

Review

Challenges and Ethical Issues Related to Non-Invasive Prenatal Testing (NIPT)

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Abstract

Non-invasive prenatal testing (NIPT) is now standard in prenatal care in many countries, even though it was introduced only about 15 years ago. Due to its rapid adoption into decades-old prenatal care plans, gynecologists, obstetricians, and the general public still struggle to understand the possibilities, benefits, and limitations of NIPT. The biggest challenge facing NIPT is that comprehensive training for healthcare professionals and independent, unbiased information for pregnant women and their families about NIPT is still difficult to access and often not adequately provided. Misunderstandings are common, such as the assumption by families who receive a negative test result that this means “The baby you are expecting will be healthy!” Therefore, the background, advantages, and limitations of NIPT are reviewed and discussed here. If users were informed in detail about the limitations of NIPT, many problems arising from false expectations and suggestions about the test's potential could be avoided. Ethical aspects of NIPT are discussed, before all the data and arguments presented lead to the conclusion that NIPT is a promising tool for prenatal care, but still needs to find its evidence-based place among other prenatal care applications.

Keywords

Non-invasive prenatal testing (NIPT); pregnant woman perspective; false-positive NIPT results; false-negative NIPT results; education programs



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1. Introduction

For the first time in human history, since about the 1970s, something that was previously only science fiction has become possible: it is now commonplace for pregnant women to obtain information about the health and genetic constitution of their unborn child [1, 2]. Besides the advances in non-invasive sonographic visualization [3], at that time (cyto)genetics started to provide reliable information about the genetic status of an individual developing child [1]. In prenatal diagnostics, invasive or non-invasive procedures can be used [1-3]. Invasive procedures involve analyzing placental or fetal tissue; this provides clear results if the unborn child has the specific genetic disorder for which it was tested. However, abnormal results in placental tissue like by CVS (chronic villi sampling) should be verified by amniocentesis [1-3]. Invasive tests also include a certain risk for the unborn child: for example, while the risk of miscarriage associated with amniocentesis was 1-3% in the 1990s, it is now only 0.1-0.3% in Western countries [2]. However, the risk of abortion associated with invasive procedures has driven the development of non-invasive tests, such as: (i) ultrasound, (ii) maternal blood testing for protein markers, (iii) first trimester screening (FTS, i.e., a combination of i and ii), and (iv) the latest tool, non-invasive prenatal testing (NIPT) [2]. All of these non-invasive procedures have one thing in common: they

- a. do not examine really fetal-derived cells,
- b. are purely doing risk assessment,
- c. only provide risk figures, and
- d. are unable to diagnose or rule out a specific genetic disorder with 100% certainty.

NIPT was introduced between 1997 [4] and 2013 [5]; it is also sometimes called non-invasive prenatal screening (NIPS) or even non-invasive prenatal diagnostics (NIPD). The latter designation should never be applied, as NIPT is not a diagnostic but a screening test [2]. It has to be mentioned that manufacturers of NIPT kits have marketed it, at least in the beginning, as a 'new diagnostic prenatal testing tool' [6].

In NIPT procedures, so-called "cell-free fetal DNA = cffDNA" is examined from the maternal serum [4], where it can be reliably detected from the 10th week of gestation. cffDNA is particularly well-suited for checking the current pregnancy exclusively, as it is removed from maternal blood shortly after the birth [2]. As we recently wrote, the clear advantages of NIPT are that it

- I. can be used earlier in pregnancy than other tests;
- II. has the potential to reach population groups that do not have access to centers offering invasive diagnostic procedures;
- III. can rule out and detect trisomy 21 with the highest probability of all non-invasive procedures—the positive predictive value (PPV) of a NIPT indicating trisomy 21 is >99% (according to manufacturer's statements and majority of published NIPT-related articles);
- IV. can provide psychological relief for a concerned pregnant woman if the NIPT result is normal, given that the rate of false-negative results is low; and
- V. can lead to early termination of pregnancy if a genetic disorder is detected using NIPT [2].

