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GENOME-WIDE NON-INVASIVE PRENATAL TESTING FOR RARE CHROMOSOMAL ABNORMALITIES: DIAGNOSTIC ACCURACY, DISCORDANT RESULTS, AND CLINICAL IMPLICATIONS

Ph.D. Thesis

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Budapest
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"Medicine is a science of uncertainty and an art of probability."

Sir William Osler

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1. LIST OF ABBREVIATIONS

- **aCGH:** Array Comparative Genomic Hybridization
- **CMG:** American College of Medical Genetics and Genomics
- **ACOG:** American College of Obstetricians and Gynecologists
- **ART**: Assisted Reproductive Technology
- **cfDNA**: Cell-free DNA
- **cffDNA**: Cell-free fetal DNA
- **CI**: Confidence Interval
- **CNV**: Copy Number Variant
- **CPM**: Confined Placental Mosaicism
- **CVS**: Chorionic Villus Sampling
- **GA**: Gestational Age
- **GW-NIPT**: Genome-Wide Non-Invasive Prenatal Testing
- **HR**: Hazard Ratio
- **MA**: Maternal age
- **MOOSE**: Meta-analysis Of Observational Studies in Epidemiology
- **MPS**: Massively Parallel Shotgun Sequencing
- **NIPT**: Non-Invasive Prenatal Testing
- **NIPS**: Non-Invasive Prenatal Screening
- **NPV**: Negative Predictive Value
- **OR**: Odds Ratio
- **PECO**: Population, Exposure, Comparators, Outcome,
- **PID**: Population, Intervention, and Diagnostic test

- **PPV**: Positive Predictive Value
- **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- **PROSPERO**: International Database of Prospectively Registered Systematic Reviews
- **PS**: Prospective Study
- **QUADAS-2**: Quality Assessment of Diagnostic Accuracy Studies 2
- **RAT**: Rare Autosomal Trisomy
- **RS**: Retrospective Study
- **SCA**: Sex Chromosome Aneuploidy
- **SNP**: Single Nucleotide Polymorphism
- **StrCAs** structural chromosomal abnormalities
- **T13**: Trisomy 13 (Patau syndrome)
- **T18**: Trisomy 18 (Edwards syndrome)
- **T21**: Trisomy 21 (Down syndrome)
- **T+No**: Trisomy + the No of chromosome (pl. T16)
- **Up**: Ultrasound Positive cases
- **UPD**: Uniparental Disomy
- **WGS**: Whole Genome Sequencing

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve to increase the effectiveness of genetic screening tests, mainly the non-invasive prenatal screening tests.

My mission is to help pregnant women and their physicians make good decisions and expert in genetic consultation.

My specific goals include investigating the effectiveness of genome-wide non-invasive prenatal testing for rare chromosomal abnormalities and examining the pregnancy outcomes of discordant, false-positive cases.

2.2. Scientometrics

Number of all publications:	7
Cumulative IF:	17.578
Av IF/publication:	2.511
Ranking (SCImago):	D1: 1, Q1: 3
Number of publications related to the subject of the thesis:	3
Cumulative IF:	15.2
Av IF/publication:	3.333
Ranking (Sci Mago):	D1: 1, Q1 2:
Number of citations on Google Scholar:	70
Number of citations on MTMT (independent):	57
H-index:	3

The detailed bibliography of the student can be found on pages 65.

2.3. Future plans

My future plans are primarily focused on the broad dissemination of the new knowledge we have published, both nationally and internationally.

Furthermore, we intend to create a user-friendly interface to ensure the practical, day-to-day applicability of these findings, thereby accelerating their integration into clinical routine.

Scientifically, I plan to analyze domestic NIPT (Non-Invasive Prenatal Testing) cases through a detailed examination of their efficacy and associated pregnancy outcomes.

3. SUMMARY OF THE THESIS

This dissertation addresses the complexities and clinical challenges arising from the increasing use of Genome-Wide Non-Invasive Prenatal Testing (GW-NIPT), particularly concerning positive results for Rare Autosomal Trisomies (RATs) and complex chromosomal abnormalities. Due to the low prevalence of these conditions, reliable data on their Positive Predictive Value (PPV) have been insufficient, complicating genetic counseling. The research consisted of two large systematic reviews and meta-analyses aimed at determining the most accurate genetic and clinical risks in GW-NIPT-positive cases, thereby aiding in genetic counseling and, in discordant cases, in planning prenatal care. The first analysis of seventeen studies, encompassing 740,076 pregnancies, precisely determined the PPV of RATs. True positive cases were determined using two different methodologies. One was a confirmed methodology, where only cases validated by genetic testing were considered true positives with a definite diagnosis, and the other was an extended methodology, where, in addition to cases confirmed by genetic testing, intrauterine fetal death and termination of pregnancy due to an abnormality confirmed by ultrasound examination were also considered true positives, where no diagnosis had been made but the fetus was probably affected.Using both a Confirmed and an Extended Method, the highest true positive rates were consistently found for Trisomy 16 (T16) and Trisomy 22 (T22). The second review, analyzing data from 681,633 pregnancies, investigated the clinical consequences of these findings. Although RAT-positive results were largely false positives (80%), approximately 35% of these were associated with adverse placenta-mediated complications, with the highest risks linked to anomalies involving chromosomes 16 and 4. Crucially, the analysis revealed a strong association between complex, multi-chromosomal GW-NIPT results and maternal malignancy, with 40% of these complex cases ultimately leading to a cancer diagnosis. This thesis concludes that discordant GW-NIPT results necessitate the implementation of chromosome-specific risk stratification in prenatal counseling and underscores the importance of a thorough differential diagnosis to exclude underlying maternal malignancies, thereby accelerating the practical application of these critical discoveries into routine clinical workflow.

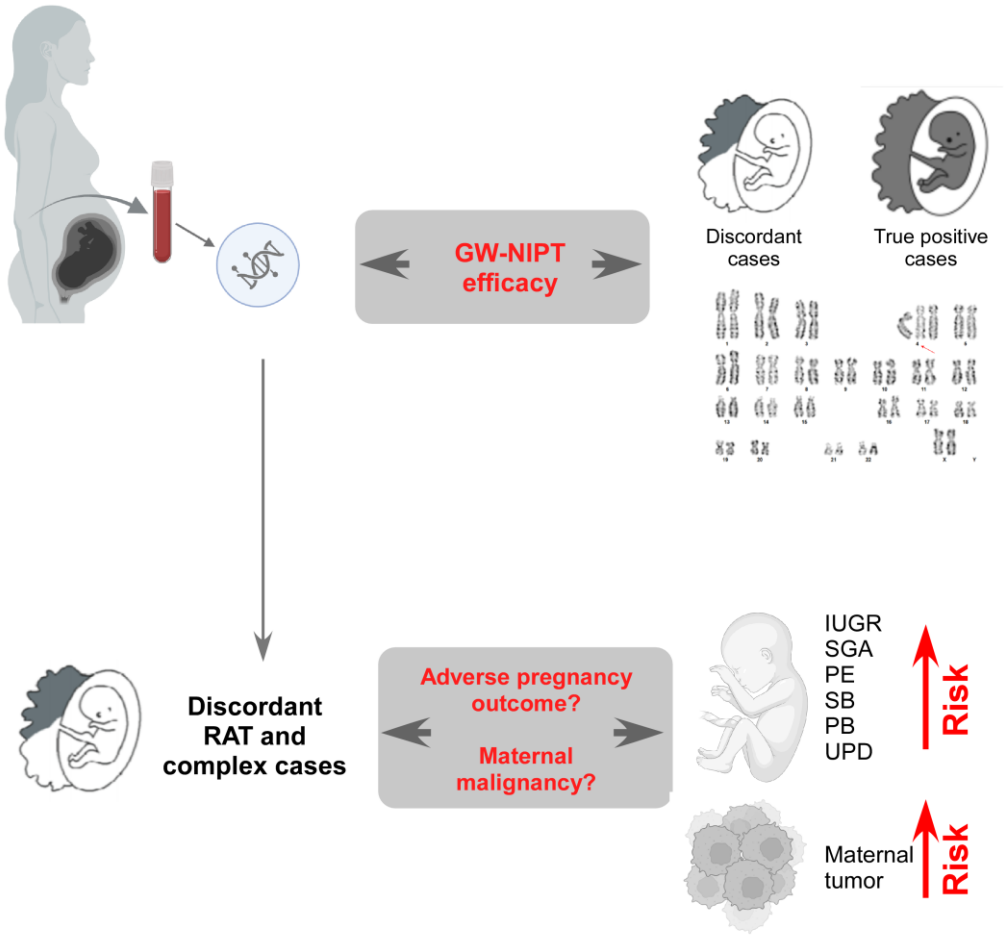
This doctoral dissertation examines the clinical and interpretative challenges associated with the increasing use of genome-wide non-invasive prenatal testing (GW-NIPT), focusing particularly on positive results for rare autosomal trisomies (RATs) and complex chromosomal abnormalities. Due to the low prevalence of these conditions, there is limited robust data on their positive predictive value (PPV) and clinical consequences, which complicates genetic counselling and prenatal decision-making.

This study comprises two systematic reviews and meta-analyses, which are designed to evaluate the diagnostic performance and clinical relevance of GW-NIPT findings. The first analysis included 17 studies encompassing 740,076 pregnancies, and estimated the PPV of RATs using two complementary outcome definitions. The confirmed approach was restricted to cases validated by invasive genetic testing representing definitive foetal diagnoses, while the extended approach also incorporated clinically relevant pregnancy outcomes suggestive of foetal involvement in the absence of cytogenetic confirmation. Across both approaches, higher confirmation rates were consistently observed for trisomies 16 and 22.

The second meta-analysis, incorporating data from 681,633 pregnancies, evaluated the clinical consequences of discordant GW-NIPT results. While most RAT-positive results were inconsistent with the fetal karyotype, a significant proportion were linked to adverse pregnancy outcomes mediated by the placenta, particularly for abnormalities involving chromosomes 16 and 4. Additionally, complex, multi-chromosomal GW-NIPT profiles were associated with an increased likelihood of underlying maternal malignancy.

In conclusion, this thesis demonstrates that discordant GW-NIPT findings may reflect biologically meaningful placental or maternal signals rather than technical artefacts. By providing chromosome-specific risk estimates, this work contributes to the evidence base that will inform the future refinement of genetic counselling and prenatal management. The novelty of this research lies in its integrated, chromosome-specific reinterpretation of GW-NIPT findings, which moves beyond a purely foetal-centric framework.

4. GRAPHICAL ABSTRACT



Abbreviations: genome-wide non-invasive prenatal test (GW-NIPT), intrauterine growth restriction (IUGR), small for gestational age (SGA), pre-eclampsia (PE), preterm birth (PB), and stillbirth (SB), uniparental disomy (UPD), rare autosomal trisomy (RAT)

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

The primary objective of this study is to critically evaluate the efficacy and screening performance of Genome-Wide Non-Invasive Prenatal Testing (GW-NIPT) in the detection of rare chromosomal abnormalities (Bianchi & Chiu, 2018; Raymond et al., 2022; Van Opstal et al., 2018). This analysis specifically entails a detailed investigation into pregnancy outcomes associated with false-positive results for rare autosomal trisomies, alongside an assessment of the prevalence and risk of underlying maternal malignancy in cases presenting with complex, multi-chromosomal GW-NIPT findings (Grati, 2014; Hartwig et al., 2017; Turriff et al., 2024).

GW-NIPT is based on the analysis of circulating cell-free DNA (cfDNA) fragments present in maternal plasma (Lo et al., 1997). These cfDNA molecules originate predominantly from apoptotic placental trophoblasts and represent a mixture of maternal and fetal genetic material. Advances in massively parallel sequencing technologies and bioinformatic modeling have enabled genome-wide interrogation of cfDNA, thereby extending the scope of non-invasive prenatal testing beyond common trisomies to rare autosomal trisomies (RATs), sex chromosome aneuploidies, and large subchromosomal copy number variations (Bianchi et al., 2014; Chiu et al., 2008; Fiorentino et al., 2017).

5.1.2. What is the problem to solve?

The aim of this study is to systematically evaluate the diagnostic accuracy of genome-wide non-invasive prenatal testing (GW-NIPT) for rare chromosomal abnormalities, and to assess the clinical significance of discordant findings (Raymond et al., 2022; Van Opstal et al., 2018). This includes their potential association with adverse pregnancy outcomes and maternal malignancies (Bianchi et al., 2015; Eggenhuizen et al., 2021; Turriff et al., 2024).

While GW-NIPT provides unprecedented genomic breadth, its clinical interpretation is inherently constrained by biological and technical factors. Because cfDNA primarily reflects placental rather than fetal genomic composition, abnormal GW-NIPT findings

may be discordant with confirmatory invasive diagnostic results (Alberry et al., 2007; Grati, 2014). Moreover, expanded genomic coverage increases the likelihood of detecting signals unrelated to fetal chromosomal status, including confined placental mosaicism and maternal genomic abnormalities, complicating clinical decision-making (Brady et al., 2016; Hartwig et al., 2017).

