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DATE	31 January 2019
REFERENCE	CGM/190131-02
SUBJECT	Update to policy report 'Editing human DNA'

Dear Mrs Van Veldhoven,

At the end of November 2018 the Chinese scientist Dr He Jiankui claimed to have created the first gene-edited (GM) humans. The twin girls are said to have been born at the beginning of November and have an alteration to their DNA that can confer resistance to HIV. This announcement injected new urgency into the international debate about human genome editing. The news has been confirmed by the Chinese authorities.

Using recent gene editing techniques such as CRISPR-Cas it is relatively simple and easy to make precisely targeted and specific alterations to DNA sequences.[1] This opens up possibilities to alter human DNA sequences in such a way that these modifications are passed on to subsequent generations, for example to prevent genetic disorders. Human genome editing is prohibited by law in most countries, including the Netherlands, and the technology raises technical, legal and ethical issues. In 2017 COGEM and the Health Council of the Netherlands published a joint report on this topic.[2]

In this letter COGEM informs you about the developments that have taken place since that earlier report and revises its recommendations in the light of these developments.

Scientist claims to have created first gene-edited humans

Earlier research in 2015 into gene editing of non-viable human embryos in the lab (in vitro) put the discussion about human genome editing onto the international agenda, although at the time clinical use seemed a long way off. The initial widespread interest and the statements from scientific and other bodies on human genome editing suggested there was a broad consensus that clinical use was premature.

However, at the end of November 2018 Dr He Jiankui of the Southern University of Science and Technology in Shenzhen, China announced that he had made the first two gene-edited humans.[3] He presented the results of his research during the Second International Summit on Human Genome Editing in Hong Kong.

Gene-edited humans: what do we know?

Dr He used the CRISPR-Cas technique to modify the DNA of human embryos.[a] The aim was to delete a specific sequence in the CCR5 gene which is known can result in a high level of resistance to the human immunodeficiency virus (HIV). This mutation occurs naturally in about 10% of the population of northern Europe.

Dr He created and modified multiple embryos from several couples with HIV-positive fathers. Of the embryos transferred to the uterus, one led to a successful pregnancy and the birth of twin girls.

During his presentation in Honk Kong Dr He said that the DNA of one of the girls had been successfully edited. In the other girl the gene editing had only been partially successful and as a result she was probably not HIV resistant. Dr He indicated that he had carried out many tests to rule out the possibility of adverse side-effects, called 'off-target effects.' He also announced that a second woman was pregnant. It is not known whether or not this second pregnancy involves a child with the same gene modification.

The hospital and university in Shenzhen to which Dr He is affiliated deny being aware of his experiment. The Chinese authorities confirmed after an initial investigation that the experiment took place.[4] Dr He has been fired by the university and placed under house arrest. An investigation into the legality of the experiment is underway and all work in his laboratory has been halted.

International condemnation of human genome editing

At the Summit in Hong Kong and in the international media the response to the news of the creation of the first gene-edited babies has been almost universally one of condemnation.

[a] Clustered Regularly Interspaced Short Palindromic Repeats combined with the enzyme Cas9 is a tool that can be used to make precisely targeted and accurate alterations to the genome of an organism.

Many scientists are of the opinion that given the risks and uncertainties surrounding the effects of germline gene editing, the experiment is technically premature.[5] From the information that has become available so far, it appears that the gene editing did not result in the intended outcome. The editing interventions are said to have resulted in variations of the naturally occurring mutation (a 32 base pair deletion) in the CCR5 gene and it is unclear whether these do indeed lead to HIV resistance. In addition, not all the cells appear to have been modified in the same way, which can lead to mosaicism, a condition in which some cells are modified and others are not. It is also difficult to establish whether or not any off-target effects have occurred, with potentially adverse consequences.

Dr He has previously made germline modifications in mice, monkeys and human embryos (in vitro). It is said that most of this work has not been accepted for publication in scientific journals, which suggests that it did not meet the quality requirements.[6] There is also criticism of the trait chosen for modification in the first gene-edited humans. In 2015 the mutation in the CCR5 gene was included in a list of naturally occurring variations in human DNA as obvious candidates for genome editing.[7] Dr He's choice seems to have been based primarily on the technical possibilities rather than on medical necessity. The CCR5 gene has been extensively studied in both animals and humans, as has the 32bp deletion which is supposed to lead to HIV resistance. The modification chosen by Dr He is a means of preventing a disease for which treatments are available. Moreover, alternatives are available that enable seropositive parents to have seronegative children. There is therefore no question of an essential medical treatment. Given the uncertainties surrounding the risks and the irreversibility of human genome editing, some bioethicists argue that the first uses should be limited to preventing serious genetic disorders that result in a short life expectancy for which no effective treatment is possible.[8]

