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A Review of Cost-Effectiveness of Preimplantation Genetic Testing for Aneuploidy

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Importance: Preimplantation genetic testing for aneuploidy (PGT-A) is an important focus area of reproductive medicine because of its potential to improve the odds of a live birth from in vitro fertilization (IVF) treatment.

Objective: Despite growing interest and use of this technology, there has been a limited, albeit growing, body of literature that has evaluated the cost-effectiveness of PGT-A for patients compared with IVF without PGT-A. This review aims to further explore this relationship and summarize current findings.

Evidence Acquisition: Studies were selected entering terms such as "PGT-A," "IVF," and "cost-effectiveness" in the PubMed database.

Results: In some studies, PGT-A has been shown to be cost-effective in older patients and patients who have experienced recurrent pregnancy loss. In other studies, PGT-A use has shown comparable live birth rates to traditional IVF while carrying a more expensive price tag. In addition, PGT-A carries risk, including embryo damage and improper embryo classification, and has significant financial cost. Specifically with regards to cost-effectiveness, considerations such as age, reproductive timeline, and economic burden have been identified.

Conclusions: Ultimately, there is incomplete data addressing factors such as mosaicism, patient perspectives of the economic cost, and patient experiences surrounding PGT-A. Further studies are needed to fully evaluate PGT-A outcomes, patient experiences, and cost-effectiveness.

Relevance: As utilization of assisted reproductive technology continues to increase, a careful analysis of the cost-effectiveness of additional genetic screening tests is critical to patient counseling and shared decision making.

Target Audience: Obstetricians and gynecologists, family physicians

Learning Objectives: After completing this activity, the reader will be better able to describe how preimplantation genetic testing for aneuploidy works; discuss the existing literature surrounding PGT-A use and its cost-effectiveness; and identify patient populations for which PGT-A might be beneficial.

BACKGROUND

Preimplantation genetic testing for aneuploidy (PGT-A) has become a prominent test in reproductive medicine.[1] With an estimated 2.3% of all infants born in the United States being conceived with assisted reproductive technologies, the use of PGT-A is rapidly expanding as an add-on to in vitro fertilization (IVF) treatment. According to the Centers for Disease Control and Prevention, in 2021, 48% of transfers involved at least 1 embryo with PGT, although the report makes no distinction between PGT-A and PGT-M.[2] Developed in the late 1980s, PGT-A represents a departure from more traditional morphology-based embryo grading, which had previously been the main selection criterion to select the best embryo for implantation. Instead, PGT-A technology involves sampling a few cells from the outer cell

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layer of the blastocyst to identify 23 pairs of chromosomes. In doing so, embryos with the correct number of chromosomes can be selected and transferred to maximize the likelihood of a live birth.[3]

The use of PGT-A has been a source of debate mostly because of the limited research regarding outcomes, along with its associated high cost. In a 2023 study looking at the economics of fertility care, Peipert et al[4] estimated that PGT-A can cost between $1150 and $1650 per embryo. The routine use of PGT-A has been evaluated by the American Society for Reproductive Medicine (ASRM). In their 2018 Committee Opinion on PGT-A, ASRM identified only 3 randomized controlled trials assessing the outcome of PGT-A. In reviewing the literature, they concluded that there was insufficient evidence to support "routine use" of PGT-A, but outlined various subsets of patients for which PGT-A could offer benefits.[3] The 2019 STAR (Single Embryo Transfer of Euploid Embryo) trial randomized over 600 patients to PGT-A versus morphology alone for single frozen thawed embryo transfer. In this study, PGT-A did not improve pregnancy outcomes as measured by the ongoing pregnancy rate at 20 weeks' gestation. However, when the analysis was limited to the group of women aged 35–40 years, although there was an increase in pregnancy rate with the use of PGT-A, this was not significant in the intention-to-treat analysis.[5] Other studies have looked at the relationship between PGT-A and socioeconomic factors. In 2021, Bedrick et al[6] evaluated the association between live birth, PGT-A, and race. Looking at a sample of 110,843 transfers of which 16% used PGT-A tested embryos, the study found that chances of live birth were equivalent with and without PGT-A.[6] As PGT-A use increases, understanding the cost-effectiveness of this add-on treatment especially in the setting of onerous IVF costs is critical.

