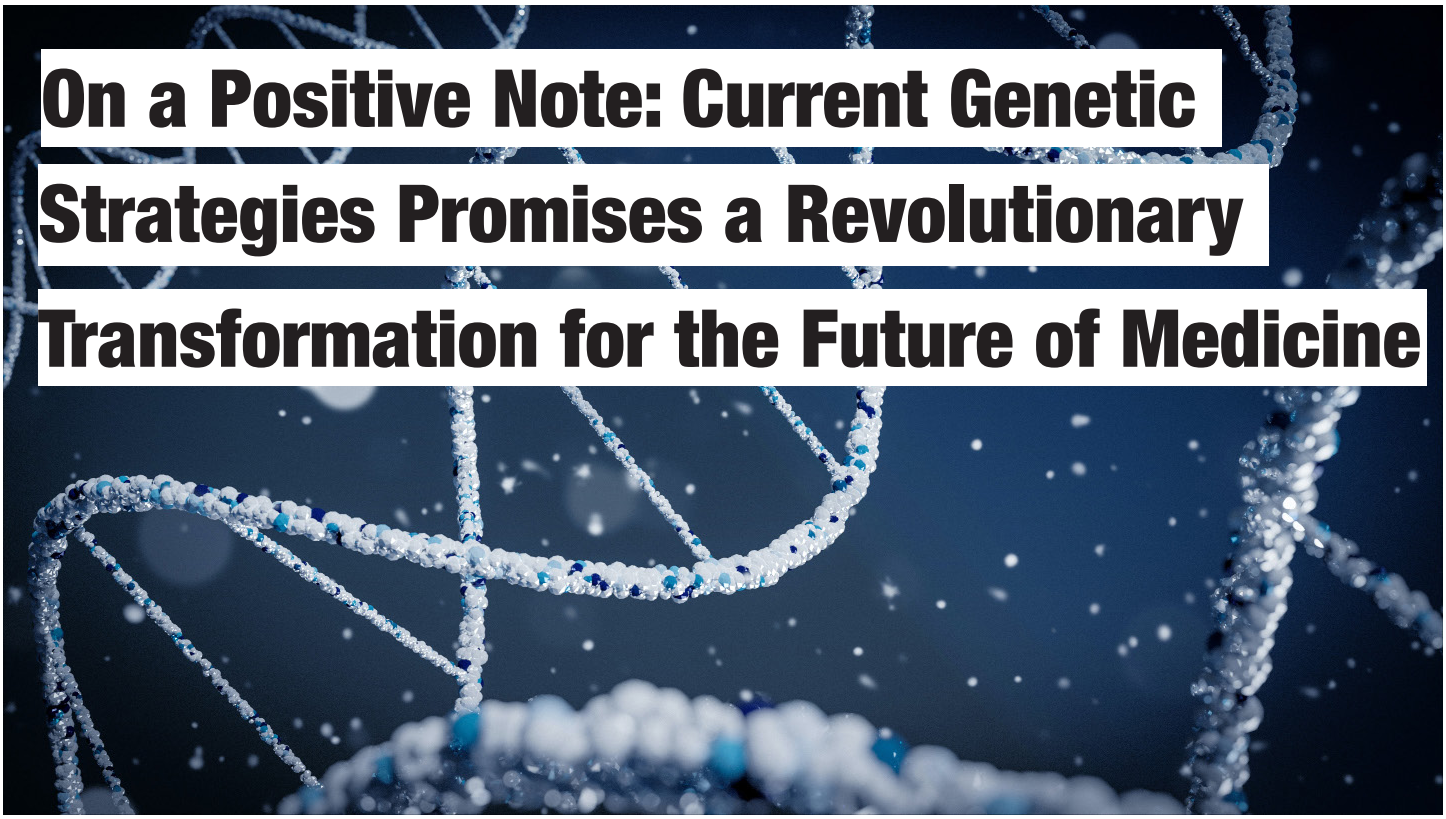
On a Positive Note: Current Genetic Strategies Promises a Revolutionary Transformation for the Future of Medicine



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For the longest time, medical problems associated with our DNA have been the hardest to correct. Genetically inherited diseases and disorders, somatic mutations both cancerous and non-cancerous, and even retroviral infections all lead to intrinsic- and extrinsic- driven modifications in our genome that can negatively impact our health. These medical issues have now re-emerged in a different light, as we optimize recently developed genetic sequencing[1-3] and editing[4-8] strategies. It is an exciting time for the field of precision medicine as it reaches new heights in characterizing diseases and acquiring viable solutions to current issues in medical genetics.[3,6]

