Germ-Line Engineering and Late-Onset Diseases: The Ethics of Self-Evolution

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Abstract

While some claim that germ-line engineering is a definite possibility, the law in Israel and in most countries states that it should be avoided. This paper suggests that using GLE in order to 'self-evolve' (when it becomes safe) is not only inevitable but also morally justified. This paper argues that,

- The great achievements of healthcare during the last century, enabling longer life, have made almost everyone prey to late-onset diseases.
- The conundrum of healthcare allocation is worsening, partly due to late-onset dysfunctional genes that have escaped the barriers of natural selection.
- Trying to free future generations from late-onset diseases (such as Alzheimer's for instance) may be considered as 'eugenics' but, if pursued freely and justly, is a noble goal.
- We will be affecting future generations whether or not we use GLE.
- By definition, GLE might be reversible; it follows therefore that GLE may not necessarily represent the dramatic change inserted in the germ line forever – as is usually suggested.
- Reproductive freedom and justice are paramount in this scenario. These values are not necessarily incompatible if the right policies are in place.

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In most countries today germ-line engineering in humans is prohibited; in Israel, a 5 year moratorium against genetic intervention in reproductive cells in humans was recently renewed for another 5 years [1]. This legislation was implemented as a result of the vast development in molecular genetics and reproductive technologies research.

Today, artificial chromosomes can be introduced into a cell and passed on when the cell divides, and onto further generations [2,3], and although the perspective of human self-design is not yet here, it is clearly visible on the horizon. According to Lee Silver [4], there is no longer any doubt among molecular geneticists that the technology to perform genetic engineering on human gametes and/or the zygote in a safe and efficient manner will be developed. Any change performed at this stage will be contained by all the cells of the embryo and will also affect the germ line, and, thus, affect future generations. The implication is that if the change is detrimental it will also harm future generations; equally, if the change is desirable it will also benefit future generations.

More recently, Gregory Stock observed that activity in four overlapping areas of research – the human genome, clinical medicine, animal transgenics, and human infertility – will bring us to germ-line genetic modifications; and that the arrival of safe and reliable germ-line technology will be the beginning of human self-design [5]. Pre-implantation genetic diagnosis, Stock believes, is the vanguard of germ-line manipulation. PGD is *not* the genetic engineering of embryos. Today PGD is used clinically to give parents the possibility of avoiding having a child affected by a genetic disease; by means of PGD, individual couples can make a free and informed decision as to whether they want to 'choose' a healthy embryo. However, one immediate implication of PGD might be to 'cure' the germ line by selecting only healthy embryos. The second implication is that PGD introduces the idea that individual couples might also make a free and informed decision as to whether they want to 'produce' a healthy embryo by manipulating their gametes and/or the zygote (when this technique becomes safe) in the first place. PGD is directly related to in vitro fertilization; and although IVF today is responsible for fewer than 1% of births in the United States and embryo selection numbers only a few hundred cases, it is widely believed that if we give the emerging technologies of PGD and IVF a decade, they will be at the cutting edge of human biological change [5].

Freeing future generations from late-onset diseases by curing these diseases in the germ line may be morally better than the alternatives and will repay, by and large, the money invested in doing so

In his book *Remaking Eden* [4], Lee Silver coined the term "self-

GLE = germ-line engineering

PGD = pre-implantation genetic diagnosis
IVF = in vitro fertilization

evolution" for the implications of new reproduction technologies and in this paper I adopt his terminology. This evolutionary perspective may help us to perceive human development as a continuum. Although human development has occurred without significant genetic change, largely as a result of cultural evolution, freeing humans from diseases as envisaged by self-evolution would involve biological development. This time however, human biological development would not be orchestrated randomly by natural selection but rather by conscious (and workable) procedures. Germline engineering and self-evolution are not equal; GLE is the technology, self-evolution a process. However, in this paper I use the terms self-evolution and GLE interchangeably.

While some researchers claim that GLE is inevitable [4,5], others argue that GLE should be avoided [6,7]. The renewal of the moratorium in Israel shows that GLE might not necessarily be inevitable and that it can be avoided by appropriate legislation. However, while this policy may now be justified because GLE is not yet safe, when this procedure does become safe the benefit of this law should be reconsidered.

