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# Non-Invasive Prenatal Tests (NIPT): Review Article

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## ABSTRACT

No single innovation in the past has made such a fast and massive effect on clinical obstetric practice as the introduction of noninvasive pre-natal screening (NIPS) for chromosomal abnormalities using fetal cell DNA in maternal plasma. In any case, the innovation of NIPS which has likewise been called noninvasive pre-natal testing (NIPT) is quickly advancing. Most clinicians will be unable to completely comprehend this new innovation to empower great clinical practice. This review will be centered around issues that have significant clinical ramifications. NIPT/S is just a screening test and every positive case must be affirmed by intrusive demonstrative strategies. Despite the fact that NIPT/S is being extended quickly to cover different chromosomes and huge chromosomal basic variations from the norm, the location rate is still unsure, and the positive prescient worth is required to be lower. Pregnant women who are at risk of chromosomal abnormalities other than basic trisomies ought to be offered a demonstrative test rather than NIPT/S. The utilization of NIPT/S as a primary Down syndrome screening test should not replace the 11–13 weeks scan.

***Keywords:*** Noninvasive prenatal screening, NIPS, NIPT, Cell- free DNA, Maternal plasma, Aneuploidy

## INTRODUCTION

### Background

Non-invasive preterm testing (NIPT), otherwise called without cell DNA testing and non-invasive preterm screening (NIPS), is a significant expansion to the scope of screening tests for fetal chromosomal irregularities. For trisomy 21 specifically, NIPT is better than other screening modalities. Nonetheless, NIPT has restrictions and complexities that mentioning clinicians and their patients ought to comprehend.

Non-invasive prenatal testing – Cell-free DNA

'fetal cell' DNA (cf DNA) comprises of short DNA pieces, which are discharged into plasma from ordinary cell turnover and are quickly cleared from flow. In a lady who is pregnant, a large portion of the cf DNA is gotten from turnover of maternal cells. Be that as it may, an extent is gotten from the external trophoblast cell layer of the placenta, which ordinarily mirrors the fetal genotype. [(1)] The level of cf DNA got from the trophoblast is named the 'fetal part'. There is a wide typical scope of fetal portion. The middle an incentive at 10 weeks of development is around 10%. [(2)]

Non-invasive preterm testing (NIPT) tests contrast in their precise strategy and there are a few distinct measures accessible in Australia; a point by point correlation is past the extent of this audit. When all is said in done, NIPT tests look at the extent of cf DNA got from explicit chromosomes. Fetal aneuploidy can make these extents go amiss from anticipated qualities, and measurable tests are applied to decide if such deviations are significant. [(3)] As most of cf DNA is maternal, the capacity to distinguish a variation from the norm of a given fetal chromosome requires adequate fetal division. Numerous NIPT measures accordingly have a fetal division cut-off level, and tests with fetal part underneath

the characterized cut-off don't deliver a result. [(4)]

NIPT can be done any time in the pregnancy from 10 weeks of gestation onwards to improve the probability of adequate fetal division. NIPT normally requires a particular solicitation structure, and can be mentioned by a clinical expert (general specialist or obstetrician) who is engaged with the patient's antenatal consideration. Preterm screening and identification of fetal chromosomal anomalies, specifically Down syndrome, has become a vital piece of obstetric consideration in numerous nations and social orders. An authoritative pre-birth analysis of fetal chromosomal variations from the norm requires an invasive system, such as amniocentesis or chorionic villus examining (CVS), to give a fetal example dependent on which the fetal hereditary status can be learned. Despite the fact that these invasive strategies are viewed as sheltered, they despite everything convey a danger of technique related premature delivery, evaluated to be beneath 1 in 300 methods in experienced hands. [(5)] So as to recognize the high-chance populace who will advantage from invasive procedures, different sonographic and maternal serum biochemical markers have been created what's more, utilized clinically in various mixes as a screening test for fetal Down syndrome. The most mainstream models are second trimester double or triple test utilizing maternal serum alpha-fetoprotein, human chorionic gonadotropin (hCG) furthermore, estriol [6] and the main trimester joined screening test utilizing ultrasound markers specifically fetal nuchal translucency estimation, biochemical markers, for example, maternal serum free beta-HCG and Pregnancy Associated Plasma Protein A (PAPP-A). Likewise, the fourfold test (with expansion of Inhibin-A) has been appeared to improve the sensitivities, consecutive and unforeseen methodologies are being adjusted in various focuses. Recently, second trimester Down syndrome screening with triple test has been supplanted by first trimester screening because of higher identification rates and prior determination of chromosomal variations from the norm, shows the revealed presentation of these normal screening tests for the preterm recognition of fetal trisomy 21. All in all, at the false positive test pace of 5%, the recognition rate for second trimester serum test, first trimester combined test and coordinated first and second trimester screening test are about 60%, 90% and 95% separately. Tragically, because of the generally low frequency of fetal trisomy 21, the positive predictive value of generally advantageous screening test is as yet 1:15 to 1:30. There has been a steady drive for building up a superior screening test, or an analytic test without hazard.

