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CRISPR Germline Engineering: Developing Embryonic Autonomy & US Regulation

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Ethical considerations and regulations of germline engineering in relation to employing the technology in clinical practice, while protecting the developing autonomy of CRISPR germline engineering recipients

Introduction

The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system is a revolutionary genomic engineering technology that is able to make direct and reliable genetic manipulations. With the rapid progression of CRISPR research, it is becoming increasingly necessary to address areas of the application of the technology that raise serious ethical concerns, particularly those pertaining to the degree to which CRISPR ought to be permitted for engineering the human germline. For genetically engineering germline cells, there is moral complexity surrounding the bioethical principle of autonomy and the future of embryos. Despite embryos not possessing autonomous decision-making capacity at the exact moment of germline engineering taking place, the decision to permanently alter the genetic information of embryos is a significant disregard of future autonomy. [6] Ethics and regulation continue to reckon with the moral claims of future children and future generations, as well as the endpoints of germline engineering.

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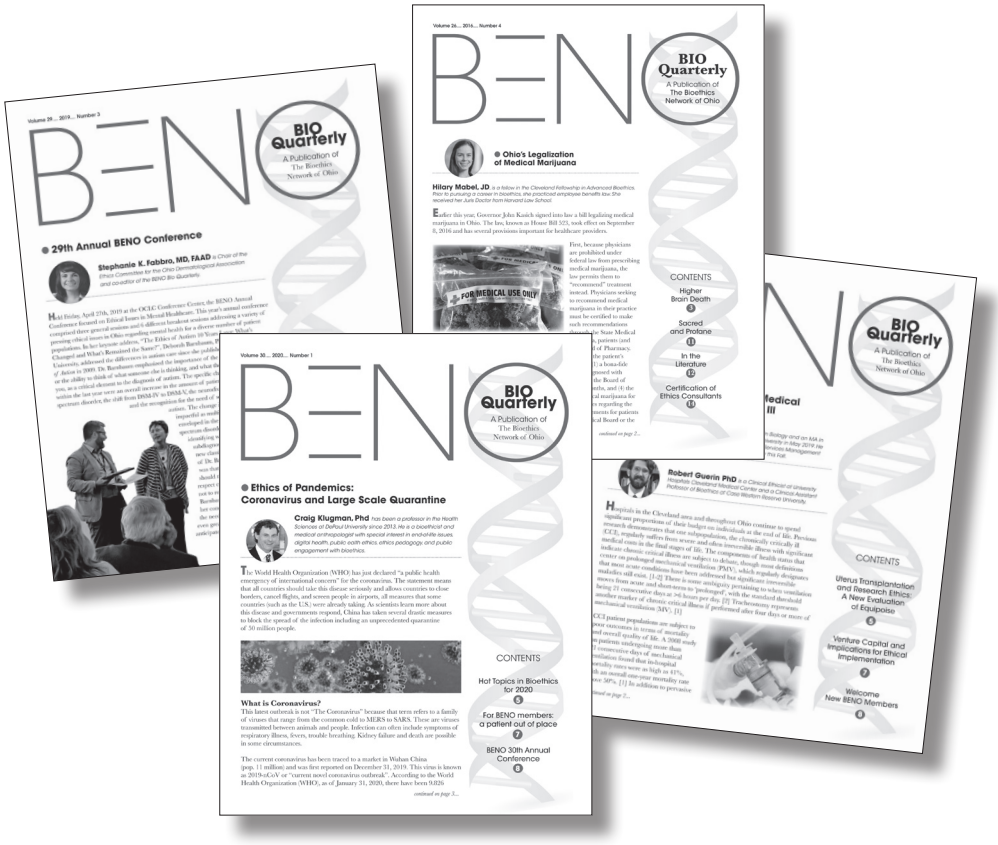

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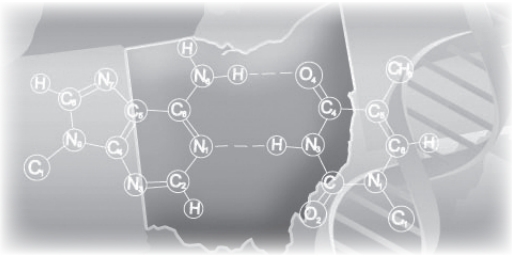

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Function and History of CRISPR

