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Report of PGDIS Task Group on status of PGT-A

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Report of PGDIS Task Group on status of PGT-A

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Abstract

The clinical utility and validity of PGT-A in IVF practice is often questioned. Some major societies have released ambiguous statements about PGT-A leaving the potential and benefits of embryo selection, enhanced by chromosome profile assessments, indeterminant. The Preimplantation Genetic Diagnosis International Society Task Group (PGDIS) has gathered the scientific information and critically evaluated the evidence about the clinical value of PGT-A. We considered technical aspects, genetic principles and clinical outcome studies and conclude that proper implementation of PGT-A does result in increased benefits for IVF embryo selection. We envision this report will remove some of the confusion surrounding PGT-A, lead to informed choices about the use of PGT-A and ultimately result in improved transfer outcomes.

Keywords

Preimplantation genetic testing for aneuploidy, misconceptions of PGT-A, aneuploidy, somatic mosaicism

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Introduction

Success in pregnancy, whether natural or IVF, is a progressive series: Initiating a pregnancy, persistence through the fetal development stages and finally, the ultimate birth of a healthy child.
In natural pregnancies, aneuploidy accounts for 3 out of 4 clinical miscarriages (Li et al 2023). Segawa et al (2017) similarly reported that 80% of week 7-10 miscarriages after IVF were aneuploid.
Data on very early pregnancy losses are lacking for natural pregnancies and so aneuploid-related sub-clinical miscarriage rates are likely being unrecognised. Madjunkova et al (2025) however reported that 36% of aneuploid IVF embryo implantations failed at the biochemical stage whereas the remainder were lost as clinical miscarriages. Tiegs et al (2020) reported that 40% of aneuploid embryos could initiate a pregnancy but also experienced a 42% loss of implantations at the very early stage with the remainder being clinical losses. Wang et al (2022) reported a 41% loss of aneuploid implantations at the sub-clinical phase. Suggesting that very early failures, while substantial, are not guaranteed.
In non-selection embryo transfer studies, arguably the most suitable and strongest PGT-A study design, Tiegs et al (2021) observed that, aneuploid embryos, while capable of initiating a pregnancy, typically failed by week 10, whereas Wang et al (2022) suggested a small minority could continue. Noninvasive prenatal blood screening has also identified various autosomal trisomies into late first trimester and early second trimester pregnancies (Scott et al 2018, Mossfield et al, 2022;) suggesting that even early clinical failures are not a barrier to aneuploid pregnancies. Finally, aneuploidy is a major cause of birth defects with Down (trisomy 21), Pateau (trisomy 18) and Edwards (trisomy 13 syndromes being well known. Several other chromosomal trisomies can cause birth defects when present even in a small fraction of the cells (Lannoo et al., EJHG, 2022). Failure at any stage of pregnancy though, is ultimately a failure of the whole process of pregnancy.
Continued reliance on pregnancy failure as a corrective solution, linked to initial poor IVF embryo selection, however, may be a poor and somewhat dated approach to IVF management.

When performing IVF with current PGT-A, it has been suggested aneuploidy deselection may improve transfer outcomes, reduce the number of miscarriages and increase the baby take home rate per transfer while simultaneously reducing the need for multiple embryo transfers. The reported high level of chromosome instability in preimplantation development though is suggested to affect the accuracy of PGT-A. These considerations are the main focus of this

current Position Statement.

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1. Safety and Accuracy of the PGT-A Procedure

Statement Key Points

- Biopsy can represent the rest of the embryo in nearly all cases
    - Sample handling is important
- Done poorly, biopsy can negatively impact on embryo potential
- Mosaicism is real but is being over reported
- PGT-A analysis has evolved into a more comprehensive chromosome screen
    - Recent approaches combine copy number analysis with genetic polymorphism analysis
- For accurate chromosome profile assembly, strictly adhering to quality practices is essential

1.1 Embryo Biopsy

To accurately analyze chromosome profiles, a genuine sample of embryo DNA is needed. The original approaches of polar body biopsy and blastomere biopsy have been substantially superseded by trophectoderm biopsy and won't be further discussed in this Statement.
Even though blastocyst biopsy involves removing multiple cells, the embryo at this stage appears to tolerate loss of more than one cell without significant detriment (Scott et al 2013). A multiple cell biopsy also improves uniformity of DNA amplification .

1.1.1 Is biopsy harmful?

Early studies on cleavage stage biopsy (Mastenbroek et al, 2007), reported a large decline in implantation potential when blastomeres were removed from a cleavage stage embryo. The extremely low implantation results reported were criticized as more likely the result of poor technique (Munne et al 2007). However, in a simple paired transfer study, it was shown that cleavage stage blastomere biopsy reduced implantation potential by nearly 40% (Scott et al

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2013).
What of the impact of trophectoderm biopsy? In a double embryo transfer study, no difference was shown between biopsied (51%) and non-biopsied (54%) embryos for sustained implantation rates. In another report from the same group (Neal et al, 2017) using single embryo transfers, even higher positive pregnancy rates (79.2%) and live birth rates (61.7%) were reported when biopsy avoided excessive cell removal. The implication of these findings is that biopsy can do harm when performed incorrectly. Inappropriate biopsy timing, prior to substantial blastocyst expansion, may also cause reduction in embryo transfer outcomes (Singh et al, 2019).
Anecdotally, a concerning recent trend suggests, that in an attempt to further minimize the impact of biopsy some groups, ignoring historical problems identified with single cell amplification, mistakenly reduce the number of cells taken, inadvertently raising the potential for minimal DNA damage/loss generating unrepresentative profiles as well as an increased potential for biases introduced during sample amplification.
In conclusion, blastocyst biopsy appears not harmful when performed properly, but variability in performance amongst clinics exists. Individual teams need to assess their own performance both in IVF and in PGT-A.

