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ESHRE/ESHG: Recommendations regarding human germ-line gene editing

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Conflicts of interests:

None

Background

Human genome editing raises high expectations & serious ethical concerns; esp. controversial is human *germ-line* genome editing (GLGE)

ESHG/ESHRE: professional responsibility to contribute to societal debate by providing

- relevant information
- normative guidance →

Background (cont.)

Invited their relevant (ethics/policy) Committees:

- Background paper &
- (joint) Recommendations on human GLGE

Status:

- accepted by the Boards, & accepted for publication by the Editors of both EJHG & Hum Reprod Online
- *provisional* Recomm.; to be regularly evaluated

Discern different contexts →

I. Non-reproductive human GLGE

No sharp demarcation *basic* – and *pre-clinical* research

A. *Basic* research

There are good reasons to allow basic research, including *human embryo* research

We should re-think the (European) Oviedo Convention, esp. its categorical prohibition of making embryos for research purposes (so-called ‘research embryos’); no fundamental ethical difference between ‘spare’ and research embryos

Non-reproductive human GLGE (cont.)

B. *Pre-clinical* GLGE?

The broader context: *responsible* innovation (requiring 'research embryos') in ART (ESHRE)

Analogy: pre-clinical testing of new medical drugs

The general framework for ART/pre-clinical (safety) studies is applicable here as well →

pre-clinical GLGE is a *necessary* condition for clinical GLGE; *but should we allow clinical GLGE?* →

II. Clinical GLGE: 1. Deontological objections?

If safe and effective, GLGE may have important benefits for prospective parents at high risk of having an affected child

Deontological objections include:

- 'It is unnatural'
  - But the moral relevance of Nature is contested, and accepting this objection would have major implications for medicine *generally*

- 'It is at odds with human dignity'
  - But difficult to see *why* in the case of *therapeutic/preventative* GLGE

Deontological objections? (cont.)

- ‘The human gene pool should be preserved as a common heritage’
  - But *which* gene pool, precisely? By the way: correcting mutations *does* preserve the gene pool …

- ‘It is at odds with respect for autonomy, as the child did not consent, and GLGE undermines its right to an open future’
  - But did *you* consent in your conception? While some types of enhancement could undermine the child’s open future, medical GLGE does not

Conclusion: these deontological objections seem to be unconvincing as *categorical* objections to GLGE

Clinical GLGE: 2. Consequentialist objections

A. Health risks

Incl. off-target and (antagonistic) pleiotropic effects

In view of the many unknowns, any clinical GLGE is premature and presently unacceptable …

… but this may change. Conditions? →

Health risks (cont.)

Future clinical GLGE can only be morally justified

- if adequate pre-clinical safety-research shows GLGE to be sufficiently safe and effective

  nb ‘how safe is safe enough?’

- if such GLGE is embedded in a formal research trajectory asap

  nb Clinical Trials Regulation EU no. 536/2014, art.90 → counter-productive effects …

Health risks (cont.)

- if embedded in long-term follow-up studies on the health of children thus conceived

  nb practical barriers/limits, e.g. lack of funding or tensions with privacy/autonomy, make this challenging

- if ‘comprehensive’ PGT of edited embryos (on the basis of WGS) would be included as a safeguard, this should be targeted at *possible off-target effects*. A possible broadening of the analysis of the raw data thus generated would raise complex additional ethical issues and needs further analysis and debate.

Consequentialist objections (cont.)

B. *Societal* concerns incl.

1. Inequity

Poverty – a large-scale moral scandal

But:

- inequity regards many other technologies;
- access to be decided on the level of society;
- (conditional) public funding, as provided for PGD in some countries, may mitigate this concern;
- no ‘leveling down’ justice (‘if equal access is not reached, *no one* should have access to the treatment’)

Consequentialist objections (cont.)

2. Undermining reproductive autonomy

But:

-GLGE may also *increase* this autonomy (see below);

-Furthermore:

- this is a well-known objection to repro-genetic technologies *generally*
- it would be problematic to *selectively* prohibit GLGE for this reason
- a challenge: guaranteeing medical and societal care and support for all affected children

Consequentialist objections (cont.)

3. Possible misuse

If (safe and effective) clinical GLGE is considered to be sound, priority should be given to the editing of highly penetrant genes for serious disorders.

Still, fears of a slippery slope; after all

- the distinction serious/less serious disorders is unclear
- the distinction therapy/prevention/enhancement is not clear-cut.

Possible misuse (cont.)

Further multidisciplinary reflection on

- demarcation of serious disorders;

- ‘designer babies’: enhancing complex traits is largely science fiction - and would run a disproportional risk of (antagonistic) pleiotropy;

- intermediate subtypes of ‘*medical enhancement’*, such as strenghtening the human immune system and editing carrier status for recessive disorders

Possible misuse (cont.)

The experience (in e.g. the UK & the Netherlands) with the regulation of PGD and other reproductive technologies may help to build a sound strategy for regulating possible future clinical GLGE, including

- a licensing system and
- obligatory regular reporting by licensed clinics about their policy/practice

in order to strenghten societal oversight.

Possible alternatives: balancing

In view of the medical and social risks of GLGE, it is important to take account of other options.

PGD may be a good alternative in most cases.

To argue, however, that ‘there is no real need for GLGE’ is a *non sequitur*, for different reasons, incl.:

Possible alternatives (cont.)

- some couples can only conceive affected children
- in some ICSI/PGD cycles, no embryo is suitable for transfer
- respect for reproductive autonomy (e.g. <embryo loss)

Alternatives (cont.)

A further ethical and societal evaluation of relevant aspects, including both health risks and societal risks, is needed in order to define indications for possible future clinical GLGE as an alternative for PGD aimed at selectively transferring an unaffected embryo.

III. Governance

An ongoing debate about material and procedural issues raised by non-reproductive and reproductive GLGE is important.

Such debate should be inclusive; apart from scientists and clinicians, other stakeholders should be invited to participate, including patients' organizations, policy makers, the public and scholars in the medical humanities.

Governance (cont.)

The current Recommendations build a first, joint, contribution of both ESHRE and ESHG to the suggested trajectory of public deliberations. The Recommendations have a provisional nature and are to be evaluated regularly and systematically.

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Literature

De Wert G, Pennings G, Clarke A, et al. Human germline gene editing. Recommendations of ESHG and ESHRE.

De Wert G, Heindryckx B, Pennings G, et al. Responsible innovation in human germline gene editing. Background document to the Recommendations of ESHG and ESHRE.

Both articles have been published in both the Eur J Hum Genet & Hum Reprod Online 2018