

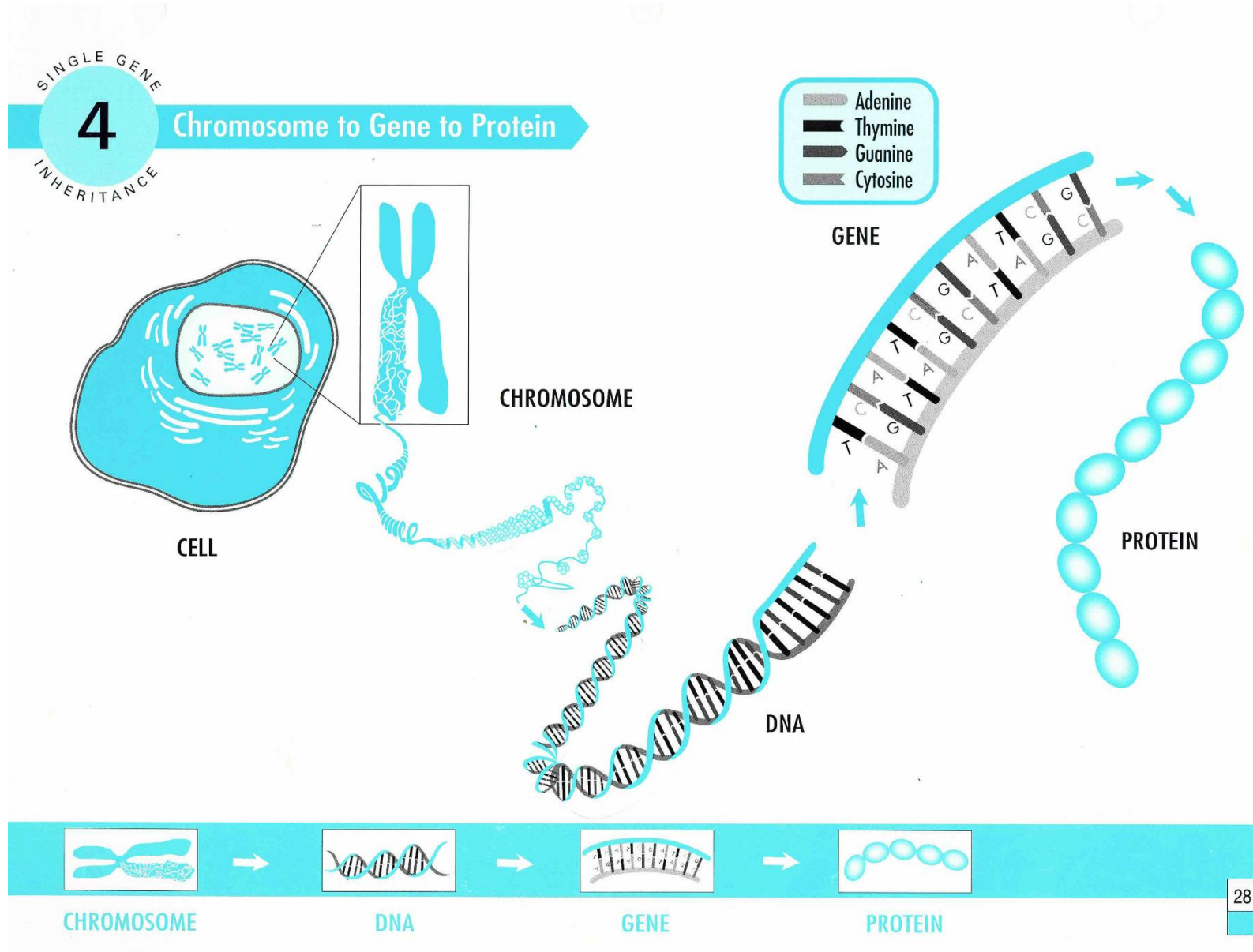


Alice Schindler, MS, CGC
Genetic Counselor, NIH/NINDS/Neurogenetics Branch

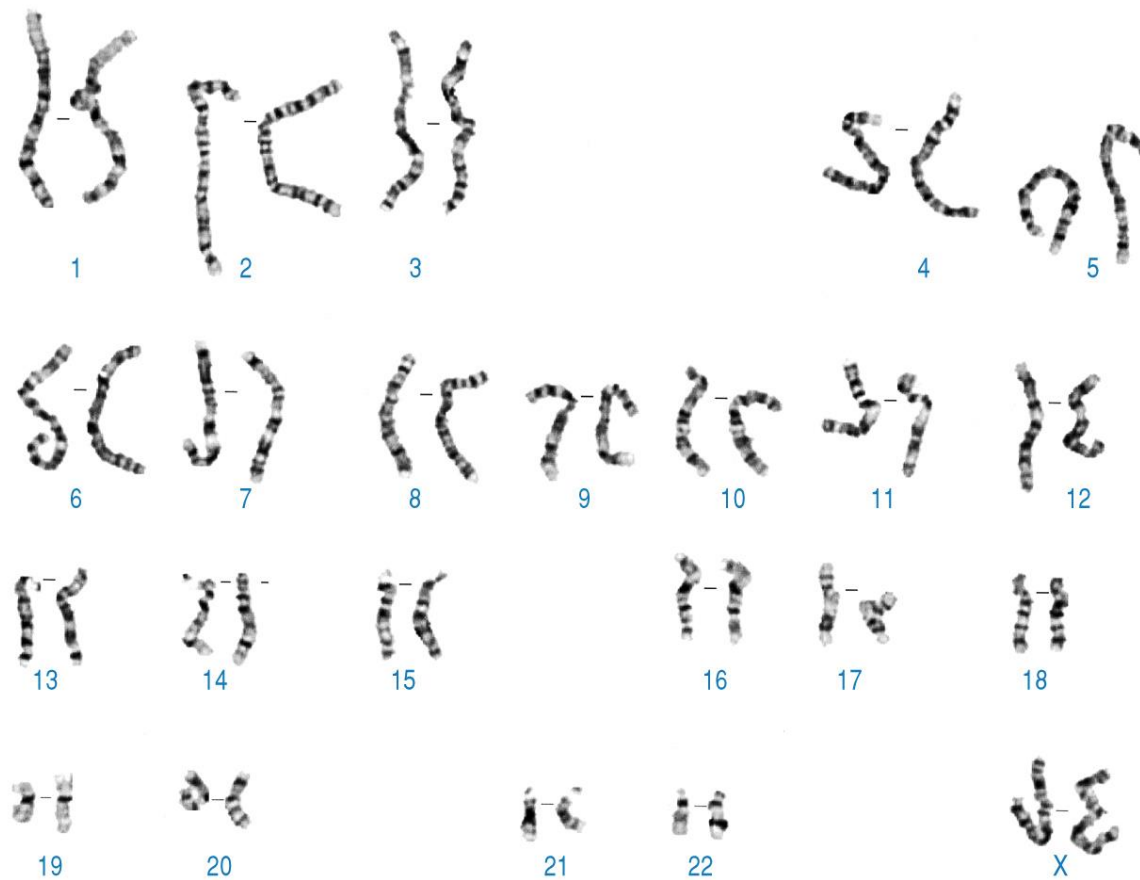
Heather Montie, PhD, Assistant Professor
Department of Bio-Medical Sciences
Philadelphia College of Osteopathic Medicine

