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ORIGINAL PAPER

CRISPR-Cas9 and He Jiankui's Case: an Islamic Bioethics Review using *Maqasid al-Shari'a* and *Qawaid Fighiyyah*

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Abstract

The discovery of clustered regularly interspaced short palindromic repeats (CRISPR) and the CRISPR-mediated protein 9 (CRISPR-Cas9) immediately revealed numerous potential therapeutic applications. Although CRISPR-Cas9 will most likely be useful for addressing issues such as genetic diseases and related medical issues, use of this modality for germline modification generates complex ethical questions regarding the safety and efficacy, human genetic enhancement, and "designer" babies. In this article, the case of the He Jiankui affair is used as an example of the potential for unregulated use of CRISPR-Cas9 technology. In 2018, Dr He Jiankui reported that he had successfully edited human embryos. This work clearly violates all international principles of bioethics. As such, the purpose of this paper is to explore the ethical challenges inherent in the use of CRISPR-Cas9 for human germline editing from the perspectives of the goals of Islamic law (Maqasid al Shari'a) and the major jurisprudential maxims (Qawaid Fiqhiyyah). We argue that from an Islamic standpoint, the therapeutic application of CRISPR-Cas9 for germline editing may be permissible if the safety and efficacy concerns are resolved and if the principles of Maqasid al-Shari'a are fulfilled.

Keywords CRISPR-Cas9 · Islamic bioethics · Gene editing · Maqasid al-Shari'a · Qawaid Fiqhiyyah

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Introduction

Introduction to CRISPR-Cas9

Gene editing is a method that permits genetic material to be added, removed, or altered at a desired site in the genome (Doudna and Charpentier 2014). Several approaches can be used to edit the genome and CRISPR-Cas9 (clustered, regularly interspaced short palindromic repeats, associated protein 9) is the most recently described. CRISPR-Cas9-mediated genome editing has been shown to be more accurate, faster, less expensive, and more efficient than other existing genome editing technologies (Cox et al. 2015).

CRISPR-Cas9 was first identified as a component of the adaptive immune system of bacterial species where it is used as a defense mechanism to protect against entry of foreign DNA (Mojica et al. 1993; Pourcel et al. 2005; van der Oost et al. 2009; van Soolingen et al. 1993). It has since been developed into a genomic editing tool (Cho et al. 2013; Cong et al. 2013; Jinek et al. 2012). The CRISPR-Cas-9 system includes the Cas9 protein and a specific RNA as two critical elements. The single guide RNA (sgRNA) is approximately 100 nucleotides in length; the Cas-9 protein binds to the guide RNA at its final 80 nucleotides (Cong et al. 2013; Mali et al. 2013).

CRISPR-Cas9 system can treat human diseases via its capacity to edit the human genome; this will also promote a larger understanding of the mechanisms of genetic disorders (Konermann et al. 2015; Zhou et al. 2014). However, several factors influence its efficacy; these must be addressed prior to its use in human subjects. Among these issues, there are concerns regarding the frequency of off-target effects of CRISPR-Cas9, the effectiveness of the homology-directed repair, the capabilities of edited cells, the immunogenicity of any CRISPR-Cas9 components used in a therapeutic setting, as well as the efficiency, specificity, and translatability of in vivo transfer methods (Zhou et al. 2014).

Several studies have revealed that CRISPR-Cas9 can be used for effective in vivo gene therapy in adult rodent models in a manner that may be translatable for human use. Gene editing has also been used to better understand single-locus genetic disorders and the prevention of more complex diseases including neurological disorders and cancer (Musunuru 2017).

It is hard to predict precisely where and how frequently the off-target effects will occur, although use of the CRISPR-Cas9 system for gene editing in single cells suggests that off-target effects are comparatively quite rare. Nevertheless, it is still possible that this method will result in a single cell with mutations introduced at an aberrant site, a finding that could lead to one of the most disconcerting complications of genome editing technology (Veres et al. 2014). The off-target effect may occur when a system designed to cleave the genome at a target site also cleaves at other sites in the genome and produces unanticipated mutations (Veres et al. 2014). Currently, there are no significant findings that focus on the safety of therapeutic CRISPR-Cas9. The only possible way to evaluate the long-term safety profile of CRISPR-Cas9-associated therapies would be via clinical trials carried out in patients who are observed for many years; at this time, these applications are limited to patients with end-stage disease in which the potential benefits greatly outweigh the risks (Musunuru 2017). Another risk associated with therapeutic use of a CRISPR-Cas9 system is inefficiencies in off- vs.

on-target effects. This may happen when the CRISPR-Cas9 generates DNA breaks with high efficiency at the desired site, ultimately resulting in an inefficient mutation rate due to homology-directed repair (HDR) (Musunuru 2017).

