Human Gene Editing: With Great Power Comes Great Responsibility

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In the twenty-first century, the world is at a crossroads for gene editing. The technology has the potential to treat anywhere between 7-50 percent of the total population, based on whether one considers those with purely genetic diseases or partially genetic diseases (e.g. diabetes) as well (Baird et al., 1988; Stevenson, 1959). Although the patients' quality of life varies depending on their genetic disease (J. S. Cohen & Biesecker, 2010), depression and reduced functional capacity are associated with life-threatening genetic diseases such as Huntington's disease (Ho et al., 2009). However, ethical quandaries plague gene editing, such as the permissibility of making "designer babies" or the ability of humans to "play God." Even therapeutic gene editing can lead to adverse events and death for patients.

Therefore, as this technology grows in capability, our society must know where to draw the line and how to use gene editing safely. How do we then distinguish responsible from reckless applications of gene editing? We cannot solely rely on medical regulatory agencies to give us the answers, as scientists, patients, bioethicists and the general public often have very different answers. Scientists, patients, and bioethicists have sometimes wanted gene editing progress at the expense of safety, and the government has not always been ready to address this. Through mistakes, society has learned that the benefits of editing must outweigh the costs, and protocols must be followed strictly. Most scientists however have advanced the field with caution and regulatory adherence. We will only consider human gene editing, and while we will address roadblocks to "designer baby" creation, we will not make moral judgements. Many questions will linger regarding the future of gene editing that will depend on progress of the field and society's evolving moral norms.

Review of Research

Previous documentary research asked people involved with the field to comment on its progress. One gene therapy researcher had positive results initially in a clinical trial followed by neutral results that rendered her work meaningless. She said she was "devastated" that the therapy failed. A gene therapy startup, Avigen, classified the timeline to an approved gene therapy as "long" and the hurdles as "bigger than expected." An analyst for an investing firm that funds gene therapies, Michael Zasloff, began to comment on the difference between acceptable and poor uses of gene editing; he claimed that treating "locally and transiently with a gene therapy is much less risky than permanently altering gene expression" (Branca, 2005).

Other groups addressed the questions around gene editing with ethical arguments rather than public survey. The Nuffield Council on Bioethics recently issued two reports on the ethics of gene editing, one general and the other focusing on embryonic gene editing before birth. The council believes that a disconnect between the rate of technological progress and the rate of regulation could be problematic. According to them, the best gene editing uses would follow current medical norms (i.e. treating disease while minimizing risk to the patient) and waiting to see if society resolves the ethical dilemmas surrounding gene editing before trying nonstandard uses (i.e. creating "designer babies"). One such dilemma in the council's view is that some "see human enhancement as an inevitable evolution in the use of technology" while others see it as a "slippery slope" that leads to the line between editing for "therapy" and "enhancement" becoming blurred. The council argued embryonic editing only has merit if a "significant risk" of genetic disease occurrence was "established prior to conception" (Nuffield Council on Bioethics, 2016, 2018). All the above work identified potential roadblocks in gene editing without

explaining how to navigate them. The present research will not answer ethical questions but will describe the evolution of editing ethics and different groups' beliefs.

Savulescu, Tanne, and others have reflected on what we learned from gene editing failures and tragedies (Savulescu, 2001; Tanne, 2000). Palmer even discussed the legality and medical liability of faulty edits long before a publicized error had occurred (Palmer, 1991). These addressed important violations of scientific ethics that establish the fundamental basis of acceptable gene editing. Meyers examined problems with the regulatory process which allowed unethical editing (Meyers, 2000). However, all these failed to name the social forces that determine what constitutes acceptable editing, or to synthesize the perspectives of these forces into one coherent document. This is the task at hand.

