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Beáta Laki
University of Pécs
https://orcid.org/0000-0002-6348-8483
laki.beata@gmail.com

Avoidance Versus Elimination. How Can We Harm Less? How Can We Do Rather Good?

Embryo Selection Through In Vitro Fertilization Versus Germline Gene Editing

1. Treatment opportunities of heritable genetic disorders – 2. Specific factors and their effects – 3. Results – 4. Conclusion

Thanks to the development of science and technology, medicine is gaining more and more knowledge. As a result of this development healing or more correctly the elimination of hereditary genetic disorders also obtains an important role.

The categories relevant to this paper can be distinguished as hereditary and non-hereditary disorders. Treating and curing non-hereditary genetic diseases formulate less, or different types of moral dilemmas. These are examined inter alia on the horizon of societal level, according to the law of self-determination, in connection with (informed) consent, or with the provision of the non-competent patient and with the notion of autonomy through its classic, yet modern medical ethical approach[1]. Of course, these interventions also face many other ethical issues (safety, harm: benefit ratio, etc.), but for the most part they are not unanswered, precisely because of the nature of the somatic procedure, which does not affect the germ line,

[1] Autonomy has an impact on all of the mentioned notions and probably self-determination is the closest to it. Self-determination means about the capability of a competent person of making decisions for personal interests, reasons.

respectively due to application of other therapies. However, in the present article, I examine the possibilities of interventions with different evaluations also from a moral point of view, precisely in the spirit of mapping and interpreting unsolvable dilemmas. In my comparative analysis, I examine the ethical aspects of germline genetic interventions and embryo selection through IVF[2] with the intent to shed light on the moral differences and possible similarities between the two. As will be seen, staying within the framework of bioethics, I will explore the pros and cons that may help us in the dilemmas of preventing or even avoiding disease in the future. I do not wish to question the importance of germline genetic interventions and the revolutionary potential they offer. However, as science is not yet at the stage where it can be made with sufficient certainty and properly laid down rules and regulations, I find it important to ethically weigh and interpret the difficulties of this only – in all likelihood – transitional period.

Numerous studies and volumes have been published and are being published continuously in the international literature, which analyse the moral aspects of each intervention. Julian Savulescu who as – probably the most significant – bioethicist deals with these areas and approaches the difficulties generated by the area from various aspects. One of the essential sources of this work[3] can be attributed to him, among other things, in which the authors do not approach the topic from the point of view I discuss here, but in many respects shed light on the ambivalent nature of this field and also the necessity of its progress and support. Not only in this paper, but in almost all those dealing with this topic, keywords emerged to remind us of the limitation, the insufficiency of our knowledge. Without claiming completeness, these are "off-target mutations", "unpredictable effects/consequences", "deletions", "safety risks", "chance of bad outcome", "expected harm", etc. All of these suggest in advance that caution about the procedure is not coincidental. But to reduce these uncertainties, we need to increase our knowledge, and so Savulescu and his co-researchers rightly and logically formulate the "principle of morally necessary research support". However, as long as the uncertainty is so significant and the consequences are often unpredictable, from my point of view, we should use other option(s) in reproductive medicine if it appears/(appear) as a suitable alternative(s). And my present paper is exploring and weighing the possibility of just that.

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[2] In Vitro Fertilization is a procedure when an egg is fertilized by sperm outside of the uterus in a test tube. It is an artificial fertilization procedure with using gametes of the prospective parents because of creating embrios that can be implanted to the mother's uterus. This procedure is mostly used because of medical reasons same as in the case of our current topic.

[3] Christopher Gynell, Thomas Douglas, Julian Savulescu. 2017. "The Ethics of Germline Gene Editing". Journal of Applied Philosophy. (34) : 498–513.

In this article I would like to examine the above-formulated issues and the individual factors by presenting and analysing the ways of avoiding, treating, and eliminating hereditary genetic disorders, as well as by interpreting key concepts. These conceptual analyses will appear primarily in the context of the interpretation of the two mentioned procedures of the title[4] that help briefly analysing the following comparisons: expected harm vs. harm reduction potential, safety, and uncertainties arising from complexity, issues of parent's freedom versus social responsibility, spontaneous mutation, and epigenetic effects, genetic diversity, the possible consequences of impacts on genetic diversity.

These aspects of analysis linked to hereditary genetic disorders are still quite broad. In some respects, they are already a narrower cross-section, and I would like to point out that problems such as non-coercion, ensuring equal access, or even non-discrimination are not what I will cover here. Instead, I will focus on how each of the procedures (IVF embryo selection and germline gene editing) can be ethically interpreted and how they relate to each other within the framework outlined by the factors listed above.

