# 2026 PCRS ANNUAL MEETING

## REPRODUCTIVE FRONTIERS: BRIDGING BIOLOGY, PRACTICE, AND POSSIBILITY

## MARCH 18-22 | RANCHO MIRAGE, CA

PACIFIC COAST REPRODUCTIVE SOCIETY

# Emerging PGT-A Technologies

Jenna Miller, MS, CGC

March 18, 2026

2026 PCRS ANNUAL MEETING

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# Disclosure Slide

- Employee
  - CooperSurgical
- Stock Shareholder (Individual stocks/Stock options; diversified mutual funds do not need to be disclosed)
  - CooperSurgical

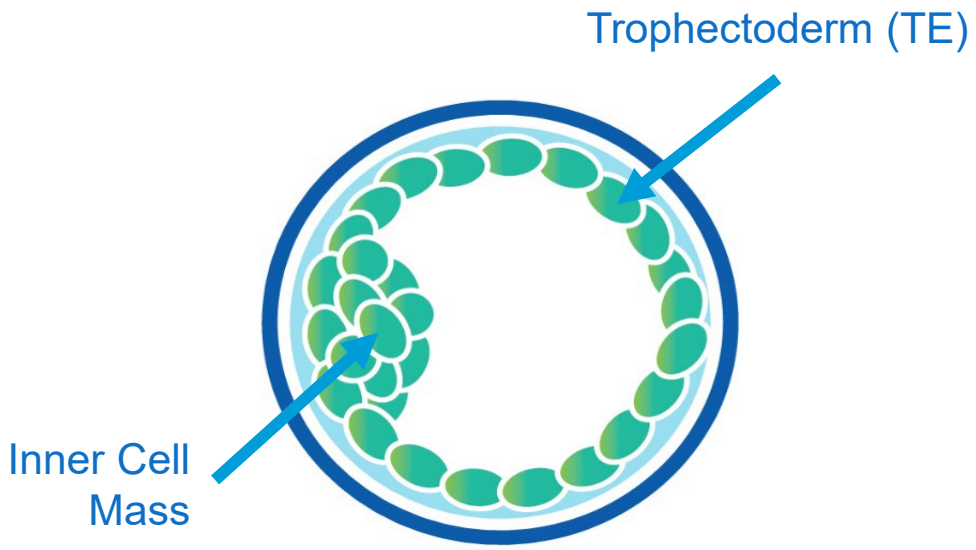
# Expected Learning Outcomes

1. Describe **primary template-directed amplification** and its applications for preimplantation genetic testing.

2. Compare the capabilities of PGT-A utilizing **NGS alone versus NGS plus SNP analysis**, particularly as pertains to haploidy/polyploidy, mosaicism and segmentals, parental confirmation and contamination identification, and microdeletions/microduplications

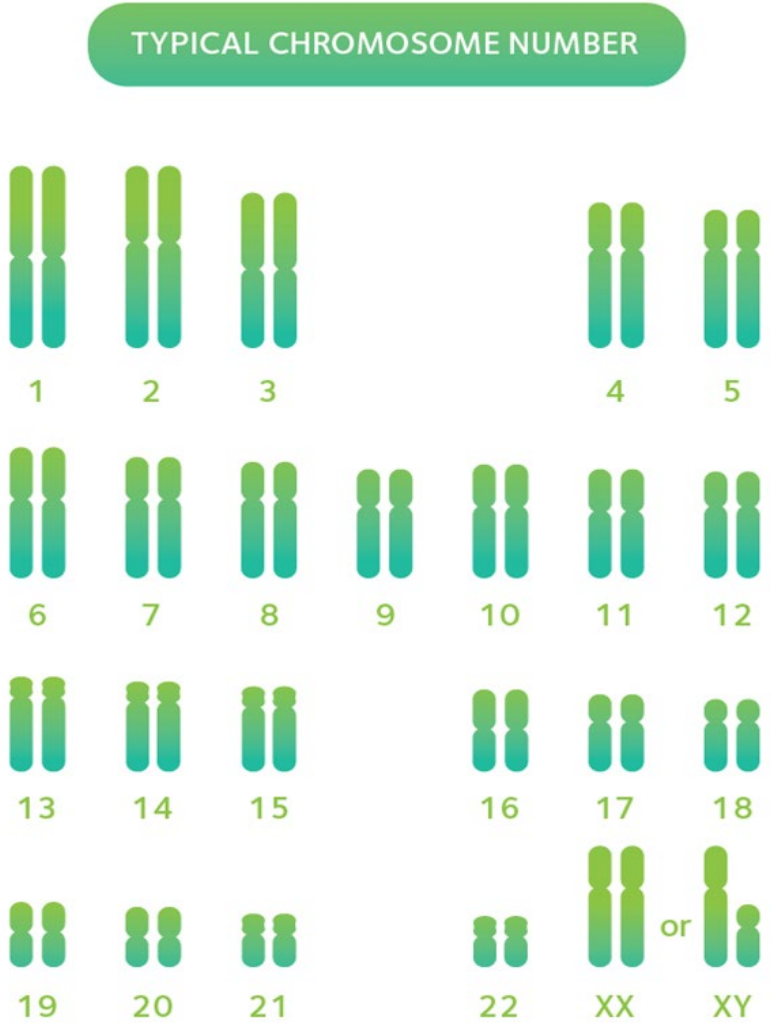
3. Utilize key questions to **critically evaluate new PGT offerings** and **identify patients who may benefit**.

# Early PGT-A




## Euploid / Normal Result:

- Expected amount of chromosomal material present
- Highest likelihood of successful pregnancy[1]

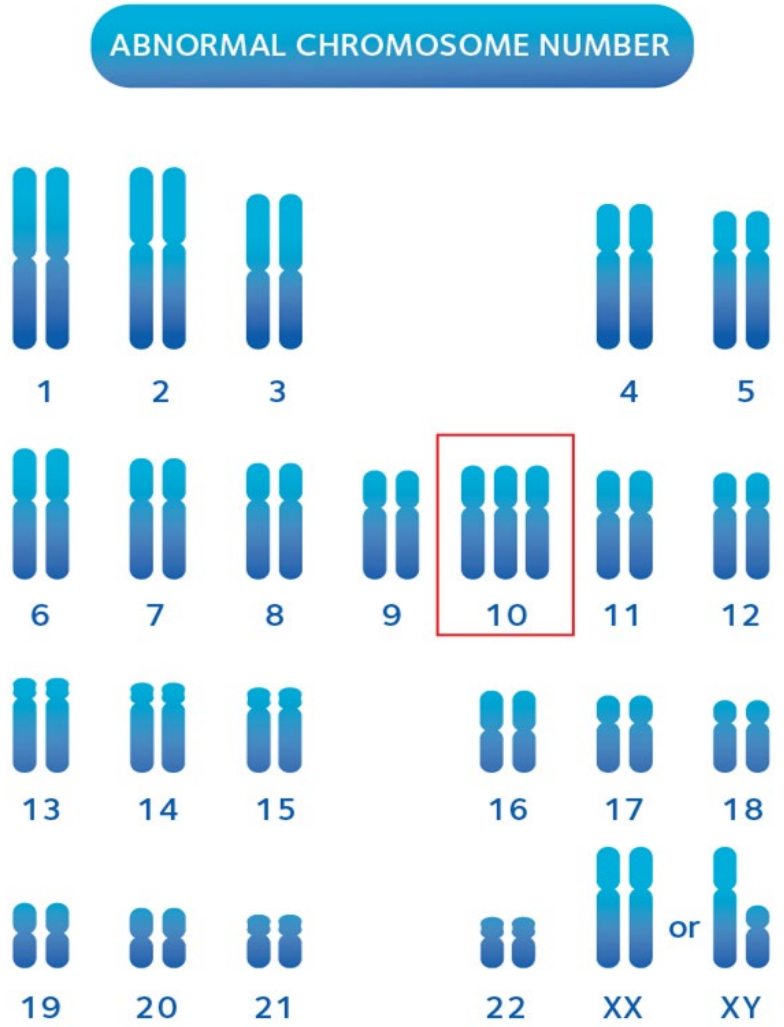



1. Tiegs, A.W., *et al.* A multicenter, prospective, blinded, nonselection study evaluating the predictive value of an aneuploid diagnosis using a targeted next-generation sequencing–based preimplantation genetic testing for aneuploidy assay and impact of biopsy. *Fert Steril*. (2021) 115:627-637.

# Early PGT-A

## Aneuploid/Abnormal Result:

- Missing/extra chromosomal material
- Found in embryos of IVF patients of any age, but risk has been shown to increase with maternal age
- May result in:[1]
  - Failed implantation
  - Miscarriage
  - Pregnancy or live birth affected with the observed abnormality

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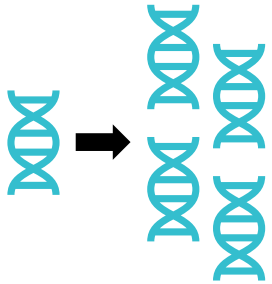
# Advances in DNA Amplification

# Modern PGT-A Laboratory Workflow

## Component methods work together to generate and analyze data

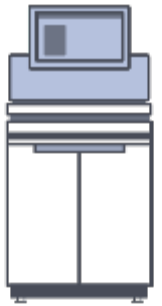
Biopsy

Genomic Amplification



Library Prep.

Sequencing



Data Analysis

Report

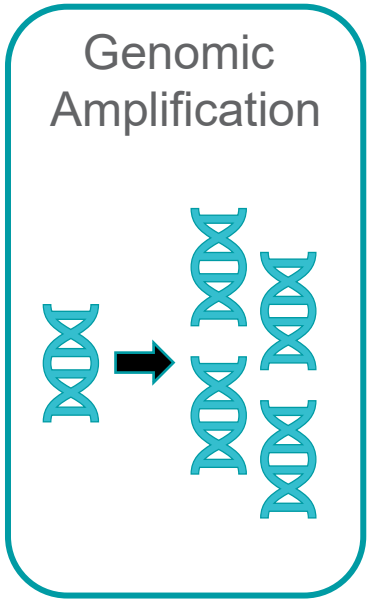
# Amplification is the first (*and most important*) step

20,000 X

5-6 Trophectoderm Cells
~50 picograms genomic DNA

→ ~1000 ng Amplified Product

- PGT-A
- PGT-M
- STR
- Sanger
- Other Assays



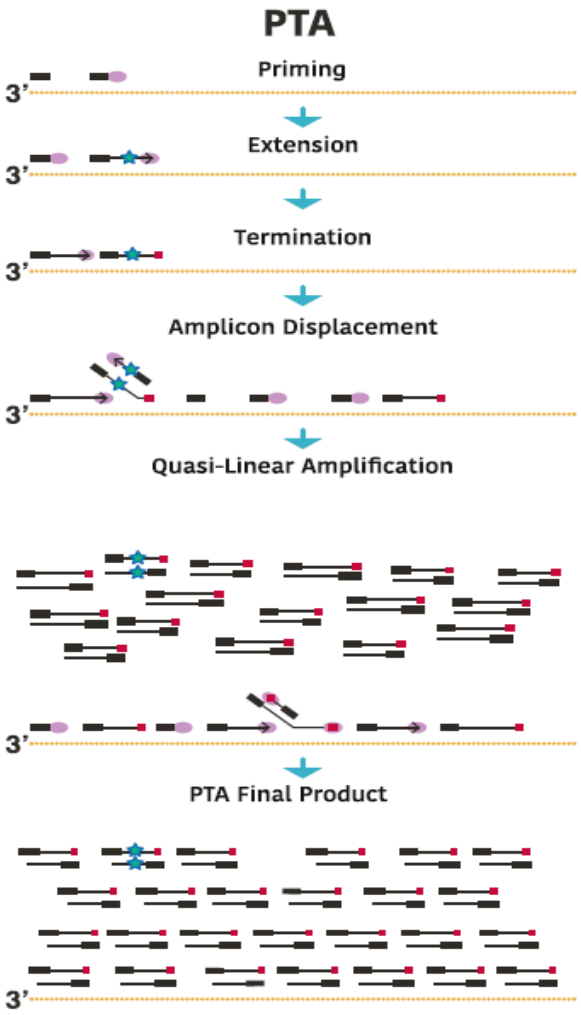

✓ Robust
*high consistency of producing results*

✓ Accurate
*high fidelity = very few errors*

✓ Complete
low bias = nearly whole genome & both alleles

# Primary Template-Directed Amplification

- Accurate, unbiased distribution of data across the entire genome

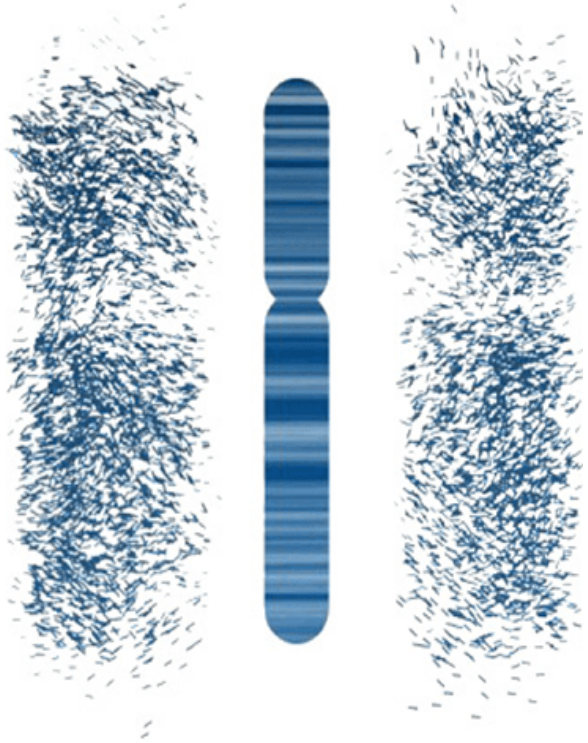



## Non-PTA

Random Priming Amplification Methods

## PTA

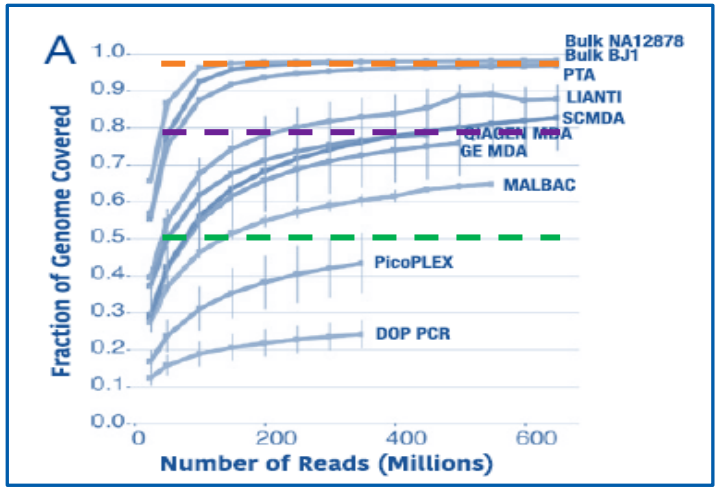
Primary Template Directed Amplification



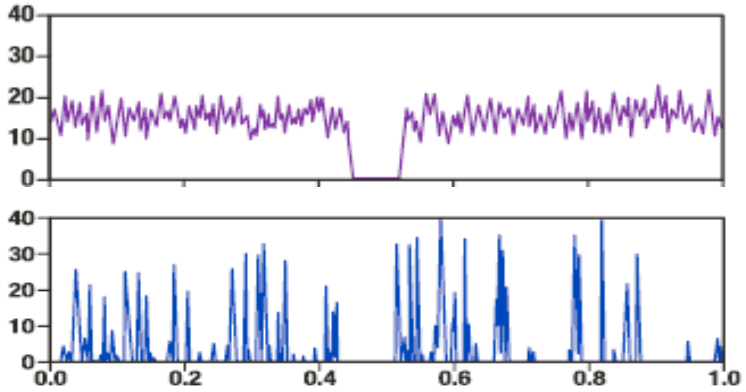
# Primary Template-Directed Amplification (PTA)

## Unbiased distribution results in more uniform (complete) genomic coverage

### Amplification of 97% of the genome



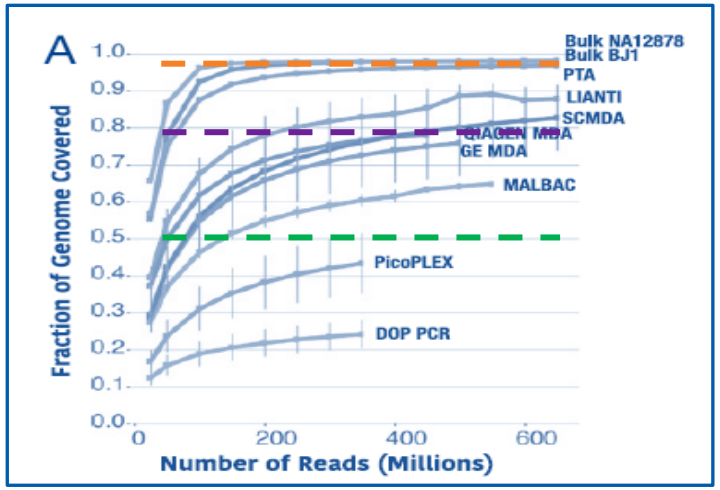

### Uniform Chromosome Coverage



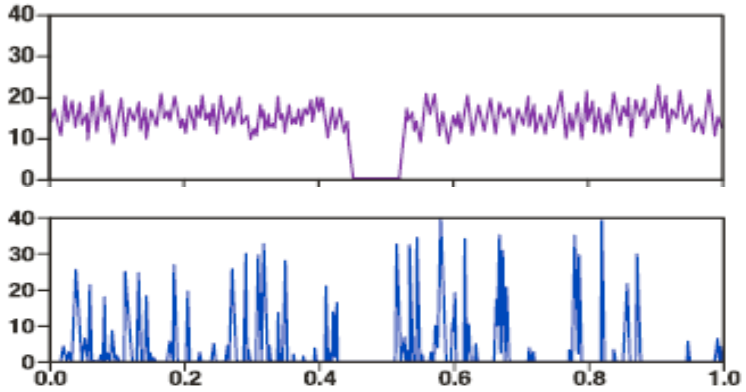
# Primary Template-Directed Amplification (PTA)

Low error propagation and full allelic discovery supports true SNP-based analysis

