World Health Organization – Research Report II

Gene Manipulation in Healthcare: Balancing Genetic Advances with Ethical Responsibility

Introduction to the Topic:

Gene manipulation has been a fast-developing field in healthcare as it refers to the modification of genetic material to try to cure, prevent or better prepare the body to fight against a disease, by including techniques such as gene editing, gene therapy and **CRISPR-Cas9**. Even though gene manipulation has the potential to cure various diseases such as cancer, cystic fibrosis, heart disease, diabetes, hemophilia and AIDS, it also generates ethical concerns among safety, informed consent and justice and equity.

Currently, gene manipulation is transitioning from research to clinical applications, and we are entering a new phase in the clinical development of **genome** editing in medicine. Due to the unresolved ethical concerns, the World Health Organization emphasizes the need of a new governance framework to implement, regulate and oversee research into the human genome.

Somatic gene therapies have already been successfully used to treat or cure HIV, sickle-cell disease (SCD) and transthyretin amyloidosis, and this technique can also be used to improve treatment for a variety of cancers. There are several risks that arise from using these techniques, using **germline** and heritable genome, which modify the genome of human embryos, causing it to be passed on to future generations, altering descendant's traits. This leads to ethical concerns regarding informed consent complexities because some of the genome alterations may affect individuals who are not born yet, making consent more challenging and confusing.

Since gene therapy is still recent and mostly in the clinical trial phase, there is a lot of uncertainty and lack of education on this topic which leads to several ethical concerns about gene manipulation, especially considering that, it involves changing the body's basic building blocks, DNA. Other causes that lead to this issue are the possible economic disparities, as these technologies may be primarily accessible to wealthier individuals creating health inequalities.

Furthermore, due to the rapid advancements in this field, editing technologies have outpaced the existing regulatory frameworks, causing ethical concerns regarding proper oversight.

