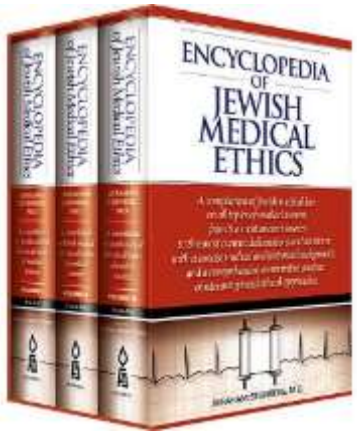
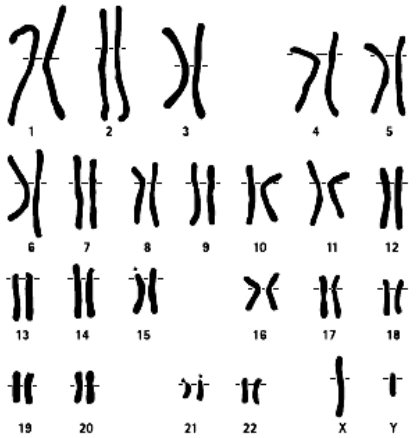
GEN-ETHICS AND HALAKHAH

Rabbi Prof. AVRAHAM STEINBERG, MD



GENETICS – SOME FACTS

- 46 chromosomes, X y
- Dominant, recessive, X-linked
- Homozygote, heterozygote
- Genotype, phenotype
- 3 billion code ‘letters’
- DNA length 2 m, wide 2 billionths of a m
- ~20,000 genes
- ~5,000 genetic syndromes



ETHICAL ISSUES IN GENETICS

- Revealing information
- informed consent
- confidentiality
- the “slippery slope”
- allocation of limited resources
- human and animal experimentation

ETHICAL ISSUES IN GENETICS

- EUGENICS
- OWNERSHIP OF GENETIC MATERIAL
- INDIVIDUAL AND MASS SCREENING
- GENETIC EDITING/ENGINEERING
- GENETIC THERAPY

THEOLOGICAL ISSUES

‘PLAYING GOD’

INTERFERENCE WITH NATURE

‘PLAYING GOD’

- genetic revolution ➔ technical not fundamental
- genetic revolution ➔ revealing existing not creating new
- where there is a plan ➔ there is a planner
- enhanced knowledge of macro- and micro-cosmos enhances the belief in the All-Mighty God

INTERFERENCE WITH NATURE

Principally permissible, perhaps required

verapo yerape, **from here one derives a healer's permission to heal** [***BK 85a***], **and we do not say -- God smites and man heals** [***Rashi,*** **loc. cit.**]

INTERFERENCE WITH NATURE

Principally permissible, perhaps required

All His work which God created to make, **is interpreted by the *Midrash* to mean that world was left incomplete for man to complete it**

INTERFERENCE WITH NATURE

Principally permissible, perhaps required

and subdue the earth **-- God gave humans power and dominion on earth to do as they wish with animals, and to build, to uproot that which is planted, etc.**

[*Ramban,* Genesis 1:28]

INTERFERENCE WITH NATURE

Qualifications

- **the actual act must not involve any inherent halakhic prohibition**
- **the act must lead to no unavoidable or irreversible result which is halakhically prohibited**
- **derived benefit should surpass the detriment**

GENETIC DETERMINISM

People tend to see genetic information as more definitive and predictive than other types of data, in the sense that "you cannot change your genes" and that "genes tell all about you."