Importantly, the rapid clinical expansion of genome-wide NIPT preceded the accumulation of robust outcome-based evidence for rare autosomal trisomies and complex genomic findings (Scott et al., 2018; Van Opstal et al., 2018). While GW-NIPT has been increasingly implemented in routine prenatal care since approximately 2019, clinically meaningful data regarding pregnancy outcomes, placental pathology and maternal conditions have only emerged subsequently (Konya et al., 2024; van Prooyen Schuurman et al., 2022).

As a result, current national and international guidelines consistently emphasize the high rate of discordant and so-called “false positive” GW-NIPT findings beyond common trisomies, highlighting their potential to generate unnecessary parental anxiety and to complicate genetic counselling and clinical decision-making (Dungan et al., 2023; Gregg et al., 2016). However, these guidelines also acknowledge the lack of comprehensive, chromosome-specific risk estimates and outcome data needed to contextualize such findings (Eggenhuizen et al., 2021; Scott et al., 2018).

The two systematic reviews and meta-analyses presented in this dissertation were designed specifically to address this critical evidence gap by disentangling technical limitations from biologically and clinically meaningful discordance.

5.1.3. What is the importance of the topic?

These studies represent the first comprehensive analyses to delineate chromosome-specific risks associated with Genome-Wide Non-Invasive Prenatal Testing (GW-NIPT) results. This information is critically important for two reasons. Firstly, during genetic counselling, the ability to accurately determine the exact genetic risk to the fetus is paramount, as it empowers prospective parents to make informed decisions regarding the necessity of confirmatory invasive testing (Bianchi & Chiu, 2018; Van Opstal et al.,

2018). Secondly, in cases identified as false positives, the determination of placental dysfunction secondary to confined placental mosaicism enables clinicians to stratify risk and establish the necessary level of surveillance and tailored prenatal care required for the remainder of the pregnancy (Eggenhuizen et al., 2021; Grati, 2014; Van Opstal et al., 2018). Importantly, reframing certain GW-NIPT results as indicators of placental pathology rather than simple analytical errors provides a biologically grounded explanation for discordance and highlights their potential prognostic relevance for pregnancy management (Eggenhuizen et al., 2021; Grati, 2014; Taglauer et al., 2014).

5.1.4. What would be the impact of our research results?

The clinical impact of our findings is twofold: they significantly contribute to reducing the psychological burden on prospective parents by providing precise risk estimates during genetic counselling, thereby facilitating more informed and autonomous decision-making (Benn et al., 2015; Lewis et al., 2016; Van Opstal et al., 2018). Conversely, in cases where a very high risk of adverse pregnancy outcomes is identified, these data directly enable the timely implementation of strict and specialized prenatal surveillance and intervention, which is essential for maximizing the potential for positive fetal outcomes (Eggenhuizen et al., 2021; Grati, 2014; Van Opstal et al., 2018).

5.2. Evolution of Genome-Wide Non-Invasive Prenatal Testing

Non-invasive prenatal testing (NIPT) based on the analysis of cell-free DNA (cfDNA) in maternal plasma has transformed prenatal screening for fetal aneuploidies. Initially developed to detect common trisomies (trisomy 21, 18, and 13), NIPT has progressively expanded toward genome-wide (GW-NIPT) approaches, enabling the detection of rare autosomal trisomies (RATs) and large subchromosomal copy number variations. Since its broader clinical implementation after 2015, GW-NIPT has been increasingly adopted as either a first-tier or contingent screening test in many countries.

While GW-NIPT offers higher analytical resolution and broader genomic coverage, its expanded scope has introduced new interpretative and clinical challenges, particularly related to findings that are discordant with confirmatory invasive diagnostic testing.

Non-invasive prenatal testing (NIPT), which is based on analysing cell-free DNA (cfDNA) in maternal plasma, has transformed the way that prenatal screening is carried out for fetal aneuploidies. Initially developed to detect the most common trisomies (trisomies 21, 18 and 13), NIPT has been shown to be more sensitive and specific than conventional biochemical screening methods (Bianchi et al., 2014; Gregg et al., 2016). This has led to a substantial reduction in unnecessary invasive procedures and pregnancy loss related to these procedures (Bianchi et al., 2014). The presence of foetal-derived cell-free DNA (cfDNA) in the maternal circulation was first described in the late 1990s, providing the biological basis for non-invasive prenatal genetic testing (Lo et al., 1997). Early clinical applications relied on targeted quantitative PCR approaches, before transitioning rapidly towards sequencing-based methodologies as next-generation sequencing technologies became widely accessible (Bianchi & Chiu, 2018).

Subsequent developments have made massively parallel sequencing (MPS)-based non-invasive prenatal testing (NIPT) possible, including low-coverage whole-genome sequencing (WGS) approaches that quantify chromosomal representation across the entire genome (Chiu et al., 2008; Lau et al., 2012). These methods use statistical frameworks, such as standardised scores (Z-scores) and likelihood-based models (including log-likelihood ratios), to infer aneuploidy by assessing deviations from the expected chromosomal dosage (Jiang & Lo, 2016). Around 2015, the introduction of genome-wide NIPT (GW-NIPT) marked a significant expansion in analytical scope, enabling the detection of rare autosomal trisomies and large subchromosomal copy number variations (Fiorentino et al., 2017; Van Opstal et al., 2018).

In parallel, alternative technical strategies have emerged, including chromosome-selective (targeted) sequencing approaches that focus on predefined chromosomes; SNP-based non-invasive prenatal testing (NIPT) that relies on allelic imbalance and haplotype modelling; and, more recently, cell-free DNA (cfDNA)-based screening for selected monogenic disorders that uses highly sensitive methods such as digital PCR. Although

these approaches differ in terms of resolution, cost and computational requirements, they are all fundamentally limited by the composite biological origin of cfDNA (Brady et al., 2016; van den Veyver & Eng, 2015).

Since its broader clinical implementation after 2015, GW-NIPT has been adopted by many countries as either a primary or secondary screening test. However, its expanded genomic coverage has introduced new interpretative and clinical challenges, particularly about results that conflict with those of confirmatory invasive diagnostic testing (Hartwig et al., 2017; Jayashankar et al., 2023).

5.3. Discordant GW-NIPT Results and Placental Mosaicism

A major limitation of GW-NIPT lies in the biological origin of cfDNA, which is predominantly derived from placental trophoblasts rather than directly from fetal tissues. As a result, confined placental mosaicism (CPM) represents the most common biological explanation for discordant NIPT results, especially in the context of RATs.

Previous systematic reviews and diagnostic accuracy studies, including our earlier meta-analysis, have demonstrated that the majority of GW-NIPT–positive RAT findings are false positives with respect to fetal karyotype, with confirmation rates often below 20%. However, labeling these findings as merely “false positive” may be misleading, as placental mosaicism itself can have clinically meaningful consequences for pregnancy outcome.

5.4. Rare Autosomal Trisomies and Placenta-Related Pregnancy Complications

Emerging evidence suggests that placental mosaicism involving certain chromosomes may impair placental development and function, leading to placenta-related pregnancy complications such as intrauterine growth restriction (IUGR), small for gestational age (SGA), pre-eclampsia (PE), preterm birth (PB), and stillbirth (SB).

Several cohort studies have reported associations between specific RATs—most notably trisomy 16—and adverse pregnancy outcomes, even when the fetus is euploid. Existing studies are heterogeneous and do not provide chromosome-specific risk estimates. As a

result, clinicians find it difficult to determine when to provide normal, enhanced, or strict prenatal care.

5.5. Uniparental Disomy

Another clinically relevant consequence of RAT-related placental mosaicism is uniparental disomy (UPD), which may arise through trisomy rescue mechanisms. UPD is of particular concern when it involves imprinted chromosomes, such as chromosomes 15 and 16, due to the risk of imprinting disorders and abnormal fetal development.

Although UPD is rare in the general population, case series and small studies suggest a disproportionately higher prevalence in pregnancies with discordant RAT findings on GW-NIPT. Systematic quantification of this risk, however, has been lacking.

5.6. Complex GW-NIPT Findings and Maternal Malignancy

In contrast to single-chromosome RAT findings, complex, multi-chromosomal abnormalities detected by GW-NIPT are unlikely to originate from placental mosaicism alone. Increasing evidence indicates that such profiles may reflect maternal genomic abnormalities, most notably occult malignancies.

Several studies have reported incidental cancer diagnoses following abnormal GW-NIPT results, raising important ethical, diagnostic, and clinical management considerations. Despite growing recognition of this phenomenon, the prevalence of maternal malignancy among complex GW-NIPT discordant cases has not been comprehensively quantified.

Overall, the available evidence indicates a significant discrepancy between the widespread clinical adoption of genome-wide non-invasive prenatal testing (GW-NIPT) and the lack of robust, outcome-based data on rare chromosomal abnormalities and complex genomic findings (Scott et al., 2018; Van Opstal et al., 2018). Although current guidelines recognise the high rate of discordant GW-NIPT results and their potential psychological and clinical implications, they lack sufficiently detailed, chromosome-specific risk estimates to inform evidence-based counselling and pregnancy management (Dungan et al., 2023; Gregg et al., 2016).

This doctoral research addresses these unmet needs by applying systematic review and meta-analytical approaches to evaluate the diagnostic performance of GW-NIPT for rare chromosomal abnormalities, as well as the clinical implications of discordant findings. Particular focus is given to adverse pregnancy outcomes and maternal malignancies. These objectives are detailed in the following section.

6. OBJECTIVES

This doctoral research aimed to systematically evaluate the clinical performance, biological interpretation and downstream implications of genome-wide non-invasive prenatal testing (GW-NIPT) in the context of rare chromosomal abnormalities.

Specifically, the thesis aimed to:

1) To determine the diagnostic performance of GW-NIPT for rare chromosomal abnormalities, including rare autosomal trisomies (RATs) and large structural chromosomal aberrations (StrCAs), by estimating their pooled prevalence, positive predictive values, and chromosome-specific variability, using systematic review and meta-analytical approaches; and
2) To characterise the biological and clinical significance of discordant GW-NIPT findings by distinguishing true fetal chromosomal involvement from placental-origin signals, such as confined placental mosaicism, and by quantifying chromosome-specific risks for adverse pregnancy outcomes, including intrauterine growth restriction, pre-eclampsia, preterm birth, and stillbirth. To characterise the biological and clinical significance of discordant GW-NIPT findings by distinguishing true foetal chromosomal involvement from signals of placental origin, such as confined placental mosaicism, and quantifying chromosome-specific risks of adverse pregnancy outcomes, including intrauterine growth restriction, pre-eclampsia, preterm birth and stillbirth.
3) The third aim was to evaluate the association between complex, multi-chromosomal GW-NIPT profiles and maternal malignancy by estimating the pooled prevalence of cancer diagnoses following discordant GW-NIPT results and describing the spectrum of underlying maternal cancers.
4) The final aim was to provide an evidence-based framework to support clinical decision-making and guideline development. This framework would integrate diagnostic accuracy, pregnancy outcome data, and maternal health implications in order to improve genetic counselling, prenatal surveillance strategies, and interdisciplinary management in pregnancies with rare or complex GW-NIPT findings.

7. METHODS

7.1. Study I.

7.1.1. Methodology and Protocol

We performed a meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). This protocol was registered in PROSPERO, the International Database of Prospectively Registered Systematic Reviews, under the identification number CRD42022377120.

7.1.2. Eligibility Criteria

All analytical studies reporting original research data were eligible for inclusion in this systematic review and meta-analysis.

To determine the appropriateness of the primary research question, the population, intervention, and diagnostic test (PID) framework was followed, where the target population was pregnant women who had undergone GW-NIPT screening, an index test where patients with GW-NIPT positive results were referred to for RATs and/or StrCAs. The diagnosis was confirmed by genetic testing of amniotic fluid, chorionic villus sampling, product of conception, or postnatal peripheral blood (Benn et al., 2015). The diagnosis was established by karyotyping, chromosomal microarray analysis, ultrasound diagnosis, or pregnancy outcome (Wapner et al., 2012). In all selected papers, the NIPT methodology used massive parallel shotgun sequencing.

The primary outcome was to test the PPV of GW-NIPT for all rare chromosomal aneuploidies and pooled for StrCAs. Secondary outcomes included the relative frequency of GW-NIPT-positive cases and true positive cases for each rare aneuploidy.

The following studies were excluded: case-control studies, case reports, case serial reports, cross-sectional studies, reviews, animal studies, cost-effectiveness studies, and studies with only data for frequent chromosome abnormalities. Studies that did not confirm RATs by invasive prenatal testing and/or postnatal karyotyping were also excluded.