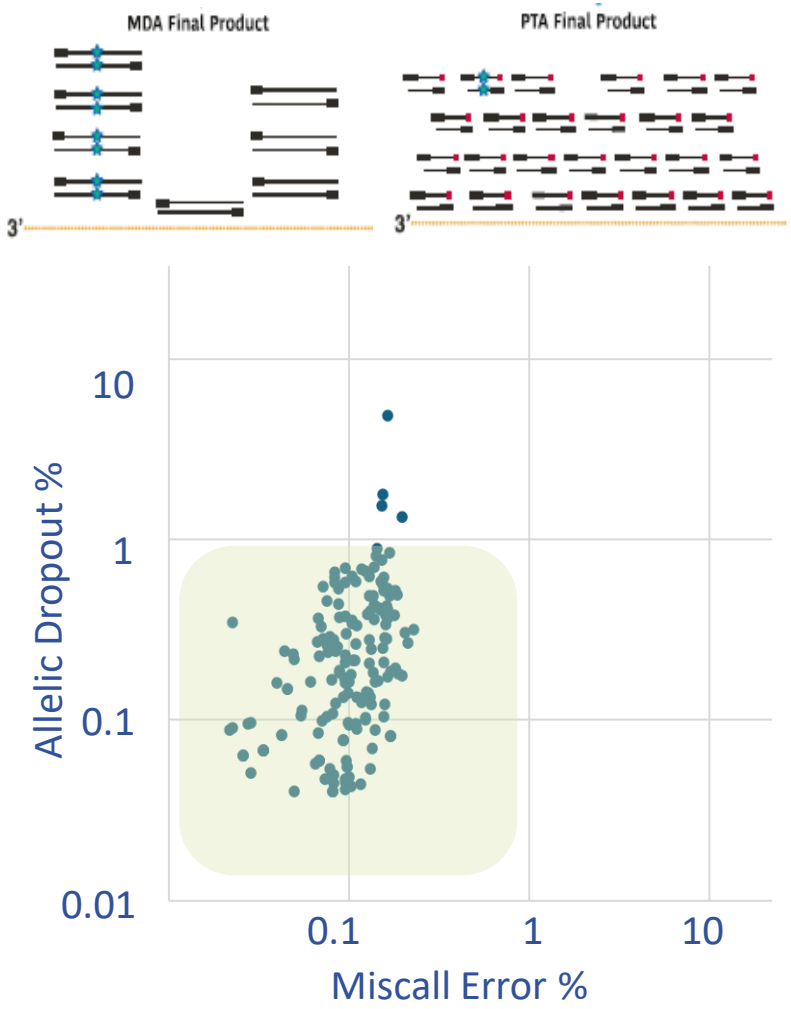
## Amplification of 97% of the genome



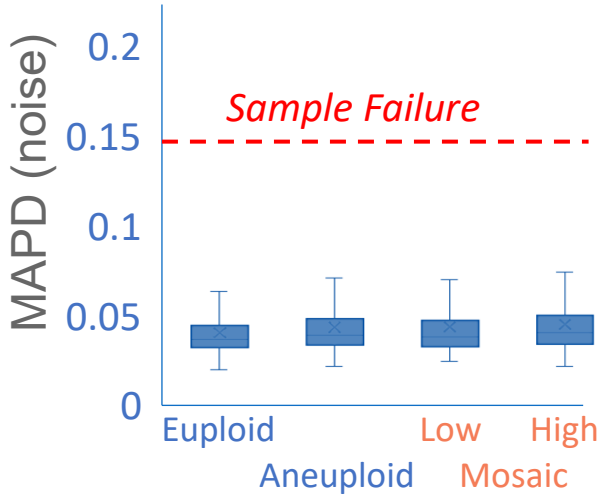

## Uniform Chromosome Coverage



## Near Zero Error or Allelic Loss

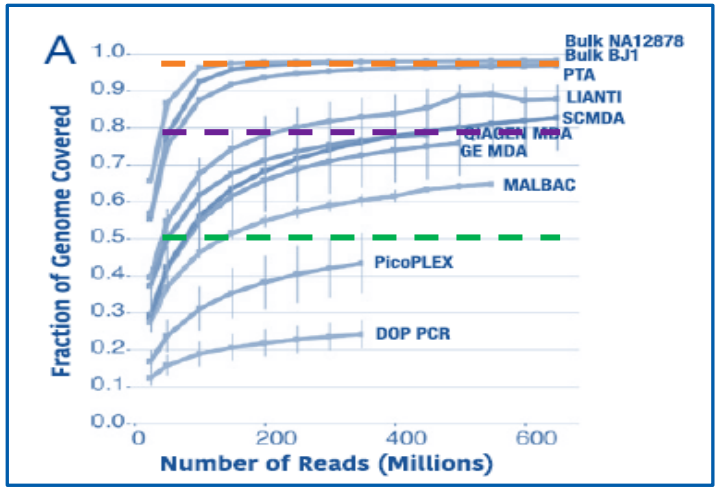



## Low Noise

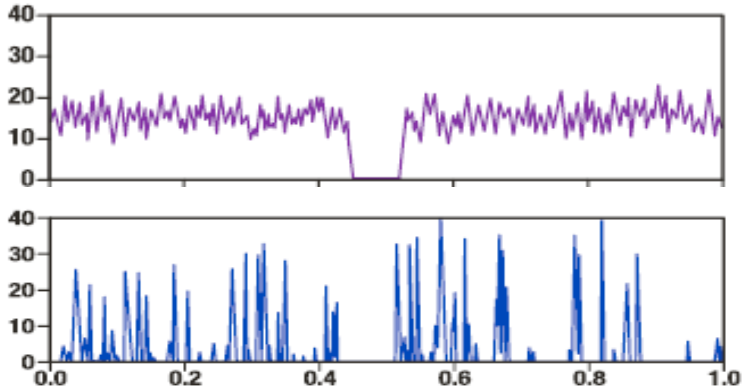


# Primary Template-Directed Amplification (PTA)

## Amplification of 97% of the genome




## Uniform Chromosome Coverage



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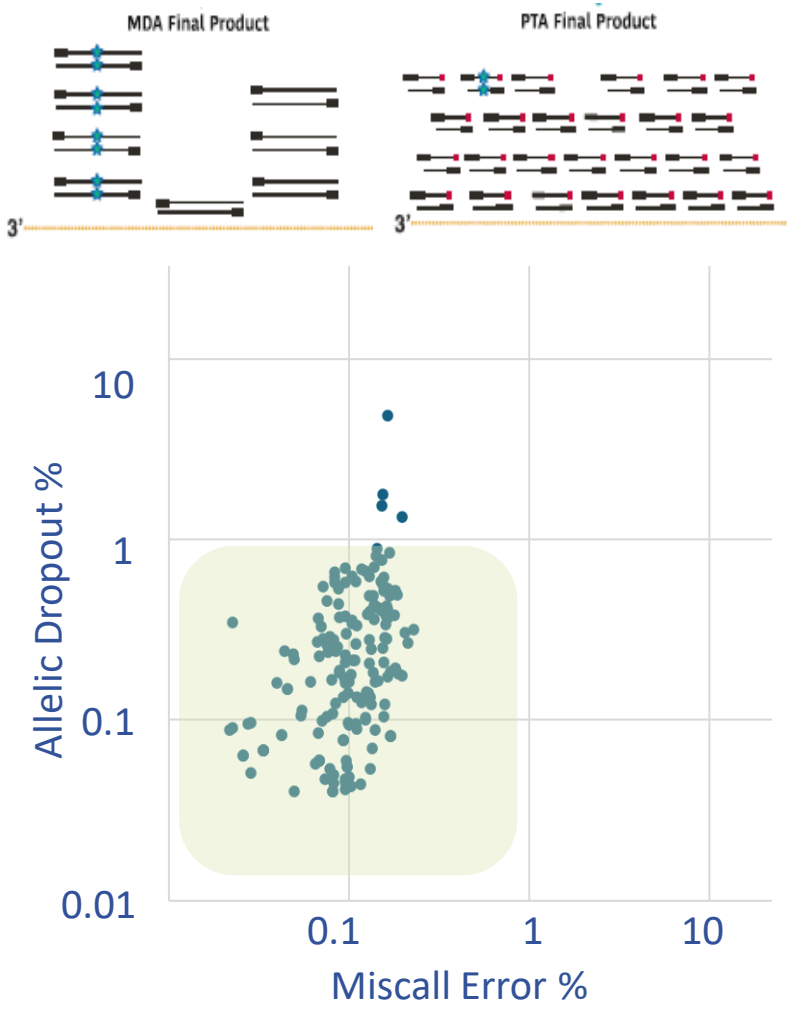
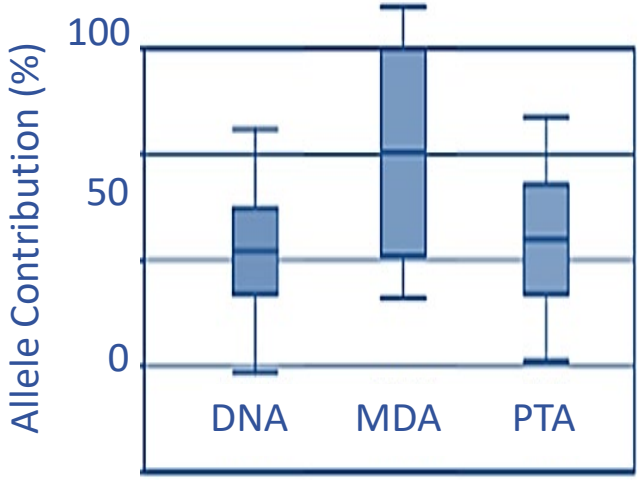
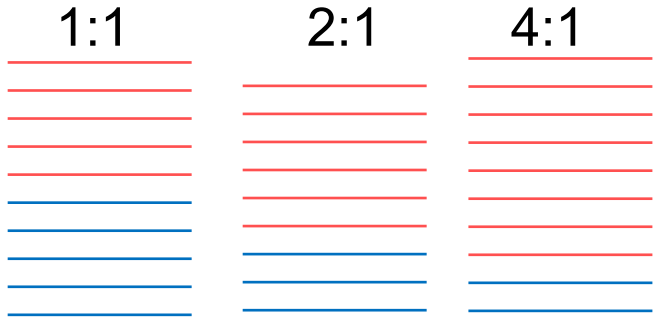



## Preserves Allelic Balance




## Ratio of alleles is maintained



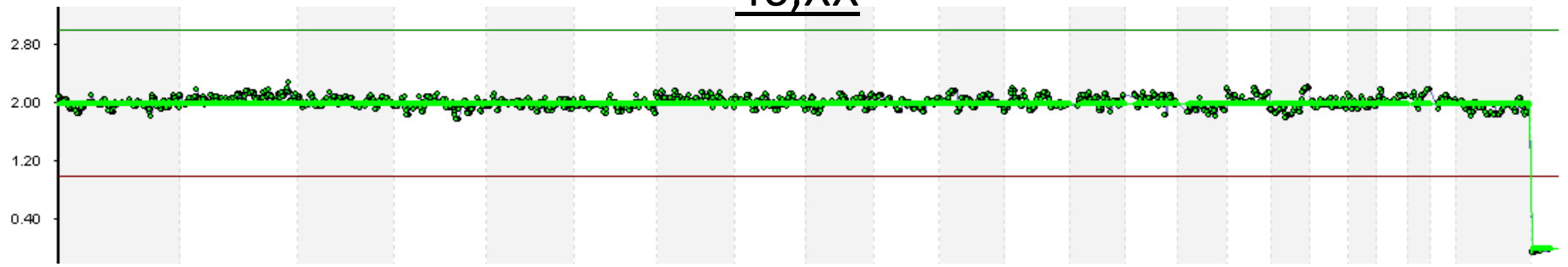
# Unprecedented performance

| Method | PTA | MDA A | Mixed Method C |
|---|---|---|---|
| Genome mapping | 97% | 88% | 55% |
| Genome recovery | 97% | 65% | 33% |
| CV of coverage | 0.8 | 1.8 | 3.2 |
| SNV sensitivity | 76% | 40% | 10% |
| SNV specificity | 94% | 93% | 65% |

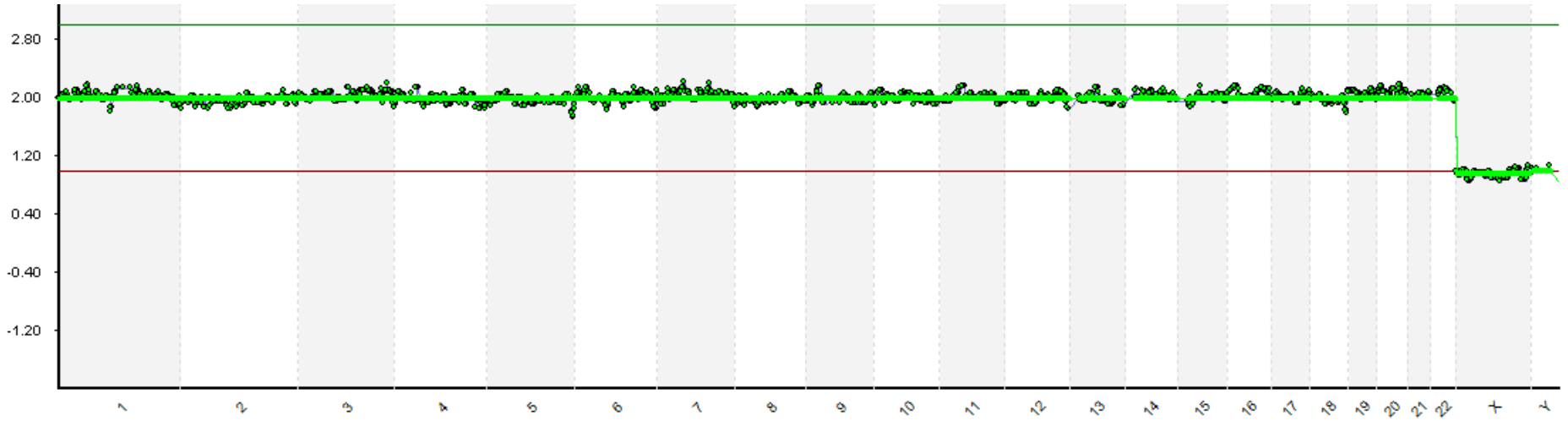
Chen C, et al. Science 2017; 356: 189–194. doi: 10.1126/science.aak9787

# From this…

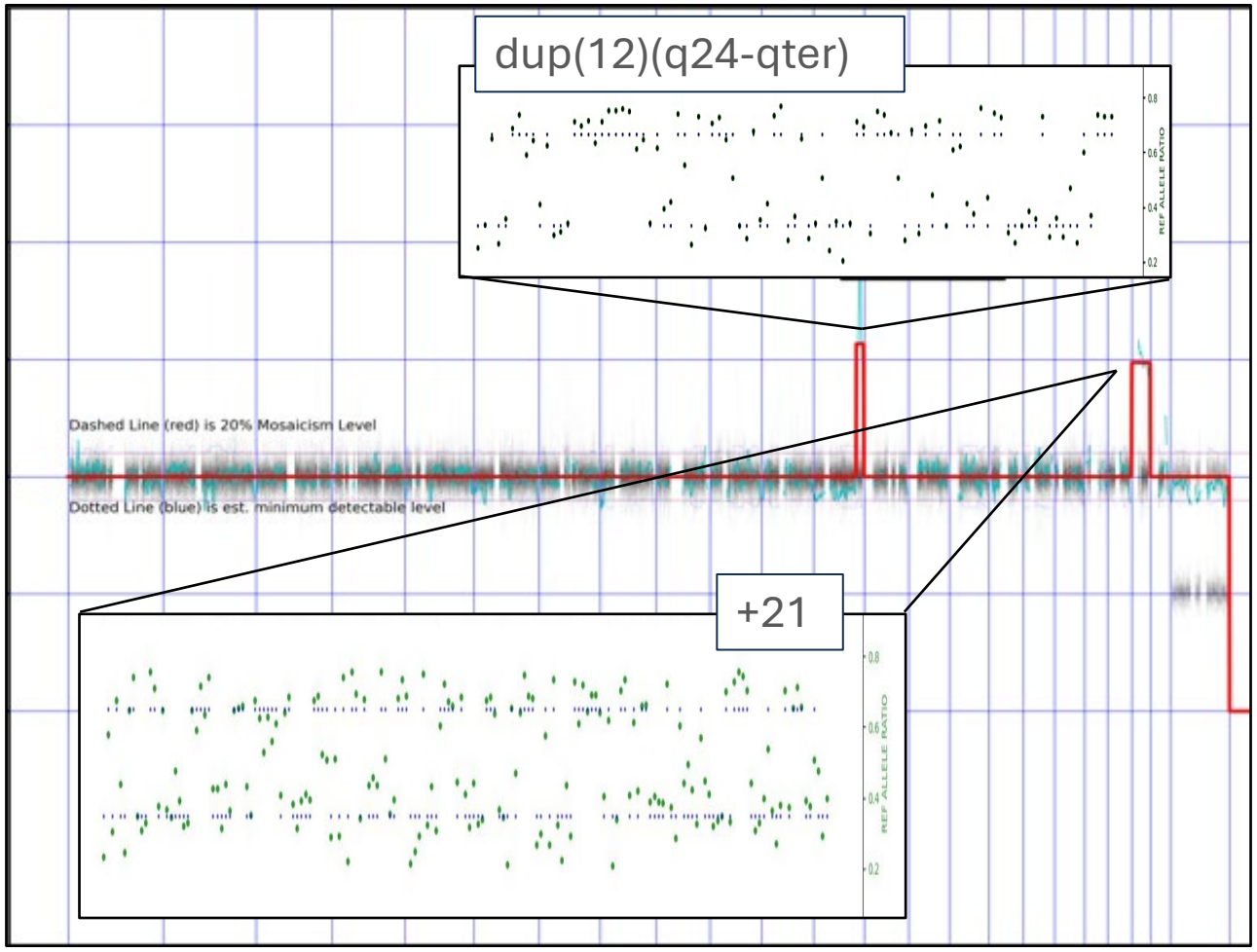
46,XX




46,XY



# ...To this




## TWO-FACTOR "AUTHENTICATION"

Tiered copy number and SNPs –
High confidence reporting through new levels of data analysis

- Locus specific,

  high depth sequencing
- 10x reduction in noise
- Up to 100K-150K SNPs

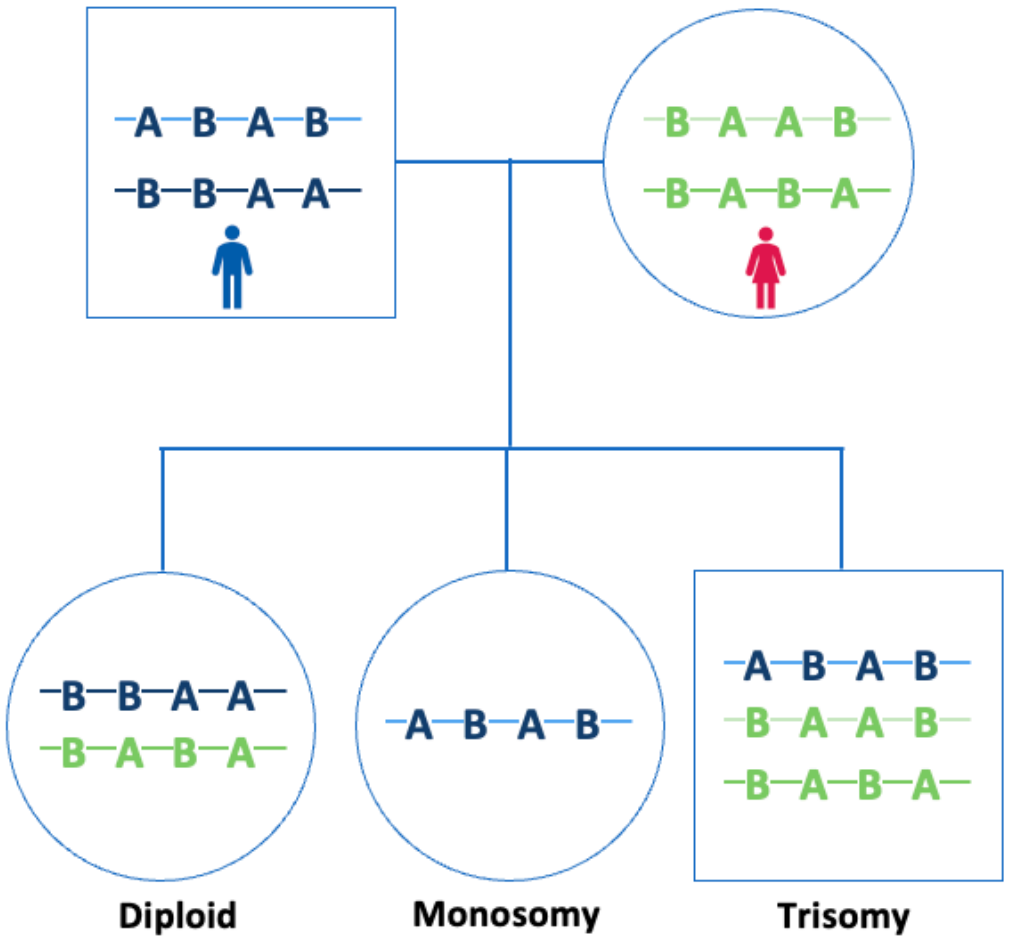
CooperSurgical internal data

# PGT-A and SNPs

# A Snippet on SNPs

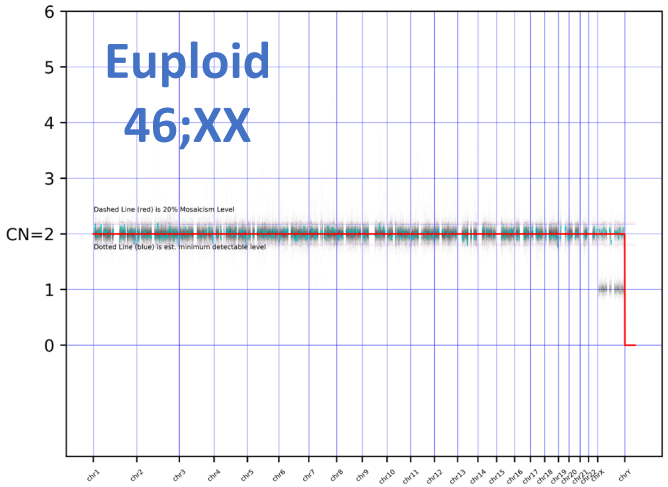
## Single Nucleotide Polymorphisms

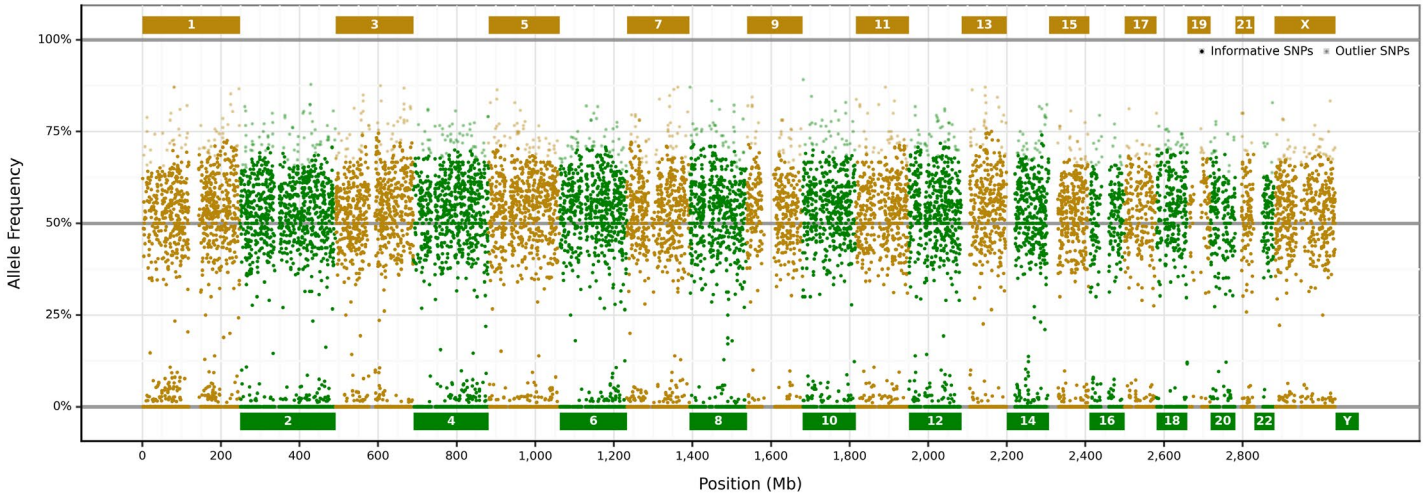
- Variation in the genome at a single nucleotide position occurring in >1% of the population
- ~10,000,000 throughout the genome, on average every 200 bp
- May be associated with traits or disorders, but most have no known function
- SNV: single nucleotide variant is a more generic synonym for less well-characterized loci
- *No two individuals** have the same pattern of SNPs*
- Exist as major and minor isoforms within a given population

