Bioethics Advisory Committee
20 YEARS OF BIOETHICS Singapore

Ethical Issues in Assisted Reproduction

The importance of Transgenerational Genomics

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Ethical Issues in Assisted Human Reproduction

IVF in Older Women

Cryopreservation of Embryos

Surrogacy

Selecting sperm for ICSI

Multiple births

Donated Eggs

Research on Embryos

Same Sex Reproduction

Human Embryonic Stem Cells

Donor Anonymity

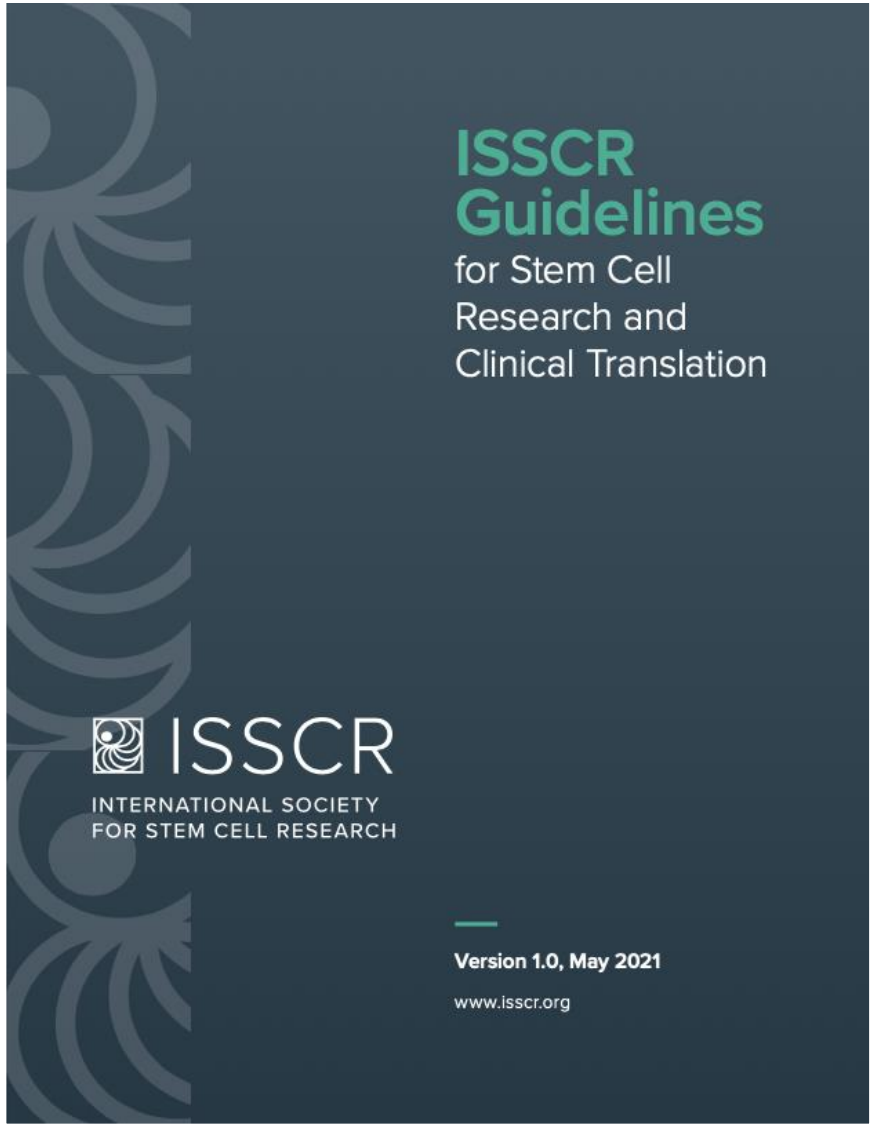
Creating Embryos for research

Human Cloning

Sex Selection

Three Parent Families

Ethical Issues in Assisted Human Reproduction



Stem cell guidelines open door to more permissive research on human embryos

Science

By Kelly Servick | May. 26, 2021 , 11:00 AM

INDEPENDENT

International guidance on 14-day limit to growing human embryos 'relaxed' by scientists

MailOnline

Scientists DROP the 14-day embryo rule - a key limit on stem cell research - in huge guideline update that could pave the way for studies on genetic disorders and miscarriage