Introduction to Islamic Bioethics

In the following part, we present an approach to Islamic bioethics that is based on the overarching theory of Maqasid *al-Shari'a* (Goals of Islamic Law) and the major *Fiqhi* (Islamic Jurisprudential) maxims. Later, we will utilize the theory of Maqasid *al-Shari'a* and the major *Fiqhi* principles to discuss the case of He Jiankui from an Islamic bioethics view. On the one hand, the Maqasid *al-Shari'a* (Goals of Islamic Law) are utilized to identify the moral decision's overall value and correctness (Padela 2019). They represent the general moral compass that guide the moral decisions through ensuring that our actions aim to achieve these goals, in accordance with them, or at least do not contradict them. On the other hand, the Fiqhi maxims represent the practical tool that provides a clear methodology that can be used to reach the legal/moral decision at stake as we will explain later. The two concepts are complimentary and sequential steps and not alternative or interchangeable. In its simplest form, the *Shari'a* goals represent the "why" and the *fiqhi* principles represent the "how."

Many ethical issues faced in modern life may not have direct references in the Muslim's main legal and moral sources, namely, al-Quran and Sunnah. Hence, Muslim scholars refer to other *Shari'a* sources, including the *ijma'*, i.e., the consensus of trusted scholars, and *qiyas*, i.e., the logical analogy of situations that no clear textual guidance (from Quran and/or Sunnah) to those that have (Thalib 2016). The latter two are known as secondary sources. The central worldview of Islam is *Shari'a*, which consists of four elements, namely, mu'amalat (transactions), *'aqidah* (creed), *'ibadah* (worship), and *akhlaq* (morality and ethics); these concepts provide flexibility and can develop according to place and time (Kamali 1989) to determine whether any individual human action is right or wrong (Laldin 2006). *Al-Shari'a* represents both the practice of Islamic law and the system of values and morality that covers all aspects of life including those that are personal, medical, and social (Sardar et al. 2003).

*Maqasid al-*Shari'a

As the name implies, the goals of *Shari'a* describe the goals that the acts should strive to achieve. These goals are classified based on varying levels of importance to human life. The first level comprises the necessities *(ḍarūriyyāt)* that include the five purposes in *Shari'a*, which are essential for one's full and entire life. These necessities are religion, life, health, intellect, lineage, and wealth (Kamali 2006). The second level includes the complementary (*hajiyyat*), which are materials or actions that fulfill human needs; these are less important than the necessities but are required to make life easier. The final level focuses on the embellishments *(tahsiniyyat*), which address human interests and factors that improve the quality of human life (Mustafa 2014).

Maqasid al-Shari'a is one of the main ethical theories in Islam, which many researchers ascribed its development to scholars like al-Shāṭibī (d. 790 AH), Al-Shāfi'ī (d. 204 AH), and Al-Juwaini (d. 478 AH). In its simplest form, it implies that Islamic

law is meant to achieve five necessities (primary needs) (*ḍarūriyyāt*) in the essence that they are needed to maintain a good quality of life. Imam al-Shatibi, known as the founder of *Maqasid al-Shari'a* theory, defined them as the "principles of religion and, subsequently, the fundamental rules to fulfill the law, and universals of faith" (Niyazee 2004). As such, *Shari'a* aims to increase the benefits for both the community and individual; it seeks to protect these benefits and facilitate and enhance human life (Padela 2019). Thus, Muslims can evaluate and resolve any ethical debate via recognition of these purposes. Shari'a's objectives are to encourage flexibility and creativity as well as dynamism as part of its practice (Melchert 2003).

Maqasid al-Shari'a includes five purposes pertaining to the preservation of *dıñ* (religion), nf*as* (life), *nasl* (progeny), '*aql* (intellect), and *māl* (wealth). The first purpose is to preserve religion (*Hifdh al-Din*), which is fulfilled through performing *Ibadah* (worship), which are necessary to promote faith and protect against the commission of sins which are causing harm to the religion.

The second purpose is the preservation of life (*Hifdh nafs)*; this purpose ensures equal respect for all human lives, promotes the quality of life, and ensures that individual life remains secured under all conditions (Kasule 2004, 2010). The third purpose is the protection of progeny (*Hifdh al-Nasl*); this purpose is fulfilled by providing health care needed for healthy pregnancy and delivery, and treatment of infertility (Kasule 2007).

The fourth purpose is the preservation of intellect (*Hifdh al-'Aql*); this purpose ensures the healthy growth of the individual's mind. Islam promotes intellectual development and well-being and makes efforts to prevent any elements that may have an adverse impact on human intellectual function (Kasule 2004, 2010). The last purpose is the preservation of wealth (*Hifdh al-Maal*); this purpose ensures that material resources (wealth) are provided with the protection and security that they require. This purpose also pertains to the means to generate and accumulate resources, as well as the fair and equitable distribution of wealth. Overall, the ethical theory of Islam can be seen as established in these five purposes of the *Maqasid al-Shari'a* that is to consider any action as ethical; it needs to not violate any of the five purposes defined by the *Maqasid al-Shari'a*.

In addition to the central role of applying *Maqasid al-Shari'a* (objectives of *Shari'a*), Islamic bioethics may also address a moral concern by applying *Al-Qawaid Fiqhiyyah* (the Fiqhi maxims/rules) (Thalib 2016), which is explained below.