Annual Kennedy Disease Association Conference
November 8, 2017

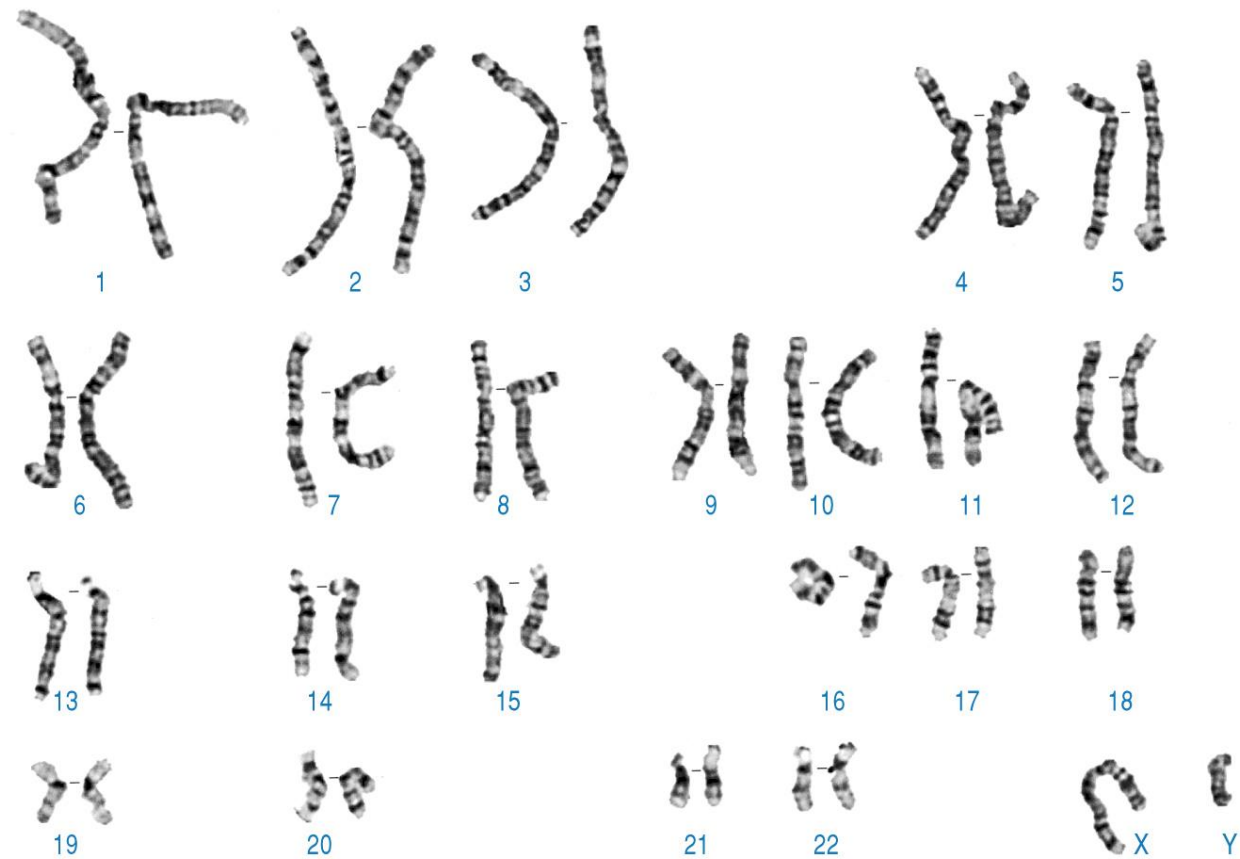
Genetics Review and Reproductive Options in Kennedy Disease



