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Review Article

Ethical Challenges and Controversies in the Practice and Advancement of Gene Therapy

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One of the most important technologies in modern medicine is gene therapy, which allows therapeutic genes to be introduced into cells of the body. The approach involves genetics and recombinant DNA techniques that allow manipulating vectors for delivery of exogenous material to target cells. The efficacy and safety of the delivery system are a key step towards the success of gene therapy. Somatic cell gene therapy is the easiest in terms of technology and the least problematic in terms of ethics. Although genetic manipulation of germline cells at the gene level has the potential to permanently eradicate certain hereditary disorders, major ethical issues such as eugenics, enhancement, mosaicism, and the transmission of undesirable traits or side effects to patients' descendants currently stymie its development, leaving only somatic gene therapy in the works. However, moral, social, and ethical arguments do not imply that germline gene therapy should be banned forever. This review discusses in detail the current challenges surrounding the practice of gene therapy, focusing on the moral arguments and scientific claims that affect the advancement of the technology. The review also suggests precautionary principles as a means to navigate ethical uncertainties.

1. Introduction

The concept of gene therapy is an experimental procedure that involves the introduction of a normal gene to compensate for a defective gene with the goal of improving a disease condition. This is achieved efficiently using viral vectors to introduce a gene of interest into target cells. Over the past decades, gene therapy has contributed significantly to the treatment of human diseases, such as cancers, cystic fibrosis, heart disease, diabetes, muscular dystrophy, hemophilia, and AIDS [1]. Historically, the first successful trials of gene therapy in humans occurred in 1990 when Ashanti DeSilva with adenosine deaminase deficiency (ADA), leading to X-linked severe combined immunodeficiency (SCID), was treated with her own blood [2]. Nine years later, gene therapy faced a devastating setback when Jesse Gelsinger, an 18-year-old boy with ornithine transcarbamylase deficiency (OTC), died after a clinical trial of therapeutic gene treatment. His death resulted from an excessive immune response after the administration of the therapeutic product. However, gene therapy has transcended beyond the sphere of failure into the arena of breakthrough. Substantial contributions have been made by gene therapy towards the treatment of human diseases. The efficient delivery of therapeutic gene by viral vectors, especially adeno-associated viruses (AAV), as well as the optimization of the delivery systems, has greatly wiped away certain negative assumptions surrounding the practice of viral gene therapy [3].

Among the first gene therapy products, Gendicine was first approved in 2003 by the Chinese Food and Drug Administration (ADA). The medication is an oncolytic virotherapeutic product used to treat neck and head carcinoma [4]. Globally, almost 2600 gene therapy products have been considered for clinical trials, of which a significant percentage have been approved [5]. Additionally, the FoCUS project by MIT suggests that 39 gene therapies will gain regulatory approval by the end of 2022 from the 2017 pipeline of 932

development candidates and this includes already approved product. Among this number, 45% of the total are expected to be utilized in the area of oncology [6].

Gene therapy can be divided into two types: germline and somatic. The distinction between these two procedures is that, in somatic gene therapy, genetic material is injected into some target cells, but the alteration is not handed down to future generations, whereas in germline gene therapy, the therapeutic or changed gene is carried down to future generations. Despite the fact that gene therapy is still in its infancy as a clinically viable therapeutic modality, ethical difficulties and conflicts must be addressed in order to avoid unethical research and health practices. The purpose of this article is to highlight the different ethical difficulties and debates that have arisen as a result of the practice and advancement of gene therapy.

2. The Approach of Gene Therapy

Gene therapy uses two approaches for therapeutic gene transfer; this includes in vivo and ex vivo gene therapy. In vivo gene therapy involves the direct introduction of the gene of interest into a patient tissue via a plasmid, nonviral or viral vectors. With ex vivo gene therapy, isolated patient cells are genetically altered outside of the human body and finally reimplanted in the same patient, or the desired proteins expressed by engineered cells are infused to the patient to introduce potentially therapeutic changes.

