# VALUE OF NON-INVASIVE PRENATAL TEST (NIPT) FOR COMPREHENSIVE FETAL ANEUPLOIDIES SCREENING

**Phan Hoang Cuc[1,✉], Hoang Thi Ngoc Lan[1]**
**Trinh Thi Que[2], Tran Hien[2], Nguyen Ba Son[2]**
*[1]Hanoi Medical University*
*[2]Medlatec General Hospital*

*The expanded NIPT for screening all fetal chromosomal aneuploidies has been widely used in clinical practice. The study was conducted on 6,104 pregnant women performing this test at Medlatec General Hospital to evaluate the values of NIPT. Sensitivity and negative predictive value reach 100%, and specificity reaches over 99.8%. The positive predictive values for trisomy 21, trisomy 18, trisomy 13, sex chromosome aneuploidies, and rare chromosome aneuploidies are 88.89%, 62.50%; 50.00%; 36.67%, and 0%, respectively. Among rare chromosome aneuploidies, trisomy 2, 4, 9, 15, 16, and 22 are reported to have adverse outcomes, while trisomy 3, 7, 8, and 20 reported no cases. Therefore, the NIPT can potentially predict adverse pregnancy outcomes for rare chromosome aneuploidies.*

**Keywords: Non-invasive Prenatal Testing, NIPT, NIPS, prenatal screening.**

## I. INTRODUCTION

Fetal chromosomal abnormalities are the leading cause of adverse obstetric outcomes and birth defects. Among live-born children, the rate of chromosomal abnormalities is approximately 1 in 150, with nearly 90% being aneuploidies. Common aneuploidies include trisomy 21, 18, and 13 (T21, T18, T13), as well as sex chromosomal aneuploidies (SCAs).[1] Additionally, among rare chromosomal aneuploidies (RCAs), trisomy 16 (T16) is often associated with adverse outcomes.[2,3] Meanwhile, trisomy 7 (T7) is the most frequently observed as high-risk, but the most favorable outcomes are reported.[4,5]

Maternal serum screening tests (double/triple test) have evolved in prenatal screening, which improved obstetric outcomes and reduced the rate of birth defects. However, these traditional screening methods still have limitations with positive predict value (PPV) ranging from 50% to 90% and false positive (FP) from 3% to 5%.[6] On the other hand, if the screening test result is high-risk, pregnant women need to undergo prenatal diagnosis such as amniocentesis to confirm. Therefore, prenatal screening needs to continuously evolve to increase PPV and reduce FP and FN, which minimize the risk of harm to mother and fetus.

Non-invasive Prenatal Testing (NIPT) is a prenatal screening test that is increasingly being adopted. NIPT is recommended to replace maternal serum screening tests completely.[7] This test is based on the analysis of cell-free DNA originating from the placenta in the mother's blood (cell fetal free DNA – cffDNA), primarily performed using next-generation sequencing (NGS). For common aneuploidies (21, 18, 13, X, and Y), the value of

*Corresponding author: Phan Hoàng Cuc*
*Hanoi Medical University*
*Email: phanhoangcuc9966@gmail.com*
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NIPT such as Se, Sp, PPV, and NPV have been shown by many studies, which surpass those of maternal serum screening tests.[6,8] However, in term of RCAs, which differ from T21, T18, T13, and SCAs, these values have not been much studied, particularly in Vietnam. Therefore, our study aimed to evaluate more about all 23 fetal aneuploidies that the NIPT can detect. We divided the analysis into two groups including common and rare aneuploidies. The value of the NIPT is confirmed by prenatal diagnostic tests in cases of high-risk NIPT results. The false negative value will also be calculated by reviewing the necessary data. In conclusion, the objective of our study is to: *Evaluate the value of the NIPT in detecting aneuploidy of all fetal aneuploidies.*

## II. MATERIALS AND METHODS

### 1. Subjects

***Data collection:*** Data were collected from the medical records of pregnant women who met the inclusion criteria below. The data collection period spanned from November 1, 2022 to September 1, 2023.

***Selection criteria:*** Pregnant women with a singleton pregnancy of at least 9 weeks, who underwent the NIPT for all fetal aneuploidies at Medlatec General Hospital.

