Navigating Fertility in CCHS

2024 CCHS FAMILY CONFERENCE
Newport Beach, CA
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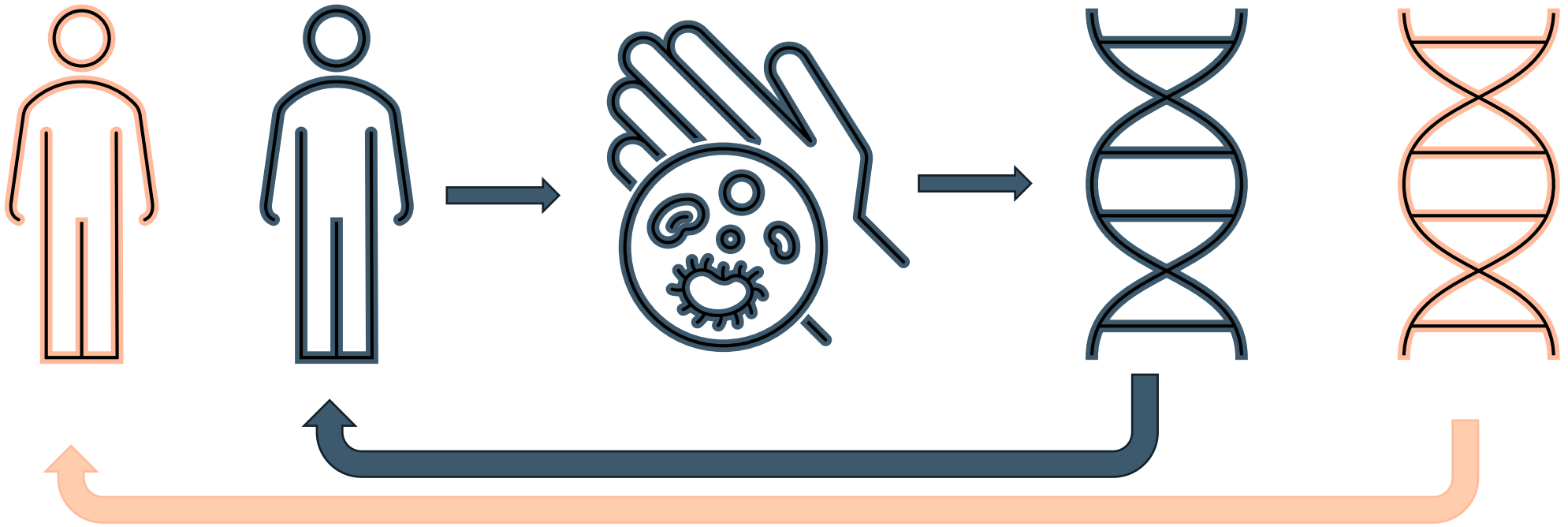
Conflict of interest

Liya is a full time salaried employee of Igenomix USA, part of VitroLife Group, a laboratory which performs PGT-M for conditions like CCHS.

