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Overview of Crispr/Cas Gene Editing for Clinical Applications potential benefits, risks and concerns

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DISCLOSURES

- No financial conflict of interest (COI)
- Co-Chair of the Ethics of Gene Modifying Technologies Working Group under the Science, Health and Policy-relevant Ethics in Singapore (SHAPES) initiative of the Centre for Biomedical Ethics, National University of Singapore (NUS)
- Member of Institutional Review Boards (IRBs) for the Defence Science Organization (DSO) and Singapore Armed Forces (SAF) and for Lee Kong Chian School of Medicine, Nanyang Technological University (NTU)
- All views and positions expressed in this presentation are my own

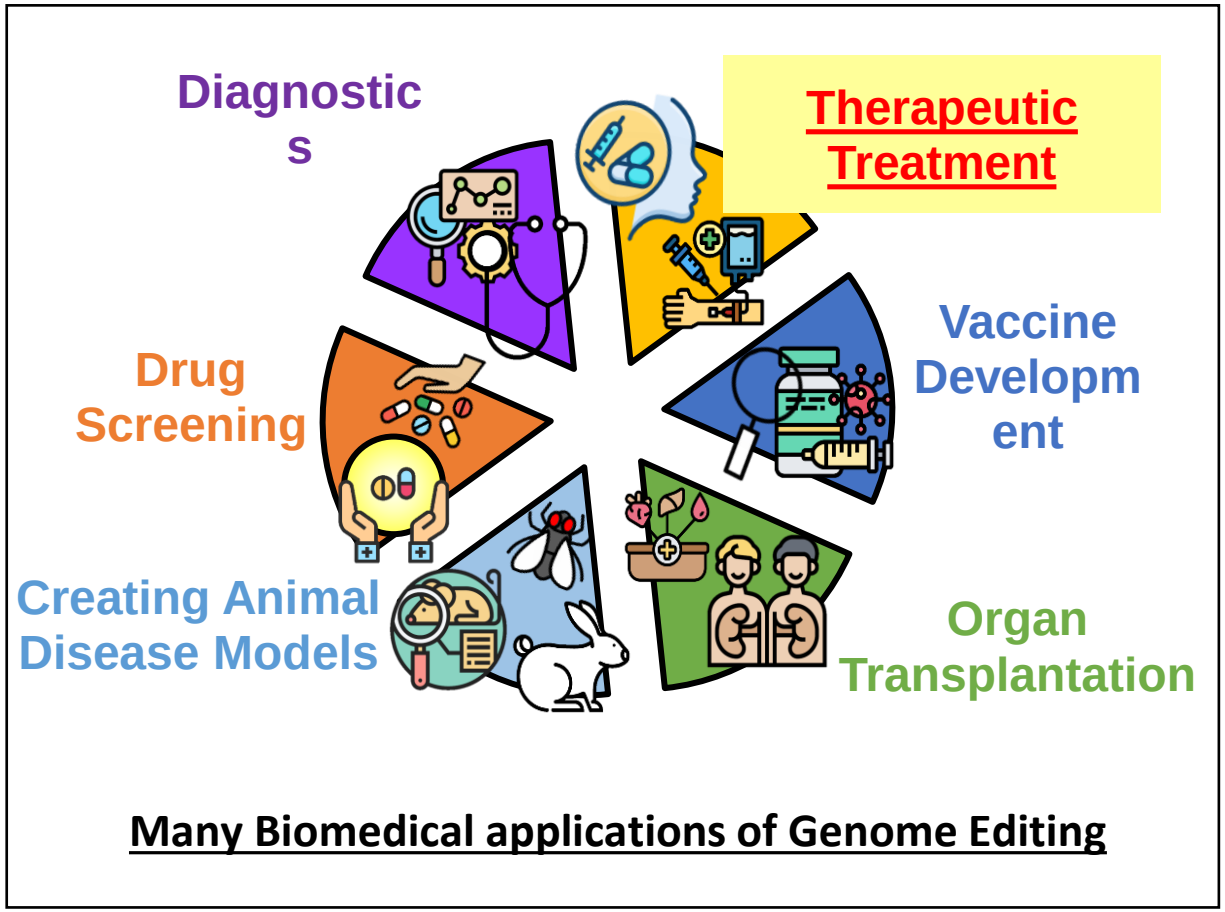
OUTLINE

1. Broad overview of gene editing in gene therapy & clinical trials
2. Potential benefits
3. Concerns (safety and ethical issues)
4. Current status in policies/governance of human genome editing

Current status of genome editing (CRISPR) in clinical translation from Bench to Bed?

Gene/Genome Editing in Humans

- Many approaches of gene editing: TALENS, zinc finger, base editing, prime editing, Crispr/Cas, etc.
- Many targets of editing: genome, epigenome, transcriptome, etc.
- Many biomedical applications: diagnostics, drug screening, creating animal disease models, therapeutic treatment