1.1.2 Is a biopsy reproducible?

Nearly all debates about accuracy revolve around the reproducibility of the test process and the final description of the embryo. Can a small part of an embryo accurately reflect the rest of the embryo? Such questioning is valid, however: i) When an embryo is assigned to be euploid or aneuploid , (typically >90-95% of all embryos tested), whole embryo analyses tend to confirm this finding (98-99%). ii) Genuine mosaic embryos though do exist and need to be considered. Although true mosaic embryos are likely <5% of all blastocyst biopsies (Katz-Jaffe et al, 2024; Saleem, 2024), higher total mosaic call rates may actually reflect artifacts of the analysis process. Treff and Marin (2021), in the largest review of "mosaic" embryo re-analyses, reported that most of these embryos (57%) were unlikely to have been mosaic and were aneuploid or euploid. With many groups suggesting 8-12% of embryos have ICN chromosome profiles, this supports the findings that actual mosaic rates are low. These observations also highlight the necessity of a reliable analysis approach (Jalas et al, 2020).

From the 8-cell stage onwards, (or even earlier)(Junyent et al , 2024) relative cell position is essentially fixed, and mosaicism, if present, is likely to be both limited and clustered (see figure 1) and not the dispersed patterns some authors have used to support their proposals of non-repeatable mosaicism analysis (Popovic et al, 2020) or models of biopsy representation (Gleicher et al 2017). This clustering constraint will apply especially to trophectoderm cells where tight

cell junctions are both present and necessary to maintain the integrity of the blastocyst.
The few studies available, using whole embryo analysis to confirm mosaicism (Marin et al, 2021), tend to show most apparent low-level mosaic embryos are actually euploid and high-level mosaics are aneuploid. Analytical errors are therefore more likely the cause of many intermediate copy number (ICN) results with only a small fraction of embryos demonstrating genuine mosaicism. The real confusion and debate about biopsy representing an embryo therefore revolves around the small percentage of embryos that are genuinely mosaic and not the 95%+ identified as an/euploid. With such a small number of mosaic embryos, excessive debate/argument around accuracy of PGT-A analysis based on perceived biological mosaicism, is only distracting and detracts from understanding the biological basis of why PGT-A is beneficial in embryo selection. The more critical concern is the correct performance of the testing process itself, to be discussed in a later section.

1.1.3 Can a biopsy describe the rest of the embryo?

It has been suggested that the genome of the embryo is not fixed but variable and capable of "self-correction", hence any early description is necessarily flawed.
It is not disputed that, in both prenatal testing and miscarriage material analysis, mosaicism is real. However, its prevalence beyond the minor levels observed in growing CVS samples (typically <10% of cells and only a few percent of samples) marks it as a rare phenomenon, not highly prevalent and possibly occurring at a later stage of embryo development. Genetic analysis of the "normal" adult population suggests that ~1 in 2000 individuals have a chromosome pattern indicative of a UPD. Logically, such individuals must have been mosaic during their development with the most likely time being during the very early embryo stage. Such evidence of aneuploid "correction" still suggests that normal birth after mosaic correction is very low (<0.2%) in the general population. Mosaic miscarriages, however, do account for an identifiable fraction of chromosomally abnormal miscarriage events and carry relevance to mosaic embryo transfers (Li et al 2023).

What about euploidy progressing to trisomy or monosomy? Similar to embryo correction, aneuploid progression would have the same model of cell distribution with limitations on when somatic variation would have a significant impact on the final embryo status.

Indirect evidence of the very low prevalence of genetic discordances between

the placental mass and the developing fetus is seen in the low false negative rates of NIPS(NIPT) (Non-Invasive Prenatal Screening/Testing). The negative predictive values for the common trisomies is typically quoted at >99.96% (1 in 2,500). Similarly, for low false positive rates. Prevalence of mosaicism in CVS samples by classical cytogenetics, is low and typically only 2-4% of samples, whereas mosaicism in amniocentesis samples is even lower at only 1-2% of amniocentesis samples (Grati et al, 2019).

It can be biased to suggest that low prevalence is a result of "self-correction" rather than the simpler explanation of an original low incidence. Taken together, mosaicism in clinical pregnancies and live births is a rare event and not reflective of the high observation claims by some authors studying embryos. Excessive somatic chromosome segregation failures in very early embryo growth will logically give a higher prevalence of prenatal aneuploidy, not the low levels typically encountered in analyses.

2. Evolution of Chromosome analysis

Statement Key Points:

- Intermediate copy number reports appear to be exaggerated in some studies
- Proper techniques are a prerequisite for accurate PGT-A detection
- low-medium grade ICNs can be transferred

PGT-A (formerly PGS) analyses evolved quickly. With increased resolution came the observation that, in some embryos, occasional chromosomes appeared to be represented by an intermediate copy number (ICN) initially proposed to be analogous to the cytogenetic observations of mosaicism seen in both normal prenatal and miscarriage material.
Confusion around what "mosaic embryo" transfer might mean clinically, led some clinics to avoid their transfer. However, reports from as early as 2015 (Greco et al 2015) clarified that small deviations in chromosome copy number appeared still compatible with successful transfer outcomes, albeit at apparently lower success rates. Individual clinics then considered their own risk management responses in determining their own transfer policy.
As technologies refined and understanding grew, PGDIS addressed the transfer of putative mosaic embryos in consecutive Position Statements in 2016, 2019 and 2022 (PGDIS Newsletter, 2016, Cram et al, 2019, Leigh et al, 2022). These statements proposed that transfer of putative mosaic embryos could be considered. From an analytical point, NGS-based ICNs of <20% should only be considered noise and within the normal range. This lower value was not a

measure of clinical significance nor of mosaicism but purely a recognition of noise associated with the initial genome amplification process and subsequent analysis.
While new technologies permit greater complexity of analysis and interpretation of chromosome status, underlying all of these tests is the requirement for appropriate quality control of: sample acquisition, sample preparation and final DNA analysis. (See Supplementary Discussion).

3. Potential value of PGT-A in embryo selection

The underlying tenet of PGT-A, that aneuploid embryos do not generally lead to a successful pregnancy, is based on the observation that aneuploidies are a major cause of failed pregnancies. Non-selection embryo transfer studies have also generally supported this view. Transfer failure as well as sub-clinical pregnancies however, are typically ignored in many analyses with only clinical pregnancies considered notable- although women all over the world still suffer disappointment after failure, especially of an early pregnancy.

While aneuploidy is the known leading cause of clinical miscarriages in natural pregnancies, the value of identifying and avoiding aneuploid embryo transfers has curiously, seen challenge by some PGT-A studies and groups.