Scientifically, CRISPR functions by the enzyme Cas9 being guided by RNA to cut DNA at specific sites. After being cut by Cas9, the DNA is reconnected by repair pathways. The most plausible method for CRISPR germline engineering in animals is for the Cas9 enzyme to be injected into an embryo in vitro. Once the CRISPR system has acted by binding the Cas9 enzyme to the DNA, cutting the DNA at specific sites, and then activating DNA repair pathways, the genetically modified embryo is implanted into the uterus. [6]

The first case of CRISPR-Cas9 in vitro human genome engineering occurred over the period of 2012 to 2013. Subsequently, in 2017, the first applications of human germline engineering occurred. In 2018, a Chinese scientist carried out a CRISPR germline engineering procedure on human embryos with the goal of making them HIV resistant. The case played an integral role in illuminating important safety and ethical issues, particularly considering that the deletion of the gene (CCR5) could be associated with unknown health implications and that the unanticipated gene edits could be passed on to future offspring. [2, 4] Essentially, CRISPR germline engineering technology is not scientifically mature for clinical use, especially on human embryos. [4] This case also evidences the demand for more stringent guidance from both ethical and legal perspectives.

CRISPR Germline Engineering Applications

CRISPR genome engineering swiftly progressed to germline engineering, and there is a high chance that human germline engineering will be offered as a clinical procedure in the future. In general, the ethical concerns pertaining to CRISPR genome engineering are linked to three specific reasons. Firstly, there are ethical concerns pertaining to the magnitude and technical scope of CRISPR technology. Secondly, there are scientific uncertainties surrounding whether genetically modified organisms might pass the genetic modifications onto future generations; therefore, there is ambiguity in being able to conduct risk-benefit analyses to assist with ethical decision-making. Thirdly, the actual biological repercussions of engineering a gene in germline cells is relatively vague; consequently, it is challenging to evaluate potential risks and benefits of CRISPR technology which impedes efficient ethical decision-making. [1] Essentially, more research is required before the benefits and harms of CRISPR germline engineering can be accurately weighed up.

In the future, CRISPR has the potential to eradicate genetic diseases, as well as be used to inactivate fatal genes that could be passed on to future generations. Though, from a safety perspective, there are a multitude of consequences of CRISPR germline engineering.

In the future, CRISPR has the potential to eradicate genetic diseases, as well as be used to inactivate fatal genes that could be passed on to future generations. Though, from a safety perspective, there are a multitude of consequences of CRISPR germline engineering. Scientifically, there are uncertainties surrounding possible damaging health effects that could be outcomes of CRISPR off-target effects. Additionally, CRISPR germline engineering has the scientific potential to express or repress genes, which has the ability to alter phenotype to give the child a "better life" in the eyes of the parents. However, what constitutes a "better life" is extremely subjective in nature and, by prioritizing parental preferences, it can be argued that the application of germline engineering neglects the autonomy of future children. [6] At the core of CRISPR germline engineering ethics are controversial issues surrounding the violation of autonomy for the recipients of the treatment, as well as the future generations.

Germline Engineering and Autonomy

Controversy around applying CRISPR to human embryos primarily stems from the ambiguity surrounding the status of human embryos in relation to personhood. It is especially relevant to concentrate on the status of embryos, given that CRISPR germline engineering occurs at the embryonic stage of development. Additionally, the sheer complexity in defining autonomy contributes to the challenge and controversy surrounding the legal status of embryos. The relationship between embryos and autonomy is multifaceted due to embryos lacking the ability to express any form of autonomy. In general, there are three stances on what the relationship between autonomy and embryonic development should be: "(1) the embryo should have the same rights as a live child, (2) parents should have complete autonomy regarding the embryo, or (3) the embryo increases in moral status with advancing gestation." [6] In addition to these perspectives of embryonic autonomy, autonomy can be regarded as being on a spectrum as an ever-changing capacity that evolves with personhood. To an extent, this is reflected in US law, where numerous states recognize embryos as "human entities with dignity and developing personhood." [6] For these reasons, embryos are

