Human Gene Therapy

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Public acceptability of gene therapy and gene editing for human use: A systematic review

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Abstract

Gene therapy and gene editing technologies are complex and it can be difficult for the public to understand their possible benefits or side-effects. However, patient and public support are critical for the successful adoption of any new technology. Given the recent advances in gene therapy and gene editing, their potential clinical benefits, and the significant attention that has been given to the first-known successful attempt at permanent and heritable changes to the human genome, a systematic review was performed to assess beliefs and attitudes towards gene therapy and gene editing for human use, and to highlight the factors that influence acceptability.

A systematic search following PRISMA guidelines was undertaken in April 2018 to identify papers examining opinions and attitudes regarding the acceptability of gene therapy and gene editing. Overall, 1561 records were retrieved from four databases (Ovid Medline, PsycINFO, Scopus, and Web of Science). Duplicates were removed, and titles and abstracts independently screened, leaving 86 full-text articles assessed for eligibility. Following full-text review, 33 were included, with 5 articles added after forwards/backwards searching. An additional 3 articles were added following an updated search in March 2019 (total n = 41).

Findings from the studies were integrated according to common themes: the impact of demographics; risks versus benefits of success; treatment specifics (e.g., medical versus other reasons; disease severity and status; somatic versus germline; mode of delivery); moral or ethical issues; and changes with time. In general, perceptions were positive, particularly for medical reasons and fatal diseases, but were also influenced by perceived risk. Somatic therapies had higher levels of acceptability than germline therapies. While available in various forms, limitations exist in the measurement of perceptions of gene therapy and gene editing.

Treatment acceptability is essential for future clinical trials, so it is important for scientists and clinicians to be clear about the risks and benefits of these technologies, and how these are communicated to the public, while encouraging education about genetic therapies to a broad range of individuals.

Keywords: Gene therapy, gene editing, acceptability, perceptions, communication, education

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Introduction

Genetic diseases are conditions caused by one or more mutations in the genome, and are ideal targets for gene therapy or gene editing; treatments designed to correct the function of the abnormal gene[1]. Gene therapy achieves this by adding a correct copy of the gene into the genome of the cells in the target organ or tissue, while gene editing alters the genome at a specific location to correct or alter the genetic sequence[2]. The premise of both of these therapeutic approaches is that the presence of the modified gene enables the expression of a correctly functioning protein, eliminating the cause of the disease and improving whole organ function.

Gene therapy and gene editing are ideally suited to monogenic inherited disorders in which mutations in a single gene are responsible for causing disease. They are also typically targeted at rare diseases for which effective treatment options are not available, and for which premature death occurs (e.g., haemophilia, cystic fibrosis). Gene therapy typically uses a vehicle—termed a gene vector—to transfer a correct copy of the gene of interest into target cells. Viral and non-viral gene vectors have been developed over the last 30 years to treat a range of intractable diseases including severe combined immunodeficiency (SCID)[3], haemophilia[4], Wiscott-Aldrich syndrome[5], metachromatic leukodystrophy (MLD)[6], spinal muscular atrophy[7], and cystic fibrosis (CF)[8, 9]. Recently, Luxturna (Spark Therapeutics) became the first FDA approved prescription gene therapy, treating Leber's congenital amaurosis, an inherited retinal disease caused by mutations in the RPE65 gene. Others such as Strimvelis (GlaxoSmithKline) for SCID, and Glybera (uniQure) for hereditary lipoprotein lipase deficiency, have been marketed, but have faced challenges due to cost[10, 11]. While *ex vivo* gene editing approaches have been developed for diseases such as haemophilia[12, 13] and immunodeficiencies[14], few successful *in vivo* techniques have been reported, primarily due to challenges associated with the delivery of the gene-editing reagents to the target cells[15].

While gene therapy and gene editing offer real hope for lasting benefit or a cure for these diseases, the delivery process and the potential for permanent changes to the host cell genome, do have potential or actual risks. A 1996 gene therapy clinical trial for X-linked SCID—a disease characterized by a lack of the IL-2 receptor that results in an impaired

adaptive immune system—used a γ-retroviral vector to deliver the IL-2 receptor gene, and resulted in improved long-term immune reconstitution and correction of the primary immunodeficiency. However, 25% of patients developed T cell acute lymphoblastic leukaemia[16, 17], an unexpected consequence of the vector inserting itself upstream of the proto-oncogene *LMO2*, resulting in its expression [17]. Gene vector designs have improved in the last 15 to 20 years, and these adverse events are now better understood and deemed extremely unlikely. However, risks remain and there are still some uncertainties about the actual risk involved. For example, Hampel and colleagues noted that "both the chances and the risks of this technology are still relatively hypothetical"[18]. In contrast, risk in other areas of medicine such as organ transplantation and stem cell therapies has become more acceptable[19], likely because the risks involved in those procedures are better understood. This suggests that the overall risk is a combination of actual and perceived risks.

There are also several ethical and philosophical issues related to gene therapy and gene editing. Both can be targeted to the somatic cells, any cell other than the reproductive cells, or to the germline cells, the reproductive cells that pass their genetic material onto their progeny. Any risks and consequences arising from somatic cell gene transfer is restricted to that particular individual. Germline gene transfer differs in that it permanently alters the sex cells of the organism. Germline alterations would be passed onto future generations, and these therapies might therefore have a much wider impact than just the treated individual[20]. Many researchers consider germline alterations to be an ethical line that should not be crossed[21]. While rare and intractable diseases are the main target of gene therapies, a future use might be functional enhancement. For example, in the future it may be possible to add or alter genes responsible for strength, endurance, speed, longevity, intelligence, hair or eye colour, or other physical traits, for non-therapeutic benefit. However, the ethics of these modifications remains questionable. As such, the ethical and moral implications of genetic therapies are likely to influence people's perceptions towards gene therapy and gene editing.

Overall, gene therapy and gene editing technologies are complex processes and it can be difficult for the public to understand their mechanisms and possible benefits and side-effects without education and clear communication[22]. However, both patient and public

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support is critical for the successful adoption of a new technology. Since gene therapy can produce permanent genetic changes, carries some inherent risks, and would ultimately be delivered to children and young patients, it is important to comprehensively assess the acceptability of gene therapy and gene editing for human use. Understanding the perceptions that people broadly hold regarding the potential risks of gene therapy and gene editing for human use is critical to consider the future viability of these treatments. In addition, patients themselves are integral stakeholders to the uptake of emerging genetic medicines. Thus, an understanding of specific factors that might influence perceptions of these technologies (e.g., mode of delivery, how therapeutic efficacy is assessed) is also essential.

Researchers have previously reviewed attitudes to biotechnology[23], gene therapy[24], and gene editing[25], however, given the recent and rapid advances in these fields, and their increasing potential to provide substantial clinical benefit, a comprehensive systematic review was deemed essential to assess the beliefs and attitudes towards gene therapy and gene editing for human use. The aim of this systematic review was to provide a broad understanding of the perceived acceptability of gene therapy and gene editing for human use and to highlight factors that influence acceptability.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed[26]. The research question, search strategy, and selection criteria were all predefined. Critical appraisal of the articles and methods for data analysis and synthesis are outlined below.

Search strategy

A systematic search was undertaken on 17 April 2018 and updated 6 March 2019 to identify papers that examined opinions and attitudes regarding the acceptability of gene therapy and gene editing. The focus was on examining perceptions of gene therapy within a broad population, with a specific focus on the ‘public’, and exploring views on gene therapy and gene editing including perceptions, attitudes, and acceptability. A search strategy was developed in consultation with a Health Sciences Librarian to increase search

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sensitivity. The following search string was adapted across four core databases: ((public OR lay OR popular* OR countr* OR communit* OR patient* OR carer* OR caregiver* OR "care giver"* OR personal OR parent*) NEAR/10 (attitude* OR accept* OR opinion* OR perception* OR view* OR belief*)) AND ((gene OR genes OR genetic* OR gene-based) NEAR/1 (addition OR edit* OR therap* OR treat* OR transfer* OR repair* OR replace* OR medicine*)). Databases used were Ovid Medline, PsycINFO, Scopus, and Web of Science.

Selection criteria

Studies were included if they were full-text, peer-reviewed articles that presented data on people's perceptions, attitudes, opinions or views on the acceptability of gene therapy or gene editing for human use. Qualitative, quantitative, and mixed-methods studies that presented primary data were included to gain a greater understanding of the research in this area. Papers from broad samples (e.g., the general population, parents, students, or those in STEM-related jobs) as well as ones that examined gene therapy in health, medical, and cosmetic settings were included. Studies were excluded if they were not peer-reviewed or available in English; if they did not measure perceptions, views, opinions or attitudes regarding gene therapy for humans; or if they focused solely on stem cell therapy, genetic testing, sex selection, or genetic enhancement without gene therapy. Studies that examined perceptions or attitudes towards gene therapy solely for agricultural purposes or animals were excluded. No date restrictions were applied.

Study selection

Overall, 1561 records were retrieved from searches on MEDLINE (n = 376), PsycINFO (n = 33), Scopus (n = 745), and Web of Science (n = 407); see Figure 1 for PRISMA diagram. Duplicates (n = 678) were removed and two authors (IP, MD) independently screened the titles and abstracts of the remaining 883 records according to the stated inclusion and exclusion criteria. A further 797 articles were removed and 86 full-text articles were assessed for potential eligibility. Based on the full-text review, 50 were excluded with reasons recorded (see Figure 1), and 33 from the initial search and a further 3 from the updated search were included (see Tables 1-3 for a summary of all included articles).

Forwards and backwards reference searches were carried out on all included studies, and an additional 5 articles were identified, resulting in a final total of 41 studies.

Critical appraisal and data synthesis

All included studies were critically appraised by two independent researchers for methodological quality using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields[27]. Where applicable this was supplemented with items from the Evaluation Tool for Qualitative Studies[28]. Average quality rating scores were calculated for each study (score range 0–1). Articles with scores ≤ 0.5 were considered low quality, with a substantial number of unfulfilled checklist criteria. Articles with scores between 0.51 and 0.8 were considered medium quality, and those with a score > 0.8 were considered high quality. Studies were not excluded or weighted in the results based on the allocated quality scores.

Results

Study characteristics

Forty one studies were included in the review (25 quantitative, 2 qualitative, and 14 mixed-method). Studies were not excluded based on the weight of evidence provided, as it was deemed essential to provide a current and complete picture of all of the evidence to date. Methodological heterogeneity was high across all of the included studies. Studies were conducted in a range of locations, with the UK (11), USA (10), Australia (6) and Japan (6) featuring most commonly. Articles were published from 1992[29] to 2019[30]: five studies[29, 31-34] were published before 2000, 14[18, 19, 35-46] between 2000 and 2010, and a further 23[30, 47-67] from 2011 onwards, demonstrating the increasing level of awareness, scientific interest and financial support for these recent advancements in gene therapy. The number of participants in each study varied from 22[38] to a large public opinion poll of 13,201 people in China[62].

Participants in the studies were from a range of sources, including; participants involved in gene therapy trials[32], international samples[30, 47, 55, 57], national samples[18, 39, 40, 42, 43, 60, 62-65, 67], people recruited from the general public[34, 35, 38, 51, 52, 59, 63], students[33, 38, 45, 49, 52, 53, 56], conference or public scientific engagement event attendees[35, 58, 59, 66], teachers[54],

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patients[36-38, 41, 44, 46, 61], parents of children with a disease[19, 38], and health practitioners[36, 46, 48, 52]. Five of the studies utilised online data collection methods[50, 51, 55, 63, 65]. Ten studies (all from 2016 onwards) specifically examined gene editing[30, 55, 57-60, 63, 64, 66, 67].

The majority of articles were rated as being of medium quality (n = 24), with eleven studies rated as high quality, and the remaining six rated as low quality. Insufficient information regarding study design and data analysis procedures were the main reasons for low-quality study ratings.

Findings from all the studies were integrated such that perceptions towards gene therapy/editing were synthesised and discussed according to common themes (see Table 1). These were: the impact of demographics; treatment specifics; risks versus benefits of success; ethical or moral issues; trust, fears or concerns; and changes over time.

Impact of demographics

Demographics impacted the overall acceptability of gene therapy, with studies investigating the impact of knowledge/education, gender, religion, and age.