However, NIPT has been introduced remarkably quickly worldwide and has unusually high financial implications [7]. It therefore seems necessary to highlight and discuss the challenges and

ethical issues of NIPT for users, i.e., pregnant women and their families, and the MDs (medical doctors) as gynecologists and obstetricians.

2. Challenges and Issues

NIPT providers and most human genetic societies strongly recommend offering NIPT always alongside pre- and post-test genetic counselling [2]. During these sessions, the couple is informed about how the test works, its advantages and pitfalls, and the consequences of positive and negative results. This also includes information about some shortcuts and challenges, as listed below.

The author of this article found that many gynecologists, obstetricians, and midwives (in Germany and other European countries, such as Austria, Croatia, Portugal, Serbia, Spain, and others) were not aware of all the listed peculiarities when asked about them. Therefore, the main challenge of NIPT is to inform and educate specialists and the public as effectively as possible on the issues discussed here. Specific challenges are highlighted after each relevant paragraph, and examples are provided in Tables for problems which came up in connection with the discussed NIPT-related challenge.

2.1 Technical Challenges

The NIPT test is based on next-generation sequencing (NGS), a relatively new approach [2, 8, 9]. Understanding NGS in detail may not be necessary to explain how NIPT works. Still, several points can lead to problems for MDs, consultants, and the public if not considered at least.

2.1.1 What Is the Significance of the Presence of Numerous NIPT Variants?

From a technical point of view, it is important to understand that dozens of variants of the test are described in the NIPT literature, but these are not always easy to distinguish [2, 8-11]:

- a. NIPT can be performed based on whole genome sequencing (WGS), which itself has at least three technical subtypes and/or can be combined with other approaches [2]. Consequently, triploidy can only be characterized by one type of NIPT, i.e., exclusively when a WGS platform based on a single nucleotide polymorphism (SNP) is used [10, 11].

Challenge 1: Physicians must be trained in the fundamentals of the various types of NIPT platforms available. Only with this knowledge will they be able to inform those they advise about the technical details of the tests they offer.

- b. NIPT can be done with commercial or in-house kits. In either situation, the technical details required for test reproducibility or for determining cut-off rates are sometimes not publicly available, or are at least very difficult to access [2, 8, 12, 13].

Challenge 2: Physicians should only offer NIPT sets if their providers specify clear cut-off rates and if the data collection is traceable.

- c. Genomic regions accessed by NIPT may cover the entire human genome for copy number variations, or only the most common second-trimester trisomies (i.e., #13, #18, #21, maybe X and Y, as well). Besides, selected microdeletion syndromes or other genetic alterations can be tested [2].

Challenge 3: The physician must clearly define the scope of the NIPT set and carefully discuss it with the pregnant couple. The test must be adapted to the couple's individual needs.

For a practical example of the consequences of the first three technical NIPT challenges, see Table 1 – Example 1.

Table 1 Four practical examples for the technical challenges of NIPT.

Example 1	Case reported by genetic counselors at the author's institute (Jena, Germany): A woman in the middle of her pregnancy had a fetus with severe sonographic findings (among others omphalocele and hygroma colli); NIPT was performed in 11th week of pregnancy, which ruled out trisomy 13, 18, and 21. At 16 weeks of pregnancy, amniocentesis revealed a karyotype of 69,XXX, i.e., triploidy. The consultant could not comprehend why trisomy 13, 18 and 21 were excluded when at the same time trisomy of complete chromosome complement was present. Apparently, the attending physician (from another institution in Germany) did not explain that it a SNP-WGS-based test was used, which triploidy could not be picked up due to technical constraints.
Example 2	In a blog post by the Australian Nuffield Council on Bioethics, which is no longer available, containing over 400 contributions from women who had good or bad experiences with NIPT [14] no post was present which indicated that any of the 400 women who posted there was aware of the fact that placental DNA is accessed. They all were convinced that "fetal DNA" was studied. This implies that this was not known to the doctors offering the test, or at least was not communicated by them.
Example 3	A woman cited in [14] reports on an avoidable misunderstanding of a no-call result as follows: "I had the NIPT done at week 10 and the result was 'high risk' for trisomy, but my fetal fraction was only 2.7%. So, I received a 'high risk' result based solely on an equation (i.e. a statistical probability) that apparently took into account my advanced age and other factors. NO DNA ANALYSIS WAS USED TO DETERMINE THIS. This was not clear to me at first, and my doctor did not explain it to me, so I was devastated and feared the worst. I had a second blood test done and repeated the test two weeks after the first test, and I received exactly the same result. It was only when I went to see a specialist in maternal-fetal medicine that I was told why the test results are very misleading in my case. The doctor reported that a low fetal proportion is not unusual in women who are overweight or obese, which applies to me. I had an ultrasound scan at week 14 and all the measurements of the neck were normal" [14].
Example 4	Another woman [14] stated the following: "We received a NIPT brochure from our doctor that indicated a PPV of 50% (i.e., 1 in 2 positive screening results is a false positive result) for Edwards syndrome if the mother is younger than 35 years of age. Had we thought about it more carefully, we would have realized that a PPV of 50% is a very low value and that we would most likely have opted for amniocentesis to obtain confirmation." This suggests that patient information gave unclear data for what PPV means, and this led to problems for the correct interpretation on reliability of NIPT.

