Complex Genetic Cases: Interactive Discussion

March 20th, 2026

2026 PCRS ANNUAL MEETING

REPRODUCTIVE FRONTIERS:
BRIDGING BIOLOGY, PRACTICE, AND POSSIBILITY

MARCH 18-22 | RANCHO MIRAGE, CA

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Presenters

Alleigh Boyd, MS, CGC
IVIRMA

Jenna Miller, MS, CGC
Cooper Surgical

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Fairfax EggBank

Disclosure Slide

- Allison (Alleigh) Boyd:
  - Nothing to Disclose
- Rawan Awwad:
  - **Employee:** Fairfax EggBank (full-time)
    Consulting Fee (e.g., Advisory Board): Mavin Clinic, LabCorp
- Jenna Miller:
  - **Employee:** CooperSurgical
    Stock Shareholder (Individual stocks/Stock options; diversified mutual funds do not need to be disclosed): CooperSurgical

Learning Objectives

- Demonstrate examples of complex genetic testing and risk assessment scenarios from a clinical, laboratory, and third-party reproduction perspectives.
- Describe the responsibilities of various entities involved in complex genetic cases.
- Suggest ways by which multi-directional interaction can help provide optimal outcomes for clients.

Outline

Case 1: DMD Carrier Status in Unaffected Male

Case 2: PGT-P vs Embryo Morphology

Case 3: Third Party Reproduction and Duty to Inform

Case 1 - DMD Dilemma

36yo female presented to care in January 2025 with h/o hypothyroidism, PCOS and 15 years of infertility

- Reported to be DMD carrier at first visit, interested in PGT-M

Duchenne Muscular Dystrophy - Positive

DMD duplication exons 54-74, Pathogenic, Heterozygous
This individual is a carrier of a pathogenic *DMD* gene variant, heterozygous for duplication of exons 54-74. Some female carriers may exhibit symptoms that range in severity. Up to 20% of carriers may have some degree of muscle weakness, ranging from mild to moderate. Approximately 8-10% of carriers are reported to have dilated cardiomyopathy that is progressive. The American Academy of Pediatrics provides recommendations for education and surveillance for female carriers of DMD-related conditions.

Duchenne Muscular Dystrophy is an X-linked condition, females will pass on the *DMD* variant to 50% of offspring; therefore, there is a 50% risk for male offspring to inherit the variant and have Duchenne Muscular Dystrophy and a 50% risk for female offspring to inherit the variant and be carriers of this *DMD* variant. Partner testing for *DMD* is not recommended.

PGT-M for DMD

Mutation presumed to be de novo or maternal in origin as father is unaffected

Case was accepted for PGT-M via linkage only due to mutation type (duplication)

Patient counseled informative relative is needed. Mother was willing to be tested but father was unwilling to be involved unless absolutely necessary. Counseled that if mother is negative, PGT-M would not be possible

Mother tested and NEGATIVE - June

Father complied with testing and POSITIVE for dup - July

Patient happy because PGT-M possible! Except…

DMD Positive Unaffected Male?

XXY?

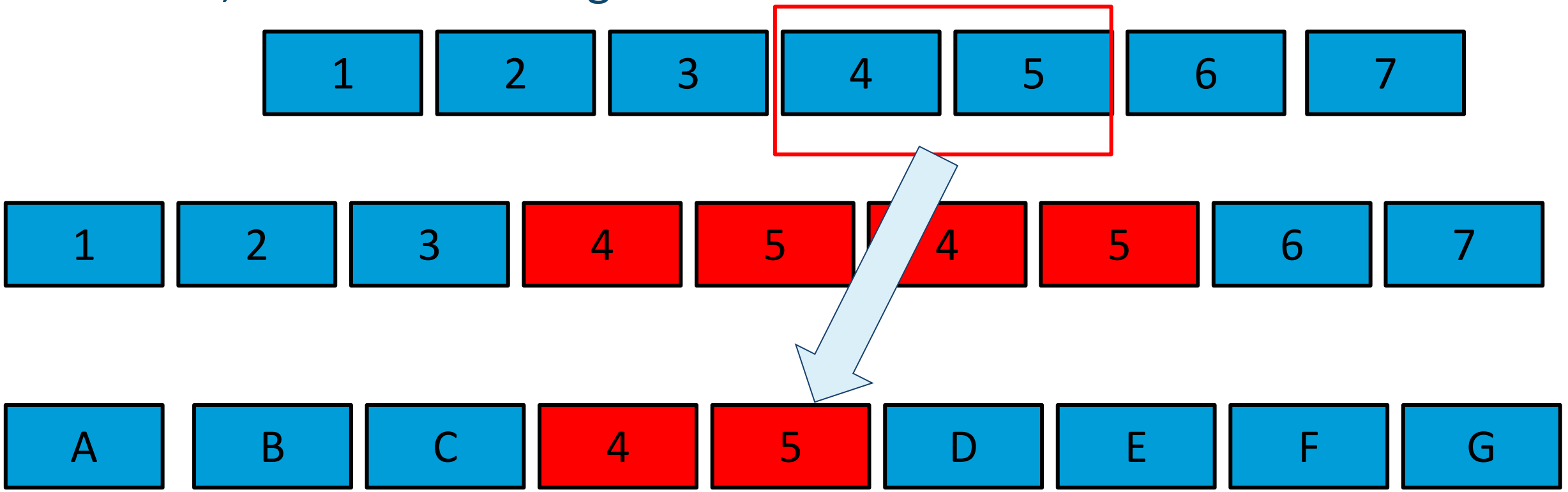
Incomplete penetrance?

