REVIEW ARTICLE

Strategies in Reducing the Economic Burden of Preimplantation Genetic Testing for Aneuploidy (PGT-A) via Morphological and Genetic Integration: A Mini Review

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Abstract

Infertility is a growing public health concern worldwide, with in vitro fertilization (IVF) is one of the most widely used treatment modalities. Preimplantation Genetic Testing for Aneuploidy (PGT-A) has emerged as a valuable tool in assisted reproductive technology (ART), to improve implantation rates and reduce the risk of miscarriage. Initially introduced in the mid-1990s with FISH-based methods, PGT-A has advanced significantly with the adoption of next-generation sequencing (NGS). Over the past two decades, it has been widely implemented in fertility clinics worlwide. However, the high cost of PGT-A continues to limit accessibility, particularly in resource-constrained settings. This mini review explores strategies to alleviate the economic burden of PGT-A, including refined patient selection, integration with morphological embryo assessment, and the emerging potential of mitochondrial DNA biomarkers. By addressing cost-effectiveness while maintaining clinical utility, these approaches may broaden access to PGT-A, ultimately improving equity and IVF outcomes.

Keywords: Infertility, assisted reproductive technologies, preimplantation genetic testing for aneuploidy (PGT-A), economic burden, in vitro fertilization

Introduction

Infertility affects millions of couples worldwide, with approximately 15% of reproductive-age couples experiencing difficulties conceiving (Luo et al. 2024). This prevalence rate aligns with global estimated reported by the World Health Organization, which identifies infertility as a significant public health concern affecting quality of life and demographic trends across population (Hillard 2015). Assisted reproductive technology (ART) has revolutionized fertility treatment, offering hope to these individuals. A key objective of ART is to maximize the likelihood of achieving a live birth while minimizing the risks associated with unsuccessful cycles and miscarriages. However, the economic burden of ART remains a major barrier to its widespread adoption.

Preimplantation Genetic Testing for Aneuploidy (PGT-A) is a new ART approach that screens embryos for chromosomal abnormalities, thereby enabling clinicians and embryologists to select euploid embryos and improve fertility outcomes. Although PGT-A has been demonstrated to improve clinical outcomes, its additional costs further limit accessibility, particularly in low- and middle-income countries (LMICs). Globally, the majority of fertility treatment expenses are borne out of pocket from patients, unlike many other costly medical interventions that are insurance-supported (Nagajyothi et al. 2025). This creates profound disparities in access to technology, particularly between high-income countries and LMICs.

Recent systematic reviews and meta-analyses suggest that PGT-A can improve live birth rates, particularly among women of advanced maternal age (>35 years), and lower miscarriage rates (Bacal et al. 2025). However, the economic burden of PGT-A restricts its widespread application. Morphological assessment of

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blastocysts, a noninvasive and cost-effective method, provides a potential complementary strategy. Traditionally, embryos are graded based on their inner cell mass (ICM), trophectoderm (TE), and degree of expansion. Although valuable, morphology alone cannot reliably predict chromosomal integrity or implantation success.

These financial constraints emphasize the importance of cost-saving strategies for fertility treatment. In a previous study, it has been demonstrated that integrating blastocyst morphology as a complementary selection tool could lead to significantly reduced number of embryos subjected to genetic testing, while maintaining favorable reproductive outcomes (Neal et al. 2018). Such integration of morphological analysis could lower laboratory expenses, reduce the frequency of repeated unsuccessful cycles, and minimize downstream costs associated with complications or multiple pregnancies.

In addition, value-based strategies such as selective application of PGT-A combined with morphology may offer the most sustainable approach. By aligning clinical effectiveness with economic efficiency, integrated protocols not only reduce the burden on patients but also support the global movement toward equitable and accessible fertility care (Neal et al. 2018; Venson et al. 2023).

Current Role of PGT-A in Assisted Reproductive Technology

PGT-A is now a central component of ART, primarily due to its capacity to identify chromosomally normal embryos prior to transfer. This screening improves implantation rates, reduces miscarriage, and decreases the time to pregnancy. Advances in next-generation sequencing (NGS) have significantly increased the accuracy and reliability of PGT-A, making it the current gold standard for chromosomal screening (Gudapati et al. 2024). Importantly, the clinical utility of PGT-A must be contextualized. While it is often recommended for women of advanced maternal age (>35 years), women with recurrent implantation failure, and those with recurrent pregnancy loss, its routine use in younger women with good ovarian reserve remains controversial with randomized controlled trials showing equivalent outcomes between PGT-A and morphology-based selection in good-prognosis patients (Munné et al. 2019).

