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“We acknowledge the Kaurna people as the Traditional Custodians of the Country we meet on. We recognise their continuing connection to the land and waters and thank them for protecting this coastline and its ecosystems since time immemorial. We pay our respects to Elders past and present and extend that respect to all First Nations people”

Artist: Jenna Oldaker, Wadawurrung artist
Artwork Description: This artwork represents the connection between our ancestors, land, sky and spirits. The spirits of those that have passed, live on in the night sky watching over us as we continue to care and learn from our beautiful Country home.

Pre-conception to pre-natal genetic testing:

Reproductive carrier screening, PGT and NIPT

Tamara Mossfield
Genetic counsellor

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Learning aims

1

Understand the role of genetics in reproduction

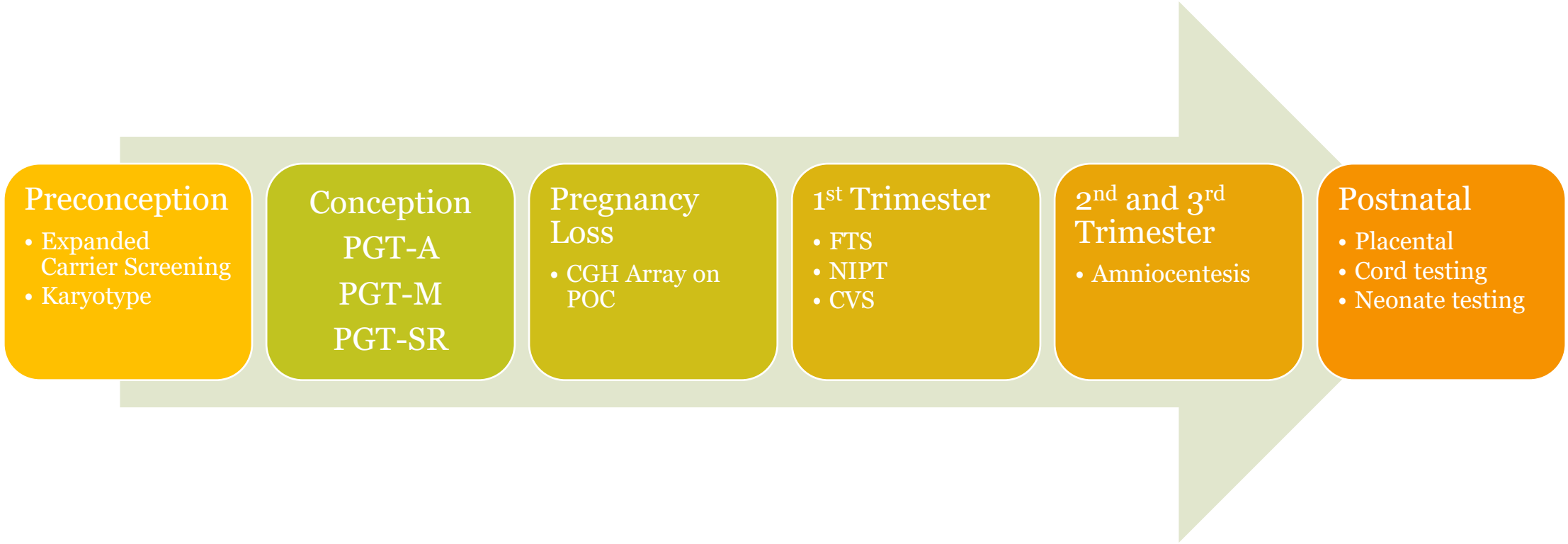
2

Outline genetic tests available from pre-conception to post-natal

3

Understand genetic testing in the context of ART

Genetic Testing in Reproduction



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Preconception

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Pre-conception Genetic Testing

Screening

Karyotyping

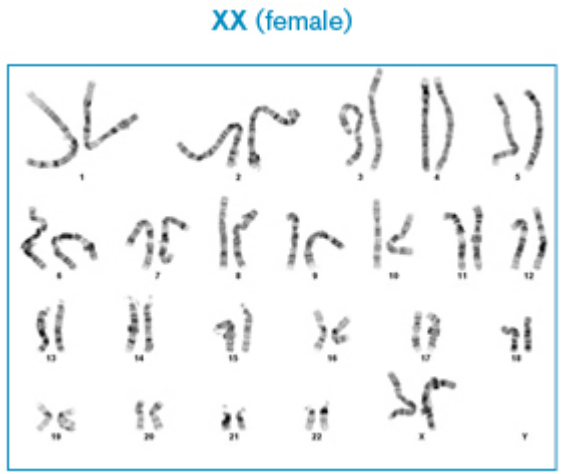
- Rec miscarriage
- Prev affected pregnancy
- FHx

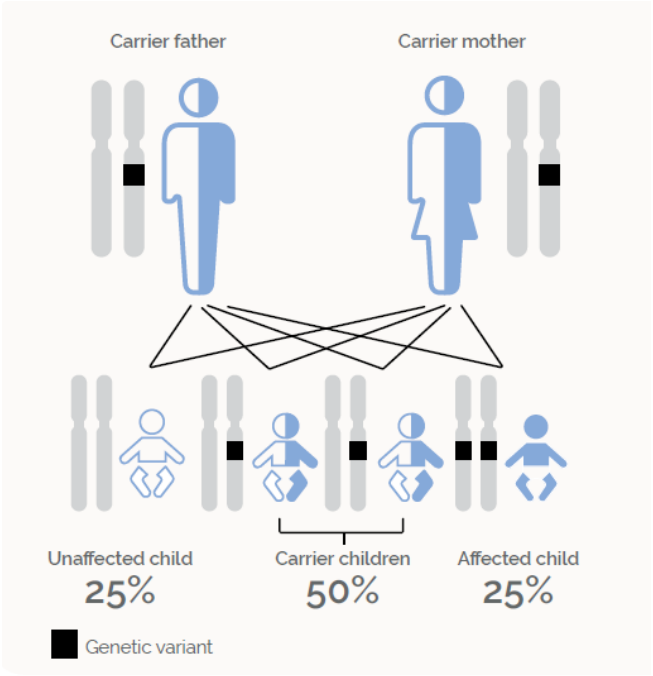
Limited/Expanded Carrier Screening

Diagnostic

Targeted testing for specific conditions

- Huntington Disease, BRCA1/2 etc
- Exome/Genome sequencing (WES/WGS) for familial conditions, congenital anomalies





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Reproductive carrier screening (RCS)

Who?

- Relevant for, and should be offered to, anyone planning a pregnancy*, regardless of family history.

What?

- A genetic test for **reproductive couples** to determine the chance of their children being affected with a **serious, childhood-onset genetic condition**

When?

- Best to test before pregnancy, but available in the first trimester.

Why?

- Most couples find out they are high-risk after a child is born. Carrier screening provides couples with family planning options. **It's all about choice.**

* The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Excellence in Women's Health

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Reproductive Carrier Screening

