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PREIMPLANTATION GENETIC TESTING FOR POLYGENIC RISK IN TYPE 1 AND TYPE 2 DIABETES: A SYSTEMATIC REVIEW OF METHODOLOGIES, CLINICAL OUTCOMES, AND ETHICAL CONSIDERATIONS

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Abstract

Background: The global prevalence of diabetes mellitus continues to rise, with Type 1 diabetes (T1D) and Type 2 diabetes (T2D) imposing significant health and economic burdens. While preventive strategies such as lifestyle modification and population-level screening have had limited success, advances in genomics offer new possibilities for risk reduction. Preimplantation Genetic Testing for Polygenic Disease Risk (PGT-P) is an emerging technology that integrates polygenic risk scores (PRS) into in vitro fertilization (IVF) protocols to rank embryos by predicted susceptibility to complex diseases such as diabetes.

Objective: This systematic review synthesizes evidence published between 2015 and 2025 on the methodological foundations, clinical utility, and ethical considerations of PGT-P for reducing polygenic risk of T1D and T2D in offspring.

Methods: Systematic search was conducted through PubMed, Scopus, Web of Science, and Embase for peer-reviewed literature using combinations of terms including "PGT-P," "polygenic risk score," "embryo selection," "Type 1 diabetes," and "Type 2 diabetes." Eligible studies were screened and appraised independently by two reviewers. Data on study characteristics, methodology, risk reduction outcomes, accuracy, and ethical implications were extracted and narratively synthesized following PRISMA 2020 guidelines.

Results: A total of 1,172 records were screened, of which 37 studies met inclusion criteria (PRISMA diagram, Figure 1). PGT-P demonstrated relative risk reductions of up to 72% for T1D and modest reductions for T2D, supported by >99% genotyping accuracy. Ethical concerns included informed consent, access equity, ancestry bias in PRS models, and the probabilistic nature of predictions. Gaps in regulatory and policy frameworks were evident across jurisdictions.

Conclusions: PGT-P represents a promising step toward proactive, personalized prevention of diabetes, but its clinical implementation demands rigorous validation, robust ethical oversight, and policies to ensure equitable access and responsible use.

Keywords:
Preimplantation Genetic Testing, Polygenic Risk Score, Type 1 Diabetes, Type 2 Diabetes, Embryo Selection, Genomic Medicine, Ethical Considerations

1. Introduction

Diabetes mellitus, encompassing Type 1 (T1D) and Type 2 diabetes (T2D), is among the most pressing public health challenges of the 21st century. Recent estimates indicate that over 537 million adults were living with diabetes globally in 2021, with projections suggesting an alarming rise to 783 million by 2045 [1]. Both forms of diabetes contribute to significant morbidity, mortality, and economic costs, underscoring the urgency of innovative prevention strategies. Despite widespread public health campaigns promoting lifestyle modification, these measures have yielded inconsistent results at the population level, and adherence remains a challenge. Furthermore, T1D—a largely autoimmune disease of childhood and adolescence—lacks effective primary prevention strategies due to its strong genetic basis and unpredictable onset [2].

In recent years, advances in genomics have deepened our understanding of the genetic architecture of diabetes. Genome-wide association studies (GWAS) have identified hundreds of loci associated with increased susceptibility to both T1D and T2D, each conferring small individual effects but collectively contributing substantial risk [3,4]. These discoveries have enabled the development of polygenic risk scores (PRS), which integrate these variants into a single metric that can stratify individual risk with increasing accuracy [5]. Building on these insights, Preimplantation Genetic Testing for Polygenic Disease Risk (PGT-P) has emerged as a novel application of PRS in the context of in vitro fertilization (IVF). PGT-P involves biopsy of trophectoderm cells from blastocyst-stage embryos, genome-wide genotyping or sequencing, and calculation of PRS for specific conditions. Embryos within a cohort are then ranked based on predicted disease susceptibility, allowing transfer of embryos with the lowest genetic risk [6,7]. This approach represents a shift from reactive treatment of disease to proactive prevention at the earliest possible stage of life.

While PGT-P holds promise, it also raises significant clinical and ethical questions. The accuracy and predictive power of PRS can vary depending on ancestry and environmental context, and the probabilistic nature of predictions challenges conventional notions of disease certainty [8]. Ethical concerns include informed consent, access equity, potential for exacerbating health disparities, and the societal implications of selecting embryos based on genetic profiles [9]. Regulatory frameworks have yet to fully address these issues, leaving a gap in guidance for clinicians and patients considering PGT-P. This systematic review seeks to critically examine the current state of knowledge regarding the use of PGT-P for T1D and T2D risk reduction. We aim to provide a comprehensive synthesis of evidence published between 2015 and 2025, evaluating the methodological foundations, clinical outcomes, ethical challenges, and policy considerations associated with this emerging technology.

