selecting for specific genetic gender traits (Nature 2018). Arguments against this proposal state that this would make it easier for institutions to discriminate based on their gender identity and reignite old gender stereotypes (Green, Benner, and Pear 2018; Nature 2018). Alternatively, genetic enhancement may lead to the abolishment of sexual dimorphism altogether, with the potential to select the best genes from each sex to create new and improved asexual beings (Kahane and Savulescu 2010). This emerging debate sparked by new enhancement technologies like HGT challenges the notion that sexual dimorphism is a natural part of life, and therefore should not be tampered with (Kahane and Savulescu 2010; Sparrow 2012). Arguments for the progression to asexuality could be classified as a more extreme form of the sex selection debate described above (Kendal 2017). In either scenario, social trends and cultural norms will undoubtedly play a strong role in gender discrimination

exacerbated by enhancive HGT procedures, as such policies affecting HGT access therefore must consider these issues going forward.

1.1.2.2 Disability discrimination

At the heart of genetic discrimination is the potential for enhancive HGT procedures to lead to either further discrimination against those who are identified with a disability *or* pressuring individuals to correct genes considered "abnormal" or maladaptive (Harris 2007a). To discuss this, one must first deliberate on what is considered 'normal'.

There are ongoing debates surrounding what is classed as 'normal' and the variances between what constitutes an enhancement or medical therapy. Norman Daniels, a well-renowned American bioethicist, describes any negative change from the 'normal' functioning of species as a disease (Daniels 2000). In his definition, therapeutic procedures reverse this process by taking a diseased state and restoring it to its 'normal' biological function. In contrast, enhancement procedures represent a positive improvement on this 'normal' function. Therefore in this thesis, an individual is said to be enhanced when a once normal individual now displays an increased capacity from that which could be reasonably predicted at birth. However, the divide between therapy and enhancement is not as clear-cut as it might initially appear. Another prominent British ethicist, John Harris, argues we use enhancements on a daily basis (Harris 2007b). Whether individuals use glasses to correct vision impairments or vaccines to prevent infection, both can be classed as an enhancement to some degree (Bostrom and Roache 2007). The ethics of enhancement will be discussed further in section 1.1.3.3 (p.25).

An additional category of human genetic modification lies in the preventative, or prophylactic capabilities of HGT. Previous literature has argued that genetic manipulation as a prevention strategy can also be classed as a genetic enhancement (Harris 2007b). However, prevention can be thought of as distinct from enhancement for two reasons. Firstly, although both are used by a 'normal' individual, enhancements are often linked with non-medical procedures, such as a change in eye colour (Harris 2007b; So et al. 2017). Alternatively, prevention is almost exclusively associated with techniques that can potentially avoid a disease or disability (Juengst 1997). Secondly, although similar to enhancement (i.e., strengthening an immune system to fight disease can be seen as both enhancement and prevention), it is easy to argue we have a moral duty to intervene using a preventative strategy so that no harm can come to an individual, the same cannot be easily done for enhancements (Resnik 2000).

The introduction of HGT therefore raises a major ethical question: should we endeavour to prevent disabilities of a genetic basis? And, if we do decide to prevent disabilities, would this not constitute as a form of eugenic practice? In Harris' 1993 paper on gene therapy and eugenics, he states it is immoral to produce children "who will be significantly harmed by their genetic constitution" (Harris 1993). In his argument, he distinguishes between the 'right' and 'wrong' form of eugenics. The wrong type is when the majority negatively influences the right of the "genetically weak" from producing. Alternatively, the 'right' type of eugenics (using the official definition of "eugenic": *pertaining or adapted to the production of fine offspring* (Murray and Little 1965) is where a couple can choose whether to have a child who is free (as reasonable predicted) from disability. This argument in favour of producing genetically strong children however fails to address both the flaws of human nature (e.g., discrimination towards one's choice of *not* selecting for a genetically strong child) and focuses on what is known as the 'medical model'[2] of disability (Reindal 2000). In other words, implementation of HGT for the purpose of 'correcting' a disability, may be seen as a value judgement about the worth of lives of people who live with the conditions for which these therapies are offered.

The dominant 'medical model' sees disability as a disadvantage, or a problem that needs to be fixed. This mode of thinking exacerbates the current divide, leaving those who identify with a disability as regularly feeling excluded or undervalued (Goering 2015). More modern arguments lead towards a more neutral model, where disability is neither a weakness nor a strength, but rather as 'normal', as often articulated by those with a 'disability' (Kent 2000; Silvers 2003). Despite the emergence of this theory, disability discrimination is still present in our society. The use of technologies such as HGT to choose against (in the case of reproduction), or correct for a disability that others perceive as 'normal' has the potential to significantly increase this type of discrimination without the careful design of policies, as disabilities are currently perceived by many as a normal part of life (Ellis 2016).

[2] The medical model of disability says people are disabled by their impairements or defferences and looks at what is 'wrong with the person, not what the person needs (Brisenden 1986).

1.1.2.3 Access to services

Concerns of genetic discriminatory behaviour leading to a "*Gattaca*"[3] future have been touted as a real possibility with the advent of HGT, where those who have not been genetically enhanced miss out on employment opportunities or cannot obtain medical insurance or bank loans due to their uncompetitive or 'normal' characteristics (Wolbring and Diep 2016; Reinsurance Group of America 2019). Why would a company hire someone who has a *predisposition* to a certain illness or disability when they have the option of employing someone who is guaranteed not to have these issues? This is morally indefensible statement, and yet, we see it all the time in our society where workers with disabilities are segregated in the workplace or not even considered for a role (Marotoa and Pettinicchio 2014). This reality is not as farfetched as it originally appears.

Inaccessibility to services has already been discussed in relation to personal genetic diagnosis and discovery (Holland and Tham 2019). Currently, millions of people are having their genome's 'read' to either predict or diagnose a genetic condition or to investigate their ancestral origins (Hogarth, Javitt, and Melzer 2008). This practice is contentious, with the risk of private companies deciding to sell an individual's genetic data to insurance companies, which in turn may increase their health insurance premiums (Blasimme, Vayena, and Van Hoyweghen 2019). In countries like America, insurance policies are vital due to the lack of free or subsidised healthcare by the government (Steinmo and Watts 1995). Without health insurance, adequate access to medical facilities is unobtainable for many Americans. In Australia, currently legislation exists that prohibits the use of genetic information by private health insurance companies, however, this is not the case for life insurance (Otlowski et al. 2019). As a temporary measure, the Australian insurance industry voluntarily created a moratorium on the use of genetic information in life insurance applications, effective from mid-2019 until mid-2024 (Desai and Jones 2019).

Commercial access and privacy restrictions relating to the storage of genetic data —as a result of either personal exploration through private entities or medical diagnosis through the public or private health system— is an issue for governments to grapple with as health moves towards precision medicine (treatment tailored to the patient), of which HGT is an exemplar. Recognising this, in 2016 the Australian Government developed its first National Health

[3] A 1997 American science fiction movie written and directed by Andrew Niccol. The film is set in a future world where societal class structures are based on genetic "purity" (Niccol 1997)

Genomics Policy Framework (AHMAC 2017). This high-level framework aims to "harness the health benefits of genomic knowledge and technology into the Australian health system in an efficient, effective, ethical and equitable way to improve individual and population health" and is the first step towards recognising and addressing some of these access issues as described above. Without regulatory and policy safeguards, this technology has the potential to impact on our human right to access services, as outlined in four Articles of the UN's Universal Declaration of Human Rights, being; the right to education (Article 26), social security (Article 22), work and equal pay (Article 23), and the right to own property (Article 17). As stated before, in our current democratic system, it is hard to believe that gene therapy or enhancement procedures will affect access to these services, yet not every country is founded on democracy, and even in a democratic society, not every employer has the same moral standards (Carucci 2016).

1.1.2.4 Issues concerning consent

Through advances in science, HGT has been positioned to treat many genetic diseases. However, with these successes have come stories of researchers pressing the boundaries of ethical research conduct. It is therefore unsurprising that informed consent to participate in genomic research, clinical trials, and its many clinical applications is also addressed within the UDHGHR (UNESCO 1997). A prime example that highlights the importance of consent in HGT research (and in human research more broadly) can be found in a recent highly-publicised experiment conducted by He Jiankui in China. He Jiankui's study was designed to assist couples where the male reproductive partner has an active human immunodeficiency virus (HIV) infection (Greely 2019). Using CRISPR (clustered regularly interspaced short palindromic repeats) technology, He Jiankui created a point mutation (Δ32) in the CCR5 gene (C-C chemokine receptor type 5) of embryonic cells to mimic a mutation that can occur naturally, but rarely, within the general population (Quillent et al. 1998). This mutation causes an absence of a cell surface protein that the HIV uses to enter the cell, therefore HIV infection cannot transpire. As part of his research, He Jiankui forged ethical review documents and deceived doctors to implant the genetically edited embryos into two women in an attempt to ensure the offspring would have 'natural' HIV resistance (Normile 2019). Based on the secretive nature of the Jiankui's research, the patient's consent was questioned (Davies 2018a).

Jiankui's embryonic research, among other scandals (such as the Gelsinger case highlighted in section 1.1.1, p. 9), directly violates Article 13, which states "the responsibilities inherent in the activities of researchers, including meticulousness, caution, intellectual honesty and integrity in carrying out their research…" (p.44). These concerns around consent are not only limited to *personal* consent, but also consent on the behalf of the unborn child (Fletcher and Richter 1996). There are many challenges when defining who has the right to consent and for what procedure, whether it be to treat a severe or mild disease, or to enhance one's own capabilities. For most medical applications, especially those which need to be done before the child reaches 18 years, parents can give consent on their child's behalf. Yet, HGT is perceived as an unnaturally invasive procedure where the aim is to modify your DNA in a permanent, and in some cases, heritable way. As such, new guidelines surrounding consent need to be considered. This was highlighted in the 2015 UNESCO Report on *Updating Its Reflection on the Human Genome and Human Rights* (UNESCO 2015), produced in response to the fast-paced nature of the field where responsibility towards future generations was highlighted as one of five key issues moving forward.

Jiankui's highly controversial research was heavily criticised for its lack of transparency and raised clear ethical issues pertaining to patient consent and welfare (Dyer 2018). Furthermore, not only was Jiankui's experiment in violation of Chinese law, it did not conform to the international norms of research conduct, demonstrating the need for international responsibility in the regulation of HGT (BBC News 2018; Cyranoski and Ledford 2018; Wang et al. 2018; Burrows 2019)

As discussed above, HGT is littered with failed and infamous experiments that have occurred within living memory. A mixture of ambition, shortcuts, blind faith and little supporting science meant that the last 40 years, have shown a number of high-profiled experiments were unsuccessful and, arguably, morally dubious (Sandhu, Keating, and Hozumi 1997). Accordingly, many scientists and members of the public are cautious about this technology (Saba, Moles, and Frewer 1998; Robillard et al. 2014; Pew Research Center 2016; McCaughey et al. 2016; Gaskell et al. 2017; Delhove et al. 2020). With gene therapy being one of the most important ethical areas of medical research, understanding public attitudes is imperative so we can be better prepare for a future with this technology.

1.1.3 Public attitudes towards human gene therapy

"Learn from me, if not by my precepts, at least by my example, how dangerous is the acquirement of knowledge, and how much happier that man is who believes his native town to be his world, than he who aspires to become greater than his nature will allow."

(Frankenstein, or, The Modern Prometheus, Mary Shelley)

HGT raises many different and, often conflicting concerns that have been the subject of public opinion studies. Particularly in the last four years, research into public attitudes of HGT has increased (Delhove et al. 2020). While research has primarily focused on public attitudes towards enhancement technologies and specific cases of therapeutic genetic modification, use of DNA and adverse societal outcomes have also been topics assessed. Below provides an overview of all surveys that were designed to assess aspects of HGT (whether this be a small subsection of the survey, or the main focus of the survey), that were published at the time of writing this thesis

1.1.3.1 Demographic associations with attitudes

Before delving into the specific attitudes, numerous studies have identified general (high-level) demographic associations with public perceptions and attitudes towards HGT. The most common of these demographic categories, being gender, age, education and religion, are summarised below.

1.1.3.1.1 Gender

Several public attitude studies have attempted to evaluate the differences between gender in attitudes towards, and perceptions, of HGT. Overwhelmingly, these studies have observed females to be more concerned or negative towards HGT and its applications (Napolitano and Ogunseitan 1999; Hampel, Pfenning, and Peters 2000; Evans, Kelley, and Zanjani 2005; Barnett, Cooper, and Senior 2007; Črne-Hladnik et al. 2009; Hudson and Orviska 2011; Črne-Hladnik et al. 2012; Xiang et al. 2015; Cebesoy and Öztekin 2016; McCaughey et al. 2016; Gaskell et al. 2017; Weisberg, Badgio, and Chatterjee 2017; Hendriks et al. 2018; Critchley et

al. 2018). For example, Hampel's 2000 study of 1,051 German participants found that only 24% of females accepted genetic engineering, compared to 40% of males. The authors attributed this variance to a gendered perception of risk.

It has been well demonstrated that females and males differ in their general perceptions of risk and trust, especially in relation to science and technology (Gustafson 1998; Slovic 1999; Henwood, Parkhill, and Pidgeon 2008; Kim, Park, and Kang 2018). Viewing risk as a social and cultural construct explains, in part, this difference[4] (Henwood, Parkhill, and Pidgeon 2008). Even though gender ideology and gendered practice is constantly evolving, the stereotypical roles of females (feminine, nurturing, emotional, accommodating, weak) and males (masculine, strong, competitive, logical) prevail and influence our sensitivity towards risk and our ability to trust (Wynne 1992; Flynn, Slovic, and Mertz 1994; Blackstone 2003; Dotti Sani and Quaranta 2017). This can be illustrated by a women's nurturing or protective role which has been associated with a heightened caution towards anything that involves risk with little benefit (Flynn, Slovic, and Mertz 1994). This gender difference will be discussed further in Chapter 9 p. 160 (the Discussion).

Despite this large body of evidence suggesting a difference between the genders, there have been a few publications that have detected no difference between male and female attitudes (Liu et al. 2011; Treleaven and Tuch 2018; McCaughey et al. 2019), and only one study that showed the opposite; namely females were more in favour of HGT than males (Wang et al. 2017). In this Chinese study, 13,201 participants (comprising of both clinicians (16%) and the general public (84%)) took part in an online survey designed to assess attitudes towards gene therapy. Contrary to other studies, women were significantly more likely to accept gene therapy when used to correct a child with an inherited disease, and in germline cells.

1.1.3.1.2 Age

Of the limited studies that assessed the relationship between age and attitudes towards HGT and gene editing, four showed a decline in acceptance as age increased (Hudson and Orviska 2011; McCaughey et al. 2016; Weisberg, Badgio, and Chatterjee 2017; Critchley et al. 2018),

[4]It is important to note that, while social and cultural constructs are major influences on the observed gender differences, these differences in risk perception are also created from a range of other complicating effects that are not discussed here as it is beyond the scope of this thesis.

with a further four finding no association (Barnett, Cooper, and Senior 2007; Liu et al. 2011; Gaskell et al. 2017; Treleaven and Tuch 2018). Only one study found older participants to be more positive towards HGT (Strong et al. 2017). To note, this differing study focused on a small cohort of 42 American participants suffering from sickle cell disease. Therefore other influencing demographic factors intensified by a small sample population may have played a part in this unusual result.

Scepticism towards science and the perception of increased risk has been demonstrated to strengthen as age increases (Slovic 1999; Dohmen, Pignatti, and Lehmann 2016; Banks, Bassoli, and Mammi 2020). Over the years, several studies have attempted to demonstrate factors such as changes in emotion (Necker and Ziegelmeyer 2016), cognitive decline (Bonsang and Dohmen 2015) and financial instability (Loewenstein 2000; Guiso, Sapienza, and Zingales 2018) as key influencers to the increased risk aversion observed in senior citizens. However, a recent study examining risk attitudes in approximately 25,000 Europeans aged 50 and older provides an alternate view (Banks, Bassoli, and Mammi 2020). Banks' et al. refines the potential factors and concludes that life-events such as health shocks, retirement, and widowhood which progressively occur as individual's age are particularly important in the development of risk aversive behaviours and attitudes.

1.1.3.1.3 Education, awareness and career

Several publications have demonstrated a positive link between favourable attitudes towards HGT and either an increased knowledge of the topic or a higher education level of the participant (Macer 1992; Macer et al. 1995; Hampel, Pfenning, and Peters 2000; Ng et al. 2000; Sturgis, Cooper, and Fife-Schaw 2005; Hudson and Orviska 2011; Črne-Hladnik et al. 2012; Robillard et al. 2014; Cebesoy and Öztekin 2016; McCaughey et al. 2016; Scheufele et al. 2017; Wang et al. 2017; Weisberg, Badgio, and Chatterjee 2017; Critchley et al. 2018; Hendriks et al. 2018). In his 2017 paper, Weisberg et al. proposed that their results suggested exposure to the topic had a positive effect on perceptions. However, several studies have opposed these findings, by either demonstrating no association (Chen and Raffan 1999; Evans, Kelley, and Zanjani 2005; Macer et al. 2007; King et al. 2010; Ganne, Garrioch, and Votruba 2015; Xiang et al. 2015; Treleaven and Tuch 2018), while only a couple have presented findings showing a negative association (Barnett, Cooper, and Senior 2007; Uchiyama, Nagai, and Muto 2018).

Barnett et al. (2007) observed that, as both education level and awareness of genetics increased, a decline in acceptance of HGT was observed.

While there has been observed association between higher education, awareness and increased support for technologies, literature has highlighted the importance of steering away from using these results as a reason to educate the public in order to address these negative attitudes. Coined by social scientists in the 1980s, the deficit model describes a communication strategy based on the notion that the public's scepticism or disinterest towards science and its applications was primarily due to a lack (or deficit) of knowledge about science and the scientific method (Pitrelli 2003; Simis et al. 2016). As a consequence, approaches to increase public awareness and positivity towards science primarily focused on the provision of knowledge, educating the public through one-way methods of communication (Stocklmayer 2013). This notion that an increased awareness and literacy directly leads to acceptance has been disproven (Einsiedel, Jelsøe, and Breck 2001).

Studies that assessed participants with a career found varied results of association with some finding a career in science or medicine as a predictor of acceptance (Macer 1992; Macer et al. 1995; Ng et al. 2000; Wang et al. 2017), yet more often than not, published studies found no relationship between the two (Chen and Raffan 1999; Macer et al. 2007; Liu et al. 2011; Ganne, Garrioch, and Votruba 2015; Xiang et al. 2015; Treleaven and Tuch 2018).

1.1.3.1.4 Religion

Several studies have found an inverse association between a participants religiosity and attitudes towards HGT (Hampel, Pfenning, and Peters 2000; Evans, Kelley, and Zanjani 2005; King et al. 2010; Hudson and Orviska 2011; Robillard et al. 2014; McCaughey et al. 2016; Scheufele et al. 2017; Critchley et al. 2018). For example, Evans et al. found Australian Catholics to be less supportive of gene therapy for the correction of both major and minor physical defects, compared to non-Catholics. While no study has yet to confirm a positive relationship (i.e., those who identify as religious are more likely to support HGT), two have identified no association (Liu et al. 2011; Xiang et al. 2015). Interestingly, both of these studies assessed young Chinese medical professionals, i.e., young nurses and doctors (n = 328; mean age = 28-33) (Liu et al. 2011) and medical students (n = 579; mean age = 22) (Xiang et al. 2015).

In Robillard's 2014 study, nearly one half of participants from America and Canada claimed that their faith or moral belief system affects how they feel personally about gene therapy. Other published work has supported this finding (Singer, Corning, and Lamias 1998). Two possible reasons to explain the formation of negative attitudes towards HGT due to one's religion or faith have been proposed by Saba et al. (1998); (1) a perception that HGT amounts to playing God and (2) their belief system rejects human improvement (Saba, Moles, and Frewer 1998). Religiosity affecting one's attitudes towards HGT is particularly prevalent when discussing embryonic and enhancement applications of HGT (McCaughey et al. 2016; Scheufele et al. 2017; Critchley et al. 2018). Religious objections of HGT have been observed throughout the past two decades, with the Catholic church actively vocalising their concerns (Moraczewski 1991). Yet recently, Pope Francis voiced his support for treating humans through genetic modification, but *only* if this will not lead to humans being treated as objects, or the creation of 'super humans' (Davies 2018b).

1.1.3.2 Procedural techniques

> *"It has now become a serious necessity to better the breed of the human race. The average citizen is too base for the everyday work of modern civilization. Civilised man has become possessed of vaster powers than in old times for good or ill but has made no corresponding advance in wits and goodness to enable him to conduct his conduct rightly."*
>
> (Sir Francis Galton, 1905)

1.1.3.2.1 Use of DNA

The use of DNA is integral to the procedural processes underpinning HGT. However to date, limited studies have assessed public attitudes towards this aspect of HGT (Bonatti et al. 2002; van Lieshout and Dawson 2016; Strong et al. 2017; Critchley et al. 2018). The use of animal DNA within research and applications of HGT has been confirmed to be conflated with concerns relating to animal welfare and rights (Einsiedel 2005; Pivetti 2007). In a 2018 Australian study by Critchley et al., females were more likely to raise concerns about the morality of animal biotechnology. Recent research has emphasised that the strength of these concerns are also influenced by factors such as the need and type of procedure (Critchley et al.

2018; van Eenennaam and Young 2018). In these studies, morality and *purpose* was shown to play a role in defining the acceptability of animal biotechnology.

The perceived 'unnaturalness' of animal and bacterial or viral DNA may also play a role in the relatively low acceptance rate towards these types of DNA (van Eenennaam and Young 2018). This fear of unnaturalness is borne out of many different factors, such as disgust, morality (e.g., whether it is perceived as 'playing God') and a naturalistic fallacy that nature is inherently good (Lull et al. 2017). While studies on public perceptions of bacterial or viral DNA for use in HGT are less prevalent, it is possible to conclude that the decrease in support is due in part to the unnaturalness or foreign nature of the material. Weisberg (2017) has previously suggested a link between the insertion of 'foreign' DNA into humans could be also akin to an enhancive procedure that is widely perceived as unacceptable (Weisberg, Badgio, and Chatterjee 2017). When the clinical indications are more serious, it is said that this can contribute to a decrease in fear or concern of unnaturalness in the individual (Lull et al. 2017). Furthermore, in Strong et al.'s 2017 study, the use of the HIV in HGT evoked negative connotations, in part due to the viruses' cultural stigma.

1.1.3.2.2 Invasiveness of the procedure

While few studies have assessed the techniques employed in HGT, two studies, almost a decade apart, observed a negative effect on attitudes with increasing invasiveness of the procedure (Blair, Kacser, and Porteous 1998; Strong et al. 2017). Both studies were designed to assess patients suffering from a chronic disease (cystic fibrosis and sickle cell disease, respectively) and family member's attitudes. In the case of Blair's study cystic fibrosis trial patients who discussed the invasiveness of the procedure represented a small section of patients all of who identified as someone with an anxiety disorder.

1.1.3.3 Therapeutic, enhancive and prophylactic applications

1.1.3.3.1 Increased severity of the clinical indication

As the severity of the clinical indication increased, acceptance of a gene therapy intervention was also found to increase in the majority of studies who assessed this (Macer 1992; Macer et al. 1995; Napolitano and Ogunseitan 1999; Ng et al. 2000; Bonatti et al. 2002; Evans, Kelley, and Zanjani 2005; Sturgis, Cooper, and Fife-Schaw 2005; Macer et al. 2007; Liu et al. 2011; Robillard et al. 2013, 2014; Xiang et al. 2015; Cebesoy and Öztekin 2016; McCaughey et al.

2016; Musunuru, Lagor, and Miano 2017; Wang et al. 2017; Hendriks et al. 2018; Uchiyama, Nagai, and Muto 2018). These results can be further divided into studies who assessed a specific disease (e.g., Alzheimer's disease or heart disease), to those who assessed a generic 'severe', 'debilitating' or 'fatal' disease. For example, Xiang et al. (2015) found that treatment by HGT of *perceived* severe diseases such as breast cancer (64%) and congenital heart disease (60%) were more acceptable than more minor diseases such as attention-deficit/hyperactivity disorder (41%) and high blood pressure (44%). Only a couple of studies appear to break this trend, showing an inverse association between severity and acceptance of HGT (Kim et al. 2006; van Lieshout and Dawson 2016). In van Lieshout and Dawson's study of Year 10 Western Australian students (n = 41), 50% indicated they would use HGT for minor diseases, compared to only 36% for a serious disease.

The dominant observed pattern of these studies (i.e., increasing severity is associated with increasing acceptance of HGT) supports previous findings which indicate individuals tend to rate the acceptability of different HGT procedures on a case-by-case basis depending on what type of illness or disability is being treated and its severity. This has been previously discussed by Gaskell et al. (2017) where he posits the issue is not with the technology itself, but its applications. Factors that play into opinion formation on a technology include whether the technology is necessary in conjunction with the perceived risks of the technology and the technology's perceived ethical concerns (Frewer, Howard, and Shepherd 1997). In addition, 'the potential for a cure', 'societal burden of the disease', 'link of a disease to a single gene' and 'public support for the research' were rated as important in the opinion formation process (Rabino 2003). Starr adds to this theory by suggesting that what people view as a tolerable or acceptable risk is approximately proportional to the perceived benefits (Starr 1969). For example, as the perceived severity of the disease increases, treatment of the disease becomes more necessary, therefore the benefits start to perceivably outweigh the identified risks of the procedure (Macer 1992).

1.1.3.3.2 Medical (therapeutic) versus non-medical applications (enhancive and prophylactic)

Enhancements, or non-medical HGT procedures are universally seen as less acceptable than all therapeutic applications (Macer et al. 1995; Napolitano and Ogunseitan 1999; Ng et al. 2000; Iredale et al. 2003; Evans, Kelley, and Zanjani 2005; Sturgis, Cooper, and Fife-Schaw 2005;

Macer et al. 2007; Robillard et al. 2013, 2014; Xiang et al. 2015; Cebesoy and Öztekin 2016; McCaughey et al. 2016; Gaskell et al. 2017; Musunuru, Lagor, and Miano 2017; Scheufele et al. 2017; Wang et al. 2017; Critchley et al. 2018; Hendriks et al. 2018; Treleaven and Tuch 2018; McCaughey et al. 2019). McCaughey's 2016 study of 12,000 participants world-wide found approximately 59% of respondents agreed with the use of HGT to cure a life-threatening or debilitating disease. This agreeability rate dropped to 43% when HGT was used for non-health (enhancement) purposes. A similar trend was observed in Sturgis et al.'s study where participants were accepting of HGT for medical purposes (73%), yet this support substantially dropped to 24% for enhancement procedures and 33% for cosmetic purposes. This decrease has also been identified for prophylactic applications, where 85% would accept HGT treatment for cardiac disease, however this decreased to 54% when HGT was used to prevent cardiac disease (Bonatti et al. 2002). Van Lieshout et al.'s study of adolescent boys was the only study to deviate from this trend, with participants showing more positive attitudes towards enhancement applications of HGT compared to medical purposes.

The fear of *creating* a new 'superior' race of humans is also ever-present when discussing human genetic modification for enhancement purposes. In 2016, the Pew Research Centre published an online survey aimed to identify attitudes towards new scientific developments that could enhance ourselves past our existing boundaries. American adults (n = 2,410) participated in the survey, of these 68% were 'very' or 'somewhat' worried about gene editing (Pew Research Center 2016), a large reason behind this is the fear of unknown consequences. While participants in this survey highlighted that we should do anything to help humankind, the fear that society will transition into a form of 'superhuman' race was observed (Pew Research Center 2016). Other public opinion research has highlighted areas of additional apprehension including fear of discrimination when creating a super-breed, and biased access to the technology leading to inequality among the community (Rabino 2003; Partridge et al. 2009; Scully, Rippberger, and Rehmann-Sutter 2004).

1.1.3.3.3 Personal experience of disease or disability

Only a couple of HGT attitude surveys have assessed whether personal experience of disease or disability plays an influencing role in perceptions towards HGT, of which a two found no association (Iredale et al. 2003; Weisberg, Badgio, and Chatterjee 2017). In Iredale's 2003 study, 22 people (divided into general public (n = 13) and people with cystic fibrosis and their

family members (n = 9)) from Wales participated in semi-structured interviews designed to assess attitudes towards gene therapy, enhancement and societal issues surrounding this technology. This study suggested that positive attitudes of gene therapy did not necessarily stem from one's health status or exposure to an affected person (in this case, close contact to a person with cystic fibrosis), although those who were affected by cystic fibrosis (either personally, or by having a close association to an affected individual) were found to be more excited for germline editing to correct disease. While overall Iredale et al. did *not* find an association, several studies have found individuals perceive their risk for a disease to be higher when a close family member has been diagnosed with a disease (Montgomery et al. 2003; Bloom et al. 2006; Chen and Kaphingst 2011). In his study, Wang et al. found participants who had a personal association with someone with an inherited or debilitating disease were more likely to accept HGT for severe diseases. This observation was supported by Strong et al. (2017) who also found parents of children with a disease of higher severity (in this case, sickle cell disease) to accept more risk.

1.1.3.3.4 Somatic versus germline editing

While some studies showed no, or an insignificant difference between attitudes relating to somatic compared to germline gene editing technologies (Macer et al. 1995; McCaughey et al. 2016; Scheufele et al. 2017; McCaughey et al. 2019), the vast majority of papers assessing this difference showed participants were more supportive of somatic editing (Napolitano and Ogunseitan 1999; Ng et al. 2000; Iredale et al. 2003; Sturgis, Cooper, and Fife-Schaw 2005; Črne-Hladnik et al. 2009, 2012; van Lieshout and Dawson 2016; Musunuru, Lagor, and Miano 2017; Wang et al. 2017; Critchley et al. 2018; Hendriks et al. 2018). Recently, 57 Australians participated in a Question and Answer panel discussion on gene editing (Treleaven and Tuch 2018). Findings highlighted high support for editing of human embryos to improve one's health, but not for enhancement purposes. Similar findings were seen in another nation-wide Australian survey of 1004 participants (using a combination of telephone and online participation) published in 2018 (Critchley et al. 2018). This survey evaluated attitudes of animal and embryo gene editing, and, like previous research, the vast majority of support for embryo editing was present for only health purposes. When questioned about 'designer babies' (a baby that has been genetically modified as an embryo in order to have specific genetic traits), support dramatically decreased (Marques, Critchley, and Walshe 2015; Critchley et al. 2018).

Previous research has shown also a higher disapproval rate for embryonic stem cell than of adult stem cell research (Nisbet 2004). In a follow up paper by Nisbet, this difference in acceptance was attributed not only to religion and ideological positions, but also concerns of the potential for science (and scientists) to adversely influence this technology (Nisbet and Goidel 2007). However slowly the approval rating is increasing, and in 2018 a Gallup poll 66% of Americans felt that germline editing for research was morally acceptable (Gallup 2018). Yet for some, manipulating an embryo is still unacceptable and should never be permitted (Araki and Ishii 2014). How the public would access and regulate such a procedure has also been highlighted by ethicists as a concern as each country has varying policies surrounding this technology.

1.1.3.4 Governance and ethics

1.1.3.4.1 Procedural risk and unknown consequences

Numerous studies have supported the proposition that the public view HGT as too risky (Macer 1992; Macer et al. 1995; Costea et al. 2009; Hudson and Orviska 2011; Črne-Hladnik et al. 2012; Cebesoy and Öztekin 2016; Strong et al. 2017; Weisberg, Badgio, and Chatterjee 2017; Hendriks et al. 2018). For example, in Hudson and Orviska's 2011 study of approximately 1000 European participants, 43% identified HGT as too uncertain and risky, citing previous HGT misfortunes such as the presence of leukaemia in patients after HGT clinical trials.

Almost equal to this number are the amount of studies that observed participant's feeling there were more benefits than risks in HGT procedures (Blair, Kacser, and Porteous 1998; Jaffé et al. 1999; Hampel, Pfenning, and Peters 2000; Kim et al. 2006; Macer et al. 2007; Xiang et al. 2015; Gaskell et al. 2017; Uchiyama, Nagai, and Muto 2018). Of these, Blair et al. reported the highest support with 87.5% of respondents (cystic fibrosis trial participants) having no concerns about the risks of HGT. In this study, the willingness for a patient to take part in a HGT clinical trial was said to be strongly related to the balance between the individual's perceptions of risk being outweighed by the benefits of the trial.

1.1.3.4.2 Consequences of natural law and other ethical and moral issues

One of the most common ethical concerns relating to HGT was the belief that the procedure was analogous to 'playing God' or 'meddling with nature' (Macer 1992; Macer et al. 1995; Blair, Kacser, and Porteous 1998; Holm and Jayson 2003; Iredale et al. 2003; Črne-Hladnik et

al. 2009; King et al. 2010; Črne-Hladnik et al. 2012; Robillard et al. 2013; Xiang et al. 2015; Wang et al. 2017; Hendriks et al. 2018). In Robillard's study 43% agreed that "interfering with genes should not be allowed as it defies nature"; (Robillard et al. 2014). Previous research has shown that on average 5-7% of individuals reject HGT primarily on the basis that it would be 'playing God' or 'unnatural' (Macer et al. 1995). This argument has also been used specifically as a reason to reject of genetic enhancement procedures (Macer et al. 1995): i.e., the unpredictable nature of 'playing God' and the perception that 'nature-modifying' technologies have an increased potential to create disastrous outcomes.

Rejection of all aspects of human gene editing has also been found to stem from the fear that replacing natural selection with deliberate selection will lead to increased inequality (Koch 2010), concerns that are also raised within fictional works such as the 1990s film *Gattaca* or Aldous Huxley's *Brave New World* (Surmeli 2012). Inequality borne from uneven resource distribution (Robillard et al. 2013), exponential population growth due to a healthier population (Robillard et al. 2014; Xiang et al. 2015), as well as less human diversity (van Lieshout and Dawson 2016; Hendriks et al. 2018) and genetic discrimination (Robillard et al. 2013; Xiang et al. 2015), have shown to be influencing factors in public attitudes of HGT and have consequences lasting for generations to come.

1.1.3.4.3 Genetically modifying embryos and children

In 2017, Gaskell et al. found that the genetic modification of adults (75%) was more accepted with the procedure being 'morally superior' to editing an unborn child (60%) in an online worldwide study (Gaskell et al. 2017). In addition, findings from a 2014 Pew survey identified two-thirds of Americans believed changing the genetic make-up of children to produce a more competitive offspring was less acceptable. The results from the Pew survey also revealed enhanced offspring was thought to lead to unwanted consequences as discussed below (Smith 2014).

Sparrow argues that parents who have the option to genetically enhance their unborn child are doing so in order to maximise the predicted general welfare of that child (Sparrow 2013). However this type of manipulation of our genetics to manufacture a 'perfect' or 'enhanced' child is fraught with danger. A world that contains so many different cultures, communities and opinions will never be able to define the 'perfect' human. Striving for a single perfect standard can easily lead to judgement and inequitable procedures that favour the connected and the

wealthy. Fear of creating a genetic 'fashion trend' that is available only to the affluent has been raised by several ethicists and academics (Fenech 2018). Unlike other fashion trends, these modifications would be permanent and possibly heritable. Anxiety that such modifications could take the human body to extreme limits, creating a trans-humans species has also been raised frequently in literature (Koch 2010).

This process also raises issues of consent not only on deciding a child's fate, but also making changes to the genome that will affect many generations. Additionally, it conflicts with some religious ideologies of citizens (Lanphier and Urnov 2015). In Iredale et al.'s study respondents raised that parents should not be discouraged from having children that will develop a severe genetic condition, and that parents do not have the right to enhance their offspring.

1.1.3.4.4 Consequences of unregulated science and human gene therapy governance

Concerns of the consequences of scientific actions is something that is clearly reflected in the public's response HGT (Couzin and Kaiser 2005; Marques, Critchley, and Walshe 2015; Nicol et al. 2017). Scientific responsibility has always been of keen interest to the public, especially in the case of HGT, and for good reason. A hasty approach to such a new science culminated in the death of Jesse Gelsinger from a severe immune response towards the viral vector used in his HGT procedure (Stolberg 1999). Fear is often felt by the public that one discovery will lead to a slippery slope of unregulated techniques that will lead to unethical and adverse consequences such as permanent disability or extreme forms of enhancements (Smith 2014).

Other issues surrounding HGT's production include high cost (Wang et al. 2017) and private companies as sole providers leading to restricted and uneven access to HGT (Iredale et al. 2003). In the 2012 Australian National Enabling Technologies Strategy Expert Forum discussed concerns around breakthroughs in this area (The Australian Institute for Commercialisation 2012). The report indicated that current technological developments are often profit driven and more importantly, raised concerns of human enhancement having no limit and being difficult to regulate. Implementing and/or maintaining strict regulations and governmental oversight has been proposed by some to avoid misuse and risks associated with HGT (Pew Research Center 2016).

Kevin Esvelt, a prominent American biologist with a research focus of genetic engineering, currently uses his reputation in the scientific community to highlight the need for ethical and responsible innovations of genetic engineering (Esvelt et al. 2014). As part of his mandate, he

proposes the creation of an 'antidote' for the proposed genetic modification *before* trials begin in order to limit unwanted permanent consequences and side-effects (Regalado 2016a). This type of research is crucial to positively develop an area that is plagued with doubt by experts and the public. It is through the actions of Esvelt and others that share a similar agenda that reinforces the responsibilities of scientists. For without scientific responsibility, this technology is prone to human rights violations due to its controversial nature, a susceptibility that is influential in formation of attitudes towards HGT.

With the variability of procedural applications (therapeutic, enhancive, and prophylactic) and a range of issues that directly impacts human rights, policy design is challenging and fraught with risks. The next section focuses on the current regulatory structures for HGT and attempts to form governance structures and international consensus. Numerous policy and regulatory strategies currently rely on governing bodies and sector peak bodies being the major decision-makers, taking little to no public opinion into account (Burstein 2003). This strategy tends to lead to problems when regulating health technologies (OECD 2017), as discussed below in Section 1.2.2 (p. 43).

1.2 A REVIEW OF THE GOVERNANCE OF EMERGING TECHNOLOGIES

This section presents a review on the current landscape of HGT policies and provides examples of how governments have incorporated public opinion into their policy design. Where none exist, examples of similar controversial medical technologies will be described alongside the strengths and failures of their governance processes. With HGT technology advancing at a rapid rate, countries are struggling to keep up with policies that directly regulate this procedure and its' consequences, as discussed below. So far, each country, organisation, institute or agency has a slightly different interpretation of what this technology encompasses, how it is regulated and the flow-on impacts it has for science and citizens. To the general public varying interpretations may appear insignificant, but in fact could lead to harmful consequences where —for example— the safety of the product might not be properly ascertained before public release, or human rights obligations surrounding this technology are not taken into account in the technology's governance structure. As this technology quickly advances, it is imperative we have close global collaboration in this complex area when drafting appropriate legislation.

1.2.1 Current policies, regulations and legislations

1.2.1.1 Current international regulation

To date, no unified policy or regulatory board exists on a global scale to regulate HGT (Isasi and Knoppers 2006; NASEM 2017). Even within western democratic countries, restrictions and policy design can vary greatly. Since the 1990s an effort has been made to coordinate an international standard of conduct for the research and implementation of HGT (Montgomery 2018; NASEM 2017; Meikar et al. 2010). Despite these attempts, formal regulation and legislation will likely never be realised on a global scale due to the fact that each country has different cultural values and economies which translates into diverse legislative and regulatory structures (Walker and Soulis 2016; Mourby and Morrison 2020; Hock, Kian, and Wah 2020). A strong example of this variation can be seen through the current global regulatory landscape on germline genetic modification where major HGT players such as China, the US and the EU have vastly different restrictions as illustrated in Figure 1 below. To begin this section, individual governance structure development of HGT regulations in these key regions are detailed.

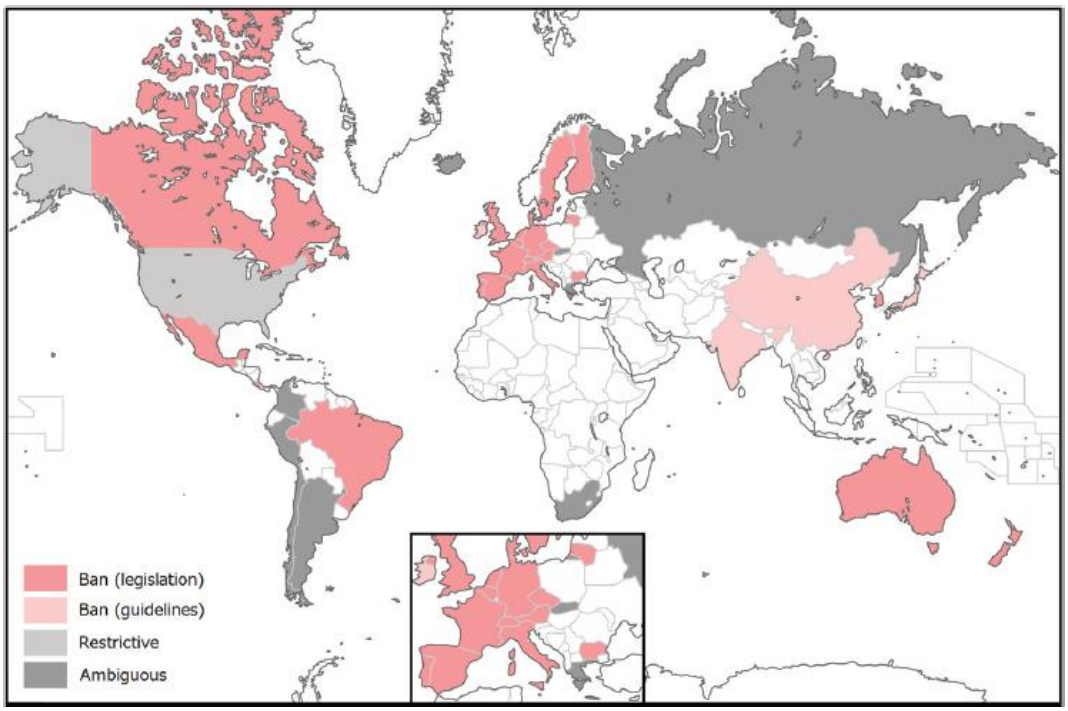


Figure 1. Map detailing differences in global regulations of human germline genetic modification (Araki and Ishii 2014).
Twenty-five countries have sanctioned legal prohibitions on germline modification (red), four countries provide recommendations or guidelines (pink). In this illustration, light grey countries have restricted its use pending further evidence, while dark grey represents ambiguous regulations.

1.2.1.2 Current regulatory frameworks

1.2.1.2.1 United States of America

Over half of all gene therapy trials worldwide are associated with US investigators and/or institutions (Hanna et al. 2017). As such, US regulations influence the research and development of the majority of HGT products. Both human clinical trial and eventual sale of these HGT products within the US are regulated by the FDA which runs rigorous tests to determine the safety and efficacy of a proposed drug (Halioua-Haubold et al. 2017; FDA 2019). Within the FDA, the Center for Biologics Evaluation and Research (CBER) is charged with regulating gene therapy products and their related devices (FDA 2019). The FDA require tests for safety, purity and potency before their sale.

The FDA is one arm of the Department of Health and Human Services (HHS) that regulates gene therapy. The other is the Office for Human Research Protections (OHRP) which ensures all human trials are reviewed and approved by the Institutional Review Boards (IRB) (HHS 2020). In addition, emerging medical technologies like gene therapy are also subject to the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) recommendations (Wolinetz 2019). This Committee provides advice through a public forum designed to discuss scientific, safety and ethical issues relating to all new technology. In the committee's Charter, public attitudes are considered as part of this review process (NIH: Office of Science Policy 2019). NExTRAC replaced the original RAC in an effort by the NIH and the FDA to streamline gene therapy regulation in order to reduce duplicative reporting structures (NIH: Office of Science Policy 2020).

1.2.1.2.2 European Union

The European Medicines Agency (EMA) oversees the evaluation and regulation of medicinal drugs within the EU. Originally, the Committee for Medicinal Products for Human Use (CHMP) provided advice to the EMA through the Gene Therapy Working Party (GTWP) on HGT products and direct or indirect issues arising from this technology (Klug et al. 2012; Halioua-Haubold et al. 2017). In 2007, the Committee for Advanced Therapies (CAT) was established on behalf of the EMA to specifically assess and approve drugs made from genetic and cellular material for the European market and provide advice to the CHMP (Cichutek 2008; Schneider et al. 2010). Representations from patients were included as part of the CAT's terms

of reference. Until its disbandment in 2012, the GTWP also reported to the CAT. Since then, this Working Group has been replaced by ad-hoc and temporary drafting groups (EMA 2012).

Distinct from other governing bodies, the EMA does not have authority to review or approve clinical trials. Instead clinical trials are authorised by national regulatory agencies, a process that can be misused to an individual countries advantage (Bender 2018). In an attempt to reduce the legislative disparity between nations, in 2019 the European Commission provided an overview of national regulatory requirements to harmonise genetically modified organisms (GMO) and medicinal product legislation across the continent. However, to date this document has not been officially adopted by the Commission (European Commission 2019). While this process was not successful, recently, overarching regulatory guidelines on clinical trials have been developed by the EU with participation from the FDA (Iglesias-López et al. 2019). The FDA currently uses this Directive as a guidance document.

The EU and the US also work together to ensure access to needed medicines occurs at a fast-tracked rate. In the EU, the EMA launched EU PRIME that works with developers of medicines which fulfil a currently unmet need within society (EMA 2016). The US equivalent, US Breakthrough Therapy, similarly is focused on the expedition of innovative medicine (FDA 2018). However, due to their varying legal frameworks, synchronisation, assessment and tracking of the requests between the two associations is difficult to achieve (Iglesias-López et al. 2019).

1.2.1.2.3 China

Compared to other Western jurisdictions, less detail is known about the current regulations emplace due to the lack of English-language literature available. While no enforced HGT regulations currently exist in China, guidelines have been created and updated since 1993 (Rosemann, Li Jiang, and Zhang 2017). The original guideline published by the Chinese Ministry of Health was titled "*An outline of Quality Controls for Clinical Studies of Human Somatic and Gene Therapy"* (Library of Congress 2015; Rosemann, Li Jiang, and Zhang 2017). This was revised in 1999 under a different title. In 2003, the China Food and Drug Administration (CDFA) released *Guidance for Human Gene Therapy Research and Its Products.* Within this document, requirements for clinical trial protocols, testing and the construction of recombinant DNA and its delivery system and ethical review are outlined.

In 2019, draft regulations were published which stated that human gene editing, gene-transfer or genetic regulation will automatically be classified as high-risk and overseen by China's State Council. Those who do not comply with these regulations could potentially be penalised by a lifetime research ban or revoking licenses (Wang, Wang, and Cai 2020). In some cases, criminal investigations may also be instigated. The draft regulations appear to be a response from He Jiankui's research (Burrows 2019).

1.2.1.2.4 Australia

Within Australia, there are several governing bodies involved in the assessment and regulation of gene therapy research, trials and products. Gene therapy research proposals must be submitted first to the Human Research Ethics Committee (HREC) for initial review (Macpherson and Rasko 2014). This task was originally supported by the Gene and Related Therapies Research Advisory Panel (GTRAP), a subcommittee of the National Health and Medical Research Council's (NHMRC) Research Committee, established in 1994 to provide HREC with advice on medical, scientific, ethical and safety issues related to gene therapy protocols (Martiniello-Wilks and Rasko 2007; Jin, Yang, and Li 2008; Macpherson and Rasko 2014). The GTRAP in turn consulted with other bodies concerned with monitoring the safety of innovative genetic manipulation techniques (Gene Manipulation Advisory Committee) or assuring the quality and safety of medicines (Therapeutic Goods Administration (TGA)) (Tribe 2012). This panel was replaced by Cellular, Tissue, and Gene Therapies Advisory Committee, however this Committee only remained for an additional three years (2006-2009). From 2009 until present day, gene therapy research and clinical trials are approved and monitored by the HREC, TGA and recorded in the Australian Clinical Trials registry (O'sullivan et al. 2019). At present, no clear policies relating specifically to HGT trials are in place in Australia. Yet, gene therapy contains many components, both ethical and technical in nature, which separates this technology from others. A guideline for HGT, similar to those seen with embryonic research in Australia, should be considered within the next few years to respond to the growing demand for this technology.

1.2.1.2.5 The future of regulation in Australia

In 2012, the Australian National Enabling Technologies Strategy Expert Forum discussed concerns around breakthroughs in this area (The Australian Institute for Commercialisation

2012). The report indicated that genetic technologies, like HGT, would be difficult to regulate. Unfortunately, this was a one-off meeting with little follow-up and no guidelines were produced. Nonetheless, an important milestone in this field was realised in November 2017, where the Council of Australian Governments (COAG) Health Council agreed to Australia's first National Health Genomics Policy Framework (the Framework) (AHMAC 2017) which acknowledges within its opening pages "the tremendous potential for genomics to contribute to early diagnosis, better targeted treatments and disease prevention" (p. i). While this framework focuses on all genomic applications impacting the health of the population, two founding principles that closely relate to HGT include "the application of genomic knowledge is ethically, legally and socially responsible and community trust is promoted" and "access and equity are promoted for vulnerable populations". This framework also recognises that there is a potential for genomic applications that currently have a more limited relevance to population health (such as HGT) to emerge. As part of this framework, these applications will be monitored with the potential to develop related policy frameworks in the future where appropriate.

1.2.1.3 Implications of ill-defined procedures

As briefly mentioned in section 1.1, there are numerous techniques that can be employed to edit DNA to either correct a problem or provide a new function. Depending on the goal, approaches include: inactivating a mutated gene, correcting the DNA sequence, replacing the abnormal gene with a (normal) copy, or the insertion of a new gene. Again, there are a couple of ways to achieve these outcomes. Subject to the target organ, affected cells may be removed, edited and then transplanted back (Crystal 1999). This process of transplantation was successfully used recently in Germany to treat a boy who suffered from epidermolysis bullosa, a rare and incurable skin condition that causes the skin to peel and blister (Fine et al. 2014). Abnormal skin cells were extracted, corrected and grown *ex-vivo* into sheets of normal skin, this new skin was transplanted back to the boy in a series of operations, with little side-effects (Servick 2017). Using an individual's own modified cells has the extra advantage of reducing the risk of forming an immune reaction to the transplant. Normal functioning genes can also be injected into the body, using a vector which contains a functional copy of the DNA sequence. This procedure is also becoming increasingly safer (Skipper and Mikkelsen 2019). In 2017, US researchers successfully used this technique in a man with Hunter's syndrome, a genetic disease that causes unusual growth and delayed development (Kaiser 2017). The variety of techniques

makes it hard to encapsulate HGT in a ‘one-size-fits-all’ definition used to regulate this technology.

1.2.1.3.1 Defining human gene therapy

Both the EMA and the FDA categorise gene therapies underneath an overarching class of medicine, known as advanced therapeutic medicinal products (ATMP). By classifying gene therapy as an ATMP, both the EMA and the FDA view gene therapy as a drug product which can be further defined as a biologic product. Alternatively in China, the Chinese Ministry of Health has authority over laws and regulations for gene therapies (Rosemann, Li Jiang, and Zhang 2017). Under this system, gene therapies are classified as high-risk “Category 3” medical technologies instead of a drug product as adopted by the FDA and the EMA.

Given HGTs biological categorisation by the FDA and EMA, the characterisation and manufacturing of these gene therapies presents its own challenges due to known variation between batches of the same product (FDA, n.d.). To rectify this, both major regulatory agencies oversee the manufacturing process and outline strict guidelines to ensure consistency of clinical performance across batches (EMA 2018). However, even within this biologic product classification, it can be difficult to differentiate between the various biological subcategories, a decision that affects the gene therapy’s regulatory framework throughout its life course (Iglesias-López et al. 2019).

Acknowledging the recent increased focus on HGT, major regulatory actors such as the FDA and the EMA have reviewed and updated their definitions and guidelines. Currently, the FDA still uses its 1993 classification, with gene therapy defined as a product:

“*that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient”*

(FDA,1993)

The EMA defines gene therapy as a biological medicinal product which fulfils the following two characteristics:

> *"[a] it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing replacing, adding or deleting a genetic sequence; [b] its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence"*
>
> (European Parliament, 2009)

While these are equivalent definitions, this technological frontier is moving fast, increasing the possibility of definitions not encompassing all variations of gene therapy products (Halioua-Haubold et al. 2017; Wirth, Parker, and Ylä-Herttuala 2013). Furthermore, the reliance on the term 'recombinant DNA' to define HGT may soon be outdated, as new technologies move away from using foreign nucleic acid sequences altogether (Mourby and Morrison 2020). As regulatory agencies try to keep pace, variations between the FDA's and the EMA's definitions may begin to arise between the organisations as neither relies on a consensus in order to develop and implement regulations. Even *within* a governing nation, adverse outcomes can occur due to misalignment of definitions.

Recently, a lack of a unifying and encompassing definition to describe the mechanisms and processes of HGT has impacted another area in the genetic modification sector. Controversially, in 2015 the US Department of Agriculture (USDA) decided not to regulate a CRISPR-edited white button mushroom which was expected to be sold in the US pending further testing (Panko 2016). The reasoning behind this decision was based on the fact that the method did not use foreign DNA from viruses or bacteria to produce the desired reduced enzyme activity which delayed mushroom browning (USDA 2015). By 2018, genetically-edited plants were excluded from regulatory oversight by the USDA altogether (Kuzma 2018). In 2019, the Australian government followed suit, opting not to regulate organisms that have been modified using certain non-invasive gene-editing methods after a review conducted by the OGTR (OGTR 2019). This decision has been described as a regulatory "middle-ground" between the weaker laws in the US and the more stringent laws adopted by the EU and China (Salleh 2019).

Unlike the FDA and the EMA, Australia's TGA has not officially adopted a definition for HGT. This is unsurprising as gene therapies are only publically accessible through a limited number of clinical trials. Clinical trials are exempt from TGA approval and therefore only need to notify the administration and ensure they follow ethical and safe practices (TGA 2020). This, however, is about to change. In 2020, an application was received by the Medical Services Advisory Committee (MSAC), a body responsible for assessing new medical services proposed for public funding in Australia (MSAC 2016a). This application proposed public funding for Luxturna, a HGT intended for the treatment of inherited retinal dystrophies, a major cause of early-onset blindness (MSAC 2020). Luxturna is the first FDA approved prescription HGT for use *in vivo* (FDA 2017). As internationally approved gene therapies increase, it is only a matter of time before a strict definition of these procedures will need to be in place. Which definition we align with is a different matter, and is of great significance to Australian governance of HGT and how each product is assessed.

Governments are witnessing fast-paced technology advancements which require increasingly complex regulatory decisions that are dictated by definitions. By having disparate policies within and between countries, collaborations and innovations may be limited due to uneven restrictions on projects and resources. Although many countries do have at least some form of regulatory oversight over genome-editing research, not all do. As a consequence, research and development into this field is highly competitive which has led to questionable, if not unethical research, as was seen in China's recent gene therapy scandal (Burrows 2019). This is compounded by the fact that HGT has numerous unknown societal consequences, which have implications that need to be addressed both nationally and through international cooperation.

1.2.1.4 Implementation of a unified framework

With different regulatory pathways and oversight, there is a clear need for countries to collectively discuss and address both the human rights and procedural challenges arising from this technology. A global unified framework will serve to standardise manufacturing, ethical research and safe utilisation for prophylactic, therapeutic or enhancement procedures. There is a spectrum of pathways one could use to create an international regulatory framework. Three broad categories of these approaches exist: (1) a transnational regulatory dialogue and networking, (2) international coordination and/or cooperation and (3) treaty-based harmonisation.

1.2.1.4.1 Transnational regulatory dialogue and networking

Transnational regulatory dialogue and networks (TRNs) describes an informal communication and learning process between different regulatory bodies (Newman and Zaring 2013); an example of this can be found between the EMA and the FDA in production of their individual guidelines on HGT. Due to the customary informality of this network, there is an inconsistent framework under which these TRNs operate (Eberlein and Grande 2005). Outputs of this network, including guidelines, are non-binding and with no international legal status (Helleiner and Porter 2010). This means that participating organisations do not need to ratify decisions or implement recommendations. For this reason, TRNs have the advantage of flexibility, speed, and are somewhat immune from the politics seen to dominate and delay treaty-based harmonisation strategies (Fenwick, Uytsel, and Wrbka 2014). Alternatively, a lack of organisational accountability and under-utilisation that pervades this process means any decisions and uptake of policies are rare. Furthermore, TRNs often fail to address implementation issues around international regulatory frameworks which act as a barrier to action (Verdier 2009).

Official TRNs which constitute membership of different regulatory government agencies are currently not as widespread. Most networks are established and run by scientists urging for consistent global regulations and guidelines that encompass all aspects and issues that arise from a technology (Verdier 2009). In France, the Association for Responsible Research and Innovation in Genome Editing (ARRIGE) initiative was launched in early 2018 (Montoliu et al. 2018). Through this initiative, thirty-five countries participated in the first meeting to discuss the ethics and governance of gene editing. Despite a promising start, to date, little tangible progress has been made by this collaboration. Like many other similar initiatives that have been created over the years, this initiative appears to have limited effect on enacting change, a characteristic inherent of TRNs (Verdier 2009; Helleiner and Porter 2010).

1.2.1.4.2 International coordination and/or cooperation

International coordination and/or cooperation are instigated to create policy designed to address issues that, in most cases, have repercussions both internal and external to a country (Ostry and Ghosh 2013); that is, implications that cross borders. In response, non-binding instruments are often developed, such as principles, guidelines or a set of standards. Increasingly this form of

international regulation is being utilised. Two major examples of international coordination include climate change (such as the Paris Climate Agreement) and in response to epi/pandemics (as orchestrated by organisations such as the World Health Organization (WHO)). However, like all approaches, there are advantages and disadvantages to this form of strategy. In the case of time-critical and clearly defined events like epidemics, a non-binding instrument allows for policy flexibility and quick action (National Research Council of the National Academies 2010). On the other hand, with slow moving and multi-faceted crises like climate change, international cooperation such as the Paris Climate Agreement tends to be exploited as a publicity stunt by leaders (Cass 2015; Hilson 2020). In 2017, *Nature* published an article that alleged none of the major nations who had signed the Paris Climate Agreement had implemented their envisioned policies and had not met their pledge to reduce their emissions target (Victor et al. 2017). This paper summarised that the short-term gains that are achieved by unilateral decision-making tend to be more seductive than pursuing long-term action that would increase global welfare. Unfortunately, with any international cooperation or coordination type approach, there is no overarching body that regulates or successfully coordinates each country's proposed actions, leaving it to the folly of short-term leaders with political agendas.

While not specifically linked to HGT, the United Nations Declaration on Human Cloning represents a legally non-binding statement that was approved by a divided UN General Assembly in 2005 (Mayor 2005). Within this statement, Member States were asked to "adopt all measures necessary to prohibit all forms of human cloning". After four years of debate, the Statement was successfully introduced. Yet countries did not alter their practices in response to the Statement (Jarrell 2006; Arsanjani 2006). In answer to this failure, a working group was established in 2008 to assess the feasibility of a binding convention to ban human reproductive cloning. This idea was largely ill-received by Member States and was put on hold until 2015 (Langlois 2017). Since then, little progress has been made.

1.2.1.4.3 Treaty-based harmonisation

The gold-standard of collective regulation is in the form of a binding treaty forged from formal negotiation (Hoffman et al. 2015). A strong example displaying the success of this approach can be found in the Council of Europe's Oviedo Convention. This Convention calls for the prohibition of genetic engineering of germline cells, an issue intrinsically linked to HGT

(Council of Europe 1997). While this Treaty is not ratified by all European countries, and regulatory enforcement is uneven across the continent, it is currently the first and only international legally binding instrument which specifically focuses on human rights in the biomedical and bioethical sector (Sykora and Caplan 2017). It builds on previous agreements and principles recognised by the European Convention of Human Rights which aims to protect the dignity and identity of all human beings with regard to the application of biology and medicine. The Convention was endorsed in 1997 Oviedo, Spain by twenty-nine European State Parties (Hondius 1997). Notable exclusions include the UK, Germany, Italy and ironically, Spain. In 2017, at the treaty's 20th anniversary, a reconsideration of the ban was put forward to the Parliamentary Assembly (Montgomery 2018). While strong arguments were made in favour of reversing the ban due to the outdated arguments originally used, the Assembly ratified its original stance and urged the remaining countries to sign the Oviedo convention (Lowthorp 2017). This is a perfect demonstration of one crucial limitation of this strategy. Once in force, amendments to reflect advancements in this sector are difficult to achieve and therefore not suited to regulate fast-changing technologies like HGT (Cho and Kelly 2012).

To date, no attempts at an international regulatory framework for HGT or surrounding issues of similar emerging genetic technologies have been completely successful (Hayakawa et al. 2016). This is not to say that there have been no beneficial outcomes achieved from previous efforts, more so that these initiatives need to be evaluated and altered to achieve their designed purpose. A crucial aspect missing from these initiatives is the lack of public participation within these processes. As argued below, public participation is a necessary step in the formation of regulatory guidelines for those policies that are controversial in nature and have the ability to affect society as a whole.

1.2.2 Public participation as part of policy formation

"Democracy is not a spectator sport, it's a participatory event. If we don't participate in it, it ceases to be a democracy"

(Michael Moore, 2009)

A technocratic society follows a socio-political structure of governance where those who are crucial to the decision-making process are selected based on their expertise (Esmark 2020).

This process was borne out of the idea that experts, such as scientists, understand more risks and impacts than politicians. This suits most first world countries which rely on 'evidence' to validate policy processes (Ingrams 2019). However, the technocratic process is arguably at odds with democracy by relying on the 'elite' to speak for the many (Gilley 2017). While this form of governance is useful for standard technologies with precedence, it falls short for those of a more novel and controversial nature, as argued below.

Arguments in favour of the technocratic process rely on the assumptions that (1) expert knowledge is the highest priority in the decision-making process, and (2) experts and science itself are value-free (Durant 1999; Esmark 2020). In reality, those who feed into the decision-making process are often the ones that are directly influenced by these regulations (for example, an academic providing advice on new regulations on their area of research) and thus have an inherent conflict of interest (Durant 1999; Abraham and Sheppard 1997; Kurki 2011). Therefore, policies created through this process are harder to justify and accept when dealing with post-normal science.

When it comes to the subjective nature of evidence, 'post-normal' sciences (high risk and ethically ambiguous science and technologies – of which HGT is an exemplar) are often considered to be the most fraught (Funtowicz and Ravetz 1994). Unlike 'normal' scientific issues for which risk assessment can be based for the most part on scientific evidence, decision-making around post-normal science has to rely on a multitude of perspectives in order to assess risks and benefits (Brossard et al. 2019) With the advancement of science, post-normal sciences are becoming increasingly present, especially within the health policy sector (Dankel, Vaage, and van der Sluijs 2017). HGT represents a commonly cited case of "post-normal science" for which "purely technical expertise is not enough to address the complexities surrounding a scientific issue that has not only technical but also social, ethical, and legal dimensions" (Brossard et al. 2019). Thus, reflecting on guideline development and policy making for the post-normal science of HGT, arguably this space can only benefit from multidisciplinary approaches. Public participation models are one way to ensure a policy framework is accountable, responsible and aligned with the dominant values of the nation.

1.2.2.1 The public participation model

Communication and deliberation of controversial scientific research and discovery desperately needs a heightened level of transparency through active dialogue with all stakeholders,

including the public (Sato and Akabayashi 2005). This is especially the case when discussing technologies that can modify our genetic make-up, as this process clearly raises many ethical and moral questions, as discussed above. To be successful both domestically and internationally, biotechnologies like HGT must establish an acceptable position in a social-political framework. It is imperative that these questions and concerns are addressed and decisions are incorporated into sound policy if we are to progress in this field and add value to people's lives through these scientific discoveries. The onus is on the academics and government to open a discussion with the public.

Gene technology is a perfect topic for public deliberation. Characteristically, it is a 'new', controversial technology containing a variety of values-based issues which would benefit from public input being included from the beginning of the process (O'Doherty and Einsiedel 2020). From its advent, ethicists and scientists have been vocal of the need for public engagement surrounding this technology (Lanphier and Urnov 2015; Nicol et al. 2017). Furthermore, public opinion surveys have repeatedly reported public calls for inclusion (Delhove et al. 2020). A 2017 conference organised by the American Heart Association identified 72% of those present would not support germline gene editing if the public remains unconsulted (Musunuru, Lagor, and Miano 2017).

To achieve a health system that is focused on the needs of its population, a decentralisation of decision-making must occur (Macklin 1993). This means moving away from central government structures and *towards* a public participation model. The main purpose for the utilisation of public participation in policy design is to ensure communities who have identified issues or who would be directly affected by the policy, are able to contribute to decisions on the planning and management of public programmes. Advocates of public participation view this contribution as an individual's democratic right and, some argue, duty to participate in practices and policies that impact them (Neuwelt 2007; G. Smith and Setälä 2018; Zakhour 2020). It is now accepted by most governments that a consultation process at crucial stages of decision-making and implementation is required (Kerley and Starr 2000). Not only is it the public's right to participate, public participation can also lead to other outcomes that are beneficial for any mature government (Macklin 1993). Main outcomes of public inclusion include accountability, and increased responsiveness, among others.

1.2.2.1.1 Accountability

Accountability and transparency is at the heart of any true democratic system. Allowing policy to be publicly scrutinised at each stage of policy development ensures standards are being met and are in line with the public's interests (Macklin 1993). Traditionally within the 20th century, accountability has been measured by audits of administrative data and reports on pre-defined outcomes of policy (Heinrich 2003). This form of accountability is generally a less complex process, where policy is assessed based on whether the program has met its expectations within a defined timeframe under a specific resource allocation (Greiling and Halachmi 2013). In addition, this model tends to rely on information being provided *to* the public in the form of publically available reports, which normally has a short-term emphasis on accountability. Recently this process is being harnessed by governments and transformed into a more dynamic model as we begin the 21st century (Fenwick and McMillan 2012).

Now in the digital age, the performance of a policy can be monitored in almost real-time. Information is more accessible to the public and as such, there is an increasing need for governments to be publicly accountable in both their planning, performance and monitoring of their policies (Greiling and Halachmi 2010). Active public participation is one way of holding the government to account, providing sound quality assurance measures with the added advantage of improved credibility and legitimacy of governmental action (Kerley and Starr 2000).

A side benefit of active public participation is public empowerment and the encouragement of its citizens to take part in, and be responsible for, their public system (Macklin 1993). It has also been shown that there is a potential for increased policy acceptance and compliance with the law when individuals feel included within governmental processes (Kerley and Starr 2000). This participatory process promotes structural development by allowing feedback from all invested parties (as a user or producer) and often leads to the transition of this improvement into more of a long-term approach (Neuwelt 2007). Furthermore, public feedback has other benefits. By creating a transparent process from a projects initial phase of development, issues can be mitigated earlier (Macklin 1993; Quick and Bryson 2016). However, this public participation through accountability will only be successful if mechanisms are in place to respond to such feedback quickly. While time consuming to develop, the benefits to society have been proven to outweigh the short-term costs and complexities initially observed (Watermeyer and Rowe 2015).

1.2.2.1.2 Responsive policies

In its basic form, policy can be framed as a response to a need within its society (Macklin 1993). Within the health system, this 'response' is often designed to balance inequalities within its population (Macklin 1993). Public participation therefore provides the government an opportunity to be more responsive to the needs of its population. By setting a framework that lets people have a say in health care directions, more appropriate care can be envisioned, particularly to those who are disadvantaged, leading to improved healthcare for all citizens (Simonsen and Robbins 2000). By using public participation within this context, the rights of people can be recognised, respected and assured, ultimately leading to better quality legislation (Kerley and Starr 2000). Government is also better positioned to respond to changing circumstances and review accordingly when a consistent public participation framework is embedded, leading to a more empowered population who will speak up when unplanned adversity arises (Simonsen and Robbins 2000; Feldman et al. 2006). Through representation and consultation, it is in the best interest of the government to support public participatory models and to begin expanding its structure to incorporate it (Macklin 1993).

1.2.2.2 Public participation in practice

Critics of the technocratic society[5] have been emboldened by the momentum shift towards participatory governance that occurred in the late 20th century (Burget, Bardone, and Pedaste 2017). Increasing use of public participation in policy has been made in Australia and abroad, however many hurdles still exist. In addition to logistical hurdles like time and cost (Rowe and Frewer 2000), this model of decision-making requires forming relationships and building trust, communication of knowledge (Rowe and Frewer 2000; Cobb 2011), and balancing varying stakeholder needs (Macklin 1993; Ross 2007). In terms of the practice of public participation, multiple models have been developed to address a wide range of policy-types and process limitations. Models range from volunteering and community campaigns to government consultations and advocacy.

[5] A technocratic society places emphasis on the opinions of experts while marginalising the role of the general population and non-experts in policy formation (Gilley 2017).

1.2.2.2.1 Responsible research and innovation – a brief overview

Responsibility of science and governance has been a major theme since the Enlightenment period (Lessem and Schieffer 2016). Despite this, research and innovation in the scientific and technological fields still functions largely separately from government and its oversight (Stilgoe, Owen, and Macnaghten 2013). While scientific freedom and autonomy is incredibly important to foster scientific innovations within a democratic society, this cannot be at the cost of accountability. To date, efforts to address scientific responsibility and its governance has been focused on the *outcomes* of science and innovation i.e., the negative and unacceptable impacts on a society. This limits a government's response to a scientific product, focusing on risk-based regulations as a 'Band-Aid' solution and is less likely to be future-orientated (Adam and Groves 2011).

Challenges when forming policy which encompasses both scientific responsibility and accountability, without restricting innovation, led to the development of the European Union's Framework on responsible research and innovation (RRI) in 2010 (European Union, n.d.; Owen, Macnaghten, and Stilgoe 2012). This framework was based on a similar evaluative framework known as Ethical, Legal and Social Aspects (ELSA), originally designed to address issues born from the Human Genome Project[6] (Knoppers, Thorogood, and Chadwick 2013). The RRI framework describes scientific research including technological development that takes into account both effects and potential impacts on society with a particular emphasis on emerging social and ethical issues. This process relies on a spectrum of societal participants, from researchers, government, business and, importantly, the public. Each actor within this framework works together throughout the research and innovation process in order to ensure its outcomes align with the public's values, needs, and the expectations of society. In practice, public participation is a major part of RRI and can lead to a variety of tangible benefits. Foremost, it allows a spectrum of perspectives to inspire design of innovative policy that is relevant to its citizens (Stilgoe, Owen, and Macnaghten 2013; Burget, Bardone, and Pedaste 2017).

[6] The Human Genome Project describes the international, collaborative research program established in 1990, whose goal was to map the entire human genome. This project was finalised in 2003 (US Department of Energy 2019).

1.2.2.2.2 Deliberative democracy in the biotechnology sphere

Deliberative democracy —a form of democracy in which deliberation is central to decision-making process— can be thought of as RRI in practice. Presently in Australia, deliberative democracy methods (such as citizen juries) are gaining traction (Russell 2017). Greater legitimacy is now being given towards this form of citizen deliberation as its methods encompass a wider representation of the public values and views compared to elected officials (e.g., policy makers) (Vandamme and Verret-Hamelin 2017).

There are many different methods of public engagement that fall under the deliberative democracy umbrella. Consensus conferences evolved from the deliberative democracy method, which has been around since the founding of democracy itself (Joss and Durant 1995). This process involves the establishment of mini-publics, organisational bodies in which diverse members of the public are randomly nominated to deliberate an issue of public concern (Smith and Setälä 2018). The Danish Board of Technology was the first to develop and use this process in a modern governance setting in an attempt to encourage policy makers to engage with the public. Interestingly, the first consensus conference was used to deliberate gene technology in industry and agriculture in 1987 (Einsiedel, Jelsøe, and Breck 2001). Since then, this process has been used in a number of countries to ascertain public opinion on many biotechnology topics including, but not limited to, gene therapy (Denmark, 1995; Belgium 2003), genetic data and testing (Germany, 2001; Denmark, 2002, Austria, 2003), and biobanking (Canada, 2009) (Nielsen 1995; The Australian Museum 1999; Einsiedel, Jelsøe, and Breck 2001; Secko et al. 2009).

However, despite its advantages, no democratic process encouraging public engagement is without flaws. Although efforts are made to ensure a wide sample of the population participates citizen attendance is generally low in numbers, (Carpini, Cook, and Jacob 2004). In addition, public deliberations still have a tendency to be represented by a slightly bias cohort of the population, with those who are willing to attend often reporting different opinions to those who do not (Fishkin and Luskin 1999). Another observed issue is those who are more outspoken tend to dominate the discussions (Jordan 2014). A capable facilitator is therefore crucial to get the best outcome from all of those who attend and scaffold the conversation appropriately (Jordan 2014).

There is also often a disconnect between the citizen deliberation and policy decisions which questions the validity of the process (Scheufele 2011). In these cases, public participation has

been separated from the formal decision-making process and is therefore perceived as more of a public relations exercise with little value (Mitton et al. 2009). As described above, the technocratic discourse focuses on risks rather than a comprehensive, holistic review of the technology in question. This focus means public participation is only usually involved *after* the decision-making process has been well-defined and framed through a risk lens (Ross 2007). Steve Rayner, a prominent British scientist argues that this then reduces discourse to risk management:

> *"The discourse of governance is reduced to a discourse of science. The discourse of science is reduced to risk. Thus the whole business of government is reduced to a discourse in risk management."*
>
> (Rayner 2003)

Rayner goes on to suggest policy should instead promote and incorporate social and cultural norms of a society rather than risk assessment in order to align with public values.

This risk frame has also been suggested to limit public participation strategies to a consensus building exercise as opposed to actually incorporating the public's concerns (Irwin 1995). To rectify this, the public need to be included *before* policy formation begins. This principle is the foundation of RRI introduced by the EU (Owen, Macnaghten, and Stilgoe 2012). Inviting the public to be present and contribute at the beginning of the research, development and agenda-making phase, is reported to encourage accountability, empowerment and is at the heart of democratic principles. It also decreases the need in controversial cases to instigate informal action by the public (Harding 1998). When public participation modes are excluded from this process, it has been shown that it is difficult for governments to maintain public trust.

While public consultation is sometimes perceived as a public relations exercise, there are cases where it has focused the attention of government and produced sound policy direction (Kerley and Starr 2000; Sato and Akabayashi 2005). Two recent public consultations are examples of where this process was successfully used to effect change in bioethical policies in both France and the UK. Les états généraux de la bioéthique (The General Public Discussion) was convened in France prior to the scheduled revision of the French Bioethics Laws in 2009 (Spranzi and Brunet 2015). This "General Public Discussion" included institutional reports, an interactive

website, public debates and three Consensus Conferences consisting of twenty-five citizens, each designed to deliberate a subset of bioethical issues. France's General Public Discussion culminated in a final report written by the participating citizens which presented recommendations that came out of this process. While criticism was directed at the limited amount of citizen recommendations that were eventually incorporated into the 1994 Law revision, citizens *were* able to express their concerns within an official forum and media coverage precipitated further public discussions within France and abroad (Spranzi and Brunet 2015; Hunyadi 2018).

The British Government has also used public participation practices to investigate the ethical issues raised from a controversial medical technique, to great effect. In 2012, the UK's Human Fertilisation and Embryology Authority (HFEA) launched a public consultation on the potential social and ethical impacts of mitochondrial replacement therapy, an illegal procedure at the time (Watermeyer and Rowe 2015). This new technology allowed those going through in vitro fertilisation (IVF) to use donor mitochondria to prevent the transmission of incurable mitochondrial diseases (Wolf, Mitalipov, and Mitalipov 2015). Specific public consultation processes included deliberative public workshops, an online survey, patient focus groups and an expert review of the safety and efficacy of the techniques. As a result of this process, in 2013 it was reported that the majority view was to use this technique as a treatment, however it should be carefully controlled (Agrawal, Burt, and Homburg 2013). Further consultation was sought on draft regulations from around the UK which lead to this experimental treatment being made legal in 2015. This lead to the Chief Scientific Adviser at the time, Sir Mark Walport, to suggest that "approval in the UK of mitochondrial donation provides a blueprint for future decisions on modifying the genome" (Hawkes 2015).

While some see the UK's consultation process as overstated in its successes (Haimes and Taylor 2017), the principle of consultation itself is not critiqued. A major criticism of this UK process was the way diverse and opposing opinion was merged into policy. Despite this, a comprehensive review of the process confirmed the overall success of the public consultation process (Watermeyer and Rowe 2015). Noted in this review, stakeholders felt the economic cost to produce the dialogue was worthwhile to prove democratic science governance works. However, like France, the public struggled to identify links between their recommendations and the final legislation.

Recently the NHMRC, on behalf of the Australia Government, initiated a similar process to review the social and ethical implications of legalising mitochondrial donation. Along with the creation of an expert working group, an extensive public consultation process was held in late 2019 that included citizen panels, webinars, written submission and public forums. In July 2020, a Position Statement from the citizen panel showed the majority view in favour of its legalisation (NHMRC 2020a). The report on all public consultation processes detailed a wider range of views and concerns that needed to be considered before moving forward (NHMRC 2020b). To note, the importance of continued community engagement was highlighted towards the end of this report. Just before the NHMRC's findings were published, Newson et al. also published research results from a separate academic-led Australian citizen jury on the use of mitochondrial DNA (Newson et al. 2019). After the jury received expert advice, the majority of participants also believed mitochondrial gene transfer should become legal within Australia, as was seen within the UK and NHMRC findings NHMRC 2020b).

1.2.2.2.3 The Australian context

As part of the federal government's National Health Strategy, throughout the 1990s, Australia published a series of background papers. A paper within this series was produced to specifically address public participation and accountability in the Australian health care system (Macklin 1993). This paper highlighted the importance of public participation to ensure accountability in its governance and acknowledged that, under the previous system, disadvantaged people had often been excluded. Without public consultation embedded within the decision-making process, only organisations and lobbying groups can be readily identified or contacted for input. This means that well-resourced groups have the highest influence within this process and, in most cases, don't naturally share the same views as the public (Lowery 2013).

Within the last couple of decades, the Australian government has actively sought to secure public stakeholder input in their decision-making processes through public advertisements and calls for submission (Macklin 1993; Kerley and Starr 2000). One way of doing this is through a Risk Impact Statement (RIS). In every policy decision within Australia, a RIS must accompany the process (Australian Prudential Regulation Authority 2020). Each RIS must contain details of consultation processes undertaken and the views elicited from major players, including, where appropriate, the public. There is also a growing role for parliamentary committees and royal commissions to conduct hearings, invite public submissions, and provide

key public consultative functions in order to form more risk-prone policies (Kerley and Starr 2000).

In the past five years there has been a number of high-profile Royal Commissions on a range of policy issues. These time-consuming and costly processes provide the government an opportunity to respond to policies that contain complex facets that are not easily solved (Heath 2017). In theory, Royal Commissions are designed to restore public trust and provide government with a list of recommendations to implement. However many commentators are critical of this style of investigation because of its often limited mandate, time and terms of reference, which are set by the initiating government (Heath 2017; Prasser 2020). Like all policy decisions, they are ultimately at the mercy of political agendas.

Other models of participation are slowly being incorporated into the Australian decision-making process. For example, South Australia holds one of the largest uranium mines in the world. In 2016, two Citizens' Juries were held in South Australia to deliberate the State's role in nuclear storage and disposal (Government of South Australia 2016). Fifty, randomly selected South Australian's took part in a week long 'trial' where expert witnesses were called to present the key issues surrounding the topic, including findings of a recent Royal Commission on the nuclear fuel cycle (Scarce 2016). After deliberation, a report was produced that identified key topics to be discussed as part of the state-wide consultation program that followed. This program included a range of consultative activities and events at over 100 sites across the state, including regional, remote and metropolitan areas. This culminated in the government's decision to remain as an exporter only, despite the jury not coming to a consensus. While lack of agreement could be *perceived* as a failure, the citizen's jury success lay in the ability of the deliberative process to engage citizens, maintain government transparency over a complex and controversial topic as well as highlight policy gaps, limitations and unresolved issues (Calyx and Jessup 2019). Importantly, reflections by jury members also highlighted the need for a more representative democratic process to deliberate these issues.

While the outcomes of the South Australia's citizen jury were generally positive, this was sadly not the case in Australia's most prominent and publicised consultative process on genetically modified crops. In 2003, InVigor® Canola —genetically modified (GM) to be herbicide resistant— was the first GM food crop to be licenced in Australia (OGTR 2018). This came after a mandatory public consultation process, which limited public submissions to *after* recommendations by the OGTR had already been finalised. This constituted a one-way process;

the OGTR provided information to the public, and within a limited scope, the public could submit their opinion (Ross 2007). Given this was the first GM crop to be grown within Australia, stakeholders and members of the public who took part in this debate and those who participated in the OGTR process have been highly critical of the InVigor® Canola decision (Ross 2007). This process did not help to lessen the publics fear that submissions are either not considered, or can be overridden based on the agenda of the day. Despite this criticism, community consultation is increasingly becoming a popular option for responsible research innovation technologies within Australia, and abroad (Von Schomberg 2013).

