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Affiliated Society Guideline

Report of the PGDIS Task Group on the status of PGT-A

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Abstract

The clinical utility and validity of preimplantation genetic testing for aneuploidies (PGT-A) in IVF practice is often questioned. Some major societies (Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology 2024) 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 (PGDIS) Task Group 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 the proper implementation of PGT-A results in increased benefits for IVF embryo selection. It is envisioned that 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.

Key words

Aneuploidy
Misconceptions of PGT-A
Preimplantation genetic testing for aneuploidies (PGT-A)
Somatic mosaicism

Introduction

Success in pregnancy, whether natural or through 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 and colleagues similarly reported that 80% of week 7–10 miscarriages after IVF were aneuploid (Segawa et al., 2017).
Data on very early pregnancy losses are lacking for natural pregnancies so aneuploid-related subclinical miscarriage rates are probably going unrecognized. Madjunkova and collaborators, however, reported that 36% of aneuploid IVF embryo implantations failed at the biochemical stage, with the remainder being lost as clinical miscarriages (Madjunkova et al., 2025). Tiegs and colleagues reported that 40% of aneuploid embryos were able initiate a pregnancy but they also experienced a 42% loss of implantations at the very early stage, with the remainder being clinical losses (Tiegs et al., 2021). Similarly, Wang and co-workers reported a 41% loss of aneuploid implantations at the subclinical phase (Wang et al., 2022). These results suggest that very early failures, while substantial, are not inevitable (Mashiko et al., 2020).
In non-selection embryo transfer studies, arguably the most suitable and strongest preimplantation genetic testing for aneuploidies (PGT-A) study design, Tiegs and colleagues observed that aneuploid embryos, while capable of initiating a pregnancy, typically failed by week 10, whereas Wang and co-workers suggested that a small minority could continue (Tiegs et al., 2021; Wang et al., 2022). Non-invasive prenatal blood screening has also identified various autosomal trisomies into late first-trimester and early second-trimester pregnancies (Mossfield et al., 2022; Scott et al., 2018), 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 13) and Edwards (trisomy 18) 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., 2022). Failure at any stage of pregnancy is, however, 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, 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 is, however, suggested to affect the accuracy of PGT-A. These considerations are the main focus of this current Position Statement.

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 embryo potential.
- •

  Mosaicism is real but is being over-reported.
- •

  PGT-A analysis has evolved into more comprehensive chromosome screening (CCS).

  - ○

    Recent approaches combine copy-number analysis with genetic polymorphism analysis.
- •

> For accurate chromosome profile assembly, is essential to adhere strictly to quality practices.

Embryo biopsy

A genuine sample of embryo DNA is needed to accurately analyse chromosome profiles. The original approaches of polar body biopsy and blastomere biopsy have been substantially superseded by trophectoderm biopsy and are not further discussed in this Position Statement.

Even though blastocyst biopsy involves removing multiple cells, the embryo at this stage appears to tolerate the loss of more than one cell without significant detriment (Scott et al., 2013). A multiple cell biopsy also improves the uniformity of DNA amplification.

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 to be 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 the implantation potential by nearly 40% (Scott et al., 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 in terms of sustained implantation rates. In another report from the same group using single-embryo transfers, even higher positive pregnancy rates (79.2%) and live birth rates (LBR; 61.7%) were reported when biopsy avoided excessive cell removal (Neal et al., 2017). 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 a 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 and increasing the potential for biases to be introduced during sample amplification.

In conclusion, blastocyst biopsy appears not to be harmful when performed properly, but a variability in performance between clinics exists. Individual teams need to assess their own performance both in IVF and in PGT-A.

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?

Although such questioning is valid, two points should be considered. First, when an embryo is assigned as euploid or aneuploid (typically over 90–95% of all tested embryos), >98% of whole embryo analyses tend to confirm this result. Second, genuine mosaic embryos do exist and need to be considered. Although true mosaic embryos probably make up fewer than 5% of all blastocyst biopsies (Katz-Jaffe et al., 2024; Saleem, 2024), higher total mosaic call rates may actually reflect artefacts 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 but were instead aneuploid or euploid. With many groups suggesting that 8–12% of embryos have intermediate copy-number (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 (Figure 1) rather than 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.

