Alternative Technologies to Germline Gene Editing

Comparison of international regulations and availabilities and their effects on practices in private clinics

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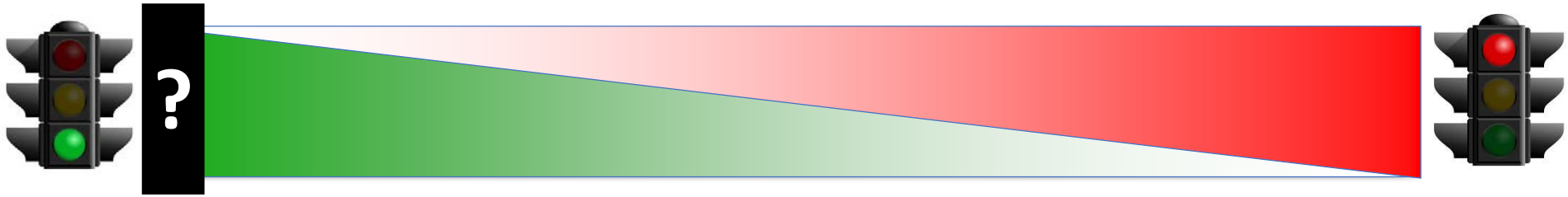
Three Broad Questions To Be Addressed

- How do regulations and availabilities of alternative technologies to GGE compare and vary internationally?
- What are the ramifications of these variations to practices in private clinics?
- Are there IVF clinics offering embryo selection for polygenic disease risk and/or desirable traits?

Types of Oversight of Technologies

- None *versus* Regulatory (policies, guidelines) *versus* Legislative (law)



Permissive/not regulated **Intermediate** **Restrictive**

Important to note that:

- This is a shifting landscape
- It is only partially visible
- It is rapidly moving

Factors Influencing International Oversight of Alternate Technologies

- Funding sources - government *versus* private
  - Government
    - Historically: more restrictive
    - Now and in the future: probably less likely to be so
- Socio-ethical, cultural and religious diversities
- Internal political factors
- The nature, type and scope of technology

Gathering of information is an ongoing effort in a changing landscape

International Regulation of Alternative Technologies

The Alternative Technologies to Germline Gene Editing

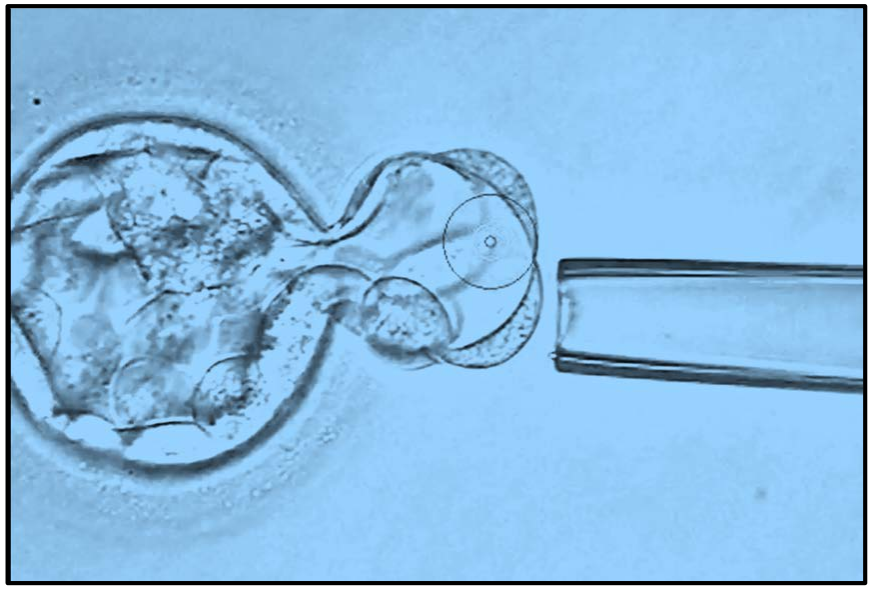
- Somatic gene editing
- PGD
  - Genetic diseases
  - Translocations
  - Non-genetic: selection based on polygenic disease risk and/or a “desired” trait(s)
- Mitochondrial Replacement Therapy (MRT)
  - Genetic diseases (e.g. Leigh syndrome, MERRF syndrome)
  - Non-genetic reasons (improved fertility outcomes)

International Regulation of Clinical Use of Somatic Gene Editing

Isasi et al 2016; Science 351:337-339

Preimplantation Genetic Diagnosis

- The current technology involves trophectoderm biopsy:

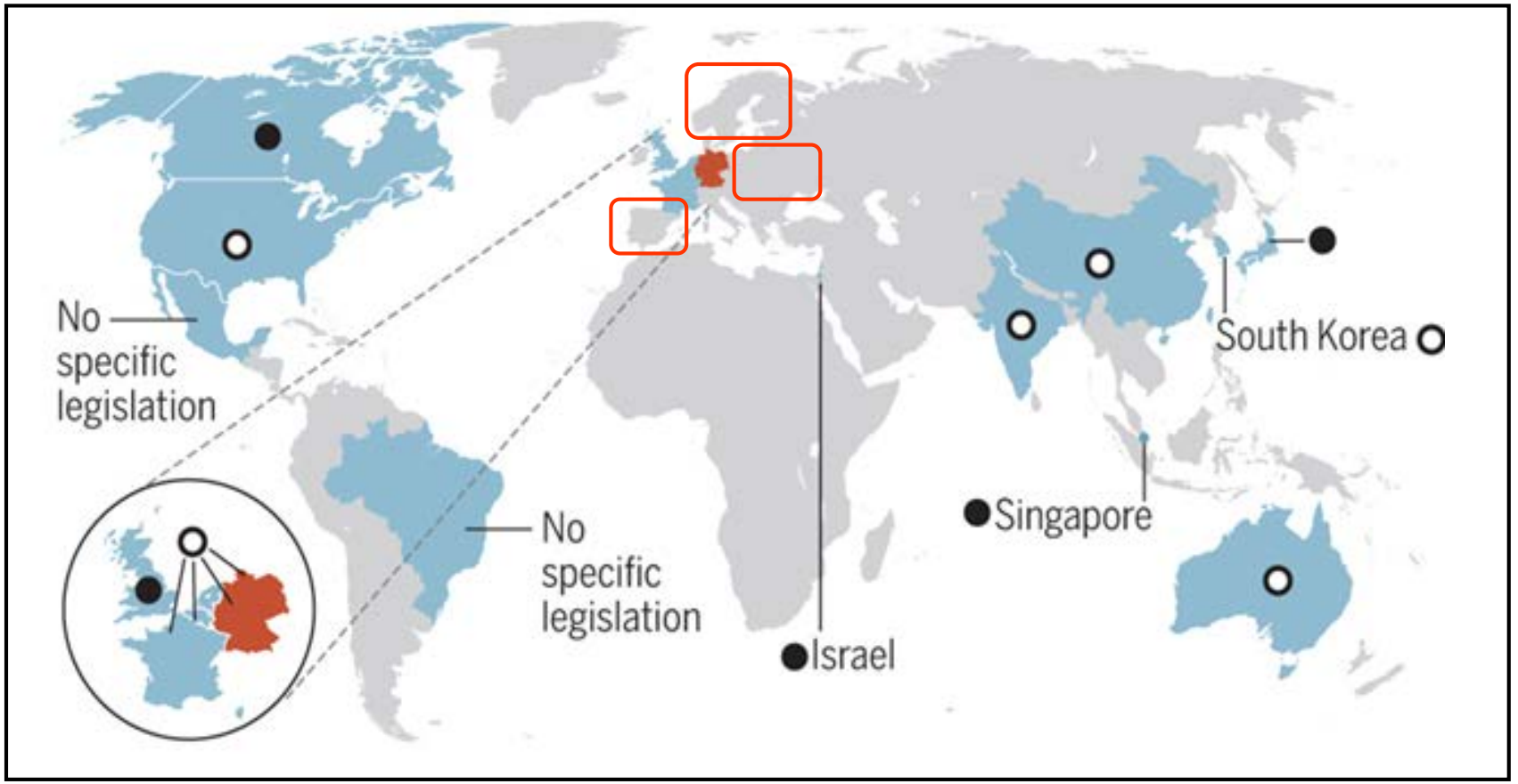


1. Several cells are removed for genetic analysis
2. The inner cell mass is not biopsied, so this is theoretically safe
3. The biopsied cells are tested for a genetic abnormality (or potentially for polygenic disease risk and/or a desired genetic trait)

- Non-invasive testing of DNA in the culture medium is under development[1-4]

[1] Feichtinger et al. 2017; Reprod Biomed Online 34(6):583-589;[2] Vera-Rodriguez et al 2018; Hum Reprod 33(4):745-756
[3] Ho et al 2018; Fertil Steril 110(3):467-475; [4] Huang et al 2019; PNAS 116(28):14105-14112

International Regulation of the Clinical Use of PGD



Permissive Intermediate Restrictive Legislation ● Regulatory

Isasi et al Science 2016;351:337-339

Mitochondrial Replacement Therapy (MRT)

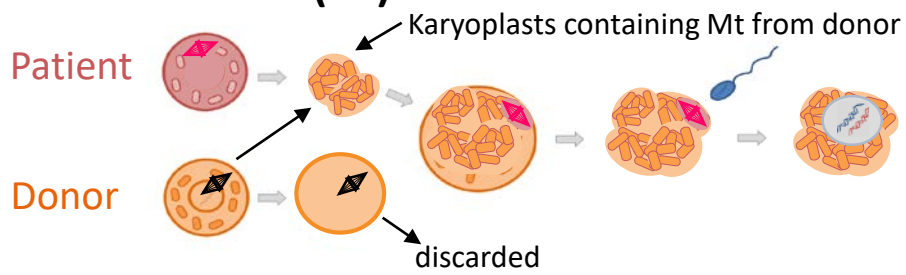
- **MRT for infertility (Cytoplasmic Transfer)**
  To boost energy production in "older" patient oocytes by transfer of cytoplasm from young donor oocytes
  - The efficacy is controversial [1-3]
- **MRT for genetic reasons (MST and PNT)**
  To replace/reduce the effect of mutated mitochondria with healthy mitochondria:
  - Maternal spindle transfer (MST)
  - Pronuclear transfer (PNT)

  Heteroplasmy is not entirely eliminated
- **In all three approaches**
  - DNA is present from a third "parent"
  - Raises concerns that MRT is a form of genetic modification that could be passed down through generations
- **International regulation of MRT is very variable**

[1] Fakih et al. JFIV Med Genet 2015;3:154; [2] Oktay K et al Reprod Sci 2015;22:1612–7
[3] Labarta et al Fertil Steril 2019 Jan;111(1):86-96

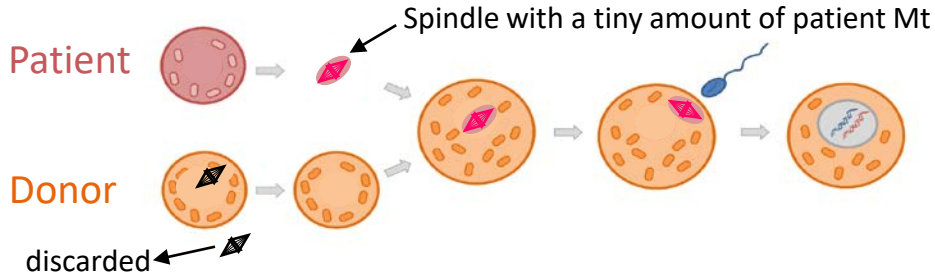
Infertility

Cytoplasmic Transfer (CT)

