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# Degree of mosaicism in trophoctoderm does not predict pregnancy potential: a corrected analysis of pregnancy outcomes following transfer of mosaic embryos

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## Abstract

**Background:** Preimplantation genetic screening (PGS) is increasingly utilized as an adjunct procedure to IVF. Recently healthy euploid live birth were reported following transfer of mosaic embryos. Several recent publications have surmised that the degree of trophoctoderm (TE) mosaicism in transferred embryos is predictive of ongoing pregnancy and miscarriage rates.

**Methods:** This is a corrected analysis of previously published retrospective data on vitro fertilization (IVF) cycle outcomes involving replacement of 143 mosaic and 1045 euploid embryos tested by PGS, utilizing high-resolution next-generation sequencing (NGS) of TE and determination of percentages of mosaicism. Receiver operating curves (ROCs) and measurement of area under the curve (AUC) were used to evaluate the accuracy of the predictor variable, proportion of aneuploid cells in a TE biopsy specimen, with IVF outcomes, ongoing pregnancy and miscarriage rates.

**Results:** Confirming findings of the previously published report we also found higher ongoing pregnancy rates (63.3% vs. 39.2%) and lower miscarriage rates (10.2% vs. 24.3%) with euploid embryo transfers than with mosaic embryo transfer. There, however, were no significant differences in ongoing pregnancy or miscarriage rates among mosaic embryo transfers at any threshold of aneuploidy. Based on AUC, TE biopsies predicted ongoing pregnancy for euploid, as well as mosaic embryos, in a range of 0.50 to 0.59 and miscarriage in a range from 0.50 to 0.66

**Conclusions:** Degree of TE mosaicism was a poor predictor of ongoing pregnancy and miscarriage.

**Keywords:** In vitro fertilization, Preimplantation genetic diagnosis, Preimplantation genetic screening, Aneuploidy, Embryo selection, Next-generation sequencing

## Background

Preimplantation genetic screening (PGS), now renamed by some as preimplantation genetic testing for aneuploidy (PGT-A), is increasingly utilized as ad-on to vitro fertilization (IVF). The original hypothesis behind PGS utilization was “*aneuploidy screening as a means to increase pregnancy rates, decrease loss rates, and establish transfer order*” [1]. Because of growing recognition that

trophoctoderm (TE) mosaicism is a common finding [2], the Preimplantation Genetic Diagnosis International Society (PGDIS) recently recommended a radical overhaul of testing methodologies and reporting of test results [3].

Since diagnostic platforms, like array comparative genome hybridization (aCGH), single-nucleotide polymorphism array, and quantitative polymerase chain reaction (qPCR) lack capacity to detect mosaicism in a single TE biopsy, next-generation sequencing (NGS), which currently detects mosaicism in excess of 20%, is the only technique recommended by PGDIS [3]. Utilizing NGS, embryos with less than 20% aneuploidy in the TE sample are, therefore, considered euploid; while those between 20

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and 80% are reported as mosaic, and those over 80% as truly aneuploid. Moreover, PGDIS guidelines suggest that embryos designated as euploid can be freely transferred, while embryos designated as aneuploid should not be transferred and, therefore, discarded [3].

Finally, mosaic embryos, at 20–80% range aneuploidy in the TE sample, may be potentially transferred, though the PGDIS notes that such transfers be performed with caution and only in absence of euploid embryos. Moreover, the society suggested an empirical hierarchy for such transfers, based on the specific aneuploidies reported in embryos [3].

A group of investigators at the 2016 World Congress on Controversies in Preconception, Preimplantation, Prenatal Genetic Diagnosis Meeting in Barcelona reached similar conclusions, advising to prioritize transfer of mosaic embryos with lower levels (20–40%) of aneuploidy in the TE sample over those with higher levels (40–70%), and defining any embryo biopsy with more than 70%

aneuploidy in its TE as aneuploid and, therefore, as not transferrable [4].

Both sets of guidelines, however, were lacking robust published clinical data in support, as are usually required for clinical diagnostic testing [5, 6]. This why a recent publication by a multi-center conglomerate of PGS reference laboratories and referring IVF centers, offering a first large data sets of clinical outcomes following transfer of mosaic blastocyst in accordance with PGDIS criteria and utilizing NGS [7], has to be viewed as a defining moment. Until these recent publications, only three groups have reported IVF cycle outcomes after transfers of mosaic embryos in a small number of cases [8–10].

