Genetic manipulation in human reproduction: what are the challenges

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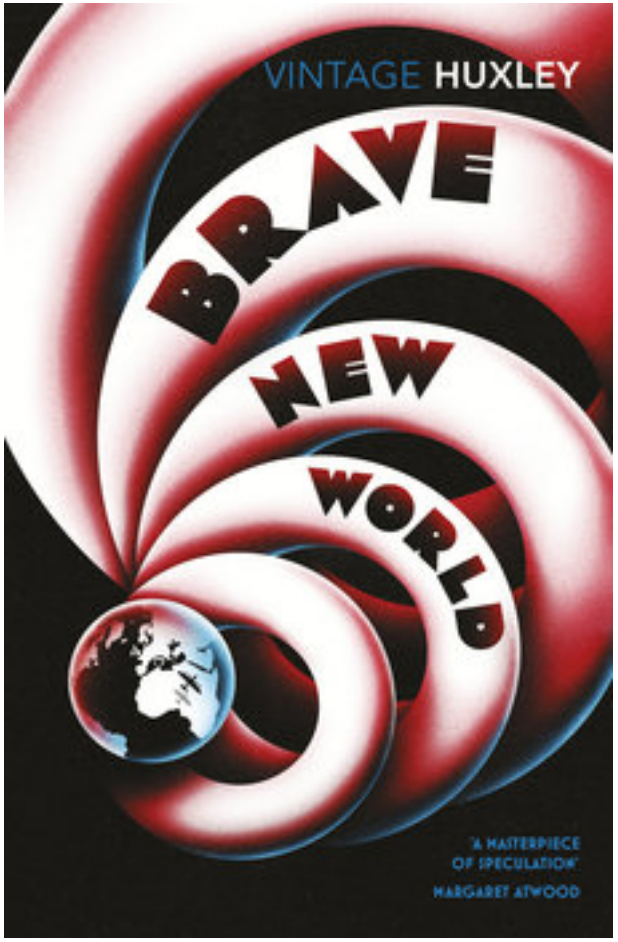
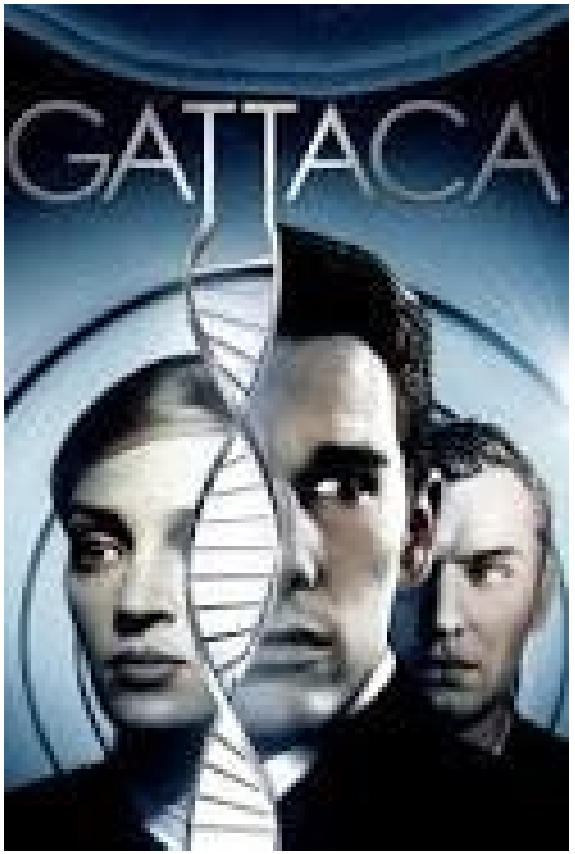
I have no conflict of interest