Emerging Issues in Assisted Human Reproduction

Expanded Preimplantation Genetic Diagnosis

Mitochondrial Replacement

Non-invasive PGT

Germline Genome Editing

Edited Synthetic Gametes

Enhanced Aneuploidy Screening

Voiding Donor Anonymity

Expanded Carrier Screening

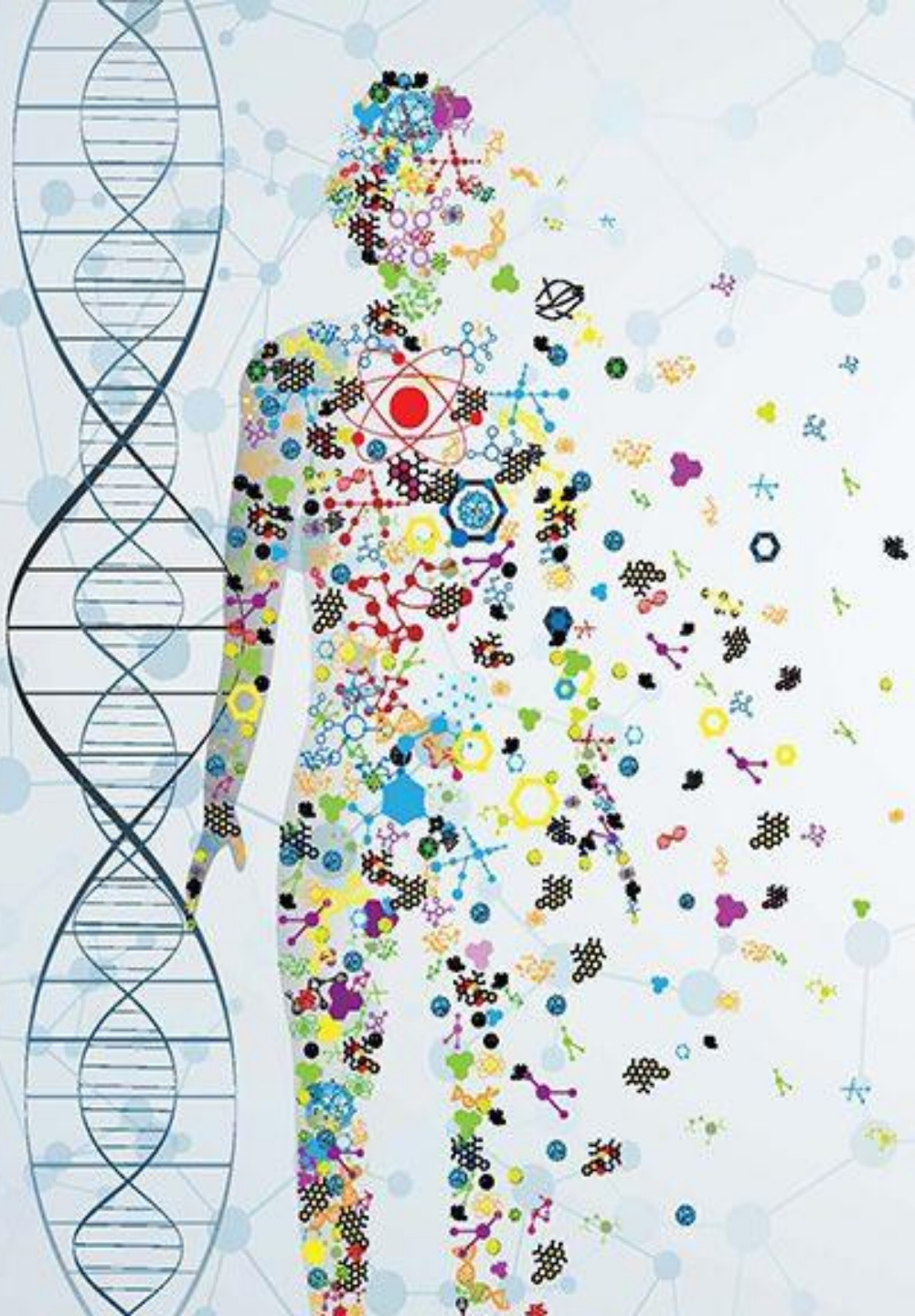
Polygenic embryo risk scoring

Genetic enhancement of embryos

Non-invasive Prenatal Testing NIPT

Non Invasive Prenatal Diagnosis NIPD

WGS of Newborns



Impact of Genomics and Personalised Medicine on ART

Increased knowledge of personal genetics allowing genetic choice before reproduction

Enhanced genetic diagnosis on embryos *in vitro*

Manipulating genes in vitro and in vivo

Appreciating the difference between personal genomics and transgenerational genomics

Preconception Testing before ART (Expanded Carrier Screening)

