Commentary

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Beginning of life ethics at the dawn of a new era of genome editing: are bioethical precepts and fast-evolving biotechnologies irreconcilable?

S. Marinelli[1], A. Del Rio[2]

[1] Università Politecnica delle Marche, Ancona; [2] Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, Rome, Italy

Abstract

The amazing and almost unimaginable advances that have unfolded over the past decades in biotechnologies (heritable germline editing in particular) have brought bioethical issues to the forefront, sparking public debate and increasing attention worldwide. Such mind-blowing progress has already resulted in major improvement and enhancements for humans, and holds the potential for even more. Technology and bioengineering have begun to take over in the life sciences industry. Man's capacity to genetically engineer the biological world is nothing short of mind-boggling in its current magnitude, and may even evolve, in a not too distant future, into attempts to fuse man and machine into a cohesive bioengineered entity; a "super human being", endowed with enhanced cognitive and physical capabilities and impervious to disease, may be not too far down the road. That will not come without caveats, however. In fact, scientific advancements at such an accelerated pace have already negatively affected our cultural, ethical, and legal values and our ability to harness the opportunities and face the dangers posed by such developments. As a matter of fact, science seems to consistently outpace public morals, ethics and policymaking, which calls for a high degree of caution and common answers. ***Clin Ter 2020; 171 (5):e407-411. doi: 10.7417/CT.2020.2249***

Key words: *heritable germline editing, CRISPR-Cas9 gene editing, genome engineering, human enhancement, bioethics*

Introduction

In recent years, the prospect of advanced genetic engineering has become much more real, owing mostly to two distinct developments. Firstly, accessible and highly sophisticated gene mapping technology has enabled scientists to gain an increasingly thorough knowledge and understanding of the human genome. Secondly a new and powerful new gene editing technology has become available, known as clustered regularly interspaced short palindromic repeat (CRISPR) and CRISPR-associated protein 9 (Cas9). Although gene editing techniques have been around for decades, e.g. experiments with zinc-finger nucleases and transcription activator-like effector-based nucleases (ZFNs and TALEN, discovered in 2005 and 2010 respectively), CRISPR constitutes a method that is considerably faster, more affordable and accurate (1, 2); it is in fact substantially more effective and closely focused than any previous gene-editing technology, in that it uses each cell's immune system to target and cut out parts of its DNA to replace them with new genetic code. Still, a mentioned earlier, heritable gene editing is an extremely controversial prospect. It is safe to say that CRISPR is already broadening the realm of what is possible in the field of genetic engineering (3). On June 21, 2016, the U.S. government announced that it had approved the first human trials using CRISPR, in this case to strengthen the cancer-fighting capabilities of the immune systems of patients suffering from melanoma and other deadly cancers (4). Major ethical quandaries recently arose from a Chinese experiment on interfering with the DNA of babies (5). That unchecked and unregulated initiative has drawn almost unanimous criticism and condemnation worldwide, which is very telling.

Germline editing and its endless, controversial potential: developing guidelines is of utmost importance

Intervening at the embryonic stage, for the purpose of germline editing, i.e. producing alterations in the gene lines in an embryo's eight or 16 cell stage (in order to eliminate the gene for a given inborn disease, for instance) could lead to heritable alterations: such changes will then be replicated in each of the resulting human being's trillions of cells and will be passed on to descendants as well. In germ-line modification procedures, which have only been carried out in experimental settings for now, the genomic editing system is mostly injected into the cytoplasm or pronuclei of zygotes or into pre-implantation embryos; genetic screening is then performed, in order to select the embryos with a corrected genomic pattern in the absence of detectable off-target genetic modifications (6). In fact, the main risk of CRISPR-Cas9 gene editing is the off-target effect of engendering unwanted DNA and "misplaced" alterations, i.e. at sites other than the intended target. This is in fact due to the fact that the technique may bring about "nonspecific

