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PCRS 2025
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Genetics in Fertility Care

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Disclosure

Employee: Inception Fertility

Learning Objectives

- Describe the objectives of genetic carrier screening in a reproductive medicine setting and illustrate some of the challenges in interpretation and clinical decision making in the patient and gamete donor populations.
- Outline the various available forms of preimplantation genetic testing (PGT) and summarize the benefits and limitations of these options.
- Review ASRM guidelines for genetic screening of gamete donors and elucidate some of the complexities of expanded carrier screening panel interpretation in the donor population.
- Define the common genetic causes of male and female infertility.

Genetics in Fertility Care

Three methods of assessing genetic risk

- Personal and family medical history review
- Genetic carrier screening
- Preimplantation genetic testing

Most often, these do not overlap. However, information or results from one of these methods may lead to additional testing prior to, during or after fertility treatment.

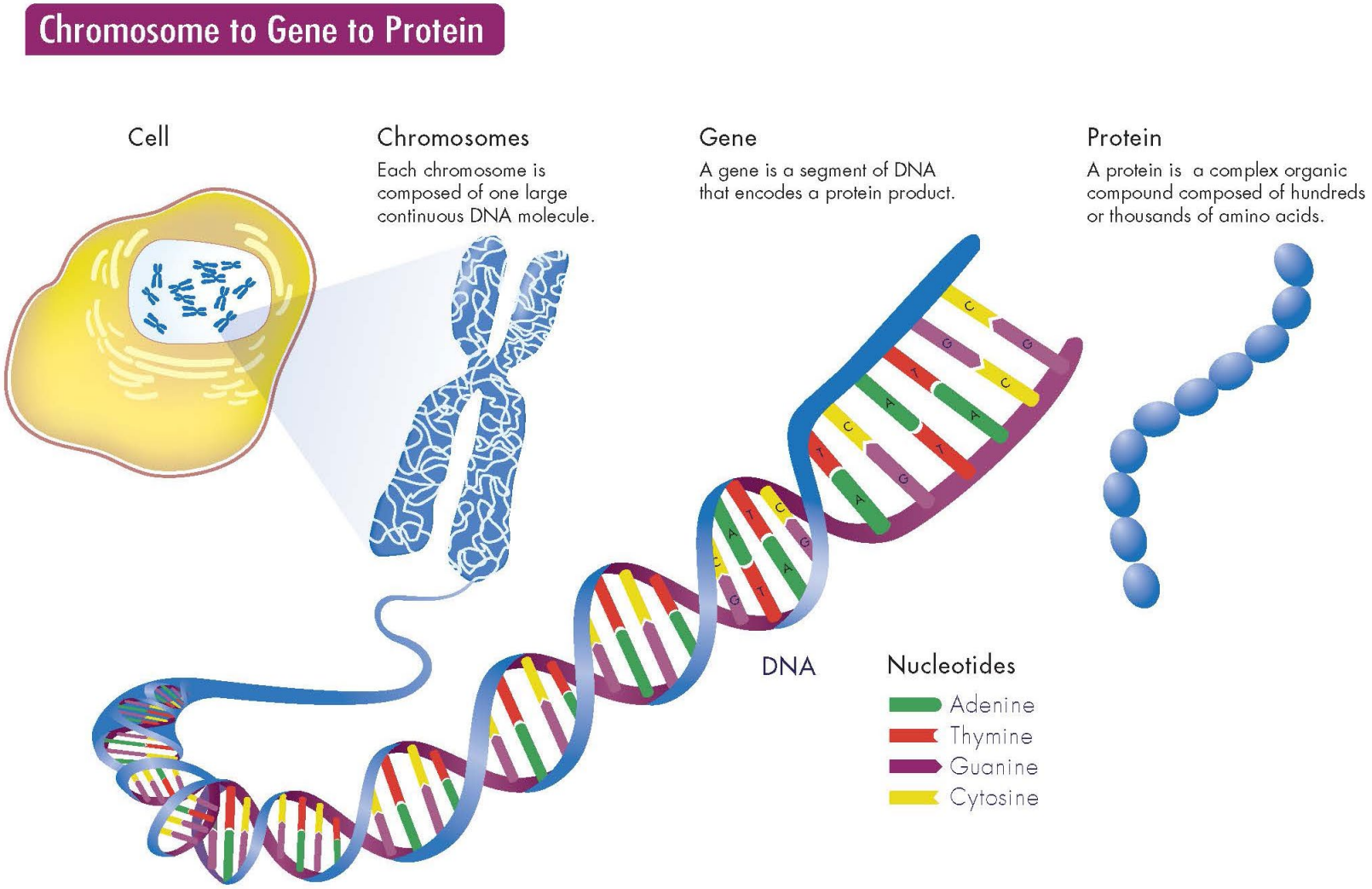
The Goal of Genetic Screening Options

The objective of offering genetic screening is to identify genetic risk and address it

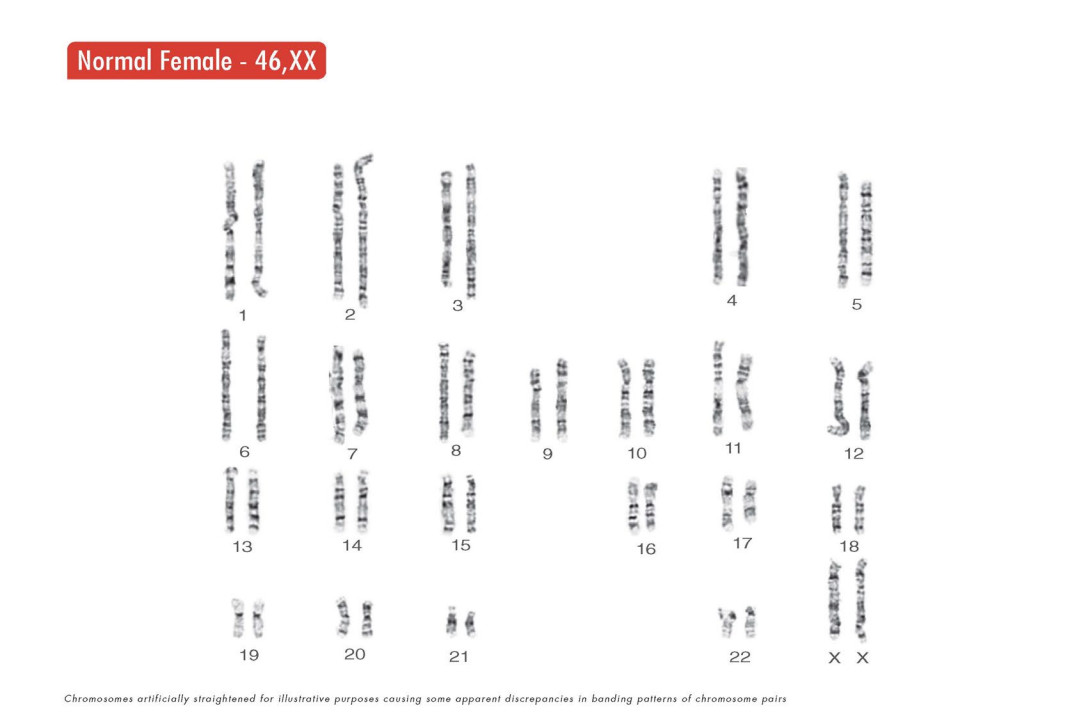
during the course of fertility treatment, if possible.

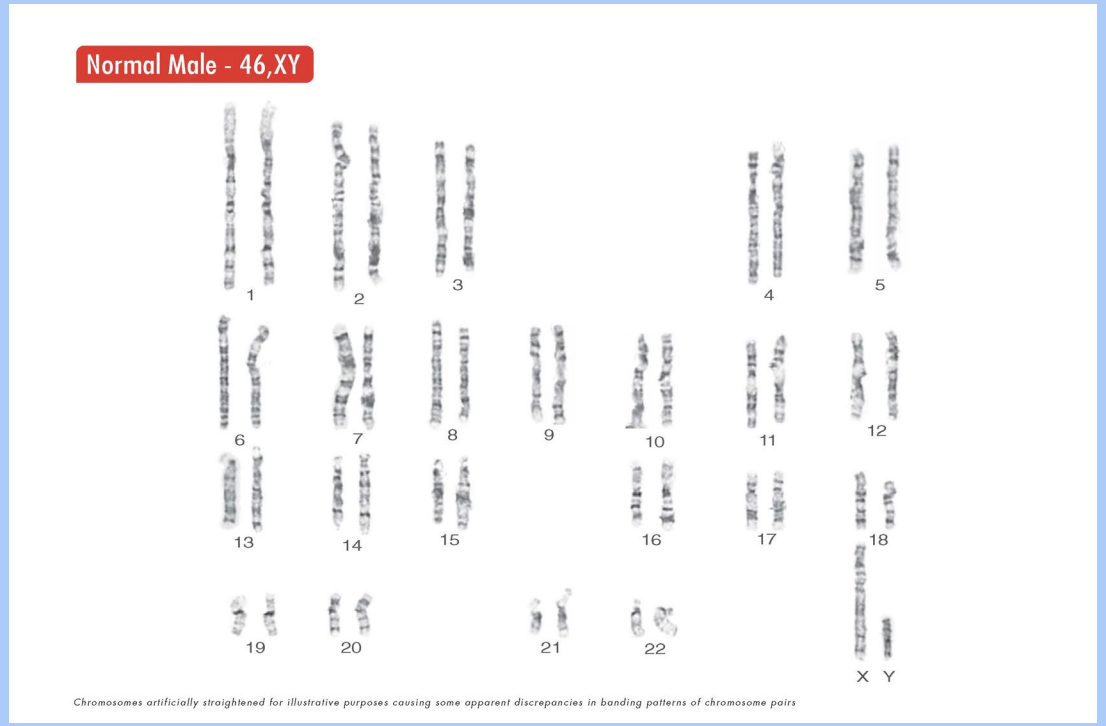
Please note: Although it may be routinely offered at your clinic, all genetic testing is optional and intended to help address genetic risk that is ***relevant and actionable for the patient***.

