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## 〈論文〉

## Debate Before Decree : Path to Overcome Japan's Scientific Stalemate on Heritable Human Genome Editing

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**Abstract**

Following the 2018 revelation from China that the first baby, or in fact twins, had been born after heritable human genome editing (HHGE), the narrative emerged in scientific and legal circles globally that an absolute and universal ban needs to be introduced with regard to the procedure. Indeed, as if in a reflect reaction to this Chinese affair, observers were seen to condemn the procedure even in principle. As the dust settled, however, from Jiankui He's shocking announcement in Hong Kong in November of that year, a more cautionary and measured approach began to emerge. Currently, with the first global recommendations on HHGE having been adopted by the World Health Organization, a consensus seems to be in the formation towards acceptance in principle, or in other words if the safety, efficacy and ethical requirements are met. Concurrently with this, the number of publications reporting experimental HHGE results has been steadily increasing. Against this backdrop, it is conspicuous that in Japan—a bioscience powerhouse, and, notably, the birthplace of the idea that a human's entire genome could be sequenced—HHGE science/research is at nil. The present article zooms in on this stasis. Invoking the cases of local human embryonic stem cell research and cadaveric organ donation, the article argues that for Japanese HHGE science to be activated and the country to fulfil its potential in this area, a broad-based bioethicists-led debate needs to be initiated.

**Keywords:** heritable human genome editing, bioethics, reproduction, public debate, science

**1. Introduction**

In May 2015, just 17 months after China claimed the monkey in the global race to genome-edit mammals (Niu *et al.* 2014), another team based there became the first to report experimental genome-editing work in humans (Liang *et al.* 2015). The embryos used in this experiment had been non-viable, or in other words, biologically speaking they did not have the capacity to develop into a fetus. However, since the world was far from having debated, let alone reached consensus, on the issue of the moral acceptability of bringing to life generically edited people who could then pass these edits onto future generations, it had proven difficult for the authors to publish it. Indeed, prior to the manuscript finally finding its way to print with the obscure *Protein and Cell*—a journal whose editorial board comprises predominantly China-based scientists, it had suffered rejection by both Nature and Science. With the results of the experiment presented demonstrating an astonishing lack

of fidelity<sup>1)</sup>, the reviewers of the first two journals had reportedly made the judgement that this work was premature even on scientific grounds. The dean of Harvard Medical School, George Q. Daley, who has revealed that he was involved in the review process of the first papers on HHGE has famously ascribed to Junjiu Huang—the lead researcher of the said experiment—potentially “deranged motivations” (Regadalo 2018, see also Daley 2018 & 2020).

Two years after the heritable human genome editing (HHGE) Rubicon was crossed with that first paper from China, another manuscript of this kind emerged on the scene from within the Oregon Health and Science University in Portland in the United States (US). Although this second paper made it through the review process of *Nature* and was published there, the claims it made were seen as, and remained, controversial. To explain, in stark contrast to the failure-ridden experiment of Liang *et al.*, the authors of this paper reported a high success rate at correcting a disease-causing mutation in a gene. In particular, the team stated that, in their experiment involving 58 embryos, the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 tool was able to replace a mutant version of the gene giving rise to the fatal heart condition known as ‘hypertrophic cardiomyopathy’ with a healthy one ‘with exceptionally high targeting efficiency’ (Ma *et al.* 2017: 416). Asserting that they have corrected the pathogenic gene mutation whilst avoiding a problem known as mosaicism—a problem whereby only some cells of an embryo have the intended gene changes, Ma *et al.* advocated the use of HHGE as a complementary therapeutic measure to Pre-implantation Genetic Diagnosis (PGD), which involves the selection of embryos for transfer into the uterus that do not carry the prospective parent’s genetic mutation. However, a group of scientists from Columbia University, the Memorial Sloan Kettering Cancer Center in New York City, and Harvard Medical School, questioned whether the mutation was fixed, offering an alternative explanation for the outcome observed by Ma *et al.* (Egli *et al.* 2017).

With the error-ridden Liang *et al.* experiment and the contested Ma *et al.* results being the only studies on HHGE, the announcement by the Chinese biophysicist Jiankui He at the time of the Second International Summit on Human Genome Editing in 2018 in Hong Kong that he had gone on to apply the CRISPR/Cas9 tool clinically came as a shock. Putting aside the many other levels at which He’s actions could be condemned (for a thorough examination of these, see Greely 2019), there had been no demonstrable and unequivocal evidence that this technique is safe and effective and thereby ready to apply in human reproduction. So overwhelming was the outcry that resulted from the He affair that scientists as well as members of the public were seen to call for an immediate and absolute moratorium on HHGE (e.g., Lander *et al.* 2019; Wolinetz & Collins 2019; Getz & Dellaire 2019; Baylis 2019; see also Wellcome Sanger Institute 2019; RS 2019; SCIMEX 2019).