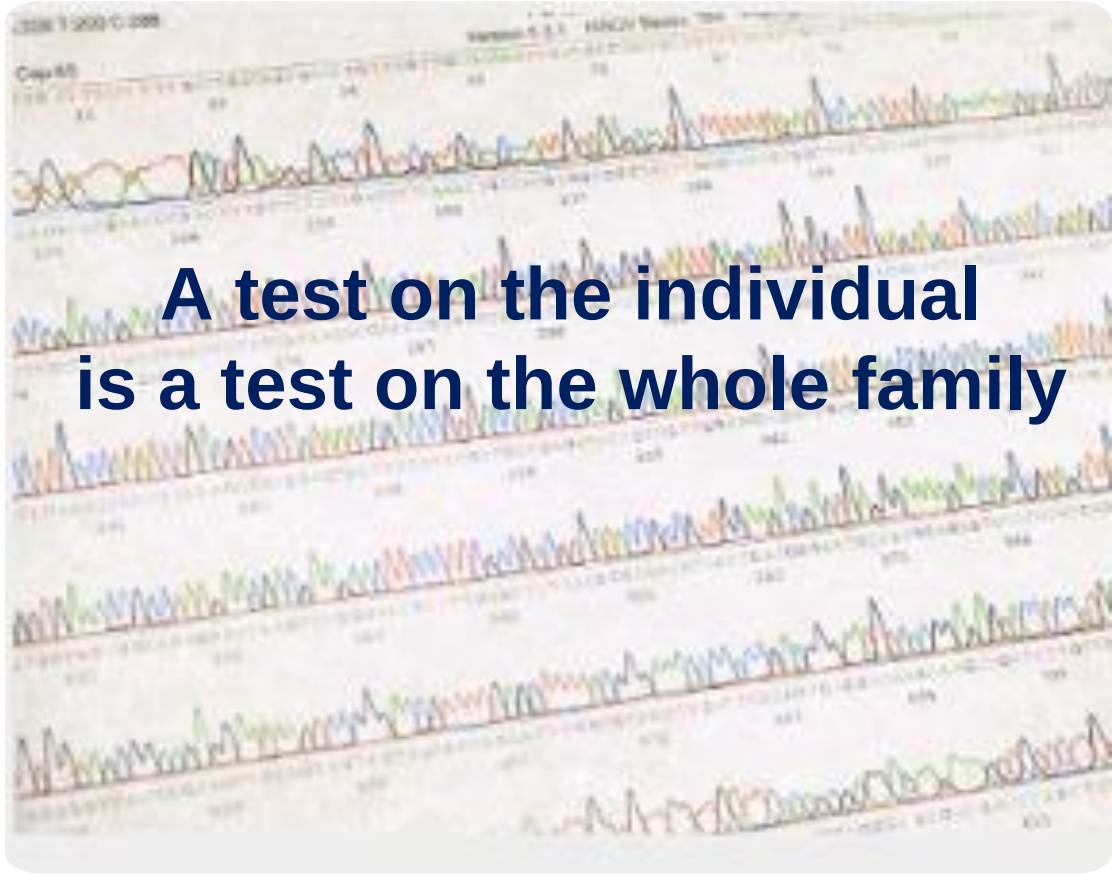
For those who already have a child with a serious monogenic condition who may be interested in avoiding the genetic disorder using PND or PGD

ECS increasingly being requested prior to ART to inform individuals or couples of possible genetic disease risks for their future offspring and their reproductive options

BUT:

Tests should be designed to achieve high clinical validity and have established clinical utility

Pre-and post-test counselling is of utmost importance



Henneman, et al., Responsible implementation of expanded carrier *Eur J Hum Genet* (2016).

Direct to Consumer Genomic testing and screening is being done with increasing frequency by the population

The four largest companies have now tested nearly 30 million people

May 2019

- **AncestryDNA** reported in that they had a database of over 15 million completed samples
- **23andMe** had tested over 10 million people
- **MyHeritage** had a database of 2.5 million people
- **FamilyTreeDNA** has over 2 million users

The number of people who have taken a DNA test is expected to grow to ~100 million by 2021

Genetic databases and donor anonymity: Kennet, Reisel and Harper. Human Reproduction, Vol 34 (9) 2019, 1848-9

Focus on REPRODUCTION

Donor anonymity 'a thing of the past'