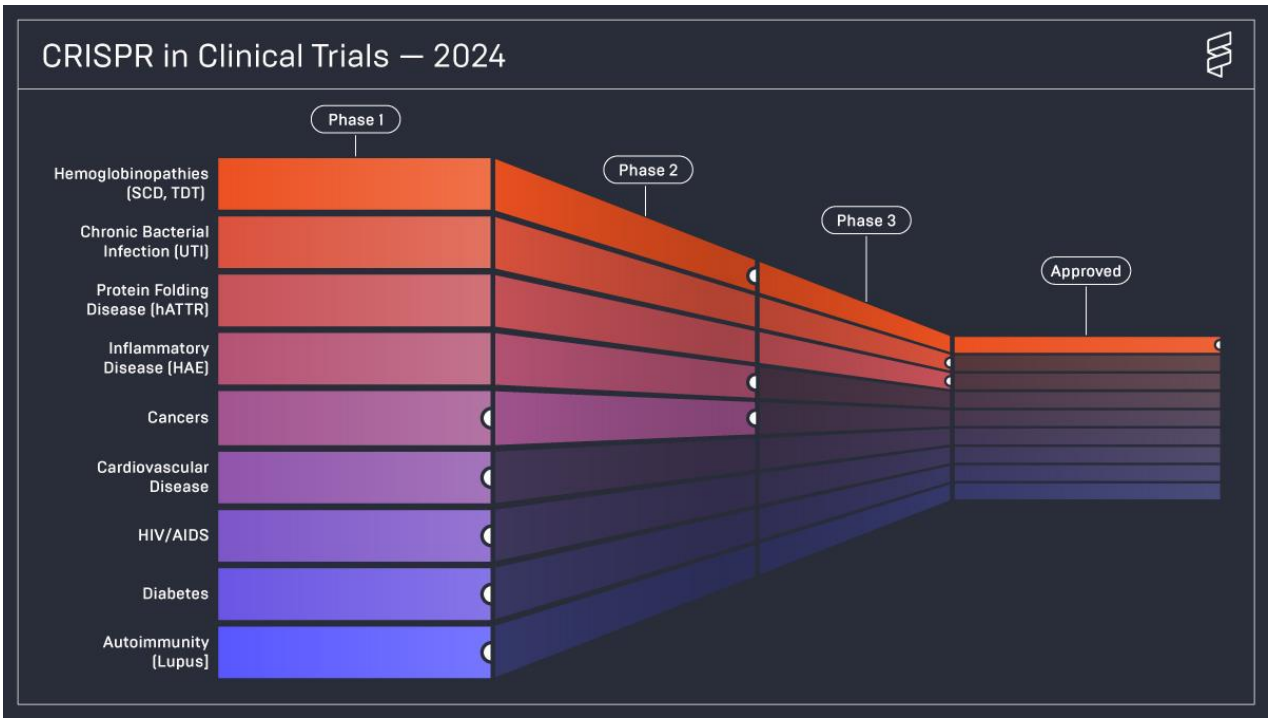

Figure 1.1 – CRISPR in Clinical Trials in 2024 (Henderson, H. (2024, March 13). CRISPR Clinical Trials: A 2024 Update. Retrieved from: https://innovativegenomics.org/news/crispr-clinical-trials-2024/)

As of 2024, Casegevy has been approved in the UK, EU, US for the treatment of beta thalassemia (TDT) and Bahrain has conditional approval. The Saudi Arabia Food and Drug Administration (FDA) is reviewing a regulatory submission, and a submission is planned to be made in Canada.

Figure 1.1 shows the use of CRISPR in clinical trials for several diseases. The one made for SCD and TDT has been approved and for both UTI and hATTR are already in phase 3. This shows evidence that gene modification has been advancing rapidly and therefore the ethical issues need to be resolved.

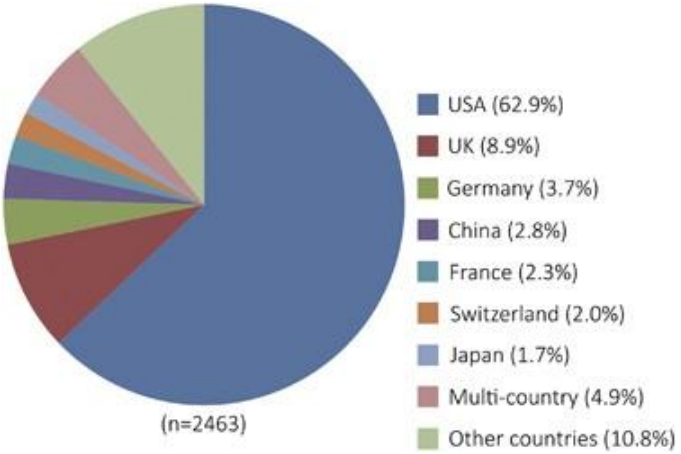

Figure 1.2 - The proportion of gene therapy clinical trials in major countries worldwide up to April 2017 (Deng, H., Wang, Y., Ding, Q., Wei, Y. (2017, September 7). Gene therapy research in Asia. Retrieved from: https://www.nature.com/articles/gt201762)

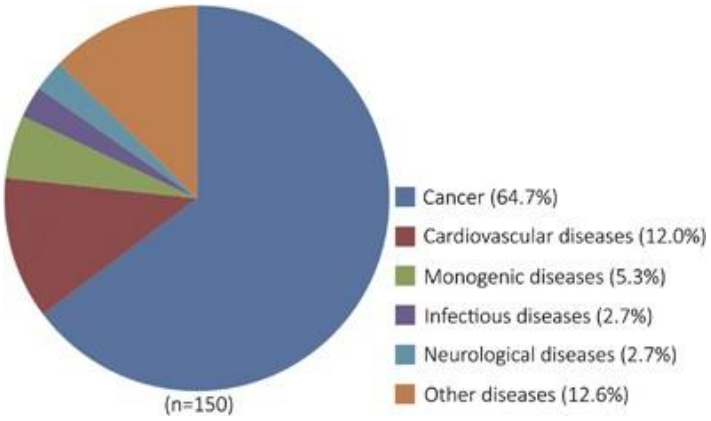

Figure 1.3 - Diseases addressed by gene therapy clinical trials in Asia up to April 2017 (Deng, H., Wang, Y., Ding, Q., Wei, Y. (2017, September 7). Gene therapy research in Asia. Retrieved from: https://www.nature.com/articles/gt201762

