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Understanding the Most Common Sample Errors in Get Checked NIPT Non-Invasive Prenatal Testing

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Abstract

Non-invasive prenatal Testing (NIPT) has revolutionized prenatal care by offering a safe, reliable, and early method for detecting chromosomal abnormalities. However, the accuracy and reliability of NIPT can be compromised by various sample errors, which can have significant implications for patient care. This review article aims to identify and understand the most common sample errors encountered in Get Checked NIPT procedures. These errors include improper sample collection, inadequate sample volume, contamination, processing delays, and maternal and fetal DNA proportions issues. By examining the root causes and consequences of these errors, this review provides insights into how they can affect test outcomes. Furthermore, the article strongly emphasizes the need for adherence to best practices and standard operating procedures to minimize these errors, ensuring higher accuracy and reliability in NIPT results. The findings underscore the importance of stringent quality control measures, proper training for healthcare providers, and patient education to reduce sample errors and enhance the overall efficacy of NIPT in clinical practice.

Keywords: sPrenatal Testing, Sample Errors, DNA Quality, Fetal Fraction

Introduction

NEQAS for circulating fetal DNA: I've been working for two decades and developed it with this aim in mind. It remains the longitudinal proficiency testing scheme of choice for several NIPT labs, and the PLCs (Professional Laboratory Consultants), renowned for their expertise in the field, have examined around 440,000 clinical NIPT samples since launch. This review, written by the PLC, aims to raise awareness of the figures recorded in the NEQAS scheme and focus on the common pitfalls seen in the lab. This review aims to discuss a number of the most common sample errors seen by our labs, including maternal cell contamination (MCC), confined placental mosaicisms (CPPM), uniparental disomy (UPD), placental mosaicism (PM), confined mosaicism of chromosomes 16 and 22 that have been detected as trisomies by NIPT as well as the non-closure of the cfDNA assay and the testing for fetus fractions to ensure an improved laboratory-to-laboratory harmonization [1-6].

NIPT is fast becoming an essential and preferred way of analyzing cell-free DNA. The highly accurate diagnosis of trisomies 21, 18, and 13 is most popular amongst patients, but the expanding ability of NIPT techniques to also detect such things as sex chromosome aneuploidies, microdeletions (MPDs) and to measure non-human material such as the Y chromosome offer increased utility and corresponding rising patient uptake [1-4]. NIPT, being non-invasive, offers a clear advantage over invasive testing for fetal aneuploidies and is thus set to become a routine part of care. There are several reasons why invasive testing is still accepted; whether it's a patient choice or sequencing failure to give results, a discussion and a working through to inform patients in an informative time of possible next steps for care is essential in all these circumstances. Of particular focus by us, dilation and curettage can sometimes be due to chromosomal aberrations and be indicative of a thyroid pregnancy or occasionally seen in mols or PMPs, which need active management [7-11].

Background of Non-Invasive Prenatal Testing (NIPT)

Non-invasive prenatal testing (NIPT) has been one of the most promising tools for prenatal care in recent years, and due to its success in detecting fetal aneuploidies, it has effectively reduced the number of invasive tests. The most important advantage of the method is that it can provide reliable results without the risk of miscarriage typical for invasive tests [10-12]. We want to demonstrate this method's increasing introduction rate and known clinical use by reporting the results of the 20,626 consecutive independent clinical cases performed at our centers. The result of this study convinced the facts in favor of its introduction in clinical use. It confirmed the possibility of extending this method to screen many more chromosomal pathologies and monogenic diseases. The increasing market diffusion of this technology has rapidly changed clinical approaches in counseling pregnant invasive tests, reducing the indication for these tests. Tests are performed on more than 20,000 pregnant women and demonstrate a high technical performance, confirming that, in an environment of mature implementation, the real-world sensitivity and specificity recently reported in population-based studies can be easily obtained [10-12]. Our huge sample confirms that the meager rate of low fetal fraction, about 1.5%, fully supports the extension of the use of this technology in the screening of many different chromosomal pathologies and monogenic diseases, with no accuracy loss [11-14]. Furthermore, the significantly reduced inappropriate results and increased diagnostic accuracy for the most common occurrence of false-negative and false-positive results usually observed in healthy screening populations highlighted with the analysis of the personalized risk assessment informed us about the future introduction of these personalized diagnostic test results will be requested and a fast test based on pre-existing country-specific databases of no matter the disease- and the pregnancy-related cases must be implemented promptly [11-14].

