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Commentary

Counselling considerations for chromosomal mosaicism detected by preimplantation genetic screening

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A B S T R A C T

The evolution of preimplantation genetic screening (PGS) for aneuploidy to blastocyst biopsy and more sensitive 24-chromosome screening techniques has resulted in a new diagnostic category of PGS results: those classified as mosaic. This diagnosis presents significant challenges for clinicians in developing policies regarding transfer and storage of such embryos, as well as in providing genetic counselling for patients prior to and following PGS. Given the high frequency of mosaic PGS results and the wide range of possible associated outcomes, there is an urgent need to understand how to appropriately counsel patients regarding such embryos. This is the first commentary to thoroughly address pre- and post-test genetic counselling recommendations, as well as considerations regarding prenatal screening and diagnosis. Current data on mosaic PGS results are summarized along with embryo selection considerations and potential outcomes of embryos diagnosed as mosaic.

Background

Preimplantation genetic screening (PGS) has evolved to become a routine part of many IVF cycles, enabling selection of euploid embryos for transfer. Implementation of the most recent PGS technologies has been shown to improve pregnancy rates per transfer in randomized controlled trials, meta-analyses, and case-controlled prospective studies. The increased resolution of PGS technologies has facilitated the identification of chromosomal mosaicism in preimplantation embryos (Fragouli et al., 2011; Munne et al., 2010). Mosaicism is the presence of two or more genetically distinct cell lines and may occur with regard to a variety of genetic changes including chromosomal aberrations, single-nucleotide variations or small insertions/deletions. Such changes can either go unnoticed or underlie genetic disease.

Chromosomal mosaicism may refer to the presence of two or more different abnormal cell lines (e.g. aneuploid/aneuploid), or a normal and an abnormal cell line (e.g. euploid/aneuploid). In contrast to an aneuploidy present in all cells of an embryo, which typically occurs via meiotic nondisjunction and is associated with increasing maternal age, mosaic aneuploidy may occur by three mechanisms. It is presumed that the majority of cases result from an initially euploid zygote that undergoes nondisjunction postzygotically, resulting in trisomic and monosomic cell lines. Other cases result from anaphase lag (failure of a chromosome to be incorporated into the newly-formed cell), resulting in the formation of a monosomic cell. Alternatively, an initially aneuploid embryo can undergo postzygotic loss (also by nondisjunction or anaphase lag) or duplication of a whole chromosome ('aneusomic rescue'). The specific method by which mosaicism arises can result in distinctly different outcomes.

Chromosomal mosaicism in pregnancies and livebirths has been reported for various types of cytogenetic aberrations including trisomies, monosomies, deletions, duplications and other rare alterations. Prenatally, placental mosaicism is identified in 1–2% of chorionic villus samples (CVS) while approximately 0.2% of amniocentesis samples,

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which directly examine fetal tissues, exhibit mosaic findings. The variety of clinical outcomes in these situations presents significant counselling challenges (Spinner and Conlin, 2014).

The emerging classification of embryos as mosaic can be attributed to two phenomena. First, the evolution from blastomere biopsy of cleavage stage embryos to trophectoderm (TE) biopsy of blastocysts has allowed for the examination of multiple biopsied cells (a necessity for recognition of mosaicism) instead of just a single cell. Second, genetic technologies for detecting chromosomal copy number variations in embryos have evolved from the use of fluorescent in-situ hybridization (FISH) to comprehensive 24-chromosome screening methods including quantitative polymerase chain reaction (qPCR), single nucleotide polymorphism (SNP) arrays, array comparative genomic hybridization (aCGH) and, most recently, next-generation sequencing (NGS). aCGH and NGS in particular are sensitive enough to detect low level mosaicism in an embryo biopsy, with early estimates demonstrating that such technologies may be capable of detecting mosaicism levels as low as 20% (Greco et al., 2015; Mamas et al., 2012). While the actual rate of mosaicism in blastocysts is not well-defined, when NGS is performed, preliminary data suggest that 10–30% of blastocyst TE biopsies may be diagnosed as mosaic (Fiorentino et al., 2014; Fragouli et al., 2015; Munne et al., 2016).

