

Clinical Utility of Targeted Essential NIPT Panels and Real-World Management Outcomes: A 3-Year Single-Center Retrospective Cohort Study (2024–2026) at Restu Ibu Sragen General Hospital

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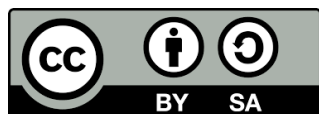
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Abstract

Targeted essential noninvasive prenatal testing (NIPT) panels, which focus on common autosomal trisomies and sex chromosome aneuploidies, offer a more affordable approach to cell-free DNA (cfDNA) screening. However, real-world evidence regarding how these results are integrated with first-trimester ultrasonography and translated into clinical management decisions in Indonesian private-practice settings remains limited. This study aimed to describe the distribution of targeted essential NIPT results, associated sonographic findings, and subsequent management pathways at a single center. We conducted a retrospective observational study of 52 consecutive patients who underwent targeted essential NIPT for trisomies 21, 18, and 13 and sex chromosome aneuploidies at Restu Ibu Sragen General Hospital between January 2024 and September 2026. Maternal demographic characteristics, gestational age at screening, nuchal translucency (NT), ductus venosus (DV) flow, screening results, and subsequent management were extracted from clinical records and summarized descriptively with Wilson 95% confidence intervals (CIs). Forty-eight patients (92.3%; 95% CI, 81.8–97.0) had low-risk results, whereas four (7.7%; 95% CI, 3.0–18.2) had high-risk results. All four high-risk cases demonstrated increased NT. Amniocentesis was deferred in all four cases, and the patients subsequently underwent serial high-resolution fetal ultrasonography and multidisciplinary counseling. Within the low-risk group, two to three patients had NT >3 mm or reversed a-wave flow in the DV, and one fetus had incidentally detected anal atresia. Targeted essential NIPT represents a practical and accessible screening option; however, it screens for a limited range of chromosomal abnormalities and should not be considered diagnostic. Its clinical utility is greatest when integrated with first-trimester and detailed fetal anatomical ultrasonography and when high-risk results are followed by structured counseling that includes the option of diagnostic testing. Because diagnostic confirmation was not obtained, positive and negative predictive values could not be estimated.



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INTRODUCTION

The discovery of cell-free fetal DNA in maternal plasma (Lo et al., 1997) laid the foundation for noninvasive prenatal testing (NIPT), which entered clinical practice in the early 2010s and has since transformed prenatal screening. Large validation studies

demonstrated that sequencing-based cell-free DNA (cfDNA) analysis outperformed conventional serum-based screening strategies for trisomy 21 (Bianchi et al., 2014; Norton et al., 2015). A meta-analysis of clinical validation studies concluded that, in singleton pregnancies, cfDNA screening could detect more than 99% of fetuses with trisomy 21, approximately 98% of those with trisomy 18, and 99% of those with trisomy 13, with a combined false-positive rate of approximately 0.13% (Gil et al., 2017). Despite this high performance, NIPT remains a screening rather than a diagnostic test. Results are probabilistic and may be discordant with the fetal chromosomal status because of confined placental mosaicism, maternal biological factors, low fetal fraction, and other biological or technical mechanisms (Grati et al., 2014; Hartwig et al., 2017; Hui & Bianchi, 2020). Accordingly, professional guidance continues to recommend genetic counseling and diagnostic testing following a high-risk cfDNA screening result rather than treating the screening result itself as a definitive diagnosis (American College of Obstetricians and Gynecologists [ACOG], 2020; Dungan et al., 2023).

First-trimester ultrasonography provides clinically important information that chromosome-specific molecular screening panels are not designed to detect. Nuchal translucency (NT) measurement at 11–13+6 weeks is a key component of first-trimester assessment, and increased NT is associated not only with aneuploidy but also with structural abnormalities, particularly congenital heart defects, and a range of genetic syndromes, even in fetuses with a normal karyotype (Nicolaides, 2011; Souka et al., 2005; Bilardo et al., 2007). Abnormal ductus venosus (DV) Doppler flow, particularly a reversed a-wave, is another marker associated with chromosomal abnormalities and congenital heart defects (Matias et al., 1998). International guidelines provide standardized recommendations for performing first-trimester ultrasonography and routine mid-trimester fetal anatomical assessment (Salomon et al., 2013, 2022). Molecular screening and ultrasonography therefore provide complementary information by addressing overlapping but distinct aspects of prenatal assessment.

