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Role of Preimplantation Genetic Testing in In-Vitro Fertilization

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Abstract

Preimplantation genetic testing (PGT), a major component of assisted reproductive technology (ART), allows embryo screening prior to implantation of in vitro fertilization (IVF) cycles. In the last 30 years, it has progressed to less restrictive chromosome assessment through fluorescent in situ hybridization to an in-depth genome assessment by next-generation sequencing. There are three broad categories of PGT - PGT-A, PGT-M, PGT-SR - each has specific objectives, e.g. to reduce the potential risk of miscarriage or the inheritance of hereditary diseases. Some indications consist of the presence of advanced maternal cloister, frequent implantation pierce or fetal dissolution, serious male factor sterility, and established abnormalities in the sovereign parents. Addition of laboratory manipulations such as trophectoderm biopsy, vitrification and optimal culture conditions has led to enhancement of accurateness and safety. There is positive evidence of benefits in specific groups, such as implantation in selected groups, fewer spontaneous pregnancies, and shorter time to pregnancy but its role in the low-risk population is controversial. Ethics and legal solutions vary depending on the country, and there is much debate over the limitation of embryo selection, fair accessibility, and justice. The existing issues deal with the mosaicism interpretation, cost management, and settling technical limitations. Non-invasive testing, embryo selection by artificial intelligence, and more accurately pinpointed genomic tools are all potential avenues of development, and there is a need to feed the introduction of these technologies into personalized reproductive care into an ethical framework.

Keywords: Preimplantation genetic testing, IVF, PGT-A, PGT-M, Assisted reproductive technology

Introduction

It is estimated that “infertility affects 8 to 12 % of all couples across the world,” not only posing a medical difficulty but also a considerable emotional, social, economic burden on the possible progenitors of a child [1]. Since its initial conception more than forty years ago, in vitro fertilization (IVF) has evolved out of an experimental innovation to become a well-established reproductive procedure with over eight million children being born across

the globe because of it [2]. Nevertheless, these success rates are low, live birth rates per cycle rates at most clinics do not exceed an average of 30-40 % [3]. Among the reasons is the fact that most embryos have chromosomal abnormalities that can reduce the chance of implanting and expose them to the likelihood of abortions [4]. This has led to incorporation of genetic screening into assisted reproductive technologies (ART) in a bid to pick out embryos that have the best possibility of initiating a healthy pregnancy. "Preimplantation Genetic Testing (PGT) refers to a set of laboratory-based methods that are employed to examine the genetic make-up of embryos created by IVF prior to transfer into the uterus [5]." Although PGT does not involve any benefit, identifying the embryos that are free of a specific chromosomal abnormality or a pathogenic gene variation, which would otherwise occur, enables more considered selection, decreasing the risk of transferring an inherited disorder, and eventually in certain patient groups, it can improve the number of offspring born [6]. The procedure was adopted initially in the initial 1990s in which embryo biopsy was allied with fluorescence in situ hybridization (FISH) to detect sex-name conditions [7]. "The use of next-generation sequencing (NGS) has made it possible to examine the genome at high resolution and is capable of detecting single-gene abnormalities and chromosomal aberrations with increased accuracy [8]."

PGT can be divided into three general categories: PGT-A to screen aneuploidy, PGT-M to detect monogenetic, and PGT-SR to screen structural chromosome rearrangement [9]. All of them fit dissimilar clinical requirements. PGT-A is commonly performed against a background of advanced maternal age or recurrent implantation failure of an exclusive embryo, or recurrent miscarriage, reflecting the observation of the increased frequency of aneuploid in elderly mothers [10]. PGT-M is applicable when a couple has an identified risk of passing on single-gene disorders, e.g. thalassemia or cystic fibrosis [11], whereas PGT-SR is especially relevant to people with balanced chromosomal translocations or inversions- changes that are commonly known to be associated with recurrent pregnancy loss [12]. Effective PGT depends on accurate embryo biopsy and accurate genetic diagnosis. "It is possible to conduct a biopsy in multiple stages: polar body biopsy prior to fertilization, cleavage-stage biopsy on day 3 or trophectoderm biopsy at a blastocyst stage on day 5 or 6 [13]." The medium used depends on reliability of diagnosis, survival of an embryo, and clinical outcome. Improvements in cryopreservation, notably the use of vitrification, have improved the workflow in that frozen embryos can be biopsied, with subsequent re-freezing without decreasing implantation capacity, allowing ample timeframe in order to conduct genetic analysis [14]. It has been shown via clinical studies that PGT use may enable higher implantation rates, reduction in the risk of miscarriage, and reduce the duration to successful pregnancy in certain subgroups [15]. But there is no consistent benefit within every population. The issue of cost-effectiveness, access difference, and ethical boundaries still exist, and an appropriate selection of cases is valuable. The history of the technology follows the one of IVF. FISH-based techniques were only able to measure just a handful of chromosomes [7] and gave partial genetic patterns and sometimes provided false negatives in the 1990s. During the 2000s, array comparative genomic hybridization (aCGH) extended testing to the chromosome set as a whole in a single test [8]. Since then NGS has become the platform of choice, providing superior resolution and mosaicism detection i.e. existence alongside in an embryo [8, 9].