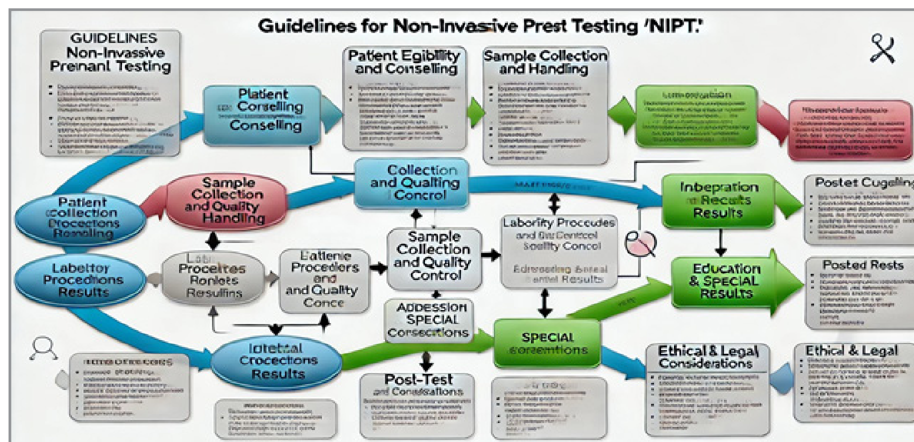

Figure 1: This flowchart provides a comprehensive overview of the guidelines for Non-Invasive Prenatal Testing (NIPT), designed to ensure NIPT's effective and ethical use in clinical practice. It is divided into several key sections, each addressing critical aspects of the testing process.

Patient Eligibility and Counseling

- **Patient Eligibility:** Identify pregnant women who are at increased risk for fetal chromosomal abnormalities, such as those with advanced maternal age, abnormal ultrasound findings, positive serum screen results, or a history of chromosomal abnormalities. Ensure NIPT is offered to eligible patients as part of their prenatal care options.
- **Pre-Test Counseling:** Provide comprehensive counseling to explain NIPT's purpose, benefits, and limitations. Discuss potential outcomes, including the possibility of false-positive and false-negative results. Emphasize the importance of confirmatory testing if NIPT results indicate potential abnormalities.

Sample Collection and Handling

- **Collection Protocol:** Train healthcare providers on the correct technique for blood sample collection using standardized collection kits. Ensure the use of appropriate tubes and adherence to proper collection procedures to avoid contamination and degradation.
- **Handling and Transportation:** Implement strict protocols for handling and transporting samples to maintain integrity. Ensure samples are kept at recommended temperatures and transported to the testing laboratory promptly.

Laboratory Procedures and Quality Control

- **Standardized Procedures:** Laboratories should use validated and standardized DNA extraction, sequencing, and analysis protocols to ensure consistency and reliability.
- **Quality Control:** Implement robust quality control measures, including regular calibration of equipment, use of internal controls, and participation in external proficiency testing programs.

Interpretation of Results

- Analytical Validation: Ensure the laboratory has validated its sensitivity, specificity, and accuracy testing methods.
- Interpretive Guidelines: Develop clear guidelines for interpreting NIPT results, considering factors such as confined placental mosaicism (CPM) and maternal mosaicism.

- Reporting: Report results clearly and concisely, indicating the likelihood of chromosomal abnormalities and the need for further confirmatory testing if necessary.

