Segmental aneuploid embryos and management strategies for transfer

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- **SIERR: Interest Group Reproductive Genetics**


Main Menu
1. Definition of segmental aneuploidies
2. Frequency at different developmental stages
3. Nature and origin of segmental aneuploidies detected in PGT
4. Transfer outcomes of segmental aneuploidies
5. Conclusions and management strategies

Background and definitions

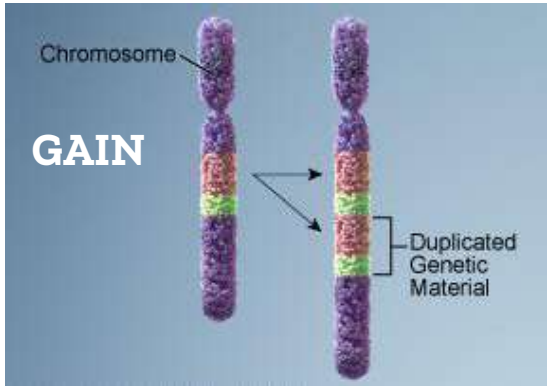
Background

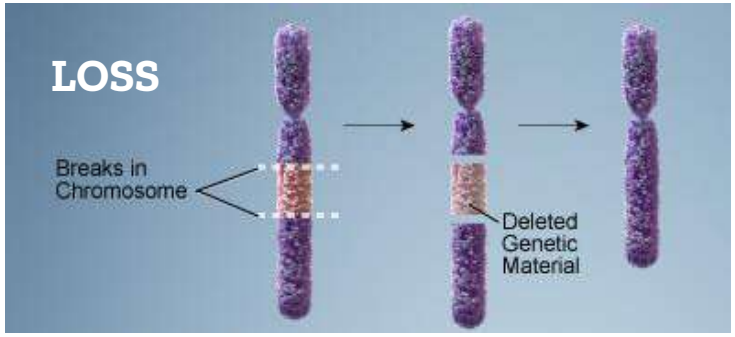
SEGMENTAL ANEUPLOIDIES in PGT

Sub-chromosomal copy number changes involving the gain or loss of a portion of the chromosome

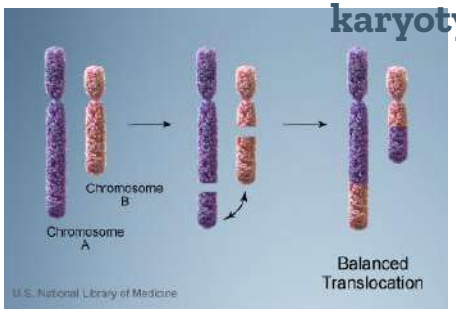
- **No clear embryologic phenotype**
- **The majority occur de novo in the embryo, involving any of the 24 chromosomes**

5-10Mb Resolution in PGT





Inherited from parents with abnormal karyotype



Mis-segregation of translocations/inversions

Expected fragments involved

Frequency of segmental aneuploidies in oocytes and preimplantation embryos

Incidence of segmental aneuploidies in oocytes, cleavage and blastocyst stage embryos

Human Reproduction, Vol.32, No.12 pp. 2549–2560, 2017
Advanced Access publication on November 8, 2017 doi:10.1093/humrep/dex324

human reproduction ORIGINAL ARTICLE *Reproductive genetics*

The incidence and origin of segmental aneuploidy in human oocytes and preimplantation embryos

D. Babariya[1,2,*], E. Fragouli[1,2], S. Alfarawati[1], K. Spath[1,2], and D. Wells[1,2]

The prevalence of SA decreases as the embryo progresses through its developmental stages

The rates of segmental aneuploidies peak in early mitotic divisions

Table III Prevalence of oocytes/embryos affected by segmental abnormality.

Stage analysis performed	Number of oocytes/embryos with a segmental aneuploidy	Ratio of loss:gain of material
Oocyte	47 (10.39%)[a,b]	0.5 (30/60)
Cleavage stage	428 (24.29%)[a,c]	1.38 (324/234)
Blastocyst	207 (15.59%)[b,c]	1.57 (168/107)

Statistical comparisons, using Fisher's exact test: (a) $P < 0.0001$; (b) $P = 0.0207$; (c) $P < 0.0001$.