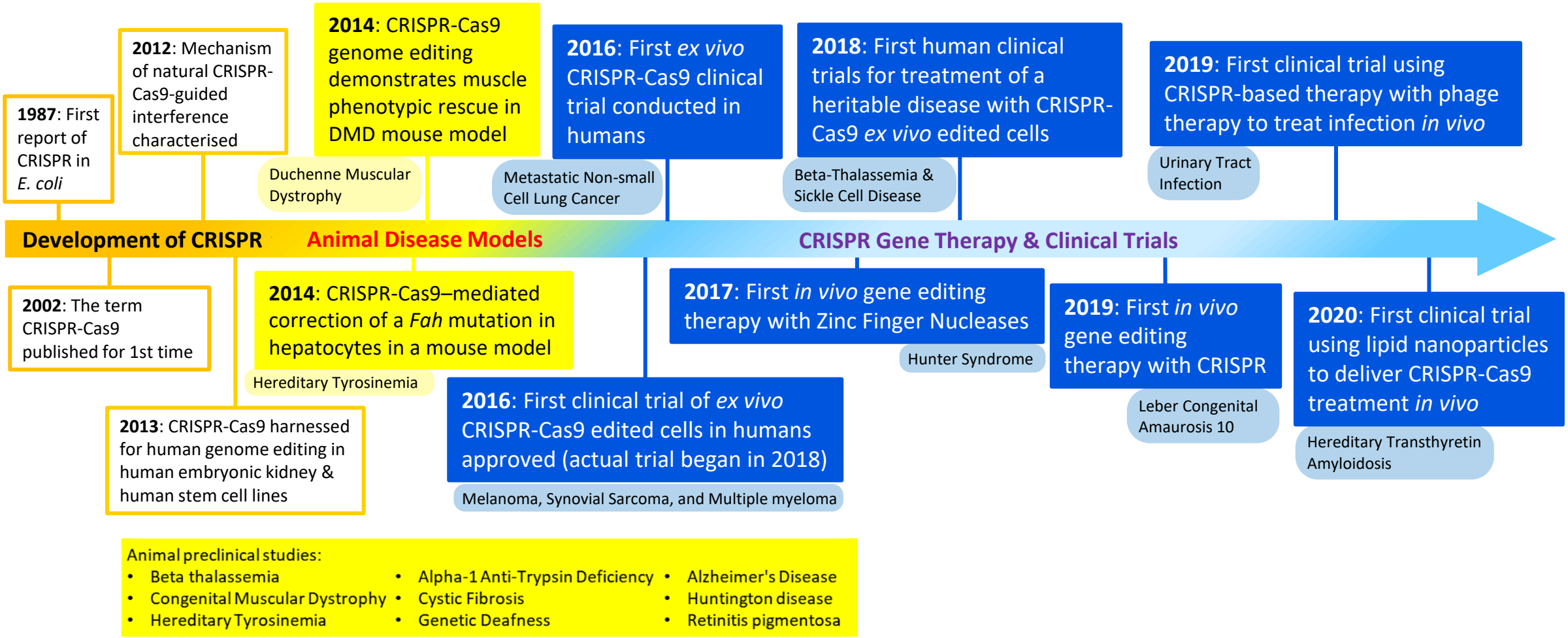
Many Biomedical applications of Genome Editing

1980: First attempted gene therapy trial (ß-thalassemia)
1987: First successful clinical therapy (SCID :severe combined immunodeficiency)

- Past 40 years from 1980s, many studies and attempts at **gene therapy**
- ***Many early stage clinical trials*** **but** ***few successful ones***
- Challenges in delivering functional genes to intended organ and achieving sufficient gene expression to make a clinical impact
- **Recent developments in gene editing tools** making them more efficient and easier to use – **clinical translation for gene therapy**?

Clinical Trials using Crispr/Cas

- Demonstration of efficacy of Crispr/Cas in pre-clinical animal studies: Duchenne muscular dystrophy (DMD), beta thalassemia, cystic fibrosis, genetic deafness, etc.
- First in human clinical trials using Crispr/Cas began in 2016 in cancers and in 2018 for monogenic disorders
- First *in vivo* (inside body) trial using zinc finger nucleases in 2017 and using Crispr/Cas in 2018



2021 and onwards .....

ViaCyte, in partnership with CRISPR Therapeutics, is currently developing **allogeneic pancreatic-lineage cells** by *ex-vivo* editing immune-modulatory genes within the stem cell line used to produce the cells to treat patients with **insulin-requiring Type 1 diabetes**. They plan to initiate a Phase 1/2 trial of the allogeneic stem cell-derived therapy with safety and efficacy assessment expected in second half of 2021.

Disease	Study title	Strategy	Study phase	Study type	Participants (No., Age)	Company
Transfusion-Dependent β-thalassemia	A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia	CTX001	Phase 1 Phase 2	Interventional	45 patients, ≥18 and ≤35 years of age	Vertex Pharmaceuticals Incorporated & CRISPR Therapeutics
Sickle Cell Disease	A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease	CTX001	Phase 1 Phase 2	Interventional	45 patients, ≥18 and ≤35 years of age	Vertex Pharmaceuticals Incorporated & CRISPR Therapeutics
β-thalassemia	iHSCs With the Gene Correction of HBB Intervent Subjests With β-thalassemia Mutations	HBB HSC-01	Early Phase 1	Interventional	12 patients, ≥ 2 and ≤ 60 years of age	Allife Medical Science & Technology Co., Ltd.
Leber congenital amaurosis LCA10	Single Ascending Dose Study in Participants With LCA10	AGN-1515 87	Phase 1 Phase 2	Interventional	18 patients, ≥ 3 Years	Allergan & Editas Medicine, Inc.

