A wholly new path via genome editing

International summit on human gene editing
Washington D.C.

Tetsuya Ishii

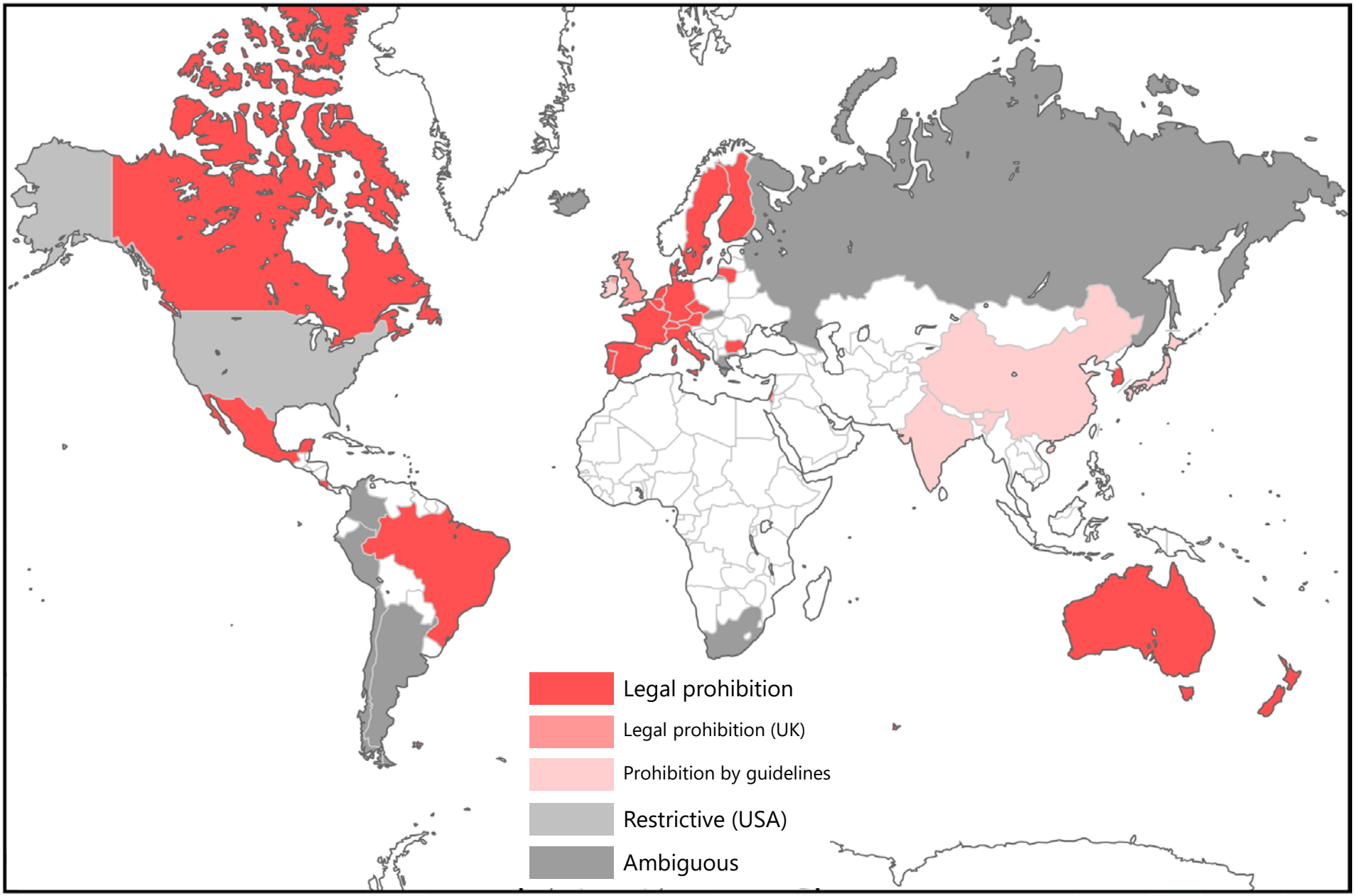
北海道大学
HOKKAIDO UNIVERSITY

Human germline gene modification

- May impact the entire body of an individual and subsequent generations.
- But, older genetic engineering has made this unrealistic.
- Moreover, this has been criticized:
  - Irremediable risks to offspring and future generations
  - Transgressions of "Natural" and "Divine laws"
  - Serious societal harms such as enhancement

Thus, there appears to be a *de facto* global consensus that human germline should not be genetically modified for reproduction.