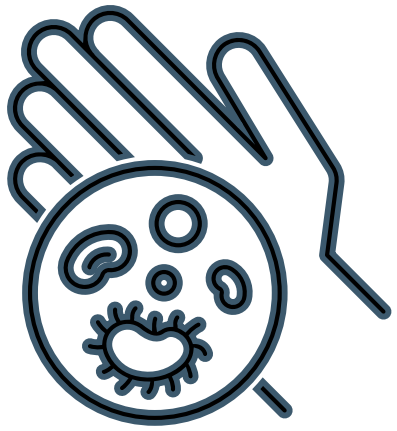
Outline

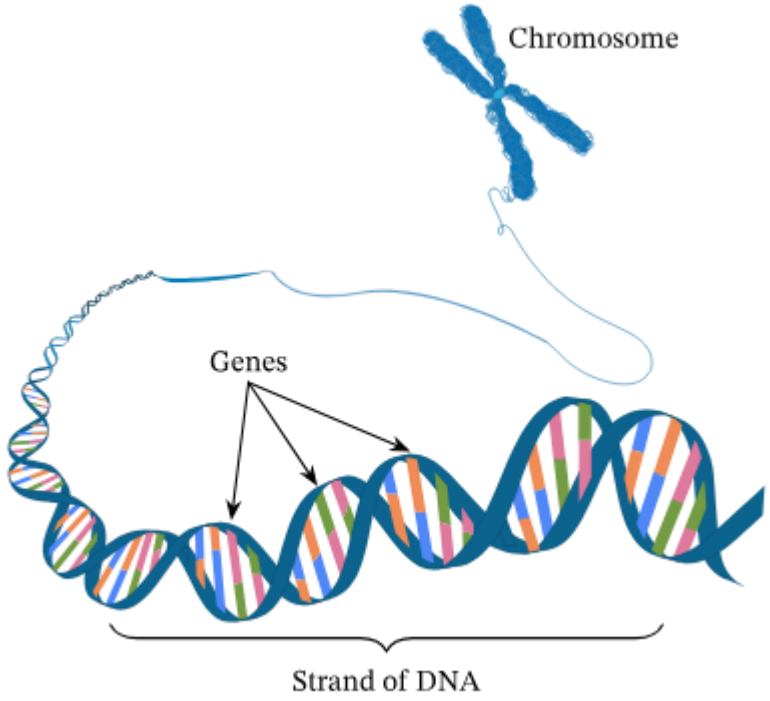
- Overview of the inheritance of Congenital Central Hypoventilation Syndrome (CCHS)
- Review recurrence rates in siblings and offspring
- Discussion of genetic testing and family planning options

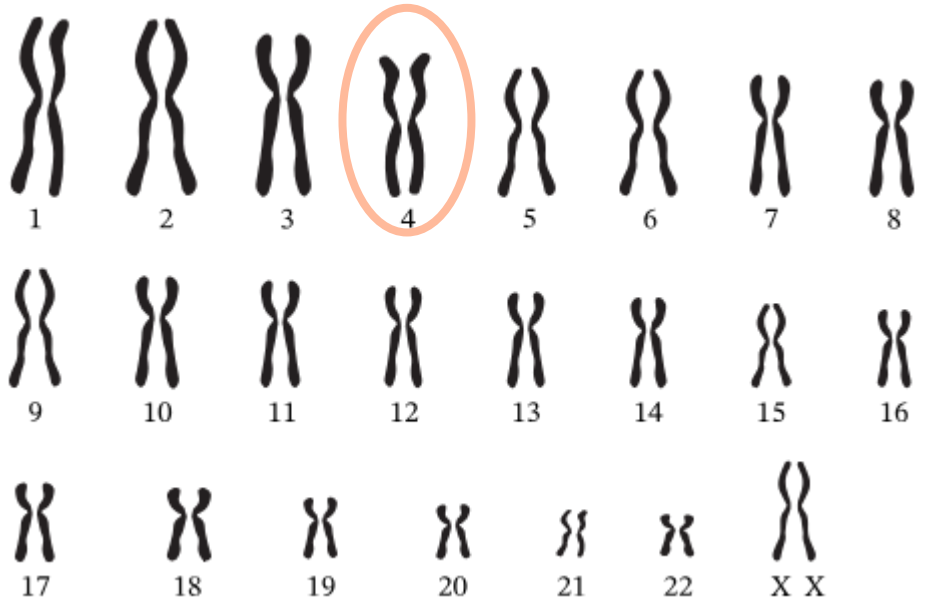
Genetics 101



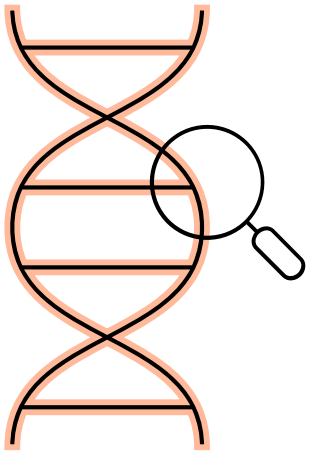
The gene assocaited with CCHS is located on chromosome 4







Pathogenic variants in PHOXB2 are associated with CCHS



Chromosome 4

PHOXB2 gene

- **Regulates autonomic nervous system (involuntary and subconcious behaviors, such as breathing, heart rate, blood glucose, body temp)**
- **Genetic variations in this gene can cause CCHS**

Pathogenic variants in PHOXB2 are associated with CCHS

Polyalanine repeat mutations (PARM)

20 alanine is typical, 25-33 alanine is expanded

… GCN – GCN – GCN – GCN – GCN …

Codes for

… Alanine – Alanine – Alanine – Alanine – Alanine …

20/25, 20/26, 20/27, etc.