The Major Fiqhi Principles (and Sub-Principles)

The *Fiqhi* maxims represent the Islamic jurisprudential maxims. They are general principles that are derived from and guided by the textual injunctions of the Qur'an and Sunnah. They are general rules under which there are sub-principles that rely on the correct interpretation of the text of the Quran and Sunnah. Ibn Al-Subki (d 771 H) defined them as universal principles that apply to many particulars from which the rulings can be understood. It has been suggested that each maxim is better seen as a principle that applies to many cases with the possibility of few exceptions (Thalib 2016). Thus, they are considered as the normative legal maxims, which have the highest degree of inclusiveness (of related branches of *Fiqh*) and are consulted as general guidelines for understanding the purposes of *Shari'a.* As such, they serve as a

universal law for all Muslims that was adopted by the majority of scholars for the understanding and interpretation of Islamic law (Thalib 2016).

Furthermore, *Qawa'id Fiqhiyyah* includes five main principles, each of which has sub-principles (Table 1 and Fig. 1); the explanation of them all is beyond the scope of this article, so we suffice with taking a few examples and apply them to the case being discussed.

Out of these sub-principles (Fig. 1), we are going to discuss the case of He Jiankui using number of these principles where applicable.

Global Ethical Concern in CRISPR-Cas9

The CRISPR tool has several technical limitations, which include the potential for limited efficiency of on-target editing (Costa et al. 2007), incorrect on- vs. off-target cleavage (Guo and Li 2015), and insufficient editing, which can result in mosaicism

Table 1 Major Fiqhi principles (maxims), their main statements, and interpretation

Major *Fiqhi* principles (maxims)	Main statement and intrepretation
A. The Principle of Intention (Q*a'idat al Qasd*)	Actions are judged by (or based upon) their intentions *(al-'umur bi maqasidiha*). Any act of human being must come from intention and be based upon his will.
B. The Principle of Certainty (Q*a'idat* Al Yaqeen)	Certainty cannot be removed by doubt (*al-yaqin la yazulu bi al-shakk*), i.e., what is known to be a fact cannot be overridden by what is doubtful.
C. Principle of Hardship (Qaidat Al Mashaqaat)	The maxim states that "Hardship begets facility" (*al-mashaqqah tajlibu al-taysir)*, where the hardship here refers where legal obligation will be lifted, and facility refers to the legal mitigation for an exception to the rule (Ruksah) where performing the rule results in hardship (Auda 2008; Thahir 2019). The basic principle is that hardship brings ease.
D. The Principle of Injury, Qaidat Al Dharar	Harm may neither be inflicted nor reciprocated in Islam *(la darar wa la dirar)*; harm must be eliminated (*al-darar yuzal)* but not by means of another harm. Harm, if it occurs, should be relieved or removed based on the following views on Harm (Zarabozo 2012): • If there are two benefits, then the higher benefit should be obtained, even if it involves losing the lesser one. • If both harm and benefit are involved, then try to get the benefit and refuse the harm • Remove harm before it occurs • Minimize harm once it occurs • Prevent further harm after it occurs
E. The Principle of Custom or Precedent, Qaidat Al Urf	Custom or precedence is a legal ruling, i.e., precedent has legal force. "Custom is authoritative" *(al-'adah muhakkamah*). What is considered customary is what is uniform, widespread, and predominant and not rare. These are the practices which are acceptable by people of sound nature, with general or universal acceptance by a country or generation. Custom in a given society can be in the form of words, actions, abstinence, or a mix of them.

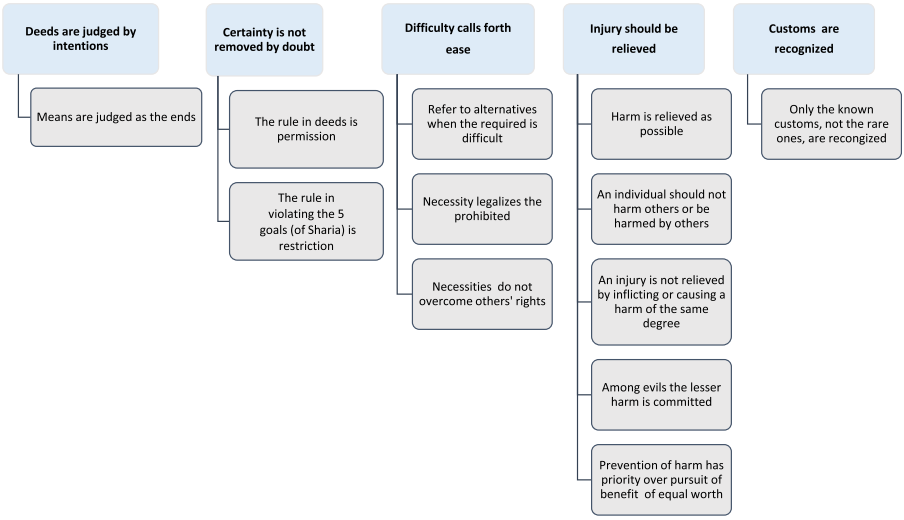

Fig. 1 Major Fiqhi principles (maxims)

(Schaefer et al. 2017). The CRISPR system offers almost unlimited therapeutic potential to address a wide range of diseases, including amyotrophic lateral sclerosis, human immunodeficiency virus (HIV) infection, cancer, and cystic fibrosis. However, it is critical to recognize that these benefits are not without potential risks. By contrast, gene editing targeting germline cells provides additional risk involving issues that might be transferred to the next generation and those to follow. As CRISPR methodology is entirely novel, there is no reliable data to elucidate the potential risks in human subjects (Brokowski and Adli 2019).