Knowledge/education

Twenty-four studies examined the impact of knowledge of gene therapy on levels of acceptance. Ten studies compared clinician/scientist/biology or medical student perceptions with those of the general public[29, 31, 33, 35, 43, 48, 52, 53, 62, 66], eight measured differences in self-reported or tested genetic knowledge[18, 39, 49, 54, 60, 64, 65, 67]), and a further ten examined differences in self-reported education levels[39, 40, 42, 47, 51, 53-55, 62, 63].

The impact of career was mixed, with four studies finding that science-oriented careers were a significant predictor of greater levels of acceptance of gene therapy[29, 31, 35, 62], whilst six studies found little to no relationship[33, 43, 48, 52, 53, 66]. In a recent study, Ganne et al. (2015) also reported no difference in the acceptance of genetic research between eye care professionals, optometry students and the general public, reporting an average 70% approval rate across all three samples[52].

Self-reported and tested knowledge of genetics was found to positively impact the acceptance of gene therapy. For example, Cebesoy et al. (2016) reported that pre-service

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teachers with a high self-reported level of knowledge had greater levels of acceptance towards gene therapy[54]. Similarly, Crne-Hladnik et al. (2012) demonstrated that female students with higher scores on a genetics knowledge test were more likely to perceive both somatic and germline gene therapy as useful[49]. However, in contrast, Evans and colleagues (2005) found that self-reported knowledge of genetics did not predict acceptance of gene therapy for a variety of applications[39]. Chen et al. (1999) noted that positive attitudes do not necessarily indicate that students have better knowledge of biotechnology, but rather that they are not aware of the risks[33]. In relation to gene editing, Uchiyama et al. (2018) found that despite self-reported low public awareness and inadequate understanding about gene editing, respondents thought that targeting disease-related genes was acceptable[67].

In relation to education levels, increased education levels were found to be a significant predictor of greater levels of gene therapy support in seven studies[40, 47, 51, 54, 55, 62, 63], whilst two studies found no relationship[39, 53], and one reported a negative relationship[42]. For example, Weisberg and colleagues (2017) reported that individuals with high school as their highest education level were less accepting of gene therapy than those with a college degree or higher[63]. In contrast, Barnett et al. (2007) found that both education level and attentiveness to issues around genetics were significant negative predictors of perceptions towards gene therapy[42].

Gender

Eighteen studies examined the impact of gender. Of those a total of 14 articles determined that women were less approving of gene therapy[18, 34, 39, 42, 45, 47, 49, 53-55, 57, 63-65]. For example, Napolitano et al. found that 58% of men and 40% of women supported somatic therapy, while 23% of men and only 16% of women expressed support for germline therapy[34]. Although Napolitano et al. (1999) did note gender-based differences for somatic and germline therapies, they did not detect an association of gender with acceptability towards specific applications[34]. One study, Liu et al. (2011), determined that gender did not impact acceptability within their cohort of oncology physicians and nurses[48], and a further two publications mirrored the sentiment that gender had no significant impact upon gene editing[30, 66]. Only a single study found women to be significantly more accepting

of gene therapy compared to men[62]. However, this was context dependent, with the applications being 1) therapy in children with an inherited disease and, 2) germline modification.

Religion

Religious affiliations of respondents were considered in ten studies[18, 39, 46-48, 51, 53, 55, 60, 64]. Religiosity was found to be a negative predictor of acceptability of gene therapy in eight of these studies[18, 39, 46, 47, 51, 55, 60, 64]. For example, Scheufele and colleagues (2017) determined that respondents with no religious affiliation reported greater support for gene therapy treatment applications compared to those with religious beliefs[60]. Similarly, both Hudson and Orviska (2011), and McCaughey et al. (2016) found religious status to be a negative predictor of the acceptance of gene therapy for a variety of applications[47, 55]. In contrast, both Xiang et al. (2015) and Liu et al. (2011) reported that religion was not related to attitudes toward genetic applications[48, 53].

Age

Overall, 26 of the 41 studies contained data on age[18, 31, 34-38, 40, 43, 45, 47, 49, 51-55, 57, 59, 61-67], but only nine specifically reported on its relationship to perceptions of gene therapy. An inverse relationship between age and acceptability of gene therapy was noted in four of the studies[47, 55, 63, 64], with younger participants being more accepting of gene therapy than older age groups. In contrast, one study found that older participants (31 years and older vs 18-30 years) had a more positive attitude toward gene transfer than younger participants, describing it as “amazing”[61]. The remaining four articles that examined age indicated that it had no effect on attitudes towards either gene therapy[42, 48] or gene editing[57, 66].

Disease status

Weisberg and colleagues (2017) found no differences in levels of gene therapy acceptance in those affected with a genetic disease or with a family history of genetic disease[63]. Similarly, Iredale and colleagues (2013) found no difference in the levels of support for gene therapy for medical applications between the public and those with cystic fibrosis (CF), but noted that families of those with CF were qualitatively more enthusiastic in their

support of germline gene therapy (i.e., "Once it is gone you would be glad to see the back of it. I would be in favour of that")[38].

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Treatment specifics

This theme examined a range of factors related to treatment, and how they affect people's perceptions. These included: medical versus non-medical applications of the technology, disease severity and status, acceptability of somatic and germline gene therapy, and mode of delivery.

Medical versus non-medical reasons for gene therapy or gene editing

A total of 21 studies specifically examined people's perceptions of gene therapy for medical (i.e, treatment or risk reduction) reasons in direct comparison to non-medical (i.e., appearance-related or enhancement) applications[30, 31, 34, 35, 38-40, 43, 50, 51, 53-58, 60, 62, 64-66]. Overall, 15 studies asked respondents their opinion on whether generalised medical vs. minor physical vs. appearance/enhancement applications should be accepted[30, 31, 35, 38, 39, 43, 50, 55-58, 60, 62, 64, 66]. Six studies compared the perceptions of gene therapy for specific applications: debilitating medical conditions (e.g., cystic fibrosis, cancer, HIV, neuromuscular disease, LCA, Parkinson's disease, sickle cell disease), mental illness (e.g., depression, schizophrenia, attention deficit disorder), minor physical conditions (i.e., cleft palate, diabetes, obesity), and non-medical reasons (intelligence enhancement, physical attributes, individual characteristics)[34, 40, 51, 53, 54, 65].

Across almost all 21 studies, in general there was substantially less support for the use of gene therapy for non-medical purposes compared to medical applications. For example, Napolitano and Ogunseitan (1999) investigated 13 different applications for gene therapy, finding greater support for treating a variety of medical and mental health issues (heritable diseases: 70%; mental retardation: 78%; delayed physical deformity: 77%), compared to both personality and appearance-related applications (baldness: 11%; hyperactivity: 29%; obesity: 32%)[34]. Robillard and colleagues (2014) found 93% of respondents believed it was acceptable to use gene therapy for Leber Congenital Amaurosis (LCA)(severe blindness at birth), compared to only 35% who believed it should be used to enhance memory[51]. Wang et al. (2017) reported greater acceptance of gene therapy for the treatment of fatal

diseases from both clinicians and the public (83% and 88%, respectively) compared to gene therapy for enhancement purposes (32% and 39%, respectively)[62].

One qualitative study was conducted using semi-structured interviews to examine the differences between medical and enhancement purposes for gene therapy. Iredale et al. (2003) found that people were more strongly opposed to the use of gene therapy for enhancement purposes, stating comments like "scientists have better things to do than to waste time on that"[38]. These opinions were echoed in more recent studies on the perceptions of gene editing, for example Scheufele et al. (2017) found 59% of respondents expressed support for human gene editing to treat human medical conditions, compared to 33% who expressed support for using these techniques to enhance or improve human abilities[60]. Furthermore, Gaskell et al. (2017) reported that 75% of respondents' reported positive evaluations of gene editing technology for adult therapy (e.g., it would lead to "improvements to quality of life"), and only 26% of respondents' comments were positive for the use of gene editing for adult enhancement[57].

Only three of the 21 studies found little indication of public discomfort with using gene therapy for what is deemed to be genetic enhancement/improvement of humans. An early study by Macer and colleagues (1995) reported that more than 50% of participants from both India and Thailand supported enhancement of physical characteristics in humans[31]. More recently, Van Lieshout and Dawson (2016) asked two small samples of Australian high school students (sample 1, n = 22; sample 2, n = 19) their position on somatic gene therapy to fight serious diseases (both samples), minor diseases (sample 1), or to enhance humans (sample 1). For sample 1, 36%, 50% and 59% were in favour of somatic gene therapy to fight serious diseases, minor diseases, and human enhancement respectively. In sample 2, 73% were in favour of somatic gene therapy to fight serious diseases[56]. Only one other text, Robillard and colleagues (2013), found some support for the use of specific applications of gene therapy for human enhancement reporting a 77% approval rate for the enhancement of normal memory function[50].

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Disease severity and availability of alternative treatments

Overall 20 studies examined opinions towards gene therapy to treat fatal or debilitating diseases compared to minor physical conditions or benign conditions. Many found that disease severity had a direct impact on acceptance of gene therapies for diseases such as incurable heart disease[37], deformity[34], neuromuscular diseases[65], Schizophrenia[40, 54, 58], Alzheimer's[50, 51, 62], Parkinson's[41], and cancer[29, 31, 43, 48, 53, 54]. More support was found for somatic therapy of fatal and debilitating diseases over less severe diseases for adults[35, 40, 55, 62] and children[55, 62]. Xiang et al. found a large proportion of respondents were accepting of gene therapy for complex and potentially severe diseases such as breast cancer (63.73%) and congenital heart disease (60.28%). However, this proportion reduced with decreasing disease severity, falling to 44.38% for hypertension and 40.59% for attention deficit hyperactivity disorder (ADHD)[53]. Similarly, 93% of respondents approved the use of gene therapy for Leber's Congenital Amaurosis, compared to 45% for ADHD[51]. Furthermore, Kim et al. (2006) found that within their sample of participants with Parkinson's disease, those who had milder symptoms seemed to be more willing to participate in gene therapy research compared to those with more debilitating symptoms[41].

As the severity of the disease increased, so too did the acceptability of gene therapy. Evans noted a 41% acceptability for a "death sentence" genetic defect[39]. Hendriks et al. found 85.2% of individuals would accept somatic gene therapy for a serious disease, such as a neuromuscular disorder, only decreasing to 66% when considering germline modification instead[65]. The same was found for severity within a specific disease, with 52% of cardiac surgery patients willing to enrol in a gene therapy trial for cardiovascular disease, and a further 33% if the heart disease was otherwise incurable[37]. Liu et al. observed increased acceptability with severity through comparison of early diagnosed cancer (63.1%) versus late stage cancer (85.1%)[48], while Uchiyama found support for therapies when the disease would either shorten life or result in long-term care[67]. In contrast, van Lieshout and Dawson (2016) reported that adolescents were more likely to be in favour of somatic gene therapy for minor (50%) in comparison to serious diseases (36%)[56].

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Four studies evaluated gene therapy versus alternative treatments[32, 36, 39, 54]. In a cohort of 16 cystic fibrosis patients, all indicated that they had a preference for gene therapy as an alternative therapy over conventional heart and lung transplantation[32]. Holm found that oncology staff deemed gene therapy (48.9%) to be a safer cancer treatment option than chemotherapy (7%), with patients (26.7%) also agreeing gene therapy was safer than chemotherapy (6.7%, with 66.7% neutral)[36].

Somatic cell gene transfer versus germline transgenesis

Seventeen papers compared the attitudes of participants towards somatic cell gene transfer, germline transgenesis or embryonic editing as three modes of therapeutic intervention[68]. There was a noteworthy difference in the acceptability of somatic gene therapy, and its benefits were largely accepted (range: 45%[34] - 98% acceptance[66]). In contrast, the use of germline transgenesis was more divisive, with many papers reporting participant wariness toward this type of therapy, resulting in a lower level of acceptability[34, 35, 38, 40, 45, 49, 56, 58, 62, 64, 65] (range: 16%[34] - 71%[35]).