Certainly, the idea of using GLE is highly controversial. For a start, only 10% of all Americans accept the science behind Darwinian evolution (interestingly, this percentage has not changed since 1980) [8]. This does not necessarily mean that those who accept Darwin's theory will also automatically accept GLE. Some authors may claim that evolution is a natural process and not a willful change made by man. On those grounds however, sound argument for and against human intervention can be discussed. But if the natural process of random genetic change is not acknowledged, this discussion cannot even begin. Secondly, while the human genome is regarded as something special and different from non-human genomes [9], we share a number of the same genes with apes, cabbages and fruit flies [10–12]. Moreover, it has been found that up to 1% of the human genome holds endogenous retroviruses, which use the human genome as their vehicle for further reproduction [13,14]. The uniqueness of the human genome is the result of a developmental process, as implied by molecular homology [10–15]. Although this process was largely at work in the past, there should be more sound argument in order to avoid further (possible) development in the future. (Some may object that a cave with paintings done by humans may be declared as "patrimony of humanity," which is a legal term indicating that something belongs to all human beings, while other caves – without human paintings – are not; however, declaring the painted cave "patrimony of humanity" – with the immediate effect of preserving it untouched – has not halted further development in human painting. By contrast, leaving the human genome untouched would clearly halt the biological development of humans.) Thirdly, self-evolution has eugenic implications, and the word 'eugenics' immediately confers everything connected to it evil and morally dubious [16–20]. Finally, while heart transplants are considered a cure and therefore morally right, genetic interventions that may avoid these transplants in the first place are regarded as "enhancement" and therefore morally wrong.

It is beyond the scope of this paper to explain Darwin's theory of evolution, and I will only remark that evolution as a natural process has not had any purpose and/or direction and as such has proceeded randomly [10–12]. Humans, however, have intervened in natural selection processes by curing and/or avoiding disease. Steve Jones [11], similarly using an evolutionary approach towards humans, also claims that humanity over the centuries has evolved with the machines that humans have built. Because of this, he remarks, human bodies have not had the *need* to evolve. However, in the developed world, ill health imposed by late-onset diseases is suggesting the contrary. We may now achieve the capability to intervene further – but this time consciously – in evolutionary processes. I contend that using GLE in order to "self-evolve" is not only inevitable but also morally justified, because the alternative may be worse.

The achievements of healthcare and late-onset dysfunctional genes

It seems that humans at both the individual and species level have reached a crucial and self-defeating point. Paradoxically, with the improvement in medical healthcare, ranging from better hygiene and better nutrition to the use of antibiotics and successful surgery, we have intervened – unknowingly – in bodily human evolution. Variation at the individual level might still be in place [15], however 'natural selection' of these variations has halted [11,12] – at least in the developed world. There is no selection whatsoever since (almost) everyone is able to reach reproductive years and reproduce. This could be an optimal and successful outcome for humans both individually and as a species. However, the improvements in medicine that have got us to this point are now, paradoxically, demanding more expensive medical care than ever [21]. We should add to the paradox of growing expenses in medicine the growing number of genetic faults in the population; for instance, the more successful we are in neonatal medicine, the greater the chance of defective children surviving and even reaching the age of fertility. Most ironically, healthcare improvements have also made us *all* 'disabled' and/or 'unfitted' in one way or another, sooner or later. This has happened because the selecting forces of evolution have spared genes whose dysfunction manifests in mature or older people primarily, due to the fact that these genes become apparent only *after* having been inherited by the next generation. Some might suggest that evolution spared these genes because they may have had some beneficial effect. However, if this were the case, higher percentages of the *same* population would be suffering from the *same* late-onset disease. If a late-onset defective gene had a protective effect but no dangers until *after* the reproductive years, selective forces would have greatly favored the incidence of this particular gene form in a population. Sickle cell anemia in the heterozygous state, for instance, protects against malaria, which explains the high incidence of this gene in certain populations. However, in the homozygous state this gene was deadly, which explains why the incidence is not higher in these populations. Yet, late-onset diseases affect some (but not all) members of a family and some (but not all) families of the same population. This may suggest that these diseases are more likely to be the result of a drifting mutation, neutral under selective forces acting before the reproduction years and therefore spared by evolution.