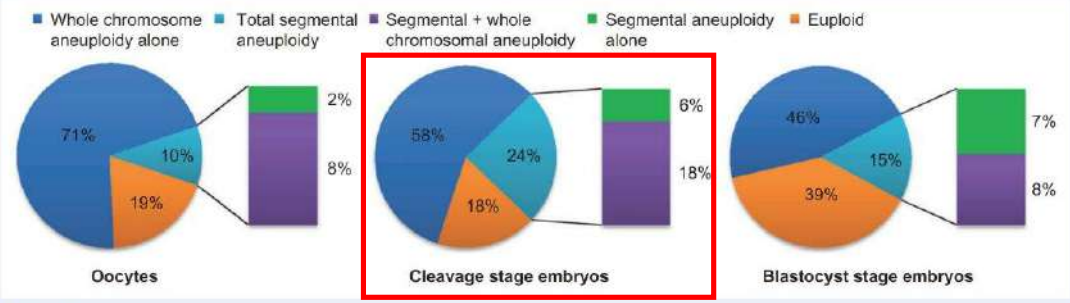


Figure 3 The frequency of segmental aneuploidy increased significantly from oocytes to the cleavage stage embryos but decreased from cleavage to blastocyst stages. Most of the segmental imbalances occurred along with other whole chromosomal aneuploidies with 8.4% (38/452) in oocytes, 18.4% (352/1762) in cleavage stage embryos and 8.1% (108/1327) at blastocyst stage. It was rare to see segmental aneuploidies occurring alone in oocytes (9/452; 1.99%) however, this was seen significantly more often at the cleavage (103/1762; 5.85%; $P = 0013$) and blastocyst stages (99/1327; 7.46%; $P < 0.0001$). No significant difference was observed in the occurrence of segmental aneuploidy alone between cleavage and blastocyst stage embryos.

Incidence and features of de novo segmental aneuploidies detected in preimplantation embryos

Incidence of segmental aneuploidy in blastocyst-stage preimplantation embryos.

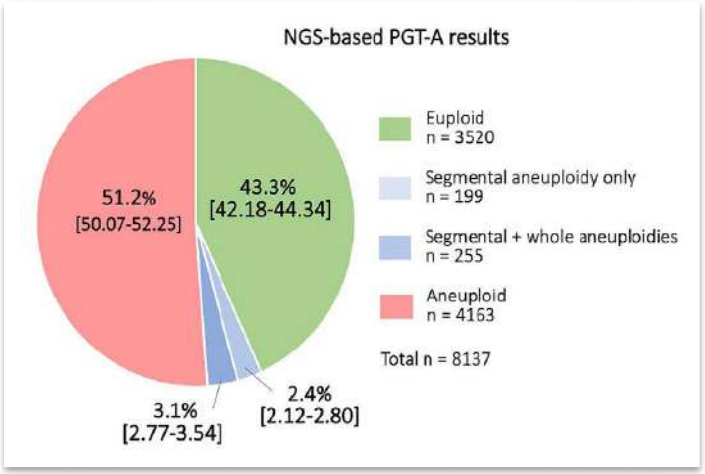
		Incidence of SA in blastocyst-stage embryos		
Reference	Total no. of blastocysts	SA-positive blastocysts	Incidence of SA	Platform
McCarty et al., 2022 (27)	89,226	2,766	3.10%	NGS
Babariya et al., 2017 (28)	1,327	207	15.60%	aCGH
Tiegs et al., 2021 (18)	2,110	186	8.82%	tNGS
Escribà et al., 2019 (26)	3,565	299	8.39%	NGS
Zore et al., 2019 (30)	377	20	5.31%	aCGH
Kubicek et al., 2019 (17)	967	54	5.58%	Karyomapping
Rechitsky et al., 2020 (35)	14,992	2,099	14.00%	NGS
Girardi et al., 2020 (24)	8,137	653	8.03%	NGS
Zuffardi et al., 2022 (31)	1,501	79	5.26%	NGS
Vialard et al., 2022 (32)	182,827	20,557	11,.24%	FAST-SeqS
Robberecht et al., 2021 (33)	1,708	97	5.68%	NGS
Zhou et al., 2018 (25)	2,095	206	9.83%	NGS
Xie et al., 2022 (21)	15,411	2,273	14.75%	NGS
Dviri et al., 2020 (34)	3,118	104	3.34%	NGS
Insua et al., 2018 (29)	3,628	314	8.65%	NGS
Mean incidence of SA	-	-	8.51%	-