Cost remains a potential barrier to the routine implementation of NIPT. Health-economic analyses suggest that its cost-effectiveness depends substantially on the unit price and its position within the overall prenatal screening strategy. For example, a real-world analysis of 140,472 women in China concluded that universal NIPT was the most effective strategy at a unit cost of RMB 600 (Liu et al., 2025). Targeted essential panels restricted to the major autosomal trisomies and sex chromosome aneuploidies have been proposed as a potentially clinically robust and economically sustainable alternative to comprehensive or genome-wide panels (Demko et al., 2022). Broader genomic coverage also involves important trade-offs. A systematic review of cfDNA screening for copy-number variants and microdeletions reported sensitivities ranging from 20% to 100% and positive predictive values ranging from 3% to 100%, while negative predictive values could not be determined in most included studies (Zaninović et al., 2022).

Evidence from Indonesia remains limited. A pilot study of sequencing-based NIPT combined with ultrasonography in pregnancies complicated by fetal anomalies

reported 100% concordance with G-banding karyotyping for trisomies 13, 18, and 21 and sex chromosome abnormalities, whereas a case of tetrasomy 9p, which was outside the targeted conditions, was identified only through karyotyping (Suardika et al., 2025). However, evidence regarding consecutive patients undergoing targeted NIPT in regional private-hospital settings remains scarce, particularly concerning subsequent clinical management when a high-risk screening result is obtained but invasive diagnostic testing is declined.

This study therefore evaluated the clinical utility, distribution of screening results, and real-world management pathways of 52 consecutive patients who underwent targeted essential NIPT at a single center. Specifically, the study aimed (i) to describe the distribution of low-risk and high-risk screening results; (ii) to characterize the sonographic findings associated with each result category, including NT and DV Doppler flow; and (iii) to document the management of high-risk screening results, with particular attention to the integration of molecular screening, patient autonomy, and advanced sonographic surveillance. Theoretically, this study contributes to the literature on NIPT implementation in resource-constrained settings. Practically, it provides evidence that may inform the integration of NIPT with ultrasonography and counseling following high-risk screening results. The findings may also inform the development of practical prenatal screening pathways that combine targeted essential NIPT with appropriate sonographic assessment, structured counseling, and access to diagnostic testing in Indonesian private-practice settings.

METHOD

Study design and setting

This retrospective, single-center observational cohort study was conducted at Restu Ibu Sragen General Hospital, Sragen, Central Java, Indonesia. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007).

Study population

All 52 consecutive patients who underwent targeted essential NIPT between January 2024 and September 2026 were included.

Non-invasive prenatal testing

The targeted essential NIPT panel assessed trisomy 21, trisomy 18, trisomy 13 and the sex chromosomes in maternal plasma. Results were reported as low-risk or high-risk according to the reporting laboratory. By design, this panel does not screen for structural malformations, sub-chromosomal copy number variants or aneuploidies of other chromosomes.

Sonographic assessment

First-trimester assessment included NT measurement and ductus venosus flow profiles. Increased NT was defined as a measurement >3 mm, and an abnormal ductus venosus profile as a reversed a-wave. Where clinically indicated, patients were referred for serial high-resolution fetomaternal ultrasound (Suardika et al., 2025). Sonographic

findings were recorded alongside the NIPT result to allow their concordance to be described.

Variables and outcomes

Variables analysed were maternal demographics, gestational age at screening, NT measurement, ductus venosus flow profile, NIPT result and subsequent clinical management, including the decision regarding invasive diagnostic testing. The primary outcome was the distribution of NIPT results (low-risk versus high-risk). Secondary outcomes were the sonographic findings within each result category and the management pathway chosen after a high-risk result.

Data collection and statistical analysis

Data were extracted from clinical and laboratory records and de-identified before analysis. Categorical variables are presented as counts and percentages with Wilson 95% confidence intervals. Given the small sample and the absence of a reference-standard result in the high-risk group, no inferential testing was performed, and sensitivity, specificity and predictive values were not calculated.

RESULTS AND DISCUSSION

Sonographic findings within the low-risk group

Within the 48 low-risk cases, two to three patients (4.2–6.3%) demonstrated increased NT (>3 mm) or a reversed a-wave in ductus venosus flow. In addition, one low-risk case involved an incidental finding of fetal anal atresia, a structural malformation that a targeted trisomy panel cannot be expected to detect.