1.2.2.2.4 Health technology assessments

In 2007, the WHO adopted Resolution WHA60.29. In this Resolution, issues arising from health technology deployment were described alongside their potential solutions (World Health Organization 2007). One of the key mitigation strategies proposed in the Resolution urged governing bodies to initiate health technology assessments (HTA) before the technology becomes publically accessible. An HTA is defined by the WHO as "the systematic evaluation of properties, effects, and/or impacts of health technology" (World Health Organization 2011). Significantly, this assessment is not confined to the scientific and technological aspects of a health device or service, but includes evaluation of the social and ethical features of the proposed intervention.

Internationally, there is a growing trend towards increased public involvement in governmental processes involving HTAs, with Australia being no exception (Whitty 2013). The Australian Government established the MSAC in 1998 to complete HTAs on all medical services proposed for public funding (MSAC 2016a). As part of the MSAC's mandate, public opinion is sought throughout the extensive HTA process (MSAC 2016b). Unfortunately, advertisement of these public consultations appear to be limited (posted to the specific MSAC application webpage) and as a consequence, these types of public consultations would be prone to receiving feedback from highly invested individuals who have been alerted of the opportunity through peak bodies (Bunea 2017). Furthermore, the HTA's public consultation form is restricted to written feedback with a pre-defined set of questions asking the respondent for general comments on the advantages and disadvantages of the proposed service (The Department of Health 2020). As highlighted in the findings of Jennifer Whitty's study, adoption of a more deliberative participatory method used to evoke active engagement on a broader scope of issues in the HTA

process is currently limited (Whitty 2013). Despite these apparent disadvantages, this form of consultation may be appropriate for the majority of HTAs that have a limited target population, as those directly affected by the service are more likely to participate (Facey et al. 2010). Nonetheless, this targeted and restricted version of public consultation in an HTA process means that for emerging technologies with expansive consequences like HGT, few members of the public are able to voice their opinion.

With the rapid advancement of genetic modifying technologies, governance of HGT will initially be under constant revision to ensure the safe use of these products. While some countries are taking part in international reviews of these governance structures, others are letting policies and guidelines lapse and become outdated. If worldwide unification of gene therapy guidelines is not currently feasible, Australia must act to update their own. Due to the controversial nature of this technology, an update in guidelines would be wise to use the well-trialled frameworks of public participation to enhance the policy decision-making process. To achieve a sound governance structure, public participation is a crucial step in this process, and is a democratic right of the public.

As discussed in this chapter, applications of HGT are diverse, with potential use as a therapy, enhancement or prevention; each of which raise ethical and moral challenges that are influenced by cultural and community values (Friedmann 1992). As such, solutions to these ethical issues do not necessarily have a 'right' answer. Each country, culture and community has a different belief or way of framing the issues. Therefore, this technology requires a set of new responsibilities to manage the more uncommon aspects of this technology, and one that should be instigated by unified global action to avoid adverse outcomes such as inequity and discrimination (Müller 1987).

Recent international implementation of similarly controversial technologies have highlighted the importance of public opinion and engagement in development of a regulatory framework. A consultation process can provide a thorough understanding of factors that influence public attitudes on a specific phenomenon (Nisbet and Scheufele 2009). It is important though that this canvassing of public opinion is well constructed and encompasses the full variety of implications. An open dialogue is particularly important for this technology as risks surrounding these procedures range from personal to societal.

As discussed, public participation does not need to be an all or nothing approach. Most governments already involve the public in some of their decision-making processes. In a less

direct way, public/consumer choice is analysed and used in the development of policy advice. While this is a time and cost-effective way to produce policy influenced by the current market, it does not account for public values that are critical to be incorporated for the more controversial technologies and innovations, such as HGT. As HGT falls under the umbrella of controversial medical technologies, it is a prime candidate for a robust and heated global debate. For this reason, and others discussed in this introduction, public input is vital to government decisions on the future of HGT (Macer et al. 1995).

1.3 SURVEY APPROACHES TO THE STUDY OF PUBLIC ATTITUDES

1.3.1 Cross-sectional surveys

While public deliberation within the HTA space is not always feasible, a major value of its inclusion is its ability to bring together a diverse range of preferences, values and interests which can be used to strengthen policy design (Street and Lopes 2017). As discussed briefly, there are limitations to large deliberative processes, including cost, the quality of deliberations, and the time taken to collect and enact change after the process concludes (Leighninger 2012; Gastil 2018). This is where cross-sectional survey studies are a useful tool to initially assess public opinion of HGT, given the broad-reaching implications of this technology (Lavrakas 2008). A cross-sectional survey allows for the collection of large and diverse cohorts, providing a snapshot of public opinion at a single point in time.

Surveys are one of the easiest ways of quickly assessing public opinion, however, the level of ease depends on the method employed (Alessi and Martin 2010; Ball 2019). Online surveys (as opposed to mail-out surveys or interviews) are one of the simplest forms of participant recruitment and have the attractive advantage of being swiftly deployed and completed at the participants convenience — a feature that has been suggested to increase response rates (Callegaro, Manfreda, and Vehova 2015; Ball 2019). This coupled with the absence of an interviewer allows the information and questions to be presented in a uniform way and reduces the risk of social desirability bias where participants respond in a way that they view as ‘publically acceptable’ (Grimm 2010; Callegaro, Manfreda, and Vehova 2015). The use of this type of survey can also mitigate the potential for outside influences on a participant’s response, unlike in a public deliberative setting where participant persuasion can occur (Leighninger 2012). However, surveys (particularly online surveys) are particularly susceptible to non-

coverage bias which may lead to a skewed sample population and in some cases, un-replicable findings (Callegaro, Manfreda, and Vehova 2015). Other limitations include self-selection bias (Eysenbach and Wyatt 2002). This form of bias describes a situation where individuals are more likely to respond if they are interested, directly affected or enticed by the incentives offered by the survey. Furthermore, survey research also lacks depth. Survey questions are standardised and tend to ask general questions that a broad range of people will understand without context. Thus the validity of survey results can be weak. However, there are limitations to all research methodologies and are considered when analysing the results.

The advantages of using an online survey format is reflected in the design of the questionnaire. Online automation allows the researcher to use skip logic as a way of personalising the process (e.g., excluding questions on topics that the participant has previously indicated they had no prior knowledge of) and allowing questions to be answered by the participant in the order intended. This flexible design also extends to the use of a variety of interactive question formats (e.g., multiple choice, open response etc.). By providing a variety of question types and ways to interact, the participant's interest is more likely to be maintained, often leading to an observed increase in the quality of a response and overall participation rates (Monroe and Adams 2012; Dolnicar, Grün, and Yanamandram 2013).

Finally, demographic correlations can be identified from cross-sectional surveys that form the basis for further research (Lau 2017). These observed correlations highlight the potential differences in the characteristics of a population, and is a useful tool to identify what matters most to people (Privitera 2014; Omair 2015). From these initial discoveries, further research investigating other aspects of public opinion —such as *why* these values are important— can be instigated.

1.3.1.1 Use of cross-sectional surveys in assessing public opinion on human gene therapy

Of the 41 published studies designed to elicit public views on HGT —of which the majority have used a cross-sectional survey method— only six have included Australian opinion of HGT (Macer et al. 1995; Evans, Kelley, and Zanjani 2005; van Lieshout and Dawson 2016; McCaughey et al. 2016; Treleaven and Tuch 2018; Critchley et al. 2018). Of these six, all have assessed issues from a limited scope and tended to focus on issues relating to the genetic modification of embryos and children. While these are crucial areas of enquiry, these subjects

are a small section of the broader issues posed by HGT, as discussed in this chapter. Attitudes towards the governance, techniques employed, and the variety of enhancement, therapeutic and prophylactic adult applications of HGT are all areas worthy of investigation. Furthermore, while other international studies have touch on certain *aspects* of these issues, none have assessed these issues together (Delhove et al. 2020). By joining the vast array of issues into the one survey, correlations can be established, shedding new light on the public's attitudes of this technology and potentially highlighting social barriers moving forward.

Our next decisions made regarding the regulation of HGT have important implications for shaping our future. This thesis expands on the current Australian literature and intends to contribute to the decision-making process by both trialling survey tools for collecting public opinion and assessing public attitudes to HGT. This preliminary study will opens doors for future research and highlights areas in need of further exploration in regulation and policy before immersive integration into our society.

This thesis was designed to build on these preliminary studies by analysing how individuals in Australia perceive and understand HGT, including their willingness to accept the wide variety of procedural applications and implications in order to provide a more complete picture of current Australian sentiment.

1.4 RESEARCH AIMS & OBJECTIVES

This thesis seeks to answer the following question:

"What is the current public awareness and attitudes towards human gene therapy in Australia?"

We hypothesise that:

"Australians have a limited understanding and awareness of human gene therapy, although they are overall optimistic when presented with this technology – as seen in other global studies"

The aim of this study was to define the public's knowledge, awareness and attitudes towards HGT in Australia. This was achieved by two surveys: (1) an Australia-wide online survey where recruitment relied on chain-sampling via major social media platforms in 2017, and (2) a survey of Australian Capital Territory (ACT) residents where a selection of households were invited to participate by a letter received in the mail in 2019.

The studies objectives were as follows:

(1) Determine the Australian public's current awareness and understanding of HGT by identifying:
    a. Whether they have heard of HGT before
    b. How they would describe HGT
    c. Their knowledge of the current use within Australia

(2) Determine the Australian public's attitudes towards:
    a. Genetic modification techniques of HGT
    b. Procedural outcomes of HGT
    c. Therapeutic, enhancement and preventative uses of HGT
    d. Governance challenges of HGT
    e. Ethical dilemmas borne from HGT

(3) Determine if there is a difference between attitudes towards one's personal use of HGT, and what is acceptable for society.

(4) Compare the results of the two different survey methods

2 Methods

This chapter details the methods designed to analyse the Australian public's attitudes and understanding of HGT. In 2017 we published a national online survey (AUST-Online), which was open for five months. Upon analysis of the data we identified areas for improvement to increase clarity and readability for the participant, eliminated questions of limited value, and added other questions which have found to be associated with public values around controversial medical technologies like HGT. We published the revised survey in 2019 as a mail-out survey to ACT residents (ACT-Mail-Out), open for one month. As discussed within this chapter, this change in recruitment strategy was undertaken to increase the likelihood of achieving a random sample of the population.

Despite the differing recruitment strategy and small variations in survey design, both the majority of questions asked, and the analysis of findings remain the same. It is for this reason that we have chosen to present each survey method alongside one another. Where methods differ, these are presented under their own headings.

2.1 METHODOLOGY SELECTED

As discussed previously in section 1.3 (p. 55), the majority of studies designed to assess public opinion of HGT have been cross-sectional online surveys, primarily due to the method's ease of dissemination and the ability to collect a large population sample in a short time period (McCaughey et al. 2016; Delhove et al. 2020). A similar approach was therefore selected for this study to conduct a robust comparison between previous findings and the findings of this research. Limitations of this approach were considered in the design of this survey, and mitigated where possible, as described below.

2.1.1 Survey design

2.1.1.1 Online Australian survey (2017)

We conducted a search of peer-reviewed literature to review previous public participation survey designs and outcomes. We then developed an Australia-wide online survey consisting of questions to identify eligible participants, basic demographic questions, and 22 substantive

questions within four overarching themes ('awareness and understanding', 'techniques and outcomes', 'therapy, enhancement and prevention applications', and 'governance and ethics'). For the purpose of this analysis, an Australian participant was a person who had self-identified as aged 18 years or over and as being current resident of Australia. An overview of the design is described in Table 1 below, and a full list of questions and response options is provided at Appendix A.

Table 1. A list of substantive and disqualification questions within the 2017 online Australian survey. 'MC' indicates multiple choice, 'OR' indicates an open response and 'TB' indicates a tick-box.

Theme	Q#	Questions	Type
Awareness and Understanding	3	Have you heard of the term Human Gene Therapy before?	MC
	4	How would you describe human gene therapy? (I.e. what does human gene therapy do?)	OR
	5	As far as you are aware, is human gene therapy already being used in Australia?	MC
	6	If you think human gene therapy is already being used in Australia, what does it treat?	OR
Techniques and Outcomes	7	How acceptable is it to treat a sick person using the following techniques?	MC
	8	How acceptable it is to treat a sick person using donated DNA from…	MC
	20	To what extent would human gene therapy be acceptable under each of these circumstances?	MC
	21	In your opinion, what kind of effect has the following had on our society?	MC
	22	How much do you think society as a whole would change if human gene therapy becomes available?	MC
	23	Overall, what kind of effect would this change have on our society?	MC
Therapy, Enhancement and Prevention Applications	9	How acceptable is it to genetically modify a person's DNA to treat a chronic illness that is a…	MC
	10	How acceptable is it to genetically modify a person's DNA to treat a physical disability that is a…	MC
	11	How acceptable is it to genetically modify a person's DNA to treat an intellectual disability that is a…	MC
	12	How acceptable is it to genetically modify a person's DNA to treat a mental disability that is a…	MC
	13	How acceptable is it to genetically modify a healthy person's DNA to enhance a trait and/or ability that is a…	MC
	14	How acceptable is it to genetically modify a healthy person's DNA to prevent...	MC
	17	Would you personally use human gene therapy to genetically modify your DNA to treat an illness?	MC
	18	Would you personally use human gene therapy to genetically modify your DNA to enhance a trait or ability? (e.g. to increase your athletic ability or intelligence)	MC
	19	Under what circumstances would you personally use human gene therapy to genetically modify your DNA?	TB
Governance and Ethics	15 &16	To what extent do you agree with the following statements relating to human gene therapy?	MC

2.1.1.1.1 Definitions

Definitions of gene therapy, enhancement and mutation were provided just after the 'awareness and understanding' themed set of questions, preceding the rest of the survey, in order to provide a general context for the participant. This ensured that all respondents had a common understanding of HGT as a therapy, and how this differed from enhancement HGT procedures. The participant was presented with the following box:

> **"Human gene therapy –** describes the prevention, treatment or cure of a disease or disorder by **genetic modification (i.e. human gene editing)** of the affected cells to correct a cellular dysfunction or to provide a new cellular function.
> Where…
> **Genes –** are made up of DNA and provide a specific function to the cell (e.g. help produce molecules called proteins).
> **Mutated genes –** are genes that directly contribute to the development of disease.
> **Enhancement human gene therapy –** is aimed at improving an already **healthy** person by **genetic modification** to confer an advantage (e.g. to increase your athletic ability)."

In addition to this section, when questions referred to a particular state of health or clinical indication (e.g., chronic illness), one or two examples of common conditions were given to demonstrate the type of disease/disability. For instance, 'severe chronic illness' examples included cystic fibrosis. In the case of questions relating to genetic modification of 'healthy' individuals (i.e., enhancive or preventative applications), examples included potential applications such as 'change of eye colour' or 'increase strength' to describe 'physical enhancements'. A full definitions list of uncommon or scientific words can be found at the beginning of this thesis on page xvii.

Throughout both surveys, questions were often split into themes on "societal use" and "personal use" While "societal use" was left undefined in this study, an assumption was made by investigators that, given its' proximity to "personal use", participants could reasonably assume that "societal use" was the opposite of "personal use".

2.1.1.1.2 Substantive questions

The majority of questions were selected and adapted from previous survey studies. By using a similar design and format, we were able to perform a comparison between observed findings from previous studies and the results from this study of Australian attitudes. In certain cases, the peer-reviewed questions in other studies were modified to investigate preferences in more detail. For example, a set of questions asked respondents to reflect on how favourable certain HGT treatments, enhancements or preventions were under a variety of different conditions. For therapeutic questions, four different categories of disease and disability were designed: chronic illness; physical disability; intellectual disability; and mental illness. These were chosen to determine if there was a difference in acceptability when treating each category with HGT. We selected each category in order to encompass a wide range of diseases and disabilities. In designing this survey, severity of the disease was a key consideration. We recognised that there is ongoing clinical and ethical debate over this concept and that views on severity may be influenced by individual experiences and values. Therefore, each disease or disability category was given three sub-categories: severe; moderate; and mild. Terminal illness was also included within the chronic illness section as the pinnacle of severity. The length of the survey was calibrated to incorporate a wide range of themes relating to HGT without compromising on data quality due to participant fatigue. Our survey is more extensive than previous surveys on the subject, allowing us to identify outcomes not discovered in other studies.

2.1.1.1.3 Demographic and co-variate questions

The survey included questions to obtain standard demographic information, including the participant's sex, education level and age, and whether the participant has children. We also asked whether the participant had been closely affected by a disease or disability. These questions were included based on identified evidence of associations from previous literature (as reviewed in section 1.1.3.1, p. 55). In addition, other questions were included that had been demonstrated in a few studies to have a relationship with HGT preferences. For example, research linking perceptions of HGT to genetically modified food/crops has been undertaken in Australia (Instinct and Reason 2015). Consequently, we included a question designed to ascertain the participant's opinion of genetically modified foods and crops, to investigate whether opinion about manipulating a plant genome is associated with opinion about human gene-editing.

At the end of the survey we included an open-ended feedback section. Quotes that were directly related to public awareness, understanding or the flow of information between government, scientists and citizens were identified and used to enhance the analysis.

2.1.1.2 Australian Capital Territory mail-out survey (2019)

While the AUST-Online survey identified some interesting findings, we observed a number of limitations. Primarily, the online survey relied on chain-sampling via major social media platforms. Partly due to this "network based" dissemination strategy, the sample was not representative of the broader Australian population (e.g., substantially higher levels of younger, female, and highly-educated respondents were observed). This biased sampling method leads to difficulties in making inferences about public perceptions across the Australian public. In order to further investigate the findings of the online survey and overcome some of the limitations identified, we conducted a revised survey. The latter was a randomised mail survey restricted to ACT residents, in order to provide a truer random sample of a small section of the Australian population. The revised survey also afforded us the opportunity to refine the survey questions to: (1) amend questions and rearrange their order to improve overall clarity; (2) exclude questions that were of little value to the analysis (this will be expanded on below); and (3) compare results of the two surveys.

The revised mail survey consisted of two questions to identify eligible participants, basic demographic and co-variate questions, and 28 substantive questions within the same four overarching themes as the online survey. A full copy of the amendments made to the online survey for the ACT-Mail-Out survey, including annotations describing the reasoning behind each amendment, can be found at Appendix B. To avoid repetition in description of methods, only a brief summary of amendments will be detailed below.

2.1.1.2.1 Substantive questions

The online survey version of Q5 ("*Do you believe human gene therapy is currently being used in Australia?*") was found to be too specific, especially as HGT research and trials to date have been limited in Australia (Ginn et al. 2018). It also did not provide us with information on how much the participant knew about the current accessibility of HGT in general (i.e., worldwide). This question was therefore split into two questions (Q5 and Q7) with Q5 having "*in Australia*" removed and Q7 being an exact replica of the online survey question for comparison. The

following open response was therefore amended to Q6: "*If you think human gene therapy is already being used, what does it treat?*".

Part of the study's objectives was to determine differences between what was deemed acceptable for *society* to use, to one's *personal* use. Through the feedback section of the AUST-Online survey, several participants highlighted the ambiguous nature of all 'acceptable' Likert questions (e.g., "*How acceptable is it to genetically modify a person's DNA to treat a chronic illness that is a…*"). Some participant's considered the way the question was framed could be interpreted as either trying to elicit a response for what they would personally use *or* what is acceptable for society as a whole. Therefore, all affected questions (i.e., questions assessing acceptability of a procedure or application) were adjusted to specify society in order to distinguish between personal and societal responses. For example, "*How acceptable is it for **society** to genetically modify a person's DNA to treat an illness that is a…"*.

As part of this amendment process, we added a personal use question under each Likert question to improve the flow of the survey, allowing the respondent to focus on one particular application or technique (e.g., chronic illness) at one time. For example, "*Would you **personally** use human gene therapy to genetically modify your DNA to treat an illness that is a…*". In the AUST-Online survey, personal use questions were asked towards the end of the survey in a tick-box format. This amendment to the survey was borne out of the belief that putting societal and personal questions adjacent to one another allowed participants to better consider the differences. This change also allowed for an analysis of differences between what an individual would be willing to accept for themselves, as opposed to what they are willing to accept for society.

2.1.1.2.2 Demographic and covariate questions

Where possible, all demographic questions were adjusted to align with the Australian Bureau of Statistics (ABS) categories. This affected questions on education and religion. In addition, questions on the participant's primary industry were revised to refer to the Australian and New Zealand Standard Industrial Classification (ANZSIC 2006) used in ABS surveys. For example, the question "*Have you ever worked in either the health or medical industry*" was replaced with "*Which of the following categories best describes the industry you primarily work in (regardless of your current position)*?" This amended question was followed by a list of options from the ANZSIC industry categories. This change was implemented in order to assess whether

other areas of work were found to have an association with certain preferences. A final adjustment was made to include a question asking respondents to confirm their political preferences in order to analyse whether there was an association between an individual's political persuasion and attitudes towards HGT.

2.2 STUDY SETTING AND PARTICIPANT PROFILE

2.2.1 Online Australian survey (2017)

The initial survey population was open to all Australian residents in late 2017 for the purpose of ascertaining a wide scope of perspectives from the Australian population. At the time the AUST-Online survey was conducted, the total population of Australia was 24.6 million. Data published 30 June 2017 from the ABS reported females made up 50.8% of this total, with the median age for Australians being 37 years (ABS 2017b). As at May 2017, two thirds of Australians (66%) had attained at least one non-school qualification such as a certificate, diploma or degree (ABS 2017a). Since questions on disease and disability may cause distress to participants, only adult residents living within Australia at the time of survey participation were eligible to participate. As the survey was only written in English, this further restricted the participant population to participants with the ability to read and answer questions in English.

2.2.2 Australian Capital Territory mail-out survey (2019)

The second survey conducted in 2019 was limited to ACT household residents in order to achieve a random population. ACT was selected given its small population, as well as being the location of the main residence of the primary investigator and her university campus. The ACT had a recorded population of 412,576, 1.6% of the total Australian population that year (ABS 2019b). As of 30 June 2019, the proportion of ACT females was 51.1%, as recorded by the ABS with the median age pf ACT residents being 35 years (ABS 2019b). As of May 2019, approximately two-thirds (68%) of Australians aged between 20-64 years had a non-school qualification (a certificate, diploma or degree) (ABS 2019a). Again, the participation was limited to English-speaking adults.

2.3 DATA COLLECTION

2.3.1 Online Australian survey (2017)

As discussed in the introduction, a cross-sectional survey collection method allowed for the sampling of large and diverse cohorts. This was desirable for an online survey as the design of the survey and the quality of the data received could be evaluated from a wide sample of Australians. Recruitment for the AUST-Online survey relied on chain-sampling through sharing on social media (Twitter, Facebook), local radio stations in Canberra and Perth, and through Australian newspaper articles. This meant that the survey evaluation could occur quickly and cost-effectively. The survey was designed and published online on the Survey Monkey® platform (SurveyMonkey Inc.," n.d.), with the participant information sheet provided on the first page of the survey (Appendix C). Participants also had the option to submit a printed survey upon request. To avoid participant information being accessed through the requesting of a printed version, participants could download the survey and anonymously post it to the surveyors without providing identifying information on the letter or envelope (advertisements to the survey stated no identifiable information was to be included on the envelope). Access to the questionnaire was available to participants for five months, ending in December 2017. This length of time was chosen to ensure enough time had passed after each advertisement round (e.g., radio) so that all possible data was collected.

2.3.2 Australian Capital Territory mail-out survey (2019)

Recruitment for the ACT-Mail-Out survey was undertaken using an implicitly weighted sampling scheme involving selection of 20 houses per ACT residential suburb at random by the principal investigator (i.e., human generated randomisation). The number of sampled households was fixed across suburbs, so the probability weighting for participants was "inversely proportional to size" of the suburb, measured by the number of households in each suburb. Due to an unfortunate miscommunication with dissertation supervisors, the investigator did not use a computer-based replicable randomisation method. Of the 120 official ACT suburbs, only 97 were inhabited at the time of survey dissemination, and therefore only these latter suburbs were included, giving a total of 1,940 houses selected. The nominated houses received a letter inviting them to participate in the survey (Appendix D). Included in the letter was a participant information sheet (Appendix E). The survey was designed and published only online on the Survey Monkey® platform. Due to an increase in incomplete/missing answers

observed in the printed versions of the AUST-Online survey, participants for the ACT-Mail-Out survey were not provided the option to complete the survey through printed forms. In addition, as information and definitions of HGT was provided at key places throughout the survey, using a printed version enhanced the likelihood that participants could scan through the document which in turn may have influenced the results in the knowledge and awareness themed questions. However, this was not found to impact the online results as less than 1% used the print option. Access to the questionnaire was available to participants for approximately three weeks, ending on 1 October 2019. It was hoped that the restricted time would create an incentive to attempt the survey soon after they received the email.

To encourage submissions, respondents to the ACT-Mail-Out survey had an option to enter a small prize draw to win one of three $50 gift cards at a large shopping centre in Canberra.[7] Those who wished to enter into the prize draw were invited to supply their email address at the end of the survey. Winners were selected at random by computer randomisation[8] after the survey had closed. Each winner was notified through their nominated email address on the same day by the principal investigator, and email addresses supplied by the participants were subsequently deleted to maintain the privacy of the participant.

2.4 DATA MANAGEMENT AND ANALYSIS UNDERTAKEN FOR BOTH SURVEYS

2.4.1 Data storage

All collected data was stored on an ANU server which was password-protected, encrypted and only accessible by the principal investigator. Hard-copies of documents were stored under lock and key and accessible only by the principal investigator and the supervisory panel. For the purposes of the candidature, the principal investigator shared data outputs with the supervisors as required. All associated material from this project will be stored for a period of five years from the date of any publication arising from this research. At the end of the storage period, any data collected is scheduled to be archived indefinitely by the principal investigator.

[7] This prize draw complied with all applicable Australian Capital Territory laws (details are provided at gamblingandracing.act.gov.au)

[8] This was done by assigning each email address a number and then using a computer pseudo-random number generator (PRNG) to randomly selecting winning numbers within the range.

2.4.2 Data coding

Questions four (Q4: "*How would you describe human gene therapy?")* and six (Q6: "*If you think human gene therapy is already being used, what does it treat?"*) in both surveys were designed as open responses with no text limit. An overall 'knowledge' score was derived from Q4 by converting each written response into numerical scores by manual revision by the principal investigator[9]. A scoring rubric can be found in Table 2. To present this data we used a bubbleplot in R studio version 3.5.0 (Wickham 2016; R Core Team 2018). The full annotated R Markdown file can be found at (Appendix F).

Table 2. Scoring rubric for the question "*How would you describe human gene therapy?"*

Score	Criteria	Participant examples from the Australia-Wide online survey
0	**No or incorrect answer** Those answers that did not relate to genetic modification or therapeutic applications at all.	*I believe it can predict what illnesses etc [sic] you might inherit*
1	**Partially correct answer** Recognised HGT involved genes in a therapeutic process but either did not explain how or provided some incorrect information.	*Changing the structure of the fibre of a living thing, be it human, animal or vegetation*
2	**Correct answer** Identify that HGT manipulates/edits/modifies genes/DNA in some way to reach a therapeutic outcome.	*Human gene therapy modifies the human genome to bring out or exclude desirable/undesirable traits*

For Q6, the respondent's answers were analysed by Survey Monkey's text analysis software to pick up the frequency of key phrases. Results were confirmed by manual revision by the principal investigator with adjustment of themes into specific diseases (e.g., cystic fibrosis), categories of diseases (e.g., blood disorder) and other identified themes (e.g., clinical trials).

[9] The principal investigator (Michel Watson) was awarded Bachelor of Science (Hons) at the University of Western Australia in the field of molecular genetics in 2013. Before transferring to the discipline of social sciences in 2017, Michel was a research assistant for several years in various molecular genetic laboratories.

2.4.3 Bivariate analysis

As no questions were compulsory, only responses which were fully completed were analysed in this study. Bivariate analysis was conducted using the IBM SPSS Statistics (version 24) software (IBM Corp 2016). For simplicity, answers on the 5-point Likert scale were treated as continuous variables with values 1-5 reflecting increasing levels of acceptability/ positivity/agreement. Responses of 'unsure' were excluded from this part of the analysis to ensure the weighted average properly reflected the strength of support — i.e., a higher score indicated a higher level of acceptability/positivity/agreement.

We conducted exploratory analysis of pairwise associations between variables of interest and identified statistically significant pairwise associations between attitudes, knowledge and demographic factors. As the variables were not normally distributed, we used non-parametric analysis of variance for this part of the analysis. For robustness testing we also applied analogous parametric tests to confirm the statistical significance results. In each case, statistical significance was confirmed in both tests, however only results from the non-parametric test are published within the results chapters.

We used the Friedman test (parametric equivalent being a one-way ANOVA) as a first step to compare groups of answers within a question (e.g. 7a, 7b and 7c) and then used the Wilcoxon Signed Rank test (parametric equivalent being a paired t-test) to compare two sets of answers from the same participant (e.g. 8a with 8c). To compare between questions (e.g., 7 to 8) which were made up of a series of sub-questions, we generated a mean score for each participant and used this mean score in the analysis. The mean score for a question reflected an aggregated measure of acceptability/positivity/agreement of the respondent.

To identify associations between a participant's answers to substantive questions and demographic categories that had two groups (e.g., male and female) we used a Mann-Whitney U-test (unpaired t-test). Finally, we used a Kruskal Wallis H-test (one-way analysis of variance) to compare answers between non-binary demographic variables (e.g., age) and participant's answers to substantive questions.

2.4.4 Multivariate analysis

We used R Studio (Version 3.5.0) for multivariate analysis (R Core Team 2018). For this analysis the substantive answers on the Likert scale were treated as ordinal response variables and we used a cumulative-link mixed model using the ordinal package in R (Christensen 2019).

This model was selected due to its ability to fit regression data that has an ordinal output variable, with allowances for random effects in the model (Christensen 2018). The variables we used in our model are shown below in Table 3. The ordinal Likert-scale answer to the question was our response variable and our explanatory variables included demographic variables, variables on the occurrence of disability/disease in the family, the participant's political preferences, HGT knowledge (both the subjective self-rating and the objective test rating) and the question being answered. To allow for within-participant correlation between answers, the model included random effects for each participant.

Table 3. Variables used in the multivariate model (cumulative-link mixed model).

	Variable	Type of variable
Response variable	Answer	Ordinal
Explanatory variables	Gender	Factor variable
	Age	Factor variable
	Education	Factor variable
	Children	Factor variable
	Industry	Factor variable
	Disability in Family	Factor variable
	Disease in Family	Factor variable
	Political preference	Factor variable
	HGT Knowledge (self-rating)	Factor variable
	HGT Knowledge (test rating)	Factor variable
	Question	Factor variable
Random-effect terms	Participant	Random effect

In order to fit the model, the data was filtered to exclude all answers of 'unsure', which left answers on the five-point Likert scale. The remaining data was set as an ordinal factor variable, with numeric values in increasing order. All answers were previously adjusted (where necessary) to guarantee consistency in coding, where a higher value reflected a greater support for the use of HGT and a lower answer reflected less support for its use. This assisted with simple interpretation of the output, by ensuring that the direction of statistical effects was comparable between questions. We produced the summary output and ANOVA table generated from the model to confirm the reliability of results. As a test of robustness of our results, we also fit a (simpler) linear mixed regression model where the Likert-scale answers were treated as continuous variables. While not an ideal model, this latter model confirmed the findings of

the primary cumulative-link mixed model. The full annotated R Markdown file, including transformation of the original data into long form, can be found at Appendix G.

2.4.5 Comparative analysis of the online Australian survey and the Australian Capital Territory mail-out survey responses

In order to analyse the benefits and limitations of each survey's design and strategy, we compared and discussed participant information such as completion rate and time taken to complete. This was followed by a comparative analysis of each survey's demographic profile to determine whether there were statistically significant differences between the two populations. This was achieved by using appropriate bivariate models as described above. This approach was also used to compare between self-rated and investigator-rated awareness and understanding themed questions located at the beginning of the survey (e.g. "*Have you heard of the term Human Gene Therapy before?"*). In cases where demographic associations to responses were identified, results from both surveys were summarised in a table format (i.e., 'yes' the association was present or 'no' it was not) and we have discussed their similarities and differences.

To note, an assumption that the public who participated in each survey was static between these time points was made in order to compare results of the two surveys. This was due to two main reasons. Firstly, we were unable to ascertain whether any developments in HGT or salient controversies between these two time points were viewed by a participant and, if it was viewed, whether the information changed the opinion of a participant. Secondly, public opinion changes slowly (Davison, 2020). This coupled with the fact that (1) HGT does not have a dominant space in the media cycle, and (2) that the two surveys were temporally close to one another, we therefore assumed that, if public opinion had changed, it would have been by a small amount and therefore reasonable to ignore

2.4.5.1 Data preparation for substantive questions

To prepare the substantive question data for analysis, questions that assessed whether a participant would personally use therapeutic, enhancive or preventative procedures deviated in design between the AUST-Online and ACT-Mail-Out surveys. In the AUST-Online survey, personal preferences were analysed by a tick box for each type of therapeutic use with moderate

and severe conditions combined (Q19: "*Under what circumstances would you personally use human gene therapy to genetically modify your DNA? (Please select all that apply)"*. In the ACT-Mail-Out survey, each severity level was separated. Therefore, to compare responses from the two surveys, moderate and severe therapeutic applications from the ACT-Mail-Out survey were averaged for each participant. In addition, participant responses to questions ascertaining to the acceptability of both mental illness and intellectual disability treatment from the AUST-Online survey were averaged to mirror the consolidated ACT-Mail-Out survey questions.

For personal preference towards the use of enhancive and preventative applications, the AUST-Online survey represented these as one individual option within Q19 (e.g., "*To enhance a trait (e.g. increase intelligence, increase athletic ability)"*). In the ACT-Mail-Out survey, this was amended to separate into the three examples for both enhancement and prevention applications (e.g. intellectual, physical, longevity). Therefore, all enhancement and prevention procedures were also averaged, respectively, to align with the AUST-Online survey questions.

The placement of questions within the survey also differed between the two surveys, and therefore must be interpreted with some caution. In the ACT-Mail-Out survey, specific categories of societal (i.e., general use) and personal use questions were located adjacent to each other, whereas in the AUST-Online survey the tick box was positioned towards the end, after ethical and moral statements were presented.

2.4.5.2 Nested ANOVA to analyse acceptability between surveys

To compare responses from questions (and sub-questions) of the AUST-Online and ACT-Mail-Out survey, we used a nested ANOVA (or hierarchical ANOVA) in R Studio. This model tested two null hypotheses; (1) that there is no difference between the averaged Likert responses of the two surveys; and if there *is* a difference (2), that this is a fixed shift in averaged Likert responses of the two surveys. This approach was chosen as trends of acceptability could be observed that would otherwise not be identified in bivariate analysis. For example, the differences in acceptability of the same question in both surveys might be significant, however this type of analysis would not show that the trend in acceptability had a similar fixed shift across all questions (i.e., not significantly different).

To prepare the data, 'unsure' answers were again excluded to ensure the weighted average properly reflected the strength of acceptability. A nested ANOVA was then run in R Studio by

importing the mean response for each question (Appendix H). As a part of this process, the mean and standard deviation score was determined for each question. This mean was imported into GraphPad Prism (version 6.01) to generate a graph (GraphPad Software Inc. 2012) where each explanatory variable (x-axis) represented one question (or sub-question), and the response variable (y-axis) reflected the Likert scale (1-5).

2.5 ETHICS APPROVAL

Ethics approval was granted by the ANU Human Research Ethics Committee (AUST-Online survey Approval Number: 2017/608; ACT-Mail-Out survey Approval Number: 2019/557). Consent of participation was obtained through submission of the response, as was described to the participant in the both the participant information sheet and at the conclusion of the survey. Importantly, participation in each survey was voluntary and the respondents were informed that they could withdraw at any time up to the submission of their response. Apart from a section where participants were able to provide their email addresses in the ACT-Mail-Out survey to be eligible for the prize draw, no personal identifying information was collected. In the event that an email address was provided for the prize draw, this information was separated from the survey response as soon as received to ensure that each answer remained anonymous when analysing the data. Only the principal investigator had access to the provided email addresses and this information was kept confidential and deleted after announcement of the winners of the lottery (a month after the survey was posted to the resident).

In designing the survey, there was acknowledgement that each survey contained questions about disability and disease which may have caused distress to participants. In the participant information sheet, participants were directed, if in distress, to consider accessing a support service such as Lifeline[10]. In addition, while recognising that the language surrounding disability is constantly changing, the terminology used in this survey was based on current Australian standards in order to mitigate issues arising from the use of insensitive language.

[10] A national charity providing all Australians experiencing a personal crisis with access to 24 hour crisis support and suicide prevention services.

Results: Overview

The next five chapters present the findings from both the 2017 AUST-Online and 2019 ACT-Mail-Out surveys. Given the vast similarities between the two surveys —in both the questions asked and the responses observed— the results from these two surveys are detailed alongside one another. To ensure results from each survey are clearly defined, headings are used to separate descriptions of each surveys stand-alone results surveys. A colour coding system of orange (AUST-Online) and blue (ACT-Mail-Out) for all tables and graphs has been incorporated.

This structure was decided upon to both avoid repetition and to clearly highlight the similarities observed. Each chapter therefore presents one theme of the survey; demographic and covariate profiles (Chapter Three) awareness and understanding (Chapter Four), attitudes towards techniques and outcomes (Chapter Five), attitudes towards therapeutic, enhancive and prophylactic applications (Chapter Six) and attitudes towards the governance and ethics of HGT (Chapter Seven). The final results chapter (Chapter Eight) details results from the multivariate analysis.

3 Results: Demographic and Co-Variate Profiles

This chapter begins by detailing analysis of the each surveys average participant response rates and times. Following, the demographic and co-variate profiles are described. In the case where covariates and demographics show a statistically significant association between one another, these are outlined in this chapter.

3.1 SURVEY POPULATION PROFILES OF BOTH SURVEYS

The AUST-Online survey was conducted in late 2017 and open to Australian residents for five months. In this time, a total of 691 participants attempted the survey, with 553 (80%) completing the questionnaire. Following, in late 2019, a revised ACT-Mail-Out survey was open to ACT residents for one month. In this time, a total of 201 participants attempted the survey, with 170 (85%) completing the questionnaire. We used a complete case analysis, where only responses which were fully completed were analysed in both surveys.

3.2 RESPONSE RATES OF BOTH SURVEYS

The AUST-Online survey had 79 questions in total (when accounting for sub-questions). As the ACT-Mail-Out survey afforded the opportunity to restructure the design to facilitate clarity, 98 questions in the ACT-Mail-Out survey were asked which equated to an additional 19 questions. While the number of questions differed between surveys, the average time spent on the survey was similar across both the AUST-Online and ACT-Mail-Out survey (20 minutes and 24 minutes, respectively).

Participants used the open-ended feedback section at the end of each survey to provide context and caveats to their answers. The section was used to enhance the interpretation of the analysis, with selected quotes presented in the discussion to add additional context to the quantitative results. In the AUST-Online survey, 200 participants (36%) took the opportunity to provide further commentary on their answers. Similarly, in ACT-Mail-Out survey, 67 (39%) provided a response. A full list of responses received for both surveys can be found at Appendix I and Appendix J, respectively.

3.3 GENDER AND AGE PROFILES OF BOTH SURVEYS

A high proportion of respondents from the AUST-Online survey were female, a trend that was also observed in the ACT-Mail-Out survey (Figure 2). While there initially appeared to be a more even spread between males and females who participated in the ACT-Mail-Out survey, a Mann-Whitney U test confirmed the two populations did not have significantly different gender proportions ($U = 3108, p = 0.379$).

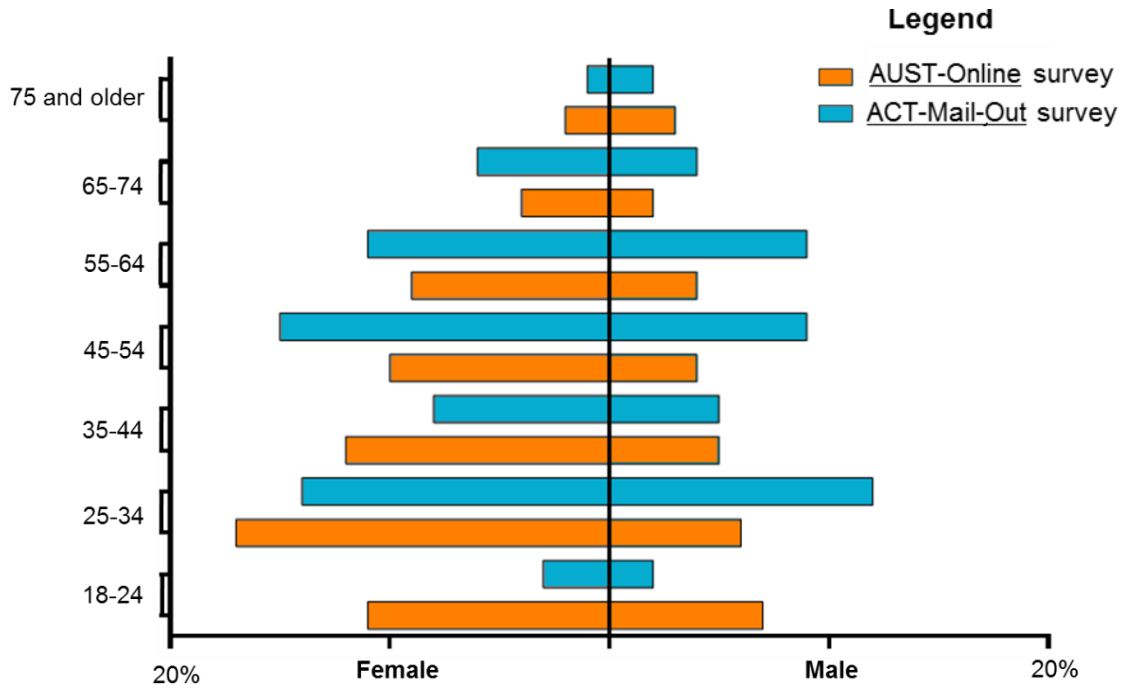


Figure 2. Age and gender profile of the AUST-Online survey and ACT-Mail-Out survey.

The most common age of respondents from the AUST-Online survey were between 18-24 years old (23%; $n = 129$), with the average age between 45-54 years (Figure 2). In the ACT-Mail-Out survey, the highest percentage of respondents were aged between 25-34 (26%; $n = 44$), with the average age being between 35-44. Further bivariate analysis determined no significant difference between both survey age profiles ($\chi^2(6) = 10, p = 0.124$).

3.4 EDUCATION PROFILE OF BOTH SURVEYS

The survey participant population of the AUST-Online survey was highly educated, with over 60% ($n = 345$) holding at least a graduate degree (Figure 3(a)). In the ACT-Mail-Out survey,

this percentage was higher, with over 75% ($n = 127$) holding a graduate degree or above (Figure 3(b)). While a larger proportion of ACT-Mail-Out survey participants had a high-level of education, there was no significant difference between both education-level profiles ($\chi^2(4) = 3, p = 0.584$).

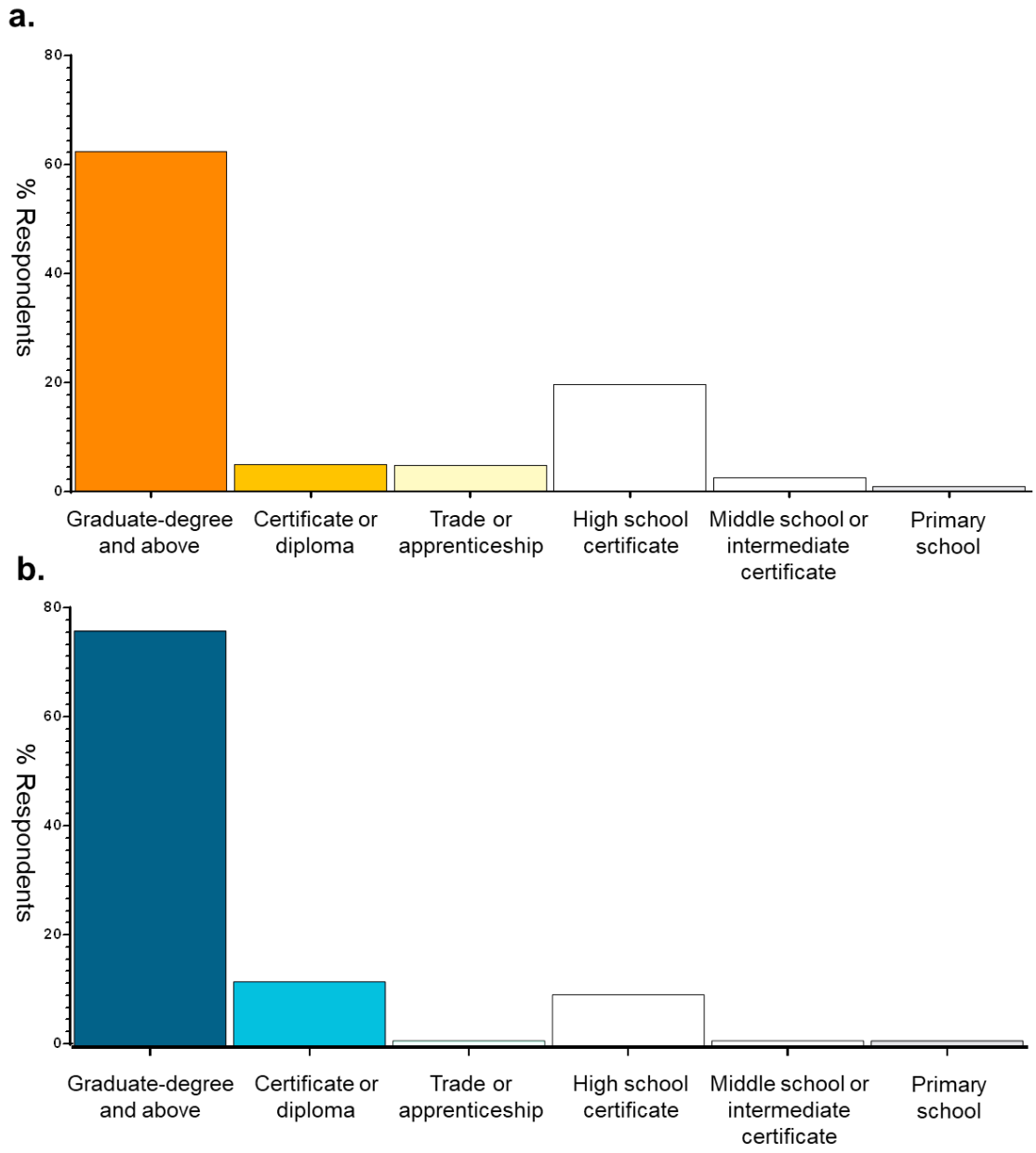


Figure 3. The highest level of education achieved by (a) AUST-Online survey and (b) ACT-Mail-Out survey respondents.

3.5 PARENTAL STATUS PROFILE OF BOTH SURVEYS

The final demographic question of interest (i.e., that showed a significant association with a substantive question), was parental status. In the AUST-Online survey, less than half of

respondents were a parent (47%; $n = 260$) (Figure 4(a)), while in the ACT-Mail-Out survey, 60% of respondents had children ($n = 104$) (Figure 4(b)). This difference however was not significant ($U = 3034, p = 0.453$).

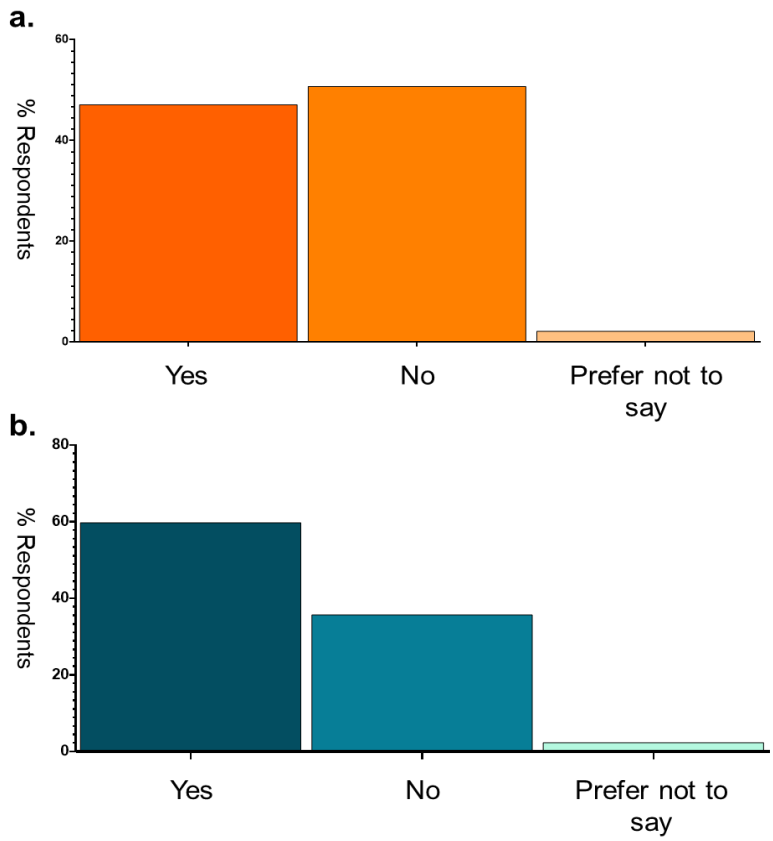


Figure 4. Percentage of respondents who indicated they were a parent in the (a) AUST-Online survey and (b) ACT-Mail-Out survey.

3.6 OTHER CO-VARIATE VARIABLES

3.6.1 Family history of disability or inherited disease of both surveys

Two co-variate variable questions showed a significant association with participant opinion asked participants whether they or anyone else in their immediate family identified as having either (1) a disability or impairment and (2) a hereditary disease that predisposes them to a serious condition. For the first question, few participants were unsure with the majority answering 'yes' in the AUST-Online survey (52%; $n = 285$)(Figure 5(a)), while in the ACT-Mail-Out survey, the majority answered 'no' (60%; $n = 101$)(Figure 5(b)). Despite this, no significant difference was observed between the two populations ($U = 2619, p = 0.344$)..

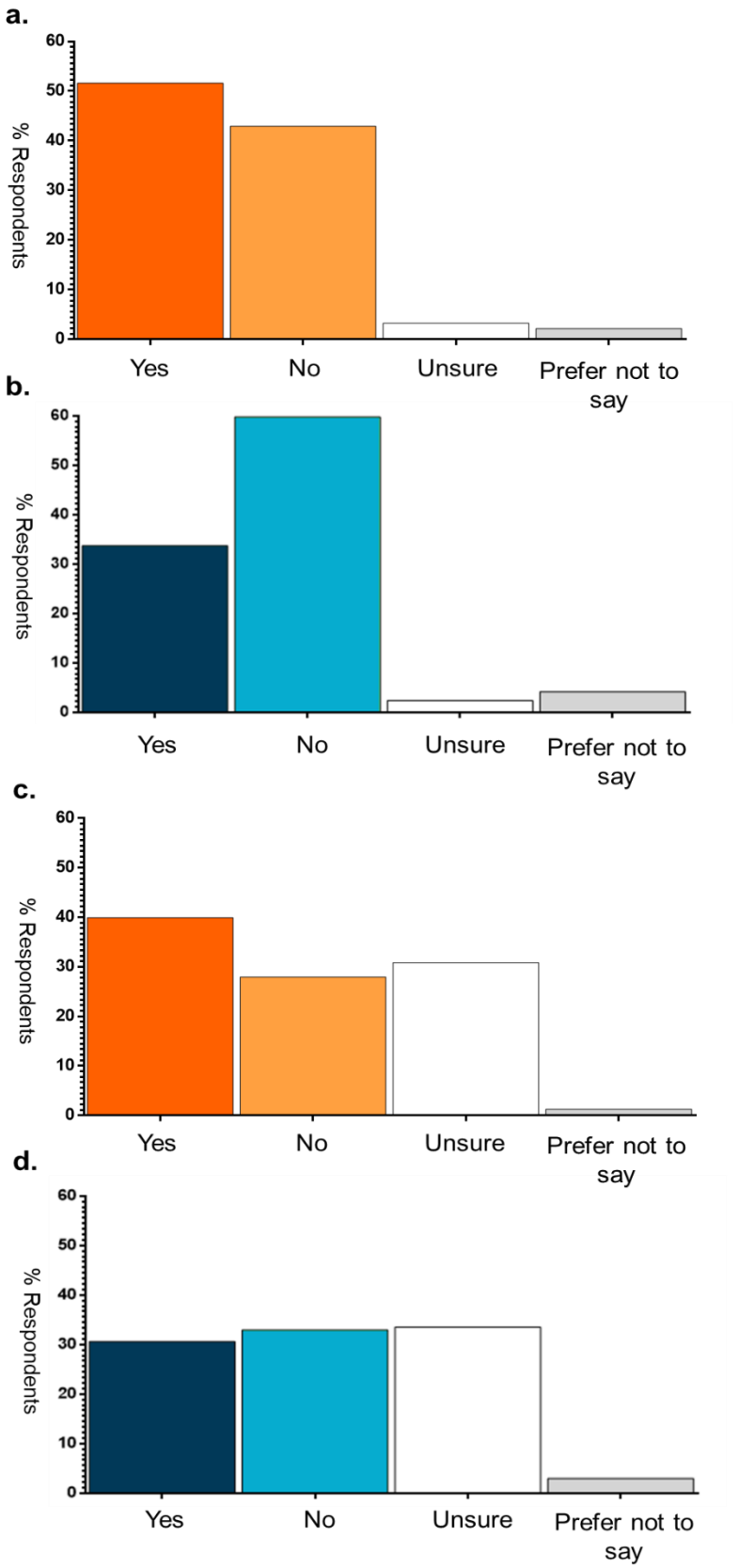


Figure 5. Percentage of respondents who had a close association with a disability or impairment in (a) AUST-Online survey and (b) ACT-Mail-Out survey. Percentage of respondents who indicated they had a close association with a hereditary disease (c) AUST-Online survey and (d) ACT-Mail-Out survey.

For an inherited disease, in both surveys a more even representation between those who said yes, no and unsure was observed for both the AUST-Online survey (Figure 5(c)), and the ACT-Mail-Out survey as shown in (Figure 5(d)). Again, no significant difference was observed ($U = 1378, p = 0.729$).

3.6.2 Attitudes towards science and technology

3.6.2.1 Online Australian survey (2017) results

As part of this study, the participant's feelings of positivity towards fields of science and technology were assessed with the question "*In your opinion, what kind of effect has the following had on our society?*". Overall, in the AUST-Online survey, 97% ($n = 534$) felt at least somewhat positive towards science. This decreased slightly to 95% when asked about technology ($n = 525$) and medicine ($n = 525$). Responses to biotechnology were significantly less (as determined by a Wilcoxon Signed Rank test) with only 71% ($n = 391$) feeling at least somewhat positive towards this field (Figure 6).

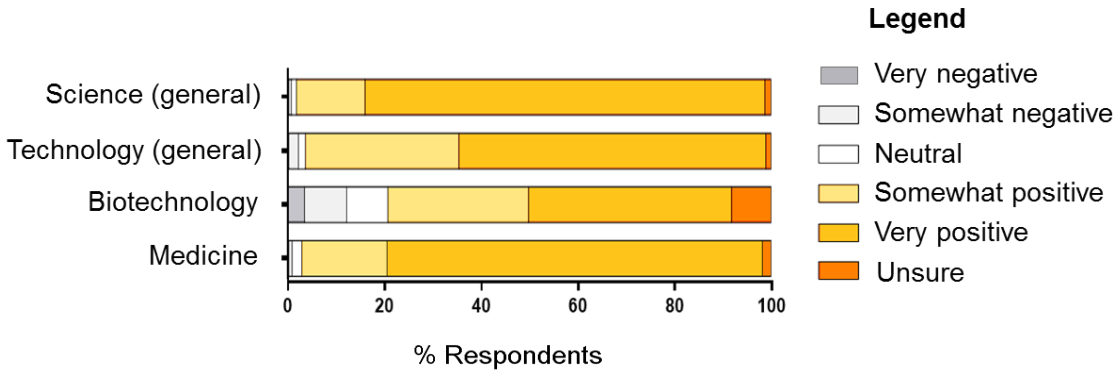


Figure 6. Distribution of AUST-Online survey participants' attitudes towards science, technology, biotechnology and medicine.

A Mann-Whitney U test conducted to ascertain differences in gender responses confirmed females in the AUST-Online survey were less likely to feel positive towards technology in general ($n_{\text{(female*positive)}} = 341\ (95\%); n_{\text{(male*positive)}} = 172\ (98\%); U = 27140,\ p = 0.002$). Biotechnology was mildly favoured by males however the p-value cut-off limits precluded this from being statistically significant. The Kruskal Wallace H-test, identified an association between increasing age and a decrease in positive feelings towards biotechnology ($\chi^2(6) = 34, p \leq 0.001$) and medicine ($\chi^2(6) = 16, p = 0.012$). Finally, as the level of

qualification increased, so too did the positive attitudes towards biotechnology ($\chi^2(7) = 22, p = 0.002$).

3.6.2.2 Australian Capital Territory mail-out survey (2019) results

In the ACT-Mail-Out survey the vast majority of participants ($94\%, n = 158$) felt at least somewhat positive towards science ($94\%, n = 158$) and medicine ($95\%, n = 161$) (Figure 7). As seen in the findings of the AUST-Online survey, responses to biotechnology were significantly less with only 72% ($n = 123$) having positive feelings towards this field. No demographic associations were observed.

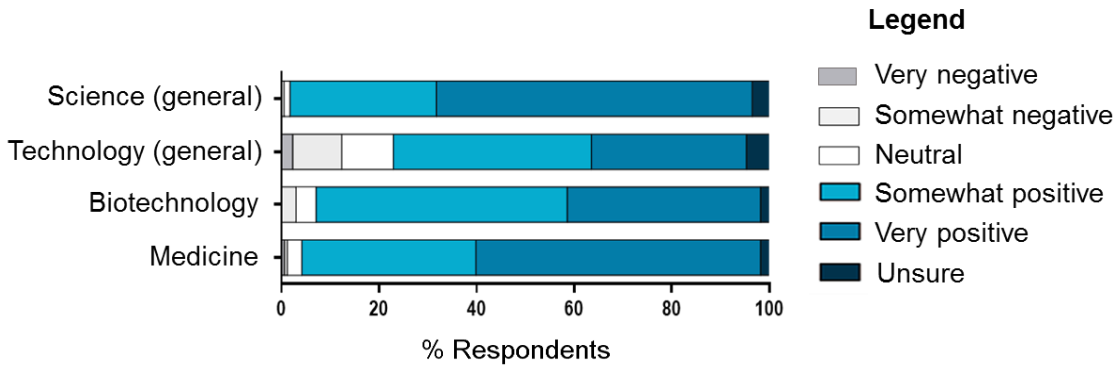


Figure 7. Distribution of ACT-Mail-Out survey participants' attitudes towards science, technology, biotechnology and medicine.

3.6.2.3 Comparison of survey results

A decrease in the rates of positive feelings was observed across the fields of science and technology, with science evoking more positive attitudes than medicine, technology and biotechnology. Based on this observation, a nested ANOVA was used to confirm that there was a significant difference in averaged Likert scores between both surveys ($p \leq 0.001$). In this case, the AUST-Online survey rates of positivity were overall higher (i.e., participants felt more positive towards each field compared to the ACT-Mail-Out survey participants) (Figure 8). Therefore, a second test was used to confirm that this difference was in fact a fixed shift (i.e., following the same trend) as the results were insignificant ($p = 0.097$). However, when accounting for participants in the ANOVA interaction model, a slightly significant result was identified ($p = 0.0497$) (i.e., no fixed shift identified). The full output for all nested ANOVAs can be found at Appendix K.

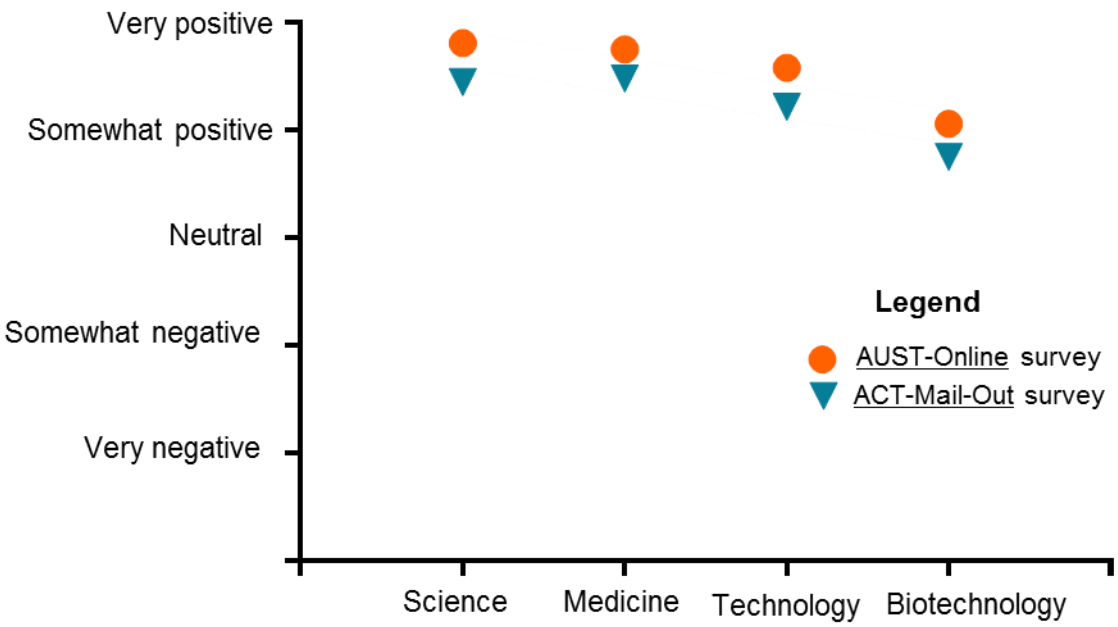


Figure 8. Averaged positivity rates towards Science, Medicine, Technology and Biotechnology.

3.6.3 Attitudes towards societal change

3.6.3.1 Online Australian survey (2017) results

A set of two questions were designed to elicit the participant's opinion and attitudes towards the change that might occur once HGT became more mainstream. For the first question (i.e, "*How much do you think society as a whole would change if human gene therapy becomes available?*", 64% ($n = 352$) of the AUST-Online survey participants indicated there would be a considerable change (Figure 9(a)). The following question ("*Overall, what kind of effect would this change have on our society?*"), 26% ($n = 142$) believed this change would be *very* positive, however almost the majority of participants (48%; $n = 259$) thought that this would only be *somewhat* positive (Figure 9(b)).

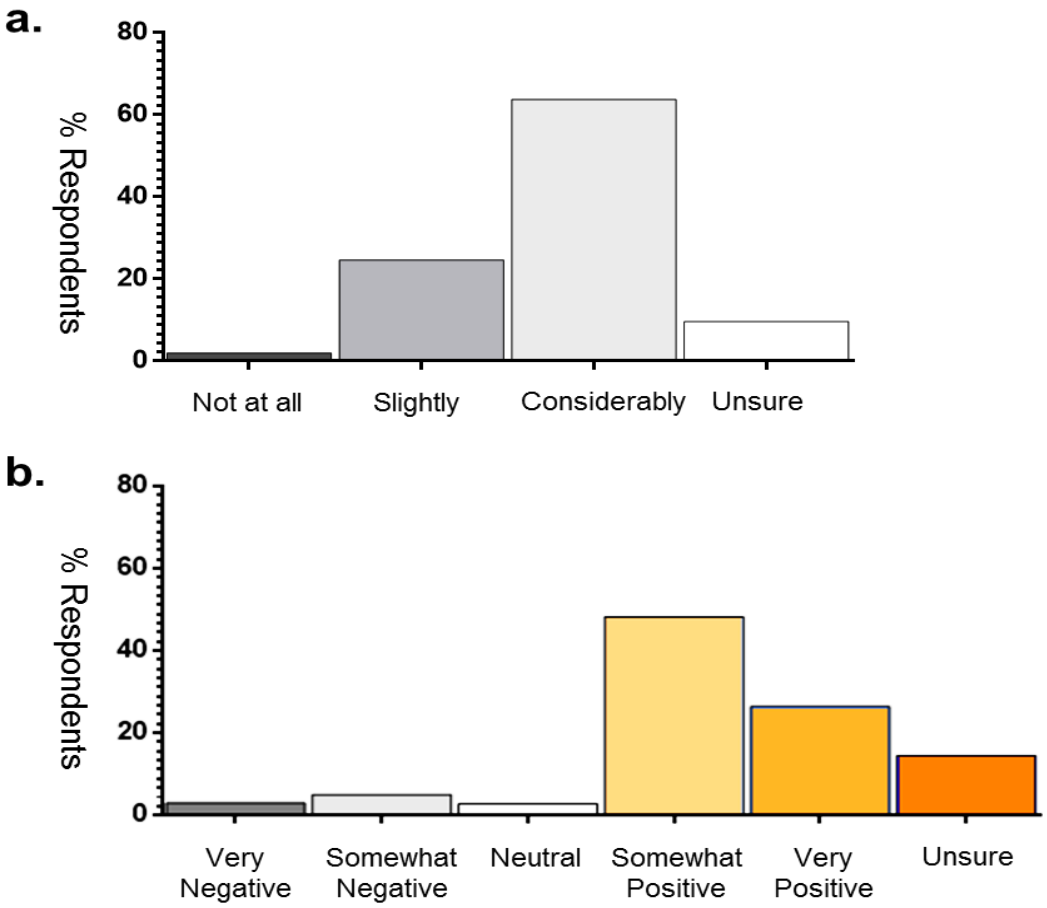


Figure 9. The percentage of AUST-Online survey respondents who feel society would change if human gene therapy were widespread.
Where (a) is percentage responses to the question *"How much do you think society as a whole would change if human gene therapy becomes available?"* and (b) is percentage responses to the question "*Overall, what kind of effect would this change have on our society?"*.

3.6.3.2 Australian Capital Territory mail-out survey (2019) results

Similar findings were observed in the ACT-Mail-Out survey, with 63% ($n = 107$) of the opinion that there would be a considerable change (Figure 10 (a)). When ACT residents responded to how positive this change would be, 18% ($n = 30$) thought this would have a very positive change, whilst 41% ($n = 69$) felt this would only be somewhat positive (Figure 10 (b)). Unlike the AUST-Online survey, gender and the participant's support (either for or against) for GM crops were both found to have a significant association to this set of questions. For how much society would change, females were more likely to feel the change would be considerable compared to males ($n_{\text{(female*considerable)}} = 65\ (67\%); n_{\text{(male*considerable)}} = 42\ (60\%); = U = 2639, p = 0.004$). Alternatively, those who supported GM crops were more likely to think the change HGT brings would be positive ($\chi^2(3) = 22, p = \leq 0.001$).

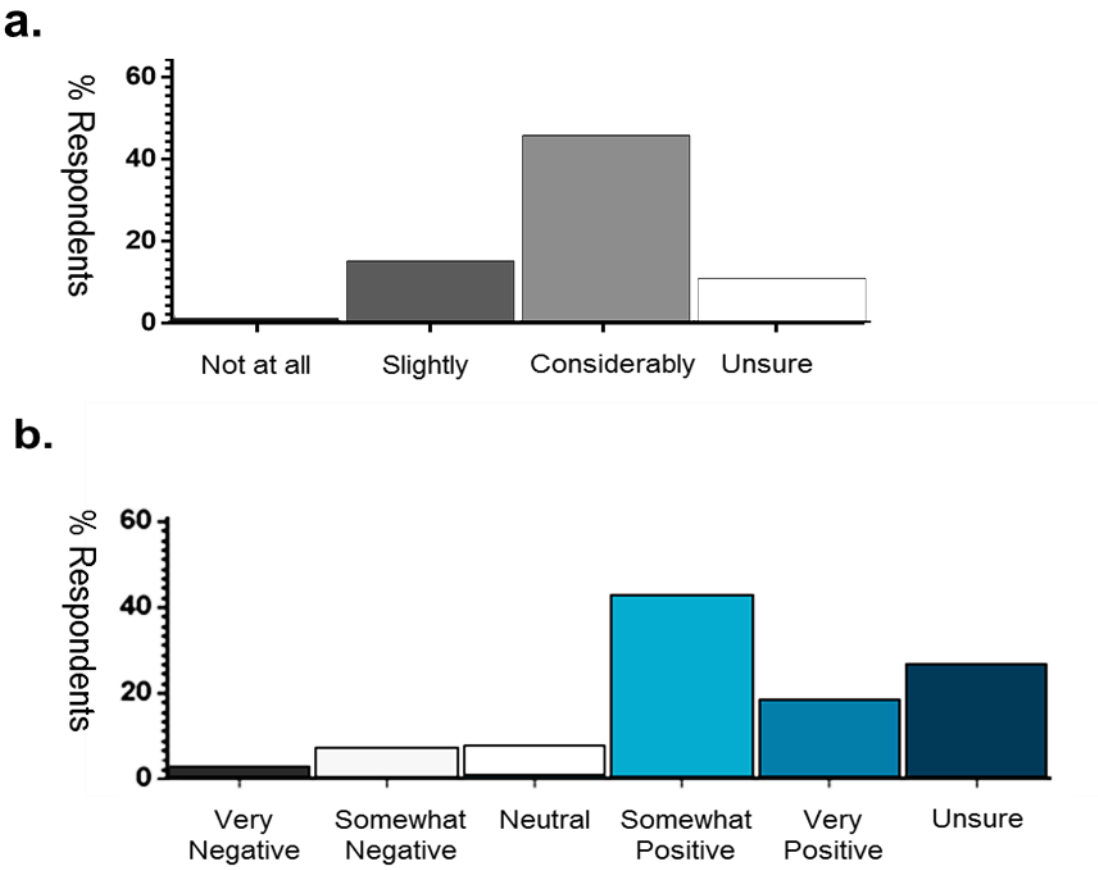


Figure 10. The percentage of ACT-Mail-Out survey respondents who feel society would change if human gene therapy were to be widespread
Where (a) is percentage responses to the question *"How much do you think society as a whole would change if human gene therapy becomes available?"* and (b) is percentage responses to the question "*Overall, what kind of effect would this change have on our society?".*

3.6.4 Attitudes towards genetically modified foods and crops

3.6.4.1 Online Australian survey (2017) results

Within the set of co-variate questions, participants were asked to respond to "*Do you personally support the use of genetically modified food/crops?*". The majority of respondents in the AUST-Online survey either moderately or completely supported genetically modified foods, 29% ($n = 160$) and 31% ($n = 171$), respectively (Figure 11). Six percent, ($n = 31$) chose 'other' and provided, in some cases, an extended response to their feeling behind genetically modified crops and food.

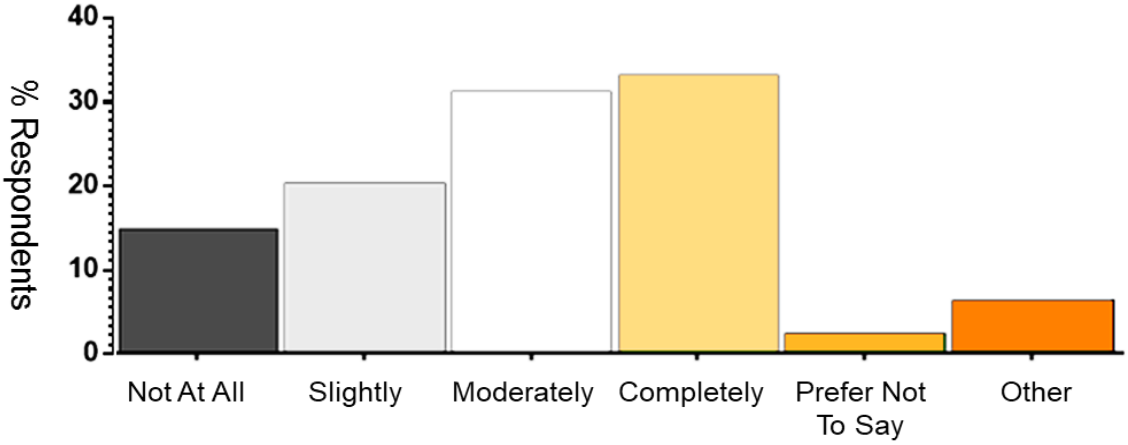


Figure 11. The percentage of AUST-Online survey respondent's strength of support for genetically modified food.

Further analysis using a Kruskal Wallace H-test found a positive association between the strength of support for genetically modified foods or crops to more positive opinions towards science in general ($\chi^2(3) = 13, p \leq 0.001$), technology in general ($\chi^2(3) = 29, p =\leq 0.001$) and medicine specifically ($\chi^2(3) = 56, p =\leq 0.001$). The strongest difference was for those who support biotechnology ($\chi^2(3) = 178, p \leq 0.001$).

3.6.4.2 Australian Capital Territory mail-out survey (2019) results

Findings from the ACT-Mail-Out survey also showed the majority of participants either completely (27%; $n = 46$) or moderately (32%; $n = 54$) supported GM food technology (Figure 12). Further analysis again found a positive correlation between the strength of support for genetically modified foods or crops to more positive opinions towards science in general ($\chi^2(3) = 12, p = 0.009$), technology in general ($\chi^2(3) = 20, p \leq 0.001$) and medicine specifically ($\chi^2(3) = 23, p \leq 0.001$). Like the AUST-Online survey, the strongest difference was for those who support biotechnology ($\chi^2(3) = 56, p \leq 0.001$). For this survey, being a parent was also found to have a significant association with GM support, where those with children were less likely to support GM food production ($n_{\text{(parent*support)}} = 196\ (80\%)$; $n_{\text{(not a parent*support)}} = 235\ (90\%)$; $U = 29708, p \leq 0.001$).

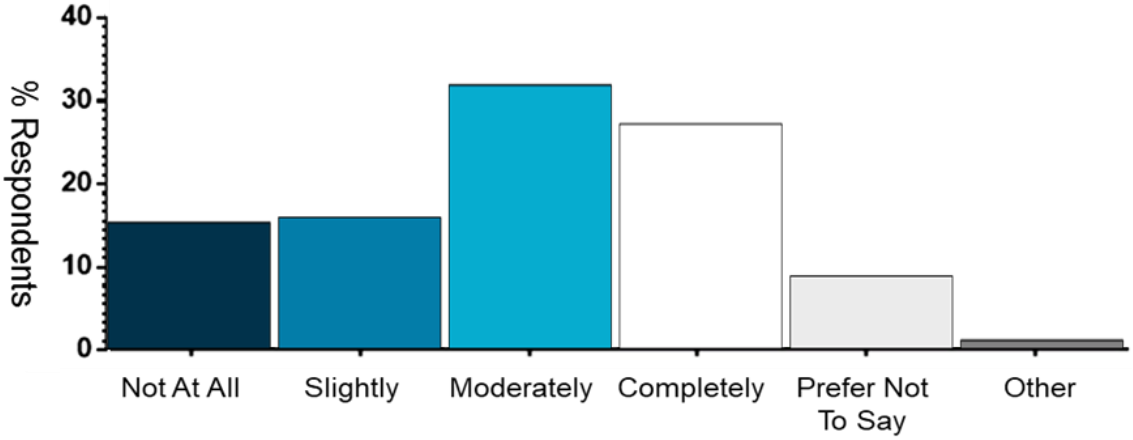


Figure 12. Percentage of ACT-Mail-Out survey respondent's strength of support for genetically modified food.

In both surveys, the majority of participants supported, to some degree, GM food or crops. To compare these two groups, a Kruskal Wallace H-test was used. No significant difference was observed ($\chi^2(3) = 7, p = 0.710$).

3.6.5 Politics

3.6.5.1 Australian Capital Territory mail-out survey (2019) results

Only the ACT-Mail-Out survey assessed the participant's political persuasion. Out of the major Australian political parties, 28% ($n = 48$) related more to the Australian Labor Party (a central-left wing political party, one of two main Australian political parties). The other major political party, the Liberal Party of Australia (a centre-right-wing Australian political party) garnered only 12% ($n = 20$) of participant support. These results were second to the Australian Greens (a minor left-wing Australian political party focused on global sustainability) where 29% ($n = 49$) of participants agreed more with this party's principles. No associations were identified between one's political persuasion and attitudes towards HGT.

3.7 CHAPTER SUMMARY

Despite the different recruitment strategies employed for each survey, the response rate and time to complete were similar, with no significant differences between key demographics (i.e.,

age, gender and education) observed. On average those who participated in each survey were highly educated young females.

Comparing co-variates to demographics identified significant positive associations between attitudes towards science, technology, medicine biotechnology, and GM food or crops for both surveys, with participant attitudes towards all fields of science being favourable in both surveys. However, females in the AUST-Online survey were less likely to feel positive towards technology.

Finally, the majority of respondents from both surveys indicated that society would experience a considerable change as HGT became more prevalent, with a small majority of participants believing this change to be "somewhat positive" when this occurs. In the ACT-Mail-Out survey females were more likely to feel the change would be considerable compared to males.

4 Results: Awareness and Understanding of Human Gene Therapy

This is the first of four chapters detailing findings from the substantive survey questions. This chapter focuses on the first 'theme' which addresses objective 1(a-c); to determine the Australian public's current awareness and understanding of HGT by identifying the following:

a. Whether they have heard of HGT before
b. How they would describe HGT
c. Their knowledge of the current use within Australia

As part of this analysis, significant demographic and co-variate associations are also described below, as is the case with the remaining results chapters.

4.1 AWARENESS OF HUMAN GENE THERAPY

Awareness of the term 'human gene therapy' was examined by personal judgement of the respondents with the results shown in Figure 13. Overall, 95% ($n = 528$) of the AUST-Online survey respondents had heard this term used before; a quarter of respondents ($n = 138$) had heard of the term but did not know what the procedure entailed.

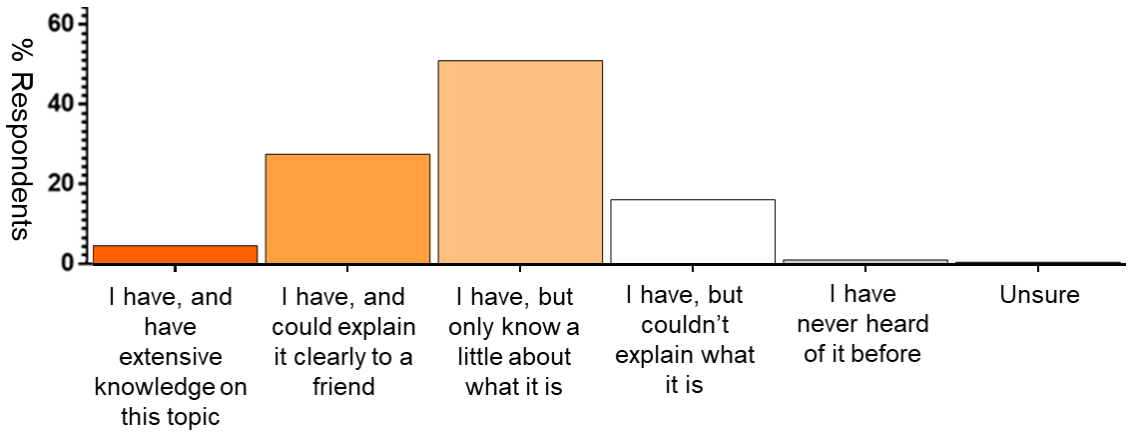


Figure 13. AUST-Online survey participants' self-rated understanding of human gene therapy.

In the ACT-Mail-Out survey, similar findings were observed, with 95% ($n = 161$) of respondents having heard of the term 'human gene therapy' (Figure 14). Just under a third of respondents ($n = 46$) had heard of the term but didn't know what the procedure involved.

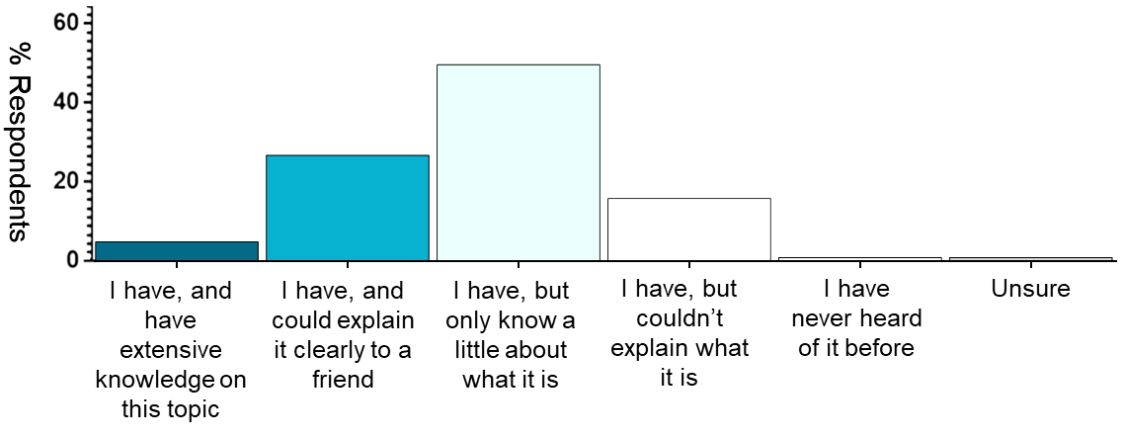


Figure 14. ACT-Mail-Out survey participant's self-rated understanding of human gene therapy.

