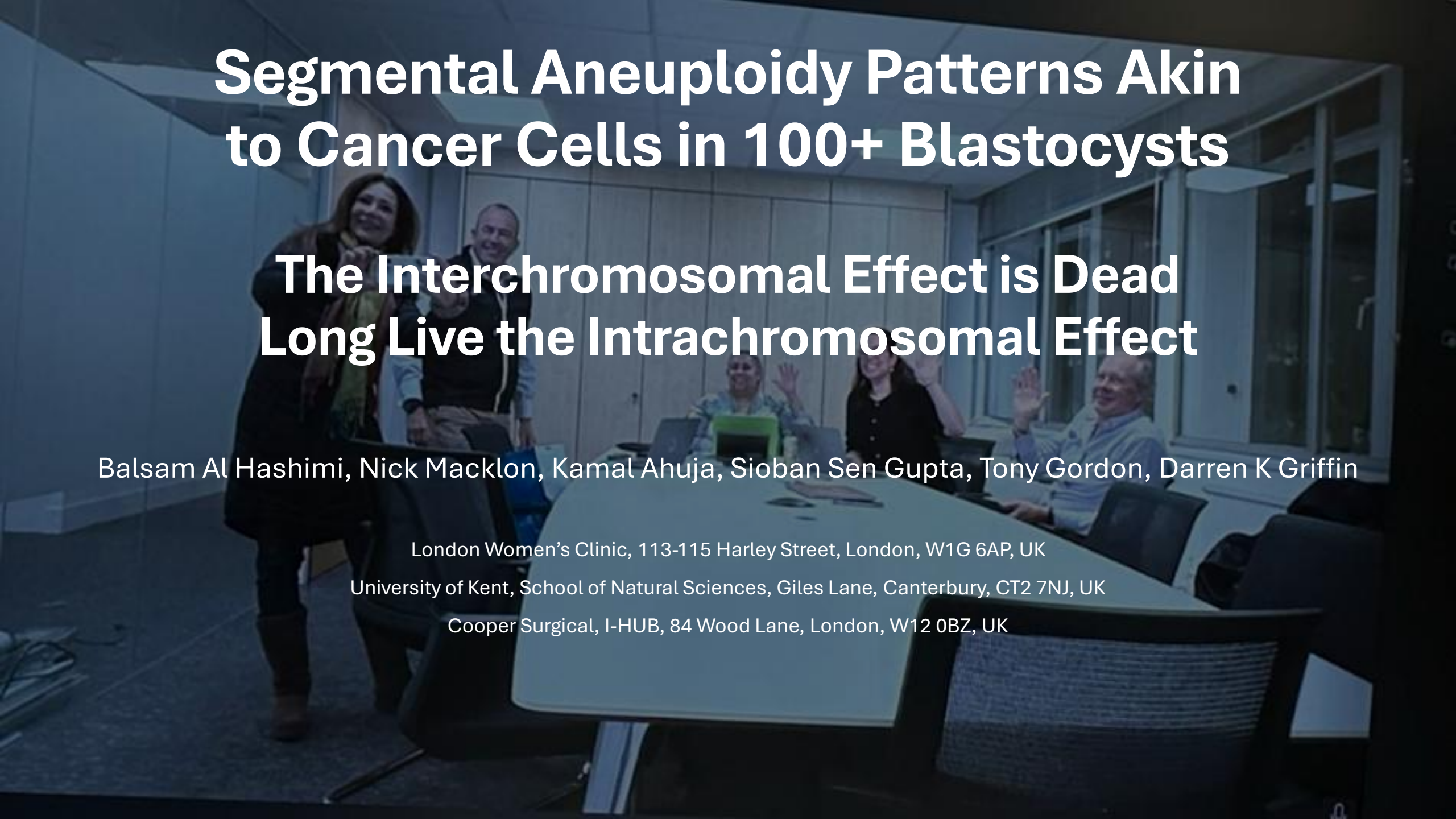

Segmental Aneuploidy Patterns Akin to Cancer Cells in 100+ Blastocysts

The Interchromosomal Effect is Dead Long Live the Intrachromosomal Effect

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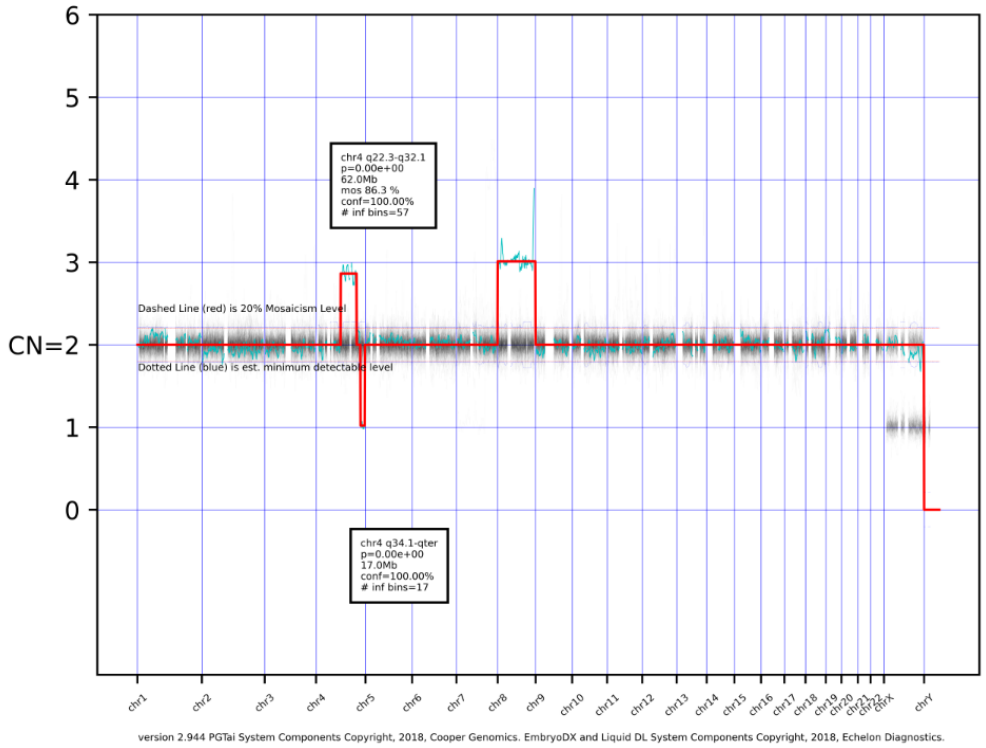
Overview

