Are some high level mosaics really meiotic aneuploidies?

Christian S Ottolini
The Evewell, London, UK
& University of Kent, Canterbury, UK

University of Kent

THE EVEWELL
OF HARLEY STREET

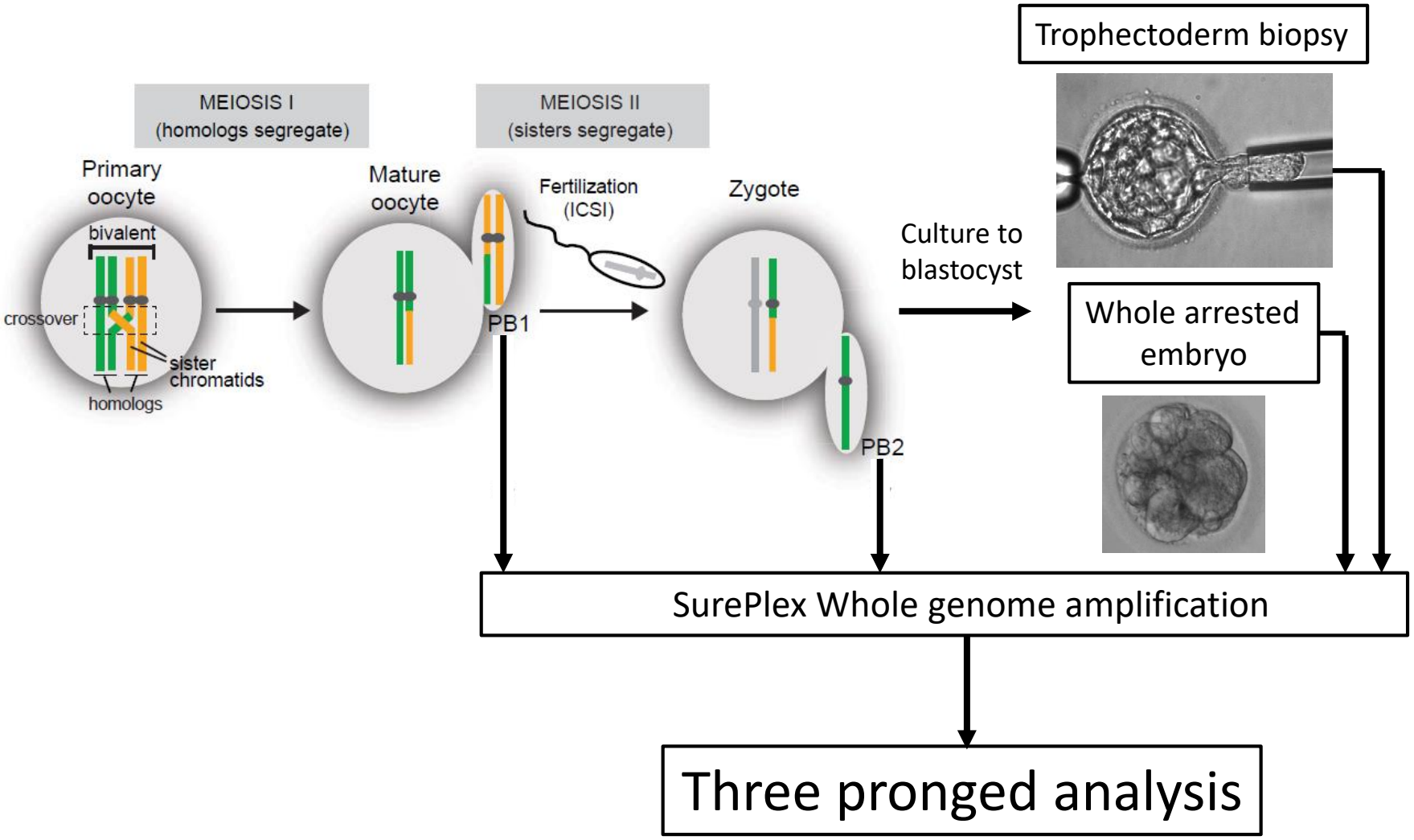
Mosaic embryos

- Mosaicism is a common feature of human preimplantation embryos and is often detected when performing PGT-A on trophectoderm biopsy samples.
- Compared to euploid embryos, mosaic embryos appear to result in a lower pregnancy rate and a higher miscarriage rate.
- “Mosaic aneuploid embryos with < 40% abnormal cells in the TE sample had an OIR of 50% compared to 27% for mosaics with 40–80% abnormal cells in the TE, and 9% for complex mosaic embryos.”