4.2 UNDERSTANDING OF HUMAN GENE THERAPY

4.2.1.1 Online Australian survey (2017) results

To determine the respondents' ability to accurately explain what HGT means, the open-ended follow up question "*How would you describe human gene therapy? (I.e. what does human gene therapy do?)*" was asked. To note, this is a respondent's nominal response, rather than a reflection of their definitive knowledge. From the AUST-Online survey, of those who indicated they could explain HGT ($n = 388$), 74% ($n = 288$) provided a correct definition (52% of the entire survey population), for example: *'It corrects genetic disorders by replacing or transforming missing or defective genes'*. Of those who gave an accurate definition of HGT, all had previously indicated they at least knew a little about HGT as shown in Figure 15.

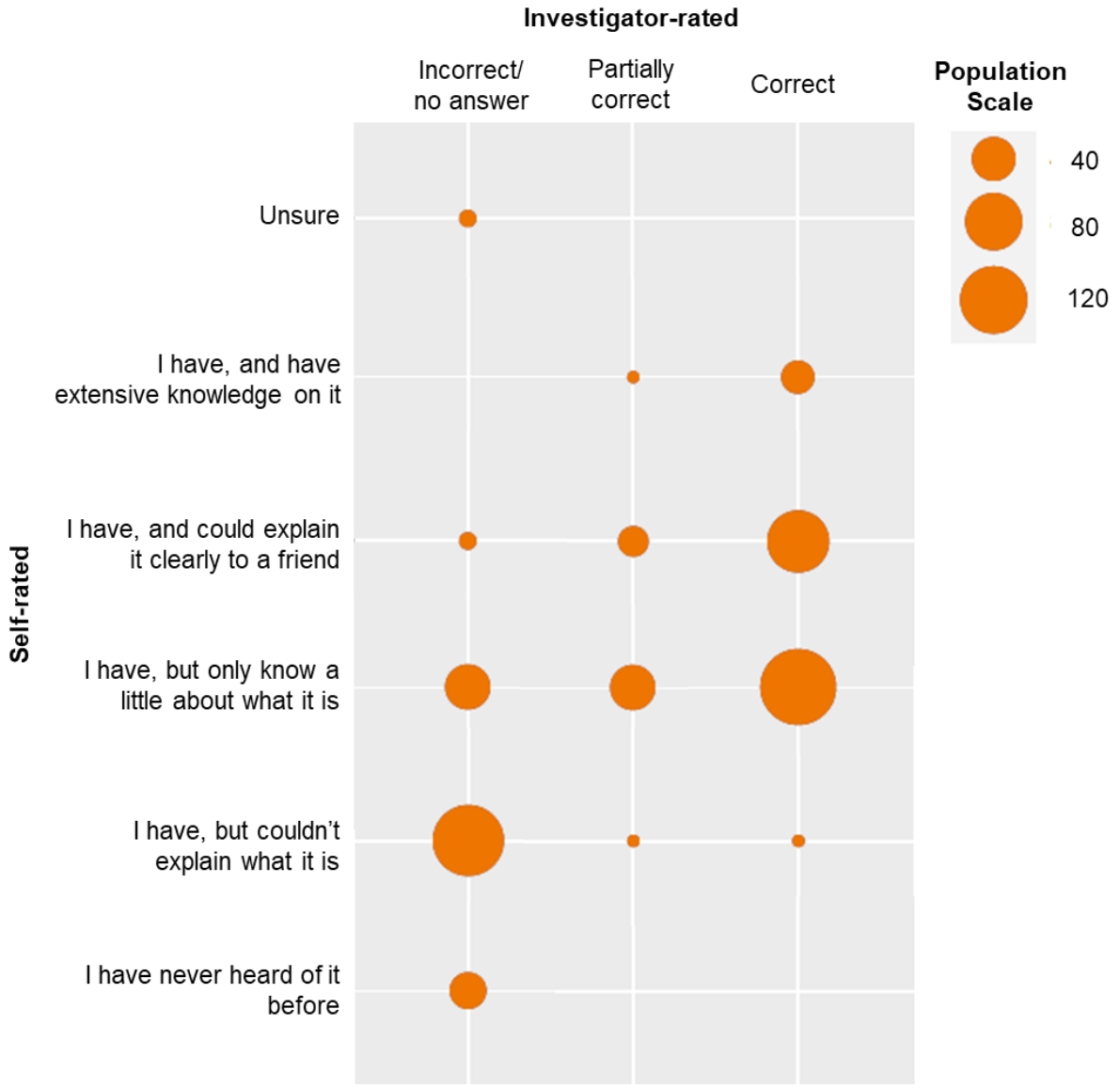


Figure 15. Bubble plot of AUST-Online survey participants' self-rated and investigator-rated understanding of human gene therapy.

Seventeen percent could offer a partially correct answer (e.g., *'It is looking into the human gene structures and finding irregularities*.'). Only one participant in the AUST-Online survey claimed they did not know how to explain HGT, yet provided a partially correct answer. Three participants provided a partially correct answer yet indicated they could explain HGT clearly to a friend while an additional respondent claimed they were an expert yet could not provide a proper definition.

Only 9% ($n = 31$) gave an incorrect answer. This did not include those who did not provide an answer at all, but did include those who gave ancillary commentary that did not address the

question (regardless of the correctness or incorrectness of that commentary). For example, the following comment was treated as an incorrect answer: *'The same as any other medical intervention. It does not stand a chance to outsmart the body's intrinsic makeup in a reliable and/or sustainable way*'. Of those who provided an incorrect answer, the majority of participants believed they knew a little about HGT. One hundred and sixty-nine participants (31%) did not provide an answer to this question at all.

Four demographic questions were shown to have a statistically significant association to a participant's awareness and understanding of HGT; these were gender, education, current or previous work in the medical industry and acceptability of genetically modified (GM) foods. On average, those who identified as males were more likely to indicate that they were aware of the term HGT ($n_{\text{(female}*\text{aware)}} = 65\ (67\%); n_{\text{(male}*\text{aware)}} = 173\ (98\%);\ U = 24878, p \leq 0.001$) and were more likely to provide a correct response ($n_{\text{(female}*\text{correct)}} = 329\ (94\%);\ n_{\text{(male}*\text{correct)}} = 173\ (62\%);\ U = 26054, p \leq 0.001$), compared to females.

As determined by a Kruskal Wallis H-test, participants in the AUST-Online survey who had obtained a higher level of education were more confident in their awareness of this technology ($\chi^2(7) = 34, p \leq 0.001$) and provided a correct definition as determined by the investigator ($\chi^2(7) = 22, p = 0.002$). This trend was also seen with those who supported GM foods ($(\chi^2(3) = 52, p \leq 0.001)$ and $(\chi^2(4) = 45, p \leq 0.001)$, respectively). Finally, those who had worked in the medical industry were on average more aware of what HGT was ($n_{\text{(works in the medical industry}*\text{aware)}} = 167(98\%);$
$n_{\text{(does not work in the medical industry}*\text{aware)}} = 344\ (9\%); U = 26204.0, p \leq 0.001$). However, this awareness did not translate into being more likely to accurately describe HGT.

4.2.1.2 Australian Capital Territory mail-out survey (2019) results

In the ACT-Mail-Out survey, 77% ($n = 131$) attempted this question with 37% ($n = 63$) providing a correct definition of gene therapy (for example *'Being able to modify a "pathogenic" copy of a human gene to restore normal gene function').* Of those who gave an accurate or partially accurate definition of HGT, all had previously indicated they had heard the term before as shown in Figure 16.

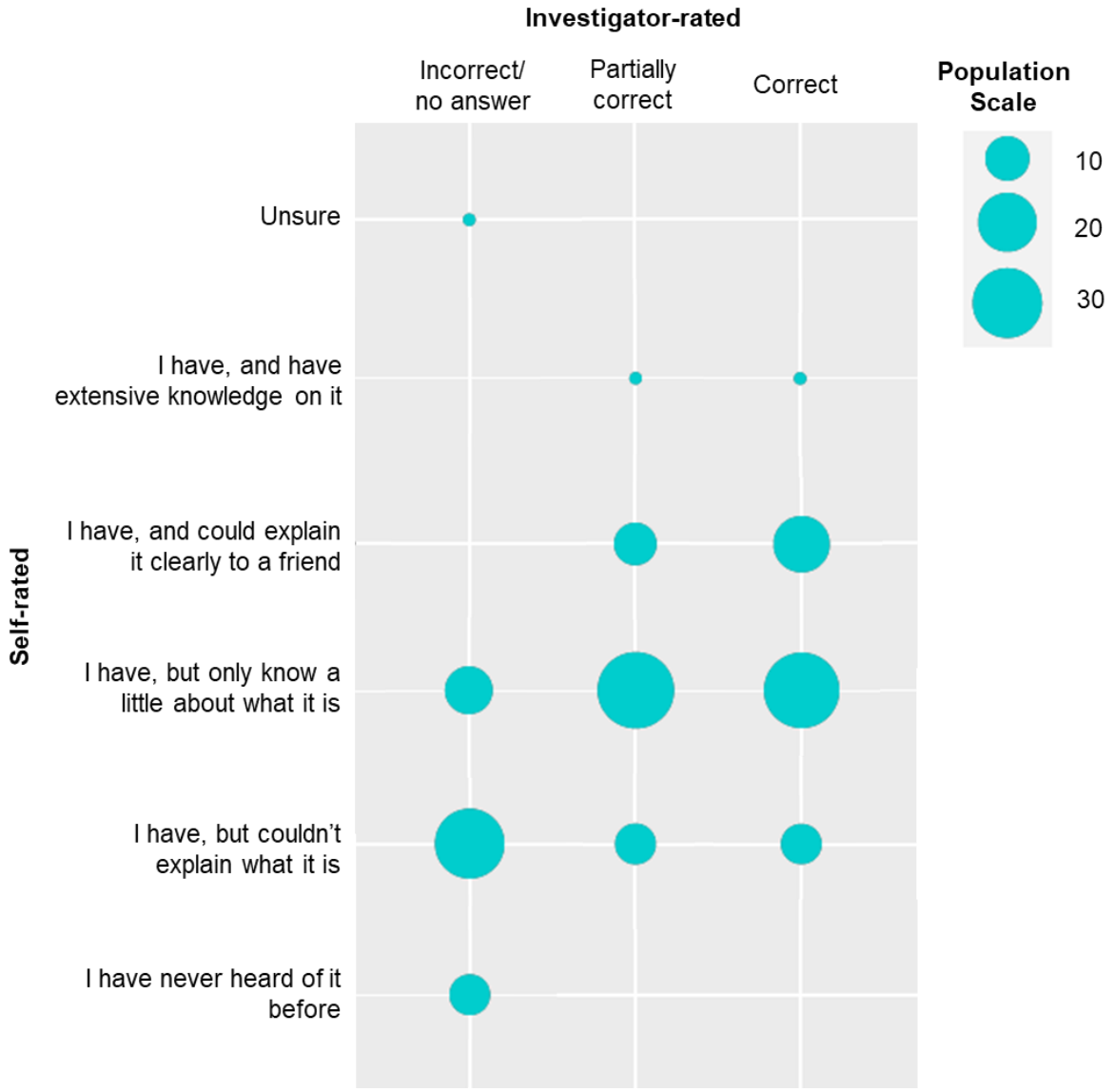


Figure 16. Bubble plot of ACT-Mail-Out survey participants' self-rated and investigator rated understanding of human gene therapy.

A partially correct answer (e.g., *'Human gene therapy uses scientific techniques that makes use of genes to treat genetic disorders*.') was provided by 33% ($n = 56$) of respondents. A total of 30% ($n = 51$) gave an incorrect answer (for example, *'A way to explain or to explore human (sic)*'). Of those who provided an incorrect answer, the majority of participants believed they had heard of HGT, but could not explain what it was (59%; $n = 30$). To note, 39 participants (23%) did not provide an answer to this question.

Only one demographic category was identified with a statistically significant association with awareness: gender. On average, females were more likely to state they were aware of the term

HGT $(n_{\text{(female*aware)}} = 91\ (95\%); n_{\text{(male*aware)}} = 67\ (96\%); U = 2808, p = 0.049)$, however, females were *not* more likely to provide a correct response.

4.2.1.3 Comparison of survey results

When comparing the findings of the two surveys, similar awareness to HGT was identified, with the findings from both surveys holding no significant difference in median scores when compared to one another using a Kruskal Wallis H-test $(\chi^2(4) = 2, p = 0.759)$. To note, unsure was excluded from this analysis to ensure a higher number reflected a higher self-rated knowledge level. For investigator-rated knowledge, the difference between each survey was again insignificant $(\chi^2(4) = 4, p = 0.215)$. Therefore no difference was determined in the actual accuracy levels (as determined by the investigator), across both survey populations.

4.3 AWARENESS OF THE CURRENT USE OF HUMAN GENE THERAPY IN AUSTRALIA

4.3.1.1 Online Australian survey (2017) results

Of those who had heard of gene therapy before in the AUST-Online survey, 31% ($n = 164$) thought that HGT was already being used in Australia to treat certain diseases. This was the correct answer. In comparison, 12% ($n = 63$) ticked 'no' with the majority of participants feeling unsure (57%; $n = 298$) as to whether this therapeutic treatment was available. Only participants who said 'yes' answered the follow up question (Figure 17).

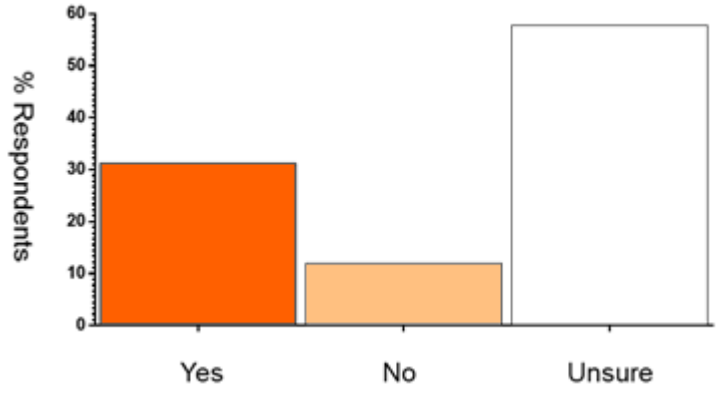


Figure 17. Knowledge of the current use of human gene therapy within Australia from the AUST-Online survey.

A third of the AUST-Online survey respondents who attempted the follow up open-ended question ("*If you think human gene therapy is already being used in Australia, what does it treat?"*) could not specifically identify the diseases they thought HGT would treat (32%; $n = 52$). Of the remaining responses, through text analysis, 33 specific diseases were identified, with the top 15 represented in (Table 4(a)). A large number of participants believed it was used to treat cancer (29%; $n = 48$), followed by cystic fibrosis 9% ($n = 14$). Seven percent ($n = 11$) cited some type of immune system disorder or blood disorder (Hemophilia B was listed in several cases). Four participants mentioned X-SCID, with one stating: *"I've heard of trials for X-SCID in the early 90s so I assume things like this are common in Australia*". A simple n-gram analysis of media articles relating to X-SCID confirmed this peak (data not shown).

Table 4. Themes raised by AUST-Online survey respondents as part of Q6: *"If you think human gene therapy is already being used in Australia, what does it treat?".*
Where (a) is specific themes, (b) is general themes and (c) is other themes raised by the participants.

a.

Specific Themes	Responses	
	%	n
Cancer	29%	48
Cystic Fibrosis	9%	14
Blood Disorders	7%	11
Immune System Disorders	7%	11
Neurological Conditions	3%	5
Down Syndrome	3%	5
Diabetes	2%	4
Heart Disease	2%	4
Liver Disease	2%	4
Musclular Dystrophy	2%	4
X-SCID	2%	4
Bone Marrow Transplant	1%	2
Lupus	1%	2
Metabolic Disorders	1%	2
Skin Issues	1%	2

b.

General Themes	Responses	
	%	n
Genetic Diseases	21%	35
Congenital (Childhood)	9%	15
Inherited Diseases	3%	6
Serious Conditions	1%	3
Chronic Disease	1%	2

c.

Other Themes	Responses	
	%	n
Clinical Trials	15%	25
Research	6%	10
Prenatal	5%	8
Used as Diagnosis	5%	8

General themes were also raised in the AUST-Online survey comment box question; 22% ($n = 35$) specified genetic diseases, 9% ($n = 15$) congenital or childhood diseases and 4% ($n = 6$) as a therapy for inherited diseases (Table 4(b)). Fifteen percent ($n = 25$) of participants thought this technology was still in clinical trials, whereas 6% ($n = 10$) believed HGT was still in a

research phase. Eight participants (5%) indicated that this therapy was used as a diagnostic tool only (Table 4(c)).

4.3.1.2 Australian Capital Territory mail-out survey (2019) results

Of all respondents who completed the ACT-Mail-Out survey, 56% ($n = 95$) thought that HGT was already being used worldwide (Figure 18 (a)). This dropped to 36% ($n = 62$) when asked if HGT was currently being used in *Australia* to treat certain diseases, with just under half of participants feeling unsure ($48\%;\ n = 82$) (Figure 18 (b)). To note, a 'yes' answer to both these questions were correct. Overall, there was a significant decrease in the surety of respondent's knowledge from global to local (Australian) use ($Z = -4.961; p \leq 0.001$).

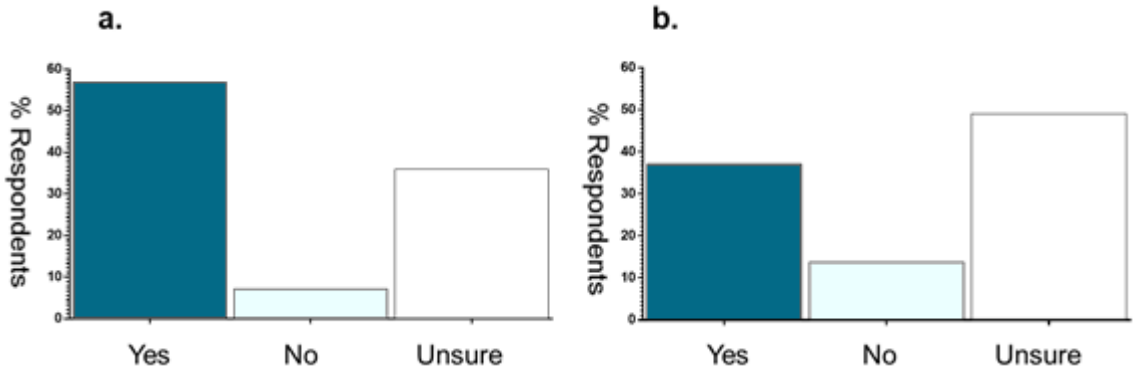


Figure 18. Knowledge of the current use of human gene therapy from the ACT-Mail-Out survey. Where (a) is globally and (b) is within Australia.

One-fifth of respondents (21%; n=26) who attempted the follow up question could not specifically identify the diseases they thought HGT would treat. Through text analysis, 15 specific diseases were identified (Table 5(a)). Again, the most popular response was 'cancer' (33%; n=40), then immune system disorders (9%; n=11) and cystic fibrosis 8% (n=10).

Table 5. Themes raised by ACT-Mail-Out survey respondents as part of Q6: "If you think human gene therapy is already being used, what does it treat?".
Where (a) is specific themes, (b) is general themes and (c) is other themes raised by the participants.

a.

Specific Themes	Responses	
	%	n
Cancer	33%	40
Cystic Fibrosis	8%	10
Blood Disorders	5%	6
Immune System Disorders	4%	5
Neurological Conditions	4%	5
HIV/AIDS	3%	4
Eye Disease/Blindness	2%	3
Muscular Dystrophy	2%	3
Parkinson's Disease	2%	3
Heart Conditions	2%	2
Skin Issues	2%	2
Enzymatic Disorder	1%	1
Infectious Disease	1%	1
Menopause	1%	1
Multiple Sclerosis	1%	1

b.

General Themes	Responses	
	%	n
Genetic Disease	20%	25
Illness/Disease	8%	10
Inherited Disease	7%	9
Serious Conditions	4%	5
Congenital (Childhood)	1%	2

c.

Other Themes	Responses	
	%	n
Research	8%	10
Embryo/Prenatal	5%	6
Diagnosis	2%	3
Clinical Trials	2%	2

As in the AUST-Online survey, general themes were also raised in this open response section; the majority of those who participated in this question (20%; $n = 25$) specified genetic diseases, 8% ($n = 10$) illness or disease and 7% ($n = 9$) as a therapy for inherited diseases (Table 5(b)). Eight percent ($n = 10$) of participants thought this technology was still in the research phase, 5% ($n = 6$) believed HGT was used for embryonic/prenatal genetic manipulation (Table 5(c)).

4.3.1.3 Comparison of survey results

Due to the amendment of the AUST-Online survey, only the awareness of *Australia's* current use of HGT was analysed in both the AUST-Online and ACT-Mail-Out survey. In Australia, the majority of participants were unsure whether the technology was in use in both the AUST-Online survey and the ACT-Mail-Out survey, with the differences between the two surveys not statistically significant ($\chi^2(2) = 5, p = 0.079$).

The top five responses that referenced a specific disease or disorder were identical in both surveys and in the same order of prevalence: Cancer, cystic fibrosis, blood disorders, immune system disorders and neurological conditions. Other themes within the top 15 included heart conditions, muscular dystrophy and skin issues (Figure 19(a)). Other more general themes recorded in both surveys are detailed in Figure 19(b).

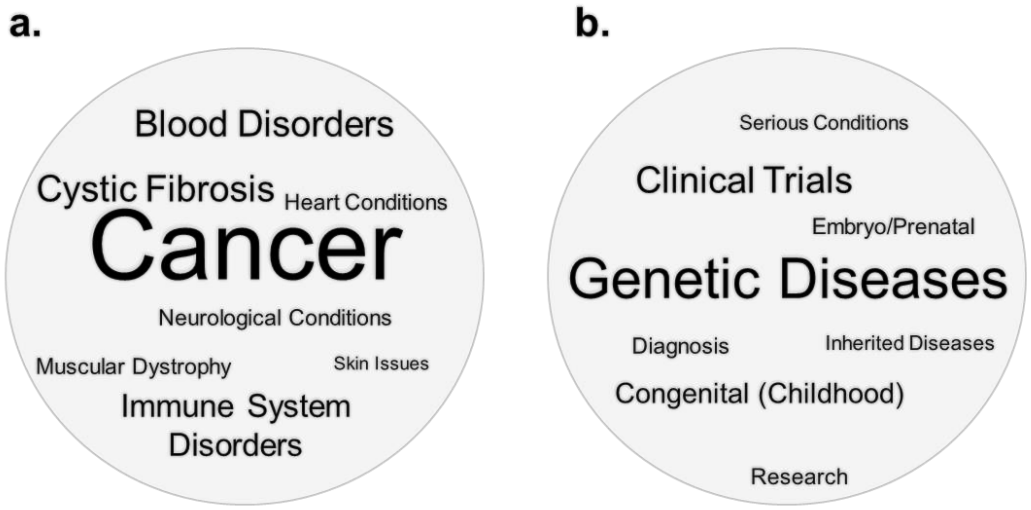


Figure 19. Common themes raised by respondents in both the AUST-Online and ACT-Mail-Out surveys for Q6: *"If you think human gene therapy is already being used in Australia, what does it treat?".*
Where (a) is specific themes and (b) is general themes

4.4 CHAPTER SUMMARY

Comparative analysis between the two surveys found no statistically significant difference between the awareness (self-rated) and understanding (investigator-rated) of participants. The majority of respondents in each survey had at least a little understanding of HGT and could provide a correct or partially correct definition. Both surveys showed significant demographic associations with gender, however disparate findings were observed: In the AUST-Online survey, males were more likely to be aware of HGT, while in the ACT-Mail-Out survey, females on average displayed a higher awareness of HGT.

Across Australia and in the ACT, the majority of participants from each survey were unsure whether the technology was used in Australia with the differences between the two surveys not statistically significant. Finally, the top five responses that referenced a specific disease or disorder that was treated by HGT were identical in both surveys: cancer, cystic fibrosis, blood

disorders, immune system disorders and neurological conditions, in order from highest to lowest rank.

5 Results: Attitudes Towards Techniques and Outcomes of Human Gene Therapy

This third results chapter details findings from the substantive survey questions relating to the theme 'techniques and outcomes'. This chapter focuses on objective 2(a-b); to determine the Australian public's attitudes towards:

a. Genetic modification techniques of HGT
b. Procedural outcomes of HGT

In addition, this chapter also focuses on objective 3; to determine if there is a difference between attitudes towards one's personal use of HGT, and what is acceptable for society. To note, this particular objective for the theme 'techniques and outcomes' was only assessed in the ACT-Mail-Out survey due to the survey design amendment process.

5.1 ACCEPTANCE TOWARDS THE USE OF DIFFERENT DNA TYPES IN HUMAN GENE THERAPY

5.1.1.1 Online Australian survey (2017) results

Participants were asked to respond to the tolerability of different types of DNA when they were used as part of the therapeutic product HGT (i.e., "*How acceptable is it to treat a sick person using donated DNA from…"*). In the AUST-Online survey, the highest participant acceptance rate was for the use of human DNA where 90% ($n = 497$) of respondents deemed this to be acceptable (Figure 20(a)). The second highest support was for artificial DNA, although acceptance was significantly less (74%; $n = 407$). The lowest support was for bacterial or viral DNA, and animal DNA where acceptance dropped to 63% ($n = 346$) and 61% ($n = 334$), respectively.

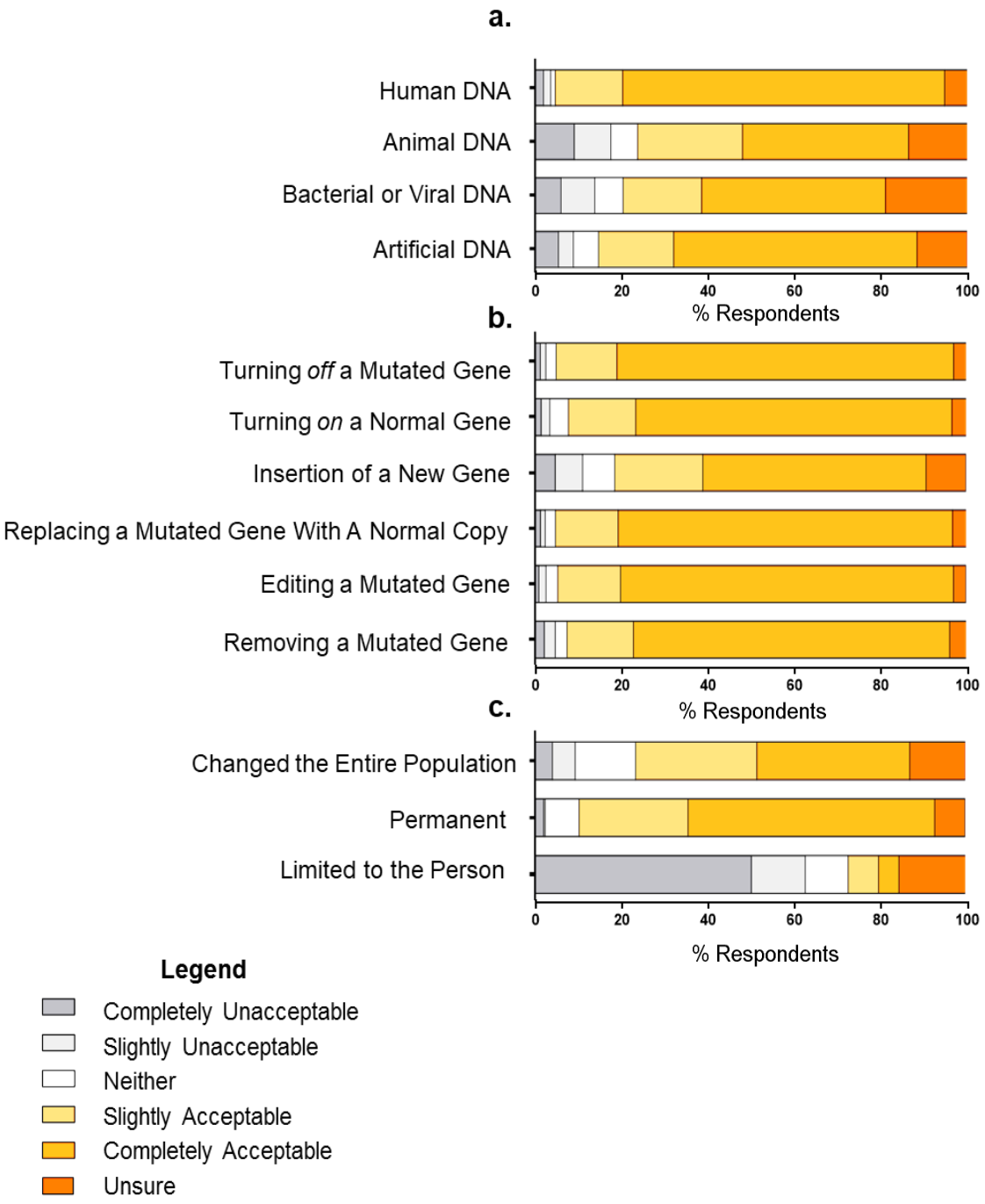


Figure 20. Distribution of AUST-Online survey participants' agreement towards techniques and outcomes of human gene therapy.
Where a) is types of DNA, (b) is techniques to modify the DNA, and (c) is outcome to the procedure.

To determine whether there was a significant difference between average acceptances of each DNA type in the AUST-Online survey, a Wilcoxon Signed Rank test was applied. Analysis revealed no significant difference between the average acceptance rates of artificial DNA, and bacterial or viral DNA. All other comparisons were identified as having significantly different average acceptance levels (Table 6).

Table 6. Wilcoxon Signed Rank test determining significant differences in the AUST-Online survey findings of societal use of DNA type.
Where 'b' indicates a score based on negative ranks and 'c' indicates a score based on positive ranks.

	Z	*p*-value
Animal DNA- Human DNA	-9.923[c]	≤0.001***
Bacterial/Viral DNA – Human DNA	-10.434[b]	≤0.001***
Artificial DNA – Human DNA	-7.799[b]	≤0.001***
Bacterial/Viral DNA – Animal DNA	-4.933[b]	≤0.001***
Artificial DNA – Animal DNA	-6.883[c]	≤0.001***
Artificial DNA – Bacterial/Viral DNA	-1.870[b]	0.061[ns]

5.1.1.2 Australian Capital Territory mail-out survey (2019) results

The same question was presented to the ACT-Mail-Out survey participants. Again, the highest acceptance was for the use of human DNA (68%; $n = 115$) (Figure 21 (a)). The second highest support was for artificial DNA, where 48% ($n = 82$) thought the use of artificial DNA was acceptable. Lowest support was for bacterial or viral DNA, and animal DNA where acceptance dropped to 47% ($n = 79$), and 40% ($n = 68$), respectively.

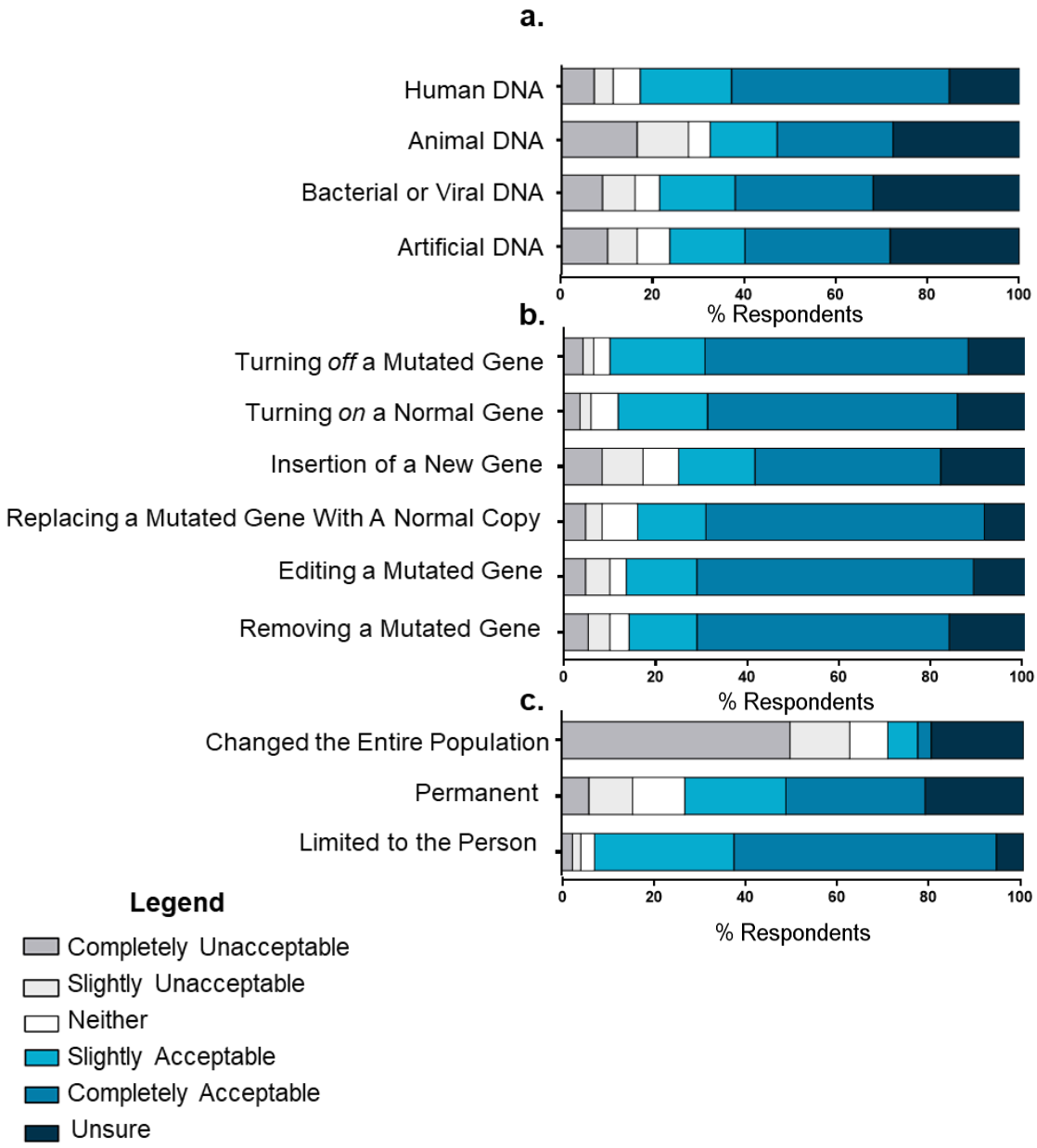


Figure 21. Distribution of ACT-Mail-Out survey participants' agreement towards societal use of techniques and outcomes of human gene therapy.
Where a) is types of DNA, (b) is techniques to modify the DNA, and (c) is outcome to the procedure.

Unlike the AUST-Online survey, participants from the ACT-Mail-Out survey were then asked to respond to whether they would *personally* use different types of DNA. For human DNA, 67% ($n = 113$) said they would (Figure 22 (a)). This rate decreased for artificial DNA, where only 46% ($n = 77$) said yes. For bacterial or viral DNA, and animal DNA, this rate dropped again to 39% ($n = 67$) and 34% ($n = 57$), respectively.

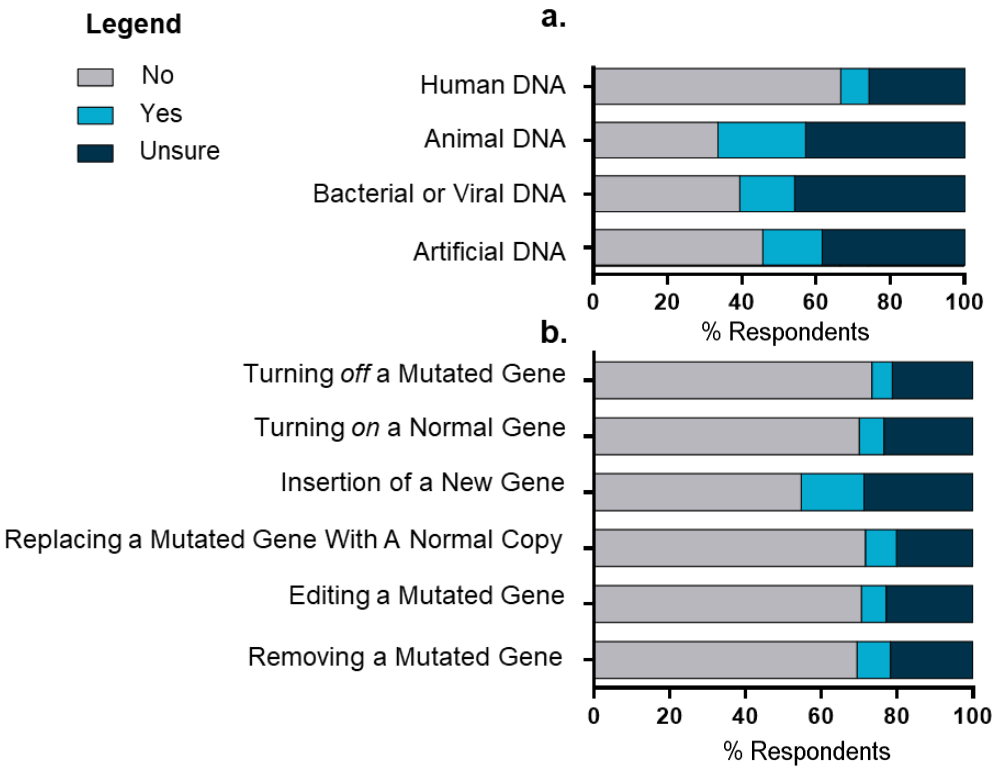


Figure 22. Distribution of ACT-Mail-Out survey participants' agreement towards personal use techniques of human gene therapy.
Where (a) is types of DNA and (b) is techniques to modify the DNA.

To determine whether there was a significant difference between average acceptances of the societal use of each DNA type, a Wilcoxon Signed Rank test was applied. Analysis revealed no significant difference between the average acceptances rate of bacterial/viral DNA compared to animal DNA or artificial DNA (Table 7). All other comparisons were identified as having significantly different average acceptance levels.

When participants were asked about whether they would *personally* use different types of DNA, only animal, and bacterial or viral DNA had the same acceptance level (i.e., insignificant difference between the two acceptance rates) as determined by the Wilcoxon Signed Rank test.

Table 7. Wilcoxon Signed Rank test determining significant differences in the ACT-Mail-Out survey findings of societal and personal use of DNA type.
Where 'b' indicates a score based on negative ranks.

	Societal Use		Personal Use	
	Z	***p*-value**	**Z**	***p*-value**
Animal DNA- Human DNA	-7.110[b]	≤0.001***	-6.230[b]	≤0.001***
Bacterial/Viral DNA – Human DNA	-5.923[b]	≤0.001***	-6.090[b]	≤0.001***
Artificial DNA – Human DNA	-5.051[b]	≤0.001***	-4.378[b]	≤0.001***
Bacterial/Viral DNA – Animal DNA	-1.844[c]	0.065[ns]	-0.803[c]	0.422[ns]
Artificial DNA – Animal DNA	-2.610[c]	0.009**	-2.719[c]	0.007**
Artificial DNA – Bacterial/Viral DNA	-1.265[c]	0.206[ns]	-2.935[c]	0.003**

A comparison *between* societal and personal use of different types and techniques used within HGT was then conducted using a Wilcoxon Signed Rank test. In each case, participants were *less* likely to find individual use acceptable compared to public use (Figure 23).

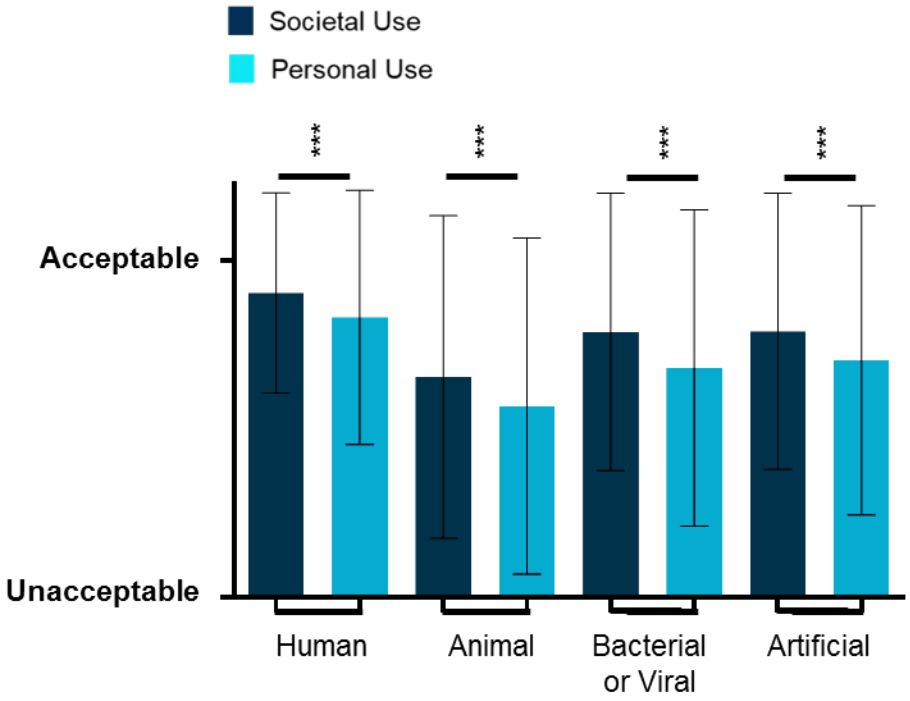


Figure 23. Wilcoxon Signed Rank test determining significant differences between societal and personal use of DNA type from the ACT-Mail-Out survey.

5.1.1.3 Comparison of survey results

A decrease in the average Likert score was observed across DNA types with human DNA being more acceptable than the use of artificial, bacterial or viral, and animal DNA. Based on this observation, a nested ANOVA was used to confirm that there was a significant difference in averaged Likert scores between both surveys ($p \leq 0.001$). In this case, the AUST-Online survey rates of acceptability were overall higher (i.e., participants felt each DNA type was more acceptable compared to the ACT-Mail-Out survey participants) (Figure 24). Therefore, a second test was used to confirm that this difference was in fact a fixed ($p = 0.257$). However, when accounting for participants in the ANOVA interaction model, a slightly significant result was identified ($p = 0.043$) (i.e., no fixed shift identified).

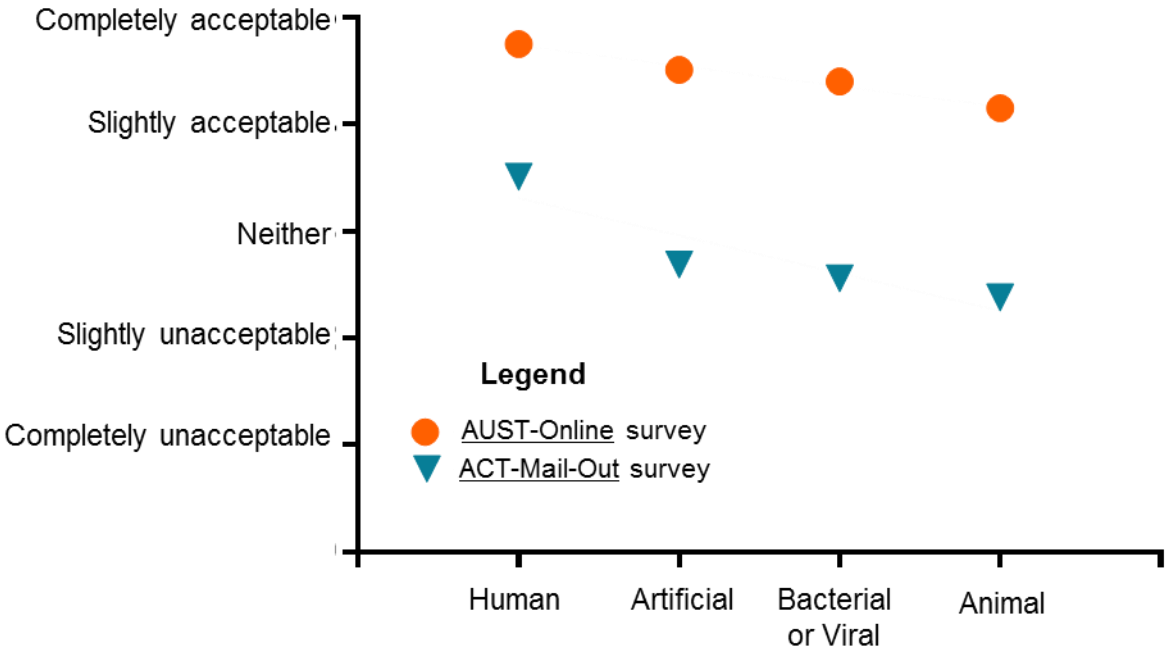


Figure 24. Averaged acceptability rates of DNA types.

5.1.1.4 Demographic associations with acceptance towards use of different types, results from both surveys

5.1.1.4.1 Gender

Further statistical tests revealed several demographic associations with attitudes towards DNA type, one of which was gender. On average, females in the AUST-Online survey were less likely to support HGT compared to males when DNA was obtained from either animals or

bacteria or viruses (Table 8). This association was also observed in the ACT-Mail-Out survey findings with the addition of human DNA being statistically significant.

Table 8. Mann-Whitney U test determining significant associations between participant attitudes towards societal use of DNA types, and gender from both the AUST-Online and ACT-Mail-Out survey.

	Human DNA	Animal DNA	Bacterial/ Viral DNA	Artificial DNA
AUST-Online survey				
Females*Acceptable (*n* (%))	326 (91%)	211 (59%)	201 (56%)	260 (72%)
Males*Acceptable (*n* (%))	160 (90%)	127 (72%)	126 (72%)	137 (77%)
Mann-Whitney U	27539	19495	18838	2398
Wilcoxon W	85169	6646	58178	73433
Z	-1.150	-3.733	-2.592	-1.318
p-value	0.250^{ns}	≤0.001***	0.010**	0.188^{ns}
ACT-Mail-Out survey				
Females*Acceptable (*n* (%))	59 (61%)	29 (30%)	37 (39%)	43 (44%)
Males*Acceptable (*n* (%))	54 (77%)	41 (59%)	41 (59%)	38 (54%)
Mann-Whitney U	2778	2238	2668	2866
Wilcoxon W	7532	6991	7324	7619
Z	-2.130	-3.845	-2.341	-1.770
p-value	0.033*	≤0.001***	0.019*	0.077^{ns}

5.1.1.4.2 Attitudes towards science and technology

Strength of support for the fields of science, technology, biotechnology and medicine were also found to have a positive statistical association with attitudes towards use of DNA in both surveys (i.e., as positivity increased for these two fields of research, so too did support for societal use of different types of DNA) (Table 9). In the AUST-Online survey, all fields were found to have a statistically significant association to all DNA types, with the exception of the technology field when compared to DNA that originated from bacteria or viruses. In the ACT-Mail-Out survey, only the fields of biotechnology and medicine were found to have a positive association.

Table 9. Kruskal Wallis H-test determining significant associations between societal use of DNA types and attitudes towards fields of science from the AUST-Online and ACT-Mail-Out survey.

		Human DNA	Animal DNA	Bacterial/Viral DNA	Artificial DNA
AUST-Online survey					
Science	χ^2	13	22	20	22
	df	4	4	4	4
	p-value	0.010**	≤0.001***	≤0.001***	≤0.001***
Tech.	χ^2	16	16	9	15
	df	4	4	4	4
	p-value	0.003**	0.003**	0.051^{ns}	0.006**
Biotech.	χ^2	28	52	31	32
	df	4	4	4	4
	p-value	≤0.001***	≤0.001***	≤0.001***	≤0.001***
Med.	χ^2	23	30	18	22
	df	4	4	4	4
	p-value	≤0.001***	≤0.001***	≤0.001**	≤0.001***
ACT-Mail-Out survey					
Biotech.	χ^2	11	15	12	12
	df	4	4	4	4
	p-value	0.022*	0.005**	0.020*	0.014*
Med.	χ^2	16	8	10	11
	df	3	3	3	3
	p-value	≤0.001***	0.037*	0.019*	0.014*

5.1.1.4.3 Age and education

For the AUST-Online survey, two more demographic categories were shown to have a significant association with attitudes. As the age of the participant increased, support for animal DNA $(\chi^2(6) = 24, p \leq 0.001)$ and bacterial or viral DNA $(\chi^2(6) = 34, p \leq 0.001)$ decreased. With education, a lower qualification levels were correlated with a higher unacceptance rate of bacterial or viral DNA for use in HGT procedures $(\chi^2(8) = 20, p = 0.009)$. This was particularly the case for those who did not complete their high school certificate.

5.1.1.4.4 GM food or crops

In the ACT-Mail-Out survey, a higher support for GM food/crops was correlated acceptance to all types of DNA within the survey for societal use (Table 10). When this question turned to acceptance of personal use, only human $(\chi^2(3) = 9, p = 0.025)$ and artificial $(\chi^2(3) = 11, p = 0.011)$ DNA showed a significant positive association with GM food support.

Table 10. Kruskal Wallis H-test determining significant associations between societal use of DNA types and strength of GMO support from the ACT-Mail-Out survey.

	Human DNA	Animal DNA	Bacterial/Viral DNA	Artificial DNA
χ^2	9	17	15	19
df	3	3	3	3
p-value	0.030*	≤0.001***	0.002**	≤0.001***

5.1.1.4.5 Parental status

Finally, those ACT-Mail-Out survey participants who did not have children were more likely to find animal $\left(n_{\text{(parent}*\text{acceptable)}} = 23\ (22\%);\ n_{\text{(not a parent}*\text{acceptable)}} = 31\ (50\%);\ U = 2618, p = 0.038\right)$ and bacterial or viral $(n_{\text{(parent}*\text{acceptable)}} = 42\ (41\%);$ $n_{\text{(not a parent}*\text{acceptable)}} = 34\ (55\%)\ ; U = 2565, p = 0.029)$ DNA acceptable for *societal use*. In the case of personal use the reverse was observed i.e, those who did have children were more likely to accept *all* types of DNA presented within the survey, except for animal DNA (Table 11).

Table 11. Mann-Whitney U test determining significant associations between personal use of DNA types and children status from the ACT-Mail-Out survey.

	Human DNA	Animal DNA	Bacterial/Viral DNA	Artificial DNA
Parent*Would use (*n* (%))	10 (10%)	25 (24%)	17 (16%)	18 (17%)
Not a parent*Would use (*n* (%))	3 (5%)	13 (21%)	7 (11%)	8 (13%)
Mann-Whitney U	2657	2734	2685	2622
Wilcoxon W	8117	8194	8145	7978
Z	-2.277	-1.759	-1.968	-2.093
p-value	0.023*	0.079^{ns}	0.049*	0.036*

5.2 PROCEDURAL TYPE

5.2.1 Acceptance towards societal use of different procedural types

5.2.1.1 Online Australian survey (2017) results

Participants were asked to respond to how acceptable certain types of HGT techniques were for societal use. In the AUST-Online survey, the lowest support was for insertion of a new gene with acceptance at 72% ($n = 399$) as detailed in Figure 20(b) (p. 101). This procedure also had

the highest ‘unacceptable’ result (11%; $n = 61$). Each other category (removing a mutated gene, editing a mutated gene, replacing a mutated gene with a normal copy, turning on a normal gene and turning off a mutated gene) had similar results with approximately 90% supporting the procedure and approximately 4% finding procedures to be unacceptable. No significant differences between the six categories was observed (data not shown).

5.2.1.2 Australian Capital Territory mail-out survey (2019) results

For the ACT-Mail-Out survey, again the lowest support was for insertion of a new gene with acceptance at 57% ($n = 96$) (Figure 21 (b), p.103). Each other category had acceptance rates of between 69% and 78%. Table 12 details significant differences in these responses as confirmed by a Wilcoxon Signed Rank test. Of note, insertion of a new gene and removing a mutated gene were found to be significantly less acceptable (with the exception of turning on a normal gene and removing a mutated gene).

Table 12. Wilcoxon Signed Rank test determining significant differences societal use and personal use of procedural types from the ACT-Mail-Out survey.
Where 'b' indicates a score based on negative ranks and 'c' indicates a score based on positive ranks.

	Societal Use		Personal Use	
	Z	*p*-value	Z	*p*-value
Editing a mutated gene - Removing a mutated gene	-2.509[b]	0.012*	-0.285[b]	0.776[ns]
Replacing a mutated gene - Removing a mutated gene	-3.451[b]	≤0.001**	-0.371[c]	0.710[ns]
Insertion of a new gene - Removing a mutated gene	-3.346[c]	≤0.001**	-3.592[b]	≤0.001***
Turning *on* a normal gene - Removing a mutated gene	-1.453[b]	0.146[ns]	-0.463[b]	0.643[ns]
Turning *off* a mutated gene - Removing a mutated gene	-2.729[b]	0.006**	-0.680[c]	0.497[ns]
Replacing a mutated gene - Editing a mutated gene	-0.811[b]	0.417[ns]	-1.221[c]	0.222[ns]
Insertion of a new gene - Editing a mutated gene	-5.597[c]	≤0.001***	-3.757[b]	≤0.001***
Turning *on* a normal gene - Editing a mutated gene	-0.887[c]	0.375[ns]	-0.275[b]	0.783[ns]
Turning *off* a mutated gene - Editing a mutated gene	-0.355[b]	0.722[ns]	-0.877[c]	0.380[ns]
Insertion of a new gene - Replacing a mutated gene	-6.367[c]	≤0.001***	-4.264[b]	≤0.001***
Turning *on* a normal gene - Replacing a mutated gene	-1.645[c]	0.100[ns]	-1.213[b]	0.225[ns]
Turning *off* a mutated gene - Replacing a mutated gene	-0.486[c]	0.627[ns]	-0.063[c]	0.949[ns]
Turning *on* a normal gene - Insertion of a new gene	-5.112[b]	≤0.001***	-3.972[c]	≤0.001***
Turning *off* a mutated gene - Insertion of a new gene	-5.458[b]	≤0.001***	-4.451[c]	≤0.001***
Turning *off* a mutated gene - Turning *on* a normal gene	-1.469[b]	0.142[ns]	-1.873[c]	0.061[ns]

ACT-Mail-Out survey participants were then asked to respond to how acceptable certain types of HGT techniques for *personal* use were. As seen when questioned about societal use of varying procedures, only 55% ($n = 93$) believed they would personally allow the insertion of a new gene as part of HGT (Figure 22(b), p.104). Each other had similar results with approximately 70%. It is therefore no surprise that insertion of a new gene compared to all other

categories for personal use, had significantly less participants saying they would personally use this technique.

A pairwise comparison between societal and personal use of different techniques was achieved by a Wilcoxon Signed Rank test. Significant differences in acceptability was identified for all categories, with participants less likely to use each technique personally, compared to their perception of societal acceptability (Figure 25).

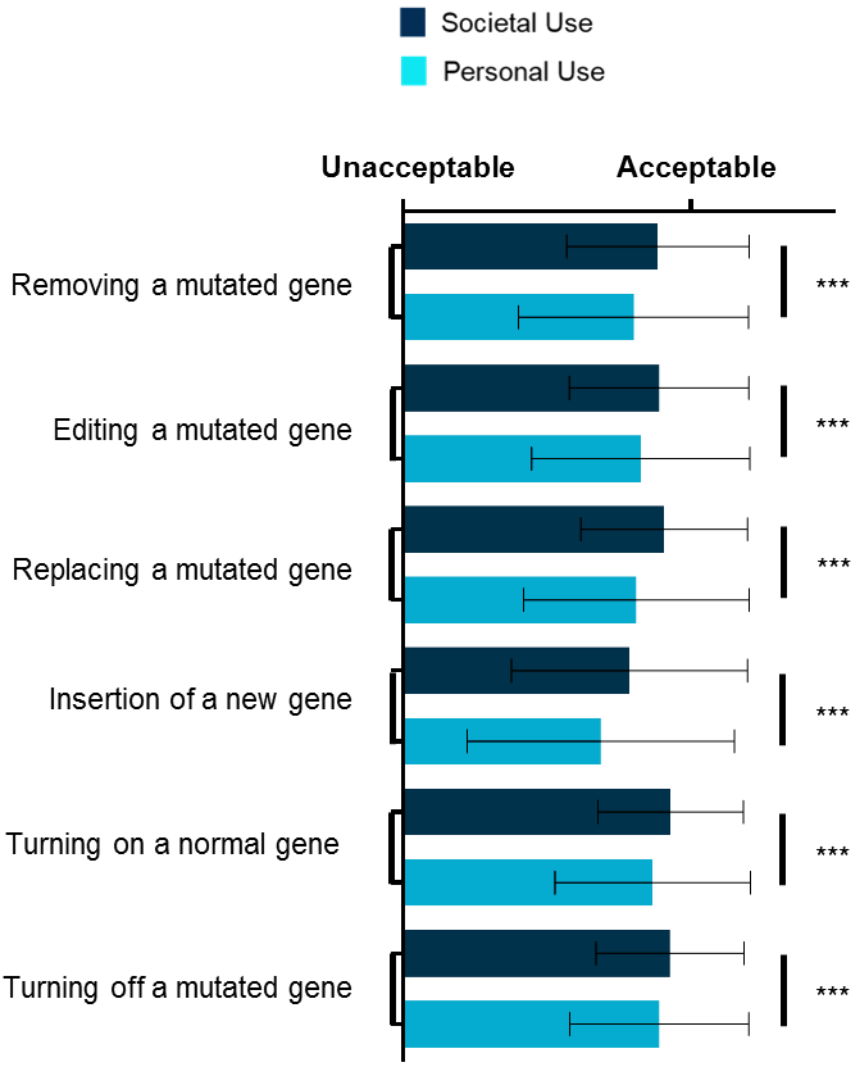


Figure 25. Wilcoxon Signed Rank test determining significant differences between ACT –Mail-Out participant's attitudes towards societal and personal use of procedural types.

5.2.1.3 Demographic associations with acceptance towards use of different procedural types, results from both surveys

5.2.1.3.1 Attitudes towards science and technology

Although no *demographic* categories analysed showed an association with acceptability of these techniques, support for the general and specific fields of science did for both the AUST-Online survey (Table 13) and ACT-Mail-Out survey (Table 14). In both surveys, on average as positivity increased for the field of technology and medicine, so too did the acceptability towards each procedural type with limited exceptions. To note, both science and biotechnology were additionally found to be significant in the AUST-Online survey findings, however this was not confirmed within the results of the ACT-Mail-Out survey.

Table 13. Kruskal Wallis H-test determining significant associations between AUST-Online survey participant's attitudes towards societal use of different procedural types and attitudes towards science, technology, biotechnology and medicine.

	Science			Technology			Biotech.			Medicine		
	χ^2	df	p-value	χ^2	df	p-value	χ^2	df	p-value	χ^2	df	p-value
Removing a mutated gene	13	4	0.013*	13	4	0.012*	10	4	0.037*	31	4	≤0.001***
Editing a mutated gene	30	4	≤0.001***	24	4	≤0.001***	31	4	≤0.001***	56	4	≤0.001***
Replacing a mutated gene	13	4	0.014*	14	4	0.008**	28	4	≤0.001***	42	4	≤0.001***
Insertion of a new gene	15	4	0.004**	17	4	0.002**	11	4	0.023*	22	4	≤0.001***
Turning on a normal gene	119	4	≤0.001***	10	4	0.043*	7	4	0.114^{ns}	29	4	≤0.001***
Turning off a mutated gene	12	4	0.019*	9	4	0.074^{ns}	10	4	0.035*	29	4	≤0.001***

Table 14. Kruskal Wallis H-test determining significant associations between ACT-Mail-Out survey participant's attitudes towards societal use of different HGT procedural types and attitudes towards technology and medicine.

	Technology			Medicine		
	χ^2	df	p-value	χ^2	df	p-value
Removing a mutated gene	13	3	0.006**	11	3	0.011*
Editing a mutated gene	10	3	0.017*	10	3	0.015*
Replacing a mutated gene	11	3	0.013*	8	3	0.042*
Insertion of a new gene	8	3	0.037*	4	3	0.288^{ns}
Turning on a normal gene	8	3	0.056^{ns}	11	3	0.011*
Turning off a mutated gene	8	3	0.044*	7	3	0.087^{ns}

5.2.1.3.2 GM food or crops

For the ACT-Mail-Out survey only, another positive association was confirmed, this being the participant's support of genetically modified foods, as shown in Table 15. Only turning off a mutated gene for personal use did have a significant association with GM foods.

Table 15. Kruskal Wallis H-test determining significant associations between ACT-Mail-Out survey participant's attitudes towards personal use of different HGT procedural types and strength of GMO support.

	Societal Use			Personal Use		
	χ^2	df	p-value	χ^2	df	p-value
Removing a mutated gene	9	3	0.031*	9	3	0.030*
Editing a mutated gene	13	3	0.005**	13	3	0.004**
Replacing a mutated gene	15	3	0.002**	9	3	0.025*
Insertion of a new gene	11	3	0.014*	17	3	0.001***
Turning on a normal gene	17	3	0.001***	11	3	0.010**
Turning off a mutated gene	13	3	0.005**	7	3	0.063^{ns}

5.3 ACCEPTABILITY OF DIFFERENT OUTCOMES

5.3.1 Online Australian survey (2017) results

The final section in this chapter focuses on outcomes of HGT. Survey participants were asked to rate a series of three potential outcomes or consequences that the procedure might have. The lowest support in the AUST-Online survey was for genetic modification that changed the entire population, with only 12% ($n = 65$) finding this an acceptable outcome (Figure 20(c), p.101). Highest acceptability was for procedures where the effect was limited to the individual with 83% ($n = 454$) of respondents finding this acceptable, and only 2% ($n = 13$) against.

Areas of significant differences in gender responses to outcomes of the procedure were discovered in the AUST-Online survey. Those who identified as female were *less* likely to support HGT if it changed the genetic makeup of the entire population (Table 16). This was also seen for age where a decrease in support was observed with increasing age of the participant for this statement ($\chi^2(6) = 34, p \leq 0.001$).

Table 16. Mann Whitney U test determining significant associations between AUST-Online survey participant's attitudes towards outcomes or consequences of human gene therapy and gender.

	If the effects were limited to the person	If the effects were permanent	If it changed the genetic makeup of the entire population
Female*Acceptable (*n* (%))	293 (81%)	216 (60%)	28 (8%)
Male*Acceptable (*n* (%))	150 (85%)	127 (72%)	35 (20%)
Mann-Whitney U	30387	30379	27069
Wilcoxon W	95007	94999	92410
Z	-.688	-.750	-2.992
p-value	0.491^{ns}	0.453^{ns}	0.003**

The final significant positive correlation observed in the AUST-Online survey was between participant's attitudes towards science**,** biotechnology and medicine, and attitudes towards different types of outcomes and consequences of HGT (Table 17).

Table 17. Kruskal Wallis H-test determining significant associations between AUST-Online survey participant's attitudes towards outcomes or consequences of human gene therapy and attitudes towards science, biotechnology and medicine.

		If the effects were limited to the person	If the effects were permanent	If it changed the genetic makeup of the entire population
Science	χ^2	25	20	7
	df	4	4	4
	p-value	<0.001***	<0.001***	0.164^{ns}
Biotech.	χ^2	25	24	37
	df	4	4	4
	p-value	<0.001***	<0.001***	<0.001***
Med.	χ^2	35	16	8
	df	4	4	4
	p-value	≤0.001***	0.004**	0.107^{ns}

5.3.2 Australian Capital Territory mail-out survey (2019) results

Findings from the ACT-Mail-Out survey confirmed the lowest acceptability rate was for genetic modification that changed the entire population, with only 9% ($n = 16$) finding this acceptable as shown in Figure 21(c), p. 103. The highest rate of acceptability was for procedures where the effect was limited to the individual with 87% ($n = 147$) of respondents finding this acceptable. When the effects were permanent, acceptability decreased to 51% ($n = 88$).

There was again a significant difference in gender acceptance rates, this time when the effects of HGT was permanent, with females less likely to accept this technique under those conditions ($n_{\text{(female}*\text{acceptable)}} = 216\ (60\%); n_{\text{(male}*\text{acceptable)}} = 127\ (72\%);\ U = 2426, p = 0.002$). When associated with GM food support, a significant association was identified for two out of the three outcomes presented (Table 18). Finally, as support for biotechnology grew, so too did support for HGT when the effects were permanent ($\chi^2(4) = 13, p = 0.010$).

Table 18. Kruskal Wallis H-test determining significant associations between outcomes or consequences of human gene therapy and GMO support from the ACT-Mail-Out survey.

	If the effects were limited to the person	If the effects were permanent	If it changed the genetic makeup of the entire population
χ^2	13	12	0.159
df	3	3	3
p-value	0.004**	0.006**	0.984^{ns}

5.4 CHAPTER SUMMARY

Attitudes towards DNA type, procedure type and potential outcomes were presented within this chapter. Participants in both surveys found the use of human DNA to treat a sick person most acceptable compared to the use of artificial DNA, bacterial or viral DNA, and animal DNA, respectively. Although, analysis revealed no significant difference between the average acceptance rates of artificial DNA, and bacterial or viral DNA in both the AUST-Online and the ACT-Mail-Out survey.

On average, females in both surveys were less likely to support HGT compared to males when DNA was obtained from either animals or bacteria or viruses. Alternatively, in both surveys, a participant was more likely to find all DNA types acceptable if they had positive attitudes towards biotechnology and medicine. When comparing differences in opinion between societal and personal use of different DNA types and procedures in the ACT-Mail-Out survey, in every example, personal use was significantly *less* acceptable.

Out of the six categories of procedural types for general use presented to the participant, the lowest support was found for insertion of a new gene, in both surveys. Only the ACT-Mail-Out survey participants were asked to respond to how acceptable certain types of HGT techniques for *personal u*se. By a significant majority, the lowest support was again seen for insertion of a new gene. In this 2019 survey, significant differences in acceptability were identified for all categories, with participants less likely to use each technique personally, compared to its general use by society. In both surveys, on average as positivity increased for the field of technology and medicine, so too did the acceptability towards each procedural type with limited exceptions. Both science and biotechnology were additionally found to be significant in the AUST-Online survey findings.

Finally, when responding to three different outcomes of HGT, the lowest support in both surveys was for genetic modification that changed the entire population. Several demographic associations were identified, however only one was observed in *both* surveys: females were *less* likely to support HGT if it changed the genetic makeup of the entire population.

6 Results: Attitudes Towards Therapeutic, Enhancive or Prophylactic Applications of Human Gene Therapy

This fourth results chapter details findings from the substantive survey questions relating to the theme 'therapy, enhancement and prevention'. This chapter focuses on objective 2(c); to determine the Australian public's attitudes towards:

c. Therapeutic, enhancement and preventative uses of HGT

This chapter also focuses on objective 3; to determine if there is a difference between attitudes towards one's personal use of HGT, and what is acceptable for society. In this case, both the AUST-Online survey and the ACT-Mail-Out survey assessed the opinions of these two categories.

6.1 SEVERITY AND TYPE OF TREATMENT APPLICATIONS

6.1.1 Online Australian survey (2017) results

Chronic illness, physical disability, intellectual disability and mental illness were used to determine the difference in the average acceptance of HGT. In all four categories of the AUST-Online survey, acceptability of HGT decreased with declining severity of the condition (Figure 26(a)). The majority of AUST-Online survey respondents believed treating a severe chronic illness was acceptable (95%; $n = 520$) yet treating a mild chronic illness was considered less acceptable (73%; $n = 504$).

Ninety-five percent ($n = 520$) found HGT to treat a severe physical disability acceptable, whereas only 77% ($n = 426$) agreed treatment for a mild physical disability was acceptable. From severe to mild, intellectual disability had a decrease in acceptability from 79% ($n = 368$) to 56% ($n = 307$) and mental illness from 84% ($n = 368$) to 54% ($n = 294$).

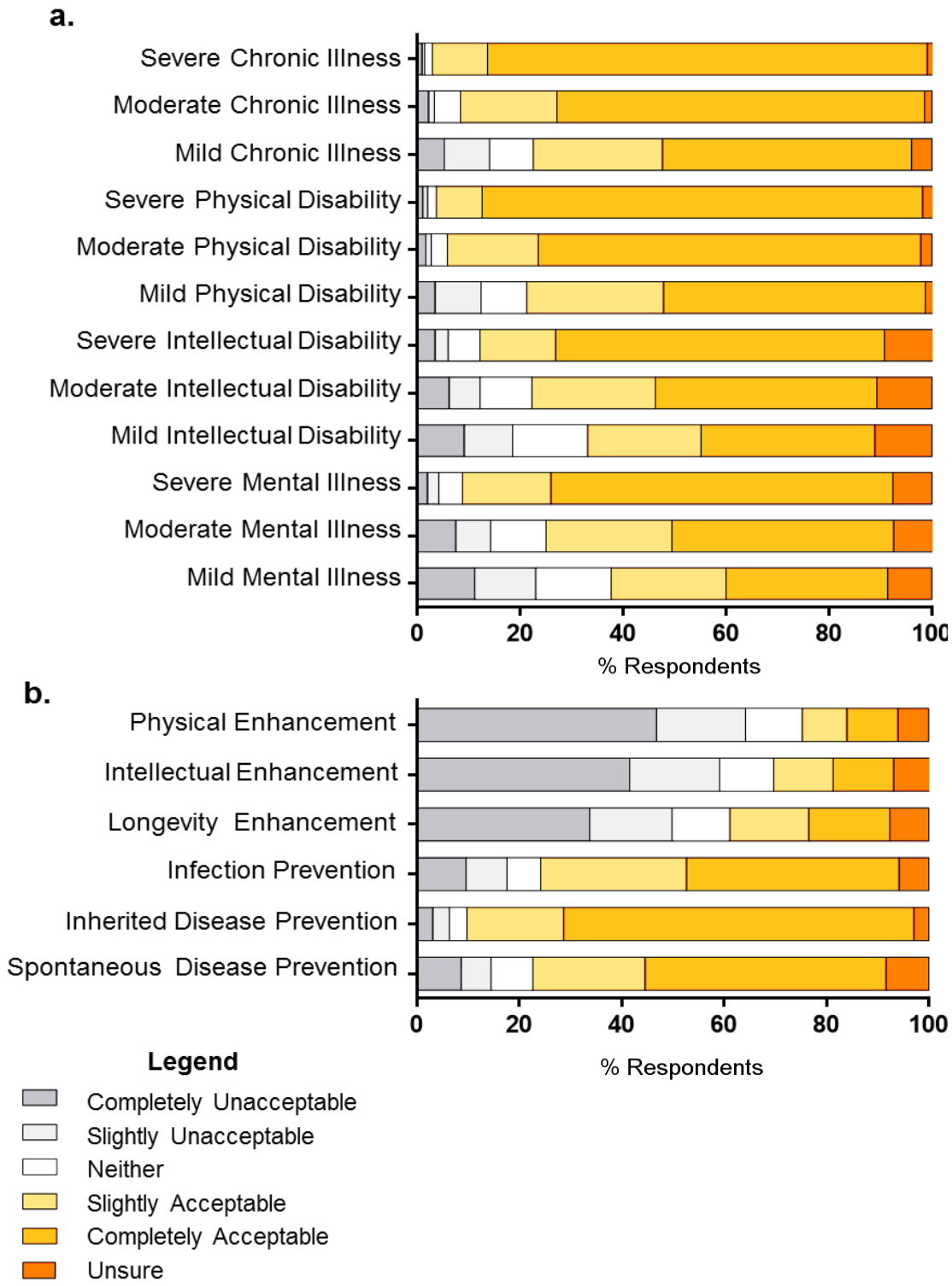


Figure 26. Distribution of AUST-Online survey participants' agreement towards human gene therapy, enhancement and prevention.
Where (a) is the percentage of respondents ranking the acceptability of using human gene therapy to treat four types of diseases (chronic illness, physical disability, intellectual disability and mental illness) with varying severity (severe, moderate and mild) and, (b) is the percentage of respondents ranking the acceptability of using human gene therapy to enhance a 'normal' trait (physical, intellectual or longevity) or to prevent certain types of disease (infection, inherited or spontaneous).

To begin the exploratory analysis of the AUST-Online survey results, a Friedman's test was applied to the data in order determine the differences in median strength of acceptability between severe, moderate and mild cases of the same disease or disability. Each severity-level of the chronic illness category was found to have a significantly different rate of acceptability ($\chi^2(1) = 236, p \leq 0.001$). This was also observed for physical disability ($\chi^2(1) = 205, p \leq 0.001$), intellectual disability ($\chi^2(1) = 206, p \leq 0.001$) and mental illness ($\chi^2(1) = 255, p \leq 0.001$). Post hoc analysis using a Wilcoxon signed-rank tests was conducted to determine the significant differences between all levels of severity in each disease/disability category. A strong significant difference was determined for each pairwise comparison, *except* between terminal illness and severe chronic illness (Table 19).

Table 19. Wilcoxon Signed Rank test determining significant differences in severity of illness or type of enhancement and prevention from the AUST-Online survey.
Where 'b' indicates a score based on negative ranks and 'c' indicates a score based on positive ranks.

	Z	*p*-value
Severe chronic illness – Terminal illness	-0.599[b]	0.549[ns]
Moderate – Severe chronic illness	-8.517[c]	≤0.001***
Mild – Moderate chronic illness	-11.749[c]	≤0.001***
Moderate – Severe physical disability	-6.712[c]	≤0.001***
Mild – Moderate physical disability	-10.862[c]	≤0.001***
Moderate – Severe intellectual disability	-9.183[c]	≤0.001***
Mild – Moderate intellectual disability	-8.359[c]	≤0.001***
Moderate – Severe mental illness	-11.067[c]	≤0.001***
Mild – Moderate mental illness	-9.962[c]	≤0.001***
Intellectual enhancement – Physical enhancement	-5.108[b]	≤0.001***
Longevity enhancement – Intellectual enhancement	-6.311[b]	≤0.001***
Longevity enhancement – Physical enhancement	-8.530[b]	≤0.001***
Inherited disease prevention – Infection prevention	-10.758[b]	≤0.001***
Spontaneous disease prevention – Inherited disease prevention	-8.119[c]	≤0.001***
Infection prevention – Spontaneous disease prevention	-2.701[c]	0.007**

6.1.2 Australian Capital Territory mail-out survey (2019) results

In the ACT-Mail-Out survey, intellectual disability and mental illness were merged. Therefore in all three categories of disability and disease, acceptability of HGT decreased with declining severity of the condition (Figure 27(a)). As seen in the AUST-Online survey, the majority of respondents believed treating a *severe* chronic illness was acceptable ($94\%;\ n = 148$). This acceptability significantly decreased for treating a *mild* chronic illness ($61\%;\ n = 103$). This pattern was also observed when comparing the acceptability of treating a severe physical disability ($86\%;\ n = 147$) to a mild physical disability ($67\%;\ n = 114$). Finally, from severe to mild, intellectual disability or mental illness also showed a decrease in acceptability from 72% ($n = 123$) to 41% ($n = 69$).

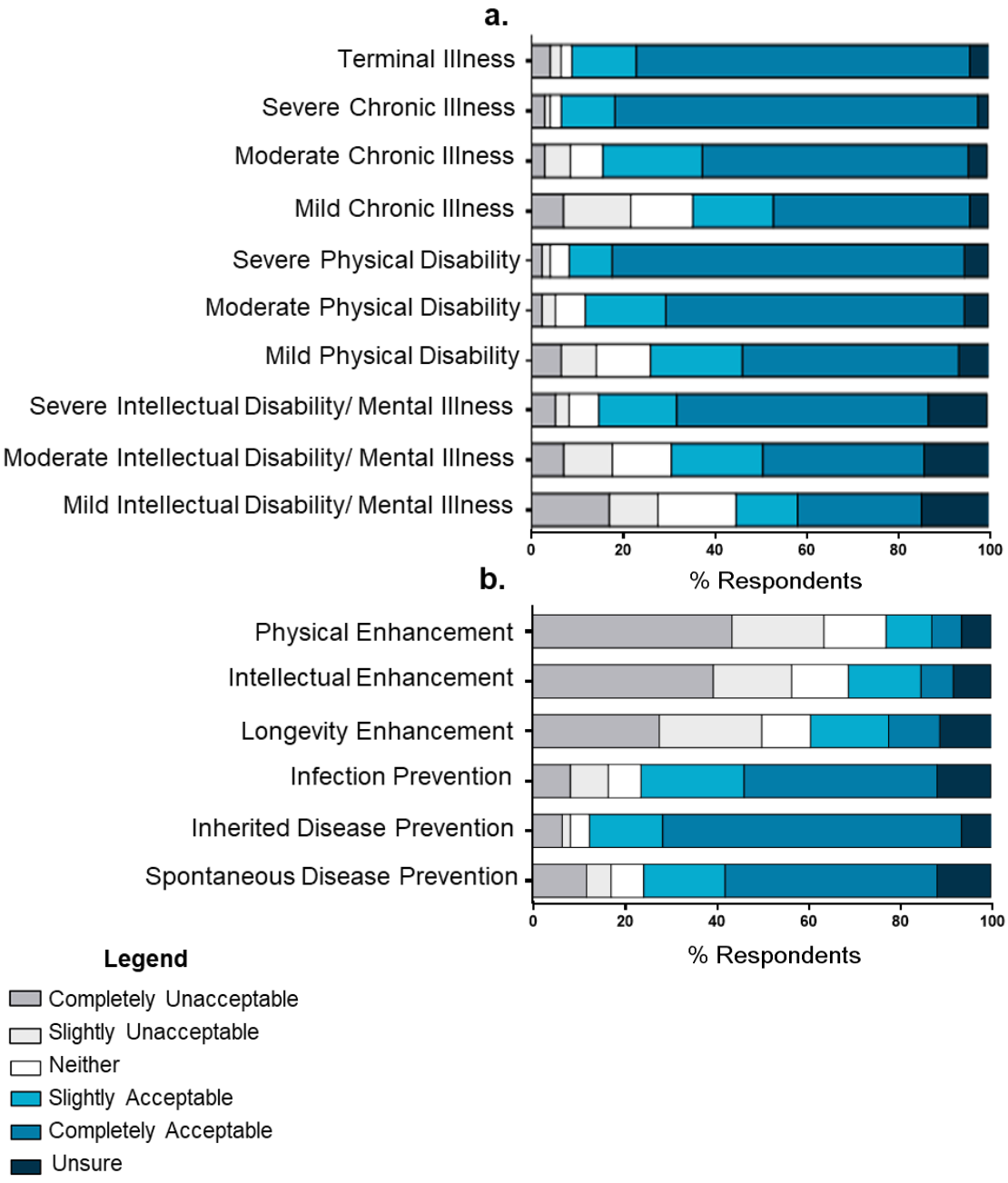


Figure 27. Distribution of ACT-Mail-Out survey participants' agreement towards human gene therapy, enhancement and prevention.
Where (a) is the percentage of respondents ranking the acceptability of using human gene therapy to treat four types of diseases (chronic illness, physical disability, intellectual disability and mental illness) with varying severity (severe, moderate and mild) and, (b) is the percentage of respondents ranking the acceptability of using human gene therapy to enhance a 'normal' trait (physical, intellectual or longevity) or to prevent certain types of disease (infection, inherited or spontaneous).

A Friedman's test was conducted, and for each case, each condition was identified as having a significantly different rate of acceptability between the severest and mildest forms of clinical indications: Chronic illness ($\chi^2(3) = 135, p = < 0.001$), physical disability ($\chi^2(2) =$

$79, p \leq 0.001$), and intellectual disability or mental illness ($\chi^2(2) = 78, p \leq 0.001$). Again, a post hoc analysis using a Wilcoxon signed-rank tests was conducted to determine significant differences between all levels of severity in each disease/disability category (Table 20). Only one comparison was identified as not statistically significant, this was between infection prevention and spontaneous prevention.

Table 20. Wilcoxon Signed Rank test determining significant differences in severity of illness or type of enhancement and prevention from the ACT-Mail-Out survey.
Where 'b' indicates a score based on negative ranks and 'c' indicates a score based on positive ranks.