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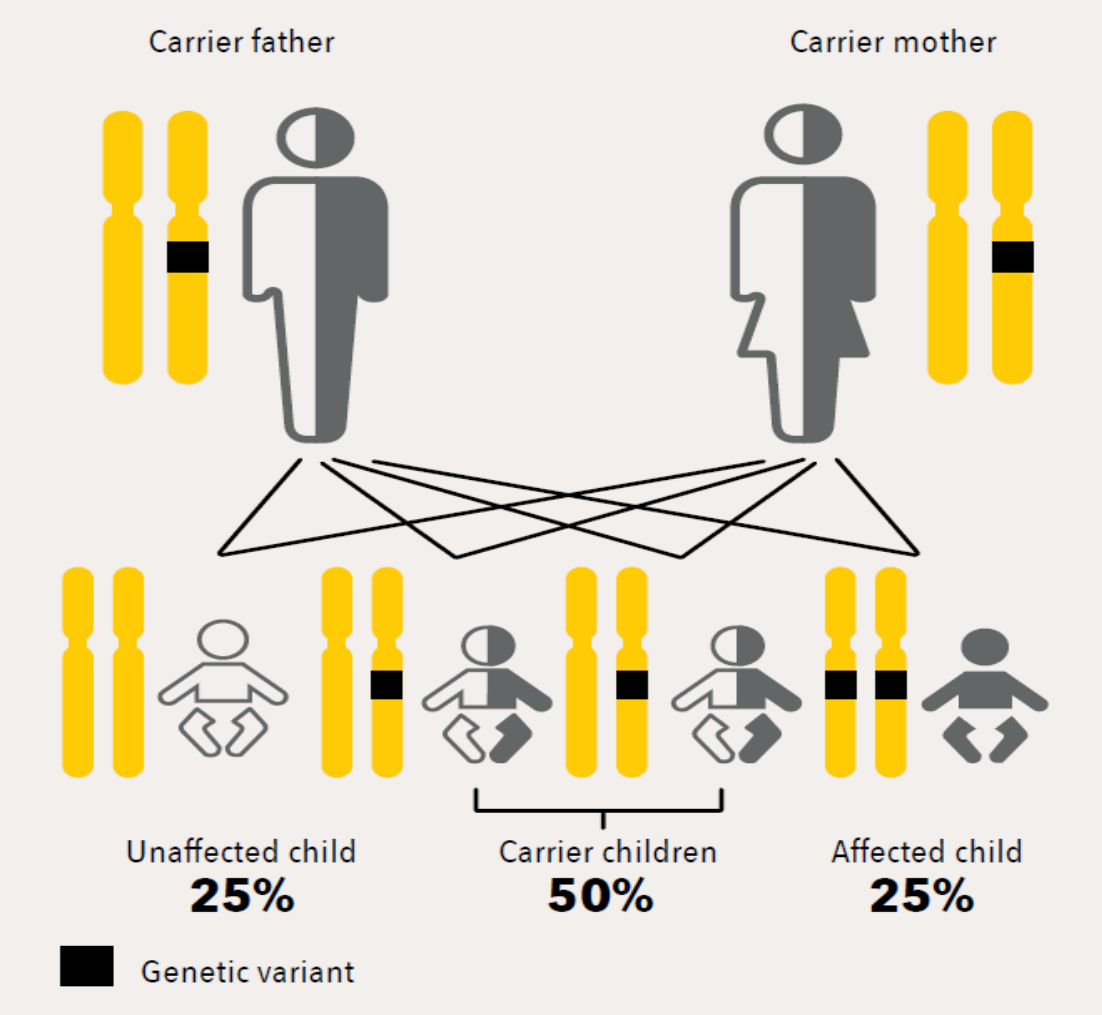
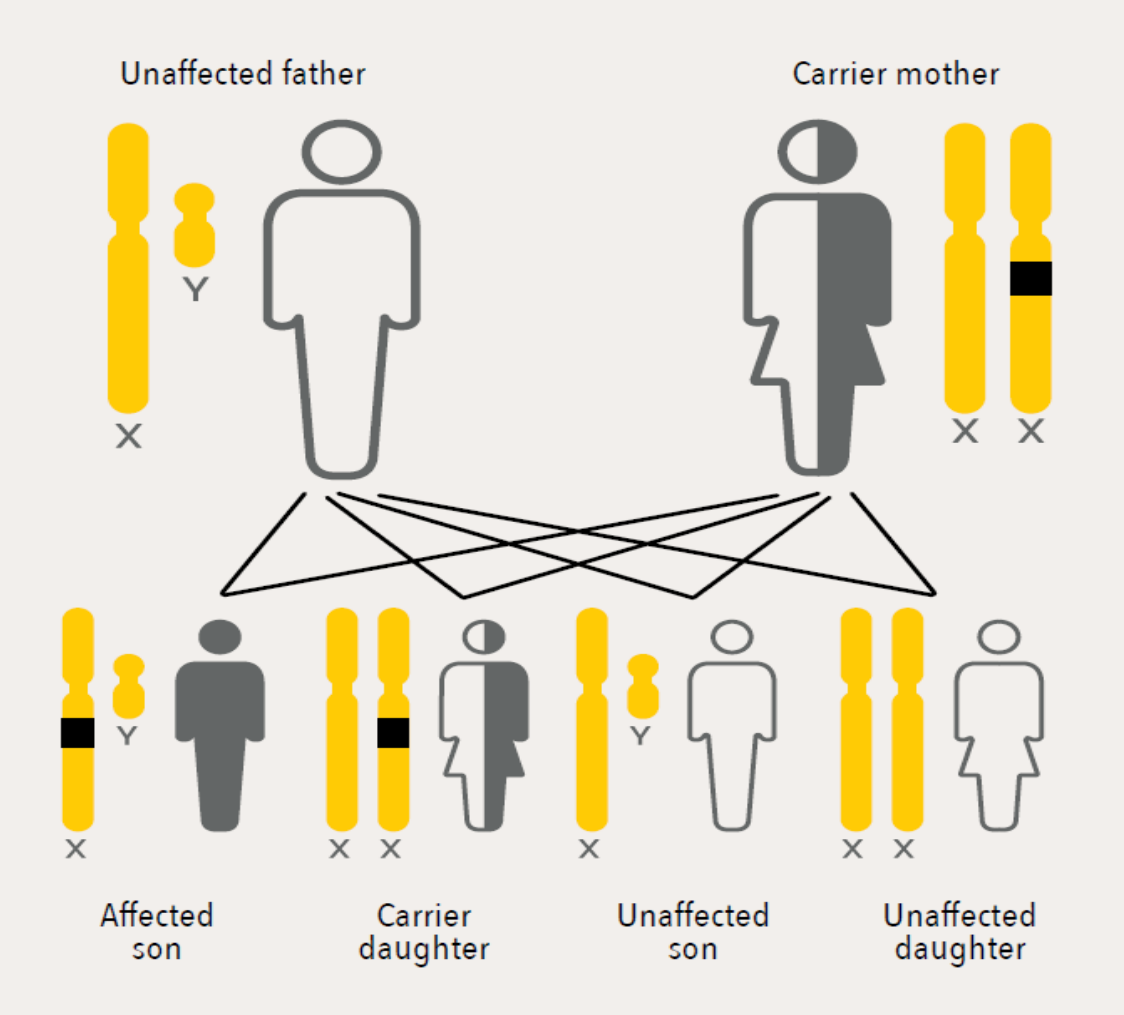
Screening a reproductive couple for **Autosomal Recessive** and **X-linked** conditions.





Reproductive Carrier Screening

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RANZCOG, 2018
Recommendation 3

Carrier screening for other genetic conditions should be offered to all women planning a pregnancy or in the first trimester of pregnancy.

*Options include screening with a **limited panel of the most frequent conditions** (e.g. cystic fibrosis, spinal muscular atrophy and fragile X syndrome) or screening with an **expanded panel** that contains many disorders (up to hundreds).*

RANZCOG: *Genetic carrier screening C-Obs 63*

Carrier screening for inherited genetic disorders	
Good practice note	Grade and supporting references
Preconception screening is preferable to antenatal screening for heritable genetic conditions as this potentially allows more options for carrier couples, including pre-implantation genetic diagnosis.	Good practice notes (consensus-based)

RANZCOG, 2018: Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions C-Obs 59

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Excellence in Women's Health

Is there only one carrier screening test?

Sample:
Blood/saliva/buccal (cheek swab)

Limited carrier screening	Expanded carrier screening
Three common genetic conditions: **Cystic fibrosis (CF)** **Spinal muscular atrophy (SMA)** **Fragile X syndrome (FXS)**	Hundreds of rare and serious, childhood onset genetic conditions (including the three common conditions)
~2-3 weeks for results	~4-6 weeks for results or more
Biological female first	Both members of reproductive couple at the same time
Bulk-billed – Medicare rebate (no out-of-pocket cost)	Out-of-pocket costs

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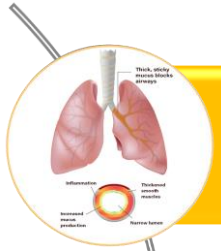
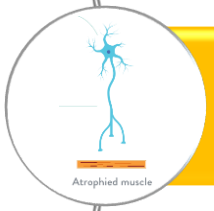
Carrier screening tests for…

Limited



Cystic fibrosis (CF)



Spinal muscular atrophy (SMA)

Fragile X syndrome (FXS)

Expanded

(including CF, SMA and FXS)

- Vision/ hearing
- Blood disorders
- Organs (liver/kidneys/lungs/brain)
- Metabolic disorders
- Developmental delay/intellectual disability
- Muscular conditions

3 gene screen What you need to know

Medicare rebate for 3 gene screen – CF, SMA and Fragile X

- Female first (to cover Fragile X (X-linked))
- If female carrier of CF or SMA > Male rebated screening
- Have to do sequentially for male to get rebate

How to order

- Most major path laboratories offering
  - Specific request forms and information sheets available
  - Use a lab with genetic counselling support

Counselling considerations

- If family history reported, indicate on form or refer on to clinical genetics/carrier screening genetic counselling services (public or private)
  - Limited to certain variants
  - More specific testing might be advised
- Fragile X associated phenotype in pre-mutation carrier females
  - Risk for POI and Fragile X tremor ataxia syndrome
- All results low risk, not no risk

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Expanded Carrier Screening

- Screening for a broad panel of conditions (generally 400+)
  - Childhood onset, severe conditions
  - Inclusion of ACMG listed genes
- Models
  - **Individual reporting** of carrier status
    - Reproductive risk summaries helpful
  - **Couple reporting** – "high risk" or "low risk" results
    - Individual carrier status not revealed
    - Mackenzie's Mission type reporting

RESULT: INCREASED REPRODUCTIVE RISK

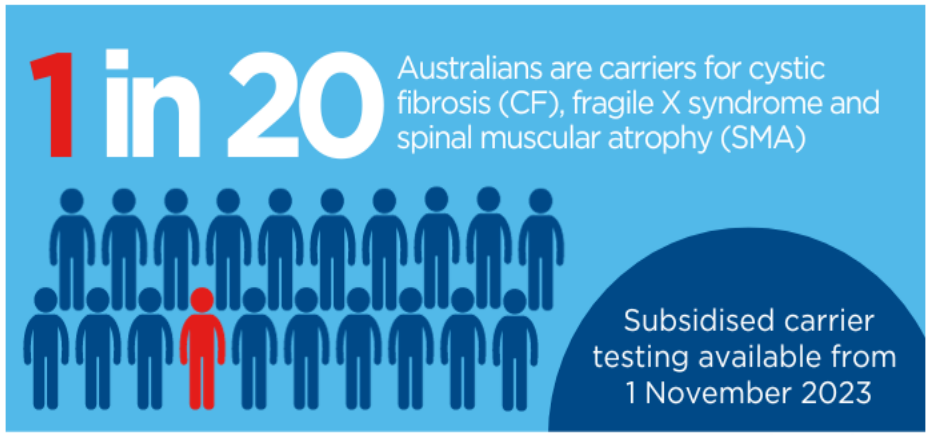
This summary combines the couple's carrier screening results to show their predicted reproductive risk of having a child with any of the tested conditions. The table below contains conditions where one or both partners screened positive. The couple screened negative for all other tested conditions. This summary provides a general risk assessment and is not intended to replace genetic counseling; risks may vary based on the specific results, ethnicity or family history.