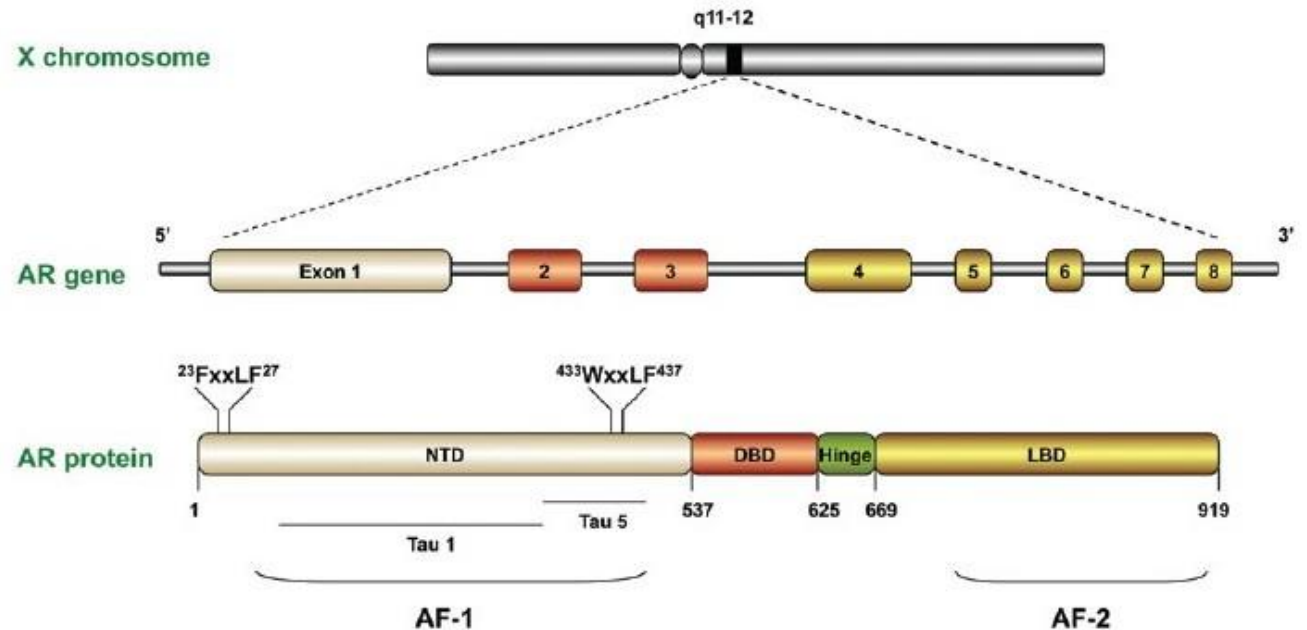
Normal Female - 46,XX



Normal Male - 46,XY

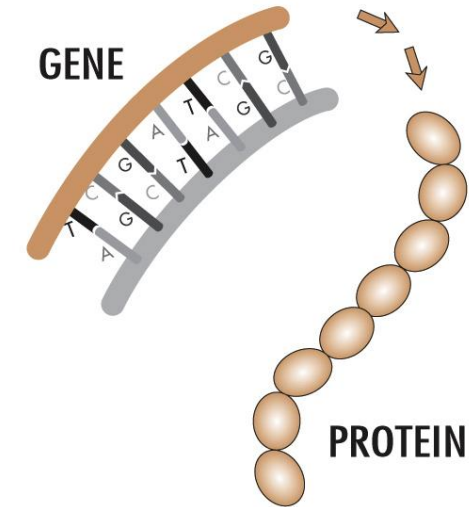


Androgen receptor gene (AR)



Trinucleotide Repeat Disorders

A **trinucleotide** is a group of 3 chemical bases within a gene. Trinucleotides code for **amino acids**. Amino acids are the building blocks of **proteins**.



TRINUCLEOTIDE C G G

Normal number of repeated trinucleotide segments within a gene = **Normal Protein Function**.



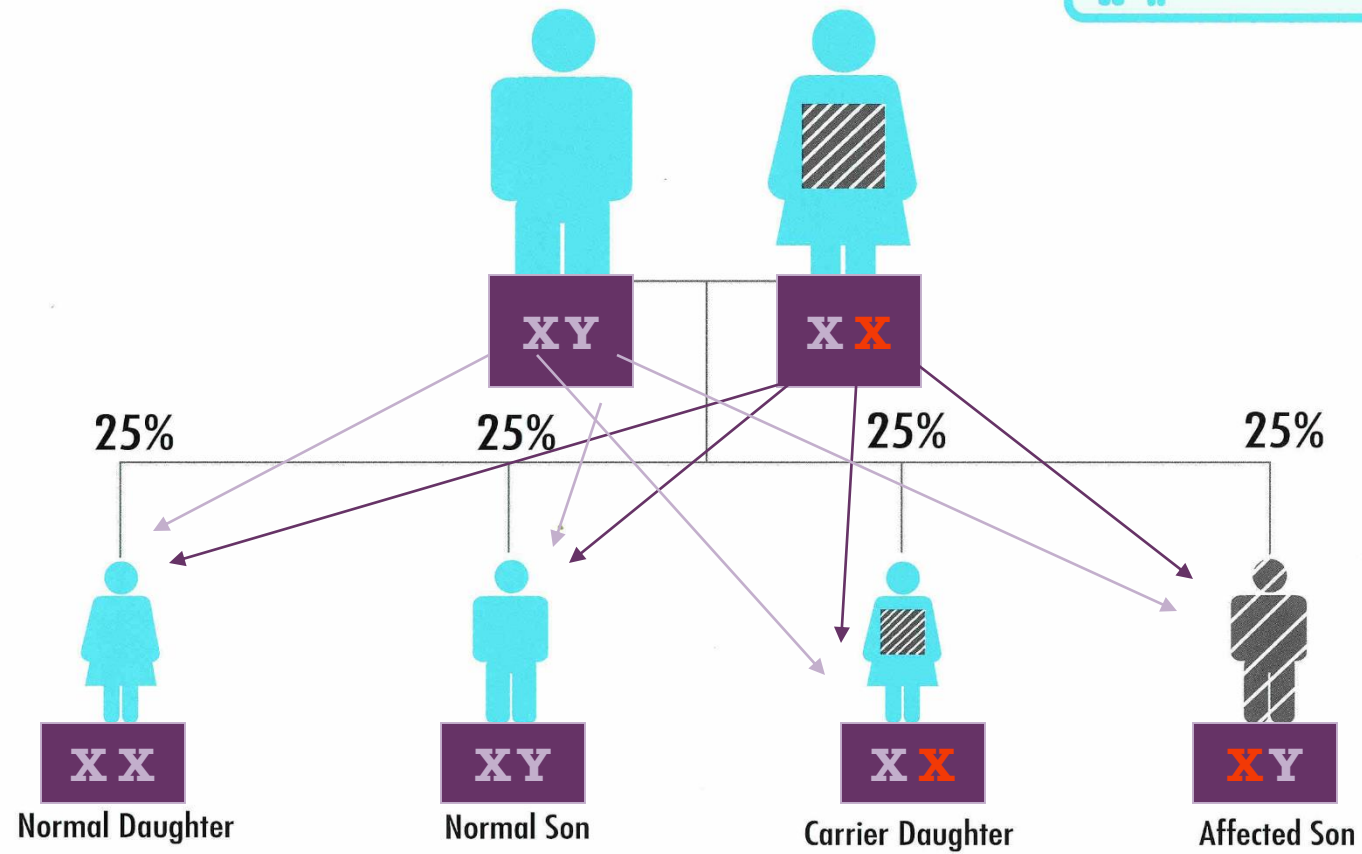
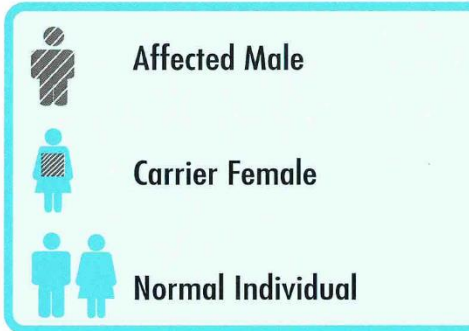
Mildly expanded number of repeated trinucleotide segments = **Normal Protein Function**.