Exceptions to the view of somatic transgenesis being more favourable were Macer et al., who only found a small difference in acceptability[31]; and both Scheufele and McCaughey who reported similar levels of support for both somatic and germline therapies[55, 60]. Iredale et al. noted differences in the willingness to personally use gene therapy for somatic (95.5%) over germline transgenesis (54.4%)[38]. This same cohort was divided when comparing the ethical differences between the two modes of therapy, with 40.9% expressing that there is no ethical disparity between somatic and germline gene therapy and 36.4% stating that the two therapies are distinct.

Mode of delivery and assessment

Overall, four studies examined perceptions towards either the mode of gene therapy delivery or how effectiveness would be assessed[32, 37, 44, 61]. Cardiac surgery patients expressed a preference for catheter-based delivery of a gene therapy product over surgical gene transfer (94% vs 80% respectively)[37]. In that same study, adenovirus was considered an acceptable gene transfer vector by 73% of patients, although the study did not assess the acceptability of other types of gene vectors[37]. Haemophilia patients clearly had a

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preference for subcutaneous administration (76.3%), with intramuscular and intravenous routes also considered positive alternatives (66.2% and 60.1% respectively)[44]. Bone marrow transplantation was the least favored administration modality, with 66.4% of patients declaring this method 'not acceptable'[44]. Individuals with sickle cell disease indicated increased apprehension upon discovery that chemotherapy would be used prior to the infusion of stem cells that had been treated with a modified HIV vector containing the therapeutic □-globin gene. This apprehension was due to both the chemotherapy and resultant side effects, and also with the use of the HIV vector as the delivery vehicle for transfer of the therapeutic gene, with individuals describing its use as 'scary'[61].

A single study analysed acceptability and assessment of gene therapy efficacy. This study used a single nasal application of DNA-liposomes in cystic fibrosis patients and noted that nine of the sixteen participants found the invasive nasal brushings, biopsies, or daily potential difference measurements to be tedious and unpleasant. These methods of outcome assessment subsequently had a direct negative bearing upon attitudes towards gene therapy[32].

Risks of gene therapy versus the potential benefits of success

This theme examined the risks and benefits of treatments and balanced these with the likely expectations that treatments would be successful. A total of 22 studies specifically examined a range of risks and benefits[18, 19, 29, 31-33, 41, 43, 44, 47, 49-51, 53, 54, 57, 59, 61-63, 65, 67], and many noted that acceptability of gene therapy or human genetic manipulation was very closely related to the risk of the intervention[50, 62, 65]. In general, there was broad support for the benefits of gene therapy for human use, however, potential risks were also important to consider. For example, Robillard et al. (2014)[51] found that 75% of a general sample of people from the USA thought that gene therapy would have positive impacts on society, 74% agreed that gene therapy would possibly provide cures for many diseases, and 54% thought that the benefits of gene therapy outweigh any harms. In a large European Union survey, Hudson and Orviska (2011)[47] found that the majority of participants thought gene therapy was useful to society, however they also had risk-related concerns. Gaskell et al. (2017) examined the public's view of gene editing, with 75% of respondents giving a positive evaluation of gene editing technology for adult

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therapy. Participants frequently thought gene editing would lead to "improvements to quality of life"; it would enable "curing dementia"; and that the "benefits outweigh[ed] the risks"[57].

When participants identified risks they included unacceptable health risks[65] and the possibility of "things going wrong" due to mistakes such as the production of leukaemia in SCID trials[47], or potential negative future consequences[61]. For example, in a study of patients with sickle cell disease, participants indicated that the risk of developing cancer following gene therapy meant they would be trading sickle cell for a potentially more serious disease[61]. Although their disease might impact their life and reduce their life expectancy, many thought it was better to continue their current treatment rather than risk developing a life-threatening condition. Others identified the risk of deliberate human germline alterations that would impact future generations[47]. Together these results suggest that it is important to understand the level of such off-target effects that participants would find acceptable for each disease[65].

Furthermore, some participants voiced disapproval that gene therapy was unnatural[31, 43], with others saying diseases have a purpose in life[65]. In a German study, Hampel et al. (2000) found that only one third of the people they interviewed thought that the risks of genetic engineering outweighed the chances of success[18]. In addition, over half of the pre-service teachers in one study either agreed or strongly agreed that "changing a person's genes is too risky, whatever the benefit might be"[54]. However, these feelings were countered in an earlier gene therapy trial reported by Blair et al. (1998), which stated that participants generally assumed that "doctors would not put them at risk"[32]. Furthermore, in a Chinese sample 41% of respondents disagreed with the statement "It is too risky to try to change people's genes" and 41% were neutral (remainder unknown)[53]. The willingness of participants to take part in a gene therapy trial also appeared to be related to their risk perception, with those that were more willing to participate also more optimistic about the potential benefits of gene therapy[41].

In a cystic fibrosis gene therapy safety trial using liposomes for delivery—where the vector is regarded as being safer than viral vectors—almost all patients thought that they had

placed themselves at no risk whatsoever by taking part[32], albeit this was prior to the SCID trials that identified the risks of genotoxity. In contrast, although cancer induction is a minor risk for gene therapy, more than half of a group of patients with haemophilia thought that the long-term perceived risk of cancer development was a major concern[44]. Kim et al. (2006) also found that participants that were willing to participate in gene therapy trials for Parkinson disease perceived less risk than those not willing to participate and were also more optimistic about the benefits to society[41].

Demographics

The interdependent relationship between risk and acceptability also varies based on demographic factors. Hampel et al. noted that men were more accepting of gene therapy, and perceived fewer risk than women[18]. In another study, women were significantly more likely to agree with the statement ''It is too risky to try to change people's genes''[53] while men were found to have higher levels of confidence in safety[47].

Risk perceptions did not vary greatly with ethnicity with the exception of one Chinese survey, which found that only 31% of respondents agreed with the statement that "The benefits of gene therapy will be greater than the harm it may cause"[53]. However, the authors did note that the greater concern of the Chinese population about gene therapy may be caused by an absence of understanding and media coverage in China[53].

Potential ethical or moral issues

The application of genome engineering requires significant ethical and moral consideration and this was a primary theme across over half of the included papers, with 24 articles discussing these issues when determining levels of acceptability[19, 29, 31, 32, 34-36, 38, 39, 43, 45-47, 49-51, 53, 56-58, 60, 62, 64, 65]. The most common ethical concern was that genetic modification was interfering with nature (unnatural)[29, 31, 32, 38, 45, 46, 49, 50, 53, 62, 65] and that it was "playing God"[29, 31, 36, 46], although some religious leaders considered it "preservation and advancement of life"[46]. As expected, gene therapy for diseases was found to be significantly more morally acceptable compared to enhancement[35, 38, 39, 50, 51, 57, 60, 62, 64]. Slovenian students considered somatic gene therapy as ranking highly in terms of usefulness and moral acceptability[45, 49]. As previously discussed, the acceptability of

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germline transgenesis is generally lower, with the potential for inadvertent germline transmission demonstrated to be of ethical concern[50].

Some of the moral concerns at a societal level include the impacts of increased longevity[51], the accompanying exponential population growth resulting from the decreased incidence of disease[51, 53], and the potential for uneven distribution of resources[50]. Further ethical considerations were related to the reduction in human diversity[56, 65] and the lack of natural selection[43, 56]. Techniques that are perceived as substantially less risky are considered more 'morally acceptable' and 'useful to society'[47, 49]. Further moral considerations included the perception that natural abilities would not be unique if people use gene therapy for enhancements[56] and may even threaten the integrity of the human species[34, 56]. There could also be a risk of losing a sense of self (personal identity), particularly in the context of gene therapy for the brain, or changes in sexual orientation as a result of gene therapy[50, 51]. In contrast, those not opposed to germline transgenesis for improved intelligence cited that it would allow users to contribute more to society, and they had concerns of falling behind if others instigated its use first[65].

A significant recurring ethical concern was whether a parent has the right to decide on the use of gene therapy, either somatic or germline, for their child. Some studies suggested that parents had no right to modify their unborn child's genes using germline therapy[44, 49, 56, 65], while others discussed the treatment of children as a parental right or duty[38, 57], or even a moral imperative towards one's offspring by not withholding the opportunity for therapy and subsequent improvement in quality of life[65]. Ninety-nine percent of respondents thought it was ethically sound to administer a gene therapy for cystic fibrosis to children (aged 6 months to 17 years), on the condition that safety was the priority[19]. The administration of gene therapy *in utero* or to a child for a fatal or debilitating disease also scored highly by the public, indicating general agreement of these uses[62]. Five other studies were in agreement with using gene therapy on children[29, 31, 34, 38, 43], with two showing more support for gene therapy in children than adults[29, 31]. Several studies showed support for *in utero* gene therapy for health-related reasons that would not result in germline transgenesis[34, 40], ones that would result in germline modification[55, 65], or ones that were embryonic but did not specify germline transgenesis[30, 64, 66].

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In some instances, the ethical division was less clear with 61% of individuals in agreement that parents could use human germline genome editing for the purpose of having a child if there was no other means to do so. This decreased to 45% when used to reduce the risk of a serious disease as opposed to being a treatment for it[58]. Iredale et al. found support for the statement that parents have the right to obtain gene therapy for their children (73%), but less support for *in utero* gene therapy where 55% agreed with the statement that "children had the right to be born with the genetic make-up they had at conception", while 27% were in disagreement, and 18% felt unsure[38].

Another interesting topic of ethical debate was the selection of participants that would be enrolled in gene therapy trials[46, 51] and the ethical responsibility to ensure accurate information for consent when participating in high-risk research[46, 51]. Participants in various studies also determined that gene therapy had the scope for generating genetic discrimination and injustice[50, 53]. The high cost of gene therapies was cited as a concern[53, 62] with the associated ethical apprehension being the creation of different classes of individuals based on who could afford gene therapy for modification purposes[51], or therapy being a privilege only for the wealthy and powerful[53].

When given the opportunity to discuss controversial scientific topics, such as gene editing, communication with a panel of topic-specific experts was shown to have no impact on the level of ethical concern for gene editing or the belief that this sort of therapeutic intervention would progress humankind. Instead, such discussions were found to significantly affect the belief that gene editing is morally acceptable, with agreement increasing following such panel discussions[59], a trend supported by others[40].

Trust, fears, or concerns

A total of 21 studies raised the topic of trust, fears and concerns related to the use of gene therapy or gene editing[18, 29, 31, 32, 35-37, 41, 42, 44, 46, 47, 50, 51, 56, 57, 61-63, 65, 67]. Most fears could be grouped into medical or trial participation concerns. Concerns related specifically to medical outcomes included infections[32, 41, 44], cancer[41, 44, 61], inflammation[41], thrombosis[44], bleeding[41], infertility[61], fear of chemotherapy[61], reactions to anesthesia[41], and contracting hepatitis[44] or HIV[61]. More generally, participants expressed concern about misuse[31],

safety[62], unacceptable health outcomes[29, 31, 47, 65, 67], adverse medical side-effects[50, 51, 62], their current disease getting worse[41], or unknown or unpredictable long-term consequences such as undesirable mutations[32, 37, 41, 50, 56, 57, 63, 65]. The acceptability of additional treatment side effects has been shown to correlate with the potential cure rate, highlighting a trade-off between side-effect/therapeutic benefit of a gene therapy treatment[36]. Participants also had concerns over being excluded from other clinical trials[41], and racial and social disparity leading to recruitment bias for clinical trials[46]. A lack of adequate information about gene therapy before a trial was also cited as a worry[50, 51]. Surprisingly, the fear of eugenics was only mentioned twice[31, 63] and does not appear to be a significant cause for concern in those considering the application of gene therapy.

Many fears and concerns were accompanied with an inherent lack of trust. These issues centred around mistrust of research[46], scientists[18], the medical system[46], and government rules and those in charge[42]. Ng et al. determined that respondents were most trusting of international regulatory bodies such as the World Health Organisation, for regulatory oversight while scientific organisations and ethics committees were deemed less favourable[35]. Religious organisations, trade unions, and political parties rated lower still in terms of trust, from a regulatory perspective[35]. Scientists expressed issues of trust surrounding the control on techniques to ensure protection from misuse[29] leaving scope for change and improvement.