	Z	*p*-value
Severe Chronic Illness – Terminal Illness	-3.118[b]	0.002**
Moderate– Severe Chronic Illness	-5.420[c]	≤0.001***
Mild – Moderate Chronic Illness	-6.332[c]	≤0.001***
Moderate – Severe Physical Disability	-2.686[c]	0.007**
Mild – Moderate Physical Disability	-6.294[c]	≤0.001***
Moderate – Severe Intellectual Disability/Mental Illness	-4.727[c]	≤0.001***
Mild – Moderate Intellectual Disability/Mental Illness	-5.460[c]	≤0.001***
Intellectual Enhancement – Physical Enhancement	-2.144[b]	0.032*
Longevity Enhancement – Intellectual Enhancement	-2.033[b]	0.042*
Longevity Enhancement – Physical Enhancement	-3.394[b]	≤0.001***
Inherited Disease Prevention – Infection Prevention	-5.808[b]	≤0.001***
Spontaneous Disease Prevention – Inherited Disease Prevention	-5.831[c]	≤0.001***
Infection Prevention – Spontaneous Disease Prevention	-0.052[c]	0.959[ns]

6.1.3 Comparison of survey results

A decrease in the average Likert score was observed with declining levels of severity in the category of chronic disease. Based on this observation, a nested ANOVA was used to confirm that there was a significant difference in averaged Likert scores between both surveys ($p \leq 0.001$). In this case, the AUST-Online survey rates of acceptability were overall higher (i.e., participants felt each chronic disease severity level was more acceptable compared to the ACT-Mail-Out survey participants) (Figure 28). A second test confirmed that this difference was in fact a fixed shift ($p = 0.529$). This result was corroborated when the ANOVA model accounted for participants ($p = 0.339$).

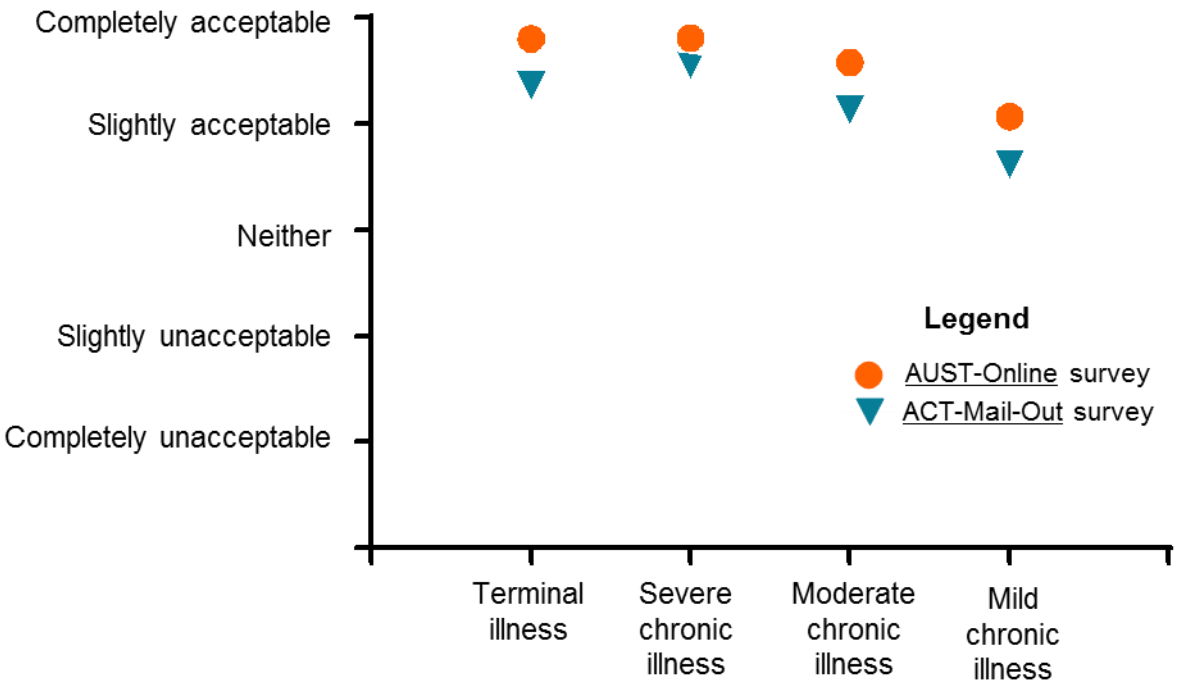


Figure 28. Averaged acceptability rates for chronic illness subcategories.

For subcategories of physical disability, a decrease in the average Likert score was also identified with declining severity levels. As observed when comparing responses from sub-categories of chronic illness in both surveys. a significant difference in averaged Likert scores was determined between both surveys ($p \leq 0.001$). The AUST-Online survey rates of acceptability were higher compared to the ACT-Mail-Out survey participants (Figure 29). A second test was used to confirm that this was a fixed shift ($p = 0.946$). An insignificant result was also observed when accounting for participants in the ANOVA interaction model ($p = 0.968$).

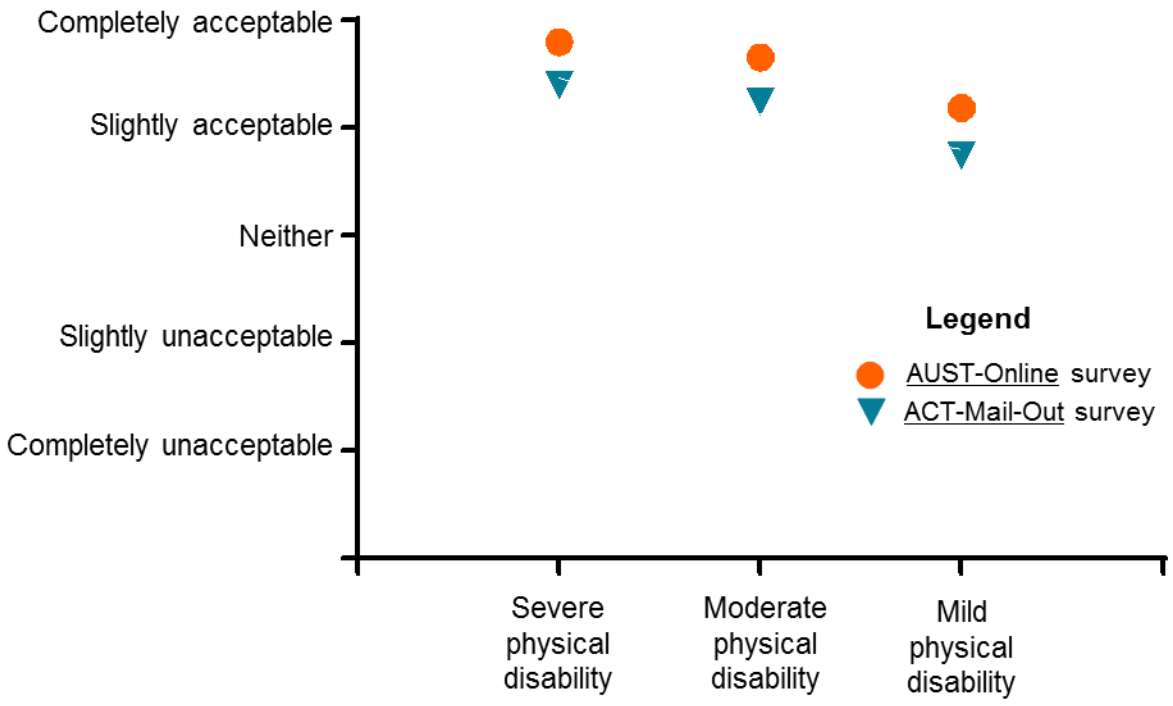


Figure 29. Averaged acceptability rates for physical disability subcategories.

In order to appropriately compare results from the two surveys, the separate categories of intellectual disability and mental illness from the AUST-Online survey were averaged to align with the ACT-Mail-Out survey. As discussed previously, when designing the ACT-Mail-Out survey, to reduce the burden on the participant, these categories were merged.

For subcategories of intellectual disability and mental illness, again a decrease in the average Likert scores with declining severity levels was identified. As before, these Likert scores were significantly different ($p \leq 0.001$), with the AUST-Online survey rates of acceptability again higher compared to the ACT-Mail-Out survey participants (Figure 30). The second ANOVA test confirmed that this difference was a fixed shift both with ($p = 0.143$) and without ($p = 0.626$) participants being included as a factor.

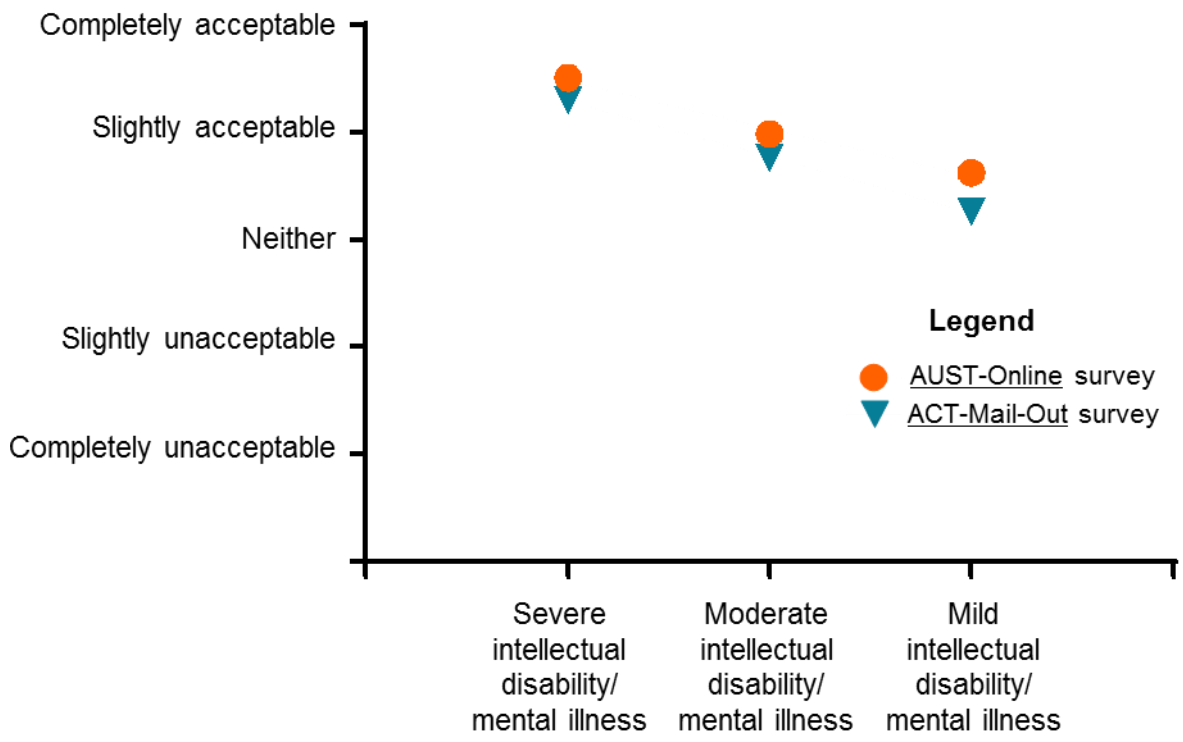


Figure 30. Averaged acceptability rates for intellectual disability or mental illness subcategories.

6.2 ENHANCEMENT APPLICATIONS

6.2.1 Online Australian survey (2017) results

The acceptability of physical, intellectual and longevity enhancement procedures using HGT was questioned within both surveys. Only 19% ($n = 103$) thought enhancing physical traits such as athletic ability or physical appearance was an acceptable use of HGT in the AUST-Online survey (Figure 26(b), p.119). Intellectual enhancement was considered slightly more appropriate with 24% (n=129) believing this procedure was 'acceptable' while the highest acceptance of gene therapy for enhancement purposes was for increased longevity (31%; $n = 172$).

When comparing the different applications of enhancement (physical, intellectual and longevity) in the AUST-Online survey, the Wilcoxon Signed Rank test indicated a significant difference in the median acceptability in each comparison (Table 19, p.120). Pairwise comparisons were also made between each category of illness/disability and enhancements. In each case, enhancement procedures were considered significantly less acceptable (Table 21, p. 131).

6.2.2 Australian Capital Territory mail-out survey (2019) results

Out of the ACT residents who took part in the survey, only 16% ($n = 28$) found physical enhancement using HGT acceptable (Figure 27(b), p.122). Intellectual enhancement was considered marginally more acceptable at 23% (n=39). Like the AUST-Online survey, the highest acceptance of rate was for enhancement to increase longevity (28%; $n = 48$). However, unlike the AUST-Online survey, a Wilcoxon Signed Rank test indicated a difference in the median acceptability only between longevity and physical enhancement ($Z = -3.394, p = 0.001$) (Table 20, p.123). Pairwise comparisons were also made between each category of illness/disability and enhancements. In each case, enhancement procedures were considered significantly less acceptable (Table 22, p. 132).

6.2.3 Comparison of survey results

In both surveys, acceptability of three enhancement procedures was measured. In each survey, longevity enhancement was deemed (on average) most acceptable, followed by an intellectual enhancement, and physical enhancement. An ANOVA confirmed a significant difference in averaged Likert scores between both surveys ($p \leq 0.001$), with the AUST-Online survey rates of acceptability again higher compared to the ACT-Mail-Out survey participants (Figure 31). The second ANOVA test confirmed that this difference was a fixed shift both with ($p = 0.893$) and without ($p = 0.995$) participants being included as a factor.

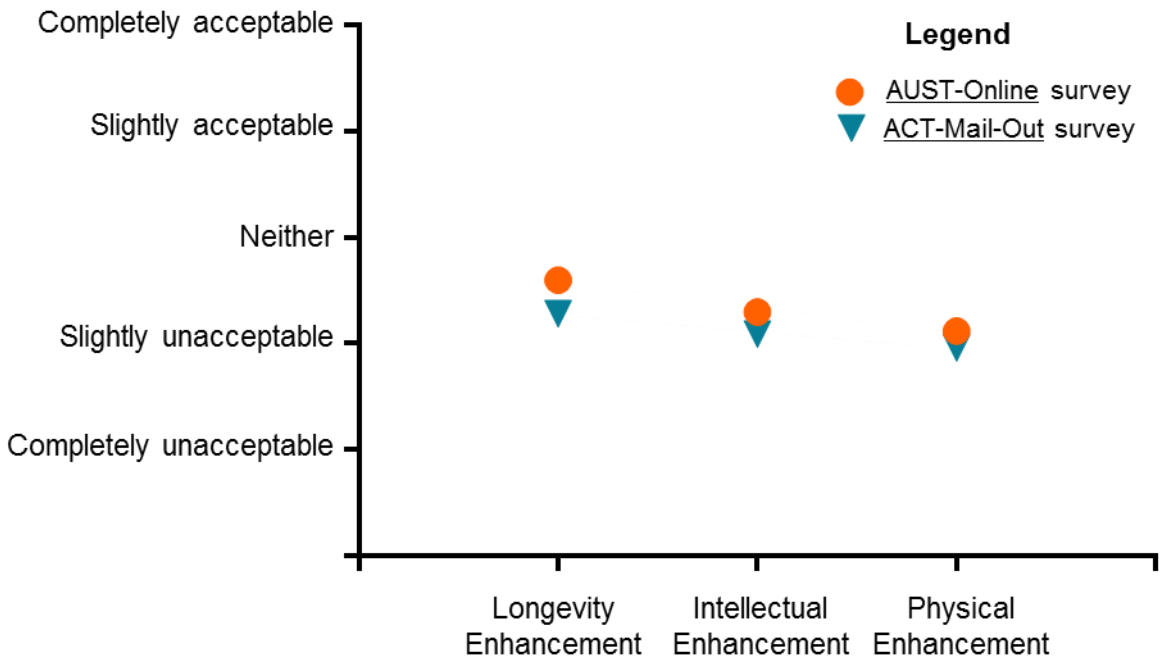


Figure 31. Average acceptability rates of three enhancement procedures.

6.3 PREVENTATIVE APPLICATIONS

6.3.1 Online Australian survey (2017) results

After enhancement procedures, participants responded to the suitability of preventative HGT applications for increasing immunity, and preventing inherited and spontaneous disease. Enhancing the immune system to prevent new infections saw 70% ($n = 386$) in favour of the technique (Figure 26(b), p.119). When asked whether they were willing to use this technology to prevent an inherited genetic disease, like breast cancer, acceptability increased to 87% ($n = 481$). Support declined again when HGT was associated to a spontaneous disease such as non-hereditary forms of cancer; 69% ($n = 381$) found this procedure acceptable. A Wilcoxon Signed Rank test determined significant differences in the median acceptability between all types of preventative procedures (Table 19, p.120). A significant difference was also observed when comparing the mean of each category of illness/disability and enhancements, with prevention less acceptable than treating a disease or illness, but more acceptable than enhancement applications (Table 21, p. 130).

6.3.2 Australian Capital Territory mail-out survey (2019) results

In the ACT-Mail-Out survey, respondents thought the prevention of an inherited genetic disease was again the most acceptable ($n = 137;\ 81\%$), followed by enhancing the immune system to prevent new infections ($n = 109;\ 65\%$) and to prevent non-hereditary diseases ($n = 108; 64\%$) (Figure 27(c), p.122). A Wilcoxon Signed Rank test indicated a significant difference between all types of preventative procedures except between infection and spontaneous disease prevention ($Z = -0.052, p = 0.959$) (Table 20, p.123). When pairwise comparisons were made between each category of illness/disability and enhancements, all categories were found to be significantly different, *except* when comparing prevention to intellectual disability/mental illness (Table 22, p,131).

6.3.3 Comparison of survey results

Due to a significant difference between the acceptability rates of each procedure, an ANOVA was used for subcategories of prevention, with results indicating a decrease in acceptance from inherited, to spontaneous, to infection prevention. There was a significant difference in averaged Likert scores between both surveys ($p \leq 0.001$), again, the AUST-Online survey rates of acceptability were higher compared to the ACT-Mail-Out survey participants (Figure 32). The second ANOVA test confirmed that this difference was a fixed shift both with ($p = 0.403$) and without ($p = 0.654$) participants being included as a factor.

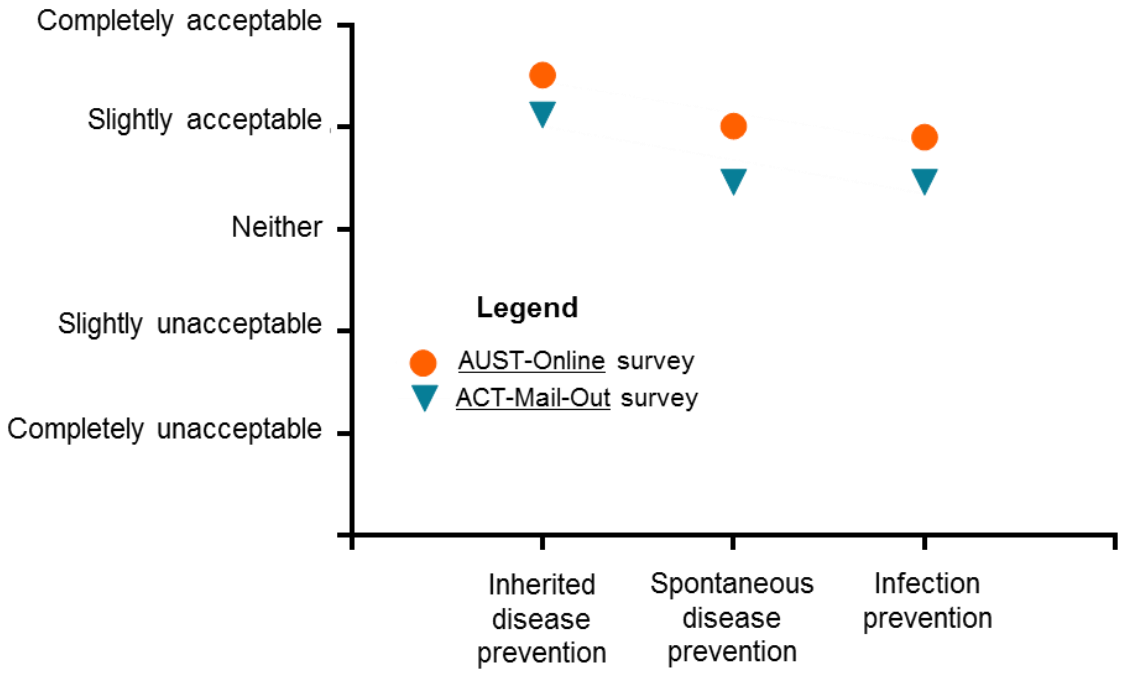


Figure 32. Averaged acceptability rates of three prevention procedures.

6.4 COMPARISON OF SURVEY RESULTS BETWEEN AVERAGED CATEGORIES OF THERAPY, PREVENTION AND ENHANCEMENT

6.4.1 Online Australian survey (2017) results

The Friedman's test additionally identified differences in acceptance between averaged scores of each category of diseases/disability (chronic, physical, intellectual and mental), data not shown. Based on this finding, a Wilcoxon signed-rank test confirmed all pairwise comparisons were significant as detailed in (Table 21).

Table 21. Wilcoxon Signed Rank test determining significant differences between averaged categories of illness/disability, enhancement and prevention from the AUST-Online survey.
Where 'b' indicates a score based on negative ranks and 'c' indicates a score based on positive ranks.

	Z	*p*-value
Physical disability – Chronic illness	-3.411[c]	<0.001***
Intellectual disability – Chronic illness	-11.207[b]	<0.001***
Mental illness – Chronic illness	-12.559[b]	<0.001***
Enhancement procedures – Chronic illness	-18.753[b]	<0.001***
Preventative procedures – Chronic illness	-9.007[b]	<0.001***
Intellectual disability – Physical disability	-12.255[b]	<0.001***
Mental illness – Physical disability	-13.637[b]	<0.001***
Enhancement procedures – Physical disability	-18.693[b]	<0.001***
Preventative procedures – Physical disability	-10.053[b]	<0.001***
Mental illness – Intellectual disability	-2.405[b]	0.016*
Enhancement procedures – Intellectual disability	-16.911[b]	<0.001***
Preventative procedures – Intellectual disability	-1.962[b]	0.050*
Enhancement procedures – Mental illness	-17.298[b]	<0.001***
Preventative procedures – Mental illness	-3.337[c]	<0.001***
Preventative procedures – Enhancement procedures	-18.111[c]	0.001***

6.4.2 Australian Capital Territory mail-out survey (2019) results

When comparing averaged therapeutic, enhancive and prophylactic categories from the ACT-Mail-Out survey, unlike the AUST-Online survey, a Wilcoxon signed-rank test identified four comparisons not to be significant as shown in (Table 22).

Table 22. Wilcoxon Signed Rank test determining significant differences between averaged categories of illness/disability, enhancement and prevention from the ACT-Mail-Out survey.
Where 'b' indicates a score based on negative ranks and 'c' indicates a score based on positive ranks.

	Z	*p*-value
Physical Disability – Chronic Illness	-0.304[b]	0.761[ns]
Intellectual Disability/Mental Illness – Chronic Illness	-0.905[c]	0.365[ns]
Enhancement Procedures – Chronic Illness	-10.127[c]	≤0.001***
Preventative Procedures – Chronic Illness	-3.621[b]	≤0.001***
Intellectual Disability/Mental Illness – Physical Disability	-1.476[c]	0.140[ns]
Enhancement Procedures – Physical Disability	-10.128[c]	≤0.001***
Preventative Procedures – Physical Disability	-14.106[c]	≤0.001***
Enhancement Procedures – Intellectual Disability/Mental Illness	-10.055[c]	≤0.001***
Preventative Procedures – Intellectual Disability/Mental Illness	-1.923[c]	0.055[ns]
Preventative Procedures – Enhancement Procedures	-9.118[b]	≤0.001***

6.4.3 Comparison of survey results

The final decline in acceptability within this section was observed across all averaged categories of therapy, enhancement and prevention in both surveys (Figure 33). Again, there was a significant difference in averaged Likert scores between both surveys ($p \leq 0.001$). While the second ANOVA test confirmed that this difference was a fixed shift ($p = 0.101$), however when accounting for participants, this turned out to be insignificant ($p = 0.019$).

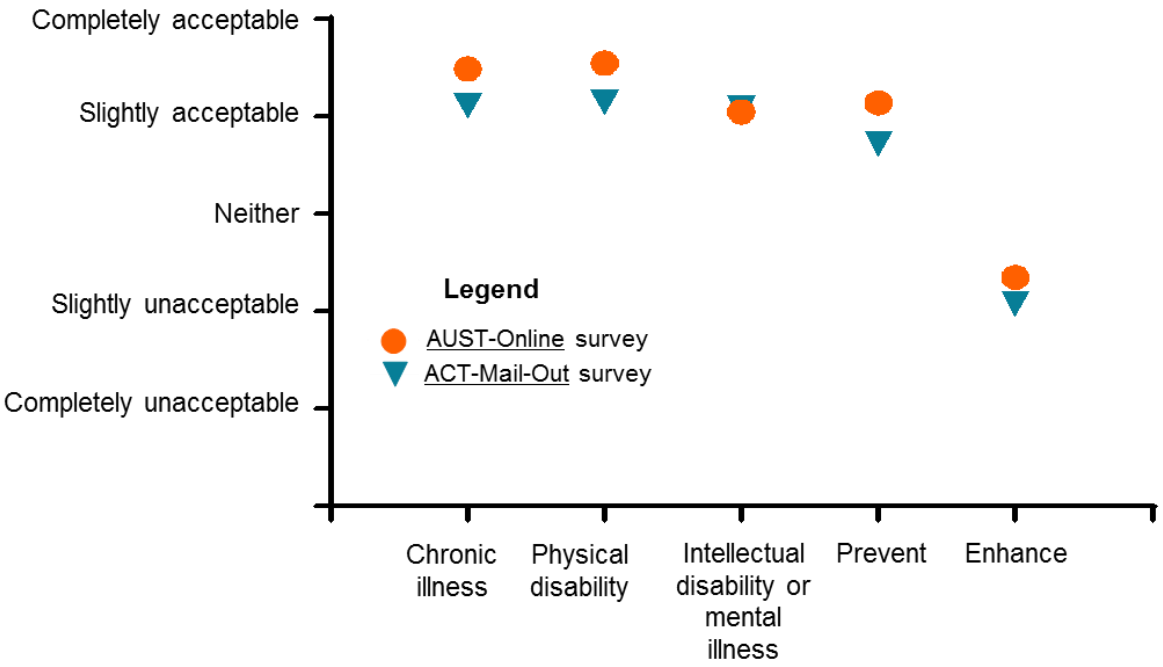
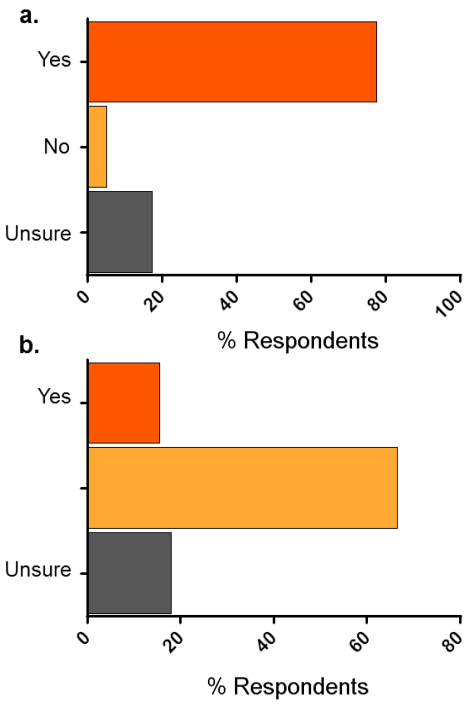


Figure 33. Averaged acceptability rates for therapeutic, enhancive and preventative categories.

6.5 ATTITUDES TO THE PERSONAL USE OF HUMAN GENE THERAPY

6.5.1 Online Australian survey (2017) results

Towards the end of the AUST-Online survey, respondents were asked if they would *personally* use gene therapy and, if so, under what conditions. Seventy-eight percent ($n = 427$) of respondents said they would use HGT as a way to '*treat a disease or disability'* while 17% ($n = 96$) remained unsure (Figure 34(a). When responding to personal use of HGT as a tool to *enhance* any human trait, 16% ($n = 86$) agreed they would whereas 66% ($n = 367$) said no (Figure 34(b)).



c.

Answer Choices	Responses	
	%	n
Terminal Illness	92	511
Moderate-to-Severe Chronic Illness	81	450
Mild Chronic Illness	55	305
Moderate-to-Severe Physical Disability	85	470
Mild Physical Disability	35	192
Moderate-to-Severe Intellectual Disability	76	422
Mild Intellectual Disability	41	225
Moderate-to-Severe Mental Illness	67	373
Mild Mental Illness	31	171
Enhancement	16	88
Prevention	76	421
Only if I could no longer manage my pain	38	208
If it is the only treatment option available	38	212
I would never use human gene therapy	3	16
Unsure	4	20
Other (please specify)	7	36

Figure 34. AUST-Online survey participant's choice to personally use human gene therapy under different circumstances.
Where (a) is the percentage of respondents who would personally use human gene therapy to treat a disease, (b) is the percentage of respondents who would personally use human gene therapy to enhance a 'normal' trait and (c) is the percentage of respondents who would use human gene therapy for specific conditions.

Next respondents in the AUST-Online survey were asked to consider several situations in which they would personally use HGT to treat, enhance or prevent a disease or disability. The highest response was for a 'terminal illness' (92%; $n = 511$), followed by 'moderate-to-severe physical disability' (85%; $n = 470$) and 'moderate-to-severe chronic illness' (81%; $n =$

450). Three percent ($n = 16$) would never use HGT and 4% ($n = 20$) were unsure of what they would choose (Figure 34(c)). Within each category, a significant decrease between moderate-to-severe was determined by a Wilcoxon Signed Rank test (data not shown).

Of those who used the 'other' option in the AUST-Online survey, 22% ($n = 8$) listed specific disease(s) or disorder(s) they would treat with HGT (e.g., '*Von Willebrand Disease and other bleeding disorders*'). Sixty-one percent ($n = 22$) provided additional caveats to them using HGT (e.g., '*Only adult stem cell, not embryonic*') and 17% (*n*=6) required more information in order to make a decision (e.g., *'Would require more information regarding safety and possible side effects'*).

To determine the similarity between the respondents rated acceptability towards societal and personal use of HGT in the AUST-Online survey, a Wilcoxon Signed Rank test was used. To achieve this analysis, all therapeutic, enhancement and preventative procedures answers were transformed into a binary response (i.e. yes: acceptable, no: unacceptable) (Figure 35). HGT procedures to treat a terminal illness or prevent a disease were the only categories where responses to societal and personal use by a respondent were aligned (i.e., the differences between each question were not significantly different). The rest of the pairwise comparisons demonstrated participants were more likely to agree with society's use of an application, but were less likely to personally use the procedure. The only exception to this was for moderate-to-severe mental illness, where participants were more likely to use HGT personally rather than for societal use.

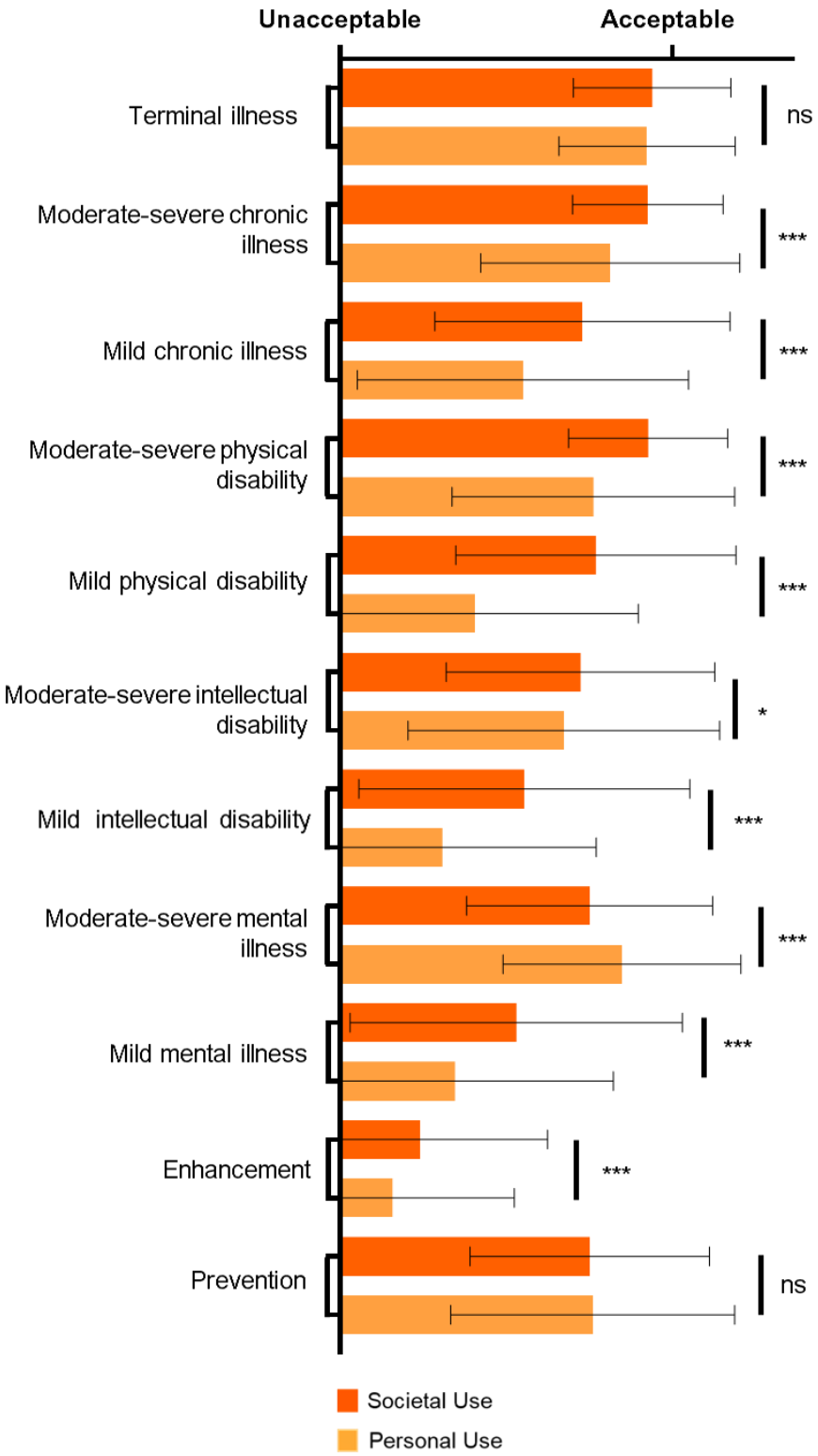


Figure 35. Wilcoxon Signed Rank test determining significant differences between averaged categories of societal and personal use of illness/disability, enhancement and prevention from the AUST-Online survey.

6.5.2 Australian Capital Territory mail-out survey (2019) results

Unlike the AUST-Online survey, throughout the ACT-Mail-Out survey, personal use and societal use questions were placed adjacent to each other. Ninety percent ($n = 165$) of ACT-Mail-Out survey respondents said they would personally use HGT as a way to treat a severe chronic illness (Figure 36). This decreased to 44% ($n = 81$) for a mild chronic illness. This declining trend of personal use from severe to mild was also observed for physical disability (86% to 47%) and intellectual disability/mental illness (75% to 35%).

Personal use of physical, intellectual and longevity enhancement procedures was 16% ($n = 27$), 21% ($n = 36$) and 28% ($n = 47$), respectively. These findings were significantly lower than results for personal use of all therapeutic applications, regardless of severity (Table 23). For personal use of prevention applications, the majority of participants indicated they would personal use HGT to prevent new infections ($54\%\ n = 90$), prevent an inherited disease ($76\%\ n = 128$) and prevent a spontaneous disease ($53\%\ n = 90$).

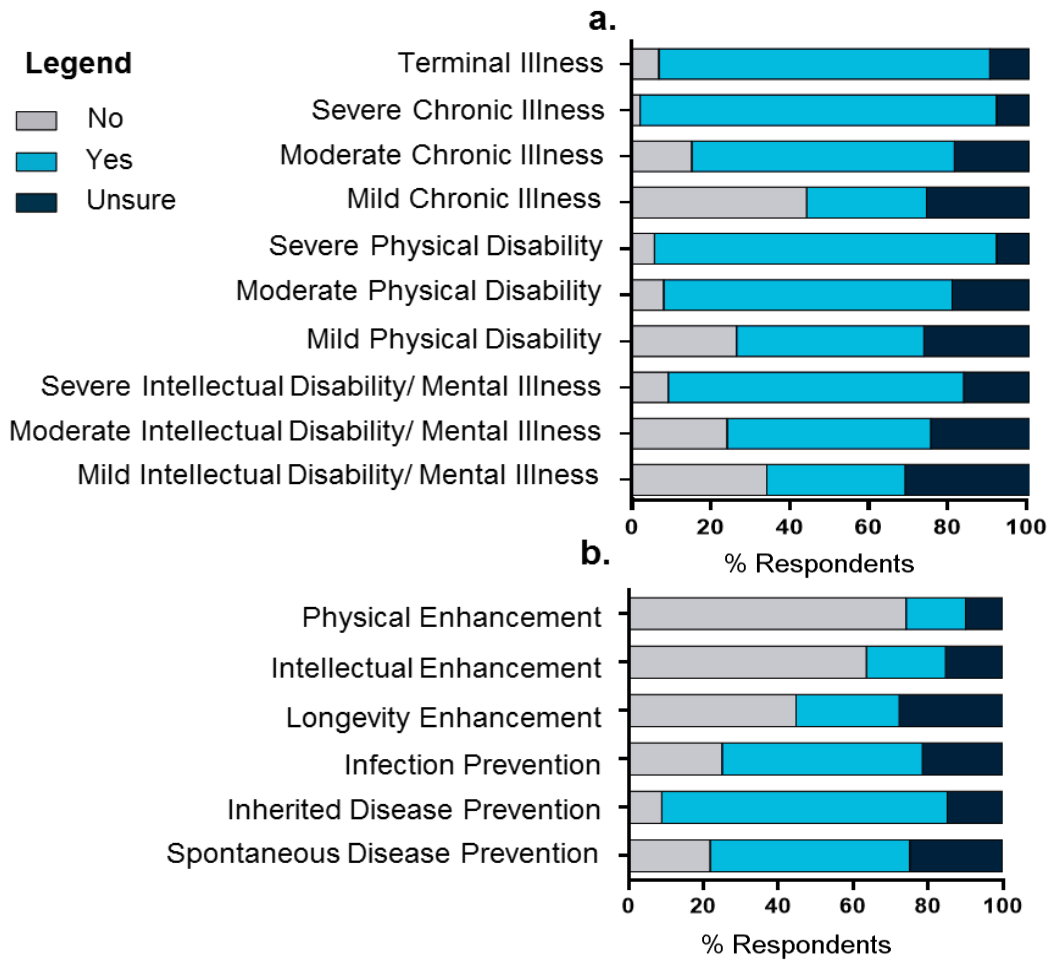


Figure 36. ACT-Mail-Out survey participant's choice to personally use human gene therapy under different circumstances.

Where (a) represents the percentage of respondents who would personally use human gene therapy to treat a disease and (b) represents the percentage of respondents who would personally use human gene therapy to enhance a 'normal' trait or prevent a disease.

A Wilcoxon signed-rank test was conducted to determine significant differences *between* what the ACT-Mail-Out survey participant would personally use at all levels of severity in each disease/disability (Table 23). Five pairwise comparisons were identified as not statistically significant, these were between terminal and severe chronic illness, each comparison between all types of enhancement procedures (i.e., physical, intellectual and longevity) and finally, between infection and spontaneous disease prevention.

Table 23. Wilcoxon Signed Rank test determining significant differences in severity of illness or type of enhancement and prevention for personal use from the ACT-Mail-Out survey.
Where 'b' indicates a score based on negative ranks and 'c' indicates a score based on positive ranks.

	Z	*p*-value
Severe chronic illness – Terminal illness	-1.828[b]	0.068[ns]
Moderate – Severe chronic illness	-5.528[c]	≤0.001***
Mild – Moderate chronic illness	-4.792[c]	≤0.001***
Moderate – Severe physical disability	-4.341[c]	≤0.001***
Mild – Moderate physical disability	-4.769[c]	≤0.001***
Moderate – Severe intellectual disability/ mental illness	-4.867[c]	≤0.001***
Mild – Moderate intellectual disability/ mental illness	-4.035[c]	≤0.001***
Intellectual enhancement – Physical enhancement	-<0.001[d]	1.000[ns]
Longevity enhancement – Intellectual enhancement	-1.205[c]	0.228[ns]
Longevity enhancement – Physical enhancement	-1.115[c]	0.265[ns]
Inherited disease prevention – Infection prevention	-4.569[b]	≤0.001***
Spontaneous disease prevention – Inherited disease prevention	-4.928[c]	≤0.001***
Infection prevention – Spontaneous disease prevention	-0.568[c]	0.570[ns]

After condensing the Likert acceptability scale of all ACT-Mail-Out survey societal questions into unacceptable (1) and acceptable (2), a Wilcoxon Signed Rank test was applied to determine statistically significant differences between acceptability towards societal use and whether they would personally use the procedure. In this case, a significant result would indicate a difference in opinion.

Strength of acceptability for societal and personal use aligned when ACT-Mail-Out survey respondents were asked to reflect on treatment of a severe chronic illness or a severe physical disability (Figure 37). This alignment of acceptability was also observed in each enhancement type. Within the prevention category, only inherited disease prevention showed a similar response between societal and personal use. The remaining categories were determined, by pairwise comparison, to be significantly different. In all cases, societal use was deemed to be more acceptability than the respondent's personal use of the procedure.

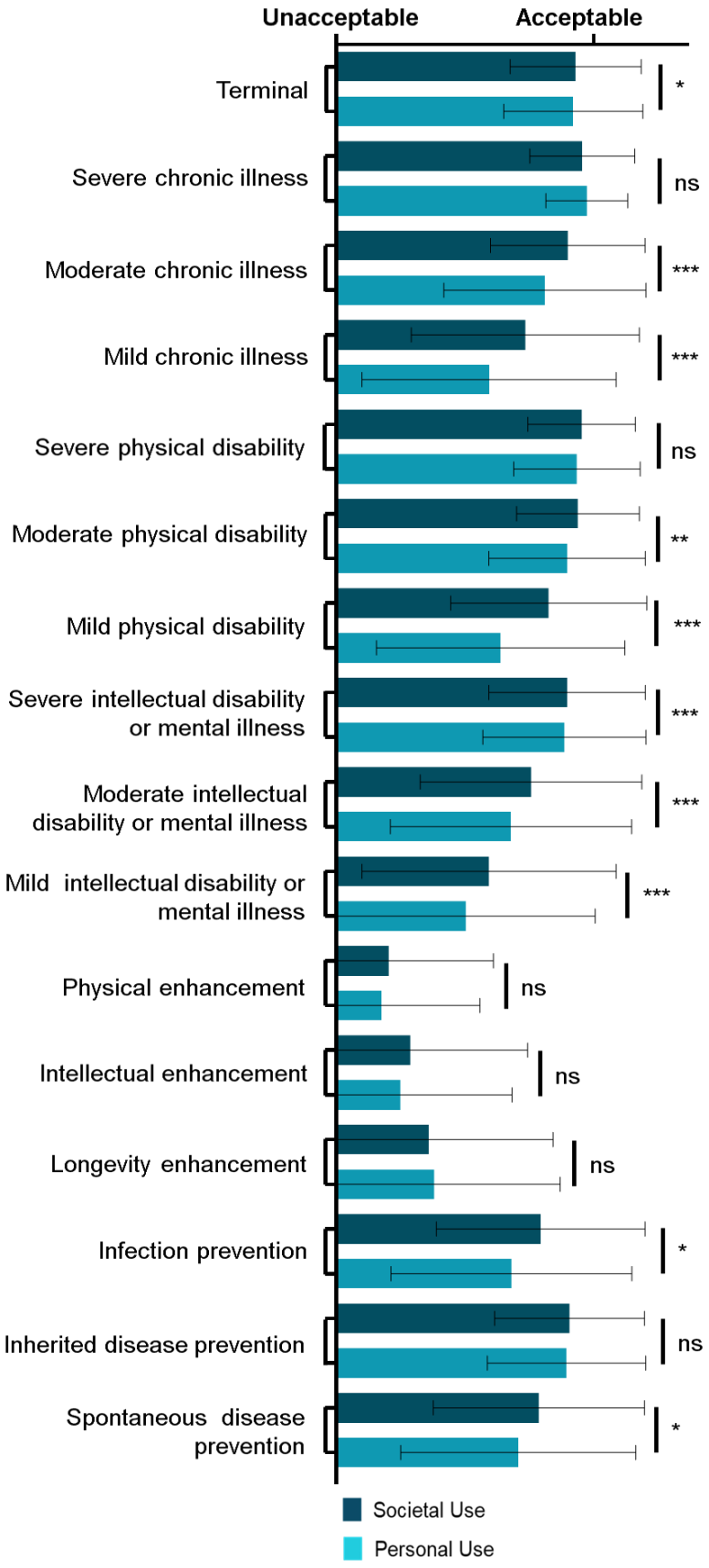


Figure 37. Wilcoxon Signed Rank test determining significant differences between averaged categories of societal and personal use of illness/disability, enhancement and prevention from the ACT-Mail-Out survey.

6.6 ASSOCIATION WITH DEMOGRAPHICS AND COVARIATES, RESUTS FROM BOTH SURVEYS

6.6.1 Gender

A non-parametric independent t-test (Mann-Whitney U-test) was conducted to initially identify whether there was an association between strength of acceptability towards procedures and demographic groups with two subcategories e.g., gender and parenthood. The AUST-Online survey found those who identified as female were less likely to accept societal use of HGT enhancement procedures for each scenario presented to them (Table 24). Females were also less likely to accept HGT to prevent infections, and prevent spontaneous (non-hereditary) disease. When participants were asked whether they would *personally* use HGT to enhance a trait females were again less likely to say 'yes' than males ($n_{\text{(female}*\text{would use)}} = 24\ (7\%)$, $n_{\text{(female}*\text{would use)}} = 58\ (33\%);\ U = 12980, p \leq 0.001$).

Table 24. Mann Whitney U test determining significant associations between societal use of enhancement and prevention procedures and gender from the AUST-Online survey.

	Physical enhance	Intellect. enhance	Longevity enhance	Prevent infection	Prevent inherited disease	Prevent spontaneous disease
Female*acceptable (*n %)*	47 (14%)	62 (18%)	79 (24%)	230 (68%)	310 (95%)	228 (70%)
Male*acceptable (*n %)*	55 (34%)	66 (41%)	90 (55%)	145 (85%)	158 (91%)	142 (84%)
Mann-Whitney U	17817	17317	15477	21231	27777	21757
Wilcoxon W	76813	74607	70423	77847	88155	74731
Z	-6.997	-7.018	-8.135	-5.109	-1.852	-4.108
p-value	≤0.001***	≤0.001***	≤0.001***	≤0.001***	0.064^{ns}	≤0.001***

6.6.2 Parental status

Participants who had children in the AUST-Online survey were more likely to agree to the societal use of HGT for severe intellectual disability ($n_{\text{(parent}*\text{acceptable)}} = 217(89\%)$, $n_{\text{(not a parent}*\text{acceptable)}} = 208\ (83\%); U = 26729, p = 0.005$). However, when responding to the acceptability of physical enhancement procedures, those with children were significantly less likely to support its use in society ($n_{\text{(parent}*\text{acceptable)}} = 42(17\%)$, $n_{\text{(not a parent}*\text{acceptable)}} = 61(23\%); U = 27352, p = 0.002$).

In the ACT-Mail-Out survey, participants who did not have children were less likely to agree to the use of HGT for terminal illness (societal use) ($n_{\text{(parent}*\text{acceptable)}} = 86(83\%), n_{\text{(not a parent}*\text{acceptable)}} = 48(79\%); U = 2629, p = 0.011$). This was also seen for personal use of a procedure to prevent an infection ($n_{\text{(parent}*\text{acceptable)}} = 30(29\%), n_{\text{(not a parent}*\text{acceptable)}} = 11(18\%); U = 2612, p = 0.012$). Interestingly, the opposite was observed for societal use to prevent an infection ($n_{\text{(not a parent}*\text{acceptable)}} = 59(57\%), n_{\text{(not a parent}*\text{acceptable)}} = 48(79\%); U = 2474, p = 0.013$).

6.6.3 Age

The participants' age profile was only an indicator in the AUST-Online survey for physical enhancement ($\chi^2(6) = 19, p = 0.004$) and infection prevention ($\chi^2(6) = 24, p \leq 0.001$) where, on average, support for both these procedures decreased with age. One respondent in the open ended feedback section of the AUST-Online survey thought this question to be '*useless'* as it had '*nothing to do with HGT'*, a disparate comment from the results.

6.6.4 GM food or crops

A Kruskal Wallis H-test was used to determine associations between responses and the strength of support for genetic modification (GM) of food. Those who supported GM technology in the ACT-Mail-Out survey were more likely to find both personal and societal use acceptable for a variety of therapeutic, enhancement and preventative applications as detailed in Table 25.

Table 25. Kruskal Wallace H-test determining significant associations between societal and personal use of therapeutic, enhancement and preventative procedures and GM food/crop support from the ACT-Mail-Out survey.

		Societal Use			Personal Use		
		χ^2	df	p-value	χ^2	df	p-value
Chronic Illness	Mild	13	3	0.004**	25	3	≤0.001***
	Moderate	ns			15	3	0.002**
Physical Disability	Mild	23	3	≤0.001***	22	3	≤0.001***
	Moderate	16	3	0.001***	11	3	0.013*
Intellectual Disability/ Mental Illness	Mild	ns			14	3	0.003**
	Moderate				14	3	0.003**
	Severe				16	3	≤0.001***
Enhancement	Longevity	11	3	0.012*	17	3	≤0.001***
	Physical	ns			17	3	≤0.001***
	Intellectual				11	3	0.013*
Prevention	Infection	32	3	≤0.001***	23	3	≤0.001***
	Spontaneous Disease	20	3	≤0.001***	23	3	≤0.001***
	Inherited Disease	15	3	0.002**	21	3	≤0.001***

6.6.5 Attitudes towards science and technology

As described in Table 26, all sectors of science mentioned within the survey (i.e., science, technology, biotechnology and medicine) had a significant positive association with longevity enhancement, physical enhancement, and all types of prevention for *societal* use in the ACT-Mail-Out survey, with the notable exception of physical enhancement only showing a positive correlation with support for technology. This trend of association was not as prevalent for *personal* use. However, strength of support for biotechnology for all prevention categories and physical enhancement was confirmed with a Kruskal Wallace H-test.

Table 26. Kruskal Wallace H-test determining significant associations between societal and personal use of enhancement and preventative procedures, and attitudes towards science, technology, biotechnology, and medicine from the ACT-Mail-Out survey.

		Societal Use			Personal Use		
		χ^2	df	p-value	χ^2	df	p-value
Science	Longevity Enhancement	13	4	0.009**	ns		
	Infection Prevention	10	4	0.044*			
	Spontaneous Disease Prevention	11	4	0.032*	1	4	0.022*
	Inherited Disease Prevention	11	4	0.032*	ns		
Technology	Longevity Enhancement	13	4	0.005**	ns		
	Physical Enhancement	10	4	0.022*	14	4	0.003**
	Infection Prevention	12	4	0.007**	ns		
	Spontaneous Disease Prevention	9	4	0.031*			
	Inherited Disease Prevention	10	4	0.015*	8	4	0.049*
Biotech.	Longevity Enhancement	15	4	0.004**	ns		
	Physical Enhancement	ns			14	4	0.007**
	Infection Prevention	21	4	≤0.001***	18	4	≤0.001***
	Spontaneous Disease Prevention	16	4	0.003**	18	4	≤0.001***
	Inherited Disease Prevention	18	4	≤0.001***	14	4	0.003**
Medicine	Longevity Enhancement	17	4	≤0.001***	ns		
	Physical Enhancement	ns			9	4	0.026*
	Infection Prevention	17	4	0.002**	ns		
	Spontaneous Disease Prevention	23	4	≤0.001***	14	4	0.003***
	Inherited Disease Prevention	22	4	≤0.001***	ns		

6.7 CHAPTER SUMMARY

Several key findings were presented in this chapter. Overall, attitudes towards each category of disease or disability showed a strong significant decrease as severity declined in both surveys. Chronic disability was considered the most acceptable for both survey participants, followed by physical disability, intellectual disability, and mental illness, respectively. Further acceptability of treatment using HGT decreased as severity of the indication decreased. A decrease was also observed when comparing general use (i.e., societal use) to personal use of each procedure, with personal use being less accepted.

This decline in acceptability was also observed for sub-categories of enhancement and prevention. In both surveys, longevity enhancement was deemed most acceptable, followed by

an intellectual enhancement, then physical enhancement. For prevention a decrease in acceptance was observed from inherited disease, to spontaneous disease, to infection prevention.

With respect to demographic associations, the AUST-Online survey showed those who identified as female were less likely to accept societal use of HGT enhancement procedures for each scenario presented to them. They were also less likely to accept HGT to prevent infections, and prevent spontaneous (non-hereditary) disease. Unlike the AUST-Online survey, several other positive associations were observed between attitudes towards HGT treatment of indications and attitudes towards GM food, science and technology in the ACT-Mail-Out survey.

7 Results: Attitudes Towards the Governance and Ethics of Human Gene Therapy

Chapter seven details findings from the final set of substantive survey questions. This chapter focuses on the theme 'governance and ethics' which addresses objective 2(d-e); to determine the Australian public's attitudes towards:

d. Governance challenges of HGT
e. Ethical dilemmas borne from HGT

7.1 GOVERNANCE

7.1.1 Online Australian survey (2017) results

Respondents were asked to review and rate their agreement towards a series of statements, five of which were related to governance of HGT. The statement ""*Human gene therapy products should only be allowed after government approval*" showed the most agreement with 75% ($n = 413$) in support of this in the AUST-Online survey (Figure 38). Alternatively, the statement "*Private companies and institutions should be allowed to research human gene therapy with no government or regulatory oversight*", showed the largest rate of disagreement (88%; $n = 483$) out of the five statements.

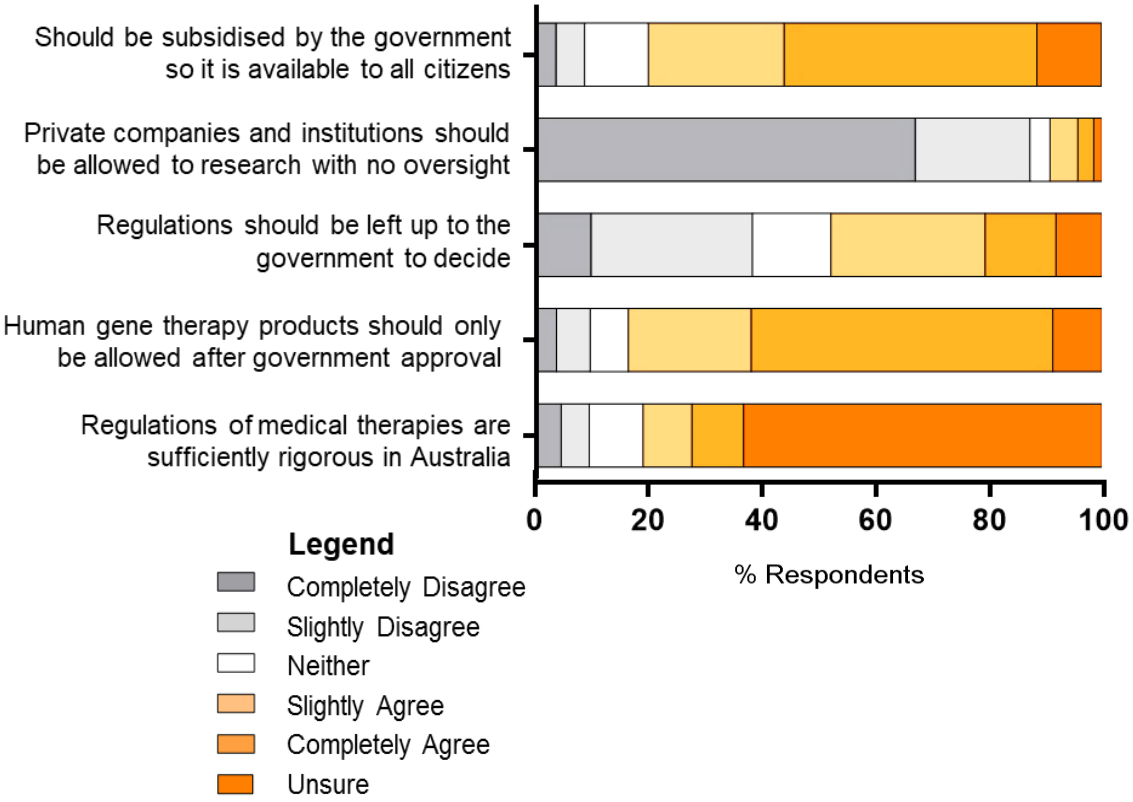


Figure 38. Distribution of AUST-Online survey participant's agreement towards statements relating to the governance of human gene therapy.

In the results of the AUST-Online survey, the highest level of education obtained was shown to have an association with two statements. As education levels increased, so too did the participants agreement with HGT being allowed only after government approval ($\chi^2(7) = 24, p \leq 0.001$). Alternatively, the opposite was the case for the statement saying that no government oversight is necessary in the AUST-Online survey ($\chi^2(7) = 27, p \leq 0.001$).

7.1.2 Australian Capital Territory mail-out survey (2019) results

The same five statements relating to issues of governance were asked in the ACT-Mail-Out survey. As with the AUST-Online survey results, only after government approval was the most accepted statement in the ACT-Mail-Out survey (85%; $n = 143$), with no government or regulatory oversight being, again, the least accepted (10% ; $n = 17$).

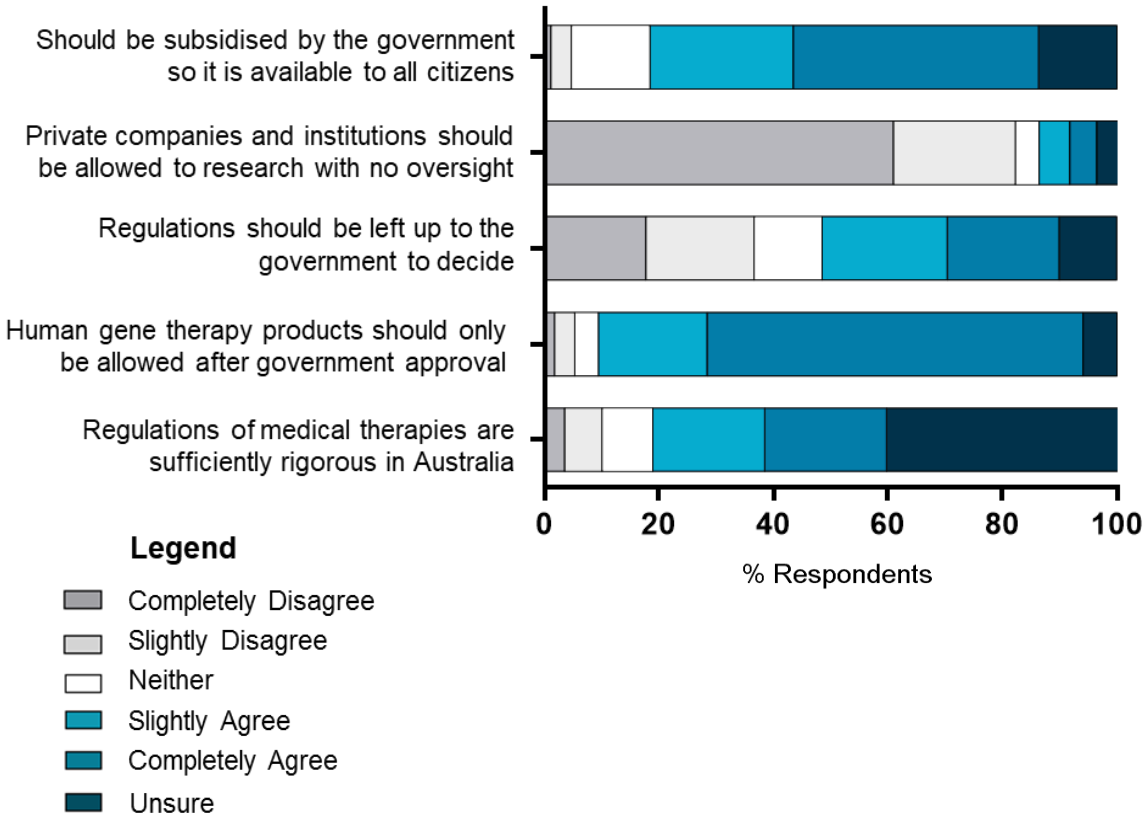


Figure 39. Distribution of ACT-Mail-Out survey participant's agreement towards statements relating to the governance of human gene therapy.

When looking at significant associations in the ACT-Mail-Out survey findings, only increasing support for technology ($\chi^2(4) = 9, p = 0.036$) and biotechnology ($\chi^2(4) = 23, p \leq 0.001$) was observed to have a positive correlation with increasing agreement towards the notion that regulations should be left up to the government to decide.

7.1.3 Comparison of results

For statements relating to the governance of human gene therapy, a decrease in the average Likert score with observed (Figure 40). While there was a significant difference in averaged Likert scores between both surveys ($p \leq 0.001$), the second ANOVA test confirmed that this difference was a fixed shift both with ($p = 0.223$) and without ($p = 0.103$) participants being included as a factor.

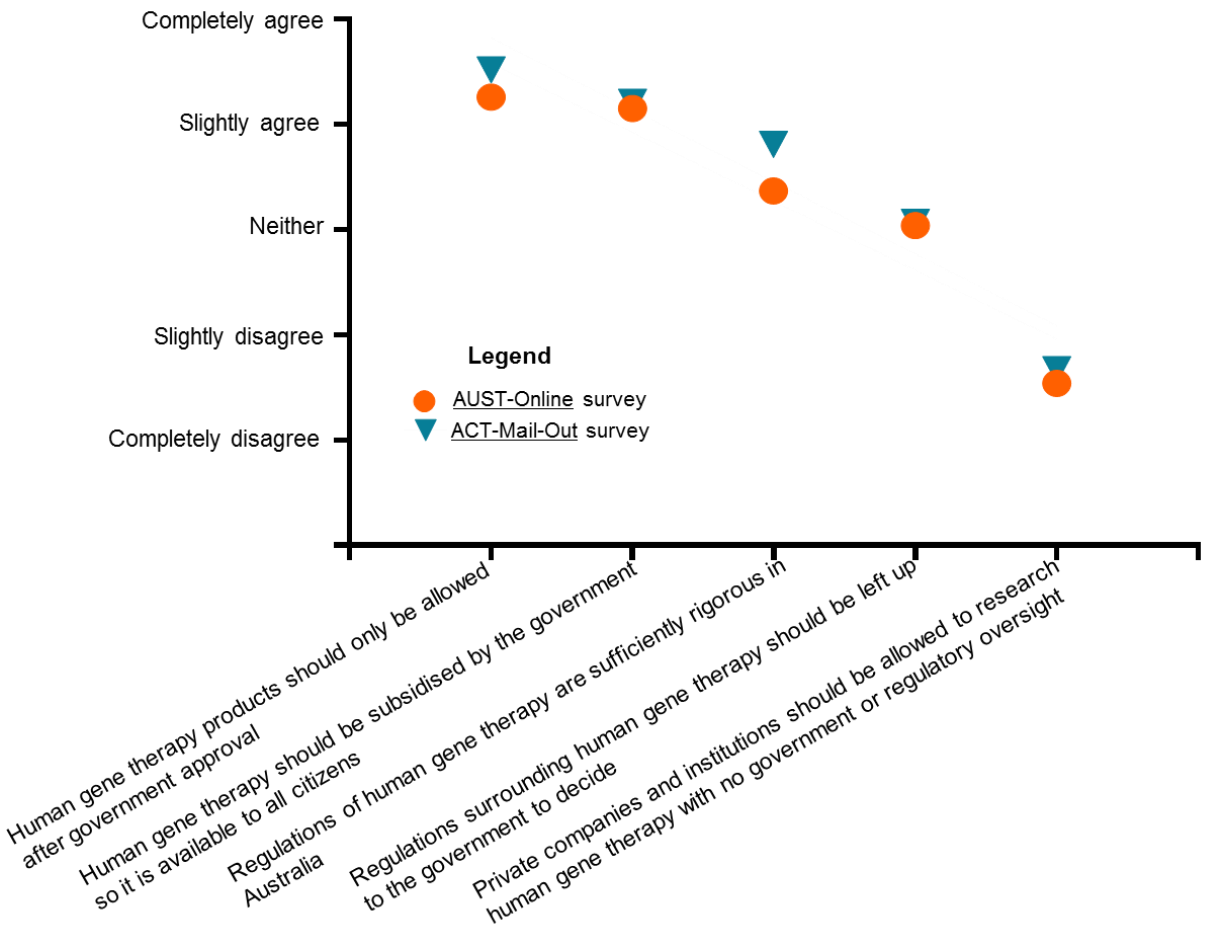


Figure 40. Averaged agreeability rates for five statements relating the governance of human gene therapy.

7.2 CONSENT

7.2.1 Online Australian survey (2017) results

Three additional statements were focused on the idea of consent. The first: *"As an individual we should be free to choose whether to personally use human gene therapy"* had the highest agreement rate at 72% ($n = 398$) (Figure 41). Responding to the statement *"The parent has the right to consent on behalf of their children to undergo human gene therapy"*, 63% ($n = 348$) agreed with this statement. The final statement in this section asked whether the respondent agreed or disagreed to the sentence *"It is the right of the individual to use human gene therapy to enhance themselves"*, this was more contentious in the AUST-Online survey where only 24% ($n = 134$) believed it was.

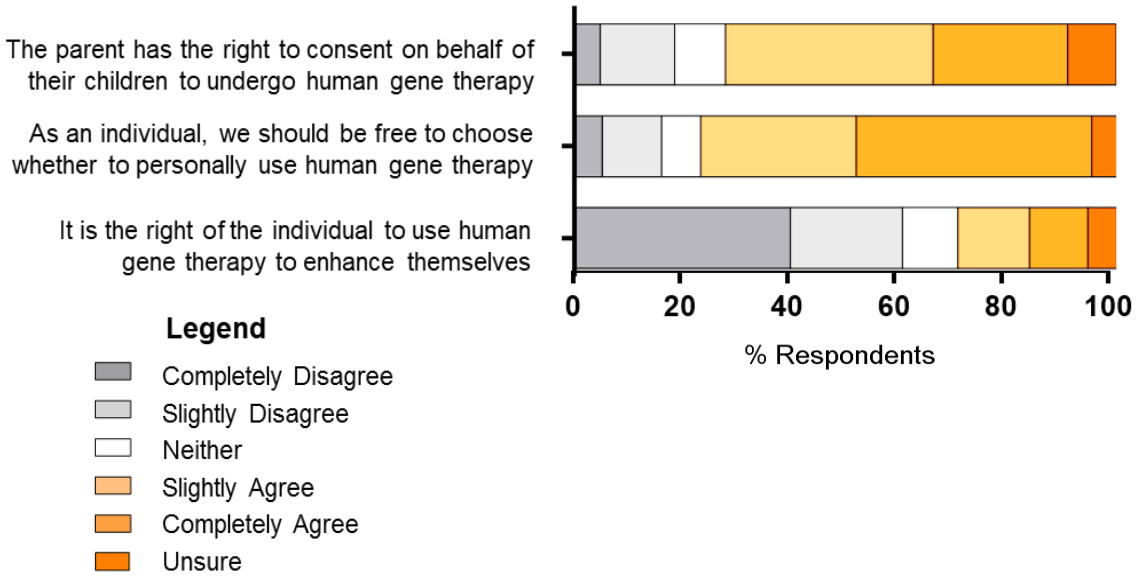


Figure 41. Distribution of AUST-Online survey participant's agreement towards statements relating to consent of human gene therapy.

As the AUST-Online survey respondent's age increased, support for the statement relating to parental consent also increased ($\chi^2(5) = 19, p = 0.002$). In addition, those who were a parent were more supportive of this statement ($n_{(\text{parent}*\text{agree})} = 194(75\%), n_{(\text{not a parent}*\text{agree})} = 146(52\%);\ U = 30067, p \leq 0.001$).

To the statement specifying it is the right of the individual to enhance, males were more likely to agree compared to females ($n_{(\text{female}*\text{agree})} = 64(18\%), n_{(\text{male}*\text{agree})} = 69(39\%);\ U = 30067, p \leq 0.001$), while support decreased with increasing age ($\chi^2(5) = 20, p \leq 0.001$).

Of those who completed the survey, 38% ($n = 209$) chose to use the feedback section to qualify their answers or further voice opinions that the survey did not cover or allow for. Forty-one individuals (20%) raised topics surrounding the need for equitable processes while 17 participants (9%) discussed themes relating to consent and personal choice. There were no demographic associations to any themes raised in the feedback section. Selected quotes will be used within the discussion section.

7.2.2 Australian Capital Territory mail-out survey (2019) results

The same trend was observed in the findings of the ACT-Mail-Out survey. The highest acceptance rating was for parental consent (69%; $n = 117$), the second for an individual has the right to choose (63%; $n = 107$) and the final, an individual can choose whether to enhance themselves (35%; $n = 59$) (Figure 42).When analysing for bivariate demographic associations, females were identified as less supportive of the statement relating to the right of an individual to enhance themselves ($n_{(\text{female}*\text{agree})} = 28(29\%), n_{(\text{male}*\text{agree})} = 31(44\%)$; $U = 2742, p = 0.038$), as was seen in the AUST-Online survey.

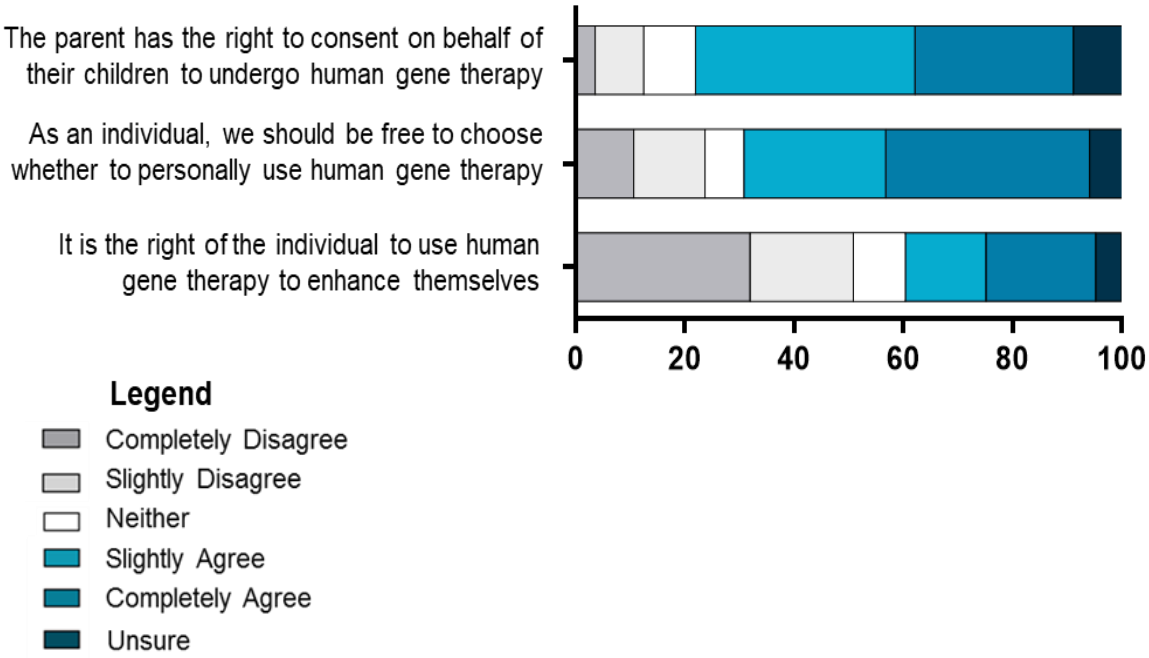


Figure 42. Distribution of ACT-Mail-Out survey participant's agreement towards statements relating to consent of human gene therapy.

7.2.3 Comparison of survey results

Answers to the three statements relating to consent from both surveys were then compared. For these statements, a decrease in the average Likert score was identified with a significant difference in averaged Likert scores between both surveys present ($p \leq 0.001$) (Figure 43). However, the second test ANOVA test confirmed that this difference was not a fixed shift either with ($p \leq 0.001$) and without ($p \leq 0.001$) participants being included as a factor.

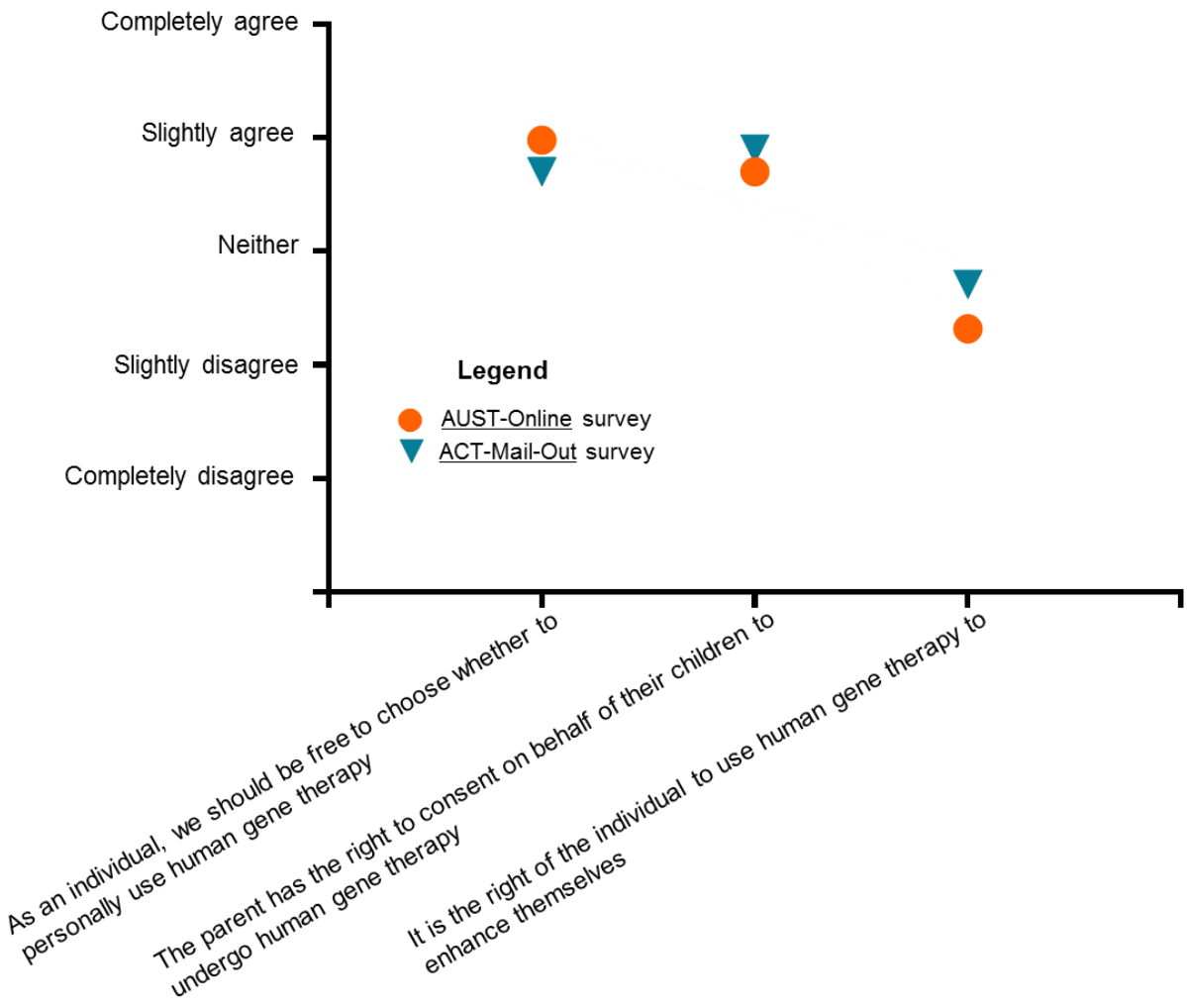


Figure 43. Averaged agreeability rates for three statements relating to concerns around consent of human gene therapy.

7.3 RISK AND NATURAL LAW

7.3.1 Online Australian survey (2017) results

A further seven statements related to the risks and responsibilities that arise from HGT. To the statement "*Human gene therapy should not be permitted as it might be used for ill intent*", only 10% ($n = 55$) agreed making it the lowest agreed to statement (Figure 44). The highest agreement was towards the statement "*Human gene therapy would improve our way of life in the future*"" where 80% ($n = 441$) agreed. Both results reflect a positive attitude towards HGT.

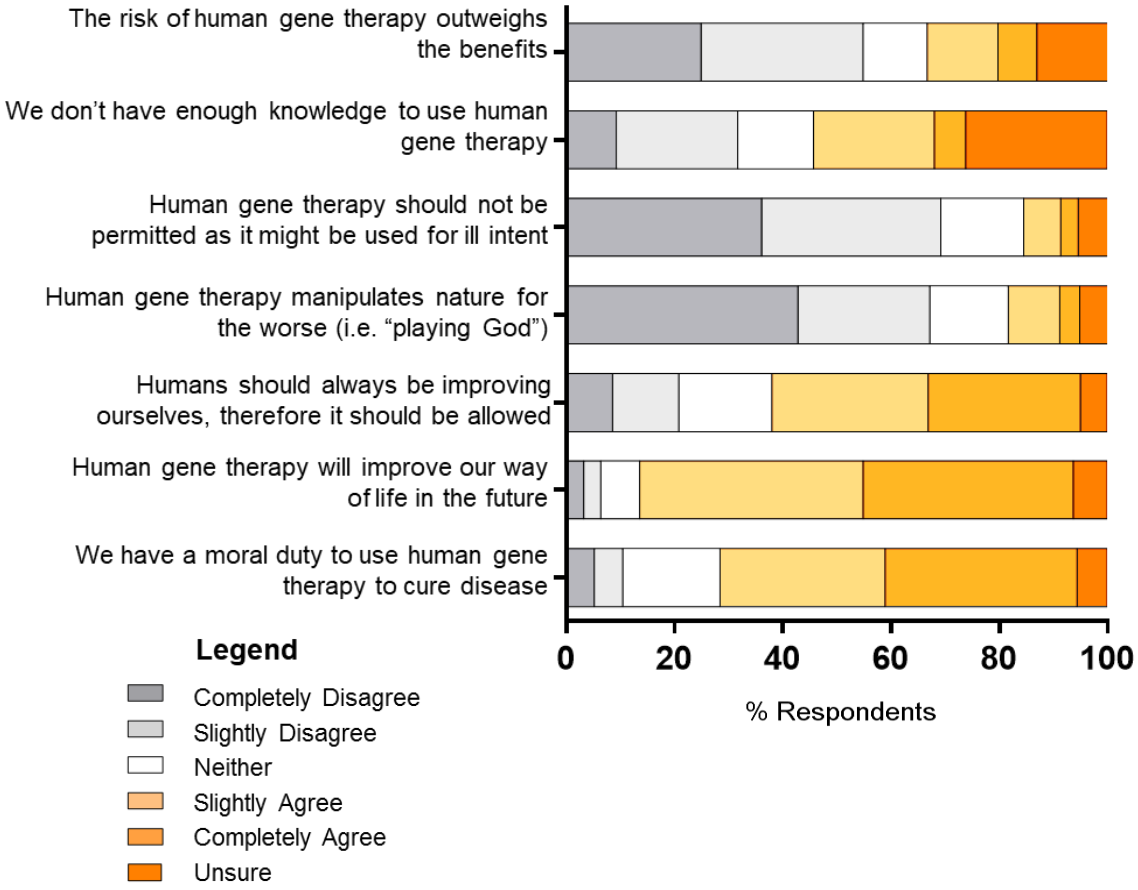


Figure 44. Distribution of AUST-Online survey participant's agreement towards statements relating to risk and natural law of human gene therapy.

To two statements saying that HGT was playing god and that it might be used for ill intent, analysis showed that females were more likely to agree with these statements (Table 27). Alternatively, males were significantly more likely to agree with the statement reflecting we have a moral duty to cure disease using this technology, and that humans should always be improving ourselves.

Finally in the AUST-Online survey, participants who indicated that they have children were more likely to support the statements that HGT might be used for ill intent ($n_{(\text{parent}*\text{agree})} = 23(9\%), n_{(\text{not a parent}*\text{agree})} = 32(11\%);\ U = 30750, p \leq 0.001$).

Table 27. Mann Whitney U test determining significant associations between attitudes towards ethical statements and gender from the AUST-Online survey.