***Exclusion criteria***

- Multiple pregnancies.
- History of blood transfusion; organ transplant; stem cell; immunotherapy; radiotherapy; chemotherapy.
- Recipient of egg donation or surrogate mother.
- Participant has been already diagnosed with fetal aneuploidy.
- Participant has been diagnosed with cancer.

### 2. Methods

**Research design**: Retrospective and cross-sectional study.

**Sample size:**

$$n = Z^2_{1-\alpha/2}\ \frac{p(1-p)}{(p\varepsilon)^2}$$

n is the sample size; $Z_{1-\alpha/2}$ is the 95% confidence level with α = 0.05. Variable Z is the Z value obtained from the corresponding Z table, with value α = 0.05, Z = 1.96; and p is the rate of detecting fetuses with aneuploidy. p = 0.0347 (the detection rate of a fetus with aneuploidy using the NIPT according to Pescia et al. (2017)).[9] Using this formula, the required sample size was calculated to be 4,750 participants.

We collected complete information from 6,048 participants, which helped our study meet the sample size standards.

**Table 1. Variables and Indicators**

| Variables | Characteristic of variables | Classify | Indicator |
|---|---|---|---|
| Maternal age | Maternal age at the time of testing (years) | Quantitative | Average maternal age |
| Gestational age | Gestational age at the time of testing (weeks) | Quantitative | Average gestational age |
| NIPT result | Low-risk or high-risk results for aneuploidies | Quantitative | Percentage of low/high-risk results in total tests |

| Variables | Characteristic of variables | Classify | Indicator |
|---|---|---|---|
| Amniotic karyotype result | Normal or abnormal results | Quantitative & qualitative | Specific results and percentage of each type in the total number of amniotic chromosome tests |

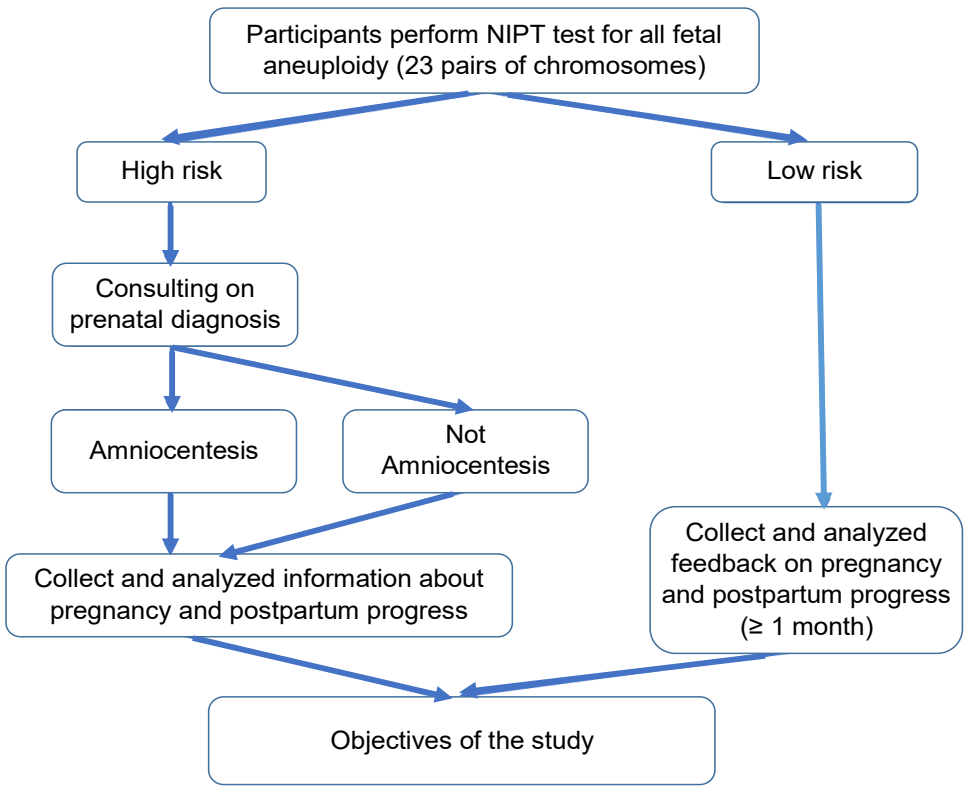


**Figure 1. Research process**

**Data processing method:** Microsoft Excel 2019 and IBM SPSS Statistic 20.

**Time and location:** The study was conducted from November 2022 to April 2023 at the Medlatec General Hospital.

### 3. Research ethics

The study was approved by the Science, Technology and Training Council of Melatec General Hospital (Number 286A/QĐ-SUB, Hanoi, November 1, 2023).