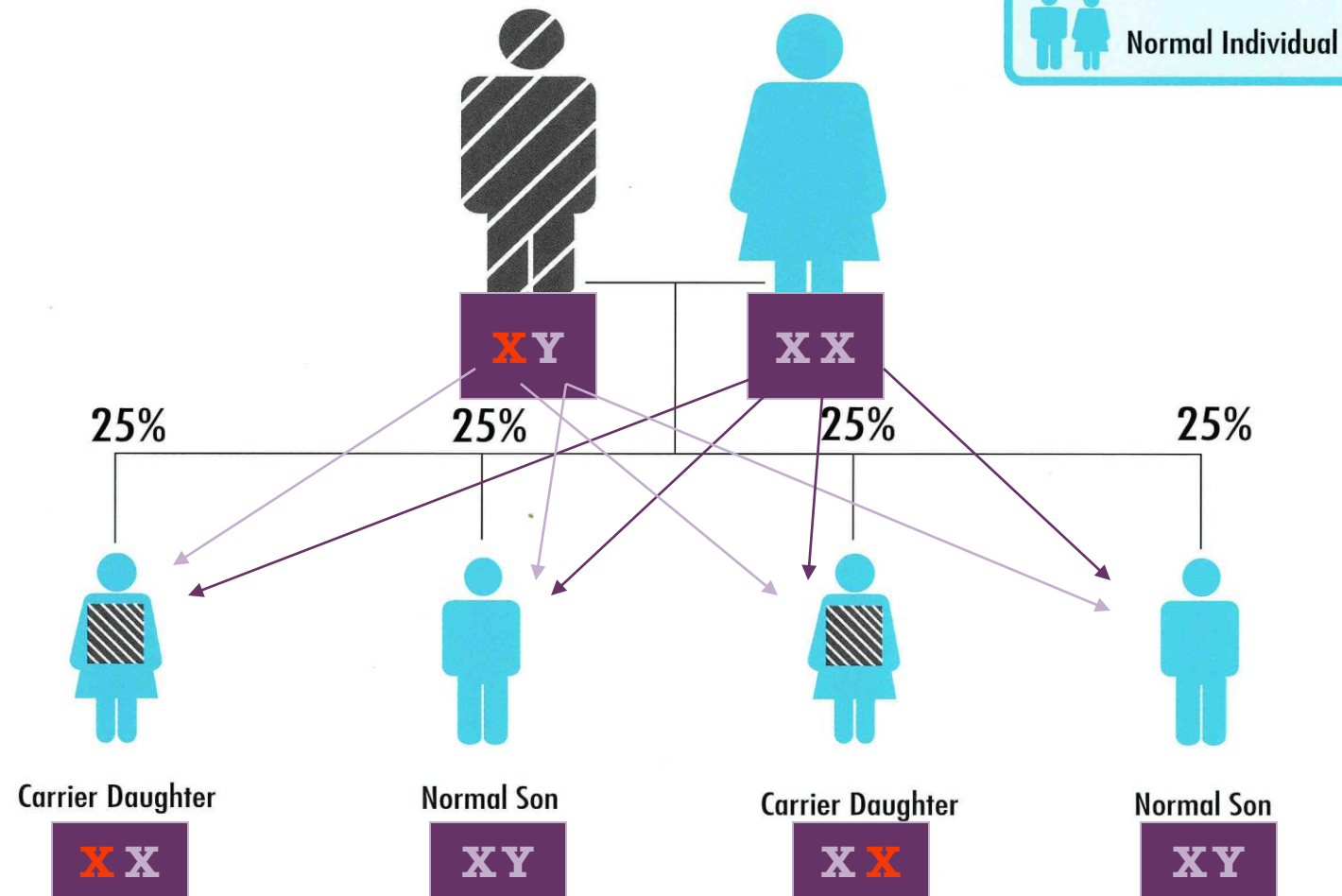
Fully expanded number of repeated trinucleotide segments = **Abnormal or Absent Protein**.



X-Linked Segregation, Carrier Mother



X-Linked Segregation, Affected Father



+ Reproductive Options

Affected Males

- 0% chance affected Sons
- 100%/obligate Carrier Daughters
- Gamete (sperm) Donation
- Gamete Selection (sperm selection for male children)
- Use No Options
- No Children
- Adoption

Carrier Females

- Have a 50% **chance** to have affected sons and carrier daughters
- Prior to Pregnancy
 - Gamete (Egg) Donation
 - Gamete Selection (sperm selection for female children)
 - Pre-implantation Genetic Diagnosis (PGD)
- During Pregnancy
 - Ultrasound (for gender)
 - CVS/Amniocentesis
 - Usually not recommended for adult onset disorders



+ Reproductive Options

Affected Males

- Will not have affected children
 - 50% Unaffected Sons
 - 50% Carrier Daughters
- Gamete (sperm) Donation
- Gamete Selection (sperm selection for male children)
- Use No Options
- No Children
- Adoption