Picchetta et al. F&S Science, 2023

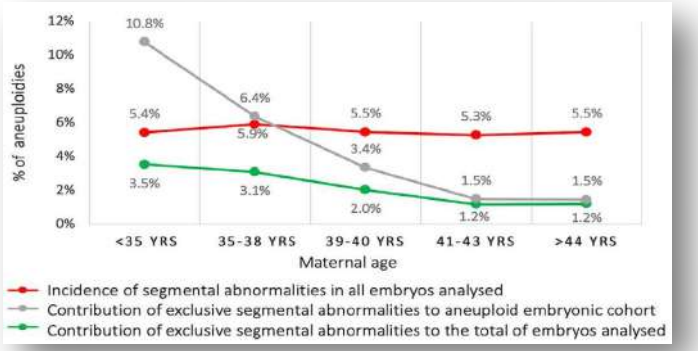
15%

3%

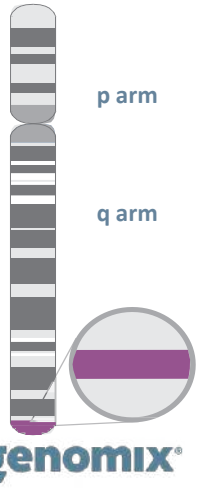
Mean incidence of SA 8.5%



Girardi et al, RJHG 2020



- SA's incidence does not increase with maternal age
- SA appear to be more frequent in the q arm
- SA are more frequently telomeric then interstitials



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Impact of segmental aneuploidies in later stages of development

- **In PRENATAL DIAGNOSIS**

Mean incidence 3.5%

Prenatal incidence of SA

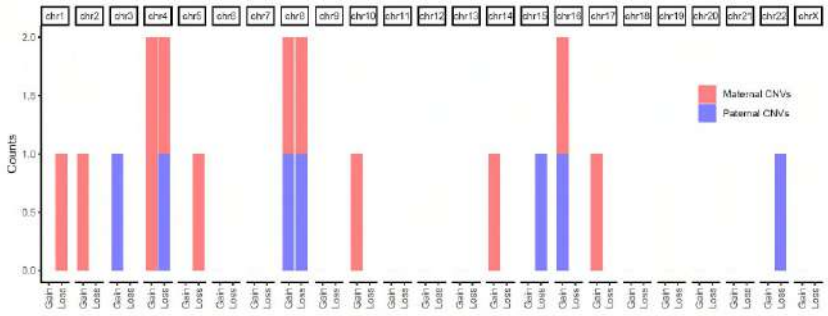
Reference	Analyzed samples	SA-positive samples	Incidence of SA	Platform
Breman et al., 2012 (65)	1,115	43	3.80%	CMA
Farcas et al., 2013 (66)	528	12	2.27%	Karyotype/FISH
Levy et al., 2014 (67)	1,861	43	2.30%	SNP array
Shen et al., 2016 (68)	436	23	5.30%	aCGH and NGS
Sahoo et al., 2017 (69)	7,396	181	2.40%	SNP array/aCGH
Wang et al., 2018 (16)	3,398	41	1.20%	CNV-Seq
Peng et al., 2019 (70)	836	40	4.80%	aCGH
Lin et al., 2020 (71)	10,377	223	2.10%	SNP array
Kowalczyk et al., 2022(72)	7,400	579	7.80%	aCGH
Mean incidence of SA	-	-	3.55%	-

Picchetta et al. F&S Science, 2023

- **In PREGNANCY LOSS**

1.3%

Size: 200kb-100Mb



Arnadottir, G.A., Jonsson, H., Hartwig, T.S. et al. Sequence diversity lost in early pregnancy. Nature (2025).

