

## Comparative Analysis of Microarray-Based and NGS-Based Cell-Free DNA for Trisomy 21 Detection in Prenatal Diagnostics: A Systematic Review

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### ABSTRACT

Advancements in prenatal diagnostics have significantly improved early detection of fetal chromosomal abnormalities, particularly through noninvasive prenatal testing (NIPT). This systematic review compares two prominent NIPT technologies—microarray-based cell-free DNA (cfDNA) and next-generation sequencing (NGS)-based cfDNA—for detecting trisomy 21 (Down syndrome). By analyzing cell-free fetal DNA in maternal blood, these methods offer crucial insights into fetal health, reducing the need for invasive procedures like amniocentesis.

The review encompasses a comprehensive search of PubMed, MEDLINE, EMBASE, and the Cochrane Library, identifying studies up to July 2023. Eight studies met the inclusion criteria, comparing the diagnostic accuracy, failure rates, and clinical implications of both cfDNA technologies.

Microarray-based cfDNA exhibited high sensitivity and specificity (99.2% and 99.8%, respectively), with lower failure rates (2.8%). NGS-based cfDNA also showed high sensitivity and specificity (99.6% and 99.9%) but had higher failure rates (up to 12.4%). While NGS-based testing offers broader genomic coverage and can detect additional chromosomal abnormalities, it also poses a higher risk of incidental findings, which may lead to overdiagnosis and parental anxiety.

This review highlights that microarray-based cfDNA is generally more cost-effective and suitable for routine prenatal screening due to its lower failure rates and high accuracy. NGS-based cfDNA, despite being more complex and costly, is advantageous for detailed chromosomal analysis in high-risk pregnancies. The choice between these technologies should consider clinical context, cost-effectiveness, and patient preferences to optimize prenatal care. Future research should aim for standardized reporting and direct comparative studies to further refine NIPT methodologies, potentially integrating hybrid approaches that combine the strengths of both technologies.

**Keywords:** cell-free DNA (cfDNA), Next-Generation Sequencing (NGS), Noninvasive Prenatal Testing (NIPT).

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### Article History

## Introduction

Prenatal diagnosis of genetic disorders has witnessed remarkable advancements in recent years, offering expectant parents the opportunity to gain critical insights into their baby's health early in pregnancy. Among the notable developments in this field, noninvasive prenatal testing (NIPT) has emerged as a transformative tool for the detection of fetal chromosomal abnormalities, with a primary focus on the most prevalent trisomy, trisomy 21, which causes Down syndrome. This novel approach has significantly reduced the need for invasive procedures like amniocentesis and chorionic villus sampling, mitigating the associated risks and anxieties (1-4). In the landscape of NIPT, two distinct technologies have taken center stage: microarray-based cell-free DNA (cfDNA) and next-generation sequencing (NGS)-based cfDNA. These technologies provide a means of analyzing cell-free fetal DNA circulating in maternal blood, offering invaluable information for early detection of trisomy 21 and other aneuploidies. The choice between these technologies bears considerable clinical significance, as it can influence the accuracy of the test, its cost-effectiveness, and the overall patient experience (5).

This systematic review delves into the comparative evaluation of microarray-based cfDNA and NGS-based cfDNA in the context of trisomy 21 detection during pregnancy. By exploring their respective principles, strengths, limitations, and clinical implications, we aim to shed light on which technology may hold superiority in enhancing prenatal care. As the pursuit of precision in prenatal diagnostics continues to drive innovation, understanding the relative merits of these two prominent methodologies becomes imperative for both clinicians and expectant parents (5-8). This review seeks to provide a comprehensive analysis of the current state of these technologies and their impact on the realm of prenatal diagnostics, ultimately contributing to the informed decision-making process in managing pregnancies at risk of trisomy 21.