7.1.3. Information Sources and Search Strategy

The systematic search was carried out in 2 stages. In the first, using MEDLINE (via PubMed) and Embase databases from November 2022 to August 2023, and in the second, updated in stages up to February 2024, supplemented by the Web of Science database. The systematic search was carried out with the following predefined search key: (nipt OR nips OR nipd OR non invasive prenatal OR cell-free) AND (rare OR aneuploidy OR trisomy OR autosomal).

No filters or language restrictions were applied during the search. Seventeen studies were available in English and one in Chinese.

For studies from the same country, we checked for overlaps and used the most recent version where found. For two studies from Australia, we were not sure that there was no overlap, so we contacted the corresponding author by email who confirmed that there was no overlap in the two databases.

7.1.4. Study Selection and Data Extraction

Two independent review authors (M.K. and A.C.) selected the articles using the EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) reference management program. Publications were first screened by title and abstract, then by full text according to eligibility criteria. A third independent review author (A.G.) resolved disagreements during the selection process.

The following data were extracted: title, first author, year of publication, study design, population screened, inclusion and exclusion criteria, and details of PID.

To estimate the accuracy of the test, we recorded the number of women screened with GW-NIPT true-positive and false-positive results overall for RATs and StrCAs (Page et al., 2021).

7.1.5. Risk of Bias and Quality of Evidence Assessment

The risk of bias was assessed (M.K. and A.C) based on the recommendations of the Cochrane Collaboration, using the Cochrane risk-of-bias tool for systematic reviews of diagnostic accuracy studies (QUADAS-2). Disagreements between data extractors were resolved by involving a third reviewer (A.G) (Whiting et al., 2011).

The quality of evidence was assessed following the recommendations of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup (Guyatt et al., 2008).

7.1.6. Data Synthesis and Analysis

In this meta-analysis, GW-NIPT results were examined on all chromosomes. We excluded the most common trisomies (T13, T18, and T21) and SCAs from the analysis, and focused only on RATs and StrCAs.

In this study, true positive cases were determined using two different methodologies. One was a confirmed methodology, where only cases confirmed by genetic testing were considered true positives, and the other one was an extended methodology, where, in addition to cases confirmed by genetic testing, intrauterine fetal death and termination of pregnancy due to an abnormality confirmed by ultrasonography were also considered true positives, as these cases were also likely to involve fetuses.

7.2. Study II.

7.2.1. Methodology and Protocol

We conducted a meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 6.0) (Higgins et al., 2019). Our findings were reported in accordance with the PRISMA and MOOSE guidelines The protocol was registered with PROSPERO, the international database of prospectively registered systematic reviews, under the identification number CRD42023392969

7.2.2. Eligibility Criteria

This systematic review and meta-analysis followed the PECO (Population, Exposure, Comparators, Outcome) framework: P-pregnant women undergoing GW-NIPT, E-false positives for RATs and complex cases, C-the general pregnant population, and O-pregnancy outcomes and maternal malignancies (Morgan et al., 2018). The primary outcome was pregnancy complications for all discordant GW-NIPT RATs, categorized by chromosome. Secondary outcomes included complex GW-NIPT-positive cases involving multiple chromosomes and maternal malignancy prevalence.

Our study investigated cases where GW-NIPT indicated RAT, but the finding was not confirmed by a subsequent diagnostic procedure (amniocentesis) and was therefore classified as discordant. All selected studies used massively parallel shotgun sequencing. However, most publications did not specify the exact platform or sequencing pipeline; therefore, only the general term MPS is used throughout this review. We included prospective and retrospective cohort studies, but excluded case-control studies, case reports, case series, cross-sectional studies, reviews, animal studies, cost-effectiveness analyses, and studies focusing only on common chromosomal abnormalities. Studies without follow-up of pregnancy outcome were also excluded. No studies were excluded because of ROB.

7.2.3. Information Sources and Search Strategy

A systematic search of five databases - MEDLINE (via PubMed), Embase, Cochrane, Scopus, and Web of Science - was conducted on August 28, 2025. The search key consisted of two domains, population and outcomes: (nipt OR non invasive prenatal) AND (malignant OR malignancy OR cancer OR preeclampsia OR IUGR OR intra uterine grow restriction OR stillbirth OR discordant OR uniparental OR UPD). No language or publication date restrictions were applied. Duplicate records were identified and removed both automatically and manually by M.K. and A.C. using EndNote X9 (Clarivate Analytics). The screening included a review by title and abstract, followed by a full-text assessment based on eligibility criteria. A third reviewer (A.G.) resolved disagreements.

7.2.4. Study Selection and Data Extraction

Data on pregnancy outcomes for controls were obtained from the relevant literature or national statistics, preferably from a similar period. Chromosomal outcomes were analyzed individually without controls. The analyzed chromosomes ranged from 1 to 22 except for 13, 18, and 21. The study focused only on RATs, so we did not process false positive common autosomal trisomies (chromosomes 13, 18, 21), sex chromosome aneuploidies, and structural abnormalities (e.g., duplications, deletions).

7.2.5. Risk of Bias and Quality of Evidence Assessment

The risk of bias was assessed by two independent investigators (M.K. and A.C) based on the recommendations of the Cochrane Collaboration, using the Quality in Prognostic

Studies tool (QUIPS) (Hayden et al., 2013). We evaluated studies based on five domains, namely: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The definition of each domain for our study can be found in Table S1 in the Supplementary Material Konya et al. 2024. Disagreements between the investigators were resolved by a third reviewer (A.G) .

7.2.6. Data Synthesis and Analysis

Statistical analyses were performed using the forestploter, dmetar and meta packages in R (version 4.1.2.), following Harrer et al (Harrer et al., 2021). A p-value <0.05 was considered significant. All analyses used a random-effects meta-analysis approach (Stijnen et al., 2010). Given the low number of studies and sparse events, we retained all eligible studies in the primary random-effects models; risk-of-bias–stratified pooling was underpowered, so we report leave-one-out influence diagnostics and interpret estimates considering QUIPS domains (Hayden et al., 2013; Hunter et al., 2014). Proportions were pooled using the generalized linear mixed-effects model of Stijnen et al. (Stijnen et al., 2010). Control data were obtained from similar geographical locations and time periods using national statistics. Pooled odds ratio (OR) with 95% confidence and p-values were calculated using the random-effects Mantel-Haenszel method (Mantel & Haenszel, 1959; Robins et al., 1986) with the Paule-Mandel tau estimator in the metabin function (Harrer et al., 2021). Heterogeneity was assessed using the I^2 statistic and the Cochrane Q tests, where I^2 values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively (Higgins et al., 2019). Results were visualized using forest plots and leave-one-out result plots. As there were fewer than ten studies per pool and reliance on external control data, publication bias analysis was not performed.

8. RESULTS

8.1. Study I: Genome-Wide, Non-Invasive Prenatal Testing for rare chromosomal abnormalities: A systematic review and meta-analysis of diagnostic test accuracy

8.1.1. Study Search and Selection

Of the 8,336 records, 17 studies were included in the meta-analysis with 740,076 GW-NIPT test analyses (Fig. 1).

Figure 1. *PRISMA 2020 flowchart representing the study selection process (Page et al., 2021)*

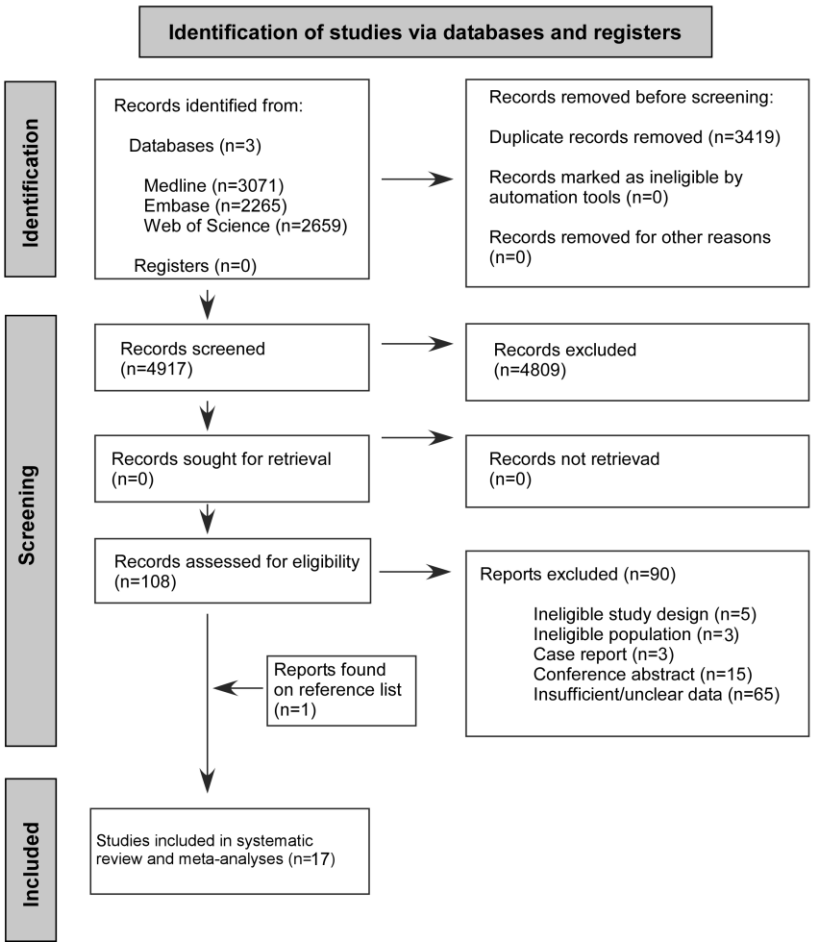


Table 1. *Basic characteristics of included studies,*

Study (year) / Study period	Country	Target population	NIPT primary screening or secondary screening	Article type	Structural variation tested	Number of investigated patients	Age mean	GA mean
Lingshan, 2020/ March 2017 to February 2020	China	high-risk pregnancies, pregnancies whose conception used ART, history of adverse reproductive outcome	primary screening	RS	no	18,016	30,0	18,0
Mossfield, 2022/ May 2021 to October 2021	Australia, Canada, Argentina, South Africa	general or high-risk	NA	RS	no	NA	36,1	11,1
Scott, 2018/ March 2015 to August 2018	Australia	singleton pregnancy, with no obvious abnormality, at a minimum of 10 weeks' gestation at sample collection	NA	PS	no	23,388	35,5	11,4

Table 1. *Basic characteristics of included studies,*

Harasim, 2022/ October 2019 to September 2021	Germany	mixed risk profile	NA	RS	yes	3,664	34,3	13,0
Schuurman , 2022/ April 2017 - April 2019	Netherland	high-risk pregnancies were not included	primary screening	RS	yes	149,318	32,9	12,4
Bogaert, 2021/ 2018 January - 2019 June	Belgium	higher-order pregnancies were not included	primary screening	RS	no	153,575	30,7	NA
Wan, 2018/ February 2015 to 2018 January	China	the pregnancy had to be above 12 gestational weeks	secondary screening	RS	no	15,362	33,0	15,0
Pertile ,2017/ NA	Australia	systematically analyzed WGS data from all chromosomes in two independent clinical laboratories	NA	RS	yes	89,817	34,6	13,8
Pescia, 2018/ NA	Switzerland	two consecutive data sets based on test reports by board-certified laboratory geneticists were retrieved from the clinical database	NA	RS	yes	6,388	NA	NA

Table 1. *Basic characteristics of included studies,*

Opstal, 2018/ April 2014 and April 2015	Netherland	high-risk pregnancies	secondary screening	RS	yes	2,527	NA	NA
Lin, 2021/ January 2014 and December 2020	China	pregnancy with a high-risk RATs report and complete clinical information	NA	RS	no	65,752	31,6	17,7
Brady, 2016/ NA	Belgium	high risk and low risk groups	NA	PS	yes	4	NA	NA
Fiorentino, 2017/ December 2015 and May 2016	Italy	pregnant women undergoing conventional cfDNA-based NIPT for common fetal aneuploidy	secondary screening	PS	yes	12,078	35,3	12,3
Basaran, 2022/ November 2013 and November 2022	Turkey	consecutive cases	NA	RS	yes	NA	34,6	17,1
Xiang, 2023/ March 2021 and March 2022	China	NIPT is a routine screening test for pregnant women at these hospitals and centers after 12 weeks of gestation	primary screening	RS	no	89,242	31,0	17,0

Table 1. *Basic characteristics of included studies,*

Zhang, 2023/ May 2018 and March 2022	China	singleton pregnancies, critical risk value of serological screening for pregnant women and high-risk value of maternal serological screening, single fetal soft markers identified by ultrasound	secondary screening	RS	yes	81,518	NA	NA
Xiaoxiao, 2023/ January 2019 and April 2023	China	high-risk cases	NA	RS	no	25,282	31,8	NA