Another objection to the choice of the CCR5 gene is that this gene is not only associated with HIV resistance, but with several other effects as well. The mutation may increase the chance of complications when the carrier is infected with certain viruses (that cause diseases such as West Nile, influenza and tick-borne encephalitis)[9,10,11] and increase the risk of adverse side-effects from the yellow fever vaccine.[12] Studies on mice with genes edited to induce the CCR5 mutation indicate improved memory and learning abilities[13] and HIV patients whose CCR5 gene has been chemically blocked are also reported to have improved cognition.[14]

Finally, there has been much criticism of the level of ethical reflection in Dr He's experiment. He claims to have paid due attention to the question of informed consent from the couples involved and that the experiment was approved by the medical ethics committee of Shenzhen Harmonicare Women's and Children's Hospital (Institutional Review Board, IRB). He consulted various international experts and published an article on ethical principles for germline gene editing.[15] However, there are uncertainties about the quality of

the information[b] and the independence of the informed consent process, which was conducted by Dr He himself. He informed the international experts he consulted of his intentions, but not[c] that he was actually carrying out the experiment.[16] He kept his research out of the public eye and knew that this was contrary to the global scientific consensus on genome editing.[5] In the meantime he was preparing to release news of his experiment to the world in a series of YouTube videos in which he explains his work and motivations.[17]

International legislation is strict, but not conclusive

In most countries human genome editing is prohibited by law.[18] In addition, various international conventions and agreements suggest there is a consensus that clinical use of genome editing is currently a step too far.[d] However, the regulations in some countries are ambiguous and conventions are not binding as long as they have not been ratified by the signatories.

Since 2015 various initiatives have been taken to facilitate discussions about the possibilities for responsible use of genome editing and the harmonising of legislation. The national academies of science in the United States, Hong Kong and the United Kingdom have twice organised a global meeting on the topic and will do this again in 2021.[19] The Association for Responsible Research and Innovation in Genome Editing (ARRIGE)[e] was launched in March 2018 in Paris with the objective of promoting a global platform for the development of responsible governance of genome editing. At the end of 2018 the World Health Organization (WHO) announced it is establishing an expert panel to develop global standards for governance and oversight of human gene editing.[20] Most of these initiatives come from the scientific community and involve consultation between scientific, legal and medical ethics experts. A group of American bioethicists are working on an initiative for a Global Observatory for Gene Editing.[21] They argue that it is not just up to scientists and other experts to decide whether or not genome editing may be used, but that this is a question for humanity as a whole to answer.[22] In short, there are numerous initiatives based on different perspectives and with different objectives.

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[b] He described his work as a project to develop an AIDS vaccine and refers only briefly to the risks and in highly technical and scientific terms. The document is said to focus on shifting responsibility away from He's team in the event of procedural problems and on the rights to images of the babies.

[c] Update: recent media outings, however, do indicate that several scientists were aware that Dr He was carrying out the trial, URL: www.the-scientist.com/news-opinion/the-us-scientists-who-knew-about-crispred-babies-65405 (accessed on 4 March 2019)

[d] These include the Oviedo Convention which contains an explicit prohibition on creating human embryos for research purposes and the modification of the human genome. The convention has been signed by 35, mostly European, countries and 6 countries (including the Netherlands) have not ratified the convention. A large number of countries have not signed the convention.

[e] Association for Responsible Research and Innovation in Genome Editing URL: www.arrige.org (accessed on 31 January 2019)

After the announcement by Dr He, however, the Global Summit concluded that the self-regulation policy launched in 2015 had failed and that legal models are not conclusive at either the international or global levels.[5] At the same time, it is generally acknowledged that a passive attitude can undermine efforts to develop responsible genome editing applications. This raises the question of what action should be taken to enable a responsible approach to genome editing.

By the same token, the question is what role the Dutch government and society can play in all this? To support and contribute to this process, in this letter COGEM makes several suggestions, preceded by some observations on the nature and scope of the international debate.

Observations on the international debate about genome editing

COGEM observes that the investigation into Dr He's experiment is still underway and an independent scientific verification of the data has not yet been completed. However, the Chinese authorities have confirmed that the experiment took place and that another woman is still pregnant with a gene-edited baby. This crosses a boundary and has not gone unnoticed in the media and in international discussions. The information presented by Dr He suggests that it is possible to genetically modify humans and that national and international rules and agreements are unable to prevent that happening.