Data from https://clinicaltrials.gov/

New CRISPR technology for Epigenome: Researchers at UC San Francisco and the Whitehead Institute develop novel CRISPR-based tools called "CRISPRoff" and "CRISPRon", allowing modification of the epigenome to **switch off or on almost any gene in human cells without editing the genetic code.**

U.S. Food and Drug Administration grants approval for an early phase, first-in-human clinical trial of a CRISPR gene correction therapy in patients with sickle cell disease **using the patient's own blood-forming stem cells**. It will be the first time clinical researchers attempt to correct the faulty beta-globin gene directly, instead of the more costly and indirect approaches such as reactivating foetal haemoglobin or using viral vectors to suppress the gene that turns off the foetal globin production at birth

√ Improvements in technology (delivery methods, multiplex base editors, etc.)
√ Further developments in approaches (Immunotherapy re-engineering T-cells, immune evasive stem cell therapy, etc.)
√ More clinical trials expected – great potential for future treating genetic diseases in clinic

Benefits and Applications

Why is Crispr/Cas9 so special for human therapeutic applications?

- More accurate, more efficient > previous approaches
- Faster and cheaper to design
- Easy to develop and use by labs
- Programmed to target anywhere in human genes
- Target for any correction – and not just replacement
- Edits (insert, delete or suppress genes)
- Diseases beyond current ability to treat
- Monogenic and complex genetic diseases
- Carriers of mutations who are unable to have a genetically related child

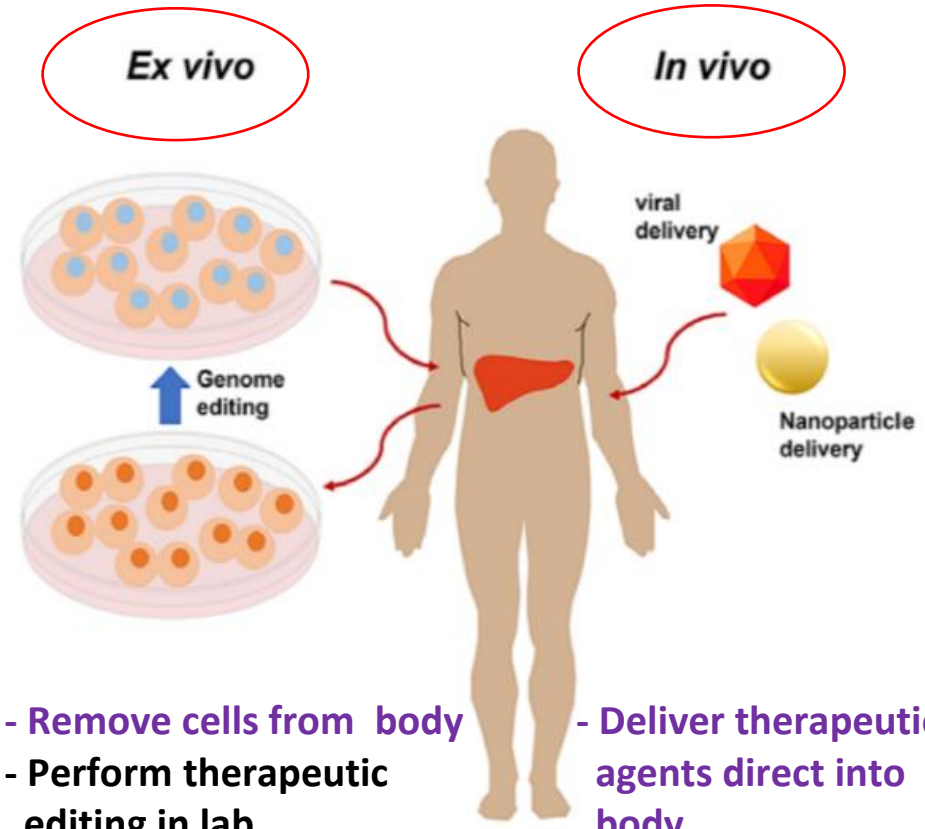
Wat are the potential benefits?