- **In the FETUS:**

0.45%*

Schlaikjær Hartwig, 2023, Lancet

- **At BIRTH:**

0.015%*

Extrapolated from UK Biobank

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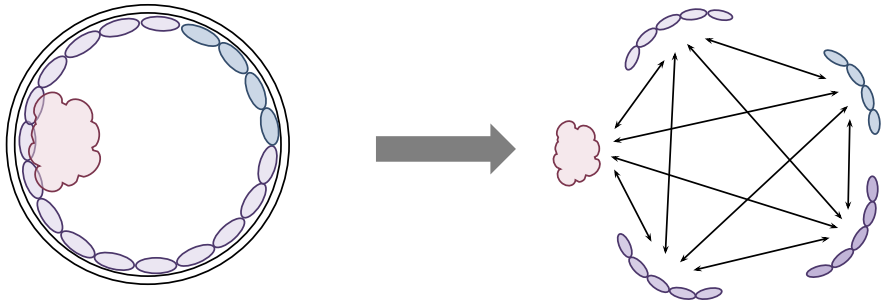
Nature and origin of segmental aneuploidies in PGT

Cell divisions origin of aneuploidies: multifocal biopsies in the research setting

Design: embryo disaggregation models and NGS-based PGT-A analysis

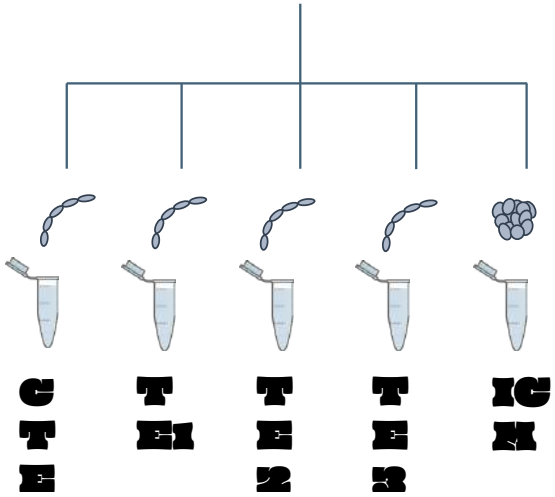
Initial PGT-A result: segmental aneuploidy



- CLINICAL TROPHECTODERM BIOPSY (TE)
- [illegible] MULTIFOCAL BIOPSIES (TE 1,2,3)

embryos donated for research

multifocal biopsies



Cell divisions origin of aneuploidies: multifocal biopsies in the research setting

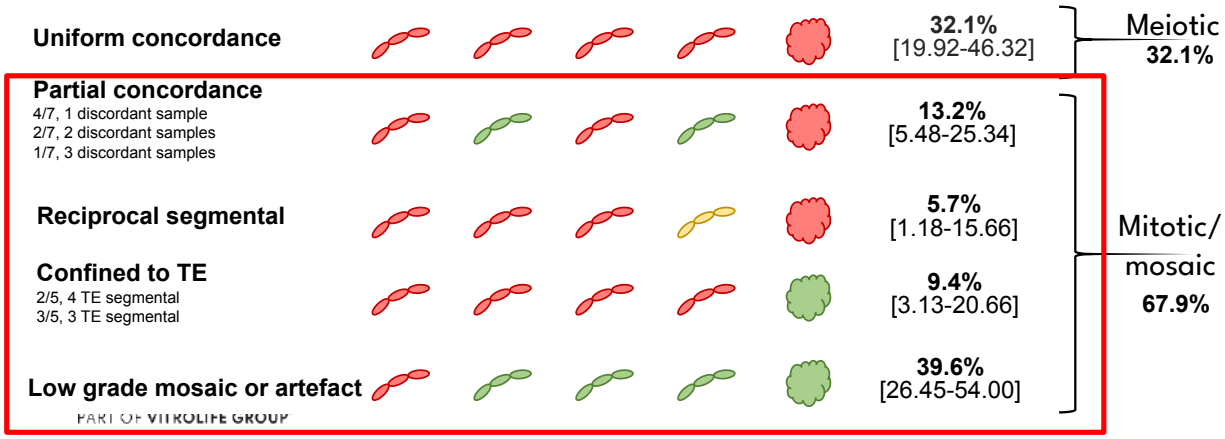
Concordance rate of SA findings in PGT-A.

