PACIFIC COAST REPRODUCTIVE SOCIETY

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INNOVATION AND INTEGRATION

THE FUTURE OF REPRODUCTIVE MEDICINE

Embryo Selection in the Genomic Era

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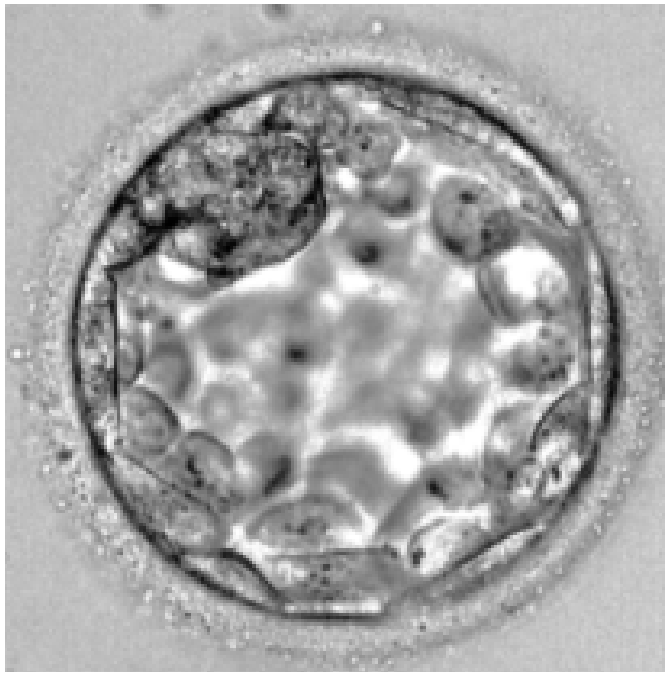
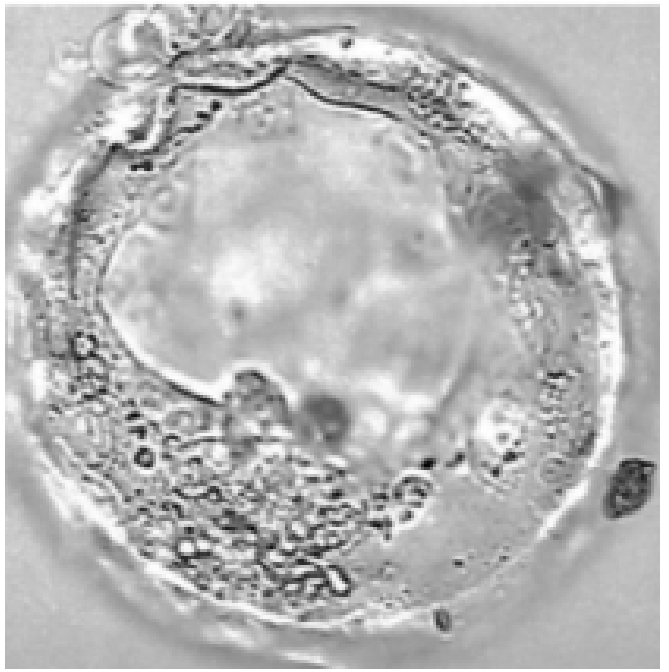
I have nothing to disclose.