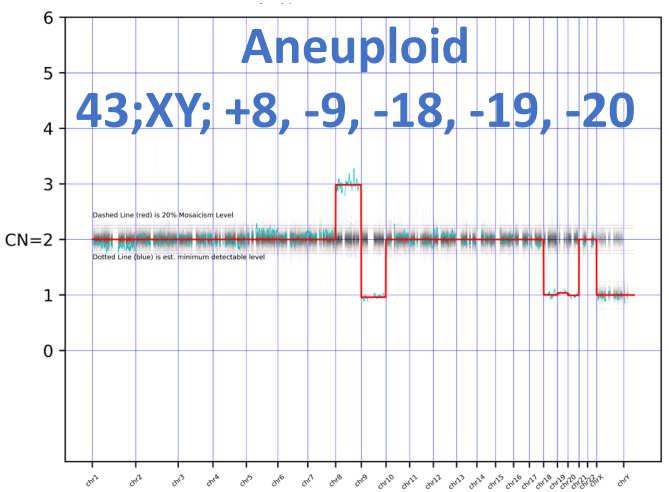


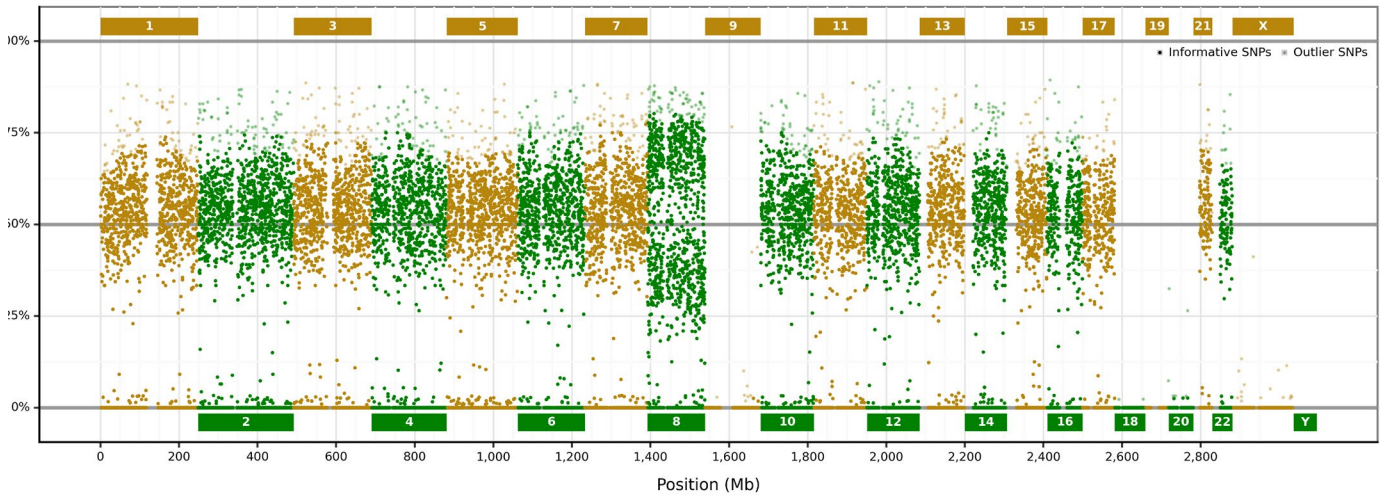

*except identical twins

# NGS + SNP Plots



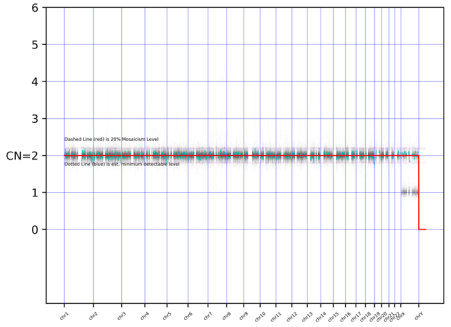



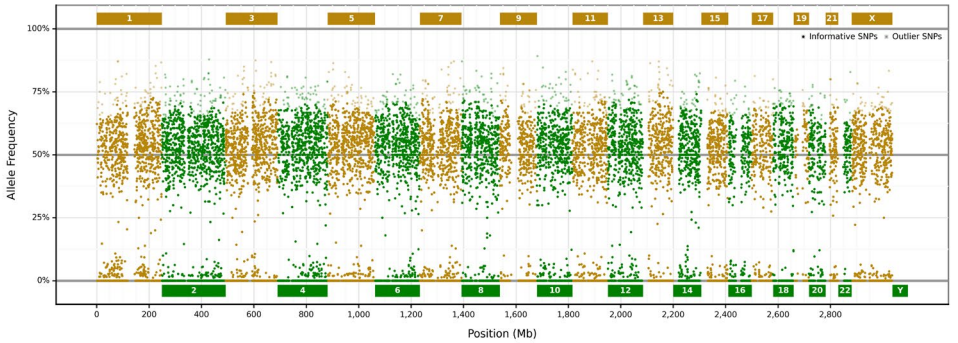



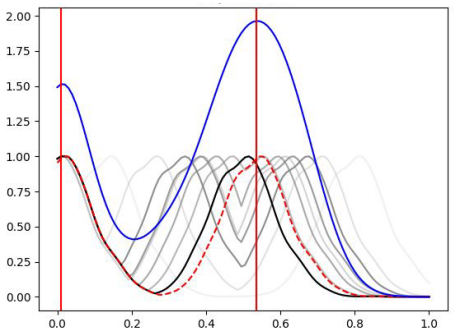



# Polyploidy Testing

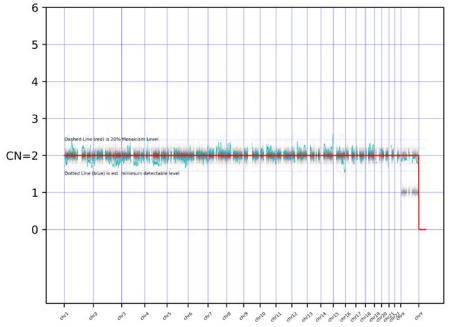
**Diploid**
**46;XX**

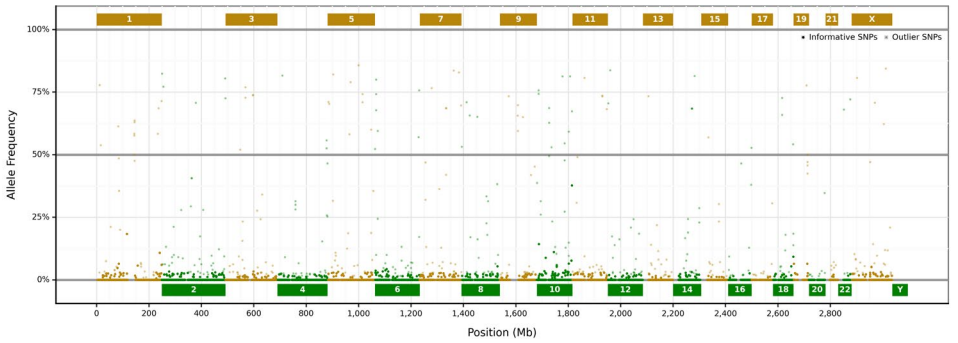


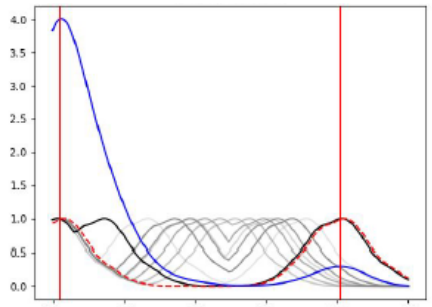



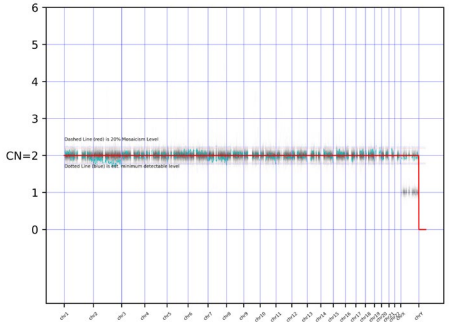
**Haploid**
**23;X**

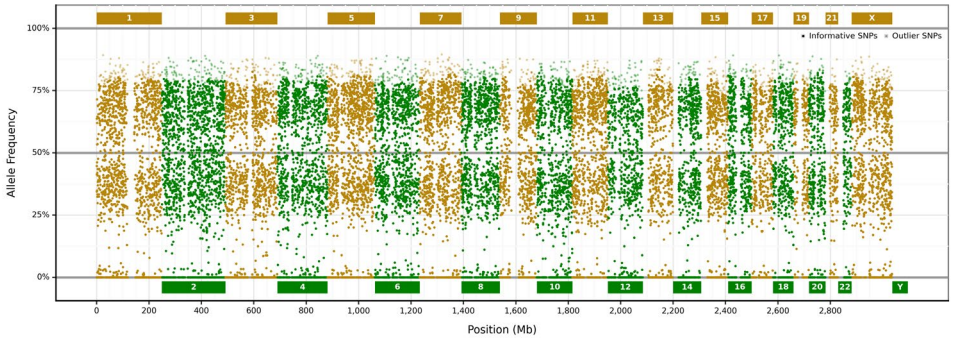


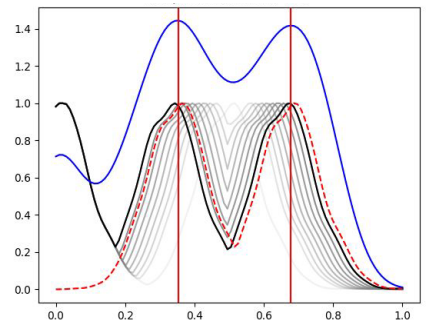



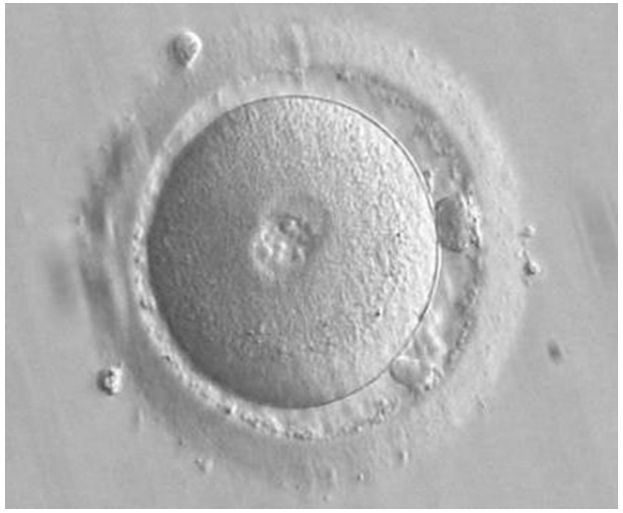
**Triploid**
**69;XXX**

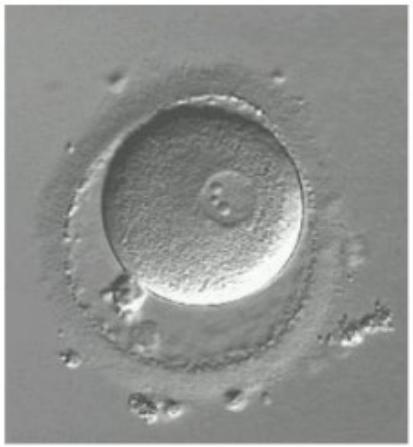


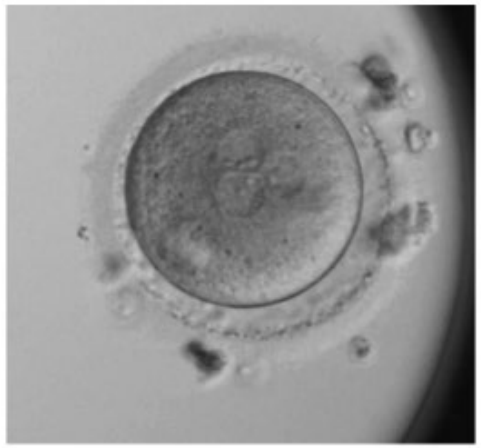



# PN Checking

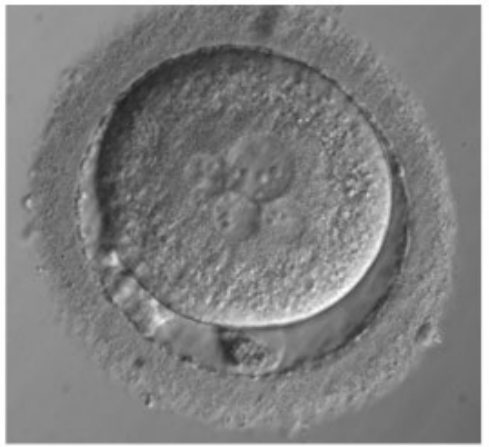




1PN



3PN



≥4PN

# Abnormal PN Outcomes

## 0PNs

- **McCallie 2024**
  - 291 0PN blastocysts
  - Haploid: 2.1%
  - Aneuploid: 41.9%
  - **Diploid/euploid: 56%**

- **Paz 2020**
  - 27 0PN blastocysts transferred
  - Implantation rate: 48%
  - Ongoing pregnancy rate: 50%
  - **13 live births (59% live birth rate)**

## 1PNs

**McCallie 2024**

- 217 1PN blastocysts
- Haploid: 36.4%
- Aneuploid: 31.8%
- **Diploid/euploid: 31.8%**

**Itoi 2015**

- 33 1PN blastocysts
- Implantation rate: 33.3%
- Clinical pregnancy rate: 33.3%
- Ongoing pregnancy rate: 27.3%
- **9 healthy live births (27.3% live birth rate)**

## 3PNs

**McCallie 2024**

- 172 3PNs
- Triploid: 50% (59% XXY; 41% XXX)
- Aneuploid: 41.9%
- **Diploid/euploid: 8.1%**

**Capalbo 2017**

- 14 2.1 PNs
- Diploid: 12 (87.5%)
- **2 healthy live births (of 3 transfers)**

Reproductive BioMedicine Online
Available online 24 October 2024, 104595
In Press, Journal Pre-proof What's this?

Article

# Reassessing the conventional fertilisation check: leveraging PGT-A to increase the number of transferrable embryos

Balsam Al Hashimi [a b c], Simon Harvey [d], Katie Harvey [e], Elena Linara-Demakakou [a], Bhavna Raikundalia [a], Orla Green [a], Darren Griffin [b], Kamal Ahuja [a], Nick Macklon [a]

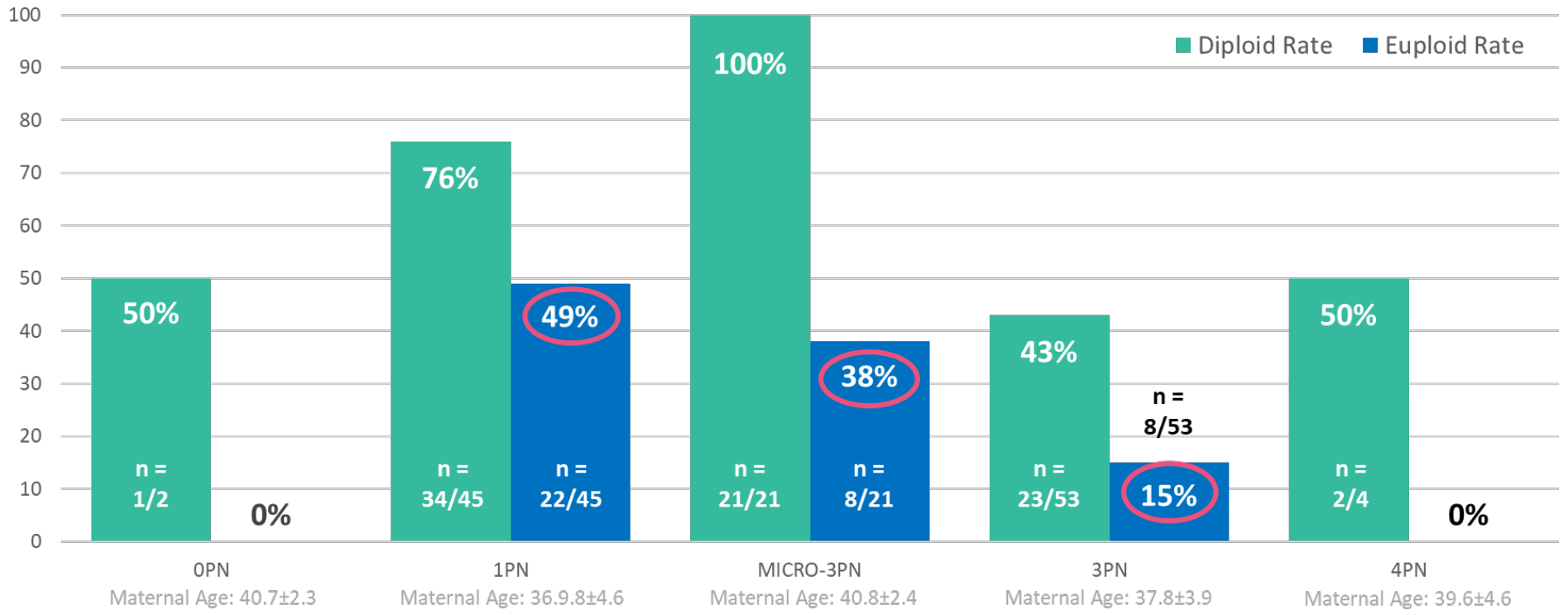
Show more



https://doi.org/10.1016/j.rbmo.2024.104595 Get rights and content

# Clinic Experience

**Retrospective, single center, ICSI and IVF Fertilized, 125 embryos**



# Pregnancy Outcomes

| | 1PN | Micro-3PN | 3PN |
|---|---|---|---|
| **Positive Bhcg** | 40% (2/5) | 100% (3/3) | 67% (2/3) |
| **Clinical pregnancy** | 40% (2/5) | 67% (2/3) | 67% (2/3) |
| **Ongoing pregnancy** | 40% (2/5) | 67% (2/3) | 67% (2/3) |
| **Live birth** | | | |
| **Patient** | 3 33% (1/3) y round IVF, 4AA-1PN-euploid | 20%( 1/5) 4AA-1PN, micro-3PN-euploid | 33% (1/3) 4AA-1PN, last attempt 3PN-euploid |

**Take home message:**

Genetic PN Checking may help those with few embryos available and help them achieve the goal of having a child.

# Origin of Aneuploidy

- Not all aneuploidy is maternally derived
- Paternal contribution to aneuploidy can be overlooked
- Can help guide informed donor decisions
- Helps to confirm whether an egg donor or sperm donor would be more beneficial

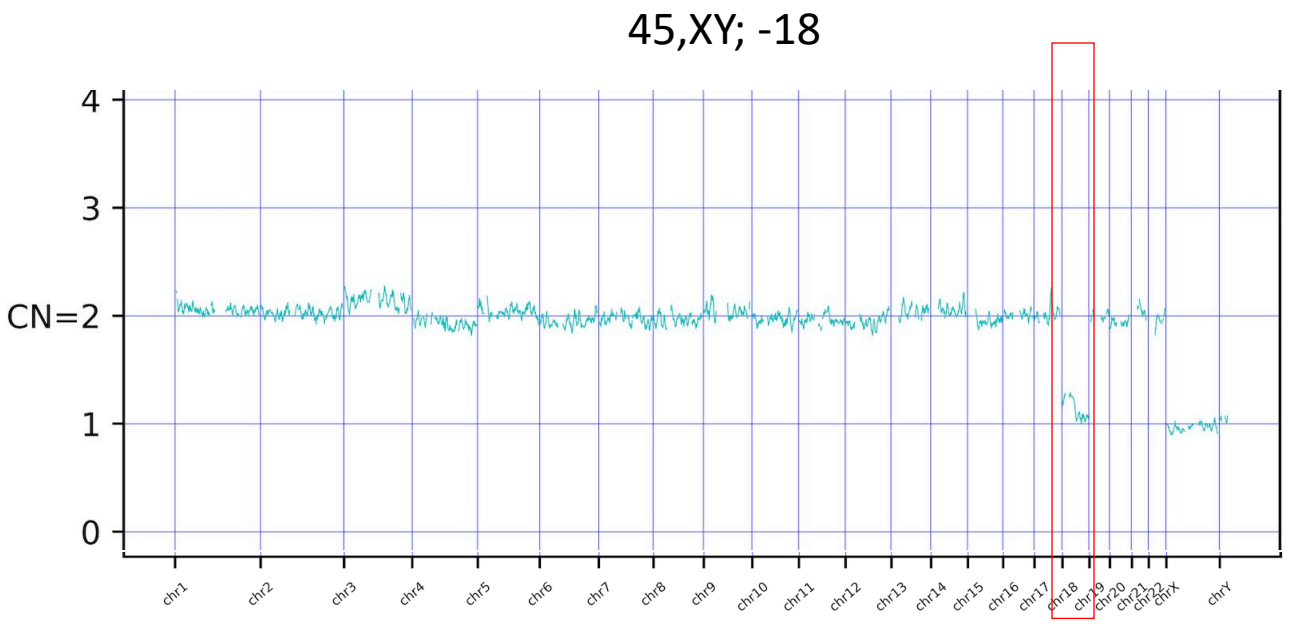

of whole chromosome aneuploidy is of paternal origin.

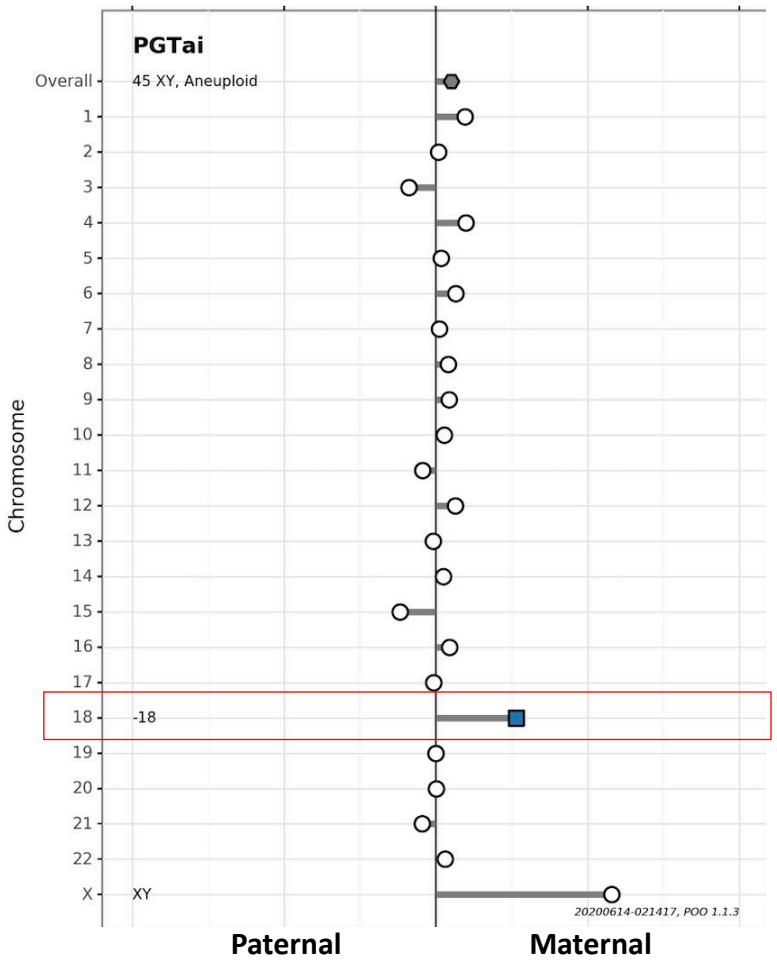
Hassold et al. 1992, Kubicek et al. 2019


of segmental aneuploidy is of paternal origin.