CONDITION	PATIENT	PARTNER	REPRODUCTIVE RISK
FMR1-related conditions including fragile X syndrome Gene: FMR1 Inheritance: X-Linked	CARRIER Variant: c.-129_-127[95] (Tandem Repeat) PERSONAL RISK ⚠	NEGATIVE No disease-causing variants detected	**Increased risk** Genetic counseling is recommended as risk depends on several factors[1]
DHDDS-related conditions Gene: DHDDS Inheritance: Autosomal recessive	CARRIER Variant: c.124A>G (p.Lys42Glu)	CARRIER Variant: c.124A>G (p.Lys42Glu)	**Increased risk** 1 in 4(25%) chance of a child with this condition
DYSF-related conditions Gene: DYSF Inheritance: Autosomal recessive	CARRIER Variant: c.5083del (p.Gln1695Serfs*27)	NEGATIVE No disease-causing variants detected	**Low risk** 1 in 124,000 (less than 0.01%) chance of a child with this condition
SLC26A2-related conditions Gene: SLC26A2 Inheritance: Autosomal recessive	NEGATIVE No disease-causing variants detected	CARRIER Variant: c.835C>T (p.Arg279Trp)	**Low risk** 1 in 12,560 (less than 0.01%) chance of a child with this condition

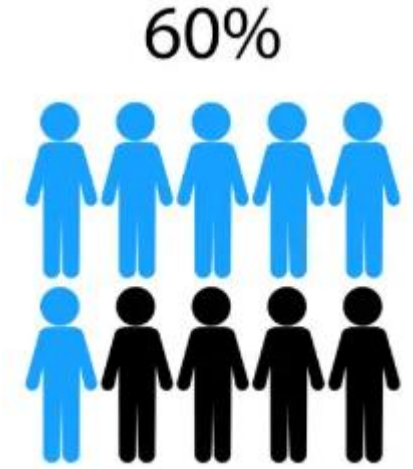
⚠ This result may impact this person's health. See the carrier screen report for more information.

(1) The chance to have a child with this condition, as well as the range/severity of symptoms, depends on several factors, including the sex of child and triplet repeat number.

Compare the pair: limited vs expanded



Approximately **1 in 240 (<1%)** Australian couples identified as high-risk of their child being born with CF, SMA or FXS



Around 3 in 5 people who have ECS will be identified as carriers of at least one condition

Approximately **1 in 50 (2%)** couples who have ECS (500+ gene screen) identified as high-risk of having a child with an inherited genetic condition

90% of carriers will have no reported family history

Westemeyer et al, 2020
ACMG, 2021
Archibald et al, 2018

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How to order?

eugene

https://eugenelabs.com/

VCGS

leaders in genetic health

https://vcgs.org.au

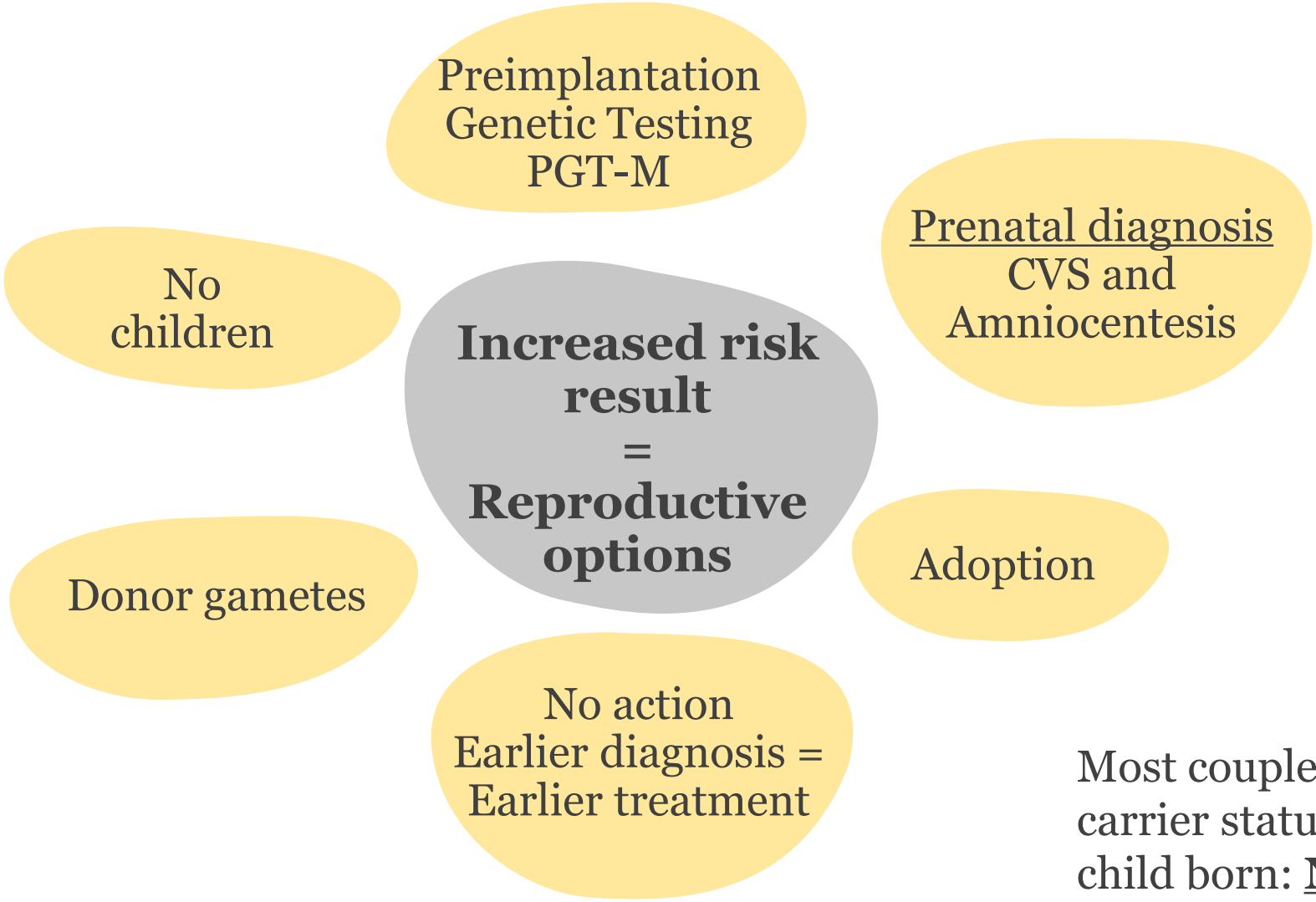
Sonic Genetics

https://sonicgenetics.com.au

lumi

https://www.lumihealth.com.au/

Genetic Carrier Screening
It's all about choice



Most couples first find out carrier status after affected child born: **No choice**

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Genea's high-risk carrier screening Genetic Counselling service

Free telehealth consultation with a Genea genetic counsellor available to *all couples with a high-risk carrier screening result* issued through any lab provider.

Discussion topics include:

- ✓ General information about the condition
- ✓ Reproductive options – including CVS and amniocentesis
- ✓ **Detailed and realistic information regarding process of Preimplantation Genetic Testing for Monogenic conditions (PGT-M)**

The benefits

- No referral required
- Free, accessible service Australia-wide
- No obligation to undertake PGT-M or prenatal testing – purpose is to provide you with the information you may need to make family planning decisions that are right for you as a couple

To refer:
Phone: 02 8484 6548
email: Genetic.counsellors@genea.com.au

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High-Risk Carrier Screen Result
Genetic Counselling Advice and Support

You have received a high-risk reproductive carrier screening result, what are your options?

If carrier screening has identified you as having an increased chance of having a child affected with one of the conditions screened, there are several reproductive options available to you, including:

1. **Test your child at birth** – there are conditions where early diagnosis and treatment can improve outcomes for a child born with certain genetic conditions.

2. **Prenatal Diagnosis** – there are tests which can be performed after you become pregnant (from around 12 weeks) called a CVS and amniocentesis. This option is highly accurate however may require you to make decisions during a pregnancy and as they are invasive, there are associated risks to the pregnancy.

3. **Pre-Implantation Genetic Testing** for monogenic conditions (PGT-M) – PGT-M is a test performed on embryos created via IVF for the condition you have an increased risk for. Only embryos identified as unaffected for the condition tested are transferred.

To obtain more information about your options and details about PGT-M, you can book a no obligation free video consultation with a Genea Genetic Counsellor.

To make an appointment please follow the QR code or email genetic.counsellors@genea.com.au
For any questions, please call 02 8484 6548

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Case Study 1

Clinical Scenario

- Sarah and Thomas: Non-consanguineous couple, English ancestry
- G1P0
- Fhx: Sarah's sister has a son with Cystic Fibrosis
- Following discussion decided to proceed with expanded carrier screening for 500+ autosomal recessive and X-linked conditions
- Expanded panel included full gene sequencing of the CFTR gene (covered the familial variant)

Case Study 1

Outcome

- Sarah was found to be a carrier of the familial CFTR variant
- Tom was found to be a carrier of oculocutaneous albinism (OCA2 gene) and not a carrier of Cystic Fibrosis

*As they are not carriers of the **same condition**, this is a **low-risk** result*

Benefits of doing expanded screening:

- Included entire CFTR gene sequencing
- Reproductive confidence

Case Study 2

Clinical Scenario

- Emma and Jacob: Non-consanguineous couple, Ashkenazi Jewish ancestry
- G3P2
- No significant Fhx reported
- Underwent free 3 gene carrier screening

Case Study 2 - Results

Outcome

- Emma and Jacob are not identified as carriers of any of the 3 conditions

*This is a **low-risk** result*

- Conceived naturally. Emma gives birth to a baby girl.
- Gaucher Disease identified on newborn screening
  - Autosomal Recessive lysosomal storage disorder
  - Trio genetic testing confirms Emma and Jacob are both carriers
  - Discussion of reproductive options for future pregnancies

Case Study 3

Clinical Scenario

- Mariam and George: consanguineous couple (first cousins), Lebanese background
- G2P1
- Increased chance of high risk result
- Following discussion, undergo expanded (500+) carrier screening