- **Genetic determinism undermines not only religion, but any humanistic moral and legal responsibility**
- **Determinism of behavior and character eliminates any effort for altruism, beneficence and responsibility, and creates anarchism and crime**
- **Genetic determinism of behavior and character is wrong even from a biological standpoint. Human characteristics are the product of complex interactions between genes and between genes and the environment.**
- **Epigenetics plays a significant role.**

DETERMINISM ⇔ FREE WILL

“Free will is bestowed upon every human being. If one desires to turn towards the good way and be righteous, he has the power to do so; if he wishes to turn towards the evil way and be wicked, he is at liberty to do so”

[***Maimonides’ Mishneh Torah, Teshuvah 5:1***]

DETERMINISM ⇔ FREE WILL

“Free will is the beginning of all human activities and approbations and of courteous conduct through which civilized societies can exist without which it would be impossible”

[*Albo’s Sefer Ha’Ikarim 1:9*]

DETERMINISM -- tendencies and motivation

- **"He who was born on *mazal* of Mars will shed blood -- either a surgeon, or a murderer, or a butcher, or a mohel"**

  [*shabbat 156a*]

- **The "story" about Moshe Rabbenu and the King of Arabya**

  [*Tiferet Yisrael, Kidushin 4:14*]

GENETICS AND HALAKHAH

IDENTIFICATION

PREVENTION

TREATMENT

IDENTIFICATION

- **Motherhood -** **exchange of babies** **mitochondrial DNA**
- **Fatherhood –** **alimony / *mamzeruth***
- **Dead person -** ***agunah/* twin towers** **Yemenite children** **anonymous person/mourning/*matzevah*** **parts of bodies/burial**
- **Forensic medicine -** **rape** **murder** **inheritance**
- **Jewish gene**

IDENTIFICATION

Halakhic debate

- **The uniqueness of individual DNA**
- **DNA as a definitive sign (סימן מובהק)**
- **The reliability of the assessment**

PREVENTION

SCREENING

- **Pre-marital diagnosis** - Dor Yesharim
- **Pre-implantation diagnosis (PGD; PGS)** -
- **Pre-natal diagnosis** - chorionic villi sampling amniocentesis
  non-invasive pre-natal testing (NIPT) ABORTION ISSUES
- **Adult diseases –** disclosure confidentiality army/business
  The story of Li-Fraumani syndrome BRCA