Concordance rate of SA in PGT-A				
Reference	**Platform**	**Embryo stage**	**Concordance rate**	**Absolute values**
Chuang et al., 2018 (47)	NGS	Blastocyst	55.50%	5/9
Popovic et al., 2019 (48)	NGS	Outgrowth 12 dpf	38.46%	5/21
Victor et al., 2019 (49)	NGS	Blastocyst	44.40%	4/9
Lawrenz et al., 2019 (50)	NGS	Blastocyst	16.70%	1/6
Navratil et al., 2020 (46)	NGS	Blastocyst	36.80%	14/38
Girardi et a., 2020 (24)	NGS	Blastocyst	32.10%	17/53
Sachdev et al., 2020 (51)	NGS	Blastocyst	0	0/12
Kim et al., 2021 (11)	NGS	Blastocyst	21.30%	36/196
Mean concordance rate	-	-	30.66%	-

Picchetta et al. F&S Science, 2023

Mean concordance rates ~30%

SEGMENTAL ANEUPLOIDIES CONFIGURATIONS

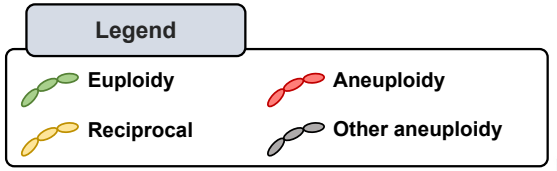



ARTICLE

Incidence, Origin, and Predictive Model for the Detection and Clinical Management of Segmental Aneuploidies in Human Embryos

Laura Girardi,[1] Munevver Serdarogullari,[2] Cristina Patassini,[1] Maurizio Poli,[1] Marco Fabiani,[1] Silvia Caroselli,[1] Onder Coban,[2] Necati Findikli,[3,4] Fazilet Kubra Boynukalin,[5] Mustafa Bahceci,[5] Rupali Chopra,[6] Rita Canipari,[7] Danilo Cimadomo,[8] Laura Rienzi,[8] Filippo Ubaldi,[8] Eva Hoffmann,[9] Carmen Rubio,[10] Carlos Simon,[11,12,13] and Antonio Capalbo[1,14,*]

Girardi et. al 2020. American Journal of Human Genetics



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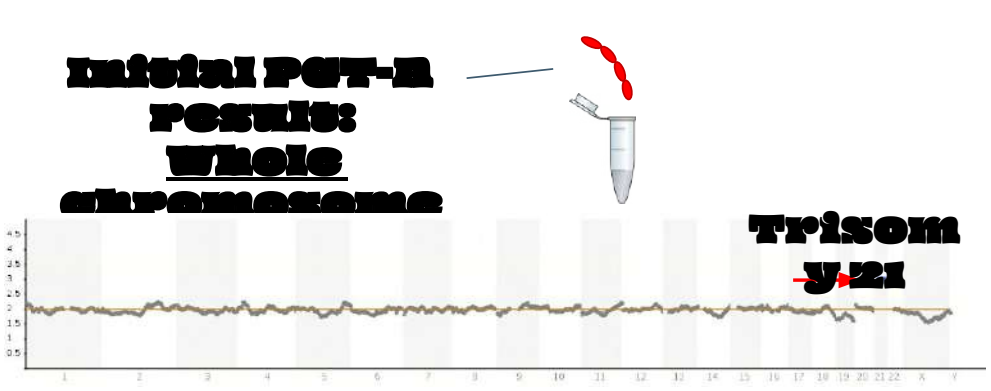
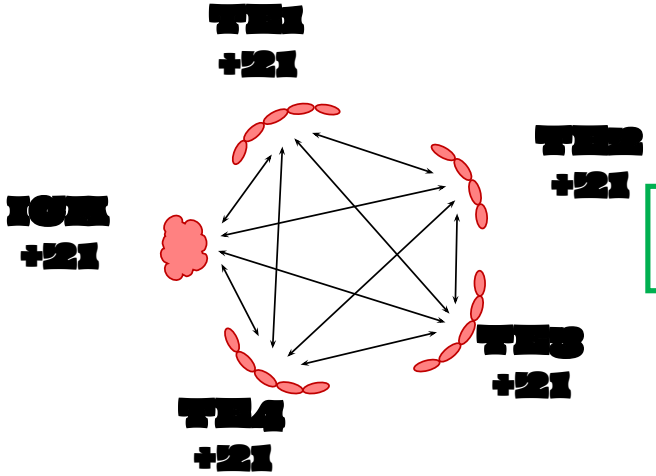
Cell divisions origin of whole chromosome aneuploidies