1. Treatment opportunities of heritable genetic disorders

In this section, I list three main groups of options for interventions that are morally different in nature. Additionally, to briefly presenting the alternatives, effectiveness, foreseeable possible consequences of each treatment alternatives (embryo selection, somatic cell genetic intervention, germline gene editing), I will also highlight their moral difficulties.

1.1. Embryo selection through IVF - the way of avoidance?

IVF, in the case of heritable genetic disorders, is practically such a disease-avoiding intervention in which, as its name implies, an egg is fertilized in vitro, then subjected to a pre-implantation genetic diagnosis before the embryo is implanted in the womb. With this examination, they can select the one (or more) embryo(s) that is not involved in the genetic disease.

When we think about it, this is an extremely simple, seemingly logical procedure, as we choose the best, against the ill or damaged ones. From this point of view, there would not even be a question of whether what we do is good or not.

[4] The two procedures are: embryo selection vis IVF and germline gene editing.

However, since these are about potential life opportunities as well, the situation is not so simple. There are different arguments against the IVF procedure that are mainly based on religious reasons and protesting artificial interference in the origin of life. Even if we accept this procedure despite all the critical remarks, we still have to face the difficulties of the fate of the so-called "orphaned" embryos, and thus the problems of the beginning, sanctity, and protection of life. These will not be discussed in detail here, I will only highlight the necessary parts of them to my analysis, but there is also a vast amount of literature on this.

If we go beyond the divisive acceptance of the procedure and focus merely on the goal to be achieved, it can be said that the intervention seems effective, yet raises several practical and moral issues. On the one hand, what happens to the embryos that carry the disorder? On the other hand, what happens when healthier embryos "arise"[5]?

We have already seen such scenarios in real life, but their acceptance or our attitude towards them are still debated. It is already known that the alternatives of handling fertilized but not needed embryos are freezing embryos for later implantation, or donation to an infertile couple, or offering for research purposes, and lastly, the destruction of it. These options, of course, can be applied only to healthy embryos. And in the case of damaged ones, only the latter two are possible.

Beyond these, however, there is also a considerable problem. Depending on the nature of the inherited disorder, embryo selection may not be able to definitively exclude the disease from the genetic line since, for example in autosomal recessive disease, the offspring, even though not ill, may still be a carrier of the disorder what means that there are chances to pass it on not only in the carrier form but also with an increased risk of developing the disease. Thus, the IVF embryo selection procedure should be repeated during the (artificial) conception of the carriers' offspring or the risk of developing the disease should be reduced in some other way. At this point, it is also perceptible, among other things, why it is more appropriate to label this procedure with the prevention, avoidance of the disease rather than with complete elimination. However, the deficiency of the method is also visible, as the disorder does not disappear; it only "hides" and thereby can be protective. And it is not a purely ethical but technical issue as well.

At the same time, if we want to concentrate on the benefits of embryo selection, it clearly does not involve any artificial intervention into the germline, in

[5] By the term "arise", I refer to the process of artificial creation, which can also be contrasted with the process of natural fertilization. Speaking of this, we can find new counterarguments, but not only against IVF, but also against all procedures that interfere with the fertilization process, and thus against germline gene editing.

the genetic stock, which would be passed on to future generations. And with this non-germline intervention the overall human species is spared from significant risk of germline modification but not from the genetic disease.

1.2. Somatic cell genetic intervention – the treatment

Somatic cells are the general cells of the body that do not play a direct role in inheritance thus such genetic intervention does not result in heritable modification. The procedure can be imagined about as they remove somatic cells from the patient than change them with specific methods to become suitable as treatment for the patient and these modified cells will be returned into the patient's body. Consequently, the appearing disorder may become treated on a somatic and at the same time individual, personalized level. Personalised since it has an impact only on the affected person and since it is a direct modification on cellular level as well. (This cannot be stated about IVF embryo selection, it is "only" a selection). It has its effect only in the given patient and ideally with better effects than with any conventional treatments, or as a previously unknown cure. Somatic gene therapies also play a significant role in current medical researche, precisely because of their enormous potential. Its ethical issues particularly concern security, safety, volunteering, accessibility.

This type of intervention could represent the actual treatment, which does not have an intergenerational effect, and thus may even shed light on the benefits. For instance, in case when the patient's body does not respond adequately to the treatment or if the procedure itself was not suitable for treating the given disorder this defect is not inherited thus the risk of bigger/more harm than it can be minimised can be significantly reduced.

