Case studies in gene editing…

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Key points

- Drive to find solutions to rare diseases is strong
  - Somatic gene therapy → ultra-rare conditions
- First uses of new technology bring considerable risks
  - IVF advanced despite major uncertainty (known/unknown)
  - Mitochondrial Replacement Therapy…
- Uses of a new technologies driven by need and demand
  - Advantages over alternatives?
- Applications in somatic gene editing: imminent
- Applications in embryo, gamete editing: feasible
  - Justification for use varies with specific indications

Case studies in gene editing: Somatic

- Genes where locus deletion is therapeutic
  - Deletion of CCR5 → resistance to HIV
  - Deletion of cep290 IVS26 in Leber's blindness→ restores normal protein, photoreceptor function
  - Deletion of Erythroid BCL11a enhancer→ reduces sickling
- Genes needing Homology Directed Repair…
    - Beta-globinopathies (Sickle cell anemia, thalassemia)

- Review and oversight of clinical applications
  - Current regulatory framework for somatic GTx adequate

Case studies in gene editing: Germline

- Parents of child with X-linked NEMO immune-deficiency
  - Seeking 2nd child via PGD → ¾ embryos unaffected
  - For 2nd child to be transplant donor to 1st → ¾ x ¼ = 3/16
  - 4 ½ cycles of IVF; 36 embryos before 2 found compatible…

Savior siblings and Fanconi anemia: analysis of success rates from the family's perspective

Juan P. Trujillo, PhD[1,2] and Jordi Surralles, PhD[1,2]

GENETICS in MEDICINE | Volume 17 | Number 11 | November 2015

Sofia Trevino

…one fit savior

8 families have elected this

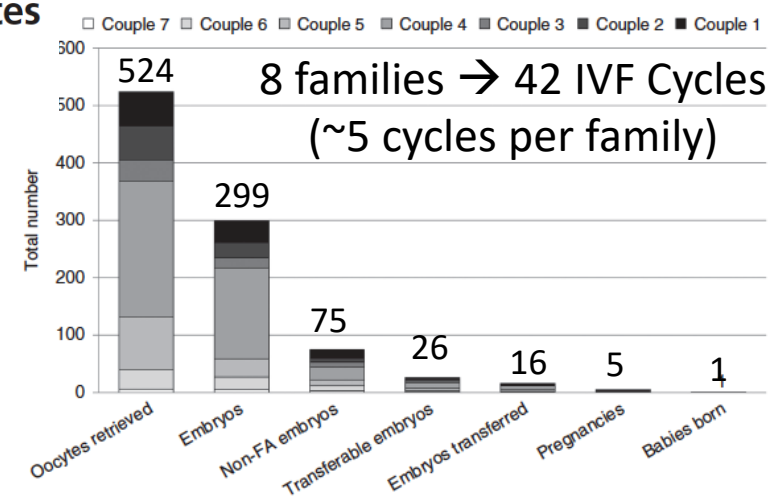
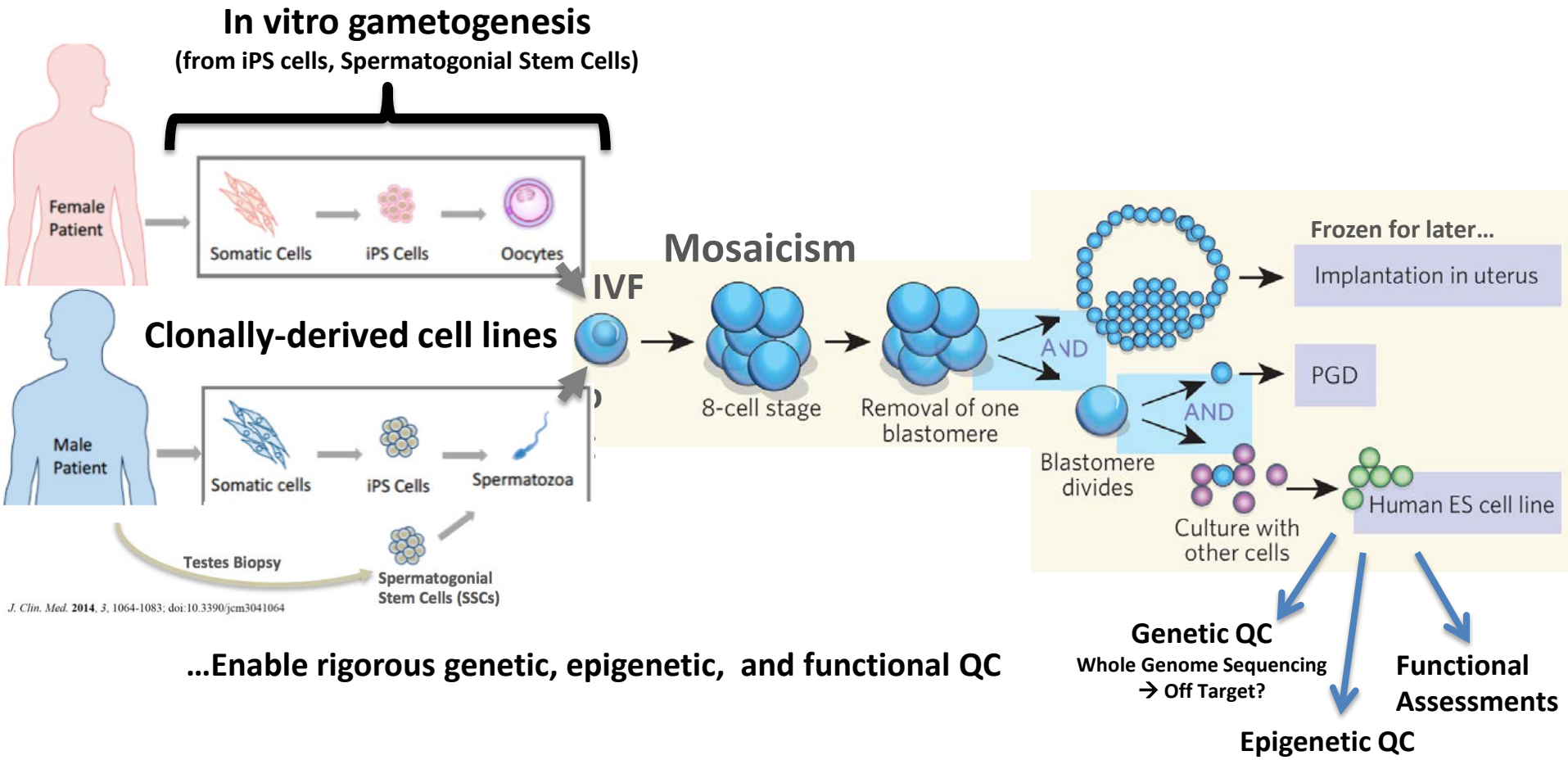