In 2017 COGEM and the Health Council of the Netherlands published the report 'Editing Human DNA: Moral and social implications of germline genetic modification.' COGEM and the Health Council of the Netherlands observed that the advances in research and the decisions based on this research should be accompanied by a social dialogue with scientists, practitioners and the wider public.

The recent developments have made the need for a social, ethical and legal dialogue even more urgent. What is needed is for the government to set an agenda and determine its position, articulating the role it wants to play (passive, reactive or proactive) in national and international initiatives concerning these developments.

Prepare now for a scenario involving the use (elsewhere) of germline gene editing

In 2015 it was stressed that a broad public debate was needed on the desirability and application of human germline gene editing. In 2018 developments seemed to take a new turn.

Various scientists and advisory bodies have concluded that Dr He's experiment was in contravention of international norms.[23]At the same time, observers state that scientific understanding of somatic and germline genetic modification is rapidly advancing and that it

is time to carefully draw up a responsible pathway towards clinical use. In a recent report, the Nuffield Council on Bioethics (United Kingdom) say that heritable genome editing interventions in humans could be ethically acceptable in some circumstances. The report underlines the importance of the welfare of a person born as a result of genome editing interventions and the need for consistency with the principles of social justice and solidarity.[24]

Given the standpoints of individual scientists, scientific organisations and advisory bodies, they seem to assume it is inevitable that heritable genome editing will eventually become clinically available. In other words, the debate has shifted from the question of 'whether' genome editing interventions should be allowed to the question of 'how' they should be done (under what conditions). The responsibility for answering this question is laid primarily at the feet of experts.[20,23] This suggests that thought should be given *now* to a scenario in which genome editing interventions are available to people elsewhere in the world irrespective of the scientific, legal and social situation in the Netherlands.

Now that a line appears to have been crossed – germline gene editing in humans – we should prepare for the possible consequences, such as the possibility of medical tourism for genome modification services. This is in line with the trend towards increasing possibilities for intervening in the human reproductive process.[f] Medical tourism for new or controversial applications tends at first to be hidden from government or regulatory bodies, which makes it difficult to gauge in advance the numbers involved or the consequences of the interventions.[25] Commercial applications may also differ from what was initially intended.[g] The suggestion that developments can no longer be prevented may give the impression that genome editing is ultimately a question of parental choice. People may be led to assume that if a technology is available, it is by definition safe and responsible. Such developments make it imperative to set up a proactive public information service in addition to the need to come to an informed judgement and take appropriate decisions at the national level.

Genome editing capabilities outstrip the tempo of the public debate

In 2015 the international media expected that it would not be long before the first gene-edited person appeared on the scene. At the time it was said that developments would move faster in Asia, possibly encouraged by geopolitical considerations.[26] Nevertheless, the world

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[f] Children have been born with genetic material from three parents, work is progressing on modifying sperm cells and a recently developed technique called I-Gonad is said to radically simplify genome editing, making it more accessible to researchers and commercial organisations.

[g] The initial argument for creating babies with genetic material from three parents was to prevent heritable genetic disorders. Later it appeared that this technique was also being used commercially to enhance fertility. Embryo screening and selection was developed with a view to implanting healthy embryos without a genetic disorder in the uterus, but is now also used for gender selection. Genome editing has always been presented initially as an opportunity to prevent heritable genetic disorders, but the first humans claimed to contain an edited genome have in fact been made resistant to a disease.

was shocked when the news broke at the end of 2018 that it had actually happened. That scientific developments do not wait for the legal, political and social climate to catch up does not mean that government and society have no choice but passive acceptance. However, research into the use of human genome editing is politically, socially and legally sensitive and so meaningful discussions are often postponed indefinitely, for example because no applications appear to be in sight.[h,i] Given the recent developments, this last argument is no longer tenable.

The profound and intergenerational implications[j] of these events make it essential that scientists, government and society form an opinion about them and come to a decision at the professional, political and individual levels about research into and application of germline gene editing in humans. Now is the time to do justice to that collective process, otherwise there is a danger that the issue of public accountability will fade into the background.