- Introduction – Segmental Aneuploidy (SA)
- Setting, study design and outcome measures
- Results
- Discussion
  - Outcomes vs. hypotheses
  - Novel findings



Unbalanced Structural Chromosomal Abnormalities

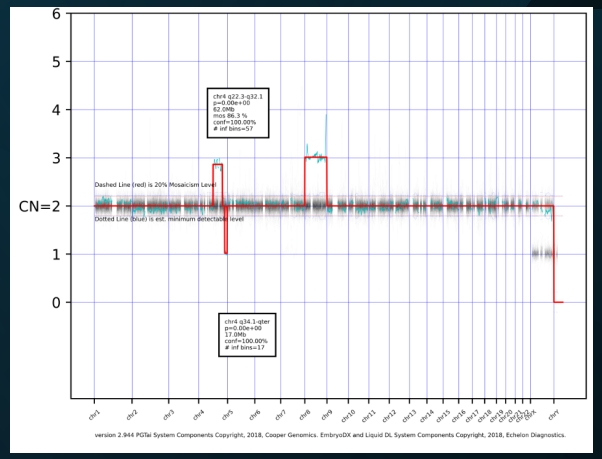
Segmental Aneuploidy (SA)

What do we Know?

- Gain or loss of parts of (not the entire) chromosome
- Similar consequences to whole chromosome aneuploidy
  - Natural and assisted reproduction
- Identified during PGT-A and PGT-SR
  - 7% of aneuploid biopsies
- Understanding its origin vital for improving ART outcomes
  - Requires exploration of its incidence and mechanisms
- Arises at meiosis or in early cleavage
  - Chromosomal breakage and recombination
- Disrupts normal embryonic development by altering gene dosage
- May be accompanied by non-disjunction event at meiosis or mitosis and/or ectopic/abnormal recombination

SA:

What Do we NOT Know?



- Parent and phase origin in human preimplantation development

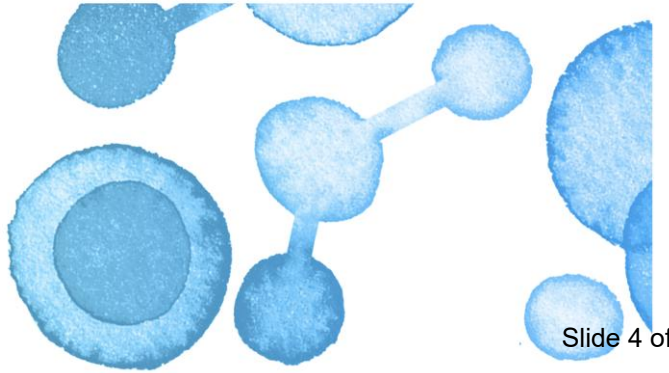
CooperSurgical®
Healthy women, babies, and families™

- Because, until recently, we did not have novel SNP-based NGS technologies to investigate it

- PGT complete (Cooper Surgical) provides those tools
  - Coupled with parental genotype
  - Provides parent and phase of origin of haploblocks
  - Interpretation similar to Karyomapping
    - Handyside et al. 2010

PGT-COMPLETE℠ TEST

From **PGT-Complete** part of **Fertility & Birth**



Purpose of this Study

To provide a reappraisal of the origin of SA in human preimplantation development through study of 100+ embryos

Two hypotheses

- SA, like whole chromosome aneuploidy, is predominantly maternal in origin
- There is broad correlation between TE and ICM
  - As has previously been reported for whole chromosome aneuploidy