Participants are completely voluntary.

Information related to participants is guaranteed to be confidential.

The research was conducted in a spirit of honesty.

Techniques and operations related to participants are guaranteed to be professional.

This research project is conducted purely for scientific purposes.

## III. RESULTS

**Table 2. General characteristics of research subjects**

| Classification | | Quantity (n) | Percentage (%) | Average ($\bar{x}$ ± SD) | Maximum | Minimum |
|---|---|---|---|---|---|---|
| *Maternal age (years)* | ≤ 29 | 3,461 | 56.70 | 29.20 ± 5.18 | 52 | 15 |
| | 30 - 34 | 1,622 | 26.57 | | | |
| | ≥ 35 | 1,021 | 16.73 | | | |
| *Gestational age (weeks)* | 9 - ≤10 | 2,387 | 39.11 | 11.02 ± 1.97 | 30,70 | 9 |
| | >10 - 21 | 3,696 | 60.55 | | | |
| | ≥ 21 | 21 | 0.34 | | | |

The average age of participants was 29.20 ± 5.18 (years old), with the oldest being 52 and the youngest being 15. The age group ≤ 35 accounts for 83.27% which is the highest rate. The average gestational age is 11.02 ± 1.97 (weeks), the maximum value is 30.7 and the minimum value is 9. The majority of participants had gestational weeks between 10 - 21 weeks with 3,696 pregnant women, accounting for 60.55%.

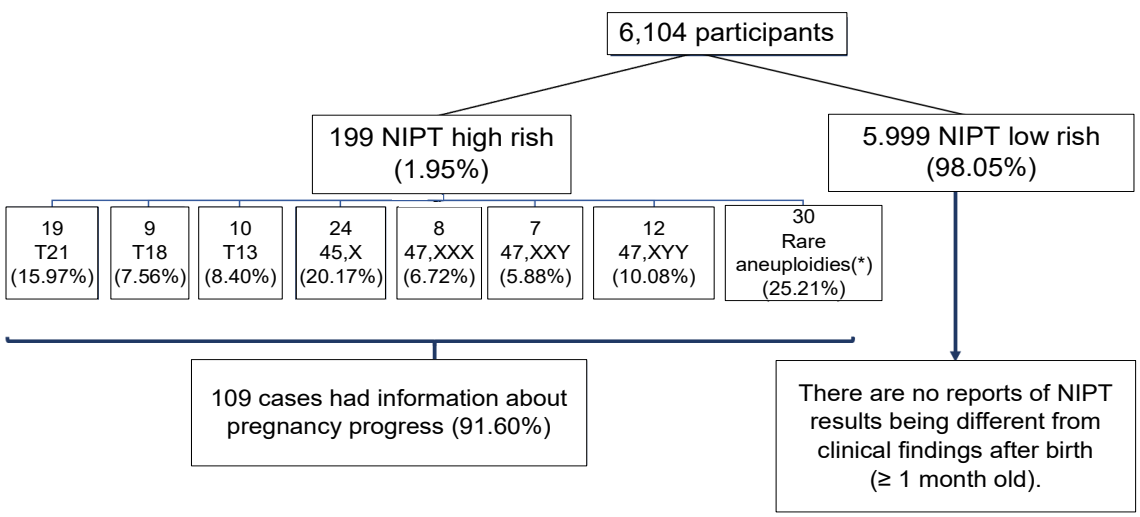


**Figure 2. Diagram of NIPT results of research subjects**

There are 6,104 participants. The result shows that 119 participants have high-risk NIPT results with aneuploidies, accounting for 1.95%. Among them, with common aneuploidies, a high-risk for Turner syndrome (45, X) is found in most cases (24 participants), followed by Down syndrome (T21) with 19 participants. There are 30 high-risk participants of rare aneuploidies, T7 and T22 are the most common with 9 and 5 cases, respectively. Of 119 high-risk cases, information from 109 participants is obtained, so 10 pregnant women are excluded from the study because they could not be contacted. There are 5,985 low-risk pregnant women, corresponding to 98.05%, of whom there were no report of adverse pregnancy and postpartum outcomes related to aneuploidy.