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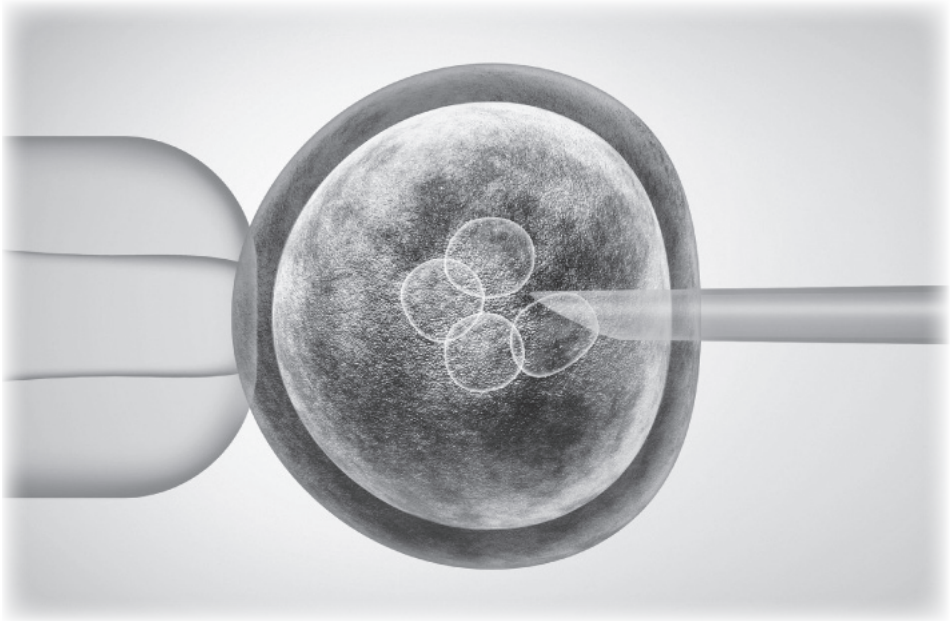
deserving of being regarded as agents with developing autonomy in ethical discussions surrounding germline engineering.

CRISPR Regulation in the United States

From a legal standpoint, government regulations in the US have enforced a ban on CRISPR germline engineering. The Consolidated Appropriations Act of 2016 forbids the US Food and Drug Administration from supporting clinical research that involves a human embryo being "intentionally created or modified to include a heritable genetic modification." [8] Despite these stringent governmental regulations, non-federal funding still allows CRISPR germline engineering to be conducted. Even though this non-federally funded research is not illegal, it still ought to adhere to bioethical principles and proper ethical guidance on CRISPR germline engineering is lacking.



At present, the policies for CRISPR germline engineering in the US are few and ambiguous. In order to deliberate the various aspects of CRISPR technology, such as legal, biomedical, and ethical, the US National Academics of Sciences, Engineering, and Medicine (NASEM) invited scientists and ethicists to gather and participate in the International Summit on Human Gene Editing in 2015. The aim of this meeting was to assess the role that CRISPR technology ought to play in human life. [1] A report issued by the US NASEM details some of the ethical implications of CRISPR germline engineering. It stresses that germline engineering should only be permissible for convincing cases that will have stringent oversight. An outcome of the meeting was that genomic edits that can be passed on to future generations would be ethically permissible under specific conditions: "In light of the technical and social concerns involved… heritable genome-editing research trials might be permitted, but only following much more research aimed at meeting existing risk/benefit standards for authorizing clinical trials and even then, only for compelling reasons and under strict oversight." Despite the US law prohibiting the federal government from funding CRISPR research involving human embryos, the NASEM report advises that germline engineering may be ethically permissible once there is a better understanding of the risks and benefits associated with CRISPR technology. [1]

Moreover, the following statement from NASEM showcases some of the considerations that are factored into the overall assessments of CRISPR germline engineering:

"Germline editing is highly contentious precisely because the resulting genetic changes would be inherited by the next generation, and the technology, therefore, would cross a line many have viewed as ethically inviolable… Policy in this area will require a careful balancing of cultural norms, the physical and emotional well-being of children, parental autonomy, and the ability of regulatory systems to prevent inappropriate or abusive applications." [7]

There appears to be unanimous agreement that potential clinical applications of germline engineering ought to involve a thorough discussion on policy and should adhere to high ethical standards. [5] However, from an ethical standpoint, it is concerning that this statement does not give mention to the developing autonomy of embryos, given that it is the future of the embryos and subsequent generations of the embryos that will be impacted by germline engineering.