A total of 2463 clinical trials were performed for several different gene therapies until 2017. According to Figure 1.2, the United States is at the forefront of gene therapy research as it has conducted 62.9% of the world with 1550 clinical trials. Followed by the United Kingdom with 8.9% and Germany with 3.7% of the total clinical trials. According to Figure 1.3, most gene therapy trials target cancer, 64.7%, followed by cardiovascular diseases, 12.0%, monogenetic diseases, 5.3% and infectious diseases, 2.7%.

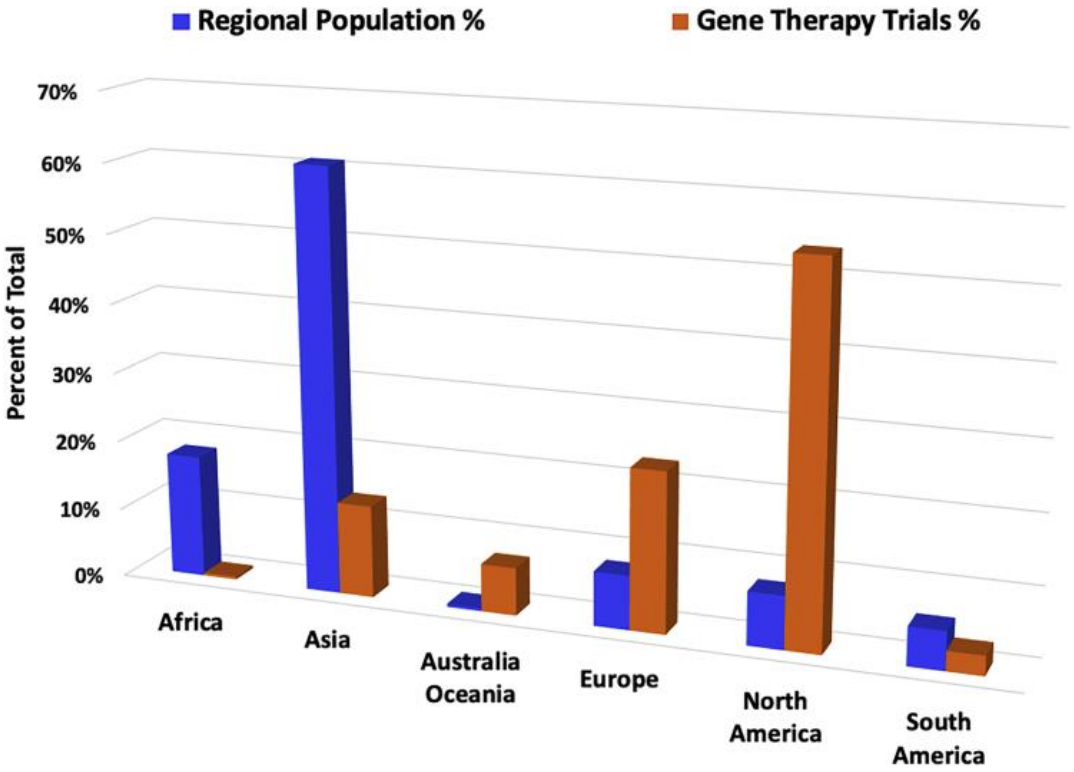

Figure 1.4 – Global gene trial distribution (Conetta, K., Bonamino, M., Mahlangu, J., Mingozzi, F., Rangarajan, S., Rao, J. (2022, April 4). Retrieved from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9171243/)

Background Information:

1960s: Bone marrow transplantation was the first step in the concept of treatment where damaged, **pathological cells** are replaced with healthy ones. This laid the groundwork for modern gene editing.

1990s: The first gene therapy was initiated to insert the gene encoding the protein into the cells of the person having hereditary health condition.

