Systematic Review

Performance Metrics of Noninvasive Prenatal Testing Panels for Dominant Single-Gene Disorders

A Systematic Review and Meta-Analysis

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OBJECTIVE: To evaluate the clinical utility and methodologic validity of noninvasive prenatal testing (NIPT) for dominant single-gene disorders by performing a systematic review and meta-analysis.

DATA SOURCES: From database inception through April 2025, we explored PubMed, EMBASE, Cochrane Library, and Web of Science.

METHOD OF STUDY SELECTION: Studies that reported NIPT panels to screen for dominant single-gene disorders with confirmation testing and involved at least 50 cases were included. The Quality Assessment of Diagnostic Accuracy Studies 2 tool was used for study appraisal. Clinical utility was evaluated by using positivity rate and positive predictive value (PPV), with pooled estimates calculated through fixed- or random-effects models. Methodologic validity was assessed through sensitivity and specificity by using a bivariate random-effects model and summary receiver operating characteristic curve analysis.

TABULATION, INTEGRATION AND RESULTS: Ten articles comprising 12,577 cases were included. Positivity rate and PPV were calculated from nine studies, with sensitivity and specificity from seven studies. The pooled positivity rate was 2.2% (95% CI, 0.8–5.6%), and pooled PPV was 93.8% (95% CI, 86.4–97.3%). The bivariate model yielded a pooled sensitivity of 94.5% (95% CI, 85.7–98.0%) and specificity of 99.7% (95% CI, 98.8–99.9%), with an area under the curve of 0.98 (95% CI, 0.94–0.99). Subgroup analysis revealed positivity rates of 0.3% in low-risk populations, 1.2% in mixed-risk populations, and 6.0% in high-risk populations. High heterogeneity was observed in the positivity rate analysis (I^2=96%). In contrast, heterogeneity was low (I^2=16%) for PPV but with publication bias being detected (P=.004).

CONCLUSION: Noninvasive prenatal testing panels for dominant single-gene disorders achieve a high PPV with high sensitivity and specificity.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO, CRD42024571768.

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Single-gene disorders are Mendelian conditions caused by mutations in one or both alleles of a gene. Up to now, there are more than 7,000 single-gene disorders with a known molecular basis, representing a significant burden on health care.[1] The prevalence of each single-gene disorder is typically less than 0.01%, but the combined prevalence is up to 1%, accounting for 5–10% of pediatric hospital admissions and childhood mortality.[2,3] Of all of these single-gene disorders, more than 60% are

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dominant single-gene disorders, with the majority attributable to de novo mutations.[4]

Noninvasive prenatal testing (NIPT) is a method based on the cell-free DNA (cfDNA) in the maternal peripheral blood to identify genetic variation that occurs in the fetus. Since the discovery of cfDNA in 1997, NIPT has undergone rapid development, particularly accelerated by the advancement of sequencing technology, which has expanded the testing scope from chromosomal aneuploidies to copy number variations and single-gene disorders of both dominant and recessive inheritance.[5–8]

Compared with the low risk of pregnancy loss in traditional diagnostic invasive testing, NIPT avoids complications associated with invasive procedures and provides an earlier detection time, as early as the 8th week of gestation.[9,10] Although the accuracy of NIPT in detecting chromosomal and subchromosomal abnormalities has been demonstrated, the diagnostic performance for single-gene disorders remains inconclusive.[11]

Several factors contribute to this uncertainty, such as limited studies with modest sample size, the diversity of sequencing and analytic methods across regions and teams, and varying NIPT panel spectrum. Noninvasive prenatal testing for autosomal recessive single-gene disorders requires highly sensitive methods to identify subtle allelic imbalances in maternal blood. In contrast to recessive disorders, which can be effectively mitigated through carrier screening and preimplantation genetic testing, de novo mutations in dominant conditions elude such preventive strategies. This inherent limitation, coupled with the progressive reduction in next-generation sequencing costs, has positioned screening panels targeting dominant single-gene disorders as an increasingly prevalent trend in prenatal screening. Accordingly, we aim to evaluate the clinical utility and methodologic validity of NIPT panels for dominant single-gene disorders by conducting a systematic review and meta-analysis.

SOURCES

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and PRISMA for diagnostic test accuracy studies.[12,13] This protocol was registered with PROSPERO (registration number: CRD42024571768) on July 22, 2024.

We searched PubMed, Cochrane Library, EMBASE, and Web of Science from inception through April 2025 for English-language peer-reviewed articles. Search terms included "noninvasive prenatal diagnosis" and "monogenic condition" with related terms. The detailed search strategy is presented in Appendix 1 (available online at http://links.lww.com/AOG/E526). Reference lists were manually screened for additional studies.