Since the manuscripts by (Munné et al. 2017; Fragouli et al. 2017) did not use standard statistical methods to assess predictive values for different degrees of mosaicism detected in TE biopsies, we reanalyzed the raw data reported by the authors. As this study will demonstrate, our analysis contradicts the conclusions of Munné et al. that

**Table 1** Predictive ability of NGS trophoctoderm biopsy for ongoing pregnancy based on proportion of abnormal cells in the specimen

	Euploid < 20% Abnormal		Mosaic ≥20% to ≤80% Abnormal		p-value	AUC
Ongoing Pregnancy	661/1045	63.3%	56/143	39.2%	< 0.0001	0.55
	Mosaic ≥20% to < 30% Abnormal		Mosaic ≥30% to ≤80% Abnormal		p-value	AUC
Age	Ongoing Pregnancy					
< 38	12/27	44.4%	22/61	36.1%	0.46	0.54
≥ 38	1/8	12.5%	21/46	45.7%	0.08	0.59
All Ages	13/35	37.1%	43/108	39.9%	0.78	0.51
	Mosaic ≥20% to < 40% Abnormal		Mosaic ≥40% to ≤80% Abnormal		p-value	AUC
Age	Ongoing Pregnancy					
< 38	22/61	36.1%	12/27	44.4%	0.46	0.54
≥ 38	10/25	40.0%	12/29	41.4%	0.92	0.51
All Ages	32/87	36.8%	24/56	42.9%	0.47	0.53
	Mosaic ≥20% to < 50% Mosaic		Mosaic ≥50% to ≤80% Abnormal		p-value	AUC
Age	Ongoing Pregnancy					
< 38	30/78	38.5%	4/10	40.0%	0.93	0.50
≥ 38	17/38	44.7%	5/16	31.3%	0.36	0.56
All Ages	47/117	40.2%	9/26	34.6%	0.60	0.52
	Mosaic ≥20% to < 60% Abnormal		Mosaic ≥60% to ≤80% Abnormal		p-value	AUC
Age	Ongoing Pregnancy					
< 38	34/86	39.5%	0/2	0.0%	0.26	0.52
≥ 38	18/44	40.9%	4/10	40.0%	0.96	0.50
All Ages	52/131	39.7%	4/12	33.3%	0.67	0.51
	Mosaic ≥20% to < 70% Abnormal		Mosaic ≥70% to ≤80% Abnormal		p-value	AUC
Age	Ongoing Pregnancy					
< 38	34/87	39.1%	0/1	0.0%	0.42	0.51
≥ 38	19/46	41.3%	3/8	37.5%	0.84	0.51
All Ages	53/134	39.6%	3/9	33.3%	0.71	0.51

AUC: area under the curve

40% mosaicism represents a significant differentiation point. Indeed, our analysis did not find significant predictability at any level of mosaicism between 20 and 80%.

## Methods

A detailed description of patient factors and molecular methods is available in the original publications, which served as data sources for our study [7, 11]. The data for 143 NGS-tested mosaic embryos that were transferred, were extracted from Additional file 1: Table S3 in the publication by Munné et al. [7]. To assess whether the degree of mosaicism at different ages affected ongoing pregnancy rates, these data were stratified for female ages < 38 and ≥ 38 years.

Data for the comparison group came from for female age well matched controls from the same publication, who had undergone transfers of 1045 euploid embryos, as determined by NGS with < 20% aneuploid cells in the TE sample [7]. This control group could not be age-stratified since only aggregate data (rather than embryo level data) were provided in the source publication.

Receiver operating characteristic curves (ROCs) and measurements of area under the curve (AUC) were used to evaluate accuracy of the predictor variable, proportion of abnormal cells in a TE biopsy specimen (i.e., percentage mosaicism) with IVF outcomes, including ongoing pregnancy and miscarriage rates.

The analysis was then performed for binary variables euploid (< 20% aneuploid cells) vs. mosaic embryos, and for various thresholds of aneuploidy, ranging from 20% to 80% in 10% increments, as detailed in Table 1 and Fig. 1.