Correspondence: Alessandro Del Rio. E-mail: alessandrodelrio70@gmail.com

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cleavage", possibly leading to mutations in non-targeted genomic sites. PGD, whole genome-wide sequencing, amniocentesis and peripheral blood test of mothers in different stages of pregnancy after transplantation may be capable of minimizing the possibility of damage arising from such interventions (7). If the risks can indeed be minimized, CRISPR could hopefully lead to the elimination of a host of diseases, before birth, in light of our ever-expanding knowledge and understanding of the genetic links to various diseases. Somatic gene editing could therefore turn out to be a game changer, not only in the treatment of a whole range of serious hereditary, particularly Mendelian, disorders, but also contribute to the genetic eradication of infectious diseases and cancer. Still, it is in our view essential to be able to rely on a widely acknowledged frame of reference, in order to effectively govern and regulate such practices. It is therefore somewhat reassuring that biotechnological advancements in genome editing have already prompted scientific institutions to devise recommendations, in light of the far-reaching ramifications such techniques will likely have in the foreseeable future. If in fact gene editing is to become a therapeutic option or a medicinal product for human use, regulations must be clearly identified and applied. The European Medicines Authority (EMA), which is in charge of supervising access of medicinal products to the market, including advanced therapy medicinal products, has laid out scientific and regulatory guidance on gene editing as an issue for its future agenda (8, 9). The European Society of Human Genetics (ESHG) and the European Society of Human Reproduction and Embryology (ESHRE) have already made a contribution in that regard as well, meant to spread information, stimulate scientific and public debate, and provide guidance. Particularly, five distinct aspects need to be addressed: the technical implications and complexities of gene editing, its various applications (whose limits are not yet fully known), relevant clinical experience regarding the handling of reproductive risk, the targeted legal regulations that need to be enacted, and the ethical and societal issues and concerns linked with germline gene editing. Given the essential nature of such elements, both ESHG and ESHRE have summoned their relevant committees (respectively, the Public and Professional Policy Committee of ESHG and the Ethics Committee of ESHRE) and taken the lead in devising a position paper and Recommendations (10).

Times not yet ripe for bioengineering at the embryonic level?

To further highlight the complexities inherent to genome editing, many of the same scientists who have hailed CRISPR's promise have also warned of the potential risks which it entails. Many National Academy of Sciences members have urged the scientific community to hold off editing embryos for now, arguing that there is not enough scientific evidence to prove the safety of making changes, at the genetic level, that can be passed down to future generations (heritable genome editing) (11). In addition, detractors have raised another concern: will the new technologies be used to edit embryos for non-therapeutic purposes? Under this scenario, parents could choose a variety of options for their unborn children, including everything from cosmetic traits, such as hair or eye color, to endowing their offspring with greater intellectual or athletic ability. Some scholars who espouse the philosophical school of thought of transhumanism see an invaluable advantage in making changes at the embryonic level. According to such an approach, in fact, that may be the area where major changes towards human enhancement become doable. As some have pointed out, in fact, it may be easier to intervene at the embryonic stage than in adults through the use of traditional drugs or machine implants (12, 13). Still, detractors have countered such claims. as many philosophers, theologians and ethicists maintain, the idea of "designer children" is alarmingly too close to eugenics, the 19th and early 20th century philosophical movement to "breed" better people (14). Eugenics ultimately inspired forced sterilization laws in a number of countries (including the U.S.) and then, most notoriously, helped provide some of the intellectual framework for Nazi Germany's murder of millions in the name of promoting racial purity (15). There also may be practical obstacles. Some have voiced the concern that there could be unintended consequences, in part because our understanding of the genome, while growing, is not even close to complete. As a matter of fact, not enough is known about how changes in the genetic code will affect development and the innumerable complexities associated with the tremendous array of human traits. Genes and proteins rarely have a single function in the genome: many cases in experimental animals where changing a 'known function' of a gene results in developmental unexpected and unwanted outcomes. Hence, These experiments obviously raise broader technical and ethical concerns. As mentioned earlier in the discussion, fears of generating "designer babies" with genetically enhanced intellectual or other traits is a major concern with germline engineering. However, the current study may reduce such fears to some extent if the embryos preferentially used the healthy parent's gene copy for the repair process instead of the exogenous DNA template. Nevertheless, fears of unjustified gene editing of human embryos appear to be justified and should be controlled, addressed and regulated by governments and society. In 2017, the National Academy of Sciences, Engineering, and Medicine, along with the National Academy of Medicine, the National Academy of Sciences and the Committee on Human Gene Editing, endorsed the view that human embryonic modification may only be allowed for the purpose of correcting mutations that cause serious disease or condition and when no reasonable alternatives exist (16). Undoubtedly, gene editing in human embryos has the potential to engendered clinical implications of unprecedented magnitude. Although there is still a lot of ground to cover before CRISPR/Cas9 techniques can become a reasonable and safe therapeutic means for clinical applications, current research points to ongoing progress and growing possibilities, on a still theoretical basis, to fix various human inborn genetic mutations and diseases that could not otherwise be cured with currently available medical therapies (17).