Post-Test Counseling and Follow-Up

- **Positive Results:** Provide genetic counseling to discuss positive NIPT findings and the next steps, including the option for invasive confirmatory testing (e.g., amniocentesis or chorionic villus sampling (CVS)).
- **Negative Results:** Reassure patients with negative results while explaining that NIPT does not detect all genetic conditions.
- **Uninterpretable Results:** Recommend a repeat test or alternative diagnostic procedures for cases with inconclusive or uninterpretable results.

Addressing Special Cases

- **Multiple Pregnancies:** Special consideration is needed for interpreting NIPT results in twin or higher-order multiple pregnancies.
- **Maternal Factors:** Be aware of maternal conditions, such as mosaicism or neoplasms, that could affect NIPT results. Provide appropriate counseling and follow-up for such cases.

Education and Training

- **Continuous Education:** Provide ongoing education and training for healthcare providers on NIPT's latest advancements and best practices.
- **Patient Education:** Develop educational materials to help patients understand NIPT's benefits and limitations.

Ethical and Legal Considerations

- **Informed Consent:** Ensure informed consent is obtained from all patients undergoing NIPT, clearly explaining the potential outcomes and implications.
- **Confidentiality:** Maintain strict confidentiality of patient information and test results by legal and ethical guidelines.

Summary

The flowchart visually represents the comprehensive guidelines for NIPT, ensuring that all aspects, from patient eligibility and sample handling to result interpretation and ethical considerations, are covered. By following these guidelines, healthcare providers and laboratories can enhance NIPT's accuracy, reliability, and ethical use, ultimately improving prenatal care and outcomes for expectant mothers and their families.

Significance of Accurate Sample Collection

In conclusion, the quality of CF-DNA is decisive for the accuracy of NIPT. Fetal mosaicism has a significant influence on the sensitivity of NIPT. Not only the pregnant women should be required to be tested again, but also amniotic fluid prenatal diagnosis can be considered to distinguish the true and false positive results of NIPT. In addition, attention should be paid to the habeas corpus test and genetic metabolic screening for the high-risk NIPT groups. The Get Checked NIPT should test multiple actively motile sperms since the X/Y different ratio of the false positive group largely corresponds to the other sex ratio of the genome, which has been noted similarly as that in the population autosomes; such a sex chromosome mismatched test result could be mainly due to mosaic chromosome maldistribution during spermatogenesis or a trisomic inner cell mass during IVF laboratory culture [5, 11-15]. Moreover, the pulsing of hysteresis drops in Nano-constrictive chips raises the difficulty for one chromosome to move faster than the other (15,16,17). Preventive prenatal medicine and prenatal genetic diagnostics are becoming increasingly popular in clinical medicine. According to medical guidelines, women who undergo screening tests can use invasive chorion villus sampling (CVS) and amniocentesis tests for genetic diagnosis. However, invasive prenatal testing can increase the risk of miscarriage, threaten the health of pregnant women, and increase the cost of medical treatments. In a clinical setting, cell-free fetal DNA (CF-DNA) from maternal plasma plays a vital role in non-invasive prenatal databases [15-17]. The previous study conducted observational cohort research to investigate the Get Checked NIPT's predictive performance and potential test failures in a single-center experience. NIPT test results data were summarized, and the specificity (Sp), sensitivity (Se), positive predictive value (PPV), and negative predictive value (NPV) were calculated for the four significant chromosomes, 13, 18, 21, and Y. The results suggest that Get Checked may be an effective tool for testing fetal aneuploidy and some sub-chromosomal aberrations. In addition, high-quality and abundant off-DNA is protected in samples stored at four °C for eight hours [4, 5, 15-17].