The current debate over the use of gene editing has been dominated by concerns about the potential risks associated with germline gene-editing techniques. These risks include the possibility of altering the DNA sequence or structure, which might lead to unwanted edit in the undesired location, or mosaicism when the editing occurs in some cells but not in others (Schaefer et al. 2017). Moreover, with gene editing in the gremlin, it can be transferred to the next generation.

The moral dilemma of germline gene editing is to ensure that it does not violate moral principles and ethical values. Informed consent is one of the main ethical issues related to this technology; obtaining a proper consent form from the person who would go under the procedure is challenging since the parents decide to apply the technique on embryos. Also, the unknown risks of germline editing might affect the child's health and his descendants. Moreover, a human enhancement that involves improving an individual's physical, mental capabilities, and overall well-being is another ethical issue. Enhancement might then lead to eugenics and generating “designer” children (Krimsky 2019a).

In 2015, a group led by Dr Huang Junjiu used CRISPR-Cas9 to alter the human β-globulin (HBB) mutation in a human zygote, which causes β-thalassemia disease. The study utilized embryos that were not suits in vitro fertilization. The group reported several issues with the technique, including off-target effect cleavage and mosaic (Liang et al. 2015). Thus, there are still significant technical issues that need to be

solved before CRISPR-Cas 9 is considered safe for any clinical use, although it is a promising approach.

In 2015, the International Summit on Human Gene Editing convened in Washington, DC, USA. The group released a consensus report that stated clearly that any clinical use of germline editing in human subjects would be considered ethically unacceptable until all safety and efficacy problems were resolved (Krimsky 2019a). In 2017, the Nuffield Council on Bioethics in the UK published a report regarding the ethical and social concern of editing germline genes and stated recommendations for using germline gene editing (Dickenson and Darnovsky 2019). Additionally, the EU clinical trial regulation prevents applying the germline gene-editing technology for research purposes (Krimsky 2019b).

In 2016, at least 11 countries proclaimed bans on human germline editing, including France, the Netherlands, Canada, Brazil, the United Kingdom, India, South Korea, Japan, Australia, Belgium, and Germany. Human germline gene editing is permitted in the United States only with specific approval from the Food and Drug Administration (Greely 2019).

Furthermore, since 2003, China has prohibited the use of human embryos in research. Thus, in China, gene editing research is permitted until day 14 of the embryo's development, and after that, any genetic editing should not be allowed (Krimsky 2019b).

Moreover, the International Islamic *Fiqh* Academy in 2013 stated a fatwa that considered the somatic gene therapy permissible as long as it would not violate the principles of *al-Shari'a*. It should also have a certainty to prevent a disease or death when there are no other treatment methods available (Mustafa 2014).

He Jiankui's Case

In 2018, Dr He Jiankui, a scientist from the Southern University of Science and Technology in China, reported successful gene editing of human embryos using CRISPR technology. Dr He announced that he modified germline cells that ultimately resulted in twin girls' birth; this goal was to protect them from HIV infection. The father was identified as HIV carrier, and the germline editing focused on generating resistance against HIV (Al-Balas et al. 2020; Wang and Yang 2019).

Several recent reviews have been published regarding He Jiankui and his actions in the bioethics literature (Isa et al. 2020; Al-Balas et al. 2020). The overall consensus has been that the experiments carried out by He Jiankui violated many moral principles. As such, the experiments performed by He Jiankui violated all known international ethical principles, for instance, respecting autonomy, beneficence, and do no harm.

The use of CRISPR-Cas9 to edit a human germline is prohibited or restricted internationally. Several reports also noted that He Jiankui had no prior experience with the use of CRISPR in embryos. However, he reported that he had conducted the CRISPR-Cas9 approach in mice and primates (Krimsky 2019a). Dr He also mentioned in his public statement the off-target effects in his experiments. However, there is not enough information about the phenomenon. Thus, He Jiankui lacked transparency with the public and the twin's parents.