Non-polyalanine repeat mutations (NPARM)

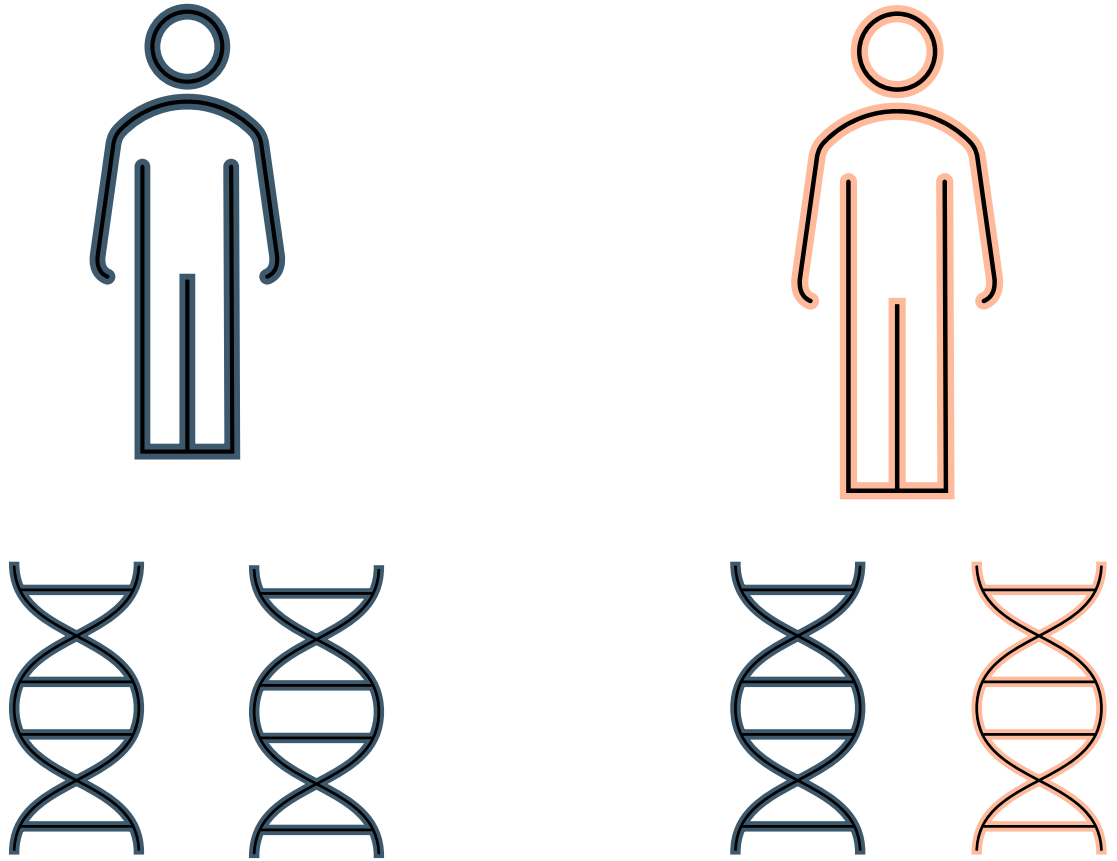
c.422G→A

“coding DNA (c), at base 422, changed from a G base to an A base”.

Whole gene or whole exon deletions (NPARM)

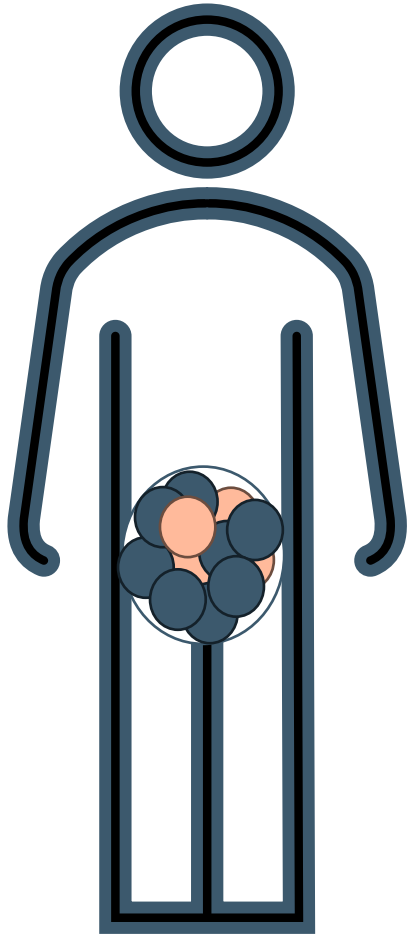
The PHOXB2 gene can be entirely or partially deleted