As the dust was settling from He’s announcement, the voice was raised from within the US and European academic community that the missteps committed by one rogue scientist should not divert from the goal of acquiring technical competency in HHGE. Since there was an unmet medical need, the argument went, a moral imperative existed to act upon HHGE science. Although the number of scholars who could be cited expressing

this idea gradually increased (e.g., Harris 2018a & 2018b, Steffann *et al.* 2018, Gyngell *et al.* 2019, Brokowski & Adli 2019, Hammerstein *et al.* 2019, Lovell-Badge 2019, Rasnich 2020, Boggio *et al.* 2020, and Greely 2021), one particularly strong exposition of it is found in a 2019 essay entitled befittingly *After the Storm—A Responsible Path for Genome Editing* (Daley *et al.* 2019). Penned by the influential trio of George Q. Daley (of Harvard's Medical School and the Boston Children's Hospital), Robin Lovell-Badge (of the United Kingdom (UK)'s flagship for discovery research in biomedicine—the Francis Crick Institute), and Julie Steffann (of Paris University and the Necker-Enfants Malades Hospital), the essay made a case for the wide range of patients who stand to benefit from this procedure: from couples where both partners carry homozygous recessive disease alleles, to partnerships where one party is homozygous for an autosomal dominant disease allele such as that for Huntington's disease, for example, to all those couples, a significant majority, who are affected by an autosomal recessive or dominant genetic disease and whom PGD (referred to above) has failed (Daley *et al.* 2019, 899)<sup>2)</sup>.

Today, whilst caution is still very much the maxim when it comes to HHGE, a moratorium on the associated science is seen as too extreme a measure. Indeed, the debate about the ethical permissibility of HHGE has gained momentum and evolved, with a trend being discernible towards acceptance in principle, or in other words, so long as safety, efficacy and ethical standards are observed. That this is the case is evidenced most clearly by the recent adoption (in July 2021) by the World Health Organization of the first global recommendations on HHGE—a step reportedly taken with a view 'to help establish [this procedure] as a tool for public health'<sup>3)</sup>. Furthermore, this development comes on the heels of three high-profile national bioethics panels—namely, the US National Academies of Sciences, Engineering and Medicine (NAS), the UK's Nuffield Council on Bioethics (NCB), and the German Ethics Council (Deutscher Ethikrat, GEC)—taking a permissive tone in their reports on the issue. To illustrate, NAS, for example, stated that:

Heritable genome-editing trials must be approached with caution, but caution does not mean they must be prohibited. If the technical challenges were overcome and potential benefits were reasonable in light of the risks, clinical trials could be initiated if limited to the most compelling circumstances, if subject to a comprehensive oversight framework that would protect the research subjects and their descendants, and if sufficient safeguards were in place to protect against inappropriate expansion to uses that are less compelling or less well understood. (NAS 2017, 134)

Similarly, NCB wrote that it is possible, indeed, to 'envisage circumstances in which heritable genome editing interventions *should* be permitted' (emphasis added) (NCB 2018, 154). As for the GEC, its members too agreed unanimously that the human germline is not categorically inviolable and considered cases where its editing should be allowed or even be considered imperative. Finally, it is precisely because the overall tone of

the discussions on HHGE in the relevant scientific and bioethics circles has shifted towards permissibility that observers of conservative, anti-HHGE, persuasion feel displeased. To cite one such observer,

... in the mainstream US and UK bioethical debate that has the greatest influence over what actually happens with science policy, the somatic/germline distinction has lost its power. For example, despite the uproar over He Jianqui's facilitation of the gestation and birth of germline modified children in China, the leadership of the Second International Summit on HGE implicitly agreed with him that it is in principle acceptable to engage in germline intervention, as long as it is safe and human subjects protections are followed. Indeed, a commission of the National Academy of Medicine, National Academy of Science, and the Royal Society recently developed a "translational pathway" for the "responsible use" of germline applications [in their 2020 *Heritable Human Genome Editing: Consensus Study Report* (NAS & RS 2020)]. (Evans 2021: 1)

Within the context of this emerging consensus regarding HHGE, it is most conspicuous that in Japan—an established leader in biomedical science and, notably, the country from where the pioneering idea sprang to sequence a human's entire genome—there is no experimental work in this area. Japanese stem cell scientists appear to be avoiding HHGE like the plague, and there are no reports of such work being conducted, or there being plans in that direction, in any of the universities or research facilities here.

