A silenced dialogue - natural science and the ethics of genomic intervention and enhancement

Anmerkung der Redaktion: Ausgehend von den rasanten Fortschritten in den Möglichkeiten der Genveränderung befasst sich die Autorin mit den damit einhergehenden Problemen der Arbeit am menschlichen Genom. Sie fordert eine umfassende, sekorübergreifende gesellschaftliche Debatte über Machbares und Wünschenswertes. Wir sind überzeugt, dass viele der Argumente auch für die bioökonomische Diskussion Gültigkeit haben, weshalb wir den Artikel in unsere Reihe aufgenommen haben. Er stellt den vorläufigen Schlusspunkt unserer Serie dar und ist uns Verpflichtung, auch in der Zukunft unseren Beitrag zur Umsetzung dieser Forderung zu leisten.

A silenced dialogue - natural science and the ethics of genomic intervention and enhancement]
The ethical and social implications of genetic enhancement have been the subject of intense debate among philosophers, theologians and social thinkers for many years. However, for a long time, researchers from the natural sciences hesitated to become seriously engaged in dialogue or debate about genetic enhancement. Theoretical discussions about the social and ethical implications of future genetic enhancement were often rejected outright as speculative thinking, completely dissociated from feasible or probable developments in science.

Hence when the German philosopher and sociologist Jürgen Habermas published his lectures on the ethical implications of genetic interventions such as pre-implantation genetic diagnosis (PGD) and genetic enhancement in his book The Future of Human Nature back in 2001 (German Edition), many researchers from the natural sciences responded to his viewpoints with silence or critique. A philosopher of biology, Lenny Moss (trained as a biochemist/biophysicist and molecular cell biologist) accused him of retreating from his earlier work, and setting "forth a thin neo-Kantian based ethics of abstention that swallows and regurgitates the media-hyped jargon of genetic programming holus-bolus" (Moss 2007).

A number of critics claimed that his theory involved a faulty conception of genetic essentialism and genetic determinism and

revealed a lack of insight into the realities of genetics and modern biomedicine. In other words, his viewpoints on genetic enhancement were not regarded as adequately informed by the actual and possible developments in science.

Many scientists simply regarded it as premature to talk about genetic enhancement altogether, because of the largely unexplored and immensely complex terrain of gene-gene interaction and the interaction between genes and environment. Furthermore, in the absence of existing or prospective safe "editing" techniques, the whole genetic enhancement debate seemed rather "fantastical" to many.

There is no doubt that the fear of being associated with "speculative thinking" or being positioned as a "conservative" or "liberal" thinker in a very polarized philosophical debate about genetic enhancement would have deterred many scientists from becoming involved in the discussion. They could undoubtedly recall incidents from the not-too-distant past, where bad publicity followed by public resistance had the effect of slowing down or halting scientific progress (through the implementation of robust regulatory schemes). Nobody could "afford" to repeat these kinds of mistakes again. Moreover, for many scientists, getting involved in humanistic research or public debates about the effects of emerging technologies (such as genetic enhancement) on our future practical and ethical life, was not part of the academic "reward scheme". In fact it would be considered by many as a bad career move to start publishing in interdisciplinary journals or the mainstream media. Only articles in high-ranking science journals counted in this extremely competitive field of research. Whatever the reason, it can be argued that a serious, frank and open-minded cross-disciplinary dialogue about the potential social and ethical implications of genetic enhancement was rarely supported by the scientific community as such.

Human genome editing - a "game changer"]
The development of Human Genome Editing is regarded by numerous scientists as a real game-changer - both as a technological advance and in terms of the prospects of germ-line genome editing and genetic enhancement. Human Genome Editing involves a number of methods for creating changes in DNA more accurately and flexibly than was previously possible. According to Martina Baumann, the editing technique CRISPR/CAS 9 (Clustered regulatory interspaced short palindromic repeats) "allows scientists to genetically 'edit' the genome sequences of higher organisms from mice to monkeys with unprecedented ease and speed, high precision and lower costs than former genome modifying tools like TALENs (Transcription activator-like effector nuclease) and ZFNs (Zinc-finger nucleases). DNA sequences may be inserted, removed or changed at virtually any position in the genome. In principle, several modifications can be performed simultaneously in one genome, which opens up the possibility of treating complex diseases or altering traits in humans that are influenced by more than one gene" (Baumann 2016, p. 139).