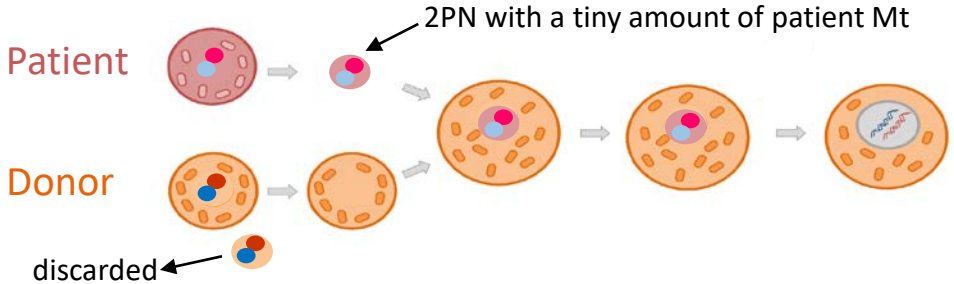


Genetic Reasons

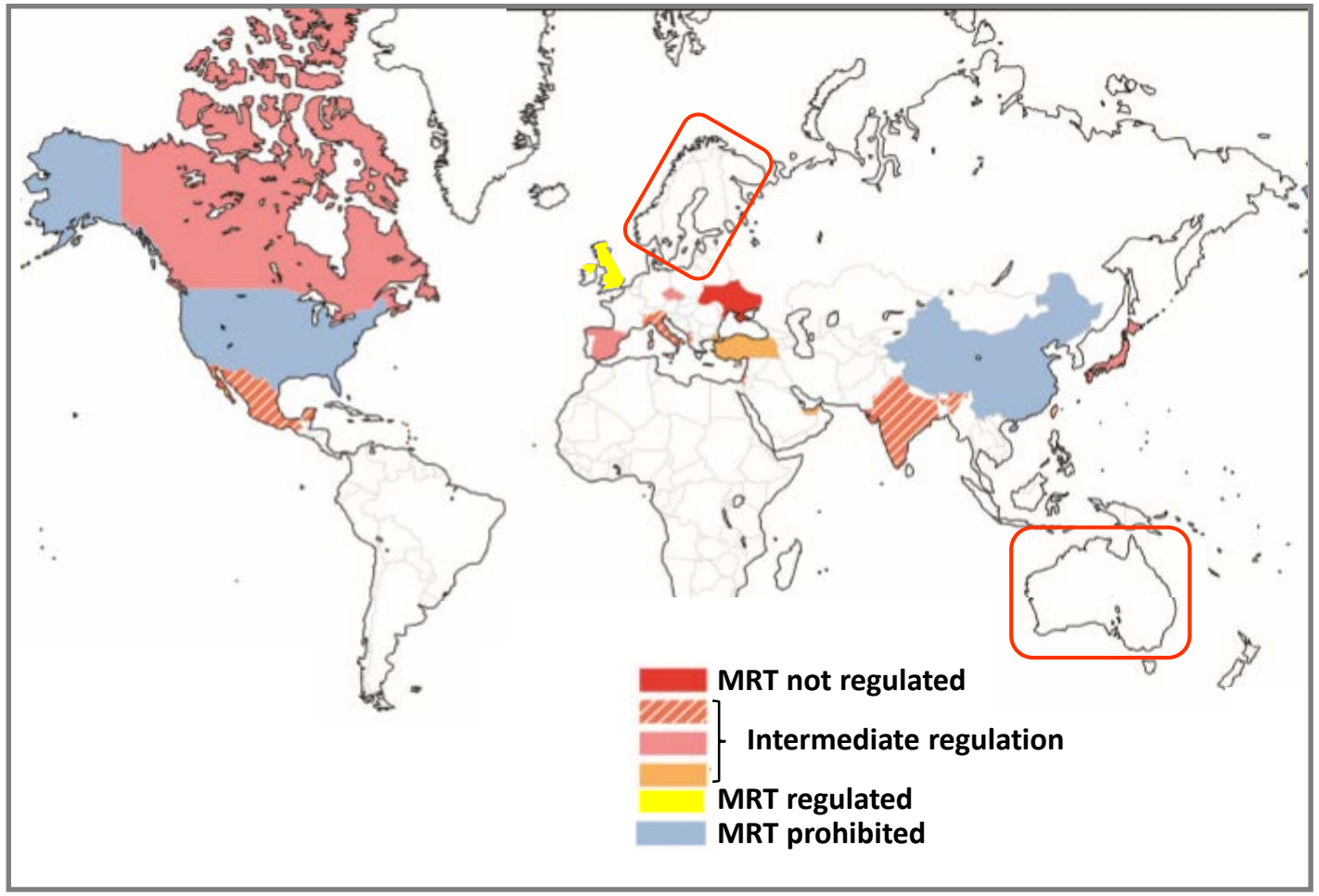
Maternal Spindle Transfer (MST)



Pronuclear Transfer (PNT)



International Regulation of Clinical Use of MRT (as of 30/3/17)



Adapted from Ishii & Hibino 2018; RBMOnline 5:93-109

Not regulated (permitted)

- Northern Cyprus and Ukraine

Intermediate regulation

- 12 countries, including Mexico and Canada

Regulated

- UK (clinic licenses allowed on a case by case basis, but only for mtDNA genetic disease, NOT for infertility)

Prohibited

- US and China

Summary: International Regulation of Alternative Technologies to Germline Gene Editing

- Somatic gene therapy (as of 2016)
  - Of the countries surveyed, all were intermediate in their regulation
- PGD (as of 2016)

  Of the countries surveyed, all were permissive except Germany, which is restrictive
- MRT (as of 2017): Much less well-defined regulatory landscape
  - Only a few countries have tight regulation
    - US and China: prohibited
    - UK: allowed on a case by case basis
  - Most have intermediate regulation
  - A few have no regulation: Ukraine and Northern Cyprus

Many countries not assessed, so available information is incomplete

Ramifications of Differing International Regulations for Alternative Technology Treatments

HARVARD
MEDICAL SCHOOL

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Medical Tourism (Cross Border Reproductive Care)

- Travel abroad by patients who are seeking certain interventions not available at home
- They will do so for various reasons:
  - Access and higher quality of care
  - Cost
  - Privacy
  - Regulation (legal and religious)
  - Law evasion is the most common reason*
- Must be weighed against risks:
  - Icreased stress
  - Safety concerns (multiple pregnancies)
- Sample movement involving:
  - Just the patient
  - The patient and samples
  - Just the samples

* Van Hoof et al 2016; Eur J Obstet Gynecol & Reprod Biol 202;101-105

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- 188 country profiles
- In/outbound medical tourist numbers
- Free entry in the IMTJ Medical Travel Directory

patient website

- Plus much much more...