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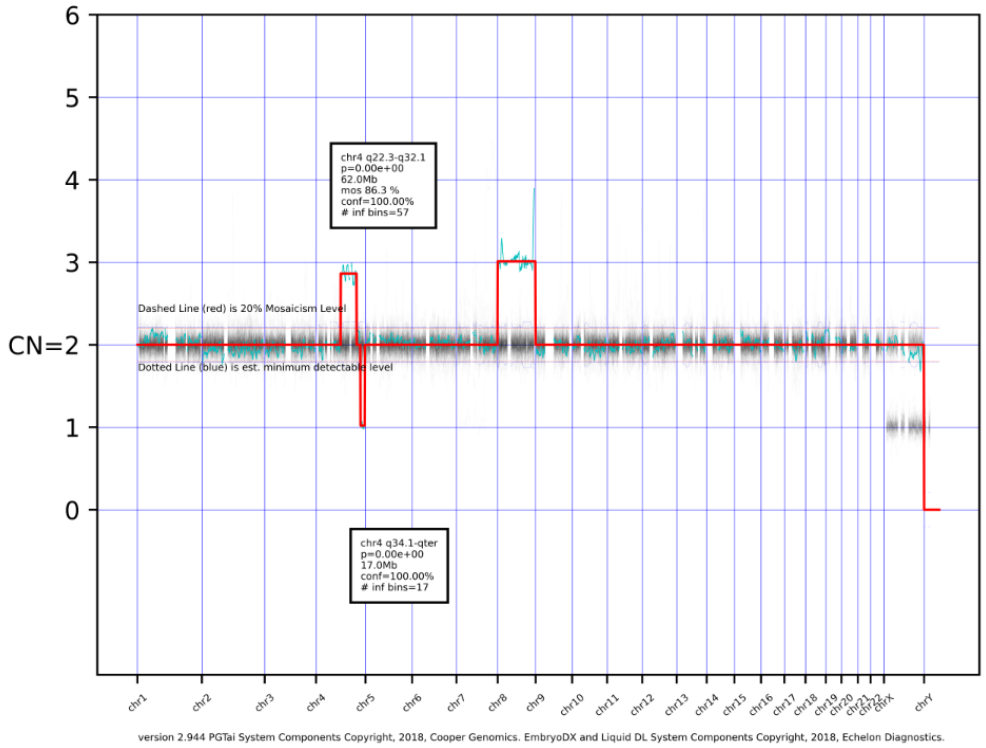

Setting

LWC Harley Street London

Undergoing routine IVF and PGT-A

Advanced Maternal Age, recurrent implantation failure or recurrent miscarriage

April 2020 – December 2024

Full IRAS ethical approval granted

University of Kent Research and Ethics Committee made fully aware of the project

None had known parental balanced translocations

Cannot rule out that a small number may have, incidentally, had e.g. a balanced translocation or inversion

Patients did not give consent for routine karyotyping

Study Design

Selected if biopsy result returned evidence of “full blown” (non-mosaic) SA	• Isolated ICM, then took a second TE biopsy (gentle “flicking” method) • Therefore examined 2xTE biopsies and ICM for all embryos

Deeper analysis to establish the origin of the error	• If algorithm detected parent of origin of gain/loss then
	  • Error was assumed to be meiotic (usually meiosis I) in origin
	  • Because SNPs from both grandparental chromosomes could be detected (gains) or loss of one set of grandparental alleles could be discriminated

Gains or losses in which parent of origin could <u>not</u> be detected	• Post-zygotic (PZ) in origin • Meiosis II loss/gain • Gain/loss was too small to determine the origin accurately (<5Mb)
102 embryos from 84 patients	• In reality, each would provide an interesting individual clinical case study

Outcome Measures

Parent and phase of origin

Concordance

- Three layers concordant
- Two of three layers concordant
- All three not concordant
- Concordance only for SA indicated
  - Non-concordance for whole chromosome aneuploidy disregarded

Did SA perpetuate a further SA on the same chromosome?

- *Intra*chromosomal effect

SA “rescue”