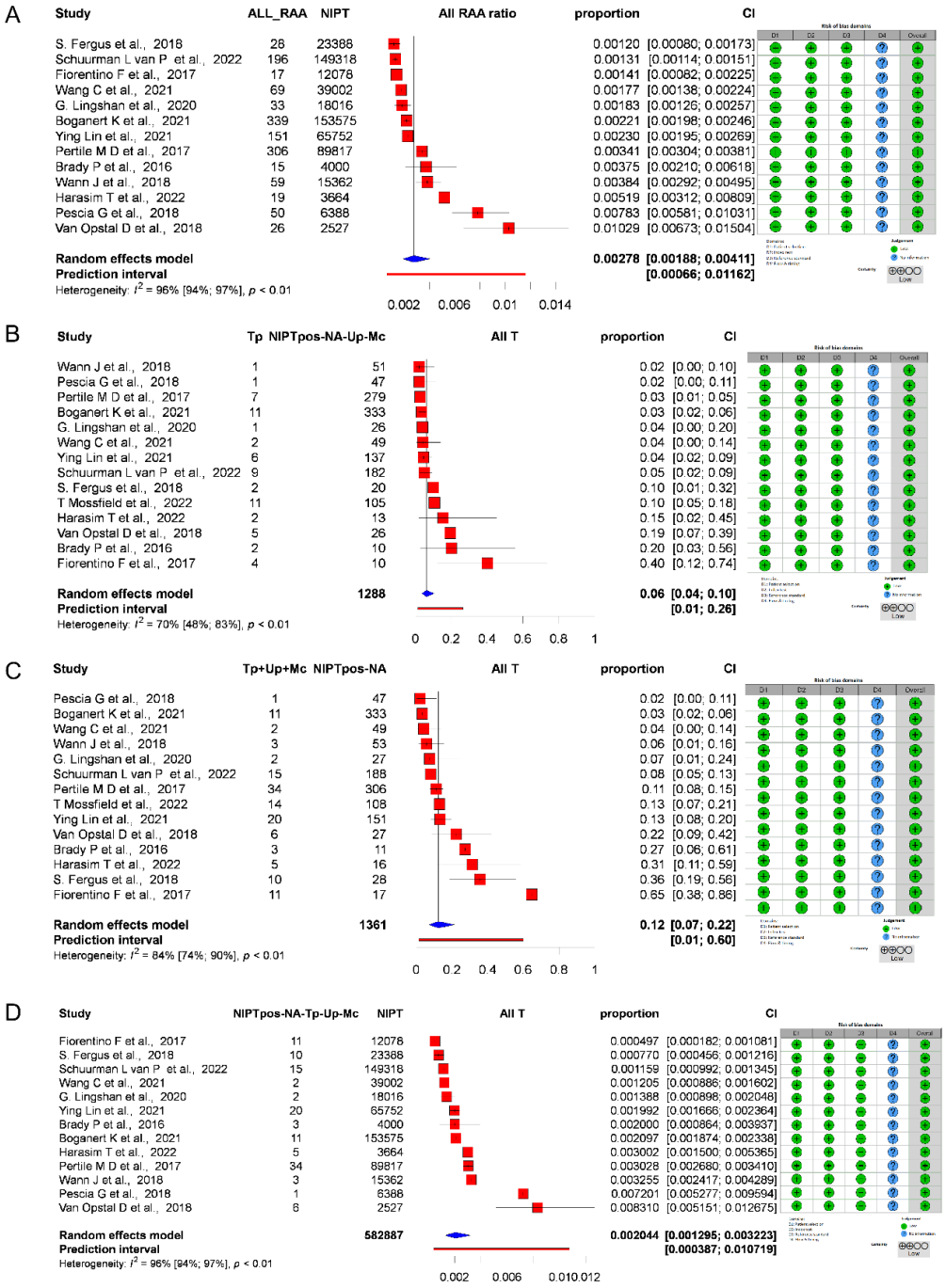
Abbreviations: *RS – retrospective study, PS – prospective study, NA – not available, GA – gestational age, NIPT – non-invasive prenatal test, WGS – whole genome sequencing, cf-DNA – cell-free DNA*

8.1.2. Primary Outcomes

8.1.2.1. Proportion and PPV of GW-NIPT positive results for RATs

For a proportion analysis, 15 studies were analyzed, and 2 studies that included only positive NIPT cases were excluded. In these 15 studies, the total GW-NIPT population was n=739,927, and 1,589 were RAT positive. The pooled proportion was 0.0026 (95% CI: [0.00196, 0.0037] PI: 0.0007; 0.0099 I^2=96 [94%, 97%]) (Figure 2A). A total of 17 studies were analyzed for PPV for all autosomal trisomies. Using the confirmed method, we found that the pooled PPV was 0.07 (95% CI: [0.04, 0.11] PI: 0.01, 0.31 I^2=76% [61%, 85%]) (Figure 2B). Using an extended method, we found that the pooled PPV was 0.13 (95% CI: [0.08, 0.20] PI: 0.02, 0.54). Heterogeneity was high, I^2=82% [73%, 85%] (Figure 2C). We also examined the proportion of false positives among all NIPT cases. The pooled FP rate among all NIPT cases was 0.0020 (95% CI: [0.0014, 0.0030] PI: 0.0005; 0.0088). Heterogeneity was high, I^2=95%[93%,96%] (Figure 2D).

Figure 2. *Forest plots representing the diagnostic test accuracy of rare trisomies*



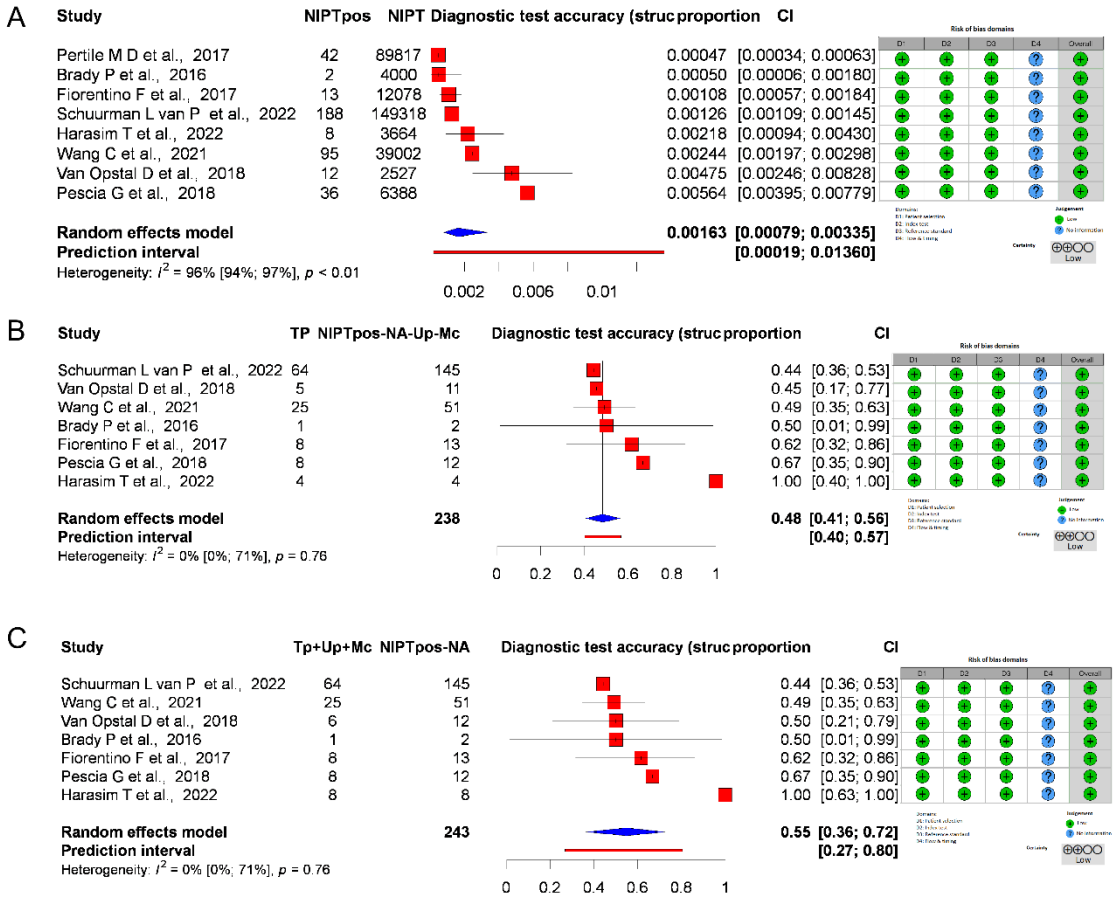
A: *Forest plot representing the pooled frequency of GW-NIPT positive results for all rare autosomal trisomies (RATs)* ***B:*** *Forest plot representing the PPV with a confirmed method for all RATs,* ***C:*** *Forest plot representing the PPV with an extended method for all RATs,* ***D:*** *Forest plot representing the pooled false positive RAT rate (Abbreviations: NIPT:*

non-invasive prenatal test, ALL_RAA: all rare autosomal aneuploidies, Tp: true positive cases, Up: Ultrasound positive cases, Mc: Miscarriage, NA: not available)

8.1.2.2. Proportion and PPV of GW-NIPT positive results for StrCAs

StrCAs were investigated in 10 studies with 388.357 cases, of which 593 were GW-NIPT positive. The pooled proportion was 0.00157 (95% CI: [0.00077, 0.00319] PI: 0.00019, 0-0.01269). Heterogeneity was high, I2=95% [93%, 97%] (Figure 3A). The pooled PPV for StrCAs using the strict method was 0.47 (95% CI: [0.31, 0.63] PI: 0.19, 0.76). Heterogeneity was I2=40% [0%, 73%] (Figure 3B). Using an extended method, we found that the pooled PPV was 0.52 (95% CI: [0.33, 0.71] PI: 0.14, 0.88). Heterogeneity was I2=41% [0%, 74%] (Figure 3C).

Figure 3: *Forest plots representing the diagnostic test accuracy of StrCAs*



A: *Forest plot representing the pooled frequency of GW-NIPT positive results for StrCAs,* ***B:*** *Forest plot representing the PPV with a confirmed method for StrCAs,* ***C:*** *Forest plot representing the PPV with an extended method for StrCAs, (Abbreviations: NIPT: non-invasive prenatal test, Tp: true positive cases, Up: Ultrasound positive cases, Mc: Miscarriage, NA: not available)*

8.1.3. Secondary Outcomes - Distribution of chromosomal aberrations by each chromosome

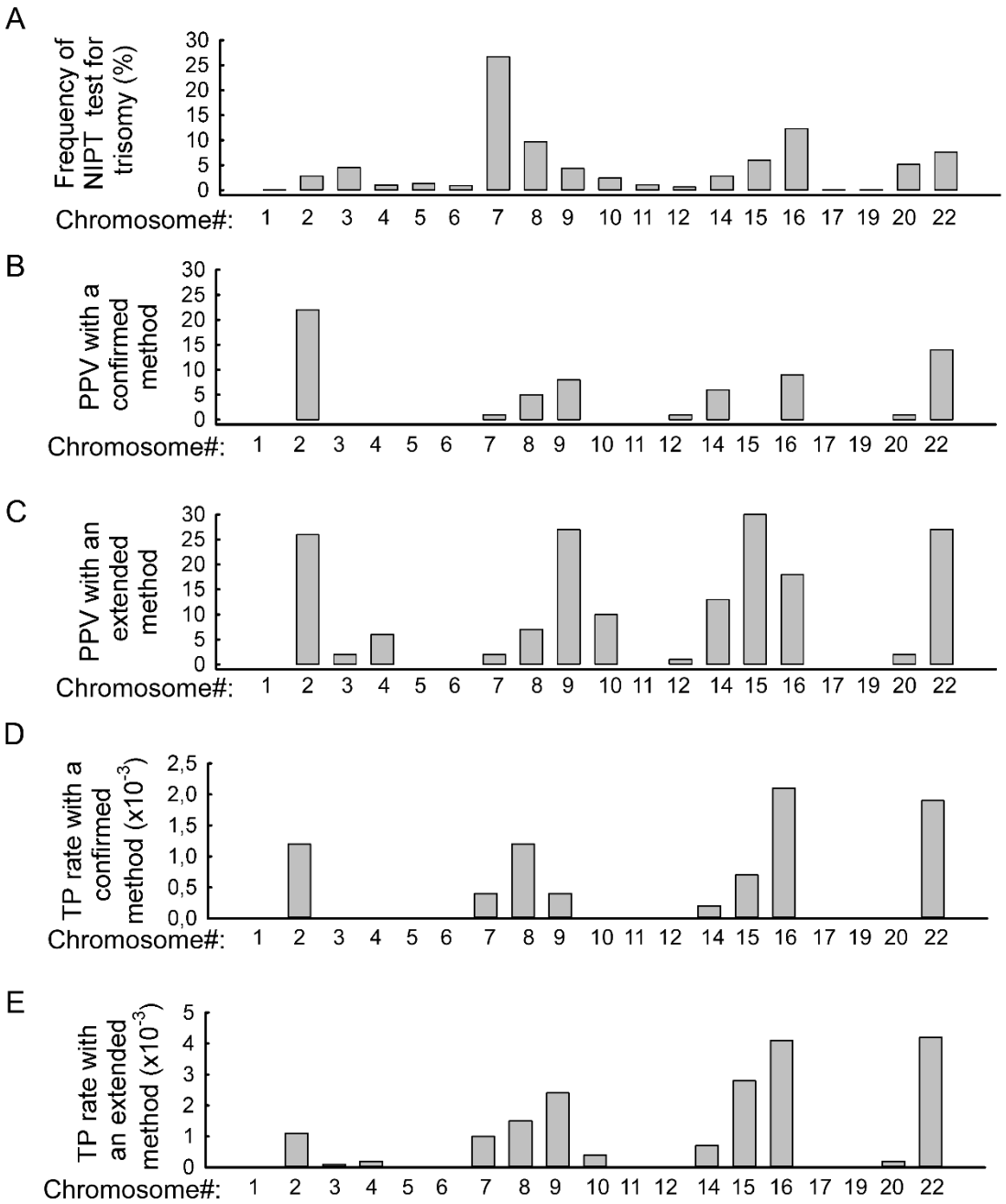
The highest number of GW-NIPT positive results was obtained for chromosome 7 trisomy (n 480), with a pooled positive ratio among all the combined T positive results of 0.27 (95% CI: [0.22, 0.31] PI: 0.154, 0.43) (Konya et al., 2024, Supplementary Figure S26). Our results show that T7 trisomy was followed by T16 (n=199), with a random-effects pooled proportion of 0.11 (95% CI: [0.09, 0.1] PI: 0. 007, 0.18) (Suppl. Figure S34), T8 (n=169) with a random-effects pooled proportion of 0.09 (95% CI: [0.08, 0.12] PI: 0.05, 0.16) (Suppl. Figure S27), T20 (n=137) with a random-effects pooled proportion of 0.07 (95% CI: [0.05, 0.09] PI: 0.04,0.13) (Suppl. Figure S37), T22 (n=134) with a random-effects pooled proportion of 0.08 (95% CI: [0.065, 0.10] PI:0.04,0.16) (Suppl. Figure S38), and T15 (n=122) with a random-effects pooled proportion of 0.06 (95% CI: [0.04, 0.08] PI:0.017, 0.18) (Suppl. Figure S33), which is considered more common.