This stasis of HHGE science in Japan could be said to be noteworthy on at least two accounts. Firstly, that Japan should shy from this science is puzzling given the country's record as the birthplace of the idea of deoxyribonucleic acid (DNA)-sequencing—an idea that became an important precursor to the so-called Human Genome Project, which was a US-led international collaborative endeavor aimed at completing the automated sequencing of a person's whole genome by the year 2000. As has already been well-documented by other scholars (e.g., Cook-Deegan 1994, Kishi 2004, Ito 2005, and Sasaki 2019), it was a Japanese scientist—University of Tokyo's Akiyoshi Wada—who proposed, as early as 1979, the creation of a machine that can rapidly sequence DNA. Even in modern times, or perhaps more now than before, Japanese bioscience occupies a top position internationally, with one recent achievement worth mentioning being the groundbreaking and Nobel Prize-winning discovery of the recipe through which adult cells can be reprogrammed (cf., Shinya Yamanaka's identification of Sox2, Oct4, Klf4 and c-Myc as the four transcription factors through which cell-reprogramming can be achieved) (Takahashi *et al.* 2007). If Japan is such an established biomedical pioneer and a scientific research powerhouse, even when it comes to the specific subject of genomes, why is it withholding from HHGE? Secondly, it is also worth pointing out that the lack of an attempt to develop HHGE as a reproductive therapy does not sit squarely with Japan's status as an *in vitro* fertilization (IVF) giant. As a glance at the data provided by the International Committee for Monitoring Assisted Reproductive Technologies

(ART) would establish, appetite for reproductive therapy in Japan is hardly lacking. Indeed, the volume of assisted reproductive activity here is second only to that of China, and those two countries register a volume of ART procedures that is an order of magnitude higher than the third largest IVF utilizer—the US (Dyer *et al.* 2016; Hu *et al.* 2020; China Registry 2020, see also Croydon 2021a & 2021b). Why would Japan resist HHGE when it is so active in ART in medically assisted reproduction in general?

With a view to gauging whether Japan is likely to play a role in the budding international endeavour of developing HHGE as a therapeutic tool in reproduction, this article zooms in on the stasis that is currently gripping the associated domestic science. To foreshadow the argument developed in the following sections, contrary to what has been said in the existing literature that the problem lies in the indolence of the politicians to promulgate a law that trumps all the outdated and often contradictory ministerial rules on HHGE experimentation, it appears likely that it is the discourse propagated by the scientists themselves about the Japanese public's being morally indifferent to the human embryo—a discourse that has persisted since the days when human embryonic stem cells (hES cells) were first isolated (in 1998)—that stands in the way of this science. By using this discourse, the article argues, the scientists are effectively shutting down public debate on the issue, thereby also stifling the science. Prior to demanding the promulgation of a law on HHGE (which would also be eventually needed as a way of delineating with clarity the boundaries to be observed), the proponents of Japanese HHGE science, the article contends, would do better to heed the insight of previous research in Japanese biomedical policymaking and focus first on stimulating a broad-based public discussion on the issue of the ethical permissibility of using HHGE in reproductive therapy.

In what follows, the article first reviews key texts from the 2000s literature on Japan's human embryonic stem cell research (hESCR). It then moves on to highlight the parallels between that literature and the current discussions on HHGE, particularly in terms of the argument that the local traditions, religious canons, and culture condition the people to regard the embryo as uninteresting and of no import. Finally, before concluding that it is a public debate that is likely to trigger the enactment of a legal decree, which could, in turn, end the existing moratorium on HHGE science here, the controlled comparison is offered between the cases of hESCR and HHGE, on the one hand, and the case of cadaveric organ donation, on the other hand.

## 2. The Moral Status of the Human Embryo in Japan: Past Literature

The possibility of editing the genome of an embryo so that the human who would develop would be unafflicted by a disease with which their parent(s) live is not the first historical juncture at which the moral status of the human embryo in Japan—i.e., whether it is considered morally inviolable or not there—has been debated. Indeed, this question became the focus of attention in several academic articles in the 2000s. Specifically, this was the era when the so-called hESCR—the research in which the embryo is used as a means

to develop cures for severely disabled people—was in its infancy worldwide, with many Christian groups in the US and across Europe launching campaigns to block it on moral grounds—the grounds that one life that has been created by God should not be sacrificed to save another. With regards to Japan, perhaps the most in-depth consideration of the local attitudes towards the human embryo during that era is that given by the medical anthropologist Margaret Sleeboom-Faulkner of Sussex University in the UK (Sleeboom-Faulkner 2008 & 2010). Guided by the question of what might be stalling hESCR in Japan, Sleeboom-Faulkner had conducted a wide range of interviews there (with scientists and other academics, doctors, housewives, etc.). She concluded that the misconception propagated by the scientists, bioethicists and their political allies, mainly out of a desire to portray their country as culturally superior to those in the West, that the human embryo is morally irrelevant to the average Japanese on the street, was suppressing the science. The moral scruples that people *do* have about the destruction of the embryo, she suggested, were being left unaddressed, and the donations of the tissue on which the research depends were, in turn, not forthcoming.

