# Introduction: Subchromosomal abnormalities in preimplantation embryonic aneuploidy screening

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The application of next generation sequencing platforms for embryonic aneuploidy screening provides enhanced resolution that allows routine evaluation of subchromosomal copy number abnormalities and mosaicism. Approximately 20% of embryos that would be designated as euploid using the conventional 24-chromosome aneuploidy screening will have evidence of a subchromosomal abnormality or mosaicism. This new information brings many challenges. Understanding the impact of these abnormalities on implantation and delivery rates is key to optimizing clinical counseling and management. (Fertil Steril® 2017;107:4–5. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** Chromosomal duplications, chromosomal deletions, subchromosomal defects, preimplantation genetic screening, embryonic mosaicism

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The last decade has the seen the evolution of clinically useful embryonic aneuploidy screening. The early failures of cleavage-stage blastomere biopsy and fluorescent in situ hybridization (FISH) are well known, and that approach to screening was inadequate to produce meaningful clinical benefit. More recently, the widespread use of trophectoderm biopsy and the use of more comprehensive and reliable analytical platforms such as single nucleotide polymorphism (SNP) array, quantitative polymerase chain reaction, and array comparative genomic hybridization (CGH) have been validated with class I data to provide improved implantation and delivery rates for much of the infertile population (1).

The principle behind embryonic aneuploidy screening was always straightforward. The age-related increase in aneuploid gestations was well established, and the logic of eliminating abnormal embryos with extremely poor reproductive potential from the pool of transferrable embryos was unassailable (2). As expected, implementing validated embryonic aneuploidy screening clinically has resulted in enhanced clinical outcomes. However, many euploid blastocysts with excellent morphologic development continue to fail to implant and progress to delivery of a healthy infant.

While the etiologies of these failures are likely quite diverse, the reality is that the outstanding outcomes attained with oocyte donation in women of all ages exceed those attained after the transfer of euploid blastocysts. This strongly suggests that many of these failures remain within the domain of the embryo.

Recently, investigators have demonstrated that other types of genetic abnormalities are present in gestations that might limit reproductive efficiency. Wapner et al., in an analysis of women whose sole indication for antenatal aneuploidy screening was advanced maternal age, demonstrated that the presence of deletions and duplication might occur as often as one in 71 pregnancies (3). That prevalence was exceedingly high and was more common than the incidence of whole chromosomal aneuploidies, which were the primary indication for their antenatal screening. This raised many questions about the impact of de novo deletions and duplications on embryonic competence. Unfortunately, most of these abnormities were too small to be detected by the analytical platforms used for embryonic aneuploidy screening at that time.

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Shortly after those data became available, next generation sequencing platforms optimized for copy number analyses of very small biologic samples were developed and implemented by several investigators. These technologies produce equivalent accuracy and precision regarding whole chromosomal aneuploidy screening but offer enhanced resolution that empowers clinical scientists to evaluate biopsy specimens for subchromosomal abnormalities at a level that had previously been unattainable.

This new and powerful tool is exciting, but the reality is that the validation studies providing definitive interpretation of the subchromosomal data are ongoing but incomplete. Still, much is known, and this information is now being incorporated into the results of clinical embryonic aneuploidy screening done by many reference laboratories. The challenge to the clinical and embryology teams receiving these reports is to fully understand their significance and how best to implement them clinically. This month's Views and Reviews focuses on these important issues.

One of the most interesting capabilities provided by the enhanced resolution of next generation sequencing is the ability to detect mosaicism within a single trophectoderm biopsy. It is important to recognize that the detection of mosaicism is limited to the mix of cells within that single biopsy. Given that a great deal of mosaicism exists that could not be detectable in a single biopsy, it is important to recognize that this does not empower comprehensive screening for mosaicism. Maxwell et al. provide a detailed description of the state of the art for detecting mosaicism, how this information may be integrated into clinical practice, and the impact on clinical outcomes. They also address the complex issue of how to counsel patients regarding their decision to use an embryo that may be mosaic. Outcomes are reduced, but many normal gestations have developed after the transfer of an embryo that appeared mosaic at the time of aneuploidy screening.

The enhanced resolution of next generation sequencing–based technologies also allows detection of duplications or deletions as small as 5 mb in size. It is most important to recognize that the substantial majority of clinically significant duplication and deletion syndromes involve abnormalities that are much smaller than 5 mb and thus would remain below the limits of resolution of contemporary screening platforms. However, it is becoming apparent that de novo duplications and deletions commonly develop in human embryos and that these embryos clearly have diminished reproductive potential. Management is not always straightforward. Most of these abnormalities are mosaic in nature, and thus some of these embryos, if transferred, will result in normal healthy offspring. Capalbo et al. review this important topic and provide insight into these findings and their clinical implications.

Preimplantation screening for chromosomal rearrangements has been validated and available for almost two decades. Screening strategies have used technologies such as FISH, SNP array, and array CGH, and all have been successful in distinguishing normal or balanced embryos from those that are unbalanced or that have inversions that might be clinically harmful. While these excellent screening options have been available, new approaches to screening now provide the ability to distinguish balanced from normal embryos. While this is unlikely to enhance clinical outcomes in those treatment cycles, it does provide an option for couples to remove the abnormality from their family's "gene pool" and thus reduce the risk that future generations will have to contend with these problems. Zimmerman et al. review the current status of screening for chromosomal rearrangements.

Finally, and perhaps most importantly, it is important for all investigators, laboratorians, and clinicians to understand that the application of these technologies is new to our field. A number of key questions remain to be answered, and class I data validating their use for detecting mosaicism and subchromosomal abnormalities are unavailable. Franasiak et al. discusses the limits of the current technology to help provide perspective on the current analytical and biologic limits of contemporary screening strategies.

These are exciting times for scientists, clinicians, embryologists, and patients. New technologies are providing powerful new insights into which factors limit human reproductive potential. The application of these screening tools should empower greater discrimination of those embryos with true reproductive potential from those that have little or none. This, in turn, should empower more efficient care while simultaneously reducing transfer order to one embryo for most patients. Eliminating polyzygotic multiple gestations would dramatically improve obstetrical and neonatal outcomes for many infertile couples who conceive through assisted reproductive technology. At the current time, significant limits on the predictive values of these technologies remain. While they may be used to enhance clinical outcomes, it is important to understand their limits and take them into consideration when counseling patients and making clinical decisions.

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