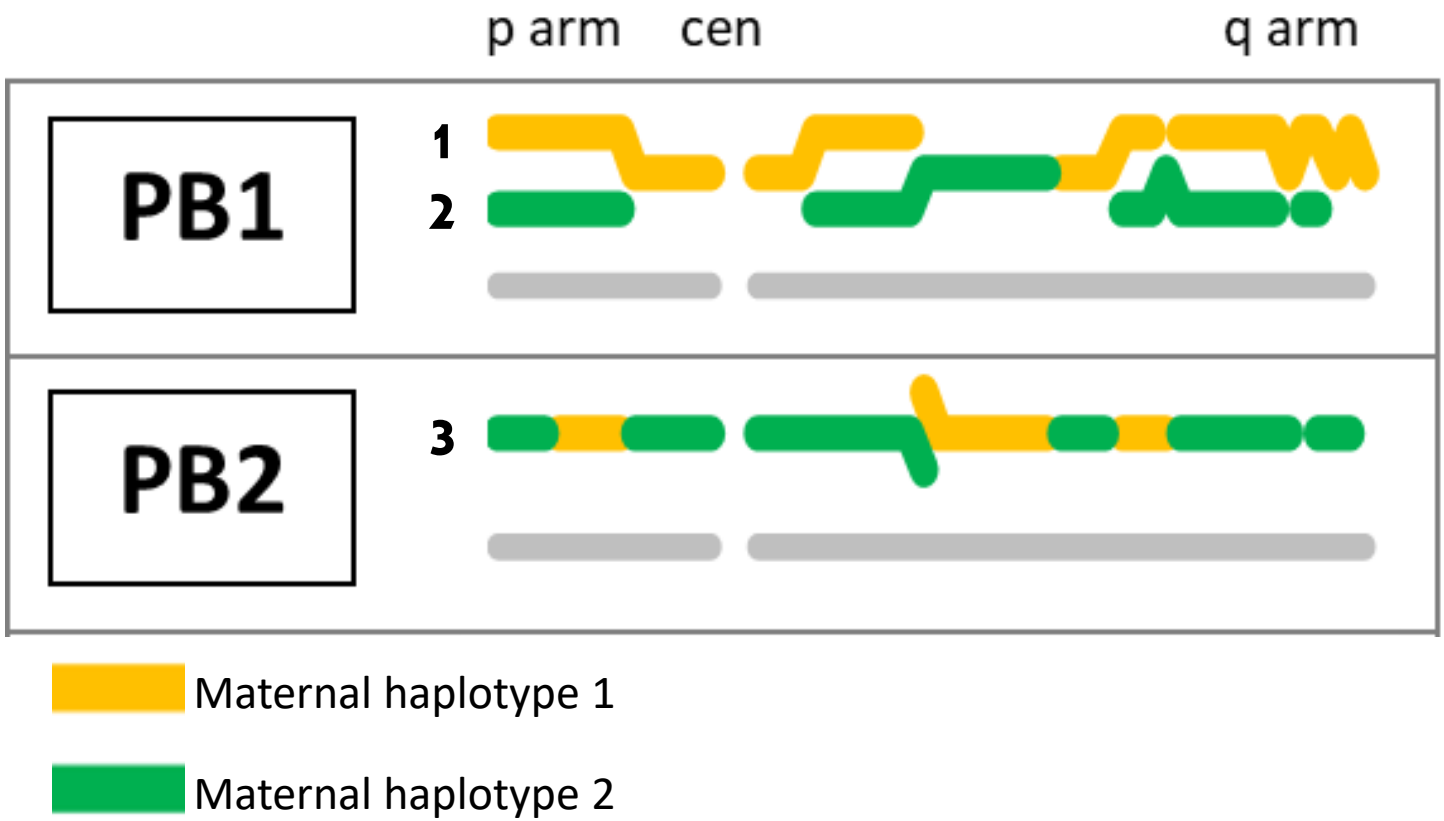
  Munné et al 2019

?????