Furthermore, his work was not focused on a devastating disease for which there are no alternative treatments. While Dr He claimed that his goal was to protect the nascent embryos from contracting HIV infection; this can be accomplished by washing the sperm of the HIV-infected father and proceeding accordingly. Furthermore, He Jiankui sought no ethical approval from his institution and did not obtain approved informed consent from his research subjects (Krimsky 2019a; Greely 2019), and subsequently violated the autonomy principle and removed the embryos' dignity value. Dr He has been involved as an active board member or investor in many companies in his region. Nevertheless, he did not disclose such information in the consent form nor inform the parents, which was considered as a conflict of interest (Krimsky 2019a). Although these research results have not been published, they highlight the potential for abuse of this technology by the international scientific community. In 2018, the Second International Summit's official statement on Human Genome Editing of the organizing committee stated that the scientific community should verify He Jiankui's claims (Krimsky 2019b). Moreover, Dr He's experiment has been considered an inadequate study, lacking ethical standards and the medical profession. The organizing committee concluded that germline editing remains a poor clinical application technique due to uncertainty and lack of a clear understanding of its risks.

After He Jiankui's announcement, more than 100 Chinese researchers reported a statement that criticized He Jiankui's work and asked the Chinese government to develop a more appropriate regulatory framework toward germline gene editing. Furthermore, the Chinese government opened an immediate investigation regarding He Jiankui's case, and they suspend him from any laboratory work (Cyranoski and Ledford 2018). In December 2019, the Chinese court sentenced He Jiankui to 3 years in prison. It was also subjected to a fine of $430,000 US dollars for illegal and unethical use of CRISPR-Cas9 technology in human embryos (Dyer 2020). Several articles have been reviewed from the Islamic perspective the He Jiankui's work. A recent paper in 2020 concluded that germline editing from an Islamic perspective is prohibited due to a lack of supporting justifications in the Muslim Jurisprudence laws (Isa et al. 2020). Another article stated that germline changes are not acceptable and cannot be applied in humans since safety and efficiency are not guaranteed (Al-Balas et al. 2020). Therefore, according to the Islamic bioethics literature, He Jiankui's failed to fulfilled Islamic Jurisprudence laws.

Discussion

CRISPR-Cas9 is a promising technology that could be implemented to improve health care quality for millions of people. However, it brings several ethical dilemmas towards its safety and germline gene editing around the world. Similarly, the Muslim world poses new moral questions that need to be answered. Islamic bioethics is concentrated on the principle of protecting human life and its values and rights. Thus, this paper will discuss the ethical issues related to He Jiankui's case based on the Islamic Bioethics.

Maqasid al-Shari'a are the general principles that can be used directly to assess any moral condition. As explained earlier, acts should be examined using *Maqasid al-Shari'a* to decide if a particular action is permissible or not from an Islamic bioethical

view. The Islamic objectives are the protection of religion, health, progeny, mind, and wealth.

He Jiankui's Case from the *Maqasid Al-Shari'a* Perspective

As far as the purpose of preserving religion is concerned, it can be seen as the group of beliefs and rules commanded by Allah that regulate human life and the relationship of humans with Allah and with one another. The CRISPR-Cas9 methodology could lead to changes in God's creation; this is another ethical issue. As CRISPR-Cas9 methodology will lead to a modification of the genetic materials and subsequent alterations in God's creation, the principle of protecting religion is not satisfied.

By contrast, CRISPR-Cas9 supporters argue that modifying God's creation is permitted within Islam in limited circumstances, including medical purposes, as these are considered to be essential changes. For example, Muslims are allowed to undergo plastic surgery in order to return body parts to their normal appearance. Thus, the CRISPR-Cas9 tool can be considered as acceptable technology from the Islamic point of view so long as it is used to treat severe genetic diseases (Isa et al. 2020). However, this permission is bound with the *Fiqh*i maxims of harm and under the necessities (*ḍarūriyyāt*) that are required to protect one's life.

Therefore, He Jiankui's experiment might open a door for the CRISPR-Cas9 application supporters to encourage using the technique in order to alter people's genomes and modify the human species nature, which can be considered changing God's creation and then as a violation of the principle of preserving the religion's objective.

Second, Muslim scholars believe that preserving human life is one of the most significant objectives of Islamic *Shari'a*. Verses of the Holy Quran state that "if anyone saves a life, it will be as though he had saved the lives of the whole humanity" (Qur'an 5:32). Nevertheless, CRISPR-Cas9 has many issues with respect to safety. As such, the use of CRISPR-Cas9 may violate the purpose of protecting life and would thus be prohibited.

Another ethical issue with the study is that He Jiankui's findings suggested a possibility of existing undesired mutations in the twin's genome because both modified and unmodified cells have appeared in their bodies, which might cause a phenomenon known as the off-target effect or mosaicism. Therefore, He Jiankui endangered the twins' lives. Furthermore, researchers also found that He Jiankui's work in one of the twins was incomplete. Therefore, that could pass health issues to the children and then affect their lives. He Jiankui violates this principle.

In addition, any modification of the genes that might lead to possible harm to future offspring would be impermissible according to the third objective of *Maqasid al-Shari'a*, which is the protection of progeny. Another ethical issue with respect to germline gene editing is informed consent. Of course, it is impossible to obtain consent from the next (unborn) generation who might be affected by this technology. Because the consent form would be obtained from the parents, and the CRISPR-Ca9 tool is a high-risk technology that might lead to unknown harm. Therefore, consent form approval can be considered as a violation of the protection of progeny objective. Furthermore, any gene-editing involving germlines from unmarried parents would be

judged as unethical as the only channel for the family in Islam is the institution of marriage (Al-Balas et al. 2020).

