SNP analysis of meiotic and mitotic aneuploidies for preimplantation genetic testing

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Declaration of interests

I am the founder of
ExOvo Genomics Ltd which licences
software, including Omnia and
AneuScan™, for comprehensive
preimplantation genetic testing

www.exovogenomics.com

Genome-wide SNP analysis for comprehensive preimplantation genetic testing

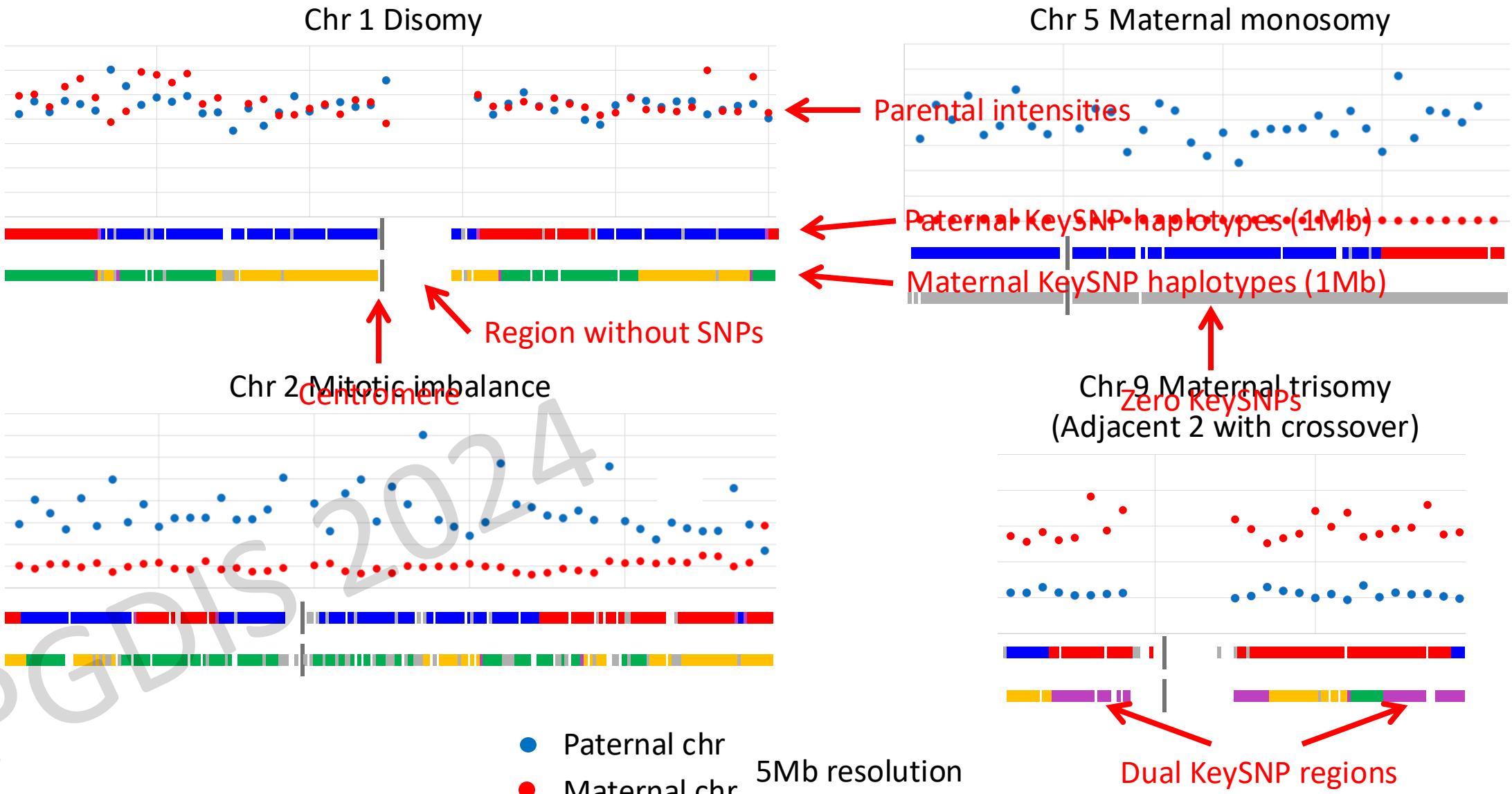
- Genome-wide SNP genotyping and karyomapping (parental haplotyping) is a universal linkage-based method for preimplantation genetic testing of monogenic disease (PGT-M) and identification of meiotic trisomies, monosomies and deletions (Handyside et al, 2010; Natesan et al, 2014)
- From 2014-2022, a large reference lab completed over 14.6K PGT-M cycles in 8.4K cases, for 4000 mutations and 900 disorders (Shadwell et al, 2022)
- Microarray-based genome-wide SNP analysis is routinely used for high resolution cytogenetics
- Combined SNP intensity and karyomap analysis of parental chromosomes allows detection of both meiotic and mitotic chromosome aneuploidies for comprehensive preimplantation genetic testing of monogenic disease, aneuploidy and structural chromosome rearrangements (PGT-M/A/SR) in a single assay

