GERMLINE GENOME EDITING IN CHINA: A TOOL TO "IMPROVE THE POPULATION QUALITY"?

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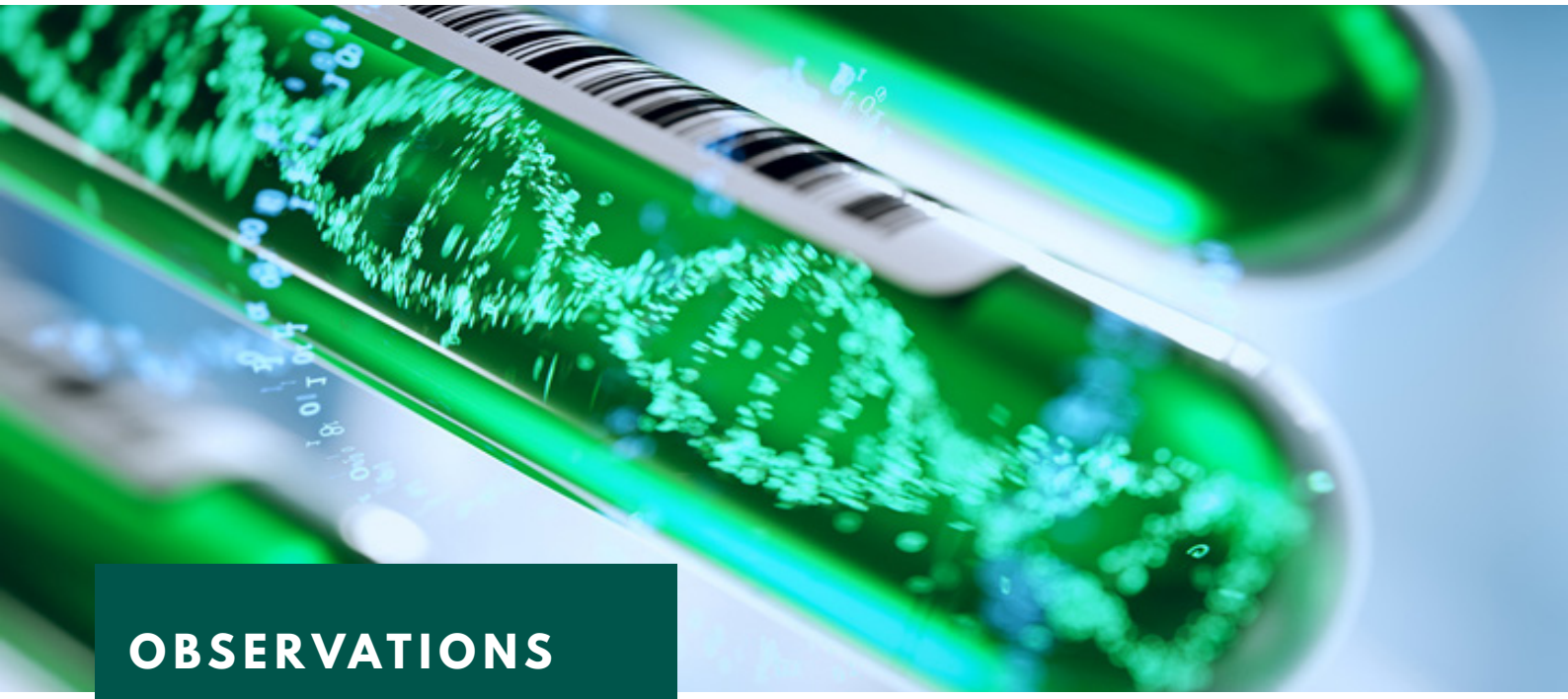

DNA molecule in test tube. iStock ID: 1042024564

OBSERVATIONS

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Is the People's Republic of China developing into the new global haven for frontier genetic research? In the last decade, China has made remarkable advancements in the field of biotechnologies and synthetic biology. Most notably, Chinese scientists have pioneered one of the most controversial applications for human beings, the so-called "germline genome editing" (GGE). This technology entails genomic changes in fertilized eggs at the earliest stages of development (zygotes) which could be permanently passed on to succeeding generations.