Some Scientists Were Not Prudent

Some scientists have valued progress at the expense of safety, and as a result, the field has learned some hard lessons. The first case of this is the infamous University of Pennsylvania clinical trial to treat ornithine transcarbamylase deficiency (OTCD) by editing the OTC gene with an adenoviral vector. During this trial in 1999, eighteen-year old patient Jesse Gelsinger died (Stolberg, 1999). This was the first public death attributable to gene editing, as the U.S. Food and Drug Administration (FDA) determined through investigation (McCarthy, 2000). The FDA admonished the Penn researchers for accepting Gelsinger into the trial when his ammonia levels were too high (Stolberg, 1999), failing to halt the study when several patients before Gelsinger "suffered serious side effects," and failing to properly train staff. One of the most damning errors was researchers' removal of two paragraphs from the original informed consent form approved by the FDA which disclosed monkey deaths in previous animal studies (Marshall, 2000). Penn researchers tried to defend the monkey deaths by saying they were not the result of

the gene therapy. The FDA disagreed, saying that the monkeys and Gelsinger both died from similar complications including disseminated intravascular coagulation (Nelson & Weiss, 2000a).

Many have commented on what went wrong with the Gelsinger case, and the consensus is that basic research ethics and protocols were discarded. Ten years after the incident, James Wilson, the lead investigator of the Penn trial, reflected on the lessons he learned from Gelsinger's death including failing to adhere strictly to protocol or to communicate with the FDA about adverse events in the clinical trial and the patients about adverse events in monkeys (Wilson, 2009). Many believed Gelsinger's treatment was due to the reckless pursuit of money, since Wilson had financial stake in the research. Alan Milstein, a nationally known bioethics litigator, says that Wilson had a patent for the edited gene, and Penn owned 33 percent of the company, Genovo, producing the edited gene (Reitz, 2008). Even Gelsinger's father, who believed the Penn researchers "didn't do anything wrong" at first, eventually came to believe the research was "all about money." He too received an out-of-court settlement from Penn for an undisclosed amount (Nelson & Weiss, 2000b). Gelsinger's father did say however that he "doesn't blame gene therapy" but rather the individual researchers (Branca, 2005). According to Wilson's 2009 report, he discusses how it is "very difficult to manage real or perceived financial conflicts of interest in clinical trials." He mentions that Genovo had yet to be well-funded and had little potential for gain for the rare disease they were treating. He states that his "primary motivation in pursuing the OTCD trial was to help children with lethal inherited diseases" (Wilson, 2009). Even though Wilson's intentions may have been pure, the fundamental error by his own admission was failure to adhere to protocol and lack of disclosure about adverse events. The FDA halted the clinical trial after Gelsinger's death (Weiss, 2000).

Over the years, more adverse events have arisen in gene therapy trials. A gene therapy for an immune disease led to one patient developing cancer (Hacein-Bey-Abina et al., 2003). Another patient, Jolee Mohr, in a rheumatoid arthritis (RA) gene therapy trial died in 2007, but the FDA determined that "the therapy played no role in the death" (Kaiser, 2007). One of the reasons there was outrage in the deaths of these patients was failure to follow protocol and ethical guidelines. However, there is another factor. For the cases of Jesse Gelsinger and Jolee Mohr, their diseases were not terminal. Some forms of OTCD are fatal, but Gelsinger had a milder form in which survival is possible with strict diet (Maestri et al., 1996; Stolberg, 1999). For Mohr, while RA is very painful and increases mortality, it can be treated with drugs and is not viewed as terminal (Wolfe et al., 1994). Since without gene therapy these two patients may have survived albeit with lower quality of life, perhaps their deaths seem senseless. Indeed, the Nuffield Council on Bioethics questions whether gene therapy "should be preferred as a treatment strategy over the best available alternative," which is diet in OTCD and drugs in RA. According to the Nuffield Council, one option is to only use gene therapy "in the absence of any alternative treatment other than palliative care for what was expected to be a fatal condition" (Nuffield Council on Bioethics, 2016). The most infamous example of reckless gene editing is discussed later.

