Gene Editing: A Brave New World?

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The author, a forensic scientist as well as an international Barrister and Attorney, is solely responsible for the contents of this article. The author has no financial conflicts of interest.

This article is a broad interdisciplinary discussion on the ethical issues surrounding history's discoveries in gene editing. The discussion addresses various points and materials found in the academic and website sources listed at the article's conclusion. The goal of this article is to open the door to critical questions and explorations of the issues at stake, both today and into the future.

Introduction
The Past As Possible Prologue

Currently, we are on the cusp of understanding and harnessing the power of our molecular biological information. Imagine a world where genetic diseases are not just manageable but curable. Then imagine a world where genetic mutations are curbed, cured or obliterated.

This article explores the relatively new and potentially societal changing Molecular Biology application CRISPR/Cas9, which provides the key to this Pandora's box of possibilities. The aim of this article is to foster a dialogue surrounding this paradigm shifting application, which has the potential to change and shape society in a myriad of ways.

In November 2018, the world was informed that Chinese scientist Dr. Jiankui He claimed he had altered the DNA of twin girls to prevent them from contracting HIV.

Effectively, Dr. He has allegedly created the first genetically designed/edited babies. However, through his announcement Dr. He has brought into focus a compendium of issues that have previously been debated in the abstract. This cauldron of issues must and should be debated on a global scale.

This field of genetic research is exploding. Nevertheless, the minefield of associative concerns needs to be brokered and broached in order to responsibly advance the applications of such a powerful and monumental tool. Coincidentally, it has been reported in January 2019 that Dr. He was fired from the Southern University of Science and Technology in Shenzhen, in China's Guandong province. His firing occurred following an investigation by officials in Guandong. The Ministry found that he broke national regulations against using gene-editing

Photo by Daniel Son

for reproductive purposes. According to an article in *Nature*, the investigation also found that Dr. He's experiment ran afoul of national Chinese regulations forbidding people with HIV from using assisted reproduction. Chinese state media agency *Xinhua* also reported that, in order to circumvent the Chinese regulations, Dr. He experimented with blood from HIV-negative volunteers.

The Advancement of Molecular Biology
How Did We Get Here?

Molecular biology research has focused on the development of technologies to efficiently and reliably document, explain, and, over time, target genes with a view of changing the genome of living cells (also known as genetic code).

In 1953, building upon the earlier research of various scientists from around Europe, Watson & Crick derived the concept of the three-dimensional, double-helical model for the structure of DNA. This was then built upon by Ray Wu of Cornell University who, between 1970 and 1973, established and then developed and applied the first method for determining DNA sequences. Frederick Sanger adopted this and then advanced this strategy to develop more rapid DNA sequencing methods at the MRC Centre, Cambridge, in 1977. Advancements in sequencing were aided by the concurrent development of recombinant DNA technology.

New methods for DNA sequencing were then developed in the mid to late 1990s and were labeled the "next-generation" or "second-generation" sequencing (NGS) methods, thereby distinguishing them from Sanger's earlier methods. In contrast to the first generation of sequencing, this technology was highly scalable, allowing the entire genome to be sequenced at once. In application, this second generation of techniques allowed the genome to be fragmented into small pieces, which were randomly sampled and then sequenced.

The mapping of an entire genome is possible because multiple fragments are sequenced at once in an automated process. This technology allows for insights into health and anthropological investigations into human origins. It thus has ushered in the realization of individualized or personalized medicine.

However, it has also opened the door to more room for error and concern. Several efforts to develop standards in the NGS field have been attempted to address these challenges, most of which have been small-scale efforts arising from individual labs. Most recently, a large organized, FDA-funded effort has culminated in what is termed the BioCompute standard, namely a more centralized construct.

Fast-forward to post-2000. The wider field of molecular biology is advancing as researchers seek to further explore the human genome. Therein begins the burgeoning interest in genome editing technology and genomic engineering.

One pillar of this expanding endeavor is "CRISPR/Cas9" or "CRISPR" which stands for **Clustered Regularly Interspaced Short Palindromic Repeats**. This technology can be programmed to target particular regions of genetic code and edit it at precise locations. This allows researchers to permanently modify genes in living cells and ultimately in organisms. This

makes it theoretically possible, in the future, to correct mutations at precise locations in the human genome, thereby potentially treating genetic origins of disease.

That this new tool is simple and easily adaptable makes it amenable to genomic editing, which is also referred to as genetic engineering. This potential was realized in 2012 by the Doudna and Charpentier labs. However, it should be noted that this powerful tool is not without its limitations.