Interestingly, T1, T17, and T19 GW-NIPT positivity was very rare. The random-effects pooled proportion for T1(n=6) was 0.003 (95% CI: [0.00, 0.0] PI: 0.00, 0.03) (Suppl. Figure S20); T17 (n=8) with a random-effects pooled proportion of 0.00 (95% CI: [0.00, 0.01] PI: 0.00,0.13) (Suppl. Figure S35) and T19 (n=1) with a random-effects pooled proportion of 0.00 (95% CI: [0.00, 0.20] PI: 0.00, 0.34) (Suppl. Figure S36).

Of a total of 1,589 GW-NIPT RAT positive cases, 87 were true positives using the confirmed method, and 174 were true positives using the extended method. With the confirmed method, the highest number of true positives was found in T16, with a random-effects pooled TP proportion among all NIPT cases of 1.7 x10-5 (95% CI: [0. 9x10-5, 3.0 x10-5] PI: 0. 9x10-5, 3.0x10-5), followed by T22, with a random-effects pooled proportion of 1.5 x10-5 (95% CI: [0. 8 x10-5, 2.8 x10-5] PI: 0. 8 x10-5, 2.9 x10-5), and T2, with a random-effects pooled proportion of 1.5 x10-5 (95% CI: [0.8 x10-5, 3.0 x10-5] PI: 0. 5 x10-5, 4.2 x10-5) (Figure 4D). With an extended method, the highest number

of true positives was confirmed in T15, with a random-effects pooled proportion of 2.9 x10-5 (95% CI: [1.0 x10-5, 8.2 x10-5] PI: 0. 1 x10-5, 7,9 x10-5), followed by T16, with a random-effects pooled proportion of 3.5 x10-5 (95% CI: [2.3 x10-5, 5.2 x10-5] PI: 2.3 x10-5, 5.2 x10-5) and T22, with a random-effects pooled proportion of 3.2 x10-5 (95% CI: [1.3 x10-5, 7.9 x10-5] PI: 2.0 x10-5, 4.33 x10-5) (Figure 4E).

Figure 4: *Column plot for visualization of the habitat of each chromosome*



A: *Column plot representing the pooled frequency of GW-NIPT positive results for all rare autosomal trisomies (RATs),* ***B:*** *Column plot representing the PPV with a confirmed method for all RATs,* ***C:*** *Column plot representing the PPV with an extended method for all RATs,* ***D:*** *Column plot representing the pooled true positive RAT rate* ***E:*** *Column plot representing the pooled true positive RAT rate*
(Abbreviations: NIPT: non-invasive prenatal test, TP: true positive cases, PPV: positive predictive value

8.2. Risk of Bias Assessment

The risk of bias was assessed (M.K. and A.C.) based on the recommendations of the Cochrane Collaboration, using the Cochrane risk-of-bias tool for systematic reviews of diagnostic accuracy studies (QUADAS-2). Disagreements between data extractors were resolved by involving a third reviewer (A.G.).

8.3. Quality of Evidence

The quality of evidence was assessed following the recommendations of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup (Guyatt et al., 2008).

8.4. Study II: Discordant findings in genome-wide non-invasive prenatal testing (GW-NIPT) for rare chromosomal abnormalities, adverse pregnancy outcomes, and maternal malignancies: a systematic review and meta-analysis

8.4.1. Study Search and Selection

Of the 2,602 records identified, 16 studies were included in the meta-analysis, comprising a total of 681,633 GW-NIPT test analyses. (Figure 5).

Figure 5. *PRISMA 2020 flowchart representing the study selection process (Page et al., 2021)*

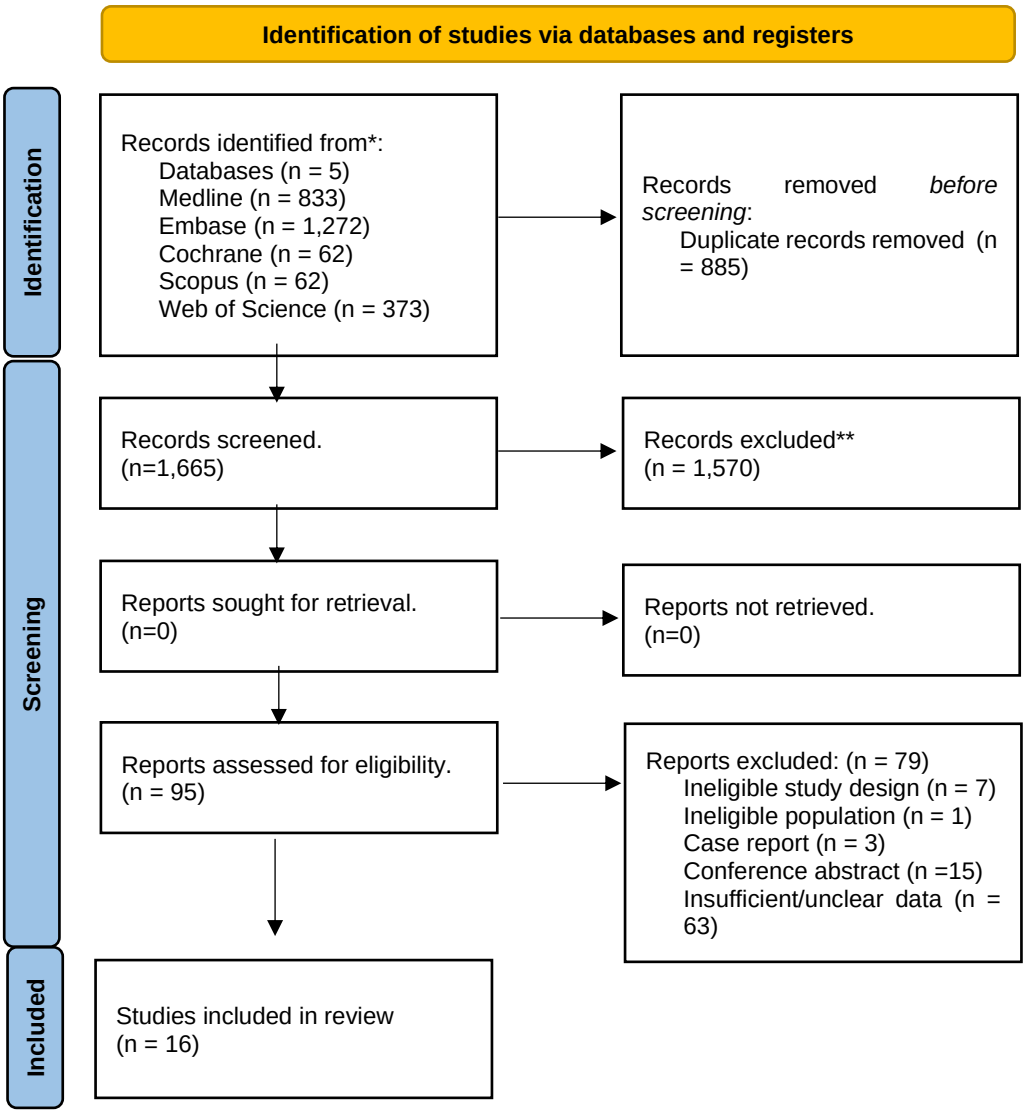


Table 2. *Basic characteristics of included studies*

Study (year) / Study period	Country	Target population	NIPT primary or secondary screening	Article type	Number of investigated NIPTs	Number of NIPT positives	Adverse Pregnancy Outcomes	Data for maternal cancer
Schuurman L, 2022/ April 2017 - April 2019	Netherland	high-risk pregnancies were not included	primary screening	RS	149,318	189	PE, IUGR, SGA, PB, SB UPD	yes
Zhang M, 2023/ May 2018 and March 2022	China	singleton pregnancies, critical risk value of serological screening for pregnant women and high-risk value of maternal serological screening, single fetal soft markers identified by ultrasound	secondary screening	RS	81,518	81	PE, IUGR, SGA, PB, UPD	no
Mossfield T, 2022/ May 2021 to October 2021	Australia, Canada, Argentina, South Africa	general or high-risk	NA	RS	NA	75	PE, IUGR, PB, SB, UPD	no
Li J 2022, Jan 2016 - June 2019	China	Patients with complex GW-NIPT results	NA	RS	NA	496	-	yes
Hong D 2023, July 2018 and June 2020	Korea	Patients with positive GW-NIPT results	NA	RS	NA	1,383	UPD	no
Ottaiano A 2023, 2018 and 2022	Italy	general or high-risk	NA	RS	100,685	27	-	yes
Lin Y, 2021/ January 2014 and December 2020	China	pregnancy with a high-risk RATs report and complete clinical information	NA	RS	65,752	142	IUGR, PB, SB, UPD	no
Harasim T, 2022/ October 2019 to September 2021	Germany	mixed risk profile	NA	RS	3,664	4	-	yes

Table 2. *Basic characteristics of included studies*

Opstal D, 2018/ April 2014 and April 2015	Netherland	high-risk pregnancies	secondary screening	RS	3,306	20	IUGR, SGA, PB, UPD	no
Scott F, 2018/ March 2015 to August 2018	Australia	singleton pregnancy, with no obvious abnormality, at a minimum of 10 weeks gestation at sample collection	NA	PS	23,388	19	IUGR, PB, SB	
Bogaert, 2021/ 2018 January - 2019 June	Belgium	higher-order pregnancies were not included	primary screening	RS	153,575	NA	UPD	no
Pertile M 2017/ NA	Australia	systematically analyzed WGS data from all chromosomes in two independent clinical laboratories	NA	RS	89,817	23	PE, IUGR, SGA, PB, SB UPD	no
Merrill M 2023, 2014-2022	USA	Most patients (79%) had multiple chromosomal aneuploidy NIPT result	NA	RS	NA	11	-	yes
Xie X, 2023/ January 2019 and April 2023	China	high-risk cases	NA	RS	6,388	42	PE, IUGR, SGA, PB, SB	no
Zhen J et al. 2025 November 2017 - May 2021	China	high-risk cases	NA	RS	59877	56	PB, SB	no
Turrif et al. 2024 December 23, 2019, - December 4, 2023	North-America	Cases that were either (1) abnormal and inconsistent with a viable fetus on sonogram, (2) abnormal and discordant with the fetal karyotype or chromosome microarray analysis, or (3) nonreportable.	NA	RS	NA	246	-	yes