Most Scientists Self-Police

While a few incidents have challenged the assumed benevolence of scientists' and their intentions, most researchers have used genetic technology ethically and even self-policed. Gene editing was born in the early 1970s in academia, but the first massive success was the company Genentech's recombinant somatostatin and insulin genes (Russo, 2003). Recombinant DNA (rDNA) is any DNA created by joining two pieces of DNA together, and recombinant genes are

essentially edited genes. Over the next twenty years, rDNA would be the foundation of gene therapy (the editing of genes for disease treatment). In 1975, the first attempt to promote responsible gene editing occurred with the 1975 Asilomar Conference on Recombinant DNA, a meeting of 140 molecular biologists in California (Powledge, 1976). The Asilomar attendees knew gene therapy may be around the corner but were not trying to regulate it yet. They believed the benefits of gene editing may be "extraordinary," but they also knew editing was risky (Powledge, 1976). The main concern of scientists at that time was the potential outbreak of pathogenic or carcinogenic bacteria, since early experiments used bacterial rDNA. They outlined different containment protocols for bacteria with varying risk levels, and they halted rDNA experiments with pathogenic or carcinogenic bacteria (Berg et al., 1975). The outcome of the conference was not formal regulation but rather a pact among scientists to self-police. By laying out their own rules for the field, they were trying to draw lines between proper and potentially dangerous gene editing. Prudence paid off, because there no biohazards or other negative events attributable to rDNA experiments for the next twenty years (Berg & Singer, 1995). Therefore, even though only 140 biologists attended the conference, the entire field apparently followed the rules. Also in 1975, the Asilomar researchers established the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH), which was tasked with regulating gene editing experiments (Rainsbury, 2000).

Self-policing occurred again when the new editing technique CRISPR-Cas9 arose, which replaced older editing methods due to increased precision and effectiveness (Jinek et al., 2012). The National Academies of Sciences, Engineering, and Medicine (NASEM) held The First International Summit on Human Gene Editing, a conference of gene editing scientists, soon after in 2015 in Washington D.C. The conference was a long overdue follow-up to Asilomar, and the

lead organizer of Asilomar, Paul Berg, organized the summit along with pioneers of CRISPR-Cas9, such as Jennifer Doudna. Attendees discussed "recent scientific developments in human gene editing and the range of ethical and governance issues associated with these advances" (NASEM, 2015). CRISPR-Cas9 may have gotten scientists self-policing again, since it got the world closer to previously unimaginable gene editing applications, such as the creation of "designer babies." A second iteration of the 2015 summit was held in 2018 in Hong Kong (NASEM, 2018).

At this second summit, Chinese researcher He Jiankui announced he used CRISPR-Cas9 to edit two embryos before implanting them in utero and allowing them to be born as twin girls. This was the first known birth of genetically-engineered children. The edits inactivated the CCR5 gene. The girls' father was HIV-positive, and the edit aimed to give the girls resistance to HIV/AIDS if father-to-child transmission occurred from sperm carrying the virus. After the babies were born without obvious health defects, he stated that he was proud to have brought "children as healthy as any other babies" into the world (He Lab, 2018). Jiankui seems to believe he did a service to the children and their parents, and the benefits of the edit in preventing potential HIV/AIDS outweighed the costs of unintended, unknown consequences.

Other scientists believed Jiankui's actions violated research ethics and the unspoken code of prudence in gene editing thrust forward by Asilomar. In response to Jiankui's experiment, The Association for Responsible Research in Genome Editing (ARRIGE) contended that "human genome edited technologies should not be permitted nor authorized until deemed safe and effective for human beings" (ARRIGE, 2018). Feng Zhang, a CRISPR-Cas9 pioneer at MIT, stated, "Society needs to figure out if we all want to do this," referring to editing embryonic genomes like Jiankui did (Bergman, 2019). Some bioethicists recommend abiding by

the precautionary principle: since the risks are unknown, we should restrict gene editing preemptively until we learn more about them (Koplin et al., 2020). Both the moratorium called for at Asilomar and the one ARRIGE is proposing now are examples of the precautionary principle. Certain bioethicists distinguish gene editing for "therapy" from for "enhancement" (Sparrow, 2019). Therapy is treatment of a disease, whereas enhancement is physical augmentation of attributes to be more "desirable" (e.g. altering height genes to permit a patient to grow taller). Enhancement editing, the creation of "designer babies," has been very controversial (Segers et al., 2019; Sparrow, 2019). Malia Fullerton, an associate professor of bioethics and humanities at the University of Washington School of Medicine, says that Jiankui's edits were "changes to prevent disease in the future as opposed to treating disease" and were an "early stage form of genetic enhancement rather than genetic treatment" (UW Medicine, 2018).