Combined karyomapping and intensity analysis for PGT of monogenic disease and aneuploidy (PGT-M/A)

- 370 cycles of PGT-M with PGT-A
- 1271 trophectoderm (TE) biopsies were processed for whole genome amplification by multiple displacement amplification (MDA) (Qiagen)
- SNP microarrays were then used for combined karyomapping and intensity analysis at approximately 300k (Vitrolife) or 700k SNP loci (Illumina) and the data analysed using custom software (Omnia/AneuScan®; ExOvo Genomics)
- Chromosome gains and losses (both meiotic and mitotic) identifiable in single samples without a phasing reference

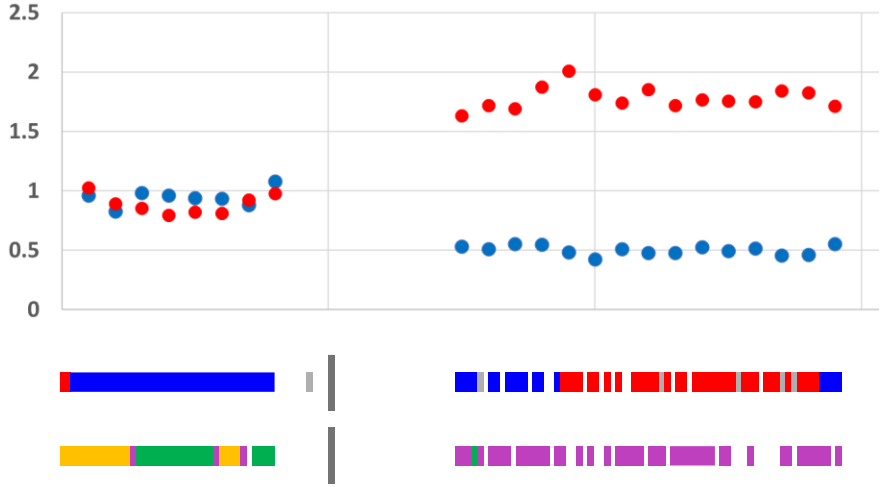
Horak and Handyside, unpublished data

(1) Whole chromosome aneuploidy

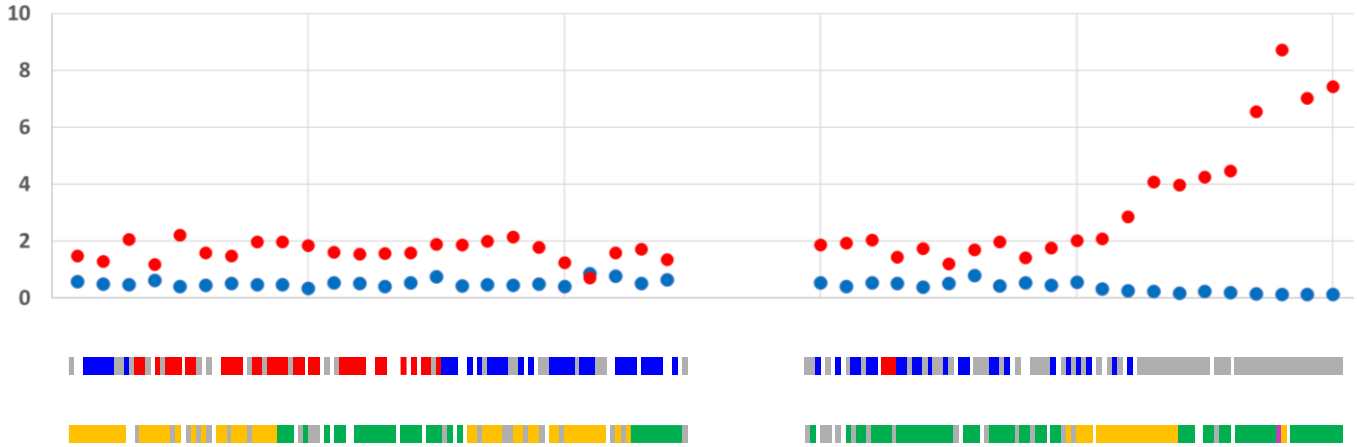


(2) Segmental aneuploidy

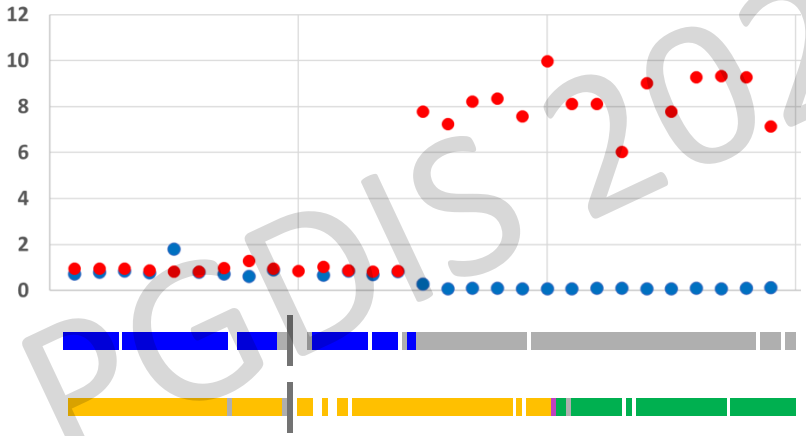
Chr 9 (Meiotic)



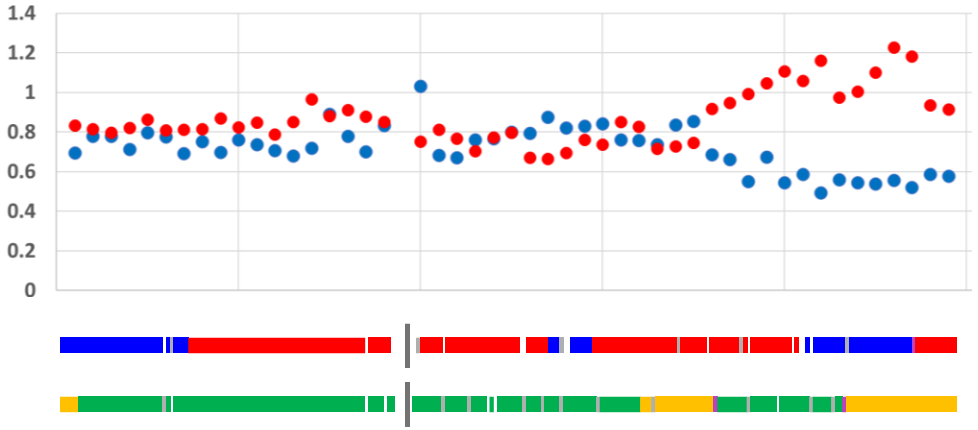
Chr 1 (Meiotic)



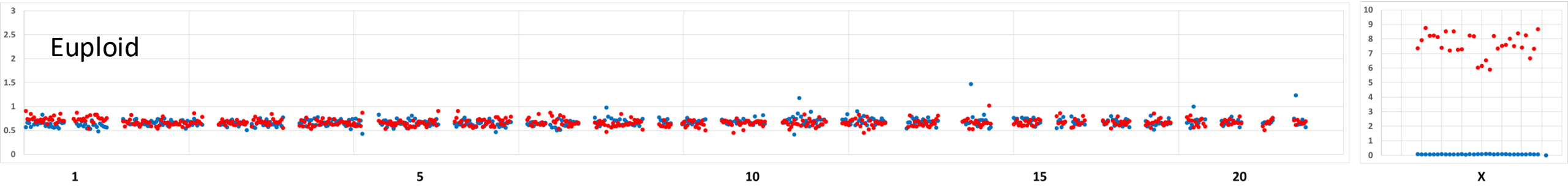
Chr 8 (Meiotic)