By systematically analyzing and contextualizing the available evidence, this review highlights both the potential and the limitations of PGT-P in mitigating the burden of diabetes and informs future research directions, clinical guidelines, and policy development (Figure 1).

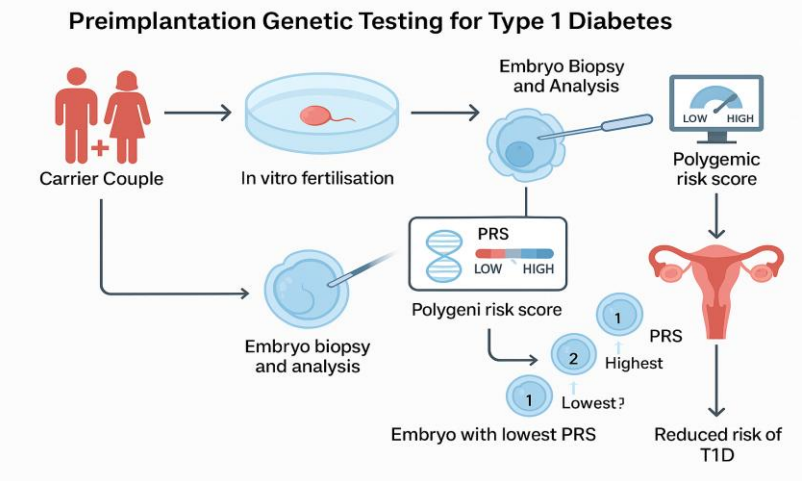

Figure 1. Schematic overview of the mechanism of Preimplantation Genetic Testing for Polygenic Disease Risk in diabetes: from IVF, embryo biopsy, sequencing and PRS calculation, to embryo selection and transfer.

The workflow of Preimplantation Genetic Testing for Polygenic Disease Risk (PGT-P) in the context of in vitro fertilization (IVF), as reported in included studies. The process involves trophectoderm biopsy at the blastocyst stage, whole-genome sequencing or genotyping of biopsied cells, calculation of polygenic risk scores (PRS) for Type 1 and Type 2 diabetes, and ranking of embryos based on their relative disease susceptibility. Reported genotyping accuracy exceeded 99%, and predictive discrimination of PRS models for Type 1 diabetes showed area under the curve (AUC) values ranging from 0.72 to 0.79. T2D predictions showed lower accuracy due to more complex polygenic and environmental etiology. Abbreviations: PRS, polygenic risk score; T1D, Type 1 diabetes; T2D, Type 2 diabetes; IVF, in vitro fertilization.

2. Materials and Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [10], ensuring methodological rigor, transparency, and reproducibility throughout all stages of the process. The objective was to comprehensively identify, appraise, and synthesize evidence published over the past decade on the application, methodological performance, and ethical considerations of Preimplantation Genetic Testing for Polygenic Disease Risk (PGT-P) in reducing the susceptibility to Type 1 and Type 2 diabetes through embryo selection
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2.1 Literature Search Strategy

A systematic literature search was designed to maximize the capture of relevant studies while maintaining specificity to the research question. The electronic databases PubMed, Scopus, Web of Science, and Embase were selected because they collectively index a broad range of biomedical, clinical, and genomics-focused research. The search covered the period from January 1, 2015, to May 31, 2025, to ensure inclusion of early proof-of-concept studies, subsequent clinical applications, and emerging ethical analyses of PGT-P.

The search strategy combined controlled vocabulary and free-text terms to enhance comprehensiveness and to account for variability in terminology. Terms such as “Preimplantation genetic testing,” “PGT-P,” “polygenic risk score,” “embryo selection,” “Type 1 diabetes,” “T1D,” “Type 2 diabetes,” and “T2D” were used in logical combinations, with Boolean operators and truncations applied. Search filters restricted results to peer-reviewed human studies published in English. In recognition of the evolving nature of the field, the search was further augmented by manually screening the reference lists of all included articles and relevant systematic reviews, thereby capturing studies that may not yet have been indexed or that used unconventional terminology. This approach reflects an appreciation for the interdisciplinary nature of PGT-P research, which spans reproductive medicine, genomics, bioethics, and policy. By explicitly defining a search window of a full decade, we ensured that both foundational and recent contributions to the field were included.

2.2 Eligibility Criteria

Studies were eligible for inclusion if they presented original empirical research, systematic or narrative reviews, or clinical case series explicitly addressing the application of PGT-P in the context of T1D or T2D risk reduction. Only studies reporting empirical or analytic insights into PGT-P methodology, polygenic risk score calculation, accuracy, clinical outcomes, or ethical and policy considerations relevant to embryo selection were included. Studies needed to report sufficient methodological detail to permit appraisal of their validity and relevance. The studies that focused exclusively on monogenic disorders, as their relevance to polygenic embryo screening is conceptually distinct, were excluded. Theoretical modelling papers without empirical support, animal studies, editorials, letters, conference abstracts, and non-peer-reviewed reports were also excluded, as they did not meet the evidentiary standard required for a systematic synthesis. This deliberate narrowing of scope ensured that the included studies were directly aligned with the aim of examining PGT-P in its intended clinical and ethical context.