Quantifiable improvements have been made as a result of these laboratory developments. PGT based on NGS has been linked with a higher implantation success in some higher risk so-called patient populations, most notably women aged 37 years and above [10]. However, the randomized data have not, across studies, demonstrated the significant increase in the rates of live births in younger women with good prognoses [15]. Findings of such nature justify the use of unique treatment approaches as opposed to universal techniques. PGT indications are clear:

"advanced maternal age", "recurrent pregnancy loss", "multiple failures at IVF", "severe malefactor infertility" and "parental chromosomal anomaly" [10, 11]. The risk of miscarriage can be reduced in couples with one member with a balanced translocation by using PGT-SR to choose the embryos with normal or balanced karyotypes [12]. PGT-M on the other hand is an alternative to prenatal diagnosis in individuals at risk of transmitting serious single gene disorders and so might later in pregnancy be faced with difficult decisions. It is also adopted unevenly across countries and depends on how regulated it is, the way it is funded and its cultural acceptance of genetic testing. In Europe, some nations restrict it to severe disease prevention, and others provide its wide use [6]. It is important to adjust treatment guidelines to regional regulations, and patient desires. The correctness is conditional upon all the stages of the process. Blastocyst stage IV tissue trophectoderm biopsy has become the norm because only a few cells are sampled, with no interference of the inner cell mass, thus increasing reliability [13]. This technique only works better than the cleavage-stage biopsy which samples only one cell [9]. DNA is subsequently amplified and examined after biopsy utilizing NGS which has high sensitivity to detect small chromosomal aberrations and mosaicism in contrast to aCGH[8]. Close attention to quality is needed, because failure to contaminate/amplify would affect findings [14]. The young women have less certain benefits, and objections still exist in the part of disposing of embryos that are labeled as mosaic [15]. This still argues regarding the possibility of PGT-A as routine or not [6, 9].

Ethics make it even more complex. One of the aspects that have been posited by the supporters is that of PGT as preventative measure against severe disease, and conversely critics fear that it may lead to non-medical selection of embryo [5]. Comprehensive counseling helps to make sure that the choices are based on medical facts as well as personal convictions. The topic could be changed by future developments. "The possibility of eliminating biopsy and enhancing acceptance may be provided by non-invasive PGT (niPGT) with the use of cell-free DNA obtained in embryo culture media [14]." Machine learning aimed at combining morphological and genetic information in a manner that would rank embryos is also under development [9]. High costs are a barrier especially in the lower-income settings. The broader access will be centralized through the creation of low-cost testing tools and sustainable financing. With the advancements in technology, a clinican should not just focus on the growth of science but also observe the guidelines in ethics that come along. This paper has the purpose of providing a comprehensive description of PGT in IVF-its track record, the present uses, technicalities, clinical outcomes, shortcomings, ethical issues, and the more recent dynamics-in order to enable patient-centered reproductive care, informed by evidence.

Evolution of Preimplantation Genetic Testing in IVF

"Preimplantation genetic testing (PGT) was proposed in the early 1990s; with the introduction of embryo biopsy in assisted reproductive technologies to test whether an individual is affected by genetic abnormalities, prior to being transferred to the uterus [16]." "Its clinical application was mostly limited then to sex determination in X-linked disorders and as a screening method to detect a relatively small repertoire of chromosomal abnormalities and fluorescence in situ hybridization (FISH) was the mainstay diagnostic method." Although innovative at the time, FISH was limited both by the limited number of chromosomes it could analyse and by being comparatively low resolution in its analyses [17]. Limitations of FISH stimulated the creation of higher genetic platforms. "This has resulted in the introduction of array comparative genomic hybridization (aCGH), where, in the late 2000s, genome-wide analysis of all chromosomes, in a single assay, was possible [18]." The use of aCGH resulted in an enhanced ability to detect aneuploidy and increased assurance of embryo selection as a critical step in the development of PGT. Nonetheless, the procedure was also invasive, involved biopsy of the embryo and the results

had a longer turnover time. All this was made easier by the advancement of IVF laboratory techniques in the same time which made PGT practice better. Improvements in the system of micromanipulation, development of embryo culture and more effective procedures of vitrification permitted removal of small cell samples safely at sufficient post-thaw viability [19]. "Procedural change has particularly been a major one with the introduction of trophectoderm biopsy at the blastocyst stage that has replaced day-3 cleavage-stage biopsy to include sampling of multiple outer-layer and achieve a better diagnostic accuracy without interfering with inner cell mass [20]."