Additionally, PGS laboratories differ in their approaches to mosaicism detection, thresholds used, classification and reporting structure. Discrimination between euploid and aneuploid samples relies on threshold values determined by statistical averages, and embryos are diagnosed as mosaic when the result falls into an 'intermediate' range between the threshold values (Scott and Galliano, 2016). Therefore, it is possible that some biopsies contain only a single cell line (euploid or aneuploid) but fall into the borderline ('mosaic') value between normal and abnormal due to overlap between mosaic and euploid (or mosaic and aneuploid) statistical ranges (Scott and Galliano, 2016). The thresholds and ranges can vary depending on the bioinformatics used by the testing laboratory. When the euploid and aneuploid ranges are narrow, biopsies diagnosed as euploid are less likely to be false-negatives (i.e. more likely to be entirely euploid) and biopsies diagnosed as aneuploid are less likely to be false-positives (i.e. more likely to be entirely aneuploid). This is consistent with early data, which has shown that a narrower euploid range is associated with improved implantation and reduced miscarriage. However, narrower euploid and aneuploid ranges mean a wider intermediate ('mosaic') range, and therefore, a greater number of embryos are given an uncertain diagnosis. Alternatively, wider euploid and aneuploid ranges decrease the percentage of results falling into the mosaic range; however, a higher frequency of false-negative or false-positive results may occur.

Clinical significance of chromosomal mosaicism

The clinical significance of chromosomal mosaicism diagnosed by PGS is not well delineated. First, embryos may have robust mechanisms of self-correction, as suggested by data showing rates of placental mosaicism to be similar between infertile and fertile women by the time of CVS (Huang et al., 2009). Second, TE cells may not always represent the cells of the inner cell mass, and other embryonic tissues may be comprised of cell lines that differ from the biopsied cells. Finally, the distribution of abnormal cells in an embryo can vary depending on the timing of mutational events and the degree of proliferation of aneuploid versus euploid cells (Spinner and Conlin, 2014). Therefore, embryos deemed mosaic by PGS have the potential to develop into a fetus that is chromosomally normal, chromosomally abnormal, or mosaic to a lesser, greater, or similar degree to that predicted by the biopsy results (Greco et al., 2015). A summary of the possible explanations for mosaic PGS results and associated risks is provided in **Table 1**.

There is sparse data regarding the transfer of embryos diagnosed as mosaic. In the only prospective study published to date, 6/18 transferred embryos with mosaic results involving different chromosomes resulted in apparently healthy live births (Greco et al., 2015). While normal karyotype studies were documented post-natally from chorionic villi, it is not known whether mosaicism persisted throughout embryonic development, and no additional follow-up on these babies was made available. While some would encourage cautious optimism regarding long-term outcomes, data is exceptionally limited at the current time.

Preliminary data suggests that embryos identified as mosaic may have a reduced chance of implantation when compared with euploid controls (Fragouli et al., 2015). Other early data sets suggest that embryonic mosaicism may play a significant role in pregnancy loss after IVF (Grifo et al., 2015), and cytogenetic and array-based analysis of

Table 1 – Potential explanations and associated risks for mosaic results following preimplantation genetic screening (PGS).

Explanation	Embryo composition	Risk assessment
Fully euploid biopsy falling into mosaic result range	Likely euploid	Low risk
Fully aneuploid biopsy falling into mosaic result range	Likely aneuploid	High risk of failed implantation, miscarriage or aneuploidy syndrome depending on chromosome involved
True mosaic (euploid/aneuploid) biopsy	Mosaic TE, euploid ICM	Low risk of poor outcome; however, possible risk of CPM (including IUGR) depending on chromosome involved
	Mosaic TE, aneuploid ICM	High risk of failed implantation, miscarriage, or aneuploidy syndrome depending on chromosome involved
	Mosaic TE, mosaic ICM	Largely unknown risk; dependent on chromosome involved, proportion of aneuploid cells, affected tissue types
Mosaic for two reciprocal aneuploid cells lines (i.e. monosomic/trisomic for same chromosome) OR for two or more different aneuploid cell lines, with no euploid cells	Likely aneuploid or mosaic for multiple aneuploidies, with no euploid cells	High risk of failed implantation, miscarriage, or aneuploidy syndrome depending on chromosome(s) involved

CPM, confined placental mosaicism; ICM, inner cell mass; IUGR, intrauterine growth restriction; TE, trophectoderm.

miscarriages following spontaneously-conceived pregnancies commonly reveal chromosomal mosaicism (Robberecht et al., 2009).