To provide more detail about the views that Sleeboom-Faulkner encountered, the members of the country's elite whom she interviewed told her that the local cultural traditions and religious canons leave the embryo in a moral vacuum. Unlike the Christian dogma that is held widely in the West that the embryo is conceived with the blessing of God, the predominant view about it amongst the Japanese public is non-religious and that it is simply the 'germ of life' (*seimei no hōga*), with the implication being that it is permissible to use embryos that would otherwise not develop into a human being (i.e., ones left over after IVF treatment, or supernumerary embryos) for positive ends, such as the development of new therapies to cure disease; and, even if the section of society that is Buddhist is considered, that religion's primary subject of concern is death, not birth (Sleeboom-Faulkner 2008: 88). There are no cultural canons prohibiting abortion in Japan, it seems to have been put forth to her; and, if it was not true that the Japanese people thought nothing about the embryo, one bioethicist apparently had informed her, the country would not have had the massive abortion rate that it has—a rate which has, moreover, been sustained for a long time. Furthermore, she documented how another academic—a high-profile professor occupying an important position in the Medical Ethics Committee at the Faculty of Medicine at the University of Tokyo, outrightly denied the relevance of any Japanese concept of 'respecting the embryo', stating to her bluntly that 'Japanese culture has never regarded abortion as a problem before, and has no reason to start worrying about it now' (Sleeboom-Faulkner 2008: 89). Contrasting their country with the US, where President George W. Bush had imposed a ban on federal funding for hESCR based on his Christian beliefs, the Japanese scientists, in particular, had reportedly expressed incredulity and dismay, claiming that such a development is impossible to imagine of Japan; because the local traditions and religious teachings do not concern themselves with the embryo, their argument had gone, the latter is left available for use in science. In their attempt to make her see that Japanese society is generally indifferent to the human embryo, these scientists also pointed out that it was only three or four minority groups which have any view whatsoever about it here,

with these being: the organizations of feminists and disabled people called the Anti-Eugenic Network (*Yūsei shisō wo tou nettowāku*), the Japanese Association for Spinal Cord Injuries (*Nihon sekizui shōgai igakkai*), and some radical Buddhist sects (e.g., the Buddhist *Ōmoto* and *Seichō no Ie*); everyone else in Japan ostensibly do not spend time concerning themselves with the embryo.

That the scientists of the time strongly felt that there is, indeed, no cultural or social reason for Japan's hESCR stagnation is confirmed by a separate piece of literature published in 2007 by a figure known as the 'father' of Japanese hES cells—Professor Emeritus of Kyoto University, Norio Nakatsuji—in the prominent international science journal *Nature*. Titling his piece 'Irrational Japanese regulations hinder human embryonic stem cell research', Nakatsuji bemoaned the unreasonably strict regulatory regime for hESCR created by the Ministry of Health, Labor and Welfare (MHLW) and the Ministry of Culture, Sports, Science, and Technology (MEXT). To cite Nakatsuji himself,

[when hES cells were isolated for the first time in 1998], many countries convened public discussions to shape policies surrounding hES cell research. With a pro-science government and *without major objections from religious or other groups* (emphasis added), Japan was recognized as one of the world's permissive countries. In principle, Japanese policies and guidelines are moderate and similar to many other countries ... [Yet, there is too much red tape]. ... hES cells cannot be studied in the same room or with the same equipment as animal cells. ... The government ethics committee warps IRB discussions. ... Certification requirements hinder training and cross-training in hES cells. ... We desperately need more rational rules that do not inhibit scientific progress. (Nakatsuji 2007)

To reiterate, for him, it was inexplicable why there are so many cumbersome and unnecessary procedures as well as unreasonable restrictions in hESCR when the public has no objections to this enterprise.