Unlike Jiankui, other scientists push the boundaries of regulation while refraining from the most controversial steps of editing human embryos: implantation into the womb and birth. Russian biologist Denis Rebrikov is one such researcher who claims that he will "not transfer an edited embryo without the permission" of the Russian Ministry of Health. However, he maintains that as "soon as we demonstrate the safety of" gene editing, the laws "will change" to permit implantation of edited embryos (Cyranoski, 2019a).

Governments Play "Catch-Up"

Regulatory agencies are particularly important players, since they control what research and clinical uses are permissible by law. However, they have been slow to do so and often regulate retroactively, especially in the case of embryonic editing. The consensus among the World Health Organization (WHO), many federal governments, and national medical regulatory agencies (e.g. the U.S. FDA) is that germline gene editing should be restricted for now (I. G.

Cohen & Adashi, 2016; Cyranoski, 2019a; Dobrovidova, 2019). Furthermore, just because there are official guidelines in place does not mean agencies enforce them. Despite the position of the Russian Ministry of Health (Dobrovidova, 2019), researchers such as Denis Rebrikov continue to contest national policy (Cyranoski, 2019a). Under a new Chinese law ostensibly in response to Jiankui's edits, researchers who implant edited germline embryos are responsible for any adverse events from the edited genes (Cyranoski, 2019b). However, Cohen notes that there is "no one providing updates on the health of the children," and therefore the outcomes of the edits "may never be headline news" (J. Cohen, 2019). Over a year after his controversial announcement, the Chinese government sentenced Jiankui and a couple colleagues to fines and up to three years in prison for "illegal medical practice" (Cyranoski, 2020). The precedent of this charge is unknown and may be the Chinese government's attempt to punish Jiankui for violating laws that do not exist yet.

Though gene therapies have existed for forty years, regulatory agencies are just beginning to approve them for clinical use. The European Medicines Agency (EMA) approved the therapies Glybera and Strimvelis (EMA, 2018a, 2018b). The FDA has now approved four gene therapies: Kymriah, Yescarta, Luxturna, and Zolgensma (FDA, 2019a, 2019b, 2019c, 2020). All of these approvals occurred in the last five years, and all of them are for editing a live patient rather than embryonic editing. The average clinical trial length for a single phase is approximately 20 months (Pregelj et al., 2015). For drugs, which follow a three-phase FDA approval process, this translates to a total approval time of five years. Though gene therapies are regulated somewhat differently from drugs, one might ask why it has taken so long for gene therapies to get approved from the time of their inception. For example, Strimvelis is an OTCD therapy, like what killed Jesse Gelsinger, and its technology has existed for twenty years before

approval in Europe and not even the U.S. yet. Regarding an RAC meeting on a 2016 gene therapy trial, a *Nature* editorial claimed that "the echoes of a trial done 17 years ago cannot be easily silenced," referring to Gelsinger's death, and that "failures could stymie CRISPR research for decades" ("Gene-therapy trials," 2016). Perhaps the mistakes of the past are the reason for slow approval for these therapies.

Patients Want Treatment

Patients with genetic diseases agree that scientists should perform experimental gene editing therapies despite safety risks. Malakkar Vohryzek, a patient with an unknown skin condition that insertion of the Dsup gene might cure (Hashimoto et al., 2016), claims that if he dies "because of an experimental treatment, it will at least help science" (Begley, 2019). Vohryzek seems to believe that the benefit of living without his skin disease outweighs the risk of possibly dying during a clinical trial. He is essentially prioritizing his quality of life over simply living. John Sabine is a patient with a mutation in the HTT gene causing his Huntington's disease, a terminal illness which may be treatable with CRISPR-Cas9 (Ekman et al., 2019). He said that patients with genetic diseases will not think "there is any moral issue" in using gene editing (Hayden, 2016).

