Tampering with the Genetic Code of Life: Comparing Secular and Halakhic Ethical Concerns

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Abstract

Over the past century, scientific advances, such as antibiotics, vaccines, and assisted reproductive technologies have dramatically transformed medicine and improved healthcare around the world. Currently, new scientific developments in genetics, such as gene editing, will further revolutionize medicine in more innovative ways. We initially discuss how gene-editing systems represent a biotechnology that has the potential to cure any of the currently incurable genetically based disease. Using a case study, we then analyze and compare secular and halakhic perspectives related to bioethical issues associated with gene-editing technologies.

Introduction

Recent scientific breakthroughs in somatic cell nuclear transfer (cloning), stem cell technologies, reproductive medicine, and genetics will transform medicine and healthcare in unimaginable ways. However, many halakhic questions arise from these new biotechnologies.[1] Questions, such as the Jewish status of a child born from a non-Jewish gestational surrogate but

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1 J. D. Loike and A. Steinberg, "Medical Ethics Series: Human cloning: a scientific and Jewish perspective," *Tradition*, 32: Aug. 1998; J.D. Loike, and M.D. Tendler, "Creating Human Embryos Using Reproductive Cloning Technologies." *Journal of Halacha and Contemporary Society*, 34: Spring, 2014.

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created from the sperm and egg of Jewish parents, have sparked considerable debate in Jewish law.[2] There are halakhic discussions regarding the Jewish status of a child conceived without human sperm but rather from an egg of a Jewish woman and from a blood or skin cell of a Jewish man.[3] How does halakhah define parenthood of a child created from three or more genetic parents? *Poskim* (halakhic decisors) will need to address the issue of halakhic parenthood in the near future, as mitochondrial replacement therapy (a procedure that requires three genetic donors to create a healthy child from a woman who suffers from a mitochondrial genetic disease)[4] is about to enter human clinical trials.

In this article, we present a new and exciting biotechnology called gene editing that scientists hope will dramatically transform and improve human health. As with other genetic technologies, the underlying science of this one is highly complicated and we have tried to present its most basic form (see addendum). However, any rabbi that will tackle the halakhic issues related to gene editing should consult with experts in genetics and molecular biology and devote adequate time to acquire a comprehensive understanding of the biology underlying this technology.

Gene-editing technologies

The basic elements of the genetic code are well known but worth a brief review to more fully understand gene editing. In the nucleus of all human cells, genetic information is encoded in approximately 3 billion base pairs distributed throughout 46 chromosomes. These base pairs represent the letters of the DNA code. A series or sequence of these base pairs can be functionally divided into genes (or the words of the DNA code) where each gene encodes the information necessary to synthesize one or several proteins. Mutations in the DNA are present in every human being and occur when a wrong base pair is encoded into a gene. If a mutation in a gene disrupts the synthesis or function of an essential protein, that individual with the genetic mutation might develop mild to severe health issues. Currently, there are over 6000 single gene disorders, such as Tay-

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2 J.D. Loike and M.D. Tendler, "Halachic Perspectives of Gestational Surrogacy," *Hakirah*, 16:115–132, 2013; J.D. Loike and M.D. Tendler, "Becoming a Surrogate for an Infertile Jewish Couple." *Journal of Halacha and Contemporary Society*, 66:5–21, 2013; J.B. Wolowelsky, and. R.V. Grazi, "Current Jewish perspectives on maternal identity." *Gynecological Endocrinology*, 301:929-930, 2014.

3 *Ibid.* 1

4 J.D. Loike, M. Hirano, and H. Margalit, "Three-Way Parenthood: dealing with the logistics of embryos created by three-parent IVF technologies that avoid the transmission of mitochondrial disease," *The Scientist*, October 1, 2013.

Sachs, cystic fibrosis, cancers, and neurodegenerative diseases that are caused by genetic mutations.

Gene-editing technology is a process to correct virtually any genetic mutation in any cell or organ by changing the base-pairs (letters) of the DNA code (see the addendum for a more comprehensive description of the various types of gene-editing biotechnologies). The origins of gene-editing technology stem from basic research in bacterial genetics in understanding how bacteria protect themselves from being infected by pathogenic viruses. These bacteria have developed a simple "immune-like system" that operates by enabling the bacteria to recognize and delete foreign genetic viral DNA to inactivate the pathogens.

The fact that gene-editing technologies were discovered from studies in bacteria supports a broad interpretation of the Mishnah in *Pirkei Avot* (5:26): *"Hafokh ba va-hafokh ba, de-kula ba*—Delve into it and delve into it, for everything is in it." The traditional interpretation of this statement is that all of the wisdom of the world can be found in the Torah, albeit often expressed cryptically and with brevity, leaving it to Torah scholars to tease out the details through diligent study. However, this principle can be applied to a Torah perspective on science as new human therapeutics can also be derived from the study of how God structured the laws of nature.[5] Knowledge leading to the discovery of new medical interventions, such as gene editing, can result from studying the biology and genetics of animals, plants and bacteria. *"Hafokh ba va-hafokh ba, de-kula ba."*

Potential Clinical Applications: The practical and clinical applications of gene editing are profound. Many diseases, such as various forms of clotting disorders, cystic fibrosis and Tay-Sachs, are caused by point mutations where one base-pair of the DNA has been miscoded, resulting in the production of dysfunctional proteins. Correcting this mutated base pair in that gene would thereby restore the production of functional proteins and prevent the onset of these diseases. Other diseases such as Fragile X and Huntington's disease are a result of a DNA region that has been replicated several times in the genome. Removing these unnecessary multiple genomic repeats via gene-editing procedures will prevent the onset of these diseases.