STUDY SELECTION

Inclusion criteria for selected studies included the following: 1) NIPT panels that used maternal cfDNA to screen dominant monogenic conditions, 2) confirmation by invasive prenatal or postnatal testing, and 3) a case series with at least 50 cases. Exclusions of studies were as follows: 1) animal studies, systematic reviews, meta-analyses, case–control studies, and case reports; 2) studies without complete datasets; and 3) conference abstracts with incomplete datasets.

After removing duplicates, two reviewers screened titles and abstracts for eligibility. Full-text screening was then independently conducted by two reviewers, with any discrepancies resolved through discussion by consulting a third reviewer. For overlapping studies with the same cohort, only the study with the largest sample size was retained.

Two reviewers independently extracted the following data: study title; authors' names; year of publication; publication type; study design; study population; geographic area; NIPT methodologies; reference standards; the count of target genes; and the overall number of single-gene disorders. To assess clinical utility, we recorded the total number of participants, positive cases for positivity rate, and all positive cases with follow-up that had true-positive results for the positive predictive value (PPV). As to methodologic validity, true-positive, false-negative, false-positive, and true-negative results were extracted.

For each individual study, we evaluated clinical utility through the assessment of positivity rate and PPV; methodologic validity was determined via sensitivity and specificity calculations.[14] Data from all eligible studies were combined to conduct the meta-analysis, thereby generating pooled estimates and 95% CIs. The 95% CI of each study for PPV was calculated using the Wilson score method to account for the high proportion values near 100%.

In conducting the meta-analysis, logit transformation was employed to handle extreme proportion values (approaching 0 and 1) in the data and ensure stable model convergence. The optimization process used a step size of 0.5 and 100 iterations to achieve computation stability. Heterogeneity assessment used fixed-effects models for metrics with low heterogeneity ($I^2<50\%$) and random-effects models for those with high heterogeneity ($I^2\geq50\%$). Because sensitivity and specificity often are inversely related, we used a bivariate random-effects model that accounts for this

correlation between two metrics. Summary receiver operating characteristic (SROC) curves were generated to visualize overall diagnostic accuracy across studies.

To explore heterogeneity sources, we conducted subgroup analysis, meta-regression, and sensitivity analysis on metrics with high heterogeneity. Population characteristics (low, mixed, high risk), commercial platform used (Vistara vs other), platform panel size (30 or less vs more than 30), and confirmatory follow-up rate (high vs low) were considered as covariates. Cohorts conducted in the general population or in populations with excluded high-risk indications were considered low-risk cohorts; those specifically targeting populations with indications were classified as high-risk cohorts. Cohorts that combined populations with indications and volunteers were categorized as mixed-risk cohorts. Based on previous studies, high-risk indications included, but were not limited to, abnormal ultrasound findings, advanced paternal age, family history, and adverse pregnancy history, but excluded pregnancies in which the mother was a known carrier of pathogenic variants for dominant single-gene disorders.[15,16] *Follow-up rate* was defined as the proportion of cases with confirmatory results by invasive testing or postnatal examination among total cases that underwent NIPT, which would be considered as high if the follow-up rate was at least 50% or low if the rate was less than 50%. Sensitivity analysis employed the leave-one-out method to identify studies that affected heterogeneity. Publication bias was assessed using funnel plots and the Egger's test, with trim-and-fill adjustments to pooled results. The trim-and-fill method is a nonparametric technique to detect and adjust for potential publication bias in meta-analysis by imputing missing studies suggested by funnel plot asymmetry and recalculating adjusted pooled estimates.[17]

Analyses were conducted with meta, metafor, and mada in R 4.4.1; $P<.05$ was considered statistically significant.

The quality of each included study was evaluated using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool.[18] This assessment was conducted independently by two reviewers using RevMan 5.4.1. Any disagreements were resolved through discussion with a third reviewer. The detailed criteria for assessment are shown in Appendix 2 (available online at http://links.lww.com/AOG/E526).

RESULTS

A flow diagram of the study-selection process is shown in Figure 1. The primary search identified a total of 2,268 articles. After eliminating duplicates, studies not relevant to the subject of interest, and articles meeting exclusion criteria, 10 articles were included. Detailed characteristics of the included articles are displayed in Appendix 3 (available online at http://links.lww.com/AOG/E526).

A total of 10 articles that reported on nine independent cohorts were included in this meta-analysis.[4,15,19–26] All included articles provided data on total cases, positive cases, true-positive results, and false-positive results; only seven of the articles provided confirmed data on true-negative and false-negative results. Westover et al,[26] although a conference abstract, was included because evaluation revealed the data were complete for analysis. Adams et al[24] and Zhang et al[25] are from the same cohort but cover different time periods with different reported data. Adams et al[24] encompassed a larger dataset (2020–2023) but reported only positive cases (true-positive results, false-positive results), suitable for calculating positivity rate and PPV. Zhang et al[25] covered an earlier subset (2016–2018) but provided complete diagnostic data (true-positive, true-negative, false-positive, and false-negative results), enabling sensitivity and specificity calculations. To avoid duplication while maximizing data utilization, we included Adams et al[24] for positivity rate and PPV analysis and Zhang et al[25] for sensitivity and specificity analysis. Eventually, nine articles[4,15,19–24,26] were included in the clinical utility analysis and seven[4,19–23,25] were included in the methodologic validity analysis.