Carrier Females

- Have a **chance** to have affected sons and carrier daughters
- Prior to Pregnancy
 - Gamete (Egg) Donation
 - Gamete Selection (sperm selection for female children)
 - Pre-implantation Genetic Diagnosis (PGD)
- During Pregnancy
 - Ultrasound (for sex)
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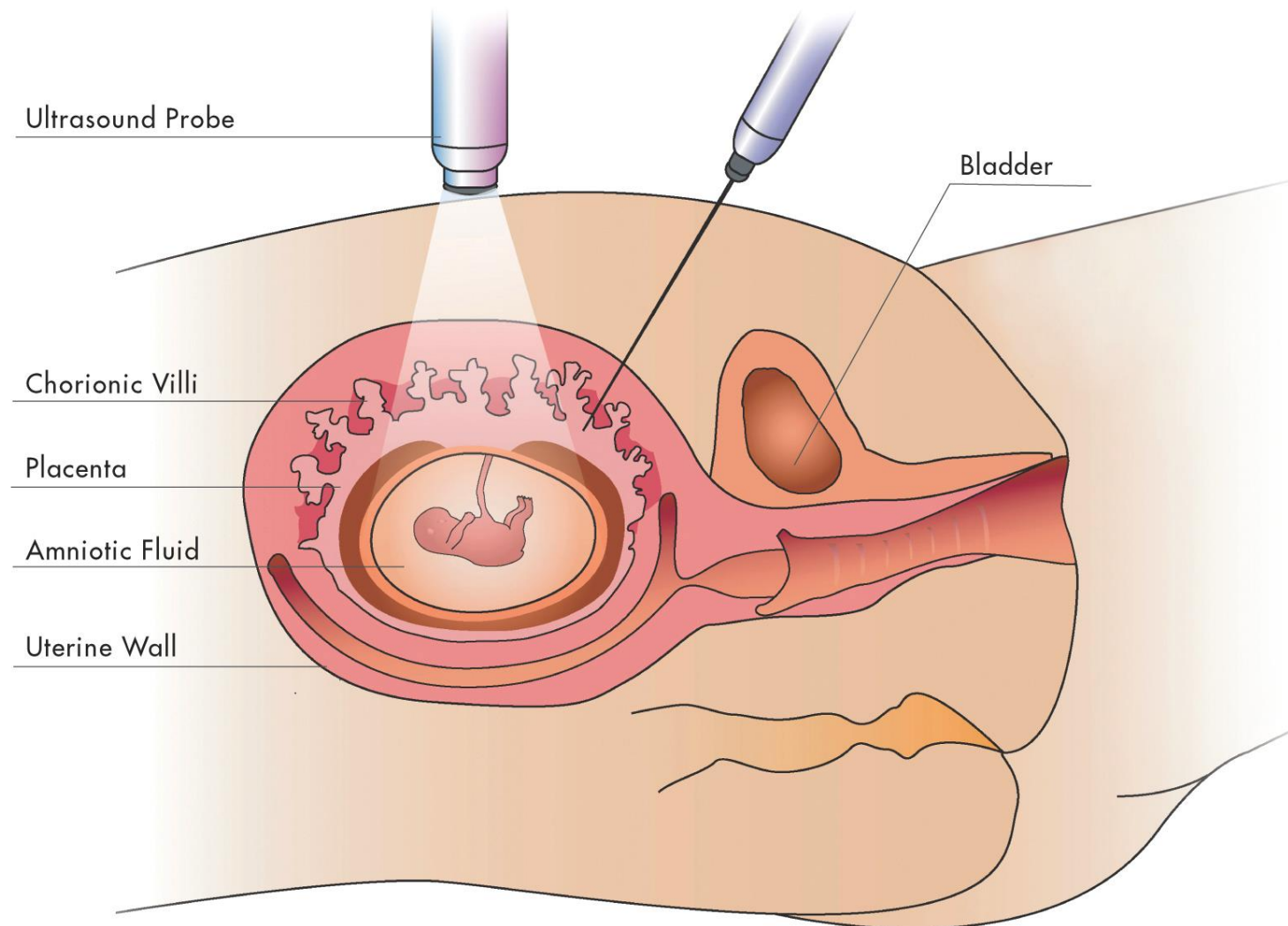
Factors affecting decision to get pre-conception or prenatal genetic testing



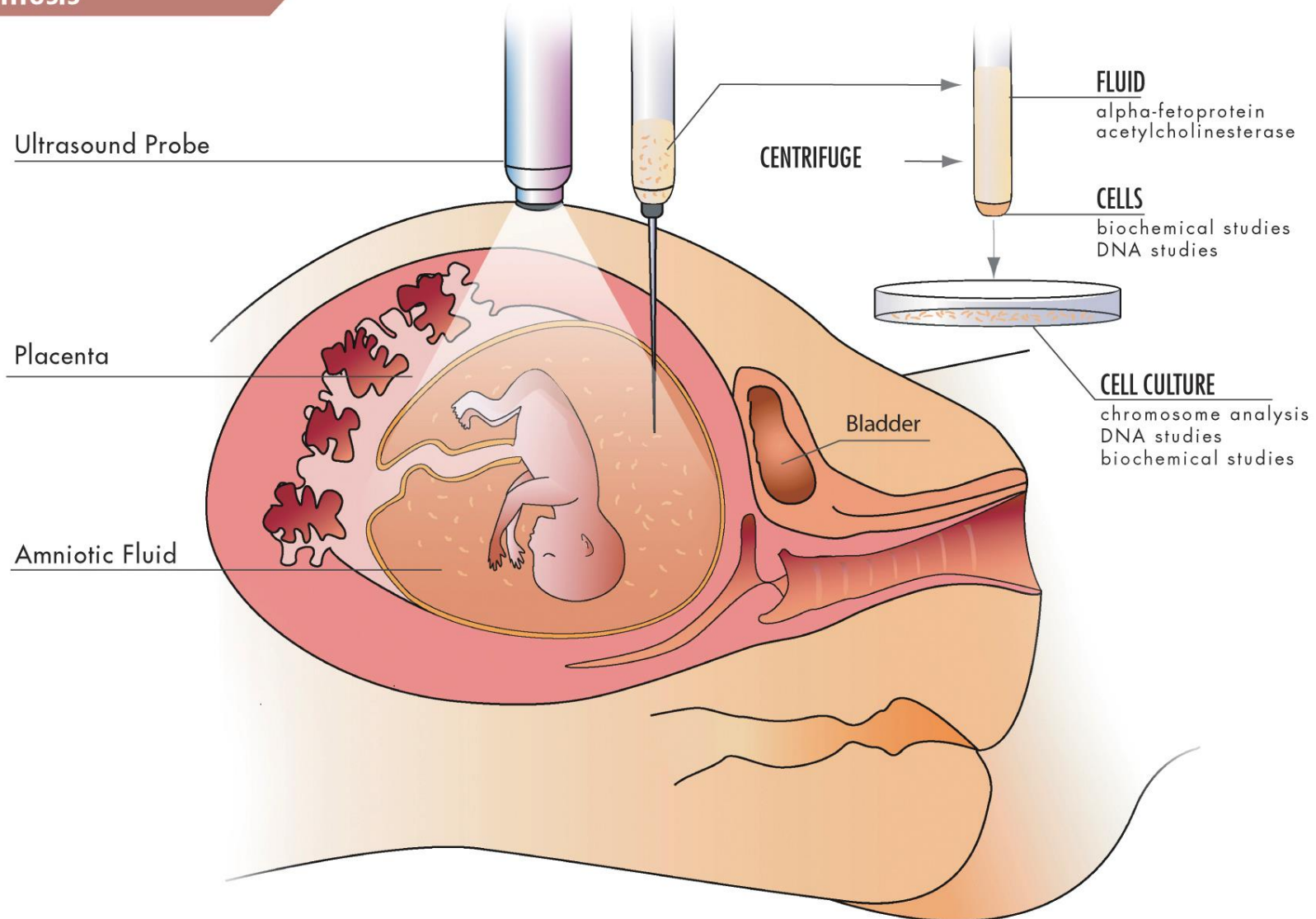
- Perceived risk
- Experience with disease
- Personality: behavioral beliefs (e.g. safety and accuracy) and perceived choice control
- SES factors
- Genetic Education and counseling
- Service delivery/Attitudes of health professionals
- Personal medical hx
- Family dynamics & what others did