The sequential advances that occurred with next-generation sequencing (NGS) offered significantly increased levels of resolution, decreased per sample expense, and the potential to recognize minimal genetic anomalies, such as segmental aneuploidies and mosaicism [21]. "NGS increased the accuracy of diagnosis, which allows the selection of embryos with the highest implantation rates and likelihoods of live birth, and has now mostly supplanted FISH and aCGH in their use in daily clinical practice." Simultaneously, the optimization of the polymerase chain reaction (PCR) techniques permitted high specificity of the detection of single-gene mutations that could be used in preimplantation genetic testing in cases of monogenic diseases (PGT-M) [22]. The addition of PCR to the NGS process has simplified the procedure to one where more conditions can be screened at once without sacrificing accuracy. New studies have been aimed at lowering invasiveness and instead non-invasive PGT (niPGT) is being analyzed where cell-free DNA can be analyzed in the embryo culture medium [23]. Not yet fully validated, niPGT could in time replace the need of biopsy, thereby eliminating some of the procedural risks, lowering financial implications, and making it accessible to all at the same time giving the same type of chromosomal information.

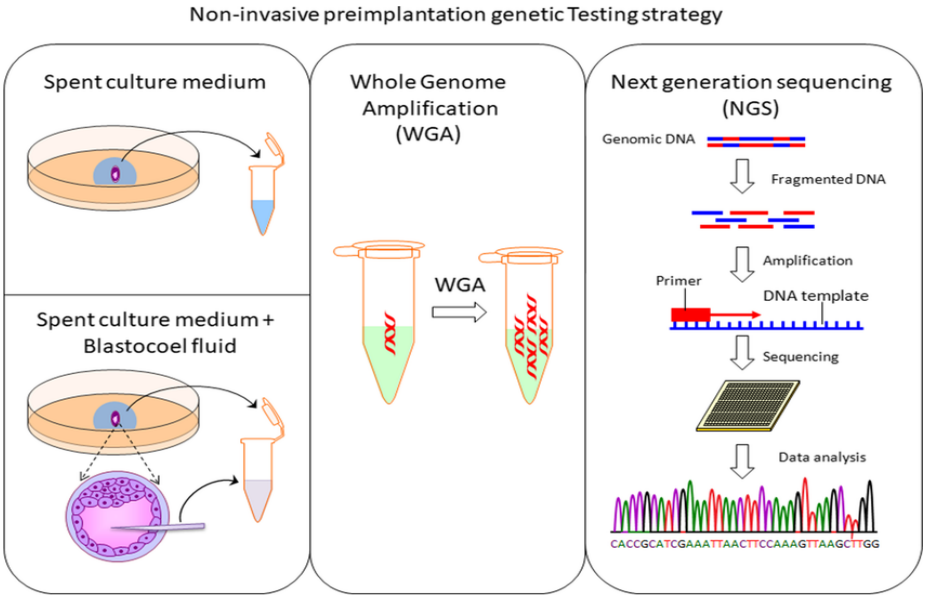


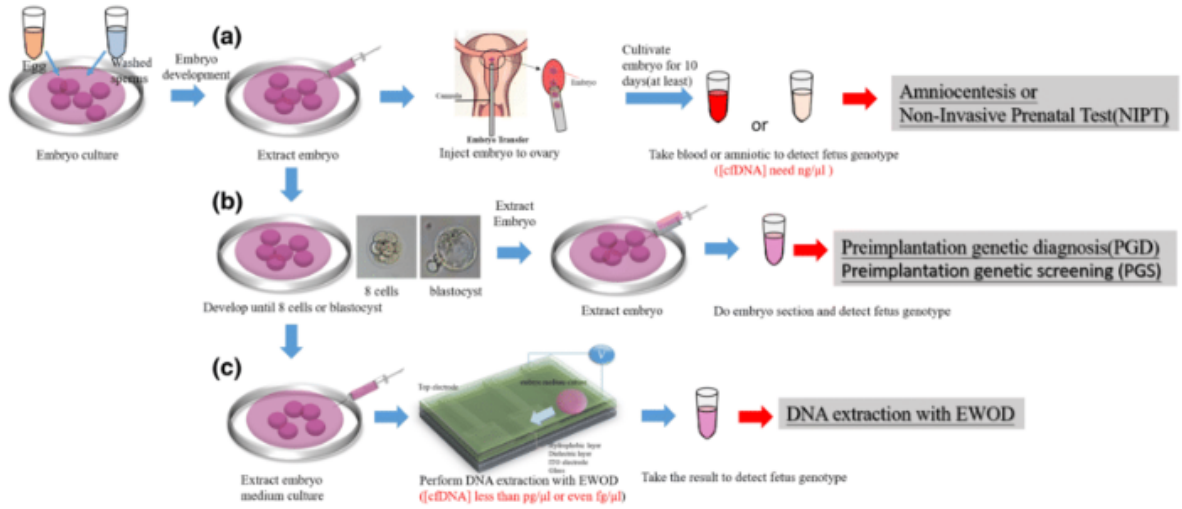
Figure 1: Non-invasive preimplantation genetic testing workflow [23]