The hope is that these new technologies will provide insight into fundamental biological processes and help treat or prevent serious genetic illness from occurring now or in the future. As the recent report by the US National Academics of Sciences and Medicine on Human Genome Editing: Science, Ethics, and Governance points out, genome editing could be used for three broad purposes: for basic research, somatic interventions, and germ-line intervention. Whereas basic research might involve work on human cells and tissue, it doesn't directly involve human subjects (unless it has the incidental effect of revealing information about an identifiable human being). This kind of basic research mostly uses somatic cells, such as skin, lung, and heart cells, but can also use germ-line (i.e., reproductive) cells, including early-stage embryos, egg, sperm, and the cells that give rise to eggs and sperm. According to the report, the latter entails "ethical and regulatory considerations regarding how the cells are collected and the purposes for which they are used, even though the research involves no pregnancy and no transmission of changes to another generation" (National Academies 2007, p. 2).

Clinical research, on the other hand, involves interventions with human subjects and hence "proposed clinical applications must undergo a supervised research phase before becoming generally available to patients" (National Academics 2007, p. 2). In most countries this area is tightly regulated. However, clinical trials have already been carried out. On 24 November 2016 David Cyranoski from Nature reported that a Chinese group had become the first to inject a person with cells that contain genes edited using the revolutionary CRISPR-Cas 9 technique. Modified cells were delivered into a patient with aggressive lung cancer as part of a clinical trial. In March 2017, a group at Peking University in Beijing hopes to start three clinical trials using CRISPR against bladder, prostate and renal-cell cancer. However, according to Cyranoski those trials had not been approved or funded yet

(Cyranoski 2016).

If one uses clinical applications that target somatic cells it will only affects the patient and not their offspring. Genome editing on the germ-line would, on the other hand, affect not only the resulting child but potentially some of the child's descendants as well.

The authors of the US National Academics of Sciences and Medicine report emphasize that with the advent of such technologies as CRISPR/CAS 9 editing has become so efficient and precise, that new applications have opened up, which no longer can be discarded as 'theoretical'. One example is germ-line editing to prevent genetically inherited disease. Another example is applications of editing for enhancement. By enhancement is meant alterations that transcend restoration or protection of health.

The debate about germ-line interventions - some perspectives]
When the potential of the CRISPR/Cas9 system was first realized, ethical concerns about the possibility of creating permanent and inheritable changes in the genome of human gametes and embryos were raised. As Sheila Jasanoff reminds us, prominent biologists were among the first to call for restraint. In March 2015, a group including David Baltimore from the California Institute of Technology and Paul Berg from the Stanford University School of Medicine, proposed a world-wide moratorium on altering the genome to produce changes that could be passed on to future generations (Jasanoff 2015). David Baltimore and his group emphasized that given the rapid developments, it "would be wise" to begin a discussion about the responsible use of this technology, addressing the societal, environmental, and ethical implications, before any attempt at germ-line genome modification was made.

The Baltimore group pleaded for a discussion of value-judgements about the balance between actions in the present and consequences in the future, which would involve the research community, relevant industries, medical centers, regulatory bodies, and the public in a shared effort to further the responsible use and development of genome engineering.

Assuming that the safety and efficacy of the technology could be assured, one of the key points to consider was, under what circumstances one would be able to make responsible use of germ-line genome modification to treat or cure severe illness in humans. Baltimore et al. explicitly asked whether it would be appropriate to use the technology to change a disease-causing mutation to a sequence more typical among healthy people? How could we be sure to avoid unintended consequences of heritable germ-line modifications with our limited knowledge about human genetics, gene-environment interactions and the pathways of disease (including the interplay between one disease and other conditions or diseases in the same patient)?" (Baltimore 2015).

Others opposed germ-line genome modification on the grounds that permitting even unambiguously therapeutic interventions could lead us down a path towards non-therapeutic genetic enhancement (Lanphier 2015). They warned against a "slippery slope" towards unregulated uses of germ-line editing and the prospects of a liberal eugenics, where parents would be free to make reproductive choices regarding the future genetic make-up of their children.

Shortly after this call for a moratorium, two papers by Chinese scientists were published, which described the use of CRISPR-Cas9 in human embryos. Even though the intervention was approved by a Chinese ethical board and had a number of measures in place to meet potential ethical concerns, it created huge controversy.

In the online German Newspaper Süddeutsche.de, Kathrin Zinkant commented that a red line had been crossed (Zinkant 2016). Even though Zinkant made it clear that the researchers had been conducting basic research of perhaps dubious quality, she urged her readers to consider this a "wake-up" call. Because of the rapid development of the field, there was no time to sit back and wait for better results to emerge. Public debate was urgently needed - even in a country such as Germany, which didn't allow such research at all. For Zinkant this was a transnational matter. Humanity as such was at stake, since these germ-line interventions would have the potential to affect future generations.