Public opinion divided; need for dialogue and awareness

In recent years public opinion surveys on topics that include human genome editing have been conducted in Europe and elsewhere in the world.[27,28] These indicate that a considerable proportion of those interviewed are positive about the use of genome editing to alleviate or prevent serious conditions. However, these surveys also reveal a reticence towards or rejection of genome editing for other purposes, for example where there is no medical necessity. Some think that that genome editing is unacceptable in any circumstances.[29] There may be a gradual shift towards public acceptance of genome editing interventions and some national and international public opinion surveys seem to suggest this.

COGEM points out that asking respondents about complex or new technological developments has its limitations, for one thing because respondents probably have little information about the issues or simply because they have not yet had the chance to form an opinion. It is therefore not possible to conclude on the basis of such opinion polls alone that public acceptance of human genome editing is growing.

Given the ongoing debate about biotechnology and genetic modification, the divisions and diversity of views about germline gene editing cannot be expected to change into a broad

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h In 2016 Edith Schippers, then the Dutch minister of health, welfare and sport, announced her intention to lift the prohibition on the creation of human embryos for research purposes in certain cases. However, this plan was shelved in the latest coalition agreement. Instead, it was agreed to stimulate discussion on this and look for alternatives. URL: https://nos.nl/nieuwsuur/artikel/2199687-nieuwe-kabinet-draait-plan-embryowet-terug-kweken-blijft-verboden.html (accessed on 31 January 2019)

i In 2018 stakeholders in the discussion on modernising biotechnology policy concluded that opinions on genome editing are sharply divided and that the topic is only relevant as input to a policy in the longer term. See KLB (2018) Eindrapport with the outcome of an exchange of views between civil society stakeholders from March to October 2018, pp 22–27

j This is what makes genome editing fundamentally different from most medical treatments and interventions, which are restricted in their effect to a single generation.

consensus. In both respects it is vital that an open dialogue takes place between people and parties with different views and professional and cultural backgrounds to explore hidden presumptions and obtain new insights. This dialogue should first and foremost facilitate the forming of opinions. Topics for discussion could include exactly what positive expectations people have and what their specific objections are, their underlying assumptions, and how developments can be managed, for example by setting conditions, enforcing rules and regulations and building stop/go moments into decision-making. Moreover, dialogue in itself will not automatically result in a consistent vision on decision-making about genome editing. It must be clear to the public if and how the outcome of the dialogue will be translated into political decisions on whether or not to relax the restrictions on fundamental research and on whether or not to permit human genome editing.

Research into and use of genome editing are inextricably linked

For various researchers in the Netherlands and elsewhere the announcement by Dr He about the clinical use of germline gene editing in humans was reason (again) to call for the use of cultured embryos: embryos specially produced for scientific research.[30] If the implications for germline genetic modification of gene editing techniques such as CRISPR-Cas are to be investigated, it is indeed important that such research is carried out at the earliest possible stage of the development of the embryo. However, there are also other arguments for using cultured embryos.[k]

COGEM points out that the discussion about scientific research into genome editing using cultured embryos cannot be divorced from the broader social debate about whether or not human genome editing should be permitted for use in clinical interventions. In practice, the difference between research and clinical use is not always clear cut and the step to application is easily made. This has been shown by the actions of Dr He, who took it upon himself as a scientist to make this step.

The discussion about the use of cultured embryos for research purposes is therefore not restricted to the safety of genome editing, but is also about the ethical aspects of scientific research, the intrinsic value of life and the responsibility of scientists to the international scientific community and to society at large. In view of the recent course of events, COGEM stresses the need for critical reflection in the training of professionals regarding their own research and that of others.

Given the profound, intergenerational and controversial implications of genome editing, scientists do not have a neutral position as pure suppliers of knowledge. The use of this

[k] Surplus embryos made available by prospective parents following an IVF treatment are less suitable because they are more developed. Besides, research on cultured embryos also serves another purpose, to obtain fundamental knowledge about human embryonic development. Therefore, this type of research is not inherently linked to the application of human germline modification.

knowledge is inextricably bound up with the discussion about the feasibility and desirability of engineering human life, and even within the scientific community and medical professions there are a number of very different views about the acceptability of human genome editing. That is why discussions within the international scientific community should not just be about acquiring new knowledge, but should also be about exploring ethical values and norms.[31] Differences in cultural values relating to scientific research and genome editing interventions should also be a part of these discussions, which must not be conducted separately or one after another, but concurrently and in interdisciplinary deliberations. They should also be conducted openly and with society as a whole. When scientists are open about their differences of opinion they are seen to be part of society as a whole, and this in turn opens up the dialogue.