Fortunately, the experience of CVS has shown that in pregnancies in which aneuploid cells appear to be limited to the placenta (confined placental mosaicism, or CPM), there is typically no apparent effect on fetal development. However, CPM of certain chromosomes is associated with an increased risk for intrauterine growth restriction (IUGR) and fetal death (Spinner and Conlin, 2014).

Fetal mosaic aneuploidy, on the other hand, can result in a broad range of outcomes, from normal/asymptomatic to severe congenital anomalies. While full fetal trisomies are only viable for certain chromosomes, mosaic aneuploidies of nearly every chromosome have been reported in liveborns, and have been associated with a wide variety of physical and mental disabilities. The outcome may be largely dependent not only on the chromosome(s) involved, but also the proportion of abnormal cells and affected tissue types, which are difficult to assess even post-natally.

Importantly, when mosaicism occurs as the result of a trisomy or monosomy 'rescue' event, there may be additional risks associated with uniparental disomy (UPD). UPD of certain imprinted chromosomes (such as, but not limited to, 7, 14, 15 and 20) is associated with genetic disorders such as Russell-Silver, Prader-Willi and Angelman syndromes, as well as nonsyndromic intellectual disability. UPD has been reported for nearly every chromosome; however, most UPD events do not result in clinical syndromes (Eggermann et al., 2015). In rare cases, UPD may also pose an increased risk of recessive genetic disease if a pathogenic mutation is located on the duplicated parental allele.

Embryo selection

It stands to reason that mosaicism detection may be a helpful tool in narrowing a cohort of embryos to those with the highest chance of being entirely euploid, thereby having the potential to increase the pregnancy rate per transfer above even that currently seen with standard PGS techniques (Munne et al., 2016). However, for patients who have only mosaic embryos available, the decision of whether to transfer or even to store such embryos can be incredibly difficult, as there are several challenges to determining the prognosis for any given mosaic result.

Recent guidelines from the Preimplantation Genetic Diagnosis International Society (PGDIS, 2016) suggest that transfer of certain mosaics is preferable to others. Specifically, these guidelines recommend that mosaic monosomies be considered prior to mosaic trisomies. While monosomies are often perceived as 'non-viable', it should be noted that every postzygotic nondisjunction event generates a monosomic cell as well as a trisomic cell; therefore, embryos that appear mosaic for a monosomy may also contain trisomic cells, and vice-versa (Scott and Galliano, 2016). As NGS cannot reliably distinguish between mosaic monosomy/euploidy and mosaic monosomy/trisomy, caution must be used in interpreting results that appear to indicate only a mosaic monosomy (Scott and Galliano, 2016). The PGDIS guidelines state that if a mosaic trisomy is considered for transfer, those involving chromosomes 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 17, 19, 20, 22, X and Y are preferred over those involving chromosomes 2, 7, 13, 14, 15, 16, 18 and 21. However, mosaic aneuploidies of virtually every chromosome have been documented in liveborns with a range of phenotypic effects. While known phenotypes – particularly Down syndrome, trisomies 13 and 18, syndromes involving sex chromosomes, IUGR and UPD syndromes – must be factored into embryo transfer decisions, it is essential to recognize that any aneuploidy can theoretically be viable in the presence of a euploid cell line. The PGDIS guidelines also recommend that the proportion of aneuploid cells be considered when contemplating transfer of an embryo diagnosed as mosaic; however, it also must be recognized that the percentage of mosaicism in the trophectoderm biopsy does not necessarily correlate with that found in the remainder of the embryo (Taylor et al., 2015).

Finally, the PGDIS guidelines do not address mosaic partial aneuploidies, for which even less data is available due to the individual rarity of each particular segmental gain or loss. In general, mosaicism of any full or partial aneuploidy could theoretically result in a live birth (with possible anomalies, depending on the percentage of abnormal cells and tissues involved) if the percentage of abnormal cells were low enough so as to not cause failed implantation or miscarriage. Clinicians will therefore encounter great difficulties in choosing 'safe' embryos that have an all-or-nothing chance of either creating a healthy baby or leading to failed implantation/miscarriage.