**Table 1. Micro deletion syndromes that can be tested using noninvasive prenatal testing**

| |
|---|
| 1p36 deletion |
| Wolf–Hirsch horn syndrome (terminal 4p deletion) |
| Cri du chat syndrome (terminal 5p deletion) |
| Langer–Gideon syndrome (8q24 deletion) |
| Jacobsen's syndrome (terminal 11q deletion) |
| Prayer–Willis and Angel man syndromes (15q11.2-q13 deletion) |
| Diverge syndrome (22q11.2 deletion) |

**Table 2. Noninvasive prenatal testing that screens for single-gene disorders**

| | |
|---|---|
| Ellaville syndrome | CHARGE syndrome |
| Cornelia de Lange syndrome | Bohring-Opitz syndrome |
| Rett syndrome | Soto's syndrome 1 |
| Schinzel-Giedion syndrome | |
| Holoprosencephaly | Craniosynostosis |

## DISCUSSION

Clinicians over the world as they receive NIPT. Generally speaking, clinical practice understanding, zones of claim to fame, open and private practice, and topography, which we accept empowers us to catch a wide scope of clinical usage issues. These information additionally give knowledge on a portion of the regular hindrances and difficulties suppliers are looking with NIPT.

One of the most striking discoveries in our examination is the extraordinary changeability in test costs both among nations and inside. We noticed that this inconstancy didn't really follow the per capita pay of the nation: Australia had the

least expensive tests overall, though Argentina had the second most elevated normal cost. Plainly, enormous inconsistencies in test cost will directly affect worldwide take-up of NIPT. As the respondent from Argentina watched, the cost of the test makes it excessively expensive for many people, and it is as yet constrained to patients who can manage the cost of it." This respondent additionally evaluated that around 0.1% of pregnant women have experienced NIPT since its presentation in Argentina in January 2013 and that "NIPT isn't assuming a critical job in routine aneuploidy screening." This announcement especially accentuates how clinical execution of NIPT in numerous nations might be confined by test costs. To be sure, numerous respondents remarked about high test costs and the exorbitance of NIPT.

It is watched variety in reactions from inside a similar nation; for instance, we noted clashing information from respondents about the accessibility of NIPT in the UK, with a large portion of the respondents detailing that NIPT isn't accessible regardless of distributed documentation of accessibility through the RAPID open area trial.16 While our constrained example of UK suppliers can't uncover across the country inclines, this disparity may reflect absence of supplier information about NIPT or may uncover lopsided accessibility of NIPT inside the UK. It was noted variable reactions inside nations for inquiries regarding whether there are plans to bring NIPT into routine antenatal consideration. This recommends policymakers should have conversations at a national level so as to coordinate the viewpoints of various partners, particularly social insurance suppliers who are offering NIPT, and illuminate all partners about designs for presentation into national projects. Such conversations may likewise help with the advancement of clear practice rules so that NIPT is utilized most adequately for every nation's needs. Our fundamental discoveries likewise affirm that proficient social orders, both national and universal, can assume an important role in controlling usage and fitting utilization of this new innovation as it enters a developing number of nations. While this examination was in progress, the International Society for Prenatal Diagnosis (ISPD) discharged a position explanation giving direction on the utilization of NIPT. [(7)] It isn't evident whether clinicians, especially from low-and center pay nations, know about these and other expert society rules and if such rules have been received in their nations.

In spite of the fact that reports show NIPT might be accessible in upwards of 90 nations, [(8)] information from three "upper-center" salary nations (Argentina, Hungary, and Turkey) and just one "lower-center" pay nation (India). [(9)] Geographically, poor inclusion of nations in the Middle East and Africa. Information is consequently slanted towards the encounters of professionals in well-resourced social insurance settings. Information likewise ought not to be viewed as illustrative of the current province of NIPT use for a whole nation. Essential objective was to check contrasts and/or likenesses in NIPT use across nations, instead of inside a specific nation. Local or commonplace contrasts by and by encompassing antenatal care and NIPT use were normal and starter discoveries from investigations of various reactions from a similar nation loan backing to that. Practices are additionally expected to be distinctive among private and open part suppliers. In addition, clinicians from different nations who we didn't review may have various encounters with NIPT use. Presently, none of the business suppliers for NIPT incorporate Rh blood testing on their test boards, in spite of the fact that without cell DNA testing for Rh blood status is accessible in numerous nations. [(10, 11)]