Changes over time

Although the gene therapy and gene editing fields have rapidly advanced over the last decade, only two papers specifically looked at changes in attitudes towards gene therapy over time[35, 43]. Both reported on public attitudes to gene therapy in Japan based on opinion surveys. Macer et al., covered surveys conducted from 1991 to 2003[43], finding that levels of optimism towards gene therapy for a serious or fatal disease remained relatively consistent over that time period. They also reported that there was little difference in attitudes towards gene therapy between the public and scientists[43]. Ng et al. reported on a subset of the same surveys from 1991 to 2000[35].

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Discussion

The purpose of this paper was to synthesise the research to date on people's perceptions of gene therapy and gene editing for human applications, and to highlight factors that influence acceptability. Key points are summarised below along with a series of recommendations to advance the work in this field.

Impact of demographic factors

Demographic factors are known to play a substantial role in influencing public perceptions relating to genetic modification. Generally, younger individuals, males, those with lower religiosity, better (self-reported) knowledge, and increased trust in scientists were shown to have more support for both gene therapy and gene editing technologies. Specifically, most studies found that younger participants were more accepting of gene therapy, possibly due to an increase in concern by older individuals and reduced exposure to the development and use of these modern technologies. Only a single study found that women were more accepting of gene therapy than men[62]. One explanation for these gender-associated differences in acceptability could be the concern that women have towards science and technology, and the increasing control that technology has over our lives suggested by some researchers[69]. While it has been shown that women are generally more risk averse than men[70], it is possible that the perceived risks of gene therapy may be more acceptable to women in certain situations, for example, when confronted with the reality of a serious or debilitating disease affecting one's offspring or children in general compared to gene therapy as a whole for adults. These differences also call for improved gender-specific educational programs to address the specific concerns more often associated with women.

Knowledge and education levels were generally significant predictors of the level of support for these technologies, however some findings were mixed. While it has been suggested that negative perceptions of gene therapy can be attributed to a lack of knowledge, the issue is more complex. Mixed results regarding the relationship between knowledge and perceptions could be due to the inconsistent way that knowledge is measured, for example through career choice or education. Self-reported and tested knowledge on genetics were found to have the most consistent results, however there

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remains a need for research to unify measurements of knowledge for consistency, clarity, and comparative analyses. Strong et al. (2017) also suggests that participant engagement over time might give opportunities to provide education; answering questions, addressing misconceptions, and allowing participants to better weigh up the risks and benefits of treatment[61]. They also recommend the use of education materials containing a combination of visual and numerical information, along with patient experiences[61].

Perceptions based on treatment specifics

Overall, there was substantially less support for the use of gene therapy for non-medical (i.e. enhancement) purposes compared to medical applications. Acceptance was lowest for non-therapeutic enhancement procedures, driven strongly by concerns such as “playing God”, “going against nature”, and also societal concerns such as disparities in resource allocation or access to procedures based on socioeconomic standing that could lead to discrimination or inequality. Gene therapy was also more acceptable for serious or fatal diseases rather than debilitating diseases (e.g. Alzheimer’s or Parkinson’s). This is likely due to the perception that gene therapy carries some risks, so the risk-benefit ratio is perceived to be inversely proportional to the severity of the disease. For some participants, the health risks were unacceptable due to the possibility of “things going wrong”, and that for patients with less severe conditions it was better to continue their current treatment rather than risking development of a life-threatening condition.

Importantly, in cases of disagreement for genetic modification for health-related applications, an absence of a complete understanding of the technologies themselves and their accompanying potential risks were cited as contributing to apprehension to their use as opposed to the actual genetic modification itself[30]. Adequate education of participants about these aspects will be of fundamental importance to its broader uptake and acceptance.

Acceptability was inversely related to the invasiveness of the delivery technique or assessment of therapeutic efficacy, however, increased discomfort or side effects arising from a gene therapy were considered acceptable for a fatal disease if there was potential for that therapy to provide a cure. An important element of patient acceptability was the

description of the mode of gene delivery (i.e., the gene vector). Describing the delivery vehicle for transfer of the therapeutic gene as an 'HIV vector' had a direct negative bearing upon attitudes towards gene therapy[61]. It is possible that if it were instead described as a 'lentiviral gene vector', then it would be less confronting, and lead to greater acceptability. However, it should be noted that this level of technical detail and the implications of using these different vector delivery methods may not be easily understandable by everyone. Education consisting of simple explanations that clearly outline the points of differences between the vector delivery systems may aid understanding to enable the public to accurately assess each therapy.

Risks versus benefits

The importance of scientists and medical personnel clearly explaining the possible risks and benefits of genetic therapies is becoming more obvious. In many studies, knowledge of gene therapy was intertwined with perceptions of its risks and benefits. For example, participants in one study remarked that including the percentage likelihood of risks was helpful for them to form their own opinions about gene therapy[61]. Willingness to take part in clinical trials was also closely related to personal risk perceptions and optimism about the potential benefits. Hudson and Orviska (2011) found that people who were more educated and had greater knowledge about gene therapy viewed it as less risky[47].

Jaffé et al. (2006) noted that they did not explicitly describe the risks of gene therapy in their study, and that providing more information to participants may have resulted in them being less accepting of risk[19]. In support of this notion, when the potential risks and side effects of a gene therapy were explicitly explained to patients with sickle cell disease they perceived the treatment less favourably[61]. Weisberg et al. (2017) also found that the support for human germline modification was slightly lower when the risks were made more explicit[63]. However, perceptions of risk and benefit are not necessarily inversely related[59], highlighting the need for open discussions with stakeholders for each application and therapy as they may have variable risk profiles.

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Trust, fears, concerns, and ethical and moral issues

Fear and concern stem mainly from the misuse of these technologies, unacceptable health outcomes, adverse medical side-effects, a current disease getting worse, or unknown or unpredictable long-term consequences such as undesirable mutations. For example participants considered germline genetic modifications such as introducing HIV resistance "a slippery slope toward other applications deemed morally unacceptable"[65]. These applications have recently become a public focus due to the use of CRISPR by Chinese Scientist Dr. Jiankui He to alter the genome of human embryos prior to implantation in order to confer HIV resistance in two infants (November 2018). This news received swift international condemnation, with the medical field saying it is irresponsible to proceed with clinical germline editing at present[71]. This type of rogue research and media attention creates mistrust of research, scientists, the medical system, government rules, and those in charge.

While there was little empirical research related to cost as a concern, anecdotally this topic is rapidly becoming one of the most frequently mentioned aspects of the gene therapy debate in public forums. As such, it is an important avenue for future research. Future research should aim to compare actual real-world costs and people's perceptions of costs for gene therapy relative to alternative therapies. It would also be interesting to assess the influence of gene therapy cost and payment models (e.g. public versus private health insurance and outcome- versus value-based pricing) on people's perceptions and acceptability.

For some people there are ongoing ethical and moral issues surrounding gene therapy and gene editing. It is therefore a moral obligation of all those involved in the development and implementation of therapeutic therapies, from scientists to policy makers to ensure that due diligence is performed with regard to the safety of these therapies, and to ensure that complex information is relayed in an understandable and transparent manner to regain trust and mitigate these current fears and concerns. The issues of mistrust amongst particular populations, especially some minority groups, also needs to be addressed as they form a barrier for the recruitment of these groups into clinical trials[46].

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The complex relationship between the use of gene therapy and its moral and ethical considerations should be at the forefront of all discussions involving genetic modification, with personal, societal, and environmental implications balanced against the potential benefit of genome modification. Continuous conversations between patients, the public, scientists, clinicians, and policy makers need to be built and maintained to deliver resolutions / agreements on how to move forward with these therapies and what would be considered "right" at a particular point in time for the world's population.

Changes over time

More than half of the papers in this review were published in the last eight years, likely owing to the maturity of the gene therapy field as a whole and also more media attention and discussions around the topic with the public. This demonstrates the increasing focus that the scientific community is placing on this type of work as a viable treatment option for a range of different complex diseases, and the importance of understanding people's perceptions towards this technology. However, since 2007, Neutral have looked at changes in perceptions over time. Collectively, from the studies reviewed it appears there is an upward trend in acceptability of gene therapy as a treatment alternative when looking at the percentage of people who were accepting, particularly for medical purposes. Some views have also changed over time based on other medical advances. For example, participants in 1999 viewed gene therapy for HIV as acceptable if it could prolong lives[33]. In 2018 a different study reported that germline modification to produce HIV resistance was not considered necessary due to the low risk of acquiring HIV[65], and the likely availability of other acceptable and effective treatments.

While the general trend for medical somatic therapy shows an increase in acceptability over time, germline modifications remain contentious and a heated source of ethical debate. Deviations from the status quo have been vehemently frowned upon with He Jiankui's editing of human embryos sparking international outcries[72] that have culminated in the Chinese government immediately tightening up regulations against germline editing[73]. Numerous cell and gene therapy committees have rebuked the act and have subsequently called for an international moratorium on the use of germline genetic modifications[74]. The expansion of gene therapies into the medical arena, coupled with

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increased media exposure are likely to change current perceptions. It will be critical to understand how the public's perception is tracking with these advancements and how much of an impact the recent gene therapy successes have had on the public's perception and willingness to participate in gene therapy clinical trials and whether there are still additional barriers that need to be overcome in the future. Future research could usefully track potential changes in perceptions over time via longitudinal methods, or by examining current versus retrospective accounts of perceptions among different samples.

Limitations and future research directions

Limitations exist with all forms of research, and the research presented in this field is no exception. In order to provide a comprehensive review, all relevant studies were included. However, it was clear that a number of misconceptions surrounding gene therapy and gene editing still exist, both among researchers and the public. For example, there were suggestions it could change sexuality [50], demonstrating that some of the studies reviewed did not understand the true purpose, capabilities, and/or reasonable applications of current gene therapy and gene editing techniques. It is likely that these misconceptions are driven by the media and sensationalised in movies (e.g., Gattaca). As such, it is essential for future research in this space to be performed by multi-disciplinary teams of gene therapy experts—including clinical researchers, basic scientists, social scientists, bioethicists and patient advocacy groups—to ensure a comprehensive understanding of perceptions of gene therapy and gene editing.

Overall, the measurement of perceptions of gene therapy and gene editing was inconsistent and there is a need for future research to employ standardised and validated forms of measurement in order to draw firm conclusions. In addition, concepts such as "risk" with regard to gene therapy have not been clearly defined within the literature, and as such, this term was used in a variety of contexts. These included general non-specific risks[57], actual risks posed by gene therapy [65], negative consequences[61], or greater philosophical risks pertaining to humankind[34, 56].

While the studies reviewed reported on data from a wide range of samples, relatively little research has been done on specific consumer groups. Future research should address this

by examining the perceptions of individuals who are closely associated with different diseases. Lastly, only two studies (that drew from the same data set) specifically reported on changes over time [35, 43]. As such, any findings related to changes should be considered with caution.

Recommendations and future directions

Public engagement can improve knowledge and change risk and benefit perceptions, but the relationship between these factors remains complex[59]. Based on the studies we reviewed, we have created the following list of recommendations and directions for future research to improve public perceptions of gene therapy.

1. Improve the standard of informed consent

Clear and consistent communication between patients, clinicians, and clinical trial managers is integral to fostering a sense of trust and empowerment to patients choosing to undergo genetic therapy. In particular, it is important to design informed consent documentation specifically for gene therapies, being mindful of the phrasing of content, terminology, and the amount of detail provided[51, 61]. Information should be engaging with complex ideas preferably portrayed with images and videos for clarity[37]. Specific attention should be given to accurately convey messaging that is often portrayed fallaciously within the media (e.g,. the generation of eugenics or designer babies). Future research should obtain insight from focus[52] and patient advocacy groups to determine any potential miscommunication of information prior to broader dissemination.

2. Use minimally invasive procedures

While invasive procedures remain the only mode of delivery for many potential gene therapies, technological advances are likely to bring about less invasive methods of delivery, and with that an expected increase in acceptability. Given the direct negative correlation between invasiveness and acceptability highlighted above[32], there must be a continuing drive to provide innovative ways to combat the current hurdles associated with non-invasive delivery of some gene therapies when alternatives may be possible.

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3. Develop greater trust

To gain public trust it is critical to deliver information to the public and potential patients that is understandable, relatable, unambiguous, and reliable[62, 65]. Greater emphasis needs to be given to the development of public engagement tools for scientists and clinicians to feel adequately equipped to engage with the public and build long-standing and honest relationships built on trust. A recent 2019 study went so far as to note that sharing visuals of scientists themselves versus innate lab objects was enough to change perceptions and garner increased trust by humanising scientists on social media[75].