International regulatory landscape: Mosaic



Araki, M. and Ishii, T. RB&E 2014;12:108.

Human germline editing needs scrutiny

Opinion

CellPress

Germline genome-editing research and its socioethical implications

Tetsuya Ishii

Office of Health and Safety, Hokkaido University, Sapporo 060-0808, Hokkaido, Japan

Genetically modifying eggs, sperm, and zygotes ('germline' modification) can impact on the entire body of the resulting individual and on subsequent generations. With the advent of genome-editing technology, human germline gene modification is no longer theoretical. Owing to increasing concerns about human germline gene modification, a voluntary moratorium on human genome-editing research and/or the clinical application of human germline genome editing has recently been called for. However, whether such research should be suspended or encouraged warrants careful consideration. The present article reviews recent research on mammalian germline genome editing, discusses the importance of public dialogue on the socioethical implications of human germline genome-editing research, and considers the relevant guidelines and legislation in different countries.

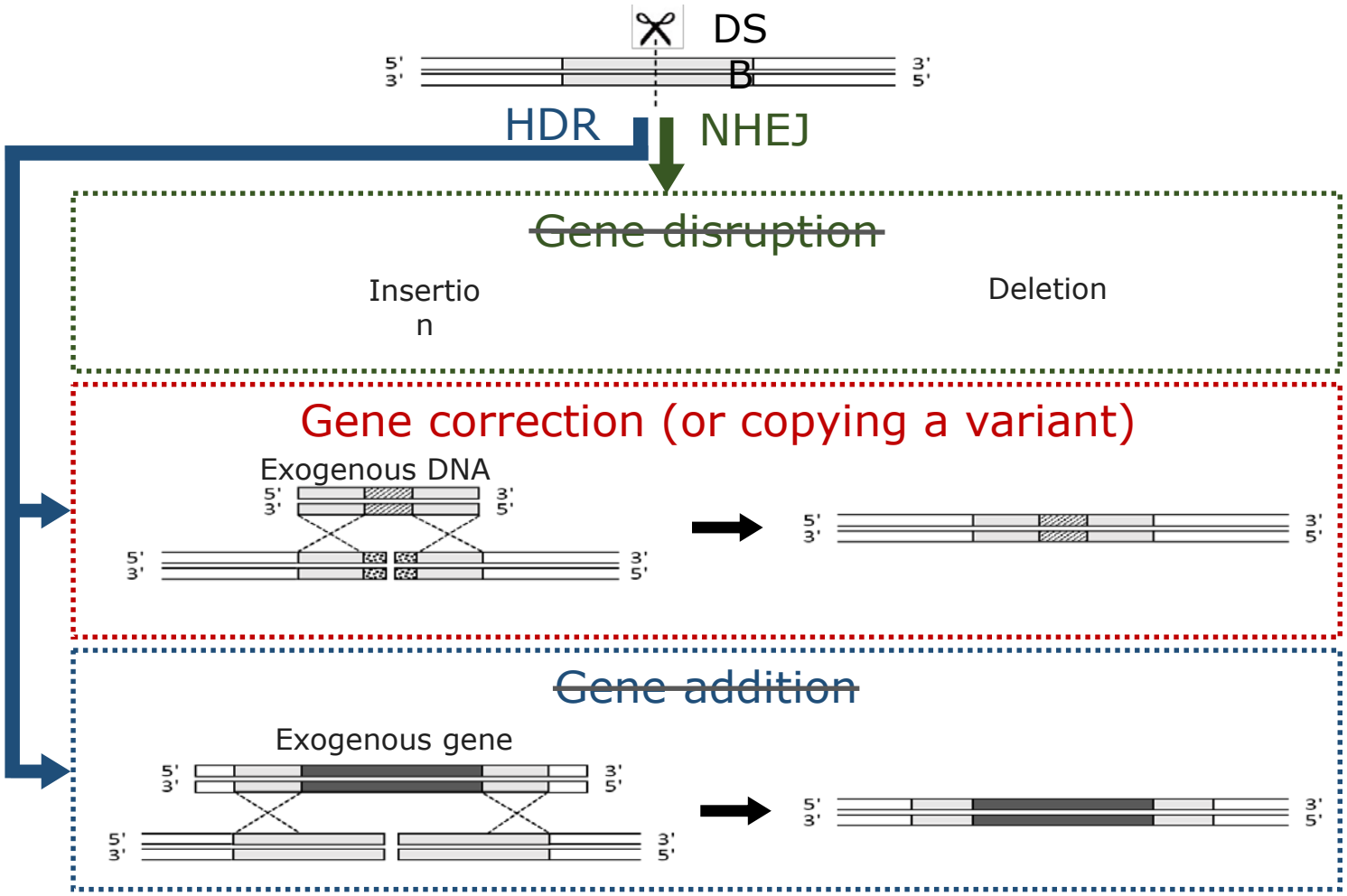
modification, and thus are now being used instead of conventional genetic engineering in many laboratories worldwide. The robustness of this genome engineering technology has made it conceivable that gene modification of the human germline (oocytes, sperm, zygotes, and embryos) (Box 1) is becoming feasible in the clinical setting [4]. However, this type of gene modification has raised tremendous debate in the context of medical beneficence, safety concerns, challenges to human dignity, and risk of abuse for eugenics or enhancement (the parental pursuit of specific traits for non-medical reasons) [5]. Consequently, many countries forbid human germline gene modification for reproductive purposes [4,6].