Arguably, heritable genome engineering presents to be the greatest controversy of the various applications of the CRISPR system. It presents added risks due to the nature of potentially transferring the genomic edits onto future generations. The report by the NASEM Committee on germline engineering stated that, in order for human germline engineering research to be ethically permissible, the following criteria should be met: "ongoing, rigorous oversight during clinical trials of the effects

of the procedure on the health and safety of the research participants; comprehensive plans for long-term, multigenerational follow up that still respect personal autonomy; maximum transparency consistent with patient privacy; continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition." [1]

In addition, the director of the US National Institutes of Health made the following statement in an attempt to address the use of CRISPR technology:

"Advances in technology have given us an elegant new way of carrying out genome editing, but the strong arguments against engaging in this activity remain. These include the serious and unquantifiable safety issues, ethical issues presented by altering the [individual's] germline in a way that affects the next generation without their consent…" [3]

It can be implied from these statements that there is recognition of the bioethical dilemma of how the process of germline engineering lacks any form of consent from the recipient of the treatment, as well as how the future generations might be affected. [6] Though the US has given some consideration to the ethical issues surrounding CRISPR germline engineering, there are no international legal or recognized policies regarding the issue. The World Health Organization created a registry to track germline clinical trials in 2019 to help improve transparency, but participation in the registry is not mandatory.

Conclusion

As CRISPR technology continues to advance, there is exciting potential for remarkable therapeutic benefits, but there is also an abundance of moral concerns. It is critically important for attention to be given to the potential power and magnitude of CRISPR germline engineering, given that it involves the genetic manipulation of cells that code reproductive cells. The application of CRISPR for germline engineering purposes in embryos presents complex ethical issues, especially with respect to the principle of autonomy. Despite embryos not possessing autonomous decision-making capacity at the exact moment of germline engineering taking place, the decision to permanently alter the genetic information of embryos is a major disregard of future autonomy of the germline engineering recipient and future affected generations. There is a significant need to control CRISPR germline engineering technology by means of bioethical concerns and considerations of autonomous decision-making in order to protect the developing autonomy of embryos. These include precautionary ethical and legal measures to ensure that CRISPR germline engineering plays a limited and responsible role in directing the course of human life.

It is critically important for attention to be given to the potential power and magnitude of CRISPR germline engineering, given that it involves the genetic manipulation of cells that code reproductive cells.

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● Case Conference: Determining Parentage in the State of Ohio for Same-Sex Couples

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The Case

Mom and Mama have been married for over a year now and are raising their 6-month-year-old daughter in northeast Ohio. Mom gave birth to their daughter after the two women went through a sperm donation center.

Mom was very ill with a flu-like illness, as was their daughter with a high fever. Because Mom was ill and could not take their daughter to the hospital, Mama gladly went. In the emergency department, all was well; they were checked in and roomed to wait for the physician. While waiting, someone came into the room to register the patient and to sign documents to treat their daughter. Upon realizing Mama was not Mom, the registrar went out, as she did not think Mama could sign for the daughter. When she returned, it was explained that only Mom could sign for the daughter.

Mama felt humiliated and angered, as she saw her role as a mother was being dismissed. Mom felt guilty that Mama had to go through the experience.

Following the hospital event, their attorney was consulted. They confirmed that Ohio law would not recognize Mama as a parent or guardian of the daughter until she formally went through the adoption process, despite being on their daughter's birth certificate.

Discussion

Although same-sex couples in Ohio are legally able to marry, adopt a child together, and have both names on their child's birth certificate, the legislation does not grant the non-biological parent the same rights granted to those within a different-sex relationship. For different-sex couples, if not adopting, the granting of parentage is given to the "natural mother and father" [1]. Paternity is granted under the conditions of presumed paternity or designation by the mother [2]. The same presumed parentage is not granted to the non-biological parent of a same-sex couple family. Here, I apply the principle of justice and feminist ethical theories to this case and the legal barrier at its heart.

In Ohio, the rights of parentage remain unequal between heterosexual and same-sex parents despite each couple's inclusion on their child's birth certificate, establishing this legislation to be discriminatory. Many states like Ohio do not recognize same-sex parentage through presumptive parentage legislation; however, in 2018, New York legally recognized a same-sex couple through presumed paternity in the case of Joseph O. v Danielle B. NY158 AD3d 767 [3]. Taking a note from Dr. Martin Luther King Jr. (1963), being unfairly or unequally applied to select groups, we can identify this legislation to be an unjust law. Unjust laws limit the full participation of those discriminated against society and its institutions [4]. In this case, the institution of family is being restricted to the biological, or "natural," parents.

This withholding from the other parent creates stress on the role and identity they hold. When an identity, such as being a parent, is not validated or respected, this can cause severe emotional trauma to their sense of self [5].