PRE-MARITAL GENETIC SCREENING

Pre-marital screening – encouraged

- **Family history**

  Talmudic sources

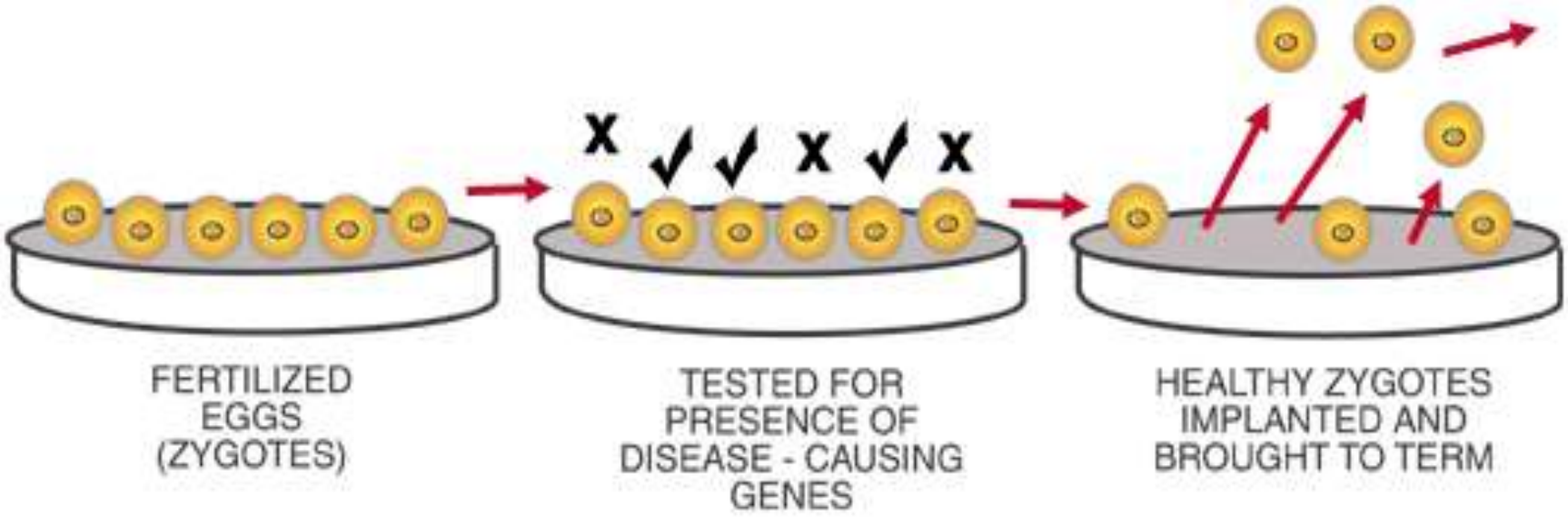
- **Tay-Sachs**

  Resonsa *Iggrot Moshe, Even Haezer* 4:10

- **Genetic screening (Dor Yesharim)**

  recessive diseases

Pre-implantation Genetic Diagnosis And Selection (PGD)



PRE-IMPLANTED FERTILIZED EGG

Respect as a human part and potential life

No human status

Consequently

pre-implantation genetic diagnosis (PGD) and discarding defective pre-embryos –

Permissible

PRE-IMPLANTATION

Respect as a human part and potential life

No human status

"he who spills the blood of a human within a human, his blood shall be spilled [Genesis 9:6] – a fetus within its mother's womb [Sanhedrin 67b]

"until 40 days after conception the fetus is mere fluid" [Yebamot 69b]

Potential life very remote

PGD - halakhah

- Rav Eliashiv principle approval = NF_1
- Rav Halberstam and Rav Neuvirt detailed approval and supervision
- Review Committee

PRINCIPLES

- Serious single gene diseases
- Serious chromosomal diseases
- Halakhically married couple

PGD - DILEMMAS

- Adult-onset disease, i.e. BRCA
- Sex selection
- Adult pregnant women, i.e., Down's
- HLA-matched baby
- 'Social' matters, i.e., IQ, aggression

NON-INVASIVE PRE-NATAL TESTING = NIPT

- Possible replacement of Invasive pre-natal diagnosis, i.e., amniocentesis and CVS
- No risk to fetus
- Use of circulating fetal DNA in maternal peripheral blood – range 3-13%
- Disappears from maternal blood within hours after delivery
- Detected as early as the 7th week of gestation, results available 1 week after sampling

NIPT – CURRENT CLINICAL USE

- **Male fetus – Y chromosome – pre-natal Dx of sex-linked diseases or congenital adrenal hyperplasia**
- **Fetal *RHD* gene – detecting RhD blood group status**
- **Fetal chromosomal aneuploidies – Down syndrome, trisomy 18, trisomy 13**
- **Fetal monogenic disease – hemoglobinopathies, hemophilia**

IN THE NEAR FUTURE

- **Scanning of the entire fetal genome non-invasively → "perfect baby syndrome"**

NIPT – ETHICAL CONSIDERATIONS POSITIVE ASPECTS

- **Safe, simple, no fetal risks – avoiding miscarriage of healthy fetus due to test (i.e., CVS, amniocentesis)**
- **Early detection – allows early reassurance if negative, and longer period for decision-making if positive; safer abortion**
- **Easily accessible – benefit a wide range of population**
- **Low cost**

NIPT – ETHICAL CONSIDERATIONS
NEGATIVE ASPECTS

- **Abuse** – for non-medical indications, i.e., sex selection, paternity testing, "for information"
- **Abortion** – for trivial and minor disorders; predispositions; carrier state; late-onset diseases; normal human variations; eugenic tendencies; "Perfect Baby Syndrome" – actually unachievable
- **Cost** – when large-scale screenings will be the norm, for information only
- **Autonomy** – increased pressure on women to perform the test
- Change in **Informed consent** – omit and cancel altogether? True informed consent?
- Change in **current scope of pre-natal screening** – missing non-genetic disorders; negative NIPT does not ensure an unaffected fetus
- **Direct-to-consumer** – no counselling; lack of individual concerns
- Change in **attitude toward the handicapped** and their families
- **Medico-legal issues** – wrongful-life law-suits
- **Slippery-slope**