**IMTJ = International Medical Travel Journal

* Van Hoof et al 2016; Eur J Obstet Gynecol & Reprod Biol 202;101-105

Medical Tourism for Assisted Reproductive Treatments

IFFS survey of 64 country respondents

Treatment	% Patients responding to question
Oocyte donation	52%
Sperm donation	45%
Embryo donation	43%
Gestational surrogacy	22%
Traditional surrogacy	9%

https://journals.www.com/grh/Fulltext2016/09000/IFFS_Surveillance.2016.1.aspx

Circumvention (of local regulation) medical tourism[1]

[1] Cohen et al 2019; Nature Biotechnol 37:589-600
IFFS = International Federation of Fertility Societies

Medical Tourism for MRT: Survey Results, 3/30/17

Country	Medical reports	Registered clinical trials	Ad on clinic website	Ad on tourism website	Country	Medical reports	Registered clinical trials	Ad on clinic website	Ad on tourism website
Canada			✓		Philippines				
China					Portugal				
Czech Republic			✓		Russia				
France					Serbia				
Georgia					[illegible]				
Germany					[illegible]ica				
Greece					South Cyprus				✓
India			✓		Spain				
Israel					Taiwan				
Italy					Thailand				
Japan			✓		Turkey			✓	
Mexico			✓		Ukraine			✓	
North Cyprus			✓	✓	UAE				
Panama					USA				

20/28 (71.4%)

= confirmed by authors via email; [illegible] = Ad for cytoplasmic transfer and/or nuclear transfer on websites offering cross-border reproductive care

Adapted from Ishii & Hibino 2018; RBM Online 5:93-109

Medical Tourism for MRT in private clinics: Example 1

Jordan – USA – Mexico

Live birth derived from oocyte spindle transfer to prevent mitochondrial disease

John Zhang [a,b,], Hui Liu [b], Shiyu Luo [c], Zhuo Lu [b], Alejandro Chávez-Badiola [a], Zitao Liu [b], Mingxue Yang [b], Zaher Merhi [d], Sherman J Silber [e], Santiago Munné [f], Michalis Konstantinidis [f], Dagan Wells [f], Jian J Tang [g], Taosheng Huang [c,*]*

[a] New Hope Fertility Center, Guadalajara, Mexico

[b] New Hope Fertility Center, New York, USA

OH 45229, USA

[d] *Department of Obstetrics and Gynecology, Division of Reproductive Biology, NYU School of Medicine, 180 Varick Street, New York, NY 10014, USA*

[e] *Infertility Center of St Louis, St Luke's Hospital, St Louis, MO 63017, USA*

[f] *Reprogenetics, 3 Regent Street, Livingston, NJ 07078, USA*

[g] *Department of Obstetrics and Gynecology, The Mount Sinai Hospital, E 101st Street, New York, NY 10029, USA*

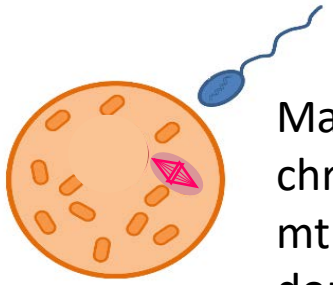
Zhang et al 2017; RMBOnline 34:361-368

Medical Tourism for MRT in private clinics: Example 1

Medical Tourism for MRT in private clinics: Example 1

- Female carrier of mtDNA mutation for Leigh syndrome with a long history of multiple undiagnosed pregnancy losses and death of 2 children as a result of this disease
- MST* was performed

Recipient, enucleated donor oocyte { }



Maternal spindle with chromosomes and ~2% mtDNA injected into donor oocyte

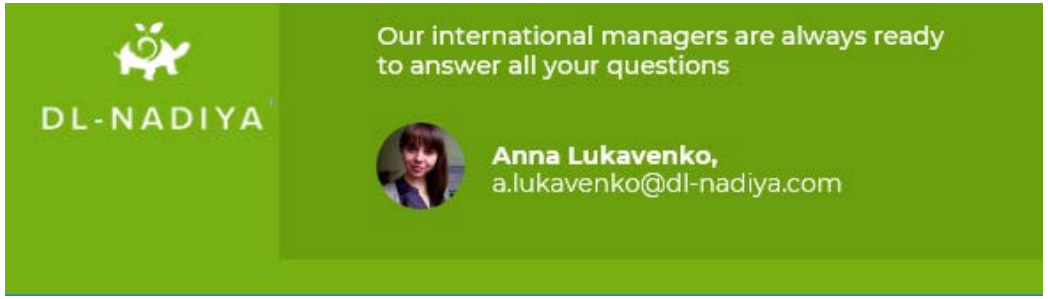
Baby's DNA mix revealed
Reardon S. Nature April 6, 2017; 544:17-18

- Son born April 6, 2016
- IRB approval obtained in Mexico for the embryo transfer
- **The US ban on MRT was circumvented but the treatment was still conducted unlawfully because:**
  - **The embryo did not meet US export license exemptions and**
  - **AMA** recommendations were not followed**