	Human gene therapy manipulates nature for the worse	We have a moral duty to use human gene therapy to cure disease	Humans should always be improving ourselves…	All research and development should be stopped …	Human gene therapy should not be permitted as it might be used for ill intent
Female*Agree (*n* (%))	60 (17%)	227 (63%)	187 (52%)	6 (2%)	43 (12%)
Male*Agree (*n* (%))	13 (7%)	130 (74%)	118 (67%)	4 (2%)	12 (8%)
Mann-Whitney U	25998	25400	25345	28333	27013
Wilcoxon W	41751	90741	89606	44086	42767
Z	-3.603	-3.937	-3.780	-2.767	-3.051
p-value	≤0.001***	≤0.001***	≤0.001***	0.006**	0.002**

7.3.2 Australian Capital Territory mail-out survey (2019) results

Similar findings was observed in the ACT-Mail-Out survey (Figure 45). The strongest agreeability towards a statement was again for HGT improving our way of life in the future (68%;$n = 116$). The lowest was for the idea that HGT would be used for ill intent (13%; $n = 22$).

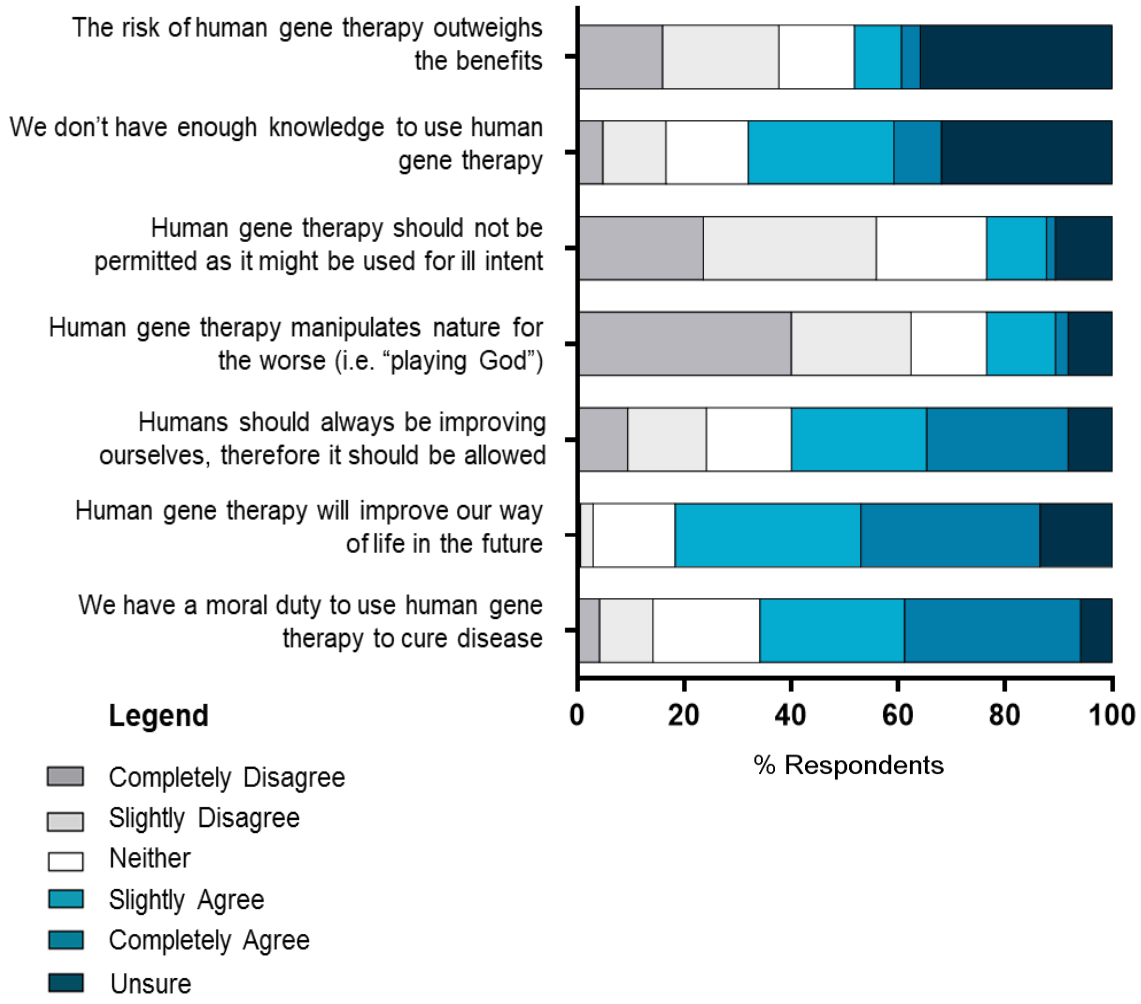


Figure 45. Distribution of ACT-Mail-Out survey participant's agreement towards statements relating to risk and natural law of human gene therapy.

It was observed through a Kruskal Wallace H-test that participants who supported medicine were more likely to support the statement; "*human gene therapy should not be permitted as it might be use for ill intent"* ($\chi^2(4) = 11, p \leq 0.001$). Four other statements within this section, showed a strong positive correlation with different areas of science, as detailed within Table 28.

Table 28. Kruskal Wallace H-test determining significant associations rate of ACT-Mail-Out survey participant agreement towards statements relating to risk and natural law, and attitudes towards science, technology, biotechnology and medicine.

	Science			Technology			Biotechnology			Medicine		
	χ^2	df	p-value	χ^2	df	p-value	χ^2	df	p-value	λ	df	p-value
Human gene therapy would improve our way of life in the future	10	4	0.034*	9	4	0.026*	18	4	≤0.001***	20	4	≤0.001***
We have a moral duty to use human gene therapy to cure disease	14	4	0.006**	17	4	0.001***	20	4	≤0.001***	19	4	≤0.001***
Humans should always be improving ourselves with the latest medical technology, therefore human gene therapy should be allowed	15	4	0.005**	25	4	≤0.001***	16	4	0.002**	13	4	0.006**
Human gene manipulates nature for the worse (i.e. playing God)	10	4	0.041*	11	4	0.015*	24	4	≤0.001***	24	4	≤0.001***

7.3.3 Comparison of survey results

The final decline in agreeability was analysed for seven statements relating to risk and natural law elements of HGT. For this set of statements, a decrease in the average Likert score was identified with a significant difference in averaged Likert scores between both surveys present ($p \leq 0.001$) (Figure 46). Like the statements relating to consent, the second test ANOVA test confirmed that this difference was not a fixed shift either with ($p \leq 0.001$) and without ($p \leq 0.001$) participants being included as a factor.

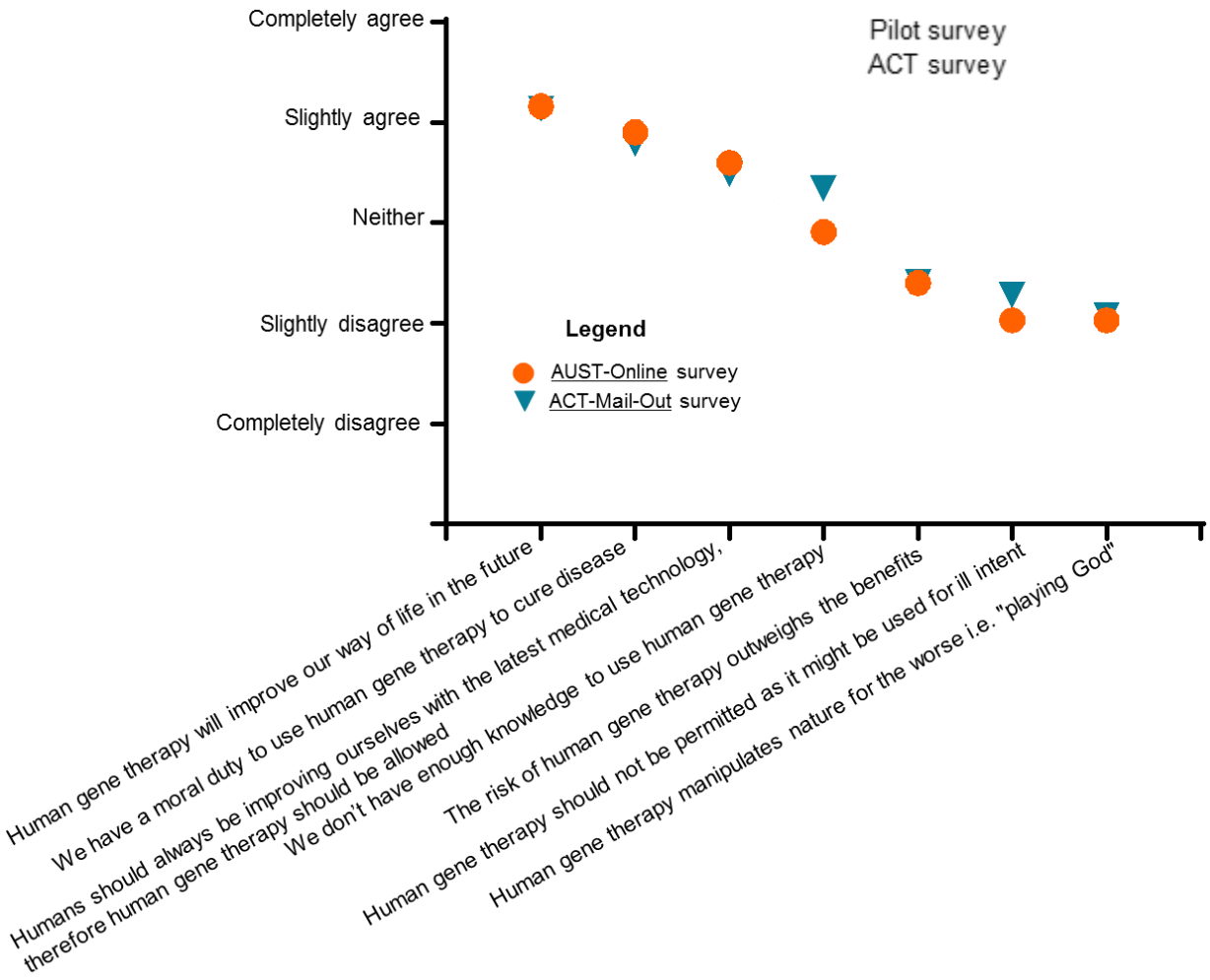


Figure 46. Averaged agreeability rates for seven statements relating to concerns about the risks and natural law of human gene therapy.

7.4 USE OF EMBRYOS

7.4.1 Online Australian survey (2017) results

In the original AUST-Online survey, *"If it required human embryo testing to develop these techniques"* was asked within the set of outcomes and consequences section, with 255 (46%) finding this procedure acceptable. To this statement, females were significantly less likely to find this acceptable than males ($n_{(\text{female}*\text{accpetable})} = 142(39\%), n_{(\text{male}*\text{acceptable})} = 84(48\%)\,; U = 27063, p = 0.005$).

7.4.2 Australian Capital Territory mail-out survey (2019) results

An additional statement was added to the original survey due to comments from the feedback section of the AUST-Online survey. To the original question posed in the AUST-Online survey, 49% ($n = 82$) of ACT-Mail-Out survey participants agreed to the use of embryos for technique development (Figure 47). To the additional statement, "*We should be able to use human gene therapies to edit an embryo in the womb",* this agreement increased to 61% ($n = 103$).

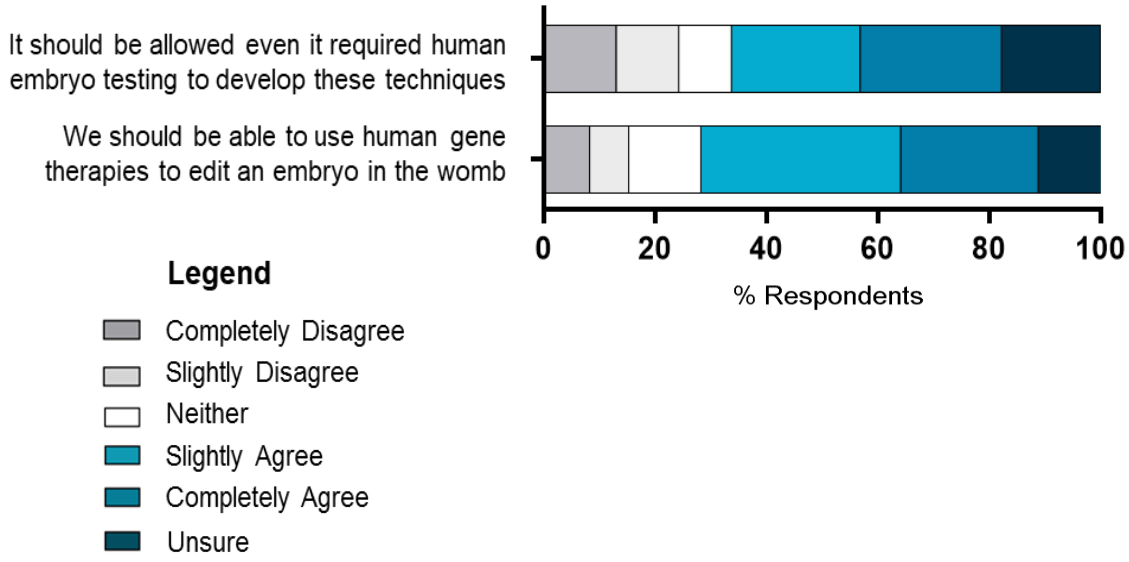


Figure 47. Distribution of ACT-Mail-Out survey participant's agreement towards statements relating to embryo use in human gene therapy.

Participants who indicated that they were not parents were more likely to support embryo testing for technology development ($n_{(\text{parent}*\text{agree})} = 43\ (42\%), n_{(\text{not a parent}*\text{agree})} = 37(60\%); U = 2577, p = 0.034$). When questioned about embryo editing to fix a trait, a positive correlation was observed been support for biotechnology and medicine and acceptability of this scenario; $\chi^2(4) = 17, p = 0.002$; and $\chi^2(4) = 11, p = 0.011$, respectively.

7.5 CHAPTER SUMMARY

Statements on governance showed a strong downward decline in agreeability that was observed across both surveys. Statements relating to strong governance and equity of this technology showed higher support than the statements that referred to the un-regulated use of this

technology or lack of consultation when designing regulations. This significant decline in support however, was not replicated in the findings of statements relating to consent, and risk and natural law.

The majority of participants felt that the right to choose and appropriate consent were important for HGT use. Although, in both surveys, females were identified as less supportive of the statement relating to the right of an individual to enhance themselves.

Finally, participants responding to statements relating to risk and natural law were overly positive of the technology and believed that HGT would improve our way of life in the future.

8 Result: Multivariate Analysis

This final results chapter details the findings of the multivariate analysis. A cumulative-link mixed model was fitted to the AUST-Online survey data to assess the impact demographic factors and co-variate factors had on a participants' attitudes towards HGT. This analysis confirmed a strong, statistically significant association with gender. In the AUST-Online survey, males were more likely to find applications and outcomes of HGT acceptable (i.e., responded with a higher Likert score) compared to females, ($p \leq 0.001$). No other relationships between demographic factors and answers were identified as having a significant association with attitudes. This result was confirmed by an ANOVA and fitting a linear regression model with a random effect term.

The same cumulative-link mixed model was fitted to the ACT-Mail-Out survey data, with exception to the inclusion of politics as a demographic variable. This analysis confirmed a statistically significant association with gender, parental status of the participant and presence of disease in the family. Males were again more likely to find all applications and outcomes of HGT acceptable compared to females ($p = 0.032^{*}$). In addition, participants who had children were *less* likely to support HGT ($p = 0.049^{*}$) while those with a history of disease within the family were more likely to support all aspects of HGT ($p = 0.029^{*}$). No other relationships between demographic factors and answers were identified as having a significant association with attitudes. The full output for both surveys can be found at Appendix L and Appendix M, respectively.

9 Discussion

This is the first Australian study that provides a of Australian's attitudes of HGT and their willingness to accept the wide variety of procedural applications and implications of this technology. Below is a discussion of findings from both surveys. Both surveys showed a strong association between gender and strength of acceptability towards all areas of HGT, which was also confirmed by multivariate analysis. Our analysis also confirmed a decline in acceptability of HGT as the severity of the clinical indication decreased in both surveys. This decline in acceptability also translated to the type of disease or disability presented to the participant, with treatment of a chronic illness the most accepted, and enhancement procedures the least accepted.

These findings are important in delineating how the public reacts to unknown and emerging controversial medical technologies that have broad consequences. In addition, these results help us to understand how governments might wish to shape regulations and policies underpinning HGT with public attitudes in mind. It has been shown that public attitudes towards a technology is one of the key factors in its subsequent development, application and governance. It is therefore crucial for these types of ethical considerations to be studied and deliberated *before* the technology affects us all (Frewer, Howard, and Shepherd 1997).

9.1 AWARENESS AND UNDERSTANDING

At the beginning of this survey, four questions were designed to assess Australian participant's perceived awareness and nominal knowledge of HGT (objective one). The below section details the discussion of these findings.

9.1.1 Awareness and understanding of the term human gene therapy

Findings from both surveys reveal a high number of participants believed they were aware of HGT and —when prompted— could demonstrate an accurate understanding of what the procedure entailed. Self-reported knowledge was shown to have a positive correlation with investigator-assessed knowledge of HGT in both surveys. While studies that directly assess public awareness and understanding of HGT are limited, one study in Japan found low self-

reported awareness and an inadequate understanding of HGT (Uchiyama, Nagai, and Muto 2018). Consequently, the results of our two surveys were unexpected, and could be attributed to either the high number of university-educated respondents, relative to their proportion in the general population, or a difference in knowledge between respondents in Australia and Japan. Alternatively, an increase in exposure to HGT-related and GMO-related media articles could be partially responsible for the increased awareness observed compared to the Japan study. While we give some hypotheses here, ultimately, any causal attribution on this difference is presently speculative, and would need to be determined in follow up studies.

From the AUST-Online survey, gender, education, previous work in the medical industry and the participant's support of genetically modified crops were shown to have a positive association with a participant's awareness and understanding of the term 'human gene therapy'. On average, males from the AUST-Online survey were more likely to be aware of the term *and* provide a correct interpretation. This is consistent with other findings that show males are more *aware* of biotechnologies compared to females (von Roten 2004; Fallows 2005; Simon 2010). Interestingly, Simon's 2010 study found males who were more educated about a certain biotechnology were more positive and accepting towards the therapy. The opposite was the case for females, where an increase in education led to more pessimistic responses. This has been supported by other studies where females are more hesitant towards scientific —and in particular, biotechnological— innovations (Gustafson 1998; Slovic 1999; Henwood, Parkhill, and Pidgeon 2008; Simon 2010; Kim, Park, and Kang 2018). Unfortunately, to the author's knowledge, assessment of the public's awareness through text-box answer has not been instigated to date, and therefore this finding cannot be qualified by previous literature.

Our AUST-Online survey also found participants who had obtained a higher level of education rated themselves as having a greater knowledge of this technology. This was also observed in those who had worked in the medical industry, who were, on average, more likely to rate their knowledge higher. Yet, in our study, this did not translate to the accuracy of their description. Previous studies have also identified an association with education level and how much the participant is aware of HGT (Macer et al. 1995; Sjöberg 2004). In addition, a similar result has been seen in additional studies where individuals from a scientific background, especially those in biological sciences, have been found to be more aware of biotechnological innovations compared to others (AbuQamar et al. 2015). A further four studies have backed up this result where participants with science-oriented careers had greater levels of acceptance of gene therapy (Macer 1992; Macer et al. 1995; Ng et al. 2000; Wang et al. 2017). Since our study did

not seek data on the type of education of the respondent, the study was unable to test the effect of educational distinctions between scientific and non-scientific fields.

In the ACT-Mail-Out survey, only gender was identified to have a positive association with HGT awareness. Overall, females were more likely to be aware of this technology, however this did not translate into greater knowledge (as rated by the investigator), nor greater awareness of the current global and domestic use of HGT. Whether these differences can be explained by the population surveyed needs further investigation.

Finally, previous studies have suggested that a lower public literacy level of techniques and applications of biotechnology, was at a minimum partly responsible for the formation of moral objections (Brankov et al. 2013). This study found no evidence that an increased awareness and literacy level of an individual directly leads to an increased acceptance, as previous studies have confirmed (Einsiedel, Jelsøe, and Breck 2001; Connor and Siegrist 2010).

9.1.2 Awareness and understanding of the current use of human gene therapy

While there were two questions requesting participants to specify whether they believed HGT was currently available, only awareness of *Australia's* current use of HGT was assessed in both surveys; a question enquiring into current global use was added to the ACT-Mail-Out survey as part of the survey revisions. Interestingly, no significant difference in rates of awareness towards Australia's use was determined between the two surveys. Findings from both surveys showed a third of the participants believed that HGT was being used in Australia to treat certain diseases, with the vast majority of respondents feeling unsure. As no other published literature to date has assessed this, a literature comparison was not possible.

The ACT-Mail-Out survey afforded the opportunity to compare participant understanding of global and domestic use of HGT. Interestingly, while over half thought HGT was in use globally, the respondent's certainty decreased significantly when questioned specifically about the Australian context. As media on Australian HGT research and clinical trials produces a small footprint within medical news, focusing on that Australian context might have influenced the high level of unsure responses received. To note, though, males were more likely to be aware of the term, this trend was not observed when investigating awareness of HGT's availability both worldwide and in Australia.

Currently in Australia, several research institutes, including the Children's Medical Research Institute, have research projects that focus on HGT (Martiniello-Wilks and Rasko 2007). While there is no database that contains specific information on gene therapy trials in Australia, the NHMRC created a clinical trials registry for Australia and New Zealand (ANZCTR 2020). Within this registry, there is currently no means to easily identify gene therapy specific trials. Despite this hindrance, as of 2017, 32 trials were currently registered in Australia (Ginn et al. 2018). In comparison, over 2,600 HGT trials are either ongoing, completed or have been approved for therapeutic use globally (Ginn et al. 2018). As such, a 'yes' answer to these questions demonstrates a correct awareness of its availability, assuming this was an informed response (Cross and Burmester 2006; Ginn et al. 2018). However to date, no confirmed gene therapy has been approved for clinical use in Australia. In 2020, an application was made to MSAC to perform a health technology assessment for Luxturna for the treatment of inherited retinal dystrophies, a major cause of early-onset blindness (MSAC 2020). No other gene therapies have been registered in the Medical Benefits Schedule (MBS) in Australia.

The follow-up question asking participants to detail what they believed HGT was currently being used for, showed large commonality between both surveys. Cancer, cystic fibrosis, heart conditions, blood, and immune system disorders all featured within the top five responses in both surveys. By a large margin, most respondents in the AUST-Online survey asserted that HGT was a treatment for cancer. This is unsurprising as gene therapies for cancer are constantly being discovered and tested in clinical trials, both in Australia and worldwide (Ginn et al. 2018). Therefore, this answer shows a correct awareness of HGT's uses (Cross and Burmester 2006; Ginn et al. 2018). In addition, with the risk of developing cancer being approximately one in three (American Cancer Society 2018), and due to the emphasis of this research in the media and the money involved in developing these treatments, 'cancer' would be a safe umbrella term to use for this answer, when unsure (Delhove et al. 2020).

Previous research has identified the availability heuristic to be a partial contributor to an individual's acceptance of genetic modifying technologies (Lull et al. 2017). That is, an individual uses a mental shortcut where easily accessible examples are used to quickly judge or form an opinion on a situation (Tversky and Kahneman 1973). These examples are usually sourced from media exposure (Scheufele 2000). Cancer (*ABC News* 2017), cystic fibrosis (Loney 2017) and heart conditions (Ma et al. 2017; Neergaard 2017) have been recently portrayed within the news. While media on cystic fibrosis did not have a direct link to HGT, early gene therapy trials were hopeful for a cure to cystic fibrosis (Jaffé et al. 1999;

Griesenbach, Geddes, and Alton 2004) as discussed in the Introduction. As such, future research that is dedicated to exploring this link is worthy of pursuit.

Surprisingly, only four respondents mentioned X-SCID treatment as this was covered extensively by the media in the late 1990s due to the beginning of multiple clinical trials (Stolberg 1999). One of the four participants mentioned:

"I've heard of trials for X-SCID in the early 90s so I assume things like this are common in Australia".

As a sizable portion of participants represented ages under 35 years, age may have played a partial role in the observed findings given their young age at the time of these highly publicised clinical trials.

9.2 TECHNIQUES AND OUTCOMES

Located throughout the survey were questions intended to ascertain public attitudes towards procedural components of HGT and their outcomes. This section details a discussion on the findings of this area of investigation which aimed to address objective two, part a. and b. (i.e., to determine the Australian public's towards genetic modification techniques of HGT and procedural outcomes of HGT). The discussion of these findings are detailed in the below section.

9.2.1 DNA type

As discussed within Chapter One (section 1.1.3.2.1, p. 24), the use of DNA is integral to many of the procedural processes underpinning HGT. It is therefore important to determine the acceptability of varying types of DNA that could potentially be used when planning policy around this technology. Results from both surveys identified concerns towards the use of different types of DNA in HGT. Although most surveyed participants were supportive of *human* DNA, the use of all other DNA types were not as well received. In addition, no significant difference in acceptability towards the use of artificial and bacterial or viral DNA for societal

use (i.e., general use) in the AUST-Online and ACT-Mail-Out survey were observed, with rates for both relatively low compared to human DNA.

This is an important finding. As highlighted previously, foreign DNA (i.e., not of human origin) is a useful tool in HGT. This is particularly the case for bacterial and viral DNA which is highly replicable, easy to manage and, in the case of viruses, used as a vector to target the cells to be modified (Horn et al. 2008). Although —as our technology advances— it is also important to discuss the possibilities of using artificial DNA as new advances emerge in synthetic DNA. Synthetic DNA can now be created within a laboratory to allow scientists to precisely design the genes needed with exact replicability, something previously not possible (Hughes and Ellington 2017).

In both surveys, females were more likely to find animal DNA less acceptable, a result that has been confirmed in previous research around animal biotechnology. In a 2019 Australian study by Critchley et al., females were more likely to raise concerns about the morality of animal biotechnology. Morality of animal biotechnology, and biotechnology in general, has previously been discussed in a 2000 paper by Evensen, Hoban, and Woodrum. In their study, it was revealed that women were less likely to recognise a personal benefit from emerging biotechnology innovations. Interestingly, this observation disappeared when awareness of the technology increased, leading the authors to propose that awareness of the technology could mitigate some of the moral objections (Evensen, Hoban, and Woodrum 2000). In Critchley's study, morality and *purpose* was shown to play a role in defining the acceptability of animal biotechnology. As no link to a procedure was provided within this survey, future research should be directed into confirming this observation. Alternatively, this result could also be partially explained by the perceived unnaturalness and immorality of animal DNA use.

This fear of unnaturalness has been suggested to arise from many different emotions, such as disgust, morality (e.g., whether it is perceived as 'playing God') and the "naturalistic fallacy" — a common fallacy that nature is inherently good (Lull et al. 2017; van Eenennaam and Young 2018). While studies on public perceptions of bacterial or viral DNA for use in HGT are less prevalent, it is possible to conclude that the decrease in support is due in part to the unnaturalness or foreign nature of the material (Frewer, Howard, and Shepherd 1997). The fact that females, in both surveys, were less likely to support the use of bacterial or viral DNA lends some weight to this theory as previous research has identified a link between acceptability of an unnatural substance and gender (Gustafson 1998). Furthermore, Weisberg (2017) has

previously suggested a link between the insertion of 'foreign' DNA into humans could be akin to an enhancive procedure that is widely perceived as unacceptable (Weisberg, Badgio, and Chatterjee 2017). When the clinical indications are more serious, it is said that this can contribute to a decrease in fear or concern of unnaturalness in the individual i.e., fears are relative to the presence of an acceptable alternative (Lull et al. 2017).

A further two demographic categories were confirmed to have a statistically significant association to attitudes towards 'animal' and 'bacterial or viral' DNA in the AUST-Online survey. These were the qualification and age of the participant. While not directly associated with HGT, scepticism towards advances in science in has also been shown to strengthen with age (Slovic 1999). In addition, recent study by Weisberg, et al. (2017) identified that older participants responded less favourably to human genetic modification research (Weisberg, Badgio, and Chatterjee 2017). In this study, as the age of the participants increased, support for the use of animal, and bacterial or viral DNA decreased.

Furthermore, participants who did not complete Year 12 (determined by an aggregated score of those who partially completed high school or received a middle school (Year 10 certificate only)) found the use of animal, and bacterial or viral DNA unacceptable. However, it is important to note that those who did not complete Year 12 made up a small subsection of the total sample size (n=21) and therefore this finding would benefit from further investigation. Nonetheless, this finding has also been reflected in other studies where an inverse relationship between qualifications and support for science and medical procedures has been reported (Barnett, Cooper, and Senior 2007; Uchiyama, Nagai, and Muto 2018). As with gender, this negative relationship was also observed in this study with attitudes towards biotechnology.

9.2.2 Procedural type

One question (with multiple sub-questions) was included to assess attitudes towards different procedures that enacted a genetic change in an organism, for example, inserting a new gene. Findings from the AUST-Online survey indicated strong support for all types of modification for societal use presented, with few disagreeing or remaining unsure about the techniques. This result demonstrated that participants did not distinguish between the acceptability of genetic editing techniques, whether this modification was to be edited, deleted or replaced. Despite lack of significant difference, insertion of a new gene received the lowest acceptance rating. It is possible that inserting a perceived 'foreign' DNA into our system may be viewed as a form of

enhancement, which as mentioned before, is widely rejected (Weisberg, Badgio, and Chatterjee 2017).

However, discordant results were observed between the AUST-Online and ACT-Mail-Out surveys when the difference between the procedural types were analysed for societal use. Where no statistical difference between the types were observed in the AUST-Online survey, results from ACT confirmed participants do distinguish between each type in terms of acceptability.

While differences in the acceptability of the six procedures assessed were only observed in the ACT-Mail-Out survey, both surveys confirmed a link between feelings of positivity towards technology and medicine, and acceptance of each procedure. No study has confirmed or even assessed this relationship to date, however this association is unsurprising as positivity has been intrinsically linked to risk perception. If an individual feels positive about technology, one would assume that the individual perceives less risks than those who feel negatively towards a technology. This particular notion was explored in a 2001 study which demonstrated this association with involuntary risk (Barnett and Breakwell 2002). Further research will need to be instigated in order to tease out this association.

9.2.3 Personal versus societal use of DNA and procedural type

Unlike the AUST-Online survey, the ACT-Mail-Out survey afforded the opportunity to investigate the differences between societal and personal use of particular procedures and techniques. For each DNA type, there was a strong decline in support from societal to personal use, this was also observed for each procedural type. While no study of HGT public attitudes to date has assessed this, it is possible that —while one may be less likely to partake in a controversial procedure (such as DNA manipulation)— there is an overriding sentiment that one's personal choice should not come at the cost of other's right to choose (Smithson 2018). This result might also be in part due to wanting scientific progress to proceed, despite one's own hesitations. When the technology becomes more mainstream and 'safer', a change in their personal preferences might occur.

A positive correlation was observed between the strength of support for GM food/crop and acceptability of DNA and procedural types in the ACT-Mail-Out survey. In the case of DNA type, this correlation was restricted to societal use only. In comparison, significance in both societal and personal use was observed for each procedural type. While this distinction will

need to be investigated further, this finding may be due to the genetic-modifying techniques employed in both GM foods and gene therapy. Previous studies have linked attitudes of genetic applications to be favourable when the application is perceived to maintain the natural order (Connor and Siegrist 2010). In contrast, a decrease in acceptability is observed for those genetic applications that are believed to change this natural order (Pivetti 2007; Lull et al. 2017). Therefore, this result adds weight to the above theory, i.e., those who are likely to support genetic change would do so across all technological areas of genetic modification, especially when focusing on the methodological aspects. However, differences do occur when questions focus on the medical and enhancement aspects of this technology, as previous studies have shown the severity of the ailment and need for the procedure is an overriding influencer as to what one deems acceptable (Condit 2010).

Apart from support for GM food/crops, positivity towards medicine showed a significant positive association with both DNA and procedural type in the ACT-Mail-Out survey findings. As these selected procedural and DNA types in the survey generally tend to be perceived as controversial due to their unnatural qualities (Gustafson 1998; Lull et al. 2017), it is possible that one's support for medicine and its progress could extend to attitudes towards gene therapy. Interestingly, biotechnology also showed a significant positive correlation for DNA type only, while the strength of positivity for the field of technology was only associated with procedural type. This distinction aligns well with the categories, with biotechnology involving the use of living organisms, such as DNA, whereas the term technology usually relates to the application of science i.e., the methods used. Based on this assumption, a positive correlation of both is an understandable finding. This positive statistically significant association was also replicated in the AUST-Online survey, and to a larger extent, with science in general and medicine specifically, where those who felt more positively towards this field were more likely to accept each technique. The same was the case for technology (except for when it was used to turn off a mutated gene) and biotechnology (except for turning on a normal gene).

The final two demographic associations observed for DNA type in the ACT-Mail-Out survey was gender and parental status. For gender, *societal use* of most DNA types were less accepted by females (as discussed above). Alternatively, those with children were less likely to support the majority of DNA types for *personal use.* While people in these two demographic categories have previously been known to perceive technological advancements with more hesitation and concern, the difference between societal use and personal use will need to be explored further. As mentioned previously, other studies have also linked gender to lower support towards

technology. It is proposed that this is due to the perception of an increased risk associated with medical procedures, coupled with the view that this type of treatment is unnatural (Gustafson 1998). In contrast, males are more inclined to worry about issues that slow scientific progress (Weisberg, Badgio, and Chatterjee 2017; Gustafson 1998).

9.2.4 Potential outcomes of human gene therapy

HGT is an innovative way of treating or enhancing the genetic make-up of an individual, but at present has a number of unknown side-effects and consequences (Hampson et al. 2018). Participants were therefore asked to rate the acceptability of a series of listed outcomes and consequences that these procedures might have, for instance, creating a permanent change in an individual. Overall, the highest approval rating was for HGT applications that were limited to the individual; the lowest was for a change in the entire population.

This last outcome piqued the interest of several participants who chose to use the feedback section to provide further commentary. One participant chose to qualify their concerns over this particular outcome:

"Homogeneity in the human population (which is essentially the ultimate ability of HGT) is both boring (!) and potentially dangerous."

Another participant raised additional concerns saying:

"We need further research to find out what could happen to a population if we eliminated these conditions entirely."

As with DNA and procedural type, when analysing potential outcomes of HGT procedures, the gender and age of the participant was associated with significantly different acceptance rates among participants in the AUST-Online survey. When assessing participants' acceptance of changing the entire population, females and those who were older were associated with a lower rate of acceptability compared to their counterparts through bivariate analysis.

To the author's knowledge, the acceptability of different HGT whole-population effects has not been studied to date. Instead, the majority of publications have focused on the outcomes of the procedure —e.g., adverse side effects. However, a common theme throughout HGT studies is that treatments which do not alter our genetic code are easier to accept and don't seem to have the same association with fear; this may be due in part to the ethical concerns and risks that arise from HGT (Robillard et al. 2014; McCaughey et al. 2016; Critchley et al. 2018).

A positive correlation was observed in the ACT-Mail-Out survey between support of GM food/crops and attitudes towards a permanent change affected by HGT (i.e., those who supported GM foods were more likely to find a permanent change more acceptable). As a permanent change instigated by the use of HGT could be perceived a 'risk' and a change to the natural order, this association also can be explained by the above theory of unnaturalness, with those supporting GM crops already supporting this notion. Interestingly, gender was also shown to be associated with this particular question, with females less likely to find a permanent change acceptable in the ACT-Mail-Out survey; no other association was observed for the other two questions.

Further follow-up studies will need to be undertaken to determine why gender was only associated with this question, and not for the other controversial outcomes of changing the entire population in the ACT-Mail-Out survey. It is possible that this was due to the fact that an entire population change is highly unacceptable, with no perceived benefit or autonomy attached to the statement; however females were less likely to find this outcome acceptable in the AUST-Online survey. On the other hand, the most accepted procedure among all participants occurred when the effects of HGT were limited to the person. This was the least controversial out of the three listed outcomes which may be due to the perception of an autonomous procedure that does not impact on others. Therefore, as the remaining two are on opposite ends of the acceptability scale, polarising views, this may explain in part why gender is not associated with these questions in the ACT-Mail-Out survey.

9.3 THERAPY, ENHANCEMENT AND PREVENTATIVE APPLICATIONS OF HUMAN GENE THERAPY

This section details a discussion on the findings of this area of investigation which aimed to address objective two, part c. (i.e., to determine the Australian public's attitude towards therapeutic, enhancement and preventative uses of HGT). Three overarching categories of

disease and disability were analysed to determine a difference in acceptability for HGT therapeutic applications. As presented in Section 1.1.2.2 (*Disability discrimination)* and 1.2.1.3.1 (*defining human gene therapy*), there is an ambiguity when trying to classify a medical procedure into a distinct group (e.g., therapeutic, enhancive, and preventative). For instance, depending on the type of cancer (present or predicted) a treatment could be classed as a therapeutic *or* a preventative. Less straight forward would be the example of Huntington's Disease, where the presence of a dominant gene ensures the individual will experience symptoms, however the late-onset nature of the disease might make a therapeutic be classed as a preventative measure. As such, the categories were designed to remain generic and high-level to avoid confusion, and attempts were made in the design of the survey to provide examples of well-known diseases that fell into one category only as a way of illustration and to provide guidance to the participant.

While the average response was positive towards this technology and higher for severe or life-threatening medical conditions, this diminished with declining severity in all three categories (chronic illness, physical disability, and intellectual disability or mental illness). An overall decrease in support for personal, as opposed to societal use (i.e., general use) was also observed within the findings of both surveys. Furthermore, multivariate analysis confirmed an association between gender and overall acceptability of applications of HGT, as discussed in this next section.

9.3.1 Decline in acceptance for severity and type of disease

Both surveys found the overall participant response was accepting towards HGT used to treat clinical indications that were considered severe or life-threatening. This acceptance however diminished with declining severity in all three categories (chronic illness, physical disability and intellectual disability or mental illness). This result is consistent with other studies that have reported similar findings across a range of different diseases (Macer 1992; Macer et al. 1995; Saba, Moles, and Frewer 1998; Bonatti et al. 2002; Macer et al. 2007; Liu et al. 2011; Robillard et al. 2013, 2014; Xiang et al. 2015; McCaughey et al. 2016; Critchley et al. 2018). As the severity of the clinical indication increased, acceptance of gene therapy interventions was also found to increase in the majority of studies who assessed it. In addition, averaged illness and disability categories differed in acceptability rates, with a chronic illness the most accepted category.

This observed pattern indicates individuals tend to rate the acceptability of different HGT procedures on a case-by-case basis depending on two overarching factors: (1) the severity of the condition and (2) the type of condition. This has been previously discussed by Gaskell et al. who suggests the issue is not with the technology itself, but its applications (Gaskell et al. 2017). Other factors that play into this decision include the necessity of the procedure in conjunction with the associated risks —both the known (e.g., quantifiable risks of procedural complications) and unknown (e.g., psychological implications of permanent changes)— and other ethical concerns (Frewer, Howard, and Shepherd 1997), all of which are issues that are incredibly prevalent when discussing HGT (Robillard et al. 2013, 2014; McCaughey et al. 2016).

To add depth to this theory, Starr suggests that what people view as a tolerable risk is approximately proportional to the real and perceived benefits of the event (Starr 1969). This suggestion is especially applicable when discussing the public acceptance of HGT, not only for treatments of different disease severities but crucially, for different disease *types*. As part of this risk assessment, the 'potential for a cure', 'societal burden of the disease' and 'link of a disease to a single gene' all have previously been rated as important in the decision-making process (Rabino 2003). Looking at each therapeutic category, chronic illness on average was significantly more acceptable than physical illness, with intellectual and mental illness the least accepted across both surveys. Presently, physical disability, intellectual disability and mental illness are frequently highly complex conditions caused by multiple genetic and environmental interactions to produce a variant phenotype that, historically, has often goes unnoticed by society (Chiurazzia and Pirozzi 2016; Procknow and Rocco 2016). Alternatively, childhood syndromes such as Down syndrome, and other chronic illnesses such as cancer are highly pervasive and publicised within the media and can be the result of one gene, and therefore a suitable target for HGT at present. These factors all play a part in influencing the risk-benefit ratio. Low severity and prevalence, combined with other ethical issues (for example, an individual's consent in the case of an intellectual disability) and risks posed by the intervention tilts the ratio towards concern, where the risks start to perceivably outweigh the benefits (Macer 1992; Hendriks et al. 2018), potentially leading to a decrease in acceptance. While this link of risk has been confirmed in other studies, the current survey design did not directly analyse this. Nonetheless, given the similarities between this study's findings and the current literature, it is likely that these aspects of an illness or disability contributed to the trend in acceptance observed within both surveys. Granted this will need to be explored further through qualitative analysis.

9.3.2 Enhancements

Genetic enhancements technologies and their implications are important topics to discuss due to the numerous ethical issues specifically related to this procedure. Improving one's abilities beyond our 'normal' limits is widely rejected around the world (Pew Research Center 2016; Dijkstra and Schuijff 2016). Both surveys confirmed this, finding all enhancive applications to have the lowest acceptance rate when compared to therapeutic and preventative procedures. This finding has also been replicated in previous studies which found enhancements less acceptable than medical therapies (Macer et al. 1995; Napolitano and Ogunseitan 1999; Ng et al. 2000; Iredale et al. 2003; Evans, Kelley, and Zanjani 2005; Sturgis, Cooper, and Fife-Schaw 2005; Macer et al. 2007; Robillard et al. 2013, 2014; Xiang et al. 2015; Cebesoy and Öztekin 2016; McCaughey et al. 2016; Gaskell et al. 2017; Musunuru, Lagor, and Miano 2017; Scheufele et al. 2017; Wang et al. 2017; Critchley et al. 2018; Hendriks et al. 2018; Treleaven and Tuch 2018; McCaughey et al. 2019).

In addition to this overall low acceptance of enhancement applications, a trend was observed *within* the enhancement category. Each enhancement example presented in the survey was found to have a significantly different acceptance rating. This finding was not only replicated within both surveys, but also in a 2014 study by Robillard et al. that found a decrease in the acceptability of gene therapy enhancements from increasing lifespan (41%), improving intelligence (39%), to improving fitness and strength (38%) in Canadian and American participants (Robillard et al. 2014). The current study confirmed this trend, although to note, both survey findings witnessed lower support for each scenario compared to Robillard's findings.

Through this study and others, enhancement procedures have been demonstrated to be more controversial than medical therapies (Rabino 2003; Robillard et al. 2013, 2014; Harris 2007b). This is unsurprising as not only are enhancive procedures deemed largely unnecessary, they are additionally accompanied with more ethical issues than therapeutic applications (Macer 1992; Rabino 2003; Hendriks et al. 2018). Previous research has highlighted the perceived lack of control (i.e., an undefined limit to human enhancement), the risk of unfair advantage, discrimination, and challenging the fundamental meaning of achievement, all as disadvantages to enhancement procedures (Resnik 2000; Rabino 2003; Koch 2010). This is compounded by fear that only the 'elite' will be able to afford enhancement technology leading to an

increasingly inequitable society (Koch 2010), an issue that is particularly present when discussing intellectual and physical enhancements.

Enhancements also raise questions of morality and mortality, including whether we have a right to 'play God' and manipulate our biology to achieve 'unnatural' outcomes (Rabino 2003; Koch 2010; Lull et al. 2017). Other moral concerns include the impacts of increased lifespan coupled with decreased disease which would contribute to a population explosion leading to further inequity due to resource demand (Robillard et al. 2014; Xiang et al. 2015). While human gene enhancements are not publicly known to be in development, technological progress will ensure this future will be realised.

9.3.3 Prevention

As discussed previously, preventative procedures occupy an unusual space between therapies and enhancements. The clinical necessity of preventive procedures isn't quite realised for an ailment that hasn't yet presented itself. While distinct from an enhancement, it can be argued that prevention is more closely aligned with this type of procedure. To bolster this assumption, previous literature has argued that genetic manipulation as a prevention strategy can be classed as a genetic enhancement (Harris 2007b). However, as discussed in section 1.1.2.2 (p. 15) , this study draws a distinction between enhancement and preventive measures for two reasons: (1) enhancements are often linked with non-medical procedures, with prevention almost exclusively associated with the avoidance of a disease or disability (Juengst 1997); and (2) it is easier to argue we have a moral duty to intervene in so that no harm can come to an individual, while the same cannot be said for enhancements (Resnik 2000). The findings of this survey placed the overall acceptance rating of preventative procedures in between therapy and enhancements, which fits in with the above assumptions well.

Under the umbrella of prevention, three different scenarios were put to the survey participants in this study. In both surveys, inherited disease prevention was the most accepted, followed by spontaneous disease prevention, and finally infection prevention. This set of results may have occurred as inherited disease prevention, while seemingly less accepted than treating the *actual* disease, is still considered closer to its therapeutic counterpart rather than with other scenarios such as spontaneous disease. In the case of inherited disease, the risk is already defined —i.e., you have inherited the condition, or are at a defined increased risk of the disease or disability (Slovic 1987). Alternatively, an un-inherited (spontaneous) disease or infection may not occur

throughout one's lifetime. As such, the necessity of intervention is diminished, which may in part explain the decrease in acceptance of HGT under these circumstances.

Unfortunately, little research has focused on somatic HGT for preventative purposes. Instead, the majority of literature has tended to focus on embryonic procedures that prevent an inherited condition (Lamberts 2017; Gurev 2017; Treleaven and Tuch 2018). This type of investigation makes it impossible to separate the morality of manipulating a human embryo with the procedure. Further research into somatic preventative applications is warranted to elicit public opinion and ascertain the reasoning behind the participant's decisions.

9.3.4 Personal use

In both surveys, *personal* use of all types of therapeutic applications were less accepted than for *societal* use, with the exception of severe chronic illness and severe physical disability in the ACT-Mail-Out survey where support remained the same. To note, questions on societal and personal use were displayed differently within each survey, with the distinction being more defined within the ACT-Mail-Out survey. Interestingly, the amended survey found a stronger statistically significant delineation between societal and personal use when it was present.

Previous research has concluded that both *severe* physical and chronic ailments are the most accepted form of HGT treatment (Robillard et al. 2014). Alternatively, despite the severity of an intellectual disability and mental illness, treatment is somewhat more controversial (Robillard et al. 2014). Therefore, this ACT-Mail-Out survey finding may be a result of the severity-level *and* relative un-controversial features of these categories.

This can also be argued for the pattern seen in preventative applications in the ACT-Mail-Out survey where inherited disease prevention was found to be insignificantly different. While preventative applications have not widely been investigated to date, there is a case to be made as to the relatively uncontroversial nature of inherited disease preventative procedures. A large contributing factor to technologies or applications deemed as controversial stem from the unknown (Frewer, Howard, and Shepherd 1997) *and* from the unnecessary (Gaskell et al. 2017). Inherited diseases (unlike the other two scenarios: spontaneous and infection, found to be significantly different in acceptance) are diagnosed (and therefore known) and, in the case of more famous inherited diseases (such as breast cancer), are often severe and therefore are more likely to be deemed as necessary by an individual. In the AUST-Online survey, personal

use of the three types of prevention and enhancement procedures were not questioned, and therefore cannot be compared.

For enhancement procedures, support was low, with no significant difference observed between personal and societal use in the ACT-Mail-Out survey. This lends strength to the above theory, this time illustrating the lower end of the spectrum. As enhancement procedures are highly controversial in nature (Bostrom and Roache 2007), both the acceptance and individual use of HGT for this purpose, might be equally as unappealing to the participant. This supports Gaskell's concept (Gaskell et al. 2017) that individual's will assess on a case-by-case basis, as summarised by one participant in the ACT-Mail-Out survey saying:

"They must be weighted on their merits and in the case of medical technologies, must be examined in the context of individual circumstance"

To date, little research has been directed towards this phenomenon (i.e., differences between personal and societal use). A 1984 study discussed the difference between personal and societal level risk judgements and concluded that these were largely distinct from one another (Tyler and Cook 1984). The paper suggests that an individual does not consistently determine personal risks from their views about society. From Tyler and Cook's study, the impersonal risk hypothesis was introduced and has been confirmed by other studies over the years (Coleman 1993; Slater and Hayes 2015). This hypothesis states that mass media exposure is likely to affect one's perception on societal views, yet does not have the same effect on an individual's perceived risk. While no studies have been specifically related to HGT, it is plausible that the media has influenced this observed divide in societal and personal acceptance as this has been the predominant communication and education medium for this technology to date (Gurev 2017). Recent positive news stories (Servick 2017; Ma et al. 2017) may have played a part in increasing societal acceptance yet has little effect on an individual risk level, in part due to other influences like the lack of necessity (Rabino 2003). This connection is therefore worth exploring in future research.

9.3.5 Demographic associations

The results of this survey showed evidence that median acceptance levels of enhancement and preventative procedures differed by gender in several question themes in the AUST-Online survey. In each case females (with the exception of inherited disease prevention) found all applications to be less acceptable. This was established through a pairwise comparison in the ACT-Online survey *and* through multivariate analysis in both surveys across all acceptability questions. As this was a major finding, this will be discussed below.

Participants in the AUST-Online study who had children were more likely to accept the societal use of HGT to treat severe intellectual disability and severe mental illness. This finding *could* be attributed to an underlying fear of intellectual disadvantage. A 1996 study detailing the results of a survey of Japan Muscular Dystrophy Association (JMDA) members, found family members were more accepting of foetal diagnosis than patients (Kaiya and Macer, 1996). The study suggests that the potential burden of looking after a person with an identified disability was an incentive to partake in practices that would lead to the early detection of a potential disability, in order to provide more choices. However, it is curious that severe physical and chronic conditions were not more likely to be accepted by parents as well. As such, this finding may be attributable to the social stigma associated with mental and intellectual disabilities (Corrigan and Miller 2004), although this association is yet to be confirmed. Opposite to the findings of this study, a recent Australian survey found that 87.5% of respondents said changing a baby's genetic make-up to make them more intelligent was taking medical advances too far (Lamberts 2017). A further finding in the ACT-Mail-Out survey showed that those who did not have children were more likely to find treatment of a terminal illness (societal only) and prevention of an infection (both societal and personal), acceptable. This has not been discussed in previous literature and therefore warrants further investigation.

For the AUST-Online survey, the only other demographic association was observed between age and attitudes towards HGT being used for either a physical enhancement or infection prevention. In both cases, there was a declining support as age increased. This finding aligns with previous findings that observed older people being more inclined to perceive risks as greater in regards to technology (Sjöberg 2000). Further research should be conducted to determine the reason and the role these differences play in HGT risk perceptions.

Finally —unlike in the AUST-Online survey— those who supported GM food/crops in the ACT-Mail-Out survey were more likely to find personal and societal uses of mild and moderate

forms of all illness and disability categories as acceptable. An unusual exception was for intellectual disability/mental illness where no societal use showed a significant association, however all three severity types for this category of personal use, were. As discussed previously, a critical finding of this survey was the diminishing support as the severity of the disease declined. In addition, support was lowest for all applications relating to intellectual disability or mental illness. Interestingly, each of these significant associations are for those applications that were less supported by participants overall, and could be due to those participants being more accepting of GM technologies transferring their support towards what others perceive as the more controversial applications as described above. A same pattern was also observed between each science sector (science, technology, biotechnology, and medicine) when associated with all enhancement and preventative procedures (as opposed to mild and moderate forms of therapies). Again, these types of procedures were viewed on average as more acceptable to those who have a higher level of trust in science and medicine.

A recent report prepared on behalf of the OGTR assessed 1,255 Australian adults. The report stated that 69% of respondents felt that biotechnology would improve our way of life in the future, whereas only 46% felt genetically modified organisms (GMOs) could do the same (Instinct and Reason 2015). Importantly, researchers found that support for GMOs were greater when the techniques used were for medical purposes such as producing insulin or vaccines. In addition, there was more support for modifications which were perceived to be less radical in nature (Instinct and Reason 2015).

9.4 GOVERNANCE AND ETHICS

This section details a discussion on the findings which aimed to address objective two, part d. and e. (i.e., to determine the Australian public's towards governance challenges of HGT and ethical dilemmas borne from HGT).

The following discussion focuses on both demographic associations isolated to this survey, and participant's comments provided within the feedback section at the end of the survey. Fifteen statements relating to previously raised concerns about the governance and ethics of HGT were presented to both sets of survey participants.

9.4.1 Governance

Previous research has identified key governance issues that have been raised by the public around emerging controversial technologies such as HGT. These concerns have, in part, stemmed from mistrust of scientists, and specific areas of scientific research (Hampel, Pfenning, and Peters 2000; Barnett, Cooper, and Senior 2007; King et al. 2010; Greiling and Halachmi 2010). It is therefore unsurprising that a regulatory barrier to HGT products in the form of government approval would be the most accepted statement out of the five within this category. The idea of a government oversight body for HGT has been previously supported by the public (Wolf, Gupta, and Kohlhepp 2009). Alternatively, at the opposite end of the agreement spectrum, no government or regulatory oversight was considered to be the least acceptable. This was also found in a Swinburne University study where there was moderate agreement (6.64 out of 10) towards the statement "*It is important for governments to regulate new technologies*" (Bruce and Critchley 2017). This may potentially be due to the pervading distrust of scientists (Hu and Deng 2018; Funk and Kennedy 2019) and their ethics committees (Ng et al. 2000).

In the results of the AUST-Online survey, these two statements (i.e., only after government approval and no regulatory oversight) were shown to be closely correlated with education levels of the participant. Responses collected for both statements demonstrated that higher education levels corresponded with a greater acceptance of government oversight when dealing with the subject of HGT. However, the same association was not observed in the ACT-Mail-Out survey findings. Nonetheless, a handful of studies have also found close correlations between lower levels of education and a decrease in trust of scientific and technological innovations (Sjöberg 2000). Sjoberg (2000) suggests that lower qualifications tend to be more sceptical of scientific advancements. In addition, previous literature has highlighted an important association between high education levels and overall trust (Borgonovi 2012; Hooghe, Marien, and Vroome 2012). Some studies have indicated that this might be due to one's intelligence being integral to discerning correctly the motivations of others (Yamagishi 2001; Sturgis, Read, and Allum 2010).

9.4.1.1 Government subsidies and patient access to the technology

As the study's findings demonstrated, an individual's right to enhance oneself is less acceptable than other therapeutic applications. This is influenced, in part, by the concern of inequitable

access to the technology, as has been shown previously in other studies (Fenech 2018; Holland and Tham 2019). One participant from the AUST-Online survey qualified their answers as follows:

> *"I think enhancement human gene therapy should *only* be available if it is (probably through government subsidy but we all know that would never happen) financially available to *everyone*. We already live in a world that benefits the rich, if money is the key to enhancement, that gap will only grow."*

Subsidising this product to guarantee its availability to all citizens was the second most accepted statement across both surveys. As discussed previously within Chapter One (section 1.1.2, p12), several disadvantages arise when access to this technology is restricted. The high cost associated with gene therapies has previously been acknowledged as a concern in two Chinese studies (Xiang et al. 2015; Wang et al. 2017). This concern is compounded by the probable risk of an increased class divide based on those who can access or afford to modify themselves and those who cannot (Robillard et al. 2014). However, public health care systems will be averse to subsidising non-therapeutic enhancements to try and correct this divide. In addition, insurers will be unwilling to support high or unknown risk technologies as they emerge (Buchanan et al. 2001). Due to the broad-reaching applications of this technology, inequality stemming from this inaccessibility could have detrimental and life-long effects for many. It is therefore reasonable that subsidies were highly supported within this survey.

Ongoing deliberations surrounding the variances between definitions of enhancement and therapeutic technologies continues. While Daniel's describes any negative change from the 'normal' functioning of species as a disease (Daniels, 2000), other ethicists argue this distinction is less clear cut (Harris, 2007). In order for government to regulate and subsidise, a health technology assessment must come to a conclusion on what 'normal' is. Ideally this definition would be one that aligns with global standards as well as public sentiment.

When discussing these results, it is important to keep in mind the uniqueness of the Australian context. In Australia, the subsidisation of many medical procedures by the Government through the MBS is expected. It is acknowledged that this is not the case for many other countries. For

example, in the US there is a heavy reliance on health insurance to access affordable healthcare. Nevertheless, in 2018, a study found 84% of Americans agreed to the statement: "*Even if it brings no immediate benefits, scientific research that advances the frontiers of knowledge is necessary and should be supported by the federal government*" (Besley and Hill 2020). Therefore, as presented in Section 1.1.2.3, patient access to this technology is a critical issue that needs to be considered when designing policy to regulate this technology. Public opinion will, and already has, played a large role in making these products more accessible to the public (Abbas 2020).

Novartis' Kymriah® (Tisagenlecleucel), is a CAR T cell therapy originally advertised for the treatment of B-cell acute lymphoblastic leukemia (ALL) [11] and was the first CAR T cell therapy to be FDA approved (Philippidis 2017). Due to Novartis' exclusive rights over the product, the cost set for this life-saving product was 450,000 CHF, well out of the price range of many (Jørgensen, Hanna and Kefalas 2020). In Europe, public opposition to the inaccessibility of Kymriah® led to Novartis relinquishing its European patent in December of 2019 due to a successful patent opposition lodgement to the European Patent Office (Abbas 2020). Now Kymriah® is reimbursed for its intended indications across the EU5 (France, Germany, Italy, Spain and the UK) (Jørgensen, Hanna and Kefalas 2020). This success highlights the real role that the public can play in improving access to innovative medical procedures.

Note that if becomes legalised ok, big market price go down. Production methods demand increases.

9.4.1.2 Government decision-making

Like other controversial technologies, members of the public and scientists have repeatedly called for all to be involved in crucial decision-making stages of HGT due to its controversial and risk-prone nature (Wilsdon and Willis 2004; Morrison and Saille 2019). An unprompted feedback section at the end of both surveys also validated this call for engagement. A number of people highlighted the desire to have more information; this took many forms. Some wanted to know more because it had sparked their interest, others believed public discussion needed to

[11] Kymriah® is now approved for two indications:

1) Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia; and
2) Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

take place around this technology. Since the public are the beneficiaries of this contentious technology, public participation is essential when designing regulations (Wetters 2008). In both surveys, the vast majority of participants preferred scientific research to be conducted after government approval. When it came to regulations being left up to the government to decide, there was almost an equal division of opinion. The desire for engagement may have played a role in the observed lower agreement towards leaving the formation of regulations solely up to the government. This particular statement was also the only governance statement associated with a co-variate category. Increasing support of technology and biotechnology was related to increasing agreement. Further inquiry should be conducted into whether this is due, in part, to the confidence of the Australian government to appropriately regulate technologies like gene therapy.

Interestingly, a large majority of respondents believed regulations around HGT are sufficiently rigorous within Australia. Previously publicised experiments have highlighted the need to regulate technologies that are controversial in nature (Esvelt et al. 2014; Regalado 2016a). One participant acknowledges this balance of scientific freedom and ensuring sound regulations, is often difficult to get right:

"There needs to be a balance between the freedom for researchers to do the work they need to do, ethical considerations and a robust regulatory environment"

As Australia does not have regulations that specifically target this emerging technology, this response correlates more to the trust bestowed on the government to ensure regulations are aligned with the best interest of the nation. Further research to determine these associations is warranted.

9.4.1.3 DNA copyright

While the design of the survey did not elicit a response on the issue of DNA copyright —unprompted in the ACT-Mail-Out survey— a number of participants raised concerns on the governance of this aspect:

"I anguish that commercial outcomes will supplant and control morality of gene therapy (e.g. copyrighting human DNA & therapies)"

This subject was brought to the fore in 2014 with the contentious Australian Federal Court ruling that allowed DNA isolated from the body to be patentable citing "The chemical and physical makeup of the isolated nucleic acid renders it not only artificial but also different from its natural counterpart." (Slezak 2014). This verdict was in stark contrast to the US Supreme Court ruling that contended DNA could not be patentable if it naturally occurs within nature (Association for Molecular Pathology (AMP) v. Myriad Genetics Inc. 2013). In Australia, a High Court challenge in 2015 reversed this decision, aligning with the US judgement (Marshall and Price 2013). This debate raised several concerns, including inhibiting scientific progress, and the immorality of patenting something that is intrinsic to oneself (Stankovic and Stankovic 2011). While this debate lay dormant in Australia since this decision, the issue has since begun to resurface due to the increased media exposure of next generation sequencing technologies and its applications (Servick 2019).

9.4.2 Consent

Arguably one of the most prominent ethical debates regarding HGT, is one of consent and freedom of choice. Three statements were designed to assess the participant's agreement towards this topic (*"The parent has the right to consent on behalf of their children to undergo human gene therapy"*, *"As an individual we should be free to choose whether to personally use human gene therapy"*, *"It is the right of the individual to use human gene therapy to enhance themselves"*). Unsurprisingly, the freedom to personally choose HGT was the most accepted statement. Alternatively, the least supported statement in this category was the right to use HGT to enhance oneself. This lower level of support for enhancement applications was a theme that was observed throughout both surveys and replicated in other studies (Robillard et al. 2013, 2014; Dijkstra and Schuijff 2016). While it is still a personal choice, enhancement procedures are still surrounded in controversy with implications far broader than those using this technology (Rabino 2003; Robillard et al. 2013, 2014; Harris 2007b) and may partially explain the difference in support between the two personal choice statements.

Less supported was the statement indicating that it was the right of the parent to decide on behalf of their child. Either *in utero* or after birth, many studies have highlighted arguments both for and against this suggestion. While many studies have proposed parents have no right to modify their child (Costea et al. 2009; van Lieshout and Dawson 2016; Hendriks et al. 2018), research has also highlighted support based on the parent's moral duty to protect their child from harm and, in some cases, provide the best possible start to their child's life even if that included enhancements (Iredale et al. 2003; Gaskell et al. 2017; Hendriks et al. 2018). Interestingly, the only demographic association (bivariate) to be confirmed was for this statement, where females from the AUST-Online survey were less supportive than males. The role of nurturer or care provider, often placed on women, has been suggested to be an influencing factor, (Siegrist 2000) where these traits are generally associated with heightened caution towards anything that involves risk with little benefit.

Consent of HGT procedures has been identified as an important issue to discuss with the public (Ormond et al. 2017). Participants used both the survey and the voluntary feedback section to describe or qualify their opinions on the ethical issues relating to consent of human genetic modification procedures in the AUST-Online survey. Some individuals used the un-facilitated open-response feedback section to properly communicate their concerns. One participant stated:

"nobody should be able to consent the use [sic] of gene therapy on a person, except that person themselves."

Another respondent also raised apprehensions around consent:

"I believe personal choice here is paramount. I would be against decisions made that will effect [sic] the genes of existing people (i.e. currently alive people with an existing gene set, not future generations)."

In addition, information to support an informed decision was important among some participants:

"All gene therapy, as with all medical treatments, should be done with the full informed consent of the individual, unless the gene therapy is to treat a condition that is preventing them from giving consent."

Within this feedback section, some respondents were also concerned with matters relating to an individual's right to consent of the procedure with one respondent stating:

"I think consent is a major factor in this kind of discussion. Medical treatment can already be administered without consent, and not always to the benefit of the patient. The potency of gene therapy renders it prone to abuse in this way"

For questions about the acceptability of consenting on behalf of children, those who had children in the AUST-Online survey were more supportive of allowing parental consent for the child (a potential reason for this is touched upon below in the demographics section (section 9.5, p. 190). However, within the feedback section, several respondents qualified their answers to say that parental consent for moderate-to-severe medical diseases is permissible, however this does not extend to mild cases or enhancement procedures. For example:

"I especially do not support unnecessary enhancements being given to children. In the case of moderate to severe disease or disability I believe parents should choose for their children but in mild cases e.g. high cholesterol or in the case of enhancements, patients should be over 18 and choose for themselves, after genetic counselling."

Although the majority of participants supported most human gene modification applications, debate around the use and regulation of this technology in relation to consent and enhancements

procedures was highlighted in this survey as something that needs to be more widely discussed amongst the general public in conjunction with the relevant authorities and experts.

9.4.3 Risk and natural law

As our understanding of genetics evolves, HGT emerges as a promising strategy to mitigate many heritable and debilitating diseases. This sentiment was reflected within both surveys, with a large proportion of survey participants sharing the view that "Human gene therapy would improve our way of life in the future". This was the most agreed to statement out of the seven within the risk and natural law category. Aligning with this sentiment, there was a low support observed for the notion that the risks outweighed the benefits of this technology. This sense of agreement towards HGT providing improvement to current treatment options and lower perception of risk observed within both surveys are potentially linked. Previous research has demonstrated the close relationship between risk, acceptability and positivity towards treatment options (Robillard et al. 2013; Wang et al. 2017; Hendriks et al. 2018). In one study, perception of risk was identified as influential to one's decision to take part in a gene therapy trial, perceiving more benefits than risks (Kim et al. 2006). In a 2000 study, a third of those interviewed believed that the risks of HGT outweigh the benefits (Hampel, Pfenning, and Peters 2000), as supported by the findings of both surveys of this study. It is therefore unsurprising that, given the high support for HGT improving our way of life in the future, participants perceived the benefits of HGT outweighing the risks.

"It is our moral duty" was the second most supported statement in this category, and arguably one of the most controversial discoveries of both surveys, with over half of participants agreeing. Recently, prominent bioethicist John Harris published a book arguing that, not only is it our moral duty to use HGT, but it is also our duty to use this technology to enhance ourselves for the public good (Harris 2007b). Due to the morally reprehensible aspects of this technology raised by the public in previous studies (Fletcher 1983; Critchley et al. 2018; McCaughey et al. 2016), there is disagreement in the literature to this particular suggestion. Further research to ascertain the reason behind this higher agreement to our moral duty would be beneficial.

In both surveys, only a tenth of participants believed this research could be used for ill intent, and therefore should not be used. This result was also observed in a recent Pew study where 9% of American's surveyed found gene editing to be morally unacceptable based on the possibility of someone abusing the technology (Funk and Hefferon 2018). Despite this

seemingly low percentage of participants who feared this outcome, this fear is not insignificant and other ethicists have shown this to be an important consideration when defining the scope of research in HGT (Regalado 2016b).

The least agreed statement linked HGT to 'playing God'. As described previously in Chapter One (section 1.1.3.4.2, p. 29), this argument centres on an old belief that manipulating nature is wrong. While most in this survey did not agree, previous findings have highlighted this as a common ethical concern raised by the public (Macer 1992; Macer et al. 1995; Holm and Jayson 2003; King et al. 2010) along with meddling with nature (Robillard et al. 2014; Xiang et al. 2015). As technological advancements continue to impact on 'nature', it would be prudent to determine if this fear of changing the natural world continues to be as pervasive as it was previously. Adding to this, in Australia there is a general low adherence to religion and therefore the fear of "playing God" might not be as prominent as in previous years, which might have impacted on the low agreement observed in this study.

Robillard posed a similar question to participants which asked if "interfering with genes should not be allowed as it defies with nature". Just under 50% agreed with this statement (Robillard et al. 2014). Previous research has shown that on average 5-7% of individuals reject HGT primarily on the basis that it would be "playing God" or "unnatural" (Macer et al. 1995). This argument has also been used as a reason for rejection of genetic enhancement procedures (Macer et al. 1995). Analysis of the survey results revealed that only a small portion of participants agreed that HGT could be considered 'playing God', with females more likely to agree with this statement in the AUST-Online survey. This will be discussed below in the demographics section of this discussion (section 9.5, p. 190). In addition, a number of participants used the open-ended response section to raise concerns about 'playing God', and altering natural law. For example:

"I also believe firmly that we shouldn't play God over evolution and modify our genes"

And:

"Human Gene Therapy could be dangerous as humans will try to play God."

As discussed by Savulescu, the concerns around 'playing God' vary (Savulescu 2009). Unlike God, scientists are not omnipotent, and therefore, might not have the knowledge needed to counteract unforeseen consequences. Furthermore, what we see as 'detrimental' genes, under environmental pressures may present with beneficial effects. Indeed, within our survey, 28% believe we do not have enough knowledge of the science behind HGT while a further 27% were unsure. In the open-ended section of the survey, scientific responsibility was also linked to the perceived shortsightedness of the researchers involved within this technology. One respondent in the AUST-Online survey warns of the unknown consequences of HGT, laying the blame at the feet of impatient scientists who wish to sustain or advance their career:

"Like the many human fabrications of which the species has little if any understanding, there will undoubtedly be serious unforeseen consequences resulting from the introduction of human gene therapy… There is just too much money and prestige at stake when measured against the immaturity and short-sightedness of those involved."

Unease surrounding the intentions of scientists were felt by others:

"I have worked as a medical research scientist and understand just how limited our knowledge about consequences is."

And:

"It's easier to create powerful technology than it is to wield powerful technology, and some of our sciences are nearly at the point where a few rogue or negligent scientists could wipe out the entire planet"

The unnaturalness of HGT was also raised in this survey. One respondent indicated nature as a force to be revered when they stated that:

"we only fool ourselves if we think we can fool nature"

Another respondent raised similar concerns, noting the ethical dilemmas this technology poses:

"...it is a very fine ethics line we walk on. Who decides where gene therapy can used? [sic] Is it 'un-natural'? Do we have the right to intervene with evolution?"

Deciding who has the 'right' to mess with nature and how this would be controlled through regulation are challenges that, while slowly being overcome (such as through the European Union's Framework on responsible research and innovation (RRI)), are still present and of clear concern to the public.

9.4.4 Use of embryos

While not in the AUST-Online survey, two additional questions relating to embryos were included within the ACT-Mail-Out survey design. This was in part due to a number of participants raising embryonic manipulation and research as a concern to be discussed within the feedback section. In this study, under half of the participants thought embryo testing for research purposes was acceptable, and over half supported the modifying an embryo's DNA. This correlates with a recent Australian study which concluded Australian's were 'comfortable' with the use of embryos for these purposes (Treleaven and Tuch 2018; Critchley et al. 2018). Other global studies have associated this application of HGT as less acceptable and more divisive among respondents (Liu et al. 2011; Hendriks et al. 2018; McCaughey et al. 2016) depending on the application and demographics of the population such as religion, socio-economic background and gender (Critchley et al. 2018). In addition, participants who indicated

that they were parents were less likely to support embryo testing for technology development, a potential factor from a perceived protective and nurturing role (Siegrist 2000).

9.5 DEMOGRAPHIC AND CO-VARIATE ASSOCIATIONS

A crucial finding of this study was the identification that gender played an overarching influencing role in attitudes towards HGT. This discovery aligns well with previous literature assessing the acceptability of HGT and its applications as well as emerging technologies in general (Napolitano and Ogunseitan 1999; Hampel, Pfenning, and Peters 2000; Evans, Kelley, and Zanjani 2005; Barnett, Cooper, and Senior 2007; Črne-Hladnik et al. 2009; Hudson and Orviska 2011; Črne-Hladnik et al. 2012; Xiang et al. 2015; Cebesoy and Öztekin 2016; McCaughey et al. 2016; Gaskell et al. 2017; Weisberg, Badgio, and Chatterjee 2017; Hendriks et al. 2018; Critchley et al. 2018). In previous surveys on issues of HGT, males were similarly found to be more in favour of gene therapy and perceived fewer risks than females (Hampel, Pfenning, and Peters 2000; Calnan, Montaner, and Horne 2005). Conversely, in another well-regarded study, gender was not found to be a key association at all (Robillard et al. 2014).

Previous studies have shown that females and males differ in perceptions of risk, and therefore trust (Gustafson 1998). Viewing risk as a social and cultural construct partially explains this difference. Although gender ideology and gendered practice are constantly evolving, the perceived roles of females and males are still prevalent today and influence our sensitivity towards risk and our ability to trust (Wynne 1992). Such influences may include socio-political factors such as power and status (Flynn, Slovic, and Mertz 1994). In addition, historical alienation and exclusion from science and technology has meant females generally perceive outcomes in these fields at a higher risk (Siegrist 2000). Attitudinal differences in gender should therefore be considered for further research to identify the strength of the above associations that potentially influence the observed gender difference.

In addition, within the ACT-Mail-Out survey findings, parenthood and a known history of disease within the family were shown to be statistically significant across all questions with a Likert scale when applied to a multivariate analysis. ACT-Mail-Out survey participants who had children were *less* likely to find all aspects of HGT acceptable than those who did not have children. While little research has been done in this area, it is easy to surmise that those with children are more cautious and averse to taking risks that have little benefit associated with the outcome due to their perceived protective and nurturing role (Siegrist 2000). A 2011 Australian

study on parental perception of risk of diseases in relation to vaccinations highlighted concepts of dread, unfamiliarity and uncontrollability when weighing up the risks of an intervention. Whether for or against vaccinations, the vast majority of participants were less willing to take risks with their children's health (Bond and Nolan 2011).

While not apparent within the bivariate analysis, those with a history of disease within the family were *more* likely to support all aspects of HGT than those who do not. Witnessing first hand someone you care about suffering, and the potential fear of what that same disease or disability might mean for yourself and your family has been shown to alter your perception of what is necessary or what risks are worth taking (Baptiste-Roberts et al. 2007; Ashida et al. 2013). In addition, while not directly related, communicating family health history has been proven to play a critical role in preventing chronic disease development in family members (Baptiste-Roberts et al. 2007). In other words, knowledge of one's family history has been shown to increase one's engagement in preventative activities (Ferrer and Klein 2015). Missing from this analysis is the perceived severity of the familial disease. This additional information would help identify if an increase in severity of a familial disease influences a person's perception of risk.

9.5.1 Support of genetically modified foods

Participants in both surveys showed majority support (i.e., either complete or moderate support) for GM foods (60% (AUST-Online) and 59% (ACT-Mail-Out)). This is slightly higher, although still comparable to a recent national Australian survey which found that nearly half of the participants (46.6%) believed it was generally safe to eat GM foods (Lamberts 2017). Another Australian report prepared, for the OGTR in 2019, showed that only 13% of respondents were completely against GM food and crops, a figure that had remained unchanged since 2017 (Cormick and Mercer 2019). In this study, the mean for those who supported the use of gene technology in food and in crops was 5.29 out of 10, with 10 being fully supportive of the technology.

Similar high levels of trust in GM foods were found in Europe. A special Eurobarometer report commissioned by the European Food Safety Authority (EFSA), found that only 27% of EU citizens were concerned about GM ingredients in food or drinks (EFSA 2019). Concern had significantly decreased compared to the 2010 Eurobarometer survey where participants were split on their attitudes towards biotechnology and genetic engineering. In addition, participants

in this earlier survey did not see the benefits of GM food, and believed it to be most likely unsafe or harmful (EFSA 2010).

Interestingly, the 2019 Eurobarometer report also highlighted an association between education and attitudes towards GM food. It was observed that those who remained in education longer, were more likely to be concerned about GM foods (EFSA 2019); 30% of participants who continued their education beyond 15 years of age were more concerned about GM food, compared to 19% who left education by the age of 15. No such association was observed in this study.

9.5.2 Support of science and technology

There is generally a high level of interest and trust in science in Australia (CSIRO 2014). As seen in this study, Bruce and Critchley found the majority of Australians trust science and technology and that it can improve the quality of one's life (Bruce and Critchley 2017). These Australian results are comparable to international literature. A survey run by the American National Science Board (NSC) indicated that Americans' overall attitudes about science was positive (NSC 2016). In Europe, a 2013 Eurobarometer survey showed that the vast majority (77%) of Europeans think that science and technology had a positive influence on society (EC 2013).

Another trend observed within this study was an association of attitudes of science and technology with gender. Females in the AUST-Online survey were less likely to feel positive towards technology in general. Lamberts (2017) observed a similar finding, suggesting that Australian males were more likely to approve of controversial scientific interventions than females. In fact, most global studies detect an accordant difference based on gender, where males rate science and technology more favourably than females (OECD 2015; Pew 2015).

As the level of qualification increased, so too did the positive attitudes towards biotechnology. In an American study by the Pew Research centre (2015), those who held a postgraduate degree were more likely to express differing views compared to those who had undertaken less formal education; however, this depended on the science topic under investigation. For example, those with a higher education are more likely to believe that eating GM good is safe, a form of biotechnology (Pew 2015). Alternatively, a study in India found that only 56 % of respondents with a lower education felt that science and technology make lives healthier, easier and more comfortable, compared to 98 % of postgraduates (NCAER 2005). This trend has also been

observed in Europe, where a strong positive correlation between attitudes towards science and technology, and level of education has been identified (ORION 2018).

9.6 COMPARISON OF SURVEY METHODS

In both surveys, regardless of recruitment methods used, a survey population skewed towards young, educated females was observed. Furthermore, no significant difference between the two survey populations were identified for all demographic and co-variate factor categories. This bias is a common theme in survey participation. Those who have a higher level of education are more likely to participate (Curtin, Presser, and Singer 2000; Goyder, Warriner, and Miller 2002). This bias has also been observed in favour of women (Curtin, Presser, and Singer 2000; Moore and Tarnai 2002), and younger people (Moore and Tarnai 2002). Based on the lack of difference between the demographics of both surveys, the time and expense to organise a state mail out survey was —in hindsight— not justified given the significantly lower response rate and similarity of population profiles, as described further in the limitations below.

While this discussion has shown that results from this study overall correlate well to domestic and international findings, the skewed demographic sample will undoubtedly impact the ability to determine the true estimate of Australian attitudes towards HGT. An effort was made to include Australian organisations and societies that held dissenting views on HGT to illustrate this alternative point of view, however, to date no societies against HGT or human gene editing are prevalent within Australia. Instead, dissenting views as raised by participants in the feedback section have been included throughout the discussion.

9.6.1 Limitations

An online survey was originally selected for recruitment due to its ability to collect responses on a large scale in a reasonable amount of time. There are, of course, inherent limitations of this procedure (Eysenbach and Wyatt 2002). As discussed above, recruitment bias is normally observed with this type of method. In addition to gender, age, and education, other specific groups are less likely to engage with this form of survey, for example those without internet access (Eysenbach and Wyatt 2002). This was observed within this survey, with highly educated females being the dominant respondents in both surveys. In addition, the majority of (56%) of respondents in the ACT-Mail-Out survey were identified as relating more to an

Australian political party of left-wing persuasion (i.e., the Australian Greens and the Australian Labor Party). While this undoubtedly would have affected the results of this study, as this was not assessed in the AUST-Online survey, we were unable to identify what the true affect was. Interestingly, a 2003 Eurobarometer survey found those who are more concerned about nature to be less optimistic about biotechnology (Gaskell, 2003). This would seem to be opposed to our findings, where attitudes to HGT were overall positive towards this form biotechnology. Future work should explore this more.

While English is the predominant language of Australia, restricting the survey to English speaking residents also contributes to this selection bias, though this is probably very minor. The recruitment survey also generated a smaller sample size than anticipated. This low sample size can introduce further bias due to the increased chance of high variability between respondent answers (Coughlan, Cronin, and Ryan 2013). The limitations were noted, with caveats provided within this discussion chapter asking the reader to interpret findings with some caution. A broader discussion of the advantages and limitations of this method was described in Chapter One (section 1.3.1, p. 56).

While a mail-out survey increases the chance of a random population, a low response rate is prevalent (Sinclair et al. 2012). To help rectify this known disadvantage, a monetary incentive was used to encourage responses, a method that has been previously shown to be successful (Edwards et al. 2009). Previous literature has explored this method and its effectiveness on increasing participation rates. A prominent theory (social exchange theory) argues that a material incentive may alter one's perception to believe the potential benefit of the gift outweighs the cost of participation. Unfortunately, this was not the case within this survey; a low response rate was observed. Due to the low sample size (and therefore large non-response), and potentially due to investigator-selected residential addresses, a skewed population was again observed. As discussed previously, this low sample size can introduce further bias due to the increased chance of high variability between respondent answers (Coughlan, Cronin, and Ryan 2013). Due to the high cost and time taken to produce and mail approximately 2,000 surveys, increasing the population size was not feasible. These limitations were taken into account when analysing and discussing the findings of this study.

Regardless of what medium and recruitment strategy, other influencing factors that affect response rates include interest in the topic (Groves, Singer, and Corning 2000) and survey fatigue (Saxon et al. 2003) from response burden due to length and complexity (Rolstad, Adler,

and Rayden 2011). In both surveys, approximately one-fifth of survey participants dropped out of the survey. One could surmise the length of the survey could be the cause of some of this. It is for this reason that the survey was predominantly restricted to Likert scale questions with two open-ended responses. While this limited the chance to qualitatively investigate influences to acceptance, the feedback allowed the participants to qualify their answers and raise additional concerns not addressed within the survey itself, with over a third in each survey accessing this option.

9.6.2 Uncertainty disclaimer

As described within the methods, unsure responses were excluded from the analysis with only answers that were on the Likert scale were used. This was to ensure each averaged category reflected the overall acceptance of the procedure (i.e., a low score (1-2) would indicate unacceptability, alternatively a high score (4-5) would signify acceptability). However, this process meant that when comparing between categories, a difference in levels of uncertainty was not reflected within the results. This also meant that, while there appeared to be a large visual decrease in acceptance, only a small decrease was recognised in some of the analyses. This approach was taken as the only other logical area where uncertainty could lie within the Likert scale was within the neutral (or neither) state. This was undesirable as neutrality suggests a position of neither for nor against the scenario, however unsure denotes the participant is undecided or confused. However, the fact that a significant decrease in severity and type of application in all scenarios analysed observed after unsure was excluded, lends weight to the observations detailed above.