Concordance between molecular and sonographic markers

Taking the two modalities together, increased NT or abnormal ductus venosus flow was recorded in six to seven of the 52 patients (11.5–13.5%). Four of these were flagged by a high-risk NIPT result, whereas the remaining two to three, roughly one-third to two-fifths of all patients with sonographic markers, had low-risk NIPT results and would not have been identified as having a potential problem by molecular screening alone.

Principal findings

In this consecutive series, 92.3% of targeted essential NIPT results were low-risk and 7.7% were high-risk. Three observations deserve emphasis. First, every high-risk result coincided with increased NT, a marker that itself carries an elevated probability of chromosomal and non-chromosomal disease. Second, amniocentesis was deferred in all four high-risk cases, so the molecular signal was never adjudicated by a diagnostic test. Third, a small number of patients with low-risk results nevertheless showed increased NT or abnormal ductus venosus flow, and one had an anorectal malformation. Taken together, these findings frame targeted NIPT as one component of an integrated pathway rather than as a stand-alone answer.

Targeted NIPT performance in context

The predominance of low-risk results is consistent with the high negative predictive value reported for essential NIPT panels in the literature (Demko et al., 2022; Gil et al., 2017). We emphasise, however, that the present dataset does not permit direct

estimation of negative predictive value, sensitivity or specificity, because reference-standard confirmation was unavailable for the high-risk group and systematic confirmation of low-risk results was not part of the study design. The observed high-risk proportion (7.7%) is also considerably higher than the pooled combined false-positive rate of about 0.13% from validation studies (Gil et al., 2017). This is what one would expect if the cohort was enriched for pregnancies with elevated prior risk, for example those referred after abnormal sonographic findings, since predictive values depend heavily on prior probability (Petersen et al., 2017). The fact that all four high-risk cases had thickened NT is compatible with such enrichment, although with only four events the estimate is imprecise (95% CI 3.0–18.2%).

These results sit comfortably alongside Indonesian pilot data showing excellent accuracy of sequencing-based NIPT for the targeted conditions when combined with ultrasound (Suardika et al., 2025). They also echo a point made in that study: excellent performance for the targeted conditions does not extend to abnormalities outside them. Table 3 places the present findings alongside the principal published evidence discussed in this paper.

Table 1. Selected published evidence compared with the present study.

Study	Design and population	Key finding	Relevance here
Gil et al., 2017	Meta-analysis of clinical validation studies of cfDNA screening in singleton pregnancies	Detection >99% (T21), about 98% (T18) and 99% (T13) at a combined false-positive rate of about 0.13%	Benchmark for the conditions covered by the panel
Suardika et al., 2025	Observational pilot in Indonesia: sequencing-based NIPT plus ultrasound in pregnancies with fetal birth defects, compared with G-banding	100% sensitivity, specificity and accuracy for T13, T18, T21 and sex chromosome abnormalities; tetrasomy 9p found only by karyotyping	Local evidence; shows the limit of targeted content
Liu et al., 2025	Retrospective analysis of 140,472 women in China who had NIPT and second-trimester serum screening	Universal NIPT was the most effective strategy at a unit cost of RMB 600	Cost-effectiveness depends on the unit price
Zaninović et al., 2022	Systematic review of 32 studies of cfDNA screening for copy number variations and microdeletions	Sensitivity 20–100%, specificity 81.62–100%, PPV 3–100%; NPV mostly not determinable	Variable validity of expanded content
Present study	Retrospective single-center cohort; 52 consecutive patients; targeted essential NIPT	92.3% low-risk, 7.7% high-risk (all with increased NT; amniocentesis deferred); sonographic abnormalities in 2–3 low-risk cases	Real-world management; NIPT and ultrasound complementary

High-risk results and the deferral of invasive testing

Because cfDNA analysis is a screening test, a high-risk result should be followed by counselling and an offer of diagnostic testing (ACOG, 2020; Dungan et al., 2023).