*MST = Maternal Spindle Transfer **AMA = American Medical Association

Medical Tourism for MRT in private clinics: Example 2

USA – Ukraine

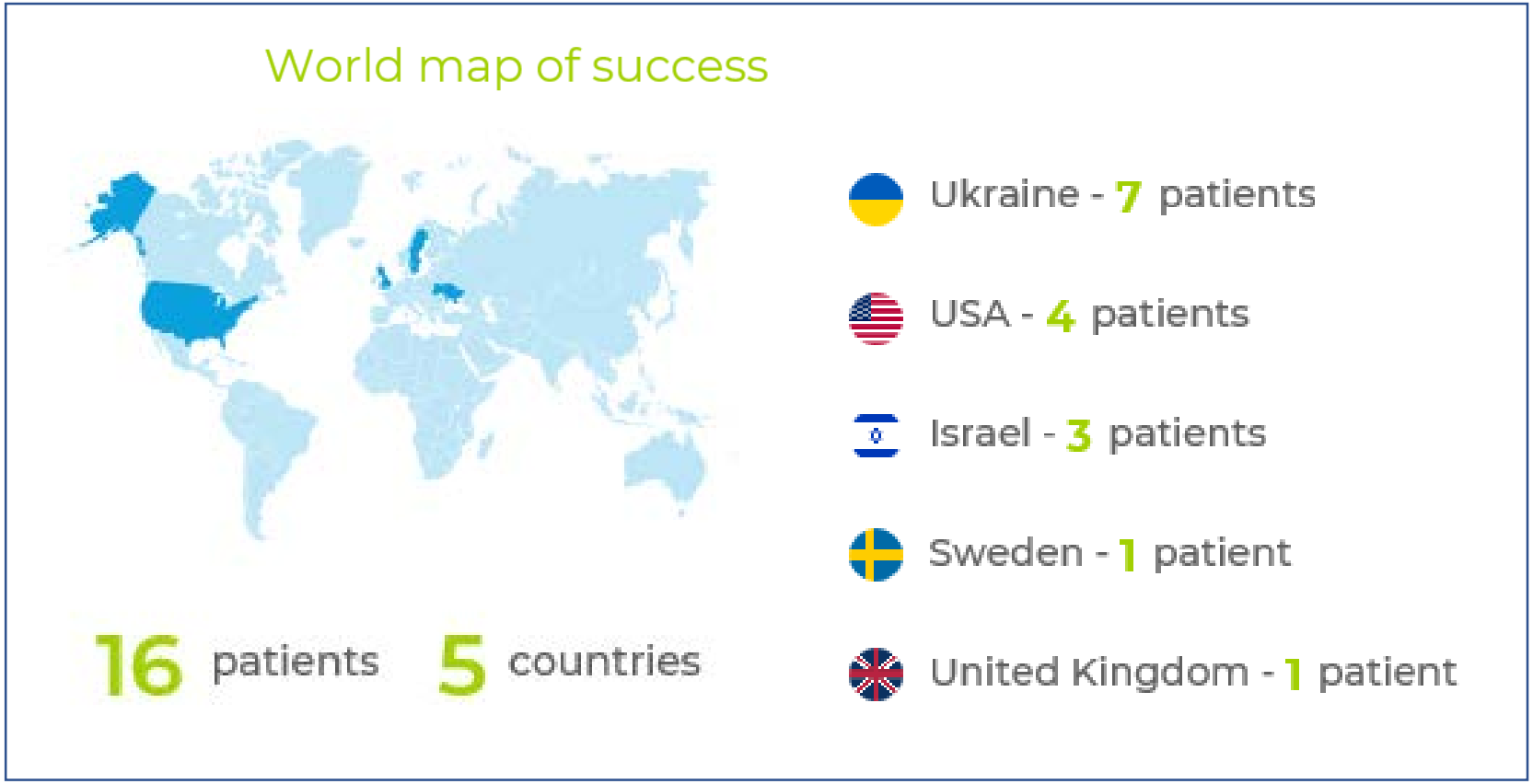


About us

Darwin Life-Nadiya is a united team of US and Ukrainian scientists who have combined experience in molecular genetics, embryology and human reproduction to develop the newest methods for achieving the pregnancy with a healthy baby in women with the high risk of mitochondrial pathology in their offspring, as well as in complicated cases of infertility forms with high genetic risk.

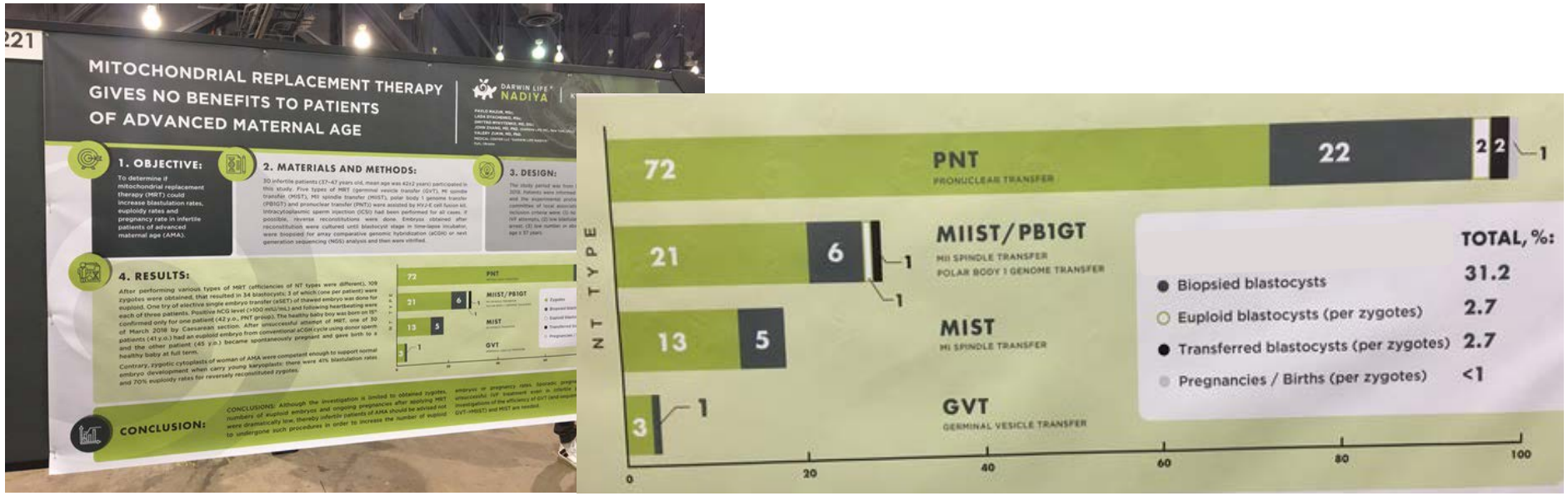
Medical Tourism for MRT in private clinics: Example 2

Nadiya Clinic, Ukraine



https://nadiya.clinic (downloaded, 3/11/19)

