Public Call for Evidence for the International Commission on the Clinical Use of Human Germline Genome Editing

1. Which diseases and conditions, if any, do you see as appropriate for human germline genome editing?

Thank you for the opportunity to provide evidence and commentary to the International Commission on the Clinical Use of Human Germline Genome Editing. The Autistic Self Advocacy Network (ASAN) - a 501(c)(3) nonprofit organization created by and for autistic people ourselves - opposes the further use and development of germline genome editing technology. Our reasons for doing so are outlined in further detail in the questions that follow.

The Autistic Self Advocacy Network (ASAN) sees no disease or condition as an appropriate target for human germline genome editing due to the potential societal and ethical implications of widespread use of the technology. The scientific community's relatively limited understanding of the long-term effects of altering any gene - particularly its effect on multiple generations of individuals - would additionally preclude the use of germline genome editing.

The Autistic Self Advocacy Network envisions a world in which all lives - including the lives of people with disabilities - have equal value. Such a world is simply not compatible with the use of technology to prevent the births of people with disabilities. Ubiquitous germline genome editing technology would, for instance, allow prospective parents of children with developmental disabilities not only to edit a prospective child's genes in order to attempt to eliminate that disability from existence before their child is even born, but also to eliminate those genes in all subsequent generations. Given the present-day use of prenatal testing to prevent the births of people with Down Syndrome, the possibility of this use is more than likely - it is **inevitable.**

Modifying specific heritable traits in an embryo or fetus - and then in all future generations of the family through the use of germline editing - possesses clear and troubling links to eugenics. The United Nations' bioethics committee, popular news outlets such as The Guardian, and eugenics historians alike have found links between twentieth century eugenics and germline genome editing. Citations: (1) United Nations Educational, Scientific, and Cultural Organization (UNESCO), UNESCO panel of experts calls for ban on "editing" of human DNA to avoid unethical tampering with hereditary traits, October 2015, https://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits; (2) Katie Hasson and Marcy Darnovsky, Gene-edited babies: no one has the moral warrant to go it alone, The Guardian (November 27, 2018, 10:01 a.m.), https://www.theguardian.com/science/2018/nov/27/gene-edited-babies-no-one-has-moral-warrant-go-it-alone; (3) Elliot Hosman, Slipping Into Eugenics? Nathaniel Comfort on the History Behind CRISPR, Biopolitical Times (July 23, 2015), https://www.geneticsandsociety.org/biopolitical-times/slipping-eugenics-nathaniel-comfort-history-behind-crispr?id=8741. ASAN maintains its strong opposition to the use of any medical procedure, practice, or technology for a eugenics-related purpose.

ASAN neither endorses nor condemns the use of gene therapy or non-heritable genome editing. There are disabilities - such as certain kinds of cancer - in which there is a general consensus by people with the disability that genome editing is permissible. Citation: Alex Lee, Gene editing isn't about designer babies, it's about hope for people like me, The Guardian (August 3, 2017, 11:51 a.m.), https://www.theguardian.com/commentisfree/2017/aug/03/gene-editing-mitochondrial-replacement-therapy-designer-babies. While Alex Lee's opinion is his own, there may be many people with his rare condition like him, and he mentions others with rare conditions seeking cures.

In such situations, the opinion and consensus of people with that disability should remain central. We expand upon our stance in this situation in further questions.

However, germline genome editing has an impact not just on the individual person with a disability but also upon future generations. This practice would therefore implicate not only the autonomy of individuals to make their own medical choices, but also impact future generations in unpredictable and troubling ways. The international scientific community also does not currently know what the full effects of even a single gene are, let alone what the long-term effect of altering a gene would be. It would be beyond irresponsible to utilize a technology on infinite generations of human subjects without a comprehensive knowledge of what it is acting upon - an understanding we simply do not have.

Conversations about genome editing have also for the most part occurred without the involvement of the disability rights community - who would crucially be among the populations most impacted by the technology. It is critical to note that those individuals with disabilities who have had the opportunity to participate have warned against the development of germline genome editing without our input, and of the deleterious effect it could have on our communities. Teresa Blankmeyer Burke, referring to the Deaf community, stated that the technology could "could mean the eradication of a particular population" and urged the scientific community to involve people with disabilities ourselves in these discussions. Citation: Teresa Blankmeyer Burke, About Us, Without Us: Inclusion in the Threat of Eradication, Impact Ethics (December 8, 2015), https://impactethics.ca/2015/12/08/about-us-without-us-inclusion-in-the-threat-of-eradication/. Disability rights advocate Alice Wong, speaking at Stanford's Medicine X conference, asked: "In the quest to eliminate suffering and pain, who has the power to decide which mutations warrant human gene editing while others are considered tolerable?" Citation: Alice Wong, Resisting Ableism: Disabled People and Human Gene Editing, presentation at the Stanford Medicine X Conference (November 1, 2017), https://www.youtube.com/watch?v=_vdeeR5DOSo (available on Youtube).