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5 The Talmud in *Pesaḥim* 112 suggests how human moral behaviors can be derived by studying behavior patterns of certain animals. The laws of nature are the expressed will of Hashem and therefore a component of the Torah that God designed to instruct mankind.

Three general types of clinical applications are at the forefront of scientific discussions related to gene-editing technology. The first is to utilize gene editing to cure individuals who have genetic mutations that cause specific diseases.[6] One procedure being considered is to obtain adult blood cells from an individual who has Hemophilia A, one of the most common genetic bleeding disorders, caused by a mutation in the blood clotting factor VIII gene. Scientists could use stem cell technology to generate stem cell lines from the patient's blood cells and apply a gene-editing system to revert the mutated DNA segment back to its operative form.[7] These genetically modified stem cells would be screened in the laboratory to ensure that proper targeted editing has been successful and that these cells can produce normal clotting factor VIII. These genetically edited cells could then be re-introduced into the patient to allow his or her liver to produce normal factor VIII and cure the person of hemophilia. A second clinical application would first package a gene-editing system into a virus that targets specific human organs to allow the gene-editing system to correct one or more specific mutations in the cells within the desired organ. For example, there are a variety of mutations that can cause liver failure, and scientists have recently implemented the above viral system to "edit" the culprit mutation and cure adult mice of a genetically based liver disease.[8] In a third type of gene-editing application, scientists corrected a specific mutation in a fertilized egg (created via in vitro fertilization)[9] of a genetically diseased mouse to cure future gestated mice of cataracts.[10]

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6 P. D. Hsu, E. S. Lander and F. Zhang, "Development and applications of CRISPR-Cas9 for genome engineering." Cell 157(6): 1262–1278, 2014.

7 C. Y. Park, J. Kim, J. Kweon, J. S. Son, J. S. Lee, J. E. Yoo, S. R. Cho, J. H. Kim, J. S. Kim and D. W. Kim, "Targeted inversion and reversion of the blood coagulation factor 8 gene in human iPS cells using TALENs." *Proc Natl Acad Sci U S A*, 111(25): 9253–9258, 2014.

8 R. Cheng, J. Peng, Y. Yan, P. Cao, J. Wang, C. Qiu, L. Tang, D. Liu, L. Tang, J. Jin, X. Huang, F. He and P. Zhang, "Efficient gene editing in adult mouse livers via adenoviral delivery of CRISPR/Cas9," *FEBS Lett*, 588 (21):3954–3958, 2014.

9 Palacios-Gonzalez, C., J. Harris and G. Testa, "Multiplex parenting: IVG and the generations to come," *J Med Ethics*, 40:11 752–758, 2014.

10 Yuxuan Wu, Dan Liang, Yinghua Wang, Meizhu Bai, Wei Tang, Shiming Bao, Zhiqiang Yan, Dangsheng Li, and Jinsong Li, "Correction of a genetic disease in mouse via use of CRISPR-Cas9." Cell stem cell 13, no. 6,659–662, 2013.

Case Study

In the Jewish community, many potential *shiddukhim* fail to materialize when genetic testing[11] reveals that both parties are carriers for Tay-Sachs, cystic fibrosis or other recessive-linked genetic diseases. If gene-editing procedures are proven to be safe, these couples could now choose to get married and have healthy children by applying these biotechnologies to their in vitro–generated embryos.

Yitzchak and Rivka decided to marry even though both are carriers of a genetic disorder, such as Tay-Sachs disease. Because they want to have a healthy child, they undergo assisted reproductive procedures in which one egg, retrieved from Rivka's ovary, is fertilized in the laboratory by Yitzchak's sperm to generate one fertilized egg. Typically, a baby will develop Tay-Sachs disease if the embryo inherits two mutated genes, one from the mother and the other from the father. In Rivka's and Yitzchak's case, there is a 25% chance that the fertilized egg will contain the two copies of the mutated gene and develop Tay-Sachs. There is also a 25% chance that the fertilized egg will have no mutated genes and never develop Tay- Sachs and finally, there is a 50% chance that the fertilized egg will inherit only one mutated gene and will live a disease-free life but will be a genetic carrier of Tay-Sachs. In this case, it was discovered that the fertilized egg inherited two mutated genes and would definitely develop the disease. Using gene-editing technologies, however, scientists in the near future will be able to correct the two mutated genes in the fertilized egg to create a child that is disease-free and not a carrier of cystic fibrosis.