Furthermore, information should be relayed frequently for the public to remain updated and feel empowered by new developments with the gene and cell therapies[46]. It is important to address any shortcomings in understanding or inaccuracies with reliable scientific content to prevent negative perceptions towards genetic therapies based on misinformation[46, 61]. It is likely that increased exposure and a continuous track record of transparency between scientists and the public would significantly improve issues of trust.

4. Develop appropriate policy frameworks for gene therapy regulation

Patients need to know that new therapies are being correctly regulated and that policy decision-makers are provided with enough up-to-date scientific insight and public participation[57] to drive these therapies forward while keeping safety a priority. Pairing current expert knowledge with a clear understanding of past errors has already provided improved guidelines for regulating gene therapies, but there is still scope for international clarity and consensus for many of their uses. Public confidence can be developed and maintained through instigation of more dynamic and open communication between the regulatory agencies that are drafting guidelines and implementing policies. This has become a realization with the recent notice by the FDA requesting formal input into their draft guidelines for the enhancement of diversity of clinical trial populations, enrolment practices, eligibility criteria, and trial designs[76]. This method of consultation and transparency specifically for gene therapy is highly recommended to improve the quality of the guidelines through constructive collective consultation and improve public trust in health agencies. It will also be essential to include post-success analyses in any future research looking at perceptions of somatic gene editing changes.

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The implications of genetic modification are not always well understood or even known scientifically, so we should continue to tread with caution while continuing to engage in global discussions on what is defined as acceptable. There is an urgency to gain international regulatory control over the use of these therapies for the right purposes, to avoid inappropriate application of genetic therapies. Currently, this is largely regulated by the Food and Drug Administration in the USA who are increasing the number of clinical reviewers for the evaluation of cell and gene therapies, and the European Medicines Agency (EMA) Advanced Therapy Medicinal Product (ATMP) who have recently completed their consultation period (July 2019) for guidelines of cell and gene therapies. Ideally, inter-agency consultation and a unified global regulatory framework should be established to streamline the regulatory process and determine which applications are deemed ethically, morally, and scientifically safe and acceptable for clinical use across geographical boundaries.

5. Provide better gene therapy education to the public and stakeholders

The rapidly changing biomedical landscape is demanding more in-depth science and biotechnology teaching, even at high school level. This shift is driven by a need to improve basic science and biotechnology knowledge[54] and bioethical principles[49] for teachers and students. Gaps in knowledge should be addressed prior to subsequent delivery of information to ensure good foundational science understanding[56]. Clinicians in relevant fields must stay up-to-date with the most current and ground-breaking gene therapy research and practice spanning oncology, ophthalmology, haemoglobinopathies, immunodeficiencies, and lysosomal storage diseases. Furthermore, knowing the factors that can influence people's perceptions will be critical to assist clinicians to act as a bridging point between patients and those developing gene therapies, and assist them to garner acceptance from patients for clinical trials.

There is an increased need and desire for the public to know more about these new and exciting genetic therapies. Opportunities to instigate multidirectional communication between the public, scientists, clinical staff, and policy decision-makers using public engagement events[59] and social media[50] will play a pivotal role in expanding public

knowledge. Training in public engagement is essential for all involved in the development and clinical administration of these therapies.

New and innovative ways of making connections between stakeholders are essential. Recently, the American Society of Gene and Cell Therapy debuted their patient education program to educate and inform patients, families, and the public about genetic diseases, therapies, and updates on clinical trials[77]. More of these initiatives must be developed in the coming years to further encourage education. Emphasis needs to be placed on finding ways to communicate, particularly with women, individuals in rural areas, older individuals, those with strong religious tendencies, and those with less education to promote gene therapy literacy competency. This will subsequently assist these groups to participate in fact-based discussions on the topic, and ensure that correct information is given to those with varying levels of understanding.

6. Each gene therapy application must be considered on its merits

Gene therapies cannot be placed under broad "blanket" regulations. It has become clear that each application will need to be assessed on its own merits and ratio of risk-to-reward[30, 65]. Policies and regulations generated should also be based on individual circumstances (risk, degree of disease severity, and medical versus enhancement), as therapies that exhibit lower risk or are for severe diseases that would have higher reward, are likely to be more acceptable, and have an easier road to clinical implementation. Each application will also need to establish the level of risk would be acceptable for patients undergoing specific gene therapy treatments in situations where acceptability is conditional (e.g., method of delivery, access to alternatives, assessment of efficacy)[65]. While acceptability has notably improved for certain applications, others still require significant ethical and legal consideration before translation toward the clinic. Currently, germline modification is banned worldwide, and is largely not ethically accepted. In our opinion, subsequent human germline editing should continue to be banned until an ethical and regulatory framework has been established and agreed upon following extensive and broad-ranging consultations with the public, scientists, clinicians, stakeholders and policy decision-makers.

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Table 1: Summary of the themes and their association to acceptability of gene therapy.

Theme	Subtheme	Acceptability	References
Demographics	Greater knowledge/education n=24	Positive n=15	18, 29, 31, 35, 40, 47, 49, 51, 54, 55, 60, 62-65
		Neutral n=7	33, 39, 43, 48, 52, 53, 66
		Negative n=2	42, 67
	Gender (women) n=18	Positive n=1	62
		Neutral n=3	30, 48, 66
		Negative n=14	18, 34, 39, 42, 45, 47, 49, 53-55, 57, 63-65
	Religion n=10	Positive n=0	
		Neutral n=2	48, 53
		Negative n=8	18, 39, 46, 47, 51, 55, 60, 64
	Age (young) n=9	Positive n=4	47, 55, 63, 64

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		Neutral n=4	42, 48, 57, 66
		Negative n=1	61
	Disease status n=2	Positive n=0	
		Neutral n=2	38, 63
		Negative n=0	
Treatment specifics	Medical over non-medical n=21	Positive n=20	30, 31, 34, 35, 38-40, 43, 50, 51, 53-55, 57, 58, 60, 62, 64-66
		Neutral n=0	
		Negative n=1	56
	Increased disease severity n=20	Positive n=18	29, 31, 34, 35, 37, 39, 40, 43, 48, 50, 51, 53-55, 58, 62, 65, 67
		Neutral n=0	
		Negative n=2	41, 56

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	Gene therapy over alternative treatments n=4	Positive n=2	32, 36
		Neutral n=0	
		Negative n=2	39, 54
	Somatic over germline transgenesis n=15	Positive n=11	34, 35, 38, 40, 45, 49, 56, 58, 62, 64, 65
		Neutral n=4	30, 31, 55, 60
		Negative n=0	
	Increased invasiveness of delivery n=2	Positive n=0	
		Neutral n=0	
		Negative n=2	32, 61
Risks of gene therapy	Too risky (risk outweighs benefit) n=22	Positive n=9	29, 31, 44, 47, 49, 54, 61, 63, 65
		Mixed (balance of risk-benefit) n=5	33, 50, 51, 59, 62

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		Negative n=8	18, 19, 32, 41, 43, 53, 57, 67
Potential ethical or moral issues	Effect of ethical and moral issues n=24	Positive n=2	40, 59
		Mixed n=4	45, 46, 49, 65
		Neutral n=0	
		Negative n=18	29, 31, 32, 34, 36, 38, 43, 45-47, 49-51, 53, 56, 62, 64, 65
Trust, fears, or concerns	Trust (lack of), fears, or concerns n=21	Positive n=0	
		Neutral n=0	
		Negative n=21	18, 29, 31, 32, 35-37, 41, 42, 44, 46, 47, 50, 51, 56, 57, 61-63, 65, 67
Changes over time	Increase in time n=2	Positive n=2	35, 43
		Neutral n=0	
		Negative n=0	

Figure Legend

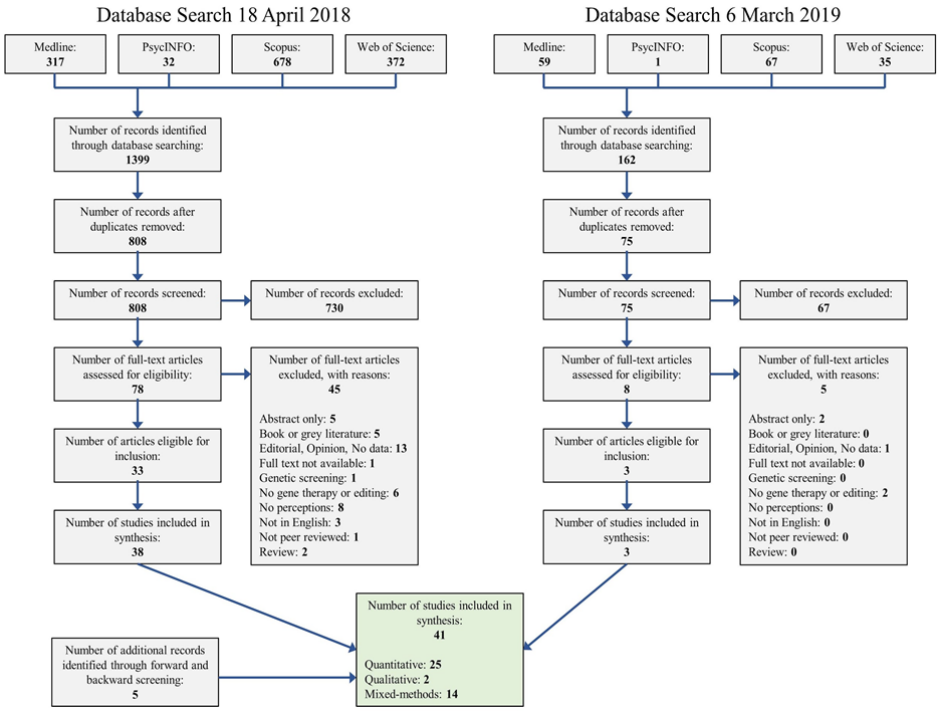

Figure 1: PRISMA flow diagram of study selection.

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Table 1:

Quantitative

Paper

Summary

Author (Year; Country)	Study design	Sample	Measure(s) of perceptions	Key Findings	Quality Rating
Barnett J, Cooper H, Senior V. (2007; UK)	Cross-sectional survey	N = 3,272; Age = 18 + years Gender ratio not specified	Four items from the British Social Attitudes Survey (validated) on whether gene therapy should be allowed for; 1: lessening aggression or violence; 2: altering sexuality; 3: reducing chances of getting breast cancer; and 4: determining the sex of an unborn baby (α = .68).	Perceptions of gene therapy positively predicted by trust (i.e. in government rules) and negatively predicted by being female, having higher education, attentiveness to genetics and beliefs in public efficacy.	Medium

Cebesoy ÜB, Öztekin C. (2016; Turkey)	Cross-sectional survey	N = 355 (113 male, 231 female, 11 not specified) pre-service teachers; Mean age = 22.04	50-item Attitudes towards Issues in Genetics Literacy Scale (ATIGLS); including items on general attitudes towards genetic applications (19 items), the use of gene therapy (10 items), and the use of somatic gene therapy, germ-line gene therapy and in-utero gene therapy (9 items).	52.6% agreed with the statement "Changing a person's genes is too risky, whatever the benefit might" and 26.2% agreed with the statement "we should never interfere with people's genes". Attitudes towards gene therapy were more favourable for more serious conditions (e.g., breast cancer, heart disease, cystic fibrosis). Participants who were more knowledgeable in genetics literacy held more favorable attitudes towards the use of genetic information, gene therapy and gene therapy applications.	High
Costea I, Isasi R, Knoppers BM, Lillicrap D. (2009; Canada)	Cross-sectional survey	N = 159 people with haemophilia (79% haemophilia A);	A 12-item self-report questionnaire (non-validated) designed for the study assessing: demographic details (4 items), knowledge (2 items),	70-72.6% believed gene transfer for haemophilia would be successful in the next 5-15 years. Success was considered as symptom-free time (range 1-12 months). Short-term safety concerns were protection against infectious agents; long-term safety concerns were developing conditions like cancer. Administration of gene therapy: 76.3% favoured	Medium