Learning Objectives

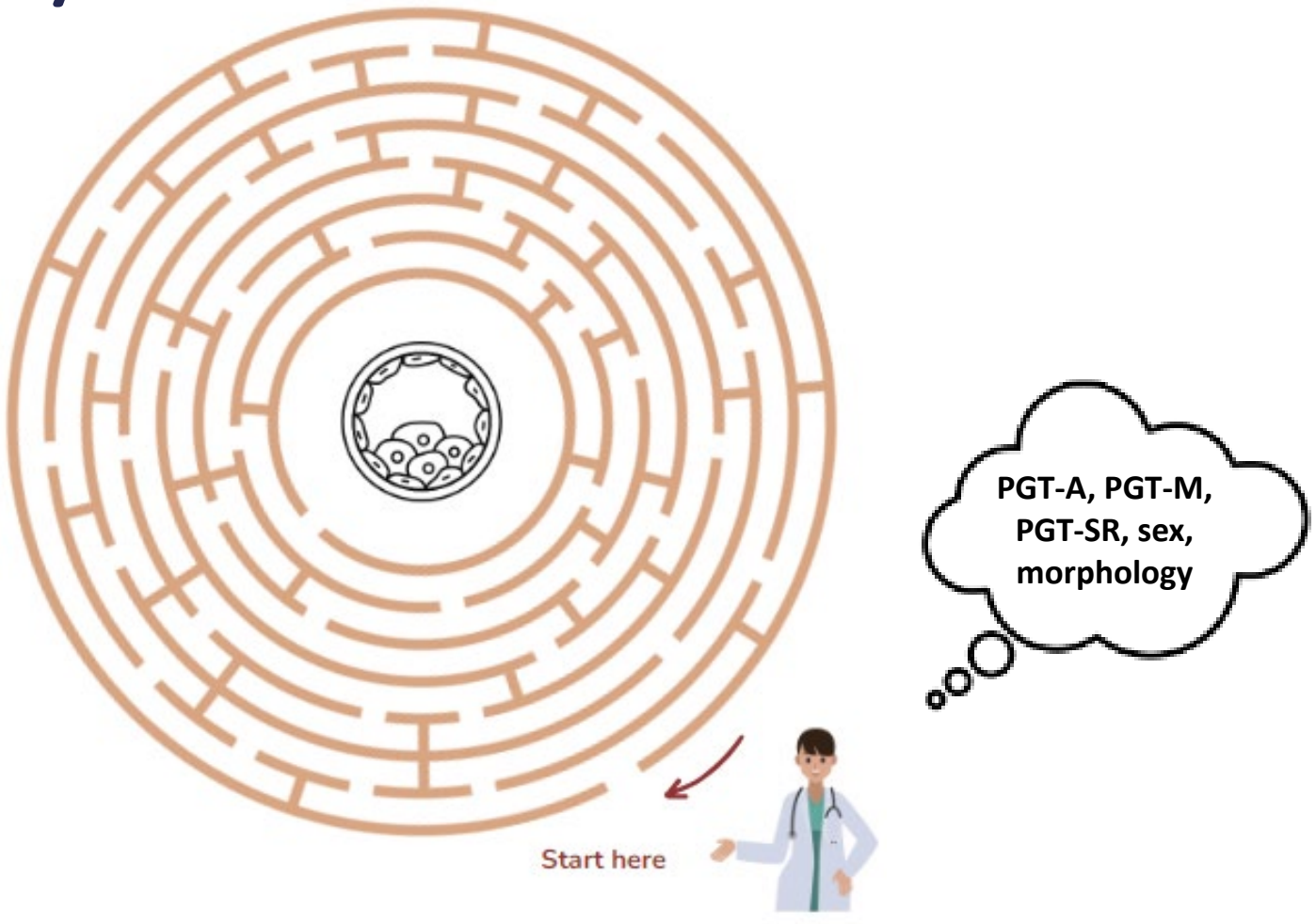
- Analyze possible results after PGT-A or PGT-M testing and their clinical significance.
- Recognize the stakeholders in decision-making surrounding embryo transfer after genetic testing and their different roles.
- Propose strategies for embryo selection after genetic testing that align with optimal patient care.