Secular bioethical concerns

Gene editing has elicited several bioethical concerns that include:

1. "Playing God" by tampering with human DNA—the genetic code of life,
2. Parents violating the principle of autonomy by altering the genetics of their child without obtaining informed consent of their child when he or she reaches legal age.
3. Eugenics or designer babies. Engaging in germ-line genetic procedures for non-medical reasons, such as changing hair color, enhancing athleticism, or modifying behavioral characteristics.[12]

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11 <https://www.jewishgenetics.org/dor-yeshorim>.

12 M.J. Selgelid, "Moderate eugenics and human enhancement." *Medicine, Health Care and Philosophy*, 17(1): 3–12, 2014.

*Tampering with human DNA***.** It is interesting that several secular bioethicists who are opposed to tampering with the code of life argue that utilizing such technology would be "playing G-d."[13] In fact, we speculate that their concern stems from their fear that our knowledge of DNA and gene editing is so rudimentary at this time, that tampering with the genetic code may inadvertently lead to harmful health consequences.[14] Several bioethicists and scientists also express concern regarding recombinant DNA technology claiming that it is perchance unethical to artificially speed up or interfere with the evolutional process. Similarly, tampering with evolution by gene editing may lead to the creation of new types of virulent pathogens or bioterror weapons.[15]

The autonomous rights of a child is an almost dogmatic principle of autonomy that bioethicists in the United States value.[16] Autonomy states that individuals have the right to choose any medical or non-medical intervention for their own bodies. This axiom is predicated on the assumption that an informed individual has the capacity and right to make any medical decision for him or herself. Parents altering a child's genetic makeup is generally viewed as unethical as it violates autonomous rights of the child. Some other examples relating to autonomy will clarify its significance. Autonomy is the legal basis used by several state legislators to sanction euthanasia or physician-assisted suicide. Religious-based circumcision is another example where several secular bioethicists propose that it is unethical to circumcise newborn children even though there may be some health benefits to the child as a result of the procedure.[17] These bioethicists propose that only when a child reaches maturity can he choose

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13 Erik Seedhouse, "Perils and Promises," *Beyond Human: Engineering Our Future Evolution* (Berlin and Heidelberg: Springer, 2014), 109–121.

14 *Ibid.* 19; S. W. Cho, et al, "Analysis of off-target effects of CRISPR/Cas-derived RNA-guided endonucleases and nickases" *Genome Res.* 24, 132–141, 2014; Y. Fu, et al, "High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells," *Nature Biotechnol*, 31, 822–826, 2013.

15 J.L. Loike and R. L. Fischbach, "Ethical Challenges in Biodefense and Bioterrorism," *J Bioterrorism & Biodefense*, S01–S12, 2013.

16 Shoukhrat Mitalipov, and Don P. Wolf, "Clinical and ethical implications of mitochondrial gene transfer," *Trends in Endocrinology & Metabolism,* 25:5–7, 2014; Alison Elizabeth Hall, et al, "What ethical and legal principles should guide the genotyping of children as part of a personalized screening programme for common cancer?" *Journal of Medical Ethics,* 40:163–167, 2014.

17 Brian J. Morris, Stefan A. Bailis, and Thomas E. Wiswell. "Circumcision Rates in the United States: Rising or Falling? What Effect Might the New Affirmative Pediatric Policy Statement Have?," *Mayo Clinic Proceedings*, Vol. 89. No. 5. Elsevier, 2014.

whether or not to be circumcised. Parents vaccinating children is the final example that elicits the ethical issue whether parents can vaccinate their children without the child's consent. In the case of parents vaccinating children, other ethical considerations trump the ethical principle of autonomy. The concern, for example, that without vaccinations, terrible infectious diseases will spread to a large segment of the population[18] justifies parents vaccinating their children.

The issue of violating the autonomy of the unborn child is considered a valid concern by secular bioethicists. Therefore, bioethicists would view it unethical to perform gene editing on the fertilized egg, fetus, or child. Rather, when a child reaches adulthood, he or she can decide whether to undergo gene editing. Similarly, secular bioethicists would not favor the use of gene-editing protocols in children to correct late-onset genetic diseases such as certain forms of cancers (e.g., breast) or neurodegenerative diseases (e.g., Huntington's disease). As these diseases do not impact the health of the child until later in life, only when the child reaches the age of consent can he or she consider undergoing these procedures. However, bioethicists are more likely to support the application of gene editing to children that have fatal or untreatable genetic diseases, such as Tay-Sachs or Fragile X.

Non-medical applications of gene editing. Currently there is no medical research institution in the United States that approves germ-line genetic therapies. There are many reasons for such caution and concerns. As mentioned above, there is great fear that this technology will tamper with the evolution of human beings. In addition, there is concern that gene-editing systems may be applied to alter or modify physical or behavioral characteristics—rather than curing diseases—and should therefore be prohibited. Finally, ethical issues related to designer babies[19] are relevant to gene-editing technologies and introduce the concern that gene-editing procedures will foster eugenics.

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18 <http://health.usnews.com/health-news/patient-advice/articles/2014/09/10/to-vaccinate-or-not-to-vaccinate>.