Despite these benefits, PGT-A remains inaccessible to many patients, mainly due to its high cost. Review shows that the procedure's financial burden varies considerably worldwide, reflecting differences in healthcare systems and market pricing. For example, in the United States, PGT-A typically costs US$15,000–150,000 per cycle (Khorshid et al. 2023). However, in India, the market price for conventional assisted reproductive technology (ART) ranged from US$4960 to US$8,497 (Arakkal et al. 2020), while in Vietnam, standard IVF procedures cost approximately US$8,549.9 (Le et al. 2018).

This wide variability underscores how PGT-A affordability is influenced not only by laboratory technology and clinical protocols but also by broader economic and healthcare contexts. In regions such as China and Malaysia, lower comparative costs may improve accessibility, whereas the higher costs in the United States continue to pose barriers to equitable access. Such disparities highlight the importance of developing integrated, cost-effective embryo selection strategies that maintain clinical value while minimizing financial strain.

Blastocyst Morphology and Integration of PGT-A in Embryo Selection

To date, blastocyst morphology remains a cornerstone of non-invasive embryo evaluation in ART. Parameters such as the inner cell mass or embryoblast quality, trophectoderm integrity, and blastocyst expansion are graded by embryologists to estimate implantation potential (Sciorio 2021). Studies indicate that high morphology grades correlate with higher live birth rates, although morphology alone cannot reveal chromosomal status (Kasaven et al. 2023). The simplicity and cost-effectiveness of morphology assessment make it especially valuable in resource-limited settings.

Following the correct embryo selection, it has been demonstrated that those with both favorable morphology and euploid status yield the highest implantation and live birth rates (Magli et al. 2016; Rubio et al. 2013). Clinical evidence demonstrates significant variations in success rates based on morphology grading. Good-quality euploid blastocyst yield statistically significantly higher implantation rates than poor-quality blastocysts (79.31% vs, 48.0%; $P<0.001$), with live birth rates following similar patterns (67.8% for good-quality vs 29.5% for poor-quality embryos) (Irani et al. 2018). These finding highlight the predictive value of morphological assessment while simultaneously revealing its limitations in identifying chromosomal abnormalities that may not manifest as morphological defects.

Nonetheless, these predictive limitations highlight the importance of integration with genetic testing such as the PGT-A. When combined with PGT-A, morphological analysis can guide clinicians regarding which embryos

should undergo testing, thereby potentially reducing the costs of the treatment. Research showed that combining PGT-A with blastocyst morphology provides a synergistic selection framework (ChéLes et al. 2020).

Clinical and Economic Comparison of Morphology Alone Versus Morphology Plus PGT-A

The debate between morphology-only and combined morphology-PGT-A approaches centers on clinical efficacy, cost-effectiveness, and patient-specific factors. Randomized controlled trials provide critical insights into this comparison. The STAR trial, a multicenter randomized study, evaluated 661 women (average age 33.7 years) with at least two blastocysts, comparing PGT-A with morphology-based selection. The results demonstrated equivalent ongoing pregnancy rates between the groups (50% PGT-A vs. 46% morphology per embryo transfer), with no significant difference in intention-to-treat analysis (41.8% vs. 43.5%) (Munné et al. 2019).

However, subgroup analysis demonstrated significant age-related differences. Among women aged 35-40 years, the use of PGT-A resulted in a significantly higher ongoing pregnancy rate compared with morphology-based selection alone (51% vs 37%, $P<0.05$) (Munné et al. 2019). This clinical benefit aligns with the higher incidence of aneuploidy observed in this age group, reported to be 64.5% in women aged 35–40 years compared with 52.0% in those under 35 ($P<0.05$**)** (Orvieto 2024).

Cost-effectiveness analyses supported selective PGT-A applications. A China-specific decision-analytic model estimated that adding PGT-A for women aged 20-37 years raises the cost per live-birth by 16.8 % (¥39 231 vs ¥33 588), but each miscarriage averted cost an additional ¥45 600. Threshold analysis indicated that PGT-A could become cost-neutral if its price fell by ¥4649.29 to ¥ 1350.71 per cycle or if the clinical pregnancy rate increased by ≥ 26 %. Thus, in resource-limited Asian settings, selective use of PGT-A (e.g., women ≥ 35 years or with repeated implantation failure) is more likely to be economically justifiable than routine application (He et al.2023). These findings suggest that while morphology remains valuable for initial screening, PGT-A provides additional benefit in specific patient populations, particularly those of advanced maternal age or with multiple available embryos.