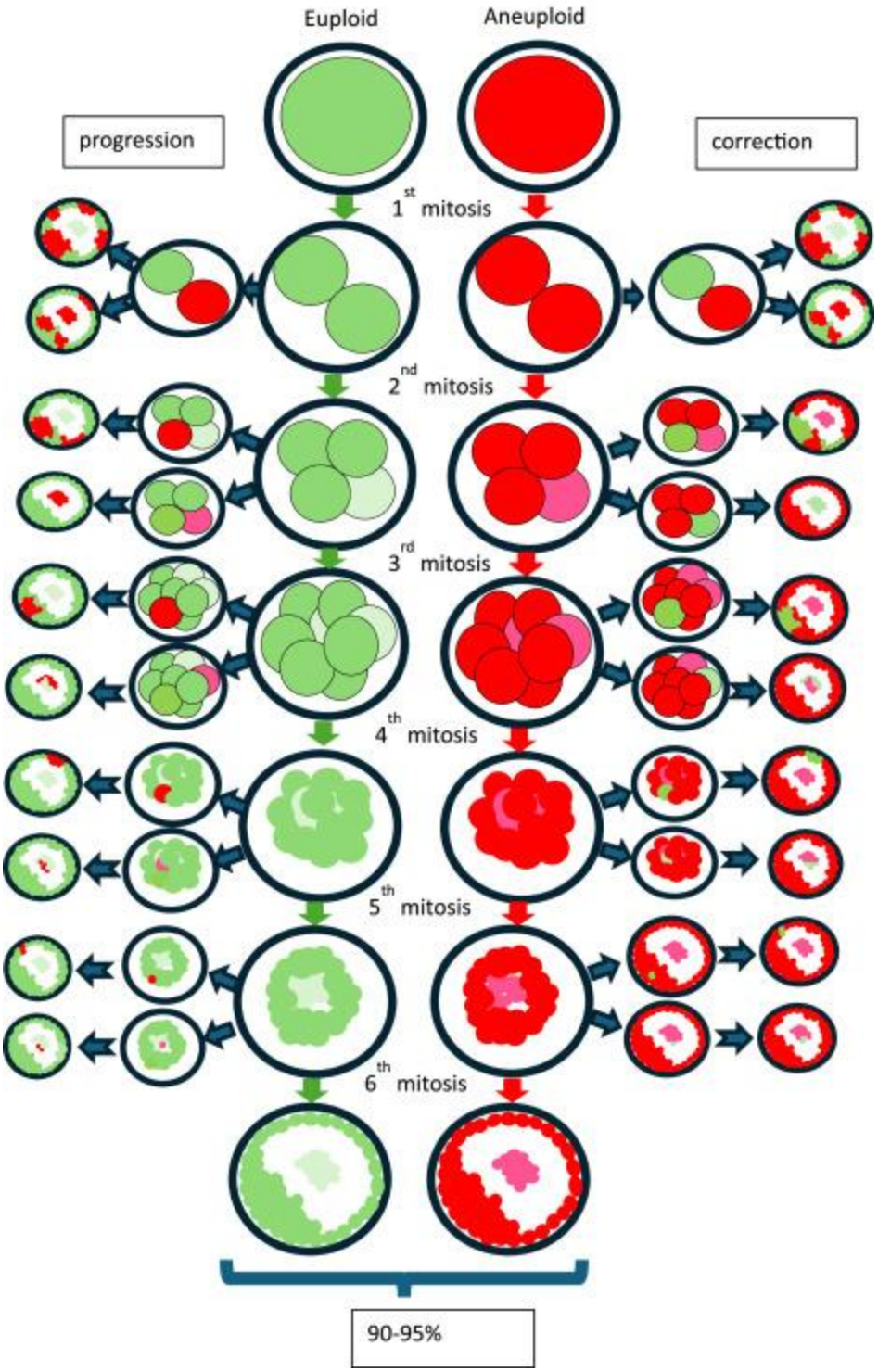

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Figure 1. Mitosis errors in early preimplantation embryos. Later mitotic errors affect fewer cells, with errors past the second mitosis tending to be geographically clumped in

the trophectoderm. Errors after the second mitosis are statistically unlikely to be biopsied and detected. Errors of mitosis involving cells destined for the inner cell mass (ICM) are less likely to be observed after mitosis 1 and unlikely to be observed after mitosis 2. Green represents euploid cells, and red represents aneuploid cells. Lighter shades reflect potential ICM cells.