(Biesecker et al., 2000; Lerman et al, 2002; Godino et al, 2013; Chen et al, 2017)

Transabdominal Chorionic Villus Sampling (CVS)



Amniocentesis





Preimplantation Genetic Testing





Day 1 Fertilized egg



Late Day 1 2-cells



Day 2 4-cells



Day 3 8-cells

Early human development *in vitro*



Day 4 Morula



Late Day 6 Hatched blastocyst



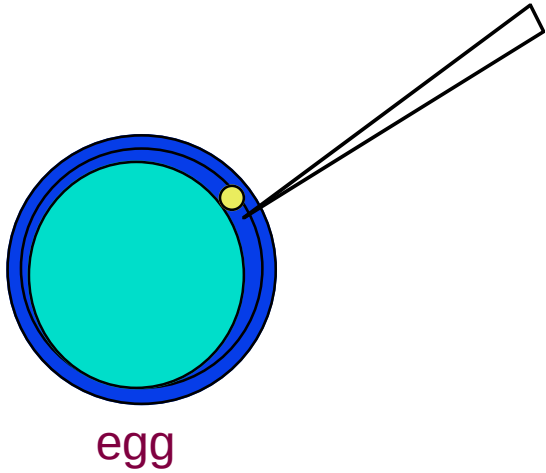
Day 6 Hatching blastocyst



Day 5 Blastocyst

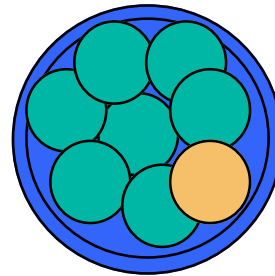


Tissues for Preimplantation Biopsy



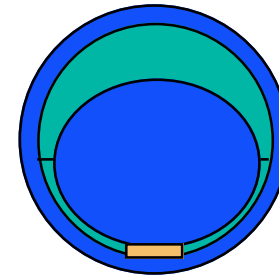
egg

Polar Body



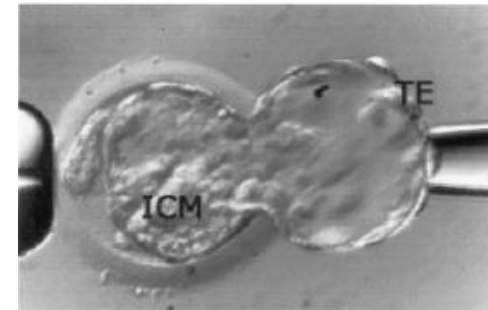
cleavage stage

* Blastomere



blastocyst

Trophectoderm





PGD-IVF

Heather Montie, PhD and John
Hanlon

+ Disclosures

- John and I made a choice together after much discussion and education about all the choices we had to have a child.
- We DO NOT believe that everyone must make the same choices that we have made (nor should any of us).
- Every individual/family has the right to make the best decision for them without any judgment or opinion inserted by others.
- We fully support everyone's decisions and are happy for anyone that chooses to not have children or to have children in any manner that is right for their family.
- We are also not spokespeople for any of the clinics or companies that are discussed in this presentation. They are only brought up because they were part of our journey.
- As a KD researcher, my choice to do PGD-IVF does NOT mean I have lost faith that we will find a therapy for KD soon.



+ Married September 2013



- Our family began with 2 dogs and a cat.
- But our fur-babies weren't enough for us.
- We were ready to expand our family.
- I was 36 when we decided to have a baby.
- “advanced maternal age”

+ Kennedy's Disease and my family



- I am an obligate carrier.
- My dad's disease course was quite aggressive and coupled with his congestive heart failure, resulted in his death at the young age of 64 (2011).
- I chose a career path to research Kennedy's Disease to help find a therapy, or even better, a cure.



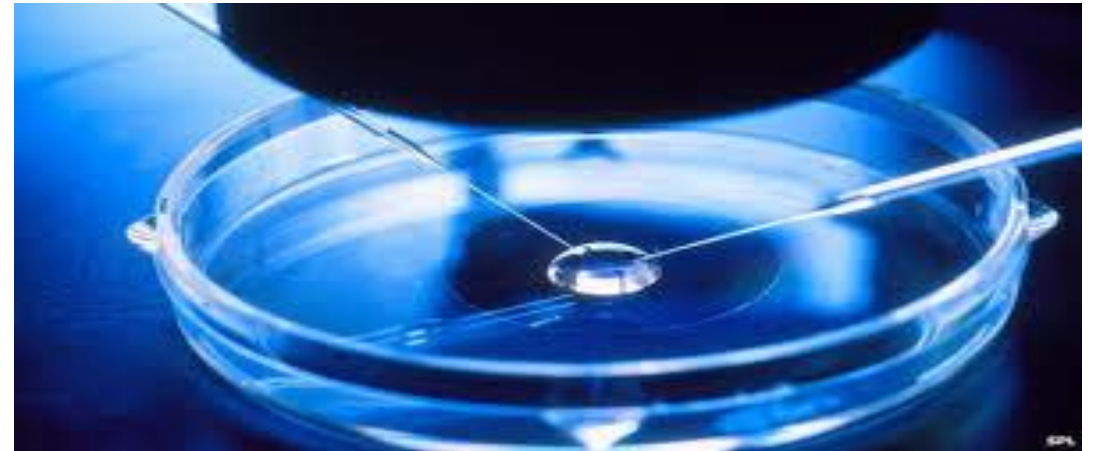
What is PGD-IVF?



- Preimplantation Genetic Diagnosis & *In Vitro* Fertilization
 - It is a screening test used to determine if genetic or chromosomal disorders are present in embryos produced through *in vitro* fertilization (IVF).
 - PGD screens embryos before they are transferred to the uterus so couples can make informed decisions about their next steps in the IVF process.
 - Embryos unaffected by the genetic or chromosomal disorder can be selected for transfer to the uterus.
- Thousands of clinical PGD cycles have been performed worldwide, resulting in the birth of thousands of healthy babies.