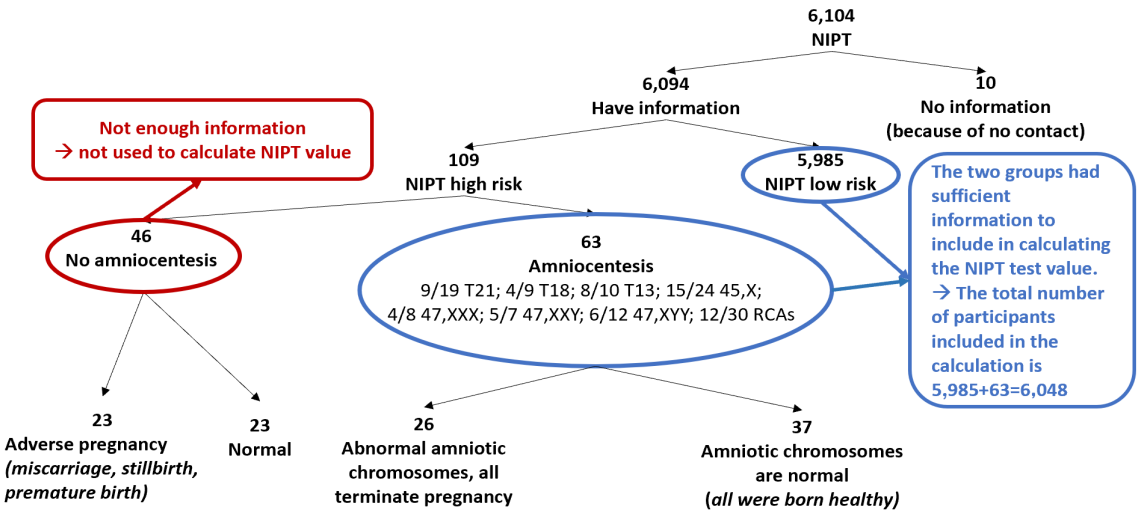


**Figure 3. Diagram summarizing data about research subjects**

There are 6,094 pregnant women who have information, including 109 high-risk cases and 5,985 low-risk NIPT cases. Of the high-risk cases, 46 participants don't offer amniocentesis and 63 participants perform amniocentesis. Cases without amniocentesis are not included in calculating the values (Se, Sp, PPV, NPV). There are only 5,985 negative cases and 63 amniocentesis groups with enough information, so the values of the NIPT in our study are calculated based on 5,985 + 63 = 6,048 (participants).

**Table 3. Value of the NIPT for comprehensive fetal aneuploidies screening**

| Values | T21 | T18 | T13 | 45,X | 47,XXX | 47,XXY | 47,XYY | RCAs |
|---|---|---|---|---|---|---|---|---|
| TP (n) | 8 | 2 | 5 | 6 | 1 | 1 | 3 | 0 |
| TN (n) | 6,053 | 6,058 | 6,054 | 6,047 | 6,058 | 6,057 | 6,056 | 6,050 |
| FP (n) | 1 | 2 | 3 | 9 | 3 | 4 | 3 | 12 |
| FN (n) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Se (%) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Sp (%) | 99.98 | 99.97 | 99.95 | 99.85 | 99.95 | 99.93 | 99.95 | 99.80 |
| PPV (%) | 88.89 | 50.00 | 62.50 | 40.00 | 25.00 | 20.00 | 50.00 | 0.00 |
| | | | | 36.67 | | | | |
| NPV (%) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

Within the scope of the study, the sensitivity and negative predictive value of the NIPT for detecting all fetal aneuploidies are 100% and the specificity is above 99.8%. The positive predictive value of the NIPT (only considering cases with amniocentesis) for Down syndrome (T21) is the highest at 88.89%, followed by Patau syndrome (T13): 62.5%, Edwards syndrome (T18): 50%, Jacob syndrome (47,XYY): 50%, Turner syndrome (45,X): 40%.