Hassold et al. 1992, Kubicek et al. 2019

# Origin of Aneuploidy




Monosomy is Paternal in Origin

**These images were generated for data visualization purposes only**

# Parent & Sibling QC


## Gamete Comparison

- Uses SNPs to track the presence of both gamete contributors' genetic material
- Confirms intended gamete sources used
- Identifies whether aneuploidy arose from oocyte or sperm
- Maternal cell & exogenous contamination
- Biparental diploid confirmation

## Sibling Comparison

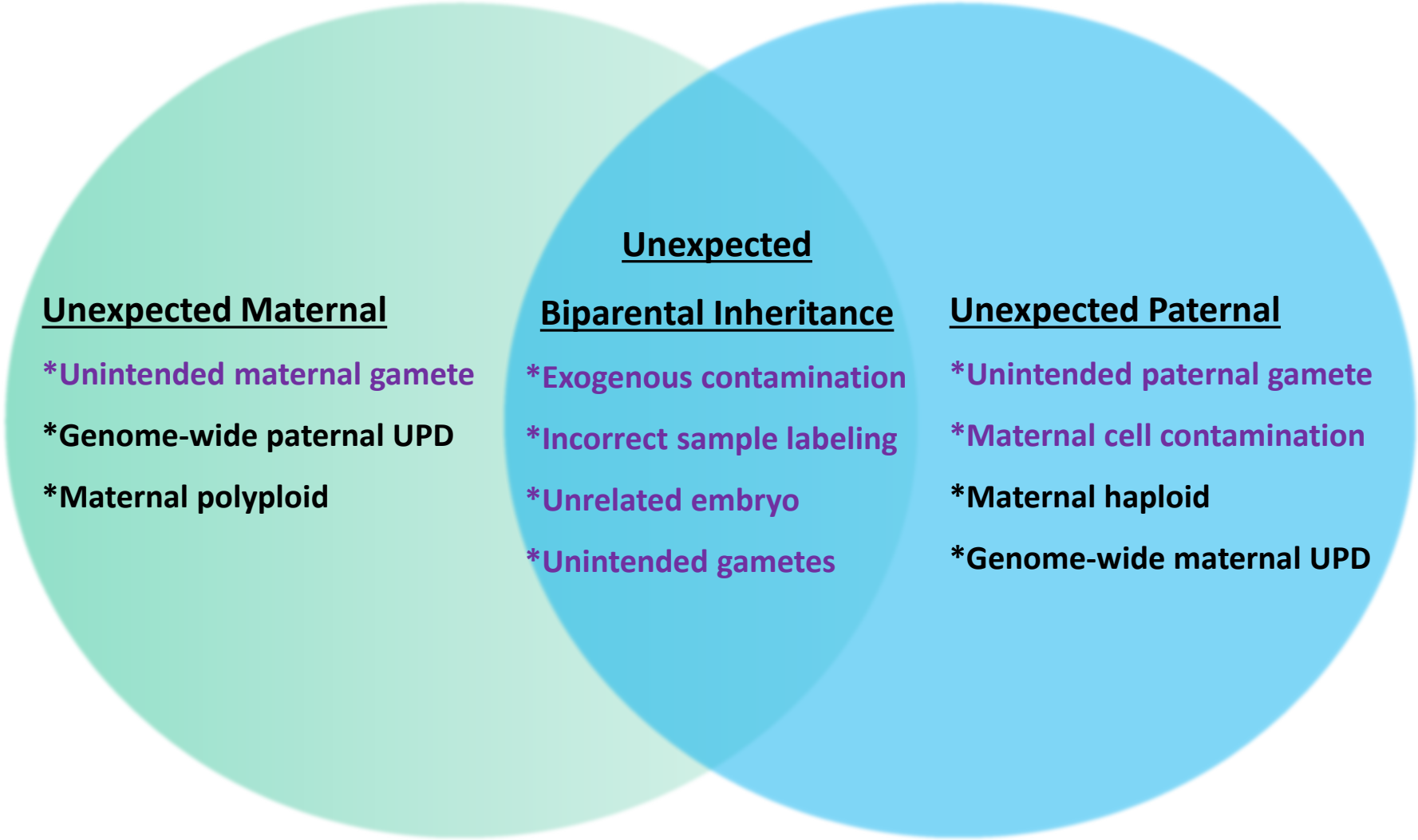
- Uses SNPs to confirm full sibling identity between embryo cohort
- Exogenous contamination
- Same embryo biopsied twice

# Possible Gamete Mismatch Causes

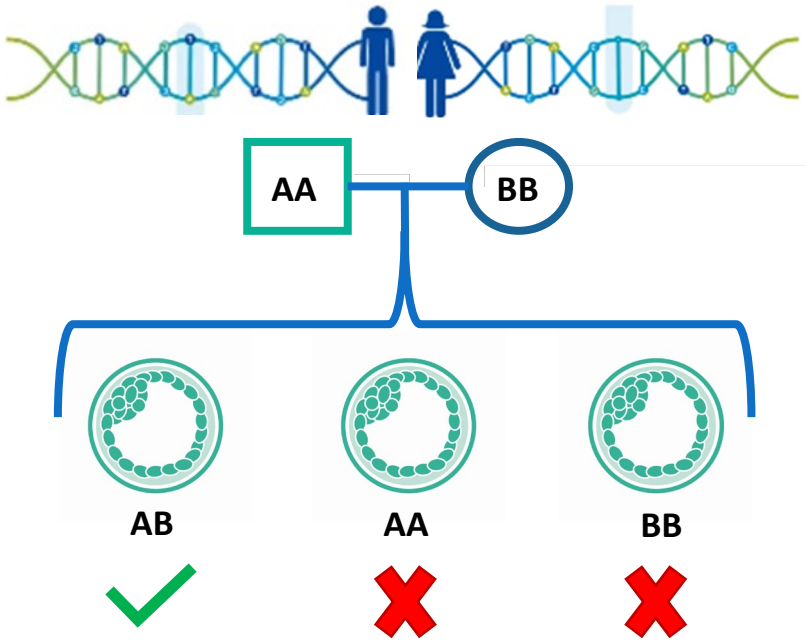
**Causes:**

**Biological**

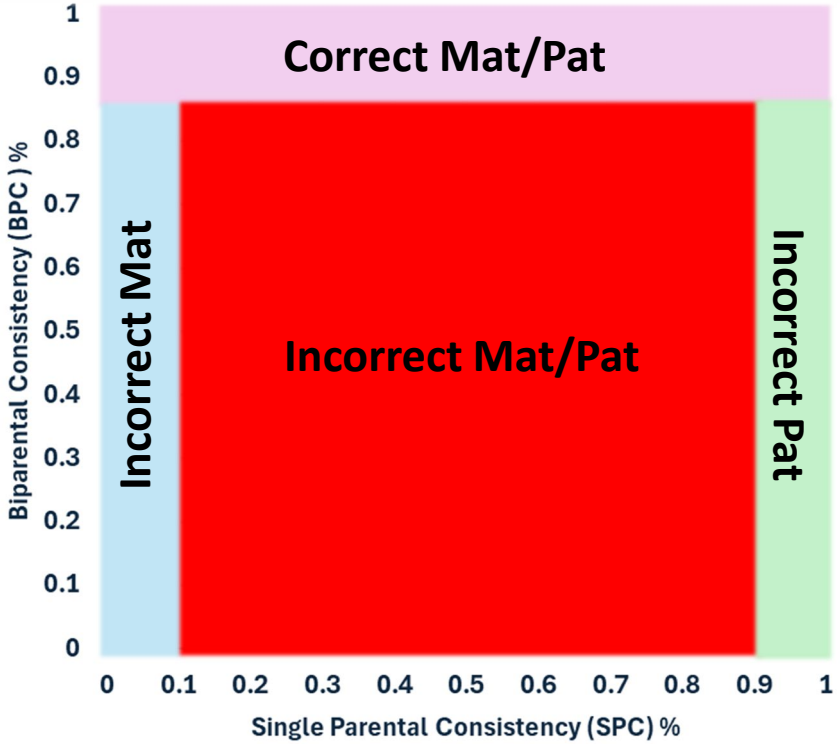
**Technical**



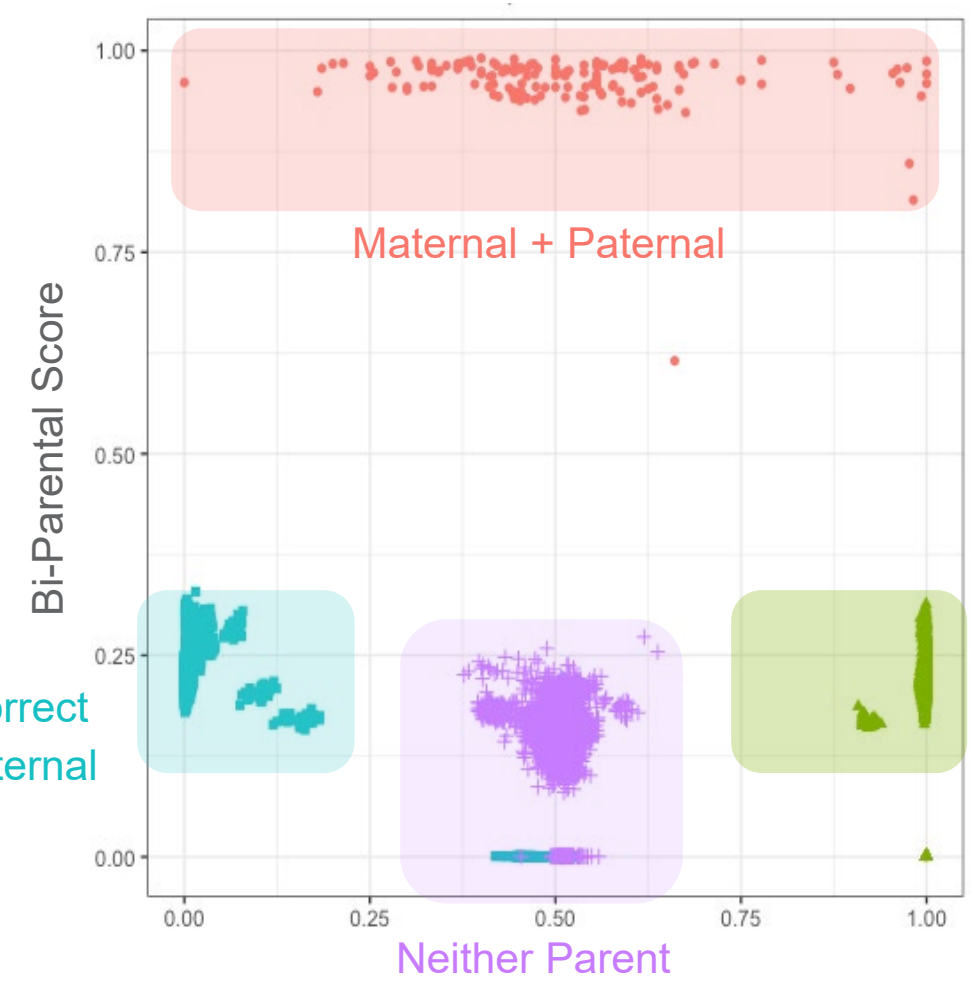
# Parent QC




- >100,000 SNPs utilized per TRIO
- Site requirements for BPC:
  - ✓ ≥30x depth
  - ✓ Overlap between Mat, Pat, and Embryo
  - ✓ Must be in diploid region
  - ✓ Must be homozygous for both parents & heterozygous for embryo



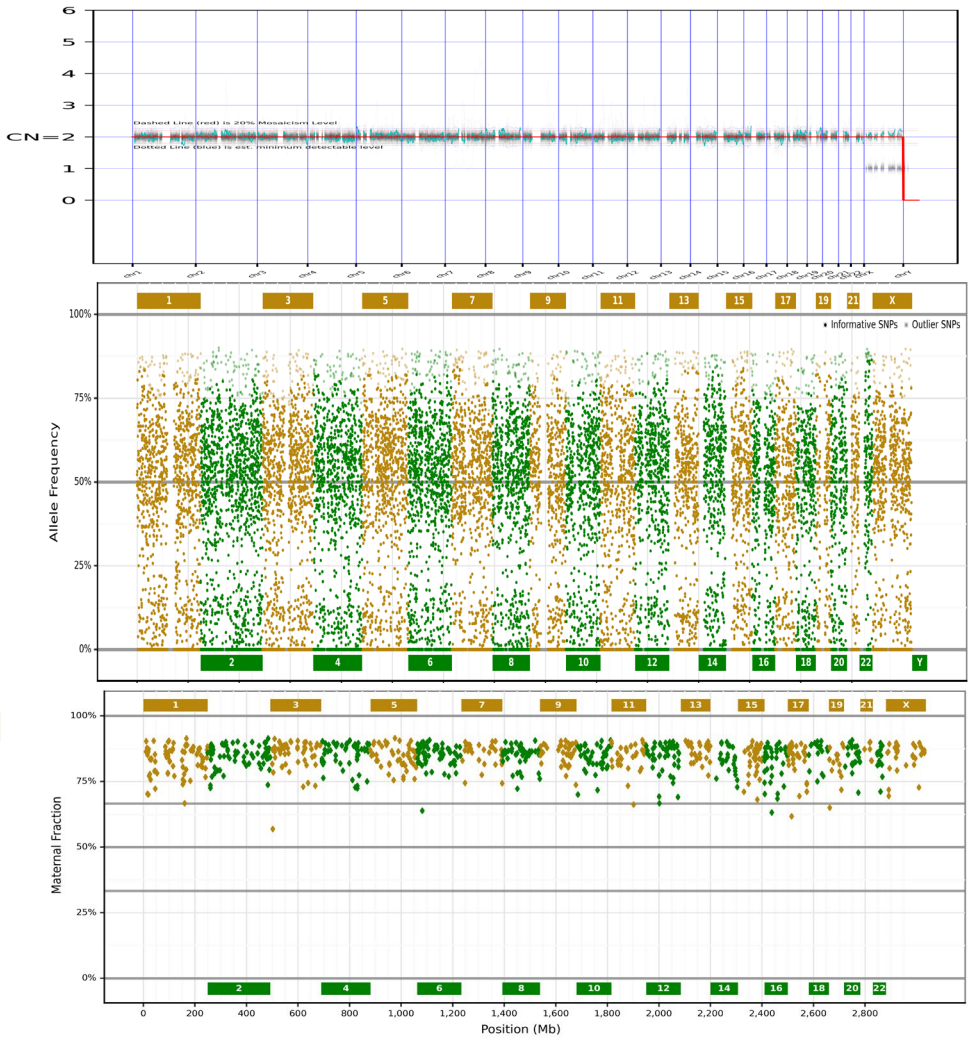
# Parent QC and Contamination




Correct Paternal

Correct Maternal

Strong Maternal Cell Contamination




Low-noise Euploid Female 46;XX

Uniform Low-Level Minor Allele “cloud”

Nearly 100% Maternal Contribution

# Sibling QC and Contamination Detection

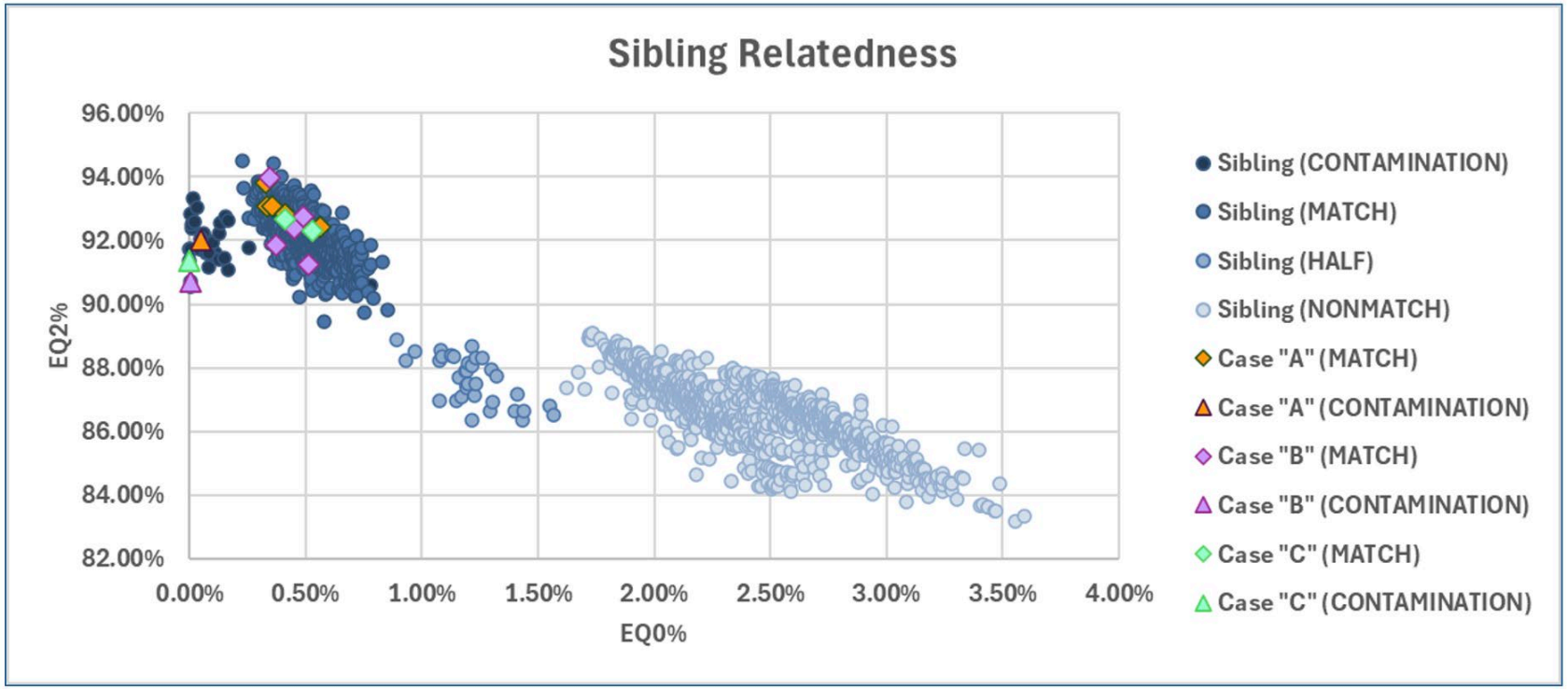
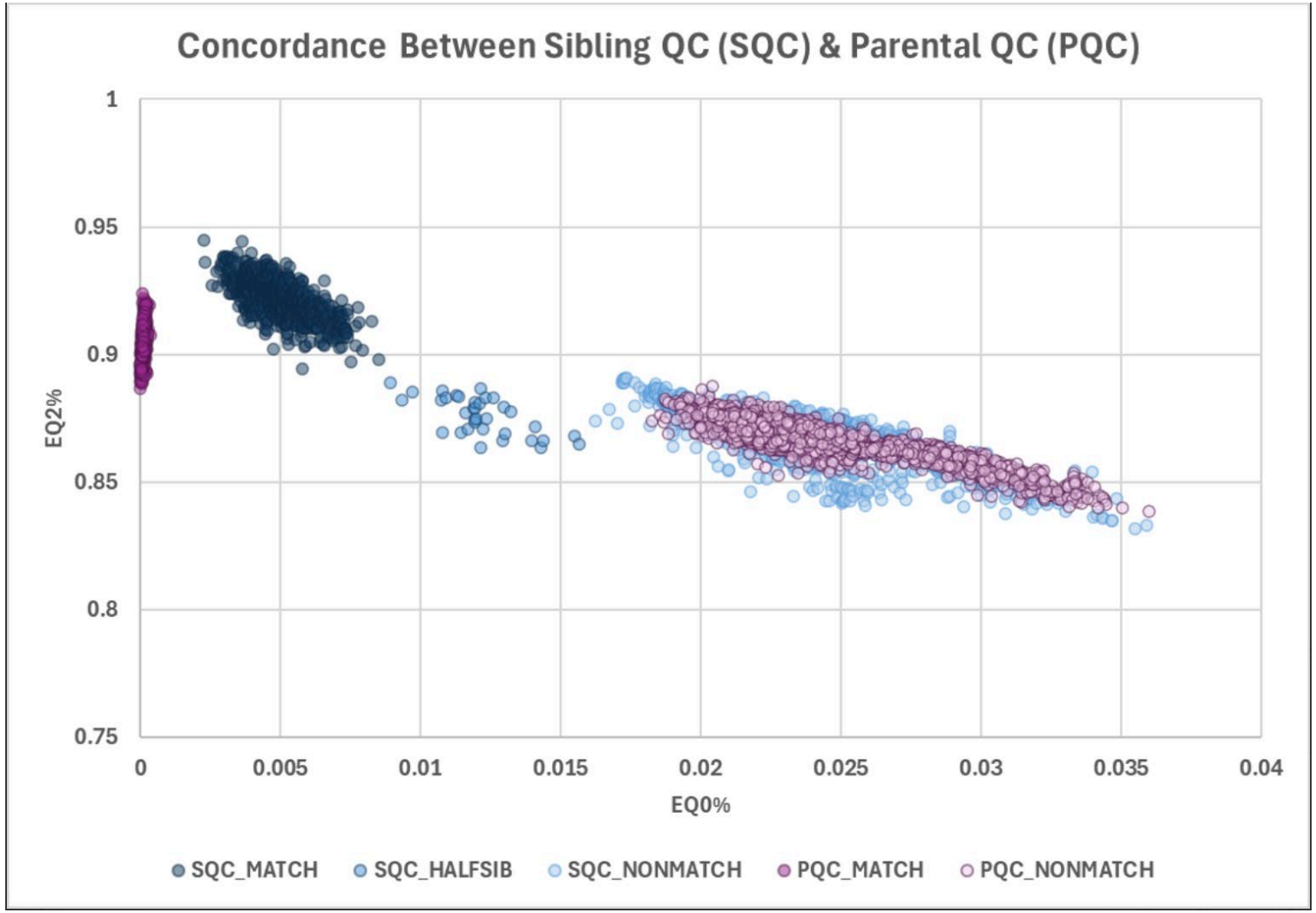
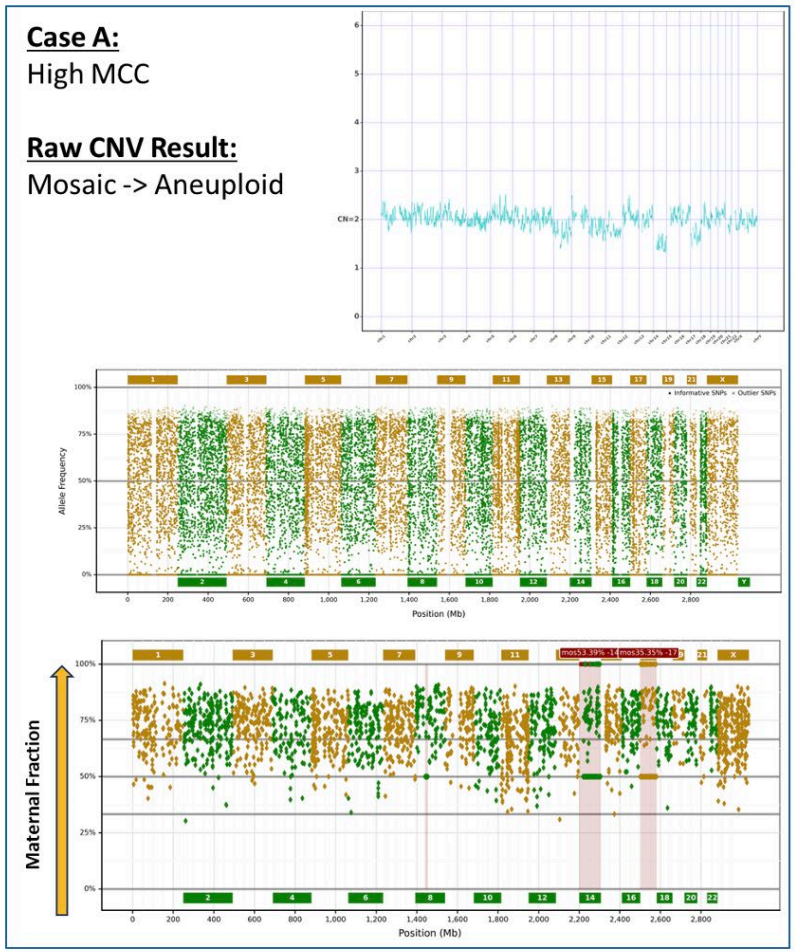