2.1.2 How Is Cell-Free Fetal DNA (cffDNA) Defined?

cffDNA is defined as “cell-free fetal DNA”, which is to say the least, a misleading designation. In the first paper reporting the discovery of this type of cell-free DNA (cfDNA), it was noted that it originates from the placenta, i.e., the trophoblast [2]. Accordingly, it does not originate from the product of conception (POC).

For sure, the fetus and placenta develop during embryogenesis from a single fertilized egg, the zygote. Nonetheless, the separation of the future placenta and embryo cells occurs at an early stage of pregnancy, occurring just a few days after fertilization. It is therefore not surprising that the placenta and fetus do not always have identical genetic makeup. Invasive diagnostic procedures using CVS indicate that in the 10th week of pregnancy, 2 to 4% of POCs have discordant placental and fetal karyotypes [12]. For a practical example of the consequences of these technical NIPT challenges, see Table 1 – Example 2.

Challenge 4: Physicians must highlight the mis-labelling of cell-free placental DNA as cell-free fetal DNA. Only if this is done in a comprehensible way will specialists later be able to explain the biological challenge described below, known as “confined placental mosaicism” (see 2.2.4.).

2.1.3 What Is the Definition of “Fetal Fraction”?

“cffDNA” constitutes merely one of two types of cfDNA present in the blood serum of a pregnant woman. The predominant source of cfDNA is apoptotic cells from the pregnant woman’s body. The “cffDNA” originating from the placenta accounts for between 3% of cfDNA in the 5th week of pregnancy and ~30% in the 40th week of pregnancy [14] and is referred to as the “fetal fraction.” In order to perform a meaningful NIPT, fetal fraction must comprise 4% or more of cfDNA [15]. If the fetal fraction in NIPT is too low, a “no-call result” is obtained, i.e., it is “not-meaningful” or not interpretable. In this case, NIPT providers usually offer a repeat test at no extra cost.

Several reasons can lead to a no-call result: (i) a small placenta or preeclampsia can be present [16], the fetus may have an intrauterine growth restriction, and in the worst case, it may be a hint of an expected premature birth [2]. A low fetal fraction is increasingly also due to maternal obesity, especially in ‘first world countries’—here, the ratio of cffDNA to maternal cfDNA shifts to the detriment of cffDNA. In affected women with high BMI (= body mass index), the NIPT error rate is up to 24.3% [17]; see Table 1 – Example 3.

Challenge 5: It is essential to inform pregnant women and their partners about the possibility of obtaining a no-call result during pretest counseling. This will help to prevent any potential distress or anxiety that may arise later on.