The few studies available, using whole-embryo analysis to confirm mosaicism (Marin et al., 2021), tend to show that most apparent low-level mosaic embryos are actually euploid and high-level mosaics are aneuploid. Analytical errors are therefore more likely to be the cause of many 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, rather than the 95% or more that are identified as (an)euploid. With such a small number of mosaic embryos, excessive debate and argument around the 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.

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' (Bolton et al., 2016), so 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 chorionic villus sampling samples (typically less than 10% of cells and only a few per cent 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 around 1 in 2000 individuals have a chromosome pattern indicative of a uniparental disomy. Logically, such individuals must have shown mosaicism during their development, with the most likely time being during the very early embryo stage. Such evidence of aneuploid 'correction' still suggests that the incidence of normal birth after mosaic correction is very low (<0.2%) in the general

population. Mosaic miscarriages do, however, account for an identifiable fraction of chromosomally abnormal miscarriage events and carry relevance for the transfer of mosaic embryos (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 for non-invasive prenatal screening/testing (NIPS/NIPT). The negative predictive value for the common trisomies is typically quoted at over 99.96% (1 in 2500). The situation is similar in terms of low false-positive rates. The prevalence of mosaicism in chorionic villus samples identified by classical cytogenetics is low, typically only 2–4% of samples, and the value for amniocentesis samples is even lower, at only 1–2% (Grati et al., 2019). It can be biased to suggest that the 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 number of claims by some authors studying embryos that there is mosaicism. An excessive number of failures of somatic chromosome segregation in very early embryo growth would logically lead to a higher prevalence of prenatal aneuploidies, and not the low levels typically encountered in analyses.

Evolution of chromosome analysis

Statement key points

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  ICN reports appear to be exaggerated in some studies.
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  Proper techniques are a prerequisite for accurate PGT-A detection.
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  Low-to-medium grade ICN embryos can be transferred.

PGT-A (formerly preimplantation genetic screening) analyses evolved quickly. With increased resolution came the observation that, in some embryos, occasional

chromosomes appeared to be represented by an 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 clarified that small deviations in chromosome copy number appeared still compatible with successful transfer outcomes, albeit at apparently lower success rates (Greco et al., 2015). Individual clinics then considered their own risk management responses in determining their own transfer policy.

As technologies refined and understanding grew, the Preimplantation Genetic Diagnosis International Society (PGDIS) addressed the transfer of putative mosaic embryos in consecutive Position Statements in 2016, 2019 and 2022 (Cram et al., 2019; Leigh et al., 2022; Preimplantation Genetic Diagnosis International Society, 2016). These statements proposed that the transfer of putative mosaic embryos could be considered. From an analytical point of view, next-generation sequencing (NGS)-based ICN of less than 20% should be considered as only noise and within the normal range. This lower value was not a measure of clinical significance or of mosaicism but purely a recognition of noise associated with the initial genome amplification process and subsequent analysis.

While new technologies permit a greater complexity of analysis (Domingo-Muelas et al., 2023, Chavli et al., 2024) and interpretation of chromosome status, underlying all these tests is the requirement for an appropriate quality control of sample acquisition, sample preparation and final DNA analysis (Supplementary Discussion).