		Mean age = 22 (*SD* = 17) Gender ratio not specified	safety (1 item), efficacy (1 item), method of adminstration (1 item), participation in clinical trials (1 item), and therapy costs (1 item).	subcutaneous; 66.2% favoured intramuscular; 60.1% favoured intravenous; 2.2% favoured bone marrow. 43.3% indicated that a therapeutic effect in humans would need to be evident before they participated in a clinical trial.	
Critchley C, Nicol D, Bruce G, Walshe J, Treleaven T, Tuch B. (2019; AUS)	Cross-sectional survey	N = 1004 (telephone n = 501; online survey n = 503) 51% female Mean age = 40.64 (online); 54.79 (telephone)	15-item (non-validated) questionnaire assessing attitudes towards various applications (enhancement, health, human reasearch; stomatic, germ line, embryos) of gene therapy.	The type of application had a greater impact on support in comaprison to cell type (i.e., somatic, germline). Support was significantly higher for use of gene therapy in medical and health-related applications in comaprison to cosmetic applications. For medical applications, support was greater for somatic cells compared to germline cells, but there was no significant difference between the use of somatic and germline cells when averaged across all applications. Younger individuals, males, lower religiousity, and those with more self-reported knowledge and trust in scientists were more likely to have more positive attitudes towards gene editing.	High

				Education, ethnicity and political orientation were not associated with general support for gene editing. Gender and ethnicity were associated with moral concerns.	
Evans MDR, Kelley J, Zanjani ED. (2005; Australia)	Cross-sectional survey	N = 1403 adult Australian citizens randomly sampled; Age not specified; Gender ratio not specified	Small number of items (number not specified) on opinions and attitudes towards germline gene therapy were from the International Social Science Survey Australia (ISSA)	Life threatening defects in children: 40% (16% definitely yes; 24% probably yes) would allow germline gene therapy vs 72% (35% definitely yes; 37% probably yes) would allow abortion. Minor defects (e.g. cleft palate): 28% (9% definitely yes; 19% probably yes) would allow germline gene therapy vs 17% (5% definitely yes; 12% probably yes) would allow abortion. Personality defect: 24% (8% definitely yes; 16% probably yes) would allow germline gene therapy vs 22% (7% definitely yes; 15% probably yes) would allow abortion. Eugenic: 9% (3% definitely yes; 6% probably yes) would allow germline gene therapy vs 5% (2% definitely yes; 3% probably yes) would allow abortion	High

				Males were more in favour of germline gene therapy for all applications. Catholics were less accepting towards using gene therapy for major and minor physical defects than non-Catholics.	
Gaskell G, Bard I, Allansdottir A, Da Cunha RV, Eduard P, Hampel J, et al. (2017; Austria, Denmark, Germany, Hungary, Iceland, Italy, Netherlands, Portugal, Spain, UK, US)	Experimental (2, context: therapy vs enhancement x 2, recipient type: adult vs prenatal)	N = 11,716 adults Age not specified; Gender ratio not specified	2-items (non-validated) in response to one of the four vignettes related to gene editing (adult therapy, prenatal therapy, adult enhancement or prenatal enhancement): "Do you think he/they made a morally acceptable decision?" and "In his/their shoes would you make the same choice?"	Gene editing more morally acceptable for therapy than enhancement and for adults rather than prenatally; these findings are consistent across countries. Females more cautious about gene editing.	Medium
		N = 1051 Germans	Non-validated (items not	33% of individuals believed that the risks outweighted the chances of success, and 20%	

Hampel J, Pfenning U, Peters HP. (2000; Germany)	Cross-sectional survey	from the general population Age not specified Gender ratio not specified	specified) telephone BioTech Survey measuring attitudes towards 10 applications of genetic engineering and approval of genetic therapy.	believed that the risks were lower than the chances. 75% approved of genetic engineering for medical applications. 24% of women approved of genetic engineering compared to men (40%). 49% of all religious people interviewed rejected genetic engineering.	Medium
Holm S & Jayson G. (2001; UK)	Cross-sectional survey	N = 44 doctors and nurses (Mean age = 33.5) N = 47 cancer patients (Mean age = 60) N = 43 relatives (Mean age =	Researcher-designed (non-validated) questionnaire assessing knowledge of gene therapy and attitudes towards gene therapy including willingness to accept side effects.	The attitude towards gene therapy were positive, and concern about gene therapy "playing God" was accepted by less than 10% of individuals. Patients/relatives perceived gene therapy to be more dangerous compared to chemotherapy. In the patient group the willingness to accept side-effects for a given improvement in cure rate was correlated to age. There was a strong belief that if gene therapy is effective it should be paid by the NHS.	Medium

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		55) Total N = 134			
Hudson J, Orviska M. (2011; Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Icelang, Italy, Latvia, Lithuania, Luxembourg, Malta,	Cross-sectional survey	N = approx. 1000 participants per EU country (25 countries); Age not specified; Gender ratio not specified	2005 Eurobarometer survey (64.3) No information is provided on the measure.	42.8% of participants tended to agree/highly agree GT was too risky 49.4% believed it was morally acceptable and 54.2% believe it is useful in society. Men vs women had higher levels of confidence in the safety of GT, as well as the perceptions of usefulness and moral acceptability. Those who reported greater knowledge about GT perceived it as less risky. Age (65+), religion, rural areas, unemployed and widowers negatively impacted acceptance; they tended to find GT riskier and less useful.	Low

Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, UK)					
Jaffé A, Prasad SA, Larcher V, Hart S. (2006; UK)	Cross-sectional survey	N = 78 parents of children with cystic fibrosis Age and gender ratio not specifed for parents Children were 60% female; age range = 6 months to 17 years	Self-report (non-validated) questionnaire in multiple choice format. Questions focused on the importance of gene therapy for CF, and the ethics of children being involved in gene therapy clinical trials.	82% of participants felt that gene therapy was the most important area of research. 56% of participants believed that gene therapy might lead to a cure, 31% expected it would alleviate symptoms but not lead to a cure, and 10% hoped for both, with 3% unsure. Almost all participants (99%) felt it was ethical to give children the opportunity to be involved in gene therapy trials, provided they were safe and carefully conducted. 91% of participants felt they would consent to their children participating in such a trial.	Low

Kim SYH, Holloway RG, Frank S, Beck CA, Zimmerman C, Wilson R, et al. (2006; US)	Cross-sectional simulated clinical trial	N = 92 participants (Parkinsons Disease); Age not specified; Gender ratio not specified	Views regarding risks and benefits (items tailored for the study) using a Risk Tolerance Score, a Personal Benefit Requirement Score, and a Social Benefit Requirement Score.	50% of participants stated they would be willing to participate in the phase I gene transfer trial. The strongest reason against participation was a perception of danger. The willing group reported a higher tolerance of research risks while perceiving lower likelihood of harm . However, the two groups did not differ in their perception of likelihood of personal benefit. Greater risk tolerance and lower risk perception predicted greater likelihood to participate in the trial.	High

Table 1:
Quantitative
Paper
Summary

Author (Year; Country)	Study design	Sample	Measure(s) of perceptions	Key Findings	Quality Rating
Liu Z-m, Liu C, Li J-y, Yu C-h, Jiang Y. (2010; China)	Cross-sectional survey	N = 328 (184 nurses, 100% female; 144 physicans, 57.6% female). Mean age = 33 (doctor); 28 (nurse)	7-item (non-validated) questionnaire that assessed attitudes regarding gene therapy (i.e., knowledge, training, recommendations for clinical trials, opinion of safety) and willingness to accept gene therapy	78% of participants thought gene therapy was safe or very safe. Demographic characteristics did not affect attitudes towards gene therapy. Those who suggested for their patients to participate in clinial trials (p<.001), who understood gene therapy as "little or none" (p =.03) and thought gene therapy was "very safe or safe" (p<.001) were more likely to accept gene therapy. Participants were more likely to recommend gene therapy	Medium

			treatment if they had cancer.	for late-stage (85.1%) vs early-stage cancer (63%).	
McCaughey T, Sanfilippo PG, Gooden GEC, Budden DM, Fan L, Fenwick E, et al. (2016; Worldwide across 185 countries)	Cross-sectional survey	N = 12,562 from 185 countries 37.9% femal e Media n age = 24	Self-report questionnaire (non-validated) with items investigating global perceptions of human genome editing applications.	59% supported gene editing to cure life-threatening diseases in children or adults and 59.4% to cure debilitating diseases 63% supported gene editing in embryos to prevent life threatening or debilibating disease. Predictors included being male, from a higher SES background, and holding a tertiary degree. 27% supported gene editing in embryos to alter a non-disease characteristic (e.g. intelligence, sporting ability, and appearance). Predictors included being male. Overall, repondents affiliated with a religious belief more likely to reject gene editing applications.	Medium
Musunuru K, Lagor WR, Miano JM. (2017; US)	Cross-sectional survey	N = 301 attendees at a Heart Association conference (74% basice	A 11-item (non-validated) survey was created in a three-point response format "yes/no/don't know"	80% supported the use of somatic genome editing in adults to prevent serious diseases 69% would agree to a genome-editing therapy that would permanently reduce the risk of coronary heart disease. 83% were opposed to somatic genome editing	Low

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		scientists) Age not specified Gender ratio not specified	assessing the application of genome editing.	to acquire desired traits such as athletic ability. 61% would accept germline genome editing for use by parents who had no other means to have a healthy biological child; 45% would accept its use to reduce the risk of a child having a serious medical condition; 2% would accept it being used to increase the odds of a child having a desired trait.	
Napolitano CL, Ogunseitan OA. (1999; US)	Cross-sectional survey	N = 246 respondents (135 female, 111 male) Age not specified	55-item survey (non-validated) assessing perceptions of the desirability, benefits, risks, and moral values associated with biotechnological and genetic engineering techniques applied to manipulate human reproduction; enhancements of human cosmetic features;	52% of male and 42% of female respondents were in favor genetic engineering to increase human longevity. 37% of respondents supported genetic engineering to improve intelligence. 78% of respondents would choose gene therapy for mental retardation in their offspring. Most males (58%) foresaw no detrimental impacts of somatic cell gene therapy, but most females (60%) disapproved. Significantly more men (23%) than women (16%) supported manipulating human germline cells.	Medium

			and germ-line and somatic gene therapy for human fetuses, children and adults.		
Ng MAC, Takeda C, Watanabe T, Macer D. (2000; Japan)	Cross-sectional survey	N = 794 (297 public; 370 scientistics; 74 Science Forum)	14-item biotechnology and bioethics survey (non-validated) assessing the perceptions of genetic engineering and attitudes towards specific applications of biotechnology	Participants were generally supportive of gene therapy (40.8%), with little difference between the public (24%) and scientists (25.6%). Forum participants were more supportive of gene therapy in general, with scientists more disapproving of enhancement. The major concerns expressed were "going against nature" and "fear of the unknown". Respondents were overwhelmingly in favor of international regulatory bodies used to regulate modern biotechnology.	Medium
Robillard JM, Roskams-Edris	Cross-sectiona	N = 467 90% from the United	Non-validated (items not specified) survey created based on findings from a previous study that examined	75% agreed that genetic treatment will have a positive impact on society and will cure a large number of diseases. 39% were in favor of using gene therapy for non-	High

D, Kuzeljevic B, Illes J. (2014; Canada, US)	l survey	States 59% aged between 19-29 years 55% female	information-seeking about gene therapy in social media (Robillard et al., 2013). The survey investigated general questions about the benefits and harms of gene therapy, the acceptability of gene therapy for various applications, the impact of gene therapy on identity, the acceptability of gene therapy for nontherapeutic applications, and the greatest area of concern when it comes to gene therapy.	therapeutic uses. The main ethical concern was exponential population growth and societal impact concerns including significantly increased longevity and creation of different classes of individuals. Lack of adequate information about gene therapy outweighed physiological concerns such as adverse medical side-effects.	
Rose KM, Korzekwa K, Brossard D,	Pre-post interventio n	Pre-test survey: N = 34	Non-validated items designed for the study. A 5-point Likert-type scale format with	Increased knowledge about genetic therapies through attending a panel influenced both risk and benefit perceptions. Perceived risks and benefits were significantly higher in the	Medi um