The 10 eligible articles were published between 2019 and 2025. Sample sizes ranged from 93 to 4,506 cases, with four studies each from China and the United States and two from Vietnam. All articles reported the pregnancy weeks at sampling, with samples obtained from the late first to mid-second trimester of pregnancy (Appendix 3, http://links.lww.com/AOG/E526). However, five cohorts had sampling performed after 18 weeks of gestation, four of which were high-risk cohorts. As it relates to the gestational age at sampling, the fetal fraction ranged from 3.0–33.0%, leading several studies to report varying no-call rates of NIPT. Although several articles did not provide no-call data, these no-call cases were not taken into calculation due to inconsistency.

Six articles used the commercial Vistara panel from Natera, which targets 30 genes that correspond to 25 conditions via capture-based next-generation sequencing with unique molecular identifiers. The other four articles used panels that cover 9–75 genes. Three studies implemented COATE-seq technology,

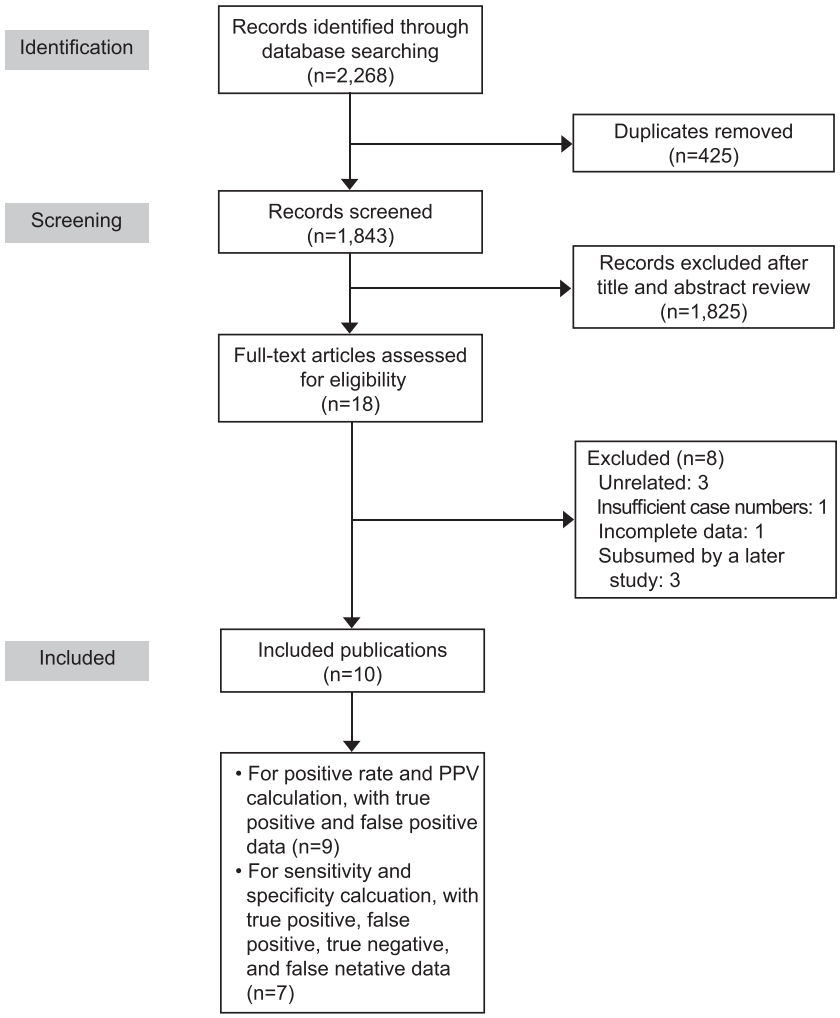

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of included articles. PPV, positive predictive value.
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and one study employed high-depth next-generation sequencing.

The quality assessment result was shown in Appendix 4 (available online at http://links.lww.com/AOG/E526). For patient selection, one of the 10 studies was high risk and one of 10 had an unclear risk. The former was a meeting abstract that lacked the description of inclusion criteria and baseline patient characteristics, and the latter had a methodologic emphasis and, thus, partially lacked details such as maternal age and more baseline characteristics. All studies showed a low risk for the index domain and reference domain. As to flow and timing, four of 10 studies were high risk and the remaining were low risk. Due to ethics consideration and participants' willingness, some studies, especially screening studies, could barely proceed with invasive confirmatory tests for all participants. As a result, an underestimation of false-negative results could have occurred. No applicability concerns existed, as we aimed to investigate in populations with different risk.