CCHS has autosomal dominant inheritance



Recurrence rates

- An affected parent has a 50% chance of passing on the condition (autosomal dominant)
- Most affected individuals have a “de novo” (new) variant
- Somatic/germline mosaicism is present in 5% - 25% of asymptomatic parents



****because of the high frequency of parental mosaicism in CCHS, a fetus should be considered at risk for CCHS even if the PHOX2B pathogenic variant detected in the proband was not identified in either parent****

Reproductive options

Pre-conception

- Preimplantation genetic testing for a monogenic condition (PGT-M) *may* be an option

Prenatal

- Chorionic villi sampling (CVS) and amniocentesis (amnio) can provide a diagnosis for a pregnancy

Testing at birth

- After birth, diagnostic testing is available

Preimplantation genetic testing for a monogenic condition (PGT-M)

- PGT-M is a genetic screening tool that is performed on an IVF embryo (prior to transfer) that identifies the presence of a specific genetic variant
- Embryos are small, therefore only tiny biopsy samples can be tested, limiting available technology
- To provide accurate and reportable results, linkage analysis (indirect methodology) must be used for this testing. This requires DNA samples from multiple generations.

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PGT-M for de novo variants

- For de novo variants, PGT-M may not be possible or recommended
- When a variant is new (de novo) in a child, and was not inherited from either parent, PGT-M has low clinical utility and technical limitations for future siblings

