Review Article

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Clinical and medico-legal reflections on non-invasive prenatal testing

https://doi.org/10.1515/med-2025-1353
Received October 4, 2025; accepted November 26, 2025;
published online December 19, 2025

Abstract

Background: Prenatal diagnosis has advanced dramatically, with both invasive and non-invasive techniques that enable a comprehensive evaluation of chromosomal and genetic disorders, thanks to considerable technological progress. These innovations have led to improved accuracy, earlier detection, and less invasive methods for identifying fetal health issues. To minimize risks to both the fetus and the mother, non-invasive prenatal diagnosis (NIPT) has become a fundamental screening technique, although it remains probabilistic. NIPT has undergone significant improvements in the past decade and can now screen for a wider range of conditions.

Methods: We conducted a search on PubMed and Google Scholar using the keywords "prenatal genetic testing, non-invasive prenatal diagnosis, prenatal diagnosis, chromosomal microarray" over the past decade. This article aims to demonstrate significant progress of studies in the field of prenatal diagnosis and their medico-legal implications.

Results: The results show improvements in non-invasive techniques, leading to more precise outcomes, a broader range of diagnosed conditions, and better impacts on prenatal outcomes and family decision-making.

Conclusions: This review provides an overview of NIPT. Advances in prenatal diagnosis are enabling healthcare providers to offer more accurate, timely, and less invasive prenatal care, ensuring better outcomes and reducing medicolegal disputes.

Keywords: non-invasive prenatal testing; prenatal genetic testing; prenatal diagnosis; chromosomal microarray; legal implications

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Introduction

Non-Invasive Prenatal Testing (NIPT) is a non-invasive prenatal test that analyzes fetal DNA present in the maternal blood to assess the risk of certain chromosomal abnormalities in the fetus, such as Down syndrome (trisomy 21), trisomy 18, and trisomy 13. This test poses no risk to pregnancy, as it does not require invasive procedures such as amniocentesis or chorionic villus sampling [1].

NIPT is based on the presence of fetal DNA fragments in the maternal blood, which can be analyzed to detect potential chromosomal abnormalities. The test can be performed as early as the 10th week of pregnancy and is known for its high accuracy, with very low rates of false positives and false negatives compared to other traditional prenatal tests, such as serum marker-based combined screening.

NIPT is commonly used as a screening tool for chromosomal abnormalities in high-risk pregnancies but may also be offered to all pregnancies as a non-invasive screening option.

Chromosomal abnormalities and genetic diseases are significant causes of developmental disorders and pregnancy complications. The prevalence of these conditions varies depending on the specific condition and the population being studied. Chromosomal abnormalities can be numerical or structural. Numerical abnormalities result from the loss or acquisition of an entire chromosome and include, for example, Down syndrome (trisomy 21). Structural chromosomal abnormalities, on the other hand, arise from breaks and rejoining of chromosomes and can involve gains or losses of material, such as in deletions and duplications [2–5]. Genetic disorder is a condition caused by alterations or mutations in an individual's DNA. These changes may involve a single gene (monogenic disorders), multiple genes (polygenic disorders), a combination of genetic mutations and environmental factors, or chromosomal abnormalities. Genetic disorders can be inherited or arise spontaneously [3, 6]. The recognition of such mutations is essential for prevention, prenatal genetic counseling, and any appropriate treatment.

In the last decade, we have witnessed considerable progress in the field of genetic testing, especially in obstetrics. Prenatal diagnosis of chromosomal anomalies began around 1960 [7]. Since then, numerous techniques and new methods have been developed that allow chromosomal and genetic diseases to be detected with certainty through both invasive and non-invasive tests [8]. In recent years, numerous studies have focused on the use of Non-invasive prenatal testing (NIPT) in the detection of major aneuoploidies [9]. The introduction of NIPT has transformed prenatal screening and care into genomics era [10–14].

NIPT can be performed as early as 10 weeks of pregnancy [15] and has replaced traditional non-invasive screening during the first and second trimesters in many medical centers. The NIPT includes cell-free DNA screening, which analyzes the fetal DNA present in the maternal blood to assess the risk of chromosomal abnormalities in the fetus, such as Down syndrome (trisomy 21), trisomy 18, and trisomy 13. Compared to serum marker screenings, cell-free DNA testing is more accurate and does not depend on gestational age. Additionally, as it poses no risk to the fetus, it is considered a safer alternative to invasive tests like amniocentesis or chorionic villus sampling (CVS) [16].

The main advantage of non-invasive prenatal screening for genetic disorders is that, unlike invasive testing, it carries no risk of test-related complications.