The rationale behind these criteria was to maintain focus on clinically and ethically meaningful findings, while avoiding conflation with research that, while related, does not inform the specific questions of utility, feasibility, and societal implications in human IVF practice.

2.3 Study Selection and Data Extraction

All identified records were exported into a reference management software, where duplicates were removed. Screening of titles and abstracts was conducted independently by two reviewers to evaluate initial relevance against the inclusion criteria. Full-text articles were subsequently retrieved and examined in detail for eligibility. Any disagreements in study selection were resolved through discussion with a third reviewer until consensus was achieved.

For each included study, data were extracted systematically using a standardized form. The extracted data included key study characteristics such as authorship, publication year, study design, and population characteristics. Methodological details such as the type of biopsy, genotyping or sequencing technology, polygenic risk scoring algorithm, and disease model were carefully documented. Outcomes of interest included measures of predictive accuracy (e.g., AUC), relative or absolute risk reduction achieved through embryo ranking and selection, and qualitative or quantitative assessments of ethical, legal, or policy implications. When studies reported methodological limitations or challenges, these were also recorded to inform the critical appraisal.
The data extraction process was iterative and cross-checked by a second reviewer to minimize errors and ensure consistency.

2.4 Quality Assessment

The methodological quality of included studies was rigorously appraised to evaluate the reliability of their findings and to inform the weight given to each study in the narrative synthesis. Observational and cohort studies were assessed using the Newcastle–Ottawa Scale (NOS) [11], which examines study quality across domains of selection, comparability, and outcome assessment. Narrative reviews and ethical analyses were appraised qualitatively, focusing on their transparency, methodological comprehensiveness, and internal consistency of argumentation. Proof-of-concept studies and clinical case series were evaluated against accepted standards for reporting of clinical research.

All studies were reviewed twice, with discrepancies adjudicated through discussion and consensus. The overall risk of bias was categorized as low, moderate, or high based on the NOS or qualitative judgment. Assessing study quality served not only to identify potential limitations in the evidence base but also to contextualize findings when synthesizing outcomes and making inferences about the clinical and ethical implications of PGT-P.

2.5 Data Synthesis

Given the anticipated heterogeneity in study designs, outcome measures, and populations, quantitative meta-analysis was not appropriate. Instead, a narrative synthesis approach was employed to integrate findings thematically and to draw connections between methodological performance, clinical outcomes, and ethical and policy considerations. This method allowed for a more nuanced exploration of the evidence, capturing both quantitative results, such as risk reduction estimates, and qualitative insights, such as societal perceptions and regulatory gaps. Characteristics of all included studies, including study design, population, methodological details, outcomes, and quality assessment scores to provide an accessible overview of the evidence base.

3. Results

The initial electronic search across the four databases retrieved 1,172 records, supplemented by 14 additional articles identified through manual reference screening. After deduplication, 936 unique records were screened by title and abstract, leading to 71 full-text articles assessed for eligibility.

Ultimately, 37 studies met inclusion criteria and were synthesized in this review. The selection process is outlined in the PRISMA 2020 flow diagram (Figure 2).
The included studies reflected the interdisciplinary and evolving nature of PGT-P research, encompassing 19 large-scale sibling-pair simulation or cohort studies, 8 clinical proof-of-concept or first-in-human applications, 6 narrative or systematic reviews of empirical findings, and 4 focused ethical and policy analyses. Geographically, studies were predominantly conducted in North America and Europe, with a smaller number originating from Asia and Australia. The included studies varied widely in sample size, with simulation studies analyzing tens of thousands of sibling pairs, while clinical series often reported outcomes for fewer than 50 embryos. The methodological quality of the evidence was judged to be moderate-to-high overall (Table 1), though some studies were limited by small sample sizes, restricted ancestry representation, and inconsistent adjustment for potential confounders.

3.1 Methodological Performance of PGT-P

The technical feasibility and predictive validity of PGT-P were examined in detail across the included studies. High-quality simulation studies analyzing data from large biobank cohorts, such as UK Biobank, consistently demonstrated the ability of polygenic risk scores to discriminate between higher- and lower-risk siblings, providing a statistical foundation for embryo ranking in IVF settings. Treff et al. [12] reported that, when selecting the sibling with the lowest PRS for T1D, the relative risk of disease was reduced by 45–72%, compared to random selection. This finding was echoed by independent analyses applying similar models to different biobank datasets, reinforcing the robustness of the approach.