What are challenges to PGT-A based on?
The existence of apparent ICN chromosome complements (whole chromosomes or segments) raised the issue of accuracy, interpretation and what the clinical significance might be. However, whole embryo studies often do not support the initial ICN analysis, suggesting that it was either localized mosaicism or, potentially, an incorrect initial analysis (Marin et al, 2021). This led to a logical proposal that the original embryo was genuinely mosaic but in a limited site or that the biopsy analysis was in some way compromised.

Capalbo et al, (2021) using a validated method for their embryo biopsy analysis, suggested that a significant percentage of the embryos they analyzed were mosaic. This was seen by some groups to challenge any clinical utility of analyzing chromosome complements. There are several aspects of note though: i) Smooth chromosome profiles presented in this latter study, potentially indicated use of quite aggressive smoothing algorithms. ii) Being a multi-center study with some centralized analysis, the authors did not acknowledge the potential of poor sample handling processes in different clinics to artefactually impact on subsequent WGA and chromosome profile generation. Many

problems can "hide" under excessive use of smoothing mathematics and the 2022 PGDIS Position Statement cautioned about approaches that "under-read and over-smoothed" because of the potential to create artefacts.

The studies (Yang et al 2021, Barad et al 2022) reporting deliberate transfers of "abnormal" embryos, misled the debate by including the transfer of mosaic embryos as "abnormal embryo" transfers. Scrutiny of the results in Yang study showed only 32 transfers with 9 recognized pregnancies (28%, 11.8% IR), 4 clinical miscarriages (44%), 5 live births (including an abnormal birth with the predicted PGT-A segmental duplication, 3 euploid births from putative mosaic embryo transfers and 1 from an unusual chromosome structure). The single euploid miscarriage was from a putative mosaic trisomy embryo suggested to have resolved although no further evidence was presented to support this assumption. Barad et al (2022), added to the former data with only 1 more birth another 6 miscarriages and another 10 failed transfers. Madjunkova et al 2025 found that of 14 aneuploid embryos with implantation, 9 resulted in clinical miscarriages and 5 were biochemical miscarriages. Most (80%) of aneuploid embryos resulted in failed implantation initiation.

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4. Statistical Analysis in PGT-A studies

Statement Key points

- Statistics is often being misused to mis represent PGT-A study results
- especially the idea of different and not different
- While charges of commercial self-interest are levelled at PGT-A use, it is quite evident that futile transfers financially benefit clinics

Reports attempting to discredit PGT-A benefits often misuse statistical interpretations to undermine any observed benefits. Statistical misuse can be accidental or covert and in the latter case may be used deceptively

4.1 The mis interpretation of "different" and "significantly different".
Authors often appear to suggest data with obvious differences are "not different" because they lacked statistical significance (<0.05). Such assertions are simplistic and potentially misleading.

4.2 Clinically Significant
Clinical significance refers to the balance point where a process is deemed relevant to a specific patient's treatment and is important in the decision-making discussion between clinician and patient. A good clinician uses all available information in assessing the benefits of any approach for the individual

patient but not necessarily for all patients in general- unless such an approach is universally beneficial. Munne and Griffin (2024) discuss the importance of patient priorities in arriving at final patient treatment plans

4.3 The meaning and implications of an "average" result

Average, by definition, lies somewhere between the best and the worst results and is a convenience in describing an outcome to a patient for counselling purposes. To be considered "informed", patients need to have some understanding of both potential positives and negatives of any treatments being proposed. PGT-A, on average, improves the likely success of the specific transfer- this is demonstrated in essentially every study. Some patients will achieve success with the first embryo transfer without any other interventions, because the clinic was successful in avoiding accidental selection of an aneuploid embryo. However, for nearly half of all patients, the first transfer will not achieve success with aneuploid embryo selection, leading to a futile transfer being a major cause for failure. Multiple-embryo transfer approaches to maintain pregnancy rates, essentially cover an inability to otherwise directly choose a euploid embryo but increase the risks of a multiple gestation pregnancy with its associated clinical complications for both pregnancy and mother (Wang et al 2025). PGT-A can reduce these latter risks by avoiding the necessity of a multiple embryo transfer approach while maintaining the likelihood of pregnancy.

4.4 Patients as individuals, as a group and their average.

When describing IVF outcomes, authors often forget the result of a transfer is for an individual patient, not a group, with a binary outcome. This can impact on how the clinician manages the specific patient if they get caught up in the debate about PGT-A. PGT-A cannot improve the outcomes for a stimulation cycle but does improve outcomes on a per-transfer-basis. Considerations about using PGT-A, become what is most important for that patient- an area where the informed clinician is the one best able to make a valued contribution. For the patient who is not concerned about the likelihood of success for any transfer, PGT-A may not be appropriate. However, for the patient who wishes to maximize the outcomes and reduce risks as much as possible, PGT-A can be considered. These are decisions that implicitly involve a properly informed patient and clinician.

4.5 Implantation Rate, Per transfer live birth rate and cumulative live birth rate
Implantation rate is the number of implantation sacs per embryo transferred. Nearly every study shows higher implantation rates (IR) when PGT-A is employed. This can only occur if a better embryo is identified by the PGT-A process.

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Several studies have shown that embryo choice, based on morphology, is typically 70-80% effective for euploid selection (Forman et al, 2013; Tiegs et al, 2021; Wang et al, 2022) for women up to ~37yo. This is different to and often incorrectly confused with average aneuploidy rates when modeling transfer outcomes (Paulson, 2019). After 37 years old, cohorts may increasingly include only aneuploid embryos raising the probability of aneuploid embryo selection. It has been observed however, that even younger women have aneuploid embryos selected for transfer (Forman et al, 2013; Tiegs et al, 2021; Wang et al, 2021; Katz-Jaffe et al, 2024) and some may also have aneuploid-only cohorts with only a minority having euploid-only cohorts.
If no improvement in IR is seen after PGT-A, in any age-group woman, then logically, the original IVF embryo selection was either100% euploid or the biopsy procedure reduced embryo potential.

4.6 Per transfer Live birth rate (LBR)

LBR is the number of patients who achieve a live birth after a transfer without consideration for the number of embryos used in any single transfer event. This will suit clinics using unselected, multiple embryo transfers.