A quick refresher on genetics



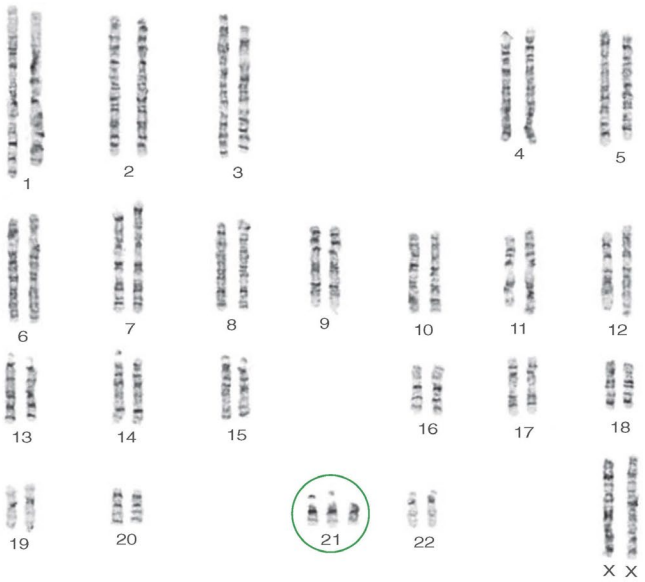
Normal human karyotypes (chromosomes)





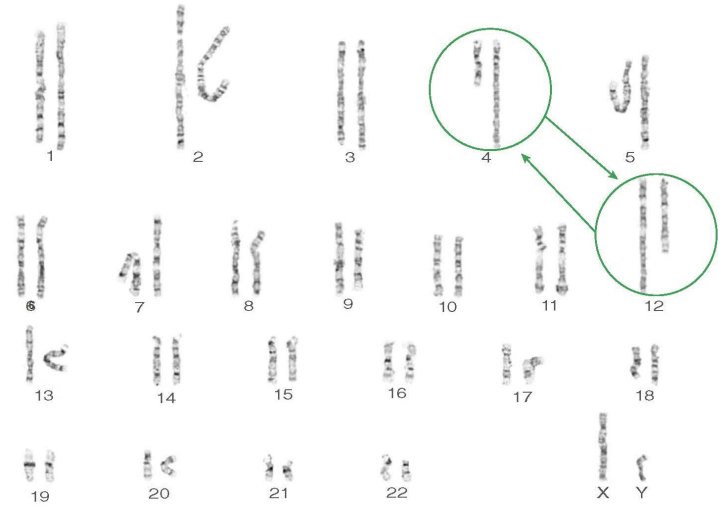
There can be differences in karyotypes

Trisomy 21 Karyotype - Down Syndrome 47,XX,+21



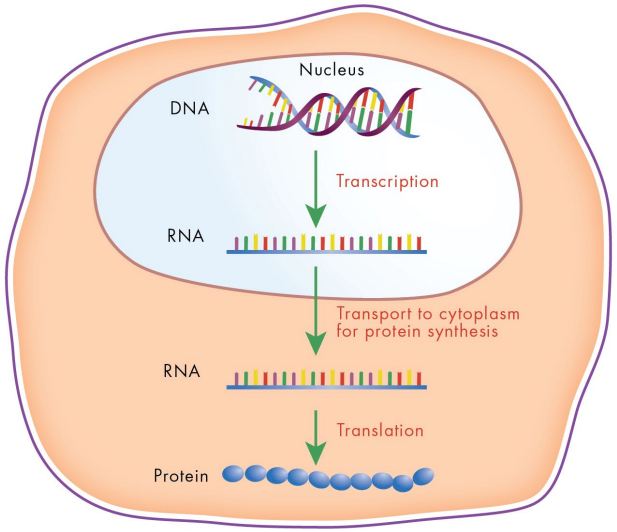
Chromosomes artificially straightened for illustrative purposes causing some apparent discrepancies in banding patterns of chromosome pairs

Balanced Reciprocal Translocation Carrier - 46, XY, t(4;12)(q24.1;q21.1)

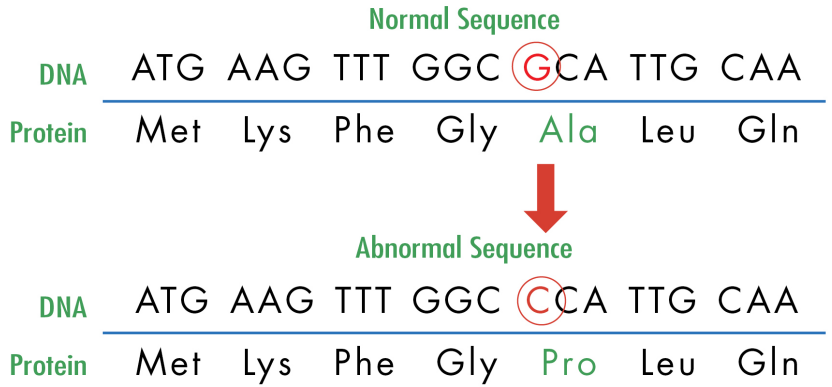


Differences in the DNA of a single gene

Central Dogma of Biology



Missense Mutation

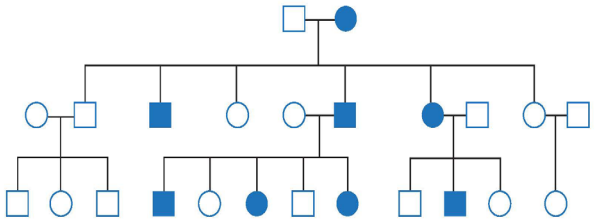


Mutation = Variant with "pathogenic" or "likely pathogenic" interpretation

Common Modes of Single Gene Inheritance

Autosomal Dominant Inheritance

Unaffected
Affected

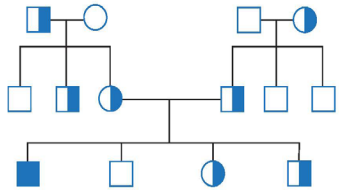


Characteristics of Autosomal Dominant Inheritance

- Multiple generations are affected.
- Males and females are equally likely to be affected.
- Male to male transmission occurs.
- Each offspring of an affected parent has a 50% chance of being affected and a 50% chance of being unaffected.

Autosomal Recessive Inheritance

Unaffected
Carrier
Affected

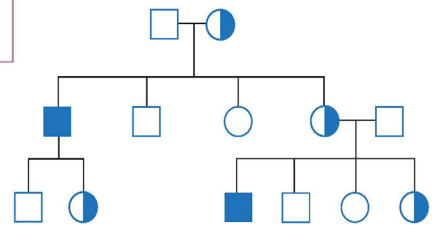


Characteristics of Autosomal Recessive Inheritance

- Greatest recurrence risk is among siblings of affected individuals.
- Males and females are equally likely to be affected.
- If parents are both carriers of mutations in the same recessive gene, each pregnancy has a 25% chance of inheriting both normal genes, a 50% chance of being a carrier, and a 25% chance of inheriting both gene mutations and being affected.
- Ethnic background and consanguinity may influence the likelihood of a specific recessive disease.

X-Linked Recessive Inheritance

Unaffected
Carrier Female
Affected Male



Characteristics of X-Linked Recessive Inheritance

- The incidence of the condition is much higher in males than females.
- All daughters of affected males will be carriers.
- The condition is never transmitted directly from father to son.
- Sons of carrier females have a 50% chance of being affected and a 50% chance of being unaffected.
- Daughters of carrier females have a 50% chance of being a carrier and a 50% chance of inheriting the normal copy of the gene.

Not all health or developmental problems are due to chromosome or single gene differences or are apparent in a patient's family history. Thus, genetic carrier screening, embryo testing and testing in a pregnancy *cannot identify all* causes of:

- developmental delays, learning problems, autism
- health problems
- birth defects
- genetic disease

Reproductive History

- Certain fertility challenges can have a genetic cause
  - Male factor infertility
    - Sperm production issues (non-obstructive azoospermia or oligospermia) – blood chromosome difference or Y chromosome microdeletions
    - Congenital absence of the vas deferens – mutations in CFTR (cystic fibrosis) genes
  - Female factor infertility
    - Primary ovarian insufficiency/early menopause - fragile X carrier or blood chromosome difference
  - Recurrent miscarriage (two or more) – blood chromosome rearrangement for EITHER partner
- Positive results for these test results may effect treatment decisions and lead to the option of embryo testing
- Other less common tests may be available based on the patient's specific fertility diagnosis

Family Medical History

If the patient is not already aware or suspecting, it's unlikely there is a genetic disease in their family. However, here are some things to ask of the patient and their reproductive partner:

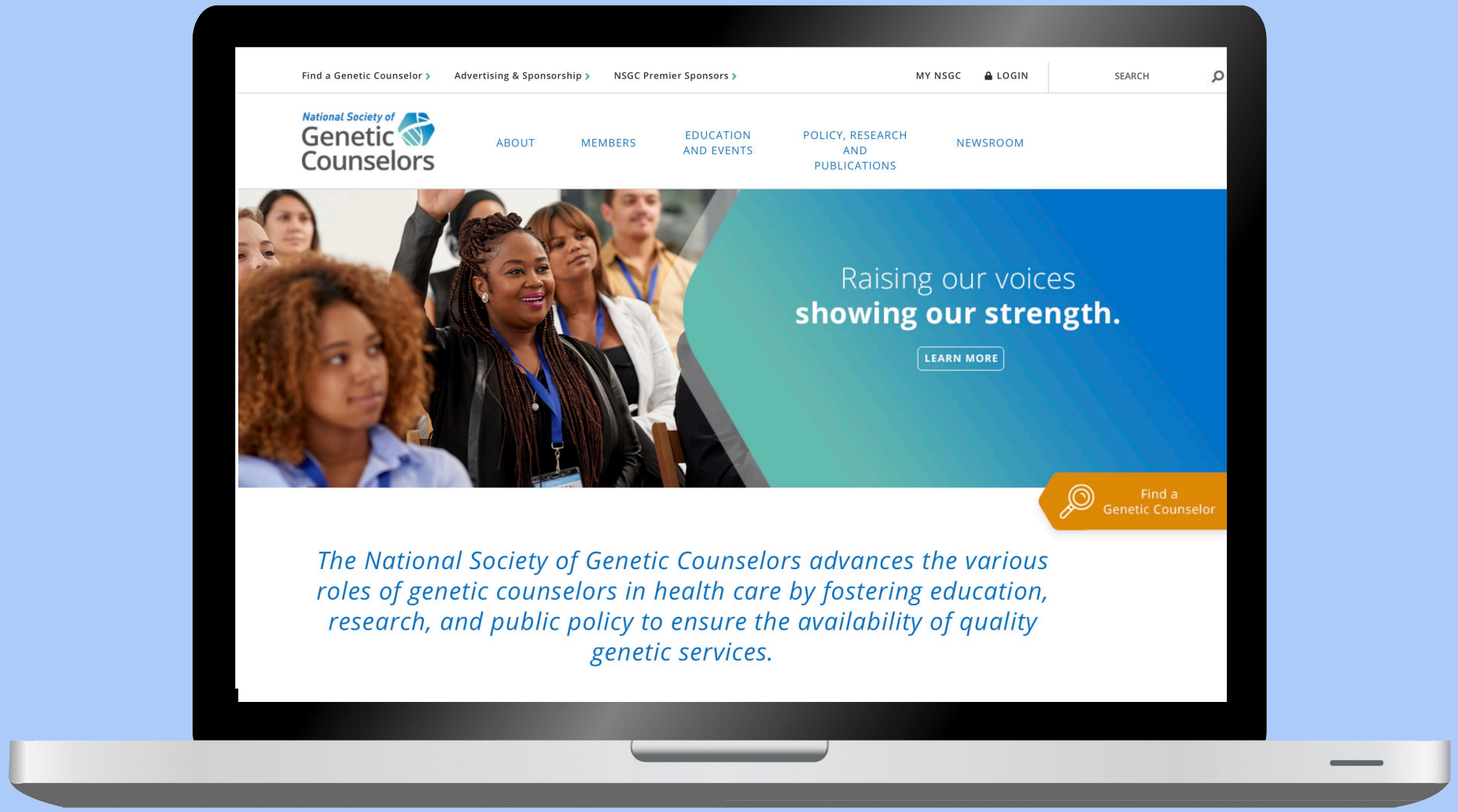
- Does anyone have a suspected or known genetic condition?
- Has anyone been told they are a carrier of a genetic condition?
- Has anyone had reproductive difficulty (recurrent miscarriages, stillbirths, infant deaths, infertility)?
- Was anyone born with a physical difference (heart defect, cleft lip, etc) or had a medical problem from a young age?
- Does anyone have developmental delays, learning difficulty, or autism?
- Are there any patterns of cancer, cancer in multiple generations or cancer at a younger age than typical?
- Do any conditions seem to "run" in the family?

Most conditions commonly seen in family histories are multifactorial:

- allergies, asthma, eczema
- late onset cancer
- late onset heart disease, high blood pressure, cholesterol disorder
- adult onset diabetes
- late onset dementia/Alzheimer disease
- autoimmune conditions
- mental health/psychiatric diagnoses
- and many others

These types of conditions may be a pattern in a family, but because they don't have a single cause, there are often no definitively predictive genetic tests.

National Society of Genetic Counselors (nsgc.org)



Genetic Carrier Screening

The objective of genetic carrier screening

In fertility care, our **OBJECTIVE** in offering carrier screening is to **identify reproductive** pairs at **risk** to have a child with a recessive or X-linked genetic disease.

The more genes we screen for, the more likely we are to identify at-risk pairs and **offer** preimplantation genetic testing for monogenic (single gene) disorders, or **PGT-M**.

Adjusting our perspective on genetic carrier screening

As genetic carrier screening panels expand, we need to shift our **PERSPECTIVE** to being more comfortable with positive results.

We are all carriers of multiple gene variants. The more genes we test, the greater the chance we will detect these variants.

Patients should be aware of this as well.

Remember and remind patients...

Family history is not predictive of carrier status

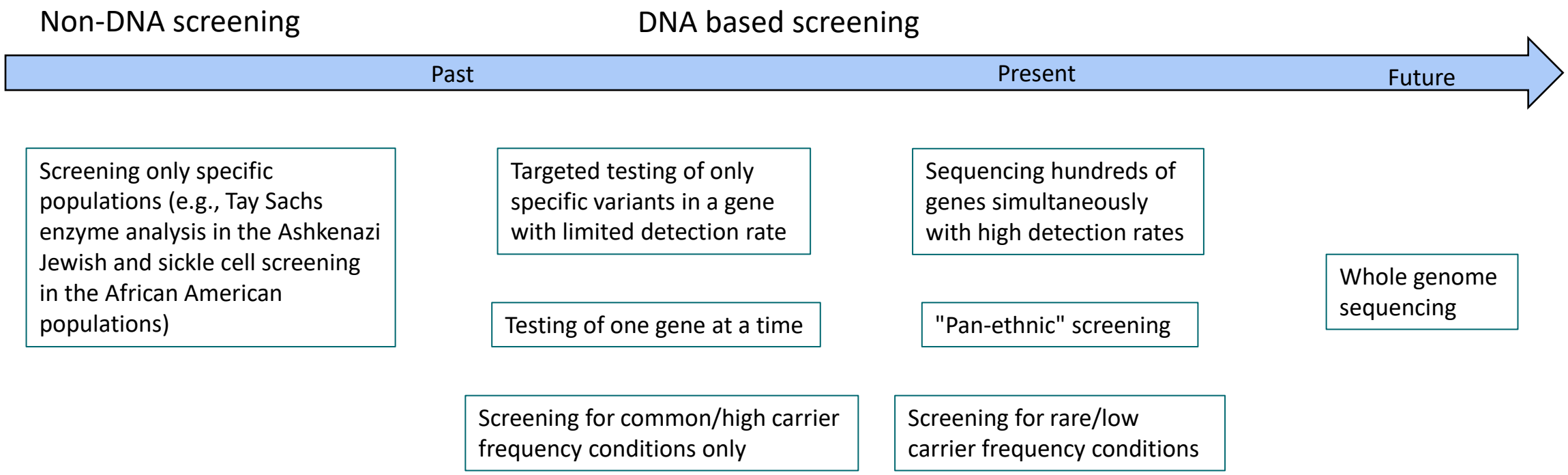
Just because a patient says they don't have a family history of
any genetic diseases does NOT mean they won't be a carrier of something on the carrier screening panel.

Most carriers of recessive and X-linked genetic conditions have no family history

Main Points of Genetic Carrier Screening

- Intended for individuals who do not have a family history of the conditions screened. More targeted testing may be appropriate for individuals with a positive family history for optimal interpretation.
- Includes screening for conditions associated with severe, childhood onset conditions for which there is no treatment or early intervention will improve outcome
- Carrier screening tests genes associated with autosomal recessive and X-linked conditions; it does not evaluate all genes/genetic conditions
- All carrier screening has limited (less than 100%) detection rate, thus:
  - A negative result means a significantly reduced (typically <1%) chance of being a carrier
  - A positive result is highly accurate (typically >99%)
  - Variant interpretation can evolve as more data is available in world-wide databases, thus an addended report may be available from the ECS lab as years pass
- Not intended to diagnose and individual with a genetic condition. However, for some genes there may be "manifesting heterozygotes" in which carriers may have some health risks

A brief history of carrier screening



Recommendations from professional organizations

2007	**ACOG Practice Bulletin 78 Hemoglobinopathies in Pregnancy** -Individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be offered carrier screening
2008	**ACMG Practice Guidelines 2008 Carrier screening in individuals of Ashkenazi Jewish descent** - Recommend that carrier screening for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease, Fanconi anemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucolipidosis IV, and Gaucher diseas for individuals of Ashkenazi Jewish descent **ACMG Practice Guidelines 2008 Carrier screening for spinal muscular atrophy** -Carrier screening for spinal muscular atrophy should be offered to all couples regardless of race and ethnicity.
2009	**ACOG Committee Opinion 432 Spinal Muscular Atrophy** - Preconception and prenatal screening for SMA is not recommended in the general population at this time **ACOG Committee Opinion 442 Preconception and Prenatal Carrier Screening for Genetic Diseases in Individuals of Eastern European Jewish Descent** -Carrier screening for TSD, Canavan disease, cystic fibrosis, and familial dysautonomia should be offered to Ashkenazi Jewish individuals before conception or during early pregnancy
2010	**ACOG Committee Opinion 469 Carrier Screening for Fragile X Syndrome** -Women with a family history of fragile X-related disorders, unexplained mental retardation or developmental delay, autism, or premature ovarian insufficiency are candidates for genetic counseling and fragile X premutation carrier screening.
2011	**ACOG Committee Opinion 486 Update on Carrier Screening for Cystic Fibrosis** -It is becoming increasingly difficult to assign a single ethnicity to individuals. It is reasonable, therefore, to offer CF carrier screening to all patients.
2013	**ACMG Position Statement on prenatal/preconception expanded carrier screening** -Provided guidance on what disease genes and mutations should be included on expanded carrier screening panels
2015	**Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine** -Expanded carrier screening can provide information about carrier status beyond population estimates and eliminates the need for ethnicity-based screening. However, this approach introduces complexities that require special consideration
2017	**ACOG Committee Opinion 690, Carrier Screening in the Age of Genomic Medicine** -Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening. **ACOG Committee Opinion 691, Carrier Screening for Genetic Conditions** -Screening for spinal muscular atrophy & cystic fibrosis should be offered to all women who are considering pregnancy or are currently pregnant. A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent)
2021	**ACMG Practice Resource Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)** Recommends a non-ethnicity based, pan ethnic approach and states that restricting carrier screening by using socially defined ethnic constructs or by self-identified ancestry is both inequitable and scientifically flawed.

https://doi.org/10.3390/soc12020033

- American College of Obstetricians and Gynecologists
- American College of Medical Genetics
- National Society of Genetic Counselors
- American Society of Reproductive Medicine
- Society of Obstetrician and Gynaecologists of Canada
- Canadian College of Medical Geneticists

Recommendation from NSGC

Received: 8 February 2022 | Revised: 20 December 2022 | Accepted: 23 December 2022

DOI: 10.1002/jgc4.1676

PRACTICE GUIDELINES

National Society of Genetic Counselors WILEY

Expanded carrier screening for reproductive risk assessment: An evidence-based practice guideline from the National Society of Genetic Counselors

Katelynn G. Sagaser[1] | Jennifer Malinowski[2] | Lauren Westerfield[3] | Jennifer Proffitt[4] | Melissa A. Hicks[5] | Tomi L. Toler[6] | Karin J. Blakemore[1] | Blair K. Stevens[7] | Lisa M. Oakes[8]

- "...ECS is superior compared to ethnicity-based carrier screening in that it both identifies more carriers of AR and XL conditions as well as eliminates a single race-based medical practice."
- "ECS should be offered to all who are currently pregnant, considering pregnancy, or might otherwise biologically contribute to pregnancy."
- "Barriers to the broad implementation of and access to ECS should be identified and addressed..."