Moreover, the moral status of the offspring born due to CRISPR-Cas9 germline editing technology is another ethical issue in the Islamic bioethics (Al-Balas et al. 2020). Moral status is defined as the level of ethical consideration and moral rights that individuals should have. Issues including the generation of embryos for research purposes and the elimination of unsuccessful embryos violate the goal of preserving human life and dignity. Nevertheless, Muslim religious scholars agreed that editing germlines before embryos are implanted in the uterus is permissible in case the technology approved for necessities (*ḍarūriyyāt*) applications because they have not yet gained the status of personhood determined by ensoulment (Fadel 2007).

As for the fourth purpose of *Maqasid al-Shari'a,* the protection of intellect, which represents the foundation of moral responsibility and free will, this objective indicates that humans are capable of selecting freely between moral and immoral, right and wrong. (*We showed him the path: whether he is thankful or not* (Qur'an 76:3)). Thus, the decision-making model with respect to the morality of CRISPR-Cas9 should be framed after assessing the possible neurological impact on the fetus and the mental health of the parents by undergoing several psychological tests.

Dr He Jiankui failed to provide an ethical approval for this procedure from his institution, nor did he obtained an approved informed consent from the research subjects (Greely 2019). He had not mentioned all the potential risks of using CRISPR to the parents, and it is also known that the parents signed on consent for developing an AIDS vaccine study, not for germline editing study. From the Islamic point of view, the consent form is not a problem because parents can decide on behalf of their progeny. According to Prophet Muhammad PBUH hadith, "You and your wealth are for your father." However, in the twin's case, they had agreed on an experiment that they do not know the future outcome for their children. Therefore, the twin's experiment did not fulfill this purpose as well (Greely 2019).

Additionally, the novelty of CRISPR-Cas9 brings new ethical concerns regarding the potential for human enhancement. This concept may include increasing the power and capacity of selected individuals beyond what has been previously limited by nature. Most Islamic scholars believe that *humans are created in their best form* (Qur'an 10:5); as such, any enhancements that increase human capabilities are considered unlawful according to the *al-shari'a* purposes and principles (Auda 2008). Also, human enhancement might violate objectives related to wealth because it may exacerbate social inequalities.

In the twin's case, the CCR5 gene is involved in developing neural networks and is responsible for cognitive function. Thus, Dr He in this way has done an experiment that might make new twins with advanced IQ and memory, which can be a human enhancement.

Furthermore, the case may also be classified according to its benefits to the twins' health care. Since we have three categories of necessity, as is discussed earlier, using CRISPR-Cas9 technology was not essential (*ḍarūriyyāt*) to protect the twin's lives since other safer solutions can be applied to eliminate HIV infection (Mustafa 2014). Dr He has not fulfilled the second level of the benefits, which is the complementary (hajiyyat), because it aimed to prevent hardship to the patients. However, the use of the gene-editing technique in twins' embryos may have many risks and complications for

them in the future. The last level of benefits is the *tahsiniyyat* (the desirable) toward the He Jiankui case, which was the ability to make the embryo healthier and more resistance to HIV infection. Again, this goal cannot be guaranteed through the use of CRISPR-Cas9 (Kamali 2006). It is important to note that this study's result was not essentially to twins' well-being, and it might lead to both a positive outcome for the twins' health and un-healthy enhancement.

Taken together, from the perspective of Islamic bioethics, any permissible use of CRISPR-Cas9 for germline editing must be in line with the principles of *Maqasid al-Shari'a*. To our assessment, the act of Dr He violates principles of preservation of human religion, life, progeny, mind, and wealth and should not be permitted.

"Sad al-dara'i," the principle is a legitimacy accepted in the Islamic community, which is well-presented in the Qur'an and Sunna and falls under the public benefit (maṣlaḥa), the jurisprudential superstructure (Mustafa 2014). There are several classifications of sad al-dara'i that depend on its possibilities: first, if the actions for sure cause harm or sins (qaṭ'i); second, if the actions have a strong belief, it causes moral distress; and third, if the actions are morally right, they may be considered correct action (Mustafa 2014). In He Jiankui's case, by utilizing this application, germline gene editing has been applied, although there are many issues towards its safety and efficiency, which provide a strong belief that it leads to risks and health issues, and consequently, it would be prohibited according to the (*sad al-dara'i*) principle to stop such activities. This application's ethical challenges cannot be ignored, such as human enhancement and changing the "God creation."

He Jiankui's Case from the Major *Fiqh*i Maxims Perspective

Islamic legal maxims are a set of rules derived from the application of *uṣūl al-fiqh* ((jurisprudence). Many Islamic scholars considered these maxims as a part of the *Maqasid al-Shari'a*. Islamic jurists developed the legal maxims into a framework of five universal maxims, including their sub-maxims that are applicable to all aspects of medical practice.