2.1.4 What Does Positive Predictive Value Mean?

To report the reliability of NIPT, the positive predictive value (PPV) has been chosen. According to Ref. [18], a PPV is “the ratio of patients who are actually diagnosed as positive to all patients with positive test results (including healthy subjects who were incorrectly diagnosed as patients). This property can predict how likely it is that someone with a positive test result is actually a patient.” It is often claimed that NIPT for trisomy 21 has a PPV of 0.99, according to the manufacturer’s

statements and the majority of published NIPT-related articles. However, in a 2022 review, the PPV value for trisomy 21 was shown to be lower, i.e., 0.95 [8]. This indicates that 9.8% of pregnancies in which trisomy 21 was initially detected are actually false positives (Table 2). The PPVs for sex chromosome aberrations (SCAs) and other trisomies, such as 13, 18, and all other rare autosomal trisomies, are between 0.54 and 0.84 (see also [19] (Table 2)). The PPVs for microdeletion syndromes are even worse [20]. Table 2 shows in detail that, for example, a PPV of 0.84 for trisomy 18 means that 18.5% of women who receive a positive NIPT result actually receive a false positive result. The significance and calculation of PPVs are unclear even to experts (see [21]); see Table 1 – Example 4.

Challenge 6: When recommending a NIPT, the physician must explain the PPV, its significance, and how many cases are false positive results.

Table 2 PPVs and underlying data taken from [14].

Chromosomal aberration	NIPT-positive cases	NIPT-false-positive cases absolute numbers/%	PPV calculated acc. to [14]
Trisomy 13	687	304/44.3	0.69
Trisomy 18	1447	268/18.5	0.84
Trisomy 21	5283	517/9.8	0.95
Rare autosomal trisomies	342	289/84.5	0.54
Sex-chromosome aberrations	1192	661/55.5	0.64

2.2 Biological Challenges

The NIPT is based on cell-free placental DNA (incorrectly referred to as “cffDNA”) that floats in blood together with maternal cfDNA. Still, in a pregnant woman's blood serum, other cfDNA populations can also be detected. These may be cffDNA due to

- A. a second fetus (twin pregnancy – see 2.3.3);
- B. an already deceased second fetus (see 2.2.1 – vanishing twin);
- C. additional maternal cfDNA with gains or losses of copy numbers originating from an yet unrecognized malignancy (see 2.2.2) and
- D. additional maternal cfDNA with gains or losses of copy numbers originating from a cryptic maternal (blood) mosaic in (see 2.2.3);
- E. a placenta with more than one cell population with or without chromosomal abnormalities that do not necessarily represent the fetal karyotype (see 2.2.4).

All of these biological facts must be known to NIPT consumers and health practitioners so that they can correctly understand the significance of normal and abnormal test results, as explained below.

2.2.1 What Are the Consequences of a Vanishing Twin for the NIPT Test?

Twins occur naturally in about one in 250 births [22]. However, in about one-third of early twin pregnancies, one of the embryos dies in the womb [23]. This dead embryo/fetus (and its placenta) can be absorbed by the mother's body without the pregnant woman noticing. Nevertheless, this apoptotic process of the disappearing twin leads to high rates of “cffDNA,” and this embryo/fetus

may not have survived due to a chromosomal abnormality [24]. The latter can now be detected in the NIPT and mistakenly attributed to the surviving single child [10, 25]; see Table 3 – Example 5.

Challenge 7: Pre-test counseling should include detailed explanations that false positive NIPT results can occur and why—and that this may also be due to the presence of a vanishing twin. In addition, an abnormal NIPT result must be cause for detailed ultrasound imaging and a search for signs of a potential vanishing twin.

Table 3 Four practical examples for biological challenges of NIPT.