In the past, when the average lifetime was 42 years or even less, dysfunctional late-onset genes did not have importance. This does not mean that everyone in the past did not live beyond their forties; certainly some survived and even lived very long lives; but the average life span of individuals of the human species has been increasing continuously. In the U.S. a child born in 1997 could expect to live for 76.5 years, about 29 years longer than a child born in 1900 [22]; and life expectancy in England has almost doubled over the last 125 years [23]. This has been *the* achievement of healthcare; however this success has also ensured that more people are now able to live long enough for defective and disabling genes to become apparent. Kidney failure, diabetes, hypercholesterolemia, heart diseases, Alzheimer's, Parkinson's, dementia, are a few late-onset congenital diseases that have been brought to the central arena of healthcare; they demand bigger budgets, and paradoxically, due to the great achievements of medical care, allow more humans to get older.

The above list is of course a loose categorization of late-onset diseases. I am aware that some of these diseases are less severe and perhaps more treatable that others. Some might also be polygenic and multi-factorial at the onset. I am grouping them here for the sake of this discussion. The point is that not everyone gets these diseases, and the fact that some people live into their nineties and beyond, completely free of disease or may have some but not the others, points to the fact that these threats have a genetic component. However, because they appear later in life and their genetic component is still unclear, these diseases (or at least some of them) have not yet been clearly categorized as "genetic," compared to other diseases that appear at birth or in childhood.

Healthcare allocation: what does "to go without" really mean?

If we free future people from late-onset diseases by using GLE, this may beg the question as to what people would be dying from. One answer is that people could die healthier. Some people do have this lucky lottery written in their genes, and these people are "naturally enhanced." They have already won the genetic lottery. On the other hand, we may try hard (and rightly so) to cure disease when and if disease appears among the unlucky, namely, those people who do not have healthy genes. However, we should acknowledge that we are getting to a crucial point in the issue of allocation of resources for healthcare.

Today there are many voices claiming that society cannot afford to offer *all* its members all the healthcare that might possibly "do them some good"; that each society has to establish priorities; or as some healthcare economists bluntly put it: "society has to decide who will get what and, by implication, who will have to go without" [24]. But then, we should also be aware of what "to go without" actually means and consider the alternatives. Because, plainly, the meaning of "to go without" is not receiving appropriate healthcare when and as required; and although none will actually murder the people on a waiting list, it necessarily follows that the outcome might be that they die. And if these deaths could be avoided by proper healthcare then their occurrence would be morally questionable. The point here is that the dilemma of resource allocation in healthcare is worsening [24–27]; this is partly due to the dysfunctional late-onset genes almost everyone carries on the one hand, and the improvement in expensive healthcare technologies on the other.

Self-evolution and Alzheimer-free people

We might now consider the alternative of self-evolution by using GLE. Evolution has proceeded randomly until now; self-evolution, by contrast, has a purpose. This approach considers the idea of GLE as a conscious, workable and *safe* strategy that could be achieved, with due research, by using genetic molecular homology to our advantage; this measure might possibly be eugenics. However, the outcome might offer a moral solution to the rapidly expanding dilemma of scarce resources in healthcare. I will return to eugenics in a moment.

If we accept Dawkins' suggestion that evolution occurs at the gene level and therefore natural selected genes are those that survive in the genetic pool [12], then self-evolution means deliberately selecting certain genes – the healthy ones – and not others, i.e., those responsible for late-onset illness. Self-evolution then refers to perceived change in humans as a continuum and contemplates these changes from a developmental point of view, because self-evolution at the individual level could eventually have effects at the species level. If more – or all – humans become Alzheimer-free by individual choice, then the genetic threat called "Alzheimer's" will no longer be a characteristic of the human species.