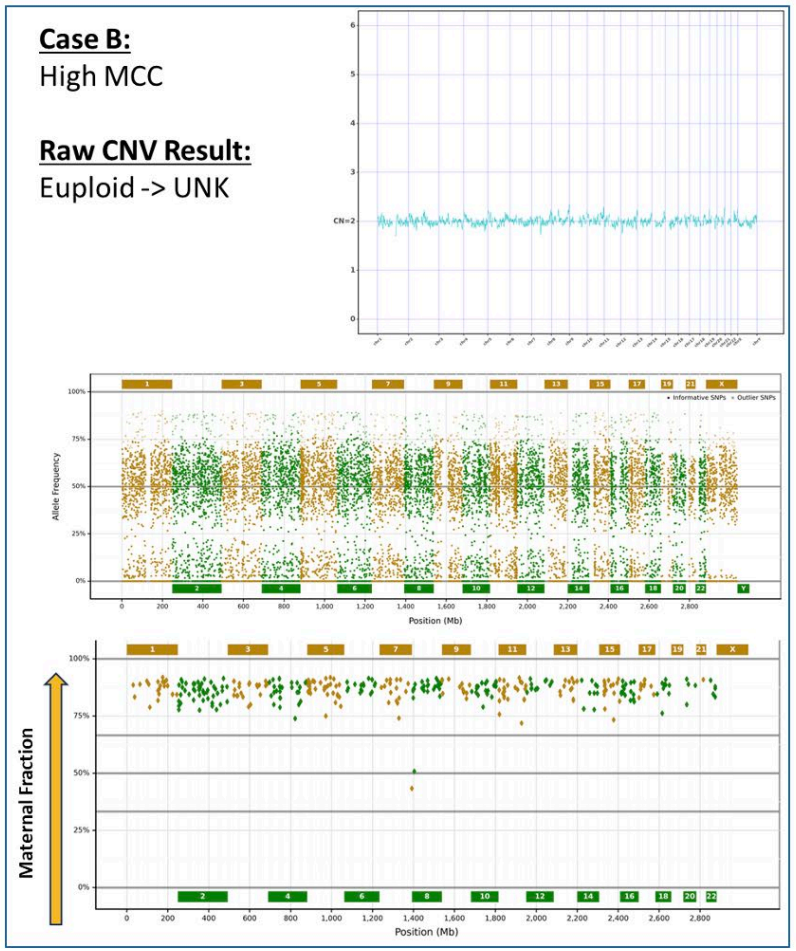

**Figure 4.** Evaluation of overlapping genotypic sites in DUO analysis across sample relationships: correct siblings (with and without detected contamination), half-siblings, and incorrect sibling pairings. Three representative cases ("A", "B", and "C") are included to illustrate variability observed.

# Sibling QC & Parental QC



# Contamination



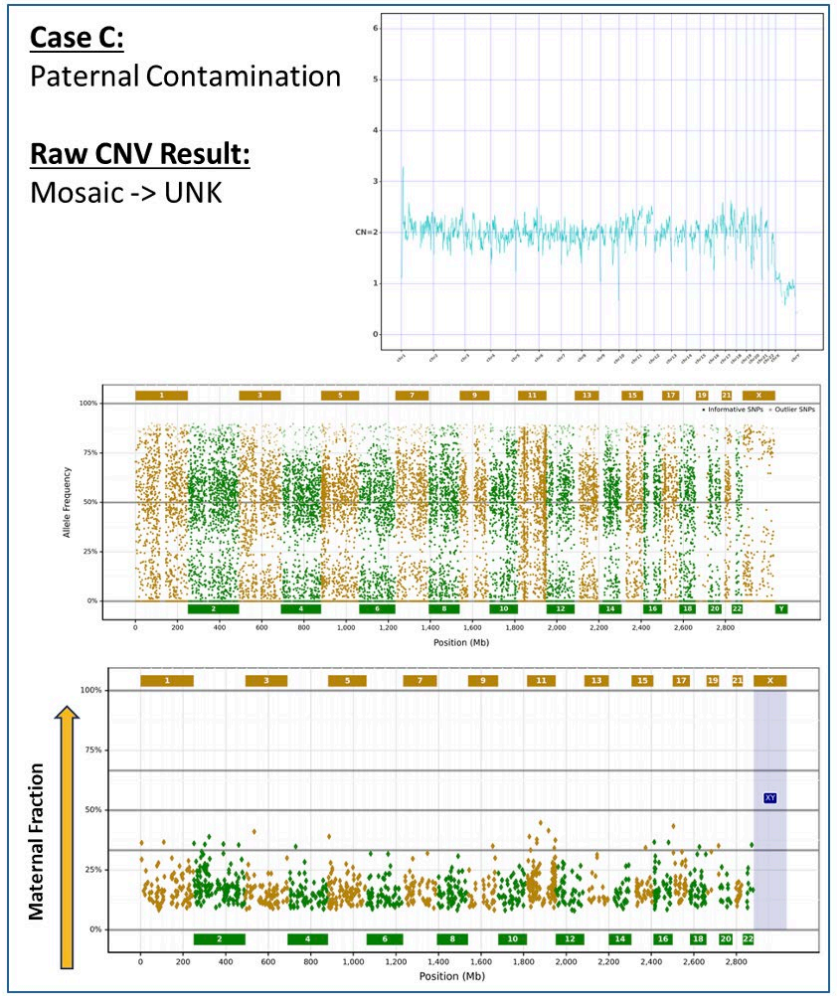




**Figure 6.** Representative contamination example cases each containing CNV, AF, and Maternal Fraction plots.

# PGT-A and SNP Analysis: Questions to Ask

- **How are you performing PGT-A** in your lab? NGS? SNPs? Both?
- Roughly **how many SNPs** are you looking at?
- **What are you able to detect** with SNP analysis? What can you not detect?
  - Haploidy/female triploidy/"PN Checking?"
  - Parent/sibling relationships?
  - Origin of aneuploidy?
  - Contamination? Maternal vs exogenous?
  - Uniparental disomy/diploidy?
  - Loss of heterozygosity?
- Do you need additional **samples from the gamete contributors?**
  - What sample types can you accept?
  - Can you perform on donor cases?
- Can you offer this testing **retrospectively?**

# PGT-A and SNP analysis: Patients to Consider

- **All patients**: new standard
- **History of SAB**, especially if triploid/molar pregnancy
- Unexpected aneuploidy
- Advanced maternal age needing **closure on autologous IVF**
- Concerned about chain of custody
- Question of correct laboratory **protocol/contamination/deception**

# Case: Recurrent Polyploidy

- Case submitted for PGT-A – 6 samples run, all returned as polyploid
- Laboratory released report to clinic and discussed suspicion for maternal cell contamination
- Clinic relayed : patient had a 7th, untested embryo transferred from the same cycle. The patient had a miscarriage and POC results revealed triploidy.
- So, 7/7 embryos all have triploidy.
- Parental buccal swabs tested for parent of origin analysis
  - 6/6 tested embryos – maternal in origin