Types of Preimplantation Genetic Testing and Their Applications

"Preimplantation genetic testing (PGT) is a general name given to a group of diagnostic methods that are aimed at evaluation of an embryo made through in vitro fertilization and before having it transferred into the uterus." The resulting classification system correlates with the genetic abnormality type being investigated, and consists of three major categories: pre-implantation genetic testing to detect aneuploidy (PGT-A), to detect monogenic disorders (PGT-M), and to detect structural chromosomal rearrangements (PGT-SR) [24]. These methods have

been tailored to meet different clinical expectations, and the determination of tackling one or the other kind of approach really depends on the genetic makeup of an individual, the past history of their reproductive life as well as the specific goals they want to accomplish. “PGT-A has the aim to identify numerical chromosomal abnormalities, or aneuploidies, the most frequent cause of failed implantation and an early miscarriage. Possibility of such errors increases steeply with progression of maternal age [25].” “PGT-A attempts to enhance implantation rates, reduce the risk of miscarriage and reduce the duration of pregnancy after selection of embryos with the appropriate chromosomal set.” “It is usually pointed out in advanced maternal age, recurrent implantation failure, recurrent pregnancy loss and in severe male factors.” By adhering to this, it aims to lower the emotional, as well as the costly expenses of repeated unsuccessful treatment processes and to improve the likelihood of a healthy infant born [26]. PGT-M is applicable in a situation where one or both of the intended parents are a known carrier of pathogenic mutation that causes single-gene disorders. It is used to detect embryos that are not affected by the particular mutation and, in this way, avoid or significantly diminish the possibility of the latter being inherited by offspring [27]. This method of testing is used in a variety of inherited diseases: autosomal recessive diseases, which include cystic fibrosis and beta-thalassemia, autosomal dominant like “Huntington's disease” and “X-linked diseases” such as “Duchenne muscular dystrophy.” Screening usually involves the use of focused molecular methods the most frequently used identifying the causative genetic variation, excessively polymerase chain response (PCR) or next-age sequencing (NGS). PGT-M could be an alternative to prenatal diagnosis in couples who have a strong family history and could avoid the difficult decisions that might be necessary later in the pregnancy.

“PGT-SR is to be used in couples where one of the partners has a balanced chromosome rearrangement e.g. translocation, inversion [28].” Carriers usually have no symptoms; however, they might give unsatisfactory gametes, where chromosomal content differs on a regular basis, which contributes to reoccurring miscarriages or congenital malformations. Such testing determines embryos that have a normal karyotype or the balanced copy of the rearrangement, hence decreasing the likelihood of the occurrence of adverse reproductive results. Similar to PGT-A, it uses the genomic platforms that provide high-resolution and can be used to detect minute imbalances across the genome. These classes of tests may be mixed in practice. “A woman of advanced maternal age who also carries a risk of a single-gene condition may be tested with PGT-A and PGT-M during the same cycle [29].” With this combined method, there are only chromosomally normal and the targeted mutation-free embryos that are chosen to increase the chances of a healthy pregnancy. Due to technological development, especially within the NGS, all PGT types have achieved an improved sensitivity and specificity level, and all genetic problems can be screened simultaneously during the same procedure [30]. “New developments in non-invasive PGT using cell-free DNA in spent embryo culture media has the possibility of eliminating the need of biopsy.” In the case of confirmation, the strategy would help in curbing procedural risk, enhance access, and maintain the swift diagnosis rates attributed to the use of PGT in modern reproductive services.



