IS THAT EUPLOID EMBRYO REALLY EUPLOID? – EMBRYONIC MOSAICISM AND ITS IMPLICATIONS ON CLINICAL OUTCOMES OF EMBRYO TRANSFERS WITH EUPLOID PGT-A RESULTS

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Background
Although PGT-A is a nearly diagnostic tool it is important to emphasize to patients that for several reasons PGT-A remains a screening technology. Through a systemic review of investigations performed in response to PGT-A result discrepancies, a relationship between discrepancies and mosaicism was identified. In most discrepancies involving confirmed mosaicism in the pregnancy, an embryo with Euploid PGT-A results was transferred. While mosaicism is not expected to be a major limitation in the validity of PGT-A results for all patients, our data suggests undetectable embryonic mosaicism is causal for PGT-A result discrepancies in a statistically relevant number of cases.

Objective
The purpose of this study was to leverage CooperSurgical's experience with internal discrepancy investigations to elucidate common findings that can be used to advance PGT-A practices for better patient and provider education and outcomes.

Materials and Methods
From May 2018 through July 2023, we received 197 discrepancy claims regarding CooperSurgical PGT-A results. PGT-A testing related to these requests was performed from 2015 to 2023. Discrepancy claims were vetted for validity and then further investigated by review of prior test data and reanalysis of embryo biopsy sample(s) via the laboratory's current PGT-A platform.

Results
From 2015-2023 the CooperSurgical laboratories ran PGT-A for ~80,000 patient cycles, with 197 discrepancies reported, a rate of all PGT-A discrepancies estimated to be <0.25%. 33 of 197 discrepancies involved clinical mosaic outcomes (17%), the majority (27, 82%) of which were transfers of embryos with Euploid PGT-A results. The majority of these 33 claims were reported in following first trimester loss and POC testing. Please see Table 1 for case details. After the 33 claims were vetted, 30 (91%) went on to investigation. All 30 investigations revealed consistent PGT-A euploid re-analysis results. Therefore, we estimate adverse pregnancy outcomes due to abnormal fetal mosaic karyotypes represent approximately ~0.03% of cycles where embryos were transferred after an initially euploid PGT-A result.

Conclusions
While undetectable abnormal embryonic mosaicism in embryos with euploid PGT-A results appears to be rare, it may be more prevalent than initially expected as well as lead to adverse pregnancy outcomes for the IVF patient. While embryonic mosaicism will not affect pregnancy outcomes for most IVF/PGT patients, this analysis highlights the importance of emphasizing to patients undergoing PGT-A that not all embryos resulting in abnormal clinical outcomes will be reported out as abnormal on PGT-A. These findings underline the continued importance of comprehensive patient counseling, and that best practice guidelines should still include the discussion and offer of prenatal diagnostic testing in pregnancies achieved via IVF with PGT-A.