2.1. Genome Editing Technologies. Genome editing techniques are considered one of the most challenging yet efficient tools for gene therapeutic approaches [7]. Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9), transcription activator-like effector nucleases (TALEN), and zinc finger nucleases (ZFN) are the most widely used genome editing tools. Genome editing in the field of gene therapy uses an in vivo or ex vivo approach with greatly increased specificity and efficiency. This is achieved by delivering the editing machinery stably into cells to edit genes, as well as making other highly targeted genomic modifications [8]. CRISPR technology offers a great promise for treating a wide range of human genetic diseases. Currently, the CRISPR/Cas9 system is the latest genome editing technology, as it is efficient and precise for genetic modification processes that include the insertion of therapeutic genes, the destruction of viral DNA, and the correction of harmful mutations [9]. Researchers have demonstrated successful proof-of-concept studies in germline and somatic gene therapy by genome editing. In 2014, Genovese and his group used CRISPR/Cas9 genome editing strategy to correct the interleukin-2 receptor subunit gamma (IL2RG) gene, which has provided a new avenue for the treatment of SCID. Another study focused on CRISPR/Cas9-mediated chromosomal inversion of the factor VIII gene in patients with hemophilia A [10]. Genome editing has now become a powerful method in the field of gene therapy. However, there are certain ethical challenges, moral, and safety concerns related to the attractive application of this technology, especially in the germline.

2.2. Germline Genome Editing. Germline gene editing (GGE) has been used as a research tool and as a therapeutic intervention. This technique has been used to modify genes of yeast, mice, plants, rodents, pigs, and primates [11]. In a recent study, gene editing was used to deactivate 62 retrovirus genes in a pig cell line, a crucial step towards creating suitable pig organs for transplantation [12, 13]. In October 2015, researchers edited a gene related to muscle growth in a beagle to double its normal muscular mass [14]. Germline gene editing has the potential to ameliorate disease phenotype from embryos, and supporters of the technique claim that it could be used as a means of disease prevention in humans. Despite the broad implications, public debate has focused on the ethics of human germline gene editing [15]. In April 2015, He, a genome editing researcher in China, used for the first time CRISPER/Cas9 genome editing technique to disable HIV-CCR5 gene that is responsible for HIV entry into target cells from an embryo and implanted into a woman [16]. DNA sequencing confirmed the deletion of the CCR5 gene, suggesting the great benefit that can be derived from germline editing. In another study, to understand the efficiency and potential off-target effect of CRISPR technology in embryo editing, Liang et al. cleaved β-globin gene of triponuclear (3PN) human zygotes using the CRISPR/Cas ribonucleoprotein. The results showed an apparent off-target effect and a low efficiency of homologous recombination directed repair (HDR) coupled with mosaicism [17]. Thus, editing a human embryo could be a useful method to eliminate defective genes and even provide HIV-positive couples the opportunity to give birth to HIV-negative children; however, some potential pitfalls, including the off-target effect and mosaicism, limit its application on humans. The safety and efficacy of genome editing tools are the main concerns for clinical application. Consequently, alternative genetic approaches that are safer and more efficient must be explored to protect people, other than changing the DNA of an embryo [18].

3. Ethical Challenges of Gene Therapy

3.1. Off-Target Mutation. The most obvious ethical debate specifically from the National Institute of Health (NIH) against GGE is the off-target effect. Off-target gene mutation could potentially result in insertional mutagenesis and gene mutation [19]. Bioethicists and researchers suggest that genome editing is new and unpredictable technology, and little is known about gene regulation and mechanisms of embryonic development; therefore, the consequences of germline therapy can be fatal [20]. Despite the fact that CRISPR/Cas proves to be an efficient tool for clinical somatic use, it has not reached the stage to be utilized in human genome editing for clinical reproductive purposes. Therefore, the apparent long-term effects cannot be overlooked [21, 22]. Genome editing performed on human embryos has a high risk of causing pathologic diseases and disabilities that can permanently affect the patient and the offspring. Although the specificity of Cas9 targeting is tightly controlled, potential off-target cleavage activity could still occur in DNA sequences and has been demonstrated in previous studies [17, 23, 24]. Nevertheless, integrating viral vectors including retrovirus, lentivirus, and even adeno-associated viruses can carry a gene of interest into a nontarget region of the host

genome which can likely result in insertional mutagenesis. A study in an animal model shows that the integration of AAV into chromosome 19 could possibly result in genotoxic effects, leading to neoplastic transformations that are prone to tumor development [25]. In addition, off-target integration has been observed in lentiviral vector systems (LV), one of the main delivery vehicles due to its high tissue tropism and long-term expression of the transgene [26]. However, refined strategies have been adapted to improve and optimize LV systems for effective and accurate gene delivery [27].