Each fetal genetic testing methods: a amniocentesis and non-invasive prenatal test (NIPT/NIPS2). b Preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS). c DNA extraction with EWOD

Figure 2: Overview of fetal genetic testing methods [30]

Indications for PGT in Clinical Practice

"Preimplantation genetic testing (PGT) is used in conjunction with in vitro fertilization (IVF) and the decision to use is based on very well-defined clinical indications." Such advice is evidence-based, given that some categories patients are at a higher risk of abnormalities in the genome of the embryos, implantation failure, and subsequent pregnancy, or other non-optimal reproductive processes [31]. Such meticulous selection of candidates enables good quality PGT to be utilized in a focused, cost-benefit and morally responsible way. Mother age is also one of the most frequent indicators of a PGT, especially PGT-A. Aneuploidy in the chromosomes of oocytes, therefore, rises extremely with age of women, mainly due to meioses division errors. Such increased aneuploidy rate leads to an increase in implantation failure risk, miscarriage, and incidents of congenital disorders development [32]. Clinicians have the ability to increase the likelihood of choosing a viable embryo in older patients by screening the embryos prior to transfer in terms of chromosomal integrity. This strategy can also reduce the interval to the achievement of successful pregnancy and lessening the amount of treatment cycles required.

Indications for HLA typing	Patients/ cycles	Cells analysed/ diagnosed	HLA-compatible embryos					Transfer cycles	Clinical pregnancies	Births/ babies	Successful stem cell transplantation
			Total	Normal	Carrier	Affected	Other				
Group I (HLA typing combined with PGD)	136/262	2367/2202 (93%)	394 (17.9%)	101 (4.6%)	175 (7.9%)	108 (4.9%)	10 (0.5%)	166	60	43/51	19
β-Thalassaemia	120/236	2132/1997	357	85	167	96	9	148	52	37/44[a,b,c]	16[d]
Wiscott Aldrich	3/4	49/43	7	3	2	1	1	4	3	3/3[e]	1
X-linked adrenoleukodystrophy	3/3	13/13	5	2	0	3	0	2	1	1/1	1
Fanconi anaemia	2/3	18/15	1	1	0	0	0	1	0		
α-Mannosidosis	1/4	35/25	2	1	0	1	0	1	0		
Gaucher syndrome	1/4	23/22	6	4	1	1	0	3	1[f]	0	
Hurler syndrome	2/3	35/28	5	2	1	2	0	2	0		
Hyper IgD	1/1	9/9	0	0	0	0	0	1[g]	0		
Glanzmann thrombasthenia	1/2	43/40	7	1	2	4	0	2	1	1/2	1
Sickle cell anaemia	1/1	5/5	2	0	2	0	0	1	1	1/1[h]	
Diamond Blackfan anaemia	1/1	5/5	2	2	0	0	0	1	1[i]		
Group II (HLA typing only)	35/65	622/539 (86.7%)	88 (16.3%)	–	–	–	–	46	14	9/11	2
Acute lymphoblastic leukaemia	15/23	215/189	26	–	–	–	–	14	5[f,i]	3/4[e,j]	
Acute myeloid leukaemia	10/17	155/128	23	–	–	–	–	14	4	2/3[i,k,l]	1
Diamond Blackfan anaemia	3/11	130/114	21	–	–	–	–	9	2[f]	1/1	1
Histiocytosis	1/3	37/33	8	–	–	–	–	3	1	1/1[h]	0
Chronic myeloid leukaemia	1/2	15/15	2	–	–	–	–	1	0		
Burkitt's lymphoma	1/2	14/9	4	–	–	–	–	2	1	1/1[h]	0
Aplastic anaemia	2/2	21/18	0	–	–	–	–	0			
Anaplastic anaemia	1/3	28/27	3	–	–	–	–	2	0		
Myelodysplastic syndrome	1/2	7/6	1	–	–	–	–	1	1	1/1[l]	0
Total	171/327	2989/2741 (92%)	–	–	–	–	–	212	74	52/62	21

HLA = human leukocyte antigen; PCD = preimplantation genetic diagnosis.
[a]Eighteen children are awaiting an appropriate time for stem cell transplantation.
[b]One transplantation could not be performed since HLA-incompatible child was born (patient consent given).
[c]One transplantation could not be performed since HLA-incompatible twins were born (patient consent given).
[d]For one patient, successful stem cell transplantation was performed, but the source cells could not be specified and the patient was lost to follow up.
[e]Two children are awaiting an appropriate time for stem cell transplantation.
[f]One pregnancy ended with missed abortion.
[g]HLA nonidentical but healthy embryo was transferred in this cycle with patient consent.
[h]One child is awaiting an appropriate time for stem cell transplantation.
[i]One pregnancy is ongoing.
[j]Twins were born preterm and cord blood was insufficient.
[k]One pregnancy was unembryonic.
[l]One affected child died before transplantation.