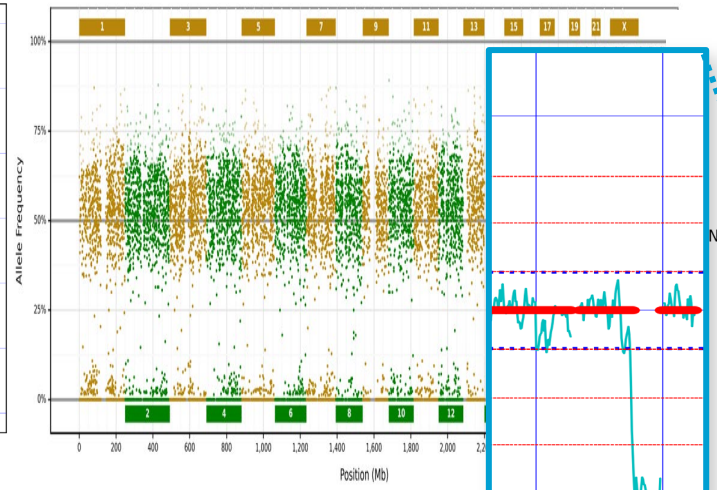
# Improved Mosaic and Segmental Calling

# Mosaic and Segmental Reporting

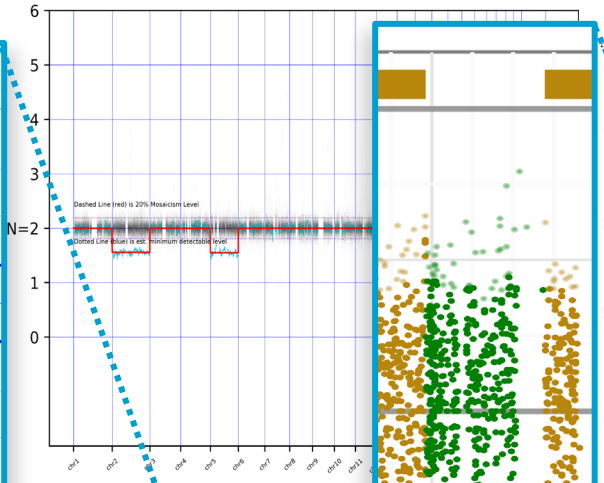
Higher confidence across all outcomes

## Euploid

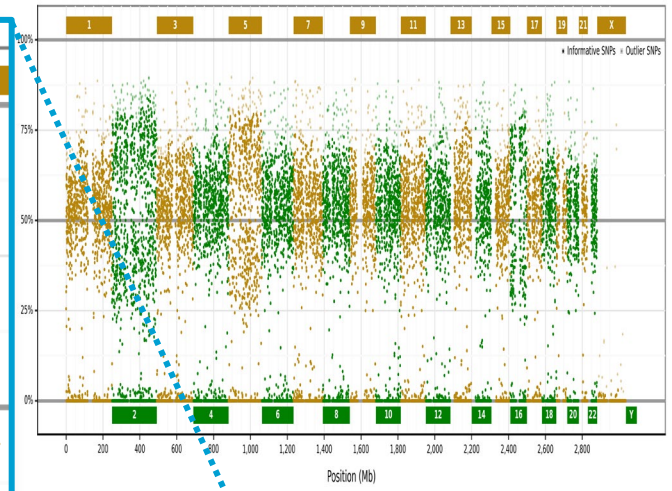

## 46;XX



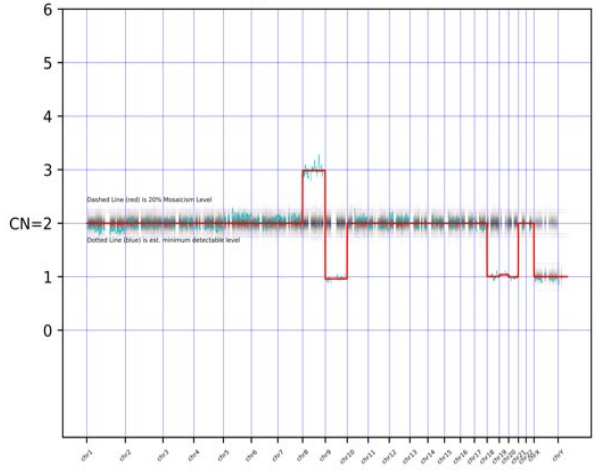

## Mosaic



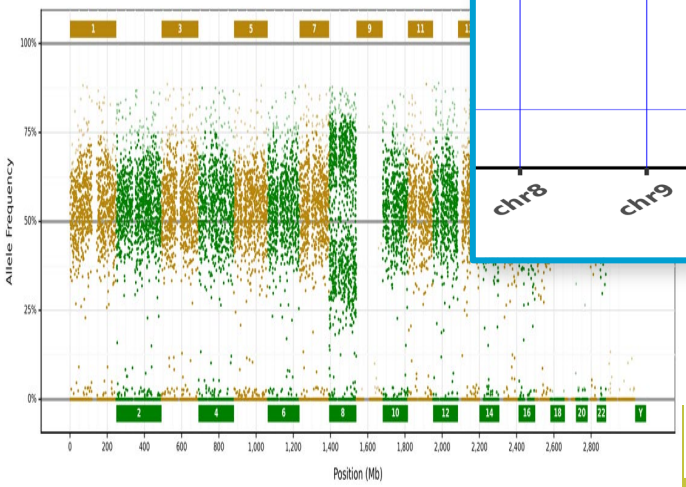

## 43;XY Mosaic -2, -5, -17



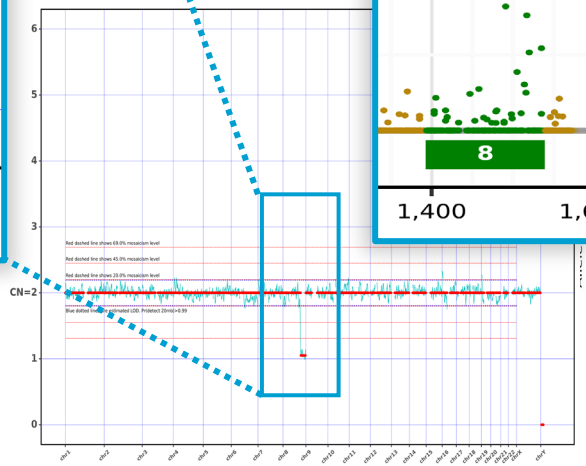

## Aneuploid



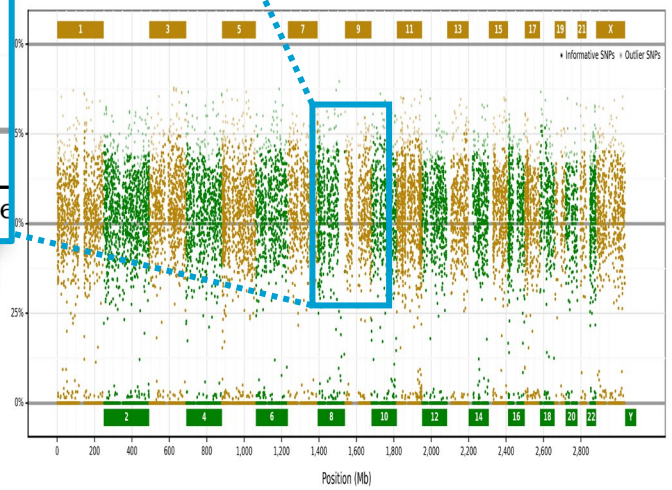

## 43;XY; +8, -9, -18,



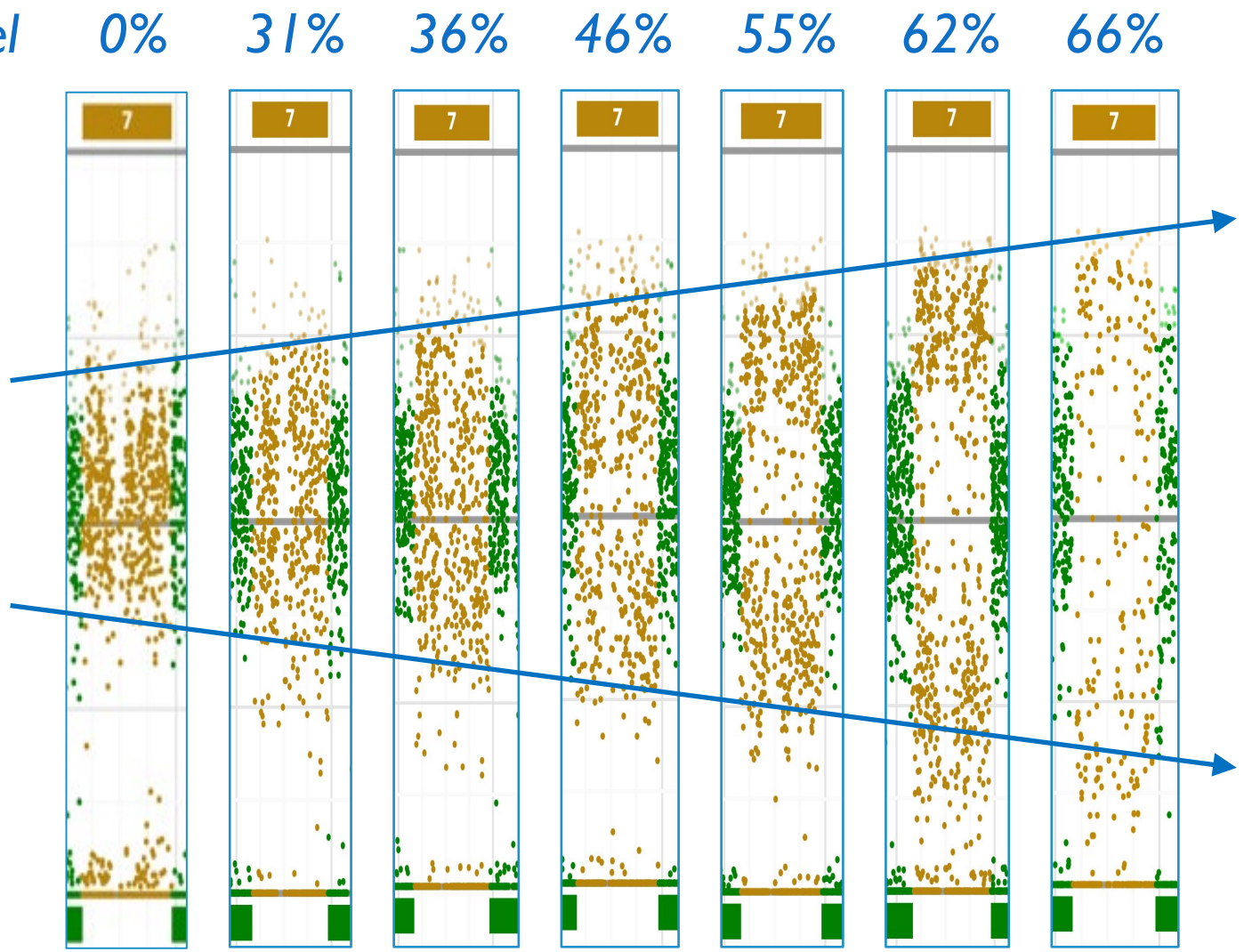

## Segmental




## 46;XX; del(8)(q23.3-qter)



# Mosaic resolution With CNV and SNP analysis



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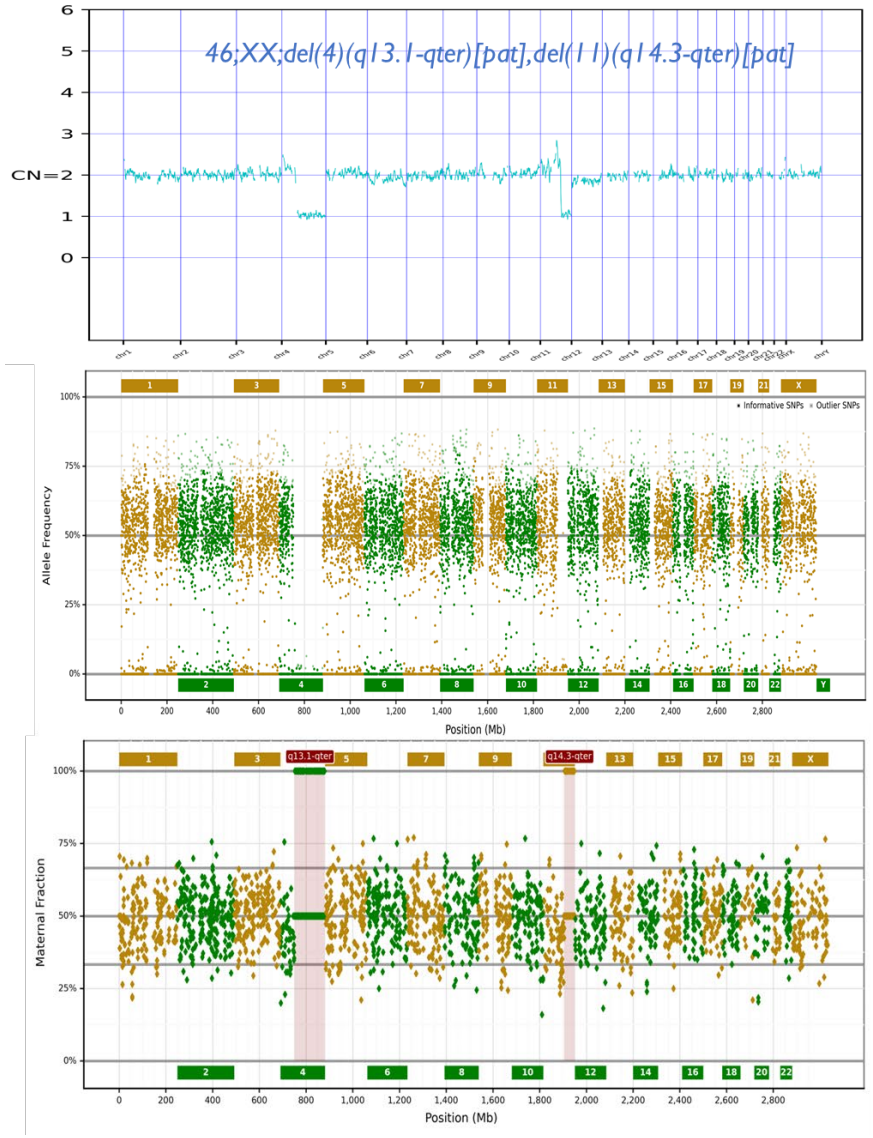
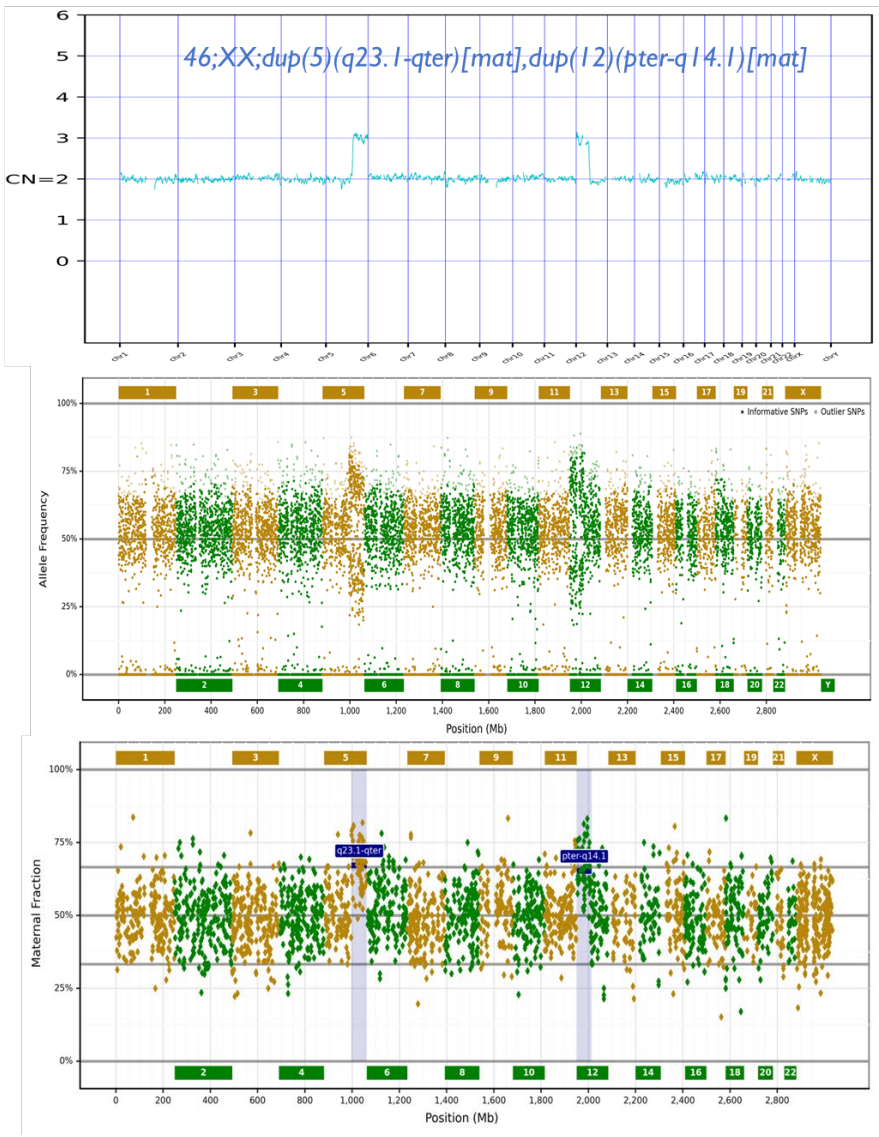
MARCH 18-22 | RANCHO MIRAGE, CA

# Improved Segmental Resolution and Confidence




Segmental Loss Resulting in Only Maternal Fraction

= Pat Deletion




Segmental Gain Resulting in Higher Maternal Fraction

= Mat Duplication

# Microdeletions and Microduplications

# Beyond Aneuploidy?

## Microdeletions and microduplications

- Microdeletions and microduplications are gains and losses of genetic material too small (<5-10 Mb) to be seen under a microscope

- Undetected microdeletions and microduplications may be associated with birth defects or developmental and intellectual disabilities[1]

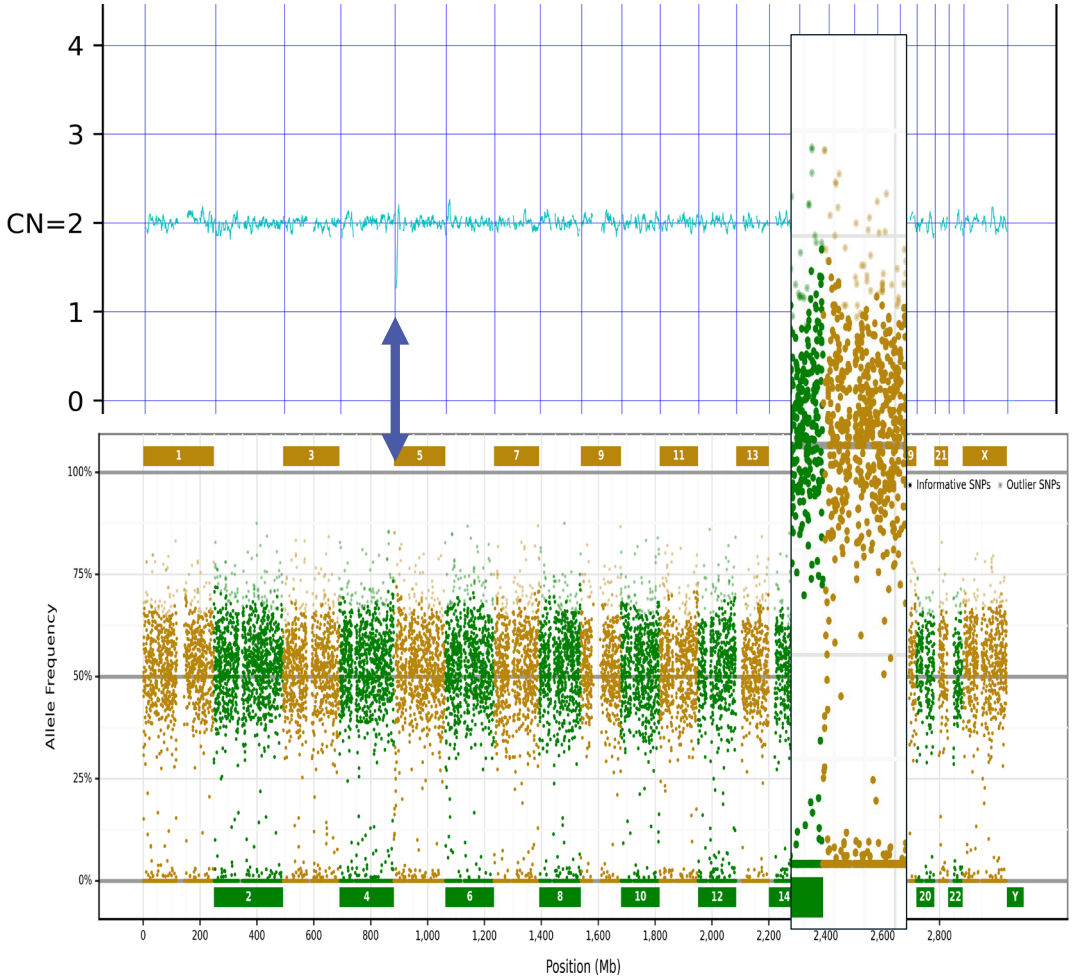
- Over 200 microdeletion / microduplication syndromes reported in the medical literature[1]

Wetzel, A.S. and Darbro, B.W., A comprehensive list of human microdeletion and microduplication syndromes. *BMC Genomic Data.* (2022) 23(1), p.82.

# Deletions and Duplication Syndromes

## Minor variation with major impact

Some chromosome abnormalities are below the resolution detectable with standard PGT-A[1]





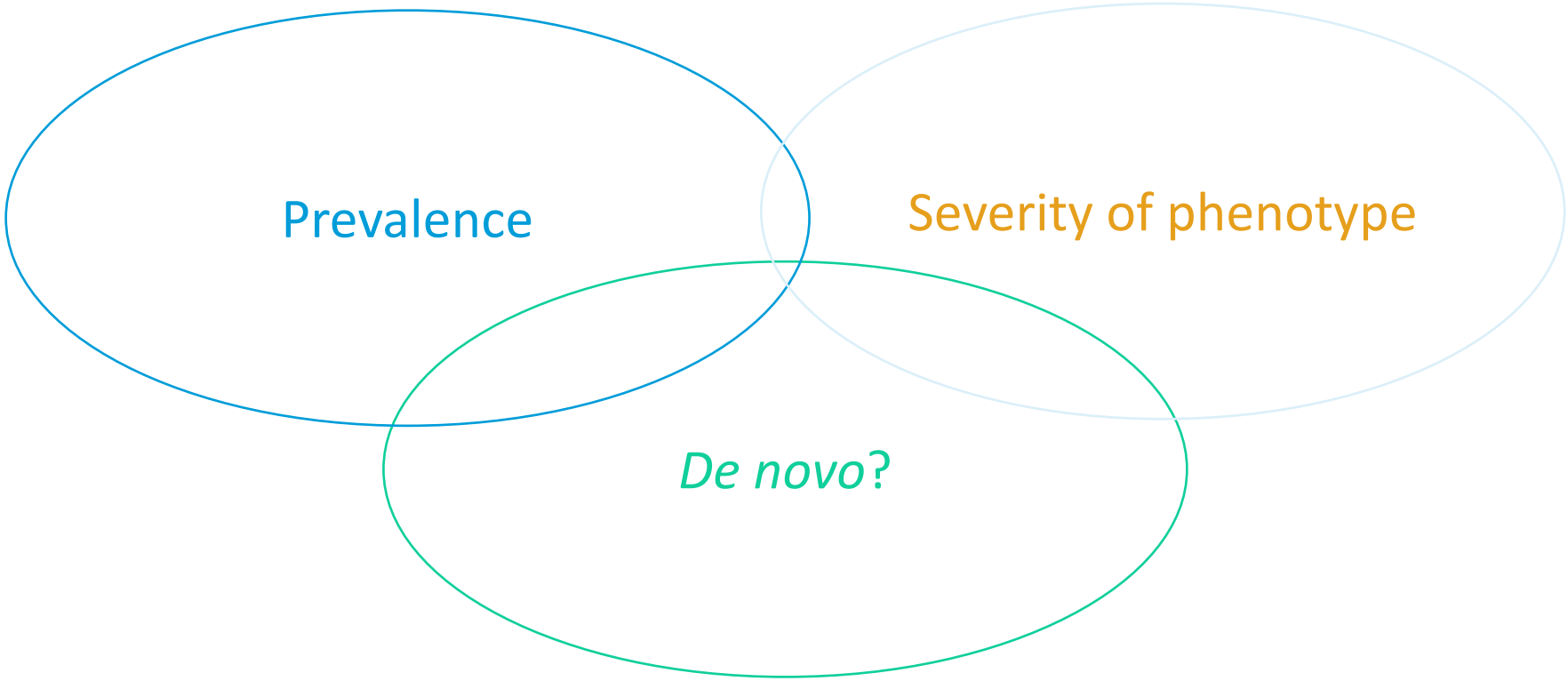
1. American College of Obstetricians and Gynecologists, (2020). Preimplantation genetic testing: ACOG Committee opinion, Number 799. *Obstetrics and Gynecology*, 135.


Source: CooperSurgical Data on file.

| | | | | |
|---|---|---|---|---|
| 1p36 Syndrome | 5q14.3-q15 Proximal | Interstitial 10q26 | 15q26 | 20q13.33 |
| ATAD3 Cluster (1p36.33) | 5q14.3-q15 Distal | Terminal 10q26 | ATR-16 (16p13.3) | 21q22 |
| 1p35 | FAP (5q22.2) | Beckwith-Wiedemann / Russell-Silver (11p15.5) | 16p13.3 | APP (21q21.3) |
| 1p32.2-p31.3 | ADLD (5q23.2) | ELP4 (11p13) | Rubinstein-Taybi (16p13.3) | Cat-eye (22q11.1-q11.21) |
| 1p21.3 | 5q31.3 | WAGRO (11p13) | Hao-Fountain Syndrome (16p13.2) | DGS/VCFS AB (22q11.2) |
| 1q21.1 TAR | Sotos Syndrome (5q35) | WAGR (11p13) | 16p13.11 BP I-II | DGS/VCFS AC (22q11.2) |
| 1q21.1 Neuro | 6p25 | Potocki-Shaffer (11p11.2) | 16p13.11 BP I-III | DGS/VCFS AD (22q11.2) |
| 1q21.1 TAR Neuro | 6p25.1p24.3 | 11q13 | 16p13.11 | DGS/VCFS BD (22q11.2) |
| 1q24-q25 Proximal | 6q12-q14.1 | Jacobsen (11q23-qter) | 16p13.11 BP II-III | DGS/VCFS CD (22q11.2) |
| 1q24-q25 Intermediate | 6q13-q14.2 | 12p13.33 | 16p12.2-p11.2 | DGS/VCFS Distal (22q11.2) |
| 1q24-q25 Distal | 6q14.1-q14.3 | 12q14 | 16p12.1 | Phelan-McDermid (22q13.33) |
| 1q41-q42 | 6q14.1-q15 | PACD (12q21.33) | 16p11.2 | SHOX (Xp22.33) |
| 1q43-q44 | 6q14.3-q16.3 | 12q24.3 | 16q22 | STS (Xp22.31) |
| 2p25.3 (MYTIL) | 6q24-q25 | 13q12.11-q12.13 | 16q24.1 | Xp21 |
| 2p21 | 6q25 | 13q12.3 | Miller-Dieker Syndrome (17p13.3) | Xp11.3 |
| NRXN1 (2p16.3) | 7p22.1 | 13q14 | SHFLD3 (17p13.3) | Xp11.23-p11.22 |
| 2p16.1-p15 | WBS (7q11.23) | Feingold Syndrome 2 (13q31.3) | 17p13.1 | Xp11.22 |
| 2p15-p14 | WBS Distal (7q11.23) | 13q32.1 | Yuan-Harel-Lupski (17p11.2) | Xq21 |
| 2p12-p11.2 | SHFM1 (7q21.3) | 13q33-q34 | CMT1A / HNPP (17p11.2) | Pelizaeus-Merzbacher (Xq22.2) |
| 2q11.2 | 8p23.1 | 14q11-q22 | Potocki-Lupski (17p11.2) | DL-ATS (Xq22.3) |
| 2q13 | 8q12 | Frias Syndrome (14q22-q23) | Smith-Magenis (17p11.2) | MR-ATS (Xq22.3) |
| Mowat Wilson (2q22.3) | 8q13 | Temple / Kagami-Ogata (14q32.2) | NF1 Type I (17q11.2) | Xq25 |
| 2q23.1 (MBD5) | 8q21.11 | Angelman / Prader-Willi BP1-3 (15q11.2-q13.1) | NF1 Type II (17q11.2) | XLAG (Xq26.3) |
| 2q31.1 | 8q22.1 | 15q11.2 BP1-2 | NF1 Type III (17q11.2) | Xq27.1 |
| 2q31.2-q32.3 | 8q22.2–q22.3 | Angelman / Prader-Willi BP2-3 (15q11.2-q13.1) | RCAD Syndrome (17q12) | Xq27.3-q28 |
| 2q33.1 | 8q23.1-q24.12 | 15q13.1-q13.2 BP3-4 | Koolen De Vries (17q21.31) | MECP2 (Xq28) |
| 2q35 | 8q24.3 | 15q13.1-13.3 BP3-5 | 17q23.1-23.2 | Xq28 (GDI1) |
| 2q37 | SRXY4 (9p24.3) | 15q13.3 BP4-5 | 17q24.2-q24.3 | Xq28 (RAB39B) |
| 3p25.3 | 9p Terminal | CHRNA7 (15q13.3) | 46 XX,XY Sex Reversal (17q24.3) | Xq28 Moyamoya |
| 3p21.31 | 9p13.3-p13.1 | MEIS2 (15q14) | 18p | AZFa (Yq11.21) |
| 3q13.31 | 9q22.3 | 15q15.3 | 18q Proximal | AZFb (Yq11.222-q11.223) |
| 3q22.1-q25.2 | 9q31.1-q31.3 | FBN1 (15q21.1) | 18q Terminal | AZFb+AZFc (Yq11.222-q11.23) |
| 3q27.3-q28 | Kleefstra Syndrome (9q34.3) | 15q24 AB | 19p13.3 | |
| 3q29 | 10p Terminal | 15q24 AC | 19p13.2 | |
| Wolf-Hirschhorn (4p16.3) | 10p15.3 | 15q24 AD | 19p13.12 | |
| 4q21 | 10p14-p12 | 15q24 BD | 19q13.11 Proximal | |
| Cri-du-chat (5p15) | HDR (10p14) | 15q24 BE | 19q13.11 Distal | |
| 5p13 | DGS2 (10p14) | Witteveen-Kolk Syndrome (15q24 CD) | 19q13.2 | |
| 5q11.2 | 10q22-q23 Syndrome | 15q24 DE | 20p13 | |
| 5q12 | SHFM3 (10q24) | 15q25 | 20p12.3 | |

# Beyond Aneuploidy?

**Microdeletions and microduplications**



# Critical syndromic regions for detection

| Microdeletion / Microduplication | Location | Length (mb) | Occurrence |
|---|---|---|---|
| Langer-Giedion Syndrome | 8q23.2–q24.1 | 10.9 | 1 / 100,000 |
| Jacobsen Syndrome | 11q23-qter | 15.4 | 1 / 100,000 |
| 2q33.1 Syndrome | 2q33.1 | 2.4 | 1 / 100,000 |
| Wolf-Hirschhorn Syndrome | 4p16.3 | 1.7 | 1 / 50,000 |
| Potocki-Lupski / Smith-Magenis Syndrome | 17p11.2 | 4.9 | 1 / 15,000 |
| Cri-du-chat Syndrome | 5p15 | 19 | 1 / 15,000 |
| 1p36 Syndrome | 1p36 | 5.5 | 1 / 5,000 |
| Angelman / Prader-Willi Syndrome | 15q11.2-q13.1 | 5.5 | 1 / 5,000 |
| DiGeorge / Velo-Cardio-Facial Syndrome | 22q11.2 | 2.6 | 1 / 2,000 |

**~ 1 / 1000 Live Births***

* Prenatal occurrence presumed to be higher

- CooperSurgical Data on file.
- medlineplus.gov/genetics/condition/
  www.orpha.net/en/disease/detail/2308
  www.natera.com/womens-health/panorama-nipt-prenata
  my.clevelandclinic.org/health/diseases

# Screening embryos could help further inform transfer decisions

- Provides more focused sequencing data than previous PGT-A[1]
- Some microdeletions and microduplications are below the resolution detectable with standard PGT-A[1]
- PGT-A, with microdeletion and microduplication detection, may offer more information for embryo transfer options

- Screening for dels/dups has presented unique challenges
  - Low resolution – short segmental CNV is difficult
  - Amplification and platform bias
  - Variable sensitivity & high false positive rates[2,3]

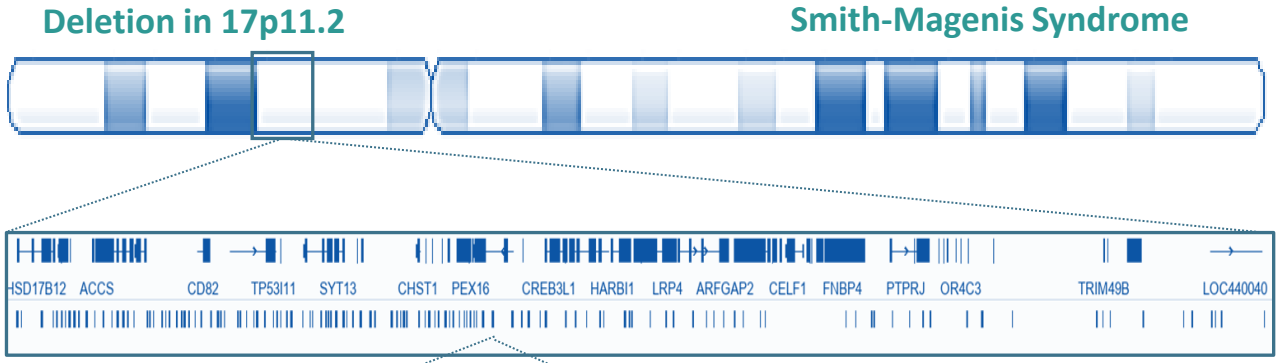
1. Weier, C., *et al.* PGT-A INCORPORATING SENSITIVE AND SPECIFIC DETECTION OF NINE RECURRENT DELETION AND DUPLICATION SYNDROMES USING HIGH RESOLUTION TARGETED SEQUENCING. *Fertility and Sterility.* (2025) 124(1), p.e30.
2. Zaninović, L., *et al.* Validity and utility of non-invasive prenatal testing for copy number variations and microdeletions: A systematic review. *Journal of Clinical Medicine.* (2022.) 11(12), p.3350.
3. Xue, H., *et al.* Efficiency of expanded noninvasive prenatal testing in the detection of fetal subchromosomal microdeletion and microduplication in a cohort of 31,256 single pregnancies. *Scientific Reports.* (2022) 12(1), p.19750.