Terminology

- Mutation = "pathogenic" or "likely pathogenic“ variant

- Heterozygous = “carrier” of a variant in one copy of their gene pair

(one copy of the *F508del* variant in the CFTR gene)

- Compound heterozygous* = two variants of a different type in the gene pair

(one copy of the *F508del* and one copy of the *W1282X* variant in the CFTR gene)

- Homozygous* = two variants of the same type in the gene pair

(two copies of the *F508del* in the CFTR genes)

** Individuals with two variants in the same recessive gene may be affected*

Essential Concepts: Detection Rate and Residual Risk

- "Detection rate" is the probability that the screening can identify a variant in a gene being tested if it is present
  - No test has a 100% detection
  - A limitation of ALL carrier screening, regardless of the laboratory and method
  - Newer DNA test methodologies have higher detection rates than older ones

- "Residual risk" is the chance that an individual might still be a carrier with a negative result
  - Calculated by knowing or estimated the carrier frequency minus the detection rate

- Carrier screening labs should provide the detection rate and residual risk with a negative result for an individual, and with a combined report, for the reproductive pair

Condition (Inheritance Pattern)	Gene	Population	Carrier Frequency	Detection Rate	Residual Risk
Cystic Fibrosis (AR)	*CFTR*	Worldwide	1 in 33	94%	1 in 520
NM_000492.3		African	1 in 58	91%	1 in 630
		Ashkenazi Jewish	1 in 24	98%	1 in 1,200
		East Asian	1 in 277	80%	1 in 1,400
		Finnish	1 in 75	93%	1 in 1,100
		European (Non-Finnish)	1 in 23	95%	1 in 440
		Native American	1 in 40	96%	1 in 1,000
Exception: Exon 10		South Asian	1 in 73	91%	1 in 800

When comparing two carrier screening results REMEMBER…

1. **Different variants in the same recessive gene of two gamete providers creates the risk to offspring.** It doesn't have to be the same variant between the two gamete sources.

> For example, a reproductive pair is at 25% risk to have a child affected with cystic fibrosis if one has a *F508del* variant in the CFTR gene and the other has a *W1282X* variant in the CFTR gene, because the *both have variants in the same gene*.

2. Because the associated condition can go by different names and sometimes one gene is associated with multiple conditions, it is important to **compare the gene names** on the report and not just the associated condition name.

> For example, a reproductive pair is at risk to have a child affected with cystic fibrosis and related conditions if one is a carrier of "*cystic fibrosis*" associated with a variant in the CFTR gene and the other is a carrier of "*CFTR related conditions*" associated with a variant in the CFTR gene, because they *both have variants in the CFTR gene*.

Genetic Counseling for Carrier Screening

- Integral to patient full understanding
  - Limitations
  - Implications for care
  - Residual risks

- Recommended for all who have ECS

- Genetic testing laboratories offer free brief results counseling with their lab-based genetic counselors for individuals who have used their test

- Lab-based genetic counselors can also support provider understanding and education

- Lab-based genetic counseling about test results is not intended to be "comprehensive genetic counseling" (i.e., does not include in depth discussion of family history, other test results or test options) as it is beyond their scope of practice

Carriers may not just be carriers

- We used to think heterozygotes ("carriers”) were unaffected with the condition
- Some people who are carriers of an autosomal recessive or X-linked conditions may have symptoms, otherwise known as **manifesting heterozygotes** (aka manifesting carriers)
- Symptoms may be considered a dominant form of the condition
- **See ECS lab interpretation**
  - Some labs have a general statement about health risks
  - Some labs will include language that specifies a variant is associated with recessive vs dominant inheritance
  - Not all labs agree on whether there are health risks associated with certain genes
- Depending on the interpretation
  - This may exclude a donor based on ASRM or our internal guidelines
  - May warrant additional medical monitoring
  - May warrant offering embryo testing (PGT-M) for patients

An example of variant interpretation

RESULT: POSITIVE

This carrier test evaluated 556 gene(s) for genetic changes (variants) that are associated with an increased risk of having a child a genetic condition. Knowledge of carrier status for one of these conditions may provide information that can be used to assist v family planning and/or preparation. Carrier screening is not intended for diagnostic purposes. To identify a potential genetic bas a condition in the individual being tested, diagnostic testing for the gene(s) of interest is recommended.

This test shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below. No othe clinically significant changes were identified in the remaining genes evaluated with this test.

RESULTS	GENE	VARIANT(S)	INHERITANCE	PARTNER TES RECOMMEND
Carrier: Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia	AIRE	c.967_979del (p.Leu323Serfs*51)	Autosomal recessive	Yes
Carrier: Xeroderma pigmentosum, variant type	POLH	c.1615del (p.Leu539*)	Autosomal recessive	Yes

RESULT: CARRIER

Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia

A single Pathogenic variant, c.967_979del (p.Leu323Serfs*51), was identified in AIRE.

What is autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia?

Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (APECED) is a condition that can be inherited in an autosomal recessive or autosomal dominant manner. To understand which condition a genetic change is associated with, a review of the entire report, including the variant details section, is recommended.

Please note that the AIRE variant identified in this individual is expected to be associated with autosomal recessive autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia.

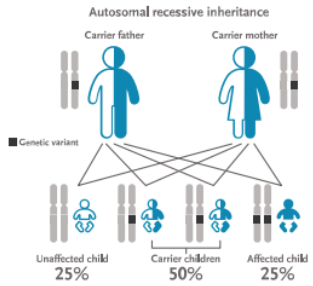
APECED is an autoimmune disease. An autoimmune condition is one in which the immune system attacks the body's own tissues and organs. One characteristic symptom of APECED is chronic fungal infections of the skin and mucous membranes (mucocutaneous candidiasis) which frequently present in infancy. Other characteristic symptoms include decreased secretion or activity of the parathyroid hormone (hypoparathyroidism) and shortage of various adrenal hormones (adrenocortical insufficiency). Both of these often present in childhood. Additional common features include premature ovarian insufficiency, reduced number of red blood cells due to insufficient vitamin B12 (pernicious anemia), loss of skin color in patches (vitiligo), hair loss (alopecia), thin enamel weakening the surface of the teeth (enamel hypoplasia), and inflammation of the cornea of the eye (keratitis). Symptoms and severity of APECED are highly variable. Prognosis depends on the severity of symptoms. Individuals with autosomal dominant APECED, which is caused by a single pathogenic AIRE variant, typically have later onset and milder symptoms or may show no obvious symptoms (reduced penetrance) compared to individuals with autosomal recessive APECED. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

Carrier testing for the reproductive partner is recommended.

If your partner tests positive:

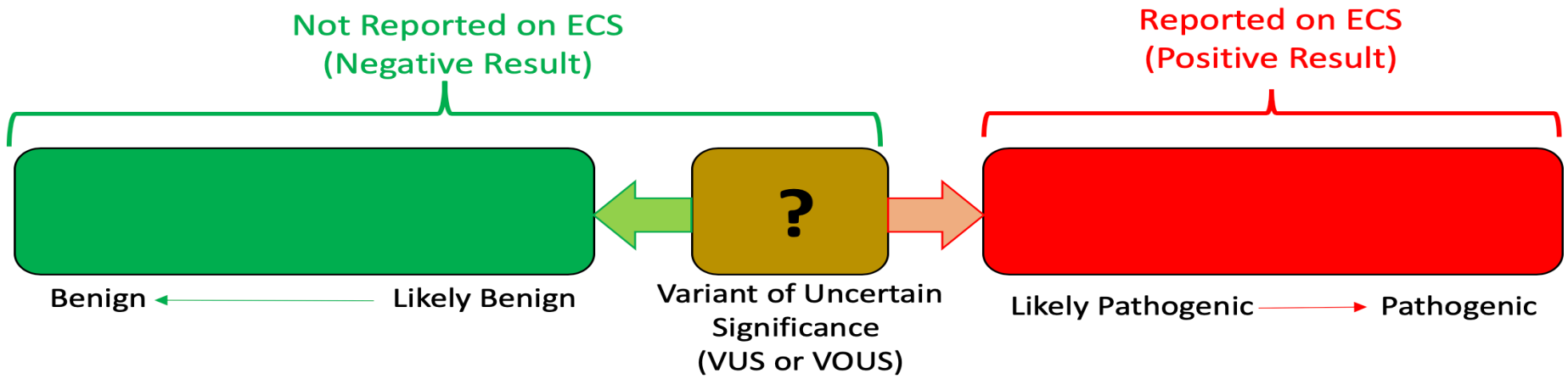
In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the AIRE gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition.