## 2- Methods

### 2-1- Search Strategy

A comprehensive search strategy was employed to identify studies comparing microarray-based and next-generation sequencing (NGS)-based cell-free DNA (cfDNA) methods for the detection of trisomy 21 in prenatal diagnostics. The search was conducted in the databases including MEDLINE, PubMed, EMBASE, and Cochrane Library. The search strategy was as follows: ((microarray-based cfDNA) OR (next-generation sequencing cfDNA) OR (NGS-based cfDNA)) AND ((trisomy 21) OR (Down syndrome))

AND (noninvasive prenatal testing OR NIPT). The search was limited to papers published in English and records from inception to July 2023.

### 2-2- Exclusion and Inclusion Criteria

Peer-reviewed records were included in the evaluation if they met the following criteria: Original research articles comparing microarray-based and NGS-based cfDNA methods for the detection of trisomy 21. Studies conducted on pregnant women undergoing NIPT for trisomy 21. Studies reported on diagnostic accuracy, including specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), and failure rates.

Studies that did not directly compare microarray-based and NGS-based cfDNA methods. Editorials, Letters to editors, Case reports, reviews, and studies lacking sufficient data on diagnostic performance metrics were excluded.

### 2-3- Study Selection

The initial search results were screened by two independent reviewers. Titles and abstracts were assessed to identify potentially relevant studies. Full-text of the included papers were retrieved and evaluated for eligibility based on the inclusion and exclusion criteria. Disagreements between reviewers were resolved by discussion.

### 2-4- Data Extraction

Two reviewers conducted data extraction independently by using a standardized data extraction form. The following information was collected from each included study.

### 2-5- Quality Assessment

The quality of the included studies was evaluated using the CONSORT (CONsolidated Standards Of Reporting Trials) guidelines for randomized controlled trials (RCTs) and the STROBE (Strengthening the reporting of observational studies in epidemiology) guidelines for observational studies. The CONSORT assessment focused on randomization, blinding, sample size, participant flow diagrams, protocol adherence, outcome reporting, and statistical methods.

### 2-6- Data Synthesis and Analysis

A qualitative synthesis of the extracted data was performed. Due to the heterogeneity in study designs, populations, and reporting of outcomes, a meta-analysis was not conducted. Instead, a comparative analysis of the diagnostic performance metrics and clinical implications of microarray-based and NGS-based cfDNA methods was presented. The STROBE

assessment for observational studies examined study design, participant details, variable definitions, data sources, bias, study size, quantitative variable handling, statistical methods, participant flow, and results presentation.

### 3- Results

#### 3-1- Study Selection

Overall, 547 papers were identified through the initial database. Following removing duplicates, 315 studies remained. Following a detailed screening of titles and abstracts, 22 studies were included for as they meet the inclusion criteria. The full texts of 12 records were then evaluated for eligibility, resulting in the inclusion of 8 studies in the final systematic review (Figure 1).

#### 3-2- Study Characteristics

The included studies varied in their design, population size, and methodology used for detecting trisomy 21. The majority were retrospective cohort studies, while others included prospective cohort studies and randomized controlled trials.

#### 3-3- Quality Assessment

The quality of the included studies was assessed using the STROBE and CONSORT. All included studies were of high quality, with a low risk of bias across domains.

Qualitative Synthesis on Comparative Performance of Microarray-Based cfDNA and NGS-Based cfDNA  
Microarray-based cfDNA demonstrated high sensitivity and specificity across multiple studies for the detection of trisomy 21. For instance, the study by Wergifossea (2019) (9) reported a sensitivity of 99.2% and a specificity of 99.8% for microarray-based methods. In comparison, NGS-based cfDNA also showed high sensitivity and specificity, with studies such as Conotte (2022) (10) reporting 99.6% sensitivity and 99.9% specificity for NGS-based methods (Table 1).

Several studies highlighted the differences in failure rates between microarray-based and NGS-based cfDNA testing. Microarray-based cfDNA methods generally exhibited lower failure rates. For example, Wergifossea (2019) (9) noted a failure rate of 2.8% for the Harmony Prenatal Test (a microarray-based method), while NGS-based methods had a failure rate of 12.4%. Conotte (2022) (10) also reported lower failure rates for microarray-based tests compared to NGS-based tests (3.2%).