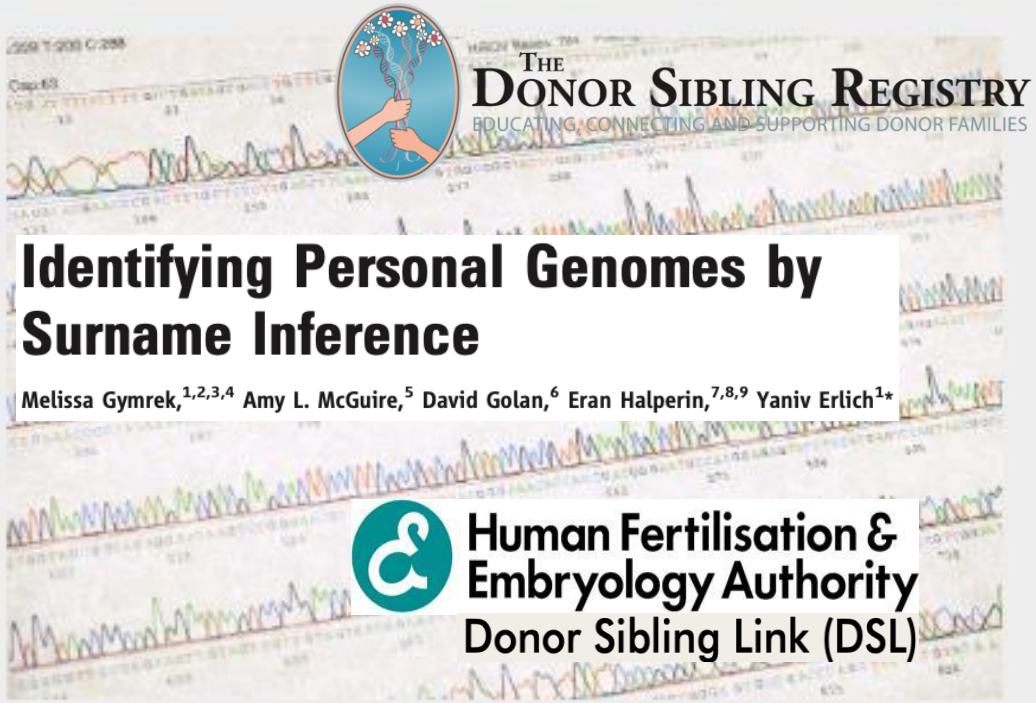
FamilyTreeDNA

Y-DNA

23andMe®

ancestry

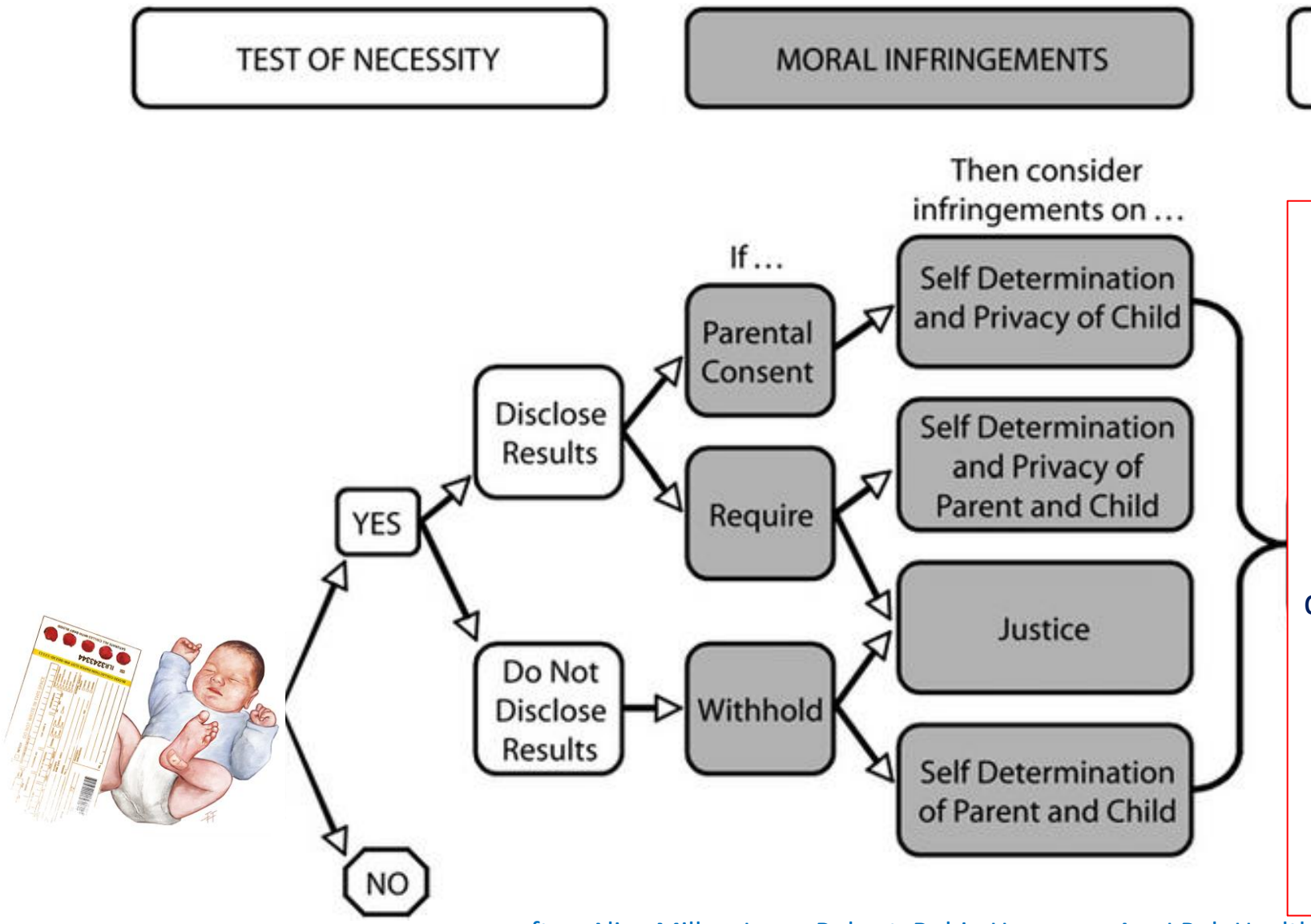
MyHeritage



Youtube - Genetic privacy: A Friend or foe. Dr Yaniv Erlich, CSO MyHeritage

Harper JC, Kennett D, Reisel D. Human Reproduction, Volume 31, Issue 6, June 2016