- Meiotic SA seen in one sample is not present in at least one other

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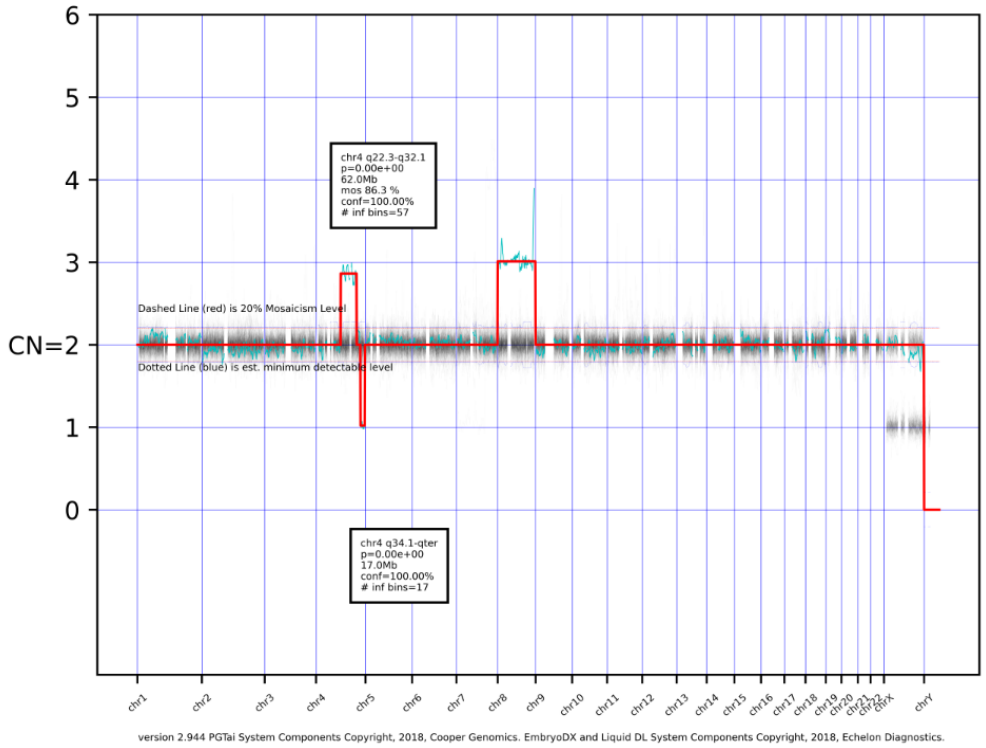
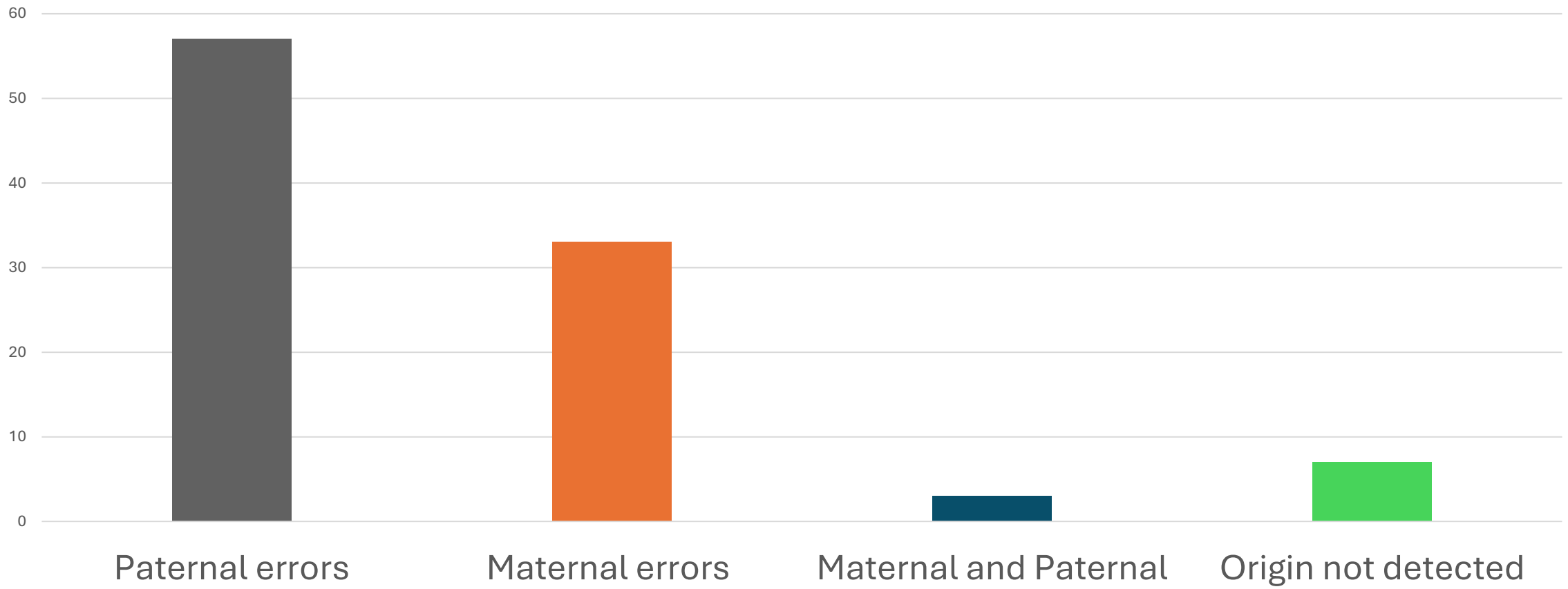