19 Scientific American – "Designing rules for designer babies," *Sci Am*, 300(5): 29, 2009; Sterckx, S., J. Cockbain, H. C. Howard and P. Borry. "'I prefer a child with ...': designer babies, another controversial patent in the arena of direct-to-consumer genomics." Genet Med 15(12): 923-924, 2013; B. Steinbock, "Designer babies: choosing our children's genes," *Lancet*, 372 (9646): 1294-1295, 2008.

Jewish Perspectives on Gene editing

Understanding science. Before presenting the halakhic perspective, it is important to highlight that the science underlying gene editing is highly complex and rabbis who address questions related to this biotechnology need a thorough and sophisticated scientific background in molecular biology, molecular genetics, cell biology and reproductive medicine.

There is a rich history of halakhic scholars who devoted time to understanding science. Many Talmudic scholars, such as the Mar Shemuel, were experts in science or medicine. In addition, Talmudic scholars and *poskim* throughout the last two thousand years relied on scientific experts in order to establish halakhic rulings. Tractate *Ḥullin* 63b states, for example, that hunters and trappers were consulted by rabbis as reliable experts in identifying kosher birds. In addition, Sanhedrin (5b) states that Rav studied with a shepherd [for 18 months to learn] which blemishes were permanent and which were temporary in order to establish the halakhic laws of *bekhor* (firstborn). *Niddah* 20b quotes Rav Zera, the leading halakhic authority of his time, who remarked: Babylonian natural laws are the cause of my refusing to rule on the halakhic status of a menstrual-blood specimen; for I thought: If I do not understand the natural laws[20] (טבעא-science), can I understand the nature of blood?" *Ḥasam Sofer*[21] addresses the issue of rabbis relying on physicians to understand the underlying science of a halakhic question, by stating,

> "In my humble opinion Ḥazal relied on the physicians regarding general [physiological] principles….you need to know much secular knowledge in many areas in order to properly understand the Torah. Their knowledge of medicine and science was critical in presenting their halakhic discussions."

Many recent *poskim*, such as Rabbi Shlomo Zalman Auerbach zt"l and Rabbi Moshe Feinstein zt"l were able to write responsa to questions arising from advances in science and medicine because they repeatedly consulted with Torah-committed doctors and scientists for technical advice.[22]

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20 The term used in this statement is טבעא translated by some Talmudic scholar as science and others, such as Jastrow, as coinage.

21 Responsa *Even Ha-Eezer* 1:30, *"Ve-khol she-kein be-nidon she-le-faneinu*."

22 R' Yonatan Eybeshutz consulted with university professors before engaging in halakhic decisions (see Ḥacham Tzvi 74–78; *Kreiti u-Pleiti*, 40:4). It is important to point out that many rabbinical scholars believed that scientific knowledge could be mastered from the Torah or *mesorah*. For example, *Midrash Tehillim* (19) quotes Shmuel as saying he is an expert in the streets of Nehardea as much as

Poskim recognize that advances in medicine and science can impact halakhah in profound ways. In the time of the Talmud, for example, parents were required to boil water on the third day after a child's *brit milah* and apply the water to the wound to promote healing.[23] It was therefore obligatory to boil water on Shabbat because not bathing him presents a serious danger to the child (*pikuach nefesh)*.[24] Rabbi Yosef Karo, however, states that in his time, they realized that there is no medical indication for bathing the infants in warm water on the third day after circumcision. [25] Thus, boiling water on the Shabbat for the newly *mal* child was viewed as biblically forbidden since the issue of *pikuach nefesh* of the newborn no longer applied. A second example is *meẓiẓa* (applying suction to increase the blood flow of the circumcision wound). The Talmud Shabbat clearly states that *meẓiẓa* of the circumcised child is based on medical considerations and is intended to prevent danger to the baby.[26] "Rav Pappa said: A *mohel* who does not perform *meẓiẓa* endangers the baby and is dismissed…it [*meẓiẓa*] is like a bandage in healing the wound." Since today, sterile techniques and antibiotics are used in *milah,* performing *meẓiẓa* to enhance healing is medically unnecessary. Thus, performing *meẓiẓa* on Shabbat for unwarranted medical reasons is biblically prohibited. A final example how medicine can impact halakhah is the current obligation to do *melakha* on Shabbat to save a premature baby born in the eighth month. In contrast, in the time of the Talmud one **would not do *melakha*** on Shabbat for a premature baby born in the eighth month because the baby was considered non-viable.[27]

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he is an expert in the 'streets' of the heavens. The Midrash asks how Shmuel knew all of that, and it answers he knew it all through the study of Torah. Rav Yonason Eyebushitz (*Kreiti u-Pleiti* 40) also states that all the laws of heaven and earth are part of Torah *she-b-'al peh*. Similarly, *Arukh ha-Shulḥan* (EH 13) states: "I will tell you a great principle: Ḥazal, besides their holiness and wisdom in the Torah, were also greater scholars in the natural sciences. See B. Breuer, F. Rosner and A. E. Glatt "A Proposal to Improve Rabbinic Decision-Making for Serious Medical Problems," *Hakirah*, 11:199–210, 2011.

23 Talmud Bavli, *Shabbat* 134b. Similarly, Rambam, *Hilkhot Shabbat* 2:14 permits boiling water on Shabbat to protect the health of the newly circumcised child.