Although it seems to be a more acceptable procedure in this respect it does not mean that it is safer as well in the sense of directly affected patient, for which, unfortunately, science provides examples. (The classic example is the case of Jesse Gelsinger – NYU Langone Health). This case is about selection of subject, informed consent and conflict of interest. But the moral issues raised by the consequence of the failed treatment, the death of the young patient who controlled his disease since his birth. And at this point we have to highlight again the safety issue that influences the ethical consideration of such treatments. Somatic gene therapy means mostly positivity from the aspect of consequentialism at the level of all of humanity, but individually, as the above-mentioned example shows, the importance of the safety factor remains indisputable. We do not risk more patients as it is necessary, and we do not risk the gene pool of humanity with not intended

but occasionally harmful and at the same time heritable consequences of germline intervention. So, we can see the pros also in connection with the society. If somatic gene editing works properly its use is undoubtable and it can become morally obligatory at the same time. But in this scenario, this is not the most efficient type of intervention – in sense of long-term effects and invested resources – if we are sure about the consequences.

1.3. Germline gene editing – the complete elimination?

Germline gene editing techniques, are germline genetic interventions, take place in germ cells that cause heritable changes in the affected genome. There are many arguments for and against them that are provoking great debates in both the scientific community and society because, on the one hand, they can have an intergenerational impact and, on the other hand, we do not know with sufficient certainty what concrete results of these changes will be. Although we want to use these as tools for morally supportable goals, and thus use them to cure diseases, more precisely to exclude them from the gene pool, at present we cannot provide a perfect result using these procedures due to our limited knowledge. The 21st century has come up with several technologies of which the CRISPR-Cas9 genetic scissors[6] seemed to be particularly promising, which removes unwanted abnormal sections from the genome based primarily on DNA repair mechanisms by cutting out and replacing segments. In 2019, an improved version, based on this operating principle, appeared on the scene, the so called "Prime Editing technique"[7]. The result of CRISPR-Cas9 intervention is difficult to predict in practice due to its frequently appearing unexpected consequences, such as deletion of certain parts of DNA, rearrangement or modification of segments, so-called appearance of off-target mutations, etc.[8], until then the Prime-editing technique appeared in science as a much more accurate and versatile intervention based on CRISPR gene editing technology. This makes it possible to write new genetic information directly to the specified

[6] The Cas9 enzyme cuts the DNA at the target site, then the cell tries to close this pause/gap again with the DNA repair mechanism and with this treating the genetic disease. This technique is used not only for germline genetic interventions but for somatic cell inteventions also.The point why it is more doubtable in case of germlone interventions is the possible failed operation of these kind of interventions and the intergenerational consequences of it.

[7] Heidi Ledford. 2019. „Super-precise new CRISPR tool could tackle a plethora of genetic diseases". Nature. https://www.nature.com/articles/d41586-019-03164-5?utm_source=fbk_nnc&utm_medium=social&utm_campaign=naturenews&sf221891291=1&fbclid=IwAR2x-nFzr-5S7IC04c1x0VFOQILmznmBf8ccWWinRgnMJ4k3nbLzXbH-vHQ (28.11.2021).

[8] Heidi Ledford. 2018. „CRISPR gene editing procedures unwanted DNA deletions". Nature. https://www.nature.com/articles/d41586-018-05736-3 (28.11.2021).

DNA site, make an intersection in the DNA strand and then insert the edited section into the target site. It is a procedure that can be used for both search and replacement. And in 2021, another technology debuted, the so-called Retron Library Recombineering (RLR)[9], and this opens new, more efficient, and safer perspectives in genetic interventions.

It is also clear from the above three examples that the development of technologies for genetic interventions has gained tremendous significance in the last few years, but certain moral questions remain about their applicability.

Due to the nature of the intervention, the term complete elimination, removal would also reflect actual intent and hopefully realizing activity, but we need to know that in the current state of science, these procedures do not always cause good, and especially are not always predictable, in case of achieving the intended goal i.e., (currently) the elimination of the disease from the genetic line of the offspring (and, of its descendants, due to the nature of the germline genetic intervention)[10].

For further discussion of the topic, it is worth briefly listing the major pros and cons of germline genetic interventions, which are the following

Among the supporting arguments, inter alia, the clinical benefit of the intervention can be interpreted in the light of irreversibility – of course, in the ideal case, if the intervention provides the expected result. This also means that no further somatic interventions are necessary. The principle of the right to life and health, according to the doctrine of duties[11], reinforces the use of the appropriate technology at our disposal. The principles of assistance and charity, in line with the doctrine of duties, also impose a moral obligation to use existing knowledge, since it is equal to an omission not to use an existing technology. If we want to refer to rights that have been called universal, we can also read the appearance of parental rights in relation to genetics, which can be discovered in Article 25 of the Universal Declaration of Human Rights:

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[9] Michael Irving. 2021. „Harvard gene-editing tool „sneaks" DNA into cells without making cuts". New Atlas. https://newatlas.com/biology/retron-library-recombineering-gene-editing-crispr/ (28.11.2021); Lindasy Brownell. 2021. „Move over CRISPR, the retrons are coming". Wyss Institute. https://wyss.harvard.edu/news/move-over-crispr-the-retrons-are-coming/ (28.11.2021); Carmen Leitch. 2021. „Are Retrons the Next CRISPR?". Labroots. URL= https://www.labroots.com/trending/cell-and-molecular-biology/20347/retrons-crispr?fbclid=IwAR1AKEHrhTjphV_xP7uPhzZWon-1HOu8BiI0EXnU8Dx_EARfymfbZC56BlaY (28.11.2021).

[10] In the present study, I only deal with interventions aimed at curing, treating and eliminating diseases, but not with enhancer, improver interventions. These raise newer and different kind of ethical issues that would lead far from my central theme.

[11] The doctrine of duties states that everyone has the right to life and health and thus to come into the world healthily. If we have the suitable technology for this, we are obliged to use it.

> Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control[12].

Further aspects, not just those involving parents but beyond them, it is worth to list as supporting arguments the universal approach that, as the intention to improve the human gene pool lies behind the interventions, these procedures should be morally supported because of the good intention.

It can be perceived that the adoption of these supporting arguments is bounded to many "ifs", and due to these doubts, it is not clear the application of germline gene editing or the moral obligation or even permissibility of their application, as long as safety, harm: benefit consideration or non-coercive access cannot be guaranteed, we cannot talk about its morally acceptable application until then. This is the argument that I would like to strengthen in the reflection of IVF's consequences.

If we want to address the counterarguments to the point of a few thoughts, we may find ourselves facing other problematic points, such as the uncertainty already mentioned, which can be derived from our inadequate level of knowledge, among other things, about the consequences. If we seek to examine further layers from the opposite side, the emergence of the genetic stock as a common property of humanity also serves as a strong counterpoint in the hands of non-supporters, because if something is common, we cannot arbitrarily decide its fate (especially if its result and consequence is not necessarily predictable) in case of it effects on others. And here we can even operate with John Stuart Mill's notion of freedom. In his work *On Liberty*[13], which is practically implied by the modern medical ethical principle of respect for autonomy in the wake of Aristotle, Mill says that our freedom cannot be restricted as long as it does not violate the freedom of others. In the case of germline genetic interventions, autonomy and freedom cannot be perfectly exercised, as we decide not only on the modification affecting the individual, but also on the genetic characteristics of the individuals of the next generations[14]. This aspect of freedom and autonomy of germline genetic interventions are expanding by additional elements if we look at the evolution as a natural process and try to change

[12] United for Human Rights. 1948. *Universal Declaration of Human Rights*, art. 25. https://www.humanrights.com/course/lesson/articles-19-25/read-article-25.html (28.11.2021).

[13] John S. Mill. 1859/2001. *On Liberty*. Kitchener: Batoche Books.

[14] I would not be immersed deeper in the issues of competence and consent. Julian Savulescu's study 2001. addresses these issues, among many others.

it through our artificial intervention. Going further in the line of counterarguments, we can also refer to the rights set out by the European Council according to which the offspring to be born has the right to come into the world without any intervention. If we follow on a more technical line, it is worth re-focusing our attention on our limited knowledge or on our existing knowledge, since our activities may exclude a gene that may be useful to its holder in some other way. We do not have to go any further, just think of the classic example, the genetic disorder responsible for sickle cell anaemia protects the carrier against malaria. Here it is evident that although this disorder causes harm, it is also beneficial. As far as the nature of genetic diseases is concerned, the fact that germline interventions may be the safest for monogenic diseases, i.e., diseases affecting one gene, cannot be ignored, but the significant percentage of genetic diseases are polygenic diseases. The complexity of that is even more unknown and so we must reckon with unwanted effect, off-target mutation, and thus a more exponential risk of a possible gene editing than in the case of monogenic ones.

It is evident that the three different types of intervention, introduced above, present different problems that we should cope with in the most ideal form for both the individual and humanity.

2. Specific factors and their effects

In this section, I focus on interpreting certain factors that help to analyse the two highlighted procedures from new perspectives also and thus help to consider which may be more ethical and why, if at all, it is possible to draw such an objective boundary.

2.1. Expected harm versus harm reduction potential

“Expected harm is the probability of a harm occurring multiplied by the magnitude of that harm. Being harmed by an intervention is being made worse off than one would otherwise have been if that intervention had not been performed”[15]. The extent of the expected harm depends on the possible consequences of the disease in the case of non-application, so its interpretation must appear at the level of individual cases (e.g., Jesse Gelsinger).