This review aims to evaluate the current literature looking at access to, use of, and cost-effectiveness of PGT-A. To identify studies for inclusion, PubMed was searched for the terms "PGT-A," "PGT aneuploidy," "PGT cost-effectiveness," and "PGT outcomes." A selection of articles was included in this review. In doing so, the review strives to contribute to the ongoing debate on the cost-effectiveness of PGT-A, as well as offer evidence-based guidance that providers can use to counsel patients.

PGT-A OUTCOMES AND COST-EFFECTIVENESS

Determining the cost-effectiveness of PGT-A relies on a clear definition of cost-effectiveness. A successful cost-effectiveness analysis must evaluate 2 components: the outcomes and the cost of the intervention compared with a similar intervention consistent with the standard of care or no intervention/expectant management. In reproductive medicine research, typical outcomes measured include, but are not limited to, clinical pregnancy rate, live birth rate, and time to live birth. However, even within the field, these outcomes can have varying definitions and parameters. In addition, the clinical pregnancy rate may not reflect the live birth rate as not all pregnancies lead to a live birth. These nuances have been studied in the reproductive medicine literature.

In their systematic review of 142 IVF randomized controlled trials published in 2013–2014, Wilkinson et al[7] reported over 800 combinations of numerator and denominator for measuring live birth rate. With these data, they concluded that only 43% of studies reporting live births as an outcome included all randomized participants in their calculations highlighting the numerous ways live birth and clinical pregnancy rate data can be obtained and published.[7] In addition, whether pregnancy rate or live birth rate is a more valuable outcome has been debated. Clarke et al[8] analyzed 67 systematic reviews representing 143 randomized controlled trials that reported both on pregnancy and live birth rate. The aim of their study was to assess whether treatment effects vary when either clinical pregnancy or live birth is used as a primary outcome. Using a kappa-statistic and odds ratio, the authors concluded that study conclusions based on pregnancy rate and live birth rate were comparable thereby validating both these parameters as IVF outcome measures.[8]

With these principles in mind, a few studies have evaluated PGT-A outcomes. In their systematic review, Simopoulou et al[9] sought to identify the type of patient that would benefit from PGT-A by analyzing whether use of PGT-A improves live birth rates. Focusing on 11 randomized controlled trials, the authors concluded that PGT-A did not improve clinical outcomes for the general population but did reduce the rate of miscarriage. In addition, when stratified by age, PGT-A was shown to improve live birth rates strictly when performed on the embryos of women over age 35.[9] The effect of patient age is also seen in the retrospective cohort study by Kucherov et al[10] analyzing 133,494 autologous IVF cycles. Their study measured cumulative live birth rate as an outcome and showed that use of PGT-A was actually associated with decreased cumulative live birth rates in the majority of patients, except those over 40.[10]

Regarding studies assessing the cost-effectiveness of PGT-A, Table 1 includes a summary of the current body of literature on the topic including study design, findings, and major limitations. Neal et al[11] used a decision analytic model with a combination of actual clinical

TABLE 1
Summary of Studies Assessing Cost-Effectiveness of PGT-A

Authors	Year Published	Study Design	Location	Sample Size	Outcomes/Highlighted Findings	Study Limitations
Murugappan et al	2015	Decision analytic model	United States	N/A	PGT-A strategy was more expensive, had a lower live birth rate, and lower clinical miscarriage rate.	Restricted to women with unexplained RPL
Collins et al	2017	Decision analytic model	United States	N/A	PGT-A is a cost-effective approach to improve live birth rate in women over 37.	Restricted to women over 37-year-old, small study (about 100 couples), single fresh embryo transfer.
Neal et al	2018	Decision analytic model	United States	8998 patients	Cumulative reproductive costs to achieve a live birth	Single oocyte retrieval, assumption miscarriage managed with D&C and that no ectopic pregnancy
Somigliana et al	2019	Theoretical model	Italy	N/A	PGT-A strategy becomes more cost-effective after age 35.	Theoretical model, no time to pregnancy analyses
Lee et al	2019	Microcosting methods, nonparametric bootstrap methods	Australia	2093 ART cycles	Cost-effectiveness improves with age and number of blastocysts.	Restricted to women over 37 years old, location, repeated cycles
Antero et al	2021	Decision analytic model	United States	N/A	Not cost-effective compared with IVF alone	Restricted to donor oocyte cycles
Lee et al	2021	Probabilistic decision tree	United States	158,665	Better live birth outcomes and economic burden in patients under the age of 35	Restricted to the United States
Nadgauda et al	2022	Review of cost-effectiveness analyses	United States	15 studies included	PGT-M consistently cost-effective; PGT-A only cost-effective in 60% of studies	N/A