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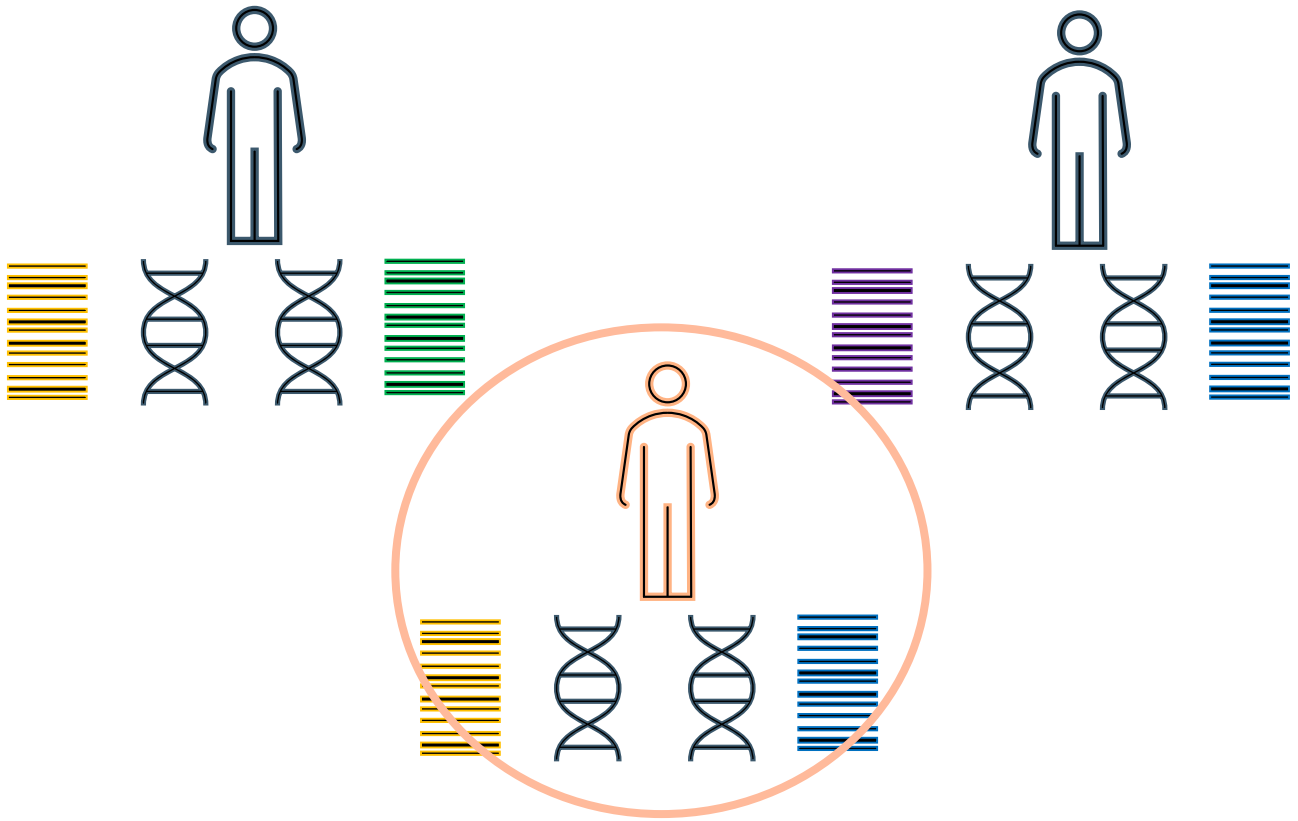
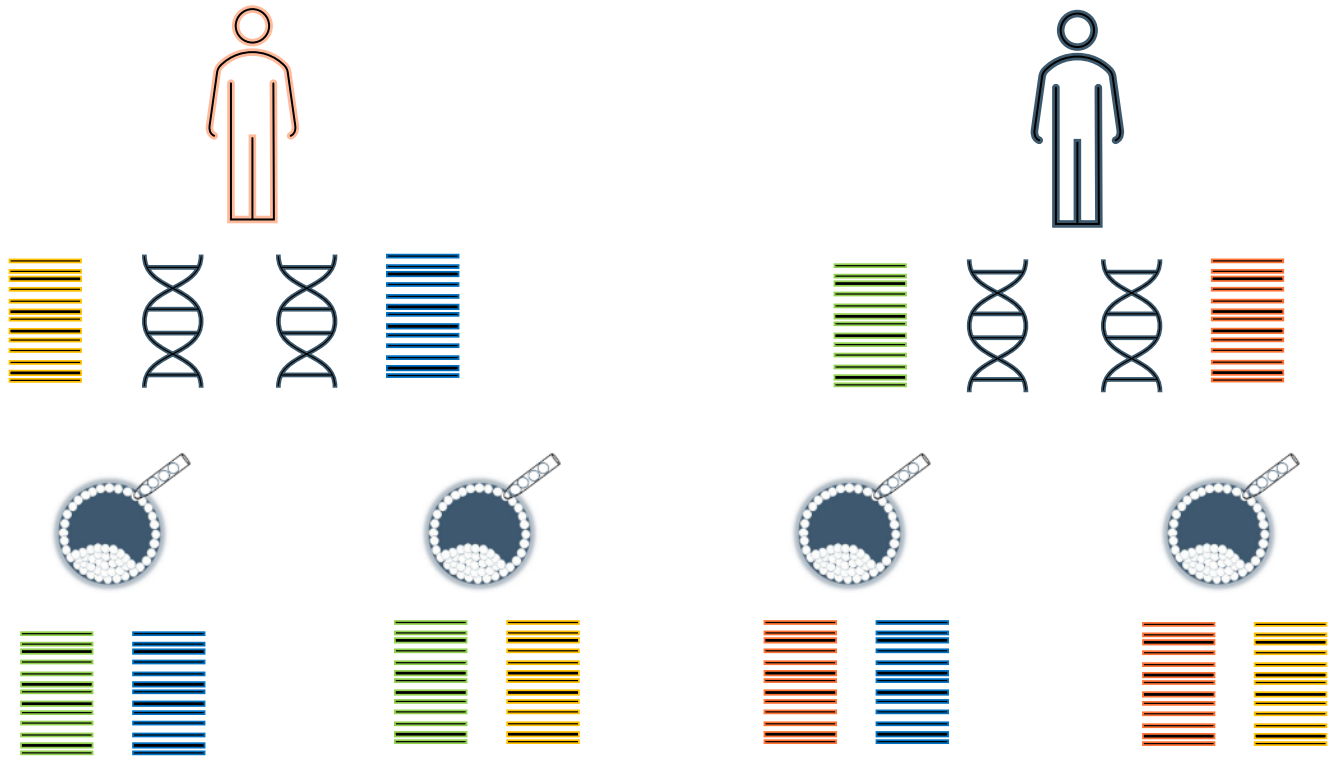