Both microarray-based and NGS-based cfDNA testing showed high detection rates for trisomy 21. However, some differences were noted in the detection of other trisomies and subchromosomal abnormalities. The

Harmony Prenatal Test and Vanadis assay (microarray-based) consistently showed high detection rates for trisomy 21. In contrast, NGS-based tests offered broader genomic coverage and detected additional subchromosomal abnormalities with high resolution (11, 12).

Incidental findings, which are genetic anomalies not related to trisomy 21, were more commonly reported in NGS-based cfDNA testing. For example, Wergifossea (2019) (9) reported incidental findings with NGS-based tests that had no clinical relevance, highlighting the potential for overdiagnosis and subsequent parental anxiety.

(Table -1)

The choice between microarray-based and NGS-based cfDNA technologies for trisomy 21 detection has significant clinical implications. Microarray-based cfDNA is preferred for its cost-effectiveness, lower failure rates, and high sensitivity and specificity for trisomy 21. NGS-based cfDNA, while more expensive and complex, provides comprehensive genomic information, making it suitable for cases requiring detailed analysis of subchromosomal abnormalities.

### 4- Discussion

The results of this systematic review provide valuable insights into the comparative performance of microarray-based cfDNA and NGS-based cfDNA technologies in the detection of trisomy 21 during pregnancy. Both methodologies have demonstrated high sensitivity and specificity, establishing them as reliable tools in noninvasive prenatal testing (NIPT). However, there are notable differences in their performance, cost-effectiveness, and clinical utility that merit a detailed discussion (13-15).

Microarray-based cfDNA testing, as reported in studies such as Wergifossea (2019) (9), exhibited high sensitivity (99.2%) and specificity (99.8%) for detecting trisomy 21. This high accuracy is crucial in minimizing false-negative and false-positive results, thereby reducing the need for follow-up invasive testing procedures. Similarly, NGS-based cfDNA testing also showed excellent sensitivity (99.6%) and specificity (99.9%) as per the findings of Conotte (2022) (10). These results highlight that both technologies are highly effective in identifying trisomy 21, ensuring that expectant parents receive accurate and reliable information about their baby's health (16-18).

One of the key differentiators between the two technologies is the failure rate. Microarray-based cfDNA testing generally exhibited lower failure rates compared to NGS-based methods. For instance, the Harmony Prenatal Test, a microarray-based method, had a failure rate of 2.8%, while NGS-based methods

reported higher failure rates, such as 12.4% in some studies. Lower failure rates are advantageous as they reduce the need for retesting, thereby alleviating anxiety and inconvenience for pregnant women. This makes microarray-based testing more favorable in clinical settings where minimizing retest rates is a priority (19-25).

NGS-based cfDNA testing provides a broader genomic coverage compared to microarray-based methods. This broader scope allows for the detection of a wider range of chromosomal abnormalities, including subchromosomal anomalies, which can be crucial for comprehensive prenatal screening. However, this also introduces the possibility of incidental findings, which can sometimes lead to overdiagnosis and unnecessary parental anxiety. Studies have shown that incidental findings are more commonly reported with NGS-based testing, underscoring the importance of careful interpretation and counseling when using this technology (19-21, 26, 27).

The choice between microarray-based and NGS-based cfDNA testing also hinges on cost-effectiveness and the clinical context. Microarray-based testing is generally more cost-effective due to its lower complexity and reduced failure rates. This makes it a suitable option for routine screening in standard prenatal care. On the other hand, NGS-based testing, while more expensive, offers detailed genomic insights that can be critical in high-risk pregnancies or when a detailed chromosomal analysis is required (28-32).

The patient experience and decision-making process are significantly influenced by the choice of testing technology. Microarray-based testing, with its lower failure rates and high accuracy, offers a straightforward and reassuring option for expectant parents. Conversely, the comprehensive nature of NGS-based testing can provide a more detailed genetic profile, which can be invaluable in certain clinical scenarios but may also necessitate more extensive genetic counseling to address potential incidental findings (33-36).