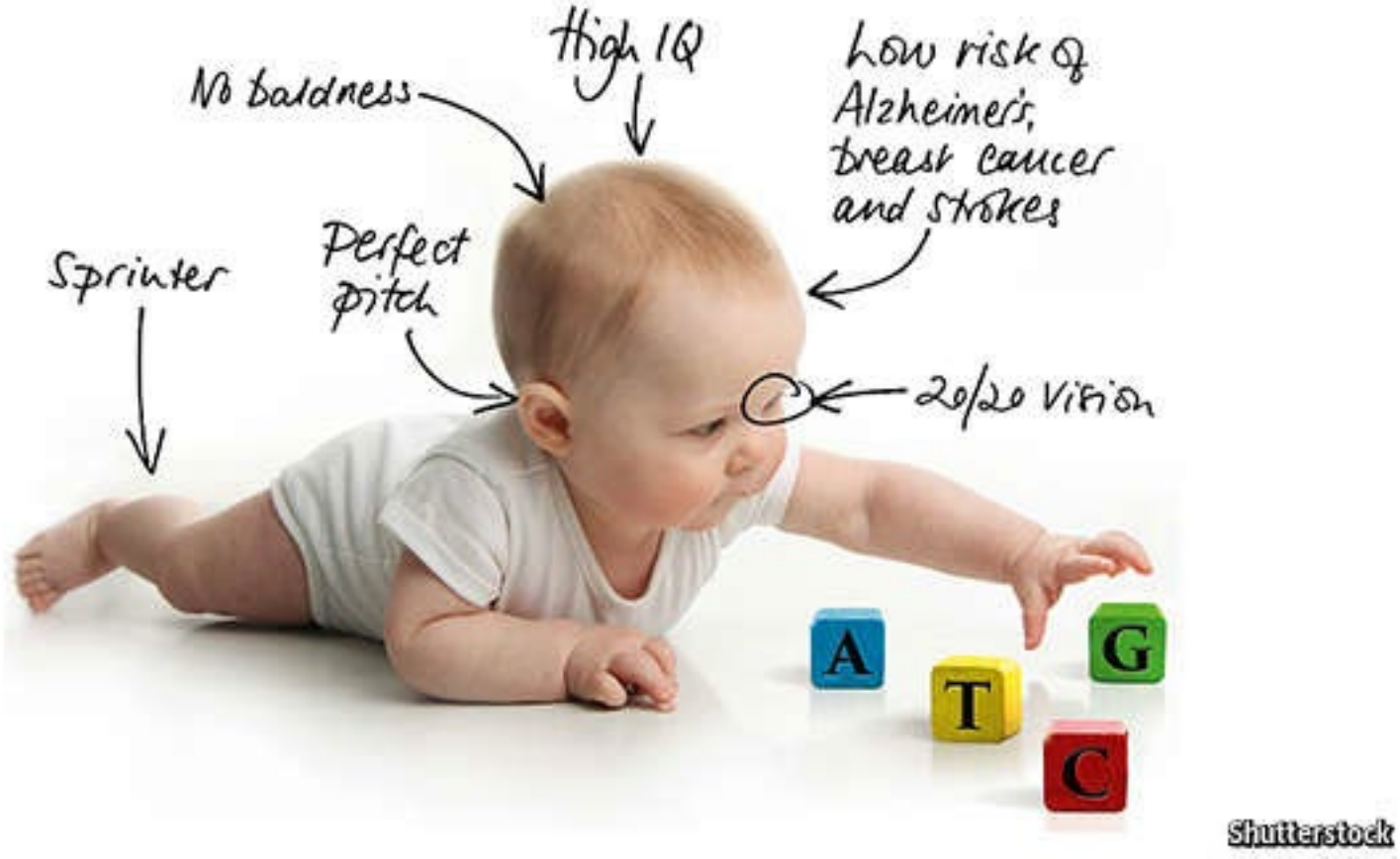
Literature and movies





Editing humanity

The Economist Aug. 22, 2015



What has already happened

Mitochondrial replacement 2016

Nana and Lulu 2018

ONE THING TO BEAR IN MIND: the IVF procedure is not changed, and the new reagents are NOT Medical Products of Human Origin