Methodology

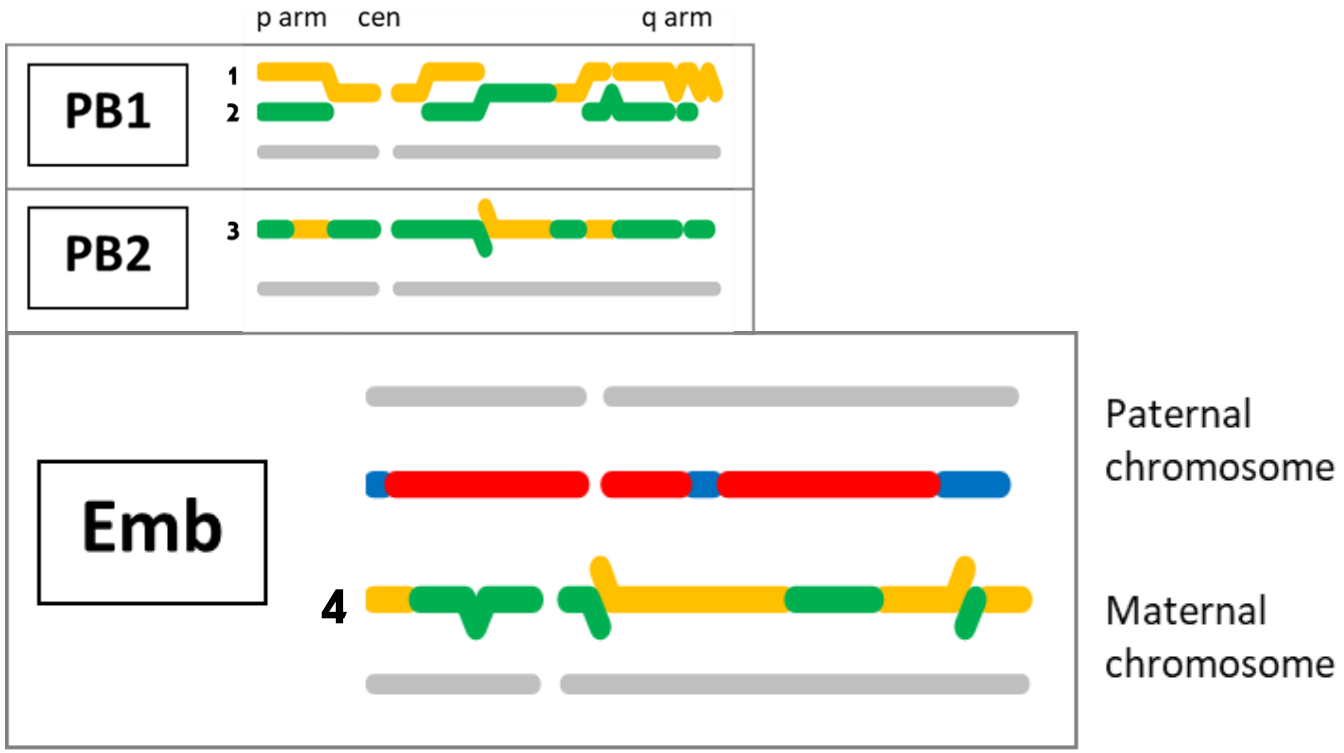


Part 1 – Polar body analysis



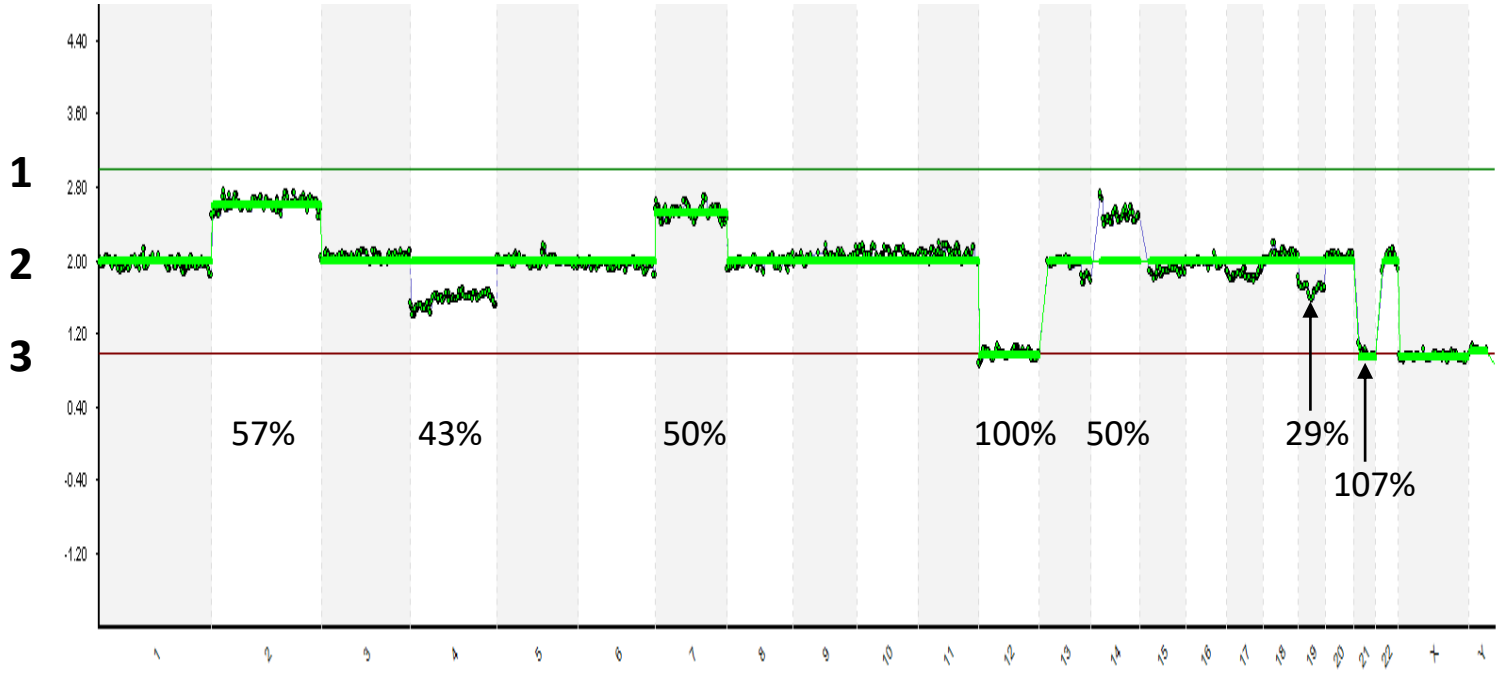
4th chromatid in the embryo

Part 2 - Karyomapping