This value is quite low in 47,XXX syndrome with 25%, and Klinefelter syndrome (47,XXY) with 20%. In particular, of high-risk RCAs, there are no case in which the NIPT results are similar to amniocentesis results. In other words, the positive predictive value of RCAs is 0%.

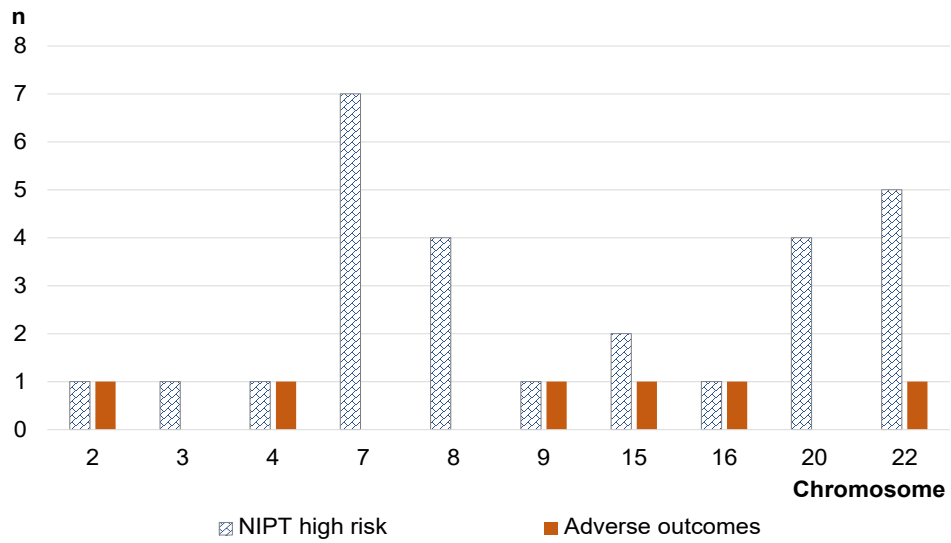


**Chart 1. Rare aneuploidy-positive NIPT cases with abnormal pregnancy**

*Adverse pregnancy outcomes include miscarriage, stillbirth, termination of pregnancy for various reasons (signs/abnormalities on ultrasound, due to abnormal amniotic karyotype), or premature birth*

There are 27 cases of high-risk NIPT for RCAs which are chromosomes 2, 3, 4, 7, 8, 9, 15, 16, 20, 22. The most common is T7. Among them, cases of T3, T7, T8, and T20 did not have adverse pregnancy outcomes. There were 6/27 cases of adverse pregnancy outcomes, including miscarriage, stillbirth, and premature birth. Aneuploidies with adverse pregnancy outcomes are associated with chromosomes 2, 4, 9, 15, 16, and 22 (1 case for each aneuploidy).

## IV. DISCUSSION

The majority of participants were younger than 35 years old, which corresponds to the marriage and reproductive age of Vietnamese women nowadays. Meanwhile, the average gestational age was 11.02 ± 1.97 weeks, aligning with the crucial role of the NIPT in early prenatal screening during the first trimester. Among the 6,104 participants, our study identified 119 individuals with high-risk NIPT results for all fetal aneuploidies, representing 1.95%. In comparison with other studies, this proportion has decreased in recent years.[9,10] The cost of the NIPT has been significantly reduced, and the effectiveness of aneuploidy screening has improved in recent years. NIPT is now recommended for alternative maternal serum screening. Additionally, NIPT results are not affected by maternal age. Our findings align with recent recommendations from ACOG and SMFM – leading Obstetrics and Genetics organizations, which advocate for aneuploidies screening by NIPT regardless of maternal age or risk factors.[7]

Our results showed that the sensitivity and negative predictive value are 100% for all fetal aneuploidies. According to E. Norton et al, the sensitivity of maternal serum tests for T21, T18, and T13 is only 78.9%, 80.0%, and 50.0%

respectively. Meanwhile, *E. Norton et al* also illustrate that the sensitivity of NIPT was 100% for all three aneuploidies (T21, T18, T13).[6] This result highlighted the superior detection ability of the NIPT in comparison with the maternal serum screening. However, these values of NIPT are not always as high as 100%.[9,11] It should be noticeable in genetic counseling because of false negative NIPT. It may be due to differences between the chromosomes of the placenta and the fetus, or issues in the sampling, performing, and analyzing. Although the possibility of missing aneuploid by NIPT is extremely low, pregnant women still need to follow up regularly with obstetric examinations and fetal ultrasounds.