Feminist ethical theories of care call our attention to the importance of recognizing the parentage identity in an already disenfranchised group, such as the LGBTQ+ community [6]. When Mama's role and identity as a mother were called into question, emotional harm ensued. Although directed toward healthcare providers, other entities (i.e., legal professionals and legislators) can benefit from this theory, which calls for listening to the voice and pain of this mother. The recognition of this pain can highlight the direction of care (or legislation) needed. Can our legislation continue to use heteronormative language when it infringes on the emotional and mental health of same-sex parents? Attention to the voices of these parents and others in the same situation would provide an overwhelming consensus on the answer: no. It is in no one's best interest to allow the legislation to continue in its current language when it violates the institution of family and identities it ascribes.

In Ohio, the rights of parentage remain unequal between hetero-sexual and same-sex parents despite each couple's inclusion on their child's birth certificate, establishing this legislation to be discriminatory.

Furthermore, utilizing a care theory can highlight another ethical implication of this case: the well-being of the child [7]. Ultimately, care was provided to the child, but there was a delay. The child's visit was an emergency case, so waiting for the authorization of the biological parent could result in harm—what the hospital's policy is in regards to pediatric emergency triage and the provision of emergent care is unknown. Can the withholding of care from a child be justified because our legislation's language does not

inherently recognize the parentage of the non-biological parent in a same-sex marriage? This situation creates tension on the roles and responsibilities of the healthcare provider. They know Mama is the mother, but the law restrains them.

Additionally, the decision of Obergefell v. Hodges, the landmark case in which the Supreme Court of the United States ruled that marriage is a fundamental right to same-sex couples was, in part, explained by the majority to protect children from the "stigma that their families are somehow lesser" [8]. This inequality contradicts the

very hopes this constitutional right aspired to establish for same-sex families and their children's health. Ultimately, the equal legal recognition of the family is essential for the societal safety net parents provide to their children.

The current Ohio legislation regarding parentage is heteronormative in its language. As a result, discrimination has continued in recognition of LGBTQ+ families. The failure to recognize and respect parent identity results in emotional and mental burden on the individual and implications on the health and care of the child. However, the voices of these families could serve as an essential catalyst to provide the appropriate care and creation of just legislation.

Author Recommendations

First, there must be a change in the language of past legislation to reflect more current laws (i.e., those which grant marriage and parenting rights to same-sex couples). The language must move away from a heteronormative stance to respect and recognize the family of same-sex couples. Specifically, Ohio Revised Codes 3111.02 and 3111.03, which establish a parent and child relationship and presumption of paternity, need their language updated. To promote this change, biomedical ethicists, healthcare providers, and legal professions should advocate that the Ohio legislative bodies protect the health and interest of same-sex families. Each professional offers a unique perspective on the highlighted issues presented in this case to call for change.

Second, healthcare providers need to be aware of the discrepancies and barriers in Ohio legislation in the case of same-sex families. They must recognize the harm both the parents and the child experience: the mental and emotional burden placed on the individual and the barriers to obtain healthcare. The values of these families and these relationships must be respected, and voices heard to direct the best choice in care for the child.

Third and finally, legislatures must act on the other implications these types of barriers in our legislation have on these families. For example, if the biological parents' family was not accepting of the other parent and fought for custody of the child if something ever happened to their son or daughter, legally speaking, had the non-biological parent not gone through the adoption process, they would not be recognized as the parent and custody could be called into question.

The case of this family helped identify several issues Ohio's current parentage legislation places on LGBTQ+ families. Biomedical ethics, healthcare providers, and legal professionals alike should advocate for change in our legislation to be more inclusive and protecting the health and well-being of these families.

Acknowledgment

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The challenges and anxiety associated with the ongoing COVID-19 pandemic are so immediate and familiar now that they require no recapitulation. BENO board members have been involved at all levels in Ohio's response to the ongoing COVID-19 pandemic, and BENO's officers and board corporately continue to watch for junctures at which our educational mission would require prompt action. BENO will continue to advocate for our discipline, for the patients, families, and clinicians we serve, and for our wider communities. Looking ahead to the happy day when this is behind us, or to the less-happy day in which this is the new normal, there will be much for healthcare ethics to learn, and there will be no better organization than BENO to elucidate those lessons for Ohio.

Regarding the Bioethics Network of Ohio Annual Conference

Theory in Action

Due to ongoing public health concerns surrounding the global COVID-19 pandemic, BENO's officers and conference planners decided in March to cancel the BENO annual conference slated for April 24th, 2020. We made the choice to cancel only after carefully weighing the emerging facts as well as our duties to our members; we regret having to cancel, as the conference was going to be excellent. As much as feasible, the 2021 annual conference will retain the topics and speakers slated for the now-cancelled 2020 conference. We look forward to seeing you in Spring of 2021!