Case Study 3 - Results

Outcome

- Mariam and George and both found to be carriers of the same GAA genetic variant
- Therefore, high risk (25%) of Pompe Disease
- Autosomal recessive condition, causes progressive weakness to the heart and skeletal muscles
- Referred to Genea for a free GC consult

Reproductive Options:

1. PGT-Monogenic
2. Prenatal Testing
3. Newborn screening (only covers certain conditions)

- Following discussions elect to proceed with IVF/PGT-M to implant an embryo with one or no copies of the GAA familial variant
- If family members are available for linkage testing, accuracy can be >99%

Conception

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Preimplantation Genetic Testing (PGT)

PGT-M (Monogenic)

- Previously Preimplantation Genetic Diagnosis (PGD)

PGT-A (Aneuploidy)

- Previously Preimplantation Genetic Screening (PGS)

PGT-SR (Structural Rearrangement)

- For balanced translocation carriers

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PGT – M

Indications

- Known genetic disorder
- Single gene target
- Exclusion testing

e.g., Huntington's disease*, BRCA1/2, cystic fibrosis

*option for exclusion testing

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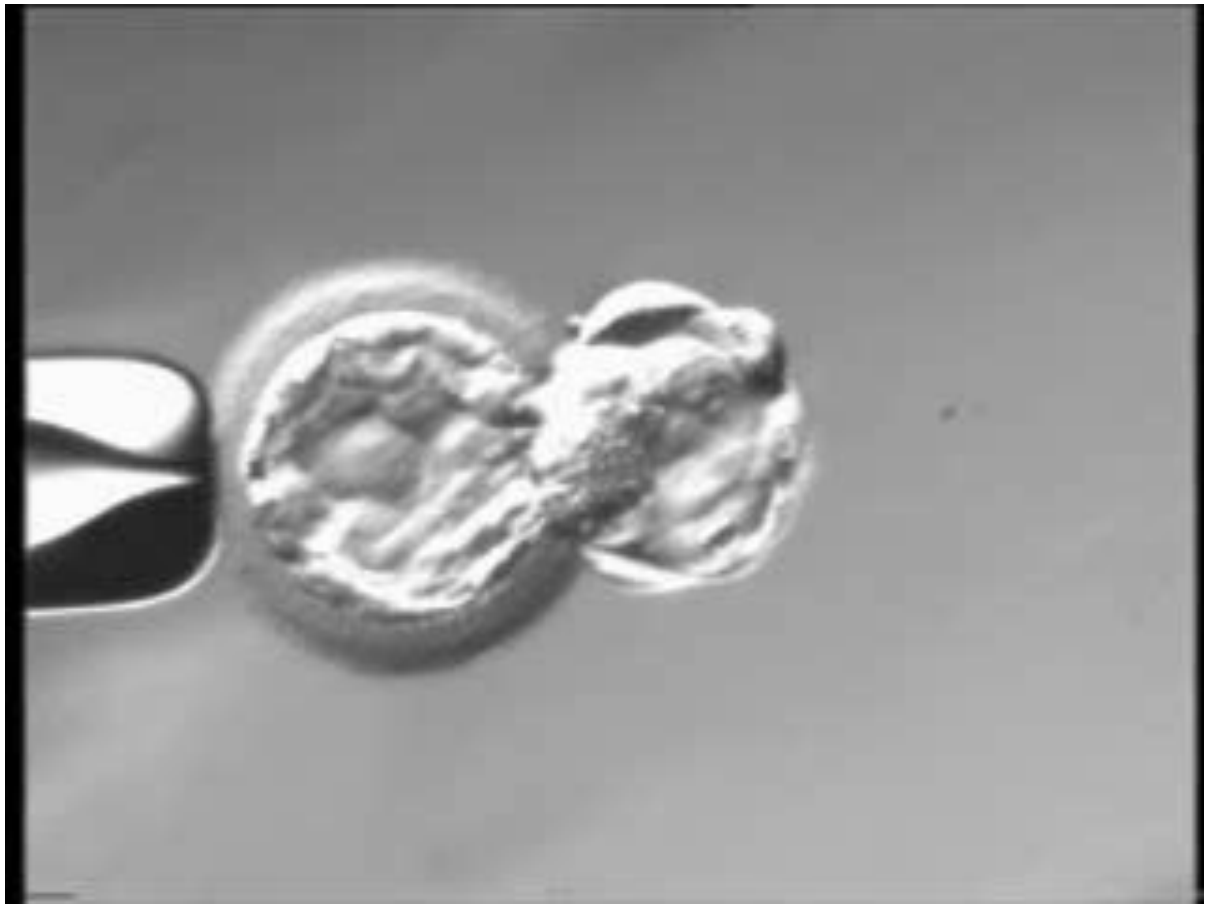
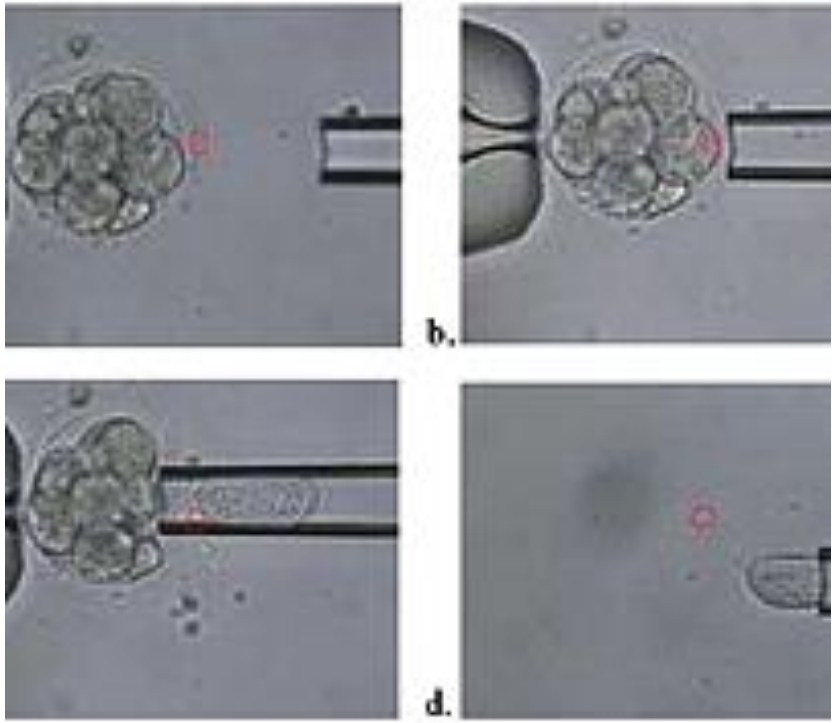
Blastocyst Biopsy

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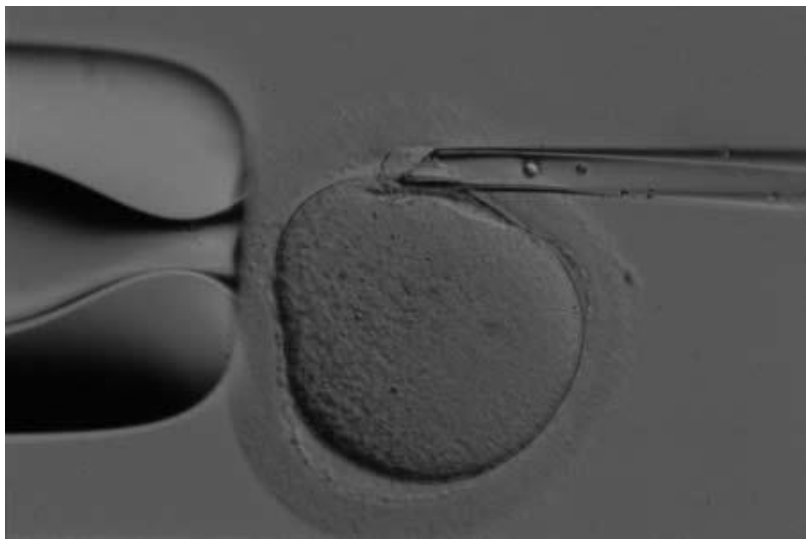

Pre-implantation Genetic Testing for monogenic/single gene disorders – PGT-M

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Genetic testing of embryos for the variants identified through carrier screening, or diagnostic genetic testing for single gene disorders running in family

Accuracy ranges from up to 90% - 99%

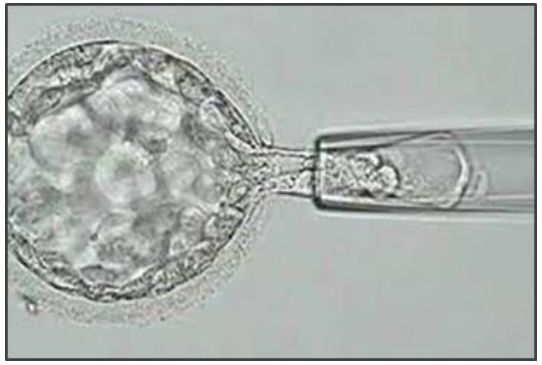
Karyomapping or PCR methods - **Familial controls required**

Work up time required – 6-12 weeks

Aneuploidy detection (PGT-A) built into platform

Misdiagnosis can occur - Confirmation via CVS/Amnio should be discussed

Advisable for couple to have genetic counselling before referring for PGT-M – for some conditions couples may not elect PGT due to mild or variable expression e.g., hearing loss variants GJB2



Pros: avoid pregnancy and birth of a child with a serious genetic condition, avoid decision whether to stop a pregnancy