Parent and Phase of Origin

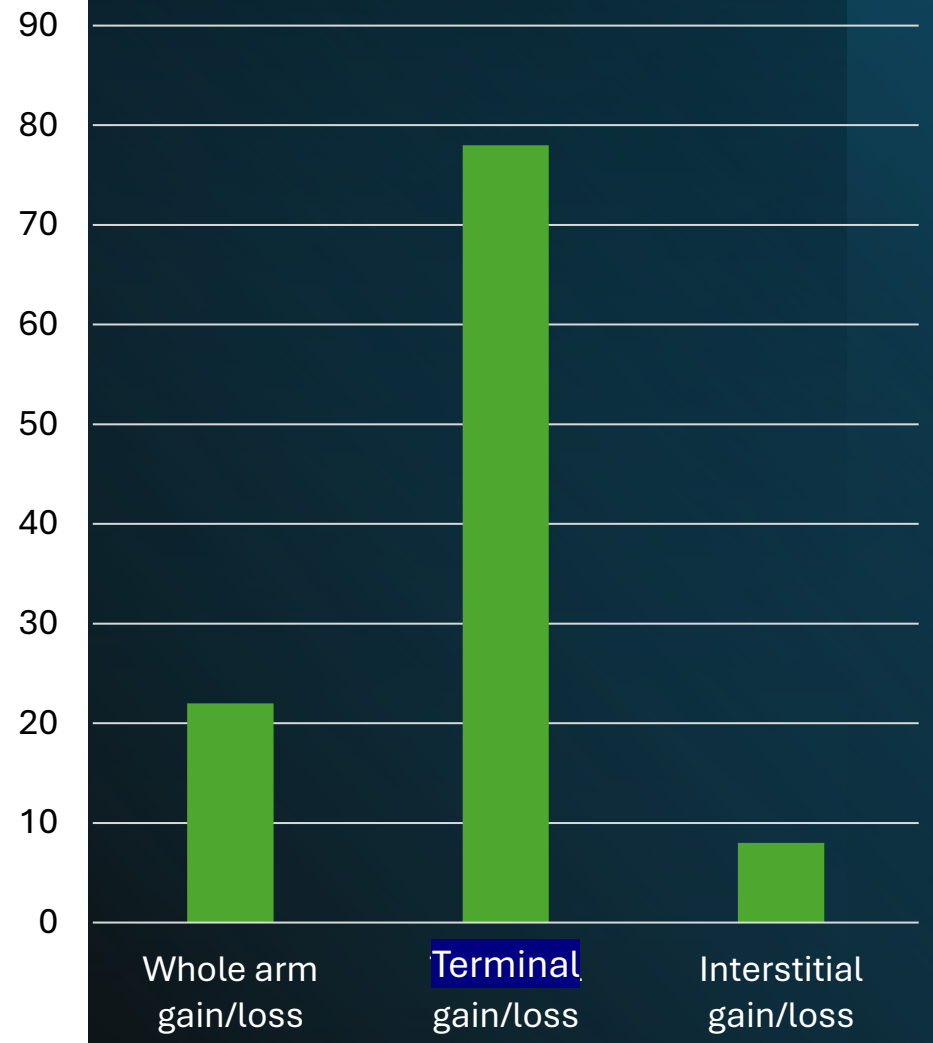


Intrachromosomal Effect and SA Rescue

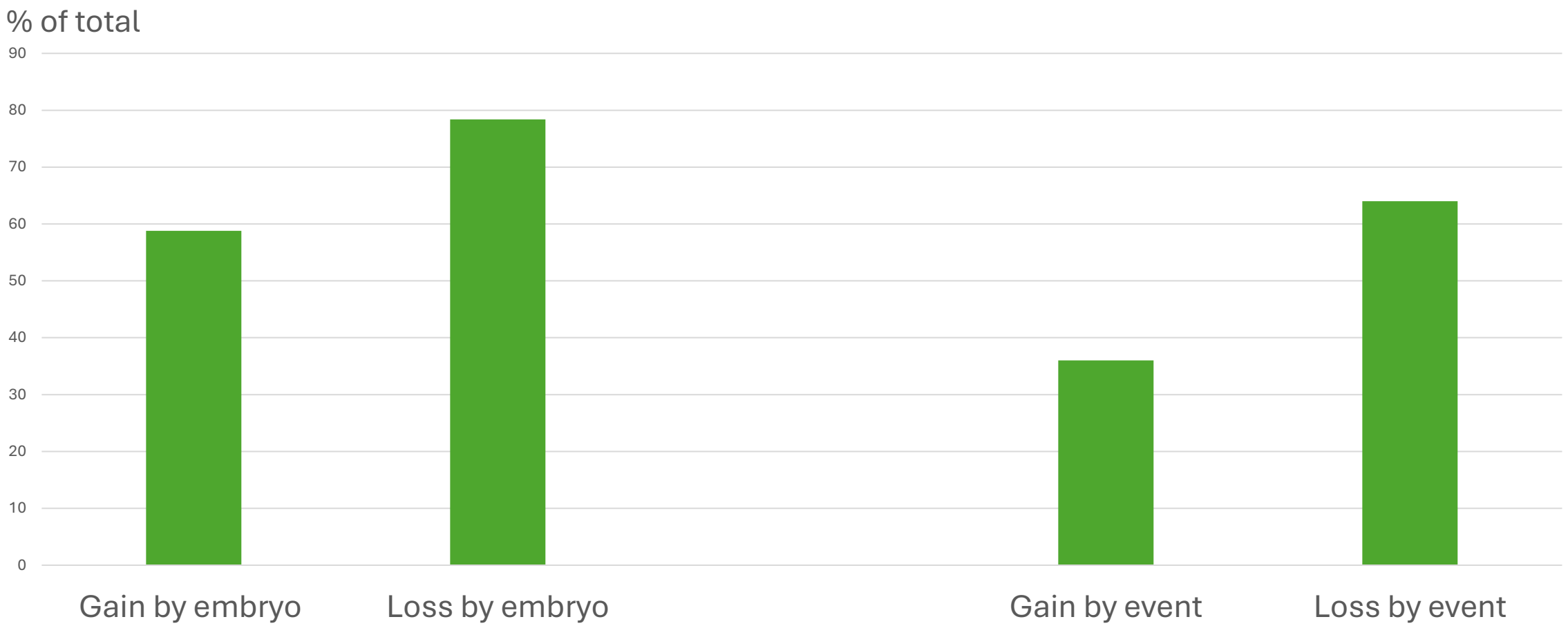
- “Intrachromosomal effect” in 46 embryos (45.1%).
  - SA had been identified in one sample, further errors of the same chromosome were apparent in at least one other
- “ SA rescue” in 40 embryos (39.2%)
  - While an error was seen in one sample (of meiotic origin)
  - Not present in at least one other
- 10 embryos (9.8%) both evidence of SA rescue *and* intrachromosomal effect