Many commentators have maintained that genome editing would also be racially and ethnically discriminatory. Black disability rights advocate Anita Cameron argued that because genetic engineering is most likely to be used by the wealthy, Black people - who are more likely to be low-income - would be less likely to use the technology and therefore discriminated against in a future where the technology is commonplace. Cameron said: "Even if there are positive aspects to human genetic engineering, due to the ableist and racist nature of health care, Black people, people of color and people with disabilities will not reap the benefits, if there are any. Instead, they'll be more likely to suffer from the negative effects, including increased discrimination, that are sure to come from this." Citation? Anita Cameron, Why I'm speaking about human genetic engineering as a Black woman with disabilities, Biopolitical Times (April 20, 2017), https://www.geneticsandsociety.org/biopolitical-times/why-im-speaking-about-human-genetic-engineering-black-woman-disabilities.

The appropriate use of genetic editing and prenatal testing are contentious topics. Nonetheless, germline editing is an untested, unsafe, eugenicist practice that has a high potential for harm and that could lead to the marginalization and elimination of many populations of people with disabilities. As a result, we cannot support this practice in any context.

2. If there were to be an appropriate use case for human germline genome editing, what evidence would be needed to proceed to first in human use?

ASAN maintains that there are no appropriate use cases for human germline genome editing. This is because the technology has a high likelihood of being used in a manner that discriminates based on race and disability. Eliminating a class of people with disabilities from existence by changing the genes that cause their disability, in all future generations, is an explicitly eugenic act. Given this, no amount of evidence would be sufficient to allow for the technology's use on human subjects or human embryos.

Non-heritable genome editing on already living humans already would require an extensive evidence base before the technology could be considered for use. Uses would have to be carefully limited to specific groups of people with disabilities who believe, as a group, that their condition is an appropriate target for gene editing. Use of genome editing to alter phenotypic traits (such as hair, skin color, the color of someone's eyes, or other aspects of their appearance such as characteristics of some disabilities) would have to be avoided and prohibited because it would inevitably be used in a racially discriminatory, ethnically discriminatory, and ableist manner.

ASAN opposes research into the viability of non-heritable genome editing that is neither requested nor desired by the specific group of people with disabilities affected. Genome editing as a technology should be utilized to help specific people, rather than for its own sake. It does not make sense for the Commission and the international scientific community to attempt to determine what evidence would be needed until it is aware of how the technology will be used.

ASAN supports conscientious, ethical research into the long-term effects of gene therapy and non-germline genome editing where requested by a specific people with disabilities, such as, for example, the effects of non-heritable gene editing to treat certain types of cancer, as urged by cancer patient groups. This is research which could at least potentially benefit people with disabilities who exist right now. It is irresponsible to bypass such efforts in favor of a far more dangerous inquiry into the elimination of genes from future populations.

3. What is the status of editing mechanisms for early stage human embryos (e.g., using different editing techniques, improving homology directed repair, etc.)? What are the factors that predict whether single nucleotide changes or other intended modifications in human embryos will be correct? To what extent will genome editing affect the viability of embryos?

ASAN does not have the requisite knowledge and/or expertise to address this question. However, we have encountered scant evidence that editing technology and knowledge of the genome is anywhere near sufficient enough to address the Commission's question.

4. What is the status of the technology for validating that a correct edit (on target characterization) has been made and that unintended edits (e.g., off target effects, mosaicism, etc.) have not occurred in a range of cell and tissue types? If possible, please provide evidence drawn from work on induced pluripotent stem cells, embryonic stem cells, and/or early stage human embryos.

ASAN does not have the requisite knowledge and/or expertise to address this question. ASAN notes that the current evidence of long-term effects and potential unintended effects of genome editing is limited, or at the very least not available to the public. ASAN urges the Commission to engage in long-term, comprehensive, longitudinal studies of any subject (including non-human subjects) of a

genome edit. It is entirely possible that an unintended effect of an edit will not present itself in some subjects until many years have passed.

5. What is the status of generating cell lines from human and non-human germline stem cells?

ASAN does not have the requisite knowledge and/or expertise to address this question.

6. How might animal models inform the editing in human embryos (inclusive of analysis of phenotypic correction)?

ASAN does not have the requisite knowledge and/or expertise to address this question.