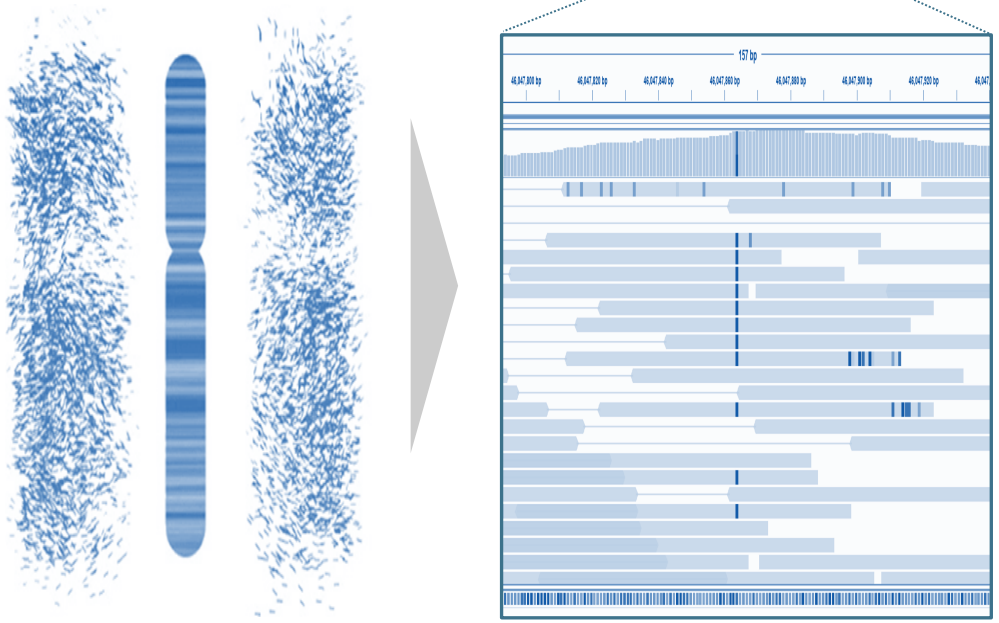
# High Resolution in Syndromic regions

**Development**
**(10K Samples)**

Pre-Clinical Validation

Clinical Evaluation




- Broadest annotated coordinates
  - *Clinical data and case studies*
  - *Account for expansion*
- Expanded SNP capture by 3-10x
  - *Selection based on minor allele frequency and uniform distribution*

**Primary Template-Directed Amplification** **Targeted NGS**

1. CooperSurgical Data on file.

# High Resolution in Syndromic regions

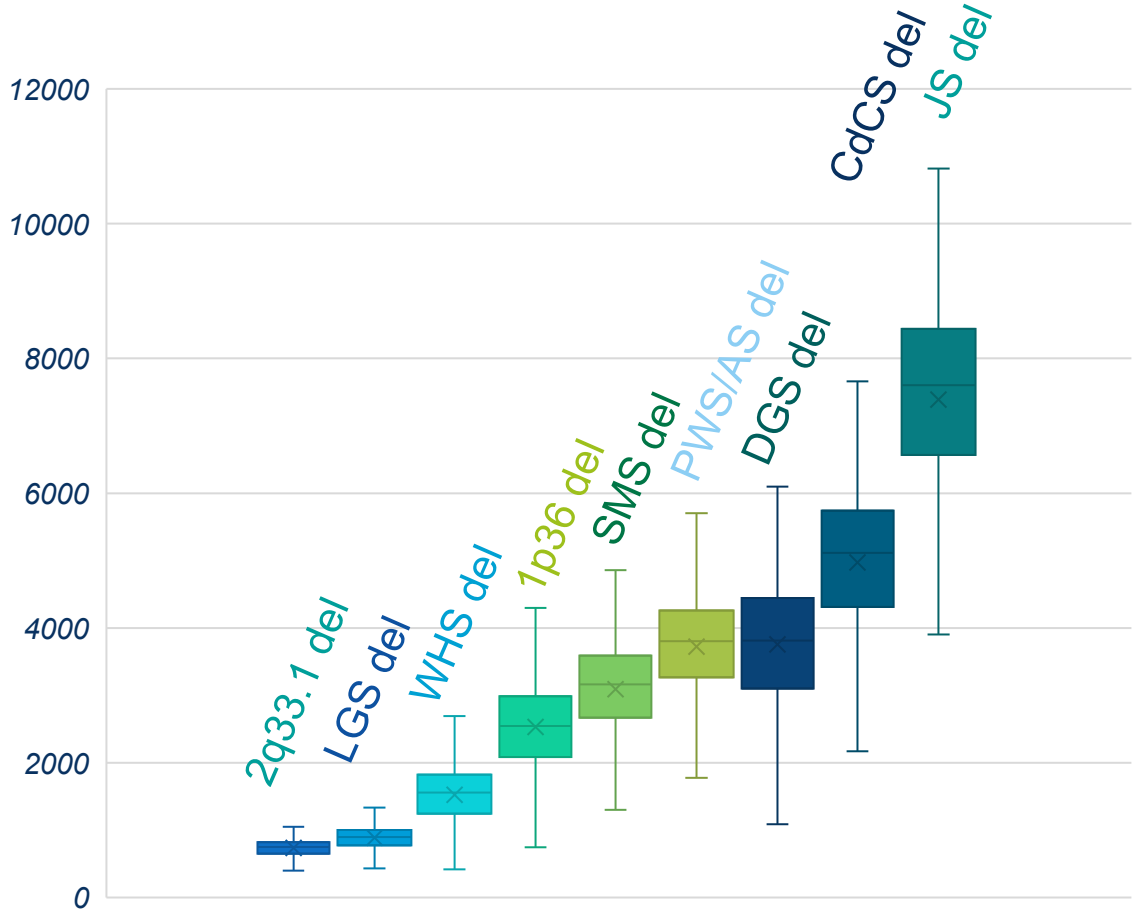
**Development**
**(10K Samples)**

- 1. Cooper Surgical Data on file.

Pre-Clinical Validation

Clinical Evaluation

Quality and Depth Filtered SNPs in each targeted region




*across all samples*

96% *of target regions generate 100+ SNPs per megabase*[1]

# *BAF* and *CNV* significance clearly define positive and negative MMS in across targeted regions[1]

Development
(10K Samples)

**Pre-Clinical Validation**
**5K Samples**

Clinical Evaluation

*Smith-Magenis Syndrome* *Deletion in 17p11.2*

**Unaffected**

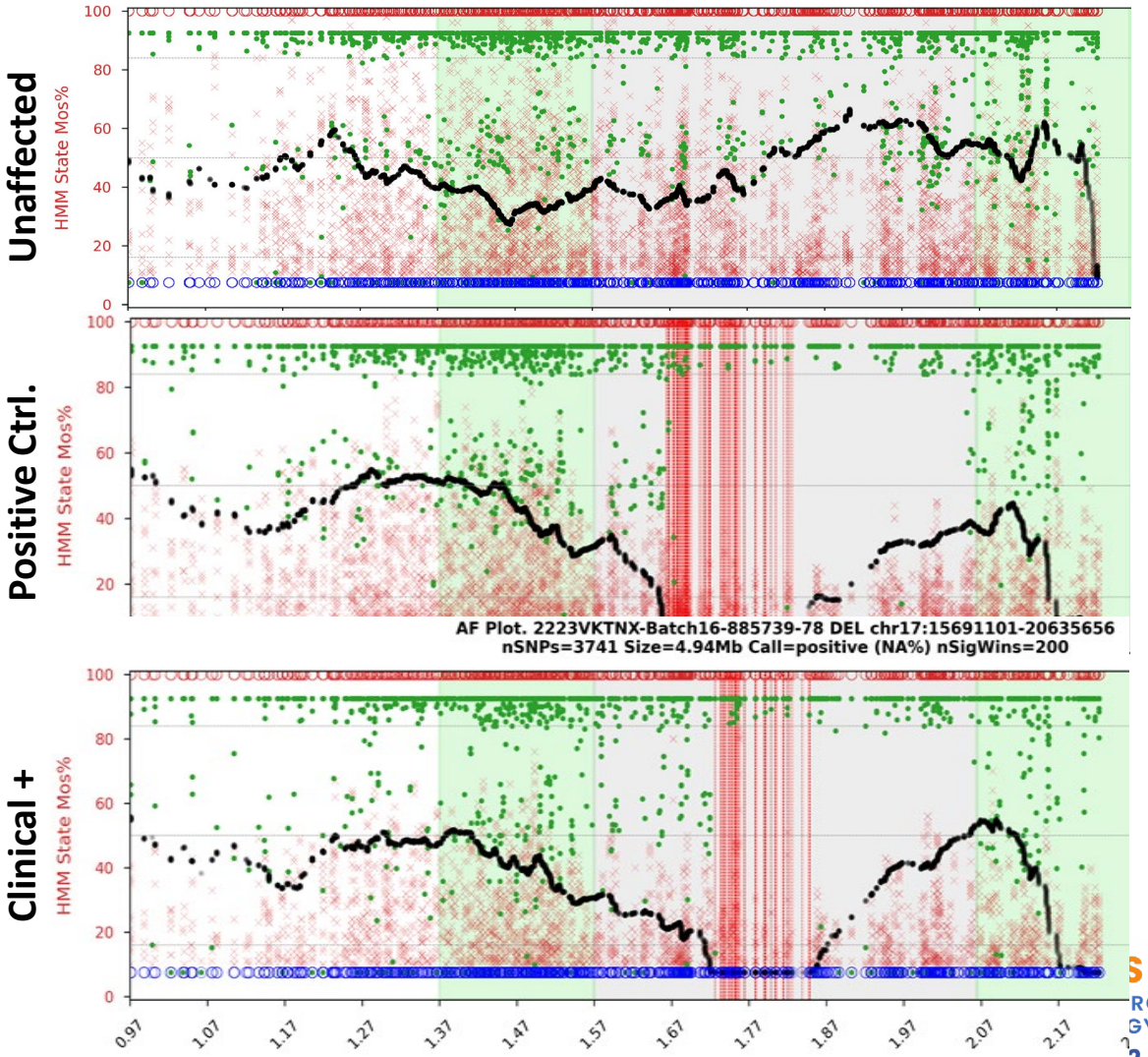
*BAF Sig: 0.259*
*CNV Sig: 1.0*
*SNPs: 2631*

**Positive Ctrl.**

*BAF Sig: 3.35E-05*
*CNV Sig: 2E-04*
*SNPs: 2041*

**Clinical +**

*BAF Sig: 3.47E-05*
*CNV Sig: 2E-04*
*SNPs: 3128*




1. CooperSurgical Data on file.

# Validation of Performance

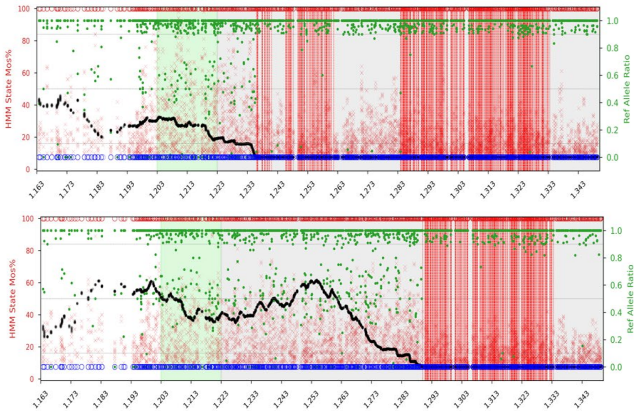
Development
(10K Samples)

**Pre-Clinical Validation**
**5K Samples**

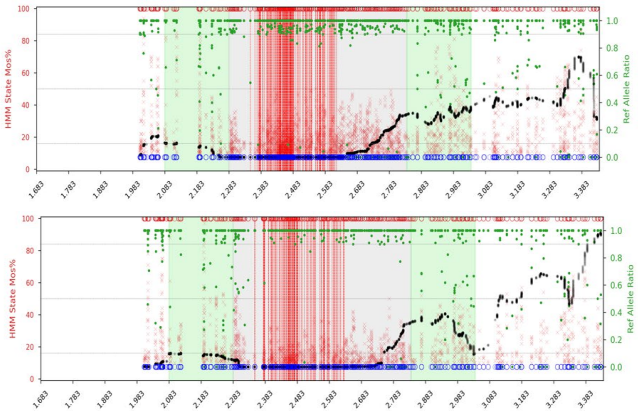
Clinical Evaluation

Control cell lines and clinical biopsies display overlapping segments across MMS target regions[1]

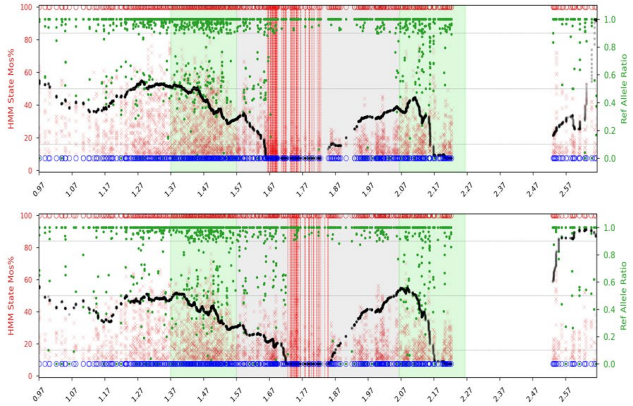
**Jacobsen Syndrome**
**Deletion in 11q23-qter**



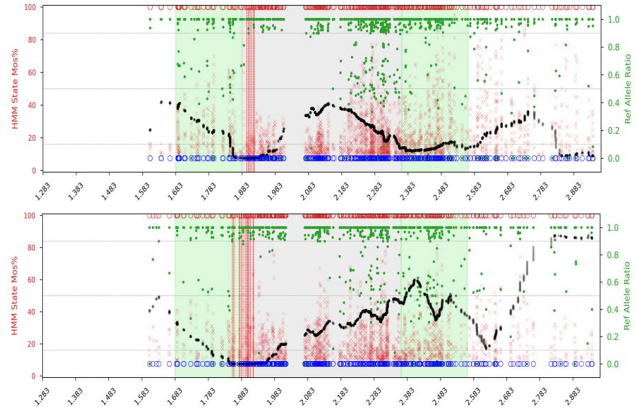

**Angelman / Prader-Willi Syndrome**
**Deletion or LoH in 15q11.2-q13.1**




**Smith-Magenis Syndrome**
**Deletion in 17p11.2**




**DiGeorge / Velo-Cardio-Facial Syndrome**
**Deletion in 22q11.2**

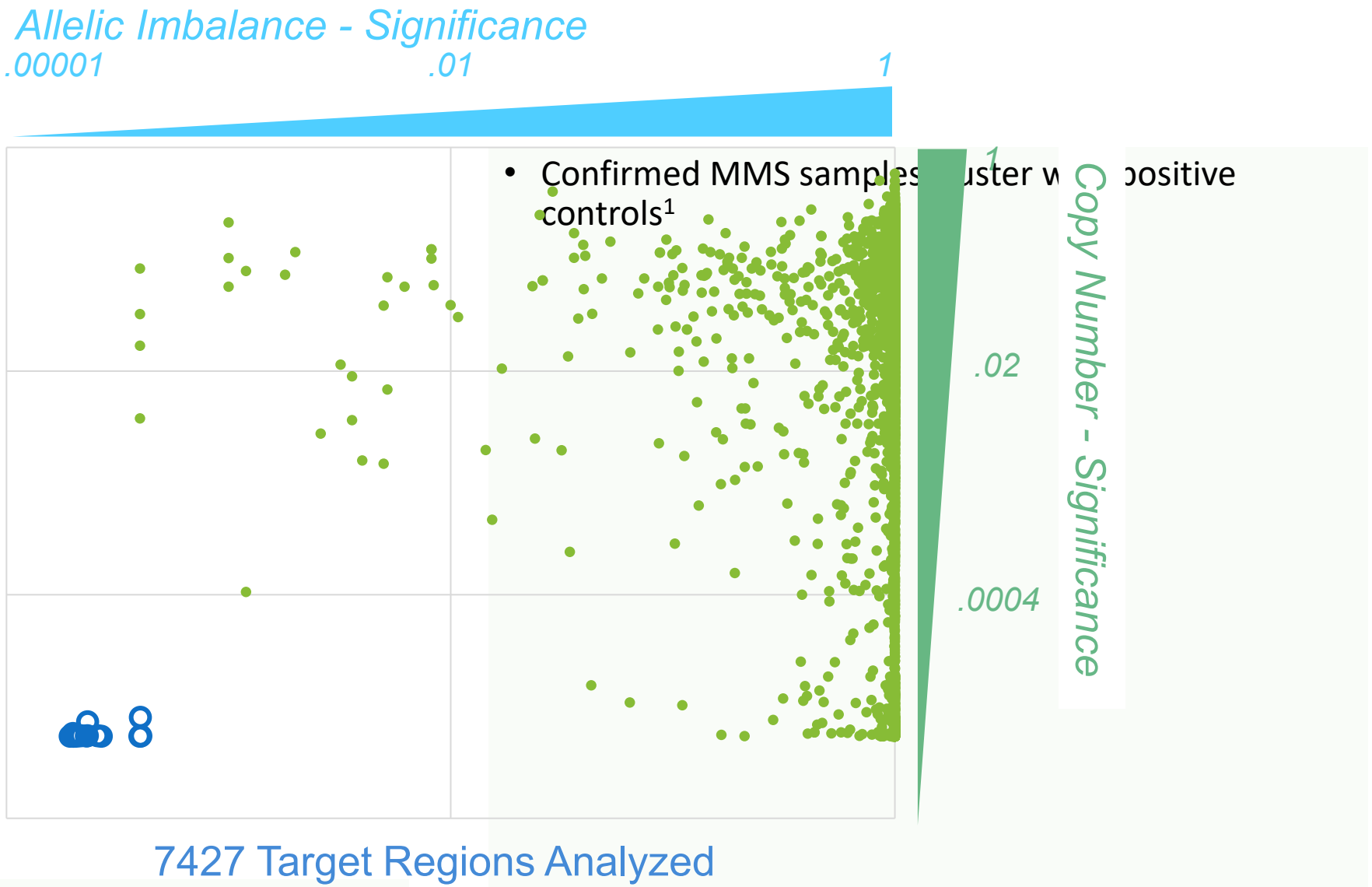



1. CooperSurgical Data on file.

Development
(10K Samples)

**Pre-Clinical Validation**
**5K Samples**

Clinical Evaluation




- Confirmed MMS samples cluster with positive controls[1]

*Negative Sample (confirmed euploid)*

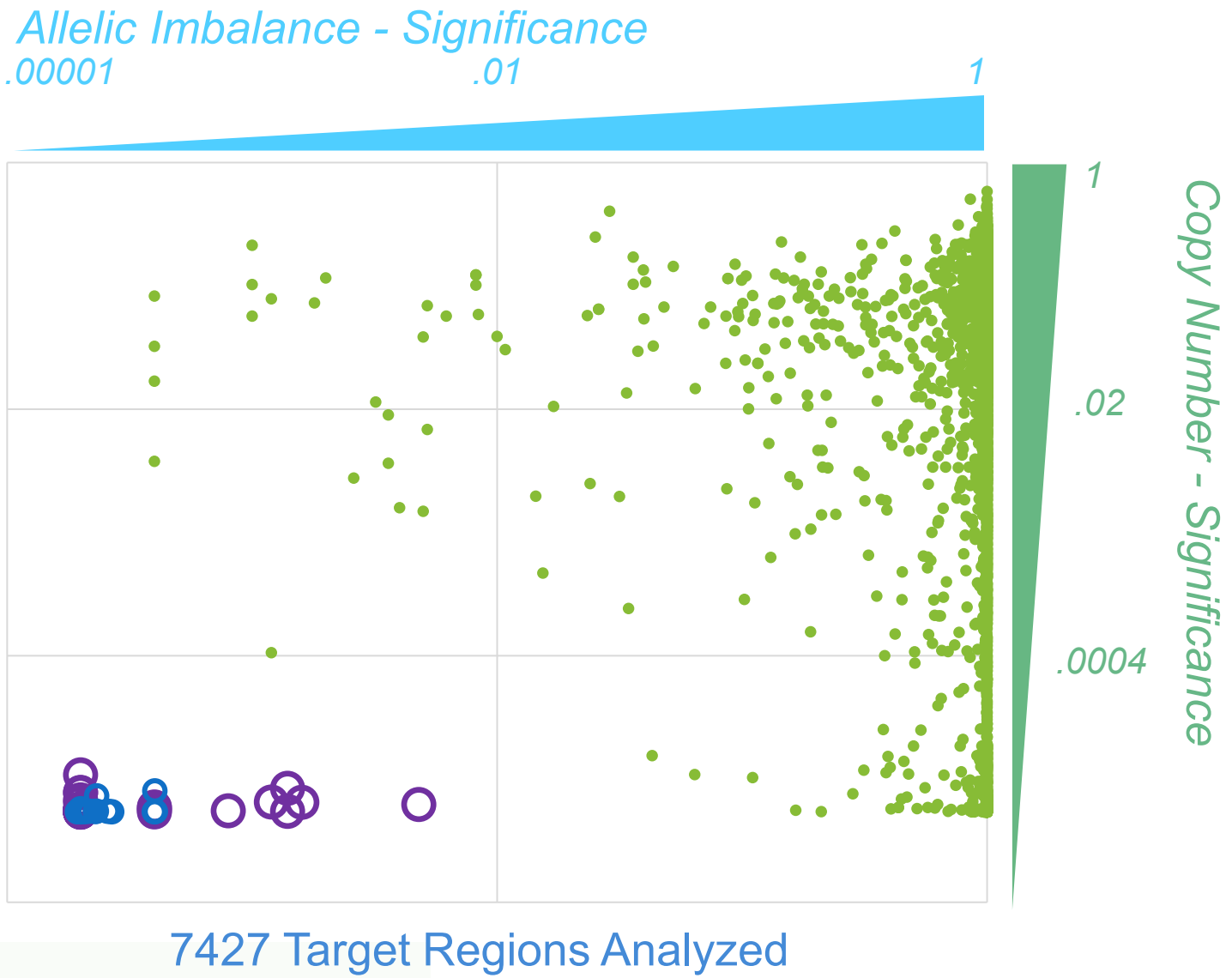
*Positive Control (MMS Cell Lines)*

- 1. CooperSurgical Data on file.

Development
(10K Samples)

**Pre-Clinical Validation**
**5K Samples**

Clinical Evaluation




- 1. CooperSurgical Data on file.