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 pregnancy. Non-selection embryo transfer studies have also generally supported this view. Transfer failures as well as subclinical pregnancies are, however, typically ignored in many analyses, with only clinical pregnancies considered notable – although women all over the world still suffer disappointment after a failure, especially that 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, been challenged 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) has raised the issue of accuracy, interpretation and clinical significance. 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 has 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 and colleagues, using a validated method for their embryo biopsy analysis, suggested that a significant percentage of the embryos they analysed were mosaic (Capalbo et al., 2021). This was seen by some groups to challenge any clinical utility of analysing chromosome complements. However, the following aspects can be noted. First, smooth chromosome profiles were presented in Capalbo and colleagues' study, potentially indicating the use of quite aggressive smoothing algorithms. Second, being a multicentre study with some centralized analysis, the authors did not acknowledge the potential for poor sample handling processes in different clinics to produce artefacts affecting subsequent whole-genome analysis and chromosome profile generation. Many problems can 'hide' under the 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 reporting deliberate transfers of 'abnormal' embryos misled the debate by including the transfer of mosaic embryos as 'abnormal embryo' transfers (Barad et al., 2022; Yang et al., 2021). Scrutiny of the results of Yang and collaborators' study showed only 32 transfers with 9 recognized pregnancies (28%, 11.8% implantation rate), 4 clinical miscarriages (44%) and 5 live births (1 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 arose from a putative mosaic trisomy embryo suggested to have resolved, although no further evidence was presented to support this assumption. Barad and co-workers added to the former data with only 1 more birth, another 6 miscarriages and another 10 failed transfers (Barad et al., 2022). Madjunkova and collaborators found that of 14 aneuploid embryos that implanted, 9 resulted in clinical miscarriage and 5 were biochemical

miscarriages (Madjunkova et al., 2025). Most (80%) of the aneuploid embryos resulted in failed initiation of implantation.

Statistical analysis in PGT-A studies

Statement key points

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  Statistics is often being misused to misrepresent PGT-A study results.
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  This is especially true for the idea of ‘different’ and ‘not different’.
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  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.

The misinterpretation of ‘different’ and ‘significantly different’

Authors often appear to suggest that data with obvious differences are ‘not different’ because they lack statistical significance ($P < 0.05$). Such assertions are simplistic and potentially misleading (Liu et al., 2024).

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 the 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. Munné and Griffin, (2024) discuss the importance of patient priorities in arriving at final patient treatment plans.

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 the 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 achieve success with the first embryo transfer without any other interventions, because the clinic was successful in avoiding the 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 of 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 the pregnancy and the 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.

Patients as individuals and as a group and their average

When describing IVF outcomes, authors often forget that 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 the risks as much as possible, PGT-A can be considered. These are decisions that implicitly involve a properly informed patient and clinician.

Implantation rate, per-transfer LBR and cumulative live birth rate

The implantation rate is the number of implantation sacs per embryo transferred. Nearly every study shows higher implantation rates when PGT-A is employed. This can only occur if a better embryo is identified by the PGT-A process.

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 approximately 37 years old. This is different from and often incorrectly confused with average aneuploidy rates when modelling transfer outcomes (Paulson, 2019). After 37 years of age, cohorts may increasingly include only aneuploid embryos, raising the probability of aneuploid embryo selection. It has been observed, however, that aneuploid embryos are selected for transfer even in younger women (Forman et al., 2013; Katz-Jaffe et al., 2024; Tiegs et al., 2021; Wang et al., 2021) and some may also have aneuploid-only cohorts, with only a minority having euploid-only cohorts.

If no improvement in implantation rate is seen after PGT-A, then logically, in any age-group woman, the original IVF embryo selection was either 100% euploid or the biopsy procedure reduced embryo potential.

Per transfer LBR

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

Cumulative live birth rate

Cumulative live birth rate (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 (Yang et al., 2012) but caused misunderstanding, with observed improvements being more correctly related to first transfer outcomes. These early misunderstandings underlie 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 that the

biopsy process does not cause harm and a per-embryo LBR is an appropriate measure of the effectiveness of PGT-A. Using CLBR comparisons, however, confuses discussions of the benefits of the prioritization of PGT-A embryo transfer (Liu et al., 2024). In all published studies comparing IVF with PGT-A/IVF, the cumulative number of transfers to produce a live birth is reduced with PGT-A (Katz-Jaffe et al., 2024; Munne and Griffin, 2024, Yan et al., 2021; Yang et al., 2021, Liu et al., 2024), suggesting that the equivalence of CLBR between PGT-A and IVF proving that PGT-A is ineffective is misleading. Not counting transfer numbers and not accepting a per-embryo live birth outcome shows the benefit of PGT-A and ignores the biology of aneuploid embryo transfer failure.