9.7 CHAPTER SUMMARY

The findings of this comparative analysis have revealed that, when accounting for all demographic factors, gender plays an influencing role in a person's overall attitudes towards applications and outcomes of HGT, with females on average less supportive of this emerging technology. In addition, a strong trend in decreasing acceptability with decreasing severity of the clinical indication was observed across all categories within both surveys. This declining trend in acceptability was also identified across major categories of HGT; therapeutic, enhancive and preventive. A final major trend was confirmed through amendment of the AUST-Online survey questions. Through separating out the questions, personal use was more robustly

analysed alongside societal use of each procedure in the ACT-Mail-Out survey. In the vast majority of cases, participants were *less* likely to personally use HGT when compared to societal use. These findings demonstrate a strong trend of acceptability that can contribute to the international body of knowledge and aid in the initial discussions on how to shape the regulations and policies that govern HGT, as summarised in the final chapter.

10 Conclusion

This thesis builds on previous research contributions to public attitudes of controversial medical technologies. Arguably the zenith of which is HGT, where there exist wide-ranging known risks, and unforeseen consequences that stem from the novelty of this procedure. Therefore, the cornerstone of this work analysed how individuals in Australia perceive and understand HGT, including their willingness to accept the wide variety of procedural applications and implications. Although previous research in this field has examined public attitudes towards HGT, the focus has tended to be on international cohorts. Prior to commencement of this thesis, limited studies had been undertaken that survey the Australian public. In addition, this previous published literature has not been as encompassing of all aspects of HGT compared to what is presented in this thesis.

There are numerous historical examples where lack of awareness of public opinion for a new technology has led to confusion and concern that has endured throughout the first critical years of implementation and widespread use. HGT in particular has a tendency to evoke public concern, in part due to the risks ranging from personal to societal implications. We are now on the precipice of having the ability to change our inherited destiny, one DNA molecule at a time. In the future many diseases and disabilities that restrict or confine us could be solved through this emerging and exciting new technology. It is a daunting prospect for most individuals to contemplate changes that are risk-prone, heritable and permanent. By assessing public attitudes, these first comprehensive consultative steps opens doors for future research and highlights areas in need of further exploration in the crucial stages before integration into our society.

Presented in this thesis were two surveys that assessed the awareness, understanding and attitudes of HGT: (1) a 2017 nation-wide social media survey of 553 Australians, and (2) a 2019 mail-out survey of 179 participants located within the ACT. The major findings shared across both surveys draw attention to strong trends in acceptability and the role that demographics, in particular gender, play in this space, as summarised below.

10.1 PUBLIC AWARENESS AND UNDERSTANDING

To date little research has focused on the current awareness and understanding of HGT within the Australian population. As such, this survey provided the perfect opportunity to assess the

current literacy levels of the public and potentially illuminate common misconceptions. The majority of participants from both surveys had heard of HGT before *and* could provide at least a partially correct definition. However, their knowledge (both self-rated and investigator-rated) did not translate into an increased awareness of the current use of HGT within Australia. While Australia has world-class medical research institutes, few HGT clinical trials and research has been undertaken to date, compared to world-leaders in this field such as America and China. Media releases therefore tend to focus on international breakthroughs. As the first HGT application edges closer towards being listed on the Medicare Benefits Schedule (Medical Services Advisory Committee 2020), communication via media, government or other platforms is one important way this controversial technology can begin to be discussed and deliberated in an open forum. Public dialogue has been something that has been vehemently advocated for by many different academics and politicians (Schneider 2017). The results from this section of the survey highlight the need to act on this now to ensure the public is fully engaged and informed of their options, potential risks and benefits of a life-changing procedure like this.

10.2 GENETIC MODIFYING TECHNIQUES

While outcomes, ethics and applications (therapeutic etc.) of HGT have received immense academic focus, little research to date has investigated public opinion of the procedural techniques used to modify the genes. This is a missed opportunity. By evaluating public opinion of the techniques that underpin the technology, a broader picture emerges that helps illuminate acceptance of HGT as a whole. In this study, participants' acceptance of DNA and technique type (insertion of a new gene etc.) were investigated. Of the four DNA types assessed within each survey, human DNA was perceived as being the most acceptable, followed by artificial, animal and finally bacterial or viral DNA. This trend in acceptance lends weight to previous theories that suggest animal welfare and unnaturalness of the method are at least two contributing factors to overall acceptance and provides a firm basis for further research into influences of public attitudes.

To the author's knowledge, no research to date has assessed DNA modifying techniques without the association of a clinical condition. This intentional separation allows for the assessment of public opinion without being linked to other influencing factors such as the severity and necessity of the intervention or other ethical issues such as consent, which contribute to one's overall acceptance. Interestingly, a high percentage of acceptance was

observed in both surveys. However, while a discernible difference in acceptance was identified between each technique within the ACT-Mail-Out survey, this was not detected within the AUST-Online survey. This disparity of results requires further research in order to confirm the accuracy of each result. It is possible that the original position at the front of the survey may have contributed to the lack of differentiation among participants. By analysing the acceptability of these different methods, these findings may help to shed new light on contributing factors to the overall acceptance of HGT.

10.3 SEVERITY AND TYPE OF CLINICAL INDICATIONS FOR THERAPEUTIC APPLICATIONS

A high level of acceptability towards HGT for severe and life limiting clinical indications have been previously observed. However, these key studies have tended to focus on specific diseases, with none as broad ranging as the study detailed within this thesis. In this study, there are three distinct groups of clinical indications explored: chronic illness, physical disability, and intellectual disability or mental illness. The findings of both surveys confirmed that where severe cases occurred, there was more acceptance across every disease or disability category measured. Acceptability then declined in line with the declining severity of the disease or disability. Another finding that was observed across both surveys was a decrease in acceptance when each overarching category (e.g., chronic illness) was averaged and compared. In each case, the use of gene therapy in chronic illness was found to be more acceptable than where a physical disability existed. Out of the three categories, intellectual disability or mental illness was deemed the most unacceptable.

These two results confirm the previously explored idea that individuals not only feel a controversial and risk-prone technology should be reserved for severe clinical indications where intervention is necessary, but also perceive different types of indications as more relevant than others. These distinctions provide up-to-date insights into Australia's risk perceptions surrounding this technology. The self-identified lack of knowledge among participants has the potential to create uncertainty about the current safety and effectiveness of this technology which may in part explain the disparity in acceptance levels between mild and severe applications. It is well documented that when one is uncertain about a technology, access restriction to those who have no other 'safer' option is often is the preferred option (Starr 1969; Rabino 2003). This outcome lends weight to previous study findings, and provides a basis for

further investigation into perceived risks and benefits of this technology. This also helps set up a framework for the Australian Government when considering new HGT applications. The first approved application sets the precedence for future applications. By identifying these public concerns, policy can adapt to include safeguards into highlighted areas of concern to ensure that the safety and well-being of the public is considered in more depth. A strong clinical necessity for the procedure is clearly an area that the public feel is important when discussing this technology.

Only three broad clinical indications were explored within this thesis. As the findings indicated an overall difference in acceptability within these three indications require further exploration into the acceptance of other types of ailments by the Australian public. As this survey was predominately based on Likert scale questions, qualitative analysis into the reasoning behind the distinctions would also benefit in further study. Standalone, these findings provide a strong confirmation of an individual's propensity to support this procedure where cases are based on (1) the severity of the condition and (2) the type of condition.

10.4 ENHANCEMENT AND PREVENTATIVE PROCEDURES

Improving one's abilities beyond our 'normal' limits by genetic manipulation has been widely rejected around the world (Robillard et al. 2014; Pew Research Center 2016; Dijkstra and Schuijff 2016). Australian surveys have tended to focus on embryonic or child enhancements which make it hard to separate acceptance rates from highly contentious issues such as consent (both for the individual and, in the case of embryos, future generations) (Lamberts 2017; Critchley et al. 2019). This study therefore set out to determine the acceptance levels for adult genetic enhancements in three different scenarios (i.e., age, physical and intellectual enhancements). These three scenarios afforded the opportunity to assess whether there were different acceptance rates under the umbrella of enhancement procedures. In both surveys, enhancements were the least accepted form of procedure when compared to therapeutic or preventative applications. Furthermore, as seen with therapeutic procedures, individuals determined the acceptance of each application on a case-by-case basis. Both are important findings that allow further insights into the Australian public's views.

To the author's knowledge, little research has been instigated into defining public acceptance of HGT *prevention* procedures in adults to date. When prevention procedures are discussed, it is usually in the form of embryonic manipulation to ensure a hereditary or genetic disorder is

not present within the unborn offspring. This procedure is also usually defined as an enhancement, rather than prevention and, as discussed previously, embryonic manipulations come with its own suite of issues that influence public attitudes. Despite this link to enhancements, it can be argued that preventative applications hold a middle ground, not as acceptable or necessary as a therapeutic procedure, yet not quite an enhancement as in most cases the application is for preventing a serious disease or disability from occurring. The findings of both surveys reflects this notion with preventative procedures more acceptable than enhancements, while less acceptable than therapeutic procedures. Adding weight to this theory was the observation that preventing a hereditary condition was the most accepted out of the three scenarios provided within the surveys (i.e., an inherited disease, a spontaneous disease that *might* occur, and infection prevention). Out of all three, an inherited disease has the lowest risk of adverse consequences as it insinuates that the gene is present and in the majority of the cases, the phenotype will occur within the individual's lifetime. This is opposed to a spontaneous disease or infection that may or may not occur depending on the prevalence of the condition or (in the case of inspection) bacteria, virus or parasite. These are important distinctions that warrant further research to confirm these influencing factors.

While HGT for preventative purposes has barely been researched to date, the similarities between prevention and enhancement cannot be ignored. As genetic enhancement technologies have wide-reaching implications, this makes public acceptance of both these applications an important topic to discuss, something that has been highlighted by the low acceptance rating observed in both surveys. Previous research has linked this decreased acceptance to concerns about disparities in resource allocation, access to the procedure, and discrimination. These findings highlight Australia's current attitudes towards the more controversial aspects of HGT. These discoveries are also important to explore and build-upon within the early stages of policy development and can aid in future research that investigates public opinion within early stages of controversial emerging technologies.

10.5 GOVERNANCE AND ETHICS

A major component that plays a pivotal role in determining an individual's acceptance of HGT, is concerns relating to the morality and ethics of HGT. Unlike other medical technologies, these unique, and broad-ranging concerns create challenges for its governance, both domestically and internationally. As such, no survey would be complete without ascertaining the public's

attitudes towards these key issues. Findings from this survey conclude that governmental oversight with public input is required for this technology to progress. Both surveys also highlighted that the overall risks of the procedure, such as misuse, inequality and adverse effects of the procedures itself, were not enough to prevent this technology from forging ahead in the eyes of the Australian public who participated. This cautious positivity observed within both surveys has been reflected worldwide. Day-by-day as technological hazards are being addressed and governments are becoming more proactive, this perception of risk appears to be decreasing. However complacency in these fundamental stages of design and development (both in a policy and technological sense) is something to avoid. There are so many aspects of this technology and its impacts yet to be discovered. Ensuring these are identified early and addressed is crucial moving forward. Surveys such as presented in this thesis are therefore vital to guarantee public opinion is consulted and incorporated.

10.6 GENDER AND OTHER DEMOGRAPHICS

Previous studies have found significant associations between demographics and acceptance towards this technology. Associations like this add perspective and insight into not only how people formulate their opinions, but importantly identifies those who feel more vulnerable. Only when identified can communities begin to address these concerns to ensure all members feel safe and not discriminated against. With this knowledge, governments are also in a better position to tailor their policy and communication strategies so that all citizens' feel informed and supported. Both surveys were the first of their kind to assess acceptance towards such a wide range of HGT applications, methods and its consequences which allowed for a robust cross-analysis between questions. For this reason, multivariate analysis was able to be performed that incorporated acceptance towards ethics, applications, outcomes and techniques. A crucial finding of this study was the identification of an overarching association between gender and attitudes of HGT. Overall, females were less likely to accept HGT. This discovery aligns well with previous literature which focus not only on HGT, but emerging technologies with ethical consequences and thus adds to the strength of this association. Throughout each survey, bivariate analysis additionally identified specific areas (e.g., use of DNA, outcomes of the technologies) where certain societal groups appeared to be more concerned than others. Apart from gender, age, education level, and parental status were among the few prevalent demographics that were highlighted as potentially having a relationship with acceptance.

10.7 RECOMMENDATIONS

There are two key recommendations that naturally emerge from this study. The first is ensuring a strong public consultative element is embedded in the design of policy, especially when it relates to controversial technologies like HGT. While this thesis has detailed government processes that already include public feedback, I don't believe it goes far enough. There appears to be no real form of public auditing that ensures the public opinion collected is considered by the policymakers. Without this transparency, it is easy for public members to be disgruntled and disheartened about these processes without understanding the true reasons why their input seemingly was not considered. The Rawlsian theory advocates for the justification of a particular position by way of reasons so that people of different moral and political persuasions find the position acceptable (Rawls 1997). It is possible to explain why certain reasons and opinion were not incorporated, and a transparent auditing process with this theory in mind would go a long way to appease public sentiment and ensure a strong Australian culture of public participation.

The second recommendation to be borne out of this thesis is that, as HGT becomes more prevalent, policy regulating this technology will need to incorporate a strong governance framework that takes into account issues of access and consent, and ensures discrimination of gender and those with disability are not unduly affected. If they are, avenues must be in place to correct this injustice. There is a fine line between policy that will impede the progress of this technology (something participants of this survey were against), and securing a safe middle-ground will be difficult given the novelty and dynamic nature of this technology. A strong definition of what constitutes enhancement (and therefore unlikely to be government subsidised) and therapeutic will need to be considered at the start of this process.

10.8 FUTURE RESEARCH

While the findings detailed in this thesis highlight strong trends in acceptance, this area of public opinion would benefit from further research. While surveys are an incredibly useful tool to obtain a large population sample in a relatively short amount of time, this method does come with drawbacks. The participants' reasoning behind their responses cannot fully be ascertained. Emerging trends from this study would therefore benefit from a qualitative analysis that builds on the key issues raised. This research could include an examination of the participant's perception of risks, both known and unknown, and under what scenarios they feel each risk is

acceptable. As awareness of a technology is integral to ensure informed consent and the formation of beliefs (whether positive or negative), research into the potential change in risk perception of HGT where an individual becomes more aware, would be a useful inquiry.

Research into demographic preferences would also be beneficial. As both surveys were slightly skewed in favour of highly educated, young females, confirmation with a more representative population of Australia would add strength to these findings. In addition, certain patterns between demographics and acceptance that emerged from bivariate analysis were not replicated in both surveys (such as demographic pairwise comparisons). Further exploration would help confirm the accuracy of these associations.

Finally, a significant difference in acceptance of societal and personal use of each procedure and technique has been identified in both surveys. As this has not been previously explored in studies focused on HGT, identifying the causal factors that underlie these differences would be valuable in order to provide a deeper understanding of an individual's risk perception.

10.9 CONCLUSION

In conclusion, this thesis has presented several findings that provide a comprehensive analysis of public opinion towards, and awareness of, different aspects of HGT. While Australian's who took part in this survey were receptive to HGT for severe therapeutic applications, this acceptance declined for enhancive, preventative and mild conditions. Furthermore, gender was found to play a key role in an individual's acceptance of HGT, a finding that was confirmed in both surveys. Overall, females were less accepting of this technology, an outcome that has been supported by previous literature.

Importantly, these findings have implications for public policy formation and ethics affecting HGT. Public policy on technologies such as HGT are in their formative stages, therefore the ethics and concerns raised by the Australian public can help develop and build upon ethically sound policy. These findings lend weight to the creation of an open dialogue between all members of society and the Government. In the future, this technology will not discriminate who will be impacted by this technology: healthy or ill, there will soon be a solution provided by HGT. However, this technology will *cause* discrimination. From issues regarding access to the technology through to human rights violations, HGT has the potential to affect people's lives and livelihoods. By assessing public opinion early, we begin the first steps in ensuring the ethical and responsible future of this life altering technology.

Appendix A: Online Australian Survey Design

1. Are you a current resident of Australia?
    a. Yes
    b. No

2. Are you 18 years or older?
    a. Yes
    b. No

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For the first section of this survey, we would like to understand how much you already know about human gene therapy.

3. Have you heard of the term human gene therapy before?
    a. I have **never** heard of it before
    b. I have, but couldn't explain what it is
    c. I have, but only know a little about what it is
    d. I have, and could explain it clearly to a friend
    e. I have, and have extensive knowledge on this topic
    f. Unsure

4. How would you describe human gene therapy? (i.e. what does human gene therapy do?)
    a. Text Box Answer

5. As far as you are aware, is human gene therapy already being used in Australia?
    a. Yes
    b. No
    c. Unsure

6. If you think human gene therapy is already being used in Australia, what does it treat?
    a. Text Box Answer

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Human gene therapy – describes the prevention, treatment or cure of a disease or disorder by **genetic modification (i.e. human gene editing)** of the affected cells to correct a cellular dysfunction or to provide a new cellular function.
Where…
Genes – are made up of DNA and provide a specific function to the cell (e.g. help produce molecules called proteins).
Mutated genes – are genes that directly contribute to the development of disease.
Enhancement human gene therapy – is aimed at improving an already **healthy** person by **genetic modification** to confer an advantage (e.g. to increase your athletic ability)

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7. How acceptable is it to treat a sick person using the following techniques (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Removing a mutated gene (e.g. cutting out the gene)
b. Editing a mutated gene (e.g. fixing a section of the gene)
c. Replacing the mutated gene with a normal copy
d. Insertion of a new gene (e.g. a gene that the person originally did not have)
e. Turning on a normal gene that was inactive (e.g. a gene that was previously silent)
f. Turning off a mutated gene that was active

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8. How acceptable is it to treat a sick person using donated DNA from… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Human DNA (e.g. from another person)
a. Animal DNA (not of human origin)
b. Bacterial or Viral DNA
c. Artificial DNA (e.g. DNA designed and created in a laboratory)

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9. How acceptable is it to genetically modify a person's DNA to treat a **chronic illness** that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Terminal illness (e.g. terminal cancer)
b. Severe chronic illness (e.g. cystic fibrosis)
c. Moderate chronic illness (e.g. heart disease)
d. Mild chronic illness (e.g. high cholesterol)

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10. How acceptable is it to genetically modify a person's DNA to treat a **physical disability** that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Severe physical disability (e.g. quadriplegic)
b. Moderate physical disability (e.g. rheumatoid arthritis)
c. Mild physical disability (e.g. short/long eye-sight, partial hearing loss)

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11. How acceptable is it to genetically modify a person's DNA to treat an **intellectual disability** that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Severe intellectual disability (e.g. severe autism)
b. Moderate intellectual disability (e.g. attention deficit disorder)
c. Mild intellectual disability (e.g. mild developmental delay)

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12. How acceptable is it to genetically modify a person's DNA to treat a **mental illness** that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Severe mental illness (e.g. schizophrenia)
b. Moderate mental illness (e.g. insomnia)
c. Mild mental illness (e.g. mild anxiety)

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13. How acceptable is it to genetically modify a **healthy** person's DNA to **enhance** a trait and/or ability that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Physical enhancement (e.g. change of eye colour, increase fitness)
b. Intellectual enhancement (e.g. increase intelligence, increase memory)
c. An enhancement that makes you age slower or live longer

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14. How acceptable is it to genetically modify a **healthy** person's DNA to **prevent**... (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Prevent new infections (e.g. immune system enhancement)
b. Prevent an inherited disease (e.g. breast cancer)
c. Prevent a potential disease that is **not** inherited (e.g. brain cancer)

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15. To what extent do you agree with the following statements relating to human gene therapy? (i.e. genetic modification) (5-Point Likert Scale; Slightly/Completely Agree/Disagree, Neither, Unsure)

a. The risk of human gene therapy outweighs the benefits
b. Human gene therapy will improve our way of life in the future
c. Regulations of medical therapies are sufficiently rigorous in Australia
d. Human gene therapy products should only be allowed after government approval
e. Human gene therapy should be subsidised by the government so it is available to all
f. Human gene therapy manipulates nature for the worse (i.e. "playing God")
g. We have a moral duty to use human gene therapy to cure disease
h. Humans should always be improving ourselves with the latest medical technology, therefore human gene therapy should be allowed
i. All research and development should be stopped into human gene therapy

16. To what extent do you agree with the following statements relating to human gene therapy? (i.e. genetic modification) (5-Point Likert Scale; Slightly/Completely Agree/Disagree, Neither, Unsure)

a. Private companies and institutions should be allowed to research human gene therapy with no government or regulatory oversight
b. The parent has the right to consent on behalf of their children to undergo human gene therapy
c. It is the right of the individual to use human gene therapy to enhance themselves (e.g. change eye-colour, athletic build, increase intelligence)
d. The benefits of human gene therapy will be greater than any harmful effects it may have
e. Regulations surrounding human gene therapy should be left up to the government to decide
f. We don't have enough knowledge to use human gene therapy
g. Human gene therapy should not be permitted as it might be used for ill intent
h. As an individual, we should be free to choose whether to personally use human gene therapy

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17. Would you personally use human gene therapy to genetically modify your DNA to treat an illness?

a. Yes
b. No
c. Unsure

18. Would you personally use human gene therapy to genetically modify your DNA to to enhance a trait or ability? (e.g. to increase your athletic ability or intelligence)

a. Yes
b. No
c. Unsure

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19. Under what circumstances would you personally use human gene therapy to genetically modify your DNA? (Please select all that apply) (Tick-box answer)

a. To treat a terminal illness (e.g. cancer, Parkinson's disease)
b. To treat a moderate-to-severe chronic illness (e.g. diabetes)
c. To treat a mild chronic illness (e.g. arthritis)
d. To treat a moderate-to-severe physical disability (e.g. blindness)
e. To treat a mild physical disability (e.g. short-sighted)
f. To treat a moderate-to-severe intellectual disability (e.g. severe autism)
g. To treat a mild intellectual disability (e.g. mild developmental delay)
h. To treat a moderate-to-severe mental illness (e.g. anorexia)
i. To treat a mild mental illness (e.g. mild anxiety)
j. To enhance a trait (e.g. increase intelligence, increase athletic ability)
k. To prevent a disease or infection (e.g. inherited breast cancer, measles)
l. If it is the only treatment option available
m. Only if I could no longer manage my pain by other means
n. I would never use human gene therapy
o. Unsure
p. Other (please specify)

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20. To what extent would human gene therapy be acceptable under each of these circumstance? (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. If the effects were limited to the person
b. If the effects were permanent (e.g. could not be reversed)
c. If it changed the genetic makeup of the entire population (e.g. Australia)
d. If it required human embryo testing to develop these techniques
e. If people could choose which diseases and conditions are affected

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21. In your opinion, what kind of effect has the following had on our **society**? (5-Point Likert Scale; Very/Somewhat Positive/Negative, Neutral, Unsure)

a. Science in general
a. Technology in general
b. Biotechnology specifically (e.g. genetically modified crops)
c. Medicine specifically (e.g. new cancer treatments)

22. How much do you think society as a whole would change if human gene therapy becomes available?

a. Not at all
b. Slightly
c. Considerably
d. Unsure

23. Overall, what kind of effect would this change have on our society?
    a. Very positive
    b. Somewhat positive
    c. Neutral (e.g. no difference)
    d. Somewhat negative
    e. Very negative
    f. Unsure

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In this last section, we would like to know a little bit more about yourself…

24. What is your gender?
    a. Female
    b. Male
    c. Other
    d. Prefer not to say

25. What is your age?
    a. 18-24
    b. 25-34
    c. 35-44
    d. 45-54
    e. 55-64
    f. 65-74
    g. 75 or older
    h. Prefer not to say

(PAGE BREAK)

26. In which Australian State/Territory do you currently reside?
    a. Australian Capital Territory
    b. Perth
    c. Western Australia (Excluding Perth)
    d. Sydney
    e. New South Wales (Excluding Sydney)
    f. Melbourne
    g. Victoria (Excluding Melbourne)
    h. Brisbane
    i. Queensland (Excluding Brisbane)
    j. Adelaide
    k. South Australia (Excluding Adelaide)
    l. Hobart
    m. Tasmania (Excluding Hobart)
    n. Darwin
    o. Northern Territory (Excluding Darwin)
    p. Prefer not to say

27. What is the highest level of educational qualification you have completed?
    a. Primary school
    b. Some high school, but no certificate
    c. Middle school/intermediate certificate (Year 10 certificate)
    d. High school certificate (Year 12 certificate)
    e. Some university, but no degree
    f. TAFE/Technical Certificate
    g. Diploma
    h. Graduate-level degree (e.g. Bachelors or Honors)
    i. Postgraduate-level degree (e.g. Masters or PhD)
    j. Other (please specify)
    k. Prefer not to say

(PAGE BREAK)

28. Which of the following categories best describes your employment status? (Please select all that apply)
    a. Employed, working full-time
    b. Employed, working part-time
    c. Employed, casual worker
    d. Not employed, looking for work
    e. Not employed, not looking for work
    f. Student
    g. Retired
    h. Not able to work
    i. Prefer not to say

29. Have you ever worked in either the health or medical industry?
    a. Yes
    b. No
    c. Unsure
    d. Prefer not to say

(PAGE BREAK)

30. Do you identify with any of the following religions?
    a. No religion
    b. Catholicism
    c. Protestantism
    d. Christianity
    e. Judaism
    f. Islam
    g. Buddhism
    h. Hinduism
    i. Inter/Non-denominational
    j. Other (please specify)
    k. Prefer not to say

31. Do you have any children?
    a. Yes
    b. No
    c. Prefer not to say

(PAGE BREAK)

32. In general, how would you rate your overall health?
    a. Excellent
    b. Very good
    c. Good
    d. Fair
    e. Poor
    f. Prefer not to say

33. Do you, or does anyone in your immediate family, identify as someone with a disability or impairment?
    a. Yes
    b. No
    c. Unsure
    d. Prefer not to say

34. Do you, or does anyone in your immediate family, have a gene that predisposes you to a serious disease such as cancer, heart disease or diabetes?
    a. Yes
    b. No
    c. Unsure
    d. Prefer not to say

(PAGE BREAK)

35. Do you personally support the use of genetically modified food/crops?
    a. Not at all
    b. Slightly
    c. Moderately
    d. Completely
    e. Other (Please specify)
    f. Prefer not to say

(PAGE BREAK)

40. How did you hear about this survey?
    a. Social Media (e.g. Facebook, Twitter)
    b. Email
    c. Letter
    d. Family
    e. A friend
    f. Other (Please specify) _____

(PAGE BREAK)

41. Before posting your responses, is there anything else you would like to share about the survey specifically or human gene therapy in general? (Text box answer)

Thank you for your participation in this survey. Your response will help clarify the current public attitudes surrounding human gene therapy in Australia and strengthen public engagement programs and policy development in this field.

Please remember, when posting your responses we ask that no identifiable information (such as your name, address, phone number etc.) is to be written on the completed survey or the return envelope. This is to protect your identity.

Appendix B: Australian Capital Territory Mail Out Survey Design

1. Are you a current resident of the Australian Capital Territory?
    a. Yes
    b. No

Q1 Comment: Amended from 'Australian State or Territory' to 'Australian Capital Territory' due to new population cohort.

2. Are you 18 years or older?
    a. Yes
    b. No

(PAGE BREAK)

For the first section of this survey, we would like to understand how much you already know about human gene therapy.

3. Have you heard of the term human gene therapy before?
    a. I have never heard of it before
    b. I have, but couldn't explain what it is
    c. I have, but only know a little about what it is
    d. I have, and could explain it clearly to a friend
    e. I have, and have extensive knowledge on this topic
    f. Unsure

4. How would you describe human gene therapy? (i.e. what does human gene therapy do?) If you have never heard of human gene therapy or are unsure, please skip this question.
    a. Text Box Answer

Q4 Comment: Included 'If you have never heard of human gene therapy or are unsure, please skip this question' as in the previous survey, participants felt they needed to provide an answer (skip logic did not always work in the AUST-Online survey).

5. As far as you are aware, is human gene therapy already being used?
    a. Yes
    b. No
    c. Unsure

Q5 Comment: Amended from 'being used in Australia' to 'being used'.

It was observed that the original question was too specific and did not provide information on how much the participant knew about the general availability of human gene therapy.

6. If you think human gene therapy is already being used, what does it treat?
    a. Text Box Answer

Q6: Comment: Altered from '…already being used in Australia' in order to be consistent with previous question.

7. Do you believe human gene therapy is currently being used in Australia?
    a. Yes
    b. No
    c. Unsure

Q6: Comment: Included from AUST-Online survey to understand if participant was aware of the Australian availability of human gene therapy.

(PAGE BREAK)

Human gene therapy – describes the prevention, treatment or cure of a disease or disorder by **genetic modification (i.e. human gene editing)** of the affected cells to correct a cellular dysfunction or to provide a new cellular function.
Where…
Genes – are made up of DNA and provide a specific function to the cell (e.g. help produce molecules called proteins).
Mutated genes – are genes that directly contribute to the development of disease.
Enhancement human gene therapy – is aimed at improving an already **healthy** person by **genetic modification** to confer an advantage (e.g. to increase your athletic ability)

(PAGE BREAK)

8. How acceptable is it for society to genetically modify a person's DNA to treat an **illness** that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)
    a. Terminal illness (e.g. terminal cancer)
    b. Severe chronic illness (e.g. cystic fibrosis)
    c. Moderate chronic illness (e.g. heart disease)
    d. Mild chronic illness (e.g. high cholesterol)

Q8, 10, 12, 14 and 16 Comment: Question location was brought forward to provide a better flow of survey themes. Added "society" into the question to be less ambiguous and distinguish between personal and societal use.

9. Would you **personally** use human gene therapy to genetically modify **your** DNA **to treat an illness** that is a… (Yes, No, Unsure)

a. Terminal illness (e.g. terminal cancer)
b. Severe chronic illness (e.g. cystic fibrosis)
c. Moderate chronic illness (e.g. heart disease)
d. Mild chronic illness (e.g. high cholesterol)

Q9, 11, 13, 15 and 17 Comment: Included to enhance the follow of the survey. This question was previously asked at the end in a tick box (previously Q17-19 in the AUST-Online survey). It is believed that putting these questions adjacent will allow participants to consider the differences better between personal and societal.

(PAGE BREAK)

10. How acceptable is it for society to genetically modify a person's DNA to treat a **physical disability** that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Severe physical disability (e.g. quadriplegic)
b. Moderate physical disability (e.g. rheumatoid arthritis)
c. Mild physical disability (e.g. short/long eye-sight, partial hearing loss)

11. Would you **personally** use human gene therapy to genetically modify **your** DNA **to treat a physical disability** that is a… (Yes, No, Unsure)

a. Severe physical disability (e.g. quadriplegic)
b. Moderate physical disability (e.g. rheumatoid arthritis)
c. Mild physical disability (e.g. short/long eye-sight, partial hearing loss)

(PAGE BREAK)

12. How acceptable is it for society to genetically modify a person's DNA to treat an **intellectual disability or a mental illness** that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Severe intellectual disability or mental illness (e.g. severe autism, schizophrenia)
b. Moderate intellectual disability or mental illness (e.g. attention deficit disorder, insomnia)
c. Mild intellectual disability or mental illness (e.g. mild developmental delay, mild anxiety)

Q12 Comment: Analysis of the AUST-Online survey revealed a decrease in strength of statistically significant difference between acceptance of intellectual disability and mental illness, compared to all other comparisons. Based on this observation, and to reduce the length of the survey, these questions were combined.

13. Would you **personally** use human gene therapy to genetically modify **your** DNA **to treat an intellectual disability or a mental illness** that is a… (Yes, No, Unsure)

a. Severe intellectual disability or mental illness (e.g. severe autism, schizophrenia)
b. Moderate intellectual disability or mental illness (e.g. attention deficit disorder, insomnia)
c. Mild intellectual disability or mental illness (e.g. mild developmental delay, mild anxiety)

(PAGE BREAK)

14. How acceptable is it for society to genetically modify a **healthy** person's DNA to **enhance** a trait and/or ability that is a… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Physical enhancement (e.g. choose eye colour, increase fitness)
b. Intellectual enhancement (e.g. increase intelligence, increase memory)
c. An enhancement that makes you age slower or live longer

15. Would you **personally** use human gene therapy to genetically modify **your** DNA **enhance** a trait and/or ability that is a … (Yes, No, Unsure)

a. Physical enhancement (e.g. choose eye colour, increase fitness)
b. Intellectual enhancement (e.g. increase intelligence, increase memory)
c. An enhancement that makes you age slower or live longer

(PAGE BREAK)

16. How acceptable is it for society to genetically modify a **healthy** person's DNA to **prevent**... (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Prevent new infections (e.g. immune system enhancement)
b. Prevent an inherited disease (e.g. breast cancer)
c. Prevent a potential disease that is **not** inherited (e.g. brain cancer)

17. Would you **personally** use human gene therapy to genetically modify **your** DNA to **prevent** … (Yes, No, Unsure)

a. Prevent new infections (e.g. immune system enhancement)
b. Prevent an inherited disease (e.g. breast cancer)
c. Prevent a potential disease that is **not** inherited (e.g. brain cancer)

(PAGE BREAK)

18. How acceptable is it for society to treat a sick person using the following techniques (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Removing a mutated gene (e.g. cutting out the gene)
b. Editing a mutated gene (e.g. fixing a section of the gene)
c. Replacing the mutated gene with a normal copy
d. Insertion of a new gene (e.g. a gene that the person originally did not have)
e. Turning on a normal gene that was inactive (e.g. a gene that was previously silent)
f. Turning off a mutated gene that was active

Q18 and 20 Comment: Added "society" into the question to be less ambiguous and distinguish between societal and personal acceptance.

19. Would you **personally use** human gene therapy that used the following techniques (Yes, No, Unsure)

a. Removing a mutated gene (e.g. cutting out the gene)
b. Editing a mutated gene (e.g. fixing a section of the gene)
c. Replacing the mutated gene with a normal copy
d. Insertion of a new gene (e.g. a gene that the person originally did not have)
e. Turning on a normal gene that was inactive (e.g. a gene that was previously silent)
f. Turning off a mutated gene that was active

Q19 and 21 Comment: Not included in the AUST-Online survey, added to identify if there was a difference between personal and societal use.

(PAGE BREAK)

20. How acceptable is it for society to treat a sick person using donated DNA from… (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. Human DNA (e.g. from another person)
b. Animal DNA (not of human origin)
c. Bacterial or Viral DNA
d. Artificial DNA (e.g. DNA designed and created in a laboratory)

21. Would you **personally use** human gene therapy that contained donated DNA from… (Yes, No, Unsure)

a. Human DNA (e.g. from another person)
b. Animal DNA (not of human origin)
c. Bacterial or Viral DNA
d. Artificial DNA (e.g. DNA designed and created in a laboratory)

(PAGE BREAK)

22. To what extent would human gene therapy be acceptable under each of these circumstance? (5-Point Likert Scale; Slightly/Completely Acceptable/Unacceptable, Neither, Unsure)

a. If the effects were limited to the person
b. If the effects were permanent (e.g. could not be reversed)
c. If it changed the genetic makeup of the entire population (e.g. Australia)

Q22 Comment: Removed the two questions relating to the use of embryos and included within the below questions (i.e. Q25).

(PAGE BREAK)

23. To what extent do you agree with the following statements relating to human gene therapy? (i.e. genetic modification) (5-Point Likert Scale; Slightly/Completely Agree/Disagree, Neither, Unsure)

a. Regulations of medical therapies are sufficiently rigorous in Australia
b. Human gene therapy products should only be allowed after government approval
c. Human gene therapy should be subsidised by the government so it is available to all citizens
d. Regulations surrounding human gene therapy should be left up to the government to decide
e. Private companies and institutions should be allowed to research human gene therapy with no government or regulatory oversight

Q23-26 Comment: Amended into themes to both enhance the flow of the survey and to shorten amount of sub-questions so the participant can visualise the answer options at all times.

24. To what extent do you agree with the following statements relating to human gene therapy? (i.e. genetic modification) (5-Point Likert Scale; Slightly/Completely Agree/Disagree, Neither, Unsure)

a. The parent has the right to consent on behalf of their children to undergo human gene therapy
b. It is the right of the individual to use human gene therapy to enhance themselves (e.g. change eye-colour, athletic build, increase intelligence)
c. As an individual, we should be free to choose whether to personally use human gene therapy

25. To what extent do you agree with the following statements relating to human gene therapy? (i.e. genetic modification) (5-Point Likert Scale; Slightly/Completely Agree/Disagree, Neither, Unsure)

a. Human gene therapy should be allowed even it required human embryo testing to develop these techniques
b. We should be able to use human gene therapies to edit an embryo in the womb
c. Human gene therapy will improve our way of life in the future
d. We have a moral duty to use human gene therapy to cure disease
e. Humans should always be improving ourselves with the latest medical technology, therefore human gene therapy should be allowed

25. To what extent do you agree with the following statements relating to human gene therapy? (i.e. genetic modification) (5-Point Likert Scale; Slightly/Completely Agree/Disagree, Neither, Unsure)

a. We don’t have enough knowledge to use human gene therapy
b. The risk of human gene therapy outweighs the benefits
c. Human gene therapy manipulates nature for the worse (i.e. “playing God”)
d. Human gene therapy should not be permitted as it might be used for ill intent

(PAGE BREAK)

27. In your opinion, what kind of effect has the following had on our **society**? (5-Point Likert Scale)
    a. Science in general
    b. Technology in general
    c. Biotechnology specifically (e.g. genetically modified crops)
    d. Medicine specifically (e.g. new cancer treatments)

28. How much do you think society as a whole would change if human gene therapy becomes available?
    a. Not at all
    b. Slightly
    c. Considerably
    d. Unsure

29. Overall, what kind of effect would this change have on our society?
    a. Very positive
    b. Somewhat positive
    c. Neutral (e.g. no difference)
    d. Somewhat negative
    e. Very negative
    f. Unsure

(PAGE BREAK)

In this last section, we would like to know a little bit more about yourself…

30. What is your gender?
    a. Female
    b. Male
    c. Other
    d. Prefer not to say

31. What is your age?
    a. 18-24
    b. 25-34
    c. 35-44
    d. 45-54
    e. 55-64
    f. 65-74
    g. 75 or older
    h. Prefer not to say

(PAGE BREAK)

32. In which ACT suburb do you currently reside?
    a. List of all suburbs (not listed due to size of list)

Q30 Comment: Included to see the spread of participating suburbs.

33. What is the highest level of educational qualification you have completed?

a. No school certificate
b. Middle school/intermediate certificate (Year 10 certificate)
c. High school certificate (Year 12 certificate)
d. Trade/apprenticeship
e. Certificate/diploma
f. University degree or above
g. Prefer not to say

Q31 Comment: Adjusted to align with ABS categories.

(PAGE BREAK)

34. Which of the following categories best describes your employment status? (Please select all that apply)

a. Employed, working full-time
b. Employed, working part-time
c. Employed, casual worker
d. Not employed, looking for work
e. Not employed, not looking for work
f. Student
g. Retired
h. Not able to work
i. Prefer not to say

35. Which of the following categories best describes the industry you primarily work in (regardless of your actual position)?

a. Agriculture, Forestry, Fishing and Hunting
a. Arts, Entertainment, and Recreation
b. Broadcasting
c. College, University, and Adult Education
d. Computer and Electronics Manufacturing
e. Construction
f. Finance and Insurance
g. Government and Public Administration
h. Health Care and Social Assistance
i. Homemaker
j. Hotel and Food Services
k. Information Services and Data Processing
l. Legal Services
m. Military
n. Mining
o. Other Education Industry
p. Other Industry
q. Other Information Industry
r. Other Manufacturing
s. Primary/Secondary (K-12) Education

t. Publishing
u. Real Estate, Rental and Leasing
v. Religious
w. Retail
x. Scientific or Technical Services
y. Software
z. Telecommunications
aa. Transportation and Warehousing
bb. Utilities (Electricity, gas, water, waste)
cc. Wholesale
dd. Prefer not to say

Q35 Comment: Replaced "Have you ever worked in either the health or medical industry" to align with ABS categories.

(PAGE BREAK)

36. Do you identify with any of the following religions?
a. No religion
b. Catholic
c. Anglican
d. Christian
e. Islam
f. Buddhism
g. Hinduism
h. Other (please specify)
i. Prefer not to say

Q36 Comment: Adjusted to align with ABS categories.

37. Do you have any children?
a. Yes
b. No
c. Prefer not to say

38. Do you, or does anyone in your immediate family, identify as someone with a disability or impairment?
a. Yes
b. No
c. Unsure
d. Prefer not to say

39. Do you, or does anyone in your immediate family, have a gene that predisposes you to a serious disease such as cancer, heart disease or diabetes?

a. Yes
b. No
c. Unsure
d. Prefer not to say

(PAGE BREAK)

40. Do you personally support the use of genetically modified food/crops?

a. Not at all
b. Slightly
c. Moderately
d. Completely
e. Other (Please specify) _____
f. Prefer not to say

41. Which Australian political party do you currently relate more to?

a. Australian Labour Party
b. Liberal Party of Australia
c. National Party of Australia
d. Australian Greens
e. Australian Democrats
f. Pauline Hanson's One Nation
g. United Australia Party
h. Australian Conservatives
i. Other (Please specific)

Q41 Comment: Included to see if political views were associated with attitudes.

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42. If you wish to take part in the lottery prize draw, please enter your email dress below. (Text box answer)

43. Before posting your responses, is there anything else you would like to share about the survey specifically or human gene therapy in general? (Text box answer)

Thank you for your participation in this survey. Your response will help clarify the current public attitudes surrounding human gene therapy in Australia and strengthen public engagement programs and policy development in this field.

Appendix C: Online Australian Survey

Participant Information Sheet

Ethics Approval Number: 2017/608

Participant Information Sheet

Description and Methodology:
This survey is being undertaken as part of an Australian National University PhD research project in science communication. The research looks at the public's attitude towards and current understanding of human gene therapy. The results of this survey will provide a snapshot of the preferences of Australian citizens in 2017. It is anticipated this knowledge will contribute to policy and regulation development in this area.

Invitations to participate will be distributed via email, the Science Alert website and social media. Completion of the survey should take approximately 15 minutes. There is a feedback section at the conclusion of the survey so that you may add comments, suggestions or concerns about the content of the survey.

Please be aware that this survey contains questions about disability and disease which may cause distress. If you are in distress, please consider accessing a support service such as Lifeline (13 11 14). The language surrounding disability is constantly changing. The terminology employed in this survey is used based on current Australian standards.

Exclusion criteria:
Participation is limited to individuals **aged 18 years or over** and be you must be a **current resident of Australia**.

Use of Data and Feedback:
The result of this project will be reported in the principal investigator's PhD thesis, and may be published in academic journals, books or news websites such as The Conversation. You will be able to access a summary of the research results at the following shared drive: https://drive.google.com/open?id=0B9n8qYWUtJarTGJNNmt0QXdrOGc

Voluntary Participation & Withdrawal:
Participation in this survey is voluntary and you can withdraw at any time up to the submission of your responses. Your submission is considered to be your consent to participate and only surveys that are completed and submitted will be used in any analysis. Once you submit your answers, your data cannot be withdrawn.

Confidentiality:
Your submission will remain anonymous. We will not collect any information that can identify individuals in anything we produce or publish.

Privacy Notice:
In collecting your personal information within this research, the ANU must comply with the Privacy Act 1988. The ANU Privacy Policy is available at https://policies.anu.edu.au/ppl/document/ANUP_010007 and it contains information about how a person can:

- Access or seek correction to their personal information;
- Complain about a breach of an Australian Privacy Principle by ANU, and how ANU will handle the complaint.

Data Storage:
All data collected will be stored on the ANU server which is password-protected, encrypted and only accessible by the principal investigator. In addition, any hard-copies of documents will be stored under lock and key, accessible only by the principal investigator and the supervisory panel.

Material from this project will be stored for a period of 5 years from the date of any publication arising from this research. At the end of the storage period, any data collected will be archived indefinitely by the principal investigator.

Contact Details for More Information:
For a downloadable version of this information sheet please click here:
https://drive.google.com/open?id=0B9n8qYWUtJarTGJNNmt0QXdrOGc

For further requests for information or queries regarding the study, please feel free to contact the following investigators:

Ms Michel Watson - Primary Investigator
Phone: +61 2 6125 7167
Email: Michel.Watson@anu.edu.au.

Dr Rod Lamberts – Supervisory Chair
Phone: +61 2 6125 0747
Email: Rod.Lamberts@anu.edu.au.

Ethics Committee Clearance:
The ethical aspects of this research have been approved by the ANU Human Research Ethics Committee (Protocol 2017/608). If you have any concerns or complaints about how this research has been conducted, please contact:

Ethics Manager
The ANU Human Research Ethics Committee
The Australian National University
Telephone: +61 2 6125 3427
Email: Human.Ethics.Officer@anu.edu.au

Appendix D: Australian Capital Territory Mail Out Survey Letter

Michel Watson
PhD Candidate

Research School of Population Health

+61 2 6125 7167
Michel.Watson@anu.edu.au

9 September 2019

Surveying community attitude towards human gene therapy

Dear Resident,

My name is Michel Watson, and I am a PhD student at the Research School of Population Health at the Australian National University (ANU). I am researching ACT resident's attitude and understanding of human gene therapy, and I want to hear from you!

Have your say by participating in a survey that forms part of my research project titled: An investigation into the potential future of human gene therapy in Australia.

Findings from this survey will help us understand how to shape the regulations and policies underpinning human gene therapy with the public's attitudes in mind. Public attitudes towards this technology is one of the key factors in its subsequent development and application, therefore it is vital that the science is communicated effectively.

If you are a current ACT resident and are 18 years or older, we want to hear from you!

Anyone and all in your household can complete the survey.

The survey **should only take 20 minutes** to complete online and is available until the 30th of September. It will look its best on your computer or tablet. The survey can be found at:

https://www.surveymonkey.com/r/N8Q6GPF

You can also enter into a prize draw to **win one of three $50 Canberra Centre gift cards** by providing your email address at the end of the survey. Please be assured that these email

addresses will only be used to contact you if you have won a prize! They will be deleted once announced.

For more information please see the participant information sheet enclosed within this envelope. If you have any other questions regarding the study please feel free to contact us:

Ms Michel Watson – Primary Investigator
Phone: +61 2 6125 7167
Email: Michel.Watson@anu.edu.au.

Dr Johanna Kurscheid – Supervisor
Phone: +61 2 6197 0076
Email: Johanna.Kurscheid@anu.edu.au

We look forward to your submission and hope you enjoy taking part in this survey!

Appendix E: Australian Capital Territory Mail Out Participant Information Sheet

Participant Information Sheet

Researcher: My name is Michel Watson, a PhD student at the Research School of Population Health at the Australian National University [ANU]. I am approaching you to invite you to participate in my research project titled:

Project Title: An investigation into the potential future of human gene therapy in Australia

General Outline of the Project:

Description and Methodology: The Research School of Population Health wishes to invite you to participate in an online survey on human gene therapy. The research looks at ACT resident's attitude towards and current understanding of human gene therapy. These findings help us to understand how to shape the regulations and policies underpinning human gene therapy with public attitudes in mind. Public attitudes towards a technology is one of the key factors in its subsequent development and application therefore it is vital that the science is communicated and deliberated effectively.

Participants: Participant's include current ACT residents who are 18 years and over.

Use of Data and Feedback: The result of this project will be reported in the principal investigator's PhD thesis, and may be published in academic journals, books or news websites such as *The Conversation*. You will be able to access a summary of the research results at the following shared drive:
https://drive.google.com/open?id=0B9n8qYWUtJarTGJNNmt0QXdrOGc

Participant Involvement:

Voluntary Participation & Withdrawal: Participation in this survey is voluntary and you may withdraw at any time up to the submission of your responses. Your submission is considered to be your consent to participate. Only surveys that are completed and submitted will be used in any analysis. Once you submit your answers, your data cannot be withdrawn.

What does participation in the research entail?: Participation in this research project involves taking part in an online survey designed to assess public attitudes and current understanding of human gene therapy. You can find the survey online with this url:
https://www.surveymonkey.com/r/N8Q6GPF

There is a feedback section at the conclusion of the survey so that you may add comments, suggestions or concerns about the content of the survey. Please note that it is permissible to refuse to answer any questions asked in this survey.

Those who wish to enter into a prize draw to win one of three $50 Canberra Centre gift cards are able to put their email addresses at the end of the survey.

Location and Duration: Completion of the survey will take place online at https://www.surveymonkey.com/r/N8Q6GPF and should take approximately 20 minutes.

Remuneration: Those who wish to enter into a prize draw to win one of three $50 Canberra Centre gift cards are able to put their email addresses at the end of the survey. The winner's email address will be selected at random, online on the 1st of October 2019. Each winner will be notified through their nominated email address on the same day by the principal researcher.

Please be assured that these email addresses will only be used to contact you if you have won a prize. They will be deleted as soon as the winner has been determined. In addition, the email addresses will be separated from your survey response as soon as possible to ensure that your answers remain anonymous when analysing the data. If you have any questions or concerns, please do not hesitate to contact the principal investigator.

Risks: Please be aware that this survey contains questions about disability and disease which may cause distress. If you are in distress, please consider accessing a support service such as Lifeline (13 11 14). The language surrounding disability is constantly changing. The terminology employed in this survey is used based on current Australian standards.

Benefits: It is unlikely that you will personally benefit from participating in this research however, the broader community would benefit from the research. These findings help us to understand how to shape the regulations and policies underpinning human gene therapy with public attitudes in mind. Public attitudes towards a technology is one of the key factors in its subsequent development and application therefore it is vital that the science is communicated and deliberated effectively.

Exclusion criteria: Participation is limited to individuals aged 18 years or over and be you must be a current resident of the Australian Capital Territory.

Confidentiality

Confidentiality: If you decide to provide your email address in order to enter your name into the lottery, information that can identify you as an individual will be collected. However, only the nominated researchers will have access to the provided email address and the investigator will keep this data confidential to the extent permitted by law. Upon announcing the winner of the lottery, all email addresses will be deleted.

Privacy Notice: In collecting your personal information within this research, the ANU must comply with the Privacy Act 1988. The ANU Privacy Policy is available at https://policies.anu.edu.au/ppl/document/ANUP_010007 and it contains information about how a person can:

- Access or seek correction to their personal information;
- Complain about a breach of an Australian Privacy Principle by ANU, and how ANU will handle the complaint.

Data Storage:

Where: All data collected will be stored on the ANU server which is password-protected, encrypted and only accessible by the principal investigator. In addition, any hard-copies of documents will be stored under lock and key, accessible only by the principal investigator and the supervisory panel.

How long: Material from this project will be stored for a period of 5 years from the date of any publication arising from this research.

Handling of Data following the required storage period: At the end of the storage period, any data collected will be archived indefinitely by the principal investigator. Please note, no identifiable information will collected or stored.

Queries and Concerns:

Contact Details for More Information: For further requests for information or queries regarding the study, please feel free to contact the following investigators:

Ms Michel Watson - Primary Investigator
Phone: +61 2 6125 7167
Email: Michel.Watson@anu.edu.au.

Dr Johanna Kurscheid – Supervisor
Phone: +61 2 6197 0076
Email: Johanna.Kurscheid@anu.edu.au

For a downloadable version of this information sheet please click here:
https://drive.google.com/open?id=0B9n8qYWUtJarTGJNNmt0QXdrOGc

Contact Details if in Distress: Please be aware that this survey contains questions about disability and disease which may cause distress. If you are in distress, please consider accessing a support service such as Lifeline (13 11 14). The language surrounding disability is constantly changing. The terminology employed in this survey is used based on current Australian standards.

Ethics Committee Clearance: The ethical aspects of this research have been approved by the ANU Human Research Ethics Committee (Protocol 2019/557). If you have any concerns or complaints about how this research has been conducted, please contact:

Ethics Manager
The ANU Human Research Ethics Committee
The Australian National University
Telephone: +61 2 6125 3427
Email: Human.Ethics.Officer@anu.edu.au

Appendix F: Bubble Plot R-Markdown Code

```
RAW_DATA        <- read.csv(file =
"C:/Users/michel/Downloads/The Human Gene Therapy Survey
2017.csv", header = TRUE);

Q3 <- RAW_DATA[,2]
Q4 <- RAW_DATA[,3]
AnswerMat <- matrix(0,nrow = 3, ncol = 6)

#Q4 <- Q4 + 1

for(i in 1:length(Q3)){
  if(!is.na(Q3[i])){
    AnswerMat[Q4[i],Q3[i]] <- AnswerMat[Q4[i],Q3[i]]+1
    }
}

Q3A <- c(1,1,1,2,2,2,3,3,3,4,4,4,5,5,5,6,6,6)
Q4A <- c(1,2,3,1,2,3,1,2,3,1,2,3,1,2,3,1,2,3)

Pops2 <- c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0)

for(i in 1:18){
  Pops2[i] <- AnswerMat[Q4A[i],Q3A[i]]
}

Pop2.data <- data.frame(Q3A, Q4A, Pops2)

library("ggplot2")

ggplot(Pop2.data, aes(x=Q4A, y=Q3A, size=ifelse(Pops2==0, NA,
Pops2))) +
  geom_point(alpha=1) +
  scale_size(range = c(1.6, 13)) +
  xlim(0.8, 3.5) +
  geom_point(color='darkOrange2')
```

Appendix G: Multivariate Analysis R-Markdown Code

```
```{r setup, include = FALSE}

knitr::opts_chunk$set(echo = TRUE);

#Load libraries
library(ggplot2);
library(tidyr);
library(dplyr);
library(stringr);
library(openxlsx);s
library(MASS);
library(lme4);

#Set plotting theme
THEME <- theme(plot.title    = element_text(hjust = 0.5, size = 14, face = 'bold'),
               plot.subtitle = element_text(hjust = 0.5, face = 'bold'));

#Create function for structure with shrtened variable names
short_str <- function(data, n = 20, ...) {
    name_vec <- names(data)
    str(setNames(data, ifelse(
    nchar(name_vec) > n, paste0(substring(name_vec, 1, n - 4), "... "), name_vec)), ...) }

```
SUMMARY

This code details the analysis of data from the AUST-Online survey (2019). The raw data was
contained in a csv file in wide form.  The raw data was imported into R and questions that were
```

not of interest were filtered out before the data was converted to long-form, a format that is suitable for analysis by regression models. A model was then fitted for the data and a summary of outputs was produced from the model.

#STEP 1 - IMPORT AND MODIFY THE DATA

First the raw data was imported from an external file. This was set as the data frame ```RAW_DATA```. The data frame contained questions with numerically coded answers that had a key in an external file. The data frame was in wide-form (i.e., it contained one row per participant, with answers to all questions by that participant shown as variables in a single row). These variables included demographic descriptors and covariates for the participants, and answers to questions on the survey.

```{r Import the raw data}

#Set the working directory
setwd("C:/ /");

#Import the data
RAW_DATA        <- read.csv(file = "The Human Gene Therapy Survey 2019.csv", header = TRUE);

```
```{r Show structure of raw data}

short_str(RAW_DATA);

``
After the data was imported, it was converted into long-form as the data frame ```DATA```.  To achieve this, participant variables were extracted separately to the answer variables, then the latter was converted into long-form. The two parts were then merged together to achieve the long-form data.  An external key was then used to substitute the numeric values of the variables with their descriptive labels, to make the meaning of the variables clearer. The variables for the answers to the survey questions were on a five-point Likert scale with a sixth category for
```

```
"unsure". After the data was converted to long-form, it was saved to the external file 'HGT
Survey 2019 (Long Form Data).xlsx'.

```{r Extract and label participant data}

#Create participant data frame
PARTICIPANTS <- data.frame(Participant                = RAW_DATA[, 1],
                           Gender                     = RAW_DATA[, 84],
                           Age                        = RAW_DATA[, 85],
                           Education                  = RAW_DATA[, 86],
                           Employment                 = RAW_DATA[, 87],
                           Children                   = RAW_DATA[, 90],
                           Disability_in_Family       = RAW_DATA[, 91],
                           Disease_in_Family          = RAW_DATA[, 92],
                           GMO_Support                = RAW_DATA[, 93],
                           Politics                   = RAW_DATA[, 94],
                           HGT_Knowledge_Self_Rating  = RAW_DATA[, 2],
                           HGT_Knowledge_Test_Rating  = RAW_DATA[, 3]);

#Label values of Gender Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$Gender[PARTICIPANTS$Gender == 1] <- "Female";
PARTICIPANTS$Gender[PARTICIPANTS$Gender == 2] <- "Male";
PARTICIPANTS$Gender[PARTICIPANTS$Gender == 3] <- "Other";
PARTICIPANTS$Gender[PARTICIPANTS$Gender == 4] <- "Prefer not to say";

#Label values of Age Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$Age[PARTICIPANTS$Age == 1]  <- "18-24";
PARTICIPANTS$Age[PARTICIPANTS$Age == 2]  <- "25-34";
PARTICIPANTS$Age[PARTICIPANTS$Age == 3]  <- "35-44";
PARTICIPANTS$Age[PARTICIPANTS$Age == 4]  <- "45-54";
PARTICIPANTS$Age[PARTICIPANTS$Age == 5]  <- "55-64";
```
```

```
PARTICIPANTS$Age[PARTICIPANTS$Age == 6]  <- "65-74";
PARTICIPANTS$Age[PARTICIPANTS$Age == 7]  <- "75+";
PARTICIPANTS$Age[PARTICIPANTS$Age == 8]  <- "Prefer not to say";

#Label values of Education Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$Education[PARTICIPANTS$Education == 1]  <- "No School Certificate";
PARTICIPANTS$Education[PARTICIPANTS$Education == 2]  <- "Middle School/Intermediate Certificate";
PARTICIPANTS$Education[PARTICIPANTS$Education == 3]  <- "High School Certificate";
PARTICIPANTS$Education[PARTICIPANTS$Education == 4]  <- "Trade/apprenticeship";
PARTICIPANTS$Education[PARTICIPANTS$Education == 5]  <- "Certificate/diploma";
PARTICIPANTS$Education[PARTICIPANTS$Education == 6]  <- "University Degree or above";
PARTICIPANTS$Education[PARTICIPANTS$Education == 7]  <- "Prefer not to say";

#Label values of Employment Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 1]  <- "Employed, working full time";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 2]  <- "Employed, working part time";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 3]  <- "Employed, casual worker";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 4]  <- "Not employed, looking for work";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 5]  <- "Not employed, not looking for work";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 6]  <- "Student";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 7]  <- "Retired";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 8]  <- "Not able to work";
PARTICIPANTS$Employment[PARTICIPANTS$Employment == 9]  <- "Prefer not to say";

#Label values of Children Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$Children[PARTICIPANTS$Children == 1]  <- "Yes";
PARTICIPANTS$Children[PARTICIPANTS$Children == 2]  <- "No";
PARTICIPANTS$Children[PARTICIPANTS$Children == 3]  <- "Prefer not to say";

#Label values of Disability_in_Family Variable
```

```
#Correspondence is taken from legend in separate file
PARTICIPANTS$Disability_in_Family[PARTICIPANTS$Disability_in_Family == 1]  <- "Yes";
PARTICIPANTS$Disability_in_Family[PARTICIPANTS$Disability_in_Family == 2]  <- "No";
PARTICIPANTS$Disability_in_Family[PARTICIPANTS$Disability_in_Family == 3]  <- "Unsure";
PARTICIPANTS$Disability_in_Family[PARTICIPANTS$Disability_in_Family == 4]  <- "Prefer not to
say";

#Label values of Disease_in_Family Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$Disease_in_Family[PARTICIPANTS$Disease_in_Family == 1]  <- "Yes";
PARTICIPANTS$Disease_in_Family[PARTICIPANTS$Disease_in_Family == 2]  <- "No";
PARTICIPANTS$Disease_in_Family[PARTICIPANTS$Disease_in_Family == 3]  <- "Unsure";
PARTICIPANTS$Disease_in_Family[PARTICIPANTS$Disease_in_Family == 4]  <- "Prefer not to say";

#Label values of GMO_Support Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$GMO_Support[PARTICIPANTS$GMO_Support == 1]  <- "Not at all";
PARTICIPANTS$GMO_Support[PARTICIPANTS$GMO_Support == 2]  <- "Slightly";
PARTICIPANTS$GMO_Support[PARTICIPANTS$GMO_Support == 3]  <- "Moderately";
PARTICIPANTS$GMO_Support[PARTICIPANTS$GMO_Support == 4]  <- "Completely";
PARTICIPANTS$GMO_Support[PARTICIPANTS$GMO_Support == 0]  <- "Unsure";
PARTICIPANTS$GMO_Support[PARTICIPANTS$GMO_Support == 5]  <- "Prefer not to say";


#Label values of HGT_Knowledge_Self_Rating Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$HGT_Knowledge_Self_Rating[PARTICIPANTS$HGT_Knowledge_Self_Rating == 1]  <- "Never
heard of it";
PARTICIPANTS$HGT_Knowledge_Self_Rating[PARTICIPANTS$HGT_Knowledge_Self_Rating == 2]  <- "Couldn't
explain";
PARTICIPANTS$HGT_Knowledge_Self_Rating[PARTICIPANTS$HGT_Knowledge_Self_Rating == 3]  <- "Explain
a little";
```

```
PARTICIPANTS$HGT_Knowledge_Self_Rating[PARTICIPANTS$HGT_Knowledge_Self_Rating == 4]  <- "Explain
clearly";
PARTICIPANTS$HGT_Knowledge_Self_Rating[PARTICIPANTS$HGT_Knowledge_Self_Rating == 5]  <-
"Extensive knowledge";
PARTICIPANTS$HGT_Knowledge_Self_Rating[PARTICIPANTS$HGT_Knowledge_Self_Rating == 6]  <- "Unsure";

#Label values of HGT_Knowledge_Test_Rating Variable
#Correspondence is taken from legend in separate file
PARTICIPANTS$HGT_Knowledge_Test_Rating[PARTICIPANTS$HGT_Knowledge_Test_Rating == 0]  <-
"Incorrect";
PARTICIPANTS$HGT_Knowledge_Test_Rating[PARTICIPANTS$HGT_Knowledge_Test_Rating == 1]  <-
"Partially Correct";
PARTICIPANTS$HGT_Knowledge_Test_Rating[PARTICIPANTS$HGT_Knowledge_Test_Rating == 2]  <-
"Correct";

```
```{r Create long-form data}

#Create answer data frame
#We only extract questions of interest in the analysis
#Some questions are omitted due to methodological decisions
ANSWERS <- RAW_DATA[, c(1, 6:9, 14:16, 20:22, 26:28, 32:34, 38:43, 50:53, 58:81, 83)] %>%
           gather(key = 'Question', value = 'Answer', -Participant);

#Create long-form data
DATA <- merge(PARTICIPANTS, ANSWERS, by = 'Participant');

#Create variables for main question and subquestion
LAST_CHAR <- stringr::str_sub(DATA$Question, -1, -1);
DATA$Main <- NA;
DATA$Sub  <- NA;
for (i in 1:nrow(DATA)) {
  DATA$Main[i] <- ifelse(LAST_CHAR[i] %in% letters,
```

```
                          stringr::str_sub(DATA$Question[i], 2, -2),
                          stringr::str_sub(DATA$Question[i], 2, -1));
  DATA$Sub[i]  <- ifelse(LAST_CHAR[i] %in% letters,
                          LAST_CHAR[i],
                          NA); }

#Move answer to last variable
DATA <- DATA[, c(1:12, 14:15, 13)]

```
```{r Show structure of data}

#Save to xlsx file
write.xlsx(DATA, 'HGT Survey 2019 (Long Form Data).xlsx');

```
```{r Show structure of data}

short_str(DATA);

```
The data frame ```DATA``` showed the data in long-form, so that there was one row for each question for each participant. The data frame contained `r nrow(DATA)` observations with `r ncol(DATA)` variables. This included the demographic variables for each participant, plus other covariates, plus the question being answered and the answer given. To assist with referencing the questions variables ```Main``` and ```Sub``` were also included to show the main question and subquestion (e.g., for question ```Q12c``` we have ```Main = 12``` and ```Sub = c```). Once the data was in long-form it was able to be fitted with a standard statistical models to describe the answer as the output.

#STEP 2 - MODEL THE DATA
```
```

In this section a cumulative-link mixed model was fitted to the long-form data. This model form was designed to deal with regression data that has an ordinal output variable, with an allowance for random effects in the model. It was able to model the ordinal answer on the Likert scale as the output, with the participant variables and the question as inputs. To allow for within-participant correlation between answers, the model included a random effect for each participant.

In order to fit the model, the data was first filtered to exclude all answers of "unsure", which left answers on the five-point Likert scale. This was set as the ordinal factor variable, with numeric values in increasing order. It was noted that answers to the questions were coded consistently to ensure that a higher value reflected greater support for the use of HGT and a lower answer reflected less support for the use of HGT. Therefore, the order of the output was comparable between questions. The model formula was set and fitted the model to the model data.

```{r Model the data - Ordinal logistic regression model}

#Filter to model data
MODEL_DATA1 <- DATA %>% filter(Answer %in% 1:5);
MODEL_DATA1$Answer <- factor(MODEL_DATA1$Answer, levels = 1:5, ordered = TRUE);

#Set model formula
FORMULA <- formula(Answer ~ factor(Gender) + factor(Age) + factor(Education) + factor(Children) +
factor(Disability_in_Family) + factor(Disease_in_Family) + factor(Politics)+
factor(HGT_Knowledge_Self_Rating) + factor(HGT_Knowledge_Test_Rating) + factor(Question) + (1 |
Participant));

#Fit cumulative-link mixed model
MODEL1 <- ordinal::clmm(FORMULA, data = MODEL_DATA1);

```
```{r Print model summary}
```

```
summary(MODEL1);

```
As an alternative and simpler model, a linear regression with a random effect term was fitted. This latter model treated the answer as a continuous random variable on a ratio scale. This was not ideal, but was a simpler model, and provided a superficial look at the relationships between the variables.

```{r Model the data - Linear regression model with random effects}

#Filter to model data
MODEL_DATA2 <- DATA %>% filter(Answer %in% 1:5);

#Set model formula
FORMULA <- formula(Answer ~ factor(Gender) + factor(Age) + factor(Education) + factor(Children)+
+ factor(politics)factor(Disability_in_Family) + factor(Disease_in_Family) +
factor(HGT_Knowledge_Self_Rating) + factor(HGT_Knowledge_Test_Rating) + factor(Question) +
(1|Participant));

#Fit model
MODEL2 <- lmer(FORMULA, data = MODEL_DATA2);


```
```{r Print model summary}

summary(MODEL2).

```

Appendix H: Nested ANOVA R-Markdown Code

```
> library(ggplot2);
> library(tidyr);
> library(dplyr);
> library(stringr);
> library(openxlsx);
> library(MASS);
> library(lme4);

#Set the working directory
setwd("C:/ ");

#Import the data
DATA <- read.csv(file = "Chronic Disease Long Form.csv", header
= TRUE);
DATA <- DATA %>% filter(Answer %in% 1:5);

#Generate models (excluding participant factor)
MODEL1 <- lm(Answer ~ factor(Severity) + factor(Survey), data =
DATA)
MODEL2 <- lm(Answer ~ factor(Severity) * factor(Survey), data =
DATA)

ANOVA <-  as.matrix(anova(MODEL1))
ANOVA

#Conduct ANOVA comparison
anova(MODEL1, MODEL2)

#Generate models (including participant factor)
MODEL3 <- lm(Answer ~ factor(Participant) + factor(Severity) +
factor(Survey), data = DATA)
```

```
MODEL4 <- lm(Answer ~ factor(Participant) + factor(Severity) *
factor(Survey), data = DATA)

ANOVA <-  as.matrix(anova(MODEL3))
ANOVA
```

Appendix I: Online Australian Survey Feedback Section

1	My understanding of the ethics of human gene therapy is that, like almost everything in science, human gene therapy is a tool that can be utilised for good or for harm. It's probably pretty hard to capture those shades of grey in a survey...
2	I have been waiting 12 years for Gene Therapy to treat my PD. I feel it is the only complete cure for this and many other dibilitating diseases
3	Bring on science
4	Good luck with your study
5	The questions with a range of radio buttons (completely acceptable, etc,) didn't seem to resize to browser window very well.
6	no
7	Human gene therapy has the potential to radically improve the survival rates of those affected by a great many conditions that at present are life altering or life ending, however the benefits need to be available to all, not just economic or geographic elites. Also, its use needs to be considered and careful given what is being altered. Side effects and benefits need to be monitored in terms of decades, not days weeks months.
8	I suspect human gene therapy will become essential to the continued survival of the human species, for better or for worse.
9	This survey was well presented and clearly worded. However, there were some questions (7-12?) that did not make it clear whether the question pertained to changing somebody else's genes or changing your own. My view changes considerably based on this distinction - i do not believe anyone has the right to modify other's genes, but if you choose to modify your own then it's little more than plastic surgery at a gene level.
10	I think it is another option to add to the arsenal - I don't think it is the magic bullet however and ere is so much we don't know that if we target a defective gene is it inadvertently targeting something else as well.
11	My main reason for rejecting the use of gene therapy for enhancements is that there is no way it will be a government supported procedure, as it has no medical applications. I'm concerned that this would mean only wealthy individuals would have access to this treatment and middle/lower class would not. Not to mention the extra issues that would arise in professional sporting
12	Must exercise extreme caution so HGT is not exploited and has strict regulation. No privatisation of it. Not an option that only wealthy people can afford.
13	Science education programs need to be ramped up in order to counter the rampant ignorance regarding gene therapy (just look at GMO debates). We also need to get actual scientists into parliament to advocate accurately for technological advances rather than relying on a layman to act as a filter.
14	There will always be risks and benefits. We just need to decide which one weighs heavier.
15	I hope with increasing science communication people can begin to understand the enormity of genetic modification - good luck with your research. Onward and upward!
16	I thinks its a good idea but it needs to b regulated n consider religion.
17	In all advances there is a counter balance. I worry that genetic engineering could be counter-positive to human frailty that makes us empathetic and caring to those less fortunate. The researches shouldn't lose sight of the humaness of us all.

18	In cases of mental or intellectual disabilities, it should be up to the individual, who knows best how this affects them during their daily life, as to whether they want to go through gene therapy. In these cases its hard to distinguish the line between illness and personality. It should not be a decision that they should be forced into.
19	human gene therapy would greatly improve life.
20	I definitely had a lot of caveats when answering. I think human gene therapy should be government subsidised to be used as medical treatments. I don't have any qualms with using it for a medical treatment, except making sure it's the last option because my guess is it would be quite costly for a long time. I think enhancement human gene therapy should *only* be available if it is (probably through government subsidy but we all know that would never happen) financially available to *everyone*. We already live in a world that benefits the rich, if money is the key to enhancement, that gap will only grow. I also think police checks are necessary for physical enhancements like strength. I would be concerned about giving enhancements to people who already use size and status to impose on other people. So in a utopia world, yes, but right now... It's hard to say. I believe that human gene therapy should be used to improve, not extend, lives past a natural age if death. We're already an overpopulated planet, and not doing very much to help care for it, without putting even more stress on it.
21	I am not sure how helpful my answers would be as I know nothing about human gene therapy. I am aware of GMO foods and if it saves people from world hunger then I am all for it. However when there are cases of genetically modified animals living inhumane lives for the benefit of the developed world it makes me extremely uncomfortable. I did click "unsure" for a few questions as I would need to know more about the side affects this would have on the individual.
22	The science is way ahead of regulation. I believe the government should delegate review of the science in this area. A review panel should be made up of experts as well as people within the community. Maybe we could then put their recommendations to a plebiscite or survey with result being binding on the government.
23	We need to be careful not to treat people with interlectual disability as a disease or a problem to be fixed. This is one of my primary concerns in this discussion (such as modifying genes to be rid of Downs Syndrome or Autism) as it is heavily stigmatizing to act as though we need to 'wipe them out'. Additionally, consent would be the major factor in anything to be changed within a person - explicit informed consent.
24	I'm a genomics researcher but have had fairly limited exposure to gene therapy so I feel that my responses might not be that accurate. For me with a lot of genetics/genomics things, I really feel that there is no society standpoint that is valid and that the individual's view is crucial. For example, I don't really agree with gene therapy because it's too new (and we don't know much about the transgenerational effects), but for someone who gene therapy is their only option for a treatment then it may be okay. Not sure if you've watched Orphan Black (it's an SBS sci-fi television show), they have a fairly long plotline spanning multiple seasons about gene therapy- might help your research? That is where I learnt a bit about gene therapy from (along with a couple of undergraduate lectures). I also think care needs to be taken when talking to the public about gene therapy as I believe that a lot of the media hypes research and may misinform public opinion, especially when inidividuals can't discern what's truly represented and what's not.
25	Fantastic survey, well designed, great PLS, good language - well done on a great research project! I've shared the link with other medical researchers (I work in medical genomics research)
26	I would permit gene therapy to treat illnesses/impairment in me on the condition that they had been adequately tested or I was in a last resort scenario.

27	It was hard to answer some of the questions because I have a different view on gene therapy for illness and preventive health strategies vs. gene therapy for cosmetic or enhancement reasons. I support the first and not the second. It seems to me that gene therapy to treat illness is analogous to plastic surgery, which is designed to help people who really need it, whereas gene therapy for eye colour or intelligence is analogous to cosmetic surgery, which is designed to make money and sell people false promises of happiness/love/success if only they look a certain way or have a certain attribute. One area in which I would support gene therapy for enhancement is for space exploration, e.g. improving radiation resistance or bone density retention for astronauts travelling to Mars. I would not support it for sporting or military use, or altering people's racial appearance, although no doubt it will be used these ways unless the way the human race manages our resources changes completely. May I suggest that for future surveys, you use the services of an editor to help clarify the way the questions are written. Some were hard to understand because of double negatives or because options did not have parallel construction. Also, the layout could have been better – I had to scroll up and down several of the longer tables because the labels across the top of the question (completely agree, somewhat agree, etc.) were no longer visible as I scrolled down to the lower items. Running the labels across the bottom of the survey would have fixed this, but if SurveyMonkey doesn't allow this, then making shorter tables is a must. If people can't see the labels any more, rather than scrolling up to double check "Which is the agree end and which is the disagree end again?" they may simply rely on their memory which could be wrong. Best of luck with your research – it was interesting to think about these issues.
28	Human gene therapy would need to be regulated, but by genetic and other experts in conversation with Government officials. There should also be room for those who are desperately willing to undergo untested therapies to help themselves and enhance research into future approved therapies. As for manipulating the whole Australian population - I think of fluoride type things as an example so do not discount whole population manipulation, but it depends on what is the therapy that is in question regarding this. There is also the question of inflicting 'best practice' by health practitioners on patients. Patients should be able to opt in or out. And if opting is a thing then opting out should be assumed unless someone acts to opt in - not the reverse. I would like to encourage this science. Thank you for your work. All the best.
29	Not enough money is spent on medical research in Australia. What research is being done is generally not communicated to the public.
30	I have coeliac disease so I'm hopeful that genetic engineering of wheat or potentially gene therapy can be used to treat my condition. Good luck with the dissertation!
31	Some of the questions were a bit vague. It makes a huge difference whether you're asking about gene therapy for medical treatment for moderate to severe disorders and illnesses vs possibly recreational uses. They are very different. I fully support safe, tested, regulated medical uses for diagnosed patients, with genetic counselling. I do not support anyone being able to buy genetic enhancements. And I especially do not support unnecessary enhancements being given to children. In the case of moderate to severe disease or disability I believe parents should choose for their children but in mild cases e.g. high cholesterol or in the case of enhancements, patients should be over 18 and choose for themselves, after genetic counselling.

32	I think it's important for the human race to get much smarter as quickly as it can so that we can start solving the problems we're creating for ourselves. It's easier to create powerful technology than it is to wield powerful technology, and some of our sciences are nearly at the point where a few rogue or negligent scientists could wipe out the entire planet (bioscience, AI, maybe nanotechnology someday). Our current institutions are pathetically inadequate at addressing these problems, eg. look at how they're handling climate change despite decades of forewarning. So yes, please figure out how to make any embryo a high-empathy genius, then maybe the Chinese or someone will start doing it to all their babies. Having said all that, I think human diversity is important. I don't want to live in a world where everyone is the same because everyone gave their children the "best" genes. A mental illness or personality flaw may suck for the person who has it, but it adds variety to the life of everyone around them. If our society were smarter we could weigh the costs and benefits here, figure out what we value, and come up with some sensible policies. I have no hope of any current society being able to do that.
33	Just a couple of small notes: The intro material says the research is examining the views of Australian citizens, but the inclusion criteria is only that you are a current Australian resident. Only mentioning in case this could be off-putting for some people (I nearly clicked away as I wasn't sure I was eligible based on the first paragraphs). Also, I found myself a little confused about what the definition of 'acceptable' was in the context of the survey (but maybe that's the point - it's all encompassing?). Either way, seems like a very interesting area to be working in and I wish you the best of luck with your PhD.
34	A very well constructed survey.
35	There are ethical issues that arise with gene therapy, and the way that we tackle these will determine whether gene therapy has a positive or negative impact on society.
36	I would like to think that gene therapy would be used to eliminate disabilities and diseases and not to enhance appearances or physical strength.
37	No
38	Most of my answers here were quite neutral as I feel the topic is loaded with nuance and more specific answers would depend on the exact biomedical and socio-cultural nature of the disease or condition that gene therapy might be used to treat. I think social context is critically important to the discussion. Obviously it would be much easier to vote in favour of gene therapy for single gene diseases with very high penetrance that are otherwise fatal than it would be for less severe conditions that have multiple risk factors or low penetrance, but even then if the therapy was low risk then perhaps it would be acceptable. Definitions of risk are also important, as different people/groups will have vastly different opinions of what constitutes a risk. In short, I think it's a very complicated issue.
39	I believe it needs to be closely regulated to protect the weakest or most vulnerable in society.
40	I think it could do amazingly good things, but do not think it should be used for fashionable choices.
41	There is a real sociological danger of human gene therapy to embolden eugenic groups, and descriminate against people with access or ethnic diversity.
42	i am not morally opposed to the idea of HGT however the rate of technological impact science has had upon the earth in the last 200 years has been phenomenal- we should take heed and proceed with great caution
43	This survey is challenging through both lack of specific knowledge of the participant - i.e. I know very little about Gene Therepy - and unformed opinions. I hope this helps progress knowledge!

44	I had to google the term to be sure what you were talking about. I don't know about the pro's and con's, but overall anything that would improve our wellbeing (and cure chronic illness) is a good thing!
45	a cautious and controlled, medically approved approach should be followed
46	Good luck in your studies.
47	Humans try to perfect things that should not always be perfected. Some "imperfections" are there for a reason. Human Gene Therapy could be dangerous as humans will try to play God.
48	I have not spent a lot of time thinking about gene therapy, but this survey really made me think about the ethics of it.
49	we don't know enough about it
50	I don't think we should put animal genes into plants and reverse
51	N/A
52	I know little to nothing at all about gene therapy. Therefore I do not know whether there are implications of human gene therapy and have answered the survey accordingly.
53	This survey made me question many things. As far as HGT goes I find it completely unacceptable to use it to change a trait like eye colour, intelligence etc. It will come down to the fact that those who have money will more likely be able to afford HTG in the future. It will create an ever further gap between the Haves and Have-nots. However, when I think about HGT helping those who are suffering from serious illnesses, I find myself questioning our existence as Human Beings. We are all meant to die at some point. I also think of the economic implications. If you can essentially extend the lives of everyone by fixing most serious illnesses, how will that impact population growth? Will we then have the resources to support that growth? How expensive will a therapy like this cost and will it be available to all? Overall, I am not sure if HGT should be available until all these (and more!) questions can be answered.
54	it's very exciting
55	I found it hard to answer some question as I did not know enough about the research to have a good understanding of the answers
56	Q 22 was unclear as the page changed and it referred to the previous question.
57	Would be wonderful for inherited childhood diseases, for instance the devastating Batten's Disease, which has affected dear friends.
58	Ideally I would need more information regarding a number of the issues posed, if I was actually in a real situation of contemplating human gene therapy. Pros and cons of such therapy versus other options, and it may differ depending on what the medical problems were.
59	I felt like there were a lot of answers I wanted to qualify. A lot of IFs. I find gene threapy fascinating and I think it holds huge promise for relieving a lot of suffering, but I worry about who uses it, and what for. Who has access to it and who doesn't. There are many ethical issues and we need openness, good public oversight, and public debate.
60	Profit motive has and continues to drive science, particularly medical science, down the wrong path. Understanding root causes of disease and living in line with our evolutionary past are the soundest forms of 'treatment' with little or no cost and no negative social or environmental impacts. Over population, technology driven agribusiness and the age of electromagnetic and chemical madness are taking their toll on our health. Declining lifespans will accelerate accordingly until we rely less on scientific breakthroughs and more on the natural patterns with which our genes evolved.
61	Survey was very interesting and has prompted me to be ready to look further into the topic. I'm ashamed to say I didn't know much about gene therapy although numerous of our children have been in inter-school debates on gentically modified crops !!