Genetic counselling considerations

Since the advent of PGS with FISH and throughout its evolution to 24-chromosome screening, ordering clinicians have had the benefit of receiving relatively straightforward results, reported as either normal (euploid) or abnormal (aneuploid). Now in the era of mosaicism, the interpretation of PGS results, education of patients and selection of embryos for transfer are more complex. That the incidence of embryonic mosaicism – or at least results falling within this range – at the blastocyst stage appears to be relatively high makes the pre-PGS and results counselling burden more daunting, and counselling challenges may persist after embryo transfer and into the prenatal and post-natal diagnosis realm. Although outcome data following transfer of mosaic embryos is largely unavailable, genetic counselling to review possible risks and outcomes should be strongly considered for any patient who is contemplating transfer of an embryo diagnosed as mosaic. Until now, specific counselling recommendations have not been published, and many IVF providers struggle with results interpretation, obtaining informed consent, embryo transfer decisions and risk assessment. This section will thoroughly address pre- and post-test genetic counselling recommendations, as well as considerations regarding prenatal screening and diagnosis. These recommendations are summarized in **Table 2**.

Pre-test counselling

Patients may have varying expectations regarding the type of information that PGS can provide. Comprehensive patient education prior to pursuing PGS is essential to ensure that patients have an adequate understanding of possible test results. If the selected test methodology includes detection and reporting of mosaicism, counselling should include information about the frequency of mosaic results (as quoted by the testing laboratory), the difficulties in identifying explanations for and interpreting such results, the limited outcome data available about mosaic embryos, clinic policies regarding the transfer and storage of mosaic embryos and the potential challenges associated with making embryo transfer decisions in the absence of clear risk information. A thorough discussion of these points

Table 2 – Summary of counselling considerations for chromosomal mosaicism detected by preimplantation genetic screening (PGS).

Laboratory and clinic policies	Laboratories performing PGS are encouraged to consider the impact of widening or narrowing the statistical range in which an embryo is diagnosed as mosaic, and to share their policies and procedures regarding the detection and reporting of chromosomal mosaicism. IVF programmes are encouraged to develop and make patients aware of their own policies regarding the transfer and storage of embryos diagnosed as mosaic. Policies should also outline programmes' plans for systematically reviewing the literature on mosaicism, revising their policies accordingly, and determining protocols for re-contact of patients when additional data become available.
Tracking of outcomes	For programmes performing transfers of embryos diagnosed as mosaic, outcomes should be documented. Laboratories performing PGS should also track prospective outcomes as pooling data from multiple centres will be necessary to generate meaningful data. However, it cannot be assumed that embryos with the same types of mosaicism would necessarily follow the same developmental paths. For babies born following transfer of embryos diagnosed as mosaic, post-natal outcome tracking may include information obtained by physical examination and cord/peripheral blood and placental karyotyping. However, even post-natally, the reliability of karyotyping is limited since the number of cells counted can preclude detection of low level mosaicism, the need for actively dividing cells limits the detection of mosaicism to certain cell types, and results from one tissue cannot be extrapolated to other tissues (Spinner and Conlin, 2014). Retrospective analysis of transfer outcomes from mosaic embryos as diagnosed by NGS-based re-analysis of stored whole genome amplification product may offer powerful data sets.
Pre-test genetic counselling	Prior to pursuing PGS, patients should be informed of the risks, benefits and limitations of the technology utilized. Patients should be provided with the option to not pursue PGS. If the technology utilized is known to identify mosaicism, patients should be informed of four possible results: euploid, aneuploid, mosaic and no result (test failure/insufficient DNA). Patients should be informed of the limited data regarding embryos diagnosed as mosaic. Patients utilizing gestational carriers may wish to inquire about their gestational carrier's willingness to transfer mosaic embryos.
Post-test genetic counselling	If euploid embryos are available, these embryos should be preferentially transferred. In the event that no euploid embryos are available for transfer and a patient is considering transferring an embryo diagnosed as mosaic, genetic counselling should be provided and should include the following points: There are several possible explanations for mosaic PGS results (**Table 1**). Such embryos may be composed of a normal and an abnormal cell line, or two or more different abnormal cell lines. Given that discrimination between euploid and aneuploid samples relies on threshold values determined by statistical averages, some embryos containing only a single cell line (euploid or aneuploid) may be misclassified as mosaic. Data regarding the significance of mosaicism identified in embryonic trophectoderm biopsies are extremely limited. Embryos diagnosed as mosaic appear to be associated with a lower implantation rate and a higher risk of miscarriage. Pregnancies resulting from conception with embryos diagnosed as mosaic may have a higher risk of prenatal and perinatal complications, due to the chance of persisting placental mosaicism. There are a small number of apparently healthy live births following conception with embryos diagnosed as mosaic. There is, however, a risk of live birth with persisting aneuploidy (in the full or mosaic state) or UPD, which could result in congenital anomalies to varying degrees. When the identified aneuploidy is associated with a known syndrome or phenotype (with particular emphasis on those involving chromosomes 13, 18, 21, X, Y), patients should be made aware of any corresponding clinical information, with the understanding that a mosaic full or partial aneuploidy involving any chromosome could have a poor outcome. Providers who are not familiar with the possible outcomes listed above may consider referring patients to a certified genetic counsellor. Gestational carriers into whom mosaic embryos may be transferred should be offered counselling on the possible outcomes and potential need for prenatal diagnosis.
Embryo selection and transfer	When selecting a mosaic embryo for transfer, additional caution is warranted for aneuploidies associated with known phenotypes, although any aneuploidy may have the potential to be viable (with associated risks) in the mosaic state. It should be recognized that the percentage of mosaicism in the trophectoderm sample, if reported, may not represent the degree of mosaicism in the remainder of the embryo and cannot be relied upon to determine risks or outcomes. Despite the possible lower implantation potential of embryos diagnosed as mosaic, single embryo transfer should be strongly considered in order to enable more accurate prenatal diagnosis and postnatal outcome reporting.
Prenatal testing considerations	Before and during a pregnancy resulting from the transfer of an embryo diagnosed as mosaic, genetic counselling should be provided to discuss the benefits and limitations of prenatal screening and diagnosis. If prenatal diagnosis is performed, the number of cells counted and analyzed should be in accordance with CLIA guidelines. If indicated, prenatal FISH, microarray and/or UPD studies may also be offered.