Example 5	As cited in [14] a woman received a call from her doctor informing her that the NIPT had revealed a 1/1 chance of having a baby with Turner syndrome and found out herself: “I had a vanishing twin who made it to week 4, two weeks behind the other, when he was discovered during my ultrasound scan at week 6 and 6 days. He disappeared and was dismissed. I have read that one of the reasons for a false positive result is an aborted twin whose DNA can remain present for up to 16 weeks.” This means: the pregnant woman had to seek explanations for her test results herself and that these were not provided by the doctor’s office performing the NIPT.
Example 6	Case from the author’s laboratory (Jena, Germany): A pregnant woman in her mid-30s underwent NIPT and received a high risk for trisomy 21. The Jena laboratory could not confirm a trisomy 21 in amniocentesis. However, medical history of the pregnant woman indicated that she had been diagnosed with myelodysplastic syndrome. It turned out at other attending physicians that this had developed into acute myeloid leukemia with acquired trisomy 21. The latter was incorrectly attributed to the fetus.
Example 7	The following post ifs from February 2022 [14]: “My NIPT test detected an increased risk of triple X syndrome (47,XXX) in the 12th week of pregnancy. I had never heard of this before, and my doctor said these tests are 99% accurate. Three days after I found out, I met with a general counselor who entered some numbers into a computer program and told me that the probability of the NIPT test result for trisomy X being a false positive is 74%. (...) My gynecologist said I shouldn’t get my hopes up, but the genetic counselor’s calculation comes to a contradictory conclusion. Can anyone share their experience with triple X syndrome detected by NIPT?” This highlights again the importance of high-quality genetic counseling being provided prior to the test. Here lacked the understanding for the reliability of NIPT in relation to the various conditions tested for by MDs.
Example 8	Several cases such as the following were investigated in the author’s laboratory, which is a molecular cytogenetic one and asked for checking of NIPT results by in amnion cells: NIPT at 11 weeks of pregnancy indicated for a trisomy 21. Sonography was normal and amniocentesis was performed at 18 weeks of pregnancy. Karyotype revealed a mosaic situation as mos 47,XN,+mar/46,XN, and the small supernumerary marker chromosome (sSMC) was characterized by molecular cytogenetics as an inv dup(21)(q11.2). Thus, it can be suggested that originally the zygote carried a trisomy 21, which was rescued during the first cell divisions. This means one of the three chromosomes 21 was either removed from the cell, or only incompletely degraded to form an sSMC 21. During development cells with a normal karyotype or with the sSMC were included into the later fetus, while trisomic cells remained in the placenta. Placenta cells with trisomy became apoptotic and ‘cffDNA’ moved into maternal blood. NIPT thus detected a hint on a trisomy 21 confined to placenta. Normal children were later born in about 10 cases like this; and comparable cases can be found in the literature as well [26].

2.2.2 Why Can NIPT Detect a Maternal Malignancy?

Cancer typically occurs in older people. However, younger individuals can also suffer from malignant diseases [27]. Since NIPT tests the cfDNA of pregnant women for chromosomal abnormalities, there is also a (small) chance that this procedure will detect chromosomal abnormalities originating from an undiagnosed tumor in the mother. According to a recent study, this probability is 0.02% [27]; see Table 3 – Example 6.

Challenge 8: It is debatable whether counseling prior to testing should also include this rare possibility of detecting a malignant disease in the mother. However, it is indisputable that every MD involved in NIPT testing must be informed of this possibility, as it is merely a variant of liquid biopsy [28, 29].

2.2.3 Why Are the Detection Rates for Sex Chromosome Aberrations (SCAs) So Low in NIPT?

More than half (55.5%) of SCAs detected by NIPT are false positives (Table 2). One reason for this is that some pregnant women have mosaic sex chromosomal conditions in peripheral blood, at least [30]. This means that 35-40% of false-positive SCA results occur in women with a karyotype of mos 46,XX/45,X/47,XXX [31]. Since NIPT compares the chromosome-specific DNA with that of the placenta, this condition is incorrectly interpreted as a numerical SCA in the fetus [32]; see Table 3 – Example 7.

Challenge 9: With regard to gender determination in NIPT, country-specific regulations must first be observed. Often sex may not be disclosed before the expiry of a certain period of time [2]. In addition, the counseling prior to the test should point out the biologically determined lower reliability of detecting SCAs compared to trisomies 13, 18, and 21.

2.2.4 What Is the Definition of “Confined Placental Mosaicism”?

Cytogenetic findings obtained from CVS (placental cells) differ from those obtained from amniocytes (fetal cells) in 2-4% of cases [2, 14]. This observation, made in invasive prenatal diagnostics for decades, has been termed confined placental mosaicism (= CPM). What CPM means can be exemplified by the possibility that a trisomy 21 may be limited to the placenta and not be present in the fetus. All conceivable variations between (a) a normal karyotype in the fetus and an aberrant karyotype in all placenta cells or (b) the other way round have been described. Therefore, at least the same range of discrepancies can be expected in NIPT results as in amniocentesis results. Furthermore, the false-positive rates must differ depending on the disease tested (such as trisomy 21 or trisomy 18 – see Table 2).