Fulfil promise of gene therapy first mooted in 1980s

Treat diseases, One time permanent cure

Two potential *targets for editing*: somatic and germline cells

1. GENE EDITING IN SOMATIC CELLS



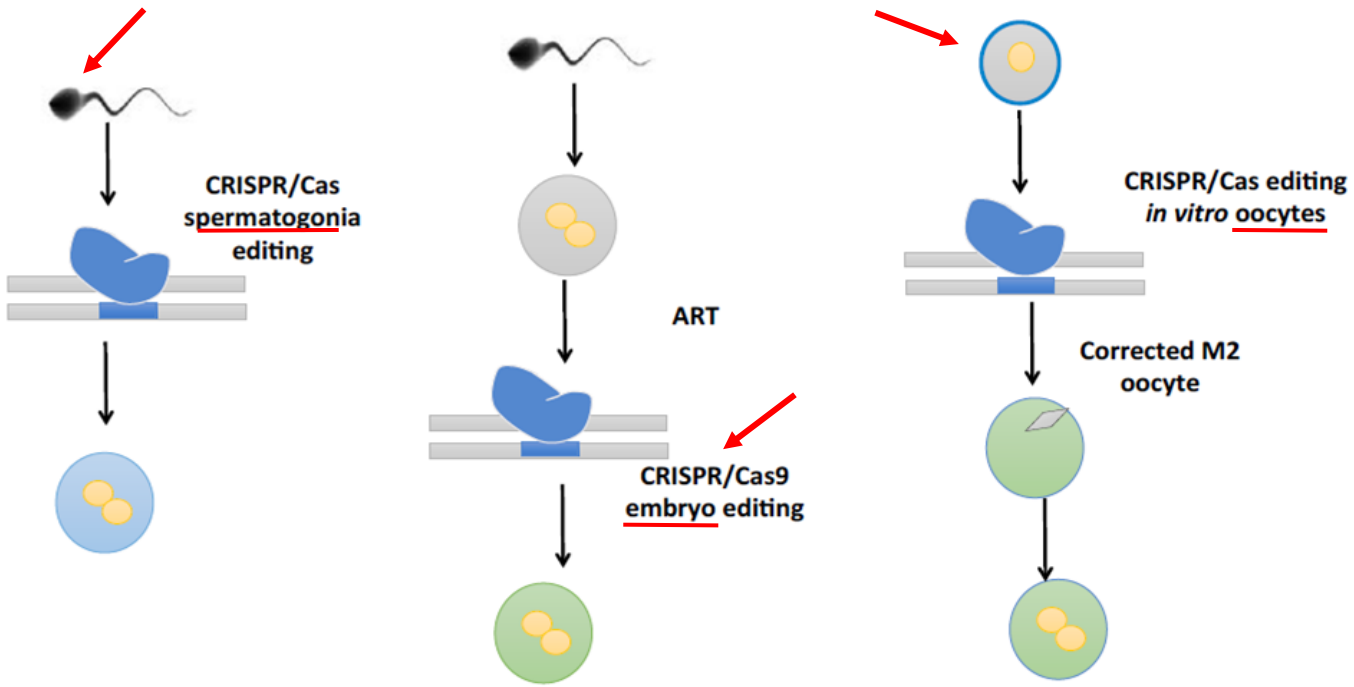
- Remove cells from body
- Perform therapeutic editing in lab
- Transfer cells back

- Deliver therapeutic agents direct into body
- Editing & correction inside cells & tissues

Hirakawa et el 2020

2. GENE EDITING IN GERMLINE (REPRODUCTIVE) CELLS

HGGE : Human Germline (Heritable) Genome Editing



ART: Assisted Reproductive Technologies

Figure 8.2 A schematic illustrating the use of CRISPR/Cas9 in sperm, oocyte and embryo genome editing. The corrected sperms and oocytes can be used in artificial reproduction techniques to produce healthy embryos.

Applications of Crispr/Cas9 in Reproductive Biology: Adapted from Khan et al 2018

2013: Mouse embryos with birth of 1st Crispr-edited mammals
2015: First report of human tripronuclear embryos (non-viable)

Treatment for couples unable to have a genetically related healthy baby?

nature BIOLOGY

April 19, 2016

Gene-Editing Research in Human Embryos Gains Momentum

Experiments are now approved in Sweden, China and the United Kingdom

By Ewen Callaway, Nature magazine on April 19, 2016

Credit: Getty Images/iStockphoto /Thinkstock (MARS)

November 28, 2018

Possible issues and concerns in clinical editing using Crispr

Possible Risks (Safety)

1. Off-target effects (inaccurate editing, unintended changes)
2. Mosaicism (mixture of corrected and uncorrected cells)
3. Immune response stimulated by Crispr/Cas
4. DNA damage activated by Crispr/Cas
5. Unknown potential side-effects in individual (take years to emerge?)
6. Technical issues (efficacy, delivery, etc.)

Other Issues (somatic & **germline)**

- Accessibility and inequalities
- Truly Informed Consent

Vulnerable subjects

Proxy consent

- Side-effects in embryos (after birth)

Unpredictable effects on future generations

- Treating a "future" person and not current patient
- Exploited for non-therapeutic (infertility, sense of smell, night vision)

Strength, speed, endurance, hair or eye color, longevity,

Eugenics: improvement of human species or "super-humans"

Altering human evolution

- Outcry lead to erosion of trust and hinder scientific developments

- Other ELSI not discussed here -

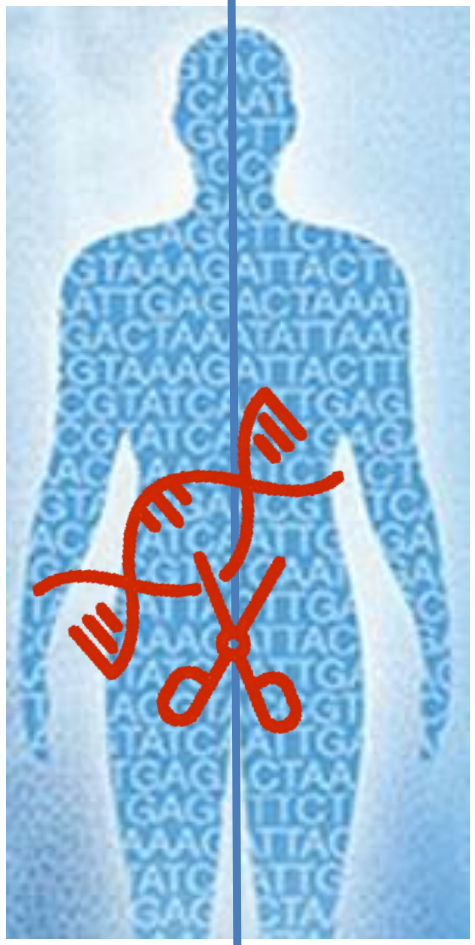
Contentious and Divided Opinions on Germline Editing