8.4.2. Primary Outcomes

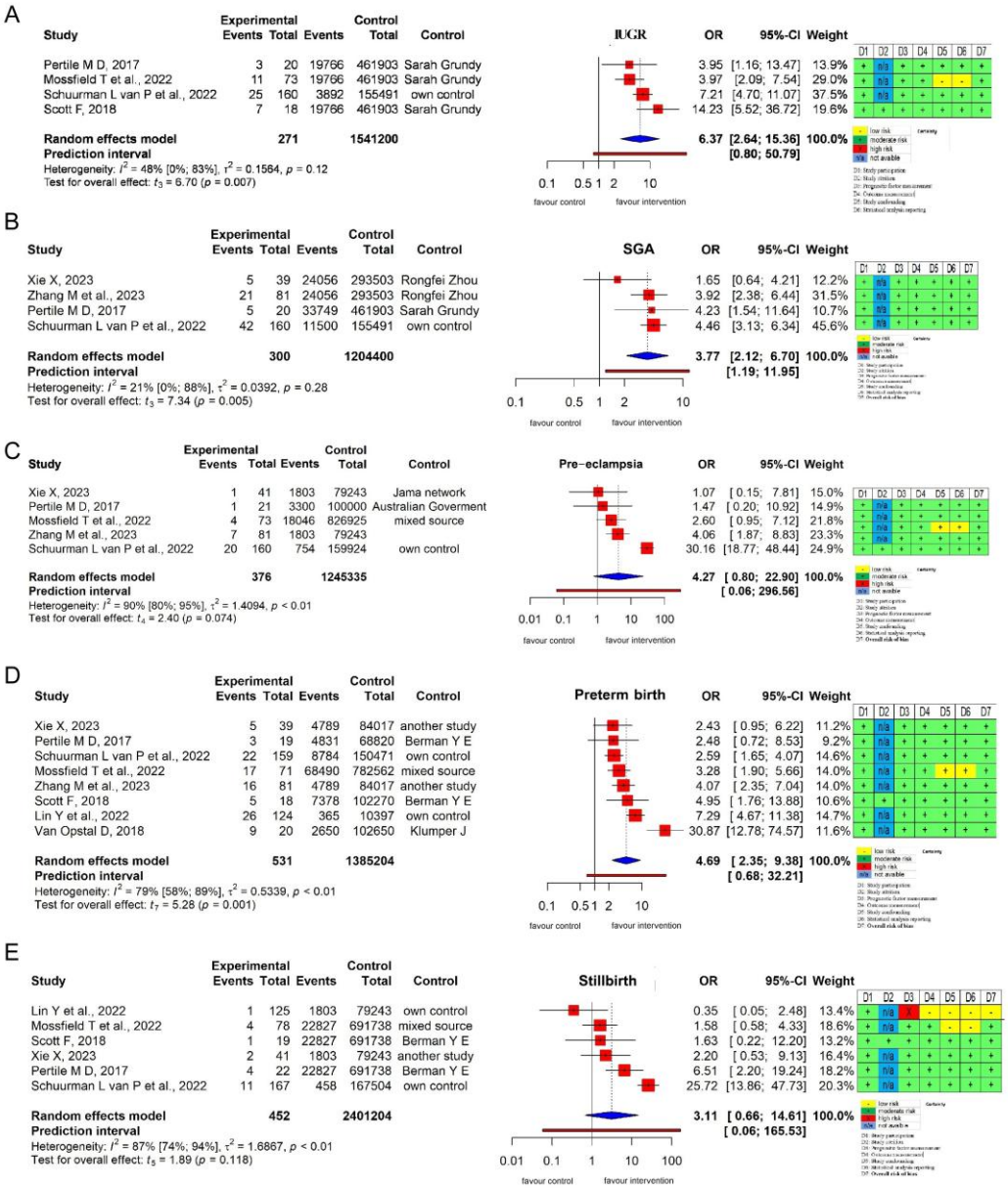
8.4.2.1. Pregnancy complications for discordant rare trisomies

A total of 681,633 GW-NIPT cases with known population numbers were included. The analysis of odds ratios (ORs) for intrauterine growth restriction (IUGR), small for gestational age (SGA), pre-eclampsia (PE), preterm birth (PB) and stillbirth (SB) was conducted across all chromosomes (Figure 6). For consistency across studies, pregnancy outcomes were defined as reported in the primary publications. Babies with a birth weight below the 3rd percentile were categorised as IUGR cases, while those below the 10th percentile were categorised as SGA. PB was analysed as an all-cause endpoint (spontaneous or iatrogenic), unless otherwise specified. SB and PE were defined as in the included studies. Studies with no suitable control group from either the original study or the national statistical authority were not included in the OR calculation.

Babies born below the 3rd percentile are considered IUGR babies; however, the cut-off may vary in some countries. A total of 46 cases of IUGR were found among 271 cases of discordant GW-NIPT in 4 studies [3, 9, 10, 20]. Women with discordant NIPT results had 6.37 times higher odds for having a baby with IUGR [OR=6.37 (95% CI: 2.64-15.36)]. There was moderate heterogeneity in the studies included (I^2 = 48%, 95% CI: 0%-83%) (Figure 6A). For PB, 9 [3, 9, 10, 18, 20, 23-26] were included with 110 cases in 568 discordant NIPT results. Similarly, women with discordant NIPT results had higher odds for PB [OR=4.60 (95% CI: 2.53-8.34)], however, the studies presented substantial heterogeneity (I^2 = 75.8%, 53.5%-87.4%) (Figure 6B). For PE, five studies were included [3, 10, 20, 24, 25] with 376 NIPT-positive cases and 33 PE diagnoses. The discordant NIPT population had 4.27 times higher odds of PE (95% CI: 0.80-22.90) compared to the comparator group. However, this large difference was not significant due to high heterogeneity (I^2 = 90%, 80%-95%) (Figure 6C). When performing the one-out analysis, omitting the study by Schuurman et al. [3] reduced the odds to 2.93, which became significant (95% CI: 1.34-6.38), and eliminated heterogeneity (Figure S80). When the size is below the 10th percentile, we refer to SGA fetuses or SGA newborns. For SGA, 4 studies were included [3, 10, 24, 25], with a total of 300 NIPT positive cases, and 73 confirmed diagnoses. The OR was 3.77 (95% CI: 2.12-6.70, PI: 1.19-11.95), with low

heterogeneity (I^2 = 21%, 0%-88%) (Figure 6D). In a one-out analysis, omitting the study by Xie X et al., the OR increased to 4.27 (95% CI: 3.57-5.09), and heterogeneity decreased to 0% (Figure S82). For stillbirth analysis, seven studies were included. There were 26 cases in a population of 492 with NIPT-positive results. The latter presented an OR of 3.25 (95% CI: 0.94-11.25, PI: 0.15-71.86), and high heterogeneity (I^2 = 85.2%, 71.5%-92.4%) (Figure 6E). Due to inconsistent reporting across studies, the pooled PB estimate should be interpreted as all-cause PB, including both spontaneous and iatrogenic events. Leave-one-out influence diagnostics indicated that one higher-risk study materially affected heterogeneity and borderline significance for PE, whereas estimates for SGA/IUGR/PB were directionally stable (Figs. S80–S82).

Figure 6. *Risk of placenta-related complications after discordant RAT-positive GW-NIPT (all chromosomes combined).*



The forest plots show the pooled odds ratios (ORs) comparing pregnancies with discordant rare autosomal trisomy (RAT) results on GW-NIPT (experimental group) with population comparators (control group).

Panels: (A) Intrauterine Growth Restriction (IUGR), (B) Small for Gestational Age (SGA), (C) Pre-Eclampsia (PE), (D) Preterm Birth (PB), and (E) Stillbirth (SB).

8.4.2.2. Pregnancy outcome per chromosome

Overall Adverse Outcomes (IUGR, SGA, PE, PB, SB)

Trisomy 16 (T16) demonstrated the highest risk for overall adverse pregnancy outcome when analyzed by chromosome. For placental mosaicism of chromosome 16, the pooled proportion was 0.84 (95% CI: [0.71, 0.92]), meaning 84% of these pregnancies were associated with an adverse outcome.

This high-risk group was followed by T4 (0.71 [0.06, 0.99]), T6 (0.66 [0.10, 0.95]), and T22 (0.59 [0.35, 0.79]). The lowest pooled proportions were observed for T8 (0.16 [0.05, 0.42]), T10 (0.17 [0.02, 0.70]), and T7 (0.26 [0.11, 0.48] This study had no statistically applicable data for chromosomes 1, 12, 17, and 19 (Figure 7A, Konya et al. 2025. Supplementary material S1-15 and S72).

Intrauterine Growth Restriction (IUGR)

For the 489 NIPT false-positive cases analyzed for IUGR (85 events), the pooled proportion was highest for T4 at 0.57 (95% CI: [0.05, 0.97]), indicating that IUGR developed in more than half of fetuses with T4 placental mosaicism. T16 also showed a high risk (0.55 [0.38, 0.71]), followed by T2 (0.40 [0.10, 0.80]). (Figure 7A, Suppl. S16-29 and S73).

Small for Gestational Age (SGA)

Based on limited data (266 NIPT false positives, 75 events), T16 carried a very high risk (pooled proportion: 0.79, 95% CI: [0.53, 0.93]). The more common trisomies (T7, T8, T20) showed a moderate risk, ranging from 0.09 to 0.20. (Figure 7A, Suppl. S50-58, S77).

Pre-eclampsia (PE)

Among 190 NIPT false-positive cases with 21 PE events, only T7, T8, T16, and T20 abnormalities had statistically significant case numbers. Of these, T16 was high risk

(pooled proportion: 0.39 [0.11, 0.77]), T20 was moderate risk (0.17 [0.02, 0.63]), while T7 and T8 were low risk (both 0.03). (Figure 7A, Suppl. S31-35 and S75).

Preterm Birth (PB)

Out of 532 NIPT false-positive cases with 103 PB events, the highest risk was observed for T2 (pooled proportion: 0.64 [0.26, 0.90]), followed by T4 (0.62 [0.14, 0.94]). T16 showed a substantial pooled proportion of 0.52 (95% CI: [0.29, 0.74]), supported by a larger dataset. Common trisomies like T7, T8, and T20 showed lower risk (0.05 to 0.14). (Figure 7A, Suppl. S36-49, S74).

Stillbirth (SB)

Due to the low frequency of SB (22 events in 371 cases), statistical interpretation is limited. The highest pooled proportions were observed for T9 (0.24 [0.05, 0.65]) and T15 (0.17 [0.04, 0.48]). The T7 group, with the highest number of cases, had a pooled proportion of 0.02 (95% CI: [0.00, 0.09]). (Figure 7A, Suppl. S59-71 and S76).

Uniparental disomy (UPD)

In our meta-analysis of 281 NIPT-positive results, we found a total of 16 UPD cases across 5 chromosomal involvements (7, 8, 15, 16, 20).

The highest pooled proportions for UPD were found for T15 at 0.22 (95% CI: [0.06, 0.55]) and T16 at 0.20 (95% CI: [0.07, 0.46]). Single cases were diagnosed at T7, T8, and T20. (Figure 7B and Suppl. S78).

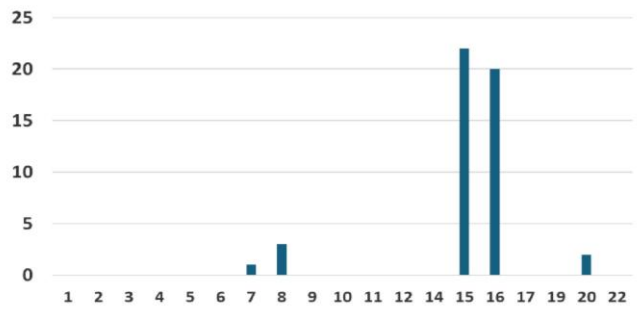
It is critical to emphasize that the identified risks for UPD in these specific chromosomes are dramatically increased compared to the general population incidence of UPD approximately 1 in 5,000–10,000 live births) (Molloy et al., 2022). So, the risks identified in this study are dramatically increased for these chromosomes.