Positive predictive value varies with the condition and with prior risk (Petersen et al., 2017), and discordant results arise through confined placental mosaicism and other biological mechanisms (Grati et al., 2014; Hartwig et al., 2017). A high-risk NIPT result accompanied by increased NT is a setting in which the probability of true abnormality is elevated but not certain. Increased NT can also reflect non-chromosomal disease (Souka et al., 2005), which is one reason chromosomal microarray, where available, adds diagnostic yield over karyotyping alone (Wapner et al., 2012).

Our findings highlight a real-world clinical challenge: patient reluctance toward invasive procedures often leads to the refusal of amniocentesis. Contemporary meta-analytic estimates of procedure-related miscarriage risk after amniocentesis are low, on the order of 0.1% (Akolekar et al., 2015), which suggests that perceived risk may exceed actual risk and that counselling should address this gap explicitly. At the same time, respect for autonomy is a core principle of prenatal care (Beauchamp & Childress, 2019). The aim of counselling is an informed choice, not compliance, and this reliance on imaging rather than genetic confirmation emphasises the balance clinicians must maintain between respecting patient autonomy and upholding evidence-based diagnostic standards. In practice this implies non-directive counselling, documentation of informed refusal, and keeping the offer of diagnostic testing open as the pregnancy progresses.

Serial high-resolution ultrasound is a legitimate risk-management adjunct in this situation, but it is not a substitute for genetic diagnosis. Sonography can detect structural and haemodynamic sequelae, but it cannot confirm a karyotype, and a reassuring scan cannot exclude an aneuploidy. Families and clinicians may therefore reach delivery with unresolved uncertainty that affects delivery planning and neonatal care. Where invasive testing is declined, a documented plan for postnatal genetic confirmation is advisable.

NIPT and ultrasound are complementary, not interchangeable

The identification of structural or sonographic abnormalities in the low-risk group illustrates a fundamental clinical truth: NIPT and morphological ultrasound are complementary, not interchangeable. Essential NIPT panels are structurally designed to target specific aneuploidies; by design they do not screen for structural malformations or specific copy number variants. Increased NT with a normal karyotype is associated with a higher risk of structural defects, especially cardiac, and of genetic syndromes, with risk rising as NT thickens (Souka et al., 2005; Bilardo et al., 2007). The >3 mm threshold used in this study lies below the 3.5 mm (approximately the 99th centile) that many programmes use to define markedly increased NT, so the low-risk cases with increased NT should be regarded as at least warranting closer evaluation. A reversed a-wave in the ductus venosus is likewise associated with chromosomal defects and cardiac abnormalities (Matias et al., 1998).

The presence of thickened NT or abnormal ductus venosus flow despite a low-risk NIPT result serves as an urgent reminder that biophysical markers retain independent diagnostic power. In these patients a detailed anatomy scan, fetal echocardiography and

consideration of diagnostic testing with microarray are appropriate irrespective of the NIPT result. In our cohort, two to three of the six to seven patients with sonographic markers had low-risk NIPT results; had sonographic assessment been omitted, these patients would have been reassured on the strength of the molecular result alone.

The incidental fetal anal atresia illustrates the same point from the structural side. Anorectal malformations can occur in isolation or as part of syndromic associations such as the VACTERL association, none of which are addressed by a trisomy panel, and they can be subtle on prenatal imaging. This supports a systematic mid-trimester morphology scan (Salomon et al., 2022) and careful wording in counselling: a low-risk NIPT result means a low probability of the specific aneuploidies tested, not a low probability of every fetal problem. The risk of false reassurance is real, and pre-test counselling should state the scope of the panel explicitly.

Scope, cost and the case for targeted panels

Targeted essential panels are a deliberate trade-off between breadth and cost. Expanded panels that include copy number variants or rare autosomal aneuploidies show heterogeneous validity, with sensitivities of 20–100% and positive predictive values of 3–100% across studies (Zaninović et al., 2022), and guidance on extended content continues to evolve (Dungan et al., 2023). Because health-economic conclusions are specific to the unit price assumed (Liu et al., 2025), a lower-cost targeted panel that captures the most common actionable aneuploidies is a reasonable choice in settings where access is constrained (Demko et al., 2022). Its limitations can be partly offset by sonographic assessment, which is relatively inexpensive and detects a different spectrum of pathology. In resource-constrained settings, this combination may provide broader practical coverage than an expanded molecular panel used alone, although this hypothesis requires formal evaluation.