Figure 3: Summary of indications, PGD results and clinical outcomes [31]

Preimplantation genetic testing is another important indication in case of recurrent implantation failure. Alternatively, this state is traditionally characterized by the impossibility of a clinical pregnancy following a couple of transfers of morphologically high-quality embryos [33]. Its etiology is however, multifactorial, but in many occasions chromosomal abnormalities contribute heavily to its cause. Where this occurs, PGT would help in selecting embryos that have normal chromosomal complement and so, increase the likelihood of implantation in later treatment cycles. Repeated pregnancy loss also makes its own appearance among the motivating factors of choosing PGT. Recurrent miscarriage can cause some couples excessive emotional and physical distress and in a large percentage of the cases, such losses can be explained by the chromosomal aberration in the embryo [34]. PGT-A might be helpful preventing occurrence of recurrence and recurring chance of miscarriage because they enable the selection of solely euploid embryos. A valid indication is also seen by severe male factor infertility; in particular, when abnormal spermatozoa are prevalent. Sperm chromosomal defects may occur in a structural or numerical form which may lead to the production of aneuploid embryos [35]. PGT provides an extra layer of protection in this environment since it screens embryos before transfer, thereby reducing the chances of transferring sperm-borne genetic defects.

Genetic abnormalities carried by the parents is an established justification of use of PGT-M or PGT-SR. In situations where both or either of the partners is a carrier of a mutation of a single-gene disorder, PGT-M has the potential of preventing the transmission of the disorder to a child [36]. Equally, those who have balanced chromosomal translocations or inversions too may be the most benefited by PGT-SR, though it allows selection of embryos with either a normal karyotype or the balanced form of the rearrangement, which decreases risk of miscarriage or birth defects. PGT can sometimes be performed on donor gametes cycles, as well- in cases where

the donor is an elderly person or has a history of genetic disease [37]. Although donor screening plans are usually quite strict, PGT provides an extra measure of security as it can certify the normality of the chromosomes or dearth of aimed mutations in the created embryos by the utilization of donor gametes.

Laboratory and Technical Advances in PGT

The genetic testing used in preimplantation (PGT) has been developed in terms of embryology, micromanipulation, and higher genomic analysis. The fact is that, at all stages of culturing embryos until the last stage genetic interpretation, gradual improvements in the laboratory procedures have continuously enhanced the precision of the diagnosis as well as its reliability [38]. The shift to trophectoderm biopsy at the blastocyst stage instead of cleavage-stage biopsy was one such transformation. This method would entail taking out a few cells of the outer layer of trophectoderm of the embryo with protecting the inner cell mass and this will lessen the possibilities of harm to the fetus developing [39]. The method makes the diagnosis more certain and minimizes sampling error present at early stages due to the analysis of several cells instead of a single blastomere. The technique has also been associated with increased rates of implantation probably because of better selection of embryos. Improvement in the conditions of embryo culture has been equally considerable. Culture of cells to blastocyst stage requires the environment to be stable and one which is physiologically suitable. The advent of time-lapse incubators and continuous observation systems has enabled laboratories to ensure accurate temperatures and gases levels, moderate the effects of the environment and record extensive morphological and morphokinetic time-lapse data that is used to assess the embryo [40].

“At a conceptual level, via the technique of next-generation sequencing (NGS), PGT diagnostic capabilities have soared.” “In comparison with the older methods e.g. fluorescence in situ hybridization (FISH) and array comparative genomic hybridization (aCGH) which has low resolution and only detects whole-chromosome aneuploidies, NGS is far more accurate by providing greater resolution and the ability to detect subchromosomal imbalances and mosaicism [41].” “PGT-A, PGT-M, and PGT-SR can be multiplexed together, performed in one assay, and simplify workflows.” A priori, the polymerase chain reaction (PCR) is still required to detect single-gene mutation in PGT-M, whereas innovative approaches, such as multiplex PCR and whole genome amplification, have offered benefits in terms of sensitivity and decreased the risk of allele drop-out or sample contamination [42]. With NGS-based method, PCR enables simultaneous evaluation of chromosomal status and monogenic disorders, which is more efficient. Tomography and the use of vitrification have also become an important part of modern PGT. Cryopreservation after biopsy allows sufficient time during which verification of comprehensive genetic analysis may be performed over time and, ultra-rapid freezing gives good post-thaw survival with full maintenance of the developmental potential of the embryo [43]. It has become a customary procedure in the laboratories at PGT to have stringent quality control over the quality of results. Double-witnessing of all cell-handling procedures, amplification with positive (coding index) and negative controls, and inter-platform duplicate checks of amplification results are protective against errors [44]. Engagement in external schemes of quality assessment also guarantees the achievement of high levels of operation and performance standards.