Figure 7*. (A): Pooled Proportions of Pregnancy Complications (Adverse Outcomes)*

A

Chromosome	Adverse outcome	IUGR	SGA	PE	PB	SB
1	NA	NA	NA	NA	NA	NA
2	45%	40%	NA	NA	60%	NA
3	29%	11%	31%	NA	11%	2%
4	71%	57%	NA	NA	71%	NA
5	30%	7%	NA	NA	1%	NA
6	60%	25%	NA	33%	20%	NA
7	26%	8%	20%	3%	12%	2%
8	16%	4%	12%	3%	4%	4%
9	42%	NA	33%	NA	14%	17%
10	17%	9%	NA	NA	6%	NA
11	50%	3%	NA	NA	43%	NA
12	NA	NA	NA	NA	NA	NA
14	NA	NA	NA	NA	NA	NA
15	50%	16%	NA	NA	11%	19%
16	84%	55%	79%	39%	55%	8%
17	NA	NA	NA	NA	NA	NA
19	NA	NA	NA	NA	NA	NA
20	29%	13%	9%	17%	12%	NA
22	59%	15%	30%	NA	22%	3%

B



- *Focus: Investigates the rate of pregnancy complications among cases where NIPT was False-Positive (FP) for a Rare Autosomal Trisomy (RAT).*
- *Stratification: Results are grouped by chromosome (Chr.).*
- *Outcomes: The "Adverse outcome" category includes Intrauterine Growth Restriction (IUGR), Small for Gestational Age (SGA), Pre-eclampsia (PE), Preterm Birth (PB), or Stillbirth (SB).*
- *Definitions: Specific definitions for IUGR (birth weight<3rdcentile), SGA (birth weight<10thcentile), and PB (all-cause) are provided.*
- *Key Data Elements: The figure shows the pooled proportion (shaded bar), the percentage, the 95% Confidence Interval (CI), and the number of FP cases ('No FP') contributing to the estimate.*

- *Caveats: "NA" means no eligible data, and caution is advised for estimates based on small denominators.*

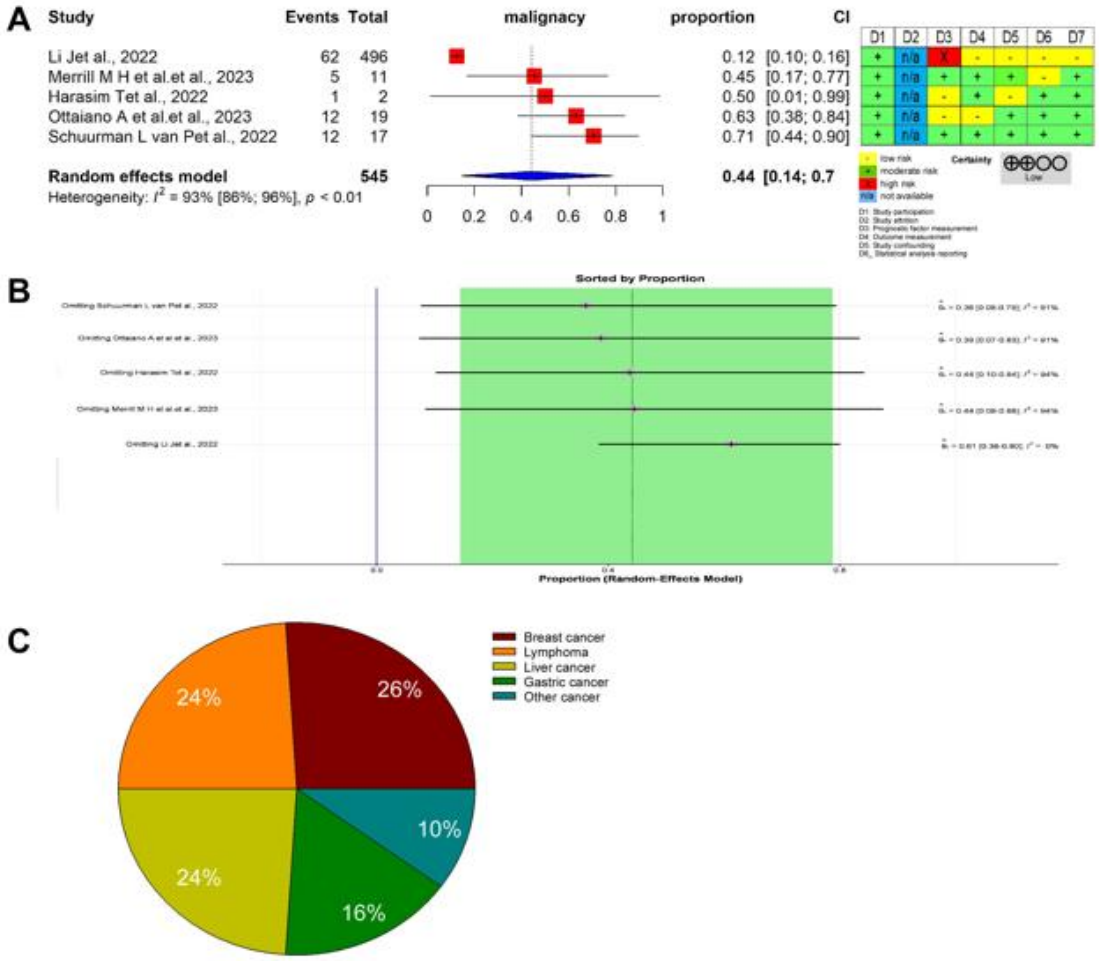
- ***(B):** Pooled Proportion of Uniparental Disomy (UPD)*
- *Focus: Investigates the proportion of UPD among cases with a discordant RAT result (positive NIPT, but not a full trisomy on definitive testing).*
- *Stratification: Grouped by chromosome.*
- *Key Data Elements: Shows the pooled proportion (percentage). The exact values and 95% CIs are in the text/supplement.*

8.4.3. Secondary Outcomes - Complex NIPT-positive cases – maternal malignancies

This study analyzed 575 complex NIPT cases, with follow-up from 6 studies. Of 575 discordant cases, 101 were associated with maternal malignancies, with a pooled proportion of 0.41 (95% CI: 0.17-0.70). Significant variation was observed between studies (12-71%), with high heterogeneity ($I^2 = 91.3\%$). (Figure 8)

The incidence of PAC is approximately 1/1,000 pregnancies [34], but in complex NIPT cases, the risk increases by a factor of 400 to 500. Of the 83 cancer cases identified, the most common were breast cancer (24%), lymphoma (24%), hepatic malignancies (16%), and gastric malignancies (10%).

Figure 8. *Maternal Malignancy and Complex Discordant GW-NIPT Results*



This figure illustrates the association between maternal cancer and genome-wide non-invasive prenatal testing (GW-NIPT) results that show complex, multi-chromosomal anomalies but are discordant (negative) with fetal testing.

A: *Pooled Proportion of Confirmed Maternal Cancer (Forest Plot)*

This forest plot displays the pooled proportion of confirmed maternal cancers found in women who had complex, multi-chromosomal GW-NIPT findings (e.g., multiple aneuploidy signals or genome-wide copy-number instability) that did not align with fetal status, ***B:*** *The results of one-out analysis,* ***C:*** *Distribution of Cancer Types (Pie Chart) This plot shows the percentage distribution of specific cancer types among all confirmed malignancies identified across the included studies.*

8.4.4. Risk of Bias Assessment

The risk of bias was assessed by two independent investigators (M.K. and A.C) based on the recommendations of the Cochrane Collaboration, using the Quality in Prognostic Studies tool (QUIPS). We evaluated studies based on five domains, namely: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The definition of each domain for our study can be found in Table S1 in the Supplementary Material. Disagreements between the investigators were resolved by a third reviewer (A.G).

9. DISCUSSION

9.1. Summary of Findings, International Comparisons (including all studies)

The clinical integration of genome-wide non-invasive prenatal testing (GW-NIPT) represents a paradigm shift in prenatal screening, moving beyond the detection of common trisomies (T21, T18, T13) toward a comprehensive assessment of the fetal and placental genomic landscape (Bianchi & Chiu, 2018). Based on the systematic review of 17 major studies covering a screening population of over 740,000 pregnancies, the findings underscore that while rare autosomal aneuploidies (RATs) and structural chromosomal abnormalities (StrCAs) are infrequent—with a pooled prevalence of approximately 0.20% to 0.26%—their identification carries profound diagnostic and prognostic implications (Konya et al., 2024). The data reveal a complex diagnostic landscape where the positive predictive value (PPV) for RATs remains generally low, averaging around 6-13% depending on the confirmation method used (Pertile, Halks-Miller, Flowers, Barbacioru, et al., 2017; Scott et al., 2018). However, this meta-analysis highlights significant variability between specific chromosomes. For instance, trisomies 16, 22, and 2 demonstrated the highest diagnostic yields, suggesting that NIPT is particularly sensitive to these specific aberrations (Benn et al., 2019; Van Opstal et al., 2018). When the diagnostic criteria were expanded to include "extended" outcomes—such as ultrasound-confirmed fetal anomalies, spontaneous miscarriages, or terminations where genetic material was not directly karyotyped but clinical evidence was overwhelming—the PPV increased significantly, particularly for chromosomes 15, 16, and 22 (Kónya et al., 2025).

A cornerstone of these findings is the clinical significance of "discordant" results, where a normal fetal karyotype follows a positive NIPT for a RAT (Hartwig et al., 2017). Traditionally viewed as "false positives," these cases are increasingly recognized as indicators of placental dysfunction, often linked to confined placental mosaicism (CPM) (Eggenhuizen et al., 2021; Grati, 2014). The meta-analysis provides robust evidence that these discordant findings are not benign; approximately 35.5% of such pregnancies resulted in adverse pregnancy outcomes (APOs). Specifically, the risk of intrauterine growth restriction (IUGR), pre-eclampsia, and preterm birth was significantly elevated in

pregnancies flagging for RATs on chromosomes 2, 11, and 16. This suggests that GW-NIPT serves as an inadvertent but valuable screening tool for placental insufficiency. Furthermore, the detection of RATs on chromosomes 15 and 16 necessitates specific follow-up for uniparental disomy (UPD), a condition that can lead to serious imprinting disorders(Hong et al., 2023). Another critical dimension identified is the correlation between complex, multi-chromosomal NIPT profiles and maternal health(Li et al., 2022). The research indicates that in 40% of cases where NIPT showed multiple or complex chromosomal aberrations, an underlying maternal malignancy was discovered, with breast cancer and lymphoma being the most prevalent. This emphasizes the role of GW-NIPT as a potential "liquid biopsy" for the mother, requiring careful ethical and clinical management (Ottaiano et al., 2024).

From an international perspective, the data synthesized in these studies reflect a global trend toward adopting expanded NIPT, though the clinical application varies by region (Jayashankar et al., 2023). Large-scale cohort studies from China, such as those by Zhen et al. (2025) (Zhen et al., 2025) and Xiang et al. (2023) (Xiang et al., 2023), provide the most substantial data regarding the prevalence of RATs in an unselected, general population, highlighting the scalability of massive parallel sequencing (MPS). In Europe, the landscape is shaped by national screening policies. The Dutch TRIDENT studies and Belgian nationwide programs (e.g., Schuurman 2022, Bogaert 2021) offer a model for integrating GW-NIPT as a first-tier screening tool, emphasizing the importance of informed parental choice and the high uptake of genome-wide reporting when offered (Van Den Bogaert et al., 2021; van Prooyen Schuurman et al., 2022). In contrast, data from countries like Italy, Germany, and Switzerland often focus on higher-risk populations or the utility of NIPT as a second-tier test following abnormal biochemical screening (Basaran et al., 2022; Fiorentino et al., 2017).

Despite these differences in healthcare delivery, the biological findings remain remarkably consistent across international borders. The recurring association between specific RATs (such as T16) and placental complications has been consistently reported across international cohorts, including studies from Australia, Europe, North America, and Asia, confirming that the clinical challenges of GW-NIPT—namely the management of mosaicism and the interpretation of rare findings—are universal (Basaran et al., 2022;

Eggenhuizen et al., 2021; Pertile, Halks-Miller, Flowers, & Barbacioru, 2017; Scott et al., 2018). The synthesis of these international results highlights a critical need for standardized global guidelines. While the technology has matured rapidly, the counseling protocols for rare findings and the management of maternal incidental findings still vary significantly. These comparisons underscore that the future of prenatal care lies in a more nuanced interpretation of genome-wide data, where the focus shifts from a simple "positive/negative" result for the fetus to a holistic assessment of the pregnancy unit, including fetal, placental, and maternal health indicators. This global evidence base confirms that while RATs are individually rare, their collective impact on prenatal management is transformative, requiring a specialized, multidisciplinary approach to genetic counseling and obstetric follow-up worldwide.

9.2. Strengths

The primary strength of this research lies in its unprecedented scale, synthesizing data from over 740,000 genome-wide non-invasive prenatal testing (GW-NIPT) analyses across diverse international cohorts. This systematic approach allowed for a high-precision meta-analysis capable of determining the prevalence and positive predictive values (PPV) of rare autosomal aneuploidies (RATs) and structural chromosomal abnormalities (StrCAs) on a chromosome-by-chromosome basis (Konya et al., 2024). A significant methodological advantage is the dual-analysis framework: by employing both a "confirmed" method (validated by genetic testing) and an "extended" method (incorporating ultrasound findings and fetal loss), the study provides a more realistic assessment of NIPT’s clinical utility in real-world settings.

Furthermore, the research extends beyond mere diagnostic accuracy to explore the prognostic value of discordant results, establishing robust links between specific chromosomal aberrations and adverse pregnancy outcomes (APOs) such as IUGR and pre-eclampsia. The systematic evaluation of complex NIPT profiles as potential markers for maternal malignancies also adds a vital dimension to maternal healthcare (Dow et al., 2021; Turriff et al., 2024). Finally, the use of advanced statistical modeling, such as random-effects generalized linear mixed models, ensures the reliability of the findings

even for extremely rare events, providing a globally representative evidence base for prenatal clinical practice.

