ASGCT responses to the WHO online consultation on the Draft Governance Framework for Human Genome Editing proposed by the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing

Submitted February 7, 2020

The committee is interested in promoting useful public education, engagement and empowerment on human genome editing. Do you know of any public engagement activities on emerging technologies (including human genome editing)? Yes/No. If yes, please detail the activity(ies) and explain whether you consider this activity(ies) useful.

Among public education efforts on human genome editing, the American Society of Gene & Cell Therapy (ASGCT) has a patient education program that contains a unit on different approaches, including gene editing. Such information has been useful, as evidenced by nearly 4,000 views of this module over a one-year period. The Society is also considering in 2020 adding information on concepts and definitions related to this issue specifically for patients, their families, and the public. ASGCT has connections with over 40 patient advocacy groups that have assisted in sharing information for patients and families. Providing scientific education on this topic could facilitate engagement of informed stakeholders on these topics.

In addition, ASGCT provides a forum for engagement of those working in the field on the issues surrounding the clinical use of germline gene editing. The Society held a daylong program on this topic at its Policy Summit in November 2019, which included presentations on the work of the WHO Committee, as well as the efforts of the International Commission on the Clinical Use of Human Germline Genome Editing. The Society is offering a session on perspectives on clinical use of germline gene editing during its Annual Meeting in May 2020 and contemplating programing in the September/October time frame for the 2020 Policy Summit.

Do you have any suggestions for effective public engagement on human genome editing? Yes/no, if yes please detail your response.

ASGCT appreciates that the Committee has identified inclusivity as an ethical principle to guide its processes. We encourage a process of genuine public engagement with multiple diverse stakeholders, including representatives with scientific, medical, patient, caregiver, policy, legal, ethical, religious, and civil societal perspectives from around the world. To further facilitate such inclusivity, the Society would encourage the Advisory Committee to identify any of these key groups that have been inadequately represented in previous comment submissions that may benefit from targeted outreach to diversify engagement.

The Society considers one of the most vital public segments to engage to be those who could be affected by gene editing technology—patients and caregivers of patients with diseases that may be

treated by gene editing. Engaging with patient advocacy groups for the provision of scientific education and receipt of input on these issues is of utmost importance. Additional highly significant stakeholders are scientific researchers with expertise in gene editing and civil societal groups that address ethical issues in society.

For future solicitation of comments, the Committee may wish to consider offering a longer response time for the completion of input. The relatively short response window for this consultation may prevent groups without a central governance structure from effectively expressing their views and/or organizations with individual members or member groups from being able to collect member input, as is the case for ASGCT.

The committee is exploring possibilities for recommending the creation of an international 'whistleblowing' mechanism for the reporting of unregistered, unethical or illegal uses of human genome editing on individuals (somatic genome editing) or germline genome editing, whether in the lab or clinically for attempts at making heritable alterations (ie reproductive uses). Do you know of any such mechanism(s) that could be useful at an international level? Yes/no. If yes, please detail the mechanism(s) and explain whether you consider this mechanism(s) desirable/practical/useful. Also, please comment on the potential objections or roadblocks to the creation of such a mechanism(s).

ASGCT supports the Committee's attention to creating a whistleblower mechanism for unethical or illegal uses of human genome editing technology. The Society would consider such a mechanism to be desirable to assist in the reporting of knowledge of research occurring outside legal, regulatory, and normative ethical practices. We would encourage the WHO to identify whether a reporting mechanism could be housed within the WHO or another international body.

ASGCT acknowledges several potential objections or roadblocks to international or supranational whistleblower mechanisms. These include:

- Obtaining international agreement on the definition of legal, regulatory, and ethical boundaries for the criteria for wrongdoing.
- Preventing reporting of false claims of wrongdoing.
- Considering role of whistleblowers in any report and subsequent investigation including confidentiality, anonymity, and protections against retaliation.
- Obtaining investigational cooperation from involved individuals, institutions, and nations and reporting allegations and findings to the same.
- Identifying the adjudication mechanism after a report is received.

The Committee is interested in understanding how to prevent instances where researchers or companies locate controversial activities in countries with weaker regulatory infrastructure for no reason other than to avoid regulation and ethics guidelines that exist in other countries. Do you have any comments on how such instances should be prevented?