4.7 Cumulative live birth rate (CLBR)

CLBR is the percentage of stimulation cycles having at least one live birth irrespective of the number of embryos transferred, number of failed transfers, total time taken and number of miscarriages. Early claims that PGT-A could improve an IVF cycle were based on a transfer cycle but caused misunderstandings with observed improvements more correctly related to first transfer outcomes. These early misunderstandings underly much of the current debate regarding the effectiveness of PGT-A.

A decrease in CLBR after biopsy would indicate a possible problem somewhere within the procedure, whereas equivalence between IVF and PGT-A in CLBR, suggests the biopsy process does not harm and a per-embryo live-birth-rate is an appropriate measure of effectiveness of PGT-A. Using CLBR comparisons though confuses discussion of the benefits of PGT-A embryo transfer prioritization. In all published studies comparing IVF to PGT-A/IVF, cumulative number of transfers to live birth is reduced with PGT-A (Munne and Griffin, 2024; Katz-Jaffe et al, 2024; Yang et al, 2021, Yan et al 2021). Suggesting that the equivalence of CLBR between PGT-A and IVF proves PGT-A is ineffective is misleading. Not counting transfer numbers and not accepting a per-embryo LB outcome shows benefit of PGT-A, ignores the biology of aneuploid embryo transfer failure. Suggesting that PGT-A is only a money grab by commercial operators is misleading. Ironically, it can be argued that clinics have a financial interest in unselected embryo transfers, since every transfer failure (fresh or

frozen) will typically result in a further frozen transfer at further expense to the patient (or financing body) since more unselected embryo transfers are required to achieve equivalence to PGT-A selected embryos. It raises the unfortunate situation that commercial interests in a clinic might sway decisions about embryo selection approaches.

4.8 Analysis of results- per protocol (PP) and Intention to treat (ITT)

Many criticisms of PGT-A studies have centered around either the study design and/or analysis of results with many critics ignoring the non-selection studies reported by several groups and overlooking the relationship between aneuploid embryos and futile transfers. Katz-Jaffe et al (2024) recently showed that, even with young patients and no bias in group formation, selection at the very start of IVF recruitment still showed significant PGT-A benefits, seriously undermining unsupported criticisms of bias in later stage selection designs.
Further debate about PGT-A efficacy then focusses on the final analysis with differences of opinion regarding the most appropriate approach: Per Protocol (PP) and Intention to Treat (ITT). Some groups promote the use of ITT analyses since it reflects real-world, typical clinic activity with its myriad variables. Other groups prefer PP analysis as logical since embryo selection is based on the applied selection process of PGT-A. Both approaches have value but differ in final evaluation. PP approaches tend to confirm the value of aneuploid embryo exclusion with higher transfer outcomes. ITT can maximize stimulation cycle outcomes but can also identify underlying problems in application of PGT-A but unfortunately fails to isolate the source of any problem.

5 Utility for Different Patient groups

Statement Key Points

- All classes of patients can benefit from PGT-A by reducing futile transfers.
- Better clinical management of RIF and RCM patients can be realized by removing aneuploidy as an underlying cause of failure

Why the debate about effectiveness of PGT-A in different patient groups?
The biological consequences of aneuploid embryo transfers are simple and relevant to all age groups: transfer failure and/or miscarriage. So, it is pertinent to consider the 5 main patient groups:

5.1Younger patients

If embryologists could always identify a euploid embryo, then PGT-A would have no practical application. However, typically, 20-30% of these women have an aneuploid embryo selected for initial transfer. Over a decade ago, Forman et al.

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(2013) demonstrated that identification of aneuploid embryos avoided futile transfers and improved the selected embryo transfer outcome(s)- again, recently demonstrated by Katz-Jaffe et al (2024). Nearly every other study suggesting no positive benefit after PGT-A in the younger patient age group, did show a small gain in transfer outcome but was severely underpowered to achieve mathematical significance.

There are intrinsic problems in seeing what should otherwise be logical and obvious. High performing clinics need very large group sizes to identify benefit significance after PGT-A. The benefits of PGT-A are there but are smaller when the initial embryo selection process is effective (see Supplementary Discussion). That is not to suggest that gains are not meaningful to patients or at least to some patients. Katz-Jaffe recently reported that even in a good clinic, benefits of PGT-A (increased IR and reduced miscarriage rate) can be observed (Katz-Jaffe et al 2024).

Average performing clinics have the potential to improve their euploid selection rates using PGT-A. It can further be suggested that, if any improvements are not observed after PGT-A, then the clinic is introducing negative impact factors such as poor embryology and/or poor biopsy technique. It is sub-performance by a clinic that reduces patient opportunities for improved outcomes by PGT-A, not the process itself.

Knowing that a transferred embryo is euploid also simplifies the identification and subsequent clinical management and decision making of genuine recurrent implantation failure (RIF) patients since PGT-A removes one major variable.

5.2 Older patients

In older patients, first transfer euploid-selection rates drop rapidly with increasing age since the number of embryos typically available decreases and the percentage of aneuploidy increases. Simple analysis (see Supplementary Discussion) shows why it was relatively easy for many studies to demonstrate better transfer outcomes with relatively small patient numbers required to reach mathematical significance when comparing older IVF-only patients to PGT-A patients.

5.3 Poor Prognosis Patients

Patients that are considered poor prognosis, typically fall into one of two groups- only a single embryo is available for transfer or all embryos are considered of very poor quality. Patients with only a single embryo available, can potentially benefit by avoiding futile transfers. This was succinctly demonstrated in a recent retrospective study by Kahraman et al (2022). In the PGT-A elective group, only ~200 out of 1100 patients were identified as having a euploid embryo, with aneuploids not transferred since likelihood of success is extremely small or zero, not wanted by the patient and clinically unacceptable. The patients that

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elected for an untested blastocyst transfer displayed implantation rates - suggestive of high aneuploid rates amongst this group. Some critical comments were misguided in suggesting lost embryo potential since the study only reported on euploid transfers or untested transfers with IR for the PGT-A group comparable to many PGT-A reports. Patients that have only very poor embryos available may or may not benefit from PGT-A. Poorer quality blastocysts have typically been observed to have higher aneuploid levels and patients could benefit from aneuploid deprioritization. However, the potential for greater embryo harm by biopsy on poor quality embryos, must be considered, although no studies looking at the impact on implantation potential by biopsy on poor embryos, have been reported. Such a study would in any case, be hampered by the generally observed poor implantation potential of non-biopsied grade 3 embryos in normal IVF. The final decision to perform PGT-A is ultimately up to the individual patient, after balanced counseling, with their own requirements and expectations being important.