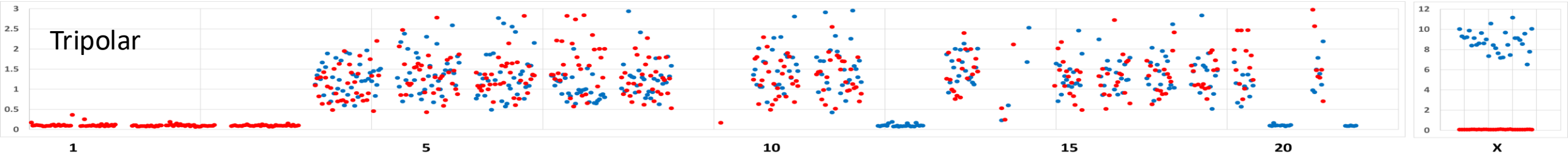


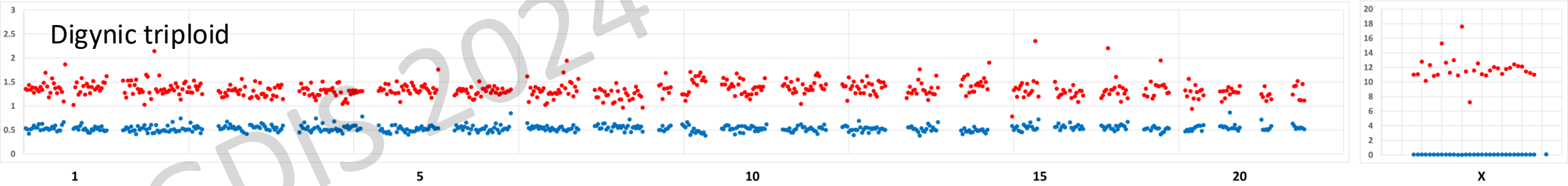
Chr 2 (Mitotic)

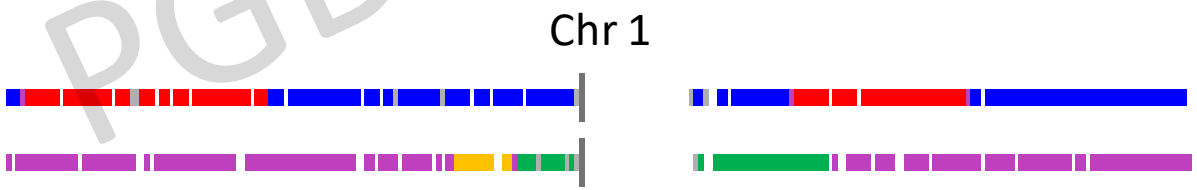


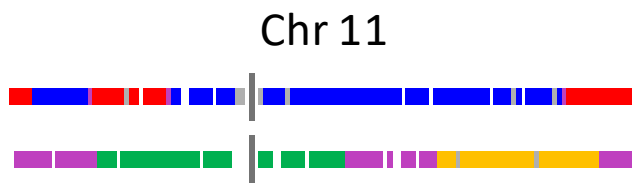
(3) Karyotype-wide abnormalities

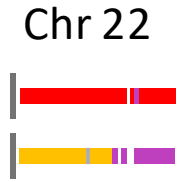












PGT-A by combined karyomapping and intensity analysis: Categorisation of biopsy samples by aneuploidy type and maternal age

Maternal age	No of biopsies	Meiotic trisomies plus any other abns	Meiotic monosomies only plus any other abns	Mitotic gains/losses	Segmental aneuploidies only	All abn	Franasiak et al (2014)	
	n	%	%	%	%	%	n	%
<30	296	6%	7%	5%	12%	29%	1652	26%
30-34	561	5%	8%	4%	15%	31%	5167	30%
35-37	239	13%	15%	4%	10%	41%	3659	37%
38-39	87	25%	16%	3%	11%	56%	2131	50%
40-43	88	26%	24%	5%	7%	61%	2367	67%
All	**1271**	**9%**	**10%**	**4%**	**12%**	**35%**	**14976**	**40%**