NIPT – ETHICAL CONSIDERATIONS CONCLUSIONS / SUGGESTIONS

SITUATIONS AND CONDITIONS TO BE APPROVED

- **High-risk pregnancies for aneuploidies and monogenetic diseases**
- **Need for counseling and informed consent – limited disease-detection; negative results does not mean necessarily a healthy baby; need for other pre-natal screening and diagnostic testing; positive results need counseling as to abortion**

NIPT – ETHICAL CONSIDERATIONS CONCLUSIONS / SUGGESTIONS

SITUATIONS AND CONDITIONS NOT TO BE APPROVED

- Low-risk pregnancies
- Routine testing
- Direct-to-consumer
- Need for rules, regulations, supervision

THANK YOU !

Questions???

GENETIC EDITING / ENGINEERING

MODERN GENETIC TECHNOLOGIES

Genetic Engineering / Genetic Modification

- **a process of inserting new genetic information into existing cells in order to modify a specific organism for the purpose of changing its characteristics.**
- **a set of technologies used to change the genetic makeup of cells, including the transfer of genes within and across species boundaries to produce improved or novel organisms.**
- **new DNA is obtained by either isolating and copying the genetic material of interest, or by artificially synthesizing the DNA.**
- **An organism that is generated through genetic engineering is considered to be genetically modified (GM) and the resulting entity is a genetically modified organism (GMO).**

MODERN GENETIC TECHNOLOGIES

Genetic Engineering / Gene Therapy

- **Genetic engineering techniques have been applied in numerous fields including research, agriculture, industrial biotechnology, and medicine.**
- **Genetic engineering has many applications to medicine that include the manufacturing of drugs, such as insulin and human growth hormone creation of model animals that mimic human conditions and gene therapy.**
- **Gene therapy is generally done by replacing defective genes with effective ones.**
- **Somatic gene therapy - clinical research using somatic gene therapy has been conducted with several diseases, including chronic lymphocytic leukemia (CLL), and Parkinson's disease.**
- **Germline gene therapy would result in any change being inheritable, which has raised concerns within the scientific community.**

MODERN GENETIC TECHNOLOGIES

Genome editing / genome editing with engineered nucleases (GEEN)

- **a type of genetic engineering in which DNA is inserted, deleted or replaced in the genome of a living organism using engineered nucleases, or "molecular scissors."**
- **these nucleases create site-specific double-strand breaks (DSBs) at desired locations in the genome.**
- **the induced double-strand breaks are repaired through nonhomologous end-joining (NHEJ) or homologous recombination (HR), resulting in targeted mutation ('edits').**
- **some specific tasks this method can carry out: targeted gene mutation; gene therapy; creating chromosome rearrangement; study gene function with stem cells; transgenic animals.**

MODERN GENETIC TECHNOLOGIES

CRISPR = Clustered regularly interspaced short palindromic repeats

- **CRISPR-Cas9 is a unique technology that enables geneticists and medical researchers to edit or modify parts of the genome by removing, adding or altering sections of the DNA sequence.**
- **It is currently the simplest, most versatile and precise method of genetic manipulation.**
- **segments of prokaryotic DNA containing short, repetitive base sequences.**
- **a prokaryote is a unicellular organism that lacks a membrane-bound nucleus (karyon), mitochondria, or any other membrane-bound organelle, i.e., bacteria.**

MODERN GENETIC TECHNOLOGIES

CRISPR = Clustered regularly interspaced short palindromic repeats

- **Some bacteria have a built-in, gene editing system similar to the CRISPR-Cas9 system that they use to respond to invading pathogens like viruses, much like an immune system.**
- **Scientists adapted this system so that it could be used in other cells from animals, including mice and humans.**
- **The CRISPR/Cas system is a prokaryotic immune system that confers resistance to foreign genetic elements that provides a form of acquired immunity.**
- **A simple version of the CRISPR/Cas system, CRISPR/Cas9, has been modified to edit genomes. By delivering the Cas9 nuclease complexed into a cell, the cell's genome can be cut at a desired location, allowing existing genes to be removed and/or new ones added.**
- **CRISPR/Cas genome editing techniques have many potential applications, including medicine and crop seed enhancement.**