Inclusive dialogue needed on the individual and collective impact of germline gene editing

The discussion about the use of genome editing includes subjects such as changing definitions of disease and health, human tissue donation, the use of cultured and surplus embryos, and social justice. To evaluate possible applications, often a seemingly clear normative distinction is made between the prevention of genetic disorders and interventions for human enhancement. COGEM observes that as knowledge and potential uses are evolving, the dividing line between prevention and enhancement is fluid; moreover, this division does not always do justice to the complexity of the functions of hereditary information (as is apparent, for example, from the multifunctionality of the CCR5 gene). From a technoscientific standpoint, therefore, healing and enhancement are not always distinct and must be considered and discussed as a continuum.

When discussing potential applications, a distinction can be made between desirability and feasibility, both from the perspective of the individual (autonomous reproductive choices) and from the perspective of the collective (what sort of society do we want to live in). The dialogue will therefore have to be both wide-ranging and specific. Although the consequences and impact of genome editing initially affect only those directly involved – patients and prospective parents with a genetic disorder – genome editing also affects subsequent generations and influences the nature of our society. It is therefore crucial that other stakeholders (scientists, medical professionals and the wider public) take part in the dialogue (a multi-actor perspective).[31]

In 2019 a two-year project will begin in the Netherlands with the aim of facilitating the social dialogue about genome editing.[1] It is an initiative by many organisations in the Netherlands concerned with medical research, ethics and debate, and will be financed by the

[1] The project *Maatschappelijke dialoog over kiembaanmodificatie* (Social dialogue on genome editing) will be carried out by a consortium consisting of Erfocentrum, Kennislink, Rathenau instituut, Centrum voor media & gezondheid, Erasmus MC, Amsterdam UMC, Community genetics en public health genomics, Nederlandse Patiëntenvereniging, Vereniging klinische genetica, VSOP and RIVM.

Dutch Ministry of Health, Welfare and Sport. This project provides opportunities to proactively facilitate the dialogue discussed above. Crucial for the success of such a process is that it is part of a transparent political decision-making process. It must be clear how and when policymakers and politicians will consider the outcomes when formulating their national and international standpoints regarding research into the clinical uses of genome editing.

Conclusions

COGEM makes the following observations regarding global developments in the field of human germline gene editing:

- The announcement of the first genetically modified humans shows that the developments in genome editing identified by COGEM in 2017 are moving more quickly than expected.
- Despite the widespread condemnation of this experiment, the international debate is shifting from the question of 'whether' germline gene editing should be allowed at all to the question of 'how' (under what conditions) it should be permitted.
- International legislation is strict, but not conclusive and developments in human genome editing will probably be hard to prevent.
- Self-regulation within the scientific community seems to have failed and has been unable to prevent a scientist taking a unilateral decision to cross the agreed boundary.
- The first applications of germline gene editing are expected to take place outside Europe. Medical tourism for genome editing can become a real possibility in future. The possibility of private parties providing commercial services in response to the individual wishes of parents cannot be ruled out.
- Given the profound and intergenerational implications of human germline gene editing, the decisions on its acceptability should be made through a collective and transparent process. Thought must therefore be given now to a scenario in which genome editing is available to people elsewhere in the world whatever the scientific, legal and social situation in the Netherlands.
- Developments in the field will eventually present the Dutch government with two concrete questions:

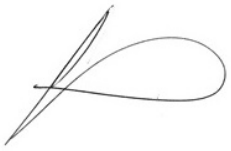
  1) Is it desirable to expand the possibilities for fundamental research on human embryos and permit the use of cultured embryos?

  2) Is it desirable to rescind the prohibition on germline gene editing to make clinical use possible?
- Both questions are intimately connected and should not be debated either in isolation (in either a scientific or societal context) or sequentially (first safety, then desirability).
- The use of scientific knowledge is inextricable bound up with the discussion about the feasibility and desirability of engineering human life. For this reason the aim should not

just be to acquire new knowledge, but also to explore values and facilitate the forming of opinions by scientists and social actors.

- The dialogue about ethical and social acceptability should also take place outside the medical and scientific communities to ensure that the final decision on whether or not to allow human germline gene editing in the Netherlands can command broad support.
- It may be possible to tie this dialogue into relevant national and international initiatives. A social dialogue will in itself be insufficient to steer developments in human genome editing. If such a public-opinion-forming process is to have any real meaning, the outcomes must be explicitly reflected in transparent political decision-making on this subject.

Yours sincerely,



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