This means that individual selection for certain alleles and not others might lead eventually to evolution of the entire species. Although this development may proceed at the individual level – as evolution proceeds (randomly) anyway, today there is a certain congruence between individual parental goals and a possible goal for the species. This may happen simply because parents want what might be "best" for their children [16] and, as Julian Savulescu has suggested [28], not choosing a fetus by means of pre-implantation diagnosis if we know (for instance) it will develop asthma may be morally justified by "procreative beneficence." As he puts it: "the morally relevant property of 'asthma' is that it is a state which reduces the well-being a person experiences." Procreative beneficence may easily include late-onset diseases since these also compromise the well-being of a person, irrespective of the age at which these diseases may appear.

The rationale for using GLE

If we could sort out the biological facts upon which self-evolution is based, then its just implementation should not be handled differently to any other procedure in healthcare. The rationale for using GLE is that:

- It is a tiny change in the molecules of DNA that may render us crippled.
- If worked out safely, GLE could avoid genetic late-onset diseases that plague people with ill health.
- Avoiding a gene that may contribute to the development of a high blood cholesterol level may be more efficient than replacing a damaged heart in surgery later on.

- Whether we intervene in the germ line or not affects future generations.
- Self-evolution is not irreversible. Similar procedures (using GLE) could be used by future generations to retrieve a gene if desired and/or needed.

I will return to the last two points in a moment.

Eugenics: back to the future?

Trying to improve the genetic make-up of humans using GLE also means 'eugenics' and the historic facts are far from reassuring [16–20]. Using eugenic ideas in modern times is round two; however, are the values behind this idea now the same values held in round one? Although using GLE for self-evolution has eugenic implications, it is important to acknowledge that a) the purpose is noble, and b) it differs completely from the racist worldview and murderous methods of the Nazis.

Eugenics is associated mainly with the atrocities perpetrated by the Nazis, although the eugenic movement in the first part of the twentieth century was widespread throughout the world. Yet this movement was inspired by the notion that not all people are created equal, and questions of justice and reproductive freedoms were ill addressed by the ideology of that era. These were the muddy ideas of the time, which finally culminated in the "racial hygiene" ideology of the Nazis. However, as Wikler and others suggest, we may learn from previous errors and thus avoid them. This means that even if the prospect of healthier human beings in the years to come might be an appropriate and defensible goal of public policy in genetics, questions of justice must be dealt with [16]. Wikler also notes that apart from the crimes of Nazi racial hygiene, infringements of reproductive freedoms were the most notable wrongs in the name of eugenics. It follows that close attention to the effect of the new genetics on these freedoms is essential [20]. But can reproductive freedoms be compatible with justice?

Liberty and reproductive choices

Liberty to make choices is an essential feature in human lives. But does this also mean that individuals should have liberty to make self-evolutionary choices? Liberty as a principle derives its moral appeal from two sources. First there is the belief that because autonomy is a vital interest, it is better for people to make their own choices, even if this is more painful for them. The other is the belief that even if paternalistic intervention is acceptable in principle as a policy, it is likely to do more harm than good on account of various human fallibilities [29]. There is no reason why the liberty of individuals to make self-evolutionary choices should be considered differently from other choices we make. Moreover, as John Harris points out [30], the best way to avoid totalitarianism and escape the possibility of racial, social or gender prejudice dictating the sort of children people have is to permit free parental choice in those matters.

Future generations

These choices, however, can certainly affect other people, primarily our own children since self-evolution is about the next generation. Is this morally permissible? Harris claims that we *already* affect our children by our choices in different ways – ranging from the partner we choose, through the age we choose to become parents (to the extent that we have the power of choice over this), to the kind of education we choose for them [30] and even the country we may choose to live in. Sometimes we do not even choose at all – a liberty that parents also have but which may have influence on the life of the child. These choices will undoubtedly affect our children, but we cannot ask their opinion, mainly because there is nobody to ask as long as they do not exist.

Our children are now born into a world in which they may live longer because of healthcare improvements. On the other hand, the bad news is that late-onset diseases might strike them. Yet nobody has thought that we had to ask these new generations what they would have preferred. We have improved the world by improving healthcare but at the same time have created a new dilemma, namely, late-onset diseases which are clearly a new plague. It is for these generations and for us now to face this new problem and resolve it. Using GLE to eliminate this new plague of ill health may of course generate new dilemmas, but this is not reason enough to avoid resolving the problems we face today. One of these dilemmas might be unrestricted longevity (in good health), however this discussion is beyond the scope of this paper.