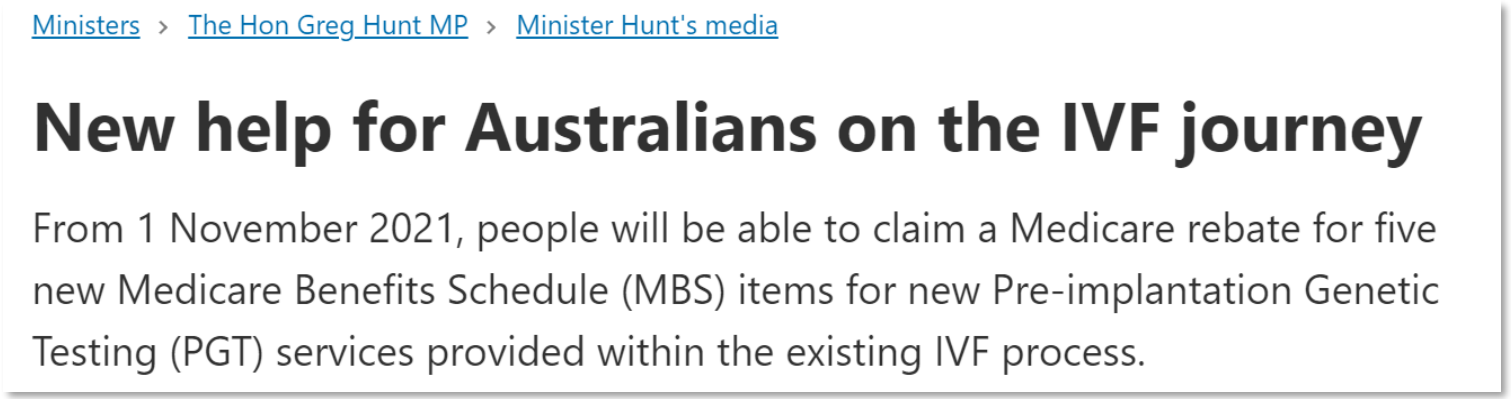
Cons: expense, medical process, no guarantee of unaffected embryos/ongoing pregnancy, need for testing other family members therefore disclosing reproductive plans

PGD: Medicare rebate

(a) the patient or the patient's reproductive partner: has an identified gene variant which places the patient **at risk of having a pregnancy affected by** a **Mendelian or mitochondrial disorder, an autosomal dominant disorder or a chromosome disorder.**

(b) **there is no curative treatment** for the disorder and there is severe limitation of quality of life despite contemporary management of the disorder.

(c) the **patient has previously had a consultation**, with a specialist or consultant physician practising as a **clinical geneticist**, that included a discussion about the disorder. Medicare rebates are restricted to one PGT test per embryo produced during a single Assisted Reproductive Treatment (ART) cycle. Genetic tests must be requested by a specialist or consultant physician. Item details found at MBS Online



Ministers › The Hon Greg Hunt MP › Minister Hunt's media

New help for Australians on the IVF journey

From 1 November 2021, people will be able to claim a Medicare rebate for five new Medicare Benefits Schedule (MBS) items for new Pre-implantation Genetic Testing (PGT) services provided within the existing IVF process.

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Patient timeline: IVF and PGT-M Cycle

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PGT (pre-treatment) – up to 2 months to "work up" the test

Referral to Fertility specialist
- Include relevant reports
- Carrier screening, genetic letters and karyotypes if done

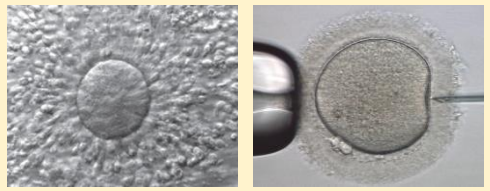
Genetic Intake in lab
- Confirm details about specific genetic disease
- Identify AFF/carrier individuals
- Discuss workup timeframe and cost with patient

Consults
- Geneticist consult
- Nursing
- Counsellor

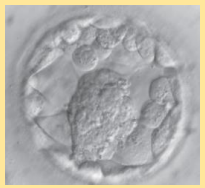
Workup
- 6-12 weeks depending on testing technique used

PGT (treatment cycle)

Egg collection /insemination



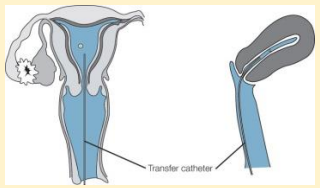
Grow to day 5/6



Trophectoderm biopsy 5-10 cells

Freeze and test biopsied cells

Transfer of unaffected embryo



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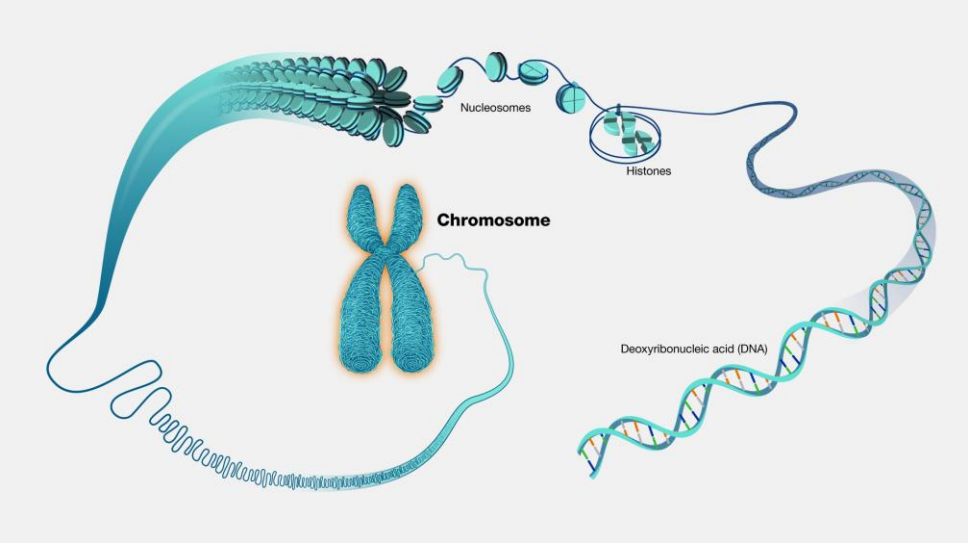
Preimplantation Genetic Testing for Aneuploidy PGT – A

Indications

- Screening
- Previous implantation failures
- Recurrent pregnancy loss



ACCEPT RPL Guidelines 2023

"There is some evidence to support the use of PGT-A and subsequent euploid embryo transfer, as a means of reducing further pregnancy loss."

- Level III-2

HFEA, 2023

- On balance, findings from high quality evidence shows this add-on is effective at reducing the chances of miscarriage for most fertility patients
- For most fertility patients, the use of PGT-A is rated red for improving the chances of having a baby.

Pre-Implantation Genetic Testing – Aneuploidy (PGT-A or PGS)

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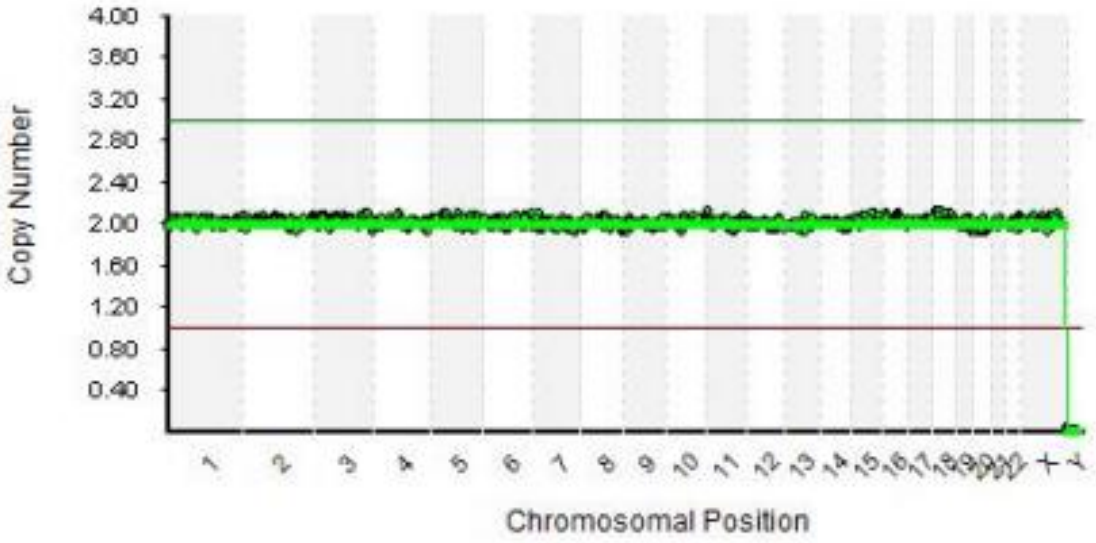
- Available to all couples having IVF
- NGS used to screen for aneuploidy on day 5/6 biopsied embryo
- 90 - 95% accurate
- Best performance in >38yr age group

Euploid (NAD)

