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)

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

Permissive  Intermediate  Restrictive  Legislative  Regulatory
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\(^1\-^4\)

International Regulation of the Clinical Use of PGD

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**

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

- 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

Adapted from Ishii & Hibino 2018; RBMOnline 5:93-109
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
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:
  - Increased stress
  - Safety concerns (multiple pregnancies)
- Sample movement involving:
  - Just the patient
  - The patient and samples
  - Just the samples

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**IMTJ = International Medical Travel Journal
# Medical Tourism for Assisted Reproductive Treatments

## IFFS survey of 64 country respondents

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<thead>
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<th>Treatment</th>
<th>% Patients responding to question</th>
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<tr>
<td>Oocyte donation</td>
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<td>Sperm donation</td>
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<td>Embryo donation</td>
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<td>Gestational surrogacy</td>
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<td>Traditional surrogacy</td>
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1 Cohen et al 2019; Nature Biotechnol 37:589-600
IFFS = International Federation of Fertility Societies

Circumvention (of local regulation) medical tourism\(^1\)

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<tr>
<th>Country</th>
<th>Medical reports</th>
<th>Registered clinical trials</th>
<th>Ad on clinic website</th>
<th>Medical reports</th>
<th>Registered clinical trials</th>
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20/28 (71.4%)

= confirmed by authors via email; 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

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,*

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Zhang et al 2017; RMBOnline 34:361-368

Jordan – USA – Mexico
Medical Tourism for MRT in private clinics: Example 1

- Mexico: Embryo transfer
- USA: Egg retrieval, MST, ICSI, embryo culture and vitrification
- Jordan: Couple’s domicile
- Vitrified embryo transported by air
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

- 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.

Our international managers are always ready to answer all your questions
Anna Lukavenko,
a.lukavenko@dl-nadiya.com
Medical Tourism for MRT in private clinics: Example 2

Nadiya Clinic, Ukraine

World map of success

16 patients 5 countries

- Ukraine - 7 patients
- USA - 4 patients
- Israel - 3 patients
- Sweden - 1 patient
- United Kingdom - 1 patient

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

Through Pioneering Clinical Research, Institute of Life IVF Center in Greece and Embryotools in Spain Achieve Global Innovation in Assisted Reproduction
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 Jadecare International, held in Beijing between 3/15 and 3/16 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.
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)

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\(^1\) Treff et al 2019; Eur J Med Genet 62:103647

downloaded 07/11/19
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 including²:

- 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
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/10.1101/626846 doi: 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**
  - 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**
  - 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

Announcing Eye Color Selection!

Welcome to eye color selection! The newest option available only at The Fertility Institutes to 21st Century “parents to be”. Parents are increasingly taking advantage of the ever-expanding role of modern genetics in providing choices concerning the health, well-being, gender and characteristics of planned pregnancies and future children.
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

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\(^1\) Sawyer et al 2013; RBMOnline 27:436-7
Embryo Selection for Other Desirable Traits

Surveys from both countries indicate:
- The majority of respondents support GGE to reduce/avoid disease risk
- A minority support GGE for child “enhancements”

For more information, please visit:
- AP-NORC Center for Public Affairs Research. Human Genetic Engineering. [link](http://apnorc.org/projects/Pages/Human-Genetic-Engineering.aspx)
- Yiwei W. Sixth Tone, Nov. 9, 2018. [link](https://www.sixthtone.com/news/1003187)
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 it is 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