As we recall, back in 2001 Habermas explicitly warned against allowing germ-line engineering, because of his fear of paternalistic, subjective and short-sighted (market-driven) interventions. In Habermas' view, irrevocable decisions over the genetic design of an unborn person would always be presumptions. A person who would potentially stand to benefit from such a decision should always

preserve the ability to say no. According to Habermas, we "overtax the finite constitution of the human spirit" by expecting that we can decide which sort of genetic inheritance will be "'the best' for the lives of our children" in the future (Habermas 2003). For Habermas it was therefore of utmost importance to uphold the principle of informed consent. Only in that way could one respect the autonomy of every single person, and protect future generations from paternalistic or well-intended but short-sighted interventions.

Some disability groups have raised concerns about the possible impact of these editing technologies on the public perception and acceptance of disabled people in the future. The question, of course, is whether parents with disabled children would feel under pressure to submit their children to editing "treatments" in the future, in order for them to live up to the new prevailing norms and standards for normal functioning in a "scientifically enlightened" society. Would parents feel compelled to "relieve" society of the economic burden of caring for the so-called "unfit" (if such care was provided by the state at all) by submitting them to available editing regimes? Would it be considered irresponsible and unethical to deny an ill or disabled child available "treatment", if such treatment was considered safe - even if this decision impacted future generations? Might disabled children start blaming their parents, and holding them responsible for missed care during the formative years of their development, if such editing opportunities were in fact publicly funded and considered a "reasonable" option?

For people at high risk of late-onset genetic diseases, there might come a time when they would feel obliged to make preventative decisions regarding their own health, in order to "live better and more independent lives in their own homes for longer", if such treatments were available. Children might start blaming their parents for irresponsible and egotistical behavior, if they didn't act on predictive genetic risk assessments, and take action to prevent their own late-onset disease. In societies with a shortage or lack of social benefits or caring facilities, this scenario might be particularly pertinent. Unfortunately, these worries cannot just be shrugged off as far-fetched. The push for prevention of chronic illness, for example, in our shrinking welfare state (with an increasing privatization of the social and public sector) is already there. Sociologists and medical philosophers are speaking about a growing individualization of the responsibility for our own health. It is therefore timely to consider carefully how these new technologies might interact with such changing sentiments and economic incentives to become an indirect "disciplinary tool".

For a number of years clinical geneticists (such as Angus Clarke) have warned that individual genetic risk profiling might gradually become required and used routinely by future employers and insurance companies in order to choose their members from among the fittest. The fear, of course, is that this would generate a genetic under-class with no access to jobs, loans or insurance. One can imagine a new kind of social control being introduced through very complex "gate-keeper" mechanisms or so-called obligatory "access points" to the practices of inclusion. It is not overly speculative to imagine that insurance companies or employers might combine big data using complex algorithms based on multiple personal data about labour, purchases, debts, credits, diet, exercise, lifestyle, sexual contacts and gene test results, to create a personal profile. Such a development would most likely generate novel forms of exclusion (Rose 2000).

The fear of exacerbating existing inequalities between rich and poor nations has been raised in discussions about both somatic and germ-line interventions, including genetic enhancement. What kinds of regulatory mechanisms should be in place, to ensure that treatments of severely ill people through somatic or germ-line interventions, or interventions for enhancement purposes, will not only be an option for the wealthy (If these kinds of treatments were considered legitimate and safe)? How could we prevent lax or non-existent regulation of germ-line interventions in certain countries from creating a "free haven" for the exploitation of poor, vulnerable citizens for risky clinical trials? How would it be possible to deter desperately ill persons from tightly regulated countries from seeking and undergoing risky clinical treatment in countries with no regulations at all? As we know, technology travels, and the medical tourism industry is already booming.

Other members of the science community and the public are of course filled with hope that terrible diseases such as cystic fibrosis or muscular dystrophy could become a thing of the past, if gene defects associated with these conditions could be corrected in the affected tissue (Parrington 2016, p. 1). The ethical principles of doing good and preventing harm run so deep in the practice of medicine, some physicians would regard it as cruel and inhumane if terrible genetic diseases could not be treated or removed from an individual suffering severe pain. (This of course assumes that such editing could be done without causing more harm than good to the individuals involved.) However, as we know, it is notoriously difficult to make utilitarian assessments about future gains and losses with regard to emerging technologies such as germ-line editing, which is why so many have opted for great restraint.