Suggesting that PGT-A is only a money grab by commercial operators is also 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.

Analysis of results – per protocol and intention to treat

Many criticisms of PGT-A studies have centred around either the study design and/or the 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 and colleagues recently showed that, even with young patients and no bias in group formation, selection at the very start of IVF recruitment still showed significant benefits of PGT-A, seriously undermining unsupported criticisms of bias in designs involving a later stage selection (Katz-Jaffe et al., 2024).

Further debate about PGT-A efficacy then focuses on the final analysis, with differences of opinion regarding the most appropriate approach: per protocol or intention to treat (ITT). Some groups promote the use of ITT analyses as these reflects the real world and typical clinic activity with its myriad variables. Other groups prefer per protocol analysis as being logical as embryo selection is based on the applied selection process of PGT-A. Both approaches have value but they differ in the final evaluation. Per protocol

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 the application of PGT-A, although it unfortunately fails to isolate the source of any problem.

Utility for different patient groups

Statement key points

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  All classes of patients can benefit from PGT-A by reducing futile transfers.
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  Better clinical management of patients with recurrent implantation failure (RIF) or recurrent miscarriage can be realized by removing aneuploidy as an underlying cause of failure.

Why the debate about the 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. Therefore it is pertinent to consider the five main patient groups.

Younger patients

If embryologists could always identify a euploid embryo, PGT-A would have no practical application. Typically, however, an aneuploid embryo is selected for initial transfer in 20–30% of these women. Over a decade ago, Forman and collaborators demonstrated that the identification of aneuploid embryos avoided futile transfers and improved the outcome(s) for the selected embryo transfers, as again recently demonstrated by Katz-Jaffe and colleagues (Forman et al., 2013; Katz-Jaffe et al., 2024) . Nearly every other study suggesting a lack of positive benefit after PGT-A in the younger patient age group showed 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 the significance of benefit after PGT-A. The benefits of PGT-A are there but are smaller when the initial embryo selection process is effective (Supplementary Discussion). That is not to suggest

that gains are not meaningful to patients, or at least to some patients. Katz-Jaffe and colleagues recently reported that, even in a good clinic, the benefits of PGT-A (increased implantation rate 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, the clinic is introducing negative impact factors such as poor embryology and/or poor biopsy technique. It is sub-performance by a clinic, and not the process itself, that reduces patient opportunities for improved outcomes with PGT-A.

Knowing that a transferred embryo is euploid also simplifies the identification, subsequent clinical management and decision making for patients with genuine RIF patients as PGT-A removes one major variable.

Older patients

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

Poor-prognosis patients

Patients who are considered to have a poor prognosis typically fall into one of two groups: only a single embryo is available for transfer or all embryos are considered to be 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 and co-workers (Kahraman et al., 2022). In the elective PGT-A group, only around 200 out of 1100 patients were identified as having a euploid embryo, with aneuploid embryos not transferred since the likelihood of success is extremely small or zero, this is not wanted by the patient and it is clinically unacceptable. The individuals who elected for an untested blastocyst transfer displayed implantation rates that

suggested high aneuploid rates among this group. Some critical comments were misguided in suggesting lost embryo potential since the study only reported on euploid transfers or untested transfers, with the implantation rate for the PGT-A group being comparable to those seen in many PGT-A reports.

Patients who have only very poor-quality 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 of poor-quality embryos must be considered, although no studies looking at the impact on implantation potential of the biopsy of poor-quality 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 counselling, with their own requirements and expectations being important.

Patients with recurrent miscarriage

This group 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 to identify the existence of other causes of miscarriage in this group and assist clinicians in initiating other studies in an expedient manner.

Patients with RIF

Finally, for individuals with RIF, PGT-A reduces futile transfers. Aneuploid embryos have a significantly reduced potential for pregnancy initiation and very high biochemical and clinical miscarriage rates, both of which can result in a false label of RIF. It was, in fact, patients with RIF who demonstrated the utility of PGT-A in the first CCS report over 15 years ago (Fragouli et al., 2008). It was seen clearly that multiple factors – blastocyst biopsy, CCS and frozen embryo transfers – combined to provide high transfer outcomes, all of which are now part of the current approach to PGT-A.