Gene editing and its potential MAP applications: an ethically sustainable substitute for preimplantation genetic diagnosis (PGD)?

Could gene-editing follow in the footsteps of other beginning-of-life technologies that used to present the same degree of complexity, from a bioethics perspective? As far as ethically controversial technologies are concerned, it is undeniable that medically-assisted procreation (MAP) has profoundly upset the traditional family model (18, 19), through practices such as gamete donation (20-22), artificial insemination (23) and egg freezing (24, 25), among others; in fact, infertile couples may now achieve parenthood by in vitro fertilization procedures which can also rely on PGD within the bounds of the law (26); in fact, access to such practices is regulated by each country with varying degrees of restrictions. In Europe, each country has shaped and enacted its own national regulations, by virtue of the margin of appreciation member states enjoy on such matters. Norms range from permissive to relatively strict. Some member states have no targeted legislation, and medically-assisted procreation is governed by general health regulatory frameworks (27). In 2004, the Italian legislature put in place a set of regulatory standards, modeled on Europe's strictest approach (28); as a result, only heterosexual couples may use the procedures; sperm donation is banned. Still, the new legislation's constitutional viability has been called into question by various Italian Constitutional Court rulings and European Court of Human Rights decisions (29, 30). Besides, the Italian Code of Medical Ethics has enshrined a set of standards for medically assisted procreation, in article 44 (31), which reflects the legal evolution of Italian jurisprudence over the years (32). Gene editing techniques are in our view likely to follow a similar legal and ethical pattern to the one that developed for MAP technologies (33).

As a matter of fact, PGD (which is currently available) and CRISPR (potentially as a future option) are two distinct techniques that pursue similar objectives: achieving better chances of a biological offspring unaffected by specific inborn disease. Although the ultimate goal may be the same (a healthy offspring), the ways in which the two techniques achieve it are different. PGD is akin to genetic testing, which screen for abnormalities in embryos, through biopsies performed at the cleavage or at the blastocyst stage, thus allowing for the selection of those at a lower risk of developing any given genetic disease (34). CRISPR/Cas9, on the other hand, are tools aimed at the modification of embryos or of gamete cells for gene therapy; the ultimate goal is to keep certain conditions from developing in the future children and in future generations, given their heritable status. PGD itself is a controversial procedure: it is not therapeutic in nature, in that it does not treat embryos; rather it is essentially selective: the embryos that will be chosen to be transferred in utero are selected through PGD. Hence, many view PGD as ethically troublesome, since it is in fact a means to select embryos that have a decreased risk of developing into a child with a genetic condition, leading to the destruction of others; in that regard, it should be noted that Article 1 of the Italian law on medically assisted procreation protects the human embryo, by recognising it as an individual with the same rights as any human being (35). Such a dynamic is therefore morally controversial for two reasons: it runs counter to the traditional priorities of medicine, because it is not aimed at curing but at 'selecting out' embryos that may develop into human beings suffering from genetic conditions; furthermore, any choice on which embryos should be selected is grounded in a value-related judgement concerning people with disabilities, as pointed out by those who espouse a critique of screening technologies that became known as the 'expressivist objection' (36). Could gene editing on human embryos even "save" embryos? Prominent scholars have made the case that gene-editing technologies could in fact result in fewer embryos being destroyed in assisted reproduction procedures. Currently, if a carrier of a genetic disease wants to have a child that will not be affected by their parent's condition, the best option is to undergo in-vitro fertilization and PGD, which make it possible to pick an embryo not affected by that condition (37). Nonetheless, this practice often involves the creation, and eventual destruction of a considerable number of "supernumerary", unwanted viable embryos which will not be implanted in the uterus and brought to term. Safe and effective gene-editing technologies, the reasoning goes, would make such a course of action obsolete; if gene editing at the embryonic level became available and widely applicable, there would be no need for carriers of genetic diseases to have large numbers of surplus embryos produces, in order to obtain healthy viable embryos for implantation in MAP procedures (38).