3.2. Genetic Mosaicism. In CRISPR germline gene therapy, the CRISPR/Cas vector is inserted immediately after fertilization so that each successive cell resulting from cleavage is genetically modified. However, the vector can persist and transcribe, making it possible to further introduce the Cas protein into parts of already engineered cells and potentially initiate another cleavage, leading to mosaicism [28, 29]. Some cells may eventually acquire edits that are different from those of other cells, leading to differences in gene copy number, causing skin, brain, and heart disorders, and impairing embryo maturation. In a study, high levels of mosaicism were observed after germline editing of a model bovine embryo using the Cas9 system [30]. This finding confirms the possibility of its occurrence in human embryos if left unregulated. Furthermore, the technological approach to testing mosaic mutations in an edited embryo may be ineffective, as the small number of cells selected for testing may not include a mosaic mutant cell [31]. In the summer of 2019, the potential effect of mosaicism emerging from the clinical application of germline editing was discussed by the US National Academy of Medicine, the US National Academy of Sciences, and the Royal Society of medicine [32]. The lack of clear evidence from experts that mosaic mutation has not occurred in a range of cell and tissue types of early-stage human embryo editing, as well as the inability of the technology to validate that a particular edit is correct and devoid of mosaic mutation could make it difficult for the public to support the application. Therefore, to ensure that germline editing is safe, all important issues and controversies should be addressed.

3.3. Informed Consent. Following the first gene therapy death recorded in a clinical trial in September 1999, the informed decision about participating in a clinical trial has gained numerous concerns. It is advisable that participants undergoing gene therapy clinical trials must be extensively educated on the potential risks and benefits associated with treatment to provide them with enough information on which to decide to participate or not without coercion [33]. A study by the National Human Genome Research Institute (NHGRI) proposed the need and importance of informed consent in CRISPR somatic genome editing after surveying patients with sickle cell disease [34]. Inasmuch as gene therapies suggest future transformation by treating many incurable diseases, the perceived benefits of the technology should not overshadow the difficulties that the patients may face in grasping long-term hazards. Although somatic gene therapy meets the need for informed consent, germline embryo editing poses a more difficult regulatory issue, that is, whether consent of a future generation is required and, if so, who should express consent because embryos cannot consent to germline intervention [35]. Moreover, the extent of authority over the embryo by the prospective parents and practitioners raises ethical debate, whether parents will be the only autonomous entity to make decisions for their unborn babies or will this be seen as usurping the interests of future generations who are unable to consent at the time of the decision [36]. Due to too many unknowns, it is uncertain what information would be required or available to properly inform prospective parents about dangers, including those for future generations [37]. This poses a significant challenge in obtaining informed consent [38]. As additional gene treatments for incurable hereditary disorders enter the consent clinic, a discussion on ethics should be started so that these issues can be discussed in a clear, fair, and balanced manner, rather than allowing any particular profession to make the final decision on where the ethical limits should be drawn [39]. It is an undeniable fact that any research which may someday prove to be a breakthrough should completely meet the ethical standards of informed consent [40].

3.4. Enhancement and Eugenics. Genetic enhancement or improvement is also a legitimate concern surrounding the application of gene therapy. Enhancement gene therapy means manipulating genes to improve the characteristics of an individual according to the interests of the person [41]. Genetic therapy, on the other hand, involves altering faulty genes to prevent or cure diseases [42]. A classic example of enhancement therapy is the injection of recombinant human growth hormone (rhGH) into children of short stature to increase the growth rate and final height [43]. However, the injection of rhGH into children of normal height in an attempt to make them taller may possibly create ethical issues. Furthermore, athletes rely on human recombinant erythropoietin (EPO) for improvement. The EPO hormone is used to induce the production of red blood cells that are used to treat kidney dialysis and anemia. However, athletes who do not have any health conditions seek EPO therapy in an attempt to improve performance in competitive events where muscles require a lot of oxygen [44, 45]. Inasmuch as some enhancement practices are considered morally unethical since it shifts from the natural, the distinction between enhancement and therapy may be a contextual issue and must be clearly understood. An enhancement application may be therapeutic and vice versa. The improvement of the height of short persons whose condition is a result of human growth hormone deficiency, as well as, enhancing the skin color of patients suffering from vitiligo indicate a therapeutic enhancement. This suggests that genetic therapy and enhancement may have common similarities [46]. Moreover, enhancement can potentially lead to eugenics. CRISPER/Cas9 offers the prospect of manipulating the germline to select human traits such as beauty, character, body formation, and intelligence. This makes it possible to create evolutionary individuals and improve the human race [47]. In 2015, the UNESCO International Bioethics Committee commented on the eugenic dangers of germline procedures. The committee suggested that the incorporation of gene editing techniques into gene therapy may possibly change the therapeutic application to racial improvement. Hence, the