It should be also noted that the amount of genetic alteration, also known as Target efficiency, is one of the most important strictures or considerations when assessing a genomic editing tool. Previous methods and tools have achieved genetic alterations anywhere ranging from 1% to 50% in human cells. By contrast CRISPR/Cas9 has reported efficiencies up to greater than 70%. However, that is in zebrafish, plants, and human stem cells ranging from 2-5%. One study purported an efficiency of 78% in one cell mouse embryos.

Another aspect of the efficiency of gene editing is the incidence of off-target mutation. This is the propensity to cut not just at its target site, but also at unintended sites with similar sequences. These off-target cuts can occur across the genome and can lead to harmful mutations that impair a cell's function or kill it outright. Off-target mutations are, generally speaking, more difficult to detect, and therefore require additional efforts such as sequencing the entire genome in order for the anomaly to be completely ruled out. The CRISPR system reduced, but has not eliminated, off-target mutations.

In a 2014 article in New England Biolabs, we are informed that the future is bright for the application of the CRISPR/Cas9 due its "simplicity, high efficiency and versatility," and additionally, its being the most "user friendly." These same researchers also commented that: "It is now clear that Cas9's potential reaches beyond DNA cleavage, and its usefulness for genome locus specific recruitment... will likely only be limited by our imagination."

Intersection: Gene Editing & Ethical Considerations

In April 2015 the first article on editing the genome of human embryos was published by researchers in China. The global response was swift; and condemnation in the form of questions abounded. The following are some examples of such responses:

"*Chinese gene-editing experiment creeps out scientists*" NBC News: https://www.nbcnews.com/health/health-news/chinese-gene-editing-experiment-creeps-out-scientists-n346916.

"*Homo sap is now a GMO. Shall we edit the genes of human embryos?*" PLOS blog: https://blogs.plos.org/onscienceblogs/2015/04/24/homo-sap-now-gmo-shall-edit-genes-human-embryos/.

"*Red alert over DNA mutation, editing of human embryos*" (Nigerian) Guardian: http://io.aibs.org/geneedit3.

The issue with this new and extremely puissant molecular biology technique, which makes gene editing faster, cheaper and more precise, is that it allows and promulgates not only the repairing of genetic mutations but includes the ability to add and alter genetic material. Because

of its potential effects, not only on the scientific community but the world at large, a group of key stakeholders led by Dr. Duodna, one of the developers of CRISPR, met in January 2015 to discuss the application's scientific, medical, legal, societal and ethical implications.

This impromptu meeting resulted in a call for a halt on human germline editing, and a large call on international dialogue for recommendations for moving forward. These calls where published in the 3 April issue of Science. An additional article of a similar nature in the same general timeframe was published by Dr. Edward Lanphier and Dr. Fyodor Urnov et al. Their article labeled human germline modification as "dangerous and ethically unacceptable."

The National Academy of Science (NAS) convened an International Summit on Human Gene Editing, which was cosponsored by the National Academy of Medicine, The Royal Society and the Chinese Academy of Sciences in early December 2015. This symposium had the sole goal of wrestling with the potential worry of human genomic editing. An article written by Beth Baker after the symposium cited that Nobel Laureate David Baltimore addressed the symposium by stating,

> We're taking on a heavy responsibility for our society because we understand that we could be on the cusp of a new era in human history... We should remember there is a larger context...-Aldous Huxley in his book *Brave New World* imagined a society built on the selection of people to fill particular roles in society with environmental manipulation to control the social mobility and behavior of the population... the warning implicit in his book is one that we should take to heart as we face the prospect of this new and powerful means to control the nature of the human population.

At the culmination of the meeting. the planning committee reached certain conclusions, namely that future research on germline and non-germline cells can continue but with the caveat that human germline editing research for the purpose of pregnancy cannot be performed. The planning committee based this on two considerations: the first being technical issues and safety, while the second considered the broader more contentious issue of societal consensus. In effect the Committee recommended that germline research should not be done simply because of the opinion of a researcher/scientist.

Unlike previous research that focused on non-germline cells of a patient with a genetic disease, the committee presciently articulated that informed consent should be considered differently for germline cell research. The Committee understood that in non-germline cell research the individual person solely considers the issue of consent. Contrast that with the issue of genomically editing a sperm, egg or embryo which would affect every cell of that unborn child and unknown future generations.