Mitochondrial diseases

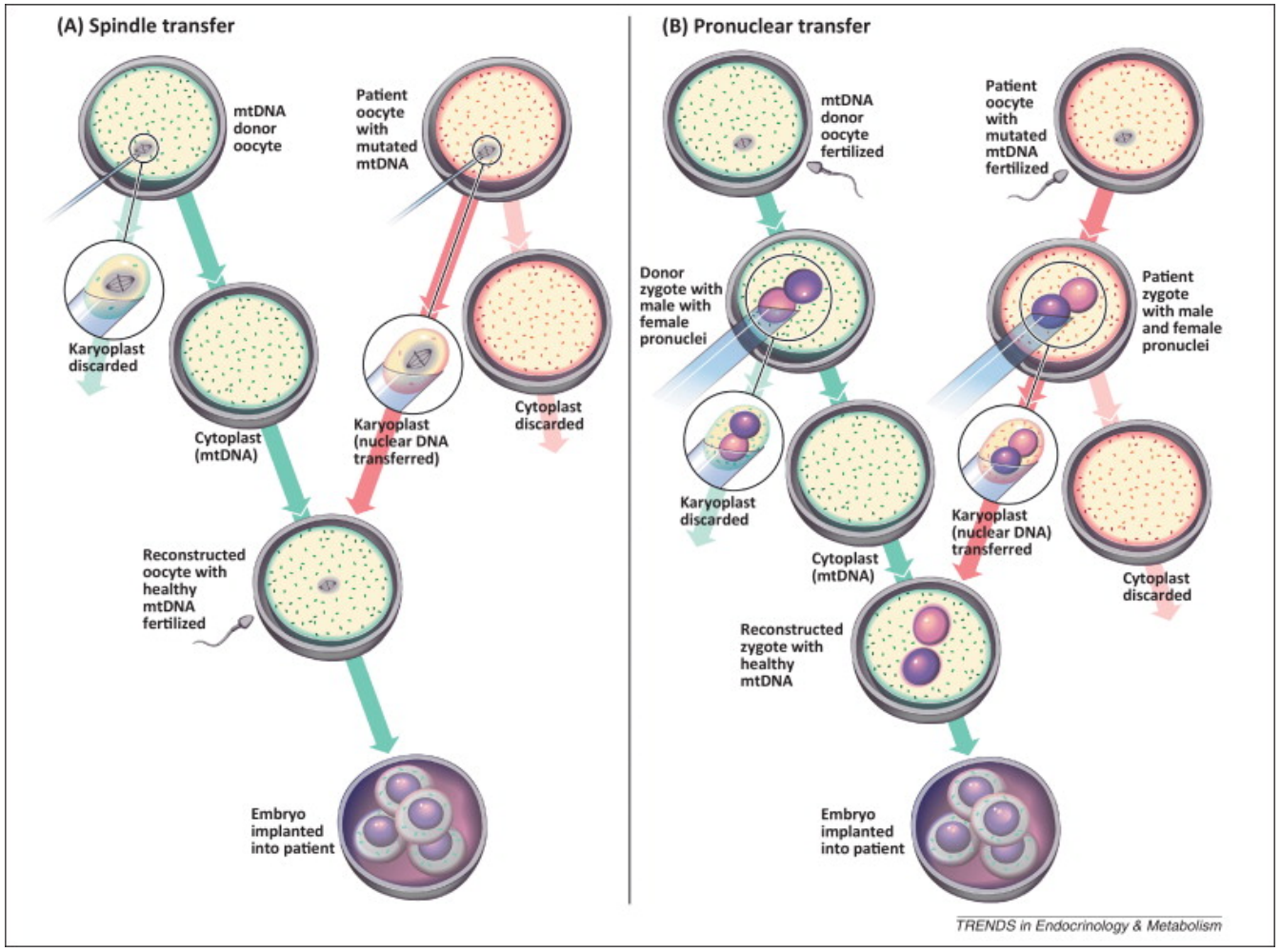
- Mitochondria – semi-autonomous organelles in practically all cells
- Maternal inheritance
- Have their own DNA; 37 genes (13 encode proteins)

2016

Exclusive: World's first baby born with new "3 parent" technique – boy born April 2016 to mother with Leigh syndrome – via spindle transfer (in Mexico) < 1% of affected mtDNA