YES
YES with caveats

- Germline editing is inevitable when safety and efficacy issues are eventually resolved
- May be the only way for genetically related offsprings if unable to produce healthy embryos
- Potentially decrease or even eliminate genetic diseases
- Moral duty to relieve or offer cure

➢ Caveats

- Engagement of all stakeholders including public
- Some form of oversight needed
- Ethical & Regulatory framework
- International consensus, harmonize policies, jurisdictions



NO
NOT
NOW/WAIT

- Not ready and moratorium needed Perhaps, may never even be ready?
- Slippery slope: somatic/germline barrier
- Ethical and moral reasons
- Other options of conceiving healthy child (PGD and IVF, fetal or *in utero* therapy)
- Benefits only to minority but impact on society (future generations & human species). Human genome is shared
- Human dignity, values and identity (attitudes about disabilities & desired traits)
- Undue pressure from vested stakeholders (patent holders, sponsors, etc.)

Current Status:
Professional Recommendations?
National Policies?
Regulations?

ASHG POSITION STATEMENT

Human Germline Genome Editing

Kelly E. Ormond,[1,19,*] Douglas P. Mortlock,[2,19] Derek T. Scholes,[3,19] Yvonne Bombard,[4] Lawrence C. Brody,[5] W. Andrew Faucett,[6,7] Nanibaa' A. Garrison,[8,9] Laura Hercher,[7,10] Rosario Isasi,[11] Anna Middleton,[12,13] Kiran Musunuru,[14] Daniel Shriner,[15,16] Alice Virani,[17,18] and Caroline E. Young[3]

With CRISPR/Cas9 and other genome-editing technologies, successful somatic and germline genome editing are becoming feasible. To respond, an American Society of Human Genetics (ASHG) workgroup developed this position statement, which was approved by the ASHG Board in March 2017. The workgroup included representatives from the UK Association of Genetic Nurses and Counsellors, Canadian Association of Genetic Counsellors, International Genetic Epidemiology Society, and US National Society of Genetic Counselors. These groups, as well as the American Society for Reproductive Medicine, Asia Pacific Society of Human Genetics, British Society for Genetic Medicine, Human Genetics Society of Australasia, Professional Society of Genetic Counselors in Asia, and Southern African Society for Human Genetics, endorsed the final statement. The statement includes the following positions. (1) At this time, given the nature and number of unanswered scientific, ethical, and policy questions, it is inappropriate to perform germline gene editing that culminates in human pregnancy. (2) Currently, there is no reason to prohibit in vitro germline genome editing on human embryos and gametes, with appropriate oversight and consent from donors, to facilitate research on the possible future clinical applications of gene editing. There should be no prohibition on making public funds available to support this research. (3) Future clinical application of human germline genome editing should not proceed unless, at a minimum, there is (a) a compelling medical rationale, (b) an evidence base that supports its clinical use, (c) an ethical justification, and (d) a transparent public process to solicit and incorporate stakeholder input.

Introduction

The American Society of Human Genetics (ASHG) Workgroup on Human Germline Genome Editing developed the present position statement and explanatory paper between August 2015 and January 2017. This group, composed of a combination of basic and clinical scientists, bioethicists, health services researchers, lawyers, and genetic counselors, worked together to integrate the scientific status of and socio-ethical views toward human germline genome editing (defined as using genome-editing techniques in a human germ cell or embryo) into this statement. The group met regularly through a series of weekly conference calls and email discussions, proposed a draft statement to the ASHG Board of Directors in April 2016, presented the draft policy statement to ASHG and European Society of Human Genetics (ESHG) members at the ASHG-ESHG Building Bridges session in May 2016, and requested comments from ASHG members in June 2016. A total of 27 comments were received, 4 of which were in opposition to the statement. All comments and recommended modifications were reviewed by the committee and discussed as part of the development of this explanatory paper, which was reviewed and approved by the ASHG Board of Directors in March 2017.

The workgroup included representation from the following professional organizations (in alphabetical order), which then also approved the position statement and paper: the Association of Genetic Nurses and Counsellors, Canadian Association of Genetic Counsellors, International Genetic Epidemiology Society, and National Society of Genetic Counselors. This resulting policy statement was then reviewed and endorsed by the following professional organizations (also listed in alphabetical order) before submission for publication: the American Society for Reproductive Medicine, Asia Pacific Society of Human Genetics (APSHG), British Society for Genetic Medicine, Human Genetics Society of Australasia, Professional Society of Genetic Counselors in Asia, and Southern African Society for Human Genetics. (The APSHG would like to add a comment that we also express a concern that in some countries with inadequate ethics committee oversight or strong institutional review boards [IRBs], the potential for abuse exists. Hence, there is a strong need to continue to educate our professionals, researchers, journal

Expert Body Statements, Policies, Guidelines for governance for HGGE

- Nuffield Council of Bioethics
- WHO Expert Advisory Committee Reports on Developing Global Standards for Governance & Oversight f Human Genome Editing
- American Society for Gene and Cell Therapy
- Japan Society of Gene Therapy
- Genome Quebec & Cnetre for Genome & Policy
- American College of Medical Genetic & Genomics
- International Society for Stem Cell Research
- Federation of European Academies of Medicine
- National Academies of Science, Engineering & Medicine (NASEM)
- And other organizations …….