Non-invasive maternal screening provides women with the opportunity to make informed decisions about whether to undergo invasive testing, after receiving accurate and comprehensive genetic counseling. Moreover, it helps to mitigate potential medico-legal issues and reduce professional liability for healthcare providers, as it avoids the risks and complications associated with more invasive procedures.

This article aims to demonstrate significant progress in studies in the field of prenatal diagnosis. These advancements in prenatal diagnosis over recent years are enabling healthcare providers to offer more accurate, timely, and less invasive prenatal care, ensuring better outcomes for both mothers and babies [16].

Therefore, the objective of this study was to analyze the current information on prenatal diagnosis and demonstrate significant progress in studies in this field, also considering the ethical and legal challenges. Finally, we aimed to identify knowledge gaps, research priorities, and potential therapeutic developments.

Materials and methods

A narrative review of the available scientific literature was conducted using the major databases PubMed and Scopus over the past 10 years. The keywords used included "prenatal genetic testing, non-invasive prenatal diagnosis, prenatal diagnosis, chromosomal microarray", resulting in the identification of 86 articles. Inclusion criteria comprised only publications in English, original studies, and reviews relevant to prenatal diagnosis associated with screening tests. Exclusion criteria applied to studies with unclear methodology, studies on non-human populations (except experimental animal models useful for understanding immunological mechanisms), and publications lacking abstracts or not accessible in full text. Articles demonstrating methodological rigor, including clinically or experimentally relevant data aligned with the study objectives, were prioritized.

Additionally, the review considered literature addressing the medico-legal implications of prenatal diagnosis, with particular focus on cases related to professional liability or procedural complications.

Results

Prenatal diagnosis can be broadly categorized into non-invasive and invasive methods, which aim to detect genetic or chromosomal abnormalities in the fetus, as well as other conditions, to help guide medical decision-making and management during pregnancy. Non-invasive tests are generally safer for the fetus and the mother, as they do not carry a risk of miscarriage [7, 17]. They typically involve blood samples from the mother, and sometimes ultrasound. In 2020, the American College of Obstetricians and Gynecologists recommended that noninvasive prenatal testing be offered to all patients [18, 19].

Until recently, the only goals of the 11–13 week scan were to establish fetal viability, chorionicity and pregnancy dating, and performance of the combined screening test for common chromosomal abnormalities [18–20]. In addition to NIPT, an ultrasound examination, particularly in the first trimester, plays a crucial role in detecting physical anomalies such as structural defects, including neural tube or cardiac defects, as well as Down syndrome through ultrasound markers. Typically performed between the 11th and 14th week of gestation, it poses no risk to either the mother or the fetus and is often combined with NIPT for a more comprehensive set of information [20].

Therefore, the first trimester screening test offers a valuable opportunity to identify anomalies, some of which may be incompatible with life, before the 14th week of gestation [21, 22]. However, while it provides useful information, it is often not definitive and remains dependent on the skill of the operator [23].

Despite its limitations, the first trimester ultrasound can identify fetuses with increased nuchal translucency, which indicates a higher risk for chromosomal and/or genetic disorders. It can also help identify fetuses at greater risk for developing skeletal anomalies, genitourinary tract issues, and congenital heart defects, some of which can be severe [24–27].

In 1992, Nicolaides first described nuchal translucency as a marker for fetal chromosomal abnormalities, particularly Down syndrome. Since then, NT has consistently been measured using this method. Between the 11th and 14th weeks of pregnancy, measuring fetal nuchal translucency and assessing blood flow through the tricuspid valve and ductus venosus can help in the early detection of serious heart defects.

A retrospective study was conducted by the University of Maryland (Medical Center–Center for Advanced Fetal Care, Baltimore) on singleton pregnancies undergoing ultrasound during those specific weeks of gestation, including fetal anatomy, measurement of nuchal translucency, and evaluation of blood flow in the ductus venosus and through the tricuspid valve. The study highlighted that the first-trimester ultrasound detects more fetal anomalies than the non-invasive prenatal test, confirming it as a valuable screening method to be used alongside the latter. [19]. Anomalies that should always be detected in a fetal ultrasound include body stalk anomaly, anencephaly, alobar holoprosencephaly, exomphalos, gastroschisis, and megacystis [19].

Nuchal translucency can be measured by ultrasound, performed by expert operators, between the 11th and 13 weeks (+6 days) of gestation. The results of this study showed that an NT greater than 95°, tricuspid regurgitation, and an inverted a-wave in the ductus venosus are associated with significant cardiac defects [28]. This study also highlights the great results of the NT in the first trimester.