[15] Julian Savulescu. 2001. „Harm, ethics committees and the gene therapy death”. Journal of Medical Ethics (27) : 148–150.

Iona Petre in his work *Future Generations and the Justifiability of Germline Engineering* comes up with a really promising and logically easy proposal, and this is the so-called harm reduction potential.

> (…) there is the possibility of altering the germline, but without automatically spreading the changes to all descendants. This could be done by introducing an artificial chromosome, which would be engineered to be non-inheritable after a certain generation (…). Ultimately, my concern is not about germline modifications as such, but about making some genetic changes indiscriminately heritable. If germline interventions may be designed in such a way that their heritability may be controlled, then there would be no successful ground for opposing them[16].

If this possibility existed, as Petre writes, there would be "no successful ground for opposing"[17] to germline genetic intervention, since unexpected consequences could also be easily addressed. And at this point too, the limitations of our scientific knowledge emerge which has a direct impact on the evaluation of applicability issues.

2.2. Safety and uncertainty

If we look at safety issues in terms of the results, potential effects, and consequences of the two procedures, it is now clear that while IVF embryo selection processes can be predicted with big certainty – especially that no specific modification activity is performed by it – our activity, which we do based on the results of diagnostic procedures, the same cannot be said about germline interventions. As we have already seen, different types of gene editing technologies can bring different unexpected consequences, which in many cases are unpredictable. It is trivially inferred from these differences that this battle will also be decided in favour of embryo selection, as its results are more predictable and safer. (Whether one or the other is more effective depends on what our goal is with that particular intervention).

Moral issues, in the name of safety, depend on our scientific knowledge and technological advancement in weighing the potential harm and benefit and evaluating this calculation as an acceptable or unacceptable risk to human(ity).

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[16] Ioana Petre. 2017. "Future Generations and the Justifiability of Germline Engineering". Journal of Medicine and Philosophy (42) : 339.

[17] Ibidem.

2.3. Parental freedom versus social responsibility

The issues of freedom and responsibility always receive considerable attention when discussing individual ethical, bioethical dilemmas, and this is no different in the present case. Examining these, the following can be established for the two procedures under comparison. On the one hand, parents should be free to decide about the conditions, circumstances of the birth of their children, thus, to choose to intervene or not in case their offspring is likely to be born with the harm of some genetic disorder. If they choose the natural way of conception, they should have the chance to decide if they so wish, to trust their child's health to nature, or to avoid disease by embryo selection, or rather complete elimination opting for this type of genetic intervention, through which they can create the best life for their unborn child, without any coercion or obligation, without fear of any future discrimination. In contrast to this relatively large freedom, it is worth mentioning the issue of social responsibility for a moment. Do the needs and interests of society not affect the freedom of parents? It would be in the fundamental interest of every community to have healthy individuals who can be useful members of society. However, if the achievement of this healthy society so-called "combination" can only be achieved through artificial intervention, can parents be obliged to use them if it is against their will, intent, or their faith and beliefs?

When social issues come to the centre of research, we inevitably find ourselves confronted with differences arising from several cultural divergences in how it affects or may affect the freedom and decision of the members of a community. If we again call for help Mill's conception of freedom, which is still relevant today, it can be said, what I have already emphasized in connection with the principle of respect for autonomy, that if an act does not harm the interests of others, it cannot be restricted. On the contrary, if the act of parents, more precisely their passive behaviour when they choose not to act, which is in the present case, the acts aimed at avoiding or eliminating the genetic damage, that can be interpreted differently at the micro and macro levels. While the micro, the nuclear, family level means the whole experience of freedom, at the macro level, that is, for society, miss to eliminate or avoid inheritable harm can also be a health threat.

If we try to relate these two factors in terms of acceptability, it can be said that if IVF embryo selection and germline genetic intervention in parental leave are at almost the same level, the same cannot apply to the terms of social responsibility. This would intend to a greater good, a more favourable result, and thus the complete elimination of the disorder. If the risk of the intervention is acceptable thus

the social interests appear along with a consequentialist ethical approach, that says choosing that procedure which results in the most good for most people[18].

2.4. Spontaneous mutation and epimutations – epigenetic effects

In this section, I highlight difficulties of unpredictable mechanisms (such as spontaneous mutations) that are not yet known completely (as epigenetics), which on the one hand, weaken and on the other hand, strengthen the consideration of application of each intervention.