U.S. National Academy of Sciences & U.S. National Academy of Medicine; the Royal Society; & the Chinese Academy of Sciences **International Summits on Human Gene Editing 2015, 2018**

Professional Societies

- **American Society of Human Genetics**
- Association of Genetics Nurses and Counsellors
- Canadian Association of Genetic Counsellors
- International Genetic Epidemiology Society
- American Society for Reproductive Medicine
- British Society for Genetic Medicine
- Human Genetics Society of Australasia
- South African Society for Human Genetics
- European Society of Human Genetics
- Professional Society of Genetic Counsellors in Asia
- **Asia Pacific Society of Human Genetics**

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SHAPES

An NUS Centre for Biomedical Ethics initiative supported by the Singapore Ministry of Health's National Medical Research Council

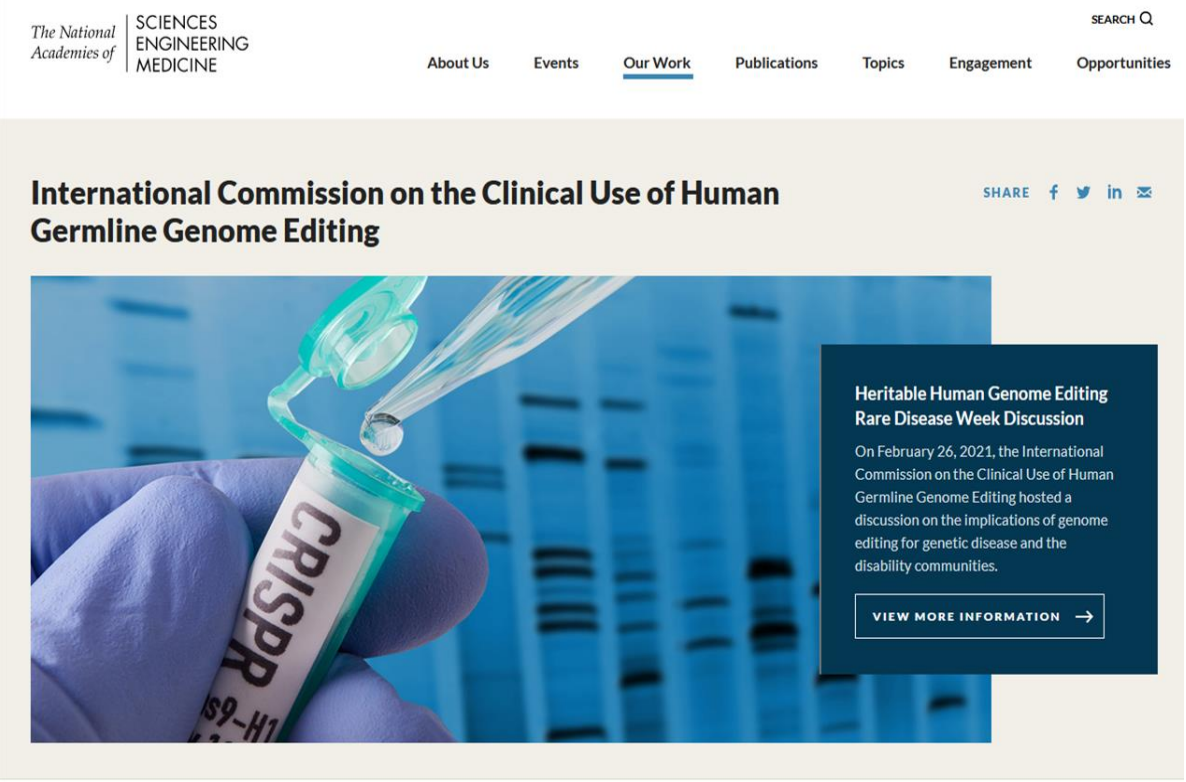
International interdisciplinary Working Group on the **Ethics of Gene-Modifying Technologies** to explore ethical issues arising in gene modifying technologies (2019)

The papers produced as part of the **SHAPES Gene Modifying Technologies (GMT) Project** supported by the **Singapore Ministry of Health's National Medical Research Council** under its NMRC Funding Initiative grant (NMRC/CBME/2016) include the following (published and under submission/review):

- "Ethical Acceptability of Preconception and Prenatal Gene Modification in the Embryo and Fetus"
- "Vulnerability and the Ethics of Human Germline Genome Editing"
- "Germline Genome Editing: Moratorium, Hard Law or an Informed Adaptive Consensus?"
- "Ethics and regulatory considerations for the clinical translation of somatic cell human epigenetic editing"
- "Germline genome modification through novel political, ethical, and social lenses"

2020: International Commission of the National Academies of Medicine, Science & Engineering (USA) & the Royal Society (UK) recently developed a "translational pathway" for the "responsible use" of germline applications

Recommended Requirements for Potential Clinical Trials of Heritable Genome Editing should society conclude that heritable human genome editing applications are acceptable



NASEM 2020

Absence of reasonable alternatives; • Restriction to preventing a serious disease or condition; • Restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to that disease or condition; • Restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects; • Availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures; • Ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants; • Comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy; • Maximum transparency consistent with patient privacy; • Continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and • Reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.