62	I am very positive about what gene therapy can do for the entire population but it is a consultative and inclusive process of development, management, regulatory, delivery and careful consultation with the community at large. This will need careful consideration and communications because at present the majority do not understand what it means, fear or reject it when it certainly can be used properly to do so much to help people in need.
63	Thank you for this survey. I took biology and chemistry in high school (in NZ) and gene therapy was not in the syllabus. Perhaps this partly contributes to my lack of knowledge about this seemingly interesting and important topic in modern society.
64	I believe that in regard to dealing with disability and illness it would be a boon, in relation to individual enhancement eg sports competition- not in favour, however there maybe future uses that would be acceptable eg space travel - enhancement of bone density or stopping of muscle wastage or longevity
65	Hope the results of this survey will be put positively to the community.
66	Each case needs to considered on its individual merits but once human gene therapy is developed it should be available for people to choose for serious problems
67	I'm not clear about how far-reaching changes to humans would be if gene therapy was restricted to the single patient. This could have an impact on future generations born to that patient, but I'm not sure whether gene therapies that are isolated and permanent can be passed on.
68	My answers are purely academic. I have reason to pause and consider if my answers would be different if I had a family member affected by a serious genetically based disease
69	Please keep up the research we know there are new things happening all the time we need people like yourselves to keep digging until you find it. Thank You
70	I feel there is an important disconnect between my answers that relate to me personally and those about gene therapy generally. I think as an individual were gene therapy to me I would seriously consider availing myself of the therapy to improve my health and wellbeing, however more generally on the topic I have reservations about what this might mean for our future (resulting in a society that resembles a dystopian future like Gattaca).
71	Information and explanation of HGTherapy in the community at large. Public education about HGT via schools and civil society would be helpful
72	Many of my answers were 'unsure' because I simply don't have the knowledge required to offer more definitive answers. I seem to have some sort of aversion to the idea of genetic enhancements (vs treatments/therapies), but I haven't yet spent enough time reflecting on this to know if there's any real moral/philosophical basis for this aversion. More knowledge may make me more or less averse to enhancement.
73	A medical development of this kind needs to be carefully and thoughtfully regulated. Both Government and the medical profession need to be involved. I would not support Medicare benefits for gene therapy to change the colour of my hair etc.
74	no
75	I really don't know enough about it to comment fairly on what I believe the effects would be.
76	This has been one of the most difficult surveys I've done. It points out my almost complete ignorance, and raises sooooo many questions I'd like to discuss (before I answered!). I begin to realise how fascinating and fraught this area is. I begin to realise how much potential there is for good, and also how much potential for harm, or even evil, and therefore how important it is to have constructive community debate about it, and what path we choose (as a community).

77	there is so much suffering in this world, science is rapidly discovering more and more wonderful answers to combat ill health, disability, etc. gene therapy could have a pivotal role in the search.
78	I had to answer "unsure" to a lot of questions as I felt I didn't know enough about human gene therapy.
79	My major difficulty in accepting is its financial cost to the health system and inequity due to affordability. I would prefer medical research to focus on the general health of the population.
80	Human gene therapy has great potential to alleviate suffering but there's also the chance that it will further exacerbate inequalities in healthcare.
81	A lot of the questions I feel need a caveat that it is up to the individual and that their intentions are for good. I believe overuse of medicine is not beneficial (for example over prescription of drugs to people who don't need them. In this case, everyday healthy people enhancing themselves)
82	A lot of my "completely agree" responses in section one assume that there is little risk involved with the therapy (ie. it doesn't have a high probability of mortality). I have said that I think it should be somewhat under government control, so that there are strict regulations surrounding risk assessment etc. I think that there will be a lot of benefit health-wise if gene therapy kicks off in a big way, but that the positive impact may have a negative impact overall on society if we choose to use it for a lot of 'enhancements', and if it should become something that only those who can afford it can access the therapy. This would of course create a very unequal divide. Thanks for the survey, I would love to know the results when complete. :)
83	I think it's an interesting field that I don't have a lot of clear opinions about yet but do expect to develop a better awareness of within my lifetime.
84	No
85	Many of the answers require a nuanced judgment by medical professionals. Regulation should be considered by a panel of suitably qualified members with sufficient knowledge in the topic. There will probably be some side affects from treatment. These will need to be weighed against any benefits. I believe as with most new treatments it will be tried on those with the least to lose and will over time progress to more routine and mundane uses as the technology improves.
86	This is such a new prospect for human health . manipulation for vanity reasons are not acceptable. The cost of care for debilitated people could be reduced and prevented.
87	Find it difficult to give governments full authority when at present they talk about CLEAN coal - NO global warming, and deceive us regarding our admission targets.
88	It's strange - I started answering that I was dead against the using GT to enhance say the sporting ability of a perfectly healthy human (ie good-bye to all meaning behind the Olympics etc), however I struggled to say I would refuse using it myself (being a healthy and moderately intelligent person) if it could increase my memory capacity - something which limits me in my work and frustrates me a great deal in life. Thanks for the moral dilemma! Having said that I am all for preventing/curing/de-symptomising diseases using GT (my son is currently undergoing a trial for the gene corrector drug Orkambi). Good luck with your study.
89	Exciting times ahead w.r.t. this especially as we, as a nation, struggle with equality
90	I would like to know more about the risks to people that human gene therapy has before I totally made up my mind whether I would be for it or not.
91	would like to be better informed about the whole programme, also need more money for research.

92	It would have been useful to provide some more info on gene therapy at the start, for example the risks involved, as it's hard to answer some of the questions without really knowing anything about the topic.
93	When I was studying biology at university a long time ago, there was a wonderful and haunting song that came out covering this topic. I recommend you look it up. Self Made Man - by David Byrne.
94	If it existed, worked, was affordable, it'd potentially immediately improve my quality of life as I have a chronic illness. I'd also be happy to spend money on products to change hair or eye colour to help fund the products that cure diseases.
95	I believe that as long as there are strong ethics around its regulation and use - not created solely or overseen by large commercial entities or governments- that the benefits to humans can be positive and significant. I believe everyone should have a choice as to whether gene therapy is a treatment option they wish to consider and I do not believe that it should be used for general enhancement of humans (ie eye colour etc). As with all technologies, medical or otherwise, its misuse and abuse will occur, to think otherwise is foolish - however I do believe that any ethics body should consist of representatives from an array of backgrounds including technology, medical, government and broader community to ensure a balance of views and to keep all parties in check.
96	Don't know enough about the subject
97	The survey poses many unrealistic scenarios and posibilities for human genetic manipulation, as GM techniques (including new GM- so'called 'gene-editing') can only be used manipulate single gene, not multi-genic traits. So, most of the outcomes that your questions imply are possible will never become clinical or commercial realities. The survey is an unrealistically positive stalking horse for HGT and its supposed benefits to human health. Previous attempts at HGT using the cut-and-paste GM techniques failed, and killed some healthy participants, such as Jesse Gelsinger. Like so-called stem cell 'therapies', egg harvesting, surrogacy, and more - now marketed on the basis of false promises, shonky evidence of efficacy, and minimal care for participants - HGT will also be oversold. It is being developed and deployed by gene jockeys and entrepreneurs with little care or concern for people. Social approaches, such as the pre-marital genetic testing and partner selection among some Jewish and Arabic communities, appears to be a more rational approach to eliminating deleterious genes. Of course, genes can still go wrong and I see no case for attempting gene therapy at any stage from egg and sperm to old age. We are much more than our genes!
98	It is a little odd that nowhere in your survey do you say whether you are talking about somatic or germline gene therapy. Both are just as possible as each other, but their ethical and societal implications are drastically different. Given the questions in your survey, it seems like you are talking about somatic gene therapy. However, since this is never stated, and given the significant recent press coverage of germline gene therapy, I think that many respondents will answer the questions on the assumption that you mean germline gene therapy. Either way, I think the lack of clarity rather calls into question the validity of the results. I would suggest re-running the survey after making it very clear exactly what kind of gene therapy you are talking about.
99	Most of the questions have answers that are highly context-dependent; it’s hard to give unequivocal answers that are really meaningful.
100	Found it very difficult to answer within the parameters without having any scientific understanding of the subject. Although we all want to be healthy and not have to face illness and disease in our, or our loved ones lives, I just wonder what the repercussions of tweeking nature will be in the long run! Healing people is great but how do you answer the ethical dilemmas and how do you keep the technology out of the hands of those who will

	profit from it - human beings do tend to upset the natural balance of things, even if we believe we are doing it for the right reasons!
101	It would be nice to have a hyperlink leading us to the best available background info on human gene therapy
102	Just on survey design, a comments section on each question or page could be helpful (although I understand how absurd the amount of data would be) As most questions I found had "yes, but" or "no, but" answers. Good luck with your research!
103	Im a student studying genetics and hope to be a genetic counselor one day!
104	I believe personal choice here is paramount. I would be against decisions made that will effect the genes of existing people (ie, currently alive people with an existing gene set, not future generations).
105	The power in gene therapy would be used by people for the worst and could not be controlled by someones who is "morally correct" as even governments aren't [Donald Trump]. The pros of curing cancer is good but too hard to control so that it wouldn't be used for selfish purposes.
106	Ticked "Couldn't explain" Then wrote - "manipulating genes to produce required results"
107	I think it would be very important to make very clear exactly what constitutes a disability/ilness and make sure people are always able to refuse. For example, asperges is currently considered to be a disability, which could make it very tempting for people to attempt a forced initiative to 'cure' people of it. However as someone who has asperges, I disagree that it is a disadvantage and would not want it to be 'cured.'
108	Any answers in "How acceptable is it.." that I gave were predicated on appropriate scientific testing and approvals
109	complex subject Several of your questions need a context to be answered yes/no
110	Legalise it completely, let us create a new and healthier humanity.
111	Some of the conditions listed aren't caused by a single genetic change (e.g mental illness), so gene therapy may not be effective as an option in some of these cases; you would require a lot of information about those disease states and expression of other factors in order to pull off gene therapies / needing a full genome sequence of an individual (because some disease manifest through multiple pathways). This could become quite costly, especially when we're talking about things that are more 'optional' e.g. enhancing traits rather than curing diseases.
112	I believe the future looks bright in terms of technological developments, however, it is a very fine ethics line we walk on. Who decides where gene therapy can used? Is it 'un-natural?'. Do we have a right to intervene with evolution? Personally, I believe it should not be used for cosmetic purposes and only used where it can improve a person's quality of life, but not influence the genetic pool of future generations. I say this because I wear two 'hats', firstly I am a science student and see this technological development as an interference with nature. These mutations often prevent deleterious alleles and mutations from being passed on to future generations. However I am also a human being and know that I personally or someone I was close to, or anyone I see suffering as a result of a debilitating illness I would want to see their quality of life improved by whatever means possible. In my mind, the compromise between my Darwinian view on the world and also being an empathetic and compassionate human being is to only apply gene therapy to diseases and medical situations where the alterations cannot be inherited. Great PhD, really interesting topic to discuss. To note: this is a topic readily discussed and included in high school science courses, particularly VCE biology so more and more students are becoming educated on this topic.
113	Should be restricted to curing and prevent disease/illness/disability for as long as possible before it unavoidably starts being used for physical/intellectual improvement.
114	no

115	I believe I am perfect even with my disability. I am already under great pressure to take various medications that I do not want to take and I am certain that the pressure to have gene therapy would be added to that. When I say pressure I mean doctors unwilling to help me with other things if I don't take the medication they have prescribed. And I'm not talking about a mental illness. I don't need medication I need time and money to do the exercises that I need to do for my health. And there it is. Time and Money. Why should the government support someone who isn't as fast or strong as everyone else. Gene therapy or euthanasia? Maybe I would take the gene therapy.
116	Tooooooovllooonnngggg
117	Wonderful medical tool requiring stringent ethical scrutiny. This is the reason why I am passionate about this survey.
118	All gene therapy, as with all medical treatments, should be done with the full informed consent of the individual, unless the gene therapy is to treat a condition that is preventing them from giving consent.
119	Some of the responses are a little limiting, for example I would only worry about 'evil' use of gene therapy if there weren't strict regulations in place, so answer depends on further information being available
120	Why does your institution feel it necessary to ascertain the level of public support for gene therapy? Are the lives of the sick, disabled, and dying up to public discussion now, do we have to have some Q&A style television show in order to ascertain whether someone should live or die? When my sister was dying of leukemia was her anti-cancer medication a subject that the Australian people have a right to decide?
121	Make it a reality please, I just swapped to this field of study.
122	Biotechnology has not made groceries cheaper for consumers (has it made multi-national companies richer?). Therefore, I only support heavy regulation and Government-only administering/delivery of gene therapy (to avoid discrimination eg poor, remote, or uninformed sectors of society). In other words, gene therapy delivered by a fair/equitable government-controlled/delivered method is the only solution.
123	Genetic engineering of crops is not human gene therapy so it's really weird to include it in the survey. It's not even good for a baseline of a person's attitudes towards genetic engineering, because all that Monsanto bad press would be nothing to the outcry if they started pulling those tricks on people who have rights, and certain country folk might be for increased crop yields but against their children being made needlessly infertile.
124	I think it's important to ensure that human gene therapy can be used by anyone. Not just rich people or those who are able to access these facilities. We should not allow further intensification between socio-economic levels
125	I note that my responses about where therapy would be acceptable are probably coloured by my own experiences with particular illnesses/disorders (I think there's more likelihood to support a potential solution when it relates directly to your own circumstances)
126	The potential for human development in this area is phenomenal, that opposition exists seems largely political than practical. Please make gene therapy available as quickly as possible
127	My only issue with human gene therapy (admittedly from a relatively uneducated perspective) is the potential for it to exacerbate existing inequalities. Economic inequality is no doubt a terrible thing, but inequality of raw physical and intellectual ability would signal the onset of a true dystopia. This cannot be a luxury for the rich. Human gene therapy should be implemented with a strict equality driven agenda or not at all.

128	When asking whether human gene therapy would impact society positively or negative there should be an answer for some of each, because I believe there would be relevant negative consequences as well as positive results. I also believe firmly that we shouldn't play God over evolution and modify our genes in such a way that poor diet and exercise wouldn't have any consequences, or to enhance traits such as athleticism or intelligence, because we are only humans after all. The complete control over our abilities would remove the sacredness of life.
129	Some questions were unclear to me. ie: does treating terminal illness indicate curing or mitigating?
130	The appropriate care needs to be taken by consenting people and their doctors, with some amount of regulation but no-one should be deprived of access to medical treatment.
131	Please cure my insufferable autism :(
132	Very difficult to answer. On the one hand I am highly optimistic about the benefits of human gene therapy if used well, on the other I am quite pessimistic about our society (runaway capital) and it's ability to make thoughtful, educated ethical decisions and providing fair access to technology when there is the lure of making huge profits.
133	Has the potential to be the next life changing discovery but at the same time could be just as detrimental if left unchecked. It has a place, but there must be boundaries.
134	Read Homo Deus.
135	If gene therapy could cure my illness I would jump at the chance!
136	My son has Type 1 Diabetes and I would love it if a cure was found.
137	I believe human gene therapy should be researched and pursued because it has the potential to greatly improve the lives of people living with chronic diseases such as cystic fibrosis or diabetes (or even spinal injury?) and to prevent disease such as inherited cancer or even cure cancer. There needs to be regulations, though, to make sure it is used appropriately and not for frivolous purposes such as eye colour and athletic performance.
138	Thanks for this. It's plain that I need to read up more if I'm to have any real clue about this. I've not maintained my sci knowledge at any high level despite enjoying it years ago, and have also forgotten *loads* of what I knew. I simply don't have enough understanding of the issues to ask the right questions or properly assess the info. (Of course, it's possible that many of my answers would still be "unsure" even if I did know!) Thanks for this opportunity to have a think about it.
139	May human gene therapy lead the way in treating and preventing serious and painful illnesses that effect my loved ones and all others that suffer
140	The survey is very broad and it was hard to answer questions categorically as there are so many "depends on" involved.
141	We only fool ourselves if we think we can fool nature. You won't find a parent of a disabled person that would change their child or whose child doesn't bring them immense joy. There are great risks if we endeavour for "the perfect human". As any scientist knows, the universe exists is chaos. Homogeneity in the human population (which is essentially the ultimate ability of HGT) is both boring (!) and potentially dangerous.
142	Like any other potent tool, gene therapy requires extemely careful consideration of practical & ethical implications. Used well it will be a boon. Used badly, a disaster.
143	For me this research is a lifeline, as a Brca2 carrier I live in hope that within the next 10 years there will be a pill or injection that my daughters can take to prevent the early onset of cancer. I don't want them to live in constant fear, where their only options are cancer or prophylactic surgery.
144	Religion should not be allowed to play any part in this. We must not allow myth to be involved in reality.

145	Like all things, there should be continual research into this field and Government regulation in some way. The benefits on society of gene editing cannot be understated and more people need to understand these benefits.
146	Therapy would have the most benefit in treating illnesses that have ongoing or deteriorating physical health eg diabetes or other conditions that have a impact on the persons ability to live and interact in society eg autism. This is provided that all conditions could return the beneficiary of the therapy to a relatively normal life style without further intervention after a period of rehabilitation. Chronic conditions from the affect of the disease that cannot be reversed have to be accepted ie peripheral neuropathy with diabetes but gene therapy would prevent further exacerbation.
147	I would prefer to be able to qualify some of my answers. Q15b is ambiguous, are the children existing or unborn?
148	Good on ANU for tackling this subject and offering the community a say via this survey. Regulation is really really important in this early stage of research so that manics (corporations) don't go crazy with it.
149	Like the many human fabrications of which the species has little if any understanding, there will undoubtedly be serious unforeseen consequences resulting from the introduction of human gene therapy. But that will not stop persons, whether natural or corporate, and their efforts to jump onto the gene therapy bandwagon. There is just too much money and prestige at stake when measured against the immaturity and short-sightedness of those involved. This survey being a prime example of such behaviour.
150	Some of the questions are currently difficult to answer as it is unclear if they are referring to the application of genetic modification to (i) disease management (e.g. diabetes) vs (ii) trait improvement (e.g. physical strength). An example has been copied out below. As such, you could be getting a biased answer as individuals moderate their answer to cover both concepts. The benefits of human gene therapy will be greater than any harmful effects it may have
151	Human gene therapy may be a threat to drug companies and how this plays out in the future may not reflect best practice medicine. This is a tricky area that requires consultation with all interested stakeholders and a sensible, directed debate without bringing religion into it.
152	Yes. A Quora participant sent me the following question: In the future will cancer and all other progressive diseases be cured by using molecularly precise, unique medicines that target the defective gene? This was my reply: It is certainly stimulating to read stories about treating cancer and other diseases by looking at the most minute targets. It is science fiction and it will always be until the microscopes are pointed to relevant targets —that is— the ballistic attack Dr Body endures each 24 hours. Health is relentlessly blown to smithereens while so many scientists are looking away. Health is vanishing and no one takes notice. What are the causes? Many indeed, and they must be rendered useless by a healthy lifestyle Dr Body really likes. By physical activity that it likes. By nutrients the doctor really identifies and takes advantage of. By allowing it the very necessary daily period without feeding, to tidy up shop and restore power. That is what it needs to smash the disease demons and let us move on full of energy. Dr Body is wise enough as to react in a positive way when the health bits have been properly applied. The proposed way to teach Dr Body how to use the immune system more strongly or efficiently is akin to teaching the earth to give us longer days. Science fiction will always be attractive. In the meantime, we'd better recognize that if Dr Body is treated with respect, health and vibrancy will ensue. Look at the causes of disease and dispose of them first. Later, point all the microscopes and telescopes in any direction and enjoy the chimera trip. I hope one day academia grants HEALTH a science degree, to produce health schools to run parallel to the medical ones.

153	I think it would be better if many of the questions could be rated positively, but only if proper control and supervision measures are in place.
154	I do query if natural selection is almost removed from the equation, how social policy should be framed and prepared to ensure ongoing support for citizens with the longer lives we are living and the increasing prevalence of lifestyle diseases. I also wonder if it will contribute to the ongoing 'instant' lifestyle we live, given if we can repair or treat anything, that the consequences of actions will not be considered.
155	Very glad you asked question about subsidies so available to all citizens, not just the people with $
156	One of our children developed Diabetes Type 1 at the age of 21 despite living a healthy athletic life beforehand. Any help including human gene therapy so she does not have to inject five times a day would make a great improvement to her career as a health professional.
157	Companies shouldn't be able to copyright or own genes. Companies shouldn't be able to copyright genetic drugs. Or maybe the copyright should become open-source after 5 years so as to limit monopolies.
158	The human race needs to truly understand what they are playing god with before making changes and how will these therapies change the generations in the future?
159	Fully support for disease treatment but not for athletic enhancement.
160	Education about the uses, benefits and problems of gene therapy needs to be undertaken through schools, print media and social media before human gene therapy is implemented. Laws and protocols need to be established by professional organisations, government agencies and community groups before human gene therapy is administered.
161	I believe it will have a positive effect on how illness/diseases are treated in the future
162	I am opposed to the use of human embryos for experimentation even if it could save my life or that of a member of family or improve the health of self or close member of family.
163	My concern is that if Gene Therapy is legalized it could easily be misused and we could become another Hitler state. I think it could be useful if it was beneficial for managing terminal illness but should never be used to make a person more handsome or athletic.Wheat has been highly genetically modified and the farmers are paid according to the gluten content of the grain.The higher the gluten content the less tolerable it is as a food source for humans and this is creating more medical issues that wouldn't be issues if the grain wasn't modified in the first place.If there are some genes that can be successfully modified to allow a baby to live a normal healthy life and the recipient can't pass the offending gene into the next generation ie ending the line of disease then it may have a place.While I don't believe humans have the right to play God I think that gene therapy could have a very restricted and useful place in medicine but definitely not in food.
164	I'm torn between thinking in would be incredible to be able to personally make modifications to yourself (the idea of self directed evolution) however i feel it would need to be heavily regulated as i could see it being abused for competitive advantage or in other negative ways
165	Am very interested in the subject, although at the age of 88 I very much doubt that it could affect my longevity even if available to me.
166	good luck!
167	only use the safest technology CRISPR is not ready for human trials yet CRISPR dangerous for off target effects only use ZINC FINGER NUCLEASE for safe and stable effects in gene editing

168	We are at a dawn of a new beginning with gene editing and therapy. Companies like Sangamo Therapeutics have already started in Vivo testing in rare diseases. If successful they will move in pediatrics and EMA is supporting them to move quickly. They plan to tackle rare diseases but their zinc finger nucleus can be used to potentially cure Alzheimer's and HIV. This would also be a start not an end. Once gene editing is mastered we can then edit those genes that cause us to age. That might be hard for people to accept the fact that death through aging is a disease which can be cured. Our society will be looked upon by future generations as primitive (cavemen) for not having embraced gene editing's benefits earlier. Good luck with your studies.
169	Human gene therapy and editing will inevitably be considered a threat by close minded religious people as it will be hard for them to accept the new reality that indeed there are cures not involving miracles, and we might not need to die if one can afford it (the cost to modify all the genes and the cost to live an extended life). Social upheaval will be inevitable.
170	I think gene therapy is worth trying in somatic cells to reduce disease burden for an individual but definitely not in the germ line cells. We don't know enough about the long term effect of changing the germ line. Also such diseases as sickle cell anaemia and thalasseamia are "protective" against malaria so we need further research to find out what could happen to a population if we eliminated these conditions entirely
171	Germline therapy must be highly regulated
172	If it helps with Multifocal Motor Nueropathy then I am all for it. Plasma treatment is good but not a permanent solution
173	I think gene therapy for the eradication of disease that is painful, degenerative or potentially terminal is great. When it comes to modification due to aesthetic preference or to gain advantage is morally wrong.
174	A lot of my answers were 'unsure' because the questions were asked in a vacuum. I'd need to know things like how much gene therapy costs, what sort of regulations would surround it (these are probably hypotheticals at this point though) before being able to form solid opinions.
175	There must be long term, rigorous studies to examine the effects of gene therapy before it is widely deployed.
176	There are a lot of grey areas. More reseach and ehtical medical guidance is needed to inform government regulations around future use. In regards to treating mental illness and intellectual disabilities the impact on personalities are of concern to me, and I have trouble conceptualizing how research into this issue could be ethically undertaken.
177	I have ethical concerns about the whole idea of perfection and the need to alter our bodies accordingly. Our fear of death results in the pouring of enormous amounts of money into medical technofixes. The money spent would be better diverted to ensuring all people have access to a hospital bed when they need it, rather than propping up a few people who can afford private health insurance.
178	My opposition to GMF and gene therapy is based on the precautionary principle AND a profound distrust of genetic reductionism. Epigenetics tells us how wrong we have been.
179	Really interesting topic I hadn't previously considered. In short, I believe gene therapy should only be used for severe disease. However, if the disease is end-stage/fatal, then I do not believe we should intervene. However if there is years of suffering/struggle ahead for the individual - then for the sake of improved quality of life, gene therapy should be used in my opinion.
180	I think this type of science is inevitable and of course some is already being used. While society will be more accepting of using genetic therapy for the cure and prevention of disease there will come a time that genetic modification for enhancing humans will be like plastic surgery is today. I just hope that it is available to all citizens at a subsidised rate so as not to create a greater divide between the rich and poor.

181	Having inherited a chronic and (currently) incurable disease that affects many people, I am so excited that gene therapy will soon transform the lives of people living with this disease. Human trials are suggesting that the disease can effectively be cured. We've been waiting a long time to see any real results so this is just very, very exciting.
182	I think the public should be able to talk about this as it affects everyone. It is too important not to talk about it with the community.
183	It has positive and negative benefits but it all comes down to the users. If the ones with the money and power get free rain then it could cause the potential to widen gaps between the poor and rich. On the flip side to ensure children and free from genetic diseases such as CF, downs etc would be a blessing.
184	I don't believe in stopping people from dying - my concern with these therapies is that they extend life without considering the social consequences of this extension. I have worked as a medical research scientist and understand just how limited our knowledge about consequences is.
185	I think consent is a major factor in this kind of discussion. Medical treatment can already be administered without consent, and not always to the benefit of the patient. The potency of gene therapy renders it prone to abuse in this way. Also I think public perceptions regarding intellectual and physical disabilities would need to be taken into account when publishing scientific research into gene therapy such that it doesn't become a new avenue for prejudice against an already heavily oppressed population.
186	I would hate to see it used the way that plastic surgery is used, now, where the skills and knowledge of doctors (mainly trained with money from the public purse) is wasted on the rich and/or stupid for superficial cosmetic surgery when there is such a need for their skills by other people who need corrective surgery to live reasonable lives. I would hope that it is something that can benefit people in developing countries as well as those in first world countries. Regulation is going to be very important - perhaps by an international body and one that is truly democratic and not influenced by industry or religious cranks.
187	Human Gene Therapy is a very difficult topic to discuss, like most scientific advancements are in terms of morals and where to draw the line. I believe research should continue into gene therapy, obviously it must be done extensively to ensure if it is eventually used, the effects would be positive and the side effects would be minimal. Regulation is definitely required. The uses of gene therapy should only be for prevention or to work against physical/mental illness and not as a way to advance a person in life/society (more intelligent). I think most important, is that nobody should be able to consent the use of gene therapy on a person, except that person themselves.
188	Science communication of new technologies needs to market the information to the masses in a way that is understandable to the layman, that is relatable and informative in order to make accurate information readily accessible and understandable to combat misinformation.
189	I have some concerns about the science, and whether it is tested enough o know what problems there might be. But the majority of my hesitations are about use of, regulation of and equity of access to the technologies.
190	The prospect of gene therapy providing cures for bleeding disorders directly affects me and I find this possibility very encouraging. I'm also excited about other illnesses can be cured in future over time.
191	Government inertia and regulation appears to hold up all medical procedures in Australia, e.g. keyhole heart surgery, stem cell treatment and many drugs that are used successfully throughout the world. Medical professionals that i have spoken to consider that Australia is 10 years behind.

192	Experimental gene therapy in the past three decades has seen spectacular failures due to haste, poor controls and regulation and over-confident researchers in the US. The work China is now doing with Human ES cells should be carefully monitored for both controls and results, if possible. Gene therapy using human ES cells will be part of the future, and rigorous controls on its us must be a concomitant. Millenia of horrendous illnesses should not be accepted as the norm if we can do something to ameliorate suffering, especially of children.
193	I have mild Hemophilia A, as does my two daughters, my mother, my brother and his two daughters.
194	I strongly support the use of gene therapy for people who have Haemophilia.
195	Please cure Haemophilia
196	Very positive about adult stem cell research, not positive about embryonic
197	All stakeholders need to be involved in regulatory process
198	I am a haemophilia A carrier, I have seen two brothers die from this and have also lost an uncle, my one remaining uncle has hep c through no fault of his own. I have a nephew with haemophilia and in my family it is classified as severe. My daughter is a carrier and two of my granddaughters possibly are as well. I have had a life that has been hard I looked after my siblings because we lived in the country and the nearest treatment hospital was in Adelaide. Unless you have had to deal with life and death you do not know the heartache of losing someone you love to pain. Anything that can make future generations cope and be pain free is a miracle in my eyes.
199	Hoping for rapid advances - we have haemophilia in our family and are excited by the prospects of a cure through gene therapy.
200	If gene therapy is used in certain cases the participant must be made aware of the outcome would be. Including any likelyhood of negative results. Participants full kowlege and permission plus, strong guidelines on where when and how it can be used.

Appendix J: Australian Capital Territory Mail Out Survey Feedback Section

1	I feel that if we can use human gene therapy to successfully treat genetic diseases, and that treatment becomes available to all Australians who need it, then that overall is a good thing. However, I do not support its use for "enhancements" in people who are otherwise well.
2	I would not personally have gene therapy as I am retired and prefer to live out my life with as few medical interventions as possible - less risky
3	Careful consideration and discussion around what is 'normal' needs to be had when thinking through these issues. As does the possible affect on health systems (in terms of cost as well as living longer).
4	I think we should get public opinion like this to help with making a decision on going ahead with gene therapy
5	It's not the existence of new technology that's problematic, it's the availability. Technological advances, like all resources of value, are unfairly distributed and will continue to be so. Nothing in the nature of gene therapy recommends it as more harmful than other technologies (especially considering technologies designed to cause harm, like guns and bombs).
6	I think our society needs to consider any options that improve the quality of our lives but I expect the government to heavily regulate any new technology that carries risk, particularly something like gene therapy. The risks, both to individuals and broader society, need to be understood and communicated before they should be accepted by society. Societal needs can override individual needs. I also have concerns that other countries will be more relaxed in their approach which could also impact on humanity. An 'arms race' of genetic modification would be a bad outcome so I'd hope (perhaps optimistically) that a global consensus forms around how it is regulated.
7	I would be interested to learn more about HGT as it appears that it could be extremely beneficial to many people who have diseases and illnesses as a result of faulty genes.
8	I am for gene therapy as a medical intervention, as long as it undergo rigorous testing and regulations. I believe enhancing healthy humans will increase the class divide even further (weathly families will be able to afford gene technology to make their kids smarter, more focused, leading to more success and wealth, as one basic example - not to mention worsening body image issues if we start selecting physical traits) and could have quite large negative impacts for society.
9	No
10	To my mind, most answers to most questions would depend on the age of the patient
11	As a species, we can manipulate our environment so we can manipulate ourselves. In the near Just to be able to get rid of diseases, disorders etc is such a huge bonus. Why should anyone suffer when we have a possible means to do good. Looking further down the path, increasing human life spend as an example will be a game changer. It'll transform our society and what we do. As we expand out from Earth, we will change as a species. Things like Gene therapy will assist our adaption to those environments.
12	Tread softly!

13	Gene therapy has the potential to revolutionise modern medicine and provide a range of interventions to significantly improve the health of many people around the globe. Unfortunately with such power - it is inevitable that this can also exacerbate the growing divide between the world's poor with limping public health services and those who can afford whatever they want. Such people with means can travel to countries with lax standards (as with plastic surgery) might go to extremes with interventions that may not all be 'therapy' but some bizarre concept of self-improvement/alteration. Other areas of cocnern = what happens when dodgy operators accidentally insert undesirable genes or edit out things they shouldn't? Could our courts fill up with more medical disasters? Science cannot always predict outcomes of interventions - expect the unexpected. For example, GM mosquitoes that were supposed to be mutant and infertile actually reproduced and genes escaped into the wild community in South America. What would happen if this occurred in human populations? Furthermore, we still do not fully understand the inter-locking complexities of the immune system, its regulation and how genetic engineering in this sphere might cause unintended seriously undesirable outcomes. e.g. we barely understand the science of gut health, genes and immune function. Therefore: proceed with caution and with as much rigorous testing as possible please. The other area for concern is that people/countries with wicked intentions could use such technology and vectors such as insects to wipe out or injure whoever they didn't like. In this way, selective gene therapy could be used on citizens against their will and to their detriment - what a terrible thought. How does the world plan to protect people from this kind of harm?
14	I think that gene therapy promises amazing advances in medicine, but am concerned about some of the ethical issues raised, including eugenics.
15	I strongly disagree with parents changing the sex of a child i.e. under 21 or attempting to change or alter certain physical characteristics of an unborn child
16	I think it was a good survey. gene therapy should benefit those who need it and not be done just to enhance ourselves
17	I feel cost is a significant factor in the use of gene therapy.
18	Really interesting survey and brought to life my feelings about the benefits of gene therapy. If it helps for example people with disabilities cancer suffers or prevents from happening its a no brainer for me!
19	There needs to be balance between the freedom for researchers to do the work they need to do, ethical considerations and a robust regulatory environment.
20	Will like to better understand Human Gene Therapy
21	It must be regulated ASAP as the technology develops so fast. ELSI research is extermelly important.
22	N/A
23	Request for email address undermines anonymity :)
24	I think there are elements missing from the questions and/or preamble about consent, effectiveness, risk:benefit and cost:benefit, the inclusion of which would allow me to make more definite answers.
25	this is really thought provoking!
26	Genetic variations are nature's way of controlling population. This occurs throughout nature. For genetic issues that are severe and not particularly viable with life it should not be interfered with. Gene therapy should be used to help alleviate negative symptoms in those who will generally live a long life.
27	no.
28	Some of the questions were too basically worded, open to interpretation. The question about "moral duty" seemed odd. There is neither a duty nor a moral obligation to apply new technologies. They must be weighed on their merits and in the case of medical technologies,

	must be examined in the context of individual circumstances. The cost of gene therapy compared to other possibly alternative treatments was not addressed in the survey. In the case of mild disabilities such as ADD, the issue of whether this was treatable by gene therapy was not addressed.
29	The reason I slightly disagree with Human gene therapy aside from the fact it plays god is that I believe the quality of life will drop because the planet has the potential to become over populated thus an increase in pollution being the only reason.
30	My views on gene thearpy is as follows. I understand that there is significant flaw in the field of medicine and treatment of illness. This is that the symptoms of the illness are being treated not the cause. For example a large portion of cancer can be prevented by changing lifestyle habits i.e. eating cleaner foods and exercising. However the medical field tries to invent new ways to treat cancer and not push policies to reduce the ease access to unhealthly food or push large scale awareness of having an healthly lifestyle. This also applies to heart disease. Gene therapy should be used in the situation were a lifestyle change cannot avoid the diease and its nature is uncontrolled e.g the small percentage of cancer cases that prevail after rigiourous lifestyle change. Gene therapy should not be used to justify our current lifestyles. How are we justifying it? By creating quick fixes for the symptoms of illness and not the root cause/reason for illness.
31	I think using human gene therapy to cure or prevent life threatening disease and illness is a natural progression in our scientific endeavours. However, I don't like the idea of using it to modify peoples eye colour, hair, height, general intelligence... I'm not sure. Hard to know where to draw the line?
32	HGT offers such great potential to improve all human lives. However, it's potential benefits (especially for non-theraputic purposes i.e genetic enhancement) mean that I am concerned that only the relatively rich will be able to enjoy its benefits to the fullest, ultimately leading to an increasingly divided society a la GATTACA, a movie I'm sure whoever is reading this is aware of :) Also if rich people live too long and endless accumulate wealth I'm not sure the economy would hold up. Cool survey and an exciting concept.
33	I wanted a choice that said "it depends on the circumstances....." - most of the answers are not so black and white!
34	Good luck with your PhD
35	I think a lot of these questions depend on the intent of use of human gene therapy - it's hard to give a catch all answer using the scales you've provided.
36	It was difficult when answering sentiment questions (positive versus negative), because I feel like there has been a mix of effects (some positive some negative) that do not equal 'neutral' (which suggests no difference/effect, rather than mixed) All the best for your research!
37	I believe that some of my answers would have been answered differently if I had been more informed about gene modification.
38	No
39	We just don't know enough about the span of effect of any gene and its complex dependencies on its environment ie. Intergene relationships.
40	I am very interested in human gene therapy - as I have a rare medical condition that I am hoping will be cured by gene therapy.
41	Well presented format, i like the Bold and Italic touches - very good for emphasis. I'm not too sure about the State of human gene therapy in general. And this Survey has shown me how complicated this field is. I'm also personally a big fan of using 'natural' methods of treating things that can be treated naturally, but if Gene Therapy can help, i think its a great initiative :)
42	Great subject for PHD - good luck
43	No

44	It's made me think more about the subject :) Must find out more!
45	I believe that if we have the ability to do so, we have a duty to save lives
46	-
47	I agree to help people suffering of deep disease after their agreement but I don't want to fall in eugenics...
48	my support for gene therapy indicated in the survey relates specifically for its use to treat disease or impairment that affects quality of life, not the general enhancement of a person or society (cf. eugenics). My non-scientific view is that there is good scope to really assist people who experience a life-limiting illness, pain in everyday life, or who are unable to fully enjoy their life due to a condition of any description. I am slightly on the fence in relation to using gene therapy to treat conditions such as autism or mental illness, unless quite severe, as I (as a partner of someone with autism/anxiety) have the view that part of it makes the person who they are, and makes society beautiful and diverse. Obviously though there is a scale in terms of impact on life. Thank you.
49	I think the development and use of this therapy should only be used to help people with genetic concerns for their offspring and for sustainable food production so that third world populations have nourishment.
50	nope
51	No
52	brilliant survey
53	I support the concept of human gene therapy if it is used for the 'right purposes' i.e curing cancer, serious chronic diseases etc. If it were ONLY used for these purposes I would be open to it being subsidised by the Government, within reason, to afford the opportunity of this therapy to all segments of our society. IF, however its use is for 'Hollywood types' to engineer themselves or their offspring for hair colour, eye colour, height, etc I would be very much against this type of therapy. To explain my stance on this is easy, if this therapy were to ever go this route it would stop being for the betterment of human beings and would rather fuel the sick fancination of our society with image. Also if human gene therapy were to be used to cure ailments that are symptoms of, just say inactivity and laziness (some, not all instances of heart disease) I would also be in opposition to this type of therapy.
54	none
55	I think it is a good idea but it will take some time for society to accept it especially those who are deeply religious.
56	I had difficulties with the questions in section 2 - those that asked whether society..... . I can't really answer for "society" - all I could do was consider what I thought the prevailing attitude was (which was difficult), or what I would choose if it was for an unknown other person (rather than me, which was the second part of those pairs of questions). Also, Q22 confused me - the question asked about limiting the effects to a single person or Australia as a whole, but also asked whether my view would change if the effect was permanent, without saying whether I should consider it in terms of an individual or the whole country
57	I hope you will obtain sufficient responses to assist with your research project. It will be interesting to see what are the implications from the results.
58	I think there is much to benefit from human gene therapy. I believe that it should only be available if it is an option for everyone (no financial barrier). I do not believe it should be available for creating the 'ideal' person - height, weight, colour, skill.
59	A lot of the questions have nuanced answers, perhaps a comment box on each to add further detail in those cases.
60	I have gone through Pre-genetic diagnosis IVF for a translocation gene I carry. I was a positive experience and i am I support the development of these technologies with appropriate research, government policy and regulation.

61	My brothers are both mentally handicapped because my parents were both carriers of the PKU gene. Although PKU is not a problem these days, the ability to remove that gene would prevent future generations from having to worry about the negative consequences.
62	I know how these surveys work. 'unsure' does not account for 'depends'. Although it is hard to quantify such a vague quality.
63	This is the next GMO ethical problem, instead it directly involves humans instead of just the food that we eat. There are tons of moral dilemmas that can be infinitely discussed on what's right or wrong. Only through experimentation will we be able to tell the negative effects of gene therapy, and by that stage it will mostly likely be too late to revert those effects.
64	I anguish that commercial outcomes will supplant and control morality of gene therapy (e.g. copyrighting human DNA & therapies).
65	Good luck!
66	no
67	I feel we should be very careful about what genetic therapy may be used for. For example, my personal case is that I am what is known as a "high functioning autistic female". I feel this has not been a drawback in my life and enables me to run my own successful small business. However, I also have Multiple Autoimmune Syndrome, which is no kind of fun since for many years it was dismissed by doctors as me being a hypochondriac. If I could change the MAS with genetic therapy, I would definitely consider it. But I wish to continue being Autistic, as I do not consider that to be a disability. Good luck with your survey!

Appendix K: Nested ANOVA Results

MODEL1: lm(Answer ~ factor(Science Type/ DNA Type/ Severity/Statements) + factor(Survey), data = DATA)

*MODEL2: lm(Answer ~ factor(Science Type/ DNA Type/ Severity/Statements) * factor(Survey), data = DATA)*

MODEL3: lm(Answer ~ factor(Participant) + factor(Science Type/ DNA Type/ Severity/Statements) + factor(Survey), data = DATA)

*MODEL4: lm(Answer ~ factor(Participant) + factor(Science Type/ DNA Type/ Severity/Statements) * factor(Survey), data = DATA)*

SCIENCE, TECHNOLOGY, BIOTECHNOLOGY AND MEDICINE

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Science Type)	3	225.24076	75.0802532	137.2249	6.353732e-83
factor(Survey)	1	19.50999	19.5099897	35.6586	2.649190e-09
Residuals	2787	1524.85921	0.5471328	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2787	1524.9				
2	2784	1521.4	3	3.4582	2.1094	0.09695

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	547	622.31829	1.1376934	2.808892	1.278947e-63
factor(Science Type)	3	222.85696	74.2856550	183.406540	2.444727e-106
factor(Survey)	1	17.16135	17.1613460	42.370268	9.291358e-11
Residuals	2240	907.27336	0.4050327	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	2240	907.27				
4	2237	904.11	3	3.1679	2.6127	0.04974 *

DNA TYPE

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(DNA Type)	3	229.67504	76.55835	51.63545	2.379239e-32
factor(Survey)	1	94.86001	94.86001	63.97916	1.925765e-15
Residuals	2433	3607.33697	1.48267	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2433	3607.3				
2	2430	3601.3	3	5.9965	1.3487	0.2568

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	544	2201.81131	4.0474473	5.269206	2.247666e-160
factor(DNA Type)	3	198.97409	66.3246975	86.345406	2.346099e-52
factor(Survey)	1	80.08466	80.0846618	104.258940	7.304256e-24
Residuals	1889	1451.00196	0.7681323	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	1889	1451.0				
4	1886	1444.8	3	6.2479	2.7187	0.04319 *

CHRONIC DISEASE

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Severity)	3	268.49366	89.4978876	109.6111	4.178483e-67
factor(Survey)	1	26.91197	26.9119656	32.9600	1.041712e-08
Residuals	2802	2287.84339	0.8165037	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2802	2287.8				
2	2799	2286.0	3	1.8099	0.7387	0.5289

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	548	1132.19069	2.0660414	3.99604	2.473324e-118
factor(Severity)	3	266.33187	88.7772887	171.70886	2.970988e-100
factor(Survey)	1	19.35847	19.3584737	37.44225	1.107123e-09
Residuals	2254	1165.36799	0.5170222	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	2254	1165.4				
4	2251	1163.6	3	1.7377	1.1205	0.3394

PHYSICAL DISABILITY

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Severity)	2	146.42318	73.2115895	93.00609	2.038340e-39
factor(Survey)	1	10.21566	10.2156630	12.97771	3.226006e-04
Residuals	2085	1641.24914	0.7871699	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2085	1641.2				
2	2083	1641.2	2	0.088152	0.0559	0.9456

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	545	962.48798	1.7660330	3.995001	2.211924e-100
factor(Severity)	2	141.18046	70.5902280	159.684446	9.538352e-64
factor(Survey)	1	13.44597	13.4459680	30.416561	4.081540e-08
Residuals	1540	680.77358	0.4420608	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	1540	680.77				
4	1538	680.74	2	0.029292	0.0331	0.9675

INTELLECTUAL DISABILITY OR MENTAL ILLNESS

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Severity)	2	245.53001	122.765005	85.28256	5.677070e-36
factor(Survey)	1	49.06263	49.062631	34.08290	6.346488e-09
Residuals	1650	2375.18970	1.439509	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	1650	2375.2				
2	1648	2373.8	2	1.352	0.4693	0.6255

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	514	1668.19901	3.2455234	4.539723	6.589857e-100
factor(Severity)	2	162.34498	81.1724909	113.541201	1.112585e-45
factor(Survey)	1	27.09308	27.0930765	37.896834	1.032736e-09
Residuals	1136	812.14528	0.7149166	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	1136	812.15				
4	1134	809.36	2	2.7818	1.9488	0.1429

ENHANCEMENT

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Enhance type)	2	77.7789605	38.8894802	18.87933914	7.536486e-09
factor(Survey)	1	0.1975446	0.1975446	0.09590025	7.568383e-01
Residuals	2002	4123.912328	2.0598963	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2002	4123.9				
2	2000	4123.9	2	0.022183	0.0054	0.9946

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	537	2945.138833	5.4844299	6.772968	2.970945e-186
factor(Enhance Type)	2	66.811925	33.4059627	41.254522	3.713164e-18
factor(Survey)	1	3.650296	3.6502958	4.507914	3.390561e-02
Residuals	1465	1186.287779	0.8097528	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	1465	1186.3				
4	1463	1186.1	2	0.18202	0.1123	0.8938

PREVENTION

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Prevent Type)	2	133.470026	66.735013	44.261346	1.543129e-19
factor(Survey)	1	1.104594	1.104594	0.732611	3.921401e-01
Residuals	2012	3033.591551	1.507749	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2012	3033.6				
2	2010	3032.3	2	1.2824	0.425	0.6538

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	543	1975.349504	3.6378444	4.977085	6.715606e-132
factor(Prevent Type)	2	117.253554	58.6267771	80.209713	8.696642e-34
factor(Survey)	1	1.843578	1.8435779	2.522275	1.124637e-01
Residuals	1469	1073.719534	0.7309187	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	1469	1073.7				
4	1467	1072.4	2	1.3292	0.9091	0.4031

THERAPEUTIC, ENHANCEMENT, PREVENTION COMPARISON

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Disease Type)	5	1438.82015	287.764031	190.44966	6.773804e-169
factor(Survey)	1	22.14003	22.140027	14.65284	1.328464e-04
Residuals	2201	3325.64852	1.510972	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2201	3325.6				
2	2198	3316.3	3	9.3948	2.0756	0.1014

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	544	2358.7992	4.3360279	4.843659	2.156797e-135
factor(Disease Type)	5	921.13855	184.2277094	205.795750	6.733194e-171
factor(Survey)	1	23.32978	23.3297804	26.061062	3.689184e-07
Residuals	1657	1483.3412	0.8951969	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	1657	1483.3				
4	1654	1474.5	3	8.8939	3.3257	0.019 *

GOVERNANCE

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Statement)	4	3325.91709	831.479272	647.42505	0.0000000000
factor(Survey)	1	14.61752	14.617521	11.38182	0.0007512025
Residuals	2961	3802.77244	1.284287	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2961	3802.8				
2	2957	3792.9	4	9.8879	1.9272	0.1032

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	551	869.26300	1.577610	1.273333	9.864273e-05
factor(Statement)	4	3276.89528	819.223820	661.218324	0.000000e+00
factor(Survey)	1	11.25238	11.252375	9.082105	2.608116e-03
Residuals	2410	2985.89639	1.238961	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	2410	2985.9				
4	2406	2978.8	4	7.0568	1.4249	0.2231

CONSENT

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Statement)	2	928.286604	464.143302	272.986845	1.075196e-105
factor(Survey)	1	3.809589	3.809589	2.240617	1.345831e-01
Residuals	2025	3442.987099	1.700241	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	2025	3443.0				
2	2023	3414.2	2	28.824	8.5394	0.0002027 ***

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	550	1396.766626	2.539576	1.79614827	3.096445e-18
factor(Statement)	2	892.687379	446.34369	315.6824391	7.55234e-115
factor(Survey)	1	0.125438	0.125438	0.08871766	7.65856e-01
Residuals	1475	2085.503850	1.413901	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	1475	2085.5				
4	1473	2058.7	2	26.856	9.608	7.15e-05 ***

RISK AND NATURAL LAW

ANOVA MODEL 1 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Statement)	6	3035.020670	505.836778	381.182400	0.0000000
factor(Survey)	1	2.666245	2.666245	2.009196	0.1564175
Residuals	4490	5958.321089	1.327020	NA	NA

ANOVA COMPARISON BETWEEN MODEL 1 AND MODEL 2 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
1	4490	5958.3				
2	4484	5933.4	6	24.92	3.1388	0.004512 **

ANOVA MODEL 3 OUTPUT

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
factor(Participant)	550	8.41191e+02	1.52943893	1.17063527	0.00600174
factor(Statement)	6	3.00711e+03	501.1843158	383.6073662	0.00000000
factor(Survey)	1	8.743063e-02	0.08743063	0.06691956	0.79588938
Residuals	3940	5.14762e+03	1.30650337	NA	NA

ANOVA COMPARISON BETWEEN MODEL 3 AND MODEL 4 OUTPUT

	Res.Df	RSS	Df	Sum of Sq	F value	Pr(>F)
3	3940	5147.6				
4	3934	5124.6	6	22.985	2.9408	0.007272 **

Appendix L: Online Australian Survey Multivariate Results

Cumulative Link Mixed Model fitted with the Laplace approximation

formula: Answer ~ factor(Gender) + factor(Age) + factor(Education) + factor(Children) + factor(Health_Work) + factor(Disability_in_Family) + factor(Disease_in_Family) + factor(HGT_Knowledge_Self_Rating) + factor(HGT_Knowledge_Test_Rating) + factor(Question) + (1 | Participant)

data: MODEL_DATA1

Random effects:

Groups	Name	Variance	Std.Dev.
Participant	(Intercept)	1.085	1.042

Number of groups: Participant 542

Coefficients:	**Estimate**	**Std. Error**	**z value**	**Pr(>|z|)**
factor(Gender)Male	0.44957	0.10869	4.136	3.53e-05***
factor(Gender)Other	0.18856	0.55528	0.340	0.734174
factor(Gender)Prefer not to say	0.69967	0.88948	0.787	0.431510
factor(Age)25-34	-1.30230	1.07105	-1.216	0.224016
factor(Age)35-44	-1.37581	1.06219	-1.295	0.195232
factor(Age)45-54	-1.41213	1.05203	-1.342	0.179501
factor(Age)55-64	-1.21171	1.05574	-1.148	0.251078
factor(Age)65-74	-1.83949	1.05383	-1.746	0.080895
factor(Age)75+	-1.64097	1.07683	-1.524	0.127536
factor(Age)Prefer not to say	-1.42402	1.07642	-1.323	0.185862
factor(Education)Prefer not to say	0.44379	0.79479	0.558	0.576586

factor(Education)Some high school	1.28490	0.60715	2.116	0.034321 *
factor(Education)TAFE/diploma	0.65873	0.35394	1.861	0.062727
factor(Education)University degree	0.54066	0.33234	1.627	0.103771
factor(Education)Year 10 high school	0.19553	0.46243	0.423	0.672417
factor(Education)Year 12 high school	0.63909	0.34380	1.859	0.063041
factor(Children)Prefer not to say	-0.45195	0.71480	-0.632	0.527208
factor(Children)Yes	0.16826	0.12970	1.297	0.194531
factor(Health_Work)Prefer not to say	0.25875	0.56638	0.457	0.647777
factor(Health_Work)Unsure	0.02381	0.78692	0.030	0.975857
factor(Health_Work)Yes	-0.08387	0.11043	-0.760	0.447533
factor(Disability_in_Family)Prefer not to say	0.65840	0.53712	1.226	0.220274
factor(Disability_in_Family)Unsure	-0.16133	0.27977	-0.577	0.564174
factor(Disability_in_Family)Yes	-0.01954	0.10369	-0.188	0.850511
factor(Disease_in_Family)Prefer not to say	-1.85736	1.54179	-1.205	0.228328
factor(Disease_in_Family)Unsure	-0.08529	0.12738	-0.670	0.503147
factor(Disease_in_Family)Yes	0.02336	0.12556	0.186	0.852411
factor(HGT_Knowledge_Self_Rating)Explain a little	-0.29116	0.19220	-1.515	0.129797
factor(HGT_Knowledge_Self_Rating)Explain clearly	-0.25070	0.22773	-1.101	0.270953
factor(HGT_Knowledge_Self_Rating)Extensive knowledge	-0.31915	0.32732	-0.975	0.329535
factor(HGT_Knowledge_Self_Rating)Never heard of it	-0.10769	0.25444	-0.423	0.672119
factor(HGT_Knowledge_Self_Rating)Unsure	-0.17847	0.78295	-0.228	0.819691
factor(HGT_Knowledge_Test_Rating)Incorrect	-0.23819	0.18496	-1.288	0.197819
factor(HGT_Knowledge_Test_Rating)Partially correct	-0.01058	0.15221	-0.070	0.944561
factor(Question)Q10b	-0.84411	0.17499	-4.824	1.41e-06 ***
factor(Question)Q10c	-2.13109	0.16384	-13.007	< 2e-16 ***
factor(Question)Q11a	-1.29801	0.17326	-7.492	6.80e-14 ***
factor(Question)Q11b	-2.41675	0.16478	-14.667	< 2e-16 ***
factor(Question)Q11c	-3.03526	0.16323	-18.595	< 2e-16 ***
factor(Question)Q12a	-1.12830	0.17379	-6.492	8.46e-11 ***
factor(Question)Q12b	-2.55611	0.16376	-15.609	< 2e-16 ***
factor(Question)Q12c	-3.27855	0.16278	-20.142	< 2e-16 ***

factor(Question)Q13a		-5.63388	0.16684	-33.768	< 2e-16 ***
factor(Question)Q13b		-5.32061	0.16602	-32.047	< 2e-16 ***
factor(Question)Q13c		-4.80285	0.16493	-29.121	< 2e-16 ***
factor(Question)Q14a		-2.63726	0.16334	-16.146	< 2e-16 ***
factor(Question)Q14b		-1.25834	0.17060	-7.376	1.63e-13 ***
factor(Question)Q14c		-2.40476	0.16534	-14.544	< 2e-16 ***
factor(Question)Q15a		-5.06786	0.16862	-30.055	< 2e-16 ***
factor(Question)Q15b		-2.34539	0.16163	-14.511	< 2e-16 ***
factor(Question)Q15c		-3.54438	0.19223	-18.438	< 2e-16 ***
factor(Question)Q15d		-1.85046	0.16968	-10.905	< 2e-16 ***
factor(Question)Q15e		-2.30763	0.16634	-13.873	< 2e-16 ***
factor(Question)Q15f		-5.75665	0.16863	-34.138	< 2e-16 ***
factor(Question)Q15g		-2.79678	0.16139	-17.329	< 2e-16 ***
factor(Question)Q15h		-3.27138	0.16121	-20.292	< 2e-16 ***
factor(Question)Q15i		-7.60707	0.18559	-40.988	< 2e-16 ***
factor(Question)Q16a		-6.86760	0.17344	-39.596	< 2e-16 ***
factor(Question)Q16b		-3.18695	0.16210	-19.661	< 2e-16 ***
factor(Question)Q16c		-5.25419	0.16533	-31.779	< 2e-16 ***
factor(Question)Q16d		-3.14446	0.16517	-19.037	< 2e-16 ***
factor(Question)Q16e	-	4.10005	0.16287	-25.174	< 2e-16 ***
factor(Question)Q16f		-4.31566	0.17082	-25.265	< 2e-16 ***
factor(Question)Q16g		-5.65974	0.16659	-33.973	< 2e-16 ***
factor(Question)Q16h		-2.52519	0.16369	-15.427	< 2e-16 ***
factor(Question)Q20a		-1.54811	0.16815	-9.207	< 2e-16 ***
factor(Question)Q20b		-2.62627	0.16392	-16.021	< 2e-16 ***
factor(Question)Q20c		-6.11247	0.17375	-35.180	< 2e-16 ***
factor(Question)Q20d		-3.61874	0.16600	-21.799	< 2e-16 ***
factor(Question)Q20e		-2.86504	0.16404	-17.465	< 2e-16 ***
factor(Question)Q21a		-0.17412	0.18847	-0.924	0.355577
factor(Question)Q21b		-1.32221	0.16805	-7.868	3.60e-15 ***
factor(Question)Q21c		-2.44007	0.16439	-14.843	< 2e-16 ***

factor(Question)Q21d	-0.52111	0.18014	-2.893	0.003819 **
factor(Question)Q22	-4.49167	0.15827	-28.379	< 2e-16 ***
factor(Question)Q23	-5.80751	0.16724	-34.726	< 2e-16 ***
factor(Question)Q7a	-0.88274	0.17618	-5.011	5.43e-07 ***
factor(Question)Q7b	-0.61836	0.17957	-3.444	0.000574 ***
factor(Question)Q7c	-0.57741	0.18043	-3.200	0.001374 **
factor(Question)Q7d	-2.08332	0.16679	-12.491	< 2e-16 ***
factor(Question)Q7e	-0.88281	0.17597	-5.017	5.26e-07 ***
factor(Question)Q7f	-0.54514	0.18093	-3.013	0.002587 **
factor(Question)Q8a	-0.68270	0.17921	-3.810	0.000139 ***
factor(Question)Q8b	-2.63656	0.16580	-15.902	< 2e-16 ***
factor(Question)Q8c	-2.30703	0.16917	-13.638	< 2e-16 ***
factor(Question)Q8d	-1.73334	0.17023	-10.183	< 2e-16 ***
factor(Question)Q9a	-0.00616	0.19413	-0.032	0.974686
factor(Question)Q9b	-0.02805	0.19146	-0.146	0.883543
factor(Question)Q9c	-1.08112	0.17160	-6.300	2.97e-10 ***
factor(Question)Q9d	-2.33844	0.16377	-14.279	< 2e-16 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:

	Estimate	**Std. Error**	**z value**
1|2	-6.879	1.180	-5.831
2|3	-5.694	1.180	-4.827
3|4	-4.784	1.179	-4.056
4|5	-3.191	1.179	-2.706

(491 observations deleted due to missingness)

Appendix M: Australian Capital Territory Survey Multivariate Results

Cumulative Link Mixed Model fitted with the Laplace approximation

formula: Answer ~ factor(Gender) + factor(Age) + factor(Education) + factor(Children) + factor(Politics) + factor(Disability_in_Family) + factor(Disease_in_Family) + factor(HGT_Knowledge_Self_Rating) + factor(HGT_Knowledge_Test_Rating) + factor(Question) + (1 | Participant)

data: MODEL_DATA1

Random effects:

Groups	Name	Variance	Std.Dev.
Participant	(Intercept)	0.7791	0.8827

Number of groups: Participant 164

Coefficients:	**Estimate**	**Std. Error**	**z value**	**Pr(>|z|)**
factor(Gender)Male	0.3569166	0.1662925	2.146	0.031848 *
factor(Age)25-34	-0.6933288	0.3938256	-1.760	0.078324
factor(Age)35-44	-0.5249005	0.4584183	-1.145	0.252199
factor(Age)45-54	-0.4774710	0.4317814	-1.106	0.268806
factor(Age)55-64	-0.4594221	0.4521941	-1.016	0.309637
factor(Age)65-74	-0.5005703	0.4859813	-1.030	0.303001
factor(Age)75+	-0.9816016	0.7082707	-1.386	0.165773
factor(Education)High school certificate	-0.2709793	0.3443236	-0.787	0.431288
factor(Education)Middle school/intermediate certificate	0.3920677	0.7508881	0.522	0.601574
factor(Education)Prefer not to say	-1.4886963	1.0096187	-1.475	0.140343
factor(Education)Trade/apprenticeship	-0.9955963	0.7295860	-1.365	0.172377
factor(Education)University degree or above	-0.2987189	0.2566160	-1.164	0.244396

factor(Children)Prefer not to say	-0.2608029	0.6031330	-0.432	0.665441
factor(Children)Yes	-0.4670652	0.2371649	-1.969	0.048911 *
factor(Politics) Pauline Hanson’s One Nation	-0.0836662	0.7311333	-0.114	0.908894
factor(Politics)Other	-0.4176689	0.3805948	-1.097	0.272462
factor(Politics)Australian Labour Party	0.1966019	0.2356429	0.834	0.404100
factor(Politics)Green	0.1088258	0.2360969	0.461	0.644844
factor(Politics)Liberal Party	0.1903910	0.2827532	0.673	0.500727
factor(Politics)National Party	-0.2847848	0.9953669	-0.286	0.774794
factor(Politics)United Australia Party	-0.0795611	0.6399883	-0.124	0.901065
factor(Disability_in_Family)Prefer not to say	-0.1704206	0.5450268	-0.313	0.754521
factor(Disability_in_Family)Unsure	0.5042347	0.5105070	0.988	0.323293
factor(Disability_in_Family)Yes	-0.2198071	0.1752014	-1.255	0.209625
factor(Disease_in_Family)Prefer not to say	0.2848726	0.6858380	0.415	0.677875
factor(Disease_in_Family)Unsure	-0.4643508	0.1975838	-2.350	0.018766 *
factor(Disease_in_Family)Yes	0.4582338	0.2098509	2.184	0.028990 *
factor(HGT_Knowledge_Self_Rating)Explain a little	0.0006560	0.2247347	0.003	0.997671
factor(HGT_Knowledge_Self_Rating)Explain clearly	-0.6422273	0.3248411	-1.977	0.048036 *
factor(HGT_Knowledge_Self_Rating)Extensive knowledge	-0.0007829	0.7318980	-0.001	0.999147
factor(HGT_Knowledge_Self_Rating)Never heard of it	-0.0683506	0.4233984	-0.161	0.871752
factor(HGT_Knowledge_Self_Rating)Unsure	3.8608216	1.1903018	3.244	0.001180 **
factor(HGT_Knowledge_Test_Rating)Incorrect	-0.3808494	0.2557821	-1.489	0.136498
factor(HGT_Knowledge_Test_Rating)Partially correct	-0.0327467	0.1948006	-0.168	0.866502
factor(Question)Q10b	-0.7625808	0.2799540	-2.724	0.006451 **
factor(Question)Q10c	-1.8384777	0.2665742	-6.897	5.32e-12 ***
factor(Question)Q12a	-1.1268617	0.2801319	-4.023	5.76e-05 ***
factor(Question)Q12b	-2.2741124	0.2663346	-8.539	< 2e-16 ***
factor(Question)Q12c	-2.9866184	0.2677482	-11.155	< 2e-16 ***
factor(Question)Q14a	-4.8841551	0.2691245	-18.148	< 2e-16 ***
factor(Question)Q14b	-4.5923412	0.2684101	-17.109	< 2e-16 ***
factor(Question)Q14c	-4.1443898	0.2679920	-15.465	< 2e-16 ***
factor(Question)Q16a	-1.9185876	0.2698153	-7.111	1.15e-12 ***

factor(Question)Q16b	-0.7693941	0.2829538	-2.719	0.006545 **
factor(Question)Q16c	-1.8163915	0.2741864	-6.625	3.48e-11 ***
factor(Question)Q18a	-1.1411423	0.2846928	-4.008	6.11e-05 ***
factor(Question)Q18b	-1.0874119	0.2821540	-3.854	0.000116 ***
factor(Question)Q18c	-1.0747495	0.2797204	-3.842	0.000122 ***
factor(Question)Q18d	-2.0661394	0.2738986	-7.543	4.58e-14 ***
factor(Question)Q18e	-1.0344949	0.2795735	-3.700	0.000215 ***
factor(Question)Q18f	-0.9545458	0.2803844	-3.404	0.000663 ***
factor(Question)Q20a	-1.4602780	0.2768560	-5.275	1.33e-07 ***
factor(Question)Q20b	-2.8828952	0.2804437	-10.280	< 2e-16 ***
factor(Question)Q20c	-2.2236805	0.2841504	-7.826	5.05e-15 ***
factor(Question)Q20d	-2.1879738	0.2797460	-7.821	5.23e-15 ***
factor(Question)Q22a	-0.9122430	0.2737634	-3.332	0.000862 ***
factor(Question)Q22b	-2.3055805	0.2731586	-8.440	< 2e-16 ***
factor(Question)Q22c	-5.4328633	0.2878242	-18.876	< 2e-16 ***
factor(Question)Q23a	-2.1603749	0.2893130	-7.467	8.19e-14 ***
factor(Question)Q23b	-0.5852593	0.2874103	-2.036	0.041718 *
factor(Question)Q23c	-1.6407608	0.2720523	-6.031	1.63e-09 ***
factor(Question)Q23d	-3.3688857	0.2704532	-12.456	< 2e-16 ***
factor(Question)Q23e	-5.7436777	0.2828125	-20.309	< 2e-16 ***
factor(Question)Q24a	-2.1345734	0.2652835	-8.046	8.53e-16 ***
factor(Question)Q24b	-3.7941604	0.2667802	-14.222	< 2e-16 ***
factor(Question)Q24c	-2.2975682	0.2675835	-8.586	< 2e-16 ***
factor(Question)Q25a	-2.7673210	0.2703697	-10.235	< 2e-16 ***
factor(Question)Q25b	-2.4085394	0.2634229	-9.143	< 2e-16 ***
factor(Question)Q25c	-1.8191367	0.2650656	-6.863	6.74e-12 ***
factor(Question)Q25d	-2.2761194	0.2615139	-8.704	< 2e-16 ***
factor(Question)Q25e	-2.7416009	0.2626846	-10.437	< 2e-16 ***
factor(Question)Q26a	-3.0301340	0.2788092	-10.868	< 2e-16 ***
factor(Question)Q26b	-4.2474397	0.2867830	-14.811	< 2e-16 ***
factor(Question)Q26c	-4.4397215	0.2680572	-16.563	< 2e-16 ***

factor(Question)Q26e	-4.8549287	0.2756535	-17.612	< 2e-16 ***
factor(Question)Q27a	-0.8952303	0.2718231	-3.293	0.000990 ***
factor(Question)Q27b	-1.5952507	0.2612150	-6.107	1.01e-09 ***
factor(Question)Q27c	-2.1264454	0.2612943	-8.138	4.01e-16 ***
factor(Question)Q27d	-0.5593426	0.2776139	-2.015	0.043923 *
factor(Question)Q29	-4.5854374	0.2746428	-16.696	< 2e-16 ***
factor(Question)Q8a	-0.3086574	0.2911224	-1.060	0.289039
factor(Question)Q8b	0.0830673	0.3029096	0.274	0.783907
factor(Question)Q8c	-1.1078965	0.2727276	-4.062	4.86e-05 ***
factor(Question)Q8d	-2.1397758	0.2641922	-8.099	5.53e-16 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:

	Estimate	**Std. Error**	**z value**
1|2	-6.1634	0.6034	-10.215
2|3	-5.0703	0.6022	-8.420
3|4	-4.2858	0.6015	-7.126
4|5	-2.7435	0.6001	-4.571

(261 observations deleted due to missingness)

References

1292.0 - Australian and New Zealand Standard Industrial Classification (ANZSIC). 2006. https://www.abs.gov.au/ausstats/abs@.nsf/mf/1292.0.

ABC News. 2017. "Leukaemia Breakthrough CAR-T Uses Children's Own Blood Cells to Attack Cancer," 2017.

Abraham, John, and Julie Sheppard. 1997. "Democracy, Technocracy, and the Secret State of Medicines Control: Expert and Nonexpert Perspectives." *Science, Technology, & Human Values* 22 (2):139–67.

AbuQamar, Synan, Qasim Alshannag, Abdelaziz Sartawi, and Rabah Iratni. 2015. "Educational Awareness of Biotechnology Issues among Undergraduate Students at the United Arab Emirates University." *Biochemistry and Molecular Biology Education* 43 (4):283–93.

Adam, Barbara, and Chris Groves. 2011. "Futures Tended: Care and Future-Oriented Responsibility." *Bulletin of Science, Technology & Society* 31 (1):17–27.

Agrawal, Rina, Elizabeth Burt, and Roy Homburg. 2013. "Time-Line in HFEA Developments and Regulatory Challenges: 20 Years of Overseeing Fertility Practices and Research in the UK." *Journal of Obstetrics and Gynaecolgy India.* 63 (6):363–69.

Alberts, Bruce, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walter. 2002. "Isolating Cells and Growing Them in Culture." In *Molecular Biology of the Cell. 4th Edition*. New York: Garland Science.

Alessi, Edward, and James Martin. 2010. "Conducting an Internet-Based Survey: Benefits, Pitfalls, and Lessons Learned." *Social Work Research* 34 (2):122–28.

American Cancer Society. 2018. "Lifetime Risk of Developing or Dying From Cancer." 2018.

Araki, Motoko, and Tetsuya Ishii. 2014. "International Regulatory Landscape and Integration of Corrective Genome Editing into in Vitro Fertilization." *Reproductive Biology and Endocrinology* 12 (1):108.

Arnold, Fred, Sunita Kishor, and T. K. Roy. 2002. "Sex-Selective Abortions in India." *Population and Development Review* 28 (4):759–785.

Arsanjani, Mahnoush. 2006. “Negotiating the UN Declaration on Human Cloning.” *American Journal of International Law* 100 (1):164–79.

Ashida, Sato, Kimberly Kaphingst, Melody Goodman, and Ellen Schafer. 2013. “Family Health History Communication Networks of Older Adults: Importance of Social Relationships and Disease Perceptions.” *Health, Education & Behaviour* 40 (5):612–19.

Association for Molecular Pathology (AMP) v. Myriad Genetics Inc. 2013, 569 U.S. 5.

Australian Bureau of Statistics. 2017a. “Attainment of Non-School Qualifications.” 6227.0 - Education and Work, Australia, May 2017. 2017. https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/6227.0Main+Features1May 2017?OpenDocument.

———. 2017b. “Feature Article: Population by Age and Sex, Australia, States and Territories.” 3101.0 - Australian Demographic Statistics, Jun 2017. 2017. https://www.abs.gov.au/ausstats/abs@.nsf/featurearticlesbyCatalogue/CCF53AA000E69954CA2582570013F5C6?OpenDocument.

———. 2019a. “Non-School Qualifications.” 6227.0 - Education and Work, Australia, May 2019. 2019. https://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/6227.0Main Features40May 2019?opendocument&tabname=Summary&prodno=6227.0&issue=May 2019&num=&view= .

———. 2019b. “Twenty Years of Population Change.” 3101.0 - Australian Demographic Statistics, Jun 2019. 2019. https://www.abs.gov.au/ausstats/abs@.nsf/0/1CD2B1952AFC5E7ACA257298000F2E76?OpenDocument.

Australian Health Ministers’ Advisory Council. 2017. “National Health Genomics Policy Framework.” Canberra.

“Australian New Zealand Clinical Trials Registry.” 2020. 2020. http://www.anzctr.org.au.

Australian Prudential Regulation Authority. 2020. “Regulation Impact Statements.” Australian Prudential Regulation Authority. 2020.

Balkwill, Frances. 2009. “Tumour Necrosis Factor and Cancer.” *Nature Reviews Cancer* 9 (5):361–71.

Ball, Helen. 2019. “Conducting Online Surveys.” *Journal of Human Lactation* 35 (3):413–17.

Baltimore, David, Paul Berg, Michael Botchan, Dana Carroll, Alta Charo, George Church, Jacob Corn, et al. 2015. “A Prudent Path Forward for Genomic Engineering and Germline Gene Modification.” *Science* 348 (6230):36–38.

Banks, James, Elena Bassoli, and Irene Mammi. 2020. “Changing Attitudes to Risk at Older Ages: The Role of Health and Other Life Events.” *Journal of Economic Psychology* 79 (1):102208.

Baptiste-Roberts, Kesha, Tiffany Gary, Gloria Beckles, Edward Gregg, Michelle Owens, Deborah Porterfield, and Michael Engelgau. 2007. “Family History of Diabetes, Awareness of Risk Factors, and Health Behaviors among African Americans.” *American Journal of Public Health* 97 (5):907–12.

Barnett, Julie, and Glynis Breakwell. 2002. “Risk Perception and Experience: Hazard Personality Profiles and Individual Differences.” *Risk Analysis* 21 (1):171–78.

Barnett, Julie, Helen Cooper, and Victoria Senior. 2007. “Belief in Public Efficacy, Trust, and Attitudes toward Modern Genetic Science.” *Risk Analysis: An International Journal* 27 (4):921–33.

BBC News. 2018. “He Jiankui Defends ‘World’s First Gene-Edited Babies.’” 2018. https://www.bbc.com/news/world-asia-china-46368731.

Beers, Britta van. 2020. “Rewriting the Human Genome, Rewriting Human Rights Law? Human Rights, Human Dignity, and Human Germline Modification in the CRISPR Era.” *Journal of Law and the Biosciences*, 1–36.

Bender, Eric. 2018. “Regulating the Gene-Therapy Revolution.” *Nature* 564 (7735):S20.

Berg, Paul, David Baltimore, Herbert Boyer, Stanley Cohen, Ronald Davis, David Hogness, Daniel Nathans, et al. 1974. “Potential Biohazards of Recombinant DNA Molecules.” *Science* 185 (4148):303.

Beutler, Ernest. 2001. “The Cline Affair.” *Molecular Therapy* 4 (5):396.

Blackstone, Amy. 2003. “Gender Roles and Society.” In *Human Ecology: An Encyclopedia of Children, Families, Communities, and Environments*, edited by Julia Miller, Richard Lerner, and Lawrence Schiamberg, 335–38. Santa Barbara: ABC-CLIO.

Blaese, Ro, Kenneth Culver, Dusty Miller, and Charles Carter. 1995. “T Lymphocyte-Directed Gene Therapy for ADAnegative SCID: Initial Trial Results after 4 Years.” *Science* 270 (5235):475–80.

Blair, Caroline, Elaine Kacser, and David Porteous. 1998. “Gene Therapy for Cystic Fibrosis: A Psychosocial Study of Trial Participants.” *Gene Therapy* 5 (2):218–23.

Blasimme, Alessandro, Effy Vayena, and Ine Van Hoyweghen. 2019. “Big Data, Precision Medicine and Private Insurance: A Delicate Balancing Act.” *Big Data & Society* 6 (1):1–6.

Bloom, Joan, Susan Stewart, Ingrid Oakley-Girvans, Priscilla Banks, and Subo Chang. 2006. “Family History, Perceived Risk, and Prostate Cancer Screening among African American Men.” *Cancer Epidemiology and Prevention Biomarkers* 15 (11):2167–73.

Bonatti, Johannes, Christa Haeusler, Alexander Klaus, Monika Fink, Angelika Hammerer-Lercher, and Günther Laufer. 2002. “Acceptance of Gene Therapy by the Heart Surgery Patient.” *European Journal of Cardio-Thoracic Surgery* 21 (6):981–86.

Bond, Lyndal, and Terry Nolan. 2011. “Making Sense of Perceptions of Risk of Diseases and Vaccinations: A Qualitative Study Combining Models of Health Beliefs, Decision-Making and Risk Perception.” *BMC Public Health* 11 (1):943.

Bonsang, Eric, and Thomas Dohmen. 2015. “Risk Attitude and Cognitive Aging.” *Journal of Economic Behavior & Organization* 112 (1):112–26.

Bordignon, Claudio, Luigi Notarangelo, Nadia Nobili, and Guiliana Ferrari. 1995. “Gene Therapy in Peripheral Blood Lymphocytes and Bone Marrow for ADAnegative Immunodeficient Patients.” *Science* 270 (5235):470–75.

Borgonovi, Francesca. 2012. “The Relationship between Education and Levels of Trust and Tolerance in Europe.” *The British Journal of Sociology* 63 (1):146–67.

Bostrom, Nick, and Rebecca Roache. 2007. “Ethical Issues in Human Enhancement.” In *New Waves in Applied Ethics*, edited by Jesper Ryberg, Thomas Petersen, and Clark Wolf, 120–52. Palgrave Macmillan.

Brankov, Tatjana, Tatjana Sibalija, Koviljko Lovre, Drago Cvijanovic, and Jonel Subic. 2013. “The Impact of Biotechnology Knowledge on the Acceptance of Genetically Modified Food in Serbia.” *Romanian Biotechnological Letters* 18 (3):8295–8306.

Brassier, Anais, Stephanie Gobin, Jean Baptiste Arnoux, Vassili Valayannopoulos, Florence Habarou, Manoelle Kossorotoff, Aude Servais, et al. 2015. “Long-Term Outcomes in Ornithine Transcarbamylase Deficiency: A Series of 90 Patients.” *Orphanet Journal of Rare Diseases* 10 (1):58.

Brisenden, Simon. 1986. “Independent Living and the Medical Model of Disability.” *Disability, Handicap & Society* 1 (2):173–78.

Brossard, Dominique, Pam Belluck, Fred Gould, and Christopher Wirz. 2019. “Promises and Perils of Gene Drives: Navigating the Communication of Complex, Post-Normal Science.” *Proceedings of the National Academy of Sciences of the United States of America* 116 (16):7692–97.

Buchanan, Allen, Dan Brock, Norman Daniels, and Daniel Wikler. 2001. *From Chance to Choice: Genetics and Justice*.

Bunea, Adriana. 2017. “Designing Stakeholder Consultations: Reinforcing or Alleviating Bias in the European Union System of Governance?” *European Journal of Political Research* 56 (1):46–69.

Burget, Mirjam, Emanuele Bardone, and Margus Pedaste. 2017. “Definitions and Conceptual Dimensions of Responsible Research and Innovation: A Literature Review.” *Science and Engineering Ethics* 23:1–19.

Burrows, Ian. 2019. “Gene-Editing Chinese Scientist He Jiankui Could Face Death Penalty, Reports Say.” ABC News. 2019. https://www.abc.net.au/news/2019-01-09/gene-editing-scientist-he-jiankui-may-face-death-penalty/10702246.

Burstein, Paul. 2003. “The Impact of Public Opinion on Public Policy: A Review and an Agenda.” *Political Research Quarterly* 56 (1):29–40.

Callegaro, Maria, Katja Manfreda, and Vasja Vehova. 2015. *Web Survey Methodology*. Sage Publications.

Calnan, Michael, David Montaner, and Rob Horne. 2005. “How Acceptable Are Innovative Health-Care Technologies? A Survey of Public Beliefs and Attitudes in England and Wales.” *Social Science & Medicine* 60 (9):1937–48.

Calyx, Cobi, and Brad Jessup. 2019. “Nuclear Citizens Jury: From Local Deliberations to Transboundary and Transgenerational Legal Dilemmas.” *Environmental Communication:*

A Journal of Nature and Culture 13 (4):491–504.

Candotti, Fabio, Kit Shaw, Linda Muul, Denise Carbonaro, Robert Sokolic, Christopher Choi, Shepherd Schurman, et al. 2012. "Gene Therapy for Adenosine Deaminase–deficient Severe Combined Immune Deficiency: Clinical Comparison of Retroviral Vectors and Treatment Plans." *Blood* 120 (18):3635–3646.

Carpini, Michael, Fay Cook, and Lawrence Jacob. 2004. "Public Deliberation, Discursive Participation, and Citizen Engagement: A Review of the Empirical Literature." *Annual Review of Political Science* 7 (1):315–44.

Carswell, Elizabeth, Lloyd Old, Robert Kassel, Sarah Green, Nancy Fiore, and Barbara Williamson. 1975. "An Endotoxin-Induced Serum Factor That Causes Necrosis of Tumors." *Proceedings of the National Academy of Sciences of the United States of America* 72 (9):3666–70.

Carucci, Ron. 2016. "Why Ethical People Make Unethical Choices." *Harvard Business Review* 12.

Casal, Paula. 2013. "Sexual Dimorphism and Human Enhancement." *Journal of Medical Ethics* 39 (12):722–28.

Cass, Oren. 2015. "Why the Paris Climate Deal Is Meaningless." *Politico*, 2015.

Cavazzana-Calvo, Marina, Salima Hacein-Bey, Genevieve de Saint Basile, Fabian Gross, Eric Yvon, Patrick Nusbaum, Francoise Selz, et al. 2000. "Gene Therapy of Human Severe Combined Immunodeficiency (SCID)-X1 Disease." *Science* 288 (5466):669–72.

Cebesoy, Ümran, and Ceren Öztekin. 2016. "Relationships among Turkish Pre-Service Science Teachers' Genetics Literacy Levels and Their Attitudes towards Issues in Genetics Literacy." *Journal of Baltic Science Education* 15 (2):159.