In contrast to the scientists' such claim, however, Sleeboom-Faulkner found through her investigation plenty of evidence suggesting that there are misgivings about the destruction of the human embryo on the part of members of the Japanese populace. Apart from the statements to this effect that she received from the housewives she interviewed, she found that it was extremely difficult for stem cell scientists to procure the vital material necessary for advancing hESCR—embryos. The scientists told her—curiously enough, in the same breath as that in which they rejected the importance of the moral status of the embryo here—that it is very rare for couples in Japan who have undergone IVF to donate their leftover embryos to science. Indeed, these interview subjects were eager to share with her how much they struggled when trying to secure the material they needed; it is so rare for Japanese couples, they seem to have lamented, to donate their embryos to science. So, clearly, if there are exhortations involved in the project to secure embryo donations for research, it cannot also be true that there exists no moral concern within the public here about the human embryo—it is a case



of either/or. Furthermore, for her, the evidence she gathered from her interviews suggested that the moral misgivings about tampering with the human embryo were there but that the scientists and their allies in the political arena were discarding them and thereby killing the prospect of a livening up that science.

### 3. The Remarkable Persistence of the ‘Japanese Uniqueness’ Argument

Today, more than a decade after the debunking of the idea that the Japanese have no moral scruples about the manipulation of the human embryo for research purposes, the same argument is being made again. This time too, the context is of a science—the HHGE one—not progressing. Japan is portrayed afresh as a unique, special case when it comes to thinking about the embryo—its culture, traditions and religious system supposedly conditioning its populace to be tolerant and supportive of the science. The embryo exists in an ethical void here, it is suggested, with the note also accompanying this claim that (very much in the style of Nakatsuji’s *Nature* article), had only an adequate regulatory framework been put in place for the scientists, as in ministerial rules that are rational, the HHGE endeavour would have undoubtedly advanced.

To cut to the chase, in a chapter in a 2020 volume *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies*, which, as the title suggests, advocates, in the context of the above-described global trend towards permissiveness, for the invigoration of HHGE science worldwide, Hokkaido University bioethicist Tetsuya Ishii, who has served on, amongst other prominent bioethics committees, the Committee on Genome Editing Technology in Medical Sciences and Clinical Applications within the Science Council of Japan (SCJ)<sup>4)</sup> (see SCJ 2017 & 2020), echoes the same arguments about Japanese traditions and human embryos that Sleeboom-Faulkner’s interviewees had expressed. Specifically, seeking to explain why HHGE does not happen in Japan, whether in terms of research or clinically, despite it being de facto legal in both these forms (‘legal’ as in no law having been put in place concerning it by the politicians), Ishii writes:

...religious beliefs are part of the discussion about human reproduction and family-building too. Some religious groups largely accept reproductive medicine, while others condemn some or all types of reproductive medicine. Often, religious beliefs shape the discussion on the acceptable use of reproductive medicine, but not so much in Japan since there is no state religion. Article 20 of the Constitution of Japan stipulates: ‘Freedom of religion is guaranteed to all. No religious organization shall receive any privileges from the State, nor exercise any political authority.’ Moreover, a [sic.] majority of Japanese are not affiliated with religion. The Pew Research Center Religion and Public Life Project 2010 showed that 57% of Japanese respondents answered that they are unaffiliated with religion, whereas 36.2% of them answered that they are Buddhists. Nearly all forms of Buddhism currently support reproductive medicine.

(Ishii 2020: 466)

To paraphrase his point, the social environment in Japan, unlike that of many other countries, is conducive to HHGE research, because the majority of Japanese people are not religious, and, as for the most significant minority of religious people, they are Buddhists, and that religion stands in support of reproductive medicine. So, *ceteris paribus*, HHGE science would be as likely to thrive in Japan as anywhere.

To provide further evidence for his theory that there is a unique Japanese, or perhaps more broadly Asian, approach to research such as HHGE, Ishii then also cites the Confucianist and Taoist traditions that are part of the cultural heritage in Japan. In particular, he explains as follows:

However, if religion is not a major factor shaping the discussion on these matters in Japan, ethics and moral [sic.] are. 'Morals' is a vague concept in Japanese, which is one of the reasons why there are no legal regulations on reproductive medicine in Japan. The English words 'morals' and 'morality', which derive from Latin 'mores', meaning 'custom', 'habits', translates to the Japanese word [virtue] (*doutoku*). However, *doutoku* also has philosophical roots in ancient Chinese Confucianism and Taoism. Those concepts are similar but not the same. Ancient Chinese Confucianism and Taoism put great value on 'ideology' and respect for authority, whereas European 'morals' value traits like freedom, equality and philanthropy. While in the West 'ethical concerns' are the soul of many biomedical regulations, in Japan it is a concern with safety and the impact that activities might have on society that is paramount. (*Ibid.*: 467)

To make more explicit the message contained in these words, the concern preoccupying people's minds in Japan when it comes to biomedicine is that of safety and the impact on society, not of ethics. This concern for safety and societal impact stems from the Japanese people's following a different system of moral principles to that of their counterparts in the West—i.e., the Confucianist and Taoist systems. That there is no concern with ethics in Japan when it comes to biomedicine, Ishii's suggestion seems to go, is attested by the fact that legal statutes ordaining for reproductive medicine do not exist at all in Japan, whether for HHGE or otherwise; all there is here in terms of regulating reproductive medicine is, as detailed in depth in other sections of his piece, safety- and technical-issue-focused bureaucratic-level regulations.