Clinical utility is associated with positivity rate and PPV, which are inherently affected by the prevalence of targeted conditions. The positivity rate after systematically pooling nine studies reached 2.2% (95% CI, 0.8–5.6%), showing high heterogeneity (I^2=96%) (Fig. 2). The pooled PPV was 93.8% (95% CI, 86.4–97%) with low heterogeneity (I^2=16%) (Fig. 3).

Methodologic validity, demonstrated by sensitivity and specificity, is independent of the prevalence, which associates just with the method accuracy itself. The sensitivity and specificity of NIPT panels for dominant single-gene disorders in seven studies were calculated and plotted on an SROC curve (Fig. 4). In this bivariate model, the balanced pooled sensitivity was 94.5% (95% CI, 85.7–98.0%) and specificity was

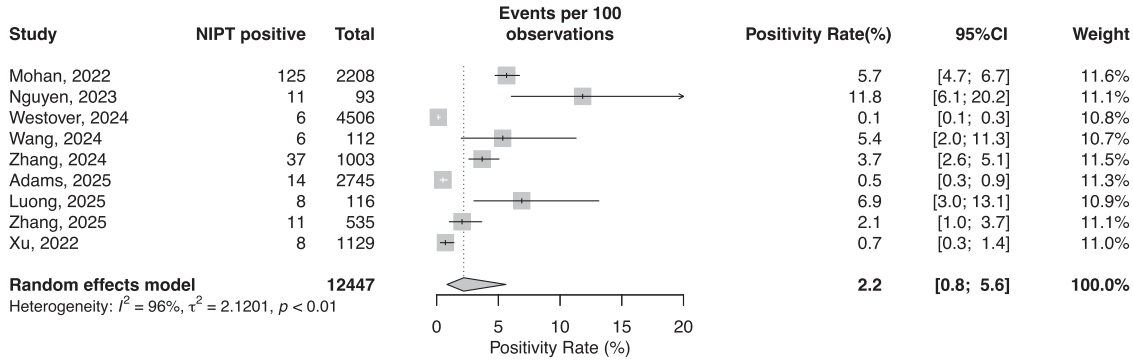

Fig. 2. Forest plots of individual and pooled positivity rates of noninvasive prenatal testing (NIPT) panels for detecting dominant single-gene disorders.

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99.7% (95% CI, 98.8–99.9%). The area under the curve equaled 0.98 (95% CI, 0.94–0.99), indicating that the diagnostic method has outstanding performance and was accurate in distinguishing between positive and negative individuals. The low heterogeneity (I^2=0%) suggests that the methodologic approaches employed across studies yielded uniformly superior performance.

Of the four metrics performed in our meta-analysis, positivity rate was the sole result with significant heterogeneity, thus warranting subgroup analysis and meta-regression for this metric alone. Initially, this was stratified into subgroups by population risk characteristics (Fig. 5). This revealed a positivity rate of 0.3% (95% CI, 0.07–1.00%) across low-risk cohorts, 1.2% (95% CI, 0.4–3.5%) across mixed-risk cohorts, and 6.0% (95% CI, 4.0–8.7%) across high-risk cohorts. Notably, high heterogeneity persisted in each population risk category. The test for subgroup difference indicated significant differences (χ^2_2 = 25.54, df=2, P<.01) between subgroups, suggesting stratification of population characteristics could partially explain the overall heterogeneity. Demonstrating a similar result, meta-regression analysis revealed that population risk was a significant moderator of the outcome, which explained 86.6% of overall heterogeneity (Appendix 5, available online at http://links.lww.com/AOG/E526). However, subgroup analysis stratified by platform, panel size and follow-up rate revealed no significant differences between subgroups. Correspondingly, meta-regression analysis indicates none of these three factors served as a significant moderator (Appendix 6, available online at http://links.lww.com/AOG/E526).

To further investigate the potential contribution of individual studies to heterogeneity, the leave-one-out method was conducted to perform a sensitivity analysis (Appendix 7, available online at http://links.lww.com/AOG/E526). For either positivity rate or PPV, the overall estimate was not affected by exclusion of any single study. The positivity rate ranged from 1.8–3.1%, and the PPV ranged from 93.2–96.8%, suggesting consistency of the findings. Omitting each study sequentially had minimal effect on