ASGCT acknowledges the difficulty in determining how to prevent instances of locating controversial activities in countries with weaker regulatory infrastructures to avoid oversight that exists in other countries. We recommend that the Committee provide recommendations on minimum standards of national oversight in its final governance framework. Consideration should be given to the development of international or regional regulations that prohibit clinical use of germline gene editing at this time, although ASGCT would require additional time to take a position on specific proposals of the creation of supranational regulatory entities.

The registry that WHO is creating may assist in creating a culture of deterrence of the initiation of controversial activities without reporting them to the registry. WHO could indicate that in addition to the registry's collection of data from countries with existing national registries (e.g., clinicaltrials.gov), it requests reporting of all gene editing clinical trials from researchers in countries without such existing data. While inappropriate research could still occur unreported in these countries, a statement of this expectation would make clear that international data collection is the norm.

The Committee has identified 5 ethical principles to guide both its work and future efforts on the effective governance of human genome editing, as follows:

- **Transparency: a commitment to share information on what is happening, how and why it is necessary;**
- **Inclusivity: a commitment to draw on the full contributions of all parts of global society, thereby providing diverse points of view, skill sets and additional methods of program management and measurement;**
- **Responsible stewardship of science: a commitment to rigorous science, to follow ethical practice in scientific and clinical conduct, and strive to maximize potential benefits while minimizing potential harms;**
- **Fairness: a commitment to fair dealings in relation to all persons and groups, and equitable access to opportunities and potential benefits, and support for efforts to encourage research and development of medical interventions that are appropriate and feasible for the widest possible range of populations; and**
- **Social justice and non-discrimination: a commitment to celebrate and promote diversity by rejecting patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age and disability.**

Do you have any comments on one or more of these 5 principles? Are there essential principles missing from this list? Yes/no, if yes please provide details. Otherwise write "no".

ASGCT supports the use of all of these ethical principles in guiding the work and future efforts of the Committee. In particular, we support consideration of the following:

Inclusivity. ASGCT encourages the Committee to continue to commit to extensive engagement among all major stakeholders, including representatives with scientific, medical, patient, caregiver, policy, legal, ethical, faith, and civil societal perspectives from around the world. This engagement may merit additional targeted outreach if responses from certain types of stakeholders are under-represented after general consultation periods have ended.

Responsible stewardship of science. In its commitment to striving to minimize potential harms, the Committee should continue to emphasize its interim recommendation that "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing." In addition, a point of agreement among stakeholders is that such applications should not proceed in the future if they are not safe. We encourage the Committee to additionally note that the clinical use of germline gene editing should not currently be allowed due to the technical scientific limitations. Those limitations, which have been well established, include incomplete efficiency and precision of on-target modification; off-target mutations; on- and off-target mutation mosaicism; and the potential interaction of novel on- and off-target mutations with existing human genetic diversity when these new alterations are passed on to future generations. As an interim goal to the establishment of broad societal consensus on the future use of this technology, we support making clear international and national statements on the current status of the *science* and continued opportunities for the expression of diverse viewpoints about the future of this technology.

The committee considers that a governance framework:

- **Is transparent, inclusive, responsible, fair, and socially just;**
- **Covers basic research that takes place entirely within a laboratory environment, including basic research on gametes and embryos; and clinical trials that enroll human participants, whether for non-heritable editing (i.e. somatic cell editing) or heritable editing (i.e. germline editing in reproduction). It also includes the emerging areas of in utero (non-heritable) genome editing on fetuses, and all types of genome editing technology, including base editing, prime editing, epigenetic editing, etc;**
- **Covers both health-related and non-health-related research;**
- **Is robust, flexible, scalable, sustainable and appropriate for use at the international, regional, national and local levels;**
- **Inspires trust by having been developed through informative and participatory approaches involving experts and non-experts;**
- **Identifies and addresses relevant issues, using a range of laws, policies, and regulatory mechanisms, developed in collaboration with the widest possible range of institutions, organizations and peoples; and**
- **Provides those who occupy specific governance roles for human genome editing with the tools and guidance they need**

Do you have any comments on these features? Are there essential features missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".