The year 2003 marks the completion of the Human Genome Project, which had taken 13 years to generate and complete the first human reference genome with a total expense of $2.7 billion dollars.[9-11] Thanks to various technological advancements and the development of parallel sequencing via microscale reactions, we have made tremendous advancements. Today, it takes less than 2 days and costs less than $1000 dollars to sequence an entire human genome.[10,12] This allowed an increase in samples and genetic diversity in our existing genome databases. As a result, statistical analyses can be conducted to efficiently identify disease-causing variants through Genome-Wide Association Studies (GWAS).[13,14]

With the expansion of human genetic variant catalogs and reduced cost of genome sequencing, the field of medical diagnostics now has the potential to enhance disease characterization with genetic-level accuracy.[10] For example, cancer was previously characterized simply based on its size and organ of origin; today, we recognize that 'same' cancer types can be unique across

individuals depending on the oncogenes involved. Given that the presence or absence of specific genes can have a significant impact on the stability and effectiveness of drugs, gene identification and characterization will provide more information on disease progression and treatment response.[15] Furthermore, this also challenges our traditional 'one-size-fits-all' approach in treating complicated genetic diseases, including cancer.[16] With reduced price and increased efficiency of genome sequencing, the 'luxury' of personalized, precision medicine (at the genetic level) is now within reach.[11]

Rather than characterizing gene functions and mutations through labor-intensive genetic knock-out studies in animals, the statistical top-down approach of GWAS has transformed current genetic research by efficiently identifying phenotype-related mutations.[14] At this rate, we will be able to identify most common disease-causing genetic variants, characterize rare ones and track novel mutations emerging in our population. In addition, it can be used to reveal genes involved in complex polygenic traits and illnesses, which will expand our understanding of non-Mendelian genetics and present the big picture behind genetic interactions.[17] Due to developments in gene-sequencing technologies, we are now at the edge of transforming the field of medical genetics as we unlock previously impervious issues.

Coincidentally, enabled by the advancements in DNA sequencing strategies, we now have a potentially viable solution to cure genetic diseases that were and will be characterized. A breakthrough emerged in 2013, when Zhang and his team realized the potential of a bacterial immune response to be used as an efficient gene-editing tool and introduced the CRISPR-Cas9 strategy.[7] Although gene modification strategies have been around for decades, this technology has also substantially increased the efficiency and reduced the price of gene editing compared to previously available techniques.[8]

As a precaution with this technique's current limitations, its direct usage for human genome modification(s) is highly restricted.[18] Nevertheless, due to its revolutionary potential in eliminating genetic diseases and predispositions, it has already made indirect ways inside medical research. In search for more effective cancer treatments, various immunotherapeutic studies are undergoing initial phases of clinical trials with very promising results.[16] The strategic utilization of genetically modified T-lymphocytes or oncolytic viruses may one day successfully eliminate cancer and provide personalized vaccines against future re-emergence.[19,20] At such an early stage of technique development, CRISPR already promises many possibilities that can revolutionize the future of medical treatment. In addition, its reduced cost and practicality has made it an invaluable tool for both medical and academic research, this increased use presents an opportunity for optimization and refinement of the technique.[6,7] Each limitation will inevitably be characterized and addressed, hopefully leading to the development of an effective genetic disease treatment.

Historically, high demand accompanied with price deflation and increased efficiency were common themes behind exponential growth,[21] similar to the trends we currently observe in genetics. Due to its promising trajectory, the field is currently receiving attention from influential and powerful investors. Cathie Wood, the CEO and founder of ARK invest, claims that "the genomic revolution is going to change healthcare as we know it, partly because of the 'good' kind of deflation" - as she alludes to Wright's law of experience curve.[21,22] With the support of both public and private sectors, funding for genetic medical research will continue to increase, which will further expedite future developments. Undeniably, these snowballing advancements are now at the cusp of undertaking revolutionary strides towards transforming the fields of medical diagnostics and treatments.

Undoubtedly, these novel discoveries and the possibilities they offer brings great bioethical and safety concerns,[18] and it would be foolish to ignore the dangers and repercussions associated with them. However, as we tackle each limitation and establish appropriate regulations, they will certainly develop into powerful tools that will surely revolutionize medicine as we know it.

Clearly, our accomplishments thus far have helped shine the light at the end of the tunnel for the endless possibilities we strive to create in medicine. Medical institutions should update current curriculums and consider these changes to better prepare future medical practitioners for the inevitable

transformation in the field of healthcare.[23] Hopefully, with our advanced understanding of these concepts and issues, we would be inspired to act by stimulating conversations and generating new ideas both within the scientific community and the general public. Together, these actions will inevitably propel us towards the promising medical future ahead.