Affecting the whole lineage

It might be said, however, that our decision to "self-evolve" our child is worse, because it will affect not only our child but also the whole lineage [31]. This means, perhaps, that if I free my child from Alzheimer's this is not only done to him but also forced upon *his* child without *his* consent. On the other hand, doing nothing, other things being equal and the intervention being safe, will have *exactly the same effect*. It will also affect my whole lineage, for if I get Alzheimer's, my child might have it, as might his progeny as well.

Some argue, however, that one may decide to eradicate a gene form because we think it causes disease, but in another environment, generations from now, the lack of this gene form (at the heterozygous state at least) may be detrimental. This might be a touching insight into the general future of humankind but a situation which, given the current choice, each of us would prefer to avoid. Naturally, parents want a healthy child, as healthy as blind nature could provide. For instance, parents would hope for a child free from a disease such as cystic fibrosis. Although the CF gene could perhaps protect future generations from an outbreak of malaria, parents would bless their good fortune if their child happens to be CF-free. It is unlikely that they would be concerned whether or not this particular child carries a CF gene; but if we consider that getting rid of this gene could be harmful for future generations then it remains unclear why this seems to be acceptable when this occurs naturally.

PGD has already made possible the idea of conscious intervention in order to make parents' hopes for having a healthy child materialize. Rightly, we should fear further harmful intervention by GLE. But as more and better knowledge accumulates, and at a

CF = cystic fibrosis

certain point we understand that getting rid of a gene may be harmful for future generations, then avoidance from safe intervention in order to insert this gene, all other things being equal, would have the same harming result and therefore cannot be better.

Finally, on this issue, there is a common but flawed notion of the dramatic and irreversible effects of GLE. This is because, by definition, GLE might not necessarily be irreversible. If it is *safely* worked out and used *once*, similar technology could also be used by future generations – even to undo what the previous generation may have done. This means that if the child is Alzheimer's-free but when he becomes an adult finds it is propitious to bequeath Alzheimer's to his son, he could always ask for the dysfunctional gene to be put *back*. We may assume, however, that in the case of the gene causing Alzheimer's this is highly improbable. The point here is that GLE may be *reversible* by its own design; therefore, changes in the germ line using GLE technology would not be as dramatic and final as usually suggested.

Side effects

One of the side effects of GLE could be prolonged longevity in good health; this can hardly be considered a bad outcome, but the consequences could be so broad that it merits a separate discussion. Other side effects of GLE could be its use for non-medical purposes, i.e., enhancements such as intelligence, character and physical traits. While some would say that these uses of GLE would be "abusing" this technology, others may argue that since "enhancement" also implies "improvement," it necessarily follows that to be enhanced by GLE would also be preferable. Some believe this would be a dangerous outcome. However, we should be aware of what exactly the danger is and address it appropriately. For if to be genetically enhanced is regarded as better then this would be a question of social justice and should be treated and dealt with as such.

Social justice

Assuming we are now convinced that self-evolution might be a good – could it be conducted justly? Moreover, could freedom of individual reproductive choice be compatible with the achievement of social justice? The answer to this question depends on the goals of social justice. The principles of equality reflect the view that it is wrong or unjust for some Fs to have G while others have not. Such inequalities must be remedied. It is clear, however, that instead of achieving equality by giving a benefit to those who lack it, one can equally achieve it by denying a benefit to those who have it. This means that egalitarian principles often lead to waste, for if there are not enough benefits to go round then whatever we have of them should be wasted rather than given to, or allowed to be retained by, some [32–34]. It follows that if the goals of social justice remain strictly egalitarian, then self-evolution might never happen because at the beginning these technologies would be expensive and few individuals would be able to afford them. Since strict egalitarian goals can be achieved by either supplying the same good for everyone or withholding it from everyone, because of egalitarian concerns, the outcome would be that the whole process of self-evolution might be avoided and, therefore, wasted. On the other hand, individuals who can afford self-evolution technologies may allow further research; so in the long run these technologies could become cheaper and affordable for more people and could become, eventually, a basic package of health – for everyone. If we basically accept that less strict egalitarian concerns can be applied to a self-evolutionary process, then John Rawls' principle of justice may be used since it permits differences between individuals insofar as they work to the advantage of the worst off [35]. This, in turn, suggests that inequality in the distribution of self-evolution is justified only if it benefits *all* people or, alternatively, only if it benefits *the least advantaged* people. From a strictly egalitarian point of view, this might not be an ideal outcome but it appears to be better than the alternatives. Most importantly, a less strict egalitarian view remains consistent with free reproductive choices.