If your partner tests negative:

A negative carrier test result reduces, but does not eliminate, the chance that a person may be a carrier. The risk that a person could still be a carrier, even after a negative test result, is called a residual risk. See the table below for your partner's hypothetical residual risk after testing negative for autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia. These values are provided only as a guide, are based on the detection rate for the condition as tested at Invitae, and assume a negative family history, the absence of symptoms, and vary based on the ethnic background of an individual. For genes associated with both dominant and recessive inheritance, the

Variant Classification



Benign or Likely Benign = Variant not known or suspected to be associated with disease
Variant of Uncertain Significance = not enough information about this variant to determine if associated with disease
Pathogenic or Likely Pathogenic = Variant known or suspected to be associated with disease

- **Only "likely pathogenic" or "pathogenic" interpretation of a variant is considered reportable and actionable with carrier screening**
- All variant classifications are reported with diagnostic testing for individuals with a clinical or family history of the condition

Variant classification can vary between labs and over time

- Variant classification dependent upon numerous variables
  - Information in world-wide variant databases
  - Some variants may not have much information in the database and labs depend on computer modeling or expected impact on gene function

- One lab may call a variant "likely pathogenic" or "pathogenic" while another lab may not, and thus not report it on carrier screening

- A variant may have more accumulated data over time, and thus be reclassified after initial reporting

- Some reclassifications may be actionable with carrier screening, while others may not
  - **Actionable**: "likely pathogenic"/"pathogenic" to "VUS"/"likely benign"/"benign" or vice versa
  - **Not actionable**:
    - "likely pathogenic" to "pathogenic" or vice versa
    - "VUS" to "likely benign" or "benign" or vice versa

Preimplantation Genetic Testing

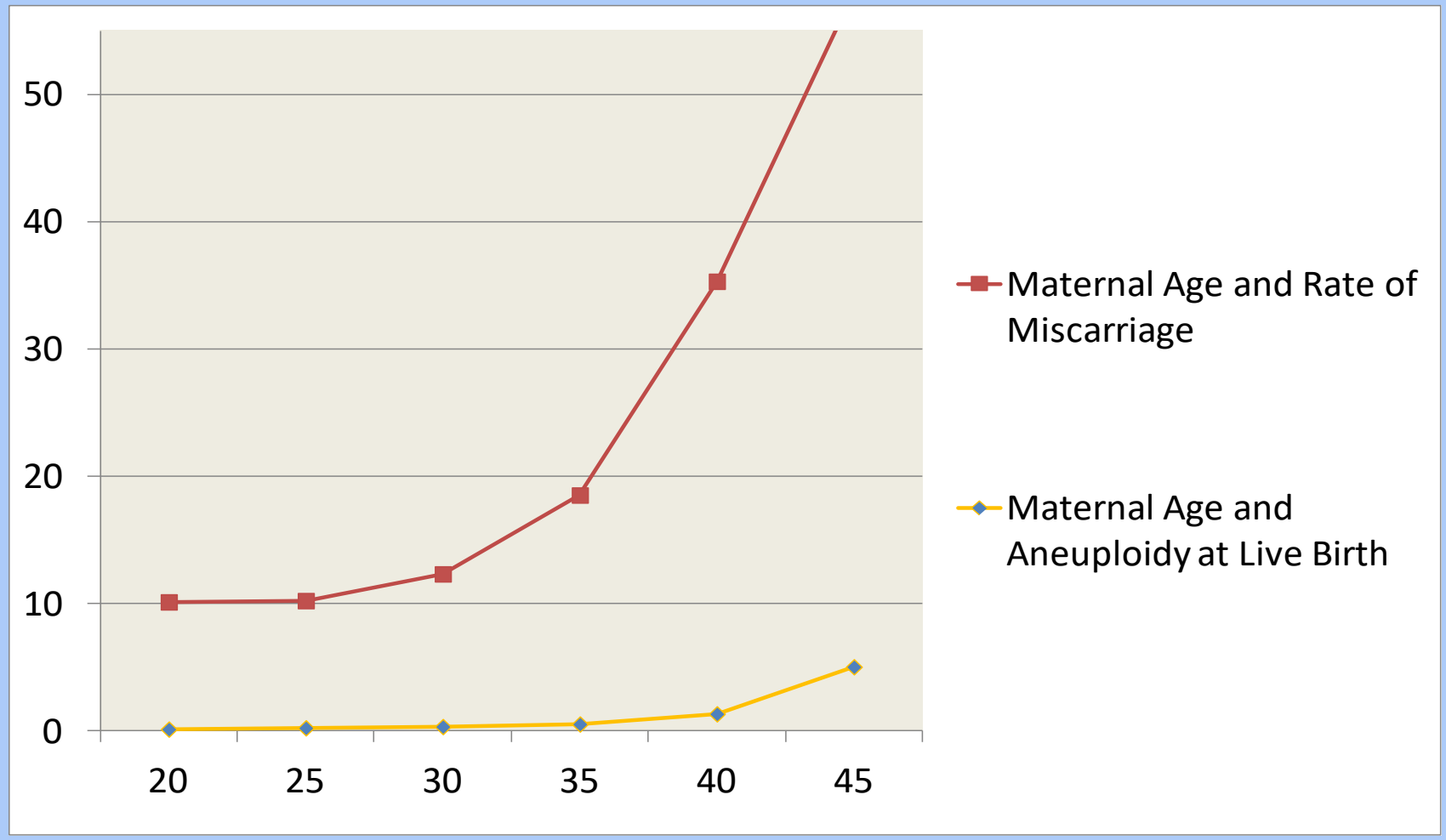
Key Considerations for Preimplantation Genetic Testing (PGT)

- Optional testing for patients doing IVF
- Considered a screening tool intended to reduce risk of embryos having specific genetic conditions
- Detection rates in high 90 percentiles; limitations in accuracy based on
  - Small amount of DNA from few cells
  - Assumption that the sample of cells tested represent remaining cells of embryo
  - Test technology
- Does not replace prenatal testing options
- Is not able to test for “everything”

PGT-A

- Preimplantation Genetic Testing for **Aneuploidy**
- Most common type of embryo testing
- Screening embryos for sporadic (not inherited) chromosome abnormalities (aneuploidy)
- Aneuploidy increases with maternal (egg) age
- Other indications for PGT-A
  - Previous pregnancy affected with aneuploidy
  - History of unexplained miscarriage
  - History of unexplained recurrent failed IVF cycles/implantation failure
  - General embryo selection/optimization of pregnancy rates

Aneuploidy and Maternal Age



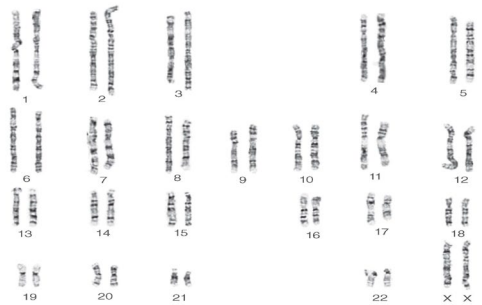
Benefits and Limitations of PGT-A

- For each **embryo transferred** that has a euploid test result:
  - Higher implantation rate
  - Reduced miscarriage risk
  - Reduced chance of fetal or newborn chromosome abnormality
  - Greater efficiency with each embryo transfer

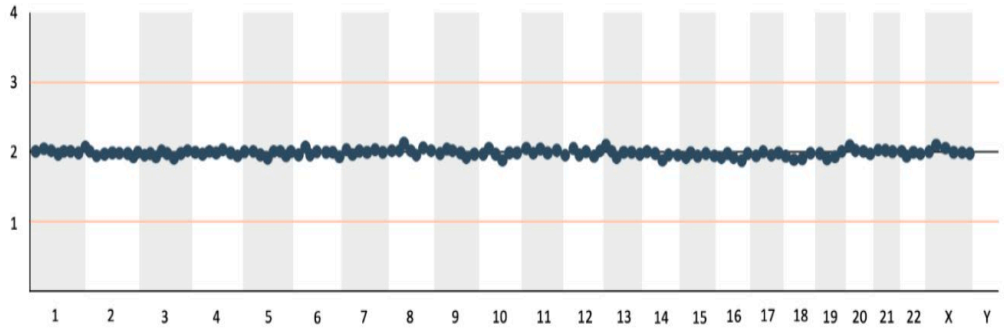
- Prenatal testing still appropriate to consider after IVF with PGT-A because:
  - PGT-A can't detect problems with fetal anatomy or growth that may be detected on ultrasound
  - Some prenatal tests, such as chorionic villus sampling (CVS) or amniocentesis ("amnio") are more accurate than PGT-A at detecting aneuploidy
  - PGT-A alone does not evaluate for single gene disorders, small copy