Creating a genetically modified embryo for the purpose of pregnancy gives birth to a compendium of ethical issues. For example, off-target genes would have to be considered if and when they occur and their frequency. Equally if the gene editing process was incomplete (for whatever reason) then a potential new set of issues and concerns emerge. Additionally, there are potential ethical and societal ramifications if function creep occurs and the technology is usurped under the guise of so-called improving humans in aesthetically pleasing ways instead of eliminating genetic disease. Further to this point, if or perhaps when the technology becomes precise enough for this thought to become viable, then questions emerge. Who decides on its

use? Who should have access to such a tool? Some, such as Ms. Beth Baker *Bioscience* editor is incredulous at the hubris in reliance on the application of this tool to circumvent the natural order and improve on the established evolutionary design.

We only have to look to our initial subject scientist, Dr. He, for a snapshot, albeit incomplete, answer to these questions.

Regarding the application of CRISPR, United States Congressman Bill Foster, PhD views it as follows: "This is in some ways, an attack from the future on our shared humanity." However, he also stated that by proactively laying the groundwork he hopes to avoid "a panicked overreaction" by his legislative counterparts.

In order to not seem completely reductive, there are many scientific and societal benefits from gene editing research. We are learning about human biology on the molecular level and the ability to eliminate debilitating genetic diseases as well as creating resistance to diseases. On a more meaningful and granular perspective, one scholar, Robin Lovell-Badge of the Francis Crick Institute, has detailed positive aspects:

...obtaining glucose and lactose tolerance in humans;

...obtaining nutritional value from currently indigestible plants;

...maintaining muscle mass in the elderly;

...and, potentially incorporating non-human traits into the human genome, such as tolerance to drought, heat or cold etc.

The possibilities are infinite. However, with these endless possibilities comes the specter of uncertainty, which fuels the present ethical quandaries.

There is a prevailing theory that common diseases affect many more genes than diseases that affect few in the population. The latter would be isolated to perhaps a single genetic mutation. Overall, the interaction of our genes is barely understood. For example, Eric Lander, the founding Director of the Broad Institute, noted that a gene that lowers an individual's risk of acquiring HIV increases that individual's risk of contracting and eventually succumbing to the West Nile Virus. Correspondingly, a gene that reduces the risk of type-1 diabetes links with a higher risk of Crohn's disease. Concomitant with uncertainty is the task of balancing risk/rewards in the context of the unborn.

Barbara Evans, a professor of law at University of Houston, elucidates that primarily the study of medical bioethics and its resultant framework tends to focus on the individual patient/research subject and the risks to that individual. For the examples detailed above as well as others, the application of CRISPR calls for a paradigm shift for the manner for which we must tackle these and other affiliated issues. It is understandable that we, as a society, must learn about and grapple with such monumental issues caused by this powerful scientific tool and its myriad of applications and uncertainties.

Dr. Baltimore posits that ethically in certain circumstances there may be no alternative. If so, then perhaps we should use CRISPR to "...help out...a yet to be born child." And that withholding the value of the modification on the basis that it might lead to other things is

"abdicating responsibility." George Church, a professor at Harvard Medical School, argued that the real battle is where to draw the line between disease prevention and other goals such as aesthetic enhancement.

Historian Daniel Kevles, an expert on eugenics, informs us that the line between disease prevention and enhancement can be blurred and even change over time, which may be dependent on what is regarded as the characteristics of health in future times. He further posits that modern efforts to improve the human species will be driven by "biocapitalism" --- a new relationship between human and capital based on technological advances and consumers. Though this phenomenon is currently exhibited in areas of assisted reproductive technology, thought should be given to the ability of the gene editing technology to be weaponized in a way inconsistent with the current application of assisted reproductive technology. Some may not agree and be in complete congruity with Kevles, and may maintain skepticism of his assessment of this particular situation. Each should draw one's own conclusions.

Social scientists at the aforementioned December 2015 NAS summit raised concerns surrounding access and decision-making specifically for people with disabilities who would or could be potentially or directly affected from the application of CRISPR. The social scientists also warned that a technique such as CRISPR should serve a broader purpose that could help eliminate or disarm social or cultural hierarchies (for example, "ableism" versus "disableism") instead of reinforcing or exacerbating them. As with anything that directly and permanently could affect the human experience, there was no general consensus reached at the Summit. However most seem to agree the need for a broad societal consensus on what will be permissible moving forward. Landers ended the aforementioned summit with this discerning comment:

> We should be very straightforward about how ignorant we are... Humility is one of the hardest challenges for any one, but especially when you have to compete for funding and attention... So it's good [to be reminded] of how much humility is appropriate in this case and how ignorant we are. Ignorance is nothing to be ashamed of -- its denial of ignorance that we should be worried about.

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