Screening Newborns for genetic disease



Carrier screening should be distinguished from **NEWBORN SCREENING PROGRAMS**

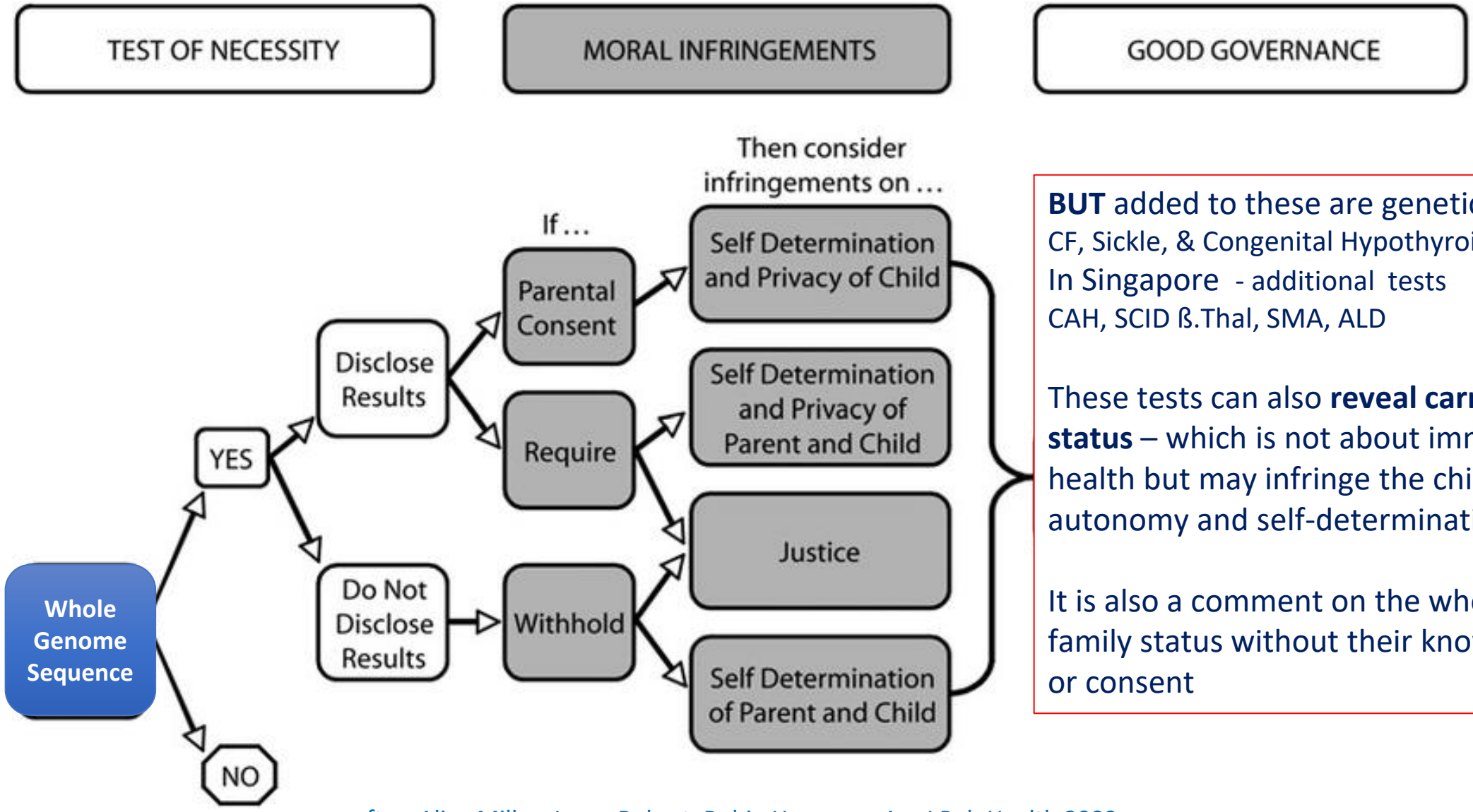
Heelprick tests aim to detect newborns with serious treatable disorders for which early treatment might be preventative.

Routine and compulsory – most for inborn errors of metabolism

after: Alice Miller, Jason Robert, Robin Hayeems. Am J Pub Health 2009

Decision tree for considering the application of public health ethics principles to incidental carrier results generated through newborn screening.

Screening Newborns for genetic disease



BUT added to these are genetic tests
CF, Sickle, & Congenital Hypothyroidism (UK)
In Singapore - additional tests
CAH, SCID ß.Thal, SMA, ALD

These tests can also **reveal carrier status** – which is not about immediate health but may infringe the child's autonomy and self-determination

It is also a comment on the whole family status without their knowledge or consent

after: Alice Miller, Jason Robert, Robin Hayeems. Am J Pub Health 2009
Decision tree for considering the application of public health ethics principles to incidental carrier results generated through newborn screening.

There is broad agreement within the genetics community that it is not acceptable to use whole genome sequencing <u>to look opportunistically</u> for a broad range of conditions in babies – especially conditions for which no treatment may be available.

https://www.nuffieldbioethics.org/publications/whole-genome-sequencing-of-babies

Testing the embryo for genetic risk

1. Recurrent: PGD (PGT-M&SR)

Associated with particular **known** inherited disorder

Cystic fibrosis; Huntington; haemophilia, mtDNA disease

With new genomic methods

Has become much more precise and reliable

Testing the embryo for genetic risk

2. Sporadic: PGS (PGT-A)

Occurs **randomly**; often age related aneuploidy.

Screening for possible loss or gain of whole chromosome e.g. (Down t21, Turner XO) or for genomic variants / new mutations.

With new genomic methods

- Rationale still valid: but in practice not wholly reliable due to **improved detection of mosaicism** – false positives.
- We have imperfect understanding of the biology of how partial **chromosome anomaly is handled during development**.
- Some aneuploidy may be normal at early stages: **many embryos are being discarded unnecessarily**.

Changing the genetic risk

Instead of just examining the genome to avoid affected births and design better treatments, why not just alter the inherited genome?