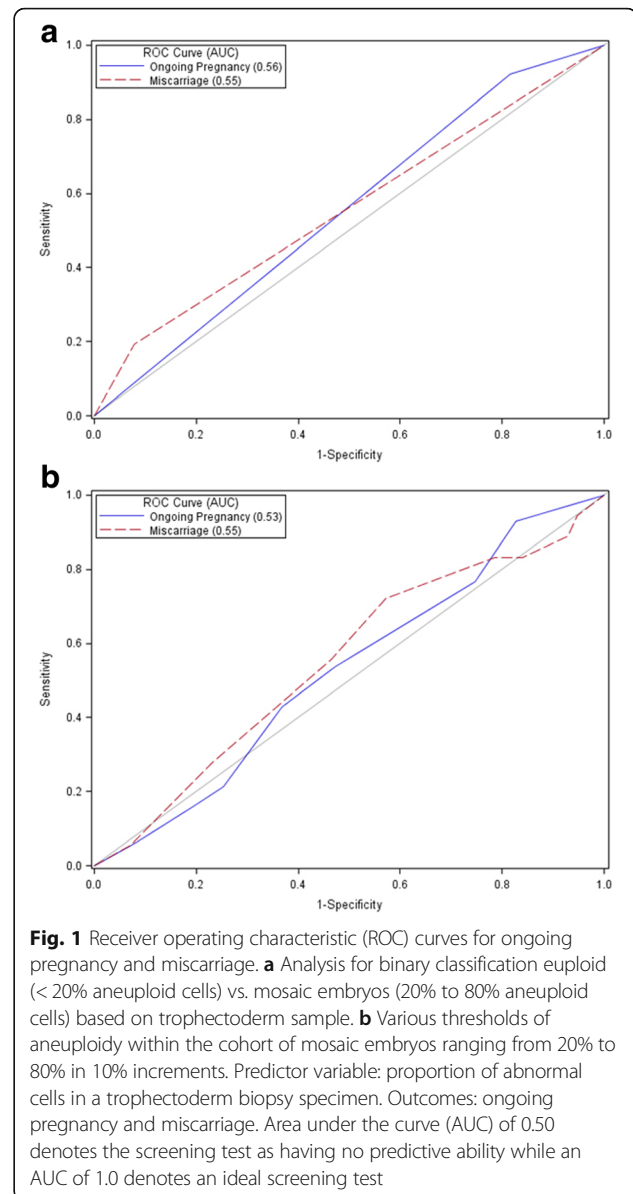
Comparisons between groups were made using chi-square tests. Statistical analyses were performed using SAS version 9.4. A  $p$ -value < 0.05 was considered statistically significant.

Since all here addressed data were already published, publicly available, and cannot be utilized to identify individual patients, this study qualified for exemption from IRB approval.

## Results

Table 1 shows the ability of TE biopsies, utilizing NGS, to predict ongoing pregnancy based on proportion of abnormal cells in each biopsy specimen. Here we confirm the findings of Munné et al. [7] that ongoing pregnancy rates were, seemingly, significantly higher following euploid embryo transfer (i.e., biopsies with < 20% aneuploidy) than mosaic embryo transfer (biopsies with 20–80% aneuploidy). Our calculation yielded a slightly lower ongoing pregnancy rate in the mosaic group than Munné et al., who reported 57 ongoing and delivered pregnancies but presented embryo level data for only 56.

Table 1 demonstrates no significant differences in ongoing pregnancy rates among mosaic transfers at any



**Fig. 1** Receiver operating characteristic (ROC) curves for ongoing pregnancy and miscarriage. **a** Analysis for binary classification euploid (< 20% aneuploid cells) vs. mosaic embryos (20% to 80% aneuploid cells) based on trophoctoderm sample. **b** Various thresholds of aneuploidy within the cohort of mosaic embryos ranging from 20% to 80% in 10% increments. Predictor variable: proportion of abnormal cells in a trophoctoderm biopsy specimen. Outcomes: ongoing pregnancy and miscarriage. Area under the curve (AUC) of 0.50 denotes the screening test as having no predictive ability while an AUC of 1.0 denotes an ideal screening test

threshold of aneuploidy. Moreover, the table demonstrates the AUC for all comparisons ranges from 0.50 to 0.59, indicating poor predictive ability of TE biopsies for ongoing pregnancies.