Nayida Clinic Ukraine: MRT Study with Oocytes of Patients of Advanced Age



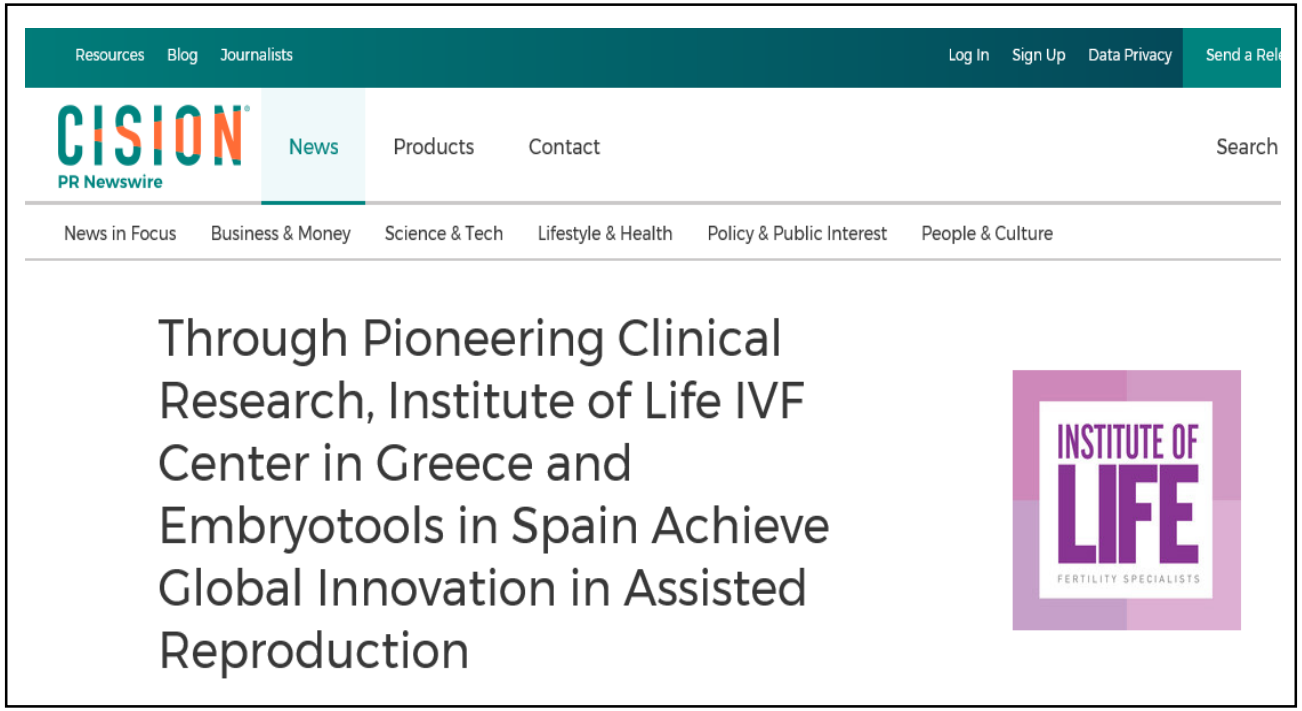
- The study failed to reveal improvement in live birth rate following MRT for women of advanced maternal age (n=30) suffering from infertility
- This is important because many programs continue to promote use of MRT to overcome infertility

Mazur et al 2019 Presented at the 2019 ASRM Scientific Congress and Expo, Philadelphia, PA, USA

Medical Tourism for MRT in private clinics: Example 3

Spain – Greece

- MST is illegal under Spanish law
- Institute of Life in Greece has been licensed to validate maternal spindle transfer in a series of clinical trials
- Embryotools in Spain is collaborating with the Institute of Life in Greece



Medical Tourism for MRT in private clinics: Example 4

INSTITUTE OF LIFE

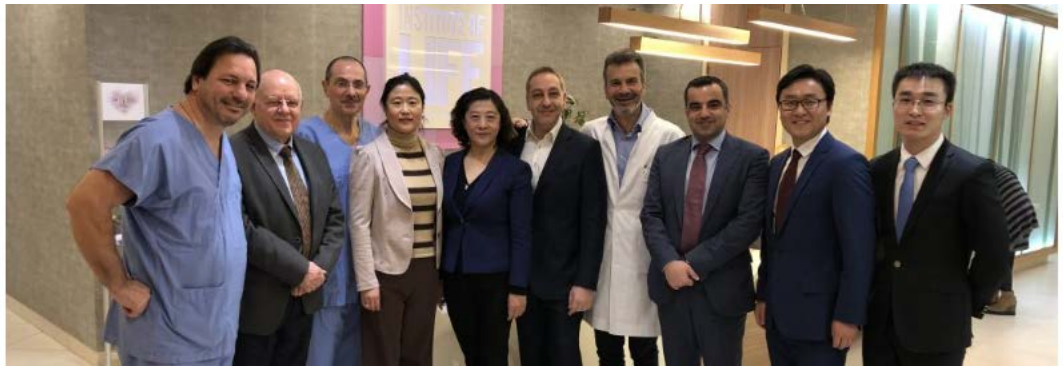
HOME TREATMENTS OUR TEAM WHY CHOOSE

Greece – China

New Strategic Partnership of the Institute of Life with Jadecare International of China

The high level of **Assisted Reproduction** in Greece is recognized globally. The **Institute of Life** has been working with the **Jadecare International Hospital** chain in China for four months now and is now receiving couples from China for IVF treatment. Under the cooperation agreement, representatives of Jadecare International visited the Institute of **Life-IASO** and representatives of the **Institute of Life** took part as invited speakers at the **4th Gynecological Conference of Jedicare International**, held in Beijing between 31/5 and 3/6 with more than one thousand gynecologists from all over China.

In his speech, **Dr. Ioannis Zervomanolakis**, Founding Member of the Institute of Life, presented the sophisticated oocyte cryopreservation techniques of our Unit. Our Scientific Advisor, **Dr. Nuno Costa Borges** presented alongside the "spindle transfer" as the last step before donating ova for women with poor quality ovaries and mitochondrial dysfunctions who want to make a child with their own genetic material.