24 *Ibid.* 1.

25 *Shulḥan Arukh, Oraḥ Ḥayyaim* 331:9. See also the comments of the Rama on this issue.

26 Talmud Bavli, *Shabbat* 133b, and see Maimonides *Hilkhot Mila*, chapter 2.

27 J.D. Loike, and M.D. Tendler, "Halacha and Bioethics," *Journal of Halacha in Contemporary Society*, 16:92–118, 2011.

The educational demand in Torah and halakhah for any aspiring rabbi is not only incredibly consuming but also a lifelong commitment. We believe that there is a dire need for our scientific and medical educators to better enable rabbis to comprehend the underlying science before addressing halakhic issues emerging from these new biotechnologies.

Before returning to the Jewish perspective of gene editing, certain principles of Jewish law must be stated.[28] First, according to halakhah, human beings serve as partners with God in the creation process,[29] but do not have absolute autonomy in utilizing medical interventions.[30] Specific halakhic guidelines delineate when patient autonomy is followed or when a Jew must submit to God's law.[31] It is widely accepted, by most *poskim,* to prohibit euthanasia even in end-of-life situations.[32] In other situations, patient autonomy does play a vital role, as in a patient with incurable cancer, who is in great pain and develops pneumonia. In this case, Rabbi Moshe Feinstein states that the question of whether one is required to treat a second illness in a terminal patient is a decision that the patient has the autonomous right to make.[33]

A second principle is articulated by Tiferet Yisrael (Rabbi Yisrael Lifshutz), who states, "Any activity that we have no reason to prohibit is permitted in halakha without having to find a reason for its permissibility,

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[28] *Ibid.* 1.

[29] Nachmanides commentary on Genesis 1:28. In addition, from a midrashic story we learn an important philosophical principle that human beings are permitted, and sometimes commanded, to alter nature in order to perfect the works of the Creator. The Talmud relates the story that Rabbi Akiva is challenged by the Roman general, Turnus Rufus, to defend the Jewish practice of circumcision, the apparent mutilation of a work of the Creator. Rabbi Akiva demonstrates to Turnus Rufus, through the comparison of kernels of "natural" wheat with man-made bread, that the works of man, as finishing touches to nature, are better than the unfinished works of the Creator (*Midrash Tanḥuma, Tazriah* 19).

[30] Alan Jotkowitz, "R. Moshe Feinstein and the Role of Autonomy in Medical Ethics Decision Making." *Modern Judaism*, 30:196–208, 2010.

[31] *Ibid.* 1.

[32] Marc Romain, and Charles L. Sprung. "End-of-Life Practices in the Intensive Care Unit: The Importance of Geography, Religion, Religious Affiliation, and Culture" *Rambam Maimonides Medical Journal*, 5:1, 2014; Alan Jotkowitz, "The Seminal Contribution of Rabbi Moshe Feinstein to the Development of Modern Jewish Medical Ethics." *Journal of Religious Ethics*, 42:285–309, 2014.

[33] Responsa *Iggerot Moshe, Ḥoshen Mishpat*, Part 2, No. 74:2; M. D. Tendler, Responsa of Rav Moshe Feinstein (New York, 1996), p. 57.

for the Torah does not mention every permissible thing but rather elaborates on only those things that are forbidden."[34] Thus, halakhah need not delineate all permissible activities.

Aside from as-yet-undefined side effects, gene-editing procedures do not involve any prohibited acts. In the case of Yitzchak and Rivka introduced above, retrieving sperm and eggs from individuals may elicit halahhic problems such as *shikhvat zera le-vatalah* in retrieving sperm and acts of *ḥavala* (inflicting injury)[35] to retrieve the egg from the ovary and using contraception in marital relations. However, many halakhic decisors rule that when such actions are preformed to correct a medical condition (such as infertility) there is no prohibition.[36] In fact, Jewish law regards infertility as a serious medical condition warranting medical intervention even when there are known health risks.[37]

Tampering with human DNA. Tampering with human DNA for medical reasons is included in the biblical directive that people are partners with God in the creation process. Therefore, according to Jewish law, there is no problem for a couple to safely correct a genetic defect in a fertilized egg.

Halakha will always consider medical risks associated with any biotechnology. Two safety concerns in current gene-editing technologies have been reported. The first is the adverse effects of targeting the wrong DNA site in the human genome and the second is the possibility of inadvertently activating cancer-like genes in the fertilized egg.[38] However, newer modifications in gene-editing procedures are being developed that will circumvent some of these safety concerns. It is likely in the near future that further revisions in gene-editing technologies will minimize any health risks to the patient.

Another issue regarding the halakhic viewpoint of tampering with the human genome is related to the principle "*kevan d-dashu beh rabim, shomer*

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34 Mishnah, *Tractate Yadayim* 4:3 #27.

35 See Rambam, *Hilkhot Rozeaḥ*, chapters 11-12 and *Shulḥan Arulh, Ḥoshen Mishpat,* chapter 426.

36 *Ibid.* 1.

