Orientation to Session

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NATIONAL ACADEMY OF MEDICINE AND
NATIONAL ACADEMY OF SCIENCES

THE ROYAL SOCIETY

Aims of session

- Part of Commission's task is to outline a framework that captures key considerations on which decisions about potential uses of human germline editing might be based

- Will briefly introduce elements on which Commission seeks input
  - Part A - categories of uses of human germline genome editing for which it might be possible to develop a responsible clinical translational pathway
  - Part B - core elements that might form part of a clinical translational pathway

- Session panelists will provide their perspectives

- Information in this session is for discussion & **does not represent conclusions of recommendations of the Commission**

Part A: Foundational questions that need to be addressed for any proposed use

Selected Scientific Questions *(partial list)*

- What is the intended clinical purpose of the human germline genome editing that is under consideration?
- Do alternative clinical approaches exist that would be likely to accomplish the intended clinical purpose?
- What specific genomic edit(s) would be required?
- What is the expected frequency of different types of off-target edits? How would potential adverse effects be assessed?
- Is there evidence whether the desired genomic edit(s) could have potentially undesirable phenotypic consequences for the edited individual or descendants with the edit?
- Have the editing and delivery technologies been extensively tested in the context of human somatic genome editing and been found to be robust, safe and effective?

Selected Societal Questions

- What are the potential non-clinical implications of the proposed use—including social, ethical, cultural, and societal issues—that should be evaluated through appropriate processes?
- What other factors—such as cost, access, and health care disparities—should be considered in evaluating the desirability of pursuing the intended use?

Initial taxonomy of potential uses

a. Monogenic conditions with life-threatening or severe health consequences
b. Monogenic conditions that increase risk of serious disease
c. Monogenic conditions that affect ‘quality of life’
d. Polygenic variation affecting serious disease risk
e. Genetic variation affecting non-disease traits
f. Novel genetic changes

Key considerations associated with types of uses

For example:

- **Nature of genome edits**. Is the proposed edit aiming to change a rare variant to a sequence commonly carried in the population?
- **Possibility of PGD as an option to conceive unaffected children**.
- **Penetrance**. Is there a high likelihood that offspring carrying the disease genotype will develop the clinical disorder?
- **Existence of effective prevention or treatment**. Do prevention or treatment options currently exist that prevent, mitigate or cure the clinical condition? Does germline genome editing fill an unmet clinical need?

Decision point

Assessment of the available base of evidence to address foundational questions and take account of the key considerations associated with types of potential uses leads to a decision point

For which potential use categories might it be possible at the present time to develop a responsible clinical translational path?

- For potential use categories in which it is possible to develop a responsible translational path, one could proceed further to develop the details of such a path
- Other potential use categories would need to be revisited at a future date in light of advances in knowledge, prior to developing any translational path.

Part B: Framework for developing a responsible translational path

- Could be developed for a potential use of human germline genome editing proceeding past Part A
- Initial list of elements forming part of a translational pathway and oversight system
  - **Legal approval** for the proposed use
  - **Adherence to normative practice guidelines, standards, and policies** for the relevant areas of scientific and clinical practice
  - **Institutional review and approval** of investigator qualifications, study design, and ethical and human subjects protections
  - **Assessment and approval by appropriate national regulatory body** in areas such as:
    - **Context of Proposed Use** (clinical condition, potential alternative therapies, etc.)
    - **Preclinical Evidence** (on- and off-target characterization, mosaicism, anticipated side effects)
    - **Clinical Evidence** (embryo results, protocols for informed consent)
    - **Other Considerations** (long-term follow-up, other social and ethical issues)
  - **Adherence to relevant outcome reporting** requirements to national or international bodies
  - **Adherence to relevant mechanisms for international coordination** for human germline genome editing that may be established
  - **Continued discussion, learning and assessment** related to the scientific, ethical, and societal considerations associated with human germline genome editing

Session structure

- Panelists have been asked to provide their perspectives and input:
    - Are the questions the right ones?
    - Does the draft taxonomy sufficiently capture potential types of uses?
    - What are the most relevant key considerations for different types of uses?
    - What else needs to be captured as part of the core elements of a responsible translational pathway?
    - How should a decision on a potential application of human germline editing be made?
- Each panelist will provide initial remarks (10 min each)
- Question and discussion period (30 min)