Economic Considerations

Incorporating blastocyst morphology and PGT-A as complementary selection tools have been shown to significantly reduce costs (Neal et al. 2018). A systematic review demonstrates that integrated ART protocols with the above approaches can deliver similar or even improved outcomes compared to PGT-A alone, with lower financial burden (Kushnir et al. 2022). It is thus recommended to develop a conceptual framework in reducing the economic burden of PGT-A through morphological pre-screening, selective application of genetic testing such as using the PGT-A, and potential integration of non-invasive biomarkers, such as the the mitochondrial DNA (mtDNA). The integrated approach could decrease the number of embryos undergoing costly testing while maintaining clinical outcomes (Figure 1). By reducing the number of embryos subjected to genetic testing, these strategies in this framework could help to decrease laboratory expenses and enhance accessibility, particularly in low-resource settings. Importantly, this cost-saving approach also aligns with the global push toward value-based healthcare, which emphasizes affordability, efficiency, and equitable access.

PGT-A and The Potential of Mitochondrial DNA as biomarker

Recently, mtDNA has emerged as a novel molecular marker in embryo selection and has gained attention as a possible adjunct to existing methods, including PGT-A. While PGT-A directly identifies chromosomal abnormalities, mtDNA measurement offers an indirect indication of embryo viability by reflecting cellular metabolic status. Several recent studies have suggested that abnormal mtDNA copy numbers may correlate with reduced implantation potential, whereas optimal levels are associated with higher embryo competence (Abdellatif et al. 2025; Chuang et al. 2023; Dickson et al. 2024). This raises the question of whether mtDNA could serve as a lower-cost alternative to PGT-A or whether it is best utilized as a complementary tool to enhance predictive accuracy.

Mitochondrial DNA (mtDNA) Testing in Embryo Selection: Economic and Clinical Considerations

The integration of mitochondrial DNA (mtDNA) testing into embryo selection algorithms presents significant cost implications that warrant careful consideration. Current mtDNA testing costs approximately US$49-199 per sample using next-generation sequencing technology, representing a substantial reduction from historical prices of US$895 in 2005 (Bettinger et al. 2019). This cost structure makes mtDNA testing considerably more affordable than comprehensive PGT-A, which ranges from US$652-150,000 per cycle depending on geographic location and healthcare system.

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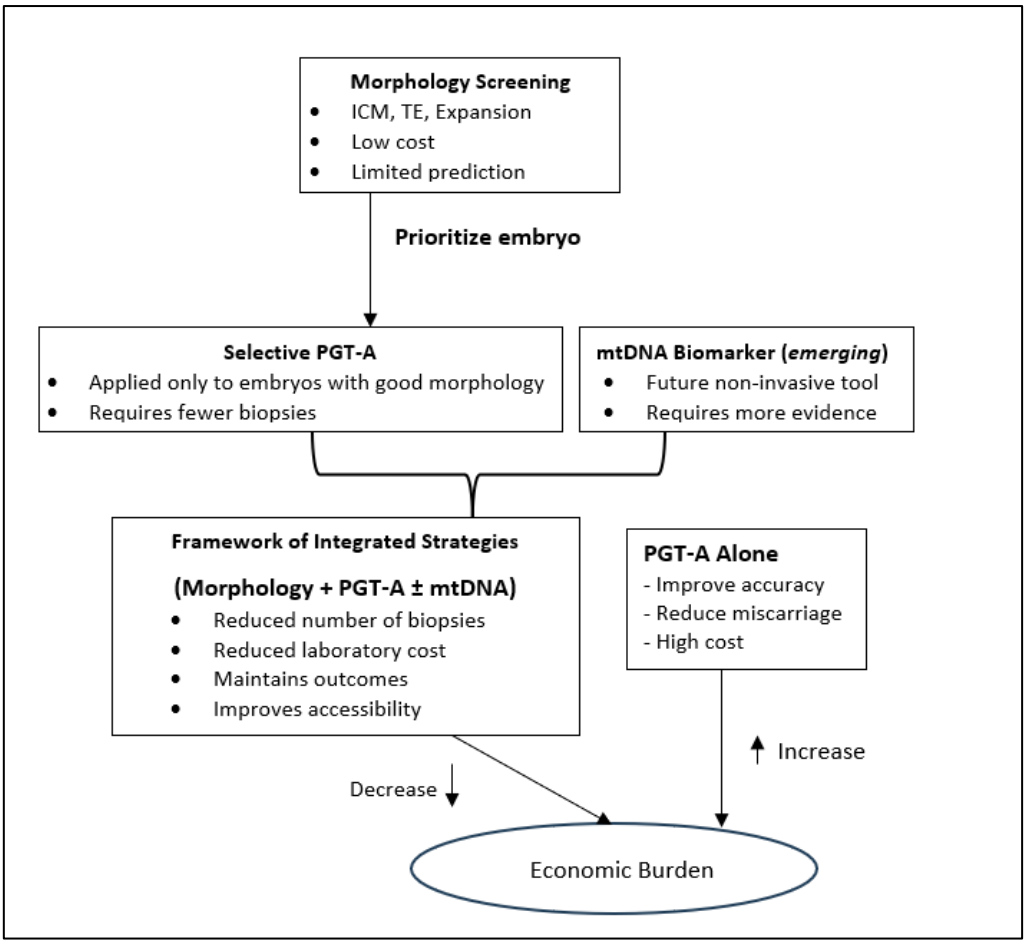

Figure 1. Framework of integrated strategies to increase cost-effectiveness of the PGT-A.