CLIA, Clinical Laboratory Improvement Amendments; FISH, fluorescence in-situ hybridization; NGS, next generation sequencing; UPD, uniparental disomy.

before embryo biopsy can help patients make informed decisions about whether or not to pursue PGS. Some patients may be dissuaded by the possibility of uncertain results, and may opt out of PGS to avoid the burden of decision-making regarding transfer or storage of embryos diagnosed as mosaic.

In considering PGS, the risks of potential misdiagnosis must be weighed against the frequency of uncertain results, and clinicians and laboratories should consider how these results may psychologically impact patients. Meldrum (2016) suggests that the uncertainty associated with mosaic results adds to the psychological burden already

carried by IVF patients. There is limited research about patient decision-making around PGS, but in one small study (Gebhart et al., 2016), 16% of patients considering PGS (*without* reporting of mosaic results) reported that the decision to accept or decline the test was difficult or extremely difficult. It seems likely that incorporating mosaicism into pre-test considerations would only increase the proportion of patients who struggle with the PGS decision.

Results of uncertain meaning, however, are not new to reproductive genetics. Chromosomal microarray, for example, has become more commonly used in addition to karyotyping for prenatal diagnosis, and identifies uncertain findings in 1–2% of cases (Westerfield et al., 2014). In one small study population, uncertain prenatal results were associated with 'emotional turmoil' (Bernhardt et al., 2012). Many participants struggled with decision-making and some regretted pursuing prenatal testing. The authors stressed the importance of thoroughly assessing couples' tolerance for uncertainty as part of the pre-test genetic counselling process. In another study, patients who had deliberated about the advantages and disadvantages of prenatal screening had less adverse emotional reactions and less difficulty making decisions following an abnormal result, compared with women who were categorized as uninformed prior to screening (Kleinveld et al., 2009). While there are obvious differences between the types of decisions made during an established pregnancy compared with those made in the preconception period, it stands to reason that pre-test educational counselling is a crucial component of any genetic testing process that has the potential to introduce impactful results of uncertain meaning.

Post-test counselling

While potentially reduced embryo implantation may be an acceptable risk for patients who otherwise do not have euploid embryos to transfer, a possible increased risk of miscarriage and unknown risk of fetal/neo-natal anomalies should be emphasized, as this information may significantly impact transfer decisions. Pregnancy loss, fetal anomalies, termination or adverse post-natal outcomes can have significant emotional and financial effects, and the time lost before a patient can pursue another cycle or alternative reproductive options is particularly relevant for patients of advanced age.