The Old Days of Embryo Selection





The Modern Day



The Future of PGT Reports

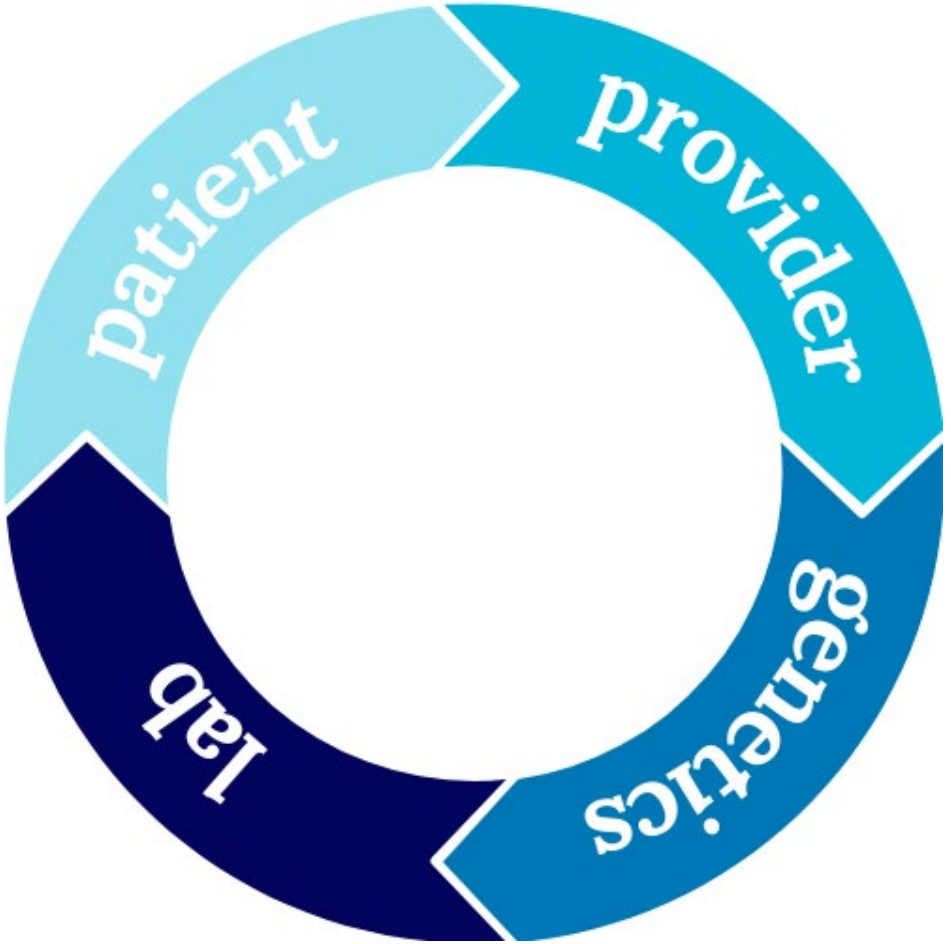
Embryo	Sample ID	Aneuploidy (PGT-A) results	Aneuploidy (PGT-A) details	Sex	Status of the maternal *FMR1* expansion haplotype (PGT-M)	Status of the *LCA5* c.516_519del AGAA variant (PGT-M)	Status of the *LCA5* c.835C>T variant (PGT-M)	Leber Congenital Amaurosis 5 interpretation (PGT-M)	Status of the *TOR1A* c.907_909delGAG variant (PGT-M)	Status of the 231kb (2,927,007-3,158,767) gain on 17p13.3
28	78855a28	Negative	No whole chromosome aneuploidy detected	Female	Negative	Heterozygous Positive	Negative	Heterozygous Positive	Heterozygous Positive	Not detected
29	78855a29	Negative	No whole chromosome aneuploidy detected	Female	Negative	Negative	Negative	Negative	Heterozygous Positive	Not detected
31	78855a31	Negative	No whole chromosome aneuploidy detected	Female	Negative	Negative	Heterozygous Positive	Heterozygous Positive	Heterozygous Positive	Not detected
32	78855a32	Negative	No whole chromosome aneuploidy detected	Male	Hemizygous Positive	Negative	Heterozygous Positive	Heterozygous Positive	Negative	Not detected
36	78855a36	Negative	No whole chromosome aneuploidy detected	Female	Negative	Negative	Heterozygous Positive	Heterozygous Positive	Heterozygous Positive	Detected
37	78855a37	Positive	-15	Male	Hemizygous Positive	Negative	Negative	Negative	Negative	Detected
38	78855a38	Negative	No whole chromosome aneuploidy detected	Female	Heterozygous Positive	Negative	Heterozygous Positive	Heterozygous Positive	Heterozygous Positive	Not detected

A Call to Action

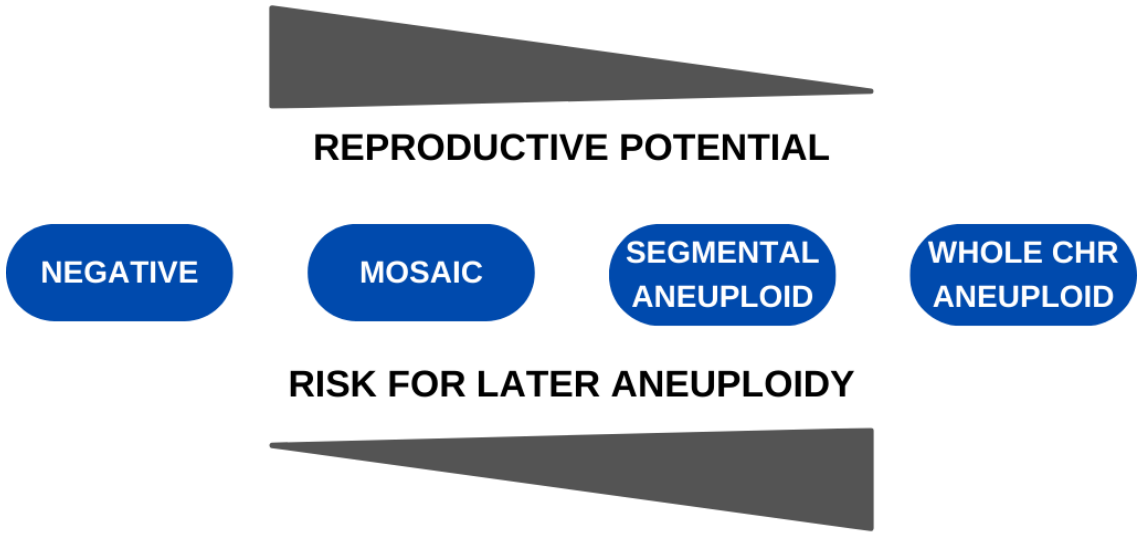
- The uptake of preimplantation genetic testing is increasing and outpacing that of prenatal diagnosis[1][2].
- Transfer of embryos with positive PGT-M results are occurring, albeit typically with adult-onset or milder conditions[3].
- Transfer of embryos with PGT-A results of unknown reproductive potential (i.e.: mosaicism or segmental aneuploidy) or of poor reproductive potential (i.e.: whole chromosome aneuploidy) are occurring[4][5].