Spontaneous mutations are mutations (mutation = "an alteration in the genetic material – the genome – of a cell of a living organism or of a virus that is more or less permanent and that can be transmitted to the cell's or the virus's descendants")[19] that have unknown causes. These are the result of faulty DNA replications. In our case, this practically means that, regardless of any intervention, spontaneous mutations can occur in the body. If we refer to the induced mutations, they already mean that these artificial changes caused by various external, environmental influences and factors and behind those there is the real intention to induce them.

In case we want to involve an additional and not necessarily controllable or predictable effect in our study, we cannot ignore the science of epigenetics, it means the following:

> The word epigenetic means literally: above or in addition to genetics. (…) Somehow the environment has an impact on gene expression and these alterations are not necessarily inherited, because they do not affect the DNA sequence (…) Epigenetics studies the cellular and physiological phenotypic trait variations caused by environmental factors that switch genes on or off and affect cell gene expression patterns. (…) The genetic background does not mean, that everything in our life is determined, rather it is the basis on which we can build our life and we can decide what we do with it. Nothing is written in advance[20].

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[18] These interests, the necessary interventions and their consideration also depend on the long-term consequences of eliminating heritable genetic damage for human gene pool, but I will address this issue in more detail in the section on diversity.

[19] Anthony J.F. Griffith. 2023. Mutation. *Britannica*. https://www.britannica.com/science/mutation-genetics (28.08.2023).

[20] Boglárka Erdélyi-Belle. 2016. "An overview of genetic terms in psychogenetic association studies". The International Society of Hypnosis Newsletter. Building Bridges of Understanding 20 (3) : 15–16.

"The epigenome consists of chemical compounds that modify, or mark, the genome in a way that tells it what to do, where to do it, and when to do it" (National Human Genome research Institute). "A change in chemical structure of DNA that does not change the DNA coding sequence" (National Cancer Institute). The effect of epigenetics on the development of diseases has not yet been proven, it cannot be ruled out in all cases, so the consideration of these possible factors may have an impact on the evaluation of genetic interventions or non-interventions. It may even make the issue of safety subject to further analysis, as the desired and unwanted effects of interventions, changes in the frequency of possible mutations, can all affect the judgment of interventions.

These kinds of unpredictability can be applied to show, even if we try to control all possible factors, participatory processes in the appearance and expression of genetic disorders, these (for the time being) coincidences are always there as possible risk factors, and thus showing that we can have a lot of influence on it, but there will probably always be some that we do not.

2.5. Genetic diversity

The goal of genetic diversity, that is, variety is to maintain adaptability and ensure survival. If known genetic harms are eliminated, genetic diversity will also be significantly reduced, from which it can be concluded that the genetic stock of the human species (or the given organism) becomes more vulnerable. However, this is not necessarily in the interest of humanity.

> Genetic diversity is important because it helps maintain the health of a population, by including alleles that may be valuable in resisting diseases, pests and other stresses. Maintaining diversity gives the population a buffer against change, providing the flexibility to adapt. If the environment changes, a population that has a higher variability of alleles will be better able to evolve to adapt to the new environment. In extreme situations (e.g. drought, disease epidemics) diversity could even mean the survival of the population[21].

Along these lines, if we think about the purpose of germline genetic intervention, it can be seen that the elimination of the disease from the genetic pool, which also reduces gene diversity, and thus also adaptability, can have a negative effect on the

[21] Theresa M. Fulton, Carlyn S.K. Buckler, Richard A. Kissel. 2011. *What is genetic diversity? The Teacher-Friendly Guide to the Evolution of Maize.* Ithaca, NY: Paleontological Research Institution. http://maize.teacherfriendlyguide.org/index.php/genetic-diversity-and-evolution (28.11.2021).

given organism. Although not all genetic disorders have some positive characteristics also, we already know several examples of duality in this regard. In all likelihood, there are far more disorders that also confer some favourable resistance on its carrier than we know today, so the complete extermination of disease may not always be in the interest of humanity[22]. In this respect, IVF embryo selection is more justified than germline genetic intervention, both scientifically and morally as it serves the interests of humanity in the light of a consequentialist attitude[23].

3. Results

In this kind of interpretation part, I would like to re-connect and compare what has been discussed and presented through a relation filter, with the help of them I would like to achieve my goal. That is, to show whether avoiding a heritable genetic disorder through IVF embryo selection or eliminating it through germline genetic intervention is more morally acceptable and supportable. If so, which one, why and under what conditions?

The interconnection of the two but organically related points can be shown more clearly by contrasting the presented factors in relation and on the other hand by showing the change of the interventions in a straight line.