Types of Chromosome Abnormality

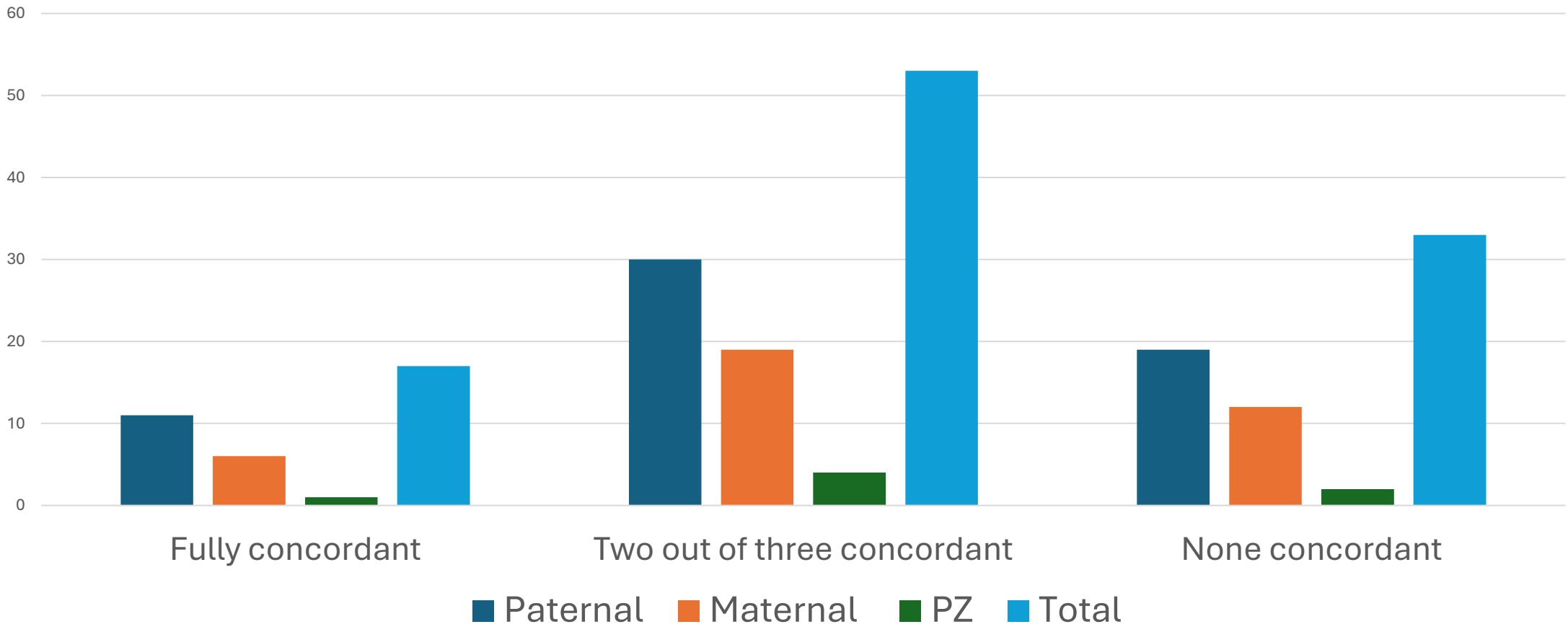
- Terminal gain/loss the most common
- Whole arm gain/loss
- Interstitial is rare
- Isochromosomes in 6 embryos (5.9%)
- Ring chromosomes in 9 embryos (8.8%)
- Parents not karyotyped but patterns consistent with a segregating inversion in 6 embryos (5.9%)
- Some echoes of cancer cells