Mild/subclinical presentation?

Pathogenicity of variant?

DMD Duplication

Duplications identified via carrier screening are *assumed* to be in tandem, within the DMD gene



DMD Duplications

15 individuals tested via high-coverage, long-read sequencing

- 11 with no clinical symptoms
  - 7/11 confirmed to be outside *DMD* and therefore not pathogenic

› Genet Med. 2025 Aug 5;27(10):101539. doi: 10.1016/j.gim.2025.101539. Online ahead of print.

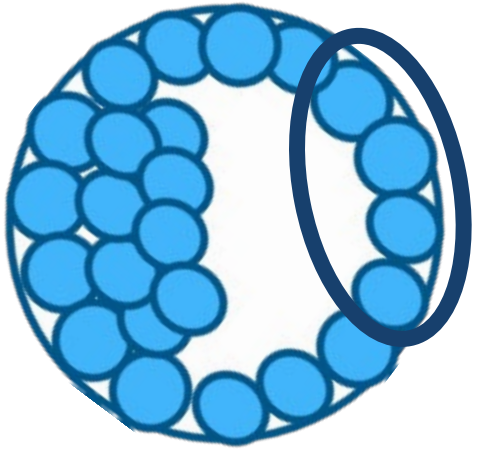
Rethinking the pathogenicity of intragenic DMD duplications detected by carrier screening: High prevalence of nontandem duplications revealed by long-read sequencing

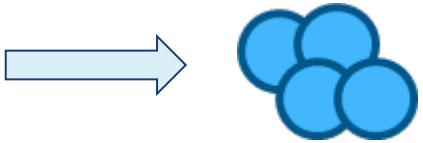
Qiliang Ding [1], Jagadheshwar Balan [2], Noemi Vidal-Folch [3], Angela M Pickart [3], Guangchao Sun [2], Jesse R Walsh [2], Ramanath Majumdar [4], Eric W Klee [5], Stephen J Murphy [4], Devin Oglesbee [3], Ross A Rowsey [3], Linda Hasadsri [6]

Affiliations + expand

PMID: 40757397 DOI: 10.1016/j.gim.2025.101539

Unclear benefit of PGT-M



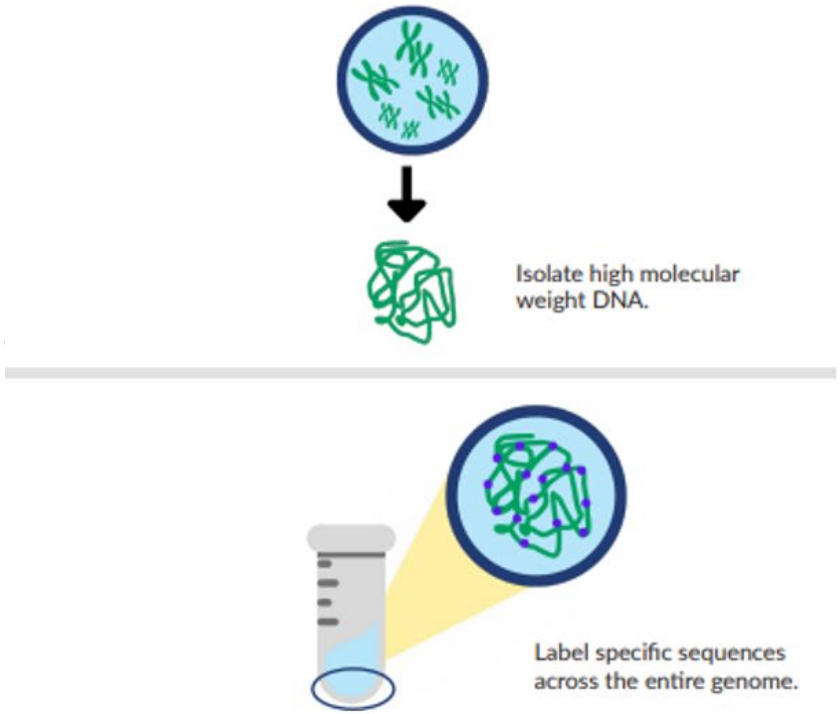


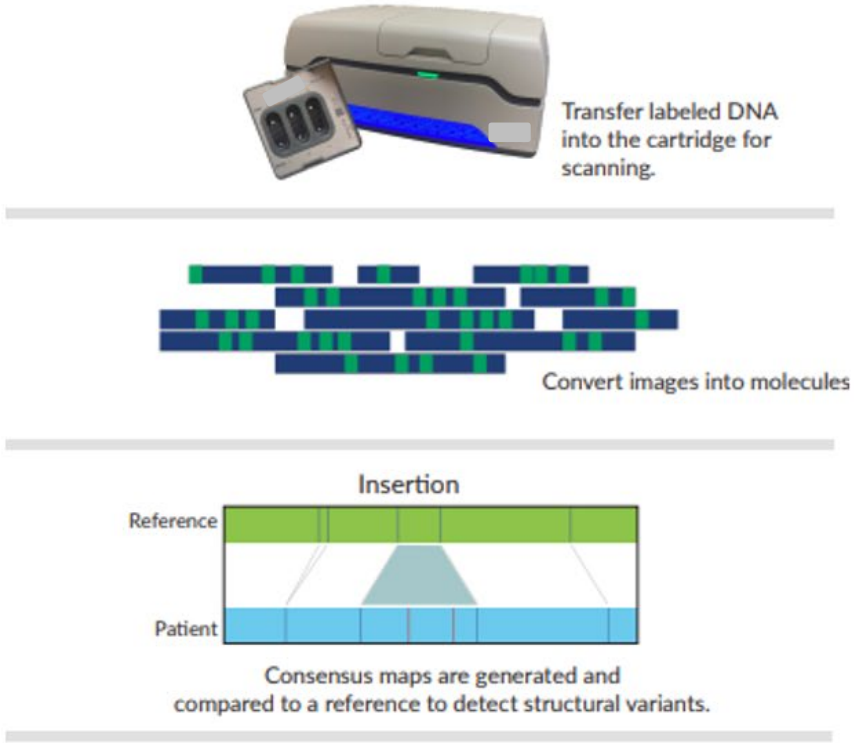
50% Paternal
Haplotype Positive

???