Could self-evolution be implemented justly?

It seems to me that this is the most crucial issue. A just healthcare has two dimensions, local and global. Both dimensions, however, have the depths of people's pockets in common. There is excellent healthcare for the haves in Brazil, which is a developing country, while 40 million have-nots in the U.S., a country that is certainly developed, do not have any kind of health insurance [36]. Therefore, in both places a just allocation could be resolved by a correct policy, for instance extending John Rawls' basic principles to healthcare as Daniels proposes [37], namely, justice requires that positive steps be taken to enhance the opportunity of those disadvantaged, such as genetic endowments, and to eliminate these disadvantages, guaranteeing fair equality of opportunity. Globally, smallpox (as a disease) was finally eradicated by a consensual policy. Of course, there are differences: smallpox was caused by a virus that was an exogenous agent, while a certain gene form – even when it may produce a faulty molecule – is an inherent form of the genome variation. However, if endogenous retroviruses have also become part of the human genome, then the distinction between exogenous agents and endogenous agents, if both are harmful, is unclear. The crux of the matter, however, is that when and if a consensual policy is in place, healthcare may also be successfully delivered even on a global scale.

It might be argued that eradicating smallpox was in the interest of the rich and the developed world because it was easily transmitted and completely deadly. By contrast, why bother with other diseases and certainly with the improvements of self-evolution for all? And yet, it seems that the developed world is already starting to feel the effects of leaving other parts of the world behind. For if in previous periods people moved from rural areas to towns in order to get food, the same is happening now on a global scale. People from poor countries are trying to enter rich countries to find a better life. So globalization of development is certainly in the interest of the developed world: if developed countries want to avoid a future avalanche of illegal immigrants and/or want to keep their way of life protected, it will certainly be in their interest to start developing the poorest parts of the world. Overall, development usually brings further development of healthcare, which means advancing the status of health, *including* genetic improvement (if wanted individually) for everyone, everywhere. Not only would this

be the right thing to do, but the money invested in so doing will, by and large, repay the investment and prevent ill health later in life.

Is this a realistic goal?

It could be argued that the goal of self-evolution for all is utopian [4]. It may be so. But from the point of view of a person living in the Middle Ages or even in the year 1900, the level and scope of healthcare in the year 2000 could also be seen as utopian. Although differences between the haves and the have-nots are huge, engines in the front usually pull whole trains behind. This means that although hospitals in rural parts of Brazil are primitive compared with other hospitals that may offer full-fledged standards of healthcare, the fact is that hospitals do exist in these areas – a service of healthcare that certainly was lacking a century ago.

By any standards of justice is this enough? Certainly it is not. But then, the alternative is that any surgery or treatment that is not available to all should be wasted and offered to none. By any account of justice this cannot be morally justified. Finally, any reasoned thinking that might suggest improving healthcare for everybody everywhere, and not only self-evolution, could be regarded as utopian in the first place, and for this matter abandoned.

Concluding remarks

I have tried to underline in this paper that, when developed safely, the gains from GLE could be enormous; however, equally, as with any medical intervention, the risks of GLE should be weighed against the benefits. While each step in this path should be monitored properly by bioethics agencies in order to avoid dangers and abuses of GLE, these agencies should make clear exactly the kind of dangers and abuses at stake in order to address them properly. This should be done on a case-by-case basis, trying to avoid preconceptions, prejudices and by keeping an open mind.

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