# Validation for Components and Analysis

Development
(10K Samples)

**Pre-Clinical Validation**
**5K Samples**

Clinical Evaluation

| Syndrome | Sensitivity | Specificity | Accuracy | Reproducibility |
|---|---|---|---|---|
| 1p36 | 100.00% | 100.00% | 100.00% | 100.00% |
| 2q33.1 | 100.00% | 100.00% | 100.00% | 100.00% |
| WH | 100.00% | 100.00% | 100.00% | 100.00% |
| CDC | 100.00% | 100.00% | 100.00% | 100.00% |
| LG | 100.00% | 100.00% | 100.00% | 100.00% |
| Jac | 100.00% | 100.00% | 100.00% | 100.00% |
| AGPR | 100.00% | 100.00% | 100.00% | 100.00% |
| SM Del | 100.00% | 99.71% | 99.74% | 100.00% |
| PL Dup | 96.43% | 99.70% | 99.22% | 96.67% |
| DGS | 98.33% | 100.00% | 99.74% | 98.48% |
| **Overall** | **99.21%** | **99.94%** | **99.87%** | **99.19%** |

- 1. CooperSurgical Data on file.

# Evaluation

Confirming accuracy and defining embryonic occurrence

- Parallel analysis using complimentary methods

  independent outcome verification to reinforce test validity

- Initial prevalence of MMS in preimplantation embryos

  support interpretation and reproductive decision-making

**53,000**

Trophectoderm Biopsies

De-Identified by 3rd party &
Retrospectively Analyzed

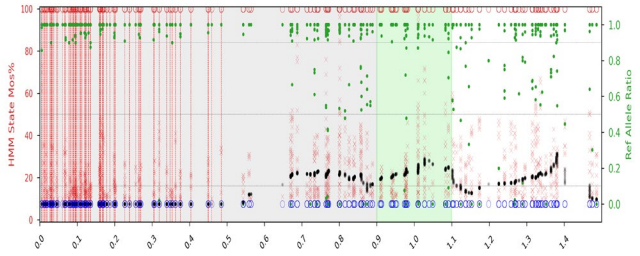
# Positive Embryos Identified

Development
(10K Samples)

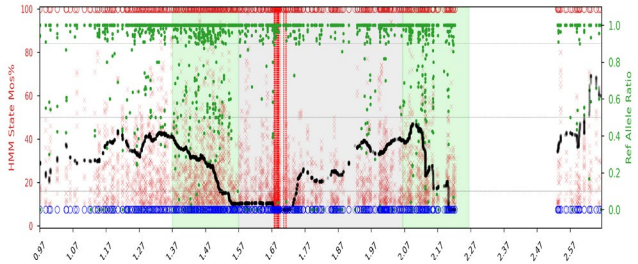
Pre-Clinical Validation
5K Samples

**Clinical Evaluation**
**53K Samples**

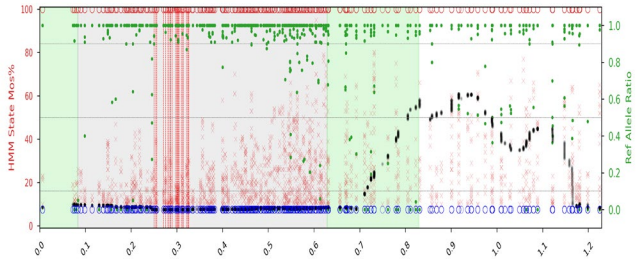
**Wolf-Hirschhorn** *4 megabases*



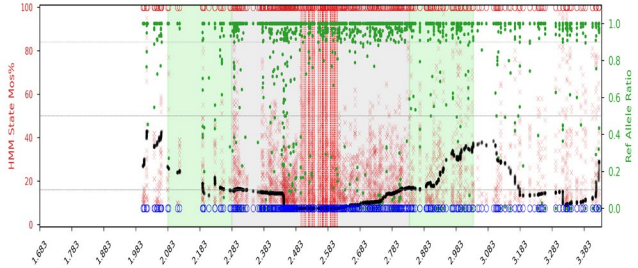

**Smith Magenis** *3 megabases*



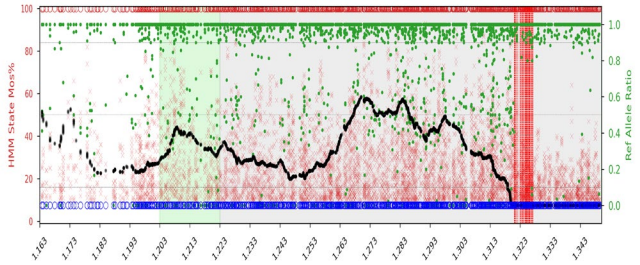

**1p36 Deletion** *4 megabases*



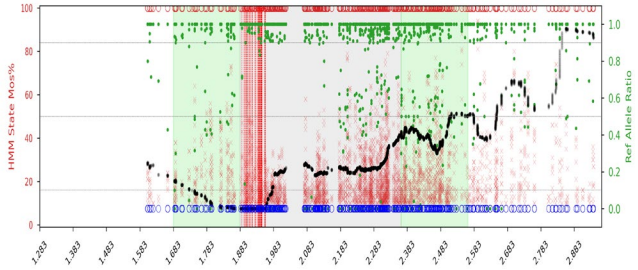

**Angelman/Prader-Willi** *3 megabases*




**Jacobsens** *3 megabases*




**22q (DiGeorge/VCFS)** *2.5 megabases*




1. CooperSurgical Data on file.

# Clinical Evaluation with Parallel Analysis Methods

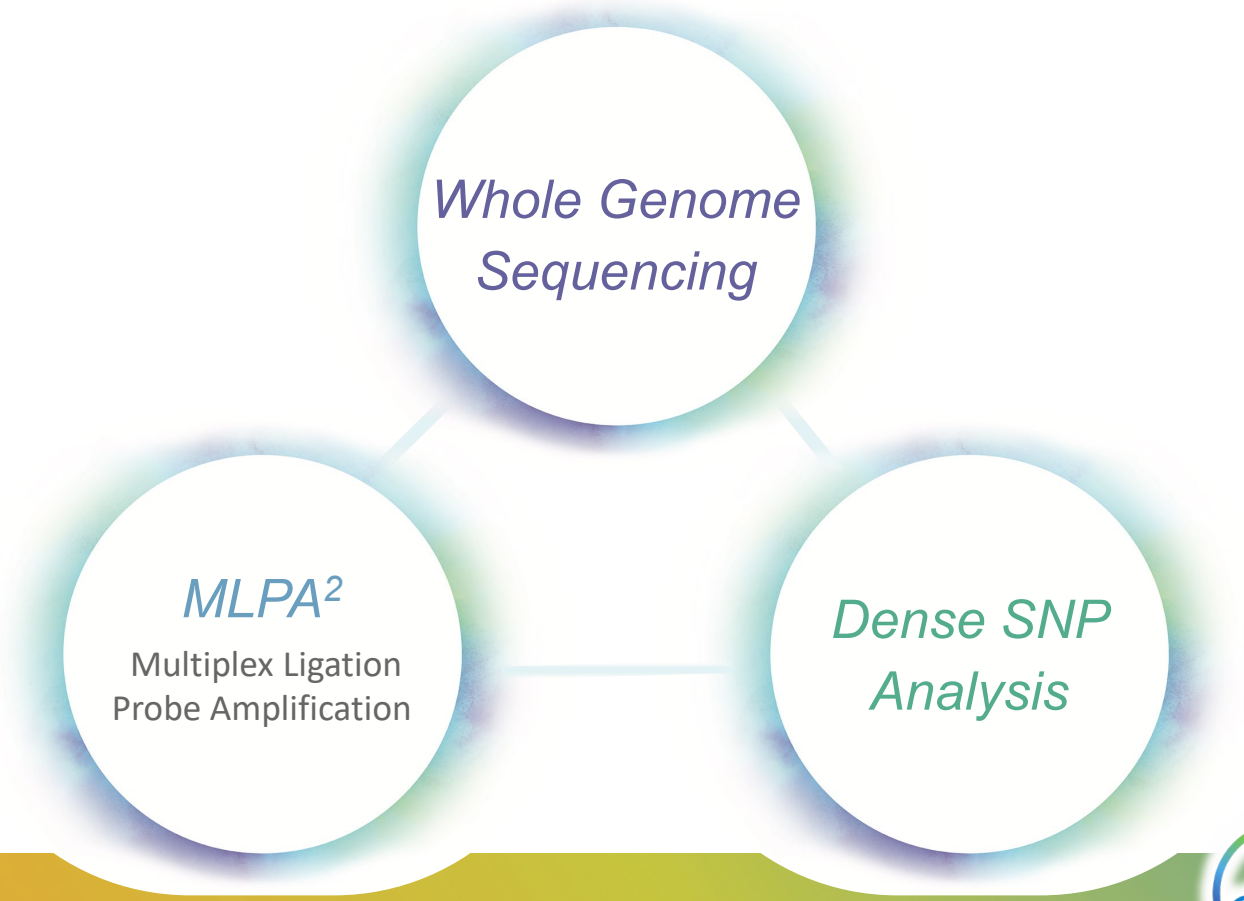
Development
(10K Samples)

Pre-Clinical Validation
5K Samples

**Clinical Evaluation**
**53K Samples**

## Confirmation Strategy

Positive and Negatives Outcomes




1. CooperSurgical Data on file.
2. Miclea et al. Diagnostic Usefulness of MLPA Techniques for Recurrent Copy Number Variants Detection in Global Developmental Delay/Intellectual Disability, Int J Gen Med. 2021

Development
(10K Samples)

Pre-Clinical Validation
5K Samples

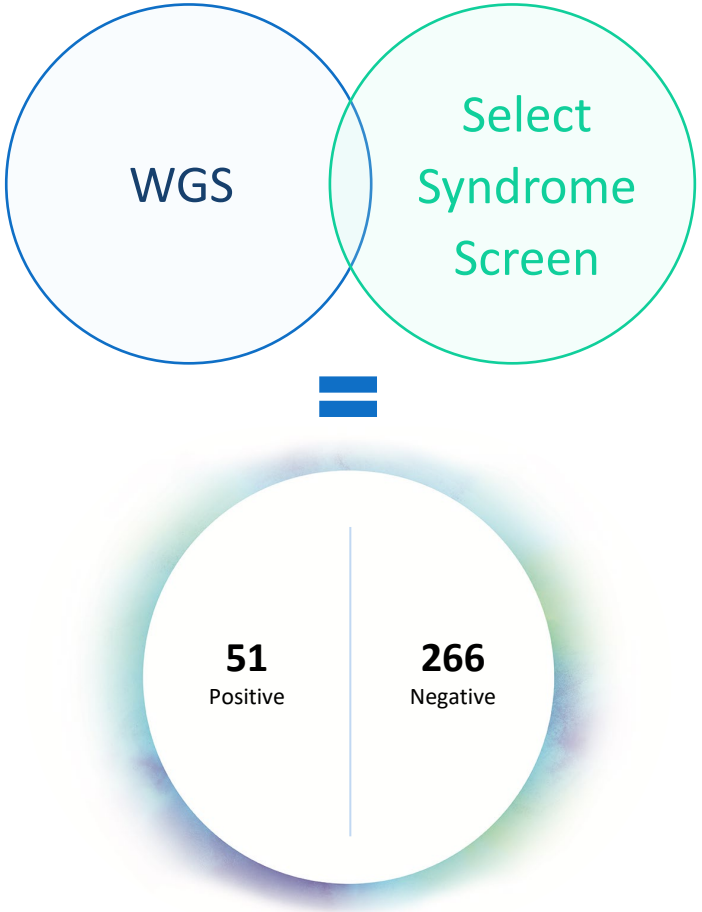
**Clinical Evaluation**
**53K Samples**

| Targeted Syndrome | Select Syndrome Screen | Whole Genome Sequencing |
|---|---|---|
| 1p36 | 10 | (10/10) 100% |
| 2q | 1 | (1/1) 100% |
| WH | 4 | (4/4) 100% |
| CDC | 7 | (7/7) 100% |
| LG | 1 | (1/1) 100% |
| Jacobsens | 10 | (10/10) 100% |
| APW | 6 | (6/6) 100% |
| SM Del | 4 | (4/4) 100% |
| PL Dup | - | - |
| DG22 | 8 | (8/8) 100% |
| Overall | 51 | (51/51) 100% |

Positive Concordance Across Individual Targets

| Negative Outcome | Select Syndrome Screen | Whole Genome Sequencing |
|---|---|---|
| All Syndromes | 262 | (262/262) 100% |

Negative Concordance Across All Targets (Embryos)




**100% Concordant**

1. CooperSurgical Data on file.

# Clinical Evaluation

| MD/MD Syndrome | Euploid | Low Level Mosaic (WC or Seg) | High Level Mosaic (WC or Seg) | Full Segmentals (w/ or w/out Mos Reg) | Whole Chromosome Aneuploidy | Collected Occurrence |
|---|---|---|---|---|---|---|
| 1p36 del | 1 in 6551 | - | - | 1 in 294 | 1 in 1642 | 1 in 2366 |
| 2q33.1 del | - | - | - | - | 1 in 9030 | 1 in 24841 |
| WHS del | 1 in 3276 | 1 in 1380 | 1 in 797 | - | 1 in 2258 | 1 in 2484 |
| CdCS del | 1 in 8735 | 1 in 1380 | 1 in 1196 | 1 in 353 | 1 in 2258 | 1 in 2615 |
| LGS del | 1 in 26204 | - | 1 in 2391 | 1 in 1764 | 1 in 18060 | 1 in 12420 |
| JS del | 1 in 6551 | - | - | 1 in 882 | 1 in 3010 | 1 in 4140 |
| PWS/AS del | 1 in 13102 | 1 in 1380 | - | 1 in 882 | 1 in 9030 | 1 in 7097 |
| SMS del | 1 in 8735 | - | - | 1 in 1764 | 1 in 4515 | 1 in 6210 |
| PTLS dup | - | - | - | 1 in 882 | 1 in 3010 | 1 in 6210 |
| DGS del | 1 in 8735 | - | 1 in 1196 | - | 1 in 3010 | 1 in 4516 |
| Combined | 1 in 936 | 1 in 460 | 1 in 299 | 1 in 93 | 1 in 334 | 1 in 444 |

# Occurrence in Transferrable Embryos

| | | |
|---|---|---|
| 1p36 del | 4 | 1 in 7494 |
| 2q33.1 del | 0 | 1 in - |
| WHS del | 12 | 1 in 2498 |
| CdCS del | 6 | 1 in 4996 |
| LGS del | 2 | 1 in 14988 |
| JS del | 4 | 1 in 7494 |
| PWS/AS del | 3 | 1 in 9992 |
| SMS del | 3 | 1 in 9992 |
| PTLS dup | 0 | 1 in - |
| DGS del | 5 | 1 in 5995 |
| | 39 | 1 in 769 |

Euploids + Mosaics

# How Could Microdels & Microdups impact the patient journey?

Ellie was offered standard PGT-A. Her IVF cycle resulted in 5 blastocysts: 2 euploid and 3 aneuploid.

Unknowingly, one of Ellie's euploid embryos had a 22q11.2 microdeletion (2.5 mb). This embryo was transferred first.

Transfer 1: Pregnant

+5 months

CHD and cleft palate identified on 19 week U/S; amniocentesis + PND confirmed 22q11.2 DS; elected for TOP

+8 months later...

Transfer 2: Pregnant

Did Not Transfer:

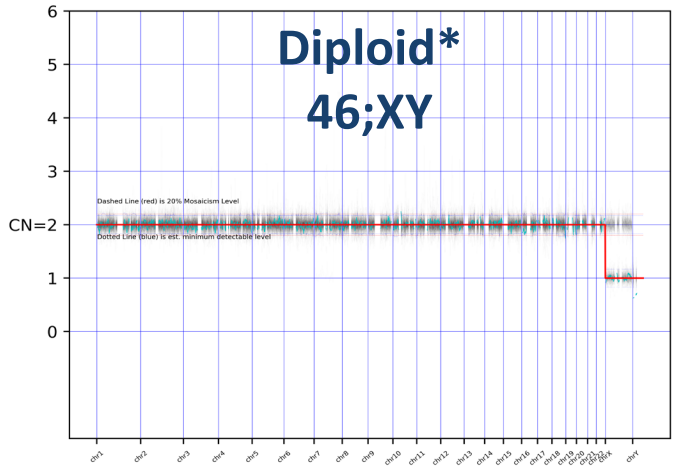
# Microdeletions/duplications: Patients to Consider

- All patients
- History of microdeletion/microduplication, in pregnancy, child, or self
- Anxious patient
- Information seeking

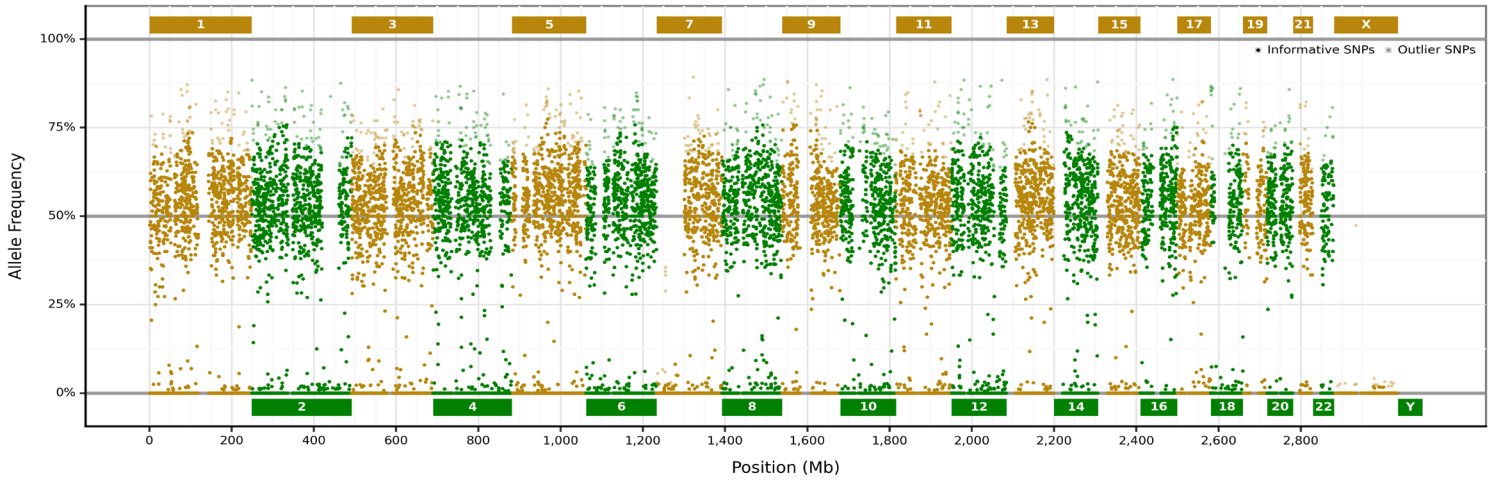
# Future Possibilities: UPD and LOH

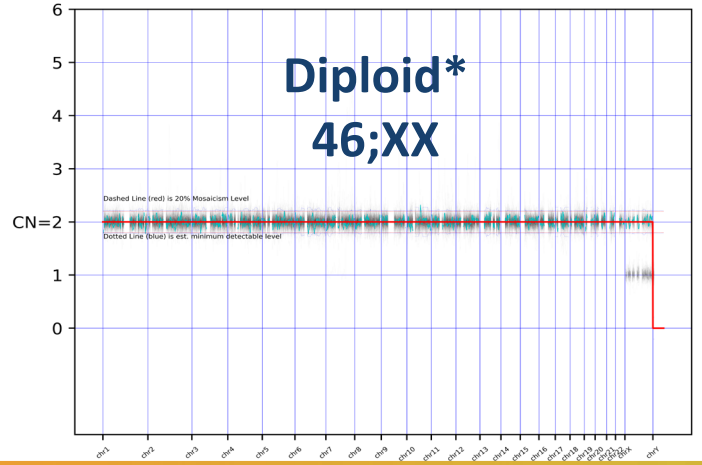
# Segmental Loss of Heterozygosity

## Single, Consanguineous and non-consanguineous LoH

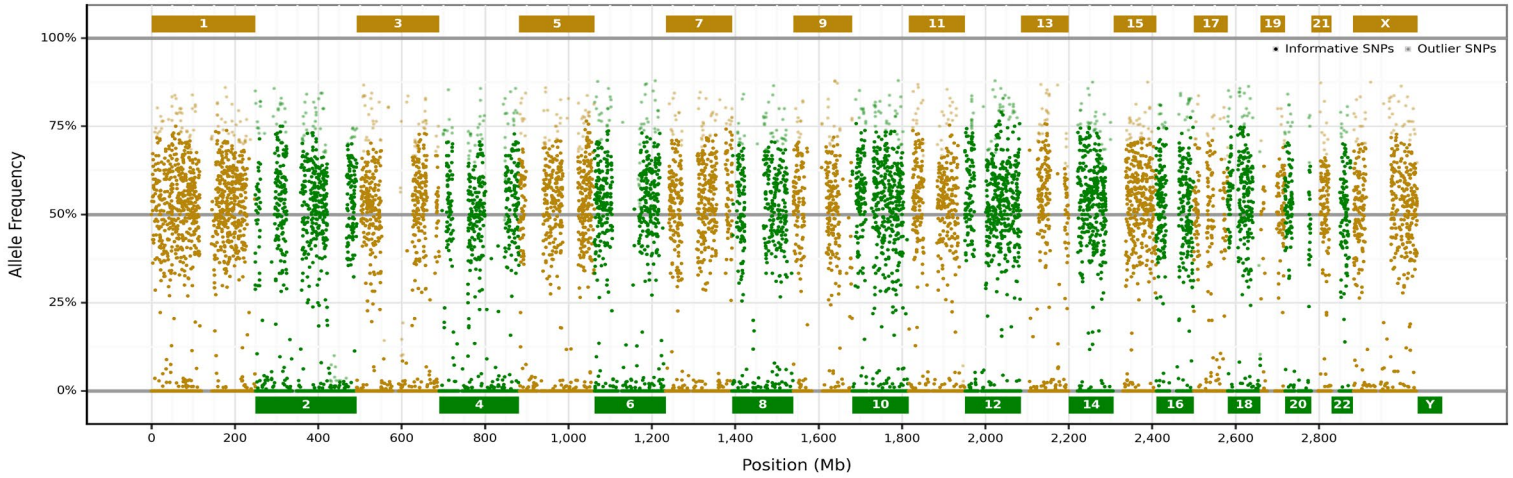



***Segmental Loss of Heterozygosity – UPD**




***Genome-wide Loss of Heterozygosity – UPD**



# Q&A