REFERENCES

1. Fedurco, M., Romieu, A., Williams, S., Lawrence, I. & Turcatti, G. BTA, a novel reagent for DNA attachment on glass and efficient generation of solid-phase amplified DNA colonies. Nucleic Acids Res. 34, e22 (2006).
2. Picelli S, Björklund AK, Reinius B, Sagasser S, Winberg G, Sandberg R. Tn5 transposase and tagmentation procedures for massively scaled sequencing projects. Genome Res. 2014 Dec;24(12):2033-40. doi: 10.1101/gr.177881.114. Epub 2014 Jul 30. PMID: 25079858; PMCID: PMC4248319.
3. Mardis ER. DNA sequencing technologies: 2006-2016. Nat Protoc. 2017 Feb;12(2):213-218. doi: 10.1038/nprot.2016.182. Epub 2017 Jan 5. PMID: 28055035.
4. Anzalone, A.V., Randolph, P.B., Davis, J.R. et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature 576, 149–157 (2019). https://doi.org/10.1038/s41586-019-1711-4
5. Chih-Che Shen, Mu-Nung Hsu, Chin-Wei Chang, Mei-Wei Lin, Jih-Ru Hwu, Yi Tu, Yu-Chen Hu, Synthetic switch to minimize CRISPR off-target effects by self-restricting Cas9 transcription and translation, Nucleic Acids Research, Volume 47, Issue 3, 20 February 2019, Page e13, https://doi.org/10.1093/nar/gky1165
6. Adli, M. The CRISPR tool kit for genome editing and beyond. Nat Commun 9, 1911 (2018). https://doi.org/10.1038/s41467-018-04252-2
7. Ran, F., Hsu, P., Wright, J. et al. Genome engineering using the CRISPR-Cas9 system. Nat Protoc 8, 2281–2308 (2013). https://doi.org/10.1038/nprot.2013.143
8. Gupta, S. K., & Shukla, P. (2017). Gene editing for cell engineering: trends and applications. Critical reviews in biotechnology, 37(5), 672-684.
9. International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature 409, 860–921 (2001). https://doi.org/10.1038/35057062
10. Wetterstrand KA. DNA sequencing costs: data from the NHGRI Large-Scale Genome Sequencing Program. http://www.genome.gov/sequencingcosts. Accessed May 8, 2022.
11. Johansen Taber KA, Dickinson BD, Wilson M. The Promise and Challenges of Next-Generation Genome Sequencing for Clinical Care. JAMA Intern Med. 2014;174(2):275–280. doi:10.1001/jamainternmed.2013.12048
12. Tucker, T., Marra, M., & Friedman, J. M. (2009). Massively parallel sequencing: the next big thing in genetic medicine. The American Journal of Human Genetics, 85(2), 142-154.
13. Klein, R. J. et al. Complement factor H polymorphism in age-related macular degeneration. Science 308, 385–389 (2005).
14. Uffelmann, E., Huang, Q.Q., Munung, N.S. et al. Genome-wide association studies. Nat Rev Methods Primers 1, 59 (2021). https://doi.org/10.1038/s43586-021-00056-9
15. Prat, A., Baselga, J. The role of hormonal therapy in the management of hormonal-receptor-positive breast cancer with co-expression of HER2. Nat Rev Clin Oncol 5, 531–542 (2008). https://doi.org/10.1038/ncponc1179
16. Nogrady, B. (2020). How cancer genomics is transforming diagnosis and treatment. Nature, 579(7800), S10.
17. Nishiguchi, K. M., Miya, F., Mori, Y., Fujita, K., Akiyama, M., Kamatani, T., ... & Nakazawa, T. (2019). Systematic detection of Mendelian and non-Mendelian variants associated with retinitis pigmentosa by genome-wide association study. bioRxiv, 859744.
18. Rossant, J. (2018). Gene editing in human development: ethical concerns and practical applications. Development, 145(16), dev150888.
19. Liu, X., Zhang, Y., Cheng, C. et al. CRISPR-Cas9-mediated multiplex gene editing in CAR-T cells. Cell Res 27, 154–157 (2017). https://doi.org/10.1038/cr.2016.142
20. Lemay, C. G., Rintoul, J. L., Kus, A., Paterson, J. M., Garcia, V., Falls, T. J., ... & Auer, R. C. (2012). Harnessing oncolytic virus-mediated antitumor immunity in an infected cell vaccine. Molecular Therapy, 20(9), 1791-1799.
21. Nagy, B., Farmer, J. D., Bui, Q. M., & Trancik, J. E. (2013). Statistical basis for predicting technological progress. PloS one, 8(2), e52669.
22. Cathie Wood: The Genomics Revolution - CRISPR. (n.d.). Www.youtube.com. Retrieved May 8, 2022, from https://www.youtube.com/watch?v=OmxWV1XvE70
23. Plunkett-Rondeau, J., Hyland, K. & Dasgupta, S. Training future physicians in the era of genomic medicine: trends in undergraduate medical genetics education. Genet Med 17, 927–934 (2015). https://doi.org/10.1038/gim.2014.208