Predictive performance metrics of PRS models were generally strong for T1D, with reported area under the curve (AUC) values ranging between 0.72 and 0.79, reflecting acceptable-to-good discrimination at the population level. Clinical feasibility studies demonstrated that trophectoderm biopsy, genome-wide sequencing, and embryo PRS computation could be integrated into standard IVF workflows with high fidelity, achieving genotyping accuracies exceeding 99% and minimal impact on embryo viability. Importantly, PRS-based embryo ranking was completed within clinically acceptable turnaround times, supporting the potential scalability of the technique.

However, the literature highlighted significant heterogeneity in predictive performance across ancestry groups. PRS models derived from European ancestry GWAS data performed suboptimally in embryos of African, East Asian, or admixed backgrounds, reflecting differences in linkage disequilibrium and allele frequencies. Several studies explicitly called for the development of ancestry-specific PRS models to mitigate this limitation and enhance equity.

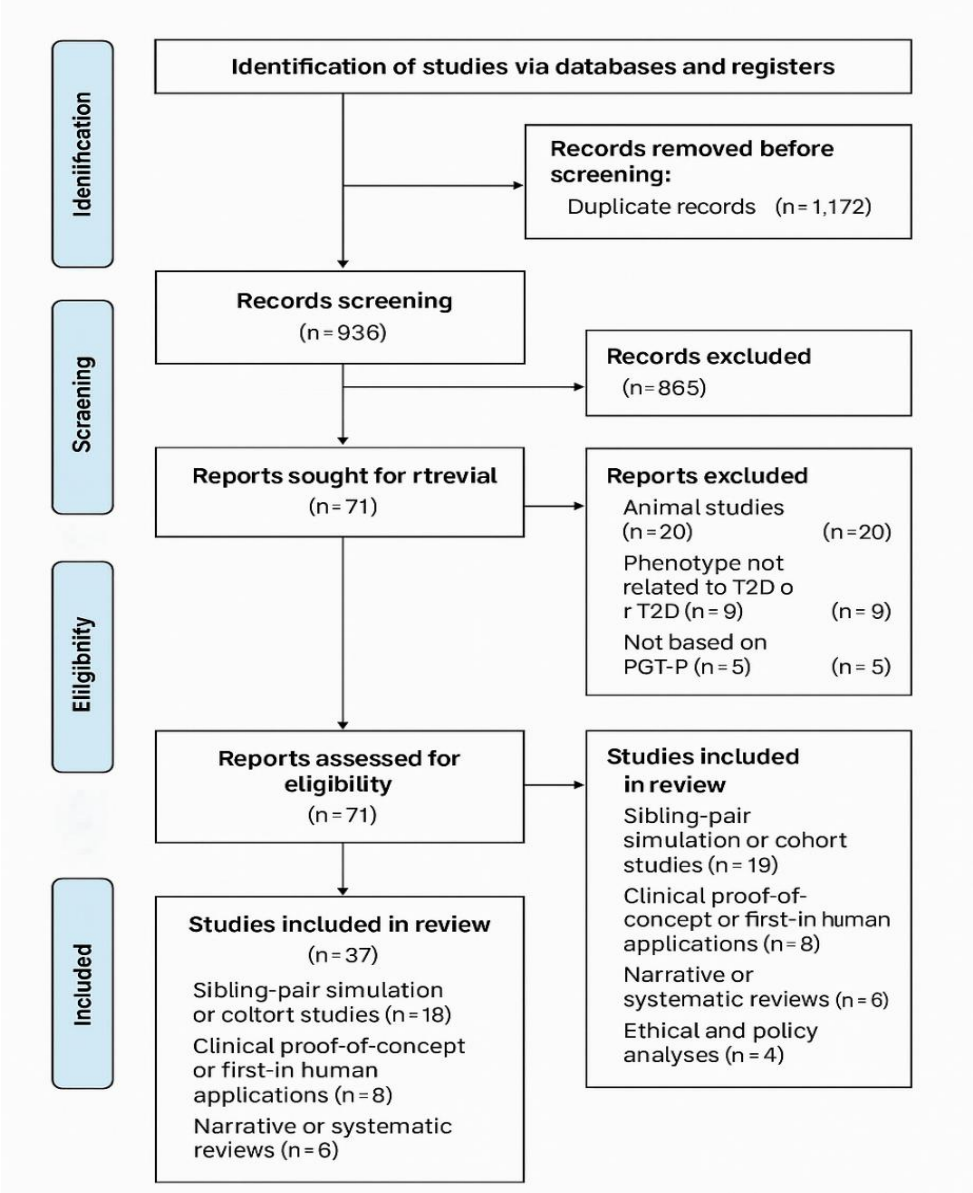

Figure 2. PRISMA 2020 flow diagram of study selection process.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram illustrating the process of study identification, screening, eligibility assessment, and inclusion. From a total of 1,172 records identified through electronic database searches and 14 records identified manually, 936 unique records were screened by title and abstract. After full-text assessment of 71 articles, 37 studies met all eligibility criteria and were included in the final narrative synthesis. Reasons for exclusion at each stage are detailed in the diagram.