equal dignity of all human beings may be altered and eventually renew eugenics [48]. To control the use of technology, an intervention aimed at altering the human genome may be performed only for preventive, diagnostic, or therapeutic purposes, and any attempt to achieve this goal should be banned [49]. Furthermore, the extent of human condition to which gene therapy is applicable should be clearly defined and properly regulated to make people aware of diseases and condition of disease that require experimental treatments. This may address concerns about equal accessibility while minimizing nontherapeutic traits enhancement. Scientific researchers should clearly state the goal of any applied or basic research involving CRISPR/Cas editing; either the research is to provide a therapeutic solution, to generate preliminary data for the development of human genome editing applications, or to just improve the expression of certain traits for nontherapeutic purposes. These distinctions are necessary in the sense that even if one opposes human enhancement therapy, there are important applications of CRISPR/Cas editing that do not serve that purpose. Nonetheless, it is crucial to emphasize that distinguishing eugenics from treatment might be difficult. For example, it is often discussed whether enhancing the immune system through gene and immunotherapeutic approaches is eugenics or not [50]. As a result, a case-by-case analysis is required to resolve numerous concerns. In fact, eugenics is rooted in a social construct which justifies discrimination and injustice against those who are genetically unfit [51]. Therefore, it is worthwhile to clarify that gene therapy, when placed in the right context, has the potential to eliminate birth abnormalities and terminal diseases.

4. Conclusion

Gene therapy has made incredible strides since its first human trial and holds great promise in medicine and health care. Even with the tragedies of early clinical trials and optimism surrounding this emerging field, many therapeutic products have been approved worldwide and are still being tested. Among the two gene therapy approaches, germline gene therapy is considered to have raised controversial arguments including off-target effects, mosaic mutation, informed consent, and eugenics. Although bioethical concerns may sound morally and socially legitimate to proponents, the public and even scientists, they are not conclusive enough to stop the good applications of gene therapy. However, to minimize public debates hampering the advancement of gene therapy, system optimization, detailed safety protocols, and critical regulatory measures must be put in place to help achieve the therapeutic goals of this technology.

Conflicts of Interest

The author declares that he/she has no conflicts of interest.

References

[1] S. Misra, "Human gene therapy: a brief overview of the genetic revolution," *The Journal of the Association of Physicians of India*, vol. 61, no. 2, pp. 127–133, 2013.

[2] R. M. Blaese, "Development of Gene Therapy for Immunodeficiency: Adenosine Deaminase Deficiency," *Pediatric Research*, vol. 33, pp. S49–S55, 1993.

[3] J. P. Gillet, B. Macadangdang, R. L. Fathke, M. M. Gottesman, and C. Kimchi-Sarfaty, "The development of gene therapy: from monogenic recessive disorders to complex diseases such as cancer," *Gene Therapy of Cancer*, pp. 5–54, 2009.

[4] W. W. Zhang, L. Li, D. Li et al., "The first approved gene therapy product for cancer Ad-p53 Gendicine: 12 years in the clinic," *Human Gene Therapy*, vol. 29, no. 2, pp. 160–179, 2018.

[5] "Corrigendum: gene therapy clinical trials worldwide to 2017: an update," *The Journal of Gene Medicine*, vol. 21, no. 9, article e3124, 2019.

[6] C. Quinn, C. Young, J. Thomas, and M. Trusheim, "Estimating the clinical pipeline of cell and gene therapies and their potential economic impact on the US healthcare system," *Value in Health*, vol. 22, no. 6, pp. 621–626, 2019.

[7] M. Alagoz and N. Kherad, "Advance genome editing technologies in the treatment of human diseases: CRISPR therapy review," *International Journal of Molecular Medicine*, vol. 46, no. 2, pp. 521–534, 2020.

[8] Q. Li, Z. Qin, Q. Wang, T. Xu, Y. Yang, and Z. He, "Applications of genome editing technology in animal disease modeling and gene therapy," *Computational and Structural Biotechnology Journal*, vol. 17, pp. 689–698, 2019.

[9] H. Li, Y. Yang, W. Hong, M. Huang, M. Wu, and X. Zhao, "Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects," *Signal Transduction and Targeted Therapy*, vol. 5, no. 1, p. 1, 2020.