Recently, representatives of the Alliance for Regenerative Medicine, a group of interested stakeholders including Cas9 developers and the International Society for Stem

Ishii, T. Trends in Molecular Medicine 2015; 21:473-81.

Approaches in human germline editing

Efficient~~, versatile~~, ~~multiplex editing~~



HDR with one gRNA policy

Ishii, T. Briefings in Functional Genomics 2015; 10.1093/bfgp/elv053

Ethical implications of HDR with one gRNA

Via HDR:

- Correcting a mutation, resulting in wild type
- Copying a naturally-occurring variant

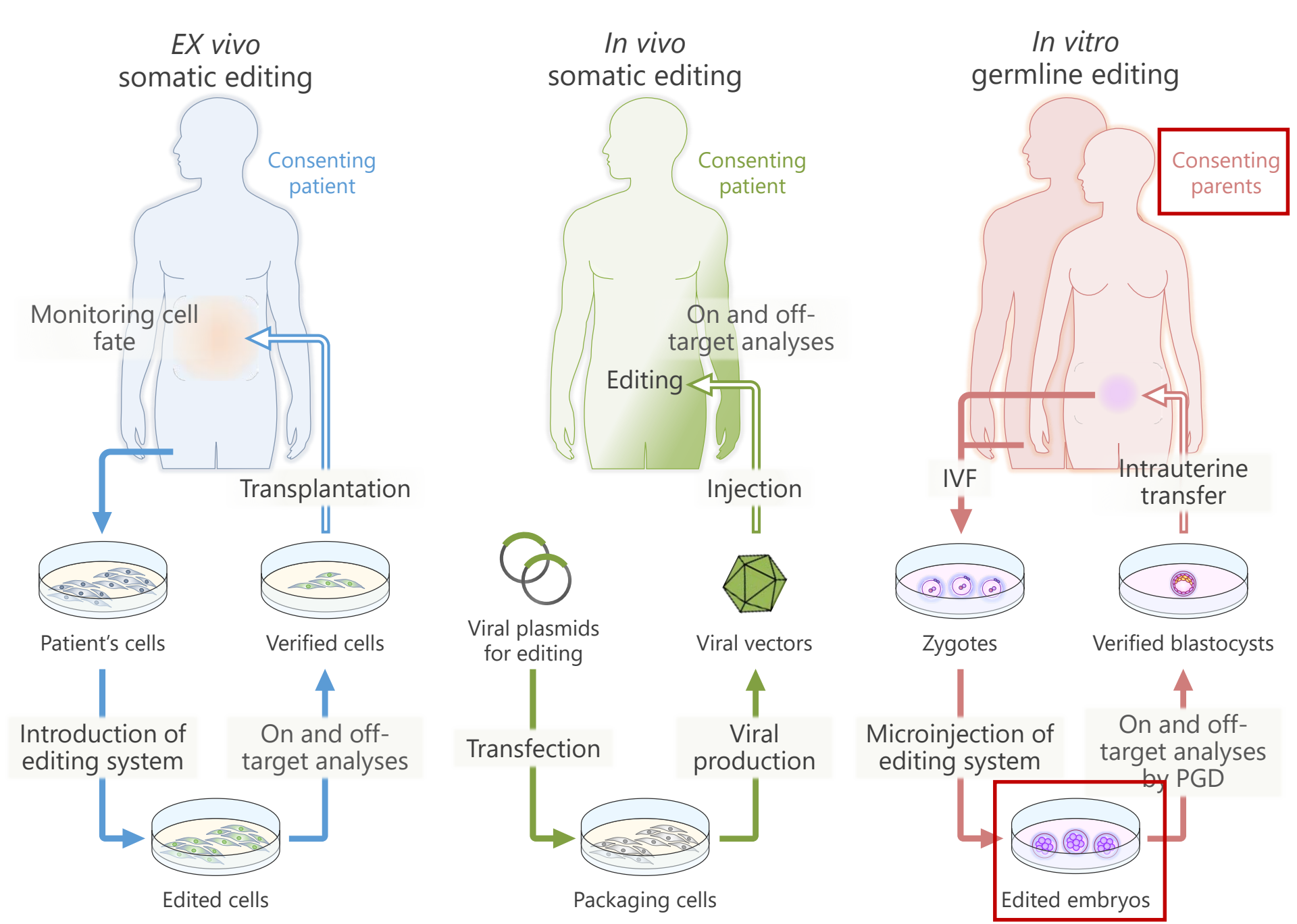
might fall under "Natural laws".

But, there is still room for consideration…

- might be contrary to the natural course of events.
- might violate divine laws, "Playing God".

Nonetheless,
this type of HDR deserves further consideration,
if the purposes are socially acceptable.

Ishii, T. Briefings in Functional Genomics 2015; 10.1093/bfgp/elv053



Araki, M. and Ishii, T. Under revision

Legitimacy of parental consent

- In ART, informed consent is obtained from prospective parent(s).

- Congenital anomaly rate in children born of ARTs has been considered largely tolerable.
  - Odds ratio of increased risk with ART vs. spontaneous conception: 1.3-1.5*

- In germline genome editing, parental consent might be justified <u>when benefits for parent(s) and/or a child exceed risks to the child.</u>

*Williams C, et al. Ultrasound Obstet Gynecol. 2010 Mar;35(3):255-9.

Four objectives of germline editing

- ○Disease prevention for healthy children
  - Rare cases of definitive inheritance of genetic disease, where PGD is not applicable.
  - Meanwhile, seem contrary to evolutionary course of event (a species corrects a mutation in the germline).

- ◎Personalized ART to enhance success rate
  - For idiopathic infertility associated with genetic conditions of parents.
  - But, likely cost higher, leading to larger reproductive disparity

- ? Enhancement for "family happiness"

- ? Eugenic uses for "a social goal"

Ishii, T. Briefings in Functional Genomics 2015; 10.1093/bfgp/elv053

What is enhanced?

A survey of 1700 women who formed their families using donor spermatozoa

Neroli Sawyer [a], Eric Blyth [b], Wendy Kramer [c], Lucy Frith [d,*]