Based on our current scientific knowledge, putting each factor in relation:

Table 1. Comparison of IVF embryo selection and Germline gene editing

	IVF embryo selection	**Relation**	**Germline gene editing**
Expected harm	less	<	bigger, uncertain
Harm reduction potential	less	<	bigger, more significant

[22] For example: sickle cell anemia and ß-thalassemia – protection against malaria; symptoms of cystic fibrosis – cholera are less severe; Tay-Sachs-diesase – protection against TBC, etc. See: Sára Tóth, Hargita Hegyesi. 2007. *Bevezetés a humángenetikába*. Budapest: Semmelweiss Kiadó.

[23] We can go much further in this line and imagine a utopian or even anti-utopian world, which could mean complete control of science, and thus even a directed evolution, where the genes we define can only appear and the complete eliminatation of genetic diseases would be the basic circumstance. This scenario can be considered a lot of things, but not sustainable, not free and especially not natural.

Safety	bigger	>	less
Parental freedom	same	=	same
Social responsibility	less	<	bigger
Spontaneous mutation	same	=	same
Epigenetic factors	same	=	same
Genetic diversity	remains, bigger	>	decrease

If we take a look at the table and summarize the facts that I introduced in the previous point we can formulate a fast but probably acceptable conclusion: the result of relation in light of our current scientific knowledge: if the above-mentioned factors and the relation between them are true IVF embryo selection has a potentially smaller negative consequence than germline gene editing currently.

It can be weird, but it seems so that the moral evaluation of embryo selection and germline genetic intervention is strongly influenced by the scientific knowledge also.

I have highlighted only a few, but extremely important factors, which show, among other things, that with the development of science and technology, this relation will change after a while and then germline gene editing techniques may come in the focus as the best and safer way of treating genetic disorders. That point will be the one when the currently quite double-sided[24] ethical difficulties become simpler and turn into just pure ethical ones without technical dimensions.

4. Conclusion

As long as the difficulties presented in this paper are not sufficiently eliminated it may be said to be relative, but also to solve this scientific-moral dilemma in determining the expected benefit and harm ratio, germline genetic interventions are not applicable morally. However, whichever is more desirable, IVF embryo selection, or germline gene editing, as we have seen, it is difficult to put on the same scale given many factors, yet I have tried to make an attempt to do so. Based on this, I concluded that as long as we are unable to achieve the appropriate level of safety due to the limi-

[24] Double sided means here that the ethical issues are influenced by scientific knowledge. The less the scientific uncertainty is the more the ethical side purely can appear.

tations of our scientific knowledge, it would be irresponsible to use germline genetic interventions, even if the expected benefits are greater but uncertain for the time being. Until this level of scientific knowledge is not reached, although IVF embryo selection also has a number of significant moral issues (and not discussed here, but also concerns rather emphatic areas those cannot be ignored such as mental and physical exertion, access to technology, etc.) however, it would be more ethical to prefer this procedure to greater benefits, citing both the principle of philanthropy, as the consequences of IVF are more visible at both the individual and societal levels.

Definitely, with the expansion of our knowledge, germline genetic intervention will gain more and more knowledge, and thus more and more certainty, yet until this happens, we should not arbitrarily apply activities that affect not only one individual, but also directly involving future generations, not least because it will also affect all of humanity as a species in a certain way but directly.

Since, in the present state, ethical judgment is not in itself, but under the influence of a function of scientific knowledge, we cannot speak of mere considerations limited to moral aspects[25]. However, this can also be seen. When we reach the level in science that germline genetic interventions can be applied with sufficient safety, a new chapter in bioethical issues will open up for humanity. It will no longer be organized primarily around expected, presumed harm and its liability issues, but even more, perhaps even purely moral, issues. From then on, science will no longer be a barrier to interventions, but society and individual interests, relations and respect for lack of coercion will appear against social responsibility. Ensuring equal access against the limited generates new focus points of discussion and analysis, which we see at the moment, but as we are not yet here, it is difficult to formulate perfectly the possible scenarios for these.

As can be seen in the above comparison and derivation, the study of moral dilemmas along germline genetic interventions in the duality of technology dependence can provide specific points of consideration according to the requirements of the present age. However, this also entails the need for continuous reinterpretation due to the constant change in science and technology until we reach the tipping point already mentioned. From then on, the components of the hitherto dual, moral dilemmas will gradually move towards the one-component, although its full achievement is unlikely, but it will be shaped by scientific progress and social interests and needs.

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[25] Lynn J. Frewer, Richard Sheperd. 1995. „Ethical Concerns and Risk Perceptions Associated With Different Applications of Genetic Engineering: Interrelationships With The Perceived Need For Regulation Of The Technology". Agriculture and human values, 48–57.