Franasiak et al (2014) Fert Stert 101, 656

Prioritisation of biopsy samples by aneuploidy type for PGT-A

Meiotic trisomies
High accuracy
Viable trisomies
Clinical syndromes

↓

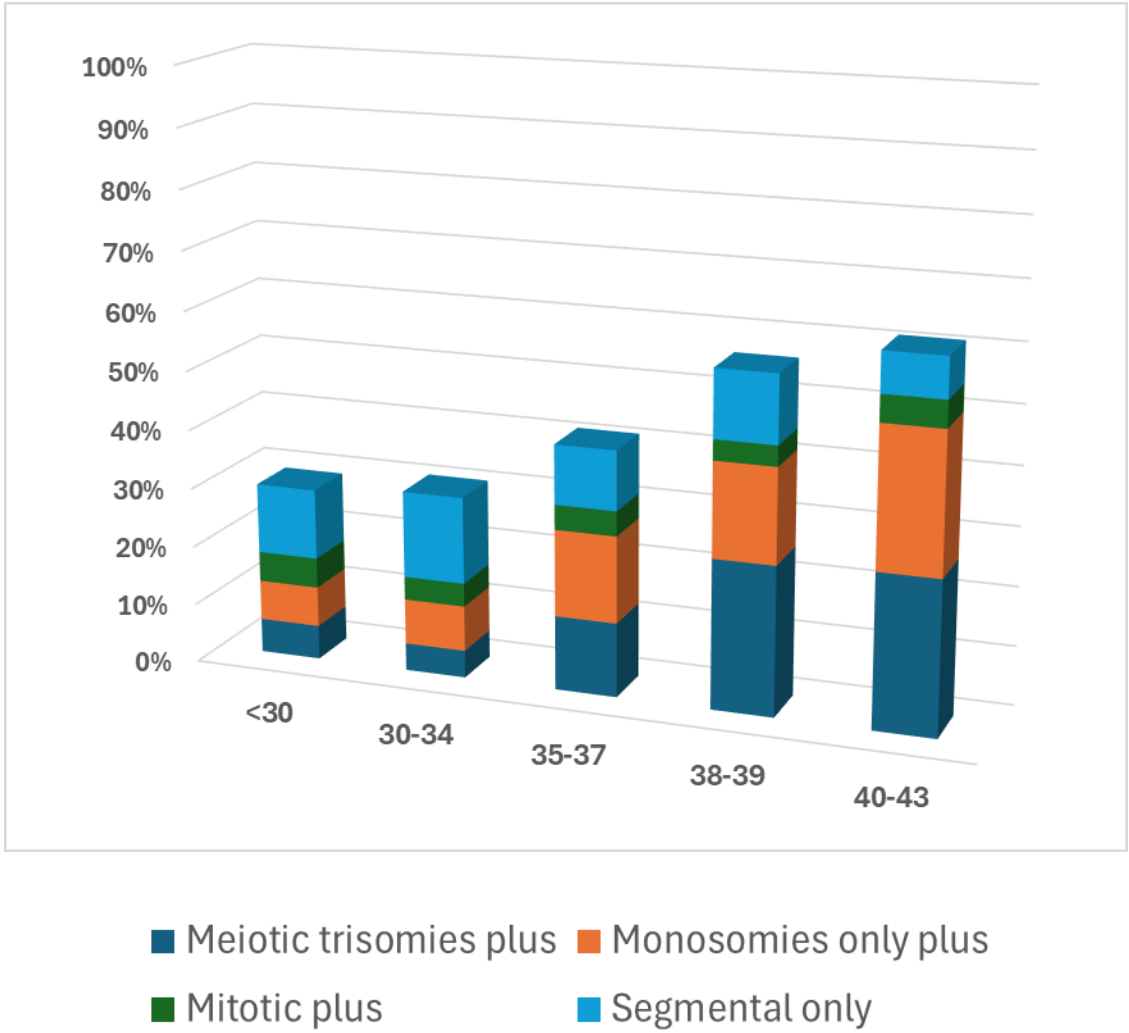
Monosomies
Presumed meiotic
Almost all lethal

↓

Mitotic aneuploidies
Mosaic gains and losses
Unknown clinical significance

↓

Segmental aneuploidies
Unknown clinical significance



Leigh et al (2022) RBMO 45, 19-25

Genome-wide SNP karyomapping and intensity analysis for PGT-A

- Single, highly versatile, universal test for linkage-based PGT-M and high resolution PGT-A and PGT-SR
- Identifies all types of abnormal fertilisation, contamination and paternity/maternity
- Applicable to single or multiple cell samples (polar bodies, blastomeres or trophectoderm biopsies)
- Compatible with isothermal (MDA) or PCR library-based methods of whole genome amplification and a range of SNP arrays

- NGS-based copy number analysis alone can result in intermediate (mosaic) copy number changes of unknown clinical significance and cannot accurately discriminate between meiotic and mitotic aneuploidies
- Combining karyomap and intensity analysis of parental chromosomes improves accuracy and allows meiotic and mitotic aneuploidies to be identified
- SNP analysis can be tailored to offer appropriate testing for different maternal age ranges to minimise the discard of viable embryos

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