REPORTED MOSAIC RATES: ARE THEY REAL OR AN ARTIFACT OF INTERMEDIATE COPY NUMBER CRITERIA CHOSEN BY PGT-A PROVIDERS?

Authors: M Gigg (1), RJ Paulson (1)

Affiliations: (1) Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: Preimplantation genetic testing for aneuploidy (PGT-A) is used in almost half of the IVF cycles performed in the United States. In 2014, next generation sequencing (NGS) was validated as a method of PGT-A, and now is the most commonly used type of DNA analysis for PGT-A. NGS involves sequencing DNA of biopsied trophectoderm cells and comparing it to a reference genome. The percentage of abnormal DNA sequenced determines if the embryo is classified as euploid, aneuploid or an intermediate copy number (ICN) designated as “mosaic”. ICN can be caused by mosaicism, mitotic state, biopsy technique, amplification bias and statistical noise. Each commercial PGT provider (CPP) can choose its own ICN criteria, or percentage of abnormal DNA sequenced, to report embryos as euploid, aneuploid, or mosaic.

Objective: To determine the effect of the chosen ICN criteria, or percentage range of abnormal DNA in the trophectoderm biopsy, on the reported rate of mosaicism.

Materials and Methods: Published rates of mosaicism performed by CPPs were collected from CPP websites and provided directly by CPP representatives. Additionally, PubMed and Google Scholar databases were used to search peer- reviewed publications with the following terms: ‘mosaic’, ‘next generation sequencing’, ‘preimplantation genetic screening’, and ‘blastocyst’. Relevant articles written in English, published from January 2015 to October 2023, and using NGS for PGT-A were analyzed.

Results: Reported rates of mosaicism from five CPPs ranged from 2.60-17.7%. Average mosaic rates from 2015-2023 were 2.57% (CPP-A), 15.8% (CPP-B), 7.40% (CPP-C), 5.76% (CPP-D), 14.0% (CPP-E). Between CPPs, ICN criteria used to designate mosaicism were separated into three groups: 20-40%, 30-70%, and 20-80%. The mean rate of mosaicism was 2.57%±0.491 for the 20-40% group, 7.82%±6.70 for the 30-70% group, and 12.6±3.81 for the 20-80% group. The difference of reported mosaicism rate between the groups was statistically significant ($p=0.000207$). Four of five CPPs further classified mosaics as low- or high-level (20-40% and 41-80% respectively for the 20-80% group, and 30-50% and 51-70% respectively for the 30-70% group), but data was only available for 3 CPPs, and not available for each year. Reported low- and high-level mosaic rates, respectively, were as follows: 7.95% and 7.88% (CPP-B), 4.91% and 2.08% (CPP-D), and 7.42% and 6.58% (CPP-E).

Conclusions: Rate of reported mosaicism correlates with ICN criteria used by CPPs to classify embryos as mosaic. The broader ICN criteria used, the higher the reported mosaic rate. Lower mosaic rates may sound appealing, but narrower ICN criteria used to classify mosaics could result in a larger proportion of embryos being reported as aneuploid. Professional organizations need to establish a standardized ICN criteria for reporting rates of overall mosaicism as well as low- and high-level mosaics.

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