Scheufele DA, Heisler L. (2017; US)	(attendance at a Human Gene Editing Panel Discussion)	Post-test survey: N = 26 Age and gender measured but not specified	questions about knowledge of genetic editing (1 item), risk perceptions (1 item), the benefit of gene editing for society (1 item), and the ethics and morality of gene editing (3 items).	post-test compared to the pre-test. Panel discussions had no significant effect on the level of concern for ethical considerations or the belief that gene editing will help human kind progress. Attendees viewed gene editing as more morally acceptable following the panel.	
Scheufele DA, Xenos MA, Howell EL, Rose KM, Brossard D, Hardy BW. (2017; US)	Cross-sectional survey	N = 1600 from national survey data; Age not specified; Gender ratio not specified	Non-validated (items not specified) YouGov survey	Respondents found somatic (64%) and germline therapy (65%) acceptable. Lower levels of acceptance for germline enhancement (26%) and somatic enhancement (39%) were observed. 59% expressed support for genome editing to treat medical conditions, while only 33% expressed support to enhance or improve human abilities. Those with low religiosity expressed support for treatment (75%) and enhancement (45%).	Low
Sturgis P,	Cross-	2000 British Social Attitudes	5-item British Social Attitudes Survey assessing attitudes towards genetic	Respondents were more likely to support gene therapy for medical purposes (73%) than for enhancement (24%), cosmetic or appearance-related purposes (33%).	Medi

Cooper H, Fife-Schaw C. (2005; UK)	sectional survey	Survey N = 3426 1999 Wellcome Trust Consultative Panel on Gene Therapy survey N = 696 Age not specified; Gender ratio not specified	science, risks and benefits, and acceptability on a variety of applications. 2-item Wellcome Trust Consultative Panel MCQ Survey analysing knowledge of genetics, as well as general attitdues towards modern and genetic science, and opinions on the applications of particular gene therapies.	Support for testing new genetic treatments on children was low (14%) but significantly increased (25%) under full information. Increased gene therapy knowledge was indicative of increased support for gene therapy for serious conditions eg. heart disease (87%) and cystic fibrosis (96%), but not for conditions such as baldness (14%).	um
Treleavan T & Tuch B. (2018; AUS)	Pre-post intervention	N = 46 (pre-panel) N = 38 (post-panel) Age = majority	Researcher-designed (non-validated; items not specified) questionnaire asessing attitudes towards heritable changes, gene editing for medical and non-health related applications.	Respondents were supportive of heritable changes to embryos for health purposes (86%) and gene editing for adults and children in clinical trials (98%). 69% were against allowing heritable changes in embryos for cosmetic/non health-related purposes. There were no demographic effects (gender, age, occupation) on attitudes.	Low

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		between 20-30 years Gender ratio not specified		Seminar attendance increased support for heritable changes in embryos for health purposes, but was not statistically significant.	
Uchiyama M, Nagai A, Muto K. (2018; Japan)	Cross-sectional survey	N = 1044 (Patients; 37% female; 20-79 years) N = 10881 (Public; 50.4% female; 20-69 years)	Non-validated (items not specified) survey created by researchers. Items asked respondents about awareness and risks of genome editing	Patients were more aware of genome editing than general adults. Overall, having an understanding of what genome editing means was related to higher acceptance rates for "may be performed for diseases that shorten a baby's life" and "may be performed for diseases that require long-term care". Perceived risks and concerns (e.g., "changing genes may have unexpected effects on the human body") were high in both groups regardless of awareness.	Medium
Wang JH, Wang R, Lee JH, Iao TWU, Hu X,	Cross-sectional survey	N = 13,201 (16.4% = clinicians; 83.6% public).	Non-validated online survey with 12-items assessing attitudes towards gene therapy.	Both clinicians and the public strongly support the use of gene therapy to treat fatal or debilitating diseases in adults and fatal disease in children. Less support from both groups for the use of gene therapy for genetic enhancement, such as increasing intelligence and physical attributes.	High

Wang YM, et al. (2017; China)		Age range: 18 to 50 years. 55.8% female (clinicians); 58% female (public)		Clinicians were more concerned about gene therapy going against nature (70.9%), followed by adverse medical side effects (68.9%), whereas the public were primarily concerned about adverse medical side effects (72.0%), followed by high cost (61.9%). Women were significantly more likely than men to accept gene therapy for use in children with inherited diseases and in germline cells. Respondents with higher education or higher self-reported income were more likely to be supportive of the use of gene therapy for severe diseases. Respondents with self-reported religious affiliations were more likely to be significantly against using gene therapy to treat genetic diseases. Respondents with personal knowledge of an individual with a fatal, debilitating or inherited disease were more accepting of gene therapy.	

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Table 1:

Quantitative

Paper

Summary

Author (Year; Country)	Study design	Sample	Measure(s) of perceptions	Key Findings	Quality Rating
Weisberg SM, Badgio D, Chatterjee A.	Cross-sectional experimental design	**Study 1** N = 1,249 43.5% female Mean age =	**Study 1** 10 researcher-designed vignettes describing "three possible uses of genetic modification: the eradication of single-gene disorders, insertion of protective genes, and insertion or replacement of genes for enhancement". Vignettes either exolicity mentioned	Participants in both studies were supportive of research into genetic modification. Men were more supportive than women. African-American participants supported	High

(2017; US)	using contrastin g vignettes	33.23 **Study 2** N = 1,244 50.5% femal e Mean age = 35.20	risks such as "unintended consequences and the possibilty of societal eugenics". Single-item question after each vignette: “Should we be actively be researching these technologies?” **Study 2** The same vignettes were used from Study 1, but the risks were presented either as the second sentence in the vignette or at the end. Single-item question after each vignette: “Should we be actively be researching these technologies?”	genetic modification research less enthusiastically than other ethnicities. Participants with a high school degree or less responded less favorably than participants with some college education. Older participants were less supportive than younger participants. The mention of risks relating to genetic modification decreased support.	

Xiang L, Xiao L, Gou Z, Li M, Zhang W, Wang H, Feng P. (2015; China)	Cross-sectional survey	N = 579 medical students and postgraduates Median age = 22 (range: 16-39) Gender ratio not specified	Non-validated survey designed for study with questions on: general attitudes toward gene therapy, its use to treat diseases of different severities or genetic enhancement, the influence of religious beliefs on attitudes toward gene therapy, main areas of concern with respect to the use of gene therapy to treat brain-related illness, the benefits and risks of gene therapy, and other ethical concerns.	39.55% of respondents were willing to undergo gene therapy, 34.89% would not, and 25.56% were undecided. The most frequent concerns were fears of adverse effects (58.54%), high cost (22.32%), and "going against nature" (19.14%). Men and ethnic minorities (rather than the Han majority) were more likely to accept gene therapy. Most respondents accepted gene therapy for more complex and severe diseases. Lower proportions of respondents were in favor of using gene therapy to improve memory or to extend lifespan. The main reported concerns were adverse side effects followed by ‘‘it goes against my beliefs". Respondents stated that religious beliefs had an effect (13.98%), did not have an effect (32.26%), or were neutral (53.76%) on their perceptions of gene therapy. Only 31.43% of respondents agreed that the benefits of	High

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				gene therapy outweighed the risks.	

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Table 2: Mixed-methods Paper Summary

Author (Year; Country)	Study Design	Sample	Measure(s) of perceptions	Key Findings	Quality Rating
Blair C, Kacser E, Porteous D. (1998; UK)	Semi-structured interviews completed at three time points (Week 1, Week 6, Week 16-18); including ratings of effectiveness.	N = 16 (6 = male, median age = 29)	Participants were asked about knowledge on gene therapy, personal benefits, fears and concerns, comparison of gene therapy to heart transplant, hopes and expectations, experiences of the treatment process and changes in attitudes and expectations. Optimism towards gene therapy as an	Patients had a mean score of 8.4 (0 = ineffective; 10 = very effective) when assessing gene therapy as a treatment for cystic fibrosis. Family and friends were often seen as the driving force behind patients taking part in experimental procedures, not necessarily shared by patients. 87.5 % had no concerns about potential risks, while 12.5% were concerned about getting worse, infections, or cancer. Patients with increased anxiety were also more likely to have concerns over the safety and promise of gene therapy. 100% of patients would prefer gene therapy	Medium

			effective treatment for cystic fibrosis (1-item non-validated measure) was measured on a Likert-type scale on a scale from 0 (ineffective) to 10 (effective).	compared to heart-lung transplantation.	
Bonatti J, Haeusler C, Klaus A, Fink M, Hammerer-Lercher A, Laufer G. (2002; Austria)	Cross-sectional mixed-methods survey	N = 150 (94 male, 56 female) heart surgery patients. Age = 38-84 years (median = 68)	A 12-item self-report questionnaire (non-validated) designed for the study assessing: 1. Basic knowledge of GT; 2. willingness to enrol in a GT trial for CVD; and 3. preferred mode of gene delivery.	52% would enrol in a clinical CVD gene therapy trial, 33% for otherwise incurable heart disease, and 13% would not consent to a gene therapy trial. Overall acceptance rate = 85%. Methods of clinical gene transfer: catheter-based (94% acceptance); surgical (80% acceptance). Adenovirus as a vector for transfer of therapeutic genes (73% acceptance). Prophylactic gene therapy for future heat disease would be accepted by 54% of patients.	Low

Chen SY, Raffan J. (2010; UK and Taiwan)	Cross sectional survey and focus groups	N = 336 (183 students in Taiwan and 153 students in the UK) Age not specified Gender ratio not specified	Researcher-designed (non-validated) questionnaire measuring knowledge and attitudes of biotechnology and genetic engineering using a Likert-type scale. Researcher-led focus group in groups using three major questions: Q1 What are your views on using HIV for gene therapy? Q2 What are your views on xenotransplantation? Q3 What are your views on the use of animals and plants in genetic engineering?	24% of Taiwanese students regarded genetic changes as beneficial compared with only 9% of UK students. In the UK, students who were studying biology demonstrated more optimistic attitudes. 72% of students studying biology, compared with 45% of those not studying biology, thought that biotechnology would not make life worse for humans. Almost all the students (95% in Taiwan, 93% in the UK) think this kind of research is worthwhile and should be supported. Most students viewed the use of HIV for gene therapy as acceptable, if it can prolong lives.	Medium
		N= 469			

Črne-Hladnik, H., Hladnik, A., Javornik, B., Košmelj, K., & Peklaj, C. (2012; Slovenia)	Cross-sectional mixed-methods survey	students 170 male; 299 female Mean age = 17 years (same sample as Črne-Hladnik et al. 2009)	Same questionnaire as Črne-Hladnik et al. (2009) with the addition of a 24-item Multiple Choice Questionnaire to measure pre-knowledge of genetics.	Females with higher pre-knowledge had significantly higher correlations with usefulnes of both somatic and germline gene therapy. Males who had higher pre-knowledge of genetics exhibited higher risk perception of germline gene therapy. Pre-knowledge was not a significant contributing factor in perceived usefulness, moral acceptability and risk perception for any other type of therapy.	Medium
Črne-Hladnik, H., Peklaj, C., Košmelj, K., Hladnik, A., & Javornik, B (2009; Slovenia)	Cross-sectional mixed-methods survey	N= 469 students 170 male; 299 female Mean age = 17 years	Questionnaire (non-validated, items not specified) asking students to evaluate the usefulness, moral acceptability and risk perception of various gene therapy applications using a 5-point Likery scale. Qualitative data was obtained by asking	There was significant moral objections to germline gene therapy compared to somatic gene therapy for hemophilia. Girls rated the usefulness of germline gene therapy significantly lower than boys, but usefulness and moral acceptability was high for all students for somatic gene therapy. Students substantiated moral acceptability of somatic gene therapy primarily on individual impact and that there were no effects on descendants. The students' strongest argument in favor of usefulness was that this treatment can provide health benefits to humans.	Medium

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reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

			students to write a few sentences to justify their answers.		
Ganne P, Garrioch R, Votruba M. (2015; UK)	Cross-sectional mixed-methods survey	STUDY 1: N = 164 (60 = undergraduate optometry students, 35 = eye care professionals, 69 = general public) Age range = 18 to >75 years Gender ratio not specfied	STUDY 1 Non-validated questionnaire (items not specificed) measuring perceptions and how they related to level of knowledge about genetics in general, eye genetics and gene therapy. Response options included multiple choice, Likert-type scales, and open-ended responses. STUDY 2 Non-validated questionnaire (items not specificed)	35% of the participants felt they understood genetics, with students and eye care professionals more confident than the public. Relatively low levels of knowledge about basic concepts in genetics and inherited eye diseases were found among all groups of participants. The majority of respondents (65%) agreed that genetics is not a frightening science. Participants across all groups (82%) felt that genetic research is necessary for progress in the field of medicine.	Medium