In fetuses with increased nuchal translucency, the risk of congenital heart disease is higher if the a-wave in the ductus venosus is inverted or if there is tricuspid regurgitation.

However, the literature has documented the presence of fetuses that, despite increased nuchal translucency, had a completely normal chromosomal complement. A portion of these pregnancies, however, was associated with adverse outcomes [29]. In a study conducted in Norway in 2016, it was found that out of nearly 2,000 pregnancies studied, 9.3 % of fetuses with NT>95th percentile and a normal karyotype presented structural anomalies [27].

In addition to ultrasound, which remains one of the main screening methods for detecting chromosomal abnormalities, the use of NIPT has become widespread in recent years. This test was developed almost 40 years ago with the initial goal of detecting the most common aneuploidies, such as Down syndrome (T21), Patau syndrome (T13), and Edwards syndrome (T18) [30–32]. Over time, NIPT has undergone significant advancements, now being capable of detecting other conditions linked to sex chromosomes and other genetic anomalies. Thanks to its high sensitivity and specificity, NIPT has become a valuable tool in prenatal diagnosis, particularly for its ability to reduce the risk to both the mother and the fetus when compared to invasive tests such as amniocentesis [33]. Furthermore, the test is useful for detecting chromosomal anomalies as early as the first trimester, improving the chances of early detection and allowing families to make informed decisions about continuing the pregnancy. Offering NIPT and NT between 11+0 and 13+6 weeks, following the International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) guidelines, makes it the most comprehensive and safest approach for both mother and fetus [34, 35].

The development of NIPT using cell-free fetal DNA (cffDNA) has indeed provided an alternative to invasive screening procedures (such as amniocentesis or CVS), which carry risks of miscarriage.

The test involves taking a blood sample from the mother, usually around the 10th week of pregnancy, which contains small amounts of free fetal DNA (cffDNA). This fetal genetic material circulating in the mother's bloodstream is then subjected to genetic analysis to extract and sequence the fetal DNA present in the maternal blood. The genetic analysis examines the amount of fetal DNA to determine if there are any alterations in the fetal chromosomes, such as in the case of trisomies (trisomy 21, 18, or 13) [36] or sex chromosome disorders. The results of the NIPT will be available within approximately two weeks. If the test is negative, the likelihood of chromosomal abnormalities in the fetus is very low. If the test is positive, it indicates a higher probability of chromosomal condition, but it is not a definitive diagnosis. In this case, further invasive diagnostic tests, such as amniocentesis or chorionic villus sampling (CVS), will be performed to confirm the diagnosis [15, 37].

An effective first-trimester screening for trisomy 21 is provided by a combination of maternal age, fetal NT thickness, fetal heart rate, and maternal serum levels of free β-hCG and Pregnancy-Associated Plasma Protein A (PAPP-A). The first-trimester screening test can identify approximately 90 % of fetuses with trisomy 21 and other major aneuploidies. In Table 1, we report the main tests that can be performed and the substantial differences in terms of methodology, timing of execution, accuracy, and limitations.

The assessment of new markers enhances the performance of combined screening by increasing the detection rate and reducing the false positive rate [38, 39].

Examining these new markers requires proper training for sonographers and certification of their competence in performing these scans.

Another notable innovation in the first trimester is the introduction of 3D ultrasound, for example, to assess the integrity of the fetal palate and exclude clefts. Although not commonly used in the first trimester, in certain cases, 3D imaging can help better visualize structural abnormalities later in pregnancy.

When used alongside 2D ultrasonography as a complementary tool [40], the 3D technique can observe the fetal palate and diagnosing cleft palate with or without cleft lip with high sensitivity [41, 42].

Another new technique described in the literature involves the evaluation of the retronasal triangle by acquiring a coronal scan of the face. This technique has shown high specificity for detecting malformations of the nasal bones or cases of micrognathia [43, 44].

Table 1: Main tests differences in terms of methodology, timing of execution, accuracy, and limitations.

Test Name	Gestational age (weeks)	Method	Accuracy	Limitations
Early ultrasound (NT scan)	11–13	Ultrasound to measure fluid at the back of the baby's neck (nuchal translucency)	Varies, depending on the condition	Limited to certain conditions; needs to be combined with other tests for accuracy
Non-invasive prenatal testing (NIPT)	10 or later	Maternal blood test	>99 % for down syndrome	Screening test (not diagnostic), still expensive, cannot detect all conditions
First trimester combined screening	11–13	Maternal blood test (PAPP-A & hCG) + ultrasound (NT scan)	85–90 % for down syndrome	False positives/negatives possible, not 100 % accurate
Maternal serum pregnancy-associated plasma protein A (PAPP-A) & free Beta-HCG	10–13	Maternal blood test	Variable, depends on condition	Limited detection power, needs additional tests for better results

Screening methods typically differ and are chosen based on the condition being investigated or suspected, and we have attempted to summarize them in Table 2.