Conclusions: the uncharted territory of genome editing requires concerted answers

Genome editing is a powerful new tool for making precise alterations to an organism's genetic material. Such techniques have been made more effective, accurate and flexible. Such a fast-moving progress have drawn interest from around the globe; the ways in which genome editing may improve human health are being explored, although the overall picture is far from complete.

Nonetheless, the speed at which these technologies are being developed and applied has compelled policymakers and stakeholders to express concerns about whether appropriate oversight and regulatory systems are currently in place in order to effectively govern these technologies, and how and when the public and should be engaged in these decisions. There are several important issues about the possible human clinical application of genome editing, including: assessing potential benefits and weighing them against the unintended risks, governing the use of genome editing, reconciling moral and societal values with clinical applications and policy decisions, and coming to terms with the decisions and differences, across various nations and cultures, that will determine how and whether such new technologies should be applied for the common good of all people and public health (16, 39). Also, any professional who feels such practices conflict with his or her conscience and moral convictions should be able to opt out, by virtue of the recognized right to conscientious objection that is upheld in most countries, where operators may choose not to be involved in controversial procedures such as abortion, assisted suicide or the prescription and provision of

emergency contraceptives, while ensuring patient rights and health are not jeopardized (40, 41). Do the benefits that genome editing will produce outweigh the risks, as prominent scholar Julian Savulescu (42) has argued? Should it be treated as any other technology in health care, or does its potential to alter human nature at the earliest stages of development make it unique? Scientists, ethicists, legislators and policy-makers need to address such questions for the sake of public health and the common good. Surely, there are solid moral and ethical reasons to continue investing in gene editing research. After all, it is worth noting that much research on gene editing can be carried out meeting global safety guidelines. For instance, research has been conducted using tripronuclear (3PN) zygotes, which have one oocyte nucleus and two sperm nuclei. Polyspermic zygotes such as these occur naturally in 2%–5% of zygotes during in vitro fertilization (IVF) clinical trials (43, 44). Such zygotes cannot develop normally in vivo, hence they are not viable in terms of implantation. That makes such trials ethically acceptable, according to some scientists (45). If in fact gene editing techniques are successful in alleviating the global burden of genetic disease and potentially cure millions worldwide, that would be in keeping with the medical principle of beneficence, to an unprecedented degree.

It is however essential that human genome editing procedures, wherever in the world they are carried out, should abide by human rights treaties and conventions, since they relate to the extremely sensitive realm of human experimentation. Total regulatory homogeneity is unlikely to be achieved: differences in cultural, religious and social priorities and values make international agreement on a single set of rules and regulations very hard to achieve. Still, should rules and regulations end up being radically divergent from country to country, both scientists and patients could resort to something akin to “fertility tourism”, i.e. travelling to nations with more permissive laws in place or ethical standards. It is just as important, however, to put and keep in place effective oversight mechanisms, conformity to international bioethical standards and targeted legislation, by which to prevent abuse and the premature application of such highly complex procedures. Finally, a reasonable degree of international harmonization of regulatory initiatives and norms is essential. Scientists must be able to share research materials and data, and the process by which such material is obtained and managed has to meet both ethical and medically safe standards of care, internationally agreed upon and harmonized from country to country, which must be the highest attainable for both research and therapy.

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