We found that the specificities were above 99.8% for all fetal aneuploidies and no value reached 100%. Studies about NIPT typically show similar percentages.[6,9,12] The high specificity and negative predictive indicated the great value of the NIPT in detecting negative cases. However, there are still false positive cases, which necessitate prenatal diagnosis if the NIPT result is high-risk.

In 119 high-risk cases, 63 chose to undergo amniocentesis. The true positive rate was 41.27%. The proportions for each aneuploidy are presented in Table 3. We compared PPV in our study with published studies in Table 4 below.

**Table 4. PPV values of NIPT in some studies**

| Authors | PPV T21 (%) | PPV T18 (%) | PPV T13 (%) | PPV SCAs (%) | | | | PPV RCAs (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | XO | XXX | XXY | XYY | |
| R.P Porreco (2014)[13] | 97.9 | 100 | 100 | 45 | 57.1 | 33.3 | 100 | |
| Grazian Pescia (2017)[9] | 95.23 | 100 | 75 | / | / | / | / | / |
| Cechuan Deng (2019)[14] | / | / | / | 18.39 | 44.40 | 39.29 | 75.00 | / |
| | | | | 32.42 | | | | |
| Wan Lu (2020)[12] | 84.67 | 58.70 | 41.94 | 33.33 | | | | |
| Zhiping Gu (2022)[15] | 94.28 | 72.22 | 50 | / | / | / | / | / |
| Yunyun Zheng (2022)[16] | 71.01 | 50 | 11.11 | 46.38 | | | | 8.33 |
| Phan Hoàng Cúc (2023) | 88.89 | 50 | 62.50 | 40 | 25 | 20 | 50 | 0 |
| | | | | 36.67 | | | | |
| Miaomiao Zhang (2023)[17] | / | / | / | / | / | / | / | 4.9* |

In our study, the PPV for T21 was the highest at 88.89%. Compared to other studies (Wan Lu: 84.67%; Zhiping Gu: 94.28%; Yunyun Zheng: 71.01%), there was no significant difference in PPV (p-value > 0.05).[12-14] Similarly, we compared the PPVs for T18 and T13 with the aforementioned studies and found comparable results. Recent studies on NIPT have shown

that the PPV for common aneuploidies ranges as follows: T21 from 70% to 95%; T18 from 50% to 70%; T13 from 10% to 65%.[12,15,16] Our results fell within these ranges. By contrast, the PPV of the maternal serum screening test was only 3.4%, according to Norton. et al.[6] The NIPT is recommended as an alternative to maternal serum screening for T13, T18, and T21, regardless of maternal age.[7]

Regarding SCAs, the overall PPV was 36.67% (45,X at 40.00%, 47,XXX at 25.00%, 47,XXY at 20.00%, and 47,XYY at 50.00%). High PPV in 47,XYY was also been reported in many studies (R.P Porreco: 100%; Cechuan Deng: 75.0%; Siping Liu: 62.5%). These studies have shown PPV ranges of 30% to 70% for 47,XXX, and 47,XXY.[10,15,16] The difference in PPV values for SCAs across different studies may be related to sample size, disease incidence in the population, study design, and number of pregnant women undergoing amniocentesis. On the other hand, the PPV of 45,X has been often low, around 20% - 40%. This can be explained that 29 out of 58 homologous genes of the X and Y chromosomes are located at the two telomeres of the chromosomes. During the sequencing process, errors can easily occur because NGS technology only sequences short DNA fragments. Evaluating both sex chromosomes simultaneously can lead to errors, especially since the Y chromosome is much smaller than the X. Furthermore, low GC content can cause low coverage of these chromosomes, leading to deviations.