Types of Sample Errors

Non-UPDs can occur in three ways: through a new-origin de novo maternal chromosome copy changes (pedia non-UPD), by paternal-origin changes, or arising from post-zygotic mitotic errors after conceptual generation (postzygotic non-UPD). Parent-derived changes typically exhibit age-related effects, such as deletions in the terminal regions of chromosomes and all chromosomes' peripheral regions. Usually, abnormalities in paternal chromosomes lead to de novo chromosome aberrations. However, in some exceptional circumstances, paternal elements may re-balance such karyotype-changing processes, leaving the child clinically normal. This phenomenon indicates that parental terminal segmental deletions and parent-involved large rearrangements are not the product of any lethal process. Moreover, it is of no vitality disadvantage to the host. If there have been deletions or inversions involving imbalances only during a post-zygotic mitotic division, normal-looking individuals free from any relevant clinical signs will not have any subsequent difficulties. Although cell-free fetal DNA is highly accurate for detecting common fetal aneuploidies, it cannot distinguish between these and maternal variants or germline copy number changes [18-20]. Here, we refer to any abnormal call related to copy number changes in the fetus, which are non-UPD type, as abnormal NIPT results (AR) (13). Abdominal AR may also be caused by 'side effects' in maternal copies and fetal anomaly combating or recurring cell-line issues [19-21]. Side effects are identified as recurrent chromosome segments when comparing pregnancy cells with parent ones or healthy control individuals with somatic cells in blood. These effects typically involve the tip or centromeric regions and are found in blood. The combative cell-line issue refers to two kinds of cells in the body with the same karyotype. An existing regular cell line shadows that of the abnormal-appearing aneuploid one, leading to an abnormal visual karyotype. During fetal aneuploidy testing, a normal karyotype is likely obtained if fetal-maternal cells are separated and G-banded after cultured. Based on the ethology, the triploidites above can be divided into true-UPD and non-UPD [19-21].

Table 1: Common Sample Errors in Get Checked NIPT (Non-Invasive Prenatal Testing)

Sample Error	Description	Impact	Mitigation Strategies
Insufficient Fetal Fraction	Fetal DNA in the maternal blood sample is below the required threshold.	This may lead to inconclusive or inaccurate test results.	Ensure proper gestational age for testing; repeat sampling if necessary.
Sample Contamination	Presence of external DNA contaminants in the sample.	It can cause false positives or false negatives, leading to incorrect diagnosis.	Strict adherence to sterile techniques, proper handling, and processing protocols.
Hemolysis	Breakdown of red blood cells in the sample, releasing cellular contents.	It may interfere with DNA extraction and amplification, affecting test accuracy.	Gentle blood draw techniques prompt the processing of samples.
Improper Sample Collection	Incorrect collection techniques, such as wrong blood tube or insufficient volume.	This can result in sample rejection or inadequate DNA yield, leading to test failure.	Training for phlebotomists on correct collection procedures, proper labeling, and sufficient sample volume.
Delayed Sample Processing	The time lag between sample collection and processing.	DNA degradation over time, potentially reducing test accuracy.	Timely transportation and sample processing, use stabilizing agents if delays are unavoidable.
Improper Storage Conditions	Exposure to extreme temperatures or improper storage.	DNA degradation, affecting test reliability.	Maintain samples at recommended temperatures, avoid freeze-thaw cycles, and use appropriate storage containers.
Technical Errors	Errors during DNA extraction, amplification, or sequencing.	This can lead to inaccurate or failed test results.	Regular maintenance and calibration of equipment, adherence to validated protocols, and quality control checks.

Contamination

The most common laboratory errors are %Hb contamination and minute Hb contamination. These are the only methods susceptible to %Hb; therefore, the laboratory error rate will be proportionally much higher if only %Hb is measured. Molecular results are somewhat less affected by minute Hb contamination as seen in two of Continue reading Dublin pilot of non-invasive prenatal DNA testing – report of a small study five cases examined but for %Hb to affect this kind of molecular testing a large part of the DNA will be degraded as well (gross Hb + +) explaining the late peak in these cases. In some cases, the QBPCR shows an extra peak at the same base position as our central peak; however, it has a peak time roughly two weeks later. Due to it being from the same base, we assume that this is a slightly more extensive rearrangement of the original peak, and in Figure 1, the extra peak is now barely visible due to our peak being even more minor. [qsa: de1375dc-a180-408c-a6ca-4af2a340b10c]. The most common cause of an abnormal DNA result is test failures due to sample quality [qsa: 99161059-1d40-446e-b495-8390e8ae27e5], either very low DNA or Hb/other contamination. Most failures are at the level of the sample collection, but about 10% are due to laboratory errors [22, 23].