Such recent developments have in particular been possible due to CRISPR/Cas9 which was initially presented in 2012. In comparison to bioengineering tools previously available, CRISPR/Cas9 is often described as being much faster, cheaper, and more precise. In 2015, a team of Chinese scientists reported—for the first time ever—their experiment on human zygotes using CRISPR/Cas9, followed by a second experiment in 2016. Both experiments were conducted in non-viable zygotes which could not have been used to establish pregnancies, in line with international regulations on human embryonic stem cell research. The third GGE experiment in 2016 involved "normal" zygotes which had the *potential* to develop into human beings. Since then, similar experiments on viable zygotes have also been carried out in the United States and United Kingdom.

However, as a pioneer of GGE, China has been heavily criticized—domestically as well as internationally—for the gradual crossing of ethical lines in its research. (Further mention of GGE experiments now refers only to CRISPR-technology ones). Some observers have argued that Chinese GGE experiments are the result of an ethical divide between China and the West. Others have strongly contested such claims, pointing out that Chinese regulations on GGE are not "lacking" but are in fact in line with international standards. Less discussed in the media, as well as in academic discourse, is the promotion of GGE research by the Chinese government: at least until late 2018, all *legal* GGE experiments in China were funded by major national institutions, including the Ministry of Science and Technology and National Natural Science Foundation of China. Therefore, these experiments on viable as well as non-viable zygotes were not just carried out in a favorable research environment with less restrictive regulations but instead directly encouraged by government agencies. This paper will refer only to *legal* experiments, thereby excluding the experiments carried out by He Jiankui. In 2018, He caused an international outcry (the "CRISPR-Baby Scandal") when he modified the genes of three newborns—the first ever genetically modified humans—as these experiments were neither legal in China nor by international regulations. This short paper seeks to explore the blurred lines between what is politically and societally envisioned and scientifically and legally permissible in the frontier field of germline genome editing in China. It summarizes a close reading of policy documents and reports and makes some suggestions for further social science research on the matter.

Global Discussions: What is Germline Genome Editing used for?

The ethics around the application of GGE are relatively new. In 2015, a number of international ethics bodies opposed its use in cases that had not resolved "the relevant safety and efficacy issues." Since its development, the technology is feared to one day be used to "improve" more complex genetically related traits such as intelligence, physical strength, or stamina. Nonetheless, in 2018 the National Academy of Sciences, Engineering and Medicine (NASEM) and the British Nuffield Council concluded that GGE should be limited to preventive measures, namely to "*correct* genetic diseases," which include

cystic fibrosis, hemophilia, cancer, and thalassemia.

In line with this view, Kang Xiangjin et al., the authors of the second ever GGE experiment underscore that "arguments for embryonic gene modification supports [sic] its clinical use despite the suggested side effects due to the overall benefit that *preventing the transmission of heritable genetic diseases* brings" (emphasis added). Genetic diseases are closely related to hereditary birth defects such as β-thalassemia. Against this backdrop, it is less surprising that the majority of GGE experiments in China aim to "correct" β-thalassemia. In the last two decades, studies have identified thalassemia as a major public health problem in southern China, affecting up to 12 million people in Guangxi and 19 million in Guangdong province.

Using GGE one day to "correct genetic diseases" still raises further questions as to why such applications are deemed plausible in the first place, not only in China but also in Europe or the United States. Why do scientists around the world aim to prevent genetic disease transmission? Why was the potential of CRISPR/Cas9 for GGE recognized so rapidly? And is the Chinese case special in this regard?