Clinical Outcomes and Efficacy of PGT

The clinical usefulness of preimplantation genetic testing (PGT) should be judged based on its impact on preeminent reproductive outcomes i.e. implantation rate, miscarriage rate, time to pregnancy, and live birth rate. “The evidence shows that when used with special attention to demographic and genetic backgrounds of selected groups of potential patients, PGT can enhance the efficiency of in vitro fertilization (IVF) by improving embryo

selection [45].” “Among the most reliable advantages that it offers is that its miscarriage rates are substantially lowered, especially when PGT-A is used.” Since aneuploidy chromosomal aneuploidy is one of the major causes of early pregnancy loss, by transferring only euploid embryos, miscarriages risk can be minimized in contrast to morphological grading alone [46]. This is best seen in women of old maternal age and partners with repeated pregnancy loss. Other important outcome measures are implantation rate. As has been demonstrated, implantation will be more likely per transfer when a chromosomally normal embryo is transferred, even in situations when morphology does not indicate high viability [47]. That justifies elective single embryo transfer as a secure option and assists to avoid high gestations without decreasing the overall effectiveness. PGT may also reduce time to pregnancy since euploid embryos are given more preference and patients conceive sooner in less number of cycles. This time-efficient nature is especially valuable to those who have to deal with age-related fertility decrease since it will reduce the financial, physical and emotional wear and tear of successive IVF attempts [48]. The most important indicator of reproductive success, the live birth rate, has grown among certain subgroups. Patients older than 37 years, repeated implantation failure, carriers of chromosomal rearrangement have cumulatively higher live birth rates per cycle started using PGT included [49]. Conversely, the younger patients with high ovarian reserve generally have little benefit, which supports the importance of accurate patient selection. In addition to the aneuploidy screening, PGT-M and PGT-SR can prevent moving such embryos that will develop into babies with pathogenic mutations or have unbalanced chromosomal faults, which contributes to having a healthy customary child and decreasing the need in using the invasive prenatal diagnostics. Improving high-resolution next-generation sequencing resulted in advancement in clinical performance with the help of observance of minor chromosomal alteration and low-rate mosaicism that is not seen through previous technologies [51]. Although that has made classification of embryos better, it is still a research issue on how to approach mosaic embryos on the most clinically effective manner. Despite the non-guaranteed nature of PGT, especially when well-selected, with the quality laboratory methodologies and suitably individualized treatment planning, it may become a decisive effort at providing timely, healthy, and successful pregnancies [52].

Ethical, Legal, and Social Perspectives

Preimplantation genetic testing (PGT) remains a controversial issue that has elicited a lot of ethical, legal, and social debate since its inception to be used as part of Routine reproductive care. Although the technology is certainly positive as it prevents the transfer of severe genetic diseases to children and enhances some aspects of reproduction, it also presents thorny issues regarding the ethical limits of embryo selection and concepts of the overall repercussions of such technology utilization [53]. The extension of acceptable indications is one of the most controversial ethical problems. The consensus on the appropriate use of PGT would be to use it in preventing serious inherited disorders, but there is a stark contrast in views when PGT is used in late-onset diseases, non-medical characteristics or selective sex. Critics warn against the implications that such applications might have in reinforcing social discrimination and aiding in the commodification of human life [54]. The supporters, however, insist on reproductive autonomy, claiming that potential parents have the right to make informed decisions regarding the genetic makeup of children and that such decisions are to be implemented within the context of ethically responsible medical practice. Another sensitive ethical issue is what happens to embryos that are unsuitable to be transferred. The detection of embryos with genetic faults as a result of PGT can bring up the decision to dispose of the embryo, donate it to research purposes, or place in long-term storage, and all of these choices are subject to both legal standards and cultural and personal preferences [55]. These choices coincide with the deep-rooted religious and philosophical opinions concerning the ethical position of the embryo.

Regulations widely differ in all the countries as in some countries regulations only allow PGT to be used under specific medical reasons, sometimes even under a case-by-case basis, but others apply it more broadly, yet apply strict licensing and quality control standards [56]. This disparity may introduce inequality of access that would lead to seeking medical care in foreign countries by some patients. The protection of genetic information privacy is another important legal aspect, as the information mentioned is particularly sensitive.

The social implication of PGT extends wider than the freedom of choice to possible implications at the population level. Opponents caution that regard to genetic selection may undermine the social acceptance of non-disabled individuals, thus, strengthening discriminatory preferences [57]. Proponents argue that the new technology can potentially decrease the occurrence of severe genetic disease, decrease long-term expenditure by the health care industry, and enhance life quality of impacted families. The barrier of cost is also very big: in most healthcare systems, PGT is not publicly funded, and it leaves access publicly limited to the individual with wealth. This gap has encouraged the demand of changes in the policy, more insurance coverage, or special subsidies on the cases which have the medical indication [58]. In every setting, broad counseling and an active principle of informed consent process is necessary to abide by the principles of good ethics. The genetic counselling should give balanced overview of the possible benefit, constraints, and risks, making the patients to make choices that suit them in relation to their needs [59]. Realistic expectations can also be built up through such discussions because although PGT holds the promise of enhancing some outcomes, it does not guarantee reproductive success either.