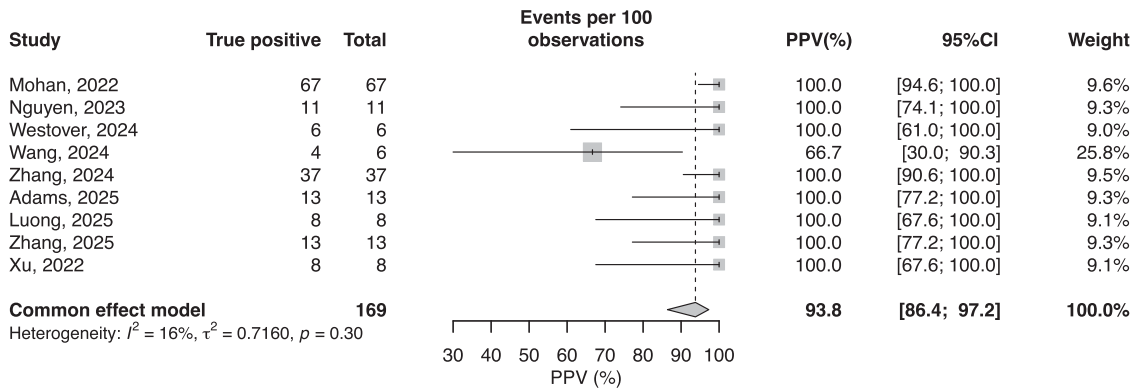

Fig. 3. Forest plots of individual and pooled positive predictive value (PPV) of noninvasive prenatal testing (NIPT) panels for detecting dominant single-gene disorders.

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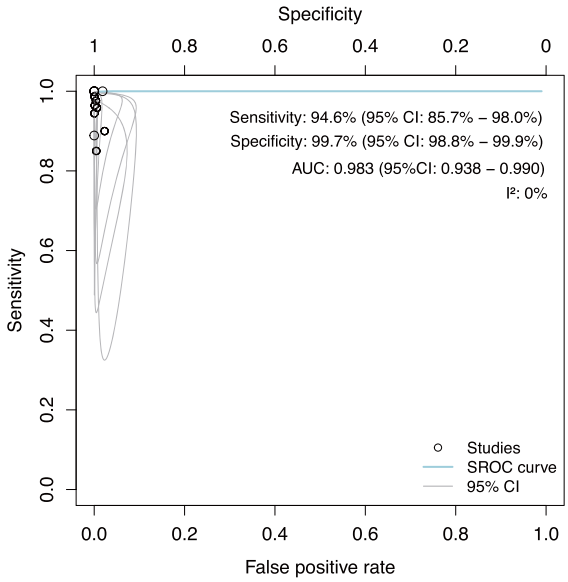

Fig. 4. The sensitivity and specificity in each study were calculated and plotted on a summary receiver operating characteristic (SROC) curve. AUC, area under the curve.

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sensitivity and specificity, which ranged from 93.1% to 96.3% and from 99.5% to 99.8%, respectively (Appendix 8, available online at http://links.lww.com/AOG/E526). These findings suggest that no single study had a disproportionate influence on the overall estimates.

Funnel plots and Egger's tests assessed publication bias for positivity rate and PPV (Appendix 9, available online at http://links.lww.com/AOG/E526). Positivity rate showed symmetric distribution with nonsignificant Egger's test (P=.143), indicating no publication bias. Positive predictive value showed marked asymmetry with significant Egger's test (P=.004). Trim-and-fill analysis estimated four missing studies, adjusting PPV to 89.4%, suggesting overestimation due to publication bias. Given the limited number of included studies for calculating sensitivity and specificity and the use of bivariate random-effects modeling with an SROC curve, publication bias was not performed by previously mentioned methods to avoid overinterpretation based on underpowered tests.

DISCUSSION

This review evaluated the performance of NIPT panels for dominant single-gene disorders from the perspectives of clinical utility and methodologic validity. Across the included studies, positivity rates and PPV were consistently reported, with a subset providing measures of diagnostic accuracy. The findings showed low heterogeneity for PPV and minimal risk of bias, supporting the overall robustness of the evidence, despite limited sample sizes. Test positivity was lowest in low-risk populations and increased progressively in mixed- and high-risk groups; PPV was uniformly high across studies. The estimates of positivity