Finally, to explain what according to Ishii accounts for the stasis of this science here, he argues that bureaucratic regulations are confusing for the concerned researchers, making it unclear if they are allowed to engage in it. He writes in particular how '[w]hen it comes to research involving human germline genome modification, the Japanese regulatory framework [as created by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labour and Welfare (MHLW)], is characterized by gaps and inconsistencies' (*Ibid.*: 442), with the definitions used in it 'often [being] at odds with scientific

understanding' (*Ibid.*: 448). 'What Japan needs', he then continues to argue, 'is a coherent, up-to-date, fundamental law that governs both basic research and medical use of human germ cells as well as embryos (*Ibid.*: 463). Then, to provide further motivation to the politicians for enacting a law in this area, he talks about the constitutional rights violated by there not being a law on this promulgated by the parliament. The stagnation of HHGE science in Japan would not end and the moratorium would not be lifted, he asserts, unless/until the politicians abandon their indolent attitude towards the issue and trump all the confusing and contradictory bureaucratic regulations with a law.

For those unfamiliar with the so-called 'Asian values' debate, this narrative might not leave an impression. However, those more familiar with the history of arguments and discussions about Japan's divergences from international norms and regimes in many an area (i.e., the so-called *nihonjin-ron* literature), the echo would be discernable. Indeed, Ishii's seems to be a cultural essentialist argument of the type that has been debunked a great many times hitherto. With his words, Ishii strongly reverberates the arguments to which Sleeboom-Faulkner alludes in her work and which she seeks to highlight as shaky. Moreover, in expressing the sentiment that it is merely the bureaucratic regime that stymies the science here and his call to politicians to act, Ishii seems to downplay the importance of a broad grassroots public debate on the ethical issues underlying HHGE science. Not only does this seem to ignore the lessons of Sleeboom-Faulkner's work on hESCR, but it also overlooks the entire section of the scholarly literature concerning Japan that debunks the simplistic cultural essentialist arguments. The upshot of this all is that nothing is done to actually explain what happens on the ground in Japan concerning HHGE science, and to thus truly advance the cause of overcoming the existing stasis in the science.

#### **4. The Crucial Role of Public Debate in Overcoming Biomedical Stalemate in Japan: A Comparison**

HHGE is not the first bioethical issue in Japan about which it has been observed that when public debate is lacking there is stasis. Indeed, the abovementioned Sleeboom-Faulkner drew an insightful comparison in her work between the case study she focused on, i.e., hESCR, and cadaveric organ donation (particularly from brain-death individuals) (Sleeboom-Faulkner 2008, 2010).

To elucidate, Sleeboom-Faulkner contrasted the two cases, highlighting that the three-decade-long moratorium that followed the infamous s-called 'Wada case'—whereby a doctor from Sapporo Medical University who performed, in 1968, Japan's first heart transplant was accused of manslaughter over the brain-death diagnosis of the donor—was only overcome when a ministerial committee directed the question to the Japanese people of what the definition of 'death' might be. Following this, a flurry of popular books appeared on the subject, with the upshot being the enactment of the 1997 Organ Transplantation Law, which, as has been documented before Sleeboom-Faulkner's writing (Morioka 2001, see also Lock 2001), left room for

interpretation to those directly concerned. The point here is that the public was invited to give their input into the policy-making process, and thereby determine how the ethical questions should be resolved. Without this, it is debatable if the moratorium would have been lifted, she argued.

In summarizing her findings, Sleeboom-Faulkner further offered the view that what makes a difference as to whether a major public debate in Japan emerges or not has to do most with how this debate is couched by the dominant group. Specifically, had the hESCR debate been put in the hands of the public in the way the debate about brain death in the 1990s was, it might have taken off and the scientific landscape might be different today. Moreover, related to the argument that Ishii presents that enacting a law for HHGE will be a watershed moment for scientific progress, Sleeboom-Faulkner hypothesizes how even if the hESCR framework promulgated by the Koizumi Cabinet was more endorsing than it actually was, in the absence of openness towards the public for debate and acknowledgement of the existing uneasiness about the utilization of embryos as a means for developing therapies, the outcome would have been the same.