data and literature-based assumptions. Gathering data from over 74 IVF centers, the study's primary outcome looked at "cumulative IVF-related costs to achieve a live birth or exhaust the embryo cohort from a single oocyte retrieval."[11] The data showed cumulative birth rates were similar in each group once all embryos are exhausted; however, PGT-A reduced the time in treatment by 4 months and led to fewer failed transfers and clinical miscarriages compared with IVF alone in patients with multiple embryos.[11] This study included over 8000 patients across a wide breadth of IVF centers thereby increasing generalizability. Putting a monetary value on this, the study estimated that for patients with greater than 1 embryo, the cost savings of PGT-A can range between $931 and $2411 when accounting for saved healthcare costs and decreased time in treatment. In addition, an age response effect on cost-effectiveness was also noted in this study.

The increased value of PGT-A in populations of older women is a consistent thread in the literature. This was further confirmed in the study by Lee et al[12] that reviewed over 100,000 IVF cycles and found that based on the cost per live birth, IVF without PGT-A was preferred in patients younger than 35. This study also estimated that the rates of intended PGT-A hover around 15%–20% of patients.[12] Building upon the hypothesis that PGT-A use in older patient populations can improve outcomes, Collins et al used a decision analytic model for women over 37 years who had undergone a successful oocyte retrieval with at least 1 blastocyst to assess cost estimates of PGT-A. The study used a sensitivity analysis and showed that PGT-A offered a 4.2 percentage point increase in live birth rate for an additional cost of $4509, yielding an incremental cost-effectiveness ratio of $105,489 per additional live birth. The incremental cost-effectiveness ratio measures the difference in costs divided by the difference in outcomes. In addition, the study suggested that this ratio is below the expected cost of achieving a live birth with IVF in this specific patient population, a value estimated to be $145,063. Therefore, this study argues that in patients over 37 years, PGT-A may be a more cost-effective solution than IVF without PGT-A given the reduced time to treatment and lower miscarriage rate.

In a similar study looking at an Australian population of "assisted reproductive technology-naive women

aged ≥37 years," Lee et al[13] used microcosting methods to determine the cost-effectiveness of PGT-A compared with morphological assessment. They concluded that the cumulative live birth rate mean healthcare costs per patient were $22,962 for the PGT-A group and $21,801 for the morphologic assessment group, yielding an incremental cost-effective ratio of $28,103 for an additional live birth with PGT-A.[13] The study also assesses a willingness to pay threshold, which the World Health Organization describes as "an estimate of what a consumer of healthcare might be prepared to pay for a health benefit."[14] The authors reported that at a willingness-to-pay threshold of $50,000 and above, there is more than an 80% probability of PGT-A being cost-effective from the healthcare perspective and a 50% likelihood from a patient perspective.[13] These conclusions are revealing because they address both the patient and healthcare costs, which are not always considered.

The impact of PGT-A on reducing miscarriages has been further studied as a cost-effective benefit. In their retrospective cohort study of 300 patients treated for recurrent pregnancy loss (RPL), Murugappan et al[15] posed the question of whether managing patients with unexplained RPL expectantly as opposed to with IVF and PGT-A would lead to improved outcomes. Their hypothesis was based on the principle that the majority of first trimester losses are caused by chromosomal abnormalities/aneuploidy and thus using PGT-A could reduce miscarriages by reducing the likelihood of an aneuploid pregnancy in a patient with RPL. The results of their decision analytic model showed a live birth rate of 53% in the IVF/PGT-A group versus 67% in the expectant management group. The clinical miscarriage rate was 7% in the PGT-A group and 24% in the expectant management group.[15] These numbers can be interpreted in various ways, but the main takeaway seems to be that while IVF/PGT-A may decrease the miscarriage rate, it did not significantly increase the live birth rate. In addition, from a cost-perspective, their model found that the IVF/PGT-A strategy was 100-fold more expensive, costing $45,300 per live birth compared with $418 per live birth with expectant management. The authors estimated that the live birth rate would need to be 91% in the IVF/PGT-A group for PGT-A to be considered cost-effective in this population.[15]