[10] B. Song, Y. Fan, W. He et al., "Improved hematopoietic differentiation efficiency of gene-corrected beta-thalassemia induced pluripotent stem cells by CRISPR/Cas9 system," *Stem Cells and Development*, vol. 24, no. 9, pp. 1053–1065, 2015.

[11] C. Gyngell, T. Douglas, and J. Savulescu, "The ethics of germline gene editing," *Journal of Applied Philosophy*, vol. 34, no. 4, pp. 498–513, 2017.

[12] D. Niu, H. J. Wei, L. Lin et al., "Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9," *Science*, vol. 357, no. 6357, pp. 1303–1307, 2017.

[13] L. Scobie, J. Denner, and H. J. Schuurman, "Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9, editorial commentary," *Xenotransplantation*, vol. 24, no. 6, p. e12363, 2017.

[14] J. Bolzon, "First gene-edited dogs reported in China: what do gene-edited dogs say about human life," *Voices in Bioethics*, 2015.

[15] J. M. Gumer, "The Wisdom of Germline Editing: An Ethical Analysis of the Use of CRISPR-Cas9 to Edit Human Embryos," *New Bioethics*, vol. 25, no. 2, pp. 137–152, 2019.

[16] D. Cyranoski and S. Reardon, "Embryo editing sparks epic debate," *Nature*, vol. 520, no. 7549, pp. 593-594, 2015.

[17] P. Liang, Y. Xu, X. Zhang et al., "CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes," *Protein & Cell*, vol. 6, no. 5, pp. 363–372, 2015.

[18] M. A. Kay, "State-of-the-art gene-based therapies: the road ahead," *Nature Reviews Genetics*, vol. 12, no. 5, pp. 316–328, 2011.

[19] G. Rubeis and F. Steger, "Risks and benefits of human germline genome editing: An ethical analysis," *Asian Bioethics Review*, vol. 10, no. 2, pp. 133–141, 2018.

[20] A. P. Cribbs and S. M. W. Perera, "Science and Bioethics of CRISPR-Cas9 Gene Editing: An Analysis Towards Separating Facts and Fiction," *Yale Journal of Biology and Medicine*, vol. 90, no. 4, pp. 625–634, 2017.

[21] F. Uddin, C. M. Rudin, and T. Sen, "CRISPR gene therapy: applications, limitations, and implications for the future," *Frontiers in Oncology*, vol. 10, p. 1387, 2020.

[22] T. Douglas, C. Gyngell, J. Harris, R. Lovell-Badge, and Group H, "Genome editing technologies and human germline genetic modification: the Hinxton group consensus statement," *The American Journal of Bioethics*, vol. 15, no. 12, pp. 42–47, 2015.

[23] L. Cong, F. A. Ran, D. Cox et al., "Multiplex genome engineering using CRISPR/Cas systems," *Science*, vol. 339, no. 6121, pp. 819–823, 2013.

[24] P. D. Hsu, D. A. Scott, J. A. Weinstein et al., "DNA targeting specificity of RNA-guided Cas9 nucleases," *Nature Biotechnology*, vol. 31, no. 9, pp. 827–832, 2013.

[25] R. J. Chandler, M. C. LaFave, G. K. Varshney et al., "Vector design influences hepatic genotoxicity after adeno-associated virus gene therapy," *The Journal of Clinical Investigation*, vol. 125, no. 2, pp. 870–880, 2015.

[26] A. Atkins, C. H. Chung, A. G. Allen et al., "Off-target analysis in gene editing and applications for clinical translation of CRISPR/Cas9 in HIV-1 therapy," *Frontiers in Genome Editing*, vol. 3, 2021.

[27] S. Mizuno, T. T. Dinh, K. Kato et al., "Simple generation of albino C57BL/6J mice with G291T mutation in the tyrosinase gene by the CRISPR/Cas9 system," *Mammalian Genome*, vol. 25, no. 7-8, pp. 327–334, 2014.

[28] W. Dong and B. Kantor, "Lentiviral vectors for delivery of gene-editing systems based on CRISPR/Cas: current state and perspectives," *Viruses*, vol. 13, no. 7, p. 1288, 2021.

[29] D. Oliver, S. Yuan, H. McSwiggin, and W. Yan, "Pervasive genotypic mosaicism in founder mice derived from genome editing through pronuclear injection," *PLoS One*, vol. 10, no. 6, p. e0129457, 2015.