Table 1: Limitations and Challenges in PGT

Limitation / Challenge	Description	References
Embryo mosaicism	Presence of both normal and abnormal cell lines within the same embryo can lead to diagnostic uncertainty and possible misclassification of embryo viability.	[60]
False positives and false negatives	Technical errors, amplification failures, or sampling bias during biopsy can produce inaccurate results, leading to viable embryos being discarded or affected embryos being transferred.	[61]
Biopsy-related risks	Although generally safe, embryo biopsy may cause cellular damage or developmental arrest in some cases, especially if performed at earlier stages or by less experienced personnel.	[62]
Cost and accessibility	High cost of PGT, often not covered by insurance or public funding, limits access to affluent patients, raising equity concerns.	[63]
Interpretation of mosaic results	Lack of universally accepted guidelines on transferring mosaic embryos leads to variable clinical practices and uncertainty in patient counselling.	[64]
Ethical concerns	Debates over embryo selection, disposal of abnormal embryos, and the expansion of PGT beyond medical necessity raise moral and societal issues.	[65]
Limited benefit in certain	In younger women or those with high-quality	[66]

populations	embryos, PGT may not significantly improve live birth rates, making its routine use debatable.	

Future Directions and Emerging Trends

Emerging Trend	Description	Potential Impact	References
Non-invasive GT (niPGT)	Uses cell-free DNA from spent embryo ulture medium or blastocoel fluid; aims to void embryo biopsy; key challenges clude low fetal DNA fraction and ontamination.	Could reduce rocedural risks, oaden access, and wer technical arriers if validated.	[67]
Advances in enomic Platforms	Higher-depth NGS, long-read equencing, and single-cell multi-omics nprove detection of segmental changes, osaicism, and phasing accuracy.	Increases agnostic precision nd expands scope to ombined romosomal and ngle-gene testing.	[68]
Mosaicism nterpretation rameworks	Risk-stratified approaches based on osaic level, affected chromosome, and atient-specific factors replace binary ormal/abnormal classification.	May reduce nnecessary embryo scard and improve ilization of mosaic mbryos.	[69]
AI-Driven mbryo ssessment	Integrates time-lapse imaging, orphokinetics, metabolic profiling, and enomic data; validated through multi-enter datasets.	Improves embryo election accuracy and upports dividualized eatment planning.	[70]
Rapid PGT Vorkflows	Microfluidic and on-instrument equencing for same-day testing to enable esh transfers.	Eliminates freeze-l cycles when not edically indicated, otentially improving utcomes.	[71]
Polygenic Risk-nformed Selection PGT-P)	Screens for multiple common variants to stimate disease risk; controversial due to nall effect sizes and ethical concerns.	Limited current ility; requires strong onsent and ethical versight.	[72]
Automation and uality Systems	Closed biopsy systems, barcoding, ontamination monitoring, and specialized roficiency testing.	Standardizes orkflows, reduces uman error, and creases reliability.	[73]

Conclusion

Preimplantation genetic testing (PGT) marks a notable advancement in reproductive medicine, allowing embryo selection to be informed by comprehensive genetic evaluation rather than morphology alone. When applied in clearly defined clinical settings—such as advanced maternal age, recurrent miscarriage, or documented genetic risk—it can improve reproductive outcomes, lessen both emotional and physical burdens, and help prevent the transmission of serious hereditary disorders.

Despite these benefits, PGT is not a one-size-fits-all solution. Its success is influenced by multiple factors, including the characteristics of the patient, the number and quality of embryos available, and the technical proficiency of the laboratory team. Ongoing challenges—ranging from the interpretation of mosaicism and management of biopsy-related risks to persistent inequities in access driven by high costs—highlight the importance of further research, standardized clinical protocols, and supportive policy measures.

The ethical and social dimensions of PGT remain central to its responsible application. Questions surrounding the permissible extent of embryo selection and the fate of surplus embryos require open public discussion and regulation that is both transparent and culturally sensitive. New innovations, such as non-invasive PGT and artificial intelligence–enhanced embryo assessment, offer the potential to broaden clinical utility while reducing procedural invasiveness.

Ultimately, the integration of PGT into IVF should follow an individualized, evidence-based framework. Such an approach must balance technological capability with strong ethical safeguards, ensuring that patients gain the advantages of scientific progress while making informed reproductive choices that reflect their values.

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