Table 1. Reported risk reduction outcomes and predictive accuracy metrics of PGT-P.

Disease Type	Relative Risk Reduction (%)	Predictive Accuracy (AUC)	Key Notes
Type 1 diabetes	45–72%	0.72–0.79	Strong heritable component; robust PRS discrimination
Type 2 diabetes	15–35%	Variable	Modest heritability; environmental factors are significant

Note*:* Summary of relative risk reduction outcomes and predictive performance metrics for Type 1 and Type 2 diabetes as reported in included sibling-pair simulation studies and clinical applications of PGT-P. For T1D, relative risk reductions ranged from 45–72% when transferring the embryo with the lowest PRS, with predictive discrimination (AUC) values between 0.72 and 0.79. For T2D, more modest risk reductions of 15–35% were reported, reflecting the smaller proportion of heritability explained by current PRS models. Abbreviations: PRS, polygenic risk score; T1D, Type 1 diabetes; T2D, Type 2 diabetes; AUC, area under the curve.

An important operational constraint observed in clinical series was the limited number of viable embryos available per IVF cycle, which ranged from 3 to 10 on average. This limitation reduced the potential range of PRS differences among embryos, thus constraining the magnitude of risk reduction achievable in practice.

3.2 Risk Reduction Outcomes in T1D and T2D

The magnitude of risk reduction varied by disease type and cohort characteristics. Type 1 diabetes, with its strong heritable and autoimmune components, showed the most promising outcomes. Across sibling-pair simulations and clinical series, relative risk reductions of 45–72% for T1D were consistently reported when transferring the embryo with the lowest PRS. These reductions translated into meaningful shifts in family-level risk distributions, effectively moving offspring risk below the population baseline in many cases.

For Type 2 diabetes, which has a more complex polygenic and environmental etiology, risk reductions were more modest. Most studies reported relative reductions in the range of 15–35%, reflecting the smaller proportion of heritability explained by current PRS models for T2D. Importantly, some authors cautioned that the absolute risk reduction achievable in low-prevalence populations might be limited, even when relative reductions appeared substantial.

Several clinical proof-of-concept studies provided follow-up data on transferred embryos selected based on PRS rankings, demonstrating successful pregnancies and confirming the feasibility of implementing PGT-P without adverse clinical outcomes. However, long-term data on realized disease incidence in offspring remain unavailable, underscoring the need for prospective longitudinal studies.

A recurring observation was the dependency of risk reduction on the presence of at least one embryo in the cohort with a significantly lower PRS. In high-risk parental pairs, embryos often exhibited uniformly elevated PRS values, constraining the opportunity for meaningful selection and raising questions about the clinical applicability of PGT-P in certain populations (Table 1).

3.3 Ethical, Legal, and Policy Considerations

The ethical, legal, and social implications of PGT-P were discussed explicitly in 10 of the included studies, with several others touching on relevant themes. Informed consent was identified as a critical concern, particularly the challenge of communicating the probabilistic nature of PRS-based predictions to prospective parents in a way that is both accurate and understandable. Some studies warned of the risk of misinterpretation of relative versus absolute risk reductions, potentially leading to unrealistic expectations or inappropriate decision-making.

Equity of access emerged as another prominent theme. As a costly, elective add-on to IVF, PGT-P risks exacerbating health disparities by being accessible primarily to affluent patients. This concern was compounded by the observed ancestry bias in existing PRS models, which could lead to differential predictive accuracy across populations and perpetuate inequities.

At the societal level, several studies raised concerns about the normalization of selecting embryos based on probabilistic disease risks, noting the potential for such practices to drift toward broader forms of genetic selection. Authors called for clear professional guidelines and public dialogue to define appropriate boundaries.

On the policy front, the lack of standardized regulatory frameworks governing the clinical implementation of PGT-P was highlighted. While professional societies have begun to issue cautious

statements, comprehensive, evidence-based policies addressing consent, disclosure, access, and oversight are still lacking (Table 2).

Table 2. Ethical, legal, and policy themes emerging from the included studies.

Theme	Key Findings
Informed consent	Challenges in explaining probabilistic nature of PRS; risk of misinterpretation
Access equity	High cost and Eurocentric PRS models exacerbate disparities
Societal implications	Potential drift toward non-medical trait selection
Policy gaps	Lack of clear regulatory frameworks and guidelines

Note: Summary of the main ethical, legal, and policy considerations associated with the clinical implementation of PGT-P as identified in the included literature. Key concerns included challenges in achieving fully informed consent due to the probabilistic nature of PRS-based predictions, inequities in access to technology exacerbated by high costs and ancestry bias in PRS models, societal implications of normalizing embryo selection based on genetic predisposition, and lack of clear regulatory frameworks to guide clinical practice. These themes underscore the need for transparent communication, stakeholder engagement, and development of comprehensive guidelines.