Gain vs. Loss

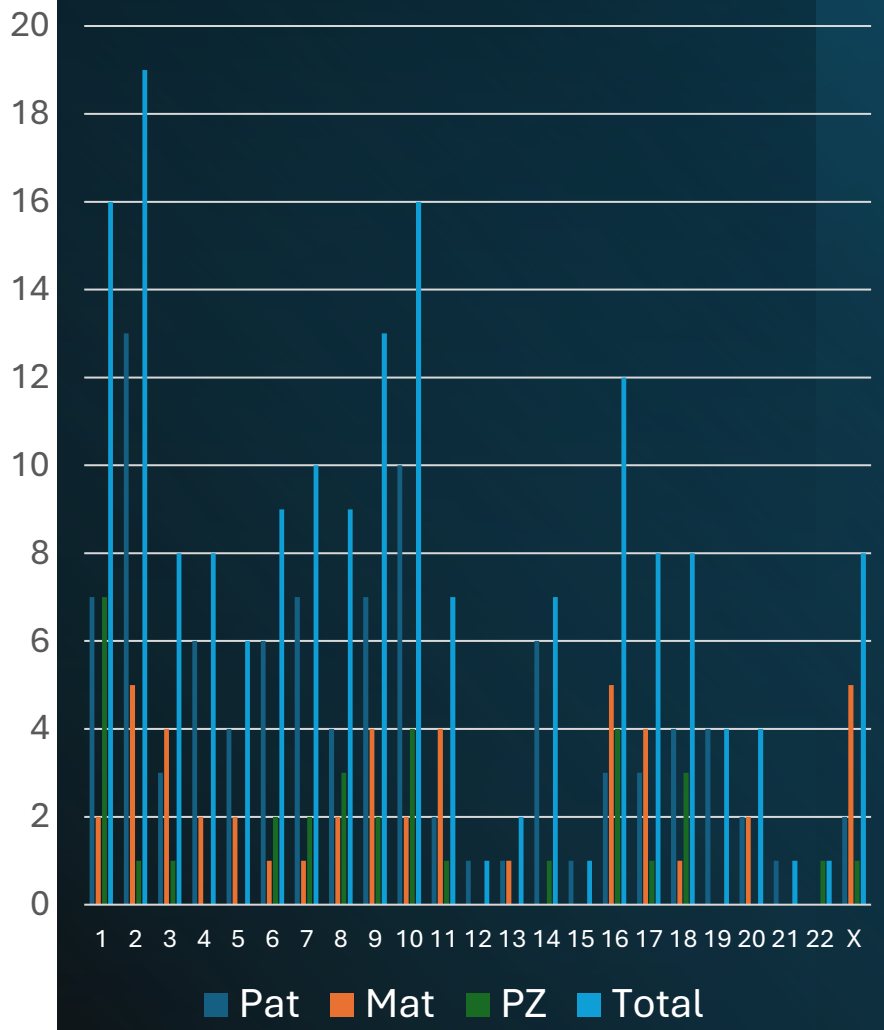

% of total
90
80
70
60
50
40
30
20
10
0
Gain by embryo
Loss by embryo
Gain by event
Loss by event

Concordance



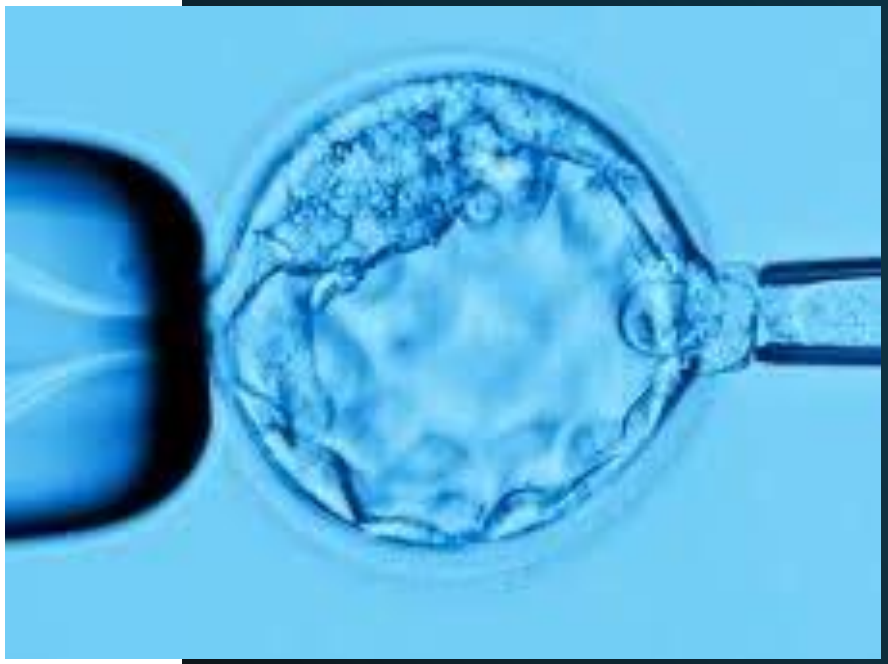
Analysis by Chromosome
Number of Errors

- All chromosomes represented at least once
- Some association with size of chromosome
  - Larger chromosomes 1 and 2 have the most
  - Smallest 21 and 22 have the least
- Chromosomes 9 and 10 perhaps over-represented
- Chromosomes 12 and 15 perhaps under-represented
- Differences do not reach statistical significance



ICM vs. TE

- All 102 embryos ascertained on the basis that there was an SA error in TE1
  - Thus there was an ascertainment bias
- Nonetheless, of these
  - 16 had euploid ICM and 16 a euploid TE2 (all but one were the same embryos)
  - 31 in the ICM and 34 in TE2 had whole chromosome aneuploidies only
- Of the 102 embryos originally diagnosed as having SA (TE1)
  - Not present in ICM of 47 embryos
  - Not present in TE2 of nearly half (50) of embryos



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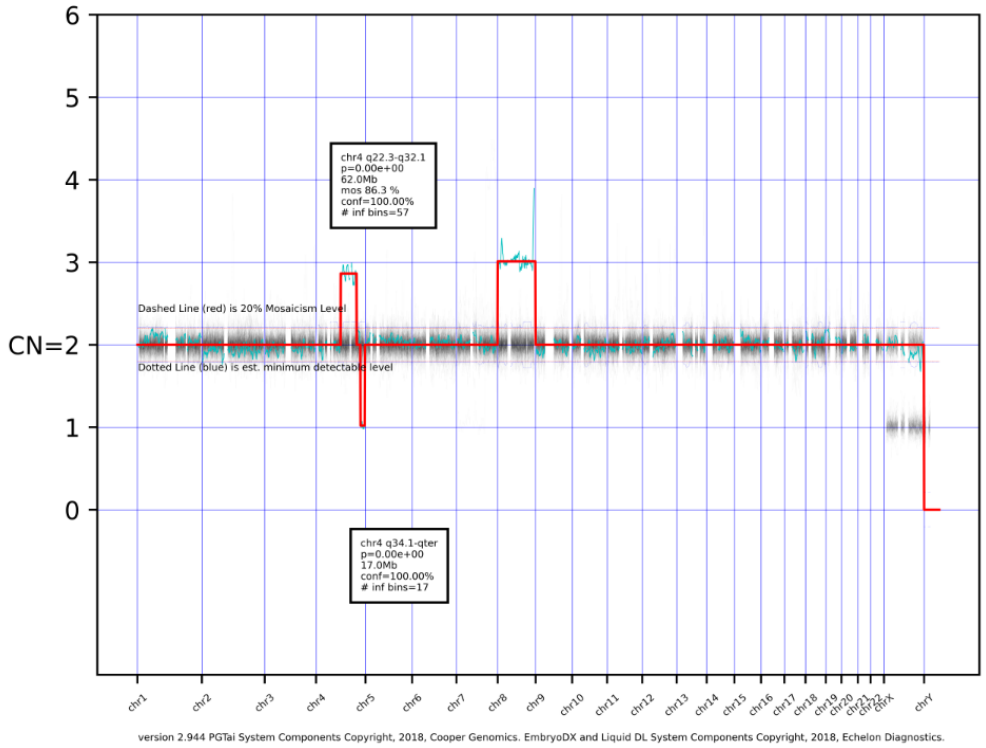