The ethical dilemmas of the twin case from the perspective of *Maqasid Al-Shari'a* have brought to the surface many Islamic major maxims and sub-maxims that support its prohibition. These maxims are as follow:

1. Principle of Intention: the main maxim is "Deeds are judged by intentions."
    1. Means are judged as the end.
2. Principle of Certainty: the main maxim is "Certainty is not removed by doubt."
    1. The rule in deeds is permission.
    2. The rule in violating the five goals (of *Shari'a*) is restricted.
3. The Principle of Hardship: the main maxim is "Hardship calls forth ease".
    "*Qa'idat al mashaqqat*" is based on the concept of "Hardship calls forth ease." Similarly, this principle has many sub-principles that can be applied to He Jiankui (Fig. 1).

1. Necessity legalizes the prohibited.
2. Refer to alternatives when the required is difficult.
3. Necessities do not overcome others' rights.

4. Principle of harm: the main maxim is "Injury should be relieved".

   a. Harm must be eliminated.
   b. An injury is not relieved by inflicting or causing harm of the same degree.
   c. An individual should not harm others or be harmed by others.
   d. Among evils, the lesser harm is committed, one should *commit* a lesser harm action to avoid *greater harm.*
   e. Prevention of harm has priority over the pursuit of the benefit of equal worth.

5. The final principle is Customs (*Uruf)*, and the maxim is "Customs are recognized", which focuses

   a. Only the known customs, not the rare ones, are recognized.

Somatic cell editing with CRISPR/Cas9 may be permissible according to individual necessity and evaluate the potential harms and benefits. It is also understood that this methodology can be considered for treatment purposes only when there are no alternative therapies. Given that, until recently, there is no specific *fatwa* (authoritative rulings on the point of Islamic law) with respect to CRISPR-Cas9 technology or in He Jiankui's case (Isa et al. 2020), we will use the five major *Fiqh*i maxims to assess it.

First, taking the first principle of intention (*al umūr bi maqāṣidihā*) that defines the purpose behind any action and states that deeds are judged by intentions (Kasule 2004; Mustafa 2014). This principle highlights the fact that the purpose underlying the use of CRISPR-Cas9 should be precisely evaluated. Accordingly, if the purpose is to treat severe genetic disorders, it would be considered as a useful purpose and under the concept of necessities (*ḍarūriyyāt*) (Greely 2019). By contrast, if the purpose of gene editing to create a "designer baby" or for mere human enhancement, this would not be acceptable (Al-Balas et al. 2020). He Jiankui violates the sub-principle that states that "means are judged as the ends" since he did not get any ethical approval to use this technology on the twin babies and cannot predict the extent to which this technology may affect their health.

Furthermore, Dr He has used the twins as human experimentation without consenting their parents. He Jiankui has modified the CCR5 gene in the twins in a different way. He has edited the two copies in one embryo, while in the other embryo, only one copy was edited.

Consequently, one of the twins still might have an HIV infection, but it might be less severe. Thus, he intended to use the twins as a means for the experiment, and subsequently, he has violated this principle.

The second consideration focuses on the principle of certainty (*Yaqīn*), which means that all the scientific knowledge regarding CRISPR-Cas9 should be evaluated so that the decision is based on evidence that ensures the safety and efficiency of the technology. Various statements from senior scholars from the scientific community have made it clear that questions regarding safety and efficiency are significant issues that currently preclude the use of CRISPR-Cas9 for human genome editing. As noted earlier, CRISPR-Cas9 is a comparatively novel application with several technical

concerns, including the potential for off-target effects, the possibility of eliminating as yet unknown but crucial functions of the targeted genes, as well as the risk that any changes made, will be transmitted to subsequent generations (Costa et al. 2007; Guo and Li 2015; Schaefer et al. 2017). Given that there is no certainty regarding the safety and efficiency of CRISPR-Cas9 as a means to treat human genetic disease (Al-Balas et al. 2020). Thus, according to the sub-principle stating that the rule in violating the five goals of (*Shari'a*) is restriction, Dr He has violated this principle.

On the other hand, supporters of gene editing technologies argue that, from the Islamic perspective, all the medical interventions are based on possibilities, which is the predominant conjecture or "overwhelming possibility" (*ghalabat al ẓann*) (Mustafa 2014). Therefore, although certainty cannot be applied with respect to CRISPR-Cas9, we might also consider the sup-principle; the rule in deeds is permission (*al aṣl fi al ashya'iashya'i al ibaḥa*), which means that all medical procedures are considered permissible until or unless their harm is defined. Another sub-principle that might support this technique's use is that certainty should not be obliterated by doubt (*al yaqiñ la yazūlu bi al-shakk*). This sub-maxim supports the position that CRISPR-Cas9 methodology may be used even though we are not sure about its safety and efficiency as long as we know that it can be effective with respect to the treatment of severe genetic diseases (Al-Balas et al. 2020).

It is unknown if the CRISPR germline editing for the CCRI gene causes other mutations or leads to serious health problems. Thus, the twin's experiment shows a violation of the certainty maxim.