Given the vagaries of the current definition of RIF and the approaches used to treat it, a simplified approach to classifying RIF, as suggested by several groups (Cimadomo et al., 2023; Pirtea et al., 2021; Hynes and Forman, 2023), 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 the subsequent patient costs of futile transfers, reduce anxiety and remove the inappropriate label of RIF. Simplification of identifying RIF would permit clinicians to proceed in a much more evidence-based approach for this group of patients and genuinely assist them in their quest for a baby, rather than using the current approach of exposing them to blind luck with undetected futile transfers.

Impact, cost-effectiveness and financial considerations

Statement key points

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  The cost-effectiveness of PGT-A is balanced against transfer costs and PGT-A testing costs.
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  Patients' 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 to identify 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 USA, where most aspects of IVF are expensive, Murugappan and colleagues reported that embryo transfers cost $3500–$12,500, with an average of $6395 (Murugappan et al., 2015). PGT-A costs varied according to individual clinics.

Is the cost of analysing the embryo(s) cost-effective? For individual, young patients in whom euploid embryos 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 a cost with no gain. However, in 20–30% of these younger women an aneuploid embryo is selected for transfer (Forman et al., 2013; Katz-Jaffe et al., 2024), so there is a subgroup, even in young patients, who could benefit, in terms of transfer success, from PGT-A. Although 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 the probability of a positive outcome.

Compared with the USA, other countries may have significantly lower transfer and PGT-A costs so the break-even cost–benefit point will vary. Clinics also approach PGT-A services differently: as a cohort analysis, as an individual per embryo cost or as 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. However, with advancing age, the cost-effectiveness of PGT-A increases and it may even be viable when PGT-A per embryo carries the same cost as a single transfer (Supplementary Discussion).

In countries where national health systems cover the IVF process, consecutive transfer approaches may be thought to be a simpler, more cost-effective approach since government coffers are subject to actual costs without commercial margins. Transfer numbers would, however, be much higher, for reasons described above. Such countries would, though, also be expected to have low 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, difficulties such as miscarriages and time to recovery, and emotional costs. Clinic resources are also unnecessarily stretched by the failure of potentially avoidable futile transfers.

Recent reports that further stirred the debate about PGT-A

Statement key points

- •

The STAR trial failed to understand the impact that individual clinics have on the final results.

- •
  Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) data show that:
  - ○
    the analysis of old data is flawed
  - ○
    recent results suggest positive outcomes after PGT-A.
- •
  UK registry data appear flawed, with poor results evident.
- •
  Cumulative live birth data are 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.
  - ○
    Cumulative live birth data can enable clinics to assess their own operation.

The STAR trial report (Munne et al., 2019) is often cited by groups suggesting that 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 being insufficient to reach significance as both groups were too small. By itself, this undermined the original intentions of the trial.
How did the trial designers underestimate the baseline parameters? They clearly underestimated the baseline performances of the participating clinic 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. Multicentre studies will always be hindered by the relative performances and participation levels of the individual clinics and add unaccounted variables in any randomized controlled trial design.

Unfortunately, in this latter study, many individual clinics did not participate at a level permitting separate analyses to be meaningful. Wang and co-workers showed that individual groups do add variability to any cohort analysis (Wang et al., 2022).

The STAR trial also reduced the 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 dataset held by SART suggested that PGT-A led to reduced outcomes (Kucherov et al., 2023; Meija et al., 2022). Both author groups used essentially the same data, which were by then 8 years old and were representative of mixed approaches in the early adoption of CCS, rather than more relevant recent data that would be more closely aligned with current practices.