In the event that a patient proceeds with the transfer of an embryo diagnosed as mosaic, counselling about the benefits, risks and limitations of prenatal screening and diagnosis should be provided. IVF providers should recognize that patients (or their gestational carriers) may receive differing information from prenatal providers who may not be familiar with embryonic mosaicism. While CVS offers the earliest prenatal diagnosis of aneuploidy, the cells obtained are placental in origin, whereas those obtained through amniocentesis are more representative of fetal tissues. However, amniocytes are derived only from the embryonic ectoderm and amnion, so even a normal amniocentesis does not exclude low-level mosaicism or aneuploid cells in other tissue types. Traditionally, fetal karyotype is established by counting chromosomes in a minimum of 20 amniocytes from at least two independent cultures, with five banded metaphase cells analysed in their entirety. As Clinical Laboratory Improvement Amendments standards dictate the counting of 50 or more cells when mosaicism is suspected, these standards may be warranted in pregnancies conceived following transfer of embryos diagnosed as mosaic. If the embryo transferred was identified as mosaic for a segmental aneuploidy, FISH or aCGH may be indicated to detect abnormalities affecting the region of interest. Prenatal UPD studies may additionally be considered, particularly in cases involving chromosomes associated with known UPD syndromes or when one parent is a known carrier of a recessive disorder for which the gene is located on the chromosome of interest. While normal prenatal diagnostic results are reassuring, patients should remain aware of their limitations.

It is essential that patients be informed of the differences between prenatal diagnosis (CVS or amniocentesis) and screening, with particular reference to cell-free DNA screening (cfDNA). Since cfDNA is derived only from placental cells, the results of this testing may not reflect the status of the fetus, and false-positive or false-negative results may occur. Many cfDNA tests only assess the risk of specific aneuploidies (typically chromosomes 21, 13, 18, X, Y) and nonetheless, test validity for mosaicism detection is unknown. While cfDNA detection of genome-wide deletions and duplications has recently become available, this testing is not recommended by the American College of Medical Genetics and Genomics (Gregg et al., 2016) as its reliability for detecting full or mosaic partial aneuploidies is unknown; the positive predictive value of abnormal results varies and may lead to patient anxiety, incorrect results interpretation and unnecessary diagnostic procedures. Additionally, fetal anomalies or 'soft markers' identified by ultrasound may be difficult to interpret in pregnancies conceived from embryos diagnosed as mosaic.

Ideally, genetic counselling regarding the challenges associated with interpretation of mosaic results, potential outcomes of mosaic embryos and prenatal testing options should be provided prior to PGS. Many patients already struggle with decisions about what to do with surplus embryos, and decision-making about transfer or storage of mosaic embryos could further complicate this issue. Some patients may therefore opt out of PGS to avoid this additional psychological burden. Post-PGS genetic counselling is of particular importance since patients could be in the position of making rushed embryo transfer decisions, such as when a euploid embryo does not survive warming and only mosaic embryos remain in storage. Cryostorage may in fact be preferred by clinics and patients who wish to postpone transfer decisions until more comprehensive outcome data are accumulated. It is prudent for clinics to develop policies addressing these situations, particularly with regard to embryo storage fees and re-contact of patients in the event of new relevant data or policy changes.

Mosaicism is only one of many new genetic counselling challenges that providers and patients will encounter with the increasing use of new genomic technologies in reproductive medicine. It will be imperative for PGD and IVF laboratories, reproductive endocrinologists, and clinical genetics providers to collaborate on designing meaningful pre- and post-test counselling protocols for fertility patients.

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REFERENCES

Bernhardt, B.A., Soucier, D., Hanson, K., Savage, M.S., Jackson, L., Wapner, R.J., 2012. Women's experiences receiving abnormal prenatal chromosomal microarray testing results. Genet. Med. 15, 139–145.

Eggermann, T., Soellner, L., Buiting, K., Kotzot, D., 2015. Mosaicism and uniparental disomy in prenatal diagnosis. Trends Mol. Med. 21, 77–87.