A Call to Action

- Most legal action to date involving PGT-M has circled around misdiagnosis[6, 7, 8].
- *Diaz v. Huntington Reproductive Center Medical Group* alleged transfer of embryo known to be CDH1+ after couple requested transfer of BRCA1+, CDH1- male. Case moved to arbitration in August 2023[9].
- Without thorough protocols in place, IVF clinics will become increasingly vulnerable to PGT-related claims.


patient
provider
genetics
lab

PGT-A



- Mosaic results:
  - Reduced reproductive potential?[5][12]
  - Low chance to result in child with mosaicism - ~1%[5]
- Segmental aneuploid results:
  - Initial reports of lower reproductive potential.
  - Chance for adverse outcome unknown.
  - Very limited information here!
- Clinics should have policies on transfer of embryos with mosaic[10] or segmental aneuploid[me] results.
  - What about sex preference?
  - What about differences in SIR due to morphology?

Importance of Genetic Counseling

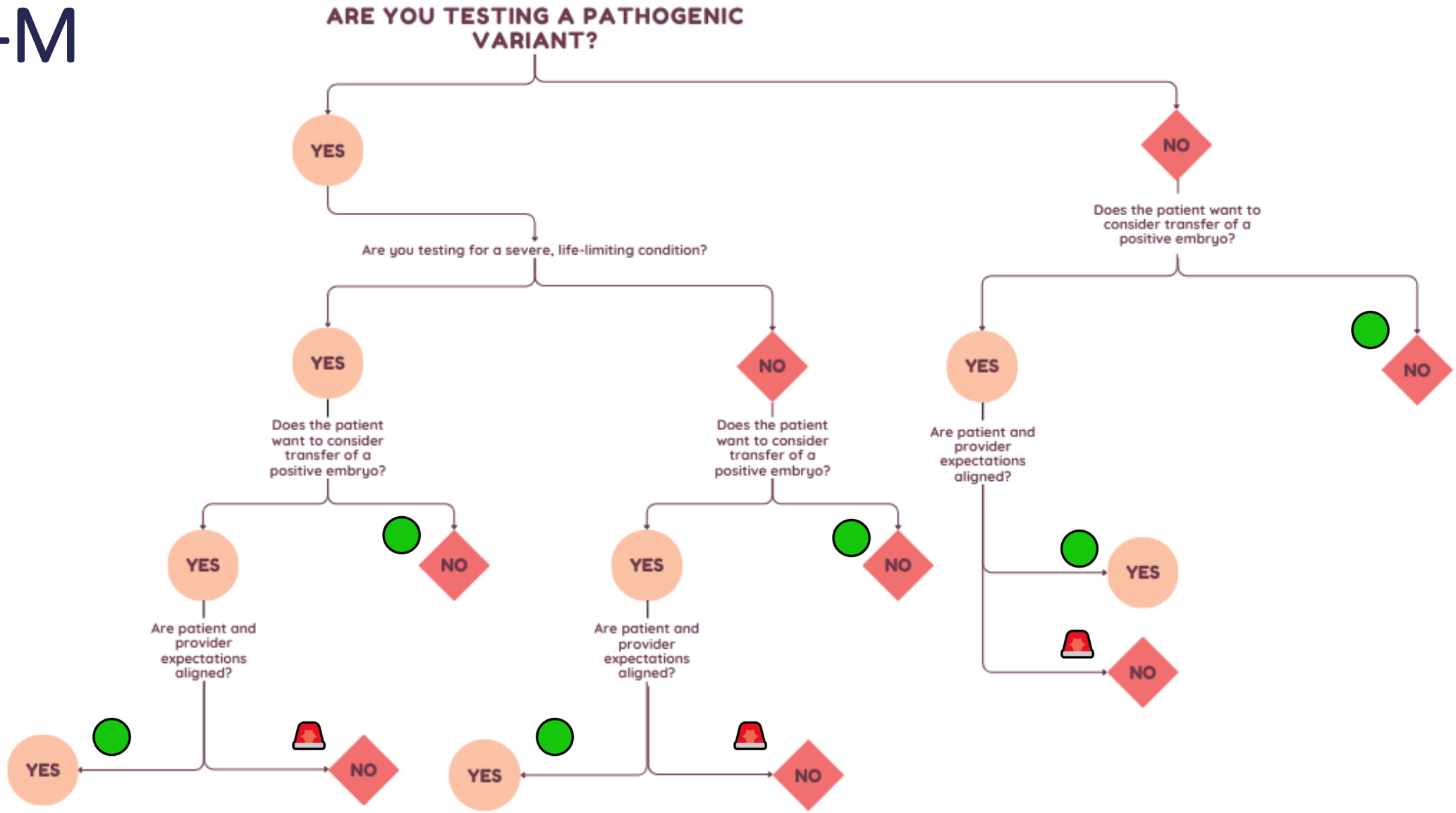
Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion

“.. patients who wish to consider transfer of an embryo diagnosed as mosaic [...] should receive comprehensive genetic counseling [by a genetics specialist] regarding this diagnosis and its uncertainties.”