Harris and colleagues attempted to address the previous limitations of SART-CORS data analysis by restricting comparisons to 2016–2019 and NGS testing (Harris et al., 2025). The primary outcome was cumulative live birth, with secondary outcomes of clinical pregnancy, miscarriage, multiple births and perinatal mortality. Analysis was on an ITT basis. They observed that the CLBR was lower in the PGT-A group but after stratification by age, the difference was reduced for individuals less than 35 years old. Paradoxically, in the older age groups (35–37 and 38–40 years) the CLBR was higher for the PGT-A groups, as were pregnancy rates and likelihood of a live birth, and miscarriage rates were substantially lower. A subgroup analysis of patients with only frozen transfers showed that 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 and collaborators also suggested that PGT-A might be associated with a modest reduction in live birth events (Roberts et al., 2022). 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, although more current than in earlier SART CORS analyses, was still dated, being from 2016–2018. The actual results presented in the supplementary tables (Tables S1 and S2, Roberts et al., 2022) raise concerns as it was

disclosed that the PGT-A results were substandard in comparison with most PGT-A comparisons available in the literature. The LBR per transfer cycle for the younger, better prognosis patients (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 against all advice from 2014 onwards, where cleavage-stage biopsy was shown not to reflect embryo potential (Scott et al., 2013).

It can be considered that the analysis of such flawed data can misrepresent modern PGT-A practices. In any case, it very tidily demonstrates that not all groups are yet at the stage where they should be offering PGT-A services. Roberts and collaborators concede that the dataset is inappropriate for the analysis of many covariates, with cumulative live births confounding live births in the first transfer – an important consideration when looking at the benefits of PGT-A (Roberts et al., 2022). 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 dataset. Additionally, it is even suggested that more recent data might reflect more recent iterations of PGT-A practices. Overall, the authors concede that the biases and limitations of registry data may affect the ability to draw useful conclusions, especially where the benefits in younger groups are likely to be less than a 5% absolute uplift in live birth events.

Munne and Griffin (2024) also used the SART database but focused instead on recent results, 2 years prior. Although limited to first transfers, they revealed that PGT-A did result in improved transfer outcomes, which has been reflected in PGT-A now being preferentially requested and performed in most US IVF cycles and 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 and co-workers presented a CLBR trial comparing IVF using the best three embryos available for transfer versus PGT-A with the best three embryos available for biopsy and euploid embryos available for transfer (Yan et al., 2021). This trial is often presented as showing that PGT-A is of no benefit. Scott and colleagues presented a critical appraisal of Yan and co-workers' study with the key elements being the disparity of transfers

available for the two groups and the failure to acknowledge the clinical utility of putative mosaic embryos (Scott et al., 2022). Scott and colleagues' conclusion was succinct in demonstrating not only the non-inferiority of PGT-A compared with IVF, but also actual equivalence in transfer outcomes and direct evidence of the non-harm of biopsy, ultimately relegating Yan and co-workers' study to a study confirming the overall safety of trophectoderm biopsy. The study itself also has a quasi-CLBR approach that is not appropriate for comparison between IVF and PGT-A.

What Scott and colleagues 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 (Supplementary Tables 3 and 4 in Yan and co-workers' paper). In addition, the cumulative live births after 1 year were numerically higher in the PGT-A group (Supplementary 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 with PGT-A selection demonstrates. Continuing controversy centres around how effective it might be within certain patient groups rather than the improved embryo selection outcomes. An improved CLBR 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 that biopsy does not cause harm, and CLBR being reduced in SART data and the UK register, suggesting that PGT-A causes 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 Position Statements and many papers over the last decade. Embryo 'self-correction', '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 embryos, were likely to be identified.

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

Counselling

Statement key points

- •
  Open discussion is important for effective counselling.
- •
  Mosaic embryo transfers are not without negative outcomes, and counselling 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 inform potential users not only 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 the 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 for the biology associated with it and for patients' expectations and concerns. Initial claims of a lack of adverse outcomes after the transfer of mosaic embryos were due to restricted datasets, probably 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 having been a routine prenatal test for over a decade now, genuine fetal mosaicism is also being observed. The simple statistic of negative predictive value for NIPS, typically described by service suppliers as approximately 99.96%, suggests a very low placental–fetal discordance. However, discordance or mosaicism is a feature of some pregnancies. Positive predictive values for NIPS are subject to other assay limitations but placental–fetal discordance is not zero. Since the PGT-A process samples only extra-embryonic cells destined for the placenta, the potential for inner cell mass/trophectoderm discordance is there but adverse outcomes are low.