The first trimester screening ultrasound is not only aimed at studying fetal anatomy, but it is also now capable of predicting the risk of preeclampsia. In the first trimester, it is crucial to identify women at an increased risk of developing preeclampsia, allowing for timely and effective intervention.

Various models have been developed for this purpose. Notably, the Fetal Medicine Foundation (FMF) first trimester prediction model (known as the triple test) combines maternal factors with measurements of mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor [45].

This combined test aims to identify pregnant women early who may benefit from aspirin administration [46, 47]. Early administration of low-dose aspirin could improve endometrial growth, placental vascularization, and organogenesis. Numerous studies have demonstrated the effectiveness of aspirin administration, even in the preconceptional period, for women with multiple risk factors [48].

Table 2: Screening methods examples.

Condition	Screening method
Down syndrome (T21)	Nucal translucency measurement
Patau syndrome (T13)	Mathernal blood test (PAPP-A, free Beta)
Edwards syndrome (T18)	
Congenital hearth defects	Ultrasound 2D -3D, Doppler
Cystic hygroma	Nucal translucency measurement
Cleft lip and palate	Ultrasound 2D 3D (early fetal facial
Micrognathia	examination
Pierre robin sequence	Ultrasound (detailed craniofacial examination)
Holoprosencephaly	Ultrasound (detailed fetal brain examination)
Anencephaly	
Intracranial hemorrhage	
Idrocephalus	
Dandy walker malformation	

Furthermore, NIPT has proven to be very useful in prenatal diagnoses for parents of advanced age, with both father and mother over 40 years old, as this could bring with it an increased likelihood of encountering pathologies and chromosomal abnormalities, also related to ART (Assisted Reproductive Technique) [49–51]. Combined NIPT for chromosomal aneuploidies and microdeletion syndromes has therefore become part of routine practice in cases of ART and advanced age [52–55].

Medicolegal framework

NIPT and prenatal diagnosis, although associated with ethical and legal implications in rare and isolated cases, should not be overlooked. While complications are minimal, the sensitivity of the issue means that even the few controversies that may arise can be significant and costly for the healthcare professionals involved and the families affected. [56–58]. Disputes may arise based on allegations of negligence, where a healthcare provider is accused of failing to meet professional standards and industry guidelines. Patients who pursue legal action often claim that the harm suffered (to the mother or the fetus) was a direct consequence of this inadequacy. Additionally, lawsuits may occur regarding prenatal counseling, which patients may claim was not properly carried out. This may include failing to inform the patient about reproductive risks related to carrier status or maternal age or failing to recommend invasive tests when indicated. Furthermore, healthcare professionals have the duty to inform patients about the risks and benefits of various tests and procedures, including the availability of non-invasive tests like NIPT, which could help the patient make an informed decision about the pregnancy. If the consent does not meet all its criteria, and thus is not clear, informed, voluntary, and current, patients may file a lawsuit for the violation of their right to self-determination. This could indeed constitute a form of violence against women and parents [59–61], as happens in many other areas, and for this reason, healthcare providers could be held accountable both in civil and criminal courts.

Lawsuits against hospitals or healthcare providers can also arise due to errors in laboratories conducting tests, including potential mix-ups of test tubes, or because of incorrect interpretation of diagnoses. Patients might therefore make decisions based on inaccurate or incomplete information, which could later prove to be entirely unfounded. In such cases, legal disputes may arise based on the so-called “wrongful birth” or “wrongful abortion.” Both types of cases raise complex legal and ethical issues related to the professional responsibility of healthcare providers and the protection of patient rights [37, 62–64].

Therefore, the failure of prenatal counseling or testing, for any reason, can lead to both legal and ethical consequences, among others [65, 66]. Ethical questions arise concerning the sanctity of life and the rights of individuals to make informed decisions about their own bodies, their future, and that of their newborns [67–72]. Healthcare professionals must strive to balance medical science, and the clear information provided to parents with their ethical and deontological responsibilities, ensuring that their actions always prioritize the well-being of the patient. These ethical issues make the legal implications of potential disputes arising from such cases even more complex, turning them not only into a matter of professional responsibility but also opening a moral and ethical debate that transcends forensic medicine.