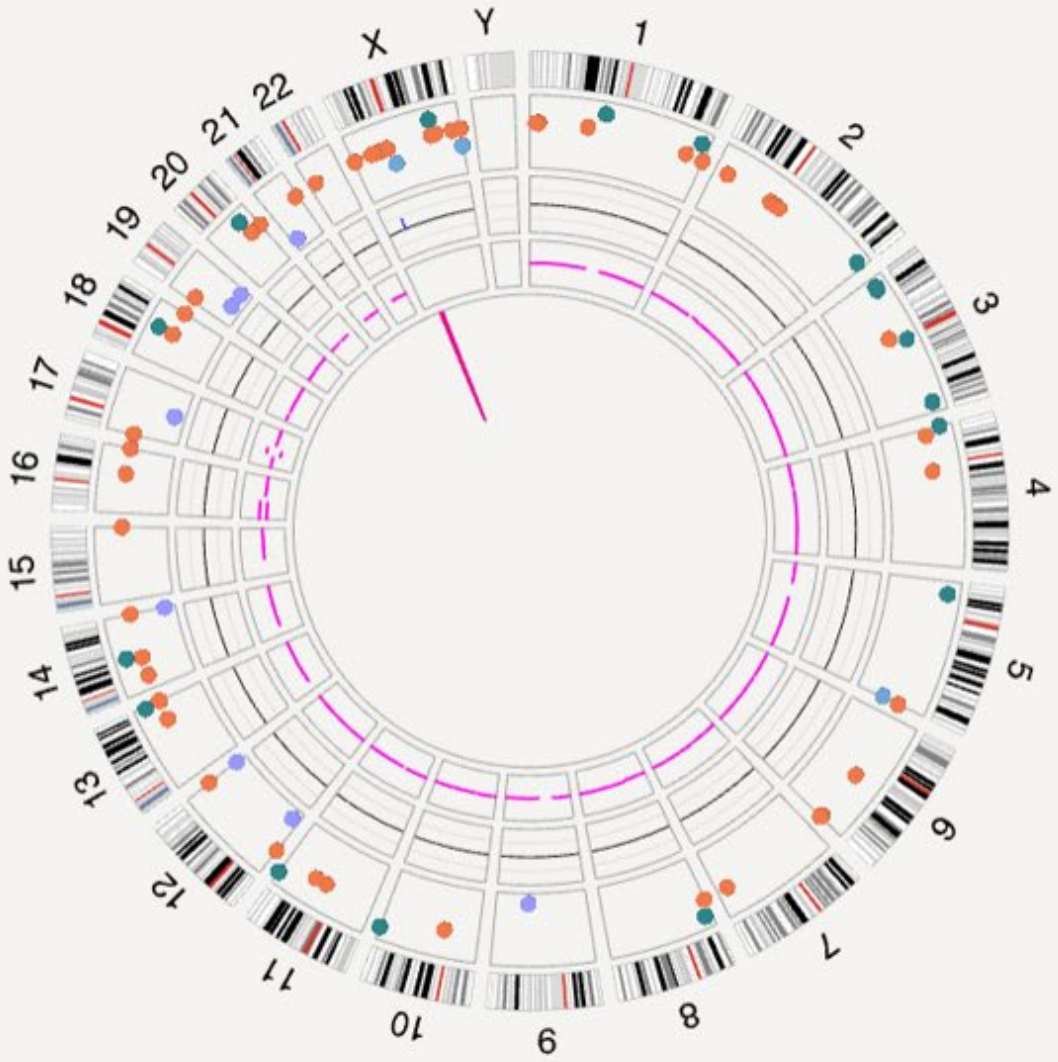
Optical Genome Mapping

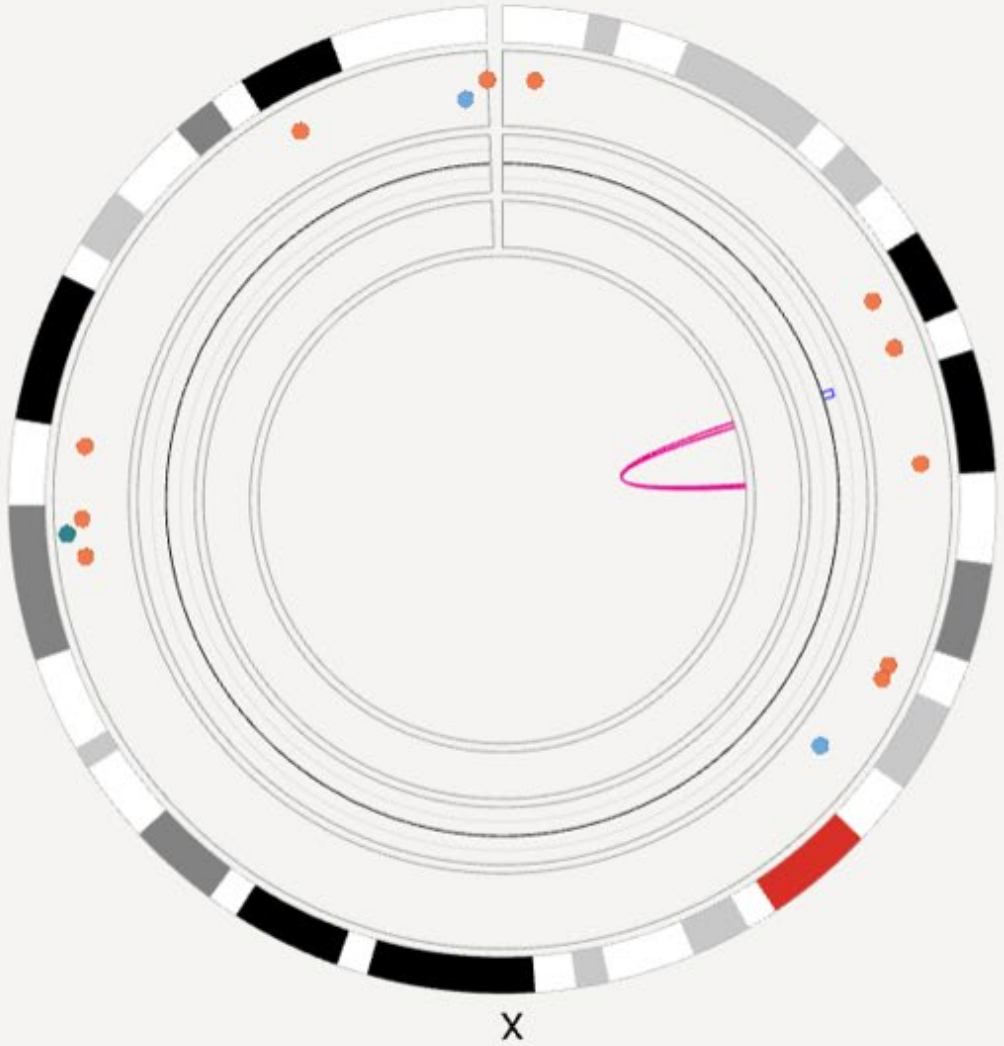
Utilizes high molecular weight DNA molecules labelled at repetitive sit with genome specific locations





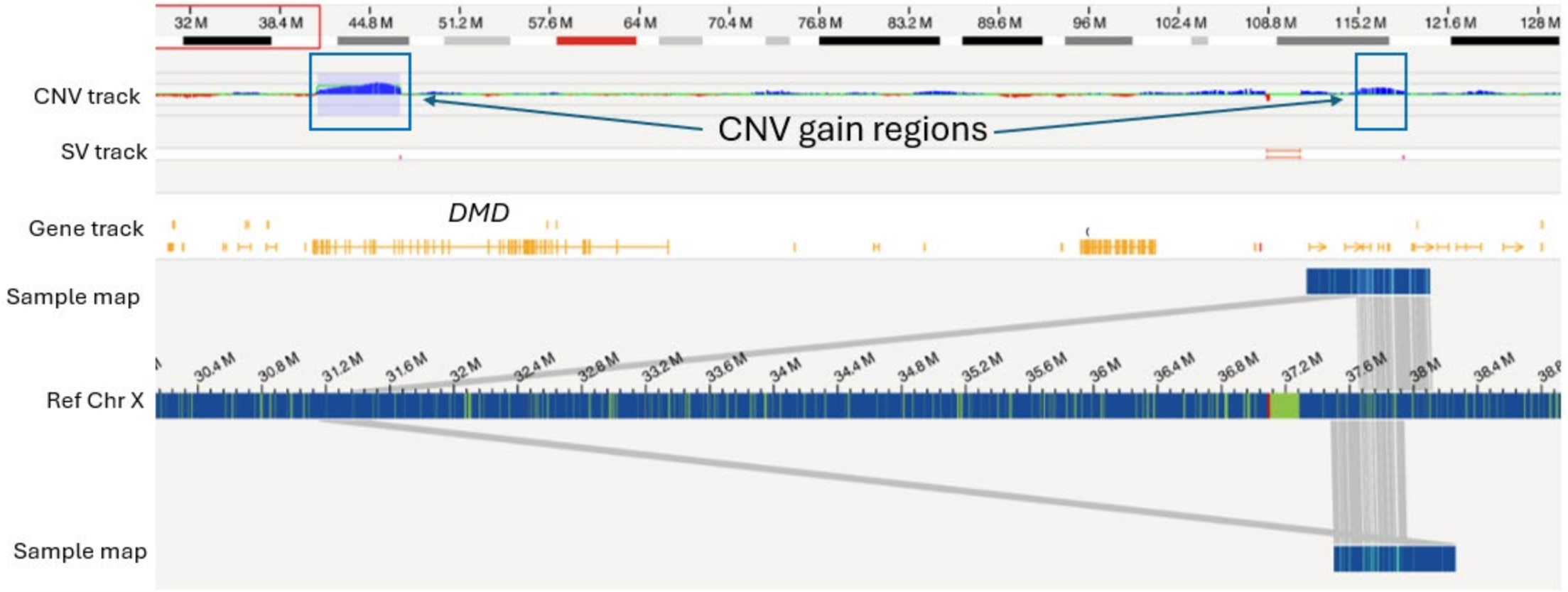
Visual provided by Nikhil Sahajpal, PhD





Visual provided by Nikhil Sahajpal, PhD

Duplication NOT in tandem!



Visual provided by Nikhil Sahajpal, PhD

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Send **rawanawwad330** to **22333**

Poll - Case 1

How would you disposition DMD positive males?