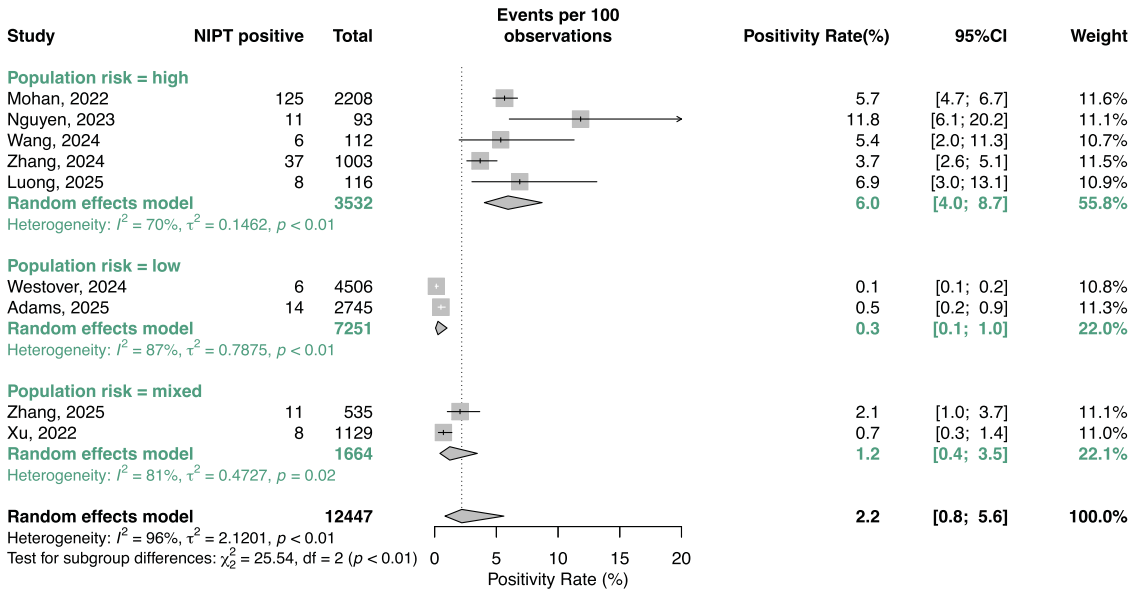

Fig. 5. Forest plots of positivity rates by subgroup analysis of population risk characteristics. NIPT, noninvasive prenatal testing; df, degrees of freedom.

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rate and PPV demonstrate the most critical concerns of clinical practice when NIPT panels are performed. Methodologic validity was further supported by the balanced combination of high sensitivity and specificity, with excellent overall discriminatory performance.

Our key finding lies in the differential positivity rates observed across populations with different risk, with meta-regression analysis substantiating significant intersubgroup differences. Recent research has shown that exome sequencing detected de novo variants with moderate or severe phenotypes in 0.7% of normal fetuses with normal G-banded karyotype or chromosomal microarray analysis.[27] Given that family history and advanced parental age were not excluded with moderate phenotypes in that study, these findings support our observed association of a positivity rate of approximately 0.27% in a low-risk population. The implementation of NIPT panels for dominant single-gene disorders as a screening modality in the general population remains contentious, partly attributed to the lack of robust empirical data in this area.[28] The positivity rate data stratified by prior risk level presented herein provides a potential evidence base for developing a more rational screening strategy. In resource-constrained health care environments, risk-stratified screening enables optimal resource allocation, thereby maximizing screening efficiency and cost-effectiveness. For patients, our findings provide clinicians with additional information for screening recommendations tailored to a specific risk profile, potentially aligning with approaches to personalize medicine and higher patient satisfaction.

The pooled PPV of NIPT panels for dominant single-gene disorders in the current study reached 93.8%, representing a result that exceeds the PPV of NIPT for chromosomal abnormalities.[29–32] The continuous advancement in sequencing and analytical technologies has led to increasing accuracy, supporting such improved PPV. Furthermore, compared with quantitative analysis based on chromosomal fragment counting used for detecting chromosomal abnormality, high-sensitivity qualitative or quantitative analysis of specific locus variants, partly like a presence-or-absence method, may in theory offer superior precision and efficiency.[33] However, the relatively small sample size of studies included in the PPV estimate may have overstated the estimate. Additionally, the presence of publication bias likely contributed to this overestimation. We attempted to correct for this by using the trim-and-fill method.

Prevalence of the conditions being evaluated was not considered in the pooled estimates, which could present a critical factor that influences the clinical utility when either very high or low, which has been emphasized in prior literature.[4,19,25] Despite the variety in panel size and composition, most panels were targeting conditions with severe outcomes and high prevalences, resulting in substantial overlap in their primary composition. Consequently, the differences in prevalence were unlikely to affect clinical utility. The minimal heterogeneity observed further supports that there were no significant intergroup differences when calculating the PPV.

The sensitivity and specificity, independent from the prevalence, were both high, with low heterogeneity. This suggests that the methodology across different NIPT panels for dominant single-gene disorders demonstrate consistently high and uniform validity. However, sensitivity and specificity can be influenced by the choice of cutoff values, yet none of the included studies explicitly reported how their cutoff thresholds were set or determined.[34] Given the low heterogeneity, it could be speculated that the potential bias introduced by cutoff variability is minimal, although it remains unknown. Given that the elimination of false-negative cases is more critical in a screening test, prioritizing sensitivity over specificity is more pivotal, which means a lower cutoff threshold.