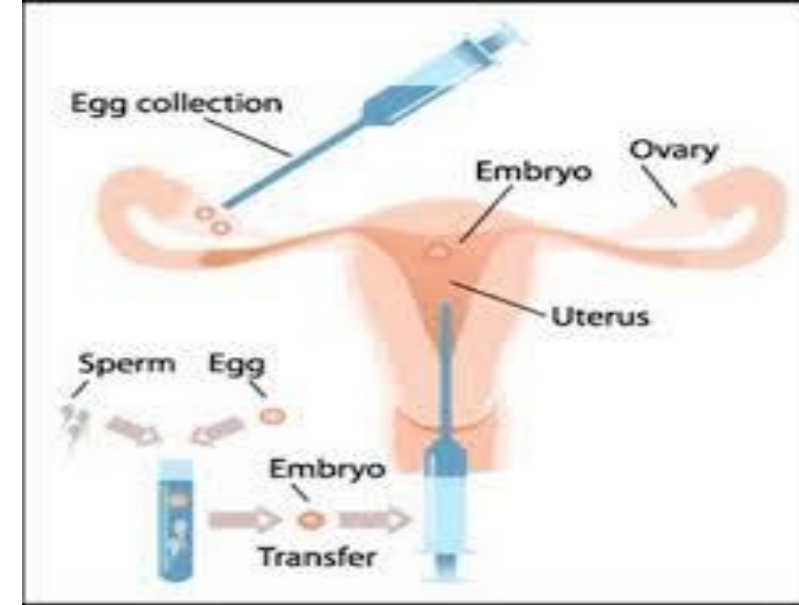
+ In vitro fertilization (IVF)

- *In vitro* fertilization (IVF) is the joining of a woman's egg and a man's sperm in a laboratory dish.
 - *In vitro* = “outside the body”
- Why is the procedure is performed?
 - to help a woman become pregnant
 - to treat many causes of infertility
 - or for genetic reasons



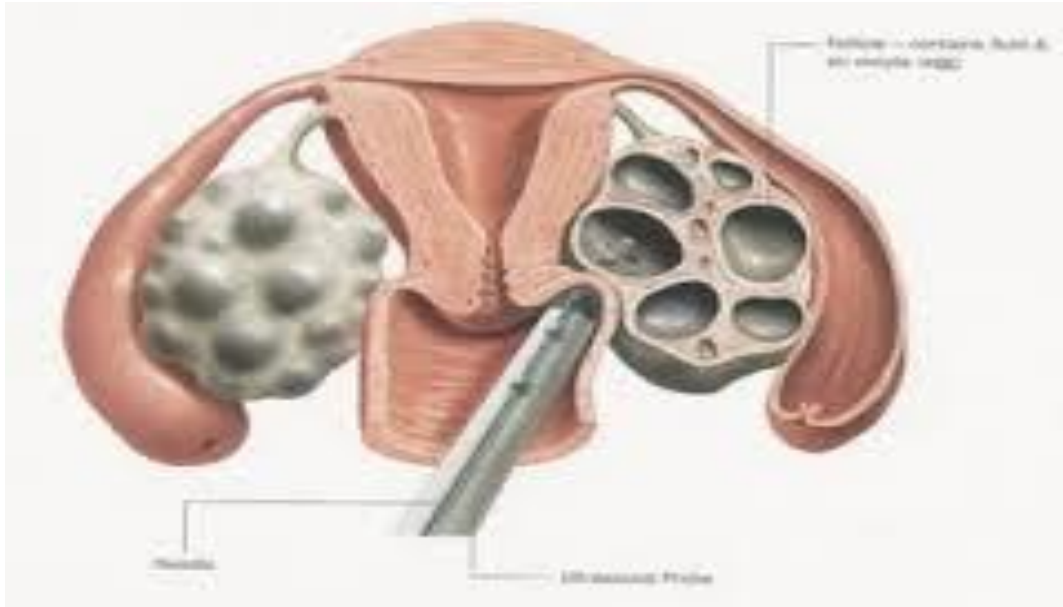
+ PGD-IVF in a nutshell

- **Genetic Counseling (1-3 months)**
 - Determine the PGD tests to be done
 - Find a company that can test your genetic condition
 - may need time for company to develop a specific test for you
- **Initial tests of mother and father** to ensure there are no inherent fertility issues that also need to be addressed. (1-2 months)
 - woman's hormone levels and cycle timing
 - ovary check (where follicles (eggs) are stored)
 - sperm health



+ PGD-IVF in a nutshell (cont.)

- Stimulation “Super-ovulation” (to induce multiple eggs to mature)
(hormone injections multiple times a day for 3-4 weeks) (2-4 months)
- Egg retrieval (anesthetized) (1 day)



+ PGD-IVF in a nutshell (cont.)

- **Fertilization** (same day as retrieval; unless choose to freeze eggs for future)

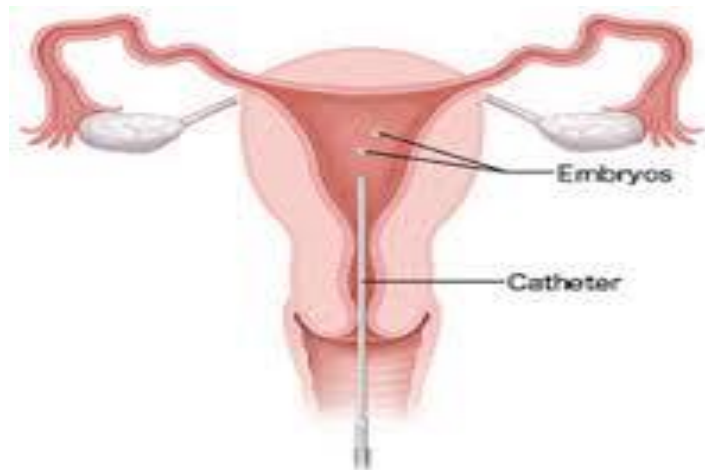
(6 days)

- Partner must be on site for their contribution
- Fertilized eggs grown in culture for 5 days
 - (to blastocyst stage)
 - calls from clinic daily to explain status
 - many embryos lost during this process (normal) (may start with 20 but end with only 5)
- at day-5, viable blastocysts have some cells removed to test
 - 2 weeks – 1 month for results
 - blastocysts are frozen



+ PGD-IVF in a nutshell (cont.)