PGT-M for NPARM variants

- For NPARM variants, it *may* be possible to use embryos as a second generation if they can be directly detected in a small sample



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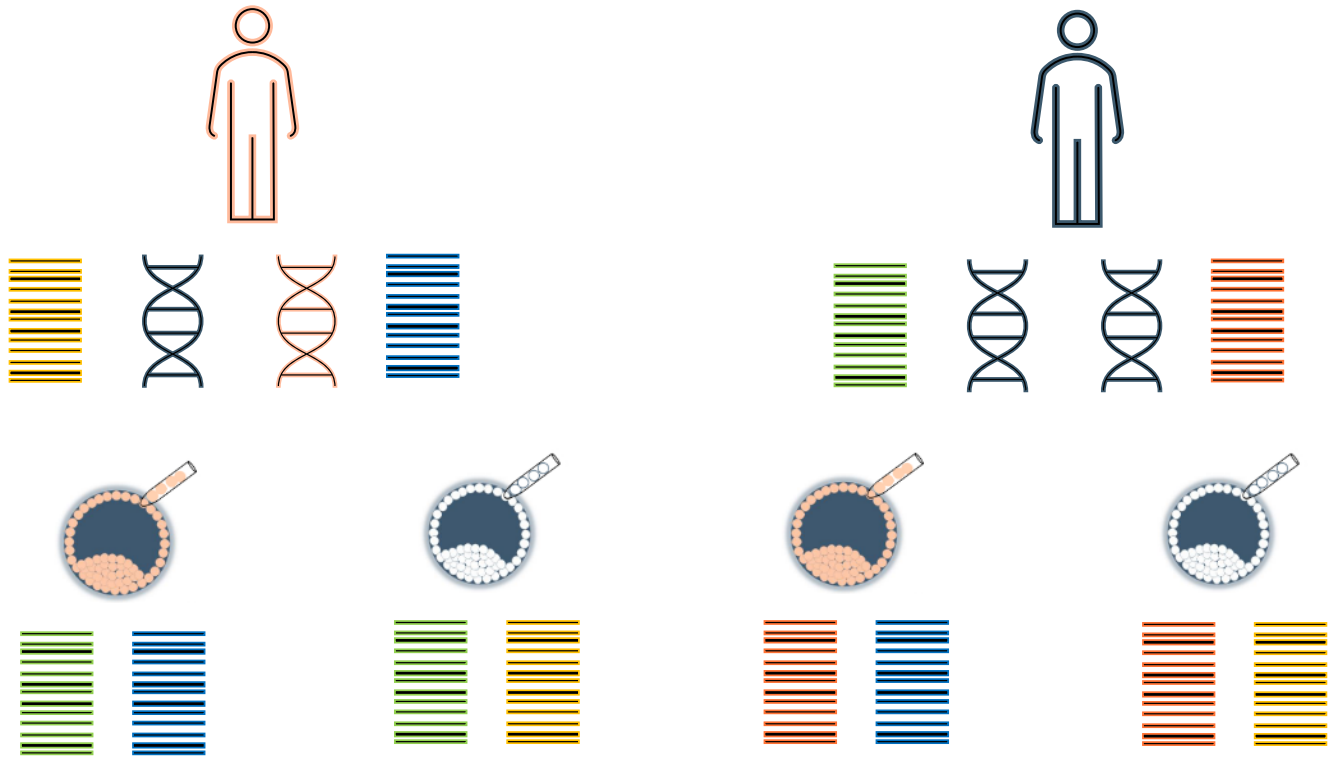
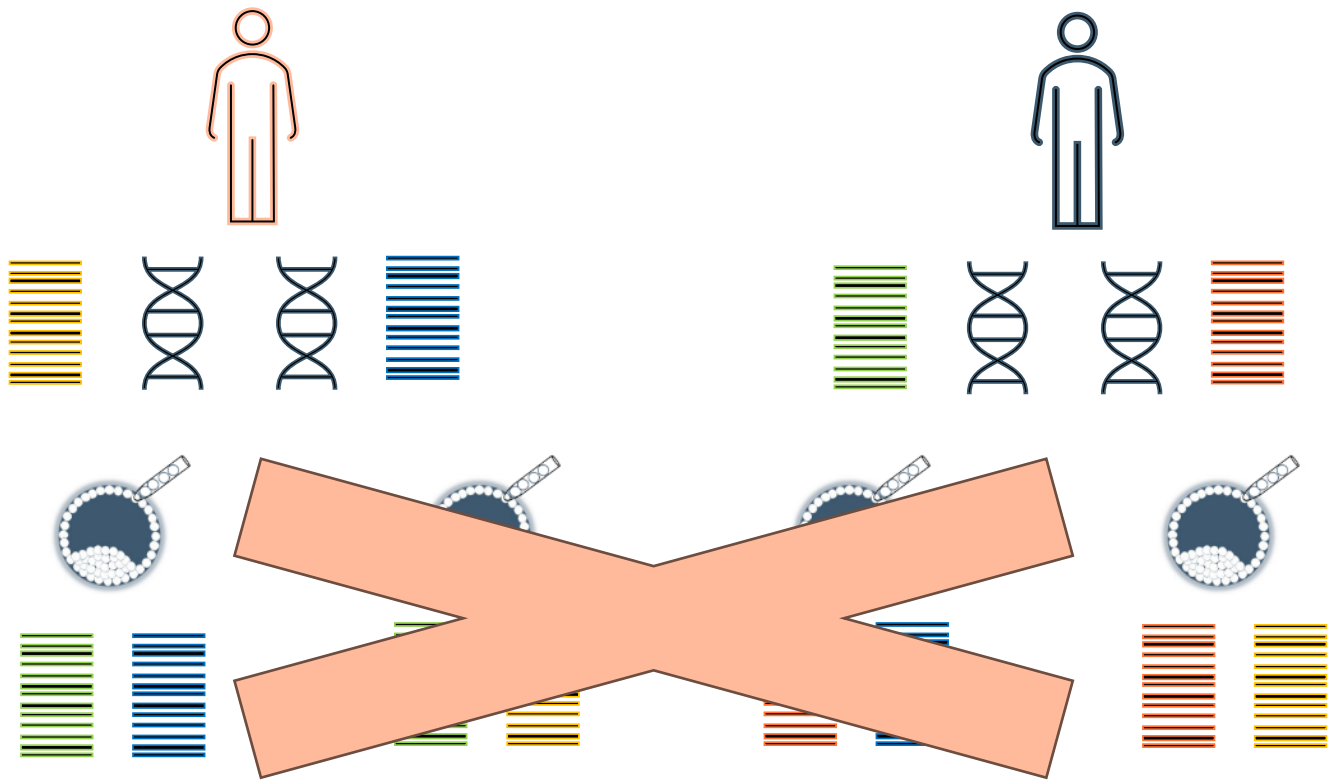