Table 2 shows the predictive ability of TE biopsies, utilizing NGS, to predict miscarriages based on proportion of abnormal cells in a single biopsy sample. Once again we confirm the findings of Munné et al. [7] that miscarriage rates were significantly lower following euploid embryo transfer than with mosaic embryo transfer. However, the table also demonstrates that the AUC is only 0.56, again indicting very poor predictive validity of a TE biopsy for miscarriages. Moreover, analysis of miscarriage risk among mosaic embryo transfers, did not find increased risk based on any threshold of aneuploidy.

**Table 2** Predictive ability of NGS trophectoderm biopsy for miscarriage based on proportion of abnormal cells in the specimen

	Euploid < 20% Abnormal		Mosaic ≥20% to ≤80% Abnormal		p-value	AUC
Miscarriage	75/736	10.2%	18/74	24.3%	0.0003	0.56
	Mosaic ≥20% to < 30% Abnormal		Mosaic ≥30% to ≤80% Abnormal		p-value	AUC
Age	Miscarriage					
< 38	5/17	29.4%	9/31	29.0%	0.69	0.50
≥ 38	0/1	0.0%	4/25	16.0%	0.66	0.52
All Ages	5/18	27.8%	13/56	23.2%	0.69	0.52
	Mosaic ≥20% to < 40% Abnormal		Mosaic ≥40% to ≤80% Abnormal		p-value	AUC
	Miscarriage					
< 38	11/33	33.3%	3/15	20.0%	0.35	0.57
≥ 38	2/12	16.7%	2/14	14.3%	0.87	0.52
All Ages	13/45	28.9%	5/29	17.2%	0.25	0.58
	Mosaic ≥20% to < 50% Mosaic		Mosaic ≥50% to ≤80% Abnormal		p-value	AUC
Age	Miscarriage					
< 38	13/43	30.2%	1/5	20.0%	0.63	0.52
≥ 38	2/19	10.5%	2/7	28.6%	0.26	0.64
All Ages	15/62	24.2%	3/12	25.0%	0.95	0.50
	Mosaic ≥20% to < 60% Abnormal		Mosaic ≥60% to ≤80% Abnormal		p-value	AUC
Age	Miscarriage					
< 38	14/48	29.2%	0/0	0.0%	–	–
≥ 38	2/20	10.0%	2/6	33.3%	0.16	0.66
All Ages	16/68	23.5%	2/6	33.3%	0.59	0.59
	Mosaic ≥20% to < 70% Abnormal		Mosaic ≥70% to ≤80% Abnormal		p-value	AUC
Age	Miscarriage					
< 38	14/48	29.2%	0/0	0.0%	–	–
≥ 38	3/22	13.6%	1/4	25.0%	0.56	0.56
All Ages	17/70	24.3%	1/4	25.0%	0.97	0.50

AUC: area under the curve

Figure 1a demonstrates ROC curves for ongoing pregnancies and miscarriages based on binary classification of embryos as either euploid or mosaic. Figure 1b shows ROC curves for ongoing pregnancies and miscarriages based on various thresholds of aneuploidy (in 10% increments, ranging from 20% to 80%) within the group of mosaic embryos. Both figures show a null line for reference with an AUC of 0.50 which denotes when a screening test has no predictive ability.

## Discussion

Our analysis confirms the previously published report which found statistically higher ongoing pregnancy rates (63.3% vs. 39.2%) and lower miscarriage rates (10.2% vs. 24.3%) with euploid embryo transfers than with mosaic embryo transfer. These findings are also consistent with a recent report by Spinella et al. [12]. However, our analysis demonstrates with ROC curves that PGS, at any threshold level of mosaicism, up to 80% aneuploidy in a

single TE biopsy as determined by NGS, has poor predictive value as a screening test for an individual embryo's ability to establish ongoing pregnancy or lead to miscarriage. Moreover, given the observed ongoing pregnancy and miscarriage rates it appears likely that in many cases aneuploidy within the TE of embryos represents a physiologic variant rather than a pathological condition. This conclusion is supported by a recent in depth literature review: "Mosaicism in Preimplantation Human Embryos: When Chromosomal Abnormalities Are the Norm" [13].