A) Eligible for transfer
B) Ineligible for transfer
C) Only eligible if no negative or carrier embryos remain
D) PGT-M is not indicated and should not be performed

PGT-M Not Indicated

DOFV - January 2025

OGM Result Disclosure - October 2025

Since PGT-M not indicated, all options available to couple

Are planning for IVF in the near future

Take Home Points

- Important to understand implications beyond “positive” variant
- Additional technologies may be available to clarify true risk, especially when family history is not consistent or PGT-M otherwise complication/unavailable
- Added time and up front costs may reduce unnecessary intervention down the line (bypassing need for PGT-M)

Case 2: Polygenics and Pathogenics

- **37 yo G6P1051 (SABx4, TAB x1 for T21)**
- **Family History**
  - Maternal father and grandfather with MI in 60s-80s
  - Maternal grandmother with breast cancer in 60s
  - Maternal cousin with cardiac anomaly
  - **Paternal uncle with colon cancer in 50s**
  - Paternal aunt with breast cancer in 70s
  - **Male partner with one adenoma noted at time of colonoscopy**

  **couple was offered referral to cancer genetics during GC consult, never pursued*
- **Testing History –** declined carrier screening ("had genome sequencing performed")

Cycle 1: Outcome

TEST RESULTS

Embryo No.	Cycle	Sample Type (Biopsy day)	Embryo results	Sex
2	-	Trophectoderm (D5)	Complex aneuploid: Trisomy 21 and 22	Male
3	-	Trophectoderm (D5)	Aneuploid: Trisomy 16	Female
5	-	Trophectoderm (D5)	**Euploid**	**Male**
6	-	Trophectoderm (D5)	**Euploid**	**Female**
7	-	Trophectoderm (D5)	**Euploid**	**Male**
1	-	Trophectoderm (D6)	**Euploid**	**Male**

Straw #:

ANALYSIS AND REPORTING: Full mosaic reporting

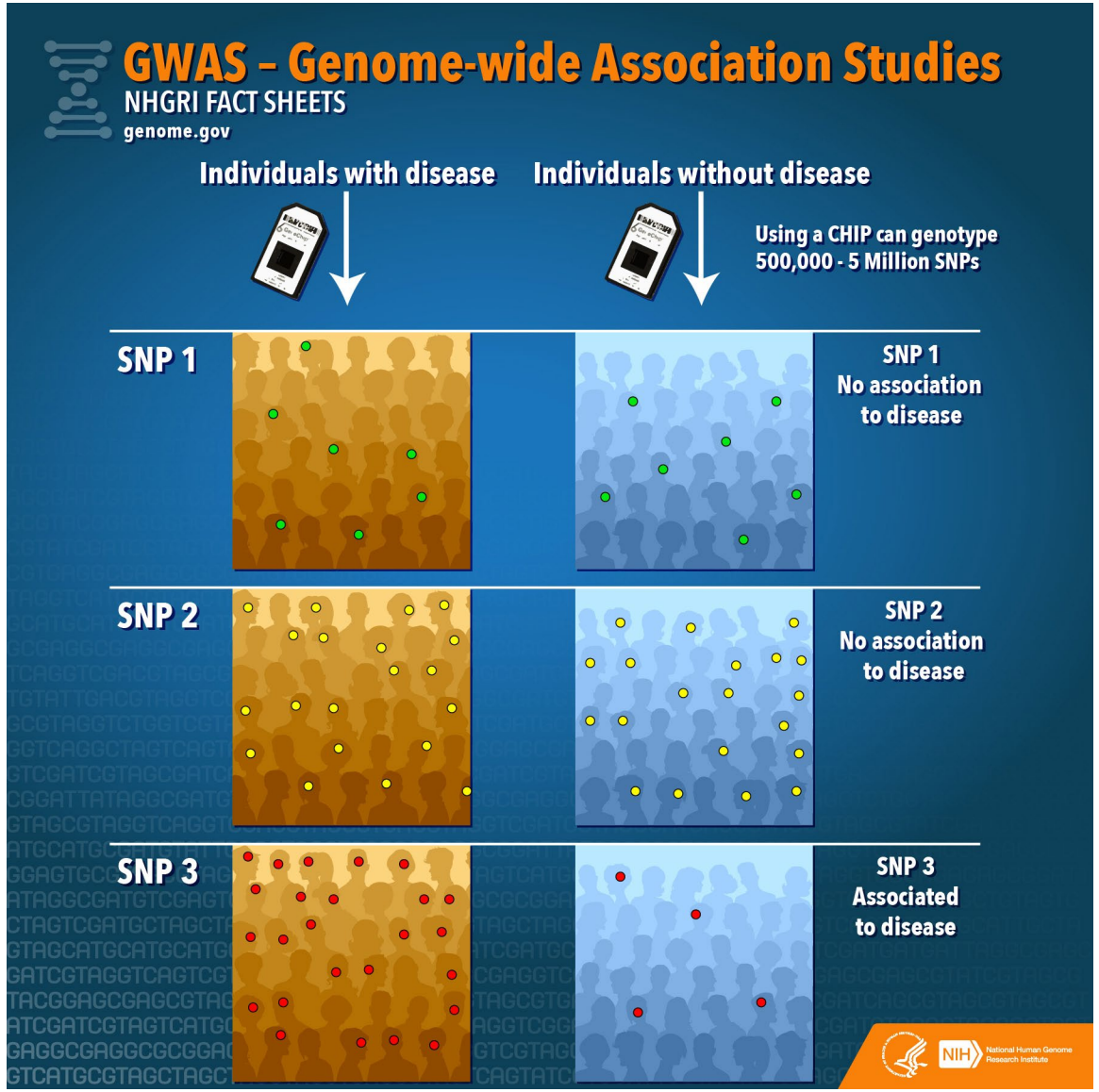
Polygenic Risk Scoring in Embryos (PGT-P)

- Data from PGT-A lab sent to private research facility for PRS for colorectal cancer
  - Existing PGT-P companies did not offer this at the time
  - PGT-A data + parental haplotypes used to calculate PRS
- Due to couple's non-European ancestry, estimate a ~25% reduction in effect size is possible.