**Positive Predictive Value (PPV)**

PPV is the probability that the fetus is truly affected when the NIPT result is positive. PPV is not only dependent on the sensitivity and specificity of a test, but also on the prevalence of disease, the expected PPV at

different disease prevalence and false positive rate assuming a detection rate of 99–100%. Changes due to varieties in recognition rate are not indicated in light of the fact that the impact is moderately little. Indeed, even at a false positive rate as low as 0.1%, a woman with a positive NIPT result will still have20–50% chance of having a normal fetus depending on whether she originally belongs to the low risk, average risker high-risk group. Therefore, NIPT must be considered as a screening test only, and all positive results must be confirmed by an invasive diagnostic test. At present, the PPV of clinical NIPT tests were reported to be 45.5–91% [(12, 13)]

**False Positive NIPT Results**

It is increasingly realized that false positive NIPT results May not be simply a technical failure, but could be due to fetal mosaicism, confined placental mosaicism , interference from a vanished twin, maternal mosaicism, maternal number variations (CNVs) in 5.2–10%. [(14)] In a detailed Study of 1033 fetuses with ultrasound anomalies, 1.8% had microscopically detectable chromosomal abnormalities other than trisomy 13, 18, 21, SCA or triploidy, and an additional 5.5% had a pathogenic CNV. [(15)] It is obvious that fetuses with structural abnormalities require further investigation down to submicroscopic level throughout the whole genome. [(16)] Some of the chromosomal abnormalities associated with structural anomalies are detectable by NIPT, such as the common aneuploidies. Some may be detectable but the detection rate is uncertain, such as rare aneuploidy or large chromosomal deletions. However, submicroscopic micro deletions or duplications less than 5 Mb are generally not detectable by NIPT except one or few micro deletions that have been specifically optimized for their detection. It follows logically that if further chromosomal investigations required in fetuses with structural abnormalities, NIPT is an inappropriate test. [(17)] While screening of Down syndrome is being moved to NIPT, one should not forget the importance of the 11–13- Week scan. A first trimester scan allows early detection of 50–60% of major structural abnormalities and assessment of the nuchal translucency. It is estimated that in 2–10% of Fetuses with nuchal translucency [3.5 mm with have a chromosomal aberration not detected by current NIPT approach. [(18)]

**Future of NIPT**

Within the next 5 years, reduction in cost will make NIPT the most cost-effective primary screening test for Down syndrome in most societies. However, the rapidity of how NIPT will replace existing publicly funded programs rely mainly on administrative and political issues of the local Government, but it is likely that this change will occur much faster than any other technologies ever used in obstetric care. It is likely that publicly funded NIPT programs will be focused only on the common aneuploidies, with or without sex chromosomal aneuploidies and NIPT outside public programs will expand to include the whole fetal genome, micro deletion/micro duplication syndromes and single gene disorders. However, the availability of such expanded NIPT will result in a slow rise in the number of invasive testing for confirmatory diagnostic tests, stimulate more ethical discussion on what conditions to be included in the expanded panel, and result in a situation in which there will be inadequate competent specialists to counsel women who are found to be high risk. We should prepare to face this change.

**A medico-legal and ethical dilemma**

New technology drives a tendency to test for an increasing number of abnormalities, but as a society we have yet to determine the conditions of offering prenatal screening. Industry is framing the testing agenda, rather than medical need or societal values. It is easy to fall into the data trap of prenatal testing, rather than

considering the values of human life in its many forms.

Currently, prenatal screening and diagnosis focuses on clinically significant disorders with well recognized phenotypes for which early diagnosis offers benefits. NIPT is potentially a powerful tool in fetal genetic diagnosis – and the range of recognizable conditions needs to be carefully evaluated to ensure there is merit in their detection; that the performance characteristics are robust and accurate; and that the testing modalities operate within ethical principles.

It is essential for clinicians to provide accurate pre-test and post-test counseling. Explaining the possibilities and limitations of prenatal testing is complex and time consuming, if poorly targeted; the new test can cause great angst and heartache for patients. It is also an area of emerging risk for doctors and the society they serve.

## CONCLUSION

Since first experience with clinical practice in Hong Kong in 2011, NIPT has immediately spread its wings over the globe. While numerous professional societies at present suggest that NIPT be utilized as a screening test, and not as a diagnostic test, its high sensitivity (true positive rate) and specificity (true negative rate) make it an alluring option in contrast to the serum screenings and invasive tests currently used. Proficient societies orders additionally suggest that NIPT be joined by hereditary directing with the goal that families can settle on educated conceptive decisions. Despite the fact that there are extra difficulties for NIPT take-up in the developing countries including the absence of healthcare services experts and foundations, the utilization of NIPT in low-asset settings might decrease the requirement for talented clinicians who perform invasive testing.

Future advances in NIPT technology promise to expand the range of conditions that can be detected, including single-gene disorders. With these advances questions of how to handle incidental findings and variants of unknown significance do arise. Moving ahead, it is mandatory that all stakeholders have their voices heard in formulating policies to ensure the ethical and equitable use of NIPT across the world.

**Conflict of interest**

All authors declare no conflicts of interest.

**Author's contribution**

Authors have equally participated and shared every item of the work.

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