Commonly utilized screening tests in reproductive medicine, such as mammograms and PAP smears for cancer screening [14], while themselves not ideal screening tests, still demonstrate far more robust clinical performance than here presented PGS data. This study reinforces previously raised concerns about the biological premise and clinical effectiveness of PGS [15–18]. It is our view that to ensure optimal outcomes for patients the reproductive medicine

community should hold commercial PGS tests to the same standards as other screening tests commonly utilized in the field. Therefore, in our opinion commercial laboratories which market PGS tests should seek regulatory approval for these tests [19].

Based on the original data set published by Munné et al. [7], our analysis may, indeed, actually still overestimate the benefits of PGS in this patient population. In the original data set, the authors indicated that 133 out of 143 mosaic embryo transfers were single embryo transfers, while 10 were double embryo transfers (such data were not provided for the control group of patients undergoing euploid embryo transfer). A higher proportion of double embryo transfers in the euploid embryo group, could, therefore, hypothetically explain the higher ongoing pregnancy rate and lower miscarriage rates observed in this group.

It is also likely that patients who produce euploid embryos have better prognoses and/or less severe underlying infertility than those who only produce mosaic embryos. This point is consistent with several recent studies which have found a correlation between proportion of aneuploid blastocysts and diminished ovarian reserve while controlling for patient age [20–22]. Finally, the original dataset does not specify the number of treated patients nor the number of tested embryos per patient in either group. It reflects only patients who reached embryo transfer, thereby excluding poorer prognosis patients who started IVF with intention of PGS but did not have any transferrable embryos following extended embryo culture, TE biopsy, cryopreservation, and thawing. The patient selection is, therefore, biased toward better prognosis patients, as previously documented in national registry data in patients undergoing IVF with PGS [23]. Additional limitations include reporting of ongoing pregnancy rates rather than live birth rates and lack of data on the health of infants conceived from mosaic embryos.

We conclude that the degree of TE mosaicism is a poor predictor of ongoing pregnancy and miscarriage. Moreover, in our ROC analysis PGS demonstrates poor clinical effectiveness for a routine screening test and, therefore, should not be routinely offered as an ad-on to IVF. Until efficacy, safety, and cost effectiveness of PGS are established it, therefore, should only be offered as an experimental test under study conditions and with appropriate informed consent.

## Additional file

**Additional file 1:** Data for 143 NGS-tested mosaic embryos that were transferred; extracted from Table S3 in the publication by Munné et al. [7]. (XLSX 17 kb)

## Abbreviations

aCGH: Array comparative genome hybridization; AUC: Area under the curve; CLIA: Clinical Laboratory Improvement Amendments; FDA: Food and Drug

Administration; IVF: In vitro fertilization; LDTs: Laboratory-developed tests; NGS: Next-generation sequencing; PGDIS: Preimplantation Genetic Diagnosis International Society; PGS: Preimplantation genetic screening; qPCR: Quantitative polymerase chain reaction; ROCs: Receiver operating curves; TE: Trophoctoderm

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## Authors' contribution

VAK, DHB, and NG developed the concept of the study; All authors contributed to data accumulation; SKD, DHB and VAK contributed to data analysis; All authors contributed to data interpretation. VAK and NG wrote the manuscript. All authors contributed to revisions of the manuscript, and approved of the final submission. VAK takes responsibility for the accuracy of the data analysis.

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## Availability of data and materials

Data were obtained from the referenced publications. Further information is available by contacting Dr. Vitaly A. Kushnir at vkushnir@thechr.com.

## Ethics approval and consent to participate

Since all here addressed data were already published, publicly available, and cannot be utilized to identify individual patients, this study qualified for exemption from IRB approval.

## Consent for publication

Not applicable

## Competing interests

V.A.K. previously served as a consultant to the CDC. N.G., D.H.B., and V.A.K. are listed as co-owners of several already awarded and still pending U.S. patents, none related to the topic of this manuscript. N.G. is a shareholder in Fertility Nutraceuticals, LLC and owner of the CHR. N.G. and D.H.B. receive patent royalties from Fertility Nutraceuticals, LLC.

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