In line with Sleeboom-Faulkner's findings about the relevance of how issues are framed here, there exists evidence demonstrating how the content of reportage on HHGE matters. In particular, an online questionnaire that investigated, in addition to a specific group of 1,044 patients and 10,881 adults in the general Japanese population, reported that although many would support the use of HHGE for disease-abatement, they are overwhelmingly concerned about the risks involved and, at the same time, do not understand the technology well (Uchiyama *et al.* 2018). Similarly, another online survey of 994 respondents living in Japan demonstrated that roughly 80% are ambivalent about HHGE, exhibiting reserved and ambiguous attitudes, registering two-sided answers, or preferring to postpone judgment (Hibino *et al.* 2019). A third survey that is particularly informative is the longitudinal one of Watanabe *et al.*, conducted over the period 2016-19, which demonstrated how knowledge of HHGE was clearly increased, but support was adversely affected by, the negative press regarding He's actions (Watanabe *et al.* 2020). Regardless of what these surveys say about the current acceptable usage of HHGE, a couple of points stand out. Firstly, the Japanese public seems to need more information on the possibilities that HHGE brings. Secondly, public opinion in the country is not yet conclusive, and is liable to change as the discussion progresses. Whilst it is only a speculative musing, were there to be more readily heard positive voices concerning the need to find a responsible pathway forward for HHGE, as there have been in the United States and the United Kingdom (e.g., Daley 2018; Daley *et al.* 2019; Harris 2018a; 2018b), perhaps there would be room for opinion to change in the other direction to that seen after the He affair. Indeed, that those scientists and bioethicists in Japan who see the advantages of HHGE research were not heard to counter the knee-jerk reactions to the latter event can only be detrimental to the quality of debate here. As with cadaveric organ donation, if the Japanese public is given a chance to both understand fully the issues, and give input into what is acceptable to them, then, at the very least, scientists would be clear about where they stand on pursuing HHGE research, and, just maybe, HHGE science in Japan would be stalled no

longer.

## 5. Concluding Discussion

This article has explored the political background of HHGE science, or rather the lack thereof, in Japan. As an alternative view to the one adopted by the SCJ and individual Japanese academics that it is a parliamentary act that would facilitate the engagement of the scientists in HHGE research, the article has attempted to make the case that for this to happen a broader public debate is first required. In support of this argument, two historical precedents have been considered, demonstrating that there is no substitute for open societal discourse in Japan when progress needs to be made on a controversial bioethical issue. Inferring from the case on cadaveric organ donation more specifically, the path to the breaking of Japan's scientific stalemate with regards to HHGE research seems to be for the public to be invited to express its views, creating an atmosphere where a plethora of perspectives can be voiced, with a subsequent acknowledgement taking place, as well as incorporation into a parliamentary draft-bill, of any anxieties and concerns that might have surfaced.

Now, an important question that follows from such a conclusion is what form a public debate in Japan on HHGE should take. Clearly, a comprehensive public response is hard to ascertain, and complete agreement is impossible. For the latter reason, early calls for a 'broad societal consensus' on HHGE globally are now seen as infeasible (Charo 2019; also see Xafis *et al.* 2021 for further discussion of the issue). At the same time, fitting with the argument of this paper, 'broad public dialogue' is still seen as an important part of the HHGE story (NAS 2018). Of course, on a domestic level in Japan, any such process must consider the peculiarities of the Japanese setting. Nonetheless, apart from looking at how this was achieved in the case of cadaveric organ donation, it is perhaps also helpful for policymakers here to look at how other countries/regions are handling the issue. On this front, for example, the European Group on Ethics in Science and New Technologies Ethics of Genome Editing has recently issued a recommendation concerning debates on the ethics of HHGE that:

Public engagement should involve a range of publics, scientists, scholars in the social sciences and humanities, ethicists, legal and policy specialists, and other experts, organised civil society, with special attention to representatives of women's rights, rights of the child, gender equality, social equality, reproductive rights and justice, disability rights, and human rights in general. (European Commission 2021, 36)

Such guidance was written 'in accordance with Article 28 "Public debate" of the Oviedo Convention of the Council of Europe and with its Committee on Bioethics' 2019 Guide to Public Debate on Human Rights and Biomedicine'. Moreover, further aiding those looking for inspiration on how to manage a public debate on

HHGE, the latter document offers concrete examples of such from 11 countries.