Implications for practice

Building on these observations and on published guidance, Table 2 outlines a pragmatic pathway that integrates targeted NIPT with sonography and preserves patient choice. It is offered as a synthesis of existing recommendations rather than as a result of this study.

Table 2. Suggested integrated pathway for targeted NIPT and first-trimester sonography.

Clinical scenario	Suggested action	Basis
Pre-test	Counsel that NIPT is a screening test for a limited set of conditions; state residual risk and the panel's scope.	ACOG, 2020; Dungan et al., 2023
All patients	Perform first-trimester ultrasound (NT, early anatomy, ductus venosus where available) irrespective of NIPT; plan a mid-trimester anomaly scan.	Salomon et al., 2013, 2022
Low-risk NIPT, normal ultrasound	Continue routine care; state that the result does not exclude conditions outside the panel.	Gil et al., 2017
Low-risk NIPT, increased NT or abnormal DV	Do not rely on NIPT for reassurance; offer detailed anatomy scan, fetal echocardiography and diagnostic testing with microarray.	Souka et al., 2005; Wapner et al., 2012
High-risk NIPT	Offer prompt diagnostic testing (karyotype or microarray) with multidisciplinary post-test counselling.	ACOG, 2020; Dungan et al., 2023
Diagnostic testing declined	Document informed refusal; keep the offer open; arrange serial ultrasound and a plan for postnatal confirmation.	Beauchamp & Childress, 2019

Strengths and limitations

Strengths of this study include the consecutive enrolment of patients, the capture of real-world management decisions rather than idealised protocol outcomes, and the joint reporting of molecular and sonographic data, which allows the complementarity of the two approaches to be seen directly. The study documents a clinically important scenario, deferral of invasive testing after a high-risk result, that is rarely reported.

Several limitations must be acknowledged. The sample is small ($N = 52$) and derived from a single private-practice center, so confidence intervals are wide and the findings may not generalise, particularly if patients were self-selected or referred after abnormal findings. The retrospective design restricts the depth and uniformity of available data. No reference-standard confirmation (karyotype, microarray or neonatal assessment) was available for the high-risk group, so positive and negative predictive values, sensitivity and specificity cannot be estimated, and the clinical truth behind the four high-risk results is unknown. The exact number of low-risk patients with increased NT or reversed DV a-wave is reported as a range. Sonographic measurements are operator-dependent, and reasons for deferring amniocentesis were recorded only as patient reluctance, so more granular data on its drivers would be valuable. Finally, no comparison was made with conventional biochemical screening or expanded NIPT panels. Larger multicentre studies with systematic outcome ascertainment are needed.

Directions for future research

Several steps would strengthen the evidence base. Multicentre registries across Indonesian hospitals could provide enough events to estimate predictive values for

targeted panels and to describe variation in practice. Prospective designs should ascertain outcomes systematically, through diagnostic testing and neonatal assessment, for both low-risk and high-risk results. Structured documentation of counselling content, and of the reasons patients decline invasive testing, would help in designing decision aids that respond to real concerns. Locally derived cost data would allow a formal comparison of targeted panels, expanded panels and contingent strategies in which NIPT is offered after sonographic risk stratification. Finally, audit of how low-risk results are communicated could test whether explicit statements about the scope of the panel reduce false reassurance.

CONCLUSION

Targeted essential NIPT panels demonstrated clinical utility as an accessible prenatal screening option. Although high-risk screening results require multidisciplinary counseling, integrating cost-effective cfDNA screening with detailed fetal ultrasonography provides a valuable approach to individualized prenatal care. Comprehensive fetal anatomical ultrasonography remains essential for detecting structural abnormalities and other fetal conditions that fall outside the scope of targeted chromosomal screening. In this cohort, the deferral of amniocentesis in all high-risk cases underscores the importance of structured, nondirective counseling and clearly documented plans for diagnostic confirmation. Such an approach supports informed patient autonomy while ensuring that the limitations of screening and the option of definitive diagnostic testing are clearly communicated.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to the conduct of the research, preparation, or publication of this article.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of this article. Onnie Wira Tama, Indah Sri Astuti and Yumita Azatin Amalia, was responsible for the conceptualization of the study, data collection and analysis, interpretation of the results, and manuscript preparation. The other authors contributed to the review, editing, and final approval of the manuscript.

GENERATIVE AI STATEMENT

The authors declare that no generative artificial intelligence was used in the preparation of this article.

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