There are several strengths in this review. We included studies with a sample size of 50 cases or more, minimizing the potential uncertainty and bias possibly caused by a small sample size. A subgroup analysis of characteristics shown to influence clinical and methodologic validity was undertaken. Finally, the subgroup analyses were stratified by risk categories, generating more clinically relevant and population-specific outcomes. Our study is not without limitations. The relatively small sample sizes in the PPV analysis introduced bias, which hindered publication bias assessment for methodologic validity. Lack of detailed risk population proportions in individual studies compromised mixed-risk cohort reliability. Finally, studies consisted of de novo cases or cases where parental carrier status was unknown at the time of testing; we were unable to assess whether test performance differs when the pregnant individual carries the pathogenic variant.

In conclusion, this review evaluated NIPT panels for dominant single-gene disorders from clinical utility and methodologic validity perspectives. These findings may provide insights into NIPT performance and support the clinical implementation of NIPT dominant single-gene disorder panels in routine prenatal care.[35]

REFERENCES

1. Chial H. Rare genetic disorders: learning about genetic disease through gene mapping, SNPs, and microarray data. Accessed June 23, 2025. http://www.nature.com/scitable/topicpage/rare-genetic-disorderslearning-about-genetic-disease-979
2. Kumar D. Medical and health aspects of genetics and genomics. In: Kumar D, Antonarakis S, editors. Medical and health genomics. Academic Press; 2016. p. 139–60. doi: 10.1016/B978-0-12-420196-5.00011-3
3. Korf BR, Pyeritz RE, Grody WW. Nature and frequency of genetic disease. In: Pyeritz RE, Korf BR, Grody WW, editors. Emery and Rimoin's principles and practice of medical genetics and genomics. 7th Ed. Academic Press; 2019. p. 47–51. doi: 10.1016/B978-0-12-812537-3.00003-2
4. Zhang J, Wu Y, Chen S, Luo Q, Xi H, Li J, et al. Prospective prenatal cell-free DNA screening for genetic conditions of heterogenous etiologies. Nat Med 2024;30:470 EP–9. doi: 10.1038/s41591-023-02774-x
5. Lo YMD, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, et al. Presence of fetal DNA in maternal plasma and serum. Lancet (London, England) 1997;350:485–7. doi: 10.1016/S0140-6736(97)02174-0
6. Saito H, Sekizawa A, Morimoto T, Suzuki M, Yanaihara T. Prenatal DNA diagnosis of a single-gene disorder from maternal plasma. Lancet 2000;356:1170. doi: 10.1016/S0140-6736(00)02767-7
7. Chiu RWK, Chan KCA, Gao Y, Lau VYM, Zheng W, Leung TY, et al. Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. Proc Natl Acad Sci USA 2008;105:20458–63. doi: 10.1073/pnas.0810641105
8. Lo YMD, Chan KCA, Sun H, Chen EZ, Jiang P, Lun FMF, et al. Maternal plasma DNA sequencing reveals the genome-wide genetic and mutational profile of the fetus. Sci Transl Med 2010;2:61ra91. doi: 10.1126/scitranslmed.3001720
9. Zhong LPW, Chiu RWK. The next frontier in noninvasive prenatal diagnostics: Cell-free fetal DNA analysis for monogenic disease assessment. Annu Rev Genomics Hum Genet 2022;23:413 EP–25. doi: 10.1146/annurev-genom-110821-113411
10. Salomon LJ, Sotiriadis A, Wulff CB, Odibo A, Akolekar R. Risk of miscarriage following amniocentesis or chorionic villus sampling: systematic review of literature and updated meta-analysis. Ultrasound Obstet Gynecol 2019;54:442–51. doi: 10.1002/uog.20353
11. Mackie F, Hemming K, Allen S, Morris R, Kilby M. The accuracy of cell-free fetal DNA -based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis. BJOG 2017;124:32–46. doi: 10.1111/1471-0528.14050
12. Salameh JP, Bossuyt PM, McGrath TA, Thombs BD, Hyde CJ, Macaskill P, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ 2020;370:m2632. doi: 10.1136/bmj.m2632
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
14. Gregg AR, Skotko BG, Benkendorf JL, Monaghan KG, Bajaj K, Best RG, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med 2016;18:1056–65. doi: 10.1038/gim.2016.97
15. Mohan P, Lemoine J, Trotter C, Rakova I, Billings P, Peacock S, et al. Clinical experience with non-invasive prenatal screening for single-gene disorders. Ultrasound Obstet Gynecol 2022;59:33–9. doi: 10.1002/uog.23756
16. Adams S, Llorin H, Maher O, Dean M, Dobson LJ, Gbur S, et al. Single gene non-invasive prenatal screening for autosomal dominant conditions in a high-risk cohort. Prenat Diagn 2023;43:1110 EP–9. doi: 10.1002/pd.6351
17. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63. doi: 10.1111/j.0006-341x.2000.00455.x
18. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Int Med 2011;155:529–36. doi: 10.7326/0003-4819-155-8-201110180-00009
19. Nguyen NY, Lu YT, Nguyen DA, Nguyen CC, Dinh LT, Tran MTT, et al. Developing and validating noninvasive prenatal testing for de novo autosomal dominant monogenic diseases in Vietnam. Per Med 2023;20:425 EP–33. doi: 10.2217/pme-2023-0076
20. Wang L, Wu X, Mou J, Ren L, Wu B, Xiang G, et al. Non-invasive prenatal detection of dominant single-gene disorders in fetal structural abnormalities: a clinical feasibility study. Arch Gynecol Obstet 2024;310:2943 EP–55. doi: 10.1007/s00404-024-07800-y
21. Luong TLA, Nguyen DA, Dao TT, Nguyen CC, Nguyen ST, Dinh LT, et al. Combined cell-free DNA screening for aneuploidies and selected single-gene disorders for pregnancies with sonographically detected fetal anomalies: detection rate and residual risk. Prenat Diagn 2025;45:70–6. doi: 10.1002/pd.6720
22. Zhang H, He J, Teng Y, Shi Q, Liu F, Peng C, et al. Non-invasive prenatal testing for dominant single-gene disorders using targeted next-generation sequencing. QJM 2025;118:344–53. doi: 10.1093/qjmed/hcaf017
23. Xu C, Li J, Chen S, Cai X, Jing R, Qin X, et al. Genetic deconvolution of fetal and maternal cell-free DNA in maternal plasma enables next-generation non-invasive prenatal screening. Cell Discov 2022;8:109. doi: 10.1038/s41421-022-00457-4
24. Adams S, Trocki OM, Miller C, Studwell C, Bombalicki M, Dobson L, et al. Routine prenatal cfDNA screening for autosomal dominant single-gene conditions. Clin Chem 2025;71:129 EP–40. doi: 10.1093/clinchem/hvae189
25. Zhang J, Li J, Saucier JB, Feng Y, Jiang Y, Sinson J, et al. Non-invasive prenatal sequencing for multiple Mendelian monogenic disorders using circulating cell-free fetal DNA. Nat Med 2019;25:439–47. doi: 10.1038/s41591-018-0334-x
26. Westover T, Rook N, James S, Lewke D, Murawsky J. Clinical utility of antenatal cfDNA screening for autosomal dominant disorders in the general population [abstract]. Am J Obstet Gynecol 2024;230:S341. doi: 10.1016/j.ajog.2023.11.656
27. Sotiriadis A, Demertzidou E, Ververi A, Tsakmaki E, Chatzakis C, Mone F. Incremental yield of exome sequencing over standard prenatal testing in structurally normal fetuses: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2025;65:552–9. doi: 10.1002/uog.29195
28. Vora NL, Langlois S, Chitty LS. Current controversy in prenatal diagnosis: the use of cfDNA to screen for monogenic conditions in low risk populations is ready for clinical use. Prenat Diagn 2024;44:389 EP–97. doi: 10.1002/pd.6469
29. Acreman ML, Bussolaro S, Raymond YC, Fantasia I, Rolnik DL, Da Silva Costa F. The predictive value of prenatal cell-free DNA testing for rare autosomal trisomies: a systematic review