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References: N/A

Case #	PGT-A Technology	CooperSurgical PGT-A Results	Clinical Results	Type of clinical outside testing	Investigation Warranted?
1	NGS	Embryo 1: mosaic partial monosomy 10q25.1-qter, XX; Embryo 2: mosaic trisomy 19, XY; Embryo 3: monosomy 22, XY; Embryo 4: trisomy 19, XX	Singleton pregnancy, mosaic deletion of 13q13.2-q34, XX	POC SNP Microarray	Yes
2	NGS	Low Level Mosaic for Trisomy 8; sex masked	Female with Trisomy 8 and Trisomy 7	POC SNP Microarray	Yes
3	NGS	High Level Mosaic for Trisomy 15 and del(20)(q11.23-qter)	Partial Trisomy 15 and UPD 15	Newborn Karyotype	No
4	NGS	Embryo 1: Complex Abnormal (-5 mos, -13 mos, -21 mos), XX; Embryo 2: Trisomy 11, XX	Singleton Euploid Female	Amniocentesis Fetal Karyotype	Yes
5	NGS	High Level Mosaic for del(20)(pter-q11.21), XX	Mosaic, interstitial duplication of 15q25.1 to q26.1), XX	Amniocentesis Prenatal SNP Microarray	Yes
6	NGS	Low Level Mosaic for Trisomy 2, XX	Mosaic Turner syndrome: 45,X[8]/46,XX[7]	Amniocentesis Fetal Karyotype	Yes
7	NGS	Euploid, XY	Mosaic Klinefelter syndrome (55%)	POC SNP Microarray	Yes
8	NGS	Euploid, XX	Mosaic Trisomy 7	POC SNP Microarray	Yes
9	NGS	Euploid, XY	Mosaic XYY/XY, mosaic trisomy 5, mosaic trisomy 20	POC SNP Microarray	Yes
10	NGS	Euploid, XY	Mosaic Partial Monosomy 4c, XY	POC Microarray	Yes
11	NGS	Euploid, XX	69,XXX/68,XXX,-21	POC SNP Microarray	Yes
12	NGS	Euploid, XX	Mosaic partial trisomy 8p, XX	POC Microarray	Yes
13	NGS	Euploid, XY	46,XY[18]/47,XY+12[1]	POC Karyotype	No
14	NGS	Euploid, XX	Mosaic trisomy 7 (22%), XX	POC SNP Microarray	Yes
15	NGS	Euploid, XX	47,XX,+8[1]/46,XX[19]	POC Karyotype	No
16	NGS	Euploid, XY	Mosaic Trisomy 21, XY	POC SNP Microarray	Yes
17	NGS	Euploid, XX	Mosaic Trisomy 17, XY	POC SNP Microarray	Yes
18	NGS	Euploid, XX	45,X[16]/47,XXX[4]	POC Karyotype	Yes
19	NGS	Euploid, XY	Mosaic 53.6Mb deletion of 8p23.3q11.23, XY	POC SNP Microarray	Yes
20	NGS	Euploid, XY	Mosaic Trisomies 7 and 19, XY	POC SNP Microarray	Yes
21	NGS	Euploid, XX	92,XXXX [4]/46,XX[16]	POC Karyotype	Yes
22	NGS	Euploid, XY	Mosaic Trisomies 8 and 14, Pathogenic Xp21.1 deletion, and multiple regions of homozygosity, XY	POC SNP Microarray	Yes
23	NGS	Euploid, XY	Trisomy 6 and Mosaic Trisomy 7, XY	POC SNP Microarray	Yes
24	NGS	Euploid, XY	Mosaic Trisomy 21 (10 cells normal, 10 cells +21)	POC Karyotype	Yes
25	NGS	Euploid, XY	Mosaic Trisomy 16, XY	POC SNP Microarray	Yes
26	NGS	Euploid, XY	46,X,+mar[3]/46,XX[7], XX	POC Karyotype	Yes
27	NGS	Euploid, XX	92,XXXX[14]/46,XX[6]	POC Karyotype	Yes
28	NGS	Euploid, XX	Mosaic Turner Syndrome (30%), XX	Amniocentesis Prenatal SNP Microarray	Yes
29	NGS	Euploid, XY	Mosaic Trisomy 21, XY	POC SNP Microarray	Yes

30	NGS	Euploid, XY	Mosaic 33.5Mb duplication of chromosome 13 and 11.3Mb terminal deletion of chromosome 18, XY	POC SNP Microarray	Yes
31	NGS	Euploid, XX	Mosaic 23.98Mb terminal deletion of chromosome 8, 45,XX,der(8)t(8;13)(p21.2; q11.2)[11]/46,XX[4]	Amniocentesis Prenatal SNP Microarray and Karyotype	Yes
32	NGS	Euploid, XX	Mosaic Turner Syndrome, XX	POC SNP Microarray	Yes
33	NGS	Euploid, XX	Mosaic Trisomies 4 and 14, XX	POC SNP Microarray	Yes

Table 1. Discrepancy cases involving clinical mosaicism.