PGT-A does not create a karyotype

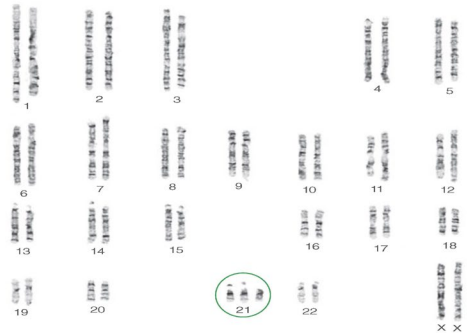
Normal female karyotype



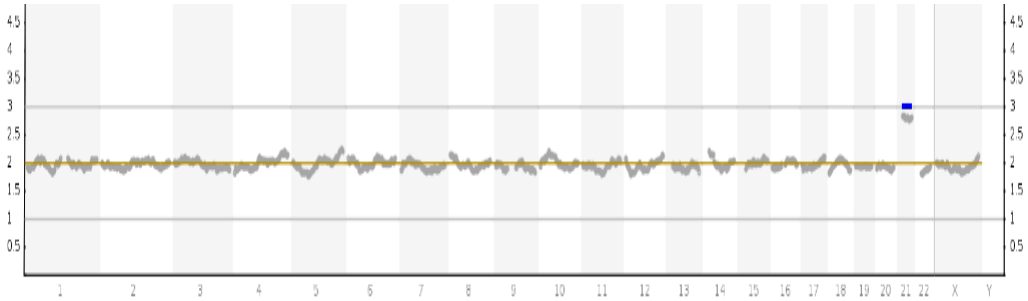
Normal female PGT-A result from NGS



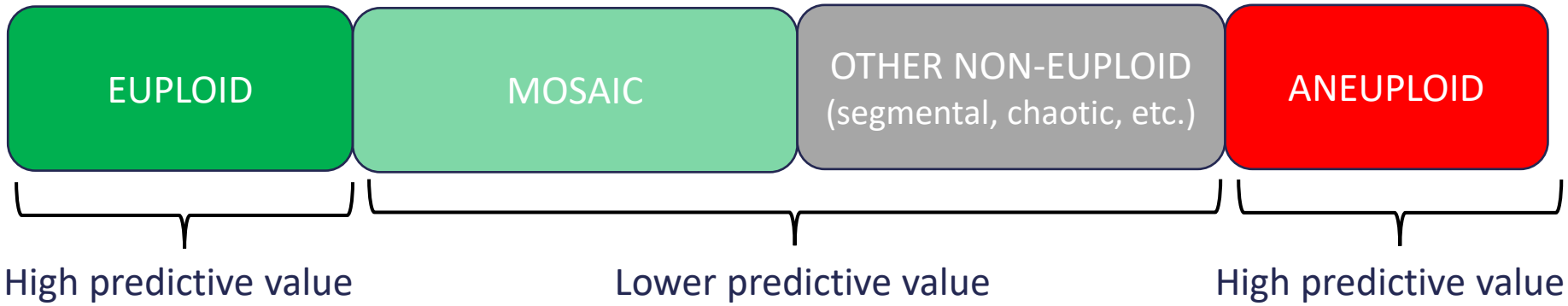
Trisomy 21 karyotype



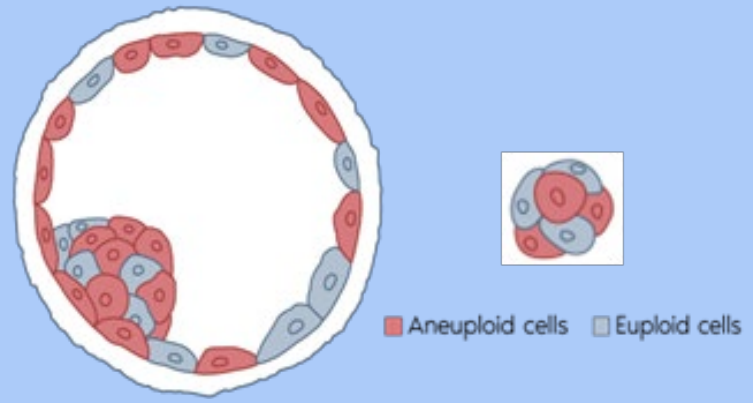
Trisomy 21 PGT-A result from NGS



Predictive Value of PGT-A Results



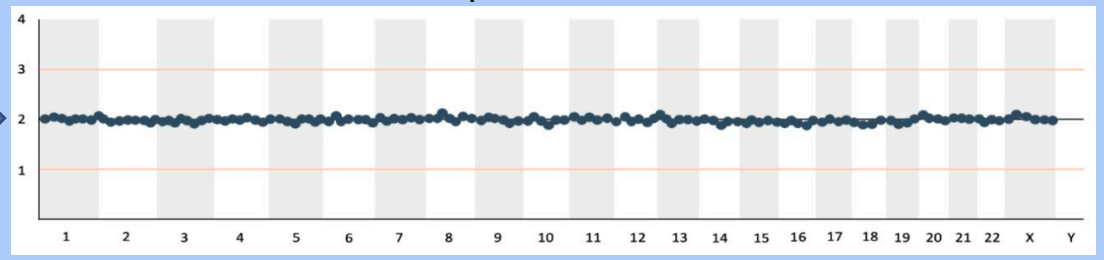
Intermediate Copy Number (Mosaicism) with PGT-A



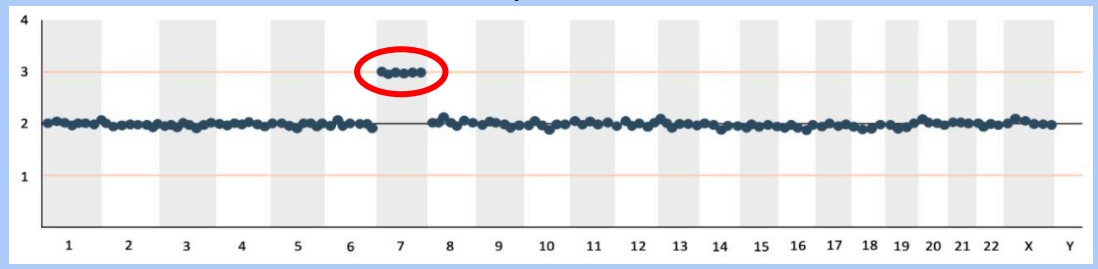
- Intermediate copy number variations in a trophectoderm biopsy containing several cells
- Does not evaluate individual cells but rather the collective amount of DNA from a group of multiple lysed cells
- Chromosomal mosaicism is presumed in PGT-A as the reason for the intermediate copy read, but not observed directly (as with a karyotype)

Euploid

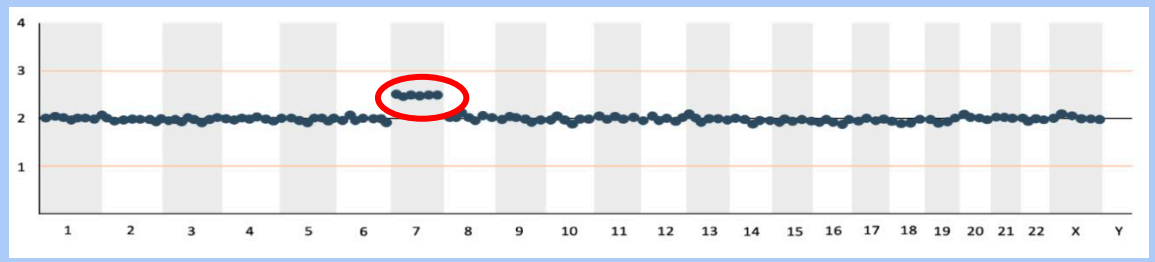
normal reference



Aneuploid



Intermediate Copy Number/"Mosaic"

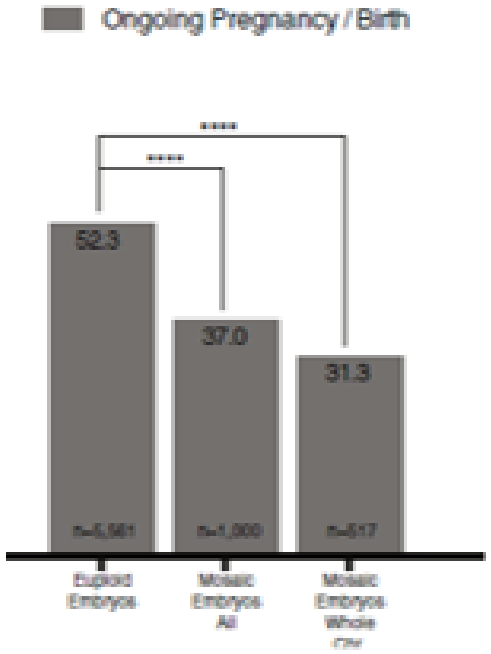


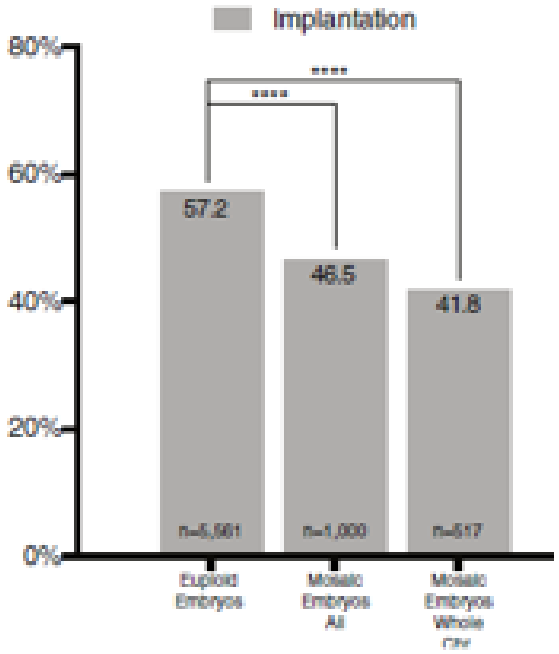
Evidence from 1000 Mosaic Embryo Transfers (F&S 2021)

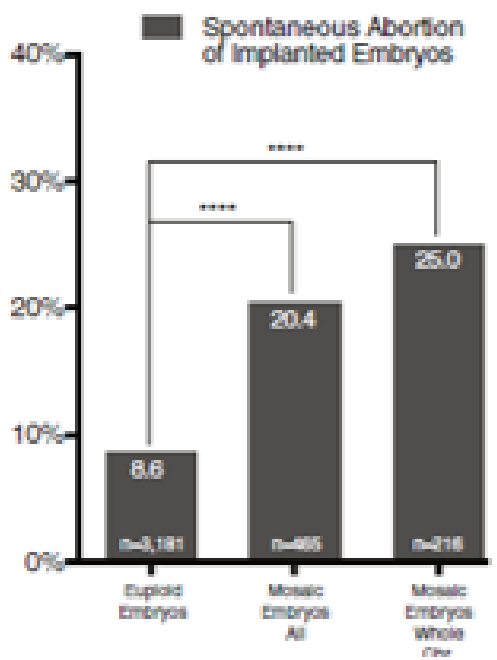
Using outcome data from one thousand mosaic embryo transfers to formulate an embryo ranking system for clinical use

Manuel Viotti, Ph.D.,[a,b] Andrea R. Victor, M.S.,[a] Frank L. Barnes, Ph.D.,[a,b] Christo G. Zouves, M.D.,[a,b] Andria G. Besser, M.S.,[c] James A. Grifo, M.D., Ph.D.,[c] En-Hui Cheng, Ph.D.,[d] Maw-Sheng Lee, M.D., Ph.D.,[d,e] Jose A. Horcajadas, Ph.D.,[f] Laura Corti, M.Sc.,[g] Francesco Fiorentino, Ph.D.,[h] Francesca Spinella, Ph.D.,[h] Maria Giulia Minasi, M.Sc.,[h] Ermanno Greco, M.D.,[h] and Santiago Munné, Ph.D.[a]