2012: CRISPR-Cas9, one of gene technology's most precise tool, was discovered by Emmanuelle Charpentier and Jennifer Doudna and were awarded the Nobel Prize in Chemistry in 2020 for this breakthrough.

2013: CRISPR-Cas9 was successfully used in genome editing in human cell cultures.

2018: After the report of twin sisters being born with edited genomes in China, authorities reaffirmed the American Society of Human Genetics (ASGH) position, which states that **in vitro** human germline genome editing is allowed.

One of the most prominent challenges regarding gene manipulation is the ethical considerations and long-term effects, as genome editing is changing the fundamental building blocks of life, and it may arise several implications as they may affect future generations. Other challenges include off-targets effects as CRISPR may edit genes other than the intended target which can lead to undesired results which might lead put the patient at risk. And, transporting the gene-editing tools to the desired location within the body requires a lot of precision and safety, which means this method needs further development. Furthermore, while attempting to correct genetic mutations, there is a risk of introducing unintentional mutations during the editing process which can lead to unexpected health issues, meaning that the overseeing and rigorous safety protocols are crucial when working with this technology.

Recent Developments:

2020: Many treatments that use gene therapy such as lipoprotein lipase deficiency therapy, melanoma therapy and Duchenne muscular dystrophy therapy, were approved by the FDA.
2021: ARCUS genome editing technology is now being used by BioSciences company in clinical trials to evaluate the clinical activities and safety of allogenic CAR T cell therapy for Non-Hodgkin Lymphoma.
2023: Casegevy is a CRISPR-based medicine that provides a cure for sickle cell disease and transfusion-dependent beta thalassemia, was approved for the first time ever by the United Kingdom's Medicines and Healthcare Products Regulatory Agency.

Focus of the Debate:

Debate should focus on the regulation and oversight of genome editing with the aim of establishing global standards to deal with the safety and ethical concerns, foster public trust and engagement, ethical boundaries by defining acceptable uses of gene manipulation and ensuring that there is equity in terms of access especially for low- and middle-income countries.

Parties Involved:

For this issue there are several parties involved such as:

United States: The United States is the leading country in terms of gene therapy research as it has the highest percentage of clinical trials performed worldwide. Also, the FDA has approved of gene therapy for several conditions, including cancer, spinal muscular atrophy, hemophilia and sickle cell disease.

United Kingdom: The United Kingdom has performed several clinical trials for genome editing and it was the first country in the world to have approval for gene editing as a potential cure for two inherited blood disorders in November of 2023.

China: In 2003, China approved the first gene therapy-based product for clinical use. Additionally, Chinese scientists were the first to use the CRISPR-Cas9 technique in a clinical trial.

European Union: Regulatory agencies in the European Union have recently approved various gene therapies, however no clinical studied on targeted germline have yet been applied in the EU as they have severely high and rigorous frameworks and regulations for overseeing the research.

Past UN Actions:

1997: The UN General Assembly endorsed the Universal Declaration on the Human Genome and Human Rights which addresses the ethical, legal and social implications of advancements in genetic research and technologies.

2014: About 40 countries discouraged or banned research on germline editing including 15 nations in Western Europe due to ethical and safety concerns.

2015: The United States, United Kingdom and China led an international effort to harmonize regulation of the application of genome editing technologies.

Possible Solutions:

Convene a small expert committee: form a small group of experts to consider the next steps for the Registry, for example improved monitoring of clinical trials using human genome editing technologies of concern.

Develop an accessible confidential reporting mechanism: work with multisector stakeholders to develop this accessible mechanism to confidentially report concerns about illegal, unregistered, unethical and unsafe human genome editing research and other activities.

Increase education, engagement and empowerment: lead regional webinars focusing on local needs in order to increase education about gene manipulation and also to increase engagement and empowerment.

Build inclusive global dialogue: Create web-based resources for reliable information on genome editing to build this inclusive global dialogue on frontier technologies by collaborating with the Science Division.