PGT-M

- PGT-M increasingly being used as an embryo ranking tool.
- Situations where PGT-M positive transfer requests may be made:
  - Variants of uncertain significance.
  - Findings associated with reduced penetrance or variable expressivity.
  - Findings that will cause a mild presentation.
- ASRM Ethics Committee recommends clinics have policies on handling these requests and defers decisions to providers[13].

PGT-M

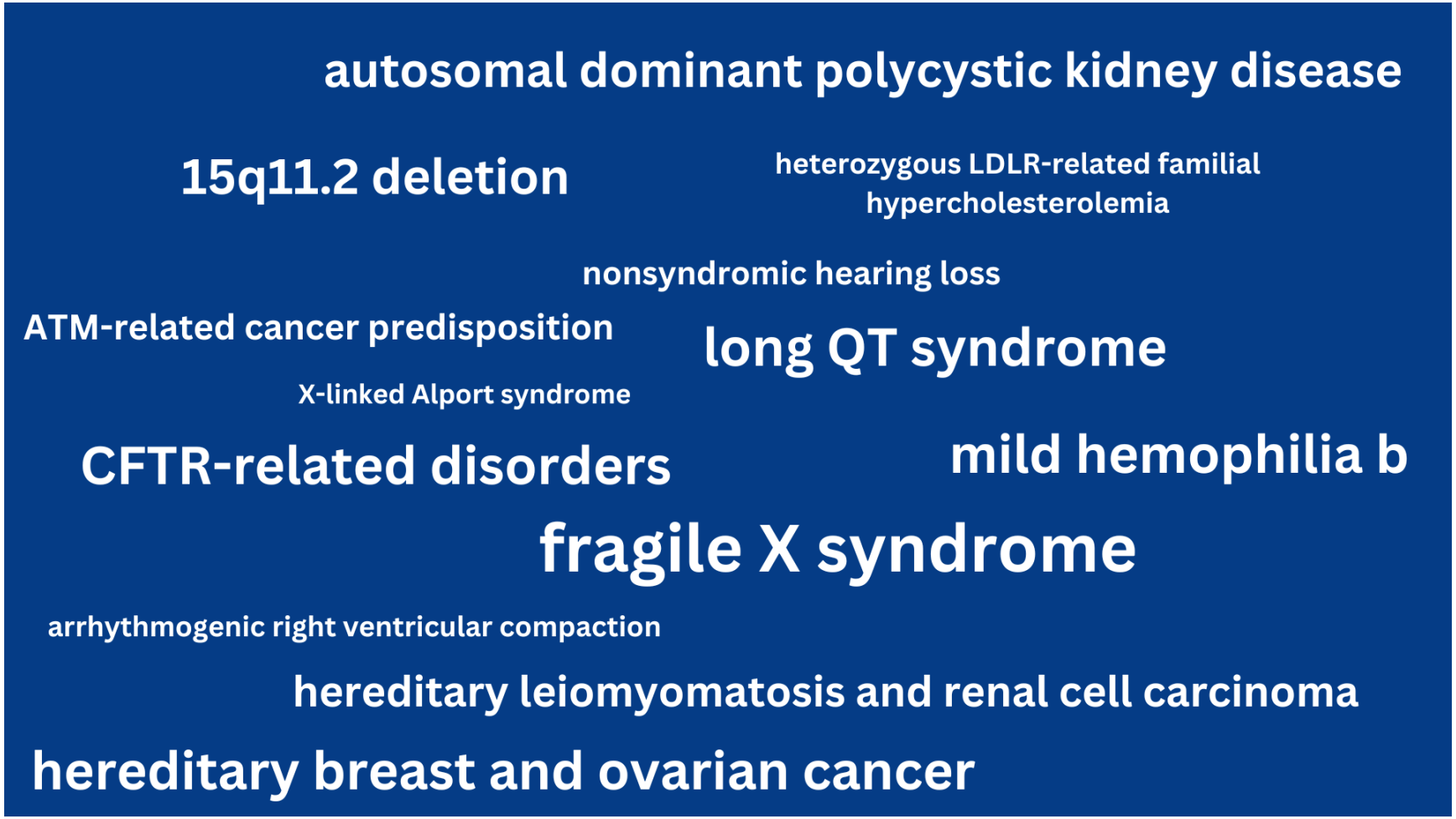

ARE YOU TESTING A PATHOGENIC VARIANT?
YES
NO
Are you testing for a severe, life-limiting condition?
Does the patient want to consider transfer of a positive embryo?
YES
NO
YES
NO
Does the patient want to consider transfer of a positive embryo?
Are patient and provider expectations aligned?
YES
NO
YES
NO
Are patient and provider expectations aligned?
YES
NO
YES
NO

Genetic Counselors Can Help!