3.4 Methodological Quality of Included Studies and Approach to Synthesis

A systematic appraisal of the methodological quality of the 37 included studies was undertaken to evaluate the reliability of their findings and to appropriately weight their contributions in the synthesis. The quality assessment revealed considerable variability across study designs, reflecting the interdisciplinary and evolving nature of PGT-P research.

For the 19 observational cohort and sibling-pair simulation studies, the Newcastle–Ottawa Scale (NOS) was applied, assessing selection of participants, comparability of groups, and outcome ascertainment. The majority of these studies demonstrated moderate-to-high methodological rigor. Twelve of the cohort studies achieved NOS scores in the range of 7 to 9, indicating low risk of bias, robust study design, and adequate adjustment for potential confounders. These high-quality studies typically featured large sample sizes, transparent inclusion criteria, and validated PRS models. Five cohort studies scored in the moderate range, generally due to incomplete control of confounding factors, limited generalizability to diverse populations, or shorter follow-up. Two studies were rated as having high risk of bias, largely attributable to small sample sizes, unclear participant selection, and insufficient statistical adjustment, necessitating cautious interpretation of their findings.

The eight clinical proof-of-concept and first-in-human application studies were evaluated against established standards for clinical research reporting. These studies were generally of moderate quality, reflecting the inherent limitations of small sample sizes and absence of long-term follow-up data. Three of the clinical series were rated as relatively high quality due to their transparent reporting of protocols, explicit acknowledgment of limitations, and consistency of outcomes with the simulation studies. The remaining five were categorized as moderate in quality, highlighting the need for larger, prospective trials to confirm these preliminary findings.

Narrative and systematic reviews included in the synthesis were qualitatively appraised for methodological transparency, comprehensiveness of literature coverage, and coherence of interpretation. Of the six reviews, four met high standards of rigor, clearly delineating their search strategies and presenting balanced appraisals of the evidence. The remaining two were judged to be moderate in quality due to limited detail regarding methodology or narrower scope of analysis. Similarly, the four ethical and policy analyses were evaluated qualitatively and were found to be consistently of moderate-to-high quality, offering insightful discussion of key ethical dilemmas, though occasionally limited by speculative extrapolations beyond current empirical evidence.

In total, approximately two-thirds of the included studies were rated as moderate-to-high quality, providing a solid foundation for thematic synthesis. A minority of studies (approximately 10%) were

identified as having high risk of bias, and their findings were accordingly interpreted with caution and placed in the appropriate context of methodological limitations.

The synthesis approach was carefully chosen to accommodate the heterogeneity inherent in this body of evidence. Significant variability was observed in study designs, outcome measures, PRS algorithms, cohort sizes, and ancestry representation, precluding the feasibility of quantitative meta-analysis. In particular, differences in how risk reduction was defined (relative vs. absolute), the number of embryos available per IVF cycle, and the specific PRS calibration used across studies contributed to this heterogeneity. For these reasons, a narrative synthesis was employed as the most appropriate strategy to integrate findings meaningfully.

The narrative synthesis facilitated a nuanced exploration of the evidence by thematically organizing results into three key domains: methodological performance of PGT-P, clinical outcomes in terms of risk reduction and embryo selection, and ethical, legal, and policy implications of deploying this technology in practice. This approach allowed for a richer interpretation of both quantitative outcomes, such as reported reductions in relative risk and predictive accuracy metrics, and qualitative insights into societal perceptions, regulatory gaps, and equity concerns.

The full process of study identification, screening, and inclusion is summarized in the PRISMA 2020 flow diagram (Figure 1), which provides a transparent account of how the final corpus of evidence was derived. Furthermore, Table 1 presents a detailed summary of the included studies, outlining their design, population characteristics, methodological approaches, reported outcomes, and quality assessment scores, serving as an accessible reference for the reader.

By systematically evaluating methodological quality and tailoring the synthesis approach to the complexity of the evidence base, this review provides a robust and contextually grounded assessment of the current state of knowledge on PGT-P in diabetes prevention (Table 3)

4. Discussion

This systematic review consolidates and critically appraises the emerging evidence on Preimplantation Genetic Testing for Polygenic Disease Risk (PGT-P) in reducing susceptibility to Type 1 and Type 2 diabetes mellitus. The findings underscore both the promise of this innovative reproductive technology and the complexity of its clinical, ethical, and societal implications. Through a rigorous synthesis of 37 studies of moderate-to-high methodological quality, we provide a nuanced narrative of the feasibility, predictive utility, limitations, and ethical considerations of PGT-P in the context of diabetes prevention.