The CRISPR Journal
Volume 3, Number 5, 2020
Mary Ann Liebert, Inc.
DOI: 10.1089/crispr.2020.0082

The CRISPR Journal

RESEARCH ARTICLE

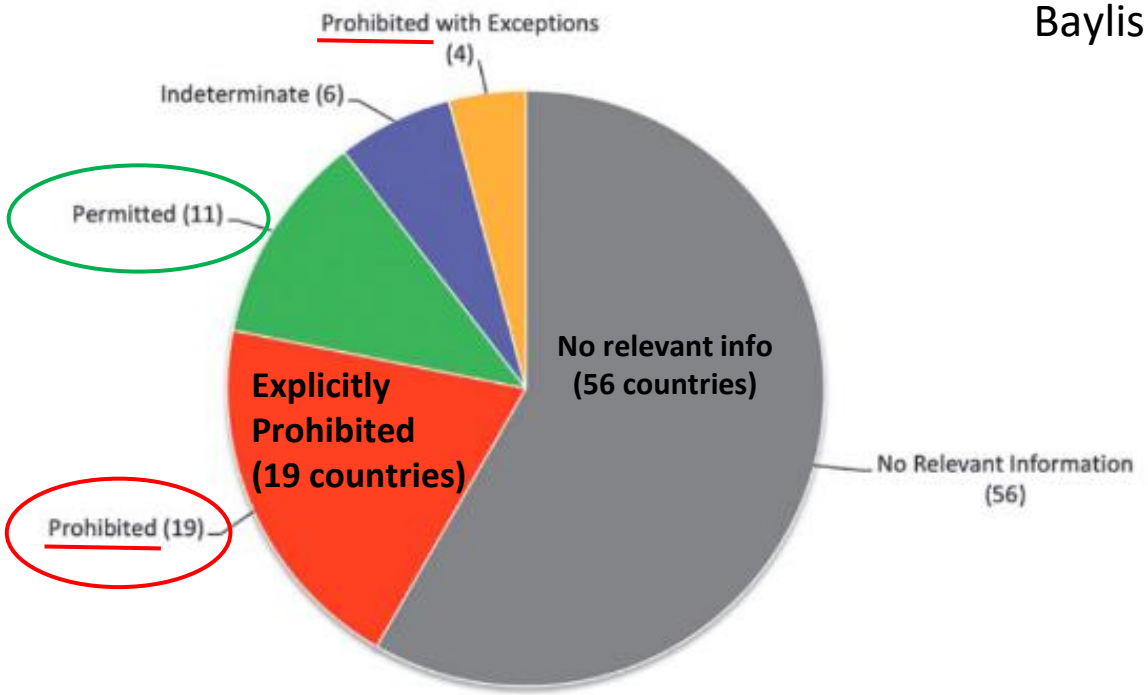
Human Germline and Heritable Genome Editing: The Global Policy Landscape

Françoise Baylis,[1,*] Marcy Darnovsky,[2,*] Katie Hasson,[2] and Timothy M. Krahn[3]

Abstract

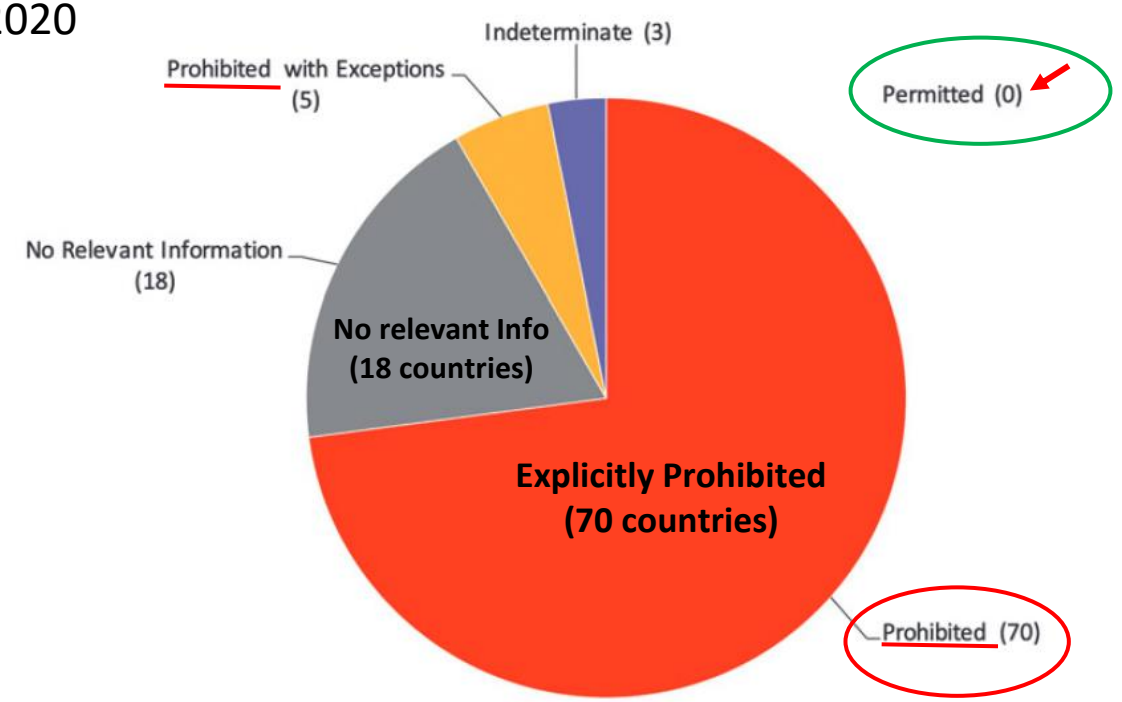
Discussions and debates about the governance of human germline and heritable genome editing should be informed by a clear and accurate understanding of the global policy landscape. This policy survey of 106 countries yields significant new data. A large majority of countries (96 out of 106) surveyed have policy documents—legislation, regulations, guidelines, codes, and international treaties—relevant to the use of genome editing to modify early-stage human embryos, gametes, or their precursor cells. Most of these 96 countries do not have policies that specifically address the use of genetically modified *in vitro* embryos in laboratory research (germline genome editing); of those that do, 23 prohibit this research and 11 explicitly permit it. Seventy-five of the 96 countries prohibit the use of genetically modified *in vitro* embryos to initiate a pregnancy (heritable genome editing). Five of these 75 countries provide exceptions to their prohibitions. No country explicitly permits heritable human genome editing. These data contrast markedly with previously reported findings.