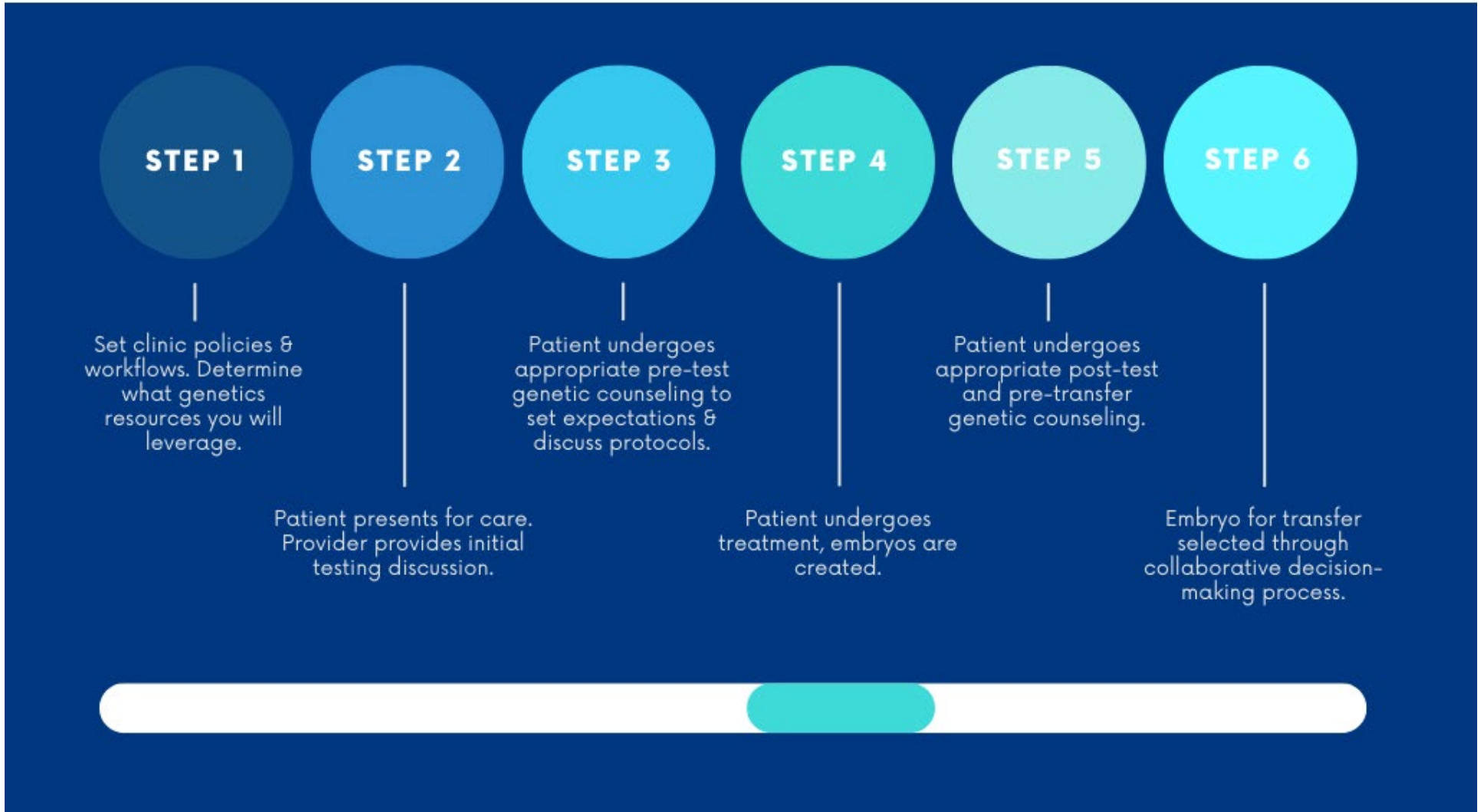
Indications and management of preimplantation genetic testing for monogenic conditions: a committee opinion

"Any patient who expresses interest in PGT-M should be offered consultation with a genetic counselor. … Ideally, patient counseling should initially be provided by a clinic-based genetic counselor…"

2023 PGT-M Positive Transfers



PGT MANAGEMENT
FOR THE MODERN IVF CLINIC



In Summary…

- Uptake of PGT is increasing and results are becoming more complex.
- A multidisciplinary approach to embryo selection ensures the best patient care.
- A clinic must have genetics support to have a successful PGT program, ideally in the form of in-house resources.

References

(1) – Roche, K., Racowsky, C., Harper, J. (2021). Utilization of preimplantation genetic testing in the USA. *Journal of Assisted Reproduction and Genetics 38*: 1045-1053.