Downloaded, 07/09/19

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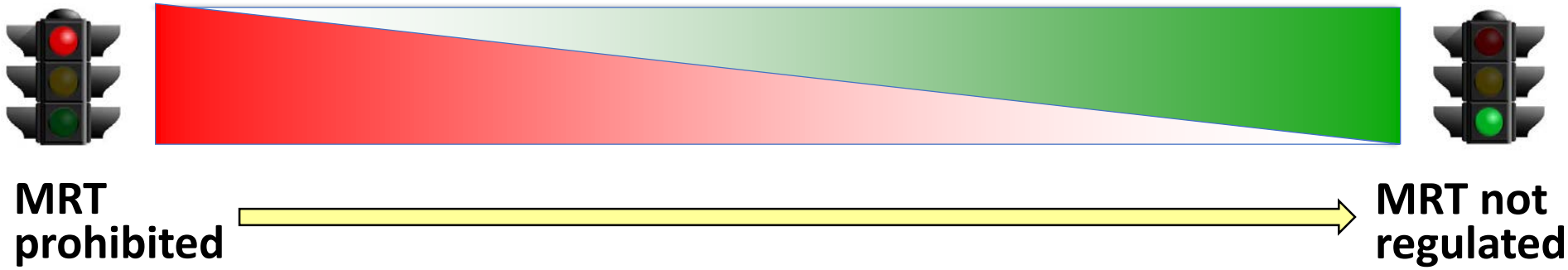
Summary: Ramifications of Differing International Regulations of Alternative Technologies

- The international variation in regulations of MRT provides the opportunity for medical tourism of patients to seek MRT treatment abroad
- There are now several examples of inter-country collaborations between private IVF clinics



Patients and samples are moving around the globe for MRT

Why Private Clinics Can Circumvent Regulations

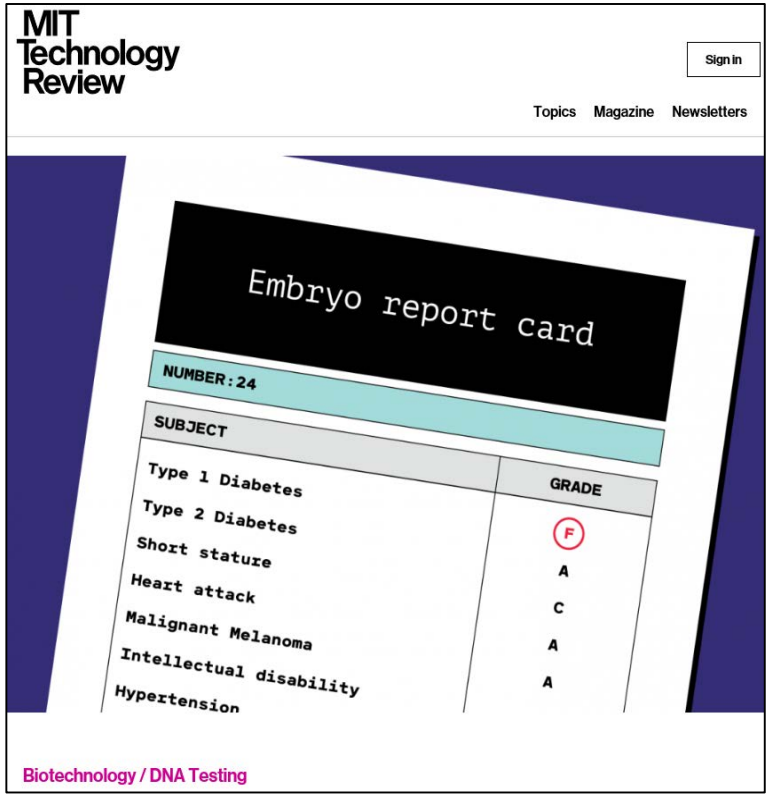
- No country prohibits citizens from obtaining medical treatment abroad (i.e. extra-territorial prohibition)
- Many countries have ambiguous or more permissive policies
- Several of these countries with ambiguous or permissive policies have excellent IVF clinics, clinicians, embryologists and scientists

Embryo Selection for Polygenic Disorder Risk and/or Desirable Traits

Embryo Selection for Polygenic Disorder Risk

- The technology is now available for polygenic disorder screening (PGT-p) in human embryos using genome-wide screening[1]
- The technology combines polygenic risk score algorithms with novel molecular biology methodologies for simultaneous prediction of:
  - Aneuploidy
  - Structural rearrangements
  - Monogenic disorders
  - Polygenic disorders

The simultaneous approaches = expanded (ePGT)



https://www.technologyreview.com/s/614690/polygenic-score-ivf-embryo-dna-tests-genomic-prediction-gattaca/
down loaded 07/11/19

[1] Treff et al 2019; Eur J Med Genet 62:103647

Embryo Selection for Polygenic Disorder Risk

- Performance has been established for hypothyroidism (AUC 0.70) and type I diabetes (AUC 0.68)[1]
- Studies indicate current applicability for several common genetic diseases including[2]:
  - Breast cancer
  - Prostate and testicular cancer
  - Basal cell carcinoma and malignant melanoma
  - Inflammatory bowel disease
  - Heart attack

[1] Treff et al 2019; Eur J Med Genet 62: 103647

[2] Lello et al Genomic Prediction of Complex Disease Risk. bioRxiv

[3] Karavani et al. http://dx.doi.org/10.1101/626846doi: bioRxiv

Embryo Selection for Polygenic Disorder Risk

- However, a very recent study suggests polygenic screening may have limited utility[1]
  - Only a marginal potential gain of embryo selection using a polygenic score estimated for height (~2.5cm) and IQ (~2.5 points)
- Lifestyle factors (diet, obesity, alcohol, smoking, exercise etc.) are major determinants of disease risk
- Available evidence does not justify testing for polygenic risk

Interpretation of polygenic risk factors keeps changing as more studies are reported

[1] Karavani et al. http://dx.doi.org/10.1101/626846doi: bioRxiv

Embryo Selection for Desirable Traits

- Obvious concerns for eugenics and possible “danger zones”
- Traits sometimes desired by a person undergoing IVF include:
  - Sex of the embryo for non-medical reasons, e.g. family balancing
  - Eye color
  - Other, e.g.
    - Height
    - Intelligence
    - Physical abilities

Embryo Selection for Desirable Traits: Gender Selection

Sex of the embryo for non-medical reasons, e.g. “family balancing”

- The ASRM Ethics Committee[1]
  - Has not reached consensus on whether it is ethical for providers to offer ART for sex selection for nonmedical purposes
- The ESHRE Task Force on Ethics and Law[2]
  - The family balancing requirement could be set at having at least one or at least more than one child of the non-requested sex in the household

ASRM = American Society for Reproductive Medicine
ESHRE = European Society for Human Reproduction and Embryology

[1] Ethics Committee of the ASRM 2015; Fertil Steril 103:1418–22
[2] Dondorp et al 2013; Hum Reprod 28(6):1448–59

Embryo Selection for Desirable Traits: Gender Selection

Over 42 countries

Embryo Selection for Desirable Traits: Eye Color

Latest Eye Color News

EYE COLOR SELECTION WITH GENETIC HEALTH SCREENING AND GENDER DETERMINATION BEGINNING AGAIN IN 2018.