and meta-analysis. Am J Obstet Gynecol 2023;228:292–305.e6. doi: 10.1016/j.ajog.2022.08.034

30. Sebire E, Rodrigo CH, Bhattacharya S, Black M, Wood R, Vieira R. The implementation and impact of non-invasive prenatal testing (NIPT) for Down's syndrome into antenatal screening programmes: a systematic review and meta-analysis. PLoS One 2024;19:e0298643. doi: 10.1371/journal.pone.0298643
31. Wen L, Zhang Y, Gao J, Hu W. The predictive value of non-invasive prenatal screening for copy number variations: a cohort study and a systematic meta-analysis. Expert Rev Mol Diagn 2023;23:713–22. doi: 10.1080/14737159.2023.2233415
32. Geppert J, Stinton C, Johnson S, Clarke A, Grammatopoulos D, Taylor-Phillips S. Antenatal screening for fetal trisomies using microarray-based cell-free DNA testing: a systematic review and meta-analysis. Prenat Diagn 2020;40:454–62. doi: 10.1002/pd.5621
33. Rose NC, Barrie ES, Malinowski J, Jenkins GP, McClain MR, LaGrave D, et al. Systematic evidence-based review: the application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. Genet Med 2022;24:1379–91. doi: 10.1016/j.gim.2022.03.019
34. Devaney SA, Palomaki GE, Scott JA, Bianchi DW. Noninvasive fetal sex determination using cell-free fetal DNA: a systematic review and meta-analysis. JAMA 2011;306:627–36. doi: 10.1001/jama.2011.1114
35. Liao J, Xu N, Gao H, Hardy T, Levy B, Mehta L, et al. Advances in prenatal cell-free DNA screening for dominant monogenic conditions: a review of current progress and future directions in clinical implementation. Prenat Diagn 2025;45:445–52. doi: 10.1002/pd.6752

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