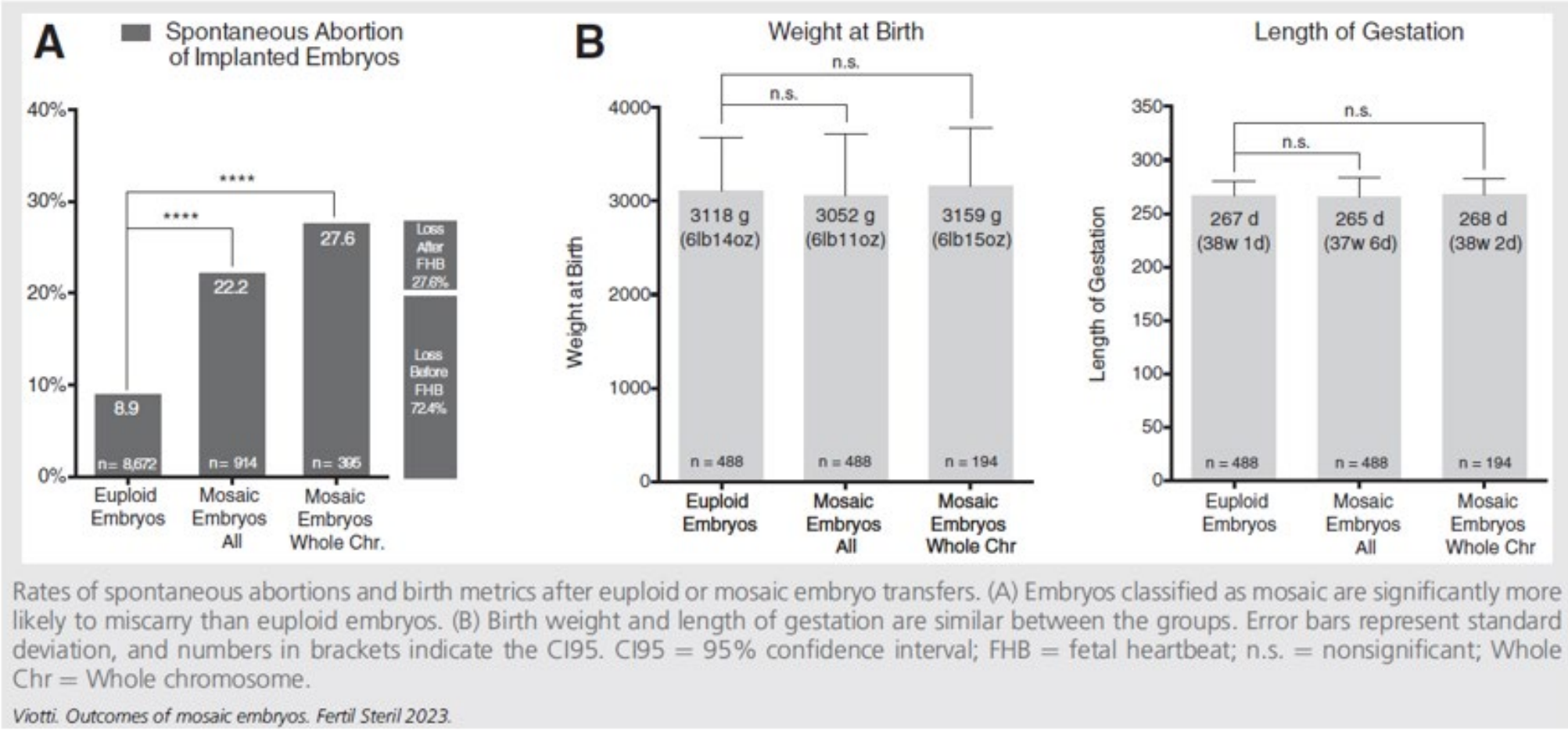
Embryos with mosaic results have lower implantation and ongoing pregnancy rates, and higher miscarriage rates







More evidence from Viotti et al 2023



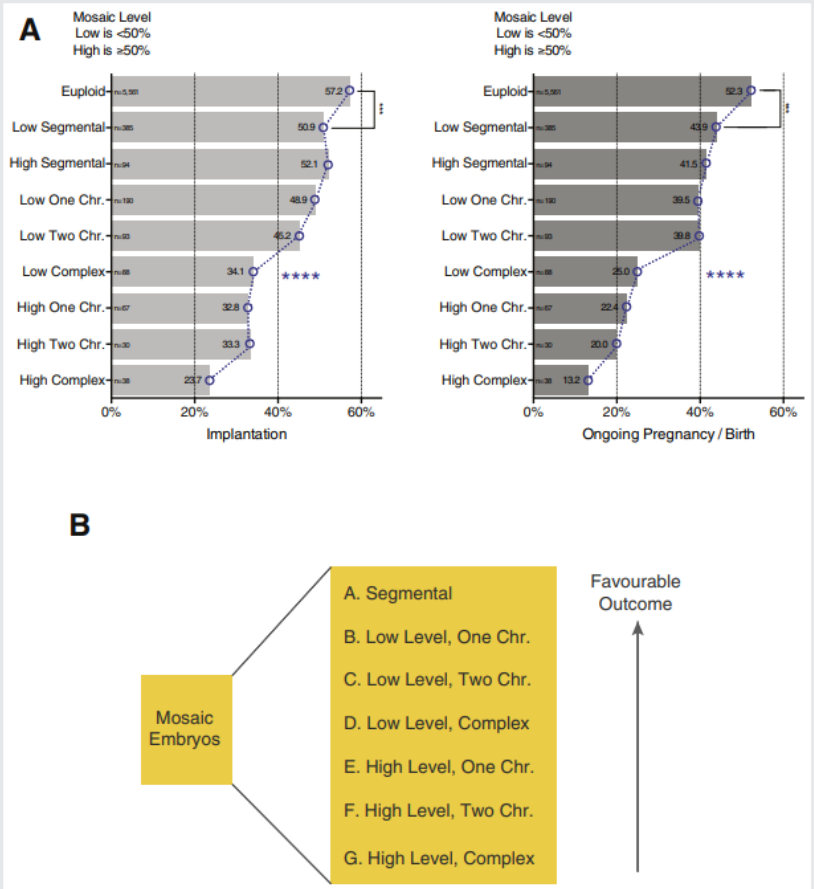
Rates of spontaneous abortions and birth metrics after euploid or mosaic embryo transfers. (A) Embryos classified as mosaic are significantly more likely to miscarry than euploid embryos. (B) Birth weight and length of gestation are similar between the groups. Error bars represent standard deviation, and numbers in brackets indicate the CI95. CI95 = 95% confidence interval; FHB = fetal heartbeat; n.s. = nonsignificant; Whole Chr = Whole chromosome.

Viotti. Outcomes of mosaic embryos. Fertil Steril 2023.

However, in ongoing pregnancies and deliveries, mosaic outcomes are similar to euploids

Guide for Ranking Embryos with Mosaic Results

FIGURE 3



Combined effect of mosaic traits on clinical outcome reveals ranking system for mosaic embryos. (**A**) Clinical outcomes of the euploid group compared with mosaic groups sorted by mosaic level and type. For mosaic level, "low" is <50%, "high" is ≥50%. Chi-square test for trend (blue dotted line and connected points) indicates statistically significant trend. (**B**) Ranking of mosaic embryo subgroups, sorted by favorable clinical outcomes. Chr. = chromosome.

Viotti. Mosaic traits affect clinical outcomes. Fertil Steril 2020.

Viotti M, et al. Using Outcome Data From One Thousand Mosaic Embryo Transfers to Formulate an Embryo Ranking System for Clinical Use. Fertil Steril 2021; 115:1212-24

Also important to consider…

…persisting mosaicism prenatally and postnatally detected

Reference	PGT-A Result	Pre/postnatal Results	Clinical Presentation
Kahraman, 2020	Mos -2 (35%)	Amnio: mosaic +2 (2/100 cells) Postnatal blood: mosaic -2 (2/100 cells)	Normal appearance of the newborn
Yang, 2021	Mos interstitial +10q11.21-q21.1	46,XY,dup(10)(q11.21-q11.23)	Coarctation of the aorta detected prenatally; "newborn deemed healthy after neonatal correction of the aorta."
Schlade-Bartusiak, *et. al.*, 2022	Mos +15, -20q11.23-qter (high level)	Postnatal karyotype: 47, XY,+del(15)(q12q23)dn with UPD15	No fetal anomalies; post natal feeding complications and airway issues
Greco, *et. al.*, 2023	Mos +1q,-7,-8,+9, -19,-20,+21 (40%)	CVS: mosaic +21 (80%) Amnio: mosaic +21 (16%)	Ultrasound anomalies, TAB
Greco, *et. al.*, 2023	Mos terminal -1p36.33-p31.1 (40%)	Amnio FISH: -1p deletion (15%)	Deletion present in 1.5% of brain cells after TAB
Viotti *et. al.*, 2024	Mos +4q32.3q34.3, -Xq27.3q28 (low level)	CVS: Mosaic +4q32.3q34.3	Normal appearance of the newborn
Viotti, ASRM 2023	Mos +15 (high level)	NIPT: Mosaic +15 POC: Mosaic +15	Ultrasound abnormalities
Viotti, ASRM 2023	Mos +21 (low level)	NIPT: +21 CVS: Mosaic +21	Ultrasound abnormalities
Viotti, ASRM 2023	Mos +17 (high level	POC: Mosaic +17	Ultrasound abnormalities

Estimated to be roughly 1%

Clarification on Segmental Aneuploidy

- An extra or missing piece of chromosome
- May also be referred to as deletion, duplication, partial monosomy or partial trisomy
- Caution with PGT-SR as segmental aneuploidy is expected to be related to parental chromosome rearrangement; associated with poor reproductive outcomes
- Can be in the mosaic and non-mosaic state – be careful not to confuse the two
- New data on non-mosaic segmental aneuploidy transfer outcomes demonstrating reproductive potential

Segmental Aneuploidy Transfer Outcomes

Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-024-03282-8

ASSISTED REPRODUCTION TECHNOLOGIES

Healthy live births achieved from embryos diagnosed as non-mosaic segmental aneuploid

Andria Besser[1] · Emily Weidenbaum[2] · Julia Buldo-Licciardi[2] · Caroline McCaffrey[1] · James Grifo[1] · Jennifer Blakemore[1]

Received: 21 August 2024 / Accepted: 1 October 2024

Abstract

Purpose To investigate pregnancy outcomes resulting from transfer of embryos with non-mosaic (NM) segmental aneuploid (SA) results following preimplantation genetic testing for aneuploidy (PGT-A).

Methods All patients who underwent frozen embryo transfer (FET) of at least one embryo with a NM-SA between March 2021 and April 2024 were retrospectively reviewed. Primary outcomes included live birth rate (LBR) and results of prenatal diagnosis. Embryos with NM-SA results were also compared to those with NM whole chromosome aneuploid (WCA) and mosaic SA results.