Policies on human germline genome editing (not for reproduction) in 96 countries



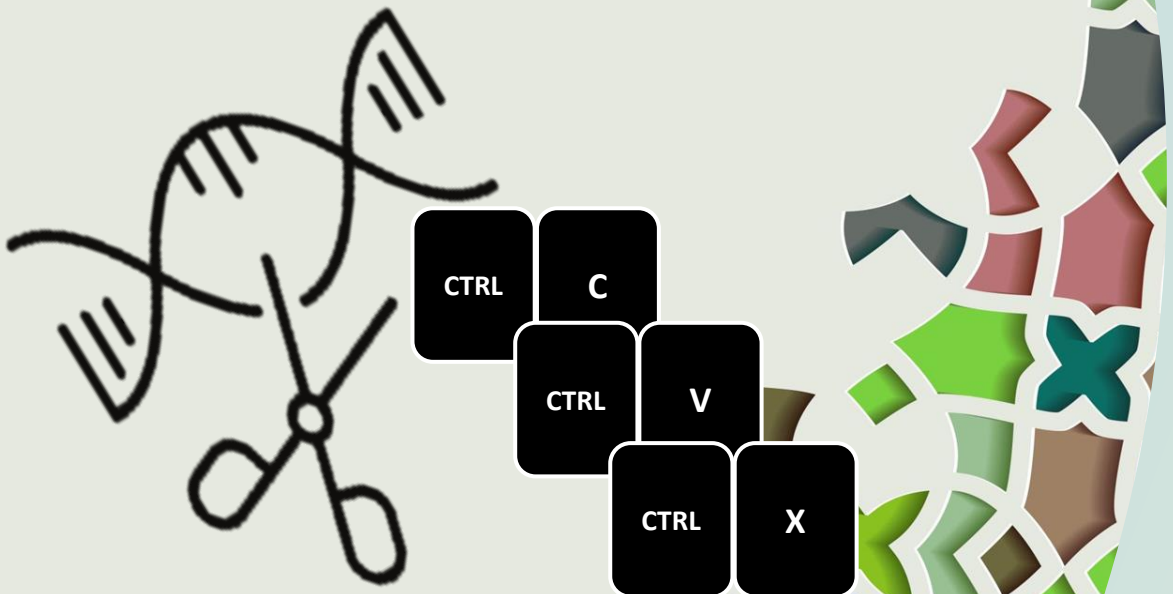
Baylis et al 2020

Policies on heritable human genome editing (for reproduction) in 96 countries



Category	Countries
11 countries permit	Burundi, China, Congo, India, Iran, Ireland, Japan, Norway, Thailand, the United Kingdom, the United States
19 countries prohibit	Albania, Austria, Bahrain, Belarus, Brazil, Canada, Costa Rica, Croatia, Germany, Greece, Lebanon, Malaysia, Malta, Pakistan, Saudi Arabia, Sweden, Switzerland, Uruguay, Vatican ...
4 countries prohibit with exceptions	Colombia, Finland, Italy, Panama
6 countries are indeterminate	Burkina Faso, Netherlands, Nigeria, Portugal, Singapore, Tunisia
56 countries have no relevant information	

Category	Countries
0 countries permit	None
70 countries prohibit	Australia, Canada, Chile, China, Estonia, Finland, France, Germany, India, Israel, Japan, Malaysia, Netherlands, New Zealand, Portugal, Qatar, Saudi Arabia, South Korea, Thailand, United Kingdom, Unites States ...
5 countries prohibit with exceptions	Belgium, Colombia, Italy, Panama, United Arab Emirates
3 countries are indeterminate	Burkina Faso, Singapore, Ukraine
18 countries have no relevant information	



Summary Comments

- The **unknown** is always likely to provoke either **high hopes or fears**
- Fatalistic and negative scenarios originally perceived or imagined may not happen

- Different families
- Different cultures
- Different governing bodies may view certain societal & ethical concerns differently *when weighing potential risks and benefits of clinical germline editing*

- Debate may be more than risk-benefit assessment?
- Consider Impact on "society" or "human race" on whole?

CONCLUDING REMARKS

1. Encourage clinical innovations & technological advances and at same time address the ethical, social and legal issues and concerns openly and robustly
2. Encourage debate and engagement, but it is important not to over-hype the expected impacts and benefits, or to sensationalize the evils or misconceptions
3. Transparent engagement of all stakeholders needed