We are pleased to announce that we are once again taking reservations from parents interested in screening their embryos for genetic health, gender and eye color. We are predicting our updated and highly accurate screening technology to be app. 90-95% predictive for eye color. Program participation requires that parents be screened genetically to determine if they carry the genes to produce a child with the eye color they seek. Call today for information: 818-728-4600 or 212-725-1177

Embryo Selection for Other Desirable Traits

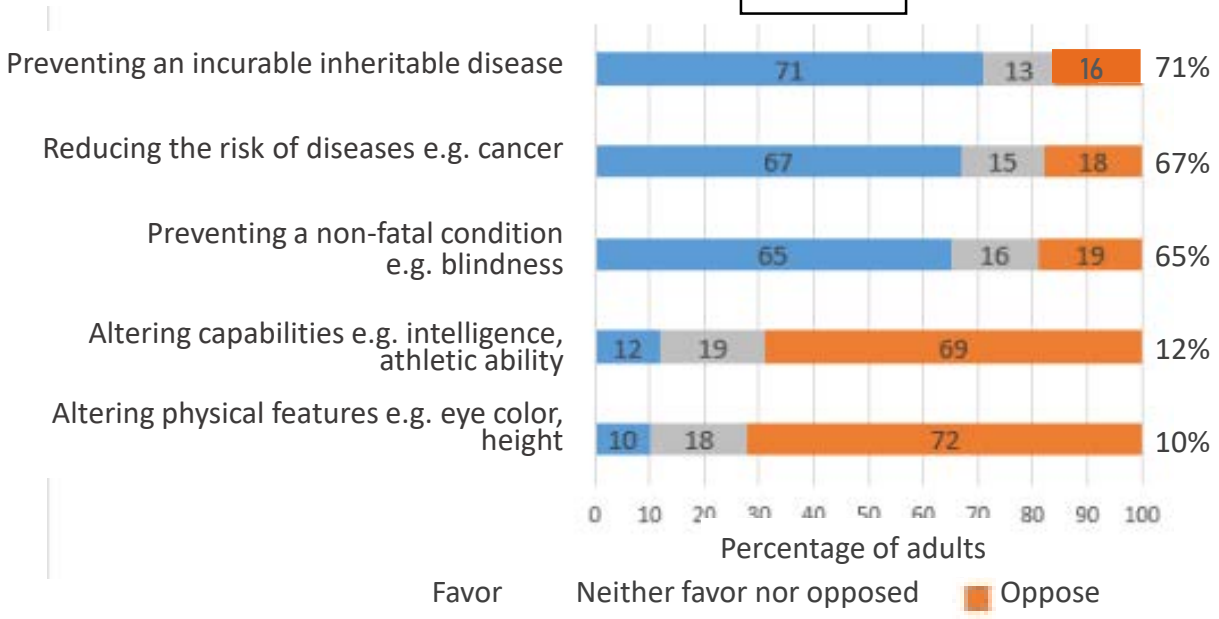
Not as prevalent as one might think:

- Survey of 1,597 women requiring sperm donation[1]
  - 50% selected for intelligence
  - 42.7% for height
  - 40.7% for ethnicity

[1] Sawyer et al 2013; RBMOnline 27:436-7

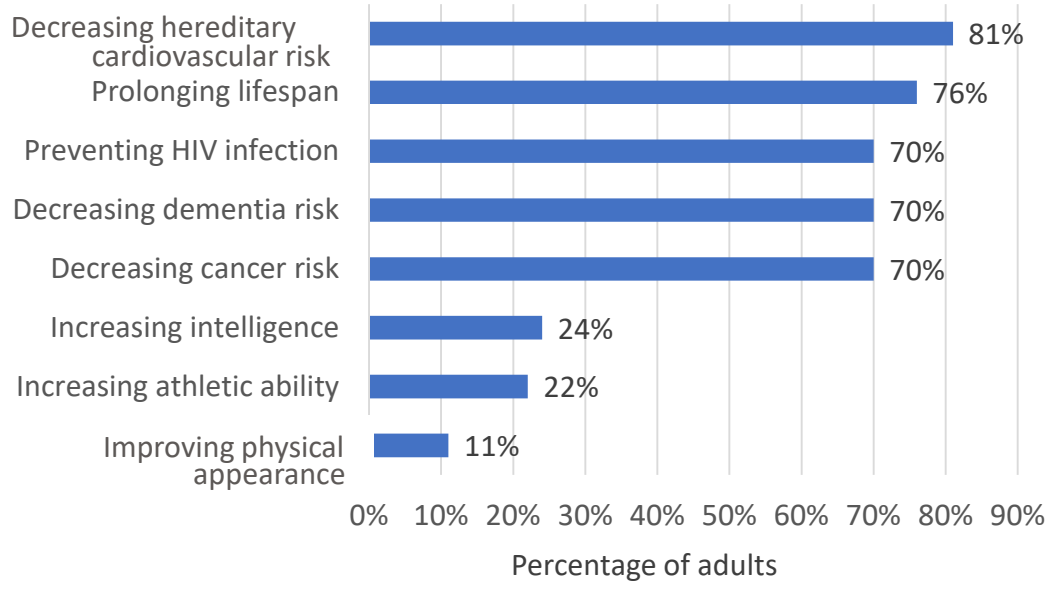
Embryo Selection for Other Desirable Traits

USA



The Associated Press-NORC Center for Public Affairs Research. Human Genetic Engineering. http://apnorc.org/projects/Pages/Human-Genetic-Engineering.aspx (US Survey)

China



Yiwei W. Sixth Tone, Nov. 9, 2018. https://www.sixthtone.com/news/1003187 Chinese Survey

Surveys from both countries indicate:

- The majority of respondents support GGE to reduce/avoid disease risk
- A minority support GGE for child “enhancements”

Thinking through the way forward ….

- The reality is that germline alterations in the human genome will likely be introduced
- Legislation often lags behind the technologies is it trying to regulate due to their rapid advancement
- It would appear that more flexible legal and operational frameworks are needed, which are adaptive to the ever-changing technologies