ASGCT finds many of these features to be broadly appropriate for a governance framework for human genome editing. Regarding the type of research to be covered by a governance framework, however, the Society needs to further assess internally its position on whether basic research on germline cells not intended for clinical use should be included in a registry, tracked separately, or not tracked. ASGCT does not currently see a need for somatic cell clinical trials to be considered part of the WHO registry, as this work is not highly distinguishable from gene therapy clinical trials and is tightly regulated around much of the world. However, should the WHO deem it necessary to include somatic cell clinical trials as part of its registry, ASGCT recommends public clarification

from the WHO that the pilot registry utilizes existing data from countries with existing national registries (e.g., clinicaltrials.gov), so as to not pose additional administrative burdens on these researchers. We acknowledge that some countries lack strong frameworks for regulating new technologies such as gene editing products, and we therefore support a Committee request for countries without existing data to submit gene editing clinical trial information to the WHO registry.

The Committee identified core elements of a governance framework, these included key *challenges* to be considered when developing oversight regimes, different *mechanisms* that may be employed individually or collectively as part of governance efforts, and a wide range of *institutions, organizations and peoples* that may need to be involved. The Committee allowed that not all of these elements will be equally important, or appropriate, in different settings and contexts. For example, different mechanisms may be a better fit in some countries than in others. Equally, different groups and individuals may be more or less pertinent, or able to engage, depending upon whether governance efforts are happening in an individual institution, or in an inter-governmental organization.

The Committee identified 8 challenges to be considered when reviewing, creating, or strengthening measures for the governance of human genome editing (see below). While not every issue will need to be specifically addressed in all resulting measures, the Committee is recommending time be set aside to consider each of them in some depth:

- **Differences in ethical views and values within and across nations**
- **Differences in social priorities within and across nations**
- **Differences in culture within and across nations**
- **Differences in public awareness, perceptions, and preferences**
- **Differences in capacity**
- **Maximising benefits**
- **Science that is dynamic and fast paced**

Do you have any comments on these challenges? Are there essential features missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".

ASGCT believes these identified challenges are reasonable for the Committee to consider as part of its draft governance framework. When addressing these issues, ASGCT recommends involvement with a broad range of stakeholders, including scientists with a high level of knowledge of gene editing technology to provide ongoing expertise as the framework is further developed. We particularly agree that the rapid pace of development of gene editing is a challenge of governance, and that maximizing the benefits of somatic cell gene editing should be a high priority when considering mechanisms for governance. We also encourage the WHO to recognize that the safety of gene editing technology for recipients may currently be assessed and should be the primary consideration for a governance framework, regardless of these challenges.

A governance framework for human genome editing might be comprised of different mechanisms. Some mechanisms will directly regulate the use of technology (such as international, regional, national or federal laws, or enforceable codes). Other mechanisms will

aim to provide indirect ways to alter behavior, change how a technology is used, and strengthen a culture of responsibility. The Committee identified 12 mechanisms that might regulate/inform the use of human genome editing, as follows:

- **Laws and regulations**
- **Professional codes of ethics, conduct and practice**
- **Funding requirements**
- **Insurance requirements**
- **Accreditation, registration, or licensing**
- **Standards and guidelines**
- **Publishing requirements**
- **Moratoria**
- **Institutional policies or guidelines**
- **Research review**
- **Licensing or marketing approval requirements**
- **Professional self-regulation**

Do you have any comments on these mechanisms? Are there mechanisms missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".

As the Committee further develops its governance framework, ASGCT would recommend prioritizing consideration of the potential use of laws and regulations; professional codes of ethics, conduct, and practice; standards and guidelines; and institutional policies or guidelines. Although these are broad categories that may encompass a variety of specific actions, ASGCT believes they are valid mechanisms meriting further discussion and detail.

ASGCT particularly supports the consideration of supranational laws and regulations that could prevent the clinical use of germline gene editing without restricting somatic gene editing applications. ASGCT generally opposes additional accreditation, registration, or licensing requirements for somatic cell editing that exceed those applied to other therapeutic products in countries with frameworks in place for regulating gene editing. We oppose utilizing restrictions in funding and publishing to enforce clinical trial reporting of somatic cell gene editing in countries in which existing systems are in place for such reporting.

ASGCT supports the collection by WHO of existing clinical trial data via its International Clinical Trials Registry Platform, which would offer a centralized source of trial information for investigators, clinicians, and the public, as long as doing so does not require additional administrative steps for researchers in countries with existing national registries.

