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Germline outline: **Preimplantation Genetic Diagnosis**
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The problem (1):
Genetic mutations in of different levels and different stages of human life that causes diseases. These mutations include:

A) Pre-birth onset mutations:
   - Aneuploidy (extra copy extra or a fragment of a chromosome; deletion of a chromosome, i.e. trisomy 21).
   - Single gene mutations that has relatively few numbers of known mutations in their sequence (i.e. Sickle cell disease).

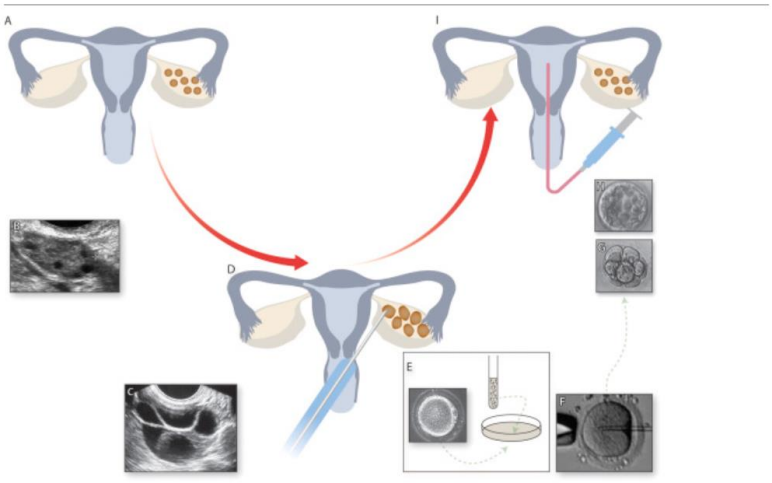
B) Post birth onset mutations:
   - Undetectable Duchenne muscular dystrophy (DMD).

Proposed solutions:
Preimplantation genetic diagnosis PGD. In essence, an embryo that is disease free escaping the possibility of gene editing.

History (2):
What is PGD?

PGD a diagnostic technique of embryos for known abnormalities or for sex selection. It is used when at least one parent is a carrier of genetical abnormality.

PGD is used with in-vitro fertilization (implementing sperm into an egg outside in a glass). The embryo then cultured at the 8-cell stage -around 5-6 days- then single cell is taken from the culture (cell biopsy) and searched for markers to specific abnormality or a disease that is known to run in the family (figure below). Note that there exists a similar testing (PGS; S= screening) where multiple failure of IVF is suspected to be caused by chromosomal abnormality (3).



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When PGD is preferable?
Unlike CRISPR, PGD efficiency is greater than 80% (4). It is a detection/selection in case of PGD versus detection/deletion or detection/correction in case of CRISPR. For example, Sickle cell anemia (caused by a mutation A>T in codon 7). In both cases, the question of the applicability of producing a sickle cell free offspring was studied; in case of PGD there has been a reported case of successful detection method of the disease that is high in accuracy (9). In the case of CRISPR, treating such mutation was done on *adult* blood cells (not germline) and the treating efficiency reached 31% (10).

Challenges to PGD:

- Mosaicism (Not all cells are healthy nor edited or diseased)
- De novo mutations in diseases such as DMD. Such diseases is a better fit to be treated by CRISPR even though the current progress is at human and mice models (7)
- Preventing diseases passaged vs lowering disease transmission (depends on the inheriting type, think myocardial diseases).
- Disease that cannot be detected early on in life.
- Certain disease has a very high rate among the embryos to start with. Diseases such as Huntington's disease.
- Termination of an ongoing pregnancy is possible.
- PGD raises some religious, cultural, and governmental issues.
- Even after diagnosis/ selection there is a chance of **miscarriage** which depends on many factors (i.e. mother age).

PGD Recommendations:

- Since PGD and IVF implementation is somewhat new health issues of kids born using such technique were studied to some extent. I haven't found a source that suggested that their mental health is different when compared with kids born in a natural way (5) nor any congential abnormalities (6).
- To favor CRISPR over PGD is possible in different ways (treatment vs enhancement).
- The use of CRISPR in addition to PGD has been discussed (8) but I couldn't find an experiment that utilized both.
- In concept, identifying the mutation sequence -keeping off-target mutation on mind- indicates the possibility to using CRISPR/Cas9 to edit the genome of germline. However, taking the efficiency of editing and compare it to the one of PGD, it doesn't make much sense using CRISPR over PGD at the current state.

Note: I didn't talk about how an abnormality is detected with PGD (e.g. DNA FISH).

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Citations:


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