9.3. Limitations

Despite the large cumulative sample size, several limitations inherent to the study of rare genetic conditions must be addressed. Although the total population is vast, the actual number of positive cases for specific rare chromosomes (e.g., trisomies 1 or 5) remains low, resulting in wide confidence intervals for certain sub-analyses. Technological heterogeneity also poses a challenge; while all included studies utilized massive parallel sequencing (MPS), variations in bioinformatics pipelines and resolution thresholds (e.g., detection limits for aberrations below 7 Mb) may have influenced the identification rates of structural abnormalities (Brady et al., 2016; Jayashankar et al., 2023).

Additionally, the potential for publication bias cannot be entirely excluded, as smaller studies may disproportionately report unusual or "successful" cases, such as rare maternal cancers, over routine false-positive results. The clinical heterogeneity introduced by varying international follow-up protocols—such as different thresholds for invasive testing or ultrasound monitoring—also impacts the uniformity of the data. Furthermore, the analysis of pregnancy complications often relied on national statistics or historical literature for control groups rather than direct, internal controls. Finally, the detection limit of standard GW-NIPT means that very small structural variations may have remained undetected, potentially leading to a slight underestimation of the total burden of chromosomal aberrations across the genome (Brady et al., 2016).

10. CONCLUSIONS

The integration of genome-wide non-invasive prenatal testing (GW-NIPT) into clinical practice represents a significant advancement in prenatal screening, providing a more comprehensive view of the fetal, placental, and maternal genomic environment (Bianchi & Chiu, 2018). This systematic review and meta-analysis demonstrate that while rare chromosomal abnormalities—including rare autosomal aneuploidies (RATs) and structural chromosomal aberrations (StrCAs)—are individually infrequent, their collective detection is of high clinical relevance. Although the positive predictive value for many of these rare findings is relatively low, specific chromosomes such as 16, 22, and 15 show a significantly higher correlation with fetal involvement, particularly when combined with ultrasound findings.

A key takeaway from this research is that "discordant" NIPT results should no longer be dismissed as mere false positives. There is clear evidence that these findings often reflect confined placental mosaicism, which serves as a potent indicator of placental insufficiency and an increased risk for adverse pregnancy outcomes like IUGR and pre-eclampsia. Furthermore, the identification of complex, multi-chromosomal patterns provides a unique window into maternal health, acting as an incidental screening tool for underlying maternal malignancies.

In conclusion, GW-NIPT should be viewed as a multi-purpose screening tool that extends beyond traditional trisomy detection. To maximize its clinical utility, international guidelines must be standardized to support healthcare providers in the complex genetic counseling and specialized obstetric management required for these rare findings. Ultimately, the transition from targeted to genome-wide screening offers a more holistic approach to pregnancy care, improving the identification of high-risk pregnancies and potentially enabling earlier interventions for both the fetus and the mother.

11. IMPLICATIONS FOR PRACTICE

The findings of this research have significant implications for the clinical management of pregnancies undergoing genome-wide non-invasive prenatal testing (GW-NIPT). First and foremost, the high rate of discordant results for rare autosomal aneuploidies (RATs) underscores the necessity of specialized genetic counseling. Clinicians must ensure that expectant parents are informed prior to testing that a positive result for a rare chromosome often does not originate from the fetus itself but may instead indicate confined placental mosaicism (CPM) or maternal factors.

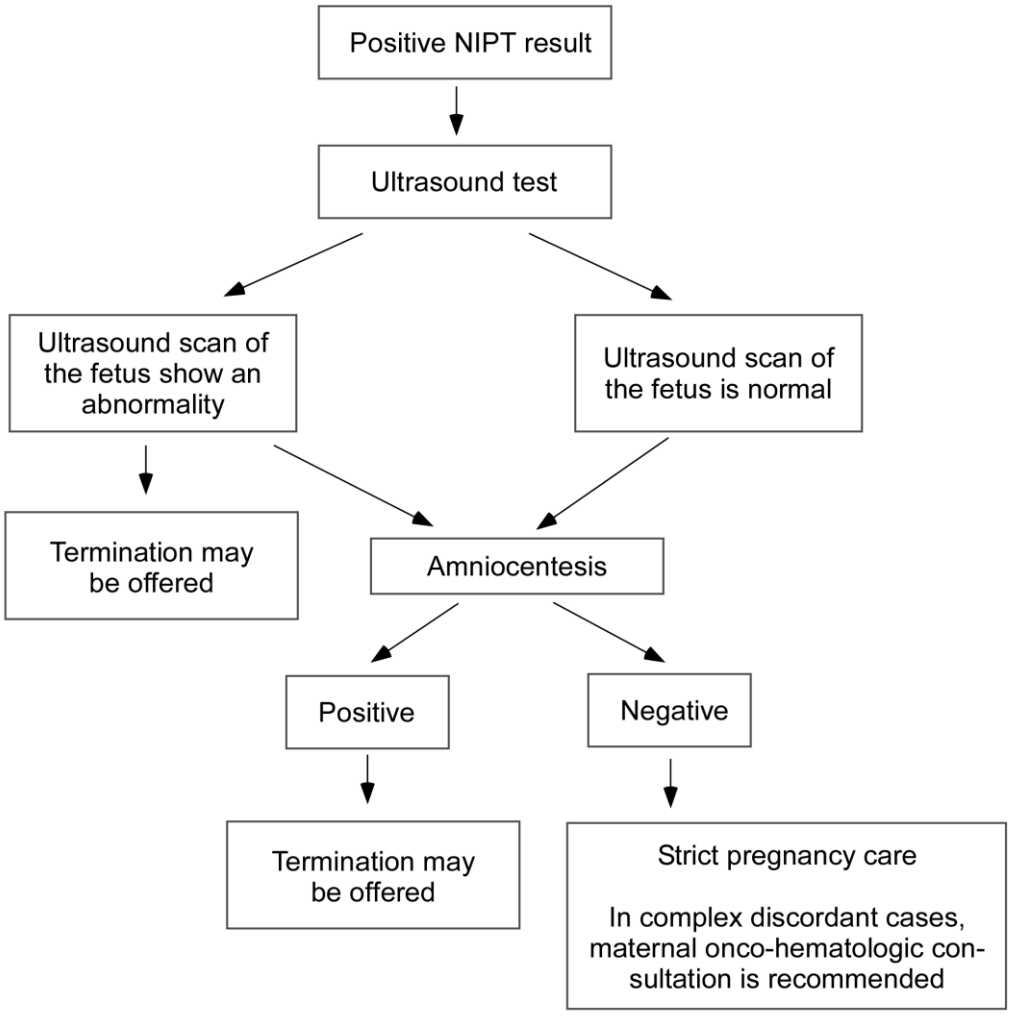
From a diagnostic perspective, the variability in positive predictive values (PPVs) suggests that clinical follow-up should be chromosome-specific. While findings involving chromosomes 16, 22, and 15 warrant immediate consideration for invasive diagnostic testing (such as amniocentesis or chorionic villus sampling) due to their higher rate of fetal involvement, other rare findings may initially be managed with high-resolution serial ultrasounds. However, because these "false positives" are strongly associated with adverse pregnancy outcomes like IUGR and pre-eclampsia, pregnancies with discordant RAT results should be classified as high-risk. This necessitates increased obstetric surveillance, including regular Doppler studies and growth scans, to mitigate the risks associated with placental insufficiency.

Furthermore, the strong correlation between complex, multi-chromosomal NIPT patterns and maternal malignancies introduces a new responsibility for prenatal care providers. When such patterns are detected, practice protocols should include a thorough maternal clinical evaluation and, if necessary, referral to oncology for further diagnostic work-up, such as whole-body MRI or specific biomarker testing. Ultimately, these implications suggest that the transition to GW-NIPT requires a multidisciplinary approach involving geneticists, maternal-fetal medicine specialists, and oncologists to ensure that both fetal and maternal health risks are addressed comprehensively.

The goal of translational medicine is to incorporate findings into routine practice as quickly as possible (Hegyi et al., 2021; Hegyi et al., 2020). Figure 9 defines a general patient follow-up guide that could serve as the basis for a broad international guideline.

Our goal is to create a user-friendly interface from difficult-to-interpret data that can be immediately integrated into daily prenatal screening.

Figure 9: *GW-NIPT positive cases – patient follow-up: recommendation for discussion regarding GW-NIPT positive cases*



12. IMPLICATIONS FOR RESEARCH

The findings of this meta-analysis not only clarify the current diagnostic performance of genome-wide non-invasive prenatal testing (GW-NIPT) but also highlight critical gaps that should guide future academic inquiry. First, there is a clear need for large-scale, prospective multicenter studies that utilize standardized bioinformatic pipelines and reporting thresholds. Current research is often limited by technological heterogeneity; therefore, future studies should focus on establishing a universal "resolution" for GW-NIPT to ensure that structural chromosomal abnormalities (StrCAs) are reported and analyzed consistently across different laboratory platforms.

Second, the robust association between discordant rare autosomal trisomies (RATs) and adverse pregnancy outcomes (APOs) warrants further investigation into the biological mechanisms of the placenta. Future research should prioritize longitudinal studies that correlate specific levels of placental mosaicism (quantified via placental site biopsies at birth) with the fetal fraction and the specific chromosome involved. This would help develop predictive models to identify which "false positive" NIPT results carry the highest risk for placental insufficiency, potentially leading to the discovery of new biomarkers for pre-eclampsia and fetal growth restriction.

Additionally, the incidental detection of maternal malignancies through complex NIPT profiles remains an emerging field. Research should move toward establishing evidence-based diagnostic algorithms for the maternal work-up. Studies comparing the cost-effectiveness and psychological impact of various screening modalities—such as whole-body MRI versus targeted biochemical markers in the event of a complex NIPT result—are essential to define the ethical and clinical boundaries of this technology.

Finally, as NIPT moves toward screening for even smaller microdeletions and microduplications, research must address the "information overload" faced by patients. Investigating the most effective methods for pre-test and post-test genetic counseling in the era of genome-wide data is vital. This includes developing decision-support tools that help parents and clinicians navigate the uncertainty associated with rare findings, ensuring that the rapid advancement of genomic technology is matched by an equally sophisticated framework for clinical interpretation and patient support.

12.1. Methodology and Study Design

This research is based on a systematic review and meta-analysis of 17 international cohorts, integrating data from over 740,000 GW-NIPT cases. The study design utilizes a random-effects, binomial generalized linear mixed model, which allows for a statistically reliable analysis of rare genetic events. A key innovation in the methodology is the implementation of a dual-outcome evaluation, distinguishing between "confirmed" results (validated by invasive testing) and "extended" outcomes (including ultrasound findings and fetal losses). This approach provides a more comprehensive assessment of the clinical utility of NIPT in real-world obstetric practice, moving beyond strictly laboratory-based validation.

13. IMPLICATIONS FOR POLICY MAKERS

The integration of GW-NIPT into national health frameworks requires a shift from a fetal-centric approach to a comprehensive "pregnancy-unit" perspective. Policy makers must prioritize the standardization of screening protocols to ensure equitable access to genome-wide reporting, establishing clear thresholds for the detection and notification of rare autosomal aneuploidies (RATs) and structural aberrations (StrCAs). Furthermore, healthcare funding and resource allocation must be adjusted; since discordant RAT results are potent indicators of placental dysfunction, policies should ensure these cases have access to specialized maternal-fetal surveillance—such as serial Doppler ultrasounds—to manage risks of IUGR and pre-eclampsia effectively. Finally, regulatory frameworks must be developed to address incidental maternal findings, creating standardized referral pathways for oncological work-ups and expanding the genetic counseling workforce to support informed reproductive choices in the era of complex genomic data.

14. FUTURE PERSPECTIVES

The future of genome-wide non-invasive prenatal testing (GW-NIPT) lies in transitioning from a purely diagnostic focus to a holistic "liquid biopsy" of the entire pregnancy unit. Advances in sequencing technology and bioinformatics are expected to lower the detection limits for submicroscopic structural variations, allowing for more precise identification of microdeletion and microduplication syndromes. Beyond chromosomal counts, the analysis of cell-free DNA methylomes and fragmentomics holds promise for developing non-invasive markers that can predict placental health and maternal vascular complications even earlier in gestation.

Furthermore, as artificial intelligence and machine learning tools are integrated into genomic pipelines, the ability to differentiate between fetal, placental, and maternal DNA origins will improve, significantly reducing false-positive rates. Research will likely expand into the ethical integration of maternal health screening, transforming NIPT into a dual-purpose tool for both prenatal care and early maternal oncology detection. Ultimately, the long-term goal is to move toward personalized prenatal management, where genome-wide data informs individualized birth plans and early interventions, ensuring the best possible health outcomes for both mother and child.

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Discordant findings in genome-wide non-invasive prenatal testing (GW-NIPT) for rare chromosomal abnormalities, adverse pregnancy outcomes, and maternal malignancies: a systematic review and meta-analysis.

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8.2 Publications not Related to the Thesis

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Scopus - Hematology Rank: Q1
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