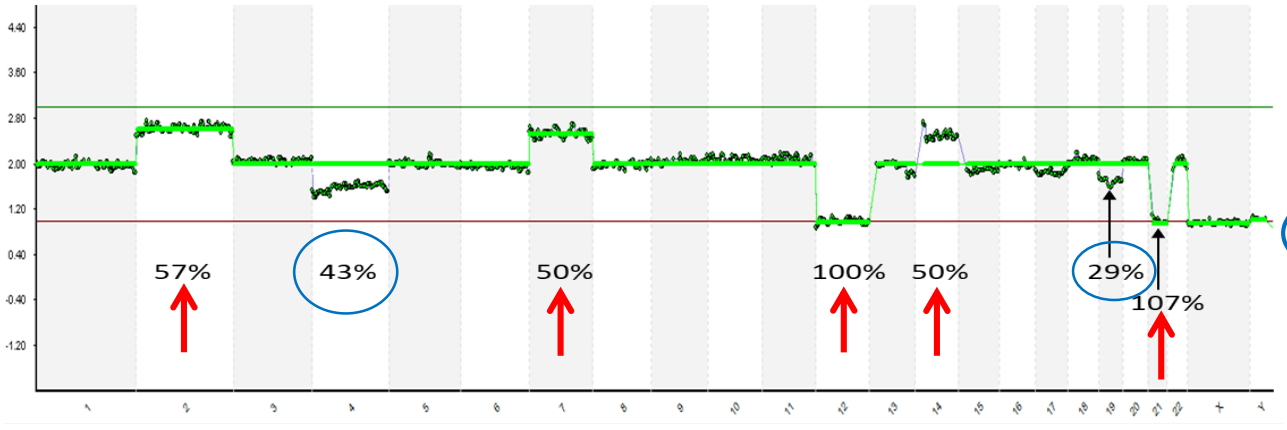
- No paternal meiotic errors observed
- Karyomapping confirmed 100% of meiotic errors identified in the polar body anaysis

