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Exploring the Chromosomal Concordance Between Trophectoderm and Inner Cell Mass Reveals a 6% 'Biological False Negative' Rate During Preimplantation Genetic Screening

Objective
Preimplantation genetic screening (PGS) at the blastocyst stage is based on the assumption that the placenta-forming trophectoderm (TE), the source of cell biopsy used for downstream examination, is an accurate representative of the inner cell mass (ICM), the group of cells that gives rise to the fetus. Previous studies exploring the rates of concordance between TE and ICM have relied on dated technologies or have suffered from small sample sizes. Here, we use NextGen Sequencing (NGS) to explore this question in a large group of embryos.

Design
50 blastocyst embryos deemed aneuploid by original TE biopsy were tested for the karyotypic profile of the ICM.

Materials and Methods
Blastocysts from freeze-all cycles were subjected to routine PGS by NGS. Embryos with full aneuploidies (complete losses or gains) were thawed and re-biopsied to isolate cells of the ICM and a second TE sample. PGS by NGS was subsequently performed on each embryo's ICM biopsy, and in case of discordance also on the second TE sample. Three analysts blindly interpreted all resulting karyotype profiles independently.

Results
From a population of 50 blastocysts originally designated as aneuploid, three cases (~6%) had euploid ICMs. For these three instances, the second TE biopsy is representative of the ICM.
A further five embryos (10%) had ICMs that contained the aneuploidy detected in the initial TE biopsy, but had additional minor karyotypic discrepancies with the original profile. For these five embryos the second TE biopsy was concordant with the original profile, suggesting that the entire TE had a different karyotypic makeup than the ICM.
The remaining 42 embryos (~84%) showed perfect karyotypic concordance between ICM and TE.

Conclusions
In ~6% of blastocysts, an initial aneuploid diagnosis is false negative, and the ICM is in effect euploid. This would help explain the reported cases in which a transferred aneuploid embryo leads to a normal and healthy pregnancy. Interestingly, in the discordant embryos the second TE biopsy often represents the ICM, meaning that a TE re-biopsy of aneuploid blastocysts might identify euploid embryos for transfer.