## 5- Limitations and Future Directions

While this review provides a comprehensive analysis, it is important to acknowledge the limitations. The heterogeneity in study designs, populations, and outcome reporting precluded a meta-analysis, and the findings are based on a qualitative synthesis. Future research should focus on standardized reporting and direct comparative studies to further elucidate the relative strengths and limitations of these technologies. Additionally, advancements in cfDNA testing technologies and the development of hybrid approaches that combine the strengths of both

microarray-based and NGS-based methods could further enhance the accuracy and utility of NIPT.

## 6- Conclusion

In conclusion, both microarray-based and NGS-based cfDNA technologies are highly effective for the detection of trisomy 21 in prenatal diagnostics, each with its own set of advantages and limitations. Microarray-based cfDNA testing is characterized by lower failure rates and cost-effectiveness, making it suitable for routine screening. NGS-based cfDNA testing offers comprehensive genomic coverage and is ideal for detailed chromosomal analysis, though it is associated with higher costs and potential for incidental findings. The choice between these technologies should be guided by clinical considerations, cost, and patient preferences, with a focus on providing accurate, reliable, and patient-centered prenatal care.

Table 1. Characteristics of included studies.

Author, Year	Objective	Key Findings	Conclusion
Wergifossea,2019(9)	Evaluate cfDNA testing methods for trisomy 21	Harmony test had a lower failure rate (2.8%) than HB-cfDNA (12.4%). Both had similar trisomy 21 detection. Rare incidental findings with HB-cfDNA had no clinical relevance.	Harmony® test had a lower failure rate and comparable trisomy 21 detection. Incidental findings with HB-cfDNA were not clinically significant.
Conotte,2022(10)	Compare Vanadis assay and Harmony Prenatal Test for trisomies	Harmony had high detection for trisomy 21 and 18. Vanadis assay detected all trisomy 21 cases. Vanadis had a higher failure rate (3.2%).	Vanadis assay showed high performance with a low failure rate in trisomy screening.
Willems,2014(13)	Evaluate Harmony test for NIPT in Belgium and the Netherlands	Harmony test had high sensitivity and low false-negative rate for trisomies 21, 18, and 13. The overall failure rate was 0.90%.	Harmony test proved reliable for trisomy detection in maternal blood in Belgium and the Netherlands.
Gnetetskaya,2018(11)	Compare Harmony and Panorama NIPTs in risk groups.	Both Harmony and Panorama showed a high sensitivity for trisomies, with differences in PPV and NPV across risk groups.	NIPT had high sensitivity, with variations in PPV and NPV in different risk groups.
Kara,2018(14)	Develop microarray-based NIPT and compare with NGS	NIPT using microarrays provided more accurate cfDNA measurements, lower assay variability, and faster analysis time than NGS.	NIPT using microarrays was more accurate and efficient compared to NGS.
Gil, 2016 (12)	The transition from combined test to cfDNA testing	The combined test had good trisomy detection. The introduction of cfDNA testing reduced invasive diagnostic procedures.	Contingent screening with cfDNA testing reduced invasive testing rates.

		especially in the high-risk group.	
Sylvie, 2017 (15)	Evaluate cfDNA as a first-tier test for trisomies	Standard screening had 83% trisomy 21 detection. cfDNA screening achieved 100% detection with 0% false-positive rate for trisomy 21. Reduced invasive testing.	cfDNA screening had high detection and reduced the need for invasive testing.
Renee, 2015 (16)	Assess targeted cfDNA analysis for trisomies	Targeted cfDNA analysis with microarray quantification showed high sensitivity and extremely low false-positive rates for common trisomies in pregnancy.	Targeted cfDNA analysis consistently demonstrated high sensitivity and low false-positive rates for common trisomies in pregnancy.

### Ethical Issue

There was no ethical issue in this review.

### Conflict of Interests

There was no conflict of interest in this study.

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