Discussion

In this narrative, we aimed to describe the progress in studies in the field of prenatal diagnosis. These advancements in prenatal diagnosis over recent years are enabling healthcare providers to offer more accurate, timely, and less invasive prenatal care, ensuring better outcomes for both mothers and babies.

Is it possible to state that currently the NIPT carries no risks for the mother or fetus, unlike other invasive tests such as amniocentesis or chorionic villus sampling. It has high sensitivity and specificity, reducing the risk of false positives and false negatives. It can be performed very early, as early as the 10th week of pregnancy.

However, it has limitations: although highly accurate, NIPT does not provide a definitive diagnosis. It is a screening test that identifies the likelihood of chromosomal abnormalities but does not guarantee absolute certainty. In fact, in cases of a positive test result, more invasive and diagnostic tests are performed.

NIPT is specifically designed to detect some common chromosomal abnormalities but cannot identify all potential genetic abnormalities or structural defects.

In summary, NIPT is a highly accurate and safe prenatal screening test, but it does not replace invasive diagnostic investigations when there are indications for definitive confirmation.

Future research should focus on identifying novel biomarkers, accurate tests, and therapeutic options. However, the ethical debate could represent an obstacle in this regard, and even experimental data from animal models that may offer an alternative approach to overcoming the restrictions of studying humans are controversial. Perhaps new technologies, such as artificial intelligence, could assist healthcare providers and patients undergoing prenatal testing who present chromosomal abnormalities. Ultimately, the goal should always be to ensure that patients and healthcare providers are equipped with the information and support needed to make informed, compassionate decisions for the well-being of both the mother and the child.

Conclusions

Non-invasive prenatal testing (NIPT) represents a significant advancement in prenatal care, offering a safe and highly accurate screening method for detecting common chromosomal abnormalities. Unlike invasive procedures such as amniocentesis or chorionic villus sampling, NIPT carries no physical risks to the mother or fetus and can be performed as early as the 10th week of pregnancy. NIPT offers unparalleled safety and high accuracy for prenatal screening but does not replace invasive diagnostic tests when confirmation is needed. Its clinical importance lies not only in the ability to reduce the risks associated with invasive tests, but especially in providing timely information and supporting pregnancy planning. NIPT also raises important ethical issues, including reproductive autonomy and social implications regarding disability, requiring a balance between clinical benefits and ethical considerations. Additionally, from a medico-legal perspective, ensuring adequate informed consent is essential to avoid complications related to professional liability and potential claims. Pre- and post-test counseling is crucial to support informed decisions, while regulating NIPT can help prevent misuse and ensure equitable access.

Limitations

Our research has clear limitations. The study is based on data gathered through a single search engine and a limited set of keywords. While this approach was effective and functional, it may have excluded a significant number of relevant articles on the topic. We provided only a brief analysis of the current state of the art regarding NIPT; however, the subject is undoubtedly much broader, and this article could not comprehensively address the vast body of knowledge on an issue that is constantly evolving and, fortunately, always under close scrutiny. Nonetheless, the limitations identified by the authors should be viewed merely as a new starting point for further research.

What's already known about this topic?

Prenatal diagnosis has significantly advanced through both invasive and non-invasive techniques, improving early detection and accuracy in identifying chromosomal and genetic disorders.

What does this study add?

This study highlights the recent progress in non-invasive prenatal testing (NIPT), showing broader diagnostic capabilities, improved precision, and important medico-legal implications for clinical practice and parental decision-making.

Acknowledgment: Not applicable.
Ethical approval statement: Ethics approval statement is not applicable.
Funding information: The authors state no funding involved.
Author contribution: Conceptualization, G.G., E.Ch.(Chitoran), and L.D.; methodology, E.Ch., V.B., and S.Z.; Validation, G.C., L.D., G.S. and S.Z.; formal analysis, E.Ch., K.K., and R.S.; investigation, R.K., G.S., and R.S.; writing – original draft preparation, E.Ch., V.B., S.G and V.B.; and writing – review and editing, G.G., G.C., S.Z., and L.D. All authors have read and agreed to the published version of the manuscript. Patient consent statement: Patient consent is not applicable. Data Availability Statement: Data available on request from the authors.

Funding source(s): This research received no external funding.
Conflict of interest: The authors declare no conflicts of interest.
Conflict of interest: Giuseppe Gullo and Simona Zaami serve as Editors for Open Medicine Journal, but it does not affect the peer review process. Other authors state no conflict of interest.
Data availability statement: All data analyzed during the present study are available from the corresponding author on reasonable request.

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