MODERN GENETIC TECHNOLOGIES

CRISPR = Clustered regularly interspaced short palindromic repeats

- **CRISPR-Cas9 has a lot of potential as a tool for treating a range of medical conditions that have a genetic component, including cancer, hepatitis B or even high cholesterol.**
- **Many of the proposed applications involve editing the genomes of somatic (non-reproductive) cells but there has been a lot of interest in and debate about the potential to edit germline (reproductive) cells.**
- **Because any changes made in germline cells will be passed on from generation to generation it has important ethical implications.**
- **Carrying out gene editing in germline cells is currently illegal in the UK and most other countries.**
- **By contrast, the use of CRISPR-Cas9 and other gene editing technologies in somatic cells is uncontroversial. Indeed they have already been used to treat human disease on a small number of exceptional and/or life-threatening cases.**

ETHICAL ISSUES IN MODERN GENETIC TECHNIQUES

- **Concerns that the technology could be used not just for treatment, but for enhancement, modification or alteration of a human beings' appearance, adaptability, intelligence, character or behavior. The distinction between cure and enhancement can also be difficult to establish.**
- **The new technologies with genome editing will allow it to be used on individuals to have "healthier children" – designer babies. In the future it may be possible to enhance people with genes from other organisms or wholly synthetic genes.**
- **Concerns about the safety of the procedure. There is a lot of work focusing on eliminating 'off-target' effects, where the CRISPR-Cas9 system cuts at a different gene to the one that was intended to be edited.**
- **Concerns that eliminating harmful genes may evoke other genes who might be more harmful.**
- **a potential weapon mass destruction, increasing the risk of the creation of harmful biological agents or products.**

ETHICAL ISSUES IN MODERN GENETIC TECHNIQUES

- **Concerns involve GM crops and whether food produced from them is safe, whether it should be labeled and what impact growing them will have on the environment.**
- **There are three main concerns over the safety of genetically modified food; whether they may provoke an allergic reaction, whether the genes could transfer from the food into human cells, and whether the genes not approved for human consumption could outcross to other crops.**
- **Concerns of unequal access to the new technologies, either between developed and developing countries, or between poor and rich individuals.**
- **Formation of animal chimeras.**

IN SUMMARY

- **Modern genetic technologies – no more 'playing G-d' than organ transplantation, modern fertility technology, antibiotics, respirators etc.**
- **Modern genetic technologies – in principle a form of permitted therapy and improvement of the world and the human being, hence no forbidden interference with nature**
- **Somatic gene engineering / editing for medical-therapeutic purposes – permissible / recommended, provided technology is safe**
- **Somatic gene engineering / editing for non-medical enhancement – forbidden**
- **Germline gene engineering / editing – at the moment forbidden**

THEOLOGICAL ISSUES

DISCUSSED IN PREVIOUS PRESENTATION

GENETICS – BRIEF HISTORY

ANTIQUITY

- Aristotle -- only father
- Talmud -- both father and mother
- 17th century -- *ovists* vs *spermists*

TREATMENT

- **Personalized Medicine**
- **Gene editing/engineering**

PERSONALIZED GEMETIC MEDICINE

PERSONALIZED MEDICINE PHARMACOGENETICS & PHARMACOGENOMICS

- Pharmacogenetics offers the prospect of an era of safer and more effective drugs, as well as more individualized use of drug therapies. The advent of pharmacogenomics--the study of how the human genome influences drug response within a person or population--has begun to drive the development of pharmaceuticals in Western medicine today.
- In many instances variation in therapy response can be attributed to genetic differences.
- Detection of the genetic differences which affect drug response, commonly referred to as pharmacogenomics, may result in further classification of diseases, and consequently, the development of 'personalized' therapies.
- Pharmacogenetics and pharmacogenomics deal with the genetic basis underlying variable drug response in individual patients.
- Numerous genes may play a role in drug response and toxicity.
- These new technologies have essentially spawned a new discipline, termed pharmacogenomics, which seeks to identify the variant genes affecting the response to drugs in individual patients.
- All of this will lead to novel approaches in drug discovery, an individualized application of drug therapy, and new insights into disease prevention.
- Pharmacogenomics may help focus effective therapy on smaller patient subpopulations