7. To what extent do different genetic backgrounds affect success and phenotypic outcomes after genome editing?

ASAN does not have the requisite knowledge and/or expertise to address this question. ASAN does recognize the urgency of investigating differences in success and phenotypic outcomes between individuals with developmental disabilities and individuals without developmental disabilities with respect to all medical care. Many, if not most, developmental disabilities - such as Fragile X Syndrome and Down's Syndrome - have a primarily genetic basis. In either case, a targeted gene therapy for another, seemingly unrelated condition may nonetheless impact someone with a developmental disability differently than someone without a developmental disability. It is therefore equally critical to account for these differences during the development of a gene editing technology, in the limited number of situations in which the use of non-heritable gene editing is appropriate.

It is also a well-known reality that women and people of color may react to medical procedures and therapies differently than white men, may present different symptoms of a condition than do white men, and may have different prognoses and rates of health conditions and disabilities than do white men. Any new gene therapy must account for these differences and must be delivered in a culturally competent and accessible manner. In particular, it is critical to ensure that when therapies are tested on human subjects, these tests include people with disabilities, women, and people of color.

8. What is the success rate of full term pregnancies following pre-implantation genetic diagnosis? What affects this (e.g., age, number of oocytes harvested, technique used, etc.)?

ASAN does not have the requisite knowledge and/or expertise to address this question.

9. What are the appropriate mechanisms for obtaining informed consent, long-term monitoring of the future children, assessing potential effects in subsequent generations, and addressing untoward effects? Are there best practices from: a) assisted reproductive technologies; b) pre-implantation genetic diagnosis; c) gene transfer research for children; d) mitochondrial replacement therapy; and e) somatic genome editing?

Germline genome editing is too new and experimental to allow the scientific community to obtain realistic informed consent to the procedure. It is impossible to convey the information required for informed consent to prospective parents, since that information does not exist. For example, although we are aware that He Jiankui unethically created the first gene-edited children and specifically modified the CCR5 gene, we have no idea what modifying CCR5 will do to the long-term health of these two children. Some scientists have speculated that the CCR5 modification may make individuals live shorter lives, may make them smarter, or may make their immune systems weaker in

response to contact with the influenza virus — and other scientists have contradicted all of these same assertions. Citation: Jon Cohen, Did CRISPR help—or harm—the first-ever gene-edited babies? Science (August 1, 2019, 11:30 a.m.), https://www.sciencemag.org/news/2019/08/did-crispr-help-or-harm-first-ever-gene-edited-babies. Each gene in the human genome has a number of complex possible effects, on both the human body and on every other gene and its expression. Without knowledge of what a genome edit would do to a potential child or individual - along with, possibly, all subsequent children in the family - it is impossible for consent to be reasonably "informed." There are therefore no appropriate mechanisms for obtaining such consent.

Obtaining informed consent to the long term future monitoring of gene-edited children would be equally difficult. As was noted by the Commission and other parties at the most recent meeting, due to the lack of information available on any of the possible side effects of a gene edit, the prospective parents would be agreeing to a "medicalized life" on behalf of their children and grandchildren. A mere survey or check-up every few years would be insufficient for the purposes of monitoring a highly new and experimental procedure. As these children and grandchildren are not yet born, they cannot possibly consent to this degree of medical monitoring.

10. How should we think about the inter-generational medical (e.g., genetic changes to the genome) and ethical implications of human germline genome editing (e.g., potential harms and benefits)? How should the rights of future generations and the wider human population be taken into account?

With respect to long-term ethical implications, we reiterate the long-stated position of the disability rights movement: that germline genome editing is a fundamentally eugenic, unethical technology which would harm our families and communities. Future decisions by the scientific community about which genes are "good" and worthy of continuation throughout the human gene pool, and which genes are "bad" and should be eliminated in all future people, are decisions about what kind of life is worth living, and have the grave potential to harm whole classes of people with disabilities.

For example, disability rights advocate Rebecca Cokley, a person with a common form of dwarfism known as achondroplasia and mother of multiple children with the same disability, expressed the common fear that genome editing would lead to the elimination of future generations of people like her and her children: "I am who I am because I have dwarfism. Dwarfs share a rich culture, as do most disability groups. We have traditions, common language and histories rich in charismatic ancestors.... Proponents of genetic engineering deliberately use vague language, such as 'prevention of serious diseases,' leading many people with disabilities to ask what, in fact, is a serious disease. Where is the line between what society perceives to be a horrible genetic mutation and someone's culture?" The same concerns exist in the autistic community. We also have a rich culture and heritage - a community - which is enhanced by the diverse support needs and ways of looking at the world of all of its members, including those with the most significant impairments.