The paper has been published, spindle transfer

20 more babies planned for 2017 -FDA - ban



Problems

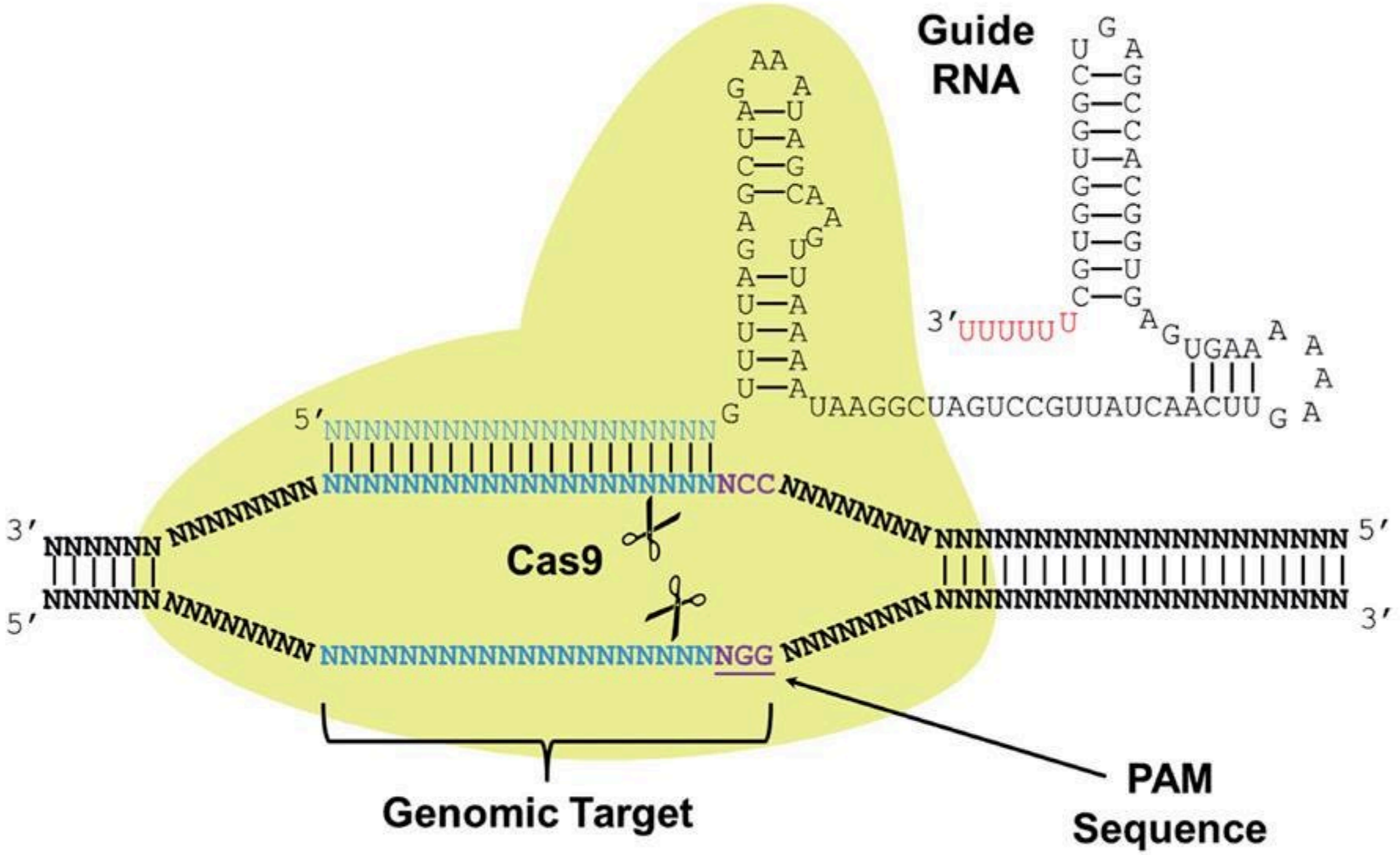
- Mitochondrial mother and nuclear mother?
- Should only male embryos be implanted to prevent transferring DNA to subsequent generations
- 150/year UK, 800/year USA
- **Newcastle scientists get permission from HFEA: 5 years**
- **5 procedures/year for 5 years**

In 2016 and 2017

- **World-First in Ukraine as 'three-Parent' Baby Born to an Infertile Couple**
- **“Three parents”, one baby, and a lot of controversy.**
- In contrast to mitochondrial diseases even if it works we do not know why
- No disease, failed IVF, pronuclear transfer