DIRECT-TO-CONSUMER COMPANIES

- More than 1,000 DNA variants associated with diseases and traits have been identified.
- Direct-to-consumer (DTC) companies are harnessing these discoveries by offering DNA tests that provide insights into personal genetic traits and disease risks.
- Genetic testing can improve lifestyle choices and increase preventive screening.
- However, understanding of the genetic contribution to human disease is far from complete.

Direct-to-Consumer - concerns:

- How the results might be interpreted, conveyed and misused.
- What tests are offered, and the time at which tests may be offered.
- No professional genetic counseling

ETHICAL CONSIDERATIONS

GENERAL ETHICAL CONCERNS

- **Clinicians and society at large are concerned about the effect genetic knowledge will have on the well-being of individual persons and groups.**
- **Understanding the social effects of genomics requires an analysis of the ways in which genetic information and a genetic approach to disease affect people individually, within their families and communities, and in their social and working lives.**
- **The most commonly expressed fear is that genetic information will be used in ways that could harm people — for example, to deny them access to health insurance, employment, education, and even loans.**
- **Genomics presents particular challenges with respect to clinicians' ethical and professional responsibilities, including the appropriate use of genomic information in the health care setting.**

GENERAL ETHICAL CONCERNS

The ethical issues raised by pharmacogenetics can be addressed under six headings:

- **(1) regulatory oversight,**
- **(2) confidentiality and privacy,**
- **(3) informed consent,**
- **(4) availability of drugs,**
- **(5) access,**
- **(6) clinicians' changing responsibilities in the era of harmacogenetic medicine.**

MODERN HISTORY

- 1865 -- Gregor Mendel
- 1900 -- Mendel was confirmed
- 1953 -- Watson & Crick -- DNA
- 1971 -- Genetic screening, USA, Tay-Sachs
- 1973 -- Genetic engineering
- 1988 -- Human Genome Project
- 1989 -- Somatic gene therapy

SPECIFIC ETHICAL ISSUES / CONCERNS

- **Patient's privacy and autonomy – how is genetic information different than any other health-related information?**