In early pregnancy, the human genome is highly flexible, if not unstable; in such early embryonic cells, before they develop into the placenta and embryo, mosaicism rates observed for chromosomal abnormalities are high [32]. Furthermore, the mechanisms by which abnormal cells develop predominantly into the placenta rather than the fetus do not yet appear to be fully understood. However, this instability may explain the remarkably high false positive rate for rare autosomal trisomies in NIPT (Table 2). As is well known, CPM is the primary cause of most false-positive and false-negative NIPT results [2]. This biological fact must be kept in mind, as it is the underlying cause of NIPT's false-positive and false-negative results; see Table 3 – Example 8.

Challenge 10: The potential discrepancy between the NIPT results from placental cells and the actual fetal karyotype (CPM) must be highlighted during pre-test counseling.

2.3 Clinical Challenges

Clinical challenges are partly the logical consequence of the above-mentioned technical and biological circumstances. The questions listed below should be addressed during the consultation prior to the test and after receiving the test results.

2.3.1 A normal NIPT Result Does Not Necessarily Guarantee a Healthy Future Baby

As already highlighted elsewhere [2], women who take the NIPT often feel that their future baby is definitely healthy if they receive a negative NIPT result. Accordingly, there is a need to explain that even if a NIPT yields normal results, only 5-10% of the possible adverse events that could lead to a somewhat affected baby are covered [2]. Three to six percent of newborns have serious congenital problems; if this group is taken as 100%, then “a chromosomal disorder is present in ~6%, teratogenic damage in ~7%, and a monogenetic or multigenetic disease in ~8% and ~25%, respectively. For the remaining ~54%, the diagnosis usually remains a lifelong condition attributed to an “idiopathic disorder,” i.e., the cause remains unclear [2]. An example from the literature can be found in Table 4 – Example 9.

Challenge 11: A couple receiving counseling must be made aware in pretest-counseling that a normal NIPT is not a stand-alone test and no diagnostic test. Depending on the individual case and possible family history, further tests may be recommended.

Table 4 Four practical examples for clinical challenges of NIPT.

Example 9	A 32-year-old pregnant woman underwent NIPT with normal results in the 15th week of pregnancy. However, abnormal biochemical test results and severely abnormal sonographic findings were present and confirmed in the 24th and 30th weeks of pregnancy. Finally, chromosome analysis of umbilical cord blood in the 33rd week of pregnancy revealed a mosaic karyotype with trisomy 18 in 61/100 cells, whereupon the pregnancy was terminated in the 34th week of pregnancy. The now examined placenta showed CPM – 33-72% of cells had trisomy 18 (six different areas were studied). Here NIPT was negative, as the overall proportion of trisomic cells in the placenta was below the detection-level. An earlier suspicion of the NIPT result, followed by amniocentesis could have led to another pregnancy management and not such a late termination of the fetus [33].
Example 10	As cited in [14] in December 2021 a pregnant woman reported a false positive NIPT result she received: “I was 38 years old and therefore considered a high-risk patient. My NIPT test showed a 15q deletion (Angelman/Prader-Willi syndrome). I was not informed about the high rate of false positive results. Abortion was recommended to me as a viable option, along with amniocentesis (which I did not accept). My daughter was born completely healthy.” A postnatal test confirmed absence of 15q deletion.
Example 11	In June 2020, a woman pregnant with twins wrote (cited in [14]): “I am currently in the 13th week of a natural twin pregnancy and have just received my NIPT test results, which are unclear in all respects. It is suspected that it has something to do with the 21st

chromosome, and it is believed that a repeat test would only lead to the same result. My extended ultrasound scan in the first trimester and my blood tests were completely normal, so this NIPT test has left all my doctors baffled. The statement that the probability of this particular situation is less than 1% is certainly not very reassuring. Furthermore, I was not even classified as a high-risk patient, and my doctor did not recommend that I have the NIPT test done. I figured that if I had the opportunity to take the test, given the 99% accuracy of the results, it would be more meaningful than any other test I could ever take. I have since had further genetic testing done for myself and have scheduled an amniocentesis for next month. It's hard to imagine how I'll make it through until then without worrying myself sick".