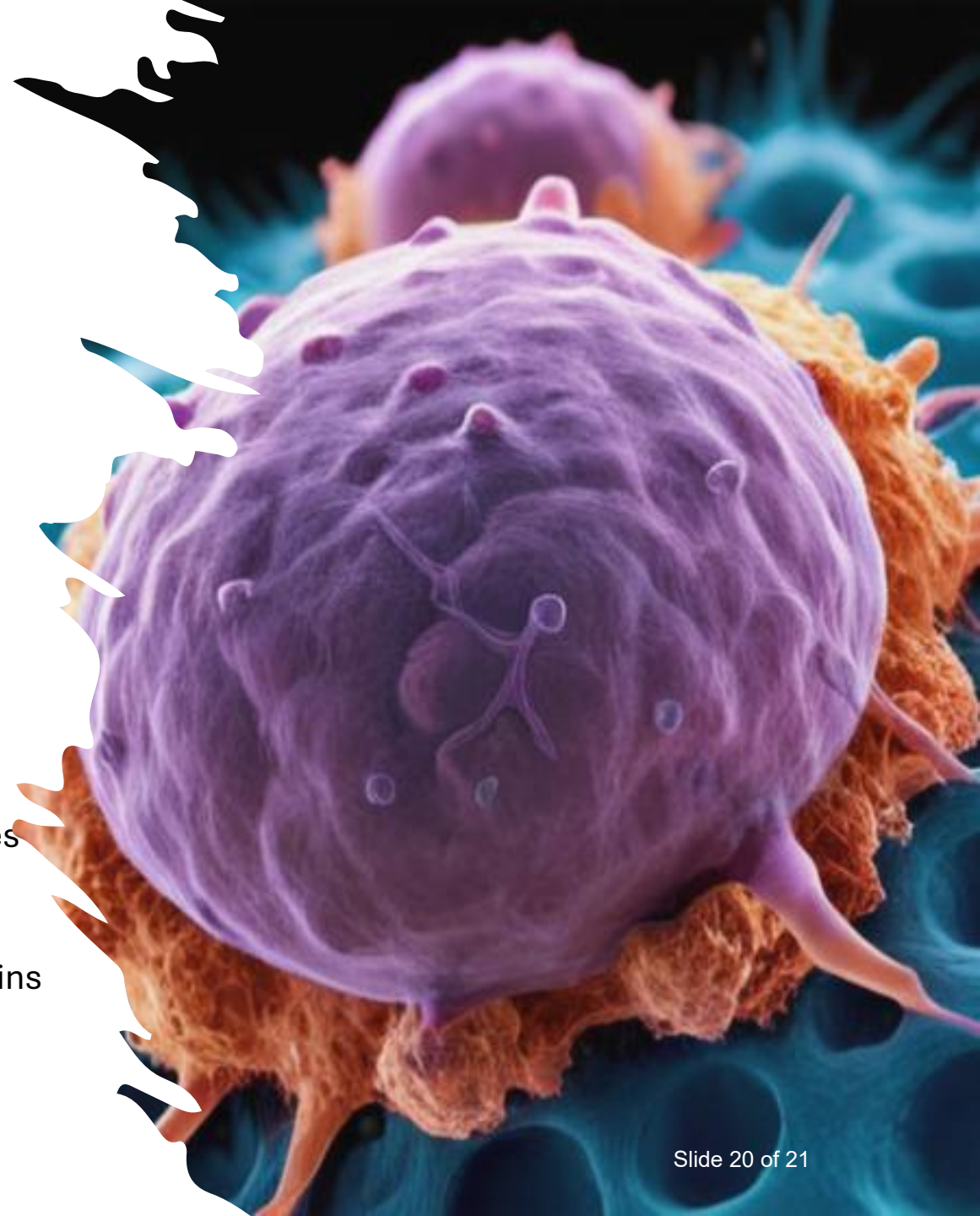
Outcomes cf. Hypotheses

- *SA, like whole chromosome aneuploidy, is predominantly maternal in origin*
- REJECTED: SA is predominantly paternal in origin

- *There is broad correlation between TE and ICM*
- REJECTED: Fully concordant was the least common category (though 2 of the three concordant was the most)

Novel Findings

- Intrachromosomal effect
  - One error perpetuates further errors on the *same chromosome*
  - Interchromosomal effect previously debunked (Griffin and Ogur 2022)
  - Related to chromothripsis?
- SA rescue
  - Whole trisomy rescue is rarely reported in preimplantation embryos
  - Unlike for whole chromosome aneuploidy, mosaicism does not arise post-zygotically
- Chromosome patterns reminiscent of cancer cells
  - Ring chromosomes, isochromosomes, terminal losses/gains
  - Helps invasive nature of blastocyst during implantation?



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