- Superovulation and retrieval may be repeated here
- At least 1 month rest for woman's cycle to settle back to normal
- Preparation for transfer of genetically normal blastocyst (hormones to prep the uterus and drugs to inhibit ovulation) (1 month)
- Transfer (1 day)



+ PGD-IVF in a nutshell (cont.)

- **Pregnancy test (9 days later)** (about 23-43% chance of pregnancy)

- If positive, CELEBRATE!



- woman must takes progesterone shots daily (thickens uterine wall) for 10 weeks to help maintain pregnancy.
- At 10-15 weeks, **chorionic villi or amniocentesis re-testing for gene anomaly** (if one chooses to do so) (can also test for chromosomal anomalies at this time) (my insurance covered this \$875)
- **In total: 6-12 months (if everything works 1st time)**
 - **plus another 37.5 weeks of pregnancy** (more time if there is a failure at any point)



IVF risks and side effects

- IVF involves large amounts of physical and emotional energy, time, and money.
- Many couples dealing with infertility suffer stress and depression.
- Fertility medicines may induce:
 - bloating, abdominal pain, mood swings, headaches, and other side effects. (memory loss, anxiety, lack of patience)
 - Most IVF medicines must be given by injection
 - several times a day
 - repeated injections can cause bruising





IVF risks and side effects (cont.)



- During the treatment:
 - many doc visits (1-3 a week) (major commitment of time)
 - blood draws and ultrasounds to check hormone levels and egg maturation
- The last week before egg retrieval is very painful.
- In rare cases, fertility drugs may cause ovarian hyperstimulation syndrome (OHSS).
 - buildup of fluid in the abdomen and chest
 - severe cases require draining of the fluid with a needle



IVF risks and side effects (cont.)



- Risks of egg retrieval include reactions to anesthesia, bleeding, infection, and damage to structures surrounding the ovaries, including the bowel and bladder.
- There is a risk of multiple pregnancies when more than one embryo is placed into the womb.
 - Carrying more than one baby at a time increases the risk of premature birth and low birth weight.
 - IVF embryos have an increased chance of dividing
 - So even if 1 is transferred; it could become twins!
 - It is unclear whether IVF increases the risk of birth defects.



Risks of failure at each stage of PGF-IVF



- Super-ovulation
 - may not lead to any mature follicles to be retrieved; or very few
- IVF may not lead to any viable blastocysts after 5 days in culture
- Genetic testing may reveal no genetically normal embryos
- Embryos may not survive thaw
- Transfer of an embryo may not lead to pregnancy
- If pregnancy is successful, there are still risks of loss that occur with any pregnancy



IVF monetary costs

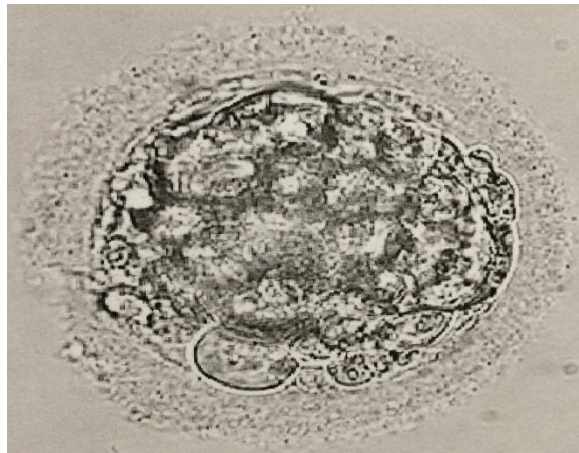


- IVF is very costly.
- Some states have laws that say health insurance companies must offer some type of coverage.
 - But, most insurance plans do not cover infertility treatment.
 - *Some* insurance plans will pay for injectable hormones. (\$5,000-\$7,000)
- Fees for a single IVF cycle include costs for medicines, surgery, anesthesia, ultrasounds, blood tests, processing the eggs and sperm, embryo storage, and embryo transfer.
- The exact total of a single IVF cycle varies, but may cost more than \$12,000 - \$19,000, plus the \$5,000-\$7,000 for hormones, plus genetic screening (\$5,000-\$6,000).

Total = \$22,000-\$32,000

A little happy note: You can deduct whatever amount is above 10% of your gross income from your federal taxes

+ Our IVF journey.....



Enson Edward Hanlon



12-13-15



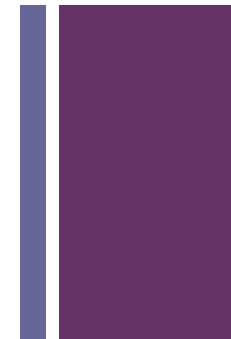
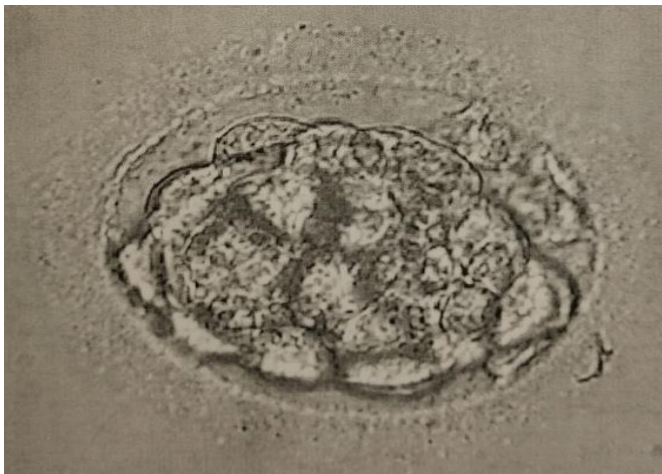


Our IVF journey.....



- We transferred a frozen embryo in January, 2017.
- Unfortunately it didn't result in a pregnancy.
- We had one embryo left.....

+ Our IVF journey: March



11-16-17!





Thanks!

- My father Edward Montie, my husband John Hanlon, our son Enson Edward Hanlon, and our daughter coming soon!
- Our whole family for their support
- RMA-Jefferson
- Genesis Genetics
- Jefferson OB/GYN
- The KDA for allowing us to share our story.



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- Alice and for being a great presentation partner.
- The whole NIH KD family for always being there for all of us!



References



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