Finally, whilst it is certainly not the job of the scientific or academic communities themselves to decide whether performing HHGE is permissible, it is one of their responsibilities to place the debate about it within the broader public on the correct footing. Concerning scientists, a neat summary of the role they can play is provided in the description of the creation of an 'informed adaptive consensus' by Kaan *et al.*:

Just as it is their professional and ethical responsibility to speak out if they believe that a particular line of research is not in the public interest, or is unethical (or both), we assert that if scientists believe that particular lines of HGGE can be ethically carried out with potential promise to humankind, they should likewise state their conscience. (Kaan *et al.* 2021)

Furthermore, scientific development needs to take place conjointly with bioethics, and it is the role of the experts in the latter field to promote such debate. Insofar as the argument of the kind made by Henry Greely, for example, that HHGE is nothing to worry about, remains obscure knowledge in Japan, the country's bioethical community could be found culpable of indolence. Indeed, given the lack of available alternatives for overcoming certain reproductive conundrums where heritable conditions are present, it seems imperative that a conversation that incorporates the arguments for HHGE is held within Japanese academia, and also extended to involve wider society. After all, if the HHGE project is to go ahead, its progress would surely benefit from the technological and biomedical capabilities that Japan could offer. Or to finish by summarizing the same point in another way, in line with the commentary offered by Japanese academic insiders in the aftermath of He's announcement suggests, it is apt to expect that in the absence of a strong affirmation on the part of those with knowledge here of the positive value that HHGE could bring to society, scientists will remain hesitant to proceed with it, to the potential detriment of the cause of alleviating human suffering.

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## 日本のヒトゲノム編集研究の行き詰まりの克服に向けて ——法律公布追及前に議論

クロイドン・シルビア

### 要旨

2018年に中国で世界初のゲノム編集赤ちゃんが誕生したことが明らかになったことを受け、科学界や法曹界では、この処置に関して絶対的かつ普遍的な禁止措置を導入する必要性があると訴えられた。しかし、ほとぼりがさめたころになって、遺伝性ヒトゲノム編集（HHGE）が倫理的に正当化できる場合もあるという考え方に主流となった。現在、世界保健機関（WHO）によってHHGEに関する最初の世界的勧告が採択され、原則的に、つまり安全性、有効性、倫理的要件が満たされれば、HHGEを受け入れるというコンセンサスが形成されつつあるようだ。同時に、HHGEの実験結果を報告する論文の数も着実に増えている。そのような中、バイオサイエンス大国であり、ヒトの全ゲノムを解読するというアイデアの発祥の地でもある日本では、HHGE科学／研究がゼロに等しいことが際立っている。本稿では、この停滞に焦点を当てる。本稿では、日本のヒト胚性幹細胞研究や死体臓器提供の事例を引き合いに出しながら、日本のHHGE科学が活性化し、この分野で日本が潜在能力を発揮するためには、広範な生命倫理学者主導の議論を開始する必要があると論じている。

**キーワード：**遺伝性ヒトゲノム編集、生命倫理、生殖、公開討論、科学

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### Notes

- 1) According to Greely, '[t]here is no "Human Germline Genome", and, to the extent there is, it has changed, is changing, and will continue to change inevitably from generation to generation, often as a result of human actions. And, in any event, not all CRISPR-induced changes should necessarily count as "changes"' (Greely 2021: 209, see also Greely 2017). For such reasons, he argues many of the objections to HHGE based on the preservation of the 'human germline' are untenable. Of the 71 embryos that survived intervention with the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 to correct the mutation causing the lethal heritable blood disorder beta thalassemia, 28 were cleaved, and only 4 contained the replacement genetic material, but with regards to these 4 embryos, a great many off-target mutations were found, and still more were envisioned.
- 2) It should be noted that Daley had previously individually gone as far as outlining what a responsible pathway for clinical translation of HHGE would look like (Daley 2018; also cited in Daley 2020). Included in this outline were both: a list of safeguards for ensuring faithful implementation, with a special focus on the chief concern about mosaicism, and a hierarchy, developed on principles of medical triage, of 'disease indications that might represent a gradation of medical necessity, and thus permissibility' (Daley 2020, 8).

- 3 ) *WHO issues new recommendations on human genome editing for the advancement of public health*, WHO News Release, 12 July 2021, available at: <https://www.who.int/news/item/12-07-2021-who-issues-new-recommendations-on-human-genome-editing-for-the-advancement-of-public-health>. For the text of the recommendations themselves, see: WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2021.
- 4 ) The SCJ has over 2,200 members representing Japan's academic community. Its activity in relation to HHGE science includes issuing calls to the government to enact legislation (SCJ 2017).