37 "This principle is derived from Genesis 30:1 that quotes Rachel saying, "Give me children, otherwise I will die" see *Netziv, Sheiltot, Parshat Naso.*

38 Melissa A. Kotterman, and David V. Schaffer. "Engineering adeno-associated viruses for clinical gene therapy." *Nature Reviews Genetics*, 2014; A. Barzel, N.K. Paulk, Y. Shi, Y. Huang, K. Chu, F. Zhang, P.N. Valdmanis, L.P. Spector, M.H. Porteus, K.M. Gaensler, and M.A. Kay, "Promoterless gene targeting without nucleases ameliorates haemophilia B in mice," *Nature*, 2014. <http://www.nature.com/nature/journal/vaop/ncurrent/full/nature 13864.html>.

petayim Hashem" (since it has become common practice that God protects those who behave as others because they trust that all will be good).[39] This principle was applied to smoking after the surgeon general's warning in 1964 about the documented severe cancer risks from smoking. At that time many halakhic decisors did not actively prohibit smoking. Why? Because at that time many people were willing to accept the medical risks of smoking due to their perceived psychological and health benefits that smoking eased tensions and improved appetite. Today, as society recognizes the severe cancer dangers and other medical risks associated with smoking, it is halakhically prohibited to smoke. Similarly, halakhic decisions regarding any medical intervention require an evaluation of the documented health dangers as well as the **perceived** health benefits associated with a biotechnology.

The therapeutic application of gene editing to correct severe diseases or life-threatening diseases would more likely be halakhically permitted than would the use of gene-editing biotechnologies to correct medical diseases where effective therapies already exist. In our case, there is no effective cure for Tay-Sachs and therefore, applying gene editing to correct this genetic disease would be halakhically acceptable. However, at this time, it may not be halakhically permissible to allow gene editing to correct hemophilia in the fertilized egg as there already exist effective therapies to treat children born with this genetic condition. In the future, if gene-editing technologies are proven to be more effective than existing therapies, then halakhah would allow gene-editing interventions for a broader range of genetic diseases.

Violating the autonomous rights of a child. It is a divine commandment for parents to care for the welfare of their children. *Kiddushin* 29a states that the father's parental obligation to teach his son how to swim is presented in the same vein as teaching his son Torah. Furthermore, the principles in

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39 Psalms 116:6 and see Tractates *Shabbat* 129b, *Niddah* 31a, 45a, *Yevamot* 12b and 71b-72a, *Avoda Zara* 30b, and *Ketubot* 39a. It is interesting that *Niddah* (31a), *Avodah Zarah* (30b) and *Ketubot* (39a) do not include the dictum of *dashu bei rabim*. There are numerous halakhic discussions on the meaning of *shomer petayim Hashem* that are beyond the scope of this article. For example, Rashi on *Ketubot* 39a states that one should not rely on *shomer petayim Hashem* when a safe alternative is available. Tosefot Rid (A.Z. 30b) and Ritva (*Yevamot* 71a) state that this applies only to unusual or minimal risks and dangers. Radak states that *dashu bei rabim* denotes the absence of any danger and requires a majority of the general public to implement *dashu bei rabim*. See also Malbim on Psalms 116:6; Rabbi Waldenberg writes that this principle applies only when life experiences indicate that people can be protected from the medical risks.

halakha of *zokhin le-adam sh-lo be-fanav* and "love your neighbor as yourself"[40] support the obligation of parents to medically care for their child without the latter's informed consent. However, parents do not have the absolute autonomous right to perform any medical intervention on their children.[41] Parents, for example, are not permitted to remove life support systems from their child who is suffering and terminally ill.

Jewish law would allow parents to apply gene editing to their embryo for serious medical reasons, such as correcting mutations responsible for Tay-Sachs, cystic fibrosis, Fragile X etc. In contrast to many secular bioethicists, halakhah would also allow parents to employ gene-editing procedures in children diagnosed for late-onset diseases, such as Huntington's disease or genetically based Alzheimer's disease. One might argue that since Huntington's and Alzheimer's disease do not affect a person until after the fourth decade of life, parents may not have the right to apply gene-editing technologies to correct these gene mutations in their children. Rather, when the child reaches halakhic maturity, he or she can choose to use gene-editing procedures to cure these mutations. However, here Halakha provides an important insight. Halakha recognizes that a healthy person would not want to develop Huntington's or Alzheimer's disease and would do everything possible to prevent onset of these diseases. Thus, halakhah would not view the parents as violating the child's right to autonomy and would permit the use of gene editing on their embryo or child, even for late-onset diseases.

Non-medical applications of gene editing. The third bioethical concern expressed by secular bioethicists is that gene editing will be used on a fertilized egg or adult for non-medical applications. If gene-editing technologies are used to change hair color from black to blond (one gene encodes this property) with minimal or no health risks, then halakhah would allow a person to use this technology for themselves. However, if minimal or serious health risks are associated with using this procedure, then halakhah would prohibit gene-editing procedures to change their own hair color or enhance athleticism without a valid medical or psychological reason. Similarly, halakhah would also prohibit non-medical applications of gene editing to their fertilized egg or child. However, if a couple has a genetic family history of short stature, then gene editing that could increase the height of a child might be deemed permissible according to

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40 Leviticus 19:18.