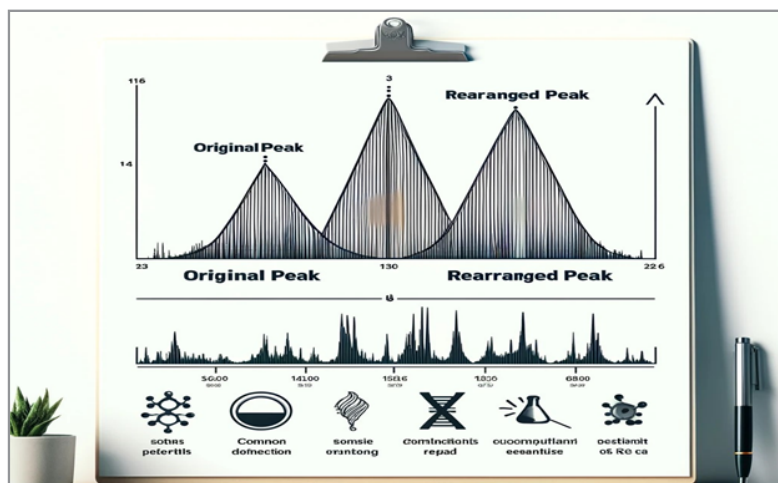

Figure 2: shows the 'Original Peak' and the 'Rearranged Peak,' along with a list of common causes of abnormal DNA results such as 'Low DNA Quality' and 'Contamination.'

Insufficient Fetal Fraction

The recently developed screening software, reported to outperform most existing tools, utilizes a measurement (called Q-score) to estimate FF and fetal cell-free DNA (cfDNA) concentration in maternal plasma, respectively. Looking ahead in molecular genomics, optimizing robust methods for FF estimation and fetal cfDNA concentration and, consequently, aneuploidy estimates, all in a unified, seamless manner, would be worthwhile. Collecting genome-wide SNP-chip data in the same plasma samples would be very helpful in understanding their impact on FF measurement and chromosome aneuploidy screening. Moreover, such detailed insights must continue to be reported in the literature. Typically, an "insufficient fetal fraction" (IFF) is the one major contributory factor to getting an "unreportable" or "no-call" result [22, 23]. Maternal weight (low and high) and blood samples drawn at early gestational age are the prominent reasons for variation in FFs. As shown in multiple studies, the correlation between FF and factors such as gestational age and BMI does not necessitate the strict implementation of universal thresholds for FF; instead, incorporating secondary algorithms and QC features in the screening software could be considered a better strategy [22, 23].