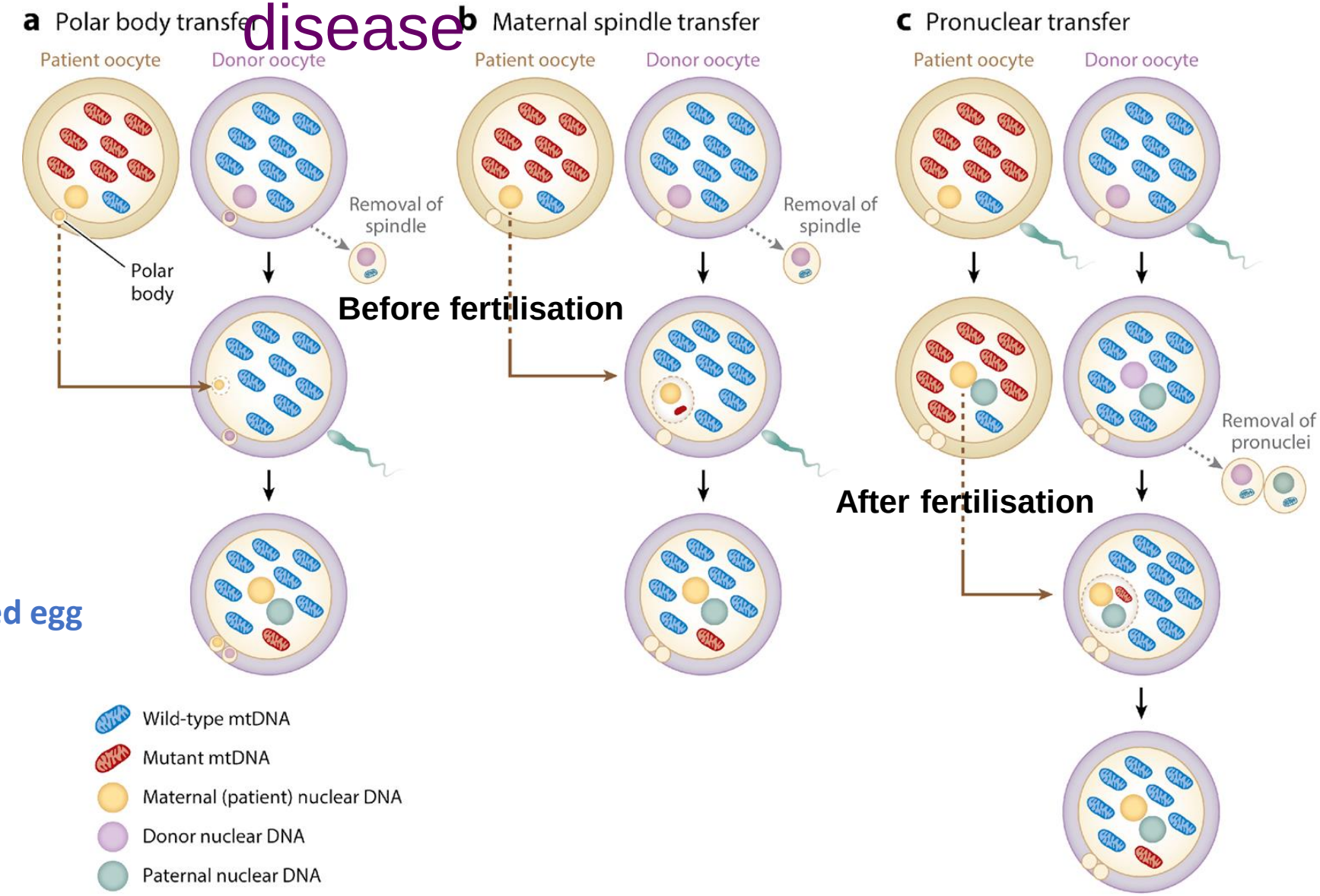
Mitochondrial replacement in mtDNA genetic disease

A Special Case

Transmitted only by the mother through her mitochondria (mtDNA not nuclear DNA)