From an economic perspective, incorporating mtDNA as a screening layer before PGT-A could improve cost-effectiveness by identifying embryos with poor metabolic profiles that are less likely to be implanted, thereby reducing unnecessary biopsy and testing. A tiered approach using mtDNA pre-screening could reduce PGT-A costs by 15-30% by eliminating embryos with compromised mitochondrial function before expensive chromosomal analysis. This represents potential savings of US$1,500-45,000 per cycle in high-cost markets, such as the United States.

However, the clinical utility of mtDNA testing remains unclear. Victor et al. (2017) demonstrated no statistically significant difference in mitochondrial DNA levels between implanted and non-implanted blastocysts, challenging the reliability of mtDNA as a standalone biomarker. The lack of specificity and consistency across patient populations limits its current application as a replacement for PGT-A (Ritu et al. 2022; Zhou et al. 2021). Consequently, mtDNA may be most valuable when integrated with PGT-A and morphological assessment, potentially reducing the number of embryos subjected to costly genetic testing while maintaining high success rates.

The economic model for mtDNA integration must balance testing costs with potential savings from reduced PGT-A utilization. If mtDNA screening costs US$100 per embryo and reduces PGT-A testing by 25%, net savings would be substantial in high-volume clinics. For example, in a cycle with eight embryos, mtDNA pre-screening would cost US$800 but could save US$3,750-37,500 in PGT-A costs, representing a favorable cost-benefit ratio. However, such savings assume that mtDNA screening accurately identifies embryos likely to fail PGT-A or exhibit reduced implantation potential, an assumption that requires further validation through large-scale clinical trials.

At present, the consensus is that mtDNA should not be considered as a replacement for PGT-A. Unlike PGT-A, which provides definitive information regarding chromosomal status, mtDNA lacks sufficient specificity and consistency across patient populations to function as a standalone diagnostic test (Ritu et al. 2022; Zhou et al. 2021). Victor et al. (2017) demonstrated that there was no statistically significant difference in mitochondrial DNA levels between implanted and non-implanted blastocysts, irrespective of whether the measurements

were obtained through NGS or qPCR analyses. Instead, mtDNA may be most valuable when integrated with PGT-A and morphological assessment, potentially reducing the number of embryos subjected to costly genetic testing while maintaining high success rates.

From a clinical standpoint, such integration aligns with the broader trend toward multi-parametric embryo evaluation, where morphology, chromosomal screening, and molecular biomarkers are combined to refine embryo selection strategies (Neal et al. 2018; Zhou et al. 2021). This approach supports a more holistic assessment of embryo viability and recognizes that no single biomarker is sufficient for reliable prediction of implantation potential. Incorporating mtDNA into multi-layered algorithms may therefore enhance decision-making efficiency, particularly in clinics managing large embryo cohorts or patients with complex reproductive profiles. As the field progresses, further research will be needed to determine how mtDNA-derived metrics can be standardized and validated across diverse clinical populations.

Ethical considerations and Legal Implication

The integration of morphology and genetic testing, including PGT-A also raises ethical and access concerns among researchers and clinicians wordwide. While combining these methods may improve clinical outcomes and reduce costs for fertility treatment, literature review shows that issues pertaining to equitable access, funding, and the broader societal impact of embryo selection remain underexplored. There is a critical need for more research to be conducted that aligns ethical considerations with clinical outcomes, particularly on PGT-A in embryo selection for fertility treatment. These future works would ensure that cost-saving innovations do not exacerbate disparities in access to reproductive technologies (Gudapati et al. 2024; L'heveder et al. 2021).

Conclusion

Improving the cost-effectiveness of PGT-A and reducing its economic burden among the patients requires a multifaceted approach, including technological innovations, selective patient application by clinicians, integrated workflow strategies, and supportive healthcare policies. Incorporating blastocyst morphology as a complementary tool has proven to enhance clinical and economic outcomes. Meanwhile, emerging biomarkers such as mtDNA could show promise but require further clinical research validation before its widespread adoption. Future research should prioritize multicenter trials, standardized protocols, and long-term outcome assessments to establish the most effective and affordable strategies for embryo selection.

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Disclosure of Conflict of Interests

The authors report no conflict of interests.

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