(2) - Poulton, A., Lewis, S., Hui, L., Halliday, J. (2018). Prenatal and preimplantation genetic diagnosis for single gene disorders: A population-based study from 1977 to 2016. *Prenatal Diagnosis 38*(12): 904-910.

(3) - Besser, A., Blakemore, J., Grifo, J., Mounts, E. (2019). Transfer of embryos with positive results following preimplantation genetic testing for monogenic disorders (PGT-M): experience of two high-volume fertility clinics. *Journal of Assisted Reproductive Genetics 36*(9): 1949-1955.

(4) - Gleicher, N., Patrizio, P., Mochizuki, L. Barad, D. (2023). Previously reported and here added cases demonstrate euploid pregnancies following by PGT-A as “mosaic” as well as “aneuploid” designated embryos. *Reproductive Biology and Endocrinology 21*(1): 25.

(5) - Viotti, M., Greco, E., Grifo, J., Madjunkov, M., Librach, C. et al. (2023). Chromosomal, gestational, and neonatal outcomes of embryos classified as a mosaic by implantation genetic testing for aneuploidy. *Fertility & Sterility 120*(5):957-966.

(6) - *Doe v. Illinois Masonic Medical Center*, 297 Ill. App. 3d 240, 696 N.E.2d 707 (Ill. App. Ct. 1998)

(7) - *Grossbaum v. Genesis Genetics Institute, LLC*, Civil Action No. 07-1359 (GEB) (D.N.J. Feb. 9, 2010)

(8) - *DOOLAN v. IVF AMERICA (MA), INC., No*, No. 993476 (Mass. Cmmw. Nov. 20, 2000)

(9) – *Jason Diaz et al. Vs. Huntington Reproductive Center Medical Group et al.,* Case Number 23STCV04530 Superior Court of California, County of Los Angeles.

(10) - Practice Commitee and Genetic Counseling Professional Group (GCPG) of the American Society of Reproductive Medicine. Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion. *Fertility & Sterility 114*(2): 246-254.

(11) - Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society of Reproductive Medicine. Indications and management of preimplantation genetic testing for monogenic conditions: a committee opinion. *Fertility & Sterility 120*(1): 61-71.

(12) – Capalbo, A., Poli, M., Rienzi, L., Girardi, L., Patassini, C., et al. (2021). Mosaic human preimplantation embryos and their developmental potential in a prospective, non-selection clinical trial. *American Journal of Human Genetics 108*(12): 2238-2247.

(13) – Ethics Committee of the American Society of Reproductive Medicine. (2017). Transferring embryos with genetic anomalies detected in preimplantation genetic testing: an Ethics Committee Opinion. *Fertility & Sterility 107*(5): 1130-1135.