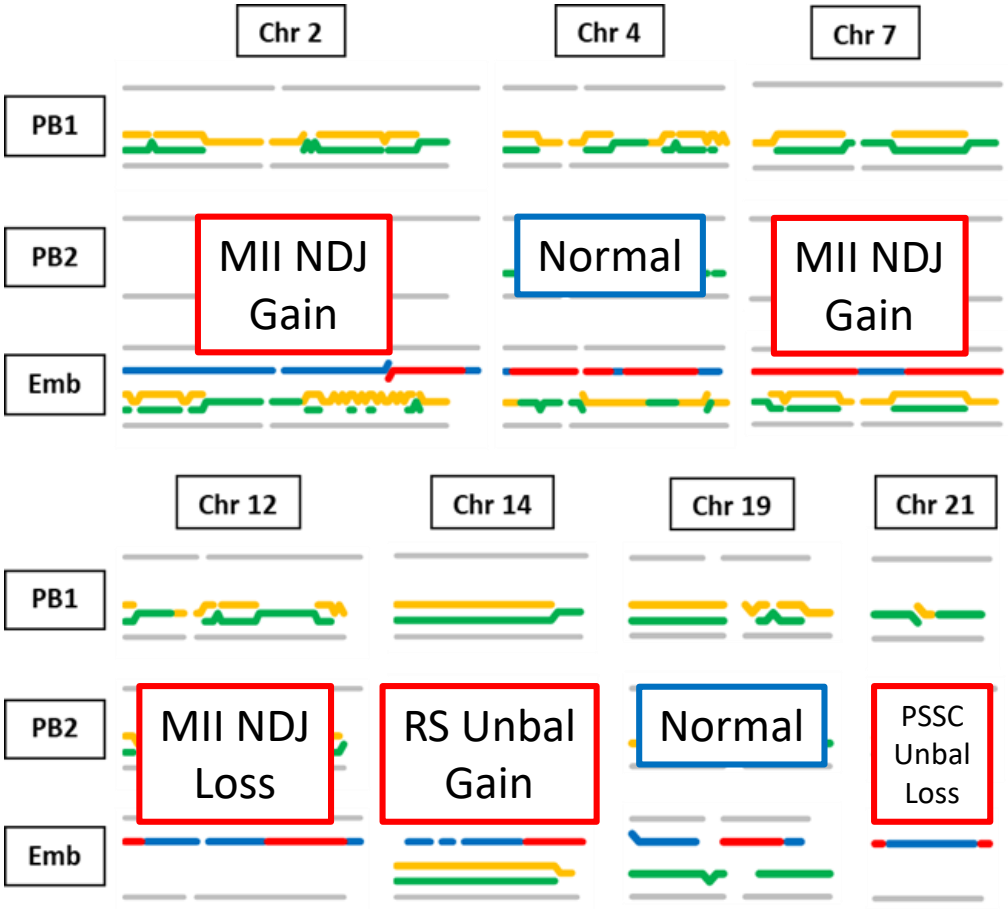
Part 3 - NGS



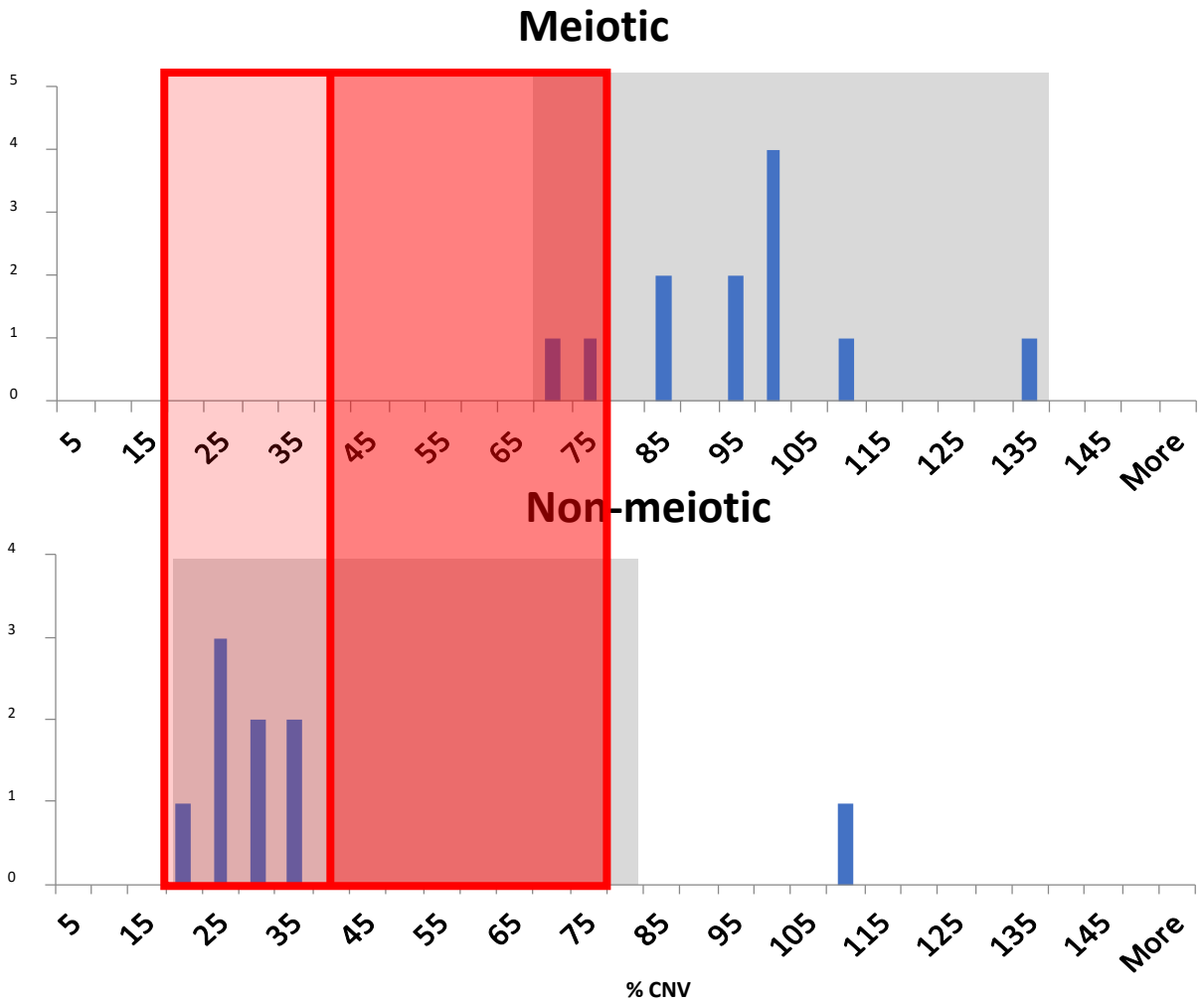
- Measure the level of copy number variations (CNVs)

Combined analysis of the 3 parts


57%
43%
50%
100%
50%
29%
107%
Non-meiotic origin
Maternal meiotic origin


Chr 2
Chr 4
Chr 7
PB1
PB2
Emb
MII NDJ Gain
Normal
MII NDJ Gain
Chr 12
Chr 14
Chr 19
Chr 21
PB1
PB2
Emb
MII NDJ Loss
RS Unbal Gain
Normal
PSSC Unbal Loss

Copy number variant (CNV) level of **meiotic vs non-mitotic** errors in TE biopsy samples



Findings

- Karyomap analysis of the trophectoderm biopsies and embryos was concordant for all of the meiotic aneuploidies identified by polar body analysis
- No paternal aneuploidies were identified by karyomap analysis in any of the embryos
- Non-meiotic changes (mosaics) were detected by NGS with predominantly low CNV levels
- All meiotic aneuploidies were detected by the NGS-based copy number analysis with a wide range of CNV levels
- **A significant portion of meiotic aneuploidies were classified as mosaic by CNV levels**

Clinical experience

- Thirteen couples consented to follow up of DNA from 21 “mosaic only” embryo biopsy samples by SNP genotyping and Karyomapping
- 63 chromosome copy number changes (both whole chromosome and segmanetal) were identified in the NGS as mosaic (range 1-13 per sample)
- 12 mosaic changes (19%) were identified as meiotic in origin in 10/21 samples (48%)*
- 5 mosaic embryos considered to be at low risk of an affected pregnancy after genetic counselling were transferred to four patients, resulting in three live births.

*This included one sample identified as a triploid with a single maternal meiotic trisomy.

Conclusions

- NGS-based copy number analysis of embryo samples robustly detects meiotic aneuploidy - not always expected 100% CNV
- NGS-based copy number analysis of embryo samples frequently detects non-meiotic CNVs, mostly in the region of low level mosaics
- **CNVs are not reliable for classifying meiotic vs mitotic errors in clinical trophectoderm biopsy samples**
- SNP genotyping and karyomapping of embryo samples is an extremely robust tool for detecting meiotic aneuploidy
- SNP genotyping is useful to confirm mosaicism identified by NGS – optimising clinical outcomes following mosaic embryo transfer

Acknowledgements

Prof. Alan H Handyside

Mr Michael S Summers
Senior Consultant,
London Women's Clinic,
London

Abeo McCollin,
London Women's Clinic,
London