		STUDY 2: N = 219 (127 = undergraduate optometry students, 77% female; 22 = eye care professionals, 45% female; 70 = general public, 59% female) Age range = 17 to >70 years	measuring exploring attitudes to genetic testing, gene therapy and knowledge about genetic services.		
Hendriks S,		N = 1013	Researcher-designed (non-validated) questionnaire measuring whether would	A majority of participants (66%) were willing to use germline modification to prevent passing on a	

Giesbertz NAA, Bredenoord, AL, Repping, S (2018; Netherlands)	Cross-sectional mixed-methods survey following a documentary	Dutch general public 54% male Age range = 11 to 90 years Mean age = 44 years	use gene therapy (yes/no) in 5 different applications (wheat for individuals with gluten intolerance; somatic modification for individuals with neuromuscular diseases; germline modification to prevent passing on a neuromuscular disease; germline modification to introduce resistance to HIV; germline modification to increase intelligence). Participants were also asked to indicate why they would or would not (open-ended question).	neuromuscular disease. Participants were least willing to use germline modification to increase intelligence of their embryo (16%). 8% considered modification unacceptable in all scenarios. Being young, male, and having watched the documentary were associated willingness to use genome modification in more scenarios. The possibility of long-term negative consequences for society, unnaturalness of genome modification, and unacceptable health risks were most frequently cited. The availability of alternatives was the most frequently mentioned reason against using genetic interventions.	Medium

King WD, Wyatt GE, Liu H, Williams JK, DiNardo AD, Mitsuyasu RT. (2010; US)	Cross-sectional survey and focus groups	N = 47 participants (16 religious leaders, 8 health care providers, 12 HIV- positive men and women, 11 community agency directors). Age range = 38.9 to 51.5 years 51% female	**Focus Group** Focus groups was conducted where the facilitator asked about: (1) general knowledge about stem cell and gene therapy research, (2) willingness to participate in this research, (3) perceptions of these treatments, and (4) opinions about stem cell and gene therapy research that might hinder or facilitate participation in this research. **Questionnaire** Prior to focus groups, participants completed a questionnaire based on previous research which	Mistrust of research and the US medical system was particularly prevalent within the African American and low income communities. Concerns raised included who was being recruited, how future effective treatments would be allocated, and the goals of HIV research. Only 28% felt that African Americans would have the same access to gene therapy as whites if this treatment was made commercially available. Following clarification that adult cells are taken from and given back to the same individual, fewer than 20% of participants believed that gene therapy using adult stem cells was morally wrong or conflicted with their religious viewpoints.	High

			measured general knowledge and moral concerns on stem cell research, opinions about treatment availability.		

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Table 2: Mixed-methods Paper Summary

Author (Year; Country)	Study Design	Sample	Measure(s) of perceptions	Key Findings	Quality Rating
Macer D, Okada Y, Nakagawa M, Chen Ng	Cross-sectional mixed-methods survey	1991: N = 1304 (551 Public, 47% female, Mean age = 39.8; 555 Scientists, 10% female, Mean age = 47.1; 198 Biology students,	Examined the perceptions of gene therapy from a variety of opinion polls conducted in Japan in 1991, 1993, 1995, 2000, and 2003	There was high gene therapy acceptance for disease prevention, with acceptance similar in 2003 as it was in 1991, and strong support to treat children. There was little difference between the public's and scientist's attitudes to gene therapy in the 2000 survey. Demographic characteristics did not influencing	Medium

MA, Inaba M. (2007; Japan)		47% female, Mean age = 22) 1993: N = 787 (352 Public, 48% female, Mean age =41.7; 435 Biology Students, 33% female, Mean age = 21.1) 1995: N = 247 (76 Public, 50% female, Mean age = 44; 171	– with a specific focus on whether participants would use gene therapy themselves to cure a fatal disease. Open-ended questions used to explore reasons.	responses to gene therapy acceptability, apart from religious views in the 1995 sample. Health risks and concerns remained relatively constant between 1993, 2000, and 2003. The most common reasons to support gene therapy were to save lives, improve quality of life, improve genes, and technological benefit. The most common disapproving reason was that it was unnatural or presented risks to one's health with concerns such as interfering with nature, playing God, health risks, risk of eugenics, and economic issues.	

		Bioethics members, 28% female, Mean age = 55.1) 2000: N = 741 (297 Public, 38% female, Mean age = 44.5; 370 Scientists, 11% female, Mean age = 50; 74 Bioethics members, 23% female, Mean age =			

		44.6) 2003: N = 379 (379 Public, 48% female, Mean age = 46.9)			
Macer DR, Akiyama S, Alora AT, Asada Y, Azariah J, Azariah H, et al. (1995; Australia, Hong Kong, India, Israel, New Zealand,	Cross-sectional mixed-methods survey	N = 6,512 (3186 general public, 1716 medical/biolo gy students, 1610 high school teachers) Age range = 20-61+	International Bioethics survey: 150-item questionnaire with 35 open-ended responses asking about attitudes towards genetic engineering, gene therapy, biotechnology, and genetic screening.	Approximately 75% supported the use of gene therapy personally. There was a general tendency for Asian countries to be more accepting of gene therapy. There were no significant demographic differences (age, sex, religion, education) in responses. 35-60% of individuas from each country would be “very willing” to undergo gene therapy for a fatal disease, and this number increases for use in children. About 5-7% of the sample rejected the use of gene therapy due to it it being "unnatural" and "playing God".	Medi um

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The Philippines, Singapore, Japan, Russia and Thailand)		8-77% female			
Macer DR. (1992, Japan, NZ, Europe, US)	Cross-sectional mixed-methods survey	Japan: 335 biology teachers, 550 scientists, 533 public NZ: 277 biology teachers, 258 scientists, 2034 public	Self-report questionnaire (non-validated) opinion surveys examining public perceptions of risks and benefits of gene therapy, clinical trials for gene therapy, and the acceptability of beginning	74% of respondents from the Japanese general population perceived genetic manipulation of human cells as unacceptable. Main reasons given: “interfering with nature” and “playing God”. Scientists were more accepting than biology teachers, and biology teachers were generally more accepting than the public. The major cited benefits included finding cures for current incurable diseases, and cancer treatment. There was a direct relationship between knowledge and acceptance. Significantly higher perception of risk from Japanese respondents,	Medium

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		US: 1273 public Age not specifie d; Gender ratio not specified	human gene therapy trials. Open-ended questions used to explore reasons.	especially amongst the public and high school biology teachers, compared to New Zealand.	
McCaughey T, Budden DM, Sanfilippo PG, Gooden GEC, Fan L, Fenwick E,	Cross-sectional mixed-methods survey	N = 12,562. 185 countries. Age range = 11-90 years (M = 32)	Researcher designed (non-validated) online survey with items on attitudes towards embryonic/gene editing for life-threatening, debilitating and non-health related (i.e., intelligence, physical appearane) purposes, assessed on 5-	Respondents who were against gene editing for health-related purposes in somatic cells or embryos, showed a higher use of the words associated with "better understanding". Respondents who agreed with genetic editing of non-health-related traits, were less likely to discuss "future generations" and more likely to cite the topic "children" in their responses. Respondents from Western backgrounds were significantly more likely to use words associated with "future generations", whilst Chinese respondents more frequently discussed the topic "better	Medi um

et al. (2019; 185 countries) 29% - United States/United Kingdom 22% - Japan or China)		37.2% female	point Likert scale (1- strongly agree, 5- strongly diagree). Additionally, one open-ended questionnaire assessed self-report factors that have infleunced attitudes towards human gene engineering (3935 qualitative text responses were analysed).	understanding". Results suggest that public resistance to somatic or embryonic gene editing does not stem from mistrust of genome modification, but rather a desire for greater understanding.	
Strong H, Mitchell MJ, Goldstein-Leever A, Shook L, Malik P,	Cross-sectional survey and focus groups	N = 42 participants with sickle cell disease Age range = 18-58 (M = 27) 48%	Self-report questionnaire (items not specified; non-validated) created for the pruposes of this study to examine general perceptions of gene therapy research. Focus-	Survey: Older participants were more positive about gene therapy. Younger participants had greater concern about side effects (i.e. fertility), and were less likely to consider gene therapy as a treatment option. Focus groups: Participants expressed negative views in using the HIV vector as a delivery system. The risk of developing cancer made participants feel they would be trading sickle cell for another potentially more chronic disease.	High

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Crosby LE. (2017; US)		male	groups were also implemented to gain an undertanding on beliefs regarding gene therapy.	Participants noted that presenting longitudinal outcomes from a larger sample sizes would give them more confidence in the reported safety, efficacy, and side effects of gene therapy. Parents of children with higher disease severity were more willing to accept more risk.	
van Lieshout E, Dawson V. (2016; AUS)	Pre-post intervention (school lesson) survey and audio recording within classroom activity	N = 41 year 10 students Age not specified 100% male	2-item questionnaire (non-validated; repeated pre and post lesson) regarding attitudes towards biotechnology on a 5-point Likert scale. Following the questionnaire, a lesson outlining a range of applications of biotechnology that affect human health was presented followed by a classroom activity where students responded	Attitudes expressed in the pre-and post-tests regarding the influence of biotechnology on human health were generally favourable. There was relatively strong support for somatic gene therapy to address diseases, but less support for addressing non-therapeutic uses. Arguments against use of gene therapy to reduce disease were based on eugenic and Darwinist arguments. Arguments for human enhancement seemed largely based on sensation. Opposition to the removal of hereditary conditions was based on social Darwinist arguments.	Medium

			(support, neutral, oppose) to 10 bioethical statements (e.g., "Somatic gene therapy to fight serious diseases is OK") . With each statement, after moving to their positions the justification from each group was recorded.		

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Table 3:
Qualitative
Paper
Summary

Author (Year; Country)	Study Design	Sample	Measure(s) of perceptions	Key Findings	Quality Rating
Iredale R, Dolan G, McDonald K, Kirk M. (2003; Wales)	Qualitative semi-structured interviews	N = 22 participants (people with cystic fibrosis or members of family *n* = 9, students and public *n* = 13) 41% female Age range =	Semi-structured interview assessing general issues about genetics, participants' health status, gene therapy (defining, perceptions, awareness of trials, willingness to paricipate in research), gene enhancement, and societal issues.	Participants were optimistic about the future of genetics. Almost all would have somatic gene therapy, and approx. half would use germline gene therapy. The majority did not approve of enhancement therapy. Participants felt that i) gene therapy should not be provided only by private companies, ii) parents should not be discouraged from having babies that will develop serious genetic conditions, iii) parents do not have a right to obtain genetic enhancement for their unborn offspring, iv) and people should not be able to have gene enhancement therapy on demand. Participants were generally in favor of the principle of using gene therapy to cure diseases. Somatic gene therapy was viewed in a	High

		16-57 years		more positive way than germline therapy. Religion was the predominant reason why participants felt there may be opposition to gene therapy. Respondents' attitudes were not related to health status or exposure to CF.	
Robillard JM, Whiteley L, Johnson TW, Lim J, Wasserman WW, Illes J.	Qualitative content analysis	NA	Content analysis of questions containing the keywords “gene therapy” from a Q&A site for a 5-year time period between January 1, 2006, and December 31, 2010. Answers were themed and coded	75% of answers regarding attitudes towards gene therapy were in favor of gene therapy. 39% were in favor of nontherapeutic enhancement uses. Examples of for and against arguments included making the most of emerging technologies and abiding by religious rules. A majority of answers (>50%) suggested that gene therapy was against nature, that it was not against religion, and that it held the potential to control evolution.	Medium

(2013; NA)			by the researchers.	Concerns revolved around possible discrimination and inequity, uneven resource allocation, and threats to genetic diversity. With regards to risks, the answers demonstrated calculation of risk-benefit and the availability of other options.	

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