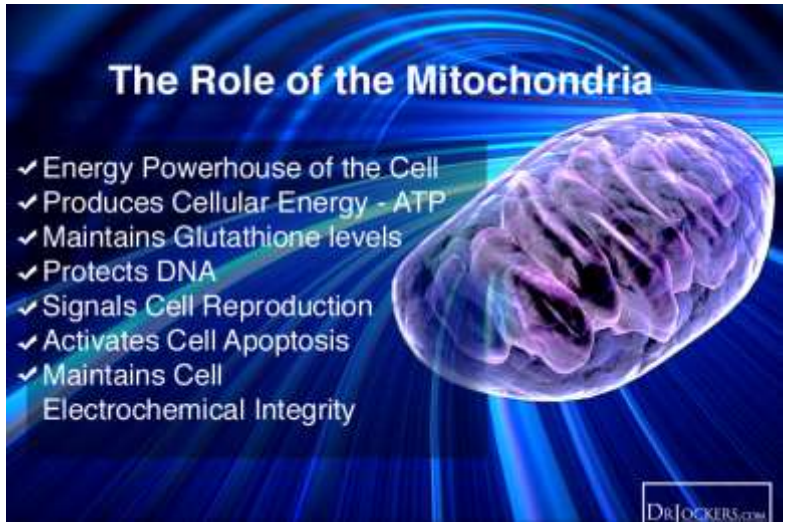
  Employees, Army, Family

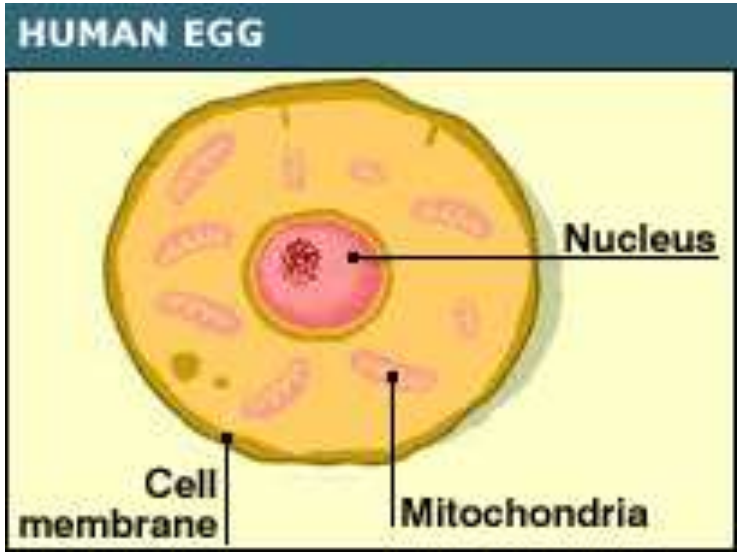
- **Beneficence – clearly advantageous?**
- **Non-maleficence – is it always harmless?**
- **Distributive justice – equal access, equity, cost, opportunity?**

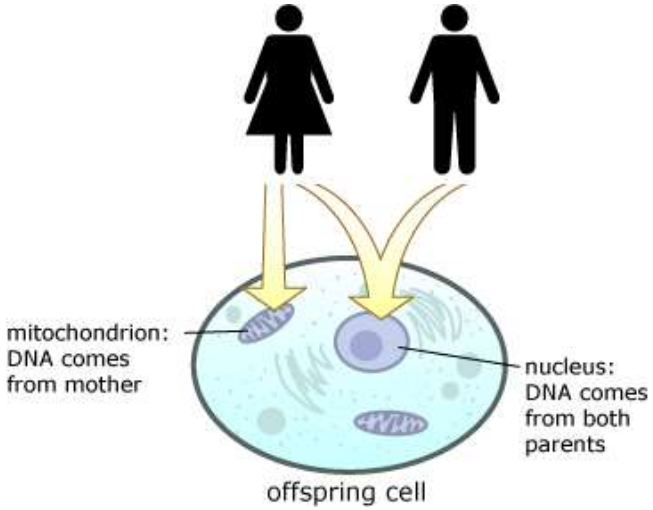
  How is it different from other expensive medical care?

- **SLIPPERY-SLOPE**

MITOCHONDRIA







NIPT – ETHICAL CONSIDERATIONS
PRINCIPLES - TENSION

INDIVIDUAL'S RIGHTS

- AUTONOMOUS DECISIONS BASED ON PERSONAL PREFERENCES
- DERIVING BENEFIT FROM AVAILABLE TECHNOLOGIES, SCIENTIFIC DISCOVERIES, ETC.
- EQUAL ACCESS TO SOCIETAL RESOURCES

⇕⇕⇕

SOCIETAL RESPONSIBILITIES

- AVOID HARM
- COST / BENEFIT CONSIDERATIONS
- MUTUALLY-SHARED MORAL AND LEGAL LIMITATIONS

NIPT – ETHICAL CONSIDERATIONS
PRINCIPLES - BALANCE

STRONG AUTONOMY ⇔ WEAK PATERNALISM

BENEFICIAL TECHNOLOGIES ARE A CLINICAL REALITY TO STAY;
HOWEVER, AVOID ABUSE AND MISCONDUCT

RULES, REGULATION AND SUPERVISION

ALLOW NIPT ➔ UNLESS STRONG MORAL CONSIDERATIONS