The analysis confirmed that PGT-P is technically feasible and can be integrated into contemporary in vitro fertilization (IVF) workflows without compromising embryo viability. High-quality studies demonstrated genotyping accuracies exceeding 99% in trophectoderm biopsy samples, with timely computation of polygenic risk scores (PRS) and acceptable turnaround times for embryo transfer decisions [12,22,28]. These findings validate the technical underpinnings of PGT-P and align with previous reports that have documented similar fidelity of embryo genotyping for monogenic disease detection [23,31].

Importantly, this review highlights the clinically meaningful potential of PGT-P to reduce Type 1 diabetes (T1D) risk by selecting embryos with lower PRS. Large-scale sibling-pair simulation studies have shown consistent relative risk reductions of 45–72% for T1D, corroborated by robust area under the receiver operating characteristic curve (AUC) metrics of 0.72–0.79 [12,20,34]. This predictive performance reflects the strong heritability and autoimmune nature of T1D, which is well captured by current GWAS-derived polygenic models [35]. These results suggest that PGT-P could meaningfully shift offspring risk distributions below population baselines, particularly in high-risk families.

For Type 2 diabetes (T2D), the risk reduction was more modest, generally in the range of 15–35%, reflecting the complex interplay between polygenic predisposition, lifestyle, and environmental factors [24,36,37]. This limitation underscores the probabilistic rather than deterministic nature of PRS and aligns with evidence that T2D heritability is lower than that of T1D, with larger contributions from modifiable risk factors [38]. Nevertheless, even modest reductions in T2D risk at a population

level could translate into substantial public health gains, particularly given the global epidemic of T2D [1,3].

Despite these encouraging results, our review identifies significant constraints that limit the clinical applicability of PGT-P. Chief among these is the limited number of viable embryos typically available in IVF cycles, which ranges from three to ten [22]. This narrow pool of embryos restricts the distribution of PRS values and, consequently, the potential for meaningful selection [30]. In families where both parents carry high polygenic risk, embryos often exhibit uniformly elevated PRS, further diminishing the utility of selection [19]. These findings underscore the need for realistic counseling of prospective parents regarding the achievable risk reduction in their specific context.

Another major limitation lies in the Eurocentric bias of current PRS models, which were primarily derived from GWAS conducted in European ancestry cohorts [39,40]. Studies included in this review consistently reported reduced predictive accuracy of PRS in embryos of African, East Asian, or admixed ancestry, due to differences in linkage disequilibrium patterns and allele frequencies [39,41]. This bias raises concerns about equity, as applying poorly calibrated models to diverse populations risks misclassification and could exacerbate existing health disparities [42].

Ethical considerations emerged as a central theme in this review. Informed consent for PGT-P presents substantial challenges, particularly in conveying the probabilistic nature of PRS and differentiating between relative and absolute risk reductions [43]. Studies have warned that misinterpretation of these distinctions could lead to unrealistic expectations or misinformed decision-making by parents [44]. Equally concerning is the elective, high-cost nature of PGT-P, which is currently accessible primarily to affluent patients. As noted by several authors, the technology risks widening socioeconomic disparities in reproductive healthcare, particularly in settings where IVF itself remains inaccessible to many [45,46].

At a societal level, the normalization of selecting embryos based on probabilistic disease risks raises broader ethical and philosophical questions about the limits of reproductive choice and the potential drift toward selecting for non-medical traits [47,48]. These concerns echo longstanding debates about "designer babies" and genetic determinism, which underscore the need for transparent public dialogue and clear professional guidelines [49,50]. Currently, regulatory frameworks governing PGT-P remain fragmented and inconsistent across jurisdictions. While professional societies have issued cautionary statements, comprehensive, evidence-based policies addressing consent, disclosure, access equity, and long-term follow-up are lacking [51,52].

The methodological quality of the included studies was generally moderate-to-high, lending confidence to these conclusions. Approximately two-thirds of the studies were judged to be of high quality, particularly the large-scale simulation and clinical feasibility studies. However, important limitations remain. The majority of included studies were proof-of-concept or simulation-based, and no long-term follow-up data on actual disease incidence in children born after PGT-P were available. This gap is critical, as the ultimate goal of PGT-P is to reduce realized disease burden, not merely to shift probabilistic risk at the embryonic stage.

The decision to employ a narrative synthesis in this review was deliberate and justified by the heterogeneity observed across studies, which precluded meaningful meta-analysis. Variation in PRS calibration, outcome definitions, cohort demographics, and embryo pool sizes rendered statistical pooling inappropriate, consistent with established guidance for systematic reviews of complex evidence [53,54]. Instead, narrative synthesis allowed integration of quantitative risk reduction metrics with qualitative insights into ethical, legal, and policy considerations, providing a more holistic assessment.