CRISPR

- clustered regularly interspaced short palindromic repeat (CRISPR),
- Defense system against viruses


Guide RNA
5′ NNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNCC
3′ NNNNNNN
NNNNNNN 5′
Cas9
NNNNNNNNNNNNNNNNNNNNNGG
3′ UUUUU
UAAGGCUAGUCCGUUAUCAACUU G A
UGAA
Genomic Target
PAM Sequence

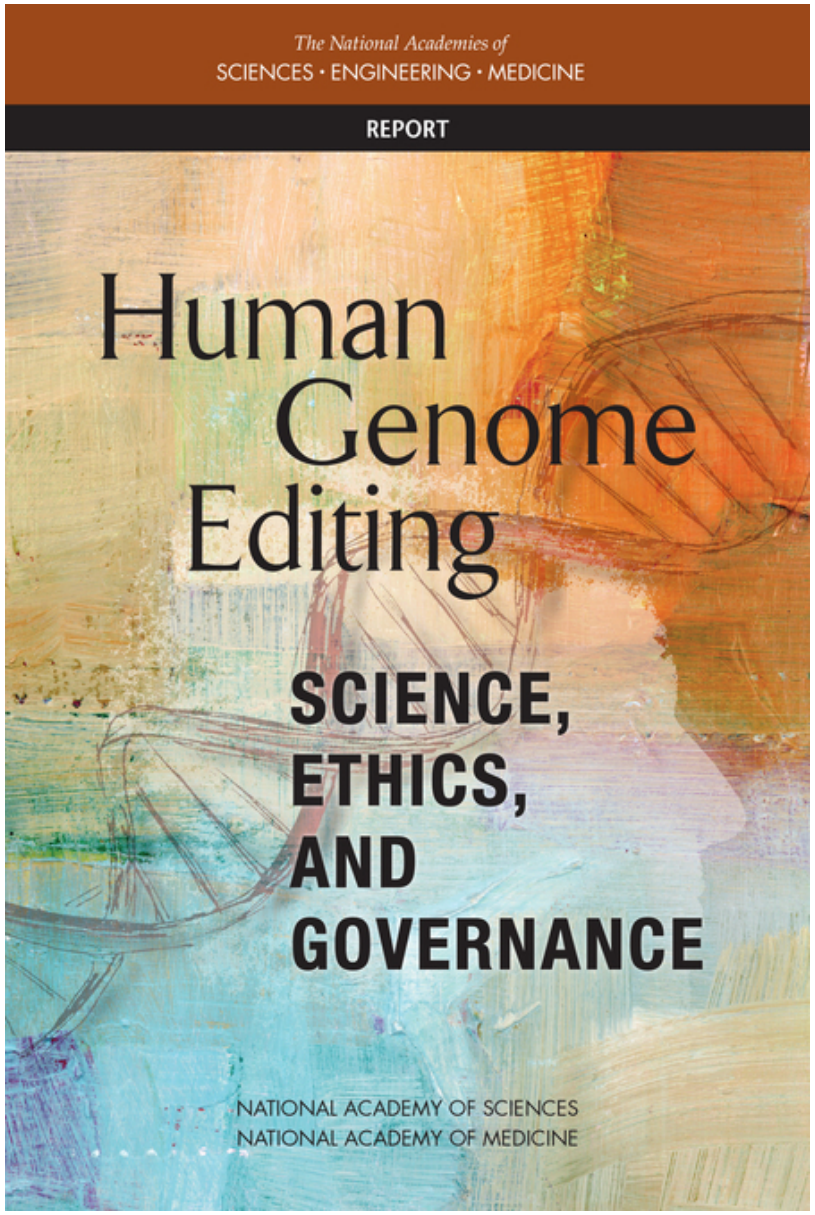
Biotechnology. A prudent path forward for genomic engineering and germline gene modification

Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church G, Corn JE, Daley GQ, Doudna JA, Fenner M, Greely HT, Jinek M, Martin GS, Penhoet E, Puck J, Sternberg SH, Weissman JS, Yamamoto KR. **Biotechnology. A prudent path forward for genomic engineering and germline gene modification**