5.4 Recurrent Miscarriage Patients

Recurrent miscarriage (RM) patients can also potentially benefit from PGT-A testing by reducing the possibility that aneuploidy was responsible for prior miscarriage events. This is logical, since over 70% of clinical miscarriages from natural pregnancies have aneuploidy as an underlying cause. Current definitions of recurrent miscarriage are weak and statistically, the probability of two consecutive aneuploid pregnancies is not trivial. PGT-A has the potential for identifying the existence of other causes of miscarriage in this group and assist the clinician in initiating other studies in an expedient manner.

5.5 Recurrent Implantation Failure Patients

Finally, for recurrent implantation failure (RIF) patients, PGT-A reduces futile transfers. Aneuploid embryos have significantly reduced pregnancy initiation potential and very high biochemical and clinical miscarriage rates- both of which can result in a false label of RIF. It was, in fact, RIF patients that demonstrated the utility of PGT-A in the first comprehensive chromosome screening (CCS) report over 15 years ago (Wells et al, 2008). It was seen clearly that multiple factors combined to give high transfer outcomes- blastocyst biopsy, CCS and frozen embryo transfers, all of which are now part of the current approach to PGT-A. Given the vagaries of current RIF definition and the approaches used to treat such, a simplified approach to classifying RIF, as suggested by Eric Forman, would be failure after a known number of euploid embryo transfers rather than the current blind approach of random embryo assignments. PGT-A would also identify "all-aneuploid" cohorts and reduce subsequent patient costs of futile transfers, reduce angst as well as remove the inappropriate label of RIF. Simplification of RIF identification will permit clinicians

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to proceed in a much more evidenced based approach for this group of patients and genuinely assist them in their quest for a baby rather than the current approach of exposing them to blind luck with undetected futile transfers.

6. Impact, Cost Effectiveness and financial considerations

Statement Key Points

- Cost effectiveness of PGT-A is balanced against transfer costs and PGT-A testing costs
- Patient hidden costs are often ignored

Failed transfers are a reality of IVF but it is recognized that aneuploid embryo transfers have much higher transfer failure rates than euploid embryos. PGT-A offers the best opportunity for identifying most of these futile-transfer embryos. An embryo transfer, fresh or frozen, has a cost- a cost that varies widely around the world. In the US, where most aspects of IVF are expensive, Murugappan et al (2015) reported that embryo transfers cost $3500-$12,500 with an average of $6,395. PGT-A costs varied according to individual clinics.

Is the cost of analyzing the embryo(s) effective? For individual, young patients where euploids are selected 70-80% of the time for the first transfer, testing would offer no obvious benefit to the individual patient with any testing just adding cost with no gain. However, 20-30% of these younger women have an aneuploid embryo selected for transfer (Forman et al, 2013; Katz-Jaffe et al, 2024) and so there is a subgroup, even in young patients, that could benefit, transfer success wise, from PGT-A. Whereas the average euploid selection rate for the young group may be high, the cost of PGT-A may be acceptable to some patients, considering a potential 20-30% gain in positive outcome probability.

Compared to the US, other countries may have significantly lower transfer and PGT-A costs and so the breakeven cost/benefit point will vary. Clinics also approach PGT-A services differently: as a cohort analysis, as an individual per embryo cost or a mixture of the two. A break-even point for PGT-A in a cost/benefit analysis, also varies according to age. For younger patients, this would be when PGT-A of a single embryo is approximately 16% of the cost of a single transfer. Whereas with advancing age, the cost effectiveness of PGT-A increases and may even be viable when PGT-A per embryo is the same cost as a single transfer . (see Supplementary Discussion for more details)

In countries where national health systems cover the IVF process, consecutive transfer approaches may be thought a simpler, more cost effective approach since the government coffers are subject to actual costs without commercial margins. Transfer numbers however, would be much higher for reasons described above. Such countries, though, would also be expected to have low

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PGT-A costs since it similarly is not subject to commercial margins. In such situations PGT-A might still be considered for its cost benefit.
The undiscussed reality in many, if not most countries, is that IVF is a commercial process- either for individual clinicians or for clinics. While some IVF groups might proffer ideologies rejecting changes in routine practice, it could be commercial realities that lead them to reject changes that could affect a clinic's bottom line where failed transfers might offer as much revenue generating potential as the initial stimulation costs.
The sequential transfer approach also does not account for individual patient costs such as time, patient inconveniences such as miscarriages and time to recovery as well as patient emotional costs. Clinic resources are also unnecessarily stretched by failures of potentially avoidable futile transfers.

7. Recent reports that further stirred the debate about PGT-A

Statement Key Points

- STAR trial failed to understand the impact individual clinics have on final results
- SART-CORS data
    - Analysis of old data is flawed
    - Recent results suggest positive outcomes after PGT-A
- UK registry data appears flawed with poor results evident
- Cumulative live birth data is misused in interpreting comparisons of IVF and IVF/PGT-A
    - The value of embryo screening is often misunderstood- it is a per transfer benefit tool
    - CLB data can enable clinics to assess their own operation

The STAR trial report (Munne et al, 2019), is often cited by groups suggesting PGT-A is not useful. There were, however, many significant flaws in this trial. The initial design, with a proposed IVF baseline of 50%, was powered to show an increased implantation and pregnancy potential of 10 percentiles. The final 60% PGT-A result was achieved but the IVF baseline was incorrect and reached nearly 60% with the small overall improvement after PGT-A insufficient to reach significance with both groups being too small. By itself, this undermined the original intentions of the trial. How did the trial designers go so wrong in baseline parameters? They clearly underestimated baseline participating clinic performances and the impact that poorer clinics may have on final averaged comparisons. The close outcomes of IVF and PGT-A embryo selections can only be a result of high IVF euploid selections and/or poor PGT-A practices losing any euploid selection benefits. Multi-center studies will always be hindered by the relative performances and participation levels of the individual clinics and add

unaccounted variables in any RCT design. Unfortunately, in this latter study, many individual clinics did not participate at a level permitting separate analyses to be meaningful. Wang et al showed that individual groups do add variability to any cohort analysis (Wang et al 2022).
The STAR trial also reduced transfer of putative mosaic embryos, losing potential positive transfer outcomes in an ITT analysis with some PGT-A patients not having a transfer and diluting positive PGT-A outcomes by an inflated denominator in the calculations.