A small subset of studies has considered the role of PGT-A in patients using donor oocytes. Antero et al[16] created a decision analytic model looking at the cost of IVF with PGT-A compared with IVF alone in achieving a live birth in donor oocyte cycles. They pursued this hypothesis given that the "highest pregnancy and live birth rates from any IVF procedure utilize donor oocytes."[16] They concluded that IVF alone with donor eggs had a net monetary benefit (NMB) of $124,044 per live birth rate compared with IVF with PGT-A using donor eggs. These conclusions support the prior literature as one must assume that donor eggs are below the age-dependent cost-effectiveness seen in other studies. Most donor eggs come from women below 35 years old, and thus PGT-A use is unlikely to be cost-effective in IVF cycles utilizing donor oocytes.

Ultimately, there are several potential factors to think about when discussing the utility and cost-effectiveness of PGT-A with patients. As summarized in the studies above, PGT-A may be a cost-effective option in certain patient populations including patients with history of miscarriages and those over the age of 35. However, discussions regarding the technology and science of preimplantation testing, the impact of mosaicism, and false-positives must be included in shared decision-making conversations with interested patients. It is important to acknowledge that PGT-A provides information that could prove incomplete and thus prevent a successful outcome. For example, in some cases, the incidence of mosaicism has been estimated to be up to 20%, and one has to wrestle with the idea that not all discarded embryos have a 0% chance of live birth.[17] Many of these mosaic embryos can likely lead to normal pregnancies, with estimates of healthy live births in up to 30% of mosaic embryo transfers.[18] In addition, although PGT-A provides information regarding aneuploidy, it does not guarantee a healthy pregnancy or future child. Further, PGT-A is considered a screening tool, with prenatal genetic testing in pregnancy still recommended, potentially adding to an already growing financial burden.

Finally, there are several limitations to the literature. Most of the studies analyzed in this review relied on mathematical models, which have underlying assumptions built into them. For example, the study by Antero et al[16] assumed a donor age under 30 years old for donor oocytes. While this may be a reasonable assumption, it may not necessarily be true, and one can argue that the true value of a study relies on whether or not it can be generalized to typical practice.[19] In addition, each study estimates different costs of PGT testing because the costs range widely, and many do not include costs to the IVF clinic such as the need to hire specifically trained embryologists or added the labor time involved in embryo biopsy and cryopreservation.[19] Still, the literature shows that there are some benefits to PGT-A, and more research should be invested in understanding the populations who appreciate improved outcomes and the cost-benefit ratio. It is important to determine whether expensive add-ons are cost-effective because this aids in patient counseling regarding benefits and

potential justifications of the costs incurred. However, as outlined by ASRM, cost-effectiveness is difficult to quantify in a field with varying insurance coverage and with IVF treatment costs being both location and clinic dependent. In the meantime, the decision to offer PGT-A testing must rely on shared decision-making between the physician and patient that includes careful consideration of patient-specific factors such as age, economic ability and willingness, infertility, and clinical history.

CONCLUSIONS

In conclusion, limited studies on PGT-A have shown that cost-effectiveness is dependent on patient age as well as economic perspective. The threshold at which it has the greatest clinical impact has varied between a maternal age of 35 and 38 years, with the overall conclusion that it benefits women who undergo IVF at a later age. In addition, there is some consensus regarding its ability to reduce clinical miscarriages, which can have an impact on societal costs and psychological burden to the patient. From an economic perspective, it is important to understand what motivates people to pursue PGT-A testing because certain aspects of PGT-A cannot be quantified. Further studies attempting to qualify patients' experiences with PGT-A and personal perception of cost-effectiveness should be undertaken.

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