41 *Ibid.* 1. When Eve became pregnant with Cain she said, "*Kaniti ish et Elokim*"—I have acquired a person from God! And therefore she called his name Cain—my possession, a *kinyan*. If parents believe they own their children, the result will not be good.

Jewish Law, because a child who is abnormally short is at a disadvantage in our society.

How would halakhah address the issue of parents using gene editing on their healthy fertilized egg or embryo to enhance or modify behavioral characteristics? Currently, there is a vast scientific literature identifying human genes that regulate intelligence, aggression, sexual orientation, and even spirituality.[42] However, using gene editing to modify behavior presents a halakhic problem. Based on existing research of the genetics of human personality, behavior, and intelligence, we cannot safely predict the outcomes of genetic manipulation of intelligence or behavior on other personality traits of an individual. Understanding the genetics related to intelligence is an excellent example. Over 150 genes have been identified that regulate human intelligence, signifying that intelligence is a highly complex characteristic.[43] In addition, enhancing intelligence would also impact other aspects of personality, emotions, behavior and even health outcomes.[44] Likewise, there are multiple genes that regulate aggression and sexual orientation that, if altered, may have far-reaching multifaceted effects on other human personality traits and behaviors.[45] We therefore propose that Halakha would prohibit, at this point in time, the utilization of gene editing to alter behavioral characteristics because of their unknown, far-reaching consequences on the personality of the individual. As science gains further knowledge regarding these issues, the halakhic prohibition may be revisited in the future. In the case of Yitzchak and Rivka, they would be allowed to correct Tay-Sachs in their fertilized egg;

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42 A.R. Sanders, E. R. Martin, G. W. Beecham, S. Guo, K. Dawood, G. Rieger, J. A. Badner, E. S. Gershon, R. S. Krishnappa, A. B. Kolundzija, J. Duan, P. V. Gejman and J. M. Bailey. "Genome-wide scan demonstrates significant linkage for male sexual orientation," *Psychological Medicine*, online at <http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=9385646&fileId=S0033291714002451>; C.G. Coll, E. L. Bearer and R. M. Lerner, eds., "Nature and nurture: The complex interplay of genetic and environmental influences on human behavior and development," *Psychology Press*, 2014.

43 M. Zhao, L. Kong and H. Qu, "A systems biology approach to identify intelligence quotient score-related genomic regions, and pathways relevant to potential therapeutic treatments." *Sci Rep*, 4: 4176. 2014.

44 I.J. Deary, A. Weiss, and G.D. Batty, "Intelligence and Personality as Predictors of Illness and Death: How Researchers in Differential Psychology and Chronic Disease Epidemiology Are Collaborating to Understand and Address Health Inequalities." *Psychological Science in the Public Interest*, 11: 53–79, 2010.

45 B. Williams, J. Myerson and S. Hale, "Individual differences, intelligence, and behavior analysis." *Journal of the experimental analysis of behavior*, 90(2): 219–231 (2008).

they would not be permitted to alter genes relating to (non-medical) behavioral traits in their fertilized egg.

Shiddukhim. *Shiddukhim* is a final concern of *poskim* that is not commonly addressed by secular bioethicists. As stated above, the application of gene-editing technologies might change decisions that couples make regarding whether or not to get married. Today, many orthodox couples are tested as carriers of genetic diseases before they even continue dating. If both parties are found to be carriers for the same recessive genetic disease, such as Tay-Sachs, they will often choose not to get married because of the high risk of having an affected child. In the future, if gene editing a fertilized egg proves to be relatively safe, then couples may opt to get married and use this technology to ensure the creation of a healthy baby. The decision by the couple, who are both carriers of a genetic disease, to get married and use gene-editing technologies to generate a healthy child, raises another important halakhic question. How would halakhah view the medical advice that the couple use birth control their whole reproductive lives to prevent the creation of a diseased child? In response to this question, it is important to highlight that many halakhic authorities allow infertile couples to use assisted reproductive technologies to create healthy babies even though the procedure may involve the potential prohibition of *shikhvat zera l-vatalah*. Thus, halakhah would allow couples, who are carriers for genetic diseases, to get married, accept a lifelong use of birth control, and utilize gene-editing technologies to correct the genetic defect in their fertilized egg.

Conclusions

Gene-editing technologies have the potential to cure a vast array of genetic diseases including Tay-Sachs, Fragile X, cystic fibrosis, and different forms of cancers, Alzheimer's disease and autoimmune diseases.[46] The dramatic successes of gene editing reported in numerous mouse models of genetic diseases provide hope that further research on these technologies will lead to innovative therapies to treat the thousands of genetic-based human diseases. Notwithstanding, more work is required to establish and improve the safety of these procedures.