Abnormal mitochondria are present in the cytoplasm of egg

Can be circumvented by transferring parental DNA into unaffected donated egg



Craven L, et al. 2017.
Annu. Rev. Genom. Hum. Genet. 18:257–75

RNA-guided genome editing using Crispr

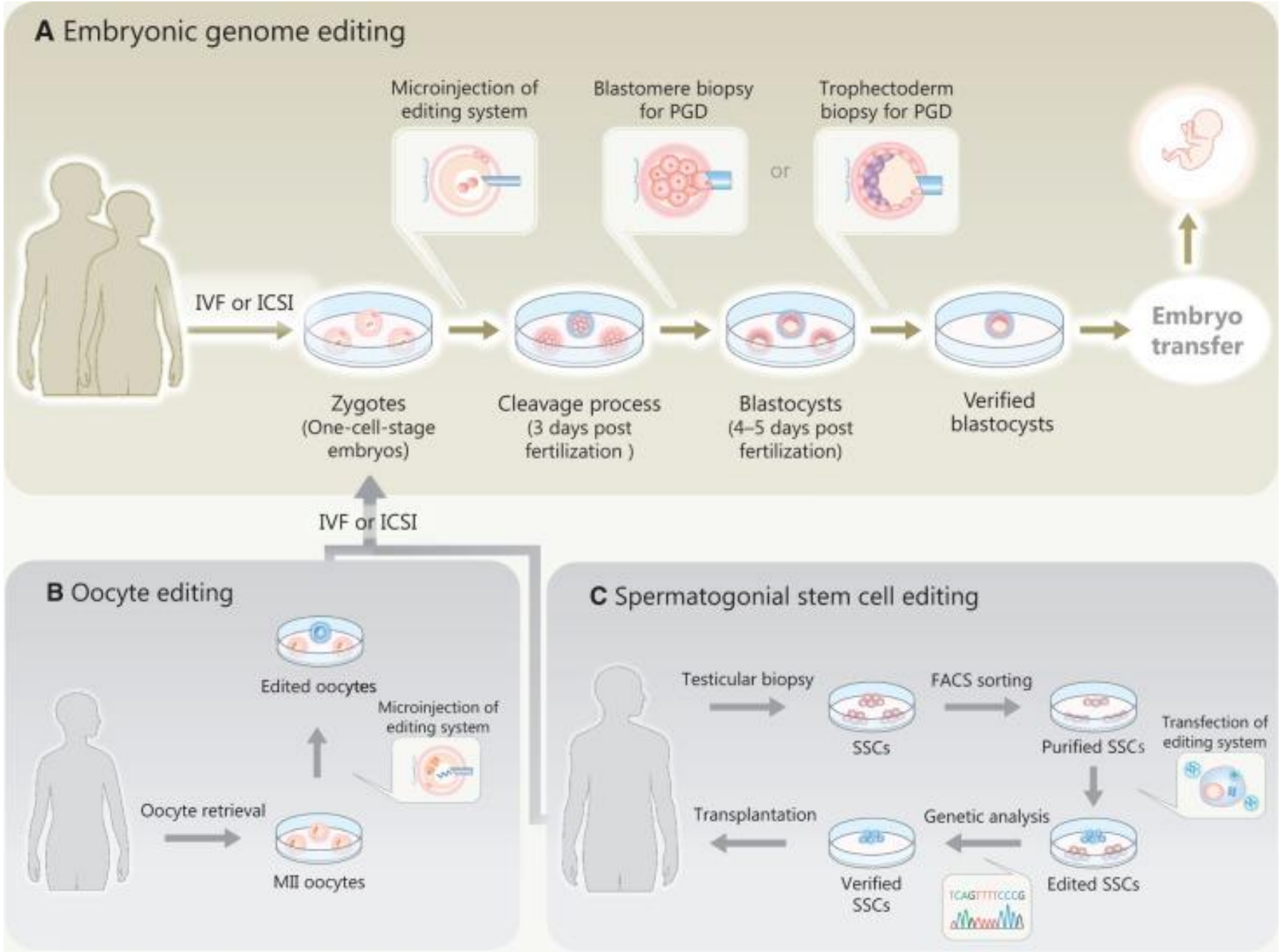
Specificity and precision is a primary concern for efficacy and safety

Genome Editongue

Intended Edit (precision)

Off target Edit (specificity)

Use on Sperm Eggs and Embryos



Ishii, T. Brief. Funct. Genomics Jan 2017

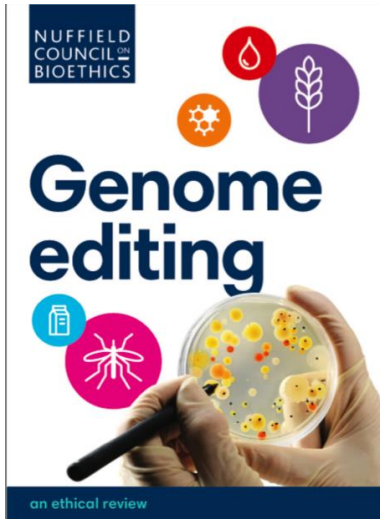
Is Genome Editing better than PGD

Advantages of editing:

- **Perhaps more embryos to biopsy**
- **Perhaps more unaffected available for transfer**

Disadvantages of editing

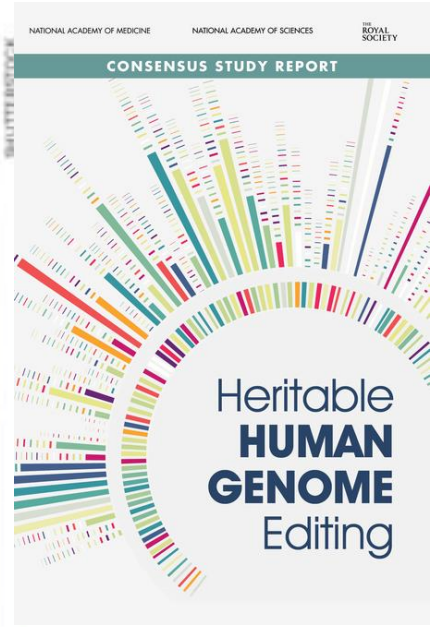
- **Efficiency of editing will have to be checked**
- **Reliability of the edit will have to be confirmed**
- **Off target effects including unexpected indels, mosaicism, aneuploidy, will have to measured and controlled for**

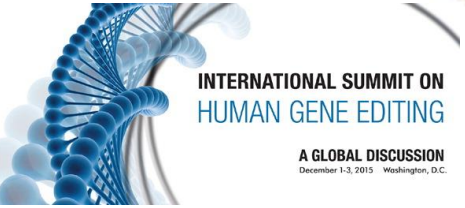


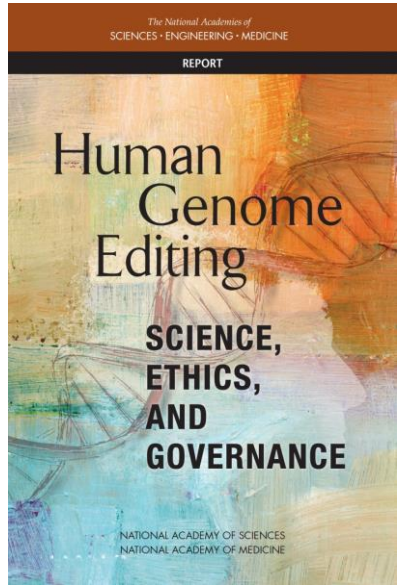
COMMENT

12 March 2015

nature International weekly journal of science







Don't edit the human germ line

Heritable human genetic modifications pose serious risks, and the therapeutic benefits are tenuous, warn **Edward Lanphier**, **Fyodor Urnov** and colleagues.