Some recent analyses of the large IVF data set held by SART suggested PGT-A led to reduced outcomes (Kucherov et al, 2023, Meija et al 2022). Both author groups used essentially the same data that was, by then, 8 years old and representative of mixed approaches in the early adoption of CCS, rather than more relevant recent data which would be more closely aligned with current practices. Harris et al (2025) attempted to address the previous limitations of SART-CORS data analysis by restricting comparisons to 2016-2019 and NGS testing. Cumulative live birth was the primary outcome with secondary outcomes of clinical pregnancy, miscarriage, multiple birth and perinatal mortality. Analysis was on an ITT basis. They observed that CLB was lower in the PGT-A group but after stratification by age, the difference was reduced for individuals <35 years. Paradoxically, in the older age groups (35-37 and 38-40 years) the CLBR was higher for PGT-A groups along with pregnancy rates, likelihood of a live birth and miscarriage rates were substantially lower. Subgroup analysis of patients with only frozen transfers showed PGT-A had higher clinical pregnancy outcomes in all age groups- raising the question of what was being performed in the total group? NGS analysis of embryos with fresh transfer can only occur through early-stage biopsy and/or delayed transfers- both of which are known to reduce pregnancy outcomes and are not part of modern PGT-A.

In a similar analysis of the UK data registry, Roberts et al (2022) also suggested that PGT-A might be associated with a modest reduction in live birth events (LBE). The authors concluded, however, that a more relevant analysis required information that was not available at that point. Closer inspection of their data raises several issues. The data period while more current than earlier analyses of SART-CORS, was still dated being 2016-2018. The actual results presented in supplementary tables (table S1 and table S2) raise concerns where it was disclosed that the PGT-A results were substandard to most PGT-A comparisons available in the literature. Live birth rate per transfer cycle for the younger, better prognosis patients

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(33.9%), were well below values considered poor in other countries. In the main text, indications about biopsy and transfer approaches, hint at cleavage stage transfers and substantial fresh transfers with most results (>91%) having an unknown stage for biopsy and transfer. This is totally contra to all advice from 2014 onwards, where cleavage stage biopsy was shown not to reflect embryo potential. It can be considered that the analysis of such flawed data can misrepresent modern PGT-A practices. In either case, it very tidily demonstrates that not all groups are yet at the stage where they should be offering PGT-A services. Roberts et al concede that the dataset is inappropriate for analysis of many covariates with cumulative live births confounding live births in the first transfer- an important consideration in looking at the benefits of PGT-A. Similarly, the inability to consider the impact of multiple embryo transfers was not available. The final description of what an effective comparison might include, excludes many of the conclusions founded on the available data set. Additionally, it is even suggested that more recent data might reflect more recent iterations of PGT-A practices. Overall, the authors concede that biases and limitations of Registry data may affect the ability to draw useful conclusions- especially where benefits in the younger groups are likely to be smaller than 5% absolute uplift in LBE.

Munne and Griffin (2024) also utilized the SART database source but focused instead on recent results from the last couple of years. Although limited to first transfers, they revealed that PGT-A did result in improved transfer outcomes which reflected in PGT-A now being preferentially requested and performed in most US IVF cycles, becoming by default, a de facto best standard of care. These latter authors further suggested how PGT-A might also result in reduced embryo losses by rescuing embryos that might have traditionally been discarded due to apparent abnormal fertilization observations.

Yan et al (2021) presented a CLBR trial comparing IVF, with the best 3 embryos available for transfer, to PGT-A with the best 3 embryos available for biopsy and euploids available for transfer. This trial is often presented as showing PGT-A is of no benefit. Scott et al (2022) presented a critical appraisal of the study with key elements being the disparity of transfers available for the two groups as well as failure to acknowledge the clinical utility of putative mosaic embryos. Scott's conclusion was succinct in demonstrating not only non-inferiority of PGT-A compared to IVF but actual equivalence in transfer outcomes and direct evidence of non-harm of biopsy- relegating Yan's study

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ultimately to a study confirming the overall safety of trophectoderm biopsy. The study itself also has a quasi-cumulative-livebirth-rate approach which is not appropriate for comparison between IVF and PGT-A. What Scott did not comment on, however, were details hidden in the appendices. For the first two transfers, PGT-A showed significantly higher positive transfer outcomes than IVF (sup table 3 and sup table 4). In addition, the cumulative live births after 1 year were numerically higher in the PGT-A group (sup table 9)- a result not presented in the final ITT discussion. The IVF group also needed more than 100 extra transfers to reach their non-inferior status.

A recent report by Viville and Aboulghar (2025), summarized many of the misconceptions surrounding PGT-A and then raised two key, very important points: 'What's it for?" and "PGT-A: what's wrong?". The precise purpose of PGT-A is to reduce transfer failure by avoiding futile aneuploid transfers which is exactly what every study comparing morphology selection to PGT-A selection demonstrates. Continuing controversy centers around how effective it might be within certain patient groups and not the improved embryo selection outcomes. Improved cumulative live birth rate was not an expectation of PGT-A but surprisingly may be an indirect benefit of current approaches. When considering what is wrong with PGT-A, the same authors cite references where cumulative rates are equal between the two selection approaches, suggesting biopsy does not cause harm, or in SART data and the UK register, CLB are reduced, suggesting PGT-A does cause harm. Weaknesses in the latter studies have been discussed above. Introducing historical perspectives around mosaic embryos and their non transfer/transfer are dated and have been the topic of several Statements and many papers over the last decade. Embryo "self-correction" or "*lineage-specific depletion of aneuploid cells" or "clonal depletion,"* is discussed in a more balanced manner but not acknowledged as a mechanism for maintaining euploidy (and possibly aneuploidy). Discussions around biopsy representation failed to critically appreciate the impact of probable cell clustering in an embryo and the variant cell numbers required to even identify clinically relevant mosaicism since only very early mosaic events, affecting a large portion of the embryo were likely to be identified.