Polygenic Risk Scoring: Background

Variants in Polygenic Risk Scoring

- Common
- Typically non-coding
- Often not the causal variant, but linked to unknown causal variant
- No clear mechanism
- Contribute to risk in an additive manner (non-dominant)
- Contribute a small amount to risk



Professional Societies' Statements

Published in final edited form as:
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Problems with Using Polygenic Scores to Select Embryos

Patrick Turley, Ph.D., Michelle N. Meyer, Ph.D., J.D., Nancy Wang, S.B., David Cesarini, Ph.D., Evelynn Hammonds, Ph.D., Alicia R. Martin, Ph.D., Benjamin M. Neale, Ph.D., Heidi L. Rehm, Ph.D., Louise Wilkins-Haug, M.D., Ph.D., Daniel J. Benjamin, Ph.D., Steven Hyman, M.D., David Laibson, Ph.D., Peter M. Visscher, Ph.D.
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SUMMARY

Companies have recently begun to sell a new service to pa
embryo selection based on polygenic scores (ESPS). Thes
predictions of health and other outcomes derived from ge
to partially predict these outcomes. This article includes a
the predictive power of polygenic scores in the context of
effects for a variety of clinical and nonclinical traits. Also
consequences of ESPS (including selecting for adverse tra
exacerbating inequalities in society, and devaluing certain
responsible communication about ESPS by practitioners a
conversation about this technology is made. (Funded by th
others.)

ESHRE supports the position of ESHG on embryo selection based on polygenic risk scores

ESHRE shares the concerns expressed by the European Society of Human Genetics (ESHG) over the use of polygenic risk scores in preimplantation genetic testing. A statement issued by the ESHG at the end of 2021 was firm in its objections that the use of PRSs in clinical practice is unproven and unethical.(1,2)

While ESHRE acknowledges that PRSs can generate useful information at the population level by identifying at-risk groups, the prediction intervals are so wide that individual predictions are highly unreliable. Thus, while benefits might be demonstrated in the future for specific patient populations, ESHRE agrees that at present there are serious scientific and ethical concerns surrounding this technology and introduction in the clinic is highly undesirable.

ESHRE's concerns, as also expressed by the ESHG, are fourfold:
* First, there are always limited embryos for genetic testing in an IVF cycle, so each one will have some heightened PRS for some characteristics or diseases. Thus, a meaningful risk reduction cannot be achieved by merely excluding embryos with very high PRSs. This is a fundamental difference from the rationale in genetic testing for monogenic diseases, in which only affected (or very high risk) embryos are de-selected to prevent a great and likely harm.
* Second, a sibling cohort of embryos evaluated by PRS will exhibit great overlap between a variety of small risk factors evident in a multitude of gene variants inherited from parental genes.
* Third, PRS are unable to include phenotypical or environmental information, which further excludes a reliable risk estimate for complex diseases.
* Fourth, interaction between the different genetic variants is poorly understood, so, for instance, embryo selection to protect against one disease may inadvertently increase risks for others.

It thus remains ESHRE's view that in the setting of embryo selection, even in cases where some analytic validity of a correlation can be demonstrated, the clinical utility of PRS remains at this time low to non-existent and cannot be supported in clinical practice.

VIEWPOINT

Check for updates

The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice

Francesca Forzano[1✉], Olga Antonova[2], Angus Clarke[3], Guido de Wert[4], Sabine Hentze[5], Yalda Jamshidi[6], Yves Moreau[7], Markus Perola[8], Inga Prokopenko[9,10,11], Andrew Read[12], Alexandre Reymond[13], Vigdis Stefansdottir[14], Carla van El[15], Maurizio Genuardi[16,17], on behalf of the Executive Committee of the European Society of Human Genetics* and the Public and Professional Policy Committee of the European Society of Human Genetics*

Polygenic risk score analyses on embryos (PGT-P) are being marketed by some private testing companies to parents using in vitro fertilisation as being useful in selecting the embryos that carry the least risk of disease in later life. It appears that at least one child has been born after such a procedure. But the utility of a PRS in this respect is severely limited, and to date, no clinical research has been performed to assess its diagnostic effectiveness in embryos. Patients need to be properly informed on the limitations of this use of PRSs, and a societal debate, focused on what would be considered acceptable with regard to the selection of individual traits, should take place before any further implementation of the technique in this population.