Mean concordance rates >98%

1. Concordance rates of SA bewteen multiple TE biopsies as well as vs ICM are significantly reduced compared to whole chromosome aneuploidies

2. Different etiology for subchromosomal alterations: more frequently mitotic in nature, arising during the first embryonic cell divisions. Mosaic in preimplantation embryos

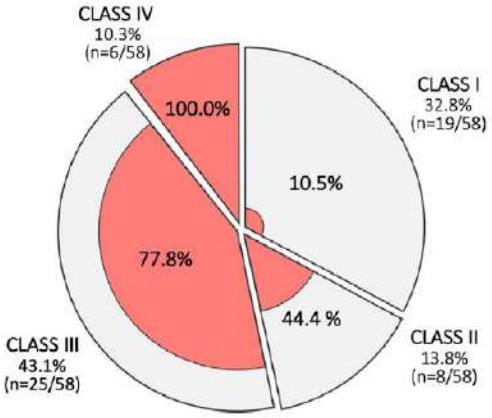
How to move to the clinical setting: additional parameters to better classify SA

Clinical application of a risk stratification model

Length of the region involved

Re-biopsy result

Correlation between cTE/scTE confirmation status, segmental size and ICM concordance



Likelihood of ICM involvement

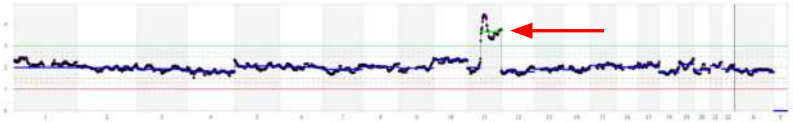
CLASS	DETAILS
I	• NOT confirmed in scTE • Length ≤80.0 Mb
II	• NOT confirmed in scTE • Length >80.0 Mb
III	• Confirmed in scTE • Length ≤80.0 Mb
IV	• Confirmed in scTE • Length >80.0 Mb

Girardi et al, RBMO 2020

Re-biopsy, euploid transfer and pregnancy follow-up

(WGA)-based NGS
PGT-A

1st Biopsy: 82.5 Mb duplication on chr



2nd Biopsy: Euploid

Viotti et al, JARG 2025

Genetic counselling + specialized informed consent outlining the associated risks

Embryo transfer

At week 13, amniocentesis was performed

Cytogenetic
46,XX

SNP microarray
arr(X,1–22) × 2

Re-biopsying the embryo can be an option for obtaining a more reliable clinical diagnosis if a SA is detected in PGT

How to move to the clinical setting: additional parameters to better classify SA

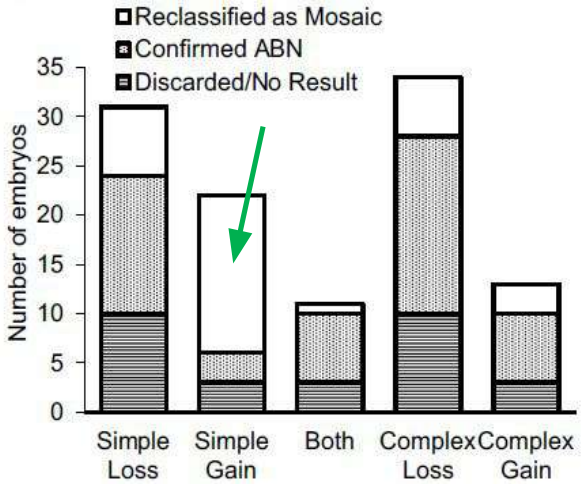
Clinical re-biopsy and type of alteration: gains vs losses

Journal of Assisted Reproduction and Genetics (2022) 39:1313–1322
https://doi.org/10.1007/s10815-022-02487-z

GENETICS

Clinical re-biopsy of segmental gains—the primary source of preimplantation genetic testing false positives

Steve Grkovic[1] · Maria V. Traversa[1] · Mark Livingstone[1] · Steven J. McArthur[1]



72.7% simple **segmental gains** were reclassified as mosaic (vs 22.6% of single loss)