PGT-M for PARM variants

- Many PARM variants and deletions cannot be directly detected in a small sample, therefore two generations of *affected* individuals would likely be required for PGT-M probe development



Limitations of PGT-M for CCHS

- 2 affected generations are required to establish linkage and create a PGT-M test (“probe”)
- For de novo variants, PGT-M may not be possible or recommended
    - **When a variant is new (de novo) in a child, and was not inherited from either parent, PGT-M has low clinical utility and technical limitations**
- For NPARM variants, it *may* be possible to use embryos as a second generation if they can be directly detected in a small sample
- Many deletions and PARM variants cannot be directly detected in a small sample, therefore two generations of affected individuals would likely be required for PGT-M probe development

- PGT-M is 98% accurate, so follow up testing in pregnancy or after birth may still be done
- PGT-M cannot predict symptoms or symptom severity

****The availability of PGT-M is situation dependent. Please speak with your healthcare provider if you have questions about the feasibility of this testing for your family.****

Prenatal testing options

Chorionic villi sampling

- A chorionic villus sampling (CVS) prenatal test assesses cells from the placenta
- Available from weeks 10 to 13 in pregnancy
- This is considered diagnostic (near 100% accurate)

Amniocentesis

- Amniocentesis (amnio) is a prenatal procedure used to collect a small sample of the amniotic fluid for testing
- Available from 14 to 20 weeks in pregnancy
- This is considered diagnostic (near 100% accurate)

Testing after birth

- Diagnostic testing is available on various sample types after birth, or when symptoms present
- Knowing a child is at risk for a specific genetic condition can aid the clinical team in shortening the diagnostic odyssey
- The sooner a diagnosis is known, the sooner treatment becomes available

Adoption

- Some families may choose to adopt gametes, embryos, or a child

Thank you!

Questions?

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