Impact of Sample Errors on Test Results

It is important to clarify at this point that samples that fail to sequence for non-invasive prenatal testing (NIPT) have two distinctively different reasons for failure: those that genuinely contain no cell-free DNA and those in which the DNA concentrations are too dilute to sequence reliably [24]. This distinction is sometimes mislabeled as a fetal fraction (i.e., the content of cell-free DNA arising from the fetus) when non-fraction-related reasons for failure are known to be significant. Although the authors recognize that cell-free fetal DNA can be responsible for samples with a genuinely meager fetal fraction (so-called fetal fraction failures), it is important to point out that the cell-free DNA is usually plastically dissipating a shallow fetal fractional signal to background, resulting in this signal being easily misinterpreted as noise since it is tiny and inaccurate, and that all too often, this type of a NIPT failure is seen; as the "genuine" fetal fraction of that sample improves (25). In this manuscript, this paper will use the terms "real failures" or very dilute sequence "low ff" mixture failures to emphasize that we are focusing on the technical reasons for how a sample can fail NIPT rather than just the content or capacity of cell-free fetal DNA in that failure. It has been several years since the NIPT technique exploded onto the prenatal testing scene, enabling thousands of expectant mothers with no prior risk factors to undergo a comparative and non-invasive prenatal test, thus preventing a considerable amount of the serious and unnecessary morbidity traditionally been, there is no comparative data to establish the performance metrics of non-invasive prenatal test (NIPT) technology, thereby promoting widespread aneuploidy screening of a previously low-risk population. Since then, a variety of real-world data from different populations and different errors has been generated that gives us an approximation of the overall accuracy of the ultra-high-throughput screens, and there have been some common ways in which samples can fail to provide high-quality data [24-26].

Preventive Measures for Sample Errors

We show that errors in the allele frequency calculation, appearing as deviations from 0% and 100% of parental alleles, are standard in prenatal diagnostics samples and are mostly related to the damage to or decomposition of DNA. Among all genetic changes, however, errors in the fragment size call identification had the most significant impact on creating a molecular karyotype. Eighty-six errors in samples showed that controlling and preventing sample errors at the pre-analytical stage is essential [15]. Therefore, we focused our analysis on the factors that could influence the final interpretation (e.g., the total amount of cfDNA, the total amount of transferred DNA, and the quality of the cfDNA used for library preparation) and the possible correlations between them. It turned out that using an additional control fragment, e.g., a 132-base pair fragment characteristic for CFTR, may help limit the errors in fragment size identification to a minimum [15, 27]. Non-invasive prenatal testing (NIPT) is a screening tool for the early diagnosis of fetal trisomies. An increasing number of laboratories are using Next Generation Sequencing and statistical algorithms to analyze maternal plasma cf-DNA. However, studies dealing with the causes of sample errors in targeted sequencing of small DNA fragments are mainly concerned with genomic DNA. Changed properties of cfDNA compared to the whole genome, probably resulting from its origin in trophoblastic cells, could affect the quality of molecular karyotype identification. This study aimed to evaluate the most common errors resulting from biochemical properties of DNA in pre-analytical steps of NIPT by using a set of reference samples (NimuP) representing cfDNA-derived control samples and under conditions of physiological pregnancy (P3 and P4) [28]. Because of the immense potential for positive predictive value, there is an exponential increase in CMA deviation, and more people are having microarray. Here, results will come back with VUS or variants of unknown significance, and the dilemma for counseling and reproductive planning can be similarly overwhelming to some couples, depending on their psychosocial makeup. Couples desiring to reduce their chance of having a child with a genetic condition may choose to undergo prenatal testing (PNT). PNT can inform about the health of the current pregnancy and the future reproductive risk. For instance, results may reveal a fetal genetic condition, which allows parents to decide whether they will terminate the pregnancy. In cases where the PNT result is typical, the family is reassured and can move forward in the pregnancy. Correctly interpreting prenatal genetic results and communicating that information effectively is critical for helping families make informed decisions about pregnancy management. This article is protected by copyright. All rights reserved [29, 30].

Conclusion

Non-Invasive Prenatal Testing (NIPT) has become the standard of care medical test during pregnancy, and approximately 15% of pregnant women can now access NIPT. However, there is an urgent need to establish guidelines for genetic counseling of NIPT results by understanding the individual parameters, including the false favorable rates. In addition to this, there are an increasing number of challenges and errors that can arise in the interpretation of NIPT, including the identification of male or maternal origin sex chromosome quaternary trisomy confined placental mosaicism (moXq/Triploidy) and the unintentional test of a maternal neoplasm. Addressing these challenges through comprehensive guidelines and enhanced interpretation protocols will improve the accuracy and reliability of NIPT, ensuring better outcomes for expectant mothers and their healthcare providers.

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