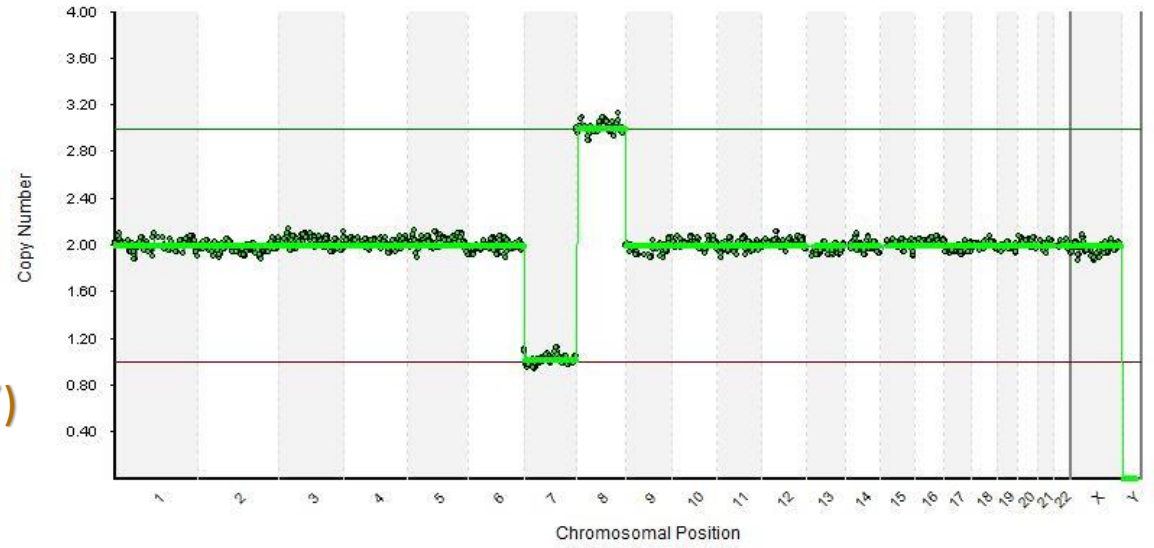


3 copies ('trisomy')

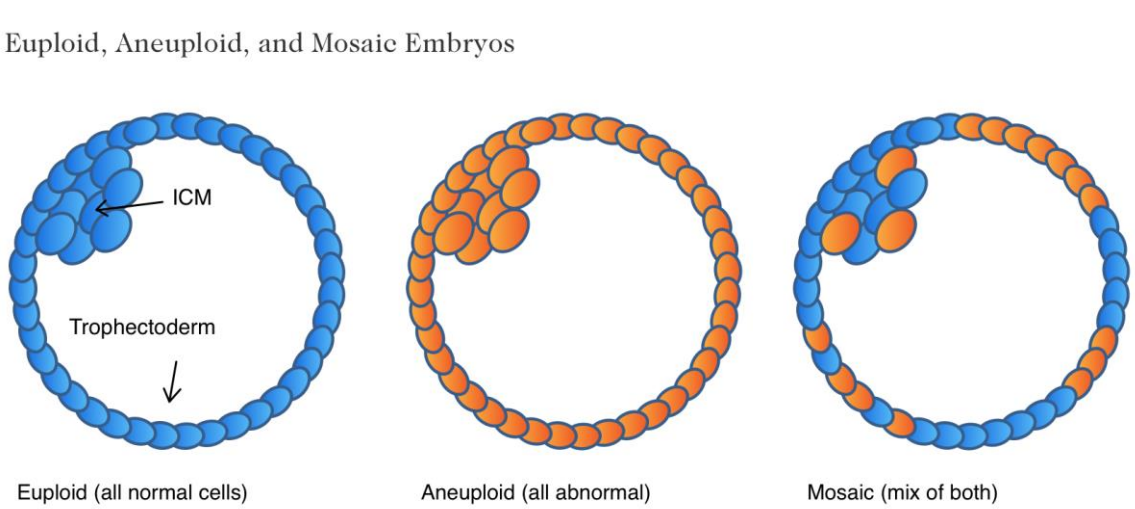
2 copies

1 copy 'monosomy')

Aneuploid (abnormal)



PGT-A Result categories



Euploid No Aneuploidy Detected (NAD)	• Preference for transfer • 95% accuracy • Prenatal screening still recommended
Aneuploid Abnormal	• Not suitable for transfer • Re-biopsy not recommended – low chance of false positive (<1%)
Mosaic embryo level of aneuploid cells detected (e.g. 40-80%)	• Available for transfer • Reduced chance implantation and live birth • Higher chance miscarriage • Small chance of pregnancy with aneuploidy • Rebiopsy not recommended • Amniocentesis recommended • Genetic counselling recommended

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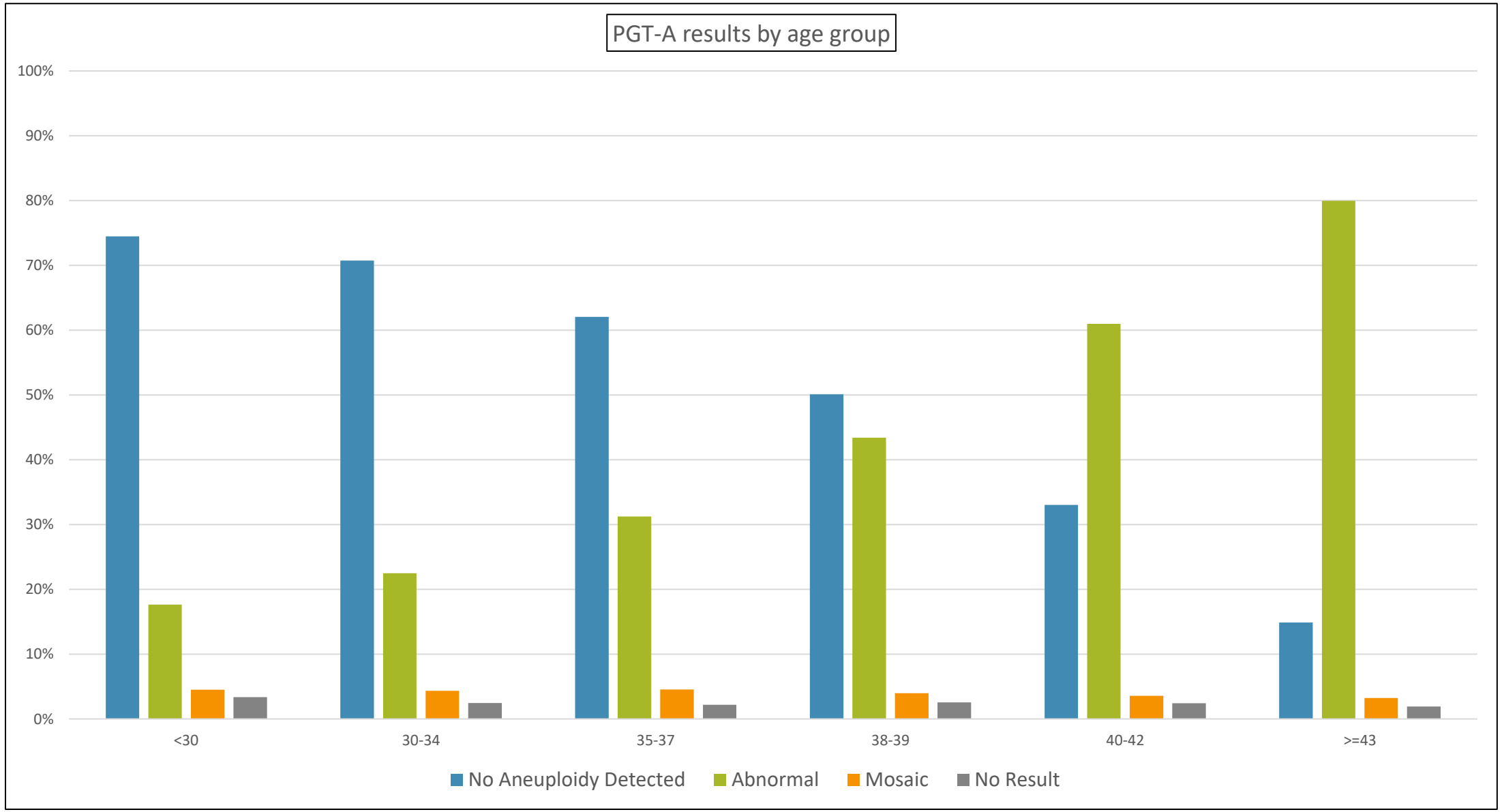

Genea data: July 2018- Dec 2023, Fresh cycles only, Women using own eggs

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Mosaic Embryos: Newborn and prenatal outcomes in the literature

- Low risk not no risk…
- Growing case reports of mosaicism persisting in ongoing pregnancy

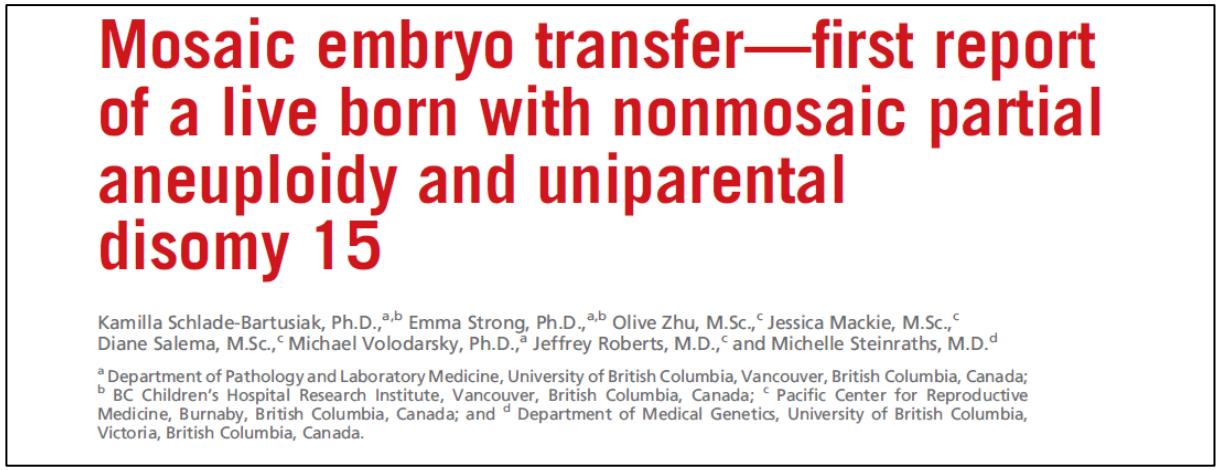
human reproduction

CASE REPORT *Reproductive genetics*

The birth of a baby with mosaicism resulting from a known mosaic embryo transfer: a case report