In this article we compared secular and halakhic perspectives on gene-editing technologies. One issue is whether patients can use these gene-

46 Zhen, Shuai, et al. "In vitro and in vivo growth suppression of human papillomavirus 16-positive cervical cancer cells by CRISPR/Cas9" *Biochemical and biophysical research communications*, 450: 1422–1426, 2014; Riya R. Kanherkar, et al, "Cellular reprogramming for understanding and treating human disease," *Stem Cell Research* 2: 67, 2014.

editing technologies at this point in time. As with other developing technologies, phase I clinical trials using gene editing will likely begin in the near future. Moreover, unlicensed and unregulated clinics in foreign countries may employ gene-editing procedures for desperate patients even before the health risks and benefits are known. Both from a secular and halakhic perspective, patients with treatable diseases are not required to volunteer for initial clinical phase I trials and should not travel to foreign unlicensed clinics that use gene-editing procedures. However, patients with diseases that are life threatening, or where no other effective therapy exists, are encouraged to volunteer in phase I gene-editing clinical trials.

The ethical issue of applying this technology to a fertilized egg highlights a fundamental difference between the secular and halakhic perspectives. Specifically, many secular bioethicists would continue to ethically object to this procedure because of their ethical concerns about germ-line therapy. Secular bioethicists have also expressed concern about, and opposition to, the tampering by scientific research with evolutionary processes. Moreover, these bioethicists do not favor medical procedures that "violate" the autonomous rights of the child. Halakha, by contrast, emphasizes the need to improve healthcare as a vital factor in allowing gene-editing technologies to be performed on the fertilized egg or fetus, and views the development of gene editing as a positive activity by humans as partners in the creation process.

At this point in time, however, both secular and halakhic ethicists would agree that gene-editing technologies should be used only to improve health and not for non-medical enhancements, especially behavior enhancements. If science gains a better understanding of the global effects of gene-editing behavioral enhancements on other personality traits of a person, then rabbinical decisors and secular bioethicists should revisit this issue.

There are two Midrashim that may be relevant to the halakhic perspective of gene editing. The Midrash states[47] that God responded to *"emet's"* (truth's) objection to the creation of man by casting *emet* to earth to understand that *emet* in heaven is absolute while *emet* on earth is relative. The moral lesson is that fallible man must accept relative truths. In other words, scientific knowledge can change over time and halakhic decisions in science and medicine must be based on current scientific knowledge.

The second Midrash[48] asks, Why does the description of creation in the Torah begin with the letter "*beit*" in *bereishit bara Elokim* and not with

47 *Midrash Rabbah* on Genesis 1:26.
48 *Midrash Rabbah* on Genesis 1:1.

"*aleph*"? Ḥazal state that Hashem saved the letter *"aleph"* for halakhic revelation in the first letter of the *aseret ha-dibrot, anokhi Hashem Elokekha*.[49] The moral message of this Midrash is a cautionary warning—that revelation and Hashem's role in the world always takes precedence over the human desire for technological development and discovery. Thus, biotechnologies that we develop, especially in reproductive medicine, are measured not by what we **can do** but by what we **may do**.

Addendum

All gene-editing technologies utilize a similar protocol that selectively removes the wrong base pair (mutation) and inserts a normal base pair in the gene of interest. At present, there are at least four gene-editing systems.[50]

1. Zinc finger nucleases.[51]
2. TALEN (Transcription Activator-Like Effector Nucleases).[52]
3. BuD—derived nucleases.[53]
4. CRISPR/Cas9 (Clustered Regularly Interspersed Short Palindromic Repeats) nucleases.[54]

All of these systems have multiple sequential components. The first component relies on either proteins or RNA to target specific sites on DNA that require editing. The second component involves a functional element called the molecular scissor, which initiates double-stranded breaks to remove a specific base-pair or region of the targeted DNA. The third element of these systems are proteins that repair the induced breaks

49 See Rabbi Jonathan Sacks at "YU Medical Ethics: Partners in Creation: Fertility, Modern Medicine, and Jewish Law," <http://curiousjew.blogspot.com/2007/10/yu-medical-ethics-partners-in-creation.html>.

50 T. Gaj, C.A. Gersbach, and C.F. Barbas III "ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering," *Trends Biotechnol*, 31, 397–405, 2013.

51 D. Carroll, "Genome engineering with zinc-finger nucleases," *Genetics* 188(4): 773–782, 2013.

52 N. Sun, and H. Zhao, "Transcription activator-like effector nucleases (TALENs): A highly efficient and versatile tool for genome editing." *Biotechnology and Bioengineering*, 110(7): 1811–1821, 2013.

53 S. Stella, R. Molina, B. López-Méndez, A. Juillerat, C. Bertonati, F. Daboussi, R. Campos-Olivas, P. Duchateau and G. Montoya "BuD, a helix–loop–helix DNA-binding domain for genome modification." *Acta Crystallographica Section D: Biological Crystallography,* 70(7): 2042–2052, 2014.

54 M.M. Harrison, B.V. Jenkins, K.M. O'Connor-Giles and J. Wildonger, "A CRISPR view of development." *Genes Dev*, 28(17): 1859–1872, 2014.

and replace the base pairs with the correct sequence encoded in the normal gene of interest. In this way each of these gene editing systems can be used to change single base-pairs or specific regions of the DNA. The major difference between these systems is how accurately they recognize and target specific sites on DNA that are to be repaired. Currently, CRISPR offers certain advantages over other editing systems, such as a shorter time required to design a specific system and the ability to target more than one region on the genome. ☙