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Reclassification of 88% segmental gains vs 37% losses

ICM involvement : 27% segmental gains vs 74% segmental losses

SEGMENTAL MONOSOMIES are more likely to be confirmed in a 2nd biopsy and in the ICM

Transfer outcomes of non-mosaic segmental aneuploid embryos

Transfer outcomes of non-mosaic segmental aneuploidies

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

Ashley W. Tiegs, M.D.,[a,b] Xin Tao, Ph.D.,[c] Yiping Zhan, Ph.D.,[c] Christine Whitehead, R.N.,[a] Julia Kim, M.D.,[a,b] Brent Hanson, M.D.,[a,b] Emily Osman, M.D.,[a,b] Thomas J. Kim, M.D.,[d] George Patounakis, M.D., Ph.D.,[a] Jacqueline Gutmann, M.D.,[e] Arthur Castelbaum, M.D.,[e] Emre Seli, M.D.,[a,g] Chaim Jalas,[c] and Richard T. Scott Jr., M.D.[a,b]

Design : Non-selection study

PGT-A platform/technology: target NGS

Number of embryos transfer: 39 embryos with uniform segmental aneuploidies

Sustained implantation rate : 30.8% (n=12/39)

Design : Retrospective/follow-up: no

PGT-A platform/technology: NGS, SNP array, Array cgh

Number of embryos transfer: 25 embryos with non-mosaic segmental aneuploidies

Live birth rate : 24.0% (n=6/25)

Prenatal testing : 4/6 live birth tested and normal (CVS, Amnio or cfDNA)

Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-024-03282-8

ASSISTED REPRODUCTION TECHNOLOGIES

Healthy live births achieved from embryos diagnosed as non-mosaic segmental aneuploid

Andria Besser[1] · Emily Weidenbaum[2] · Julia Buldo-Licciardi[2] · Caroline McCaffrey[1] · James Grifo[1] · Jennifer Blakemore[1]

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What do we know about transfer outcomes of uniform whole chromosome aneuploidies

Table 1. Published non-selection and cohort study outcome data involving transfer of full aneuploid embryos for whole chromosomes

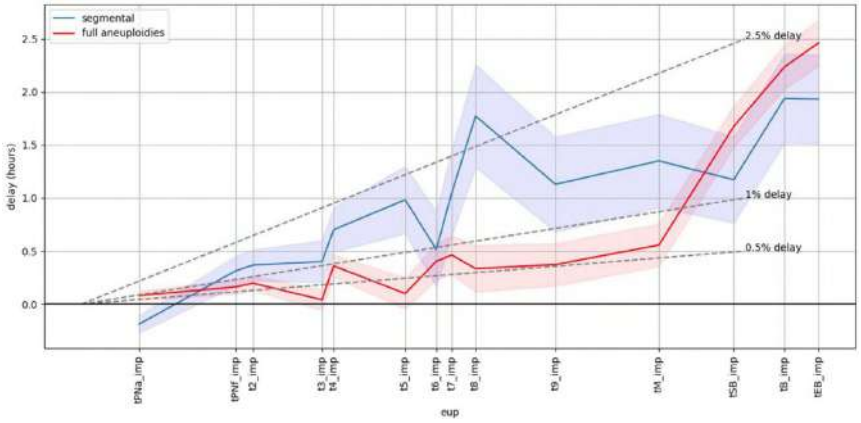
Study	Design	Transfers of uniformly aneuploid embryos n[a]	Miscarriage rate % (n, 95% CI)	Lethality rate % (n, 95% CI)
Scott et al., 2012 (45)	blinded	95	33.3% (2/6) (4.3%–77.7%)[b]	95.8% (91/95) (84.5%–99.4%)
Tiegs et al., 2021 (40)	blinded	102	100% (24/24) (85.8%–100%)	100% (102/102) (96.5%–100%)
Wang et al., 2021 (41)	blinded	44	75.0% (6/8) (34.9%–96.8%)	95.5% (42/44) (84.5%–99.4%)
Yang et al., 2022 (44)	blinded	6	100% (6/6) (54.1%–100%)	100% (6/6) (54.1%–100%)
Barad et al., 2022 (46)	unblinded	106	85.7% (6/7) (42.1%–99.6%)	99.1% (105/106) (94.9%–99.9%)
Total	N/A	353	86.3% (44/51) (73.7%–94.3%)	98.0% (346/353) (96.0%–99.2%)

[a]Embryos with at least one whole-chromosome aneuploidy in the uniform range (non-mosaic).
[b]Post-transfer polar body analysis revealed likely mitotic (mosaic) origin of the aneuploidy detected through PGT-A.