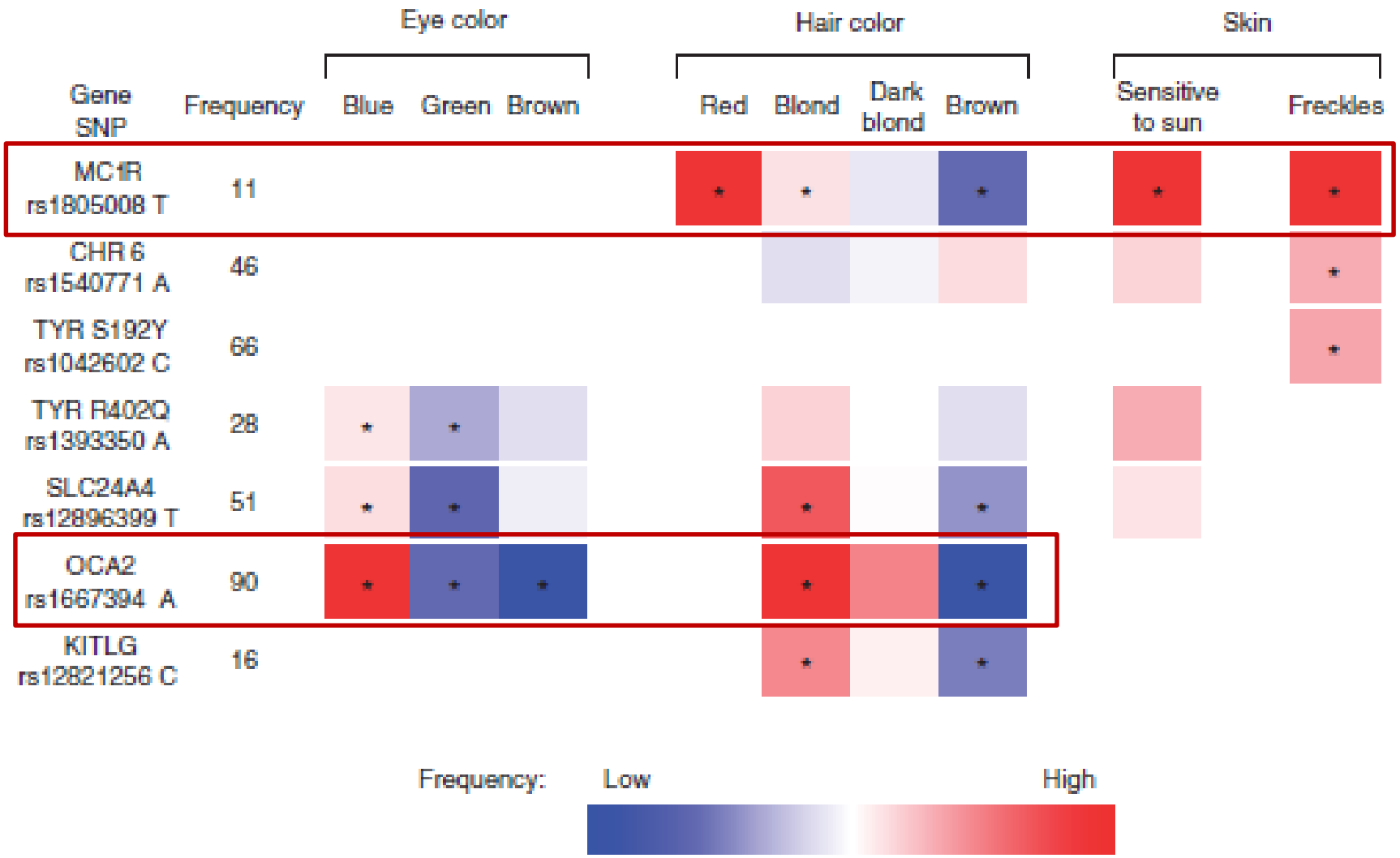
[a] School of Health Sciences, University of Ballarat, University Drive, Mount Helen, Ballarat, Victoria 3353, Australia; [b] University of Huddersfield, Queensgate, Huddersfield, West Yorkshire HD1 3D, UK; [c] Donor Sibling Registry, PO Box 1571, Nederland, CO 80466, USA; [d] Institute of Psychology, Health and Society, University of Liverpool, The Waterhouse Blds, Brownlow St, Liverpool L69 3GL, UK

* Corresponding author. *E-mail addresses:* neroliann@gmail.com (N Sawyer), e.d.blyth@hud.ac.uk (E Blyth), wendy@donorsiblingregistry.com (W Kramer), Frith@liverpool.ac.uk (L Frith).

Other than health,
women wanted to know the intelligence, height and ethnicity of sperm donors.