While the transfer of mosaic embryos was initially reported to have few negative outcomes, recent discussions have been a bit more open with significant adverse events now being openly described (Viotti et al 2023). As with all methods, poor performances can negatively impact on results and subsequent interpretations. This is an operator variable, not a PGT-A variable. This situation is indirectly acknowledged by major society statements regarding the use of PGT-A as not being appropriate for "routine use". Societies must balance their opinion across a variety of clinics and differing levels of expertise within those clinics. All statements concede, however, that in some clinics positive benefits are observed but in some patient groups these benefits are not as

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pronounced. The negative conclusions proffered by Viville and Aboulghar (2025) are unsupported by many of their own discussion points or aspects.

8. Counseling

Statement Key Points

- Open discussion is important for effective counseling
- Mosaic embryo transfers are not without negative outcomes and counseling might be adjusted accordingly
- PGT-A can be an important addition for some patients but should be raised with all patients
- Errors are a possibility and must be discussed
- Clinics and clinicians have absolute rights regarding their own risk management strategies

Effective counselling must not only inform potential users of the opportunities available with PGT-A but also of the limitations of current technologies. As greater use is made of the different technologies of PGT-A, groups around the world are seeing benefit in reduced numbers of transfers needed to achieve pregnancy. However, rarer occurrences, such as mosaicism and aneuploid rescue are also being revealed. Discussions surrounding euploid embryo transfers and aneuploid embryo transfers tend to be simpler, whereas the transfer of confirmed mosaic embryos has a deeper level of complexity- both in the biology associated with it as well as patient expectations and concerns.. Initial claims of no adverse outcomes after the transfer of mosaic embryos were due to restricted data-sets, likely a consequence of exaggerated numbers of mosaic embryos as well as limited outcome data (possibly restricted by potential litigation). With larger outcome series, more negative outcomes are being openly presented. With NIPS now being a routine prenatal test for over a decade, genuine fetal mosaicism is also being observed. The simple statistic of Negative predictive Value (NPV) for NIPS, typically described by service suppliers as ~99.96%, suggests a very low placental/fetal discordance. However, discordance or mosaicism is a feature of some pregnancies. Positive Predictive Values (PPV) for NIPS is subject to other assay limitations but placental/fetal discordance is not zero. Since the PGT-A process samples only extra embryonic

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cells destined for the placenta, the potential for ICM/trophectoderm discordance is there but adverse outcomes are low.

What of the possible transfer of embryos considered aneuploid? The results of transfer of genuine aneuploid embryos showed high transfer failure rates, high miscarriage rates and occasional abnormal live births (Yang et al, et al, 2022). Similarly, the very small but limited follow up after mosaic embryo transfers reported by Capalbo et al. (2021) may misguide discussions between clinicians, counsellors and patients. More informative though are the non-selection studies where abnormality was identified post transfer (Scott et al, 2012; Tiegs et al, 2021; Wang et al, 2021, Madjunkova et al, 2025). In these studies, the potential for abnormal embryos to initiate a pregnancy was clearly identified as was their typical sub clinical and clinical miscarriages with very few putative abnormal embryos resulting in a normal live birth. The earlier study from Scott et al. (2012) suggested that potentially up to 4% of abnormal embryos may undergo mitotic normalization (a number seen to be similar in Wang et al, 2021) whereas a later study from the same group reported 100% failure (implantation failures and miscarriages) for all transferred aneuploid embryos. The birth of chromosomally abnormal babies as well as the low presence of UPD individuals in the general population, are direct evidence that all chromosomally abnormal zygotes fail, but the actual number of successes appear to be very small. The question does arise though, as to whether chromosomally abnormal embryos could be considered for transfer? For some patients this is not a consideration whereas for others, it might be their last hope. Counselling in such cases needs to be both well informed and non-directive so the patient benefits most from whatever decision follows.

What of post implantation testing? All major IVF societies recommend prenatal testing. For reasons discussed previously, normalcy of an embryo and subsequent fetus cannot be guaranteed by PGT-A. Fetal/placental mosaicism and natural pregnancies are both genuine features of the real world and need to be considered by all parties involved when discussing pregnancy testing. It is apparent though that PGT-A can reduce the likelihood of initiating a pregnancy with a chromosomally abnormal embryo and similarly, appropriate well-informed considerations can be made after the transfer of an apparent mosaic embryo.

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It should also be noted that some false negative PGT-A results could be the consequence of a natural pregnancy, occurring during the PGT/IVF treatment. While well-known, this topic remains under-discussed. Such pregnancies remain often undiscovered and undisclosed.

All testing procedures have a potential for error. This may include sample mix-ups in the clinic or laboratory, analytical errors, interpretation errors, result transcription errors or communication errors. Every clinic and laboratory have their own procedures to minimize the risk of such an occurrence, but it cannot be zero. An error can result in an inappropriate embryo being transferred or a suitable embryo being misclassified and rejected for transfer. Fortunately, in a well operating practice, such errors are few. Counseling must include a balanced discussion of each of these areas in a manner that does not alarm the patient nor avoid the possibility. Natural pregnancies also cannot be excluded.

With the focus on maximizing the number of embryos available for transfer, some PGT-A approaches bring the possibility of utilizing what would have been considered unsuitable embryos (Handyside et al 2024). Some of these embryos would already have been considered in routine (no PGT-A) IVF since transfer, freezing and biopsy are all based on some minimal requirement of advanced embryo development. This new approach offers patients the possibility of maximizing outcomes per retrieval. With this opportunity though, comes some caveats. The level of counselling and understanding required is increased compared to otherwise simple euploid selections. The possibility of adverse events does increase when known aneuploid embryos are transferred and counselling must take this into account. The extended counselling must include all aspects relevant to the patient, the clinic and the treating clinician. In some countries this may raise litigation risks to an unacceptable point and autonomy for such decision making cannot be removed from either the clinic or the treating clinician.

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9. Conclusions

The biological basis of why PGT-A assisted embryo selection,(viz aneuploid identification), may be beneficial, is not logically challengeable.