Q&A

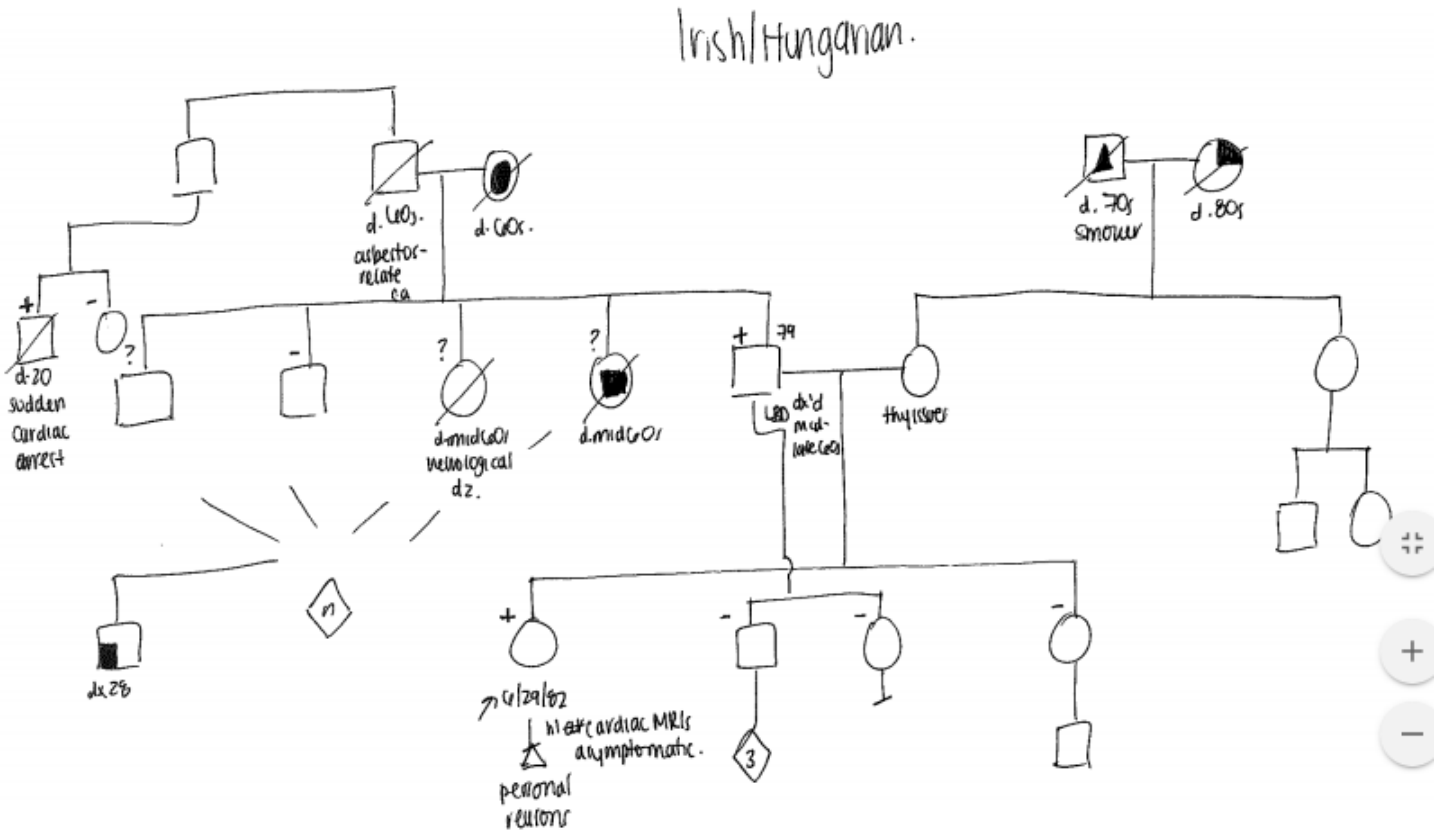
Case-Based Learning

- 39-year-old female, G1P0010 presents for fertility preservation.
  - Medical history significant for PKP2-related arrhythmogenic right ventricular cardiomyopathy (ARVC) and history of R oophorectomy due to complex cysts.
  - AFC 8, AMH 1.48, FSH 4.7
- Patient pursues EOC and 12 M2s frozen.
- Patient presents a year later for embryo creation with donor sperm – no embryos frozen.
- Patient pursues 1 IVF with PGT-A/M cycle:
  - 11/10/10 – 6 biopsied.
  - 4 aneuploid, 2 PGT-A negative and PGT-M positive.
- Patient declines additional IVF cycle, wants to transfer PGT-M positive.

Case-Based Learning

- Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC):
  - Autosomal dominant
  - Cardiomyopathy characterized by fibrofatty replacement of myocardium of the right side of the heart.
  - Symptoms can include heart palpitations, syncope or sudden death.
  - Typically presents in adulthood.
  - Management includes surveillance to monitor cardiac tissue changes and arrhythmias, beta-blockers, anti-arrhythmia agents, catheter ablations and ICD placement.
  - Prognosis is good with proper treatment.

Case-Based Learning



Case-Based Learning

- Do you transfer the PGT-A negative, PKP2 positive embryos?
- Patient approved to transfer PKP2+ embryo, FET planned.
- Patient changes her mind and goes onto pursue 4 additional IVF with PGT-A/M cycles:
  - IVF #2 – 10/6/6 – 1 biopsied – aneuploid
  - IVF #3 – 13/12/8 – 4 biopsied – 2 aneuploid, 2 PGT-A neg/PGT-M pos
  - IVF #4 – 17/13/11 – 4 biopsied – 2 PGT-A neg/PGT-M pos, 1 seg aneu/PGT-M neg, 1 seg aneu/PGT-M pos
  - IVF #5 – 16/10/10 - 4 biopsied – 2 aneuploid, 1 PGT-A/M neg, 1 PGT-A neg/PGT-M pos

Case-Based Learning

- Embryo Inventory:
  - Embryo 20 – PGT-A negative male, PKP2 heterozygous – D5 5AA
  - Embryo 21 – PGT-A negative female, PKP2 heterozygous – D5 5AB
  - Embryo 36 – PGT-A negative male, PKP2 heterozygous – D6 5AA
  - Embryo 42 – PGT-A negative female, PKP2 heterozygous – D6 4BB
  - Embryo 53 – PGT-A negative male, PKP2 heterozygous – D6 6BA
  - Embryo 57 – SegAneu male, PKP2 heterozygous – del(18q11.2-q23)(57.7Mb) – D5 5BB
  - Embryo 58 – SegAneu male, PKP2 negative – del(15q25.1-q26.3)(23.7Mb) – D6 4BC
  - Embryo 59 – PGT-A negative female, PKP2 heterozygous – D6 5BB
  - **Embryo 69 – PGT-A/M negative male – D6 5BB**
  - Embryo 74 – PGT-A negative female, PKP2 heterozygous – D6 6BA