Sawyer N. et al. Reprod Biomed Online. 2013 Oct;27(4):436-47.

Enhance visible traits in children



Yoshimi K., et al. Nat Commun 2014; **5:**4240.
Kamaraj B., Purohit R. Biomed Res Int. 2014; 2014:905472. Sulem P, et al. Nat Genet. 2007 Dec;39(12):1443-52.

Enhancement of visible traits : Unjustifiable

1. Could enhance the child's life by providing a socially favored appearance, BUT also could affect the child's health.
   * Consider plastic surgery.
2. Serious discord may occur within a family, if the child does not exhibit that characteristic.
   *Parents likely value child's appearance.
3. The child may suffer distress because it was imposed through means other than a blood relationship.

Ishii, T. Briefings in Functional Genomics 2015; 10.1093/bfgp/elv053

Eugenic uses for a social goal

- ~~Negative eugenics~~

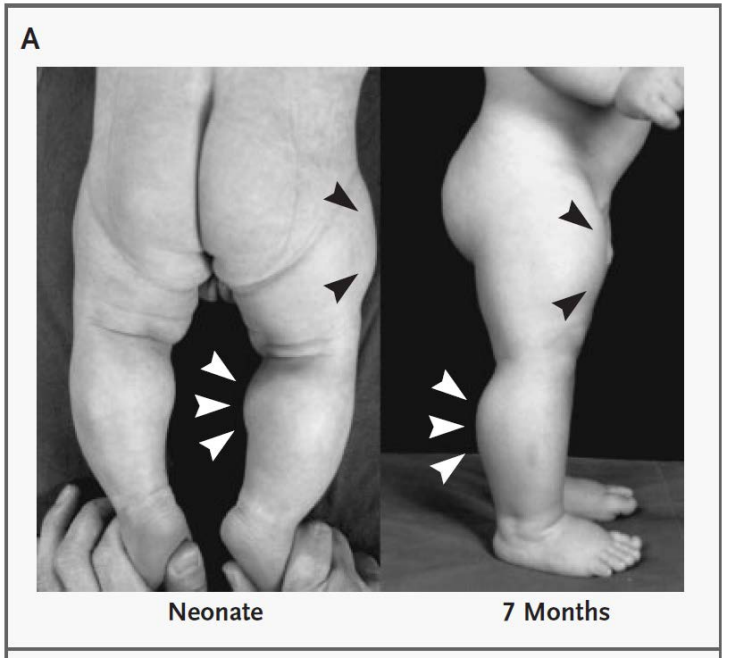
Applying a sex distortion system (using customized nucleases to induce DSBs in X chromosome during spermatogenesis) to a specific group.

→ Crime against humanity

- Positive eugenics

Copying of a naturally-occurring *MSTN* variant, to create a number of people with muscle hypertrophy.

→ human production, not reproduction



Schuelke M., et al.
N Engl J Med (2004) 350:2682-2688.