Results Out of 25 NM-SA embryos transferred, the LBR was 24%. Prenatal diagnosis by amniocentesis and/or chorionic villus sampling was performed in 3/6 pregnancies, and results were normal. Embryos with duplications produced more live births compared to those with deletions. NM-SA embryos had a significantly higher ongoing pregnancy (OP)/LBR compared to embryos with NM-WCA results and a significantly lower OP/LBR compared to embryos with mosaic SA results; however, when compared to embryos with high-level SA mosaicism > 40%, the OP/LBR was not significantly different.

Conclusion Embryos with NM-SAs can result in euploid live births, albeit at reduced rates compared to those with mosaic SAs. These data can be used to aid in patient counseling about PGT-A results and embryo transfer decisions.

- 25 embryos with non-mosaic segmental aneuploidy transferred
- Some had addtl mosaic findings
- 17 SETs, 8 DETs
  - 6 with mosaic
  - 2 with euploid
- **6 apparently healthy live births (24%)**
  - 3 isolated seg
  - 3 seg + mos
  - Prenatal diagnosis performed for 3 with normal results
  - 1 euploid on rebx

A quick primer on PGT-A and Mosaicism

Hear from one of the world experts on non-euploid embryo transfer outcomes

Andria Besser, MS, CGC

tomorrow morning at 8am!

What do we do with these complexities?

- What are the clinic policies on transfer of embryos with mosaic or other non-euploid results?
- Is the clinic policy documented and known to all embryology and clinical staff?
- Is the clinic policy shared with all patients PRIOR to IVF-PGT cycle start?
- Are non-euploid embryos kept in cryopreservation and for how long?

ASRM PAGES

Transferring embryos with genetic anomalies detected in preimplantation testing: an Ethics Committee Opinion

Ethics Committee of the American Society for Reproductive Medicine

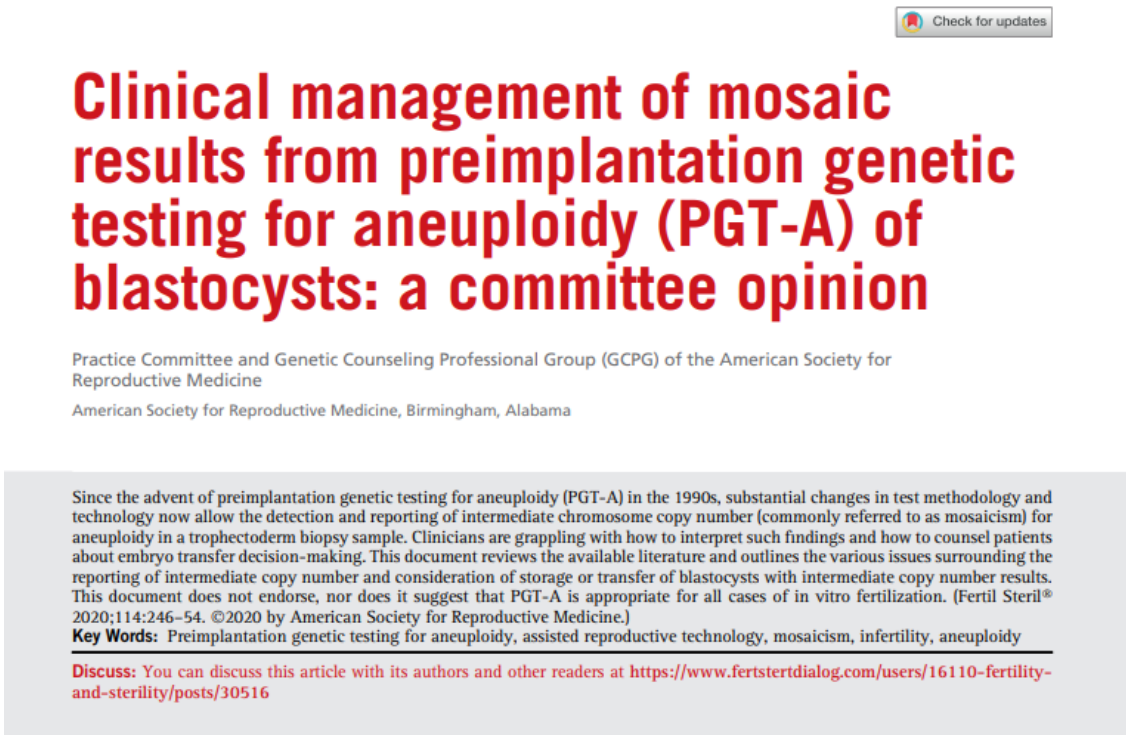
American Society for Reproductive Medicine, Birmingham, Alabama

Patient requests for transfer of embryos with genetic anomalies linked to serious health-affecting disorders detected in preimplantation testing are rare but do exist. This Opinion sets out the possible rationales for a provider's decision to assist or decline to assist in such transfers. The Committee concludes in most clinical cases it is ethically permissible to assist or decline to assist in transferring such embryos. In circumstances in which a child is highly likely to be born with a life-threatening condition that causes severe and early debility with no possibility of reasonable function, provider transfer of such embryos is ethically problematic and highly discouraged. (Fertil Steril® 2017;107:1130–5. ©2017 by American Society for Reproductive Medicine.)

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/14893-23835

"Fertility clinics are strongly encouraged to draft and make available to all patients written policies on whether or not the program agrees to the transfer of embryos with known health-affecting genetic anomalies.

…these policies should be the product of an informed, deliberative, and collaborative process that includes all relevant clinic personnel."



Check for updates

Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion

Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Since the advent of preimplantation genetic testing for aneuploidy (PGT-A) in the 1990s, substantial changes in test methodology and technology now allow the detection and reporting of intermediate chromosome copy number (commonly referred to as mosaicism) for aneuploidy in a trophectoderm biopsy sample. Clinicians are grappling with how to interpret such findings and how to counsel patients about embryo transfer decision-making. This document reviews the available literature and outlines the various issues surrounding the reporting of intermediate copy number and consideration of storage or transfer of blastocysts with intermediate copy number results. This document does not endorse, nor does it suggest that PGT-A is appropriate for all cases of in vitro fertilization. (Fertil Steril® 2020;114:246–54. ©2020 by American Society for Reproductive Medicine.)

Key Words: Preimplantation genetic testing for aneuploidy, assisted reproductive technology, mosaicism, infertility, aneuploidy

First published 2020
Updated version pending publication 2023

- Euploid embryos should be prioritized
- Patients should consult with geneticist/genetic counselor prior transfer of mosaic (non-euploid) embryos with ample time to consider currently known risks/benefits
- Prenatal and postnatal follow up genetic counseling and testing consideration recommended

PGT for Inherited Conditions

- PGT-M
  - Screening for specific **single gene** conditions (aka "**monogenic**" disease)
  - Typically done when the genetic condition in the family or for which parents are carriers is associated with significant medical and/or developmental risk in offspring
  - Gene and specific variant(s) need to be known to set up testing in embryos

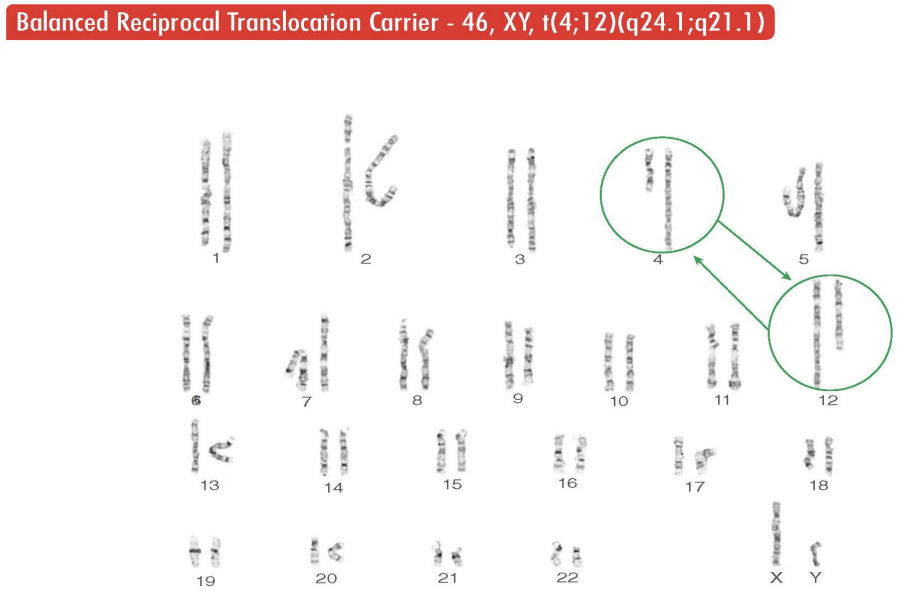
- PGT-SR
  - Screening of specific inherited aneuploid based on parent's **structural rearrangement**
  - Embryos at increased risk for chromosomal imbalance related to parent's chromosome rearrangement
  - Parents' karyotypes must be known to set up additional testing in embryos

NOTE: These types of PGT typically include PGT-A

PGT-M requirements

- Need to know the inheritance pattern, gene and gene variant
- Requires review with the PGT lab before case can be accepted
- Often requires patients' family members to provide DNA samples
- Requires lead time for the PGT lab to accurately set up testing
  - ask PGT lab for details
  - often more than one month from the time family member samples are received
  - "Fast Track" option may be available

PGT-SR



- Chromosome rearrangements in a parent lead to higher change of imbalance in gametes and therefore embryos
- Breakpoints for rearrangements and size of chromosome segments unique to the patient/family
- Review of the case with PGT lab necessary to ensure proper set up and accurate reporting
- PGT-SR typically does not differential normal from balanced configuration

PGT lab genetic counselors

- What they are **able to provide**
  - Pretest PGT education for patients
  - Support for clinicians in understanding PGT results
  - Post-test PGT results review for patients; especially important when considering a NEET

- What they **cannot provide**
  - Discussion of clinic specific SOPs
  - Direction on which embryo should be transferred first

Summary

- Three means of assessing genetic risk in a reproductive setting:
  1. Personal and family history review
  2. Genetic carrier screening of patients/gamete donors
  3. Preimplantation genetic testing of embryos

- Genetic counselors can be an essential part of the fertility care team to ensure:
  - Proper assessment of genetic risk
  - Offering and coordination of appropriate genetic tests
  - Interpretation of genetic test results
  - Facilitation of patient decision making regarding genetic testing
  - Supporting the care team with genetic testing for patients/donors

Q&A