Debates about the positive value of PGT-A in embryo selection, however, have seen negative responses that are often developed around reports involving poor study design, poorly executed technique and/or covert biases in statistical presentations. PGT-A is for a single purpose: identify aneuploid embryos and any lengthy discussion about misconceptions surrounding putative mosaic embryos and their transfer are either historical or misleading. Importantly, clinics are responsible for their own risk management and transfer strategies and need appropriate information based on current knowledge.

9.1 Biopsy as representative of the embryo

1. The biopsy will identify the embryo as an average and is likely to reflect the embryo as a whole. While somatic mosaicism may exist in some limited situations, it should not confound most interpretations.
2. A vast majority of embryos are simple euploid or aneuploid although identifiable mosaicism might occur occasionally. Much of the reported mosaicism however, appears to be artifact associated with sample handling and analysis.
3. Very early mitotic errors (cleavage stage) are likely to be identifiable via a trophectoderm biopsy whereas later changes less so but are also less likely to confuse analysis interpretation. Upon survival, early mitotic errors would be present in a large fraction of the embryo whereas later errors, less likely so.

9.2 Accuracy of analysis

Several technical issues may impact on the analytical accuracy of a biopsy analysis. It is important to avoid DNA degradation since it can cause bias in the subsequent amplification and skew results. All PGT-A interpretations should include review of analytical quality measures to confirm reliability of the analysis and avoid incorrect identification of aneuploidy or mosaicism. The testing platforms utilized are standard and share well validated performances with prenatal testing. Final analysis and interpretations may vary according to each testing group and might need independent validation.

9.3 PGT-A benefits

Until other approaches for identification of aneuploid embryos exist, PGT-A can be of benefit to all categories of patients. Transfer of an aneuploid embryo is

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typically futile with few benefits and potentially significant negative clinical, emotional and economic consequences.

9.3.1 For young women

Until embryology can identify aneuploid embryos with near 100% accuracy, younger women may benefit from PGT-A. The final decision to use PGT-A is a personal preference that includes understanding the probability of potential gains.

9.3.2 For older women

Patients of higher ages have a higher probability of benefiting from using PGT-A. As with younger women, the final decision is a personal preference

9.3.3 Other categories

All category of patients can benefit from a reduction in any futile transfers associated with aneuploid embryos

9.4 Patient counseling

Since all groups of patients can potentially benefit from PGT-A, all patients should be offered the opportunity of PGT-A assisted embryo selection. This necessitates clinicians being informed, unbiased and non-directive in their consultations and appropriate specialist counseling is also available.

9.5 PGT-A in current practices

Until other effective approaches to identify aneuploid embryos exist, PGT-A offers the best way to reduce futile transfers and improve outcomes for all classes of patients and so should be discussed as an option with every patient seeking IVF for infertility treatment. Discussion as to which patients are best served by PGT-A should be made by informed clinicians after consideration of the individual patient's wants, needs and desires.

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Declaration of Interest

DL, RJS, DSC, ZFC, YG, KX, LS, JLS, GH, SK, LG, JRV, DW, report no direct conflict of interest regarding PGT-A services.

SR, AK, TG, CR supply commercial PGT-A services

AHH, SM provide or hold commercial interest in embryo testing

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Legend to figure

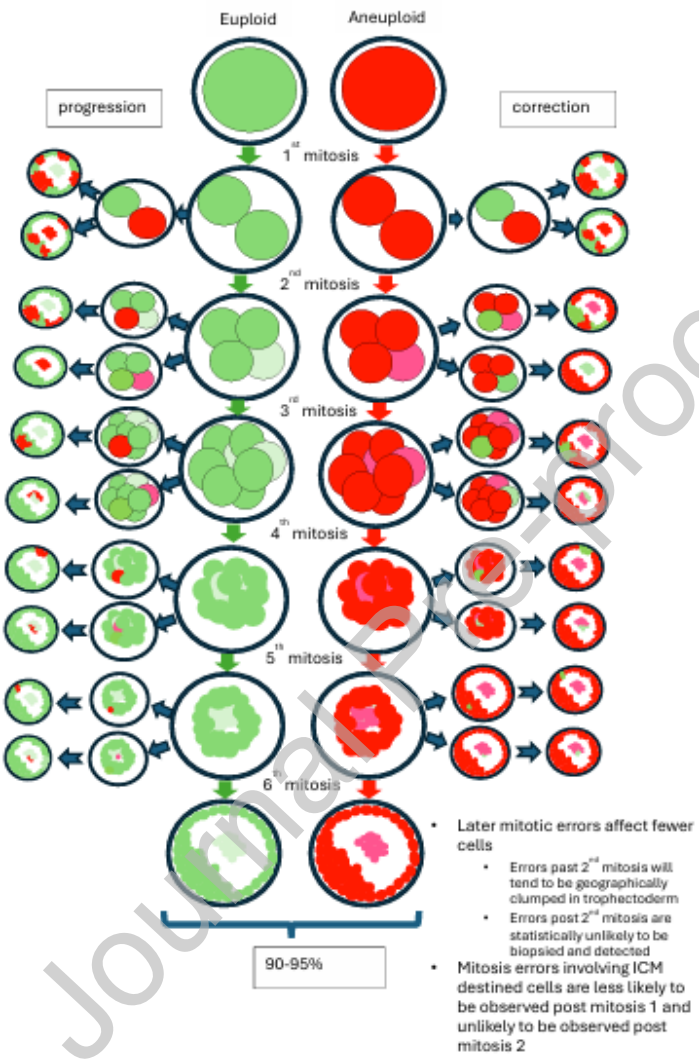

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Figure 1 Mitosis errors in early preimplantation embryos

Biography

Don Leigh is a past President of PGDIS. He has a PhD from University of NSW (1986) and has been performing PGT since 1998. Currently he is in southern

China and is involved in both training for PGT and development of fundamental methods to improve laboratory outcomes.

Key message

Improved IVF embryo selection in modern PGT-A, is based on sound biological principles but this is debated and genuine objective discussion has become distorted. This presentation clarifies the underlying tenets of positive embryo selection and assists clinicians, counselors and laboratory staff in improving patient embryo transfer outcomes.

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