Semra Kahraman*, Murat Cetinkaya, Beril Yuksel, Mesut Yesil, and Caroline Pirkevi Cetinkaya

Istanbul Memorial Hospital, Assisted Reproductive Technologies and Reproductive Genetics Center, Piyale Pasa Bulvari 34385, Sisli, Istanbul, Turkey



Mosaic embryo transfer—first report of a live born with nonmosaic partial aneuploidy and uniparental disomy 15

Kamilla Schlade-Bartusiak, Ph.D.,[a,b] Emma Strong, Ph.D.,[a,b] Olive Zhu, M.Sc.,[c] Jessica Mackie, M.Sc.,[c] Diane Salema, M.Sc.,[c] Michael Volodarsky, Ph.D.,[a] Jeffrey Roberts, M.D.,[c] and Michelle Steinraths, M.D.[d]

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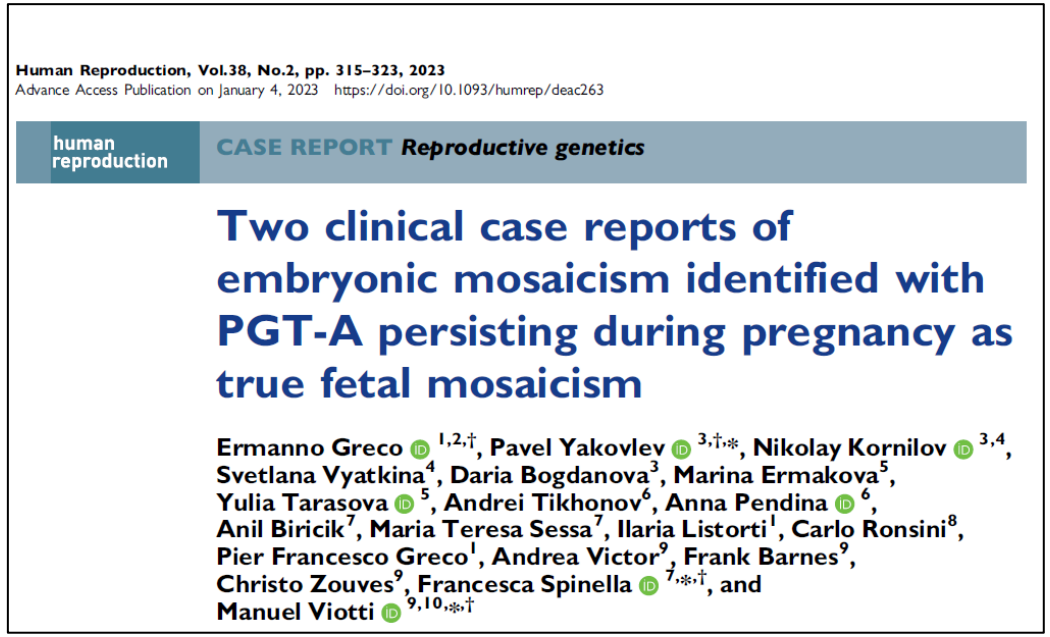

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human reproduction

CASE REPORT *Reproductive genetics*

Two clinical case reports of embryonic mosaicism identified with PGT-A persisting during pregnancy as true fetal mosaicism

Ermanno Greco [1,2,†], Pavel Yakovlev [3,†,*], Nikolay Kornilov [3,4], Svetlana Vyatkina[4], Daria Bogdanova[3], Marina Ermakova[5], Yulia Tarasova [5], Andrei Tikhonov[6], Anna Pendina [6], Anil Biricik[7], Maria Teresa Sessa[7], Ilaria Listorti[1], Carlo Ronsini[8], Pier Francesco Greco[1], Andrea Victor[9], Frank Barnes[9], Christo Zouves[9], Francesca Spinella [7,*,†], and Manuel Viotti [9,10,*,†]

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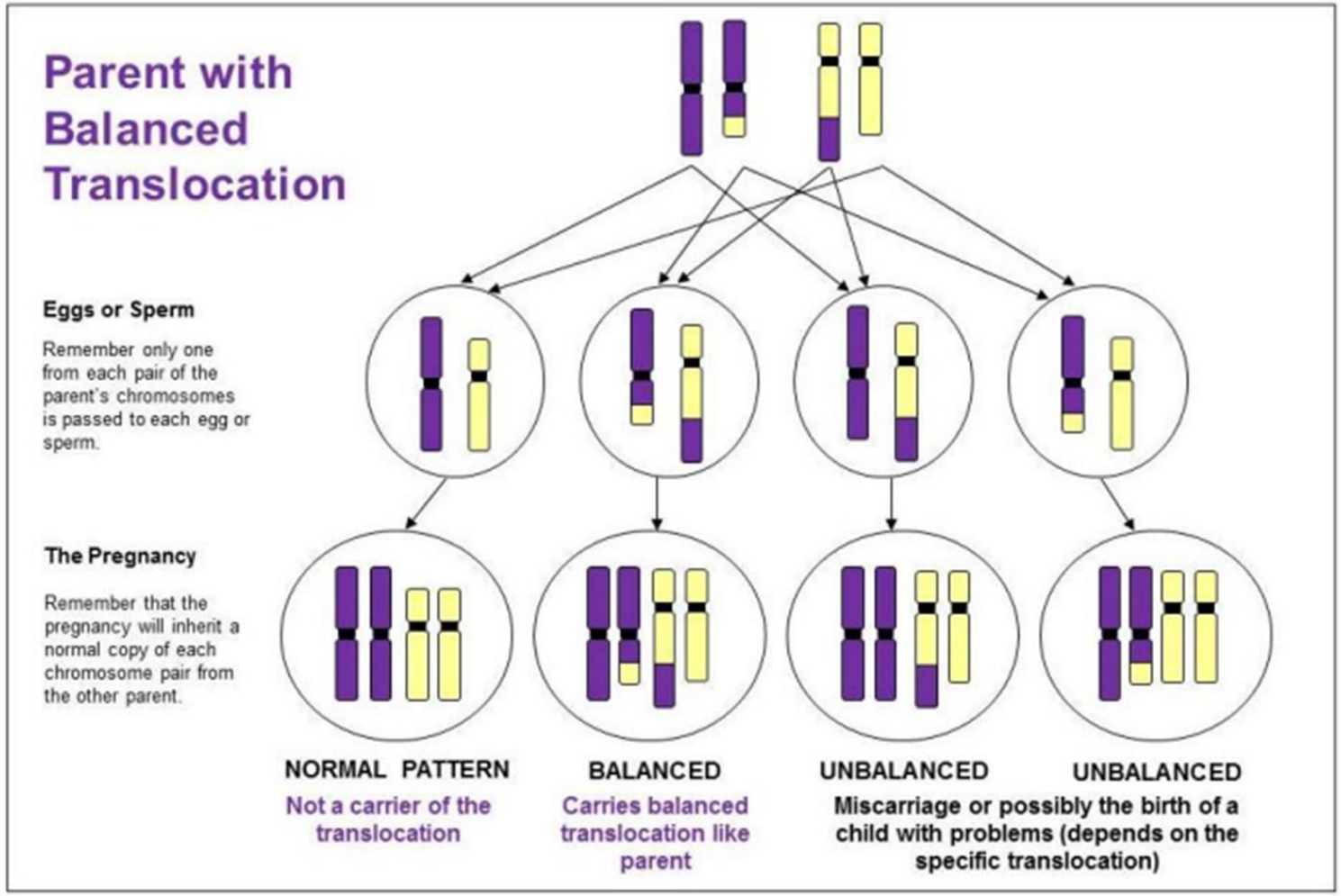
Preimplantation Genetic Testing for Structural Rearrangments
PGT – SR

Balanced Translocations



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PGT Structural rearrangements (PGT-SR)

- Indications – inversions, balanced translocations
- Pre-implantation Genetic Testing option for parental balanced translocation carriers
- 95-99% accurate
- NGS testing to identify unbalanced vs balanced embryos
- Generally no test work up required
- Additional testing requires work up, extra time and cost
  - **Breakpoint testing** can identify translocation carrier embryos vs embryos without the balanced translocation
    - only an option if enough embryos available
  - **UPD** – can confirm biparental inheritance
- Screens all other chromosomes at the same time