Lethality rate: 98%

Research and future perspectives

Adding time-lapse and morphokinetic analysis to predict segmental aneuploid embryos



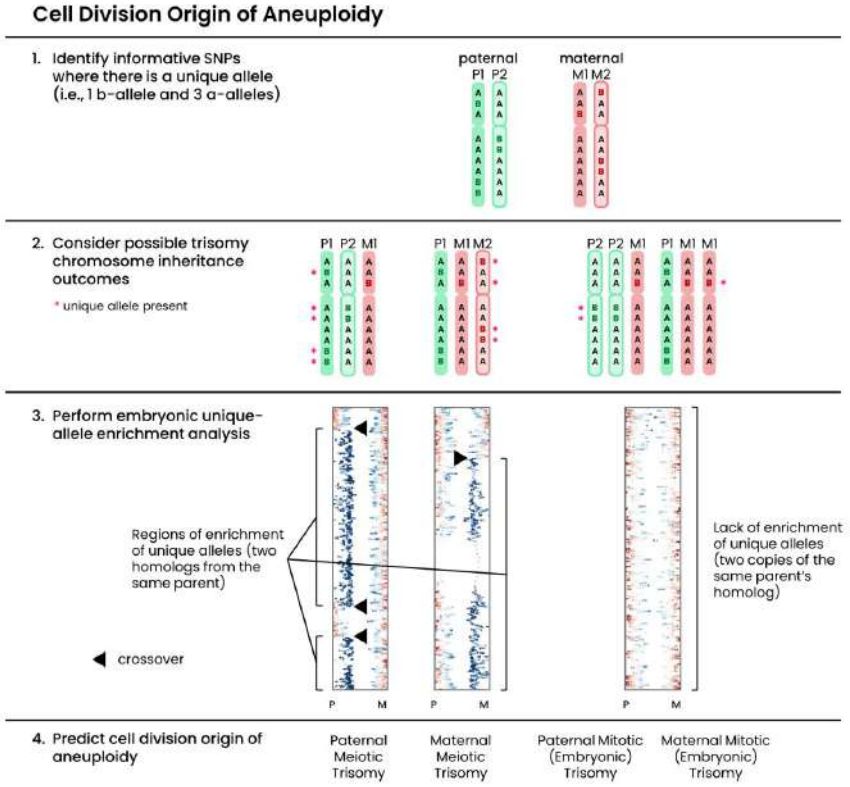
Figliuzzi et.al, Fertil Steril 2025

Blastocysts with SA and WCA exhibit a delay in reaching the expanded blastocyst-stage compared with euploid.

SA embryos have a distinct morphokinetic signature

Segmental score: specificity 92.5% sensitivity 20.0%

Adding genotyping data and parental DNA analysis in PGT to better predict the origin of aneuploidy



conclusions and management strategies for transfer

Conclusions and management strategies for transfer

Historically, embryos diagnosed as segmental aneuploid have been categorized alongside whole chromosome aneuploid embryos and considered unsuitable for transfer.

SA should be considered as a separate category compared to WCA and should be subjected to <u>different interpretation</u> and ad-hoc management strategies.

MANAGEMENT STRATEGIES FOR UNIFORM SEGMENTAL ANEUPLOIDIES

- Deletions/duplications can be associated with **a <u>wide range of phenotypes</u>: genetic syndromes, embryonic lethality, miscarriage, no clinical consequences**

- Transfer outcomes of uniform segmental aneuploidies are limited but…transfer "**may be considered**" as 25-30% success rate is significantly different from <1% of uniform WCA

- The assessment of a **second TE biopsy** can enhance predictivity on ICM constitution and empowering the decision-making process

- <u>Risks associated</u> with double round of <u>re-biopsy</u> and vitrification should considered and commented

All patients should receive genetic counselling and close monitoring

THANKS FOR YOUR ATTENTION