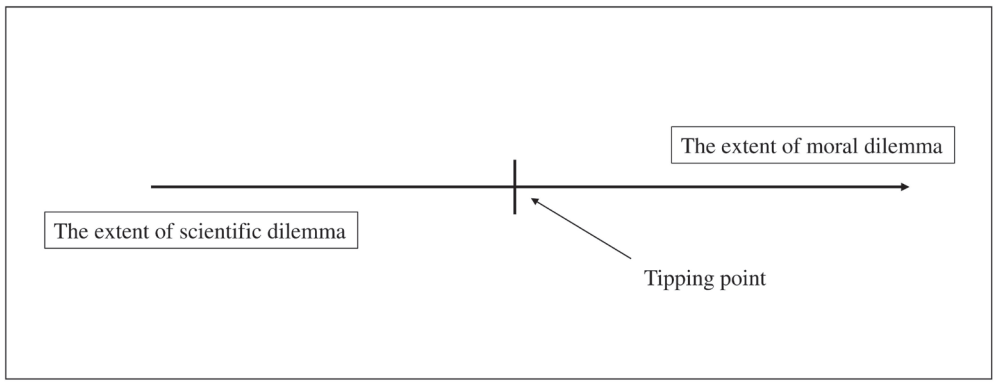

Figure 1: Tipping point

To summarize, continuous monitoring is needed, which may seem simple, yet it is an extremely complex task due to the many factors involved. However, the point does not lie in this complexity, but rather in the so-called transitional period during which we still have alternative ways to treat and/or avoid a certain level of genetic harm. If we look at this scale for a moment, somatic genetic intervention is in the most acceptable place. Although its application also places limitations on the present and future of the disorder. This is followed in the row by IVF embryo selection with all its moral aspects, which I have discussed above. And finally, the application of germline interventions ranks third (but first in terms of effectiveness). The positive thing about current restrictions[26] is that germline interventions should not be approved as emergency/coercive solutions, but – even if they are not as effective – there are alternatives until the right moment comes. This is why it can be said that when these procedures become more and more widely permitted, we can also be sure of their safety. Or the other way around, it can spread more applications once they are suitably safe.

We are moving on a scale that will be the new starting point when our scientific knowledge will be enough to stop playing a role. And in the meantime, the limitations arising from our defined knowledge cannot be ignored.

From the above derivation, we can conclude that until the discussed turning/tipping point due to the duality of scientific-moral dilemmas, the intervention to avoid genetic abnormalities through IVF embryo selection is more acceptable than the complete exclusion by germline genetic interventions.

[26] International Commission on the Clinical Use of Human Germline Genome Editing. 2020. *Heritable Human Genome Editing*. Washington, DC: The National Academies Press. www.nap.edu (28.11.2021).

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Abstract: The present article focuses on hereditary genetic disorders which is specified and evaluated through comparative analysis. This comparison extends on highlighting a few factors in connection with avoidance through IVF embryo selection procedure and elimination, removal through germline gene editing. Focusing on the later listed factors the author introduces a new perspective of moral evaluation of the mentioned procedures. With the explanation of the dilemma, according to showing the factors and with the analysis of their effects the paper concludes that it is conceivable based on the factors discussed here that avoiding the appearance of genetic disease through IVF embryo selection is morally more acceptable, given the current state of science and technology, than the direct modification, intervention into the germline.

Keywords: IVF embryo selection, germline gene editing, safety, expected harm, responsibility, freedom.

Streszczenie: Unikanie versus eliminacja. Jak można mniej szkodzić? Jak można postępować lepiej? Selekcja embrionów w procedurze zapłodnienia *in vitro* versus edycja genetycznej linii zarodkowej. Przedmiotem niniejszego artykułu jest dziedziczne zaburzenie genetyczne, które zostało określone i ocenione w oparciu o analizę porównawczą. Komparacja ta rozwija się przez naświetlenie kilku czynników związanych z unikaniem procedury selekcji i eliminacji embrionów podczas zapłodnienia *in vitro*, a zastąpieniem jej edycją genetycznej linii zarodkowej. Koncentrując się na kilku czynnikach, tekst przedstawia nową perspektywę oceny moralnej wspomnianej procedury. Z wyjaśnieniem dylematu, zgodnie z przedstawionymi czynnikami i analizą ich skutków, autorka dochodzi do konkluzji, zgodnie z którą wyobrażalne jest, bazując na przedstawionych czynnikach, unikanie wystąpienia choroby genetycznej nie przez selekcję embrionów podczas *in vitro*, ale na drodze bardziej moralnie akceptowalnej. Według autorki, uwzględniając aktualny stan nauki i technologii, jest to możliwe przez interwencję w linię zarodkową.

Słowa kluczowe: selekcja embrionów podczas zapłodnienia *in vitro*, edycja genetycznej linii zarodkowej, pewność, przewidywalne szkody, odpowiedzialność, wolność.