Glossary and Key Terms:

CRISPR-Cas9: Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein (CRISPR-Cas9) is a gene-editing technology that corrects error in the genome.

Genome: The entire set of DNA instructions found in a cell; it consists of 23 pairs of chromosomes.

Somatic gene therapy: Involves the introduction of a human gene into a living person's **somatic cells**.

Somatic cells: Any cell of a living organism other than the reproductive cells.

Germline: Refers to the sex cells (eggs and sperm) that sexually reproducing organisms use to pass on their genomes from one generation to the next.
In vitro: When something is performed outside of a living organism for example in a test tube.
Pathological cells: Cells that are affected by a disease

Bibliography and Useful Links:

Ayanoglu, F., Elçin, A., Elçin, Y. (2020, April 2). Bioethical issues in genome editing by CRISPR-Cas9 technology. Retrieved from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7129066/

Conetta, K., Bonamino, M., Mahlangu, J., Mingozzi, F., Rangarajan, S., Rao, J. (2022, April 4). Retrieved from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9171243/

Deng, H., Wang, Y., Ding, Q., Wei, Y. (2017, September 7). Gene therapy research in Asia. Retrieved from: https://www.nature.com/articles/gt201762

Faltus, T., Beriain, I. (2023, March 14). The EU legal framework on clinical trials directed to therapeutic germline gene alteration: A critical and systematic analysis. Retrieved from: https://journals.sagepub.com/doi/10.1177/09685332231154586?icid=int.sj-full-text.similar-articles.2

Fernholm, A. (2020). The Nobel Prize in Chemistry 2020. Retrieved from: https://www.nobelprize.org/prizes/chemistry/2020/popular-information/

Henderson, H. (2024, March 13). CRISPR Clinical Trials: A 2024 Update. Retrieved from: https://innovativegenomics.org/news/crispr-clinical-trials-2024/

Imperial College Healthcare NHS Trust. (2023, November 16). UK medicines regulator approves world-first gene-editing treatment for blood disorders. Retrieved from: https://www.imperial.nhs.uk/about-us/news/uk-medicines-regulator-approves-world-first-gene-editing-treatment-for-blood-disorders

Kenter, M. (2018, November 13). Is it time to reform oversight of clinical gene therapy in the EU? Retrieved from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6303196/

Mayo Clinic. (2024, April 23). Gene Therapy. Retrieved from: https://www.mayoclinic.org/tests-procedures/gene-therapy/about/pac-20384619

N.A. (n.d.). CRISPR and the future of healthcare: Promise and challenges. Retrieved from: https://sanogenetics.com/resources/blog/crispr-and-the-future-of-healthcare

National Library of Medicine. (n.d.). What are the ethical issues surrounding gene therapy? Retrieved from: https://medlineplus.gov/genetics/understanding/therapy/ethics/

NIH. (2017, August 3). What are the Ethical Concerns of Genome Editing? Retrieved from: https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/ethical-concerns

Ojiambo, M., Pharm, B. (2023, December 11). What's Hot in 2024: CRISPR Treatments. Retrieved from: https://www.criver.com/eureka/whats-hot-2024-crispr-treatments

Petraitytė, G., Preikšaitienė, E., Mikštienė, V. (2021, August 17). Genome Editing in Medicine: Tools and Challenges. Retrieved from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9133615/

Redman, M., King, A., Watson, C., King, D. (2016, April 8). Retrieved from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4975809/

UNESCO. (2023, April 20). UNESCO cautions against reckless application of gene editing. Retrieved from: https://www.unesco.org/en/articles/unesco-cautions-against-reckless-application-gene-editing

UNESCO. (n.d.). Universal Declaration on the Human Genome and Human Rights. Retrieved from: https://www.unesco.org/en/ethics-science-technology/human-genome-and-human-rights

WHO. (2021, July 12). WHO issues new recommendations on human genome editing for the advancement of public health. Retrieved from: https://www.who.int/news/item/12-07-2021-who-issues-new-recommendations-on-human-genome-editing-for-the-advancement-of-public-health