In evaluating the value of NIPT for RCAs, 11 participants underwent amniocentesis and all had normal amniotic karyotypes, resulting in a PPV of 0%. Of the remaining 16 pregnant women who did not undergo amniocentesis, 6 pregnancies had adverse outcomes (1/1 T2, 1/1 T4, 1/1 T9, 1/1 T16, 1/3 T15, 1/5 T22). Low PPV for RCAs has also shown in most studies (Yunyun Zheng: 8.33%; Miaomiao Zhang: 4.9%).[14,17] Currently, NIPT is commonly used for screening T21, T18, T13, and SCAs, but extending this test for RCAs is still controversial. The PPV for RCAs is considered to be lower than that of common aneuploidies, which may lead to unnecessary interventions for prenatal diagnosis. Most major Obstetrics and Genetics Organizations do not recommend screening RCAs. Therefore, studies on the value of screening for RCAs are necessary to inform clinical practice guidelines. A low PPV implies a high false positive rate, likely due to the low prevalence of fetuses with RCAs, most of which are placental mosaics. It is also noticeable that the samples from chorionic villus sampling, *Grati FR et al.* indicated CPM for RCAs was not associated with an increased risk of fetal abnormalities.[2] Therefore, choosing the method of specimen collection during invasive diagnosis is important. Most high-risk NIPT cases for RCAs with positive amniocentesis results were low mosaicism (13% - 29%), as shown in some studies (Zhu et al., 2021, Ting Hu et al., 2022).[18,19] This can explain why fetal miscarriages occur before amniocentesis. Thus, the PPV of the NIPT is affected because amniocentesis was not performed for confirmation. High-risk RCA cases may involve pure trisomy, fetal and placental mosaicism, segmental imbalances, and UPDs (uniparental disomy) (Siping Liu et al., 2022, Miaomiao Zhang et al., 2023).[10,17] These results suggest a new direction in prenatal diagnosis for high-risk RCA cases, such as microfragmentation methods like SNP array and CNV-seq. The limitation of our study is that we could only evaluate prenatal diagnosis results at the chromosomal level, potentially missing some abnormalities.

Several rare aneuploidies frequently analyzed by other researchers were also observed in our study. First, T7 was the most common high-risk NIPT case, with the most favorable pregnancy outcomes. Yiming Qi et al. found that 29/29 T7 cases had normal amniotic karyotypes. This study also evaluated 8/29 placentas and indicated that CPM was the leading cause of false positives, with CPM of T7 causing fewer adverse pregnancy outcomes.[4] On the other hand, the study of Zhu et al. analyzed UPD7 in NIPT cases of high-risk for T7. This result indicated these fetuses were unlikely to have UPD7 because no positive UPD7 cases were recorded.[18] Our study reported 9 cases of T7, with no adverse pregnancy outcome. From this analysis, we found that high-risk NIPT outcomes for T7 are generally positive. Additionally, high-risk NIPT for T16 has frequently been reported to be associated with adverse obstetric outcomes. Grati et al. extrapolated data from the placenta to NIPT and showed that placental mosaicism for T16 is strongly associated with an increased incidence of low birth weight and preterm birth, while other RCAs were less associated with adverse obstetric outcomes.[2]

Our study has several limitations. Firstly, the assessment of low-risk cases who have no aneuploidy for over a month may be inaccurate. The reason is that aneuploidy manifestations can appear long after birth, such as sex aneuploidies. Additionally, postnatal evaluations were inconsistent, as different experts performed at different times. However, given our large sample size and limited resources, our research team could not further refine the postnatal assessment and could only conduct the retrospective study. Secondly, excluding 56 cases (10 cases of no contact and 46 cases of incomplete information) from calculations may cause errors. Thirdly, in the rare aneuploidy group, considering only the 63 cases of amniocentesis results in a PPV value of 0%. However, if the cause of adverse outcomes in this group were known exactly, the PPV value would likely be higher. This limitation could be revised if all pregnancies underwent amniocentesis or fetal samples were collected for cases of early fetal loss. Nevertheless, this is challenging to achieve with a large sample size that is geographically and temporally dispersed, and with limited resources as in our study.

## V. CONCLUSION

The NIPT has a high value in screening for common aneuploidies (T21, T18, T13, and SCAs). For RCAs, NIPT can potentially predict adverse pregnancy outcomes. Prenatal diagnosis must be performed in high-risk NIPT cases. Pregnancy monitoring and fetal ultrasound need to always be maintained.

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