European Journal of Human Genetics; https://doi.org/10.1038/s41431-021-01000-x

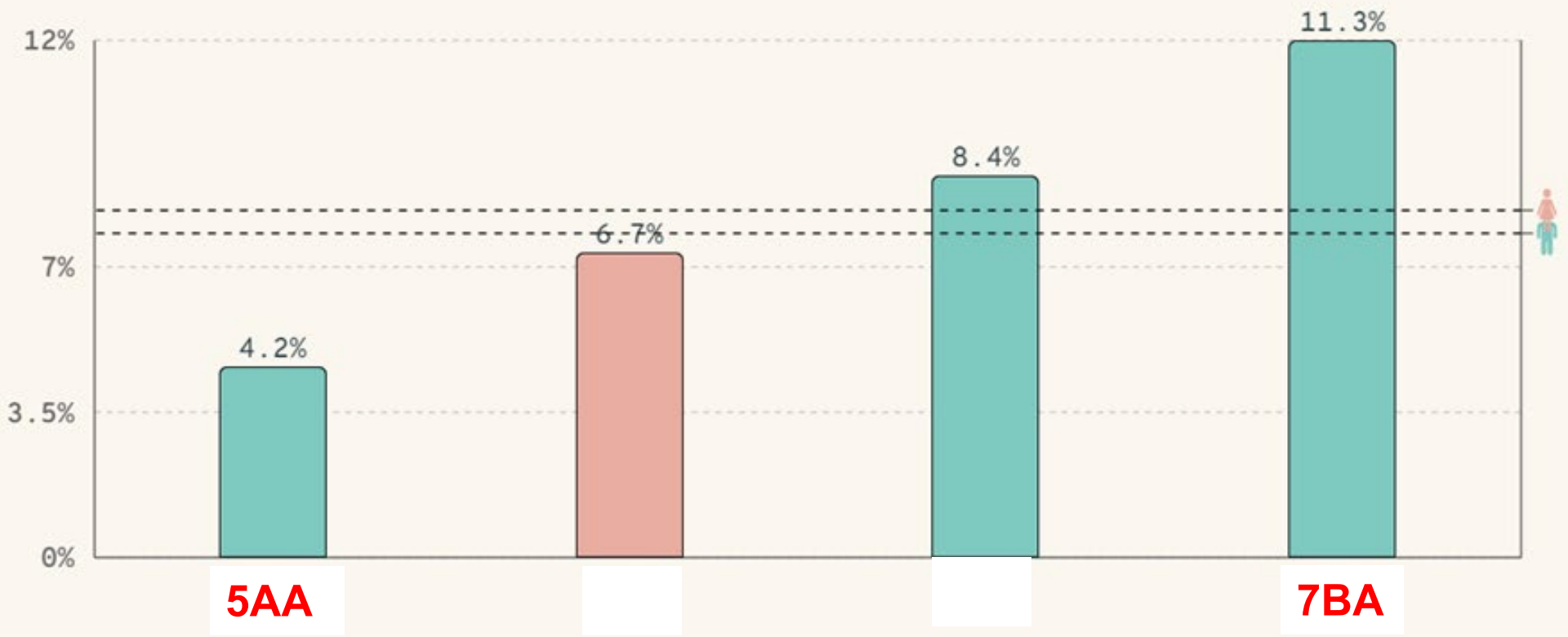
ACMG STATEMENT

Clinical utility of polygenic risk scores for embryo selection: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)

Theresa A. Grebe[1,2], George Khushf[3], John M. Greally[4], Patrick Turley[5,6], Nastaran Foyouzi[7], Sara Rabin-Havt[8], Benjamin E. Berkman[9], Kathleen Pope[10,11], Matteo Vatta[12], Shagun Kaur[1,2]; on behalf of the ACMG Social, Ethical, and Legal Issues Committee[13]

Disclaimer: This statement is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. Adherence to this statement is completely voluntary and does not necessarily assure a successful medical outcome. This statement should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, clinicians should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen.
Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this statement. Clinicians also are advised to take notice of the date this statement was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures. Where individual authors are listed, the views expressed may not reflect those of authors' employers or affiliated institutions.

Lifetime risk Colorectal Cancer



1 - arrested
2 - fragmented morula
3 - morula
4 - cavitating morula
5 - early blast
6 - blast
7 - expanded blast
8 - hatching blast
9- fully hatched

What to Transfer?

- Patients have a male preference
- Clinic wants to transfer embryo 5
  - Embryo grade: 7BA
  - Highest PRS at 11.3%
- Patients want to transfer embryo 7
  - Embryo grade: 5AA
  - Lowest PRS at 4.2%
- Clinic policies
  - Lab's prerogative which embryo to transfer within preferred sex
  - "Abnormal embryo transfer" permitted

1 - arrested
2 - fragmented morula
3 - morula
4 - cavitating morula
5 - early blast
6 - blast
7 - expanded blast
8 - hatching blast
9- fully hatched

Transfer 1

- Embryo 7 (lowest PRS) transferred
- Pregnant following SET
- Aneuploidy screening low risk @ 10w
- Ultrasound at 12w showed cystic hygroma, total body lymphedema, and single great vessel
- CVS pursued for fetal sequencing and microarray
  - **De novo heterozygous PATHOGENIC variant in *PTPN11*,c.182A>G (p.Asp61Gly)**
  - **Diagnosis: Noonan Syndrome**
- Expanded carrier screening elected
  - **Concordant GJB2 carriers**
- TOP

Cycle 2: PGT-A + PGT-M

- Pursued clinical PGT-M for GJB2 with PGT lab
  - Also sent DNA from cycle 1 biopsies to research lab
- Underwent a second cycle to generate additional embryos
  - 2 additional euploid, unaffected male embryos identified

Research vs Clinical PGT-M Results: Cycle 1

Offspring	Maternal Inheritance	Paternal Inheritance	Affected Status
Born Child	No missense	No deletion	Unaffected
	Missense	Deletion	Affected

TEST RESULTS

Embryo No.	PGT-M Results c.109G>A & c.235del, GJB2	PGT-A Results Aneuploidy screening	Sex
	At-risk	Complex aneuploid	Male
			Female
			Male
			Female
			Male
			Male