Chinese biophysicist Dr He Jianku stunned the world that he has created twin girls by IVF genome editing and embryo transfer, born in Oct 2018.

Corrected *CCR5,* a gene that might reduce susceptibility to HIV

Addresses a social construct; not about avoiding a serious genetic disease

Transgenerational Genomics and ART

Preconception

Preconception testing for recurrent genetic disease
Consanguinity risk

Whole Genome Sequencing to screen for any genetic disease

Preimplantation

PGT for monogenic disease (PGD)

PGT for sporadic aneuploidy

MRT for mtDNA disease & infertility

Genome editing of gametes

Genome editing of embryos

Postnatal

Extended but limited heel-prick gene test

Whole Genome Sequencing of newborns

Genetic identification of gamete donors

Prenatal

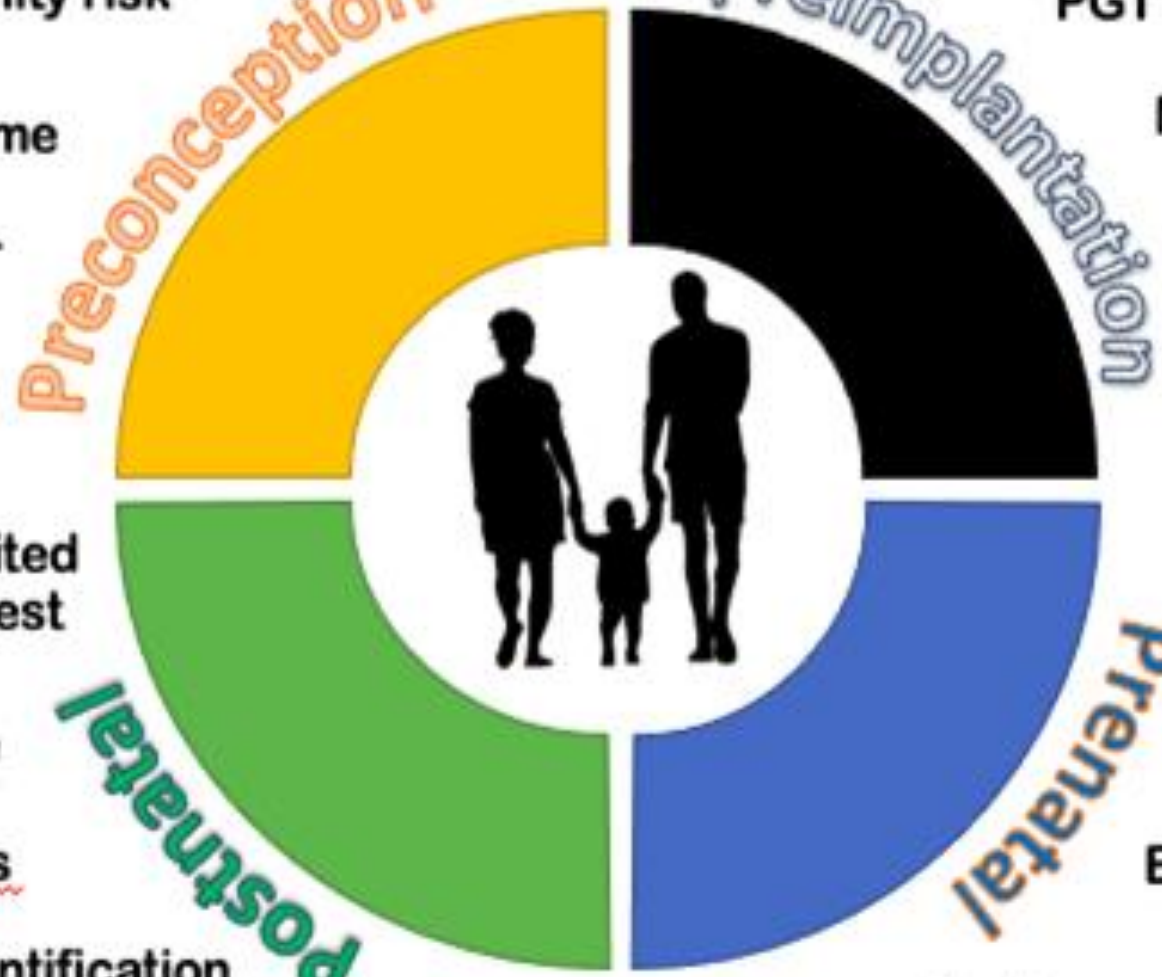
Non-Invasive Prenatal Testing

Non-Invasive Prenatal Diagnosis

Exome sequencing in ultrasound detected anomaly

In utero gene editing / therapy

Transgenerational Genomics and ART



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Transgenerational Genomics and ART

Integration of Clinical Genetics & Comprehensive Laboratory Service


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