- Science. 2015 Apr 3;348(6230):36-8

Baltimore et al..1

„Strongly discourage…any attempts at germline modification for clinical application in humans while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations….This will enable pathways to responsible uses of this technology, if any, to be identified”



PDF]Genome editing: an ethical review - Nuffield Bioethics

nuffieldbioethics.org/wp-content/uploads/

Genome editing and human reproduction social and ethical issues

Human Genome editing Science, ethics, and Governance

- absence of reasonable alternatives;
- restriction to editing genes that have been convincingly demonstrated to cause or strongly predispose to a serious disease or condition;
- credible pre-clinical and/or clinical data on risks and potential health benefits;
- ongoing, rigorous oversight during clinical trials;
- comprehensive plans for long-term multigenerational follow-up; and
- continued reassessment of both health & societal benefits and risks, with wide-ranging, ongoing input from the public.

Oviedo

Article 13 –An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

Article 18 – 1 Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo.

2 The creation of human embryos for research purposes is prohibited

What must be addressed

How to engage the public in a discussion

GENETIC ALLIANCE UK/Progress Educational Trust/Welcome – Basic understanding of genome editing

Media

What about the germline? – Oviedo

Ethical trials – watch for several generations? (Cwik, NEJM)

Acceptability of germline interventions (Church,2017; Steffann et al., 2018)

How to do GLOBAL regulation ????

Nature March 22, 2018

1) A global observatory for gene editing

Sheila Jasanoff and J. Benjamin Hurlbut call for an international network of scholars and organizations to support a new kind of conversation.

2) Rethink public engagement for gene editing*The breadth of social and moral questions raised requires a new architecture for democratic debate, insists Simon Burall*g

.

Problem of education

- GMOs, vaccines, stem cell treatments …
- EDUCATION AND INFORMATION
- Jaime Metzl „The whole species must inform the debate before any genetic revolution is unleashed” – Financial Times article

Problem of oversight

- Mexican baby – “prepared” in US, then everything in Mexico
- Problem of “genetic enhancement” tourism?

So far

Cells with introduced modifications used to treat a baby with leukemia

Removal of about 50 retroviral genomes from porcine DNA, cells then pigs

In vitro Huntington disease gene removed

Nana and Lulu

He – 19.11 2018

- He Jiankui announces the birth of twins – their genomes had been edited - CCR5 gene inactivation – to protect against HIV
- The girls' father is a carrier
- Press, youtube, presentation at conference, no paper
- 8 -> couples; 22 embryos, 16 edited, 1 twin pregnancy

Mice, then monkeys

- In one twin both CCR5 genes inactivated (del4, ins 1), in the second twin one (del 15)
- No other changes?
- Informed consent murky

He – November 2018

- CCR5 –HIV entry into cells
- del32/del32 (2-4% European population) resistant to most HIV strains
- AIDS cured after bone marrow transplant from del32/del32 donor

  Berlin patient and London patient

  But no transfer from father in IVF

  CCR5 also has other functions

CCR5-Δ32 is deleterious in the homozygous state in humans

- : 03 June 2019 *Nature Medicine* (2019)
- Xinzhu Wei & Rasmus Nielsen
- We use the genotyping and death register information of 409,693 individuals of British ancestry to investigate fitness effects of the *CCR5*-Δ32 mutation. We estimate a 21% increase in the all-cause mortality rate in individuals who are homozygous for the Δ32 allele.

WHO expert advisory committee on developing global standards for governance and oversight of Human Genome editing

Registry for anything to do with human genome editing (somatic and germline)

WHO International Clinical Trials Registry Platform (ICTRP). The ICTRP gathers the trial registration data sets provided by primary registries.

Oversight and governance

Education, engagement and empowerment

What's next

- Therapy and enhancement
- This is not so simple – muscle in muscular dystrophy and muscle in healthy person/athlete
- CCR5 –HIV resistance – enhancement/therapy
- Premature
- Whether and when – monogenic diseases but there are other methods
- Russia – Denis Rebrikov – HIV+ mothers; deaf couples -> children who are not deaf