The US report on germ-line genome editing]

It has come as a surprise to some that the US report doesn't recommend a total ban on clinical trials using germ-line editing. The report states that if such interventions can be proved safe, and if numerous criteria are met to ensure that such gene editing is regulated and limited, it could potentially be used to treat rare, serious diseases. The authors are aware that some of the listed criteria are "necessarily vague". For example, they mention that clinical trials using heritable germ-line editing should be permitted only 1) in the absence of reasonable alternatives or 2) to prevent a serious disease or condition. They emphasize that what counts as 'serious disease or condition' and what defines "reasonable alternatives" will be interpreted quite differently in societies with diverse historical, cultural and social characteristics. They also suggest that physicians and patients will interpret them according to the specifics of individual cases. The report specifically advocates for a principle-based ethics, pointing to the well-known bioethical principles of beneficence, non-maleficence, autonomy and justice as a common morality framework for reflecting on the applications of genome editing. Such a framework allows scope for individual interpretation based on the particular values, beliefs and goals of a society or culture.

When it comes to the question of enhancement, the report recommends that there should be "reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition" (ibid.). In other words, the report does not support uses of germ-line intervention for enhancement purposes. But it does point to the difficulties of making a clear-cut distinction between normal function/disability and treatment/enhancement.

How one might balance and prioritize the general principles in various local contexts and circumstances of germ-line genome editing is not discussed in any detail in the report. In fact one could argue that the bioethical principles are so broadly construed that they might even allow for conflicting decisions. As the report makes clear, what counts as reasonable (as in "reasonable alternatives") and what the characteristics are of "serious" disease is very culture-specific and hence open to varied interpretations. By promoting a number of criteria respecting the plurality of world-views, the authors seem to accept that the uses of germ-line interventions might vary from country to country or even within countries.

Peter Mills, one of the authors of the Nuttfield Council's report on Genome Editing from 2016, having read the US report, argues that "What we have here is ethics in the laboratory rather than ethics in the field" (Mills 2017). He laments the fact that the bioethics literature is often "transfixed by aporetic debates over liminal questions (treatment/enhancement, normal function/disability), in an attempt to make them categorical for juridical (or quasi-juridical) processes" (Ibid.). What is left out of the equation are important questions about the impact of genome editing and germ-line intervention on "discourses, institutions and jurisdictions; how it might creep across distances both functional and geographical; what incumbent techniques and counterfactual possibilities it might displace; to what moral transformations it might inure; and what mitigations can be foreseen against its negative externalities" (Mills 2017).

A democratic dialogue about non-therapeutic uses of genome editing?]

The debate about genetic enhancement has, as mentioned in the beginning of this essay, a long philosophical trajectory. There is no doubt that many philosophers would ask, what is genuinely new about the recent developments in science? Many would deny that the basic bioethical questions and perspectives on genetic enhancement have changed in any substantial way. The US report seems to point in that direction. Others would alert us to the fact that important techno-scientific perspectives - such as those elaborated above - need to inform a thorough investigation and debate about the ethical and social implications of the new genome editing techniques.

The Nuffield council report from the UK and the US National Academies of Sciences and Medicine report on genome editing seem to signify that a cross-disciplinary ethical debate about gene editing applications such as somatic and germ-line enhancement is finally underway. In Germany, the Ethical Council and a number of private organizations such as The Schader Stiftung invites experts from various sciences and institutions to speak about the issue. They form discussion groups, promote dialogue with the public, define practical tools for ethical assessment and seek to bring a measure of objectivity to the debate on genome editing. The

Ethical Council is also actively seeking dialogue with the ethics committees of other countries.

Scientists are now writing extensively about the possible applications of genome editing in international journals, newsletters and through various media and broadcasts. They are also addressing the need for interdisciplinary and public debate about the social and ethical implications of this research. Within a very brief period of time, the debate has thus become part of mainstream news. There is no talk about ?genetic programming holus-bolus' anymore, although this kind of research might very well be hyped, as so many novel research agendas have been in the past.

Indeed, scientists from the natural sciences now seem to be setting the agenda for when and how the joint discussion about the ethical and social implications of genome editing should take place. The question is whether they should also be given priority in judging which questions and which aspects of this discussion around the ethical and social aspects of genetic enhancement are worth attending to? How can we make sure that the fears, hopes, beliefs, values and norms of the public are in fact taken into account when we discuss and make decisions about the future of genome editing? How are we going to ensure that important public viewpoints are not simply discarded, because they might be considered as putting a brake on research, or slowing down scientific progress in a highly competitive world?

It is crucial that a framework for a democratic dialogue about novel genome editing techniques is agreed upon and carried out in a timely fashion. The participation and engagement of the scientific community in this process is essential. "Slowing down" research may be needed to find out what lurks in the interstices, as the Belgian philosopher Isabelle Stengers would say. A multi-faceted, timely and comprehensive dialogue about the responsible use of these new technologies is something we owe to each other, and not least, to our descendants.

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