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Prenatal

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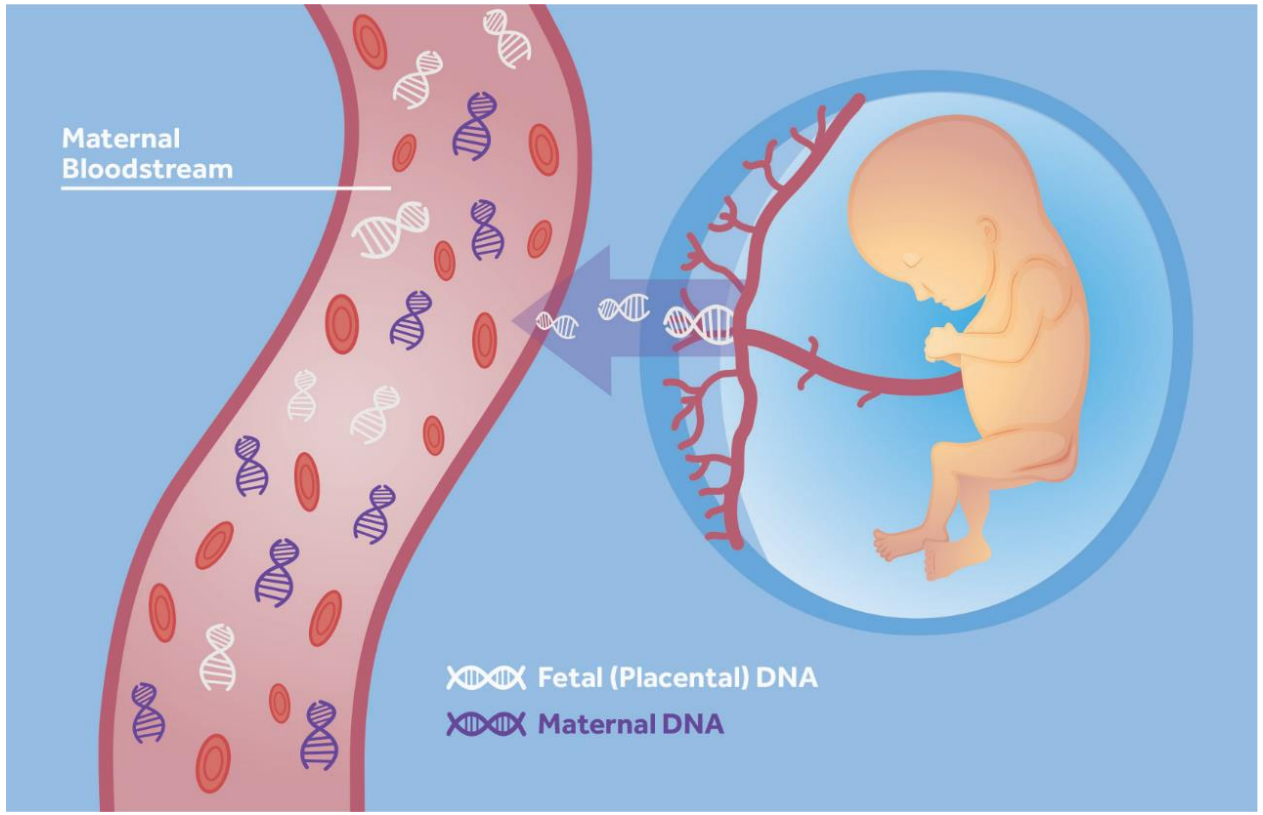
Non-Invasive Prenatal Testing

NIPT – How does it work



- Maternal blood test from 10 weeks gestation
- Many providers offering different levels of screening
  - Common aneuploidies or all chromosomes, microdeletions
- Whole Chromosome Screen
  - common and rare aneuploidies
  - segmental aneuploidies

Whole Genome NIPT

- WGS/NGS based technology
- Common Trisomies -21, 13 and 18
- Sex/Sex Chromosome variations

→**Rare autosomal aneuploidies (RAAs)**

  - Prevalence: ~1 in 300
  - PPV ~4.1-23%

→**Partial deletions/duplications (>7Mb) (Segmental Aneuploidies)**

  - PPV ~30-47%

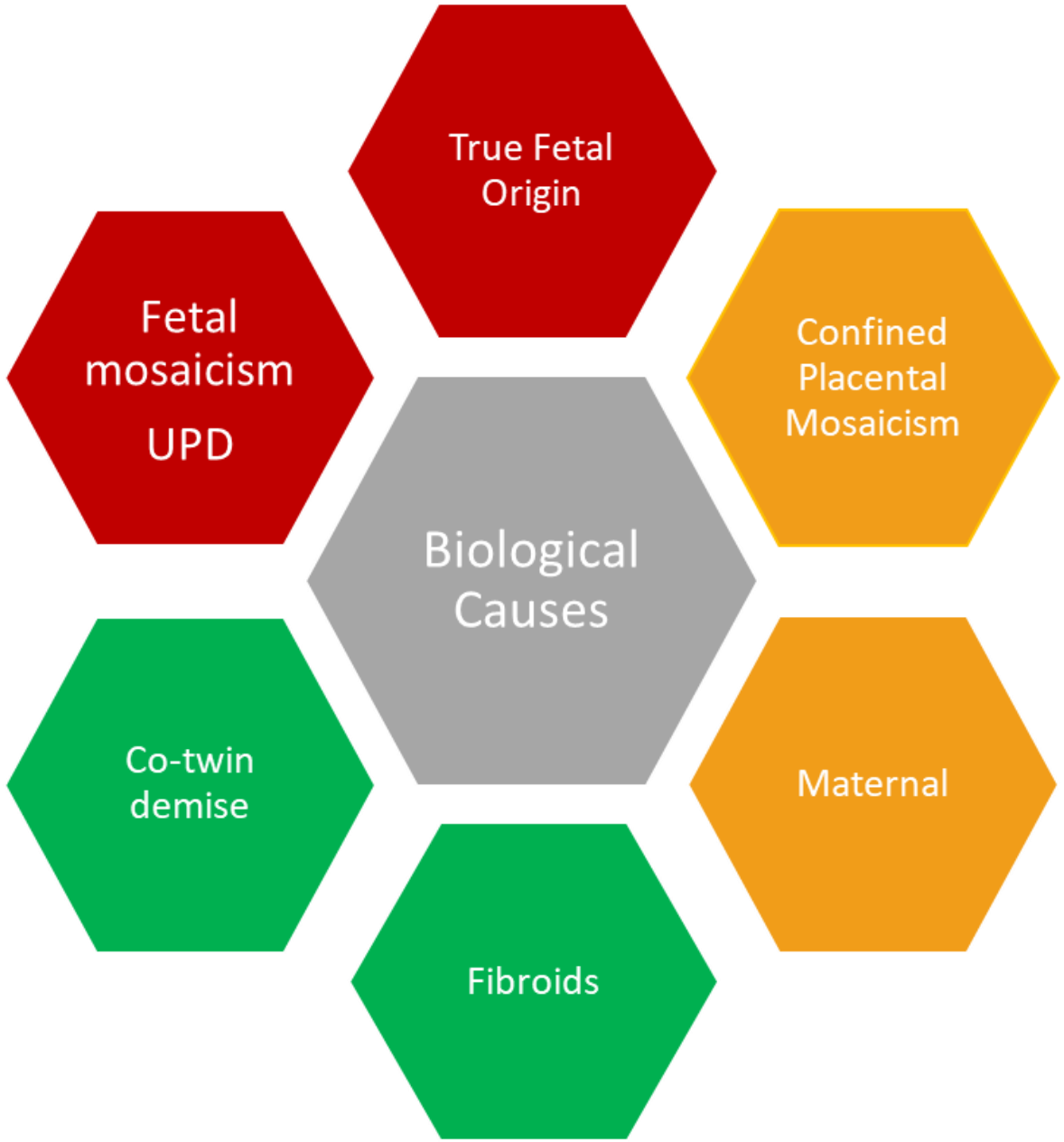
- Some services able to offer screening for unbalanced **translocations**

Figure S4. **Typical autosome-wide profiles for a healthy NIPT sample.**

Figure S6. **Typical autosome-wide profiles for a trisomy 21 NIPT sample.**

Ramen et al (2019)

Counselling Considerations for a High Risk NIPT result



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NIPT: What do couples need to know?

Screening not diagnostic
Importance of including ultrasound (11-14 week ultrasound & morphology scan)
Amniocentesis over CVS in the setting of normal US findings
Accuracy for Trisomy 21 versus inaccuracy of other aneuploidies
Possible anxiety / false reassurance
Multiple test fails = increased risk aneuploidy
Not the same as carrier screening – doesn't screen for Cystic Fibrosis, Fragile X etc.
Possibility of identifying maternal chromosomal issue

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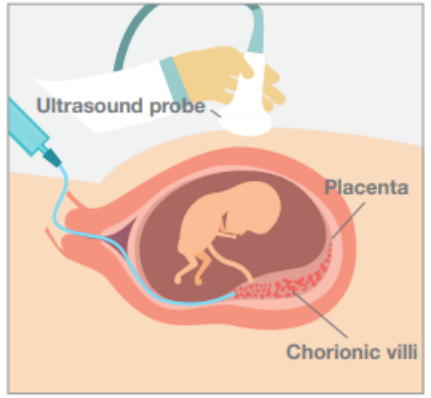
Prenatal diagnosis
CVS and Amniocentesis

Diagnostic for aneuploidy and single gene disorders

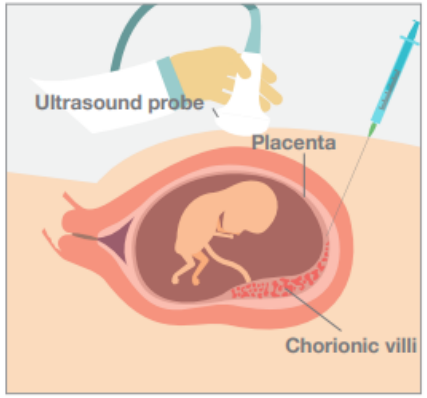
- **CVS**
  - 11-14 weeks gestation
  - Risks ~1% miscarriage
  - ~2 week result TAT

- **Amniocentesis**
  - 15 weeks onwards
  - Risks ~0.5% miscarriage
  - ~2 week result TAT, maybe longer

Prenatal diagnosis may require test work up for rare conditions identified on carrier screening
<u>= Increase in wait times for results</u>

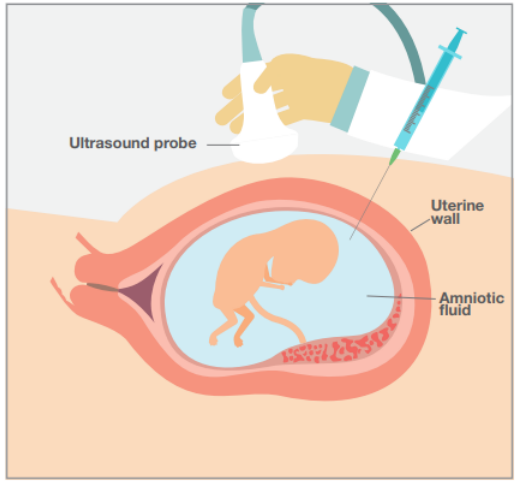


Transcervical CVS



Transabdominal CVS

Amniocentesis



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Thank you