Jerrod, a patient who actually received gene therapy in a clinical trial for glycogen storage disease (GSD), said that he "felt like a prisoner" in his own body. After the therapy produced positive results, he declared he was "not a prisoner" in his own body anymore and that he could sleep peacefully "without worrying about dying in the middle of the night." He hopes they can "put this [gene therapy] out on the market for everyone to use" and that he does not want "any other kid" to endure what he "went through as a kid" (UConn Health, 2018, 2019).

The Public Wants Progress

Novartis, a global pharmaceutical company, conducted street interviews to ask the general public their perceptions of gene editing. Some interviewees knew what gene editing was while others did not. One interviewee, the daughter of a cancer patient, said, "Maybe if my mom had tried something like this, she still might be around." She seems to believe cancer treatment is a worthy application of gene editing that is worth the risk. Another man declared gene editing gives people with genetic disease a "new sense of control," and yet another instructed the interviewer (a scientist with the company) to go use gene editing "on more stuff" and "get it to work" as quickly as possible. When asked about her main concerns over gene editing, one woman said that researchers may not know what genes they modify or "what the future consequences" of the edit are (Novartis, 2019). Novartis stands to gain financially from gene therapies they are developing, and it is conceivable they posted these interviews on their YouTube channel as a kind of advertisement to foster public support for gene therapies. The public seems optimistic about the massive benefits of gene editing but unsure if it can meet expectations.

Biohackers favor the widespread dissemination of gene editing technology out of the ivory tower of academia and into the general public. Most have no professional training in biological sciences, but they conduct do-it-yourself (DIY) biological experiments ("Garage biology," 2010). Biohacker Josiah Zayner claims that if gene editing "is just in the hands of a few people, and nobody else is using it, then it can't have the power that it really needs to have." Zayner sparked controversy in 2017 when he injected himself with edited genes and again in 2018 when he tried to replace his entire gut microbiome (Atlantic, 2018; Zayner, 2017). Zayner is also the CEO of a company known as The ODIN, which sells DIY CRISPR-Cas9 kits for

editing human cells among others (Zayner, 2017). The FDA has stated that DIY human gene editing kits are illegal (FDA, 2017), but the ODIN continues to sell them. Zayner stated, "Science is stuck in this paradigm" of "not experimenting with humans." He asked why people are "so afraid" of "some experiments?" (Atlantic, 2018) Zayner seems to think that hesitance for human trials is misplaced and that changing attitudes towards them is essential for progress.

Make Mistakes, Grow, and Move Forward

Scientists have made mistakes with gene editing, and sometimes that has killed people or caused them pain. The scientific community admonishes these people and tries to self-regulate. Regulatory agencies may not be keeping up with the pace of development of gene editing technology and may have even slowed progress in this field to catch up. Over the last forty years we have seen the gene editing field arise, form its own ethical guidelines, err, readjust those guidelines, and continue advancing to produce something of lasting impact for humanity. The lesson we can learn from gene editing is that the rules governing a field are fluid and continually formed by technological, social, and political forces. We must also try to learn from our mistakes rather than repeating them, as Jiankui may have copied Wilson's recklessness. Slow, steady, and safe progress wins the race.

These lessons could apply to Boeing's recent 737 MAX scandal, for example. Though the 737 MAX design violated safety precautions in favor of financial progress (Gelles, 2019), the company can learn from its mistake and take the time to prioritize lives in addition to profit in future designs. Perhaps if they pursue long-term valuation instead of trying to shortcut the system, they will better succeed. Finally, some areas for future investigation include interviewing FDA officials and gene therapy scientists to ask them if tragedies have actually slowed down progress. A detailed plan of how to test gene edits iteratively for safety would

solve many of the field's roadblocks. A survey of the general public of their desire to have "designer babies" would answer if we as a species want to go down that road.

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