Chinese Discourses on "Improving the Newborn Population"

Public and scientific discourse in China around human genetic disease is not a recent phenomenon but can be traced back to the late 1970s. As the foundation for Chinese modernization efforts, population governance set the national goal of reducing the population size while simultaneously "raising its quality." Guided by neo-Malthusian thought and informed by the forecast in the "The Limits to Growth" (1972), the Chinese government enacted the one-child policy to address the "problem" of Chinese "overpopulation." Likewise, officials declared to increase "population quality" (人口素质) by "improving" the three areas that doctrinally define human "quality": health (or physiology), education, and ideology. Beginning in the early 1980s, the state promoted the notion of "superior birth and child rearing" (优生优育) to encourage the creation of a healthier cohort. To do so, officials introduced a series of eugenic policies to reduce the number of birth defects. These policies eventually culminated in a national law called "Eugenics and Health Protection Law" of 1993 which was, after massive international critique, relabeled as "Law on Maternal and Infant Health Care" (LMIHC) in 1994. However, the character and aim of this law remained clear in its eugenic intents.

As Article 1 of the LMIHC precisely states, "this Law is formulated in accordance with the Constitution with a view to ensuring the health of mothers and infants and improving the quality of the newborn population." For this purpose, the LMIHC introduced mandatory premarital health check-ups to ensure that newborn children would not be affected by "serious genetic disease." In practice, this implied that couples were obliged to undergo genetic counseling prior to marriage to prove that they were not carriers of genetic diseases. Unless they have been issued such a positive health certificate, couples would not be given permission to marry unless

they would approve voluntary sterilization (Art. 10) and if applicable, pregnant women carrying genetic disease would voluntarily abort their fetus according to informed consent (Art. 18, 19). Through these mechanisms, political decision-makers aimed to ensure that only certain, "healthy" offspring would be born.

Mandatory health check-ups were suspended in 2003. Nonetheless, until today the use of assisted reproductive technologies (ART) in China must comply with the stipulations of the LMIHC. This means that in-vitro fertilization and sperm banking must ensure that no genetic diseases are transmitted using these technologies. This also applies broadly to research activities, which may someday serve for practical application, such as human embryonic stem cell research and GGE which are both classified as ART.

International Measures toward Birth Defect Prevention

Efforts to prevent hereditary birth defects are not unique to China; similar government initiatives have also been implemented elsewhere, notably in the Middle East including the Republic of Cyprus (in 1983), Iran (in 1997), Saudi Arabia (in 2004), and the United Arab Emirates (in 2011).

Certain birth defects such as α-thalassemia are strongly linked to under-five mortality, and are therefore part of the Millennium Development Goal 4 of the United Nations (UN) to lower the global under-five mortality rate. In 2010, the World Health Assembly (WHA) accordingly endorsed a resolution on birth defects to standardize international surveillance and to provide preventive care for families and persons concerned. The resolution also recommended all stakeholders to establish appropriate Community Genetic Services offering genetic counseling for couples. These international developments are in some ways similar to the stipulations of China's LMIHC, albeit less centered on the population and more on the interests of each individual being. In the international discussion as well as in China, birth defects such as thalassemia, which usually develop into chronic diseases, are viewed as a heavy burden on the public health system. And yet as far as we know, this burden has not been translated into public funding of GGE experiments anywhere in the world except in China. Major policy guidelines show that experiments to prevent genetic disease transmission have been envisioned by Chinese policy-makers years before they have been made public. This in particular includes China's Five-Year-Plans and the "Roadmap to 2050" (from now "Roadmap"), a highly ambitious 18-volume white paper series released by the Chinese Academy of Sciences (CAS) in 2010.

Evidence of GGE in China's Future Aspirations to "Improve the Population Quality"

GGE may play a significant future role in population "improvement" as highlighted in three areas in the Roadmap. First, in reference to the UN Millennial Development Goals, the Roadmap stresses the "great importance to the research on population control and reproductive health." In the field of public health, "safe contraception and birth defects prevention" are listed as

the "first of five priority subjects" for China's mid and long-term research and development. Second, the Roadmap proposes to employ ART to eliminate "embryos with genetic defects [...] before transfer" to avoid the "[...] birth of infants with genetic diseases." It also suggests to "[...] actively carry out *prenatal interventional therapy* for birth defects of known causes, including surgery therapy and *gene therapy*" (emphasis added). Lastly the Roadmap strongly encourages researchers as well as policy-makers to focus on synthetic biology. Shortly after its publication, China emerged as a global leader in synthetic biology, including biomedical engineering, as well as the first place using one of its most versatile applications, CRISPR/Cas9, in human zygotes.