Figure 1 Graphical representation of accumulated embryology and genetic data from 38 in vitro fertilization (IVF) cycles using preimplantation genetic diagnosis (PGD) with human leukocyte antigen (HLA) typing in seven families with Fanconi anemia (FA).

Coupling gene editing to PGD may improve efficiency, reduce cycles

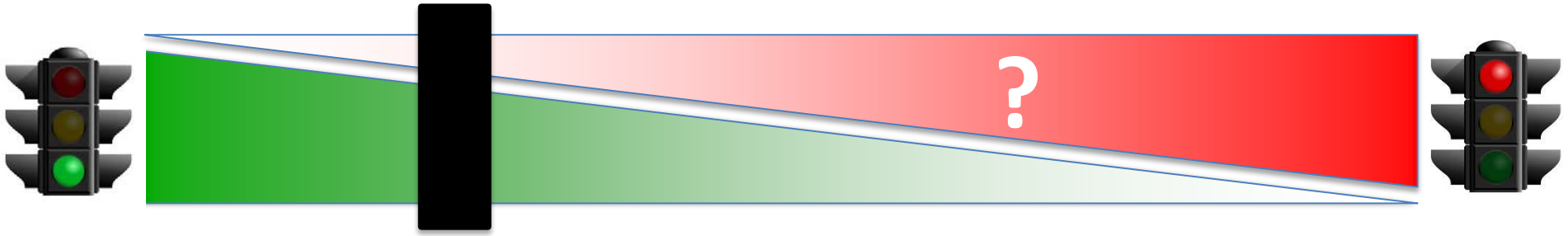
Assessing safety of gamete or embryo gene modification



…Enable rigorous genetic, epigenetic, and functional QC

Figures adapted from Simpson JL Nature 2006 and Ishii T J Clin Med 2014

Justification for germline editing varies…



Disease prevention

- Huntington's
- Tay Sachs
- Cystic Fibrosis
- Sickle cell anemia

Consider alternatives…

PGD

Somatic therapy

When no alternative…

Couples, both affected

Homozygous recessive

Autosomal dominant

HZ Auto Dominant

Infertility

Modifying Disease Risk

- HIV resistance (CCR5)
- Heart disease (PCSK9)
- Alzheimer's disease (APP A673T/+)
- Cancer (BRCA1/2)
- Resistance to global pandemics…

NATURE VOL. 326 12 MARCH 1987

Homozygotes for Huntington's disease

Nancy S. W[illegible], Anne B. Young, Christopher E. Tanz‡,
Helen Travers§, Simon Starosta-Rubinstein†,
John B. Penney†, S. Robert Snodgrass‖, Ira Shoulson¶,
Fidela Gomez#, Maria A. Ramos Arroyo**,
Graciela K. Penchaszadeh*, Humberto Moreno††,
Kerin Gibbons‡, Ann Faryniarz‡, Wendy Hobbs‡,
Mary Anne Anderson‡, Ernesto Bonilla††,
P. Michael Conneally‡‡ & James F. Gusella‡

"Enhancements"

- Muscularity (MSTN)
- Eye color, height?
- Learning and memory
  https://www.dnalc.org/view/1390-Genes-for-Learning-and-Memory.html
- https://www.cog-genomics.org/

- Complex traits:
  - Most Challenging

Permissible vs impermissible applications?