Offspring	M
Born Child	N
	M
	N
	N
	N

TEST RESULTS

Embryo No.	PGT-M Results c.109G>A & c.235del, GJB2	PGT-A Results Aneuploidy screening	Sex
2	At-risk	Complex aneuploid	Male
3	Carrier	Aneuploid	Female
5	**Carrier**	**Euploid**	**Male**
6	**Carrier**	**Euploid**	**Female**
7	**Carrier**	**Euploid**	**Male**
1	At-risk	Euploid	Male

No missense	Deletion	Carrier
Missense	Deletion	Affected

Second Cyc

TEST RESULTS

Embryo No.	PGT-M Results c.109G>A & c.235del, GJB2	PGT-A Results Aneuploidy screening	Sex
	Carrier	**Euploid**	**XY**

TEST RESULTS

Embryo No.	PGT-M Results c.109G>A & c.235del, GJB2	PGT-A Results Aneuploidy screening	Sex
1	**Carrier**	**Euploid**	**XY**
3	At-risk	Complex aneuploid	XX
6	At-risk	Euploid	XX
7	Carrier	Low mosaic	XX
8	**Carrier**	**Euploid**	**XY**
9	Non-carrier	Aneuploid	XX
10	At-risk	Low mosaic	XX

See detailed results for PGT-M and PGT-A tests in following pages.

Transfer 2

- Euploid carrier male transferred
- Healthy baby born!

Take Home Points

Polygenic risk scoring is not designed to take rare variants into account

- Did not address GJB2 carrier status
- Did not address de novo Noonan
- If pursuing PGT-P, ask lab

No test (PGT-A, PGT-M, PGT-P, morphology) is a panacea

When poll is active respond at PollEv.com/rawanawwad330
Send **rawanawwad330** to **22333**

POLL - Case 2

1. Would your clinic permit a patient to pursue PRS for their embryos?
2. Would your clinic permit a patient to transfer a low PRS, lower grade embryo over a high PRS, higher grade embryo?

A. Yes
B. No

Case 3 - Duty to Inform in Third Party Reproduction

Donor reports
recent Dx of anxiety
+ ADHD @ 27

Egg bank notifies
clinics + recipients

Outcomes:

- Several healthy births and euploid frozen embryos.
- Mild delays for 2 children.

1 baby with overgrowth, delays
Molecular testing confirms
Beck Fahrner Syndrome (BFS)

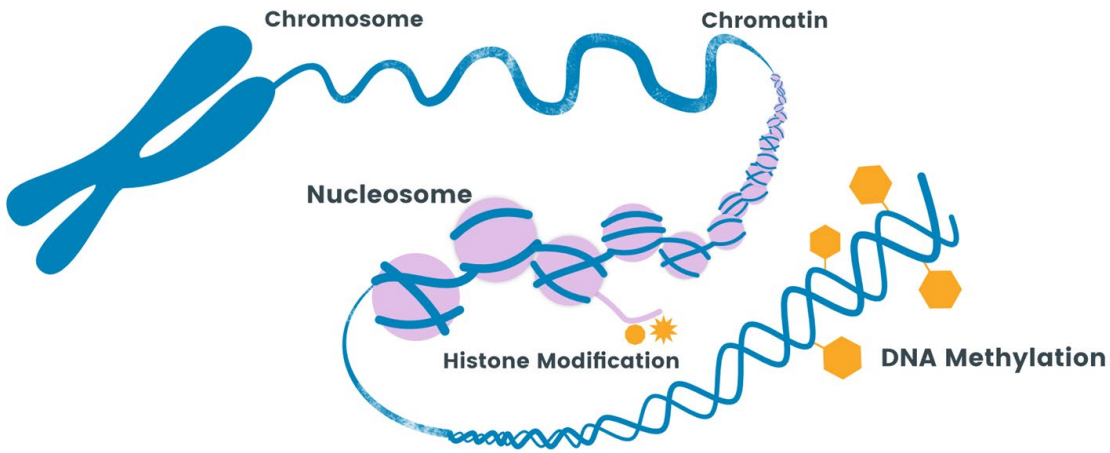
Beck Fahrner Syndrome (BFS)

Clinical Features:

- AD with variable expressivity
- ID / Developmental delay
- Epilepsy
- Neurobehavioral features: autism, anxiety, and ADHD
- Refractive errors
- Hearing loss
- Growth abnormalities, mostly macrocephaly and overgrowth

Molecular Analysis:

- *TET3* gene testing
- Methylation signal analysis



Affected Donor-Conceived Child

- Positive variant in TET3, classified as VUS
- Positive methylation signal
- Recipient did not reach out to bank because “donor’s history is negative for BFS features”

Case Investigation

- Donor's mother: previously reported history of anxiety
- No other personal or family history of any BFS features
- Donor tested positive for:
  - same VUS as affected child
  - positive TET3 methylation signal
- Notifications resulted in multiple child evaluations and PGT-M requests

Points to Consider

- Duty to inform
  - Recipients sign agreement with bank to report medical updates.
  - What obligation does a pediatric/fertility/genetics clinic have to inform a gamete bank?
  - What obligations do testing labs have to inform banks? Example: duo whole genome sequencing on donor-conceived embryos without donor sample.

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Poll

- Should clinics handling donor-conceived pregnancies/offspring be mandated to report findings with increased recurrence risk to biological relatives to the gamete bank?

  A. Yes
  B. No
  C. I don’t know

Take Home Points

- Encourage your patient to share medical updates with the gamete bank.
- Official guidelines are needed to address nuances of medical update management in third party reproduction.

Q&A