The principle of injury (*Ḍarar*) evaluates the harm that might be caused by CRISPR-Cas9 and its application for human germline editing. The primary maxim is that no harm should be inflicted (*al ḍarar yuzāl*) (Kasule 2004; Thahir 2019; Zarabozo 2012; Kamali 2006; Mustafa 2014). By applying sub-maxims under this principle, which are that any harm that might result from treatment should be minimized (harm is relieved as possible) (*al ḍarar yudfa'u bi qadr al imkān*) and (an individual should not harm others or be harmed by others) (*yjb 'an la yadura alshakhs alakhar 'aw yadura bih alakharun*), we will find that the He Jiankui case is not in conformity with these principles as well because the side effects and potential harm cannot be predicted and therefore cannot be minimized or prevented.

This principle also links to the beneficence that is expected with respect to the patient and to the community as a result of using this tool according to these sup-principles (An injury is not relieved by inflicting or causing harm of the same degree) (*al ḍarar la yuzāl bi mithlihi*) and (prevention of harm has priority over pursuit of the benefit of equal worth). Thus, the priority is to avoid harm over the search for something of equal or same beneficence (Mustafa 2014). As mentioned earlier, the possible harm that may result from using this tool is not yet fully understood; as the risk cannot be explained to the next generation, this tool would be considered impermissible from the perspective of Islamic bioethics (Al-Balas et al. 2020) and the He Jiankui case violates this principle.

On the other hand, according to the sub-principle, *"al dharar al ashadd yuzaalu bi al dharar al akhaff"* (among evils the lesser harm is committed), the possibility of treating serious disease with CRISPR-Cas9 outweighs the possibility of a minor disease or defect, and as such, it should be considered as acceptable both ethically and from an Islamic standpoint (Dayan 2019). However, with no certainty about the CRISPR-Cas9

safety and efficacy, it is challenged to determine which action might lead to more harm, the suffering from a severe disease, or the applying germline editing with the unknown consequences.

Using the principle of necessity (*Ḍarūra*) one could state that utilizing this technique is necessary in order to prevent harm, notably in cases where there are no alternatives (necessity legalizes the prohibited) (*al ḍarūrāt tubīḥ u al maḥḍūrāt*) and (refer to alternatives when the required is difficult) (Kasule 2004; Thahir 2019; Zarabozo 2012; Kamali 2006; Mustafa 2014). Therefore, scientists should discuss all alternatives, including their safety and availability, to justify their CRISPR-Cas9 gene editing selection as optimal therapy. From the Islamic perspective, CRISPR-Cas 9 in the case of Dr He is not considered to be a necessity in many cases as alternative treatments are available that are associated with less risk and potential harm. Notably, Dr He claimed that CRISPR-Cas9 gene editing would protect the embryos from paternally driven HIV infection; however, the alternative approach, which includes washing the sperm of the HIV-infected father, is undoubtedly the choice that will incur less potential harm (Krimsky 2019a). Therefore, He Jiankui's case has violated several sub-maxims under this maxim such as "necessities do not overcome others' rights," for example, human rights and dignity, since Dr He has failed to obtain an acceptable consent form from the twin's parents (Krimsky 2019a).

The Principle of Custom *('Urf)* refers to utilizing traditions and customs when making an ethical decision concerning any new issues (*al 'āda muḥakkama*). This principle would suggest that all members of the medical and scientific research community must come to a consensus on this issue; this principle also implies that CRISPR-Cas9 also needs to be accepted by laypeople and that it cannot be specifically against Islamic rules (Kamali 2006; Mustafa 2014). From the Islamic view, this principle was not fulfilled because, at this time, efficacy in communities worldwide stand against the use of CRISPR-Cas9 for editing human germlines (Al-Balas et al. 2020). As such, Dr He has violated this principle. Under this maxim, a sub-principle states that "only the known customs, not the rare ones, are recognized" (*faqat aleadat almaerufat, walaysat aleaddat alnnadirat, almuetaraf biha*). Thus, Dr He has not fulfilled this sub-principle as his case is considered a rare and unusual case (Mustafa 2014).

Conclusion

From a Islamic perspective, the CRISPR-Cas9 technique to edit human germline is not prohibited since it can be applied to protect human lives and health. However, it is not only about the technology but also how it might be utilized; thus, He Jiankui's work's main problem was the lack of scientific justification and supporting evidence of its safety and efficiency.

In conclusion, for moral decisions regarding the use of CRISPR-Cas9 technology for human germline editing based on Islamic law, we highlight a few critical points:

- Decisions from an Islamic perspective rely on the application of *Maqasid al-Shari'a* and *Qawaid Fiqhiyyah* as the sources of ethical guidelines for the evaluation of

novel technologies, including CRISPR-Cas9 from the Islamic bioethics' perspective.
- Multi-disciplinary experts, including geneticists, *Shari'a* law specialists, bioethicists, and social scientists, will need to work together to generate appropriate ethical, religious, and moral conclusions regarding the use of CRISPR-Cas9 in the Muslim world.
- CRISPR-Cas9 may be permissible for therapeutic applications, including germline editing, based on necessity, once concerns regarding safety and efficiency have been resolved.

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