[30] S. L. Hennig, J. R. Owen, J. C. Lin et al., "Evaluation of mutation rates, mosaicism and off target mutations when injecting Cas9 mRNA or protein for genome editing of bovine embryos," *Scientific Reports*, vol. 10, no. 1, p. 22309, 2020.

[31] H. Ledford, "CRISPR babies: when will the world be ready," *Nature*, vol. 570, no. 7761, pp. 293–296, 2019.

[32] National Academies of Sciences Engineering and Medicine, "Committee on Human Gene Editing: Scientific Medical and Ethical Considerations, & National Academies of Sciences Engineering and Medicine (U.S.)," in *Human Genome Editing: Science, Ethics, and Governance*, The National Academies Press, 2017.

[33] E. C. Jonlin, "Informed consent for human embryo genome editing," *Stem Cell Reports*, vol. 14, no. 4, pp. 530–537, 2020.

[34] S. Desine, B. M. Hollister, K. E. Abdallah, A. Persaud, S. C. Hull, and V. L. Bonham, "The meaning of informed consent: genome editing clinical trials for sickle cell disease," *AJOB empirical bioethics*, vol. 11, no. 4, pp. 195–207, 2020.

[35] J. Smolenski, "CRISPR/Cas9 and germline modification: new difficulties in obtaining informed consent," *The American Journal of Bioethics*, vol. 15, no. 12, pp. 35–37, 2015.

[36] Z. K. Shinwari, F. Tanveer, and A. T. Khalil, "Ethical issues regarding CRISPR mediated genome editing," *Current Issues in Molecular Biology*, vol. 26, no. 1, pp. 103–110, 2018.

[37] E. Lanphier, F. Urnov, S. E. Haecker, M. Werner, and J. Smolenski, "Don't edit the human germ line," *Nature*, vol. 519, no. 7544, pp. 410-411, 2015.

[38] A. Caplan, "Getting serious about the challenge of regulating germline gene therapy," *PLoS Biology*, vol. 17, no. 4, p. e3000223, 2019.

[39] J. Kahn, "Informed consent in human gene transfer clinical trials," *Human Gene Therapy*, vol. 19, no. 1, pp. 7-8, 2008.

[40] L. P. Nijhawan, M. D. Janodia, B. S. Muddukrishna et al., "Informed consent: issues and challenges," *Journal of Advanced Pharmaceutical Technology & Research*, vol. 4, no. 3, pp. 134–140, 2013.

[41] T. Friedmann, "Genetic therapies, human genetic enhancement, and eugenics," *Gene Therapy*, vol. 26, no. 9, pp. 351–353, 2019.

[42] M. Cavazzana-Calvo, A. Thrasher, and F. Mavilio, "The future of gene therapy," *Nature*, vol. 427, no. 6977, pp. 779–781, 2004.

[43] E. Graber, E. O. Reiter, and A. D. Rogol, "Human growth and growth hormone: from antiquity to the recominant age to the future," *Frontiers in Endocrinology*, vol. 12, article 709936, 2021.

[44] S. De Marchi, M. Pirisi, and G. F. Ferraccioli, "Erythropoietin and the anemia of chronic diseases," *Clinical and Experimental Rheumatology*, vol. 11, no. 4, pp. 429–444, 1993.

[45] S. T. Provatopoulou and P. N. Ziroyiannis, "Clinical use of erythropoietin in chronic kidney disease: outcomes and future prospects," *Hippokratia*, vol. 15, no. 2, pp. 109–115, 2011.

[46] F. Kamm, *What is and is not wrong with enhancement*, 2006.

[47] C. Schmidt, "Temprian therapeutics: developing a gene-based treatment for vitiligo," *Nature*, 2020.

[48] H. T. Greely, "CRISPR'd babies: human germline genome editing in the He Jiankui affair," *Journal of Law and the Biosciences*, vol. 6, no. 1, pp. 111–183, 2019.

[49] International Bioethics Committee, "Report of the International Bioethics Committee IBC on Updating Its Reflection on the Human Genome and Human Rights. FINAL RECOMMENDATIONS," *Law and the human genome review*, no. 43, pp. 195–199, 2015.

[50] I. De Miguel Beriain, "Legal issues regarding gene editing at the beginning of life: an EU perspective," *Regenerative Medicine*, vol. 12, no. 6, pp. 669–679, 2017.

[51] N. Bostrom and R. Roache, "Ethical issues in human enhancement," *New Waves in Applied Ethics*, pp. 120–152, 2008.