Ishii, T. Briefings in Functional Genomics 2015; 10.1093/bfgp/elv053

ART legislation in G8 and China

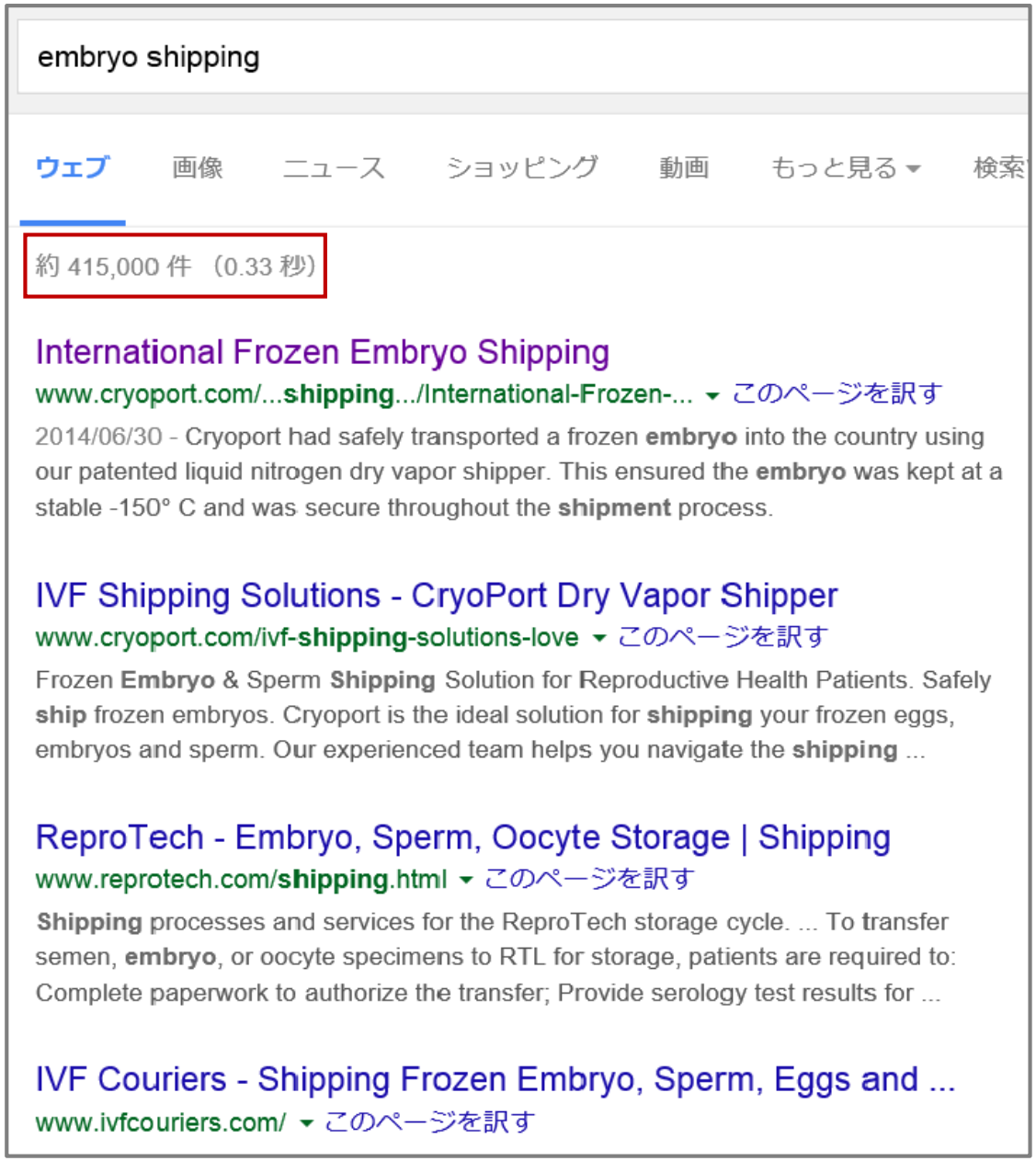
	ART centers 2007	Centers/M	ART-specific national law	Prohibition of reproductive cloning by national law	Prohibition of GGM by national law
Canada	26	0.79	Yes	Yes	Yes
Russia	69	0.48	No	Yes	Ambiguous
UK	70	1.15	Yes	Yes	Yes
France	104	1.68	Yes	Yes	Yes
Germany	118	1.44	Yes	Yes	Yes
Italy	202	3.47	Yes	Yes	Yes
China	358	2.65	No	No	No
USA	483	1.60	Yes	No	No
Japan	606	4.74	No	Yes	No

Only Japan, USA, China (and Russia) face troubles of enhancement (or eugenics)?

Ishii, T. Briefings in Functional Genomics 2015; 10.1093/bfgp/elv053

No

- ART tourisms are available.
- Embryo shipping services are also available.



Whittaker A.M.
Reprod Biomed Online 2011; 23:609-617.

Is it right time to move to a wholly new path?

- YES

  Please propose more measures
  in addition to HDR & one gRNA policy.

- NO

  So, what is needed for global society?

Public dialogues needed in each country

北海道大学
HOKKAIDO UNIVERSITY

June 6, 2015. Sapporo. “Science intervening in life”

Selecting and modifying human embryos and its social implications

http://costep.hucc.hokudai.ac.jp/costep/contents/article/1344/