Chandler, Randy, and Charles Venditti. 2016. "Gene Therapy for Metabolic Diseases." *Translational Science of Rare Diseases* 1 (1):73–89.

Chang, Patricia. 1994. "The Somatic Tissue." In *Somatic Gene Therapy*. CRC Press.

Check, Erika. 2002. "Gene Therapy: A Tragic Setback." *Nature* 420 (6912):116–18.

Chen, L. S., and K. A. Kaphingst. 2011. "Risk Perceptions and Family History of Lung Cancer: Differences by Smoking Status." *Public Health Genomics* 14 (1):26–34.

Chen, Shao-Yen, and John Raffan. 1999. “Biotechnology: Student’s Knowledge and Attitudes in the UK and Taiwan.” *Journal of Biological Education* 34 (1):17–23.

Chiurazzia, Pietro, and Filomena Pirozzi. 2016. “Advances in Understanding – Genetic Basis of Intellectual Disability.” *F1000 Research* 5 (1):Rev-599.

Cho, Sungjoon, and Claire Kelly. 2012. “Promises and Perils of New Global Governance: A Case of the G20.” *Chicago Journal of International Law* 12 (2):498.

Christensen, Rune Haubo B. 2018. “Cumulative Link Models for Ordinal Regression with the R Package Ordinal.” *Journal of Statistical Software*.

Cichutek, Klaus. 2008. “Gene and Cell Therapy in Germany and the EU.” *Journal Für Verbraucherschutz Und Lebensmittelsicherheit* 3 (1):73–76.

Cline, Martin. 1985. “Perspectives for Gene Therapy: Inserting New Genetic Information into Mammalian Cells by Physical Techniques and Viral Vectors.” *Pharmacology & Therapeutics* 29 (1):69–92.

Cline, Martin, Howard Stang, Karen Mercola, L. Morse, Ruth Ruprecht, Jeffrey Browne, and Winston Salser. 1980. “Gene Transfer in Intact Animals.” *Nature* 284:422–25.

Cobb, Michael. 2011. “Creating Informed Public Opinion: Citizen Deliberation about Nanotechnologies for Human Enhancements.” *Journal of Nanoparticle Research* 13 (4):1533–48.

Coleman, Cynthia-Lou. 1993. “The Influence of Mass Media and Interpersonal Communication on Societal and Personal Risk Judgments.” *Communication Research* 2 (1):205–42.

Condit, Celeste. 2010. “Public Attitudes and Beliefs About Genetics.” *Annual Review of Genomics and Human Genetics* 11:339–59.

Connor, Melanie, and Michael Siegrist. 2010. “Factors Influencing People’s Acceptance of Gene Technology: The Role of Knowledge, Health Expectations, Naturalness, and Social Trust.” *Science Communication* 32 (4):514–38.

Corrigan, Patrick, and Frederick Miller. 2004. “Shame, Blame, and Contamination: A Review of the Impact of Mental Illness Stigma on Family Members.” *Journal of Mental Health* 13 (6):537–48.

Costea, Irina, Rosario Isasi, Bartha Knoppers, and David Lillicrap. 2009. “Haemophilia Gene

Therapy: The Patients'perspective." *Haemophilia* 15 (5):1159–61.

Cotrim, Ana, and Bruce Baum. 2008. "Gene Therapy: Some History, Applications, Problems, and Prospects." *Toxicologic Pathology* 36 (1):97–103.

Coughlan, Michael, Patricia Cronin, and Frances Ryan. 2013. "Survey Research: Process and Limitations." *International Journal of Therapy and Rehabilitation: Research Methodology Series* 16 (1):9–15.

Council of Europe. 1997. "Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine."

Couzin, Jennifer, and Jocelyn Kaiser. 2005. "As Gelsinger Case Ends, Gene Therapy Suffers Another Blow." *Science* 307 (5712):1028b.

Critchley, Christine, Dianne Nicol, Gordana Bruce, Jarrod Walshe, Tamara Treleaven, and Bernard Tuch. 2018. "Predicting Public Attitudes Toward Gene Editing of Germlines: The Impact of Moral and Hereditary Concern in Human and Animal Applications." *Frontiers in Genetics* 9 (1):704.

Črne-Hladnik, Helena, Aleš Hladnik, Branka Javornik, Katarina Košmelj, and Cirilia Peklaj. 2012. "Is Judgement of Biotechnological Ethical Aspects Related to High School Students' Knowledge?" *International Journal of Science Education* 34 (8):1277–96.

Črne-Hladnik, Helena, Cirilia Peklaj, Katarina Košmelj, Aleš Hladnik, and Branka Javornik. 2009. "Assessment of Slovene Secondary School Students' Attitudes to Biotechnology in Terms of Usefulness, Moral Acceptability and Risk Perception." *Public Understanding of Science* 18 (6):747–58.

Cross, Deanna, and James Burmester. 2006. "Gene Therapy for Cancer Treatment: Past, Present and Future." *Clinical Medicine & Research* 4 (3):218–227.

Crystal, Ronald. 1999. "In Vivo and Ex Vivo Gene Therapy Strategies to Treat Tumors Using Adenovirus Gene Transfer Vectors." *Cancer Chemotherapy and Pharmacology Volume* 43 (1):S90–99.

Culver, Kenneth. 1994. *Gene Therapy: A Handbook for Physicians*. *Mary Ann Liebert*. New York.

Curtin, Richard, Stanley Presser, and Eleanor Singer. 2000. “The Effects of Response Rate Changes on the Index of Consumer Sentiment.” *Public Opinion Quarterly* 64 (4):413–28.

Cyranoski, David, and Heidi Ledford. 2018. “Genome-Edited Baby Claim Provokes International Outcry.” *Nature* 563:607–8.

Daniels, Norman. 2000. “Normal Functioning and the Treatment-Enhancement Distinction.” *Cambridge Quarterly of Healthcare Ethics* 9 (3):309–22.

Dankel, Dorothy, Nora Vaage, and Jeroen van der Sluijs. 2017. “Post-Normal Science in Practice.” *Futures* 91:1–4.

Davies, Kevin. 2018a. “He Said What Now?” *The CRISPR Journal* 1 (6):358–62.

———. 2018b. “Unite to Cure: CRISPR Comes to the Vatican.” *The CRISPR Journal* 1 (3):213–16.

Delhove, Juliette, Ivana Osenk, Ivanka Prichard, and Martin Donnelley. 2020. “Public Acceptability of Gene Therapy and Gene Editing for Human Use: A Systematic Review.” *Human Gene Therapy* 31 (1–2):20–46.

Desai, Tarishi, and Hayley Jones. 2019. “Life Insurance Industry Bans Itself from Using Genetic Test Results.” *The McCabe Centre for Law & Cancer*, 2019.

Dickson, David. 1981. “NIH Censure for Dr. Martin Cline: Tighter Rules for Future Research Plans.” *Nature* 291:369.

Dijkstra, Anne, and Mirjam Schuijff. 2016. “Public Opinions about Human Enhancement Can Enhance the Expert-Only Debate: A Review Study.” *Public Understanding of Science* 25 (5):588–602.

Dohmen, Thomas, Hartmut Pignatti, and Norberto Lehmann. 2016. “Time-Varying Individual Risk Attitudes over the Great Recession: A Comparison of Germany and Ukraine.” *Journal of Comparative Economics* 44 (1):182–200.

Dolnicar, Sara, Bettina Grün, and Venkata Yanamandram. 2013. “Dynamic, Interactive Survey Questions Can Increase Survey Data Quality.” *Journal of Travel & Tourism Marketing* 30 (7):690–99.

Dotti Sani, Giulia, and Mario Quaranta. 2017. “The Best Is Yet to Come? Attitudes Toward Gender Roles Among Adolescents in 36 Countries.” *Sex Roles* 77 (1–2):30–45.

Durant, John. 1999. “Participatory Technology Assessment and the Democratic Model of the Public Understanding of Science.” *Science and Public Policy* 26 (5):313–19.

Dyer, Owen. 2018. “Researcher Who Edited Babies’ Genome Retreats from View as Criticism Mounts.” *British Medical Journal* 363 (1):k5113.

Ebenstein, Avraham. 2010. “The ‘Missing Girls’ of China and the Unintended Consequences of the One Child Policy.” *Journal of Human Resources* 45 (1):87–115.

Eberlein, Burkard, and Edgar Grande. 2005. “Beyond Delegation: Transnational Regulatory Regimes and the Eu Regulatory State.” *Journal of European Public Policy* 12 (1):89–112.

Edwards, Phillip, Ian Roberts, Mike Clarke, Carolyn DiGuiseppi, Reinhard Wentz, Irene Kwan, Rachel Cooper, Lambert Felix, and Sarah Pratap. 2009. “Methods to Increase Response to Postal and Electronic Questionnaires.” *Cochrane Database of Systematic Reviews* 3.

Eenennaam, Alison van, and Amy Young. 2018. “Public Perception of Animal Biotechnology.” In *Animal Biotechnology*, edited by Heiner Niemann and Christine Wrenzycki, 257–63. Springer, Cham.

Einsiedel, Edna. 2005. “Public Perceptions of Transgenic Animals.” *Revue Scientifique et Technique-Office International Des Epizooties* 24 (1):149.

Einsiedel, Edna, Erling Jelsøe, and Thomas Breck. 2001. “Publics at the Technology Table: The Consensus Conference in Denmark, Canada, and Australia.” *Public Understanding of Science* 10 (1):83–98.

Ellis, Gerry. 2016. “Impairment and Disability: Challenging Concepts of ‘Normality.’” In *Researching Audio Description*, 33–45. London: Palgrave Macmillan.

Esmark, Anders. 2020. “Technocracy at a Glance.” In *The New Technocracy*, 3–4.

Esvelt, Kevin, Andrea Smidler, Flaminia Catteruccia, and George Church. 2014. “Emerging Technology: Concerning RNA-Guided Gene Drives for the Alteration of Wild Populations.” *Ecology, Chromosomes and Gene Expression* 3:e03401.

European Commission. 2013. “What You Need to Know about Biosimilar Medicinal Products.”

———. 2019. “Medicinal Products for Human Use Containing or Consisting of GMOs: Interplay between the EU Legislation on Medicinal Products and GMOs.”

European Medicines Agency. 2012. “Committee for Advanced Therapies’ Activities Streamlined.” 2012.

———. 2016. “PRIME: Priority Medicines.” 2016. https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines .

———. 2018. “Guideline on the Quality, Non-Clinical and Clinical Aspects of Gene Therapy Medicinal Products.”

European Parliament. 2009. *Directive 2009/120/EC, Annex I, Part IV*.

European Union. n.d. “Responsible Research and Innovation.” https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation.

Evans, Mariah, Jonathan Kelley, and Esmail Zanjani. 2005. “The Ethics of Gene Therapy and Abortion: Public Opinion.” *Fetal Diagnosis and Therapy* 20 (3):223–34.

Evensen, Christian, Thomas Hoban, and Eric Woodrum. 2000. “Technology and Morality: Influences on Public Attitudes toward Biotechnology.” *Knowledge, Technology & Policy* 13 (1):43–57.

Eysenbach, Gunther, and Jeremy Wyatt. 2002. “Using the Internet for Surveys and Health Research.” *Journal of Medical Internet Research* 4 (2):E13.

Facey, Karen, Antoine Boivin, Javier Gracia, Helle Ploug Hansen, Alessandra Lo Scalzo, Jean Mossman, and Ann Single. 2010. “Patients’ Perspectives in Health Technology Assessment: A Route to Robust Evidence and Fair Deliberation.” *International Journal of Technology Assessment in Health Care* 26 (3):334–40.

Fallows, Deborah. 2005. “How Women and Men Use the Internet.” http://www.pewresearch.org/wp-content/uploads/sites/9/2005/12/PIP_Women_and_Men_online.pdf.

Fay, Nikta, and Nelly Panté. 2015. “Nuclear Entry of DNA Viruses.” *Frontiers in Microbiology* 6:467.

Fehse, Boris, and Ingo Roeder. 2008. “Insertional Mutagenesis and Clonal Dominance: Biological and Statistical Considerations.” *Gene Therapy* 15 (2):143–53.

Feldman, Martha, Anne Khademian, Helen Ingram, and Anne Schneider. 2006. “Ways of

Knowing and Inclusive Management Practices." *Public Administration Review* 66:89–99.

Fenech, Lisa. 2018. "Creating the Perfect Human Race: How Far Will We Go for Designer Families?" *Family Court Review* 56 (1):150–64.

Fenwick, Mark, Steven Van Uytsel, and Stefan Wrbka. 2014. "Introduction: Networks and Networked Governance." In *Transnational Business and the Law*, 3–9. Springer Berlin Heidelberg.

Fenwick, and Janice McMillan. 2012. "Public Participation and Public Service Modernization: Learning from New Labor?" *International Journal of Public Administration* 35 (6):367–78.

Ferrer, Rebecca, and William Klein. 2015. "Risk Perceptions and Health Behavior." *Current Opinion in Psychology* 5 (1):85–89.

Ferrua, Francesca, and Alessandro Aiuti. 2017. "Twenty-Five Years of Gene Therapy for ADA-SCID: From Bubble Babies to an Approved Drug." *Human Gene Therapy* 28 (11):972–81.

Fine, Jo-David, Leena Bruckner-Tuderman, Robin Eady, Eugene Bauer, Johann Bauer, Cristina Has, Adrian Heagerty, et al. 2014. "Inherited Epidermolysis Bullosa: Updated Recommendations on Diagnosis and Classification." *Journal of the American Academy of Dermatology* 70 (6):1103–26.

Fishkin, James, and Robert Luskin. 1999. "Bringing Deliberation to the Democratic Dialogue." In *The Poll with a Human Face: The National Issues Convention Experiment in Political Communication*, 3–38.

Fletcher, John. 1983. "Moral Problems and Ethical Issues in Prospective Human Gene Therapy." *Virginia Law Review* 69 (3):515–46.

Fletcher, John, and Gerd Richter. 1996. "Human Fetal Gene Therapy: Moral and Ethical Questions." *Human Gene Therapy* 7 (13):1605–14.

Flinn, Aisling, and Andrew Gennery. 2018. "Adenosine Deaminase Deficiency: A Review." *Orphanet Journal of Rare Diseases* 13 (1):1–7.

Flynn, James, Paul Slovic, and C. K. Mertz. 1994. "Gender, Race and Perception of Environmental Health Risks." *Risk Analysis* 14:1101–8.

Food & Drug Administration. n.d. “Biological Product Definitions.” https://www.fda.gov/media/108557/download.

———. 1993. “Federal Register Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products.” *Federal Register* 58 (197):53248-.

———. 2017. “FDA Approves Novel Gene Therapy to Treat Patients with a Rare Form of Inherited Vision Loss.” FDA News Release. 2017.

———. 2018. “Breakthrough Therapy.” 2018. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

———. 2019. “Center for Biologics Evaluation and Research (CBER).” 2019. https://www.fda.gov/about-fda/fda-organization/center-biologics-evaluation-and-research-cber.

Frewer, Lynn, Chaya Howard, and Richard Shepherd. 1997. “Public Concerns in the United Kingdom about General and Specific Applications of Genetic Engineering: Risk, Benefit, and Ethics.” *Science, Technology, & Human Values* 22 (1):98–124.

Friedmann, Theodore. 1992. “A Brief History of Gene Therapy.” *Nature Genetics* 2 (2):93–98.

Friedmann, Theodore, and Richard Roblin. 1972. “Gene Therapy for Human Genetic Disease?” *Science* 175 (4025):949–55.

Funk, Cary, and Meg Hefferon. 2018. “Public Views of Gene Editing for Babies Depend on How It Would Be Used.”

Funk, Cary, and Brian Kennedy. 2019. “Public Confidence in Scientists Has Remained Stable for Decades.” Pew Research Center. 2019. https://www.pewresearch.org/fact-tank/2019/03/22/public-confidence-in-scientists-has-remained-stable-for-decades/.

Funtowicz, Silvio, and Jerome Ravetz. 1994. “Uncertainty, Complexity and Post-normal Science.” *Environmental Toxicology and Chemistry: An International Journal* 13 (12):1881–85.

Gaj, Thomas, Shannon Sirk, Sai-lan Shui, and Jia Liu. 2016. “Genome-Editing Technologies: Principles and Applications.” *Cold Spring Harbor Perspectives in Biology* 8 (12):a023754.

Galanello, Renzo, and Raffaella Origa. 2010. “Beta-Thalassemia.” *Orphanet Journal of Rare Diseases* 5 (11).

Gallup, Inc. 2018. “Stem Cell Research.” 2018. https://news.gallup.com/poll/21676/Stem-Cell Research.aspx.

Ganne, Pratyusha, Robert Garrioch, and Marcela Votruba. 2015. “Perceptions and Understanding of Genetics and Genetic Eye Disease and Attitudes to Genetic Testing and Gene Therapy in a Primary Eye Care Setting.” *Ophthalmic Genetics* 36 (1):50–57.

Gaskell, George, Imre Bard, Agnes Allansdottir, Rui Vieira da Cunha, Peter Eduard, Juergen Hampel, Elisabeth Hildt, et al. 2017. “Public Views on Gene Editing and Its Uses.” *Nature Biotechnology* 20 (8):1038–52.

Gaspar, Bobby, Emma Bjorkegren, Kate Parsley, Kimberly Gilmour, Doug King, Joanna Sinclair, Fang Zhang, et al. 2006. “Successful Reconstitution of Immunity in ADA-SCID by Stem Cell Gene Therapy Following Cessation of PEG-ADA and Use of Mild Preconditioning.” *Molecular Therapy* 14 (4):505–13.

Gastil, John. 2018. “The Lessons and Limitations of Experiments in Democratic Deliberation.” *Annual Review of Law and Social Science* 14 (1):271–91.

Gaudet, Daniel, Julie Méthot, and John Kastelein. 2012. “Gene Therapy for Lipoprotein Lipase Deficiency.” *Current Opinion in Lipidology* 23 (4):310–20.

Gershoni, Moran, and Shmuel Pietrokovski. 2017. “The Landscape of Sex-Differential Transcriptome and Its Consequent Selection in Human Adults.” *BioMed Central Biology* 15 (7).

Gilley, Bruce. 2017. “Technocracy and Democracy as Spheres of Justice in Public Policy.” *Policy Sciences* 50:9–22.

Ginn, Samantha, Ian Alexander, Michael Edelstein, Mohammad Abedi, and Jo Wixon. 2013. “Gene Therapy Clinical Trials Worldwide to 2012–an Update.” *The Journal of Gene Medicine* 15 (2):65–77.

Ginn, Samantha, Anais Amaya, Ian Alexander, Michael Edelstein, and Mohammad Abedi. 2018. “Gene Therapy Clinical Trials Worldwide to 2017: An Update.” *The Journal of Gene Medicine* 20 (5):e3015.

Giri, Isabelle, Olivier Danos, and Moshe Yaniv. 1985. “Genomic Structure of the Cottontail Rabbit (Shope) Papillomavirus.” *Proceedings of the National Academy of Sciences* 82 (6):1580–84.

Goering, Sara. 2015. “Rethinking Disability: The Social Model of Disability and Chronic Disease.” *Current Reviews in Musculoskeletal Medicine* 8 (2):134–38.

Government of South Australia. 2016. “Get to Know Nuclear: Discover. Discuss. Decide.” 2016. https://nuclear.yoursay.sa.gov.au/know-nuclear.

Goyder, John, Keith Warriner, and Susan Miller. 2002. “Evaluating Socio-Economic Status (SES) Bias in Survey Nonresponse.” *Journal of Statistics Stockholm* 18 (1):1–12.

GraphPad Software Inc. 2012. “GraphPad Prism Version 6.01 for Windows.” California: GraphPad Software Inc.

Greely, Henry. 2019. “CRISPR’d Babies: Human Germline Genome Editing in the ‘He Jiankui Affair.’” *Journal of Law and the Biosciences* 6 (1):111–83.

Green, Erica, Katie Benner, and Robert Pear. 2018. “‘Transgender’ Could Be Defined Out of Existence Under Trump Administration.” *The New York Times,* 2018.

Green, Michael, Richard Treisman, and Tom Maniatis. 1983. “Transcriptional Activation of Cloned Human β-Globin Genes by Viral Immediate-Early Gene Products.” *Cell* 35 (1):137–48.

Greiling, Dorthea, and Arie Halachmi. 2010. “Accountability and Governance Issues: Introduction.” *Public Administration Quarterly* 34 (3):264–70.

———. 2013. “Accountability and Organisational Learning in the Public Sector.” *Public Performance & Management Review* 36 (3):380–406.

Griesenbach, Uta, Duncan Geddes, and Eric Alton. 2004. “Gene Therapy for Cystic Fibrosis: An Example for Lung Gene Therapy.” *Gene Therapy* 11 (1):S43–50.

Griffiths, Anthony. 2009. “Recombinant DNA Technology.” *Encyclopaedia Britannica*. https://www.britannica.com/science/recombinant-DNA-technology.

Grimm, Pamela. 2010. “Social Desirability Bias.” In *Wiley International Encyclopedia of Marketing*. John Wiley & Sons, Ltd.

Groves, Robert, Eleanor Singer, and Amy Corning. 2000. “Leverage-Saliency Theory of

Survey Participation." *The Public Opinion Quarterly* 64 (3):299–308.

Guiso, Luigi, Paola Sapienza, and Luigi Zingales. 2018. "Time Varying Risk Aversion." *Journal of Financial Economics* 128 (3):403–21.

Gurev, Sarah. 2017. "CRISPR in Popular Media: Sensationalism of Germline Editing in Human Embryos." *Intersect* 10 (2).

Gustafson, Per. 1998. "Gender Differences in Risk Perception: Theoretical and Methodological Perspectives." *Risk Analysis* 18 (6):805–11.

Hacein-Bey-Abina, Salima, Christof von Kalle, Manfred Schmidt, Françoise Le Deist, Nicolas Wulffraat, Elisabeth McIntyre, Isabelle Radford, et al. 2003. "A Serious Adverse Event after Successful Gene Therapy for X-Linked Severe Combined Immunodeficiency." *New England Journal of Medicine2* 348 (3):255–56.

Haimes, Erica, and Ken Taylor. 2017. "Sharpening the Cutting Edge: Additional Considerations for the UK Debates on Embryonic Interventions for Mitochondrial Diseases." *Life Sciences, Society and Policy* 13 (1):1–25.

Halioua-Haubold, Celine-Lea, James Peyer, James Smith, Zeeshaan Arshad, Matthew Scholz, David Brindley, and Robert MacLareng. 2017. "Regulatory Considerations for Gene Therapy Products in the US, EU, and Japan." *Yale Journal of Biology and Medicine* 90 (4):683–93.

Hampel, Jürgen, Uwe Pfenning, and Hans Peter Peters. 2000. "Attitudes towards Genetic Engineering." *New Genetics and Society* 19 (3):233–49.

Hampson, Grace, Adrian Towse, Steven Pearson, William Dreitlein, and Chris Henshall. 2018. "Gene Therapy: Evidence, Value and Affordability in the US Health Care System." *Journal of Comparative Effectiveness Research* 7 (1):15–28.

Hanna, Eve, Cécile Rémuzat, Pascal Auquier, and Mondher Toumi. 2017. "Gene Therapies Development: Slow Progress and Promising Prospect." *Journal of Market Access and Health Policy* 5 (1):1265293.

Harding, Ronnie. 1998. *Environmental Decision Making: The Roles of Scientists, Engineers and the Public*. Sydney: The Federation Press.

Harris, John. 1993. "Is Gene Therapy a Form of Eugenics?" *Bioethics* 7 (2–3):178–87.

———. 2007a. “Disability and Super-Ability.” In *Enhancing Evolution: The Ethical Case for Making Better People*, 72. Princeton University Press.

———. 2007b. “Enhancement Is a Moral Duty.” In *Enhancing Evolution: The Ethical Case for Making Better People*, 32–36. Princeton University Press.

Hawkes, Nigel. 2015. “UK’s Approval of Mitochondrial Donation Shows How Decisions on Gene Editing Can Be Made.” *British Medical Journal* 351:h6745.

Hayakawa, Takao, Ian Harris, Jeewon Joung, Nobuo Kanai, Shin Kawamata, Srinivasan Kellathur, Junichi Koga, et al. 2016. “Report of the International Regulatory Forum on Human Cell Therapy and Gene Therapy Products.” *Biologicals* 44 (5):467–79.

Heath, Jared. 2017. “Key Trends and Lessons from Australian Royal Commissions and Inquiries.” Corrs Chambers Westgarth. 2017.

Heinrich, Carolyn. 2003. “Outcomes–Based Performance Management in the Public Sector: Implications for Government Accountability and Effectiveness.” *Public Administration Review* 62 (6):712–25.

Helleiner, Eric, and Tony Porter. 2010. “Making Transnational Networks More Accountable.” *Economics, Management & Financial Markets* 5 (2):158–73.

Hendriks, Saskia, Noor Giesbertz, Annelien Bredenoord, and Sjoerd Repping. 2018. “Reasons for Being in Favour of or against Genome Modification: A Survey of the Dutch General Public.” *Human Reproduction Open* 3 (1):hoy008.

Henwood, Karen, Karen Parkhill, and Nick Pidgeon. 2008. “Science, Technology and Risk Perception: From Gender Differences to the Effects Made by Gender.” *Equal Opportunities International* 27 (8):662–76.

Hilson, Chris. 2020. “Hitting the Target? Analysing the Use of Targets in Climate Law.” *Journal of Environmental Law* 32 (2):195–220.

Hock, Sia Chong, Sia Ming Kian, and Chan Lai Wah. 2020. “Global Challenges in the Manufacture, Regulation and International Harmonization of GMP and Quality Standards for Biopharmaceuticals.” *Generics and Biosimilars Initiative Journal* 9 (2):52–63.

Hoffman, Steven, Grazia Caleo, Nils Daulaire, Stefan Elbe, Precious Matsoso, Elias Mossialos, Zain Rizvi, and John-Arne Røttingenh. 2015. “Strategies for Achieving Global Collective

Action on Antimicrobial Resistance." *Bulletin of the World Health Organisation* 93 (12):867–76.

Hogarth, Stuart, Gail Javitt, and David Melzer. 2008. "The Current Landscape for Direct-to-Consumer Genetic Testing: Legal, Ethical, and Policy Issues." *Annual Review of Genomics and Human Genetics* 9 (1):161–82.

Holland, Peter, and Tse Leng Tham. 2019. "To Test or Not to Test: Drug and Genetic Testing in the 21st Century Workplace." *Contemporary HRM Issues in the 21st Century*, 137–47.

Holm, Soren, and Gordon Jayson. 2003. "What Do Patients, Their Relatives and Medical Staff Know about Genetic Therapy?" *Bulletin of Medical Ethics* 173 (1):13–19.

Hondius, Frits. 1997. "Protecting Medical and Genetic Data." *European Journal of Health Law* 4 (4):361–88.

Hooghe, Marc, Sofie Marien, and Thomas de Vroome. 2012. "The Cognitive Basis of Trust. The Relation between Education, Cognitive Ability, and Generalized and Political Trust." *Intelligence* 40 (6):604–13.

Horn, Nancy, Jennifer Meek, Gregg Budahazi, and Magda Marquet. 2008. "Cancer Gene Therapy Using Plasmid DNA: Purification of DNA for Human Clinical Trials." *Human Gene Therapy* 6 (5):565–73.

Hu, R., and H. Deng. 2018. "A Crisis of Consumers' Trust in Scientists and Influence on Consumer Attitude." In *International Association of Agricultural Economists*, Q01-Q16.

Hudson, John, and Marta Orviska. 2011. "European Attitudes to Gene Therapy and Pharmacogenetics." *Drug Discovery Today* 16 (19):843–47.

Hughes, Randall, and Andrew Ellington. 2017. "Synthetic DNA Synthesis and Assembly: Putting the Synthetic in Synthetic Biology." *Cold Spring Harbor Perspectives in Biology* 9 (1):a023812.

Hunyadi, Mark. 2018. "Critical Approach to Bioethics." In *Treaty of Bioethics*, edited by Emmanuel Hirsch and François Hirsch, 51–63. Eres.

IBM Corp. 2016. "IBM SPSS Statistics for Windows." Armonk, NY: IBM Corp.

Iglesias-López, Carolina, Antonia Agustí, Mercè Obach, and Antonio Vallano. 2019. "Regulatory Framework for Advanced Therapy Medicinal Products in Europe and United

States.” *Frontiers in Pharmacology* 10.

Ingrams, Alex. 2019. “Public Values in the Age of Big Data: A Public Information Perspective.” *Policy & Internet* 11 (2):128–48.

Instinct and Reason. 2015. “Community Attitudes to Gene Technology.”

Iredale, Rachel, Gina Dolan, Kevin McDonald, and Maggie Kirk. 2003. “Public Attitudes to Human Gene Therapy: A Pilot Study in Wales.” *Public Health Genomics* 6 (3):139–46.

Irwin, Alan. 1995. *Citizen Science: A Study of People, Expertise and Sustainable Development*.

Isasi, Rosario, and Bartha Knoppers. 2006. “Mind the Gap: Policy Approaches to Embryonic Stem Cell and Cloning Research in 50 Countries.” *European Journal of Health Law* 13 (1):9–25.

Jackson, David, Robert Symons, and Paul Berg. 1972. “Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia Coli.” *Proceedings of the National Academy of Sciences* 69 (10):2904–9.

Jaffé, Andrew, Andrew Bush, Duncan Geddes, and Eric Alton. 1999. “Prospects for Gene Therapy in Cystic Fibrosis.” *Disease in Childhood* 80 (3):286–89.

Jarrell, Channah. 2006. “No Worldwide Consensus: The United Nations Declaration on Human Cloning.” *Georgia Journal of International and Comparative Law*, no. 1:205–30.

Jin, Xi, Yi-Da Yang, and You-Ming Li. 2008. “Gene Therapy: Regulations, Ethics and Its Practicalities in Liver Disease.” *World Journal of Gastroenterology* 14 (15):2303–7.

Jordan, Thomas. 2014. “Deliberative Methods for Complex Issues: A Typology of Functions That May Need Scaffolding.” *Group Facilitation: A Research and Applications Journa* 13:50–71.

Joss, Simon, and John Durant, eds. 1995. *Public Participation in Science: The Role of Consensus Conferences in Europe*. NMSI Trading Ltd.

Juengst, Eric. 1997. “Can Enhancement Be Distinguished from Prevention in Genetic Medicine?” *The Journal of Medicine and Philosophy* 22 (2):125–42.

Kahane, Guy, and Julian Savulescu. 2010. “The Value of Sex in Procreative Reasons.” *The American Journal of Bioethics* 10 (7):22–24.

Kaiser, Jocelyn. 2017. “A Human Has Been Injected with Gene-Editing Tools to Cure His Disabling Disease. Here’s What You Need to Know.” *Science*, 2017.

Kendal, Evie. 2017. “The Perfect Womb: Promoting Equality of (Fetal) Opportunity.” *Journal of Bioethical Inquiry* 14 (2):85–194.

Kent, Deborah. 2000. “Somewhere a Mockingbird.” In *Prenatal Testing and Disability Rights*, edited by Erik Parens and Adrienne Asch, 57–63. Washington, DC: Georgetown University Press.

Kerley, Bill, and Graeme Starr. 2000. “Public Consultation: Adding Value or Impeding Policy?” *Agenda: A Journal of Policy Analysis and Reform* 7:185–92.

Kim, Scott, Robert Holloway, Samuel Frank, C. Beck, C. Zimmerman, Renee Wilson, and Karl Kieburtz. 2006. “Volunteering for Early Phase Gene Transfer Research in Parkinson.” *Neurology* 66 (7):1010–15.

Kim, YoungHo, InKyoung Park, and SooJin Kang. 2018. “Age and Gender Differences in Health Risk Perception.” *Central European Journal of Public Health* 26 (1):54–59.

King, William, Gail Wyatt, Honghu Liu, John Williams, Anthony DiNardo, and Ronald Mitsuyasu. 2010. “Pilot Assessment of HIV Gene Therapy-Hematopoietic Stem Cell Clinical Trial Acceptability among Minority Patients and Their Advisors.” *Journal of the National Medical Association* 102 (12):1123–30.

Kirubarajan, Abirami, Jia Lu, and John-Paul Oliveria. 2017. “Vectors Have Both Magnitude and Direction: Considerations for Viral versus Non-Viral Vectors in Gene Therapy.” *Gene Editing and Personalized Medicine* 8 (1):29–31.

Klug, Bettina, Patrick Celis, Melanie Carr, and Jens Reinhardt. 2012. “Regulatory Structures for Gene Therapy Medicinal Products in the European Union.” In *Methods in Enzymology*, 507:337–54. Academic Press.

Knoppers, Bartha Maria, Adrian Thorogood, and Ruth Chadwick. 2013. “The Human Genome Organisation: Towards next-Generation Ethics.” *Genome Medicine* 5 (4):38.

Koch, Tom. 2010. “Enhancing Who? Enhancing What? Ethics, Bioethics, and Transhumanism.” *The Journal of Medicine and Philosophy* 35 (6):685–99.

Kohn, Donald. 2002. “Adenosine Deaminase Gene Therapy Protocol Revisited.” *Molecular*

Therapy 5 (2):96–97.

Kurki, Milja. 2011. “Democracy through Technocracy? Reflections on Technocratic Assumptions in EU Democracy Promotion Discourse.” *Journal of Intervention and Statebuilding* 5 (2):211–34.

Kuzma, Jennifer. 2018. “Regulating Gene-Edited Crops.” *Issues in Science and Technology* 35 (1):80–85.

Lamberts, Rod. 2017. “The Australian Beliefs and Attitudes towards Science Survey.” Canberra, Australia.

Langlois, Adèle. 2017. “The Global Governance of Human Cloning: The Case of UNESCO.” *Palgrave Communications* 3 (1):1–8.

Lanphier, Edward, and Fyodor Urnov. 2015. “Don’t Edit the Human Germ Line.” *Nature* 519 (7544):410.

Lau, Francis. 2017. “Methods for Correlational Studies.” In *Handbook of EHealth Evaluation: An Evidence-Based Approach*, 213–26. University of Victoria.

Lavrakas, Paul. 2008. “Cross-Sectional Survey Design.” In *Encyclopedia of Survey Research Methods*. Thousand Oaks: Sage Publications.

Lederberg, Joshua. 1963. “Molecular Biology, Eugenics and Euphenics.” *Nature* 198 (4879):428–29.

Leighninger, Matt. 2012. “Mapping Deliberative Civic Engagement.” In *Democracy in Motion: Evaluating the Practice and Impact of Deliberative Civic Engagement*, 28. Oxford University Press.

Lenzi, Rebecca, Bruce Altevogt, and Lawrence Gostin. 2014. “Oversight of Gene Transfer Research.” In *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee*, 41–44. Washington DC: National Academies Press.

Lessem, Ronnie, and Alexander Schieffer. 2016. *Integral Research and Innovation: Transforming Enterprise and Society*. CRC Press.

Li, S.D., and L Huang. 2006. “Gene Therapy Progress and Prospects: Non-Viral Gene Therapy by Systemic Delivery.” *Gene Therapy* 13 (18):1313–19.

Library of Congress. 2015. “Restrictions on Genetically Modified Organisms: China.” 2015. https://www.loc.gov/law/help/restrictions-on-gmos/china.php.

Lieshout, Emile van, and Vaille Dawson. 2016. “Knowledge of, and Attitudes towards Health-Related Biotechnology Applications amongst Australian Year 10 High School Students.” *Journal of Biological Education* 15 (3):329–44.

Liu, Zi-ming, Chang Liu, Jun-ying Li, Chun-hua Yu, and Yu Jiang. 2011. “The Attitude of Oncology Physicians and Nurses to the Acceptance of New Drugs for Gene Therapy.” *Journal of Cancer Education* 26 (2):248–53.

Lodish, Harvey, Arnold Berk, Lawrence Zipursky, Paul Matsudaira, David Baltimore, and James Darnell. 2000. “Viruses: Structure, Function, and Use.” In *Molecular Cell Biology. 4th Edition.* New York: W. H. Freeman and Company.

Loewenstein, George. 2000. “Emotions in Economic Theory and Economic Behavior.” *American Economic Review* 90 (2):426–32.

Loney, Georgia. 2017. “Cystic Fibrosis Patients, Families Angry over Latest Refusal to Subsidise Drug Orkambi.” *ABC News*, 2017.

Lowery, David. 2013. “Lobbying Influence: Meaning, Measurement and Missing.” *Interest Groups & Advocacy* 2:1–26.

Lowthorp, Leah. 2017. “CGS at the Oviedo Convention’s 20th Anniversary.” Center for Genetics and Society. 2017.

Lull, Robert, Dietram Scheufele, Kathleen Jamieson, and Dan Kahan. 2017. “Understanding and Overcoming Fear of the Unnatural in Discussion of GMOs.” In *The Oxford Handbook of the Science of Science Communication*, 413. New York: Oxford University Press.

Lundstrom, Kenneth. 2018. “Viral Vectors in Gene Therapy.” *Diseases* 6 (2):42.

Lynch, Carmel, Monika Clowes, William Osborne, Alexander Clowes, and Dusty Miller. 1992. “Long-Term Expression of Human Adenosine Deaminase in Vascular Smooth Muscle Cells of Rats: A Model for Gene Therapy.” *Proceedings of the National Academy of Sciences* 89 (3):1138–42.

Ma, Hong, Nuria Marti-Gutierrez, Sang-Wook Park, Jun Wu, Yeonmi Lee, Keiichiro Suzuki, Amy Koski, et al. 2017. “Correction of a Pathogenic Gene Mutation in Human Embryos.”

Nature. https://doi.org/doi:10.1038/nature23305.

Macer, Darryl. 1992. “Public Acceptance of Human Gene Therapy and Perceptions of Human Genetic Manipulation.” *Human Gene Therapy* 3 (5):511–18.

Macer, Darryl, Shiro Akiyama, Angeles Tan Alora, Yukiko Asada, Jayapaul Azariah, Hilda Azariah, Maureen Boost, et al. 1995. “International Perceptions and Approval of Gene Therapy.” *Human Gene Therapy* 6 (6):791–803.

Macer, Darryl, Yoshihiro Okada, Makoto Nakagawa, MaryAnn Chen Ng, and Masakazu Inaba. 2007. “Changing Hopes and Concerns about Gene Therapy in Japan.” *Journal of Commercial Biotechnology* 13 (3):209–22.

Macklin, Jenny. 1993. “Healthy Participation: Acheiving Greater Public Participation and Accountability in the Australian Healthcare System.” *Background Paper (National Health Strategy (Australia) No. 12*.

Macpherson, Ignacio, María Roqué, and Ignacio Segarra. 2019. “Ethical Challenges of Germline Genetic Enhancement.” *Frontiers in Genetics* 10 (1):767.

Macpherson, Janet, and John Rasko. 2014. “Gene Therapy Clinical Trials: The Australian Path to the End of Suffering.” *The Journal of Cell Therapy* 16 (4):S51–52.

Maeder, Morgan, and Charles Gersbach. 2016. “Genome-Editing Technologies for Gene and Cell Therapy.” *Molecular Therapy* 24 (3):430–46.

Maginnis, Melissa. 2018. “Virus–Receptor Interactions: The Key to Cellular Invasion.” *Journal of Molecular Biology* 430 (17):2590–2611.

Mali, Shrikant. 2013. “Delivery Systems for Gene Therapy.” *Indian Journal of Human Genetics* 19 (1):3–8.

Maniatis, Tom, Sim Gek Kee, Argiris Efstratiadis, and Fotis Kafatos. 1976. “Amplification and Characterization of a β-Globin Gene Synthesized in Vitro.” *Cell* 8 (2):163–82.

Marotoa, Michelle, and David Pettinicchio. 2014. “Disability, Structural Inequality, and Work: The Influence of Occupational Segregation on Earnings for People with Different Disabilities.” *Research in Social Stratification and Mobility* 38:76–92.

Marques, Mathew, Christine Critchley, and Jarrod Walshe. 2015. “Attitudes to Genetically Modified Food over Time: How Trust in Organizations and the Media Cycle Predict

Support.” *Public Understanding of Science* 24 (5):601–18.

Marshall, Eliot. 1999. “Gene Therapy Death Prompts Review of Adenovirus Vector.” *Science* 286 (5448):2244–45.

Marshall, Eliot, and Michael Price. 2013. “U.S. Supreme Court Strikes Down Human Gene Patents.” *Science*.

Martiniello-Wilks, Rosetta, and John Rasko. 2007. “Cell and Gene Therapy in Australia.” *Cytotherapy* 9 (3):209–21.

Mayor, Susan. 2005. “UN Committee Approves Declaration on Human Cloning.” *The British Medical Journal* 330:496.

McCaughey, Tristan, David Budden, Paul Sanfilippo, George Gooden, Eva Fenwick Li Fan, Gwyneth Rees, Casimir MacGregor, et al. 2019. “A Need for Better Understanding Is the Major Determinant for Public Perceptions of Human Gene Editing.” *Human Gene Therapy* 3 (1):36–43.

McCaughey, Tristan, Paul Sanfilippo, George Gooden, David Budden, Eva Fenwick, Gwyneth Rees, Casimir MacGregor, et al. 2016. “A Global Social Media Survey of Attitudes to Human Genome Editing.” *Cell Stem Cell* 18 (5):569–72.

Medical Services Advisory Committee. 2016a. “About MSAC.” 2016.

———. 2016b. “Public Consultation.” 2016. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/Factsheet-08.

———. 2020. “1623 - Voretigene Neparvovec (Luxturna) for the Treatment of Biallelic RPE-65-Mediated Inherited Retinal Dystrophies.” MSAC Applications. 2020. http://msac.gov.au/internet/msac/publishing.nsf/Content/1623-public.

Meikar, Oliver, Matteo Da Ros, Heidi Liljenbäck, Jorma Toppari, and Noora Kotaja. 2010. “Accumulation of PiRNAs in the Chromatoid Bodies Purified by a Novel Isolation Protocol.” *Experimental Cell Research* 316 (9). Elsevier Inc.:1567–75. https://doi.org/10.1016/j.yexcr.2010.02.023.

Mercola, Karen, Menashe Bar-Eli, Howard Stang, Dennis Slamon, and Martin Cline. 1982. “Insertion of New Genetic Information into Bone Marrow Cells of Mice: Comparison of Two Selectable Genes.” *Annals of the New York Academy of Sciences* 397 (1):272–80.

Mercola, Karen, Howard Stang, Jeffrey Browne, Winston Salser, and Martin Cline. 1980. "Insertion of a New Gene of Viral Origin into Bone Marrow Cells of Mice." *Science* 208 (4447):1033–35.

Mitton, Craig, Neale Smith, Stuart Peacock, Brian Evoy, and Julia Abelson. 2009. "Public Participation in Health Care Priority Setting: A Scoping Review." *Health Policy* 91 (3):219–28.

Modell, Bernadette. 1977. "Total Management of Thalassaemia Major." *Archives of Disease in Childhood* 52 (6):489.

Monckton, Darren. 2019. "Manage Risk of Accidental Gene Editing of Germline." *Nature* 568:458.

Monroe, Martha, and Damian Adams. 2012. "Increasing Response Rates to Web-Based Surveys." *Journal of Extension* 50 (6):6TOT7.

Montgomery, Guy, Joel Erblich, Terry DiLorenzo, and Dana Bovbjerg. 2003. "Family and Friends with Disease: Their Impact on Perceived Risk." *Preventive Medicine* 37 (3):242–49.

Montgomery, Jonathan. 2018. "Modification of the Human Genome: Human Rights Challenges Raised by Scientific and Technological Developments." In *20th Anniversary of the Oviedo Convention: Relevance and Challenges*. Strasbourg, France: Council of Europe.

Montoliu, Lluis, Jennifer Merchant, François Hirsch, Marion Abecassis, Pierre Jouannet, Bernard Baertschi, Cyril Sarrauste de Menthière, and Hervé Chneiweiss. 2018. "ARRIGE Arrives: Toward the Responsible Use of Genome Editing." *The CRISPR Journal* 1 (2):128–29.

Moore, Danna, and John Tarnai. 2002. "Evaluating Nonresponse Error in Mail Surveys." In *Survey Nonresponse*, 197–211. New York: John Wiley & Sons.

Moraczewski, Albert. 1991. "The Human Genome Project and the Catholic Church." *International Journal of Bioethics* 2 (4):229–34.

Morrison, Michael, and Stevienna de Saille. 2019. "CRISPR in Context: Towards a Socially Responsible Debate on Embryo Editing." *Nature Humanities & Social Sciences Communications* 5 (1):1–9.

Mourby, Miranda, and Michael Morrison. 2020. “Gene Therapy Regulation: Could in-Body Editing Fall through the Net?” *European Journal of Human Genetics Volume* 28 (1):979–981.

Müller, Hermann. 1987. “Human Gene Therapy: Possibilities and Limitations.” *Cellular and Molecular Life Sciences* 43 (4):375–78.

Mulligan, Richard, Bruce Howard, and Paul Berg. 1979. “Synthesis of Rabbit Beta-Globin in Cultured Monkey Kidney Cells Following Infection with a SV40 B-Globin Recombinant Genome.” *Nature* 277:11.

Murray, James, and William Little. 1965. *The Shorter Oxford English Dictionary*. Third. Oxford : Clarendon Press.

Musunuru, Kiran, William Lagor, and Joseph Miano. 2017. “What Do We Really Think about Human Germline Genome Editing, and What Does It Mean for Medicine?” *Circulation: Cardiovascular Genetics* 10 (3):e001910.

Napolitano, Carol, and Oladele Ogunseitan. 1999. “Gender Differences in the Perception of Genetic Engineering Applied to Human Reproduction.” *Social Indicators Research* 46 (2):191–204.

National Academies of Sciences, Engineering, and Medicine, National Academy of Medicine, National Academy of Sciences, and and Ethical Considerations Committee on Human Gene Editing: Scientific, Medical. 2017. “Somatic Genome Editing.” In *Human Genome Editing: Science, Ethics, and Governance.*, 83–110. Washington DC: National Academies Press.

National Academies of Sciences Engineering and Medicine. 2017. “International Research, Oversight and Regulations.” In *Human Genome Editing: Science, Ethics, and Governance*, 262. National Academies Press.

National Health and Medical Research Council. 2020a. “Mitochondrial Donation Community Consultation Citizens’ Panel Position Statement.” Canberra.

———. 2020b. “Mitochondrial Donation Community Consultation Report.”

National Insitutes of Health: Office of Science Policy. 2019. “Amended Charter: Novel and Exceptional Technology and Research Advisory Committee (Formerly Recombinant DNA Advisory Committee).”

———. 2020. “Recombinant DNA Advisory Committee Archives.” 2020. https://osp.od.nih.gov/biotechnology/recombinant-dna-advisory-committee/.

National Insitutes of Health. 1976. *Recombinant DNA Research — Guidelines*. United States.

National Research Council of the National Academies. 2010. “National and International Coordination and Collaboration.” In *Defending Planet Earth: Near-Earth-Object Surveys and Hazard Mitigation Strategies*, 93–97.

Necker, Sarah, and Michael Ziegelmeyer. 2016. “Household Risk Taking after the Financial Crisis.” *The Quarterly Review of Economics and Finance* 59 (1):141–60.

Neergaard, Lauran. 2017. “First Embryo Gene-Repair Holds Promise for Inherited Disease.” *ABC News*, 2017. http://abcnews.go.com/Technology/wireStory/safe-repair-disease-causing-gene-human-embryos-48991523.

Neuwelt, Pat. 2007. *Community Participation Toolkit: A Resource for Primary Health Organisations*. Wellington: Steele Roberts Ltd Publishers.

Newman, Abraham, and David Zaring. 2013. “Regulatory Networks: Power, Legitimacy and Compliance.” In *Interdisciplinary Perspectives on International Law and International Relations. The State of the Art*, 244–65. Cambridge University Press.

Newson, A. J., S. de Lacey, D. K. Dowling, S. Murray, C. M. Sue, D. R. Thorburn, L. Gillam, and C. Degeling. 2019. “Public Attitudes towards Novel Reproductive Technologies: A Citizens’ Jury on Mitochondrial Donation.” *Human Reproduction* 34 (4):751–757.

Ng, Mary Ann, Chika Takeda, Tomoyuki Watanabe, and Darryl Macer. 2000. “Attitudes of the Public and Scientists to Biotechnology in Japan at the Start of 2000.” *Eubios Journal of Asian and International Bioethics: EJAIB* 10 (4):106–13.

Niccol, Andrew. 1997. *Gattaca*. United States.

Nicol, Dianne, Lisa Eckstein, Michael Morrison, Jacob Sherkow, Margaret Otlowski, Tess Whitton, Tania Bubela, et al. 2017. “Key Challenges in Bringing CRISPR-Mediated Somatic Cell Therapy into the Clinic.” *Genome Medicine* 9 (1):85.

Nielsen, Ragnar Heldt. 1995. “Consensus Conference on Gene Therapy.”

Nisbet, Matthew. 2004. “Public Opinion about Stem Cell Research and Human Cloning.” *Public Opinion Quarterly* 68 (1):131–54.

Nisbet, Matthew, and Robert Goidel. 2007. “Understanding Citizen Perceptions of Science Controversy: Bridging the Ethnographic—survey Research Divide.” *Public Understanding of Science* 16 (4):421–40.

Nisbet, Matthew, and Dietram Scheufele. 2009. “What’s next for Science Communication? Promising Directions and Lingering Distractions.” *American Journal of Botany* 96 (10):1767–78.

Normile, Dennis. 2019. “Chinese Scientist Who Produced Genetically Altered Babies Sentenced to 3 Years in Jail.” *Science*.

O’Doherty, Kieran, and Edna Einsiedel. 2020. “Introduction.” In *Public Engagement and Emerging Technologies*, edited by Kieran O’Doherty and Edna Einsiedel, 1–7. Vancouver: UBC Press.

O’sullivan, Gabrielle, Zlatibor Velickovic, Michelle Keir, Janet Macpherson, and John Rasko. 2019. “Cell and Gene Therapy Manufacturing Capabilities in Australia and New Zealand.” *Cytotherapy* 21 (12):1258–73.

Office of the Gene Technology Regulator. 2018. “Genetically Modified (GM) Canola in Australia.”

———. 2019. *Gene Technology Amendment (2019 Measures No. 1) Regulations 2019*.

Omair, Aamir. 2015. “Selecting the Appropriate Study Design for Your Research: Descriptive Study Designs.” *Journal of Health Specialties* 3 (3):153–56.

Onodera, Masafumi, and Yukio Sakiyama. 2005. “Adenosine Deaminase Deficiency as the First Target Disorder in Gene Therapy.” *Expert Opinion on Investigational Drugs* 9 (3):543–49.

Organisation for Economic Co-operation and Development. 2017. *New Health Technologies Managing Access, Value and Sustainability*. Paris: OECD Publishing.

Ormond, Kelly, Douglas Mortlock, Derek Scholes, Yvonne Bombard, Lawrence Brody, Andrew Faucett, Nanibaa’ Garrison, et al. 2017. “Human Germline Genome Editing.” *The American Journal of Human Genetics* 101 (2):167–76.

Orth, G., F. Vielle, and J. P. Changeux. 1967. “On the Arginase of the Shope Papillomas.” *Virology* 31 (4):729–32.

Ostry, Jonathan, and Atish Ghosh. 2013. “Obstacles to International Policy Coordination, and How to Overcome Them.”

Otlowski, Margaret, Jane Tiller, Kristine Barlow-Stewart, and Paul Lacaze. 2019. “Genetic Testing and Insurance in Australia.” *Australian Journal of General Practice* 48 (3):96–99.

Owen, Richard, Phil Macnaghten, and Jack Stilgoe. 2012. “Responsible Research and Innovation: From Science in Society to Science for Society, with Society.” *Science and Public Policy* 39 (6):751–60.

Panko, Ben. 2016. “CRISPR-Edited Mushroom Dodges U.S. Regulators.” *Science*, 2016.

Papadopoulos, Nikolaos, Philip Bates, Philip Bardin, Alberto Papi, Shih Leir, David Fraenkel, Jon Meyer, et al. 2000. “Rhinoviruses Infect the Lower Airways.” *Journal of Infectious Diseases* 181 (6):1875–84.

Partridge, Brad, Mair Underwood, Jayne Lucke, Helen Bartlett, and Wayne Hall. 2009. “Ethical Concerns in the Community about Technologies to Extend Human Life Span.” *The American Journal of Bioethics* 9 (12):68–76.

Peng, Xizhe. 1991. *Demographic Transition in China: Fertility Trends since the 1950s.* Oxford: Clarendon Press.

Pew Research Center. 2016. “U.S. Public Wary of Biomedical Technologies to ‘Enhance’ Human Abilities.” *Pew Research Center*.

Pitrelli, Nico. 2003. “The Crisis of the ‘Public Understanding of Science’ in Great Britain.” *Journal of Science Communication* 2 (1):F01.

Pivetti, Monica. 2007. “Natural and Unnatural: Activists’ Representations of Animal Biotechnology.” *New Genetics and Society* 26 (2):137–57.

Prasser, Scott. 2020. “How Royal Commissions Can Both Help and Hinder.” The Centre for Independent Studies. 2020.

Privitera, Giovanni. 2014. “Survey and Correlational Research Designs.” In *Research Methods for the Behavioral Sciences*, edited by Frederick Gravetter and Lori-Ann Forzano, 225–60. Sage Publications.

Procknow, Greg, and Tonette Rocco. 2016. “The Unheard, Unseen, and Often Forgotten: An Examination of Disability in the Human Resource Development Literature.” *Human*

Resource Development Review 15 (4):379–403.

Quick, Kathryn, and John Bryson. 2016. “Theories of Public Participation in Governance.” In *Handbook of Theories of Governance*. Edward Elgar Publishing.

Quillent, Caroline, Estelle Oberlin, Joséphine Braun, Dominique Rousset, Gustavo Gonzalez-Canali, Patricia Métais, Luc Montagnier, Jean-Louis Virelizier, Fernando Beretta, and Alberto Arenzana-Seisdedos. 1998. “HIV-1-Resistance Phenotype Conferred by Combination of Two Separate Inherited Mutations of CCR5 Gene.” *The Lancet* 351 (9095):14–18.

R Core Team. 2018. “R: A Language and Environment for Statistical Computing.” Vienna, Austria: R Foundation for Statistical Computing. http://www.r-project.org/.

Rabino, Isaac. 2003. “Gene Therapy: Ethical Issues.” *Theoretical Medicine and Bioethics* 24 (1):31–58.

Radcliffe, Shawn. 2016. “Controversy Over Choosing Sex of Child Using IVF.” *Healthline*, 2016.

Ramamoorth, Murali, and Aparna Narvekar. 2015. “Non Viral Vectors in Gene Therapy- An Overview.” *Journal of Clinical and Diagnostic Research* 1 (9):GE01.

Rayner, Steve. 2003. “Democracy in the Age of Assessment: Reflections on the Roles of Expertise and Democracy in Public-Sector Decision Making.” *Science and Public Policy* 30 (3):163–70.

Regalado, Antonio. 2016a. “Meet the Moralist Policing Gene Drives, a Technology That Messes with Evolution.” *MIT Technology Review*, 2016.

———. 2016b. “Top U.S. Intelligence Official Calls Gene Editing a WMD Threat.” *MIT Technology Review*, 2016.

Reindal, Solveig. 2000. “Disability, Gene Therapy and Eugenics - a Challenge to John Harris.” *Journal of Medical Ethics* 26 (1):89–94.

Reinsurance Group of America. 2019. “Genetics and Insurance: Challenges and Opportunities II.”

Resnik, David. 2000. “The Moral Significance of the Therapy-Enhancement Distinction in Human Genetics.” *Cambridge Quarterly of Healthcare Ethics* 9 (3):365–77.

Rinčić, Iva, Amir Muzur, and Stephen Sodeke. 2018. “Sex Selection, Gender Selection, and Sexism.” In *Clinical Ethics At the Crossroads of Genetic and Reproductive Technologies*, 113–30.

Robbins, Paul, and Steven Ghivizzani. 1998. “Viral Vectors for Gene Therapy.” *Pharmacology & Therapeutics* 80 (1):35–47.

Robillard, Julie, Dylan Roskams-Edris, Boris Kuzeljevic, and Judy Illes. 2014. “Prevailing Public Perceptions of the Ethics of Gene Therapy.” *Human Gene Therapy* 25:740–46.

Robillard, Julie, Louise Whiteley, Thomas Wade Johnson, Jonathan Lim, Wyeth Wasserman, and Judy Illes. 2013. “Utilizing Social Media to Study Information-Seeking and Ethical Issues in Gene Therapy.” *Journal of Medical Internet Research* 15 (3):e44.

Rogers, Stanfield. 1971. “Change in the Structure of Shope Papilloma Virus-Induced Arginase Associated with Mutation of the Virus.” *Journal of Experimental Medicine* 134 (6):1442–52.

Rogers, Stanfield, A. Lowenthal, H. G. Terheggen, and J. P. Columbo. 1973. “Induction of Arginase Activity with the Shope Papilloma Virus in Tissue Culture Cells from an Argininemic Patient.” *Journal of Experimental Medicine* 137 (4):1091–96.

Rolstad, Sindre, John Adler, and Anna Rayden. 2011. “Response Burden and Questionnaire Length: Is Shorter Better? A Review and Meta-Analysis.” *Value in Health* 14 (8):1101–8.

Rosemann, Achim, Soochow Li Jiang, and Xinqing Zhang. 2017. “The Regulatory and Legal Situation of Human Embryo, Gamete and Germ Line Gene Editing Research and Clinical Applications in the People’s Republic of China.”

Rosenberg, Steven. 1992. “Gene Therapy for Cancer.” *Journal of the American Medical Association* 268 (17):2416–19.

Rosenberg, Steven, Paul Aebersold, Kenneth Cornetta, Attan Kasid, Richard Morgan, Robert Moen, Evelyn Karson, et al. 1990. “Gene Transfer into Humans—immunotherapy of Patients with Advanced Melanoma, Using Tumor-Infiltrating Lymphocytes Modified by Retroviral Gene Transduction.” *New England Journal of Medicine* 323 (9):570–78.

Rosenberg, Steven, French Anderson, Michael Blaese, Patrick Hwu, John Yannelli, James Yang, Suzanne Topalian, Douglas Schwartzentruber, Jeffrey Weber, and Stephen Ettinghausen. 1993. “The Development of Gene Therapy for the Treatment of Cancer.”

Annals of Surgery 218 (4):455–63.

Ross, Kerry. 2007. “Providing ‘Thoughtful Feedback’: Public Participation in the Regulation of Australia’s First Genetically Modified Food Crop.” *Science and Public Policy* 34 (3):213–225.

Roten, Fabienne Crettaz von. 2004. “Gender Differences in Attitudes toward Science in Switzerland.” *Public Understanding of Science* 13 (2):191–99.

Rowe, Gene, and Lynn Frewer. 2000. “Public Participation Methods: A Framework for Evaluation.” *Science, Technology, & Human Values* 25 (1):3–29.

Russell, Wendy. 2017. “The Macro--impacts of Citizen Deliberation Processes.”

Saba, Anna, Anna Moles, and Lynn Frewer. 1998. “Public Concerns about General and Specific Applications of Genetic Engineering: A Comparative Study between the UK and Italy.” *Nutrition & Food Science* 98 (1):19–29.

Salleh, Anna. 2019. “CRISPR Editing of Plants and Animals Gets Green Light in Australia. Now What?” *ABC News*, 2019.

Sambrook, Joseph, Heiner Westphal, P. R. Srinivasan, and Renato Dulbecco. 1968. “The Integrated State of Viral DNA in SV40-Transformed Cells.” *Proceedings of the National Academy of Sciences* 60 (4):1288–95.

Sandhu, Jasbir, Armand Keating, and Nobumichi Hozumi. 1997. “Human Gene Therapy.” *Critical Reviews in Biotechnology* 17 (4):307–26.

Sato, Hajime, and Akira Akabayashi. 2005. “Bioethical Policymaking for Advanced Medical Technologies: Institutional Characteristics and Citizen Participation in Eight OECD Countries.” *Review of Policy Research* 22 (4):571–87.

Savulescu, Julian. 2001. “Harm, Ethics Committees and the Gene Therapy Death.” *Journal of Medical Ethics* 27 (3):148–50.

———. 2009. “Genetic Interventions and the Ethics of Enhancement of Human Beings.” In *Readings in the Philosophy of Technology*, edited by David Kaplan, 2nd ed., 426–28. Rowman & Littlefield Publishers Inc.

Saxon, Diane, Dean Garratt, Peter Gilroy, and Clive Cairns. 2003. “Collecting Data in the Information Age: Exploring Web-Based Survey Methods in Educational Research.”

Research in Education 69 (1):51–66.

Scarce, Kevin. 2016. “Nuclear Fuel Cycle Royal Commission Report.”

Scheufele, Dietram. 2000. “Agenda-Setting, Priming, and Framing Revisited: Another Look at Cognitive Effects of Political Communication.” *Mass Communication and Society* 3 (2–3):297–316.

———. 2011. “Modern Citizenship or Policy Dead End? Evaluating the Need for Public Participation in Science Policy Making, and Why Public Meetings May Not Be the Answer.” *Joan Shorenstein Center on the Press, Politics and Public Policy Research Paper Series*, Paper# R-34.

Scheufele, Dietram, Michael Xenos, Emily Howell, Kathleen Rose, Dominique Brossard, and Bruce Hardy. 2017. “US Attitudes on Human Genome Editing.” *Science* 357 (6351):553–54.

Schneider, Christian, Patrick Celis, Paula Salmikangas, Bernd Jilma, Bruno Flamion, Lyubina Racheva Todorova, Anna Paphitou, et al. 2010. “Challenges with Advanced Therapy Medicinal Products and How to Meet Them.” *Nature Reviews Drug Discovery* 9 (3):195–201.

Schomberg, Rene Von. 2013. “A Vision of Responsible Research and Innovation.” In *Responsible Innovation: Managing the Responsible Emergence of Science and Innovation in Society*, 51–74.

Scully, Jackie, Christine Rippberger, and Christoph Rehmann-Sutter. 2004. “Non-Professionals’ Evaluations of Gene Therapy Ethics.” *Social Science & Medicine5* 58 (7):1415–25.

Secko, David, Nina Preto, Simon Niemeyer, and Michael Burgess. 2009. “Informed Consent in Biobank Research: A Deliberative Approach to the Debate.” *Social Science & Medicine* 68 (4):781–89.

Servick, Kelly. 2017. “A Boy with a Rare Disease Gets New Skin, Thanks to Gene-Corrected Stem Cells.” *Science*, 2017.

———. 2019. “Controversial U.S. Bill Would Lift Supreme Court Ban on Patenting Human Genes.” *Science*.

Shampo, Marc, and Robert Kyle. 2003. “Paul Berg—American Nobel Laureate.” *Mayo Clinical Proceedings* 78 (11):1435.

Sheridan, Cormac. 2011. “Gene Therapy Finds Its Niche.” *Nature Biotechnology* 29 (2):121–28.

Sherman, Erik. 2017. “Genetic Engineering Will Make Income Inequality Much Worse.” *Forbes*, 2017.

Shukla, Vaishali, Enrique Seoane-Vazquez, Souhiela Fawaz, Lawrence Brown, and Rosa Rodriguez-Monguio. 2019. “The Landscape of Cellular and Gene Therapy Products: Authorization, Discontinuations, and Cost.” *Human Gene Therapy Clinical Development* 30 (3):102–13.

Siegrist, Michael. 2000. “The Influence of Trust and Perceptions of Risks and Benefits on the Acceptance of Gene Technology.” *Risk Analysis* 20 (2):195–203.

Silvers, Anita. 2003. “On the Possibility and Desirability of Constructing a Neutral Conception of Disability.” *Heoretical Medicine and Bioethics* 24 (6):471–87.

Simis, Molly, Haley Madden, Michael Cacciatore, and Sara Yeo. 2016. “The Lure of Rationality: Why Does the Deficit Model Persist in Science Communication?” *Public Understanding of Science* 25 (4):400–414.

Simmons, Danielle. 2008. “Genetic Inequality: Human Genetic Engineering.” *Nature Education* 1 (1):173.

Simon, Richard. 2010. “Gender Differences in Knowledge and Attitude towards Biotechnology.” *Public Understanding of Science* 19 (6):642–653.

Simonsen, William, and Mark Robbins. 2000. *Citizen Participation in Resource Allocation*. Boulder: Westview Press.

Sinclair, Martha, Joanne O’Toole, Manori Malawaraarachchi, and Karin Leder. 2012. “Comparison of Response Rates and Cost-Effectiveness for a Community-Based Survey: Postal, Internet and Telephone Modes with Generic or Personalised Recruitment Approaches.” *BMC Medical Research Methodology* 12 (1):132.

Singer, Eleanor, Amy Corning, and Mark Lamias. 1998. “Trends: Genetic Testing, Engineering, and Therapy: Awareness and Attitudes.” *The Public Opinion Quarterly* 62

(4):633–64.

Sjöberg, Lennart. 2000. “Factors in Risk Perception.” *Risk Analysis* 20 (1):1–12.

———. 2004. “Principles of Risk Perception Applied to Gene Technology: To Overcome the Resistance to Applications of Biotechnology, Research on Risk Perception Must Take a Closer Look at the Public’s Reasons for Rejecting This Technology.” *EMBO Reports* 5 (1S):S47–51.

Skipper, Kristian, and Jacob Mikkelsen. 2019. *Toward In Vivo Gene Therapy Using CRISPR*. *CRISPR Gene Editing*. Humana Press, New York.

Slater, Michael, and Andrew Hayes. 2015. “Injury News Coverage, Relative Concern, and Support for Alcohol-Control Policies: An Impersonal Impact Explanation.” *Journal of Health Communication* 20 (1):51–59.

Slezak, Michael. 2014. “Genes Still Patentable in Australia as Appeal Rejected.” *New Scientist*, 2014.

Slovic, Paul. 1987. “Perception of Risk.” *Science* 236 (4799):280–85.

———. 1999. “Trust, Emotion, Sex, Politics, and Science: Surveying the Risk-Assessment Battlefield.” *Risk Analysis* 19 (4):689–701.

Smith, Aaron. 2014. “U.S. Views of Technology and the Future.”

Smith, Graham, and Maija Setälä. 2018. “Mini-Publics and Deliberative Democracy.” In *The Oxford Handbook of Deliberative Democracy*, 300–314.

Smithson, Michael. 2018. “Trusted Autonomy Under Uncertainty.” In *Foundations of Trusted Autonomy*, 185–201. Springer, Cham.

So, Derek, Erika Kleiderman, Seydina Touré, and Yann Joly. 2017. “Disease Resistance and the Definition of Genetic Enhancement.” *Frontiers in Genetics* 8 (1):40.

Sparrow, Robert. 2012. “Human Enhancement and Sexual Dimorphism.” *Bioethics* 26 (9):464–75.

———. 2013. “Sexism and Human Enhancement.” *Journal of Medical Ethics* 39 (12):732–35.

Spranzi, Marta, and Laurence Brunet. 2015. “The French Bioethics Public Consultation and the Anonymity Doctrine: Empirical Ethics and Normative Assumptions.” *Monash Bioethics*

Review 33 (1):18–28.

Stankovic, Bratislav, and Mirjana Stankovic. 2011. “The Selfish Patent.” *Journal of Law, Technology and the Internet* 3 (1):67–92.

Starr, Chauncey. 1969. “Social Benefit versus Technological Risk.” *Science*, 1232–38.

Steinmo, Sven, and Jon Watts. 1995. “It’s the Institutions, Stupid! Why Comprehensive National Health Insurance Always Fails in America.” *Journal of Health Politics, Policy and Law* 20 (2):329–72.

Stilgoe, Jack, Richard Owen, and Phil Macnaghten. 2013. “Developing a Framework for Responsible Innovation.” *Research Policy* 42:1568–80.

Stocklmayer, Susan. 2013. “Engagement with Science, Models of Science Communication.” In *Communication and Engagement with Science and Technology: Issues and Dilemmas: A Reader in Science Communication*, edited by John Gilbert, Sue Stocklmayer, and Susan Stocklmayer, 19–38. New York: Routledge.

Stolberg, Sheryl. 1999. “The Biotech Death of Jesse Gelsinger.” *New York Times Magazine*, 1999.

Street, Jackie, and Edilene Lopes. 2017. “Deliberative Methods to Involve Patients in HTA.” In *Patient Involvement in Health Technology Assessment*, 165–73.

Strong, Heather, Monica Mitchell, Alana Goldstein-Leever, Lisa Shook, Punam Malik, and Lori Crosby. 2017. “Patient Perspectives on Gene Transfer Therapy for Sickle Cell Disease.” *Advances in Therapy* 34 (8):2007–21.

Sturgis, Patrick, Helen Cooper, and Chris Fife-Schaw. 2005. “Attitudes to Biotechnology: Estimating the Opinions of a Better-Informed Public.” *New Genetics and Society* 24 (1):31–56.

Sturgis, Patrick, Sanna Read, and Nick Allum. 2010. “Does Intelligence Foster Generalized Trust? An Empirical Test Using the UK Birth Cohort Studies.” *Intelligence* 38 (1):45–54.

Sudbeck, Kristine. 2012. “The Effects of China’s One-Child Policy: The Significance for Chinese Women.” *Nebraska Anthropologist* 27 (1):43–60.

Sun, Majorie. 1981. “Cline Loses Two NIH Grants.” *Science* 214 (4526):1220.

Surmeli, Hikmet. 2012. “Examination the Effect of Science Fiction Films on Science Education

Students' Attitudes towards STS Course." *Procedia - Social and Behavioral Sciences* 47:1012–16.

"SurveyMonkey Inc." n.d. San Mateo, California, USA. www.surveymonkey.com.

Sykora, Peter, and Arthur Caplan. 2017. "The Council of Europe Should Not Reaffirm the Ban on Germline Genome Editing in Humans." *EMBO Reports* 18 (11):1871–72.

Szybalska, Elizabeth Hunter, and Waclaw Szybalski. 1962. "Genetics of Human Cell Lines, IV. DNA-Mediated Heritable Transformation of a Biochemical Trait." *Proceedings of the National Academy of Sciences* 48 (12):2026–34.

Tatum, Edward. 1966. "Molecular Biology, Nucleic Acids, and the Future of Medicine." *Perspectives in Biology and Medicine* 10 (1):19–32.

Terheggen, H. G., A. Lowenthal, F. Lavinha, and J. P. Colombo. 1975. "Familial Hyperargininaemia." *Archives of Disease in Childhood* 50 (1):57–62.

Terheggen, H. G., A. Lowenthal, F. Lavinha, J. P. Colombo, and Stanfield Rogers. 1975. "Unsuccessful Trial of Gene Replacement in Arginase Deficiency." *European Journal of Pediatrics* 119 (1):1–3.

Terheggen, H. G., A. Schwenk, A. Lowenthal, M. Van Sande, and J. P. Colombo. 1969. "Argininaemia with Arginase Deficiency." *Lancet* 294 (7623):748–49.

The Australian Institute for Commercialisation. 2012. "Enabling Technology Futures: A Survey of the Australian Technology Landscape."

The Australian Museum. 1999. "Gene Technology in the Food Chain : Lay Panel Report." Canberra.

The Department of Health. 2020. "Consultation Survey on MSAC Application 1628: Alpha-1-Antitrypsin Genotyping."

The United Nations Educational Scientific and Cultural Organization. 1997. "Universal Declaration on the Human Genome and Human Rights." http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html.

———. 2015. "Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights." Paris.

Therapeutic Goods Administration. 2020. “Clinical Trials.” Australian Government Department of Health. 2020. https://www.tga.gov.au/clinical-trials.

Thomas, Clare, Anja Ehrhardt, and Mark Kay. 2003. “Progress and Problems with the Use of Viral Vectors for Gene Therapy.” *Nature Reviews Genetics* 4 (5):346–358.

Tomanin, Rosella, and Maurizio Scarpa. 2004. “Why Do We Need New Gene Therapy Viral Vectors? Characteristics, Limitations and Future Perspectives of Viral Vector Transduction.” *Current Gene Therapy* 4 (4):357–72.

Topp, W. C., D. Lane, and Robert Pollack. 1981. *Transformation by SV40 and Polyoma Virus in DNA*. Edited by J. Tooze. *Tumor Viruses*. Cold Spring Harbor: Cold Spring Harbor Press.

Travis, John. 2015. “Making the Cut.” *Science* 350 (6267):1456–57.

Travlos, Gregory S. 2006. “Normal Structure, Function, and Histology of the Bone Marrow.” *Toxicologic Pathology* 34 (5):548–65.

Treleaven, Tamara, and Bernard Tuch. 2018. “Australian Public Attitudes on Gene Editing of the Human Embryo.” *Journal of Law and Medicine* 26 (1):204–7.

Tribe, David. 2012. “Gene Technology Regulation in Australia: A Decade of a Federal Implementation of a Statutory Legal Code in a Context of Constituent States Taking Divergent Positions.” *GM Crops and Food: Biotechnology in Agriculture and the Food Chain* 3 (1):21–29.

Tüzmen, Şükrü, Yasemin Baskın, Ayşe Feyda Nursal, Serpil Eraslan, Yağmur Esemen, Gizem Çalıbaşı, Ayşe Banu Demir, Duygu Abbasoğlu, and Candan Hızel. 2018. “Techniques for Nucleic Acid Engineering: The Foundation of Gene Manipulation.” In *Omics Technologies and Bio-Engineering: Towards Improving Quality of Life*, 247–315. Academic Press.

Tyler, Tom, and Fay Cook. 1984. “The Mass Media and Judgments of Risk: Distinguishing Impact on Personal and Societal Level Judgments.” *Journal of Personality and Social Psycholog* 47 (4):693–708.

Uchida, Eriko, Hiroyuki Mizuguchi, Akiko Ishii-Watabe, and Takao Hayakawa. 2002. “Comparison of the Efficiency and Safety of Non-Viral Vector-Mediated Gene Transfer into a Wide Range of Human Cells.” *Biological and Pharmaceutical Bulletin* 25 (7):891–

97.

Uchiyama, Masato, Akiko Nagai, and Kaori Muto. 2018. “Survey on the Perception of Germline Genome Editing among the General Public in Japan.” *Journal of Human Genetics* 63 (6):745–48.

United Nations. 1948. “Universal Declaration of Human Rights.” https://www.un.org/en/universal-declaration-human-rights/.

US Department of Agriculture. 2015. “Request for Confirmation That Transgene-Free, CRISPR-Edited Mushroom Is Not a Regulated Article.”

US Department of Energy. 2019. “Human Genome Project Information Archive 1990–2003.” 2019. https://web.ornl.gov/sci/techresources/Human_Genome/index.shtml.

US Department of Health & Human Services. 2020. “Office for Human Research Protections.” 2020. https://www.hhs.gov/ohrp/.

“US Proposal for Defining Gender Has No Basis in Science.” 2018. *Nature* 563 (5):7729.

Vandamme, Pierre-Etienne, and Antoine Verret-Hamelin. 2017. “A Randomly Selected Chamber: Promises and Challenges.” *Journal of Public Deliberation* 13 (1).

Verdier, Pierre-Hugues. 2009. “Transnational Regulatory Networks and Their Limits.” *Yale Journal of International LAw* 34 (1):113.

Victor, David, Keigo Akimoto, Yoichi Kaya, Mitsutsune Yamaguchi, Danny Cullenward, and Cameron Hepburn. 2017. “Prove Paris Was More than Paper Promises.” *Nature* 548:25–27.

Vorburger, Stephan, and Kelly Hunt. 2002. “Adenoviral Gene Therapy.” *The Oncologist* 7 (1):46–59.

Wade, Nicholas. 1980. “UCLA Gene Therapy Racked by Friendly Fire.” *Science* 210:509–11.

———. 1981. “Gene Therapy Pioneer Draws Mikadoesque Rap.” *Science* 212 (4500):1253.

Walker, Chris, and Tina Soulis. 2016. “Global Regulatory Strategy.” In *Global Pharmaceutical and Biologics Regulatory Strategy, Second Edition*, 187–204. Regulatory Affairs Professionals Society.

Wang, Chen, Xiaomei Zhai, Xinqing Zhang, Limin Li, Jianwei Wang, and De-pei Liu. 2018.

"Gene-Edited Babies: Chinese Academy of Medical Sciences' Response and Action." *The Lancet* 393 (10166):25–26.

Wang, Dawei, Kang Wang, and Yujia Cai. 2020. "An Overview of Development in Gene Therapeutics in China." *Gene Therapy* 27 (1):338–48.

Wang, Jiang-Hui, Rong Wang, Jia Hui Lee, Tiara W.U. Iao, Xiao Hu, Yu-Meng Wang, Lei-Lei Tu, et al. 2017. "Public Attitudes toward Gene Therapy in China." *Molecular Therapy-Methods & Clinical Development* 6 (1):40–42.

Watermeyer, Richard, and Gene Rowe. 2015. "Evaluation of the Project: Mitochondria Replacement Consultation."

Watson, James, and Francis Crick. 1953. "A Structure for Deoxyribose Nucleic Acid." *Nature* 3 (171):737–38.

Weisberg, Steven, Daniel Badgio, and Anjan Chatterjee. 2017. "A CRISPR New World: Attitudes in the Public toward Innovations in Human Genetic Modification." *Frontiers in Public Health* 22 (5):117.

Wetters, Kirk. 2008. "Preface: The Opinion Machine." In *The Opinion System: Impasses of the Public Sphere from Hobbes to Habermas*, xi.

Whitty, Jennifer. 2013. "An International Survey of the Public Engagement Practices of Health Technology Assessment Organizations." *Value in Health* 16 (1):155–63.

Wickham, Hadley. 2016. *Ggplot2: Elegant Graphics for Data Analysis*. New York: Springer.

Wilsdon, James, and Rebecca Willis. 2004. *See-through Science. Why Public Engagement Needs to Move Upstream*. London: Demos.

Wilson, James. 2005. "The First Commercial Gene Therapy Product." *Human Gene Therapy* 16 (9):1014–15.

———. 2009. "Lessons Learned from the Gene Therapy Trial for Ornithine Transcarbamylase Deficiency." *Molecular Genetics and Metabolism* 96 (4):151–57.

Winckler, Edwin. 2002. "Chinese Reproductive Policy at the Turn of the Millennium: Dynamic Stability." *Population and Development Review* 28 (3):379–418.

Wirth, Thomas, Nigel Parker, and Seppo Ylä-Herttuala. 2013. "History of Gene Therapy." *Gene* 525 (2):162–69.

Wivel, Nelson, and Leroy Walters. 1993. “Germ-Line Gene Modification and Disease Prevention: Some Medical and Ethical Perspectives.” *Science* 262 (5133):533–38.

Wolbring, Gregor, and Lucy Diep. 2016. “The Discussions around Precision Genetic Engineering: Role of and Impact on Disabled People.” *Laws* 5 (3):37.

Wolf, Don, Nargiz Mitalipov, and Shoukhrat Mitalipov. 2015. “Mitochondrial Replacement Therapy in Reproductive Medicine.” *Trends in Molecular Medicine* 21 (2):68–76.

Wolf, Susan, Rishi Gupta, and Peter Kohlhepp. 2009. “Gene Therapy Oversight: Lessons for Nanobiotechnology.” *The Journal of Law, Medicine & Ethics* 37 (4):659–84.

Wolinetz, Carrie. 2019. “Introducing the NExTRAC.” National Insitutes of Health: Office of Science Policy. 2019. https://osp.od.nih.gov/2019/04/24/introducing-the-nextrac/.

World Health Organization. 2007. *WHA60.29: Health Technologies*.

———. 2011. “Health Technology Assessment of Medical Devices: WHO Medical Device Technical Series.”

Wynne, Brian. 1992. “Risk and Social Learning: Reification to Engagement.” In *Social Theories of Risk*, edited by Sheldon Krimsky and Dominic Golding, 275–97. Westport, CT: Praeger Publishers.

Xiang, Liangcheng, Lihong Xiao, Zhongping Gou, Wei Zhang Mei Li, Haiping Wang, and Ping Feng. 2015. “Survey of Attitudes and Ethical Concerns Related to Gene Therapy among Medical Students and Postgraduates in China.” *Human Gene Therapy* 26 (12):841–49.

Xin, Hao. 2006. “Gendicine’s Efficacy: Hard to Translate.” *Science* 314 (5803):1233.

Yamagishi, Toshio. 2001. “Trust as a Form of Social Intelligence.” In *Russell Sage Foundation Series on Trust: Trust in Society*, edited by Karen Cook, 121–147. Russell Sage Foundation.

Zakhour, Sherif. 2020. “The Democratic Legitimacy of Public Participation in Planning: Contrasting Optimistic, Critical, and Agnostic Understandings.” *Planning Theory* 1 (1):0–22.

Zhang, Shu-Yuan, You-Yong Lu, and Zhao-Hui Peng. 2012. “Recombinant Adenoviral-P53 Agent (Gendicine®): Quality Control, Mechanism of Action, and Its Use for Treatment of Malignant Tumors.” In *Recent Advances in Cancer Research and Therapy*, 215–43.

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