Another way to govern human genome editing technologies is by encouraging, fostering changes in the behavior of those involved in doing the research. The Committee has identified some mechanisms that can be used to have that effect. Mechanisms that foster changes in the behavior of those involved in doing the research:

- **Public education, engagement and empowerment initiatives and activities**
- **Academic and professional training**

- **Academic, professional, and other conferences and information sharing opportunities**
- **Academic, professional and other (e.g., financial) incentives**
- **Technical advances or strategies**

Do you have any comments on these mechanisms? Are there mechanisms missing from the list? Yes/No, if Yes please provide details. Otherwise, write "No".

ASGCT particularly supports the consideration of public education, engagement, and empowerment initiatives; and academic, professional, and other conferences and information sharing opportunities. The Society is pleased to be involved in providing some of these resources and opportunities. These mechanisms should not be utilized in isolation from other oversight mechanisms, however, since they alone do not serve as a sufficiently strong or clear indication of the currently inappropriate nature of the clinical use of germline germ editing. Together with other oversight mechanisms, education and engagement efforts may foster awareness and ongoing dialogue.

A number of different types of institutions, organizations and peoples can play important roles within a governance framework. Some of these may be directly involved with establishing governance mechanisms. This may differ by country and mechanism. For example, in some countries industry organizations can feed into the development of regulations. In other places this does not happen. Different institutions, organizations and peoples may also be involved with enforcing or implementing different mechanisms. For example, in some cases members of the general public may sit on research ethics review committees. In other cases, they may not. Furthermore, different institutions, organizations, and peoples may have other roles in participating in governance, for example, through education, engagement or empowerment initiatives, other forms of training, or shaping public perceptions.

The Committee identified an illustrative list of 17 different institutions, organizations, and peoples that can play important roles within a governance framework:

- **Institutions undertaking human genome editing research**
- **Governments**
- **Health care institutions**
- **Industry associations and other representative bodies**
- **Professional scientific organizations**
- **Publishers of research findings**
- **Scientists including clinician-scientists**
- **Clinicians**
- **‘Citizen scientists’, ‘biohackers’, and their communities**
- **Funders of research**
- **International organizations**
- **Advisory and review boards**
- **Civil society and interest groups**
- **Legal practitioners and academics**
- **Patient groups and those who might be affected by human genome editing**

- **Science fiction writers, game designers, and TV and movie companies**
- **Social media activists**

Do you have any comments on this list? Are there institutions, organizations or people missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".

ASGCT considers a broad and inclusive process to be critical in the construction of the Committee's proposed governance framework. The Society recommends further definition of relevant stakeholders, however. We question the degree of relevance of science fiction writers, game designers, and entertainment media. While we recognize the influence these individuals and companies may have over cultural discussion, ASGCT does not consider their input to be highly germane to the subject matter or vital to inclusive dialogue. In addition, we recommend excluding the category of biohackers, since we question whether engagement would be productive with those who, by definition, exploit genetic material experimentally without regard to accepted ethical standards or for criminal purposes. Relevant social media activists are likely already included within other groupings, such as patient groups and civil society groups.

In addition, ASGCT suggests further clarification of additional categories. Governments is a broad term that may include a variety of stakeholders. The Society considers governmental regulatory bodies and health authorities to be the most relevant governmental entities to play a role in a governance framework. Similarly, health care institutions and clinicians that provide clinical trials and/or *in vitro* fertilization would be the relevant health care institutions in this process. Industry representatives and scientists should include those who research gene editing and/or are developing gene-edited products, as well as those who engage in bioethical research. International organizations should be further defined as international nongovernmental organizations that work on matters of science, technology, health, and/or bioethics, including an emphasis on gene editing. Civil society and interest groups that should be included are those that have ethical/human rights and/or medical/health interests or missions, which would include faith organizations and secular human rights organizations. Relevant legal practitioners and academics are similarly those who work at the intersection of issues of health, medicine, technology, and bioethics. We appreciate the inclusion of professional scientific organizations, as one whose members engage in gene editing research.

FINAL COMMENTS. Is there anything else you think the Committee should be considering in terms of the governance of human genome editing? Yes/No, if Yes please provide details. Otherwise, write "No".

ASGCT applauds the Committee for addressing this important and challenging scientific, ethical, and societal issue. We appreciate this opportunity to be supportive of these efforts and to provide feedback throughout this process, as well as the opportunity the WHO provided for representatives of the Society to engage by phone regarding the WHO registry pilot project.