A further drive that may embrace GGE technology to "improve the population quality" is China's medium-term goal: to achieve "Socialist Modernization" by 2035. In this context, China's 14th Five-Year-Plan (2021–2025) aims to "formulate a long-term development strategy on population," to "raise the level of services for better natal and prenatal care" and to "increase the quality of the population." In 2014, Tian Xueyuan, the former director of the Chinese Academy of Social Sciences, noted that the quality of newborns does not only affect distinct families, but rather the nation as a whole. Both the "birth of excellent individuals" and "the low birth rate" (i.e., population control including the one-child policy) are considered as an "integral part of the solution to China's population problem." In late 2018, Tian further emphasized this view stating that due to China's demographic transition, modernization is increasingly relying on enhancing productivity and therefore on "improving population quality," which also includes the "physical population quality" i.e., health.

Conclusion: GGE to Prevent Birth Defects Globally?

The international discourse around GGE explores CRISPR/Cas9 technology as a permanent solution to prevent hereditary birth defects at the earliest stage of human development. While this goal appears to be an international consensus, we still know little about the extent to which the political motivations behind it are similar or different in the respective countries that are conducting research on GGE. In China, efforts to advance GGE research are directly linked to the political desire of population management, nation building, modernization, and therefore the legitimacy of the political system. The legislation regulating ART in China originates from a eugenic discourse that seems less pronounced in Chinese public today but nonetheless, in its juridified form (the LMIHC), mandates everyday medical practices e.g., sperm banking, maternal education, genetic counseling, and IVF in order to politically control reproduction, and ultimately to create desired national citizens. The concepts that in turn make these methods tangible and measurable, especially that of "population quality," are what make the Chinese discourse unique. So why, if the technology was internationally condemned as a transgression of ethical norms, was it pioneered in China? I argue that it was because reproduction is

viewed instrumentally in China. What is more, political decision-makers as well as scientists apparently view a lack of control over these processes at the population level as a threat to modernization efforts.

International discourse, however, appears to be irresolute on where to draw the boundaries between eugenics and ethically acceptable application. What leads us to believe that international birth defect prevention measures advocated by organizations such as the UN and WHO are not eugenic? What role does eugenics play in international discussions on birth defects prevention? And how did we get to the point historically where the UN and WHO's measures to prevent birth defects are recognized as a public health necessity that is deemed different from the perils of 19th and 20th century eugenics?

These questions seem to be more significant as current developments in GGE research suggest that as a result of the "CRISPR-Baby Scandal," international bodies such as the WHO aim to introduce guidelines and regulations instead of a global ban on GGE. As this type of genetic research bears consequences for humanity on a previously unimaginable scale, a social science observation of the structures and norms in which Chinese GGE experiments are taking place seems urgently necessary and relevant to hard-science approaches. On the one hand, this includes the ethics of GGE research especially in relation to eugenics, but also the investigation of political concepts such as "population quality" as well as the legal framework guiding GGE research (such as the LMIHC). To gain a complete understanding of the subject, our analyses must be contextualized in the field of international sciences, asking to what extent GGE experiments are in line with the recommendations of international actors such as the WHO. Investigating these issues could bring new answers to the question of which ways the Chinese research environments differ (or are even unique) in comparison to other pioneers in research and therefore why they might favor kinds of research that some have criticized as "unethical." Finally, this does not only pertain to GGE experiments, but in a broader sense also entails a wider array of ethically questionable experiments such as the gene-editing and cloning of monkeys in which China emerged as a global leader.

Further Readings

Greenhalgh, Susan. 2010. *Cultivating Global Citizens: Population in the Rise of China*. Cambridge, MA: Harvard University Press. Cambridge.

Sleeboom-Faulkner, Margaret. 2010. "Eugenic Birth and Fetal Education: The Friction Between Lineage Enhancement and Premarital Testing Among Rural Households in Mainland China." *The China Journal* (64), 121–41.

Wahlberg, Ayo. 2018. *Good Quality: The Routinization of Sperm Banking in China*. Oakland, CA: University of California Press.

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