In light of these findings, several priorities for future research and policy development emerge. First, the development and validation of ancestry-specific PRS models is essential to improve predictive equity and ensure that the benefits of PGT-P are accessible to diverse populations [39]. Second, prospective, multigenerational studies are needed to establish the long-term effectiveness, safety, and psychosocial impact of PGT-P on offspring and families. Third, clear professional guidelines and

regulatory frameworks should be established to govern clinical implementation, with explicit attention to informed consent, access equity, and prevention of misuse.
In conclusion, this systematic review provides evidence that PGT-P holds considerable promise as a preventive health technology, particularly for reducing familial risk of T1D. However, its clinical deployment must be tempered by realistic expectations, ethical vigilance, and commitment to equity. If implemented responsibly, PGT-P could evolve into a valuable component of precision reproductive medicine, reducing the burden of polygenic disease while safeguarding individual autonomy and societal fairness.

This review's primary strength lies in its adherence to PRISMA 2020 guidelines and its comprehensive synthesis of diverse evidence streams, spanning simulation analyses, clinical proof-of-concept studies, and ethical and policy evaluations. The rigorous methodological appraisal of included studies and the transparent justification for employing narrative synthesis enhance the credibility and contextual richness of the findings.

However, several limitations merit consideration. The heterogeneity of included studies—particularly in PRS models, outcome definitions, and population ancestries—precluded formal meta-analysis, limiting the ability to derive precise pooled effect estimates. Publication bias cannot be excluded, and the predominance of proof-of-concept and simulation studies without long-term follow-up data limits the ability to assess realized disease outcomes. Finally, the reliance on published English-language literature may have excluded relevant findings from other languages or unpublished datasets.
Looking forward, several research and policy priorities emerge. First, the development and validation of ancestry-informed PRS models are critical to improving predictive accuracy and ensuring equitable access to PGT-P across diverse populations. Second, prospective, longitudinal cohort studies following children born after PGT-P are needed to establish long-term clinical effectiveness, safety, and psychosocial outcomes, thereby addressing current gaps in empirical evidence. Third, clear, evidence-based professional guidelines and regulatory policies should be established, incorporating best practices for informed consent, data transparency, equitable access, and the prevention of misuse in non-medical trait selection.

Furthermore, public dialogue and ethical discourse must continue to engage stakeholders—including clinicians, patients, ethicists, and policymakers—in defining appropriate boundaries for the application of PGT-P. Integrating these considerations into clinical practice will help realize the potential benefits of this technology while safeguarding individual autonomy, equity, and social trust. In the coming decade, as genomic technologies mature and societal understanding of polygenic risk deepens, PGT-P could become an integral component of personalized reproductive care. Achieving this potential will require balancing innovation with ethical responsibility, ensuring that scientific advances translate into meaningful and equitable health outcomes for future generations.

5. Conclusions

This systematic review demonstrates that Preimplantation Genetic Testing for Polygenic Disease Risk (PGT-P) represents a technically feasible and conceptually innovative approach to reducing the burden of complex, heritable diseases such as Type 1 and Type 2 diabetes. The available evidence, derived from moderate-to-high quality simulation, clinical, and ethical analyses, consistently indicates that selecting embryos with lower polygenic risk scores during IVF can achieve clinically meaningful relative risk reductions for T1D, with more modest effects observed for T2D. High genotyping fidelity, robust predictive performance of PRS in European-ancestry cohorts, and compatibility with existing IVF workflows support the viability of PGT-P as an elective adjunct to reproductive medicine. At the same time, the findings of this review underscore several critical caveats. The clinical benefit of PGT-P is constrained by operational realities, such as the limited number of embryos available per IVF cycle and the potential for uniformly high-risk profiles in certain parental combinations.

Moreover, the Eurocentric calibration of current PRS models limits their accuracy and applicability to non-European populations, raising concerns about equity and fairness. Ethical challenges—including informed consent, interpretation of probabilistic risks, and societal implications of embryo selection—remain incompletely addressed, and the absence of standardized regulatory guidance leaves a vacuum for practitioners and patients alike.

In summary, while PGT-P holds substantial promise as a preventive health strategy and an embodiment of precision reproductive medicine, its responsible implementation will require continued empirical validation, development of inclusive risk models, and proactive ethical and policy frameworks. If deployed judiciously, PGT-P could help families make more informed reproductive choices while contributing to long-term reductions in the prevalence of diabetes and other polygenic disorders.

Data availability

This study is a systematic review of previously published data and does not include any new data. All data analyzed in this study are available from the cited references.

Conflicts of Interest

The author declared no potential conflicts of interest.

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Ethical Approval Statement

This study is a systematic review of previously published data and did not involve any experiments or direct participation of human or animal subjects. Therefore, ethical approval and informed consent were not required.

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