What of the possible transfer of embryos considered aneuploid? The results of the transfer of genuine aneuploid embryos showed high transfer failure rates, high miscarriage rates and occasional abnormal live births (Yang et al., 2021). Similarly, the very small but limited follow-up after mosaic embryo transfers reported by Capalbo and colleagues may wrongly guide discussions between clinicians, counsellors and patients (Capalbo et al., 2021). More informative, however, are the non-selection studies where abnormality was identified after transfer (Madjunkova et al., 2025; Scott et al., 2012; Tiegs et al., 2021; Wang et al., 2021). In these studies, the potential for abnormal embryos to initiate a pregnancy was clearly identified, as were their typical subclinical and clinical miscarriages, with very few putative abnormal embryos resulting in a normal live birth. The earlier study from Scott and colleagues suggested that potentially up to 4% of abnormal embryos may undergo mitotic normalization (similar to the number reported by Wang and co-workers), whereas a later study from the same group

reported 100% failure (implantation failures and miscarriages) for all transferred aneuploid embryos (Scott et al., 2012; Wang et al., 2021).

The birth of chromosomally abnormal babies as well as the low presence of uniparental disomy individuals in the general population are direct evidence that all chromosomally abnormal zygotes fail, but the actual number of successes appears to be very small. The question arises, however, of 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 the reasons discussed previously, the normalcy of an embryo and the 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, however, 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.

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. Although well known, this topic remains under-discussed. Such pregnancies often remain undiscovered and undisclosed.

All testing procedures have a potential for error. This may include sample mix-ups in the clinic or laboratory, analytical errors and errors in interpretation, result transcription or communication. Every clinic and laboratory has their own procedures to minimize the risk of such occurrences, but this cannot be zero. An error can result in an inappropriate embryo being transferred or a suitable embryo being misclassified and rejected for transfer. Fortunately, such errors are few in practices that are operating well. Counselling must include a balanced discussion of each of these areas in a manner that does not alarm the patient or avoid the possibility of errors. 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., 2025). Some of these embryos would already

have been considered in routine (no PGT-A) IVF as transfer, freezing and biopsy are all based on some minimal requirement of advanced embryo development (McCoy et al., 2023). This new approach offers patients the possibility of maximizing outcomes per retrieval.

With this opportunity, though, come some caveats. The level of counselling and understanding required is increased compared with otherwise simple euploid selections. The possibility of adverse events increases 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.

Conclusions

The biological basis of why PGT-A-assisted embryo selection (i.e. the identification of aneuploidy) 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 techniques and/or covert biases in statistical presentations. PGT-A is for a single purpose – to 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.

Biopsy as representative of the embryo

- •

  The biopsy will identify the embryo as an average and is likely to reflect the embryo as a whole. Although somatic mosaicism may exist in some limited situations, it should not confound most interpretations.
- •

  A vast majority of embryos are simple euploid or aneuploid, although identifiable mosaicism occasionally occurs. Much of the reported mosaicism, however, appears to be an artefact associated with sample handling and analysis.

- •

  Very early mitotic errors (cleavage stage) are likely to be identifiable via a trophectoderm biopsy, whereas later changes are less identifiable but are also less likely to confuse interpretation of the analysis. Upon survival, early mitotic errors would be present in a large fraction of the embryo, whereas later errors are less likely to be.

Accuracy of analysis

Several technical issues may impact the analytical accuracy of a biopsy analysis. It is important to avoid DNA degradation as it can cause bias in the subsequent amplification and skew the results. All PGT-A interpretations should include a review of analytical quality measures to confirm the reliability of the analysis and avoid incorrect identification of aneuploidy or mosaicism. The testing platforms used 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.

Benefits of PGT-A

Until other approaches to identify aneuploid embryos exist, PGT-A can be of benefit to all categories of patients. Transfer of an aneuploid embryo is typically futile, with few benefits but potentially significant negative clinical, emotional and economic consequences.

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.

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.

Other categories

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

Patient counselling

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

PGT-A in current practice

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

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Appendix. Supplementary materials

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Data availability

No data was used for the research described in the article.

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Don Leigh is a past President of PGDIS. He has a PhD from the University of New South Wales (1986) and has been performing PGT since 1998. Currently, he is in southern China and is involved in both training for PGT and the 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, counsellors and laboratory staff in improving patient embryo transfer outcomes.
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