Fiorentino, F., Bono, S., Biricik, A., Nuccitelli, A., Cotroneo, E., Cottone, G., Kokocinski, F., Michel, C.E., Minasi, M.G., Greco, E., 2014. Application of next-generation sequencing technology for comprehensive aneuploidy screening of blastocysts in clinical preimplantation genetic screening cycles. Hum. Reprod. 29, 2802–2813.

Fragouli, E., Alfarawati, S., Daphnis, D.D., Goodall, N.N., Mania, A., Griffiths, T., Gordon, A., Wells, D., 2011. Cytogenetic analysis of human blastocysts with the use of FISH, CGH and aCGH: scientific data and technical evaluation. Hum. Reprod. 26, 480–490.

Fragouli, E., Alfarawati, S., Spath, K., Tarozzi, N., Borini, A., Wells, D., 2015. The developmental potential of mosaic embryos. Fertil. Steril. 104, e96.

Gebhart, M.B., Hines, R.S., Penman, A., Holland, A.C., 2016. How do patient perceived determinants influence the decision-making process to accept or decline preimplantation genetic screening? Fertil. Steril. 105, 188–193.

Greco, E., Giulia Minasi, M., Fiorentino, F., 2015. Healthy babies after intrauterine transfer of mosaic aneuploid blastocysts. N. Engl. J. Med. 373, 2089–2090.

Gregg, A.R., Skotko, B.G., Benkendorf, J.L., Monaghan, K.G., Bajaj, K., Best, R.G., Klugman, S., Watson, M.S., 2016. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet. Med. 18, 1056–1065.

Grifo, J., Colls, P., Ribustello, L., Escudero, T., Liu, E., Munne, S., 2015. Why do array-CGH (ACGH) euploid embryos miscarry? Reanalysis by NGS reveals undetected abnormalities which would have prevented 56% of the miscarriages. Fertil. Steril. 104, e14.

Huang, A., Adusumalli, J., Patel, S., Liem, J., Williams, J., 3rd, Pisarska, M.D., 2009. Prevalence of chromosomal mosaicism in pregnancies from couples with infertility. Fertil. Steril. 91, 2355–2360.

Kleinveld, J.H., Ten Kate, L.P., van den Berg, M., van Vugt, J.M., Timmermans, D.R., 2009. Does informed decision making influence psychological outcomes after receiving a positive screening outcome? Prenat. Diagn. 29, 271–273.

Mamas, T., Gordon, A., Brown, A., Harper, J., Sengupta, S., 2012. Detection of aneuploidy by array comparative genomic hybridization using cell lines to mimic a mosaic trophectoderm biopsy. Fertil. Steril. 97, 943–947.

Meldrum, D.R., 2016. Lightening the burden of care in assisted reproductive technology. Fertil. Steril. 105, 1144–1145.

Munne, S., Wells, D., Cohen, J., 2010. Technology requirements for preimplantation genetic diagnosis to improve assisted reproduction outcomes. Fertil. Steril. 94, 408–430.

Munne, S., Grifo, J., Wells, D., 2016. Mosaicism: 'survival of the fittest' versus 'no embryo left behind. Fertil. Steril. 105, 1146–1149.

PGDIS, 2016. Preimplantation Genetic Diagnosis International Society (PGDIS) position statement on chromosome mosaicism and preimplantation aneuploidy testing at the blastocyst stage. http://pgdis.org/docs/newsletter_071816.html. (Accessed 9 January 2016).

Robberecht, C., Schuddinck, V., Fryns, J., Vermeesch, J.R., 2009. Diagnosis of miscarriages by molecular karyotyping: benefits and pitfalls. Genet. Med. 11, 646–654.

Scott, R.T., Jr., Galliano, D., 2016. The challenge of embryonic mosaicism in preimplantation genetic screening. Fertil. Steril. 105, 1150–1152.

Spinner, N.B., Conlin, L.K., 2014. Mosaicism and clinical genetics. Am. J. Med. Genet. C Semin. Med. Gen. 166C, 397–405.

Taylor, T.H., Wing, R., Griffin, D.K., 2015. A technique to 'map' mosaicism at the blastocyst stage using comprehensive chromosome screening. Fertil. Steril. 104, e274.

Westerfield, L., Darilek, S., van den Veyver, I.B., 2014. Counseling challenges with variants of uncertain significance and incidental findings in prenatal genetic screening and diagnosis. J. Clin. Med. 3, 1018–1032.