ASAN believes that eliminating genetic disability in future generations in essence eliminates these vibrant communities in generations to come. As noted, disability is a social and cultural identity and inheritance for many of us, rather than merely a loss of ability or a barrier preventing us from interacting with the world. We urge the Commission to pay close attention to the concerns of the disability rights community and our reasons for believing germline genome editing to be discriminatory and unethical.

With respect to the rights of the wider human population, the elimination of types of disability from the genome using germline genome editing - a likely product of its widespread

availability - may have long-term negative effects on human tolerance of difference, human diversity, and the cultural and social development of humanity as a whole. People with disabilities have made a myriad of contributions to the wider world. Our extinction is too high a price to pay for the advancement of genome editing technology.

Finally, it is important to consider the likelihood that genetic diversity, including genes that are currently seen as disfavoured, is critical to human survival. Genes that may lead to disability in typical modern conditions may be advantageous in unanticipated ways in the future. For example, certain genes may confer resistance to diseases that do not currently exist, help individuals survive harsh conditions or starvation, or lead to behaviors that may be adaptive in future conditions. It is impossible to predict which conditions humanity may face in the future. By eliminating genes from future generations, we may therefore be undermining humanity's future ability to survive.

11. What international oversight structures would need to be in place to facilitate, in a responsible way, a path forward for germline genome editing?

ASAN argues that there is no responsible path forward for the use of germline genome editing at all. The procedure has potentially racist and strikingly ableist implications which would negatively impact the long-term future of the international disability rights community. As such, no international oversight structures could make any path forward for germline genome editing ethical or responsible.

Additionally, it is quite unlikely that an international oversight structure would be fully able to govern germline genome editing. For example, although the United Nations or another international body could develop a Convention on the Ethical Use of Germline Genome Editing, countries could simply choose not to sign and/or ratify the Convention. Even if we assume that all interested countries signed and ratified such a document, international standards, even when binding, can remain unenforced. For example, although a great many countries have signed and ratified the Convention on the Rights of People with Disabilities, very few of these countries have made substantial progress towards enforcing Article 12 of the Convention, which requires that States Parties take "appropriate measures to provide access by persons with disabilities to the support they may require in exercising their legal capacity." Citation: Convention on the Rights of Persons with Disabilities art. 12, December 13, 2006, U.N. Doc A/RES/61/106, 6, 2515 U.N.T.S. 3, 78. Some individual countries are also quite likely to interpret any international governing standards such as to allow whatever action they take, regardless of whether the standards actually do so. Regardless of the presence or absence of international standards, individual organizations or persons will exist who defy them, who will face little accountability. Citation: See Ed Pilkington, UN calls for investigation of US school's shock treatments of autistic children, The Guardian (June 2, 2012 2:29 p.m.), https://www.theguardian.com/society/2012/jun/02/un-investigation-shock-treatments-autism?newsfeed=true.

ASAN therefore argues that the best prevention method for unethical uses of germline genome editing is not oversight but rather a general international condemnation and moratorium on research on germline editing. Although widespread condemnation likely would not wholly eliminate the technology's surreptitious development, it would impose sanctions and negative consequences on the responsible parties.

12. Are there any topics or issues that are not covered by the above questions that you think the Commission should attend to during its deliberations?

The Autistic Self Advocacy Network remains concerned that this meeting of the International Commission did not involve the input of people with disabilities ourselves. In fact, the meeting rarely contemplated the serious medical and ethical implications that germline genome editing has for our community, which have been described extensively in prior questions. While the Deaf advocate Teresa Blankmeyer Burke was present at the meeting and provided the Commission with verbal comments, there appeared to be only a few members of the disability rights community physically present at most. This leaves out the voices of disability communities that are largely opposed to the very concept of "cure," such as Deafness, dwarfism, and intellectual and developmental disabilities. The majority of the discussion concerned the medical and/or scientific barriers to the development of germline genome editing, rather than the ethical implications of the technology. Additionally, most of the questions listed in this feedback form are medical, rather than ethical questions.

Under these circumstances, the Commission cannot say that they have given the perspective of our community a proper hearing, nor have they presented us with an opportunity to provide significant feedback on the technology's vast potential for harm. ASAN urges the Commission to:

(1) specifically invite disability rights organizations as speakers at the next meeting of the Commission;

(2) widely disseminate the time and place of the next meeting to the disability rights community and offer additional overflow rooms and means of physically and virtually attending the meeting;

(3) offer substantial opportunities for written comments that more directly address the moral and ethical implications of germline genome editing and invite the specific expertise and perspectives of the disability community, and conduct further exploration of these concerns.

Thank you for the opportunity to comment on this important technological advancement, its implications, and on a meeting of this Commission. For more information on ASAN's position on germline genome editing please contact Sam Crane, our Director of Legal and Public Policy, at scrane@autisticadvocacy.org.