Example 12 The following lengthy post from Australia (published in April 2020 and cited in [14]) illustrates how much tested women crave information that should normally be provided by the doctor offering the test: "We agreed to have the NIPT test done, and a week later the doctor called and asked us to come in as soon as possible to get the results. High risk for trisomy 13; the doctor said the test was accurate and the hospital would contact us within 24 hours to discuss further testing and next steps, but we should be prepared that we had never heard of this condition before, as babies with trisomy 13 do not survive. The wait was agonizing, and we called the hospital every day for four days to get an appointment. Finally, I spoke to a genetic counselor who was wonderful, made an appointment for two weeks later (the referral hadn't come through yet) and suggested doing another ultrasound to give us more information and make the two-week wait easier. Our ultrasound was "perfect," with no signs of trisomy 13. The woman who did the ultrasound still said that the NIPT test was more conclusive than what she could see, but that was a glimmer of hope. When I went back to the doctor, she told us that the ultrasound was not reliable because we were only in the 11th week of pregnancy (at the time of the ultrasound) and that we should prepare for invasive diagnostics. At the first appointment at the hospital, there was a professor, a doctor, and two midwives in the room, and I asked about the reliability of the test and the statistics provided. They said that the test was still relatively new and that not enough was known about it yet, but in their experience, less than 50% of babies in my situation (risk assessment but ultrasound without signs) actually had a genetic disorder. At my second appointment at the hospital, there was another ultrasound and the amniocentesis. The team of doctors and nurses was positive. Two days later, they called with the results and said that the baby did not have trisomy 13, Down syndrome, or Edwards syndrome. To say that we are relieved would be an understatement. When my doctor received more information, she was shocked. I don't feel that we were adequately informed and that we should have been offered counseling before the NIPT test. It was only through the genetic counselor and the hospital that we learned that the NIPT test is a "screening test" and not a "diagnosis." My doctor never mentioned this and assured us that the test was 99% accurate. Before we contacted the genetic counselor, my husband and I considered terminating the pregnancy rather than risking a non-viable pregnancy. I am now in my 17th/18th week and have spent half the time since I found out about my pregnancy with stress and real mental health issues that I have never suffered from before. I know that my doctor did her best with the information she had, but doctors who offer this test need to be better trained and informed."

2.3.2 The Implications of an Abnormal NIPT Result for the Health of Future Offspring Require Further Elucidation

As much as 9.8% to 84.5% of abnormal NIPT results are false positives (Table 2) – these rates vary depending on the disease tested. This constitutes the primary rationale for concluding that an anomalous result in NIPT does not inherently indicate adverse outcomes for the future infant. Furthermore, we recently calculated the incidence of truly positive NIPT results, as well as the prevalence of newborns diagnosed with the corresponding conditions [14]. Notably, this calculation indicated that 90% of the aborted fetuses (by intervention) would have been aborted naturally. The subjects would not have survived birth, and an induced abortion would not have been necessary [34]; see Table 4 – Example 10.

Challenge 12: As demonstrated by others and summarized by us [2, 8, 14], a positive NIPT result for MD means a high level of care for the pregnant woman. In addition to the comprehensive counseling provided before and after the test to address the potential outcomes, including positive test results, it is recommended that subsequent counseling sessions be scheduled to address any remaining inquiries or concerns the woman may have.

2.3.3 Why Not to Test Twin Pregnancies?

Twins occur naturally in only 1/250 births; however, due to the increasing use of artificial insemination, this rate has risen to 1/30 births in the USA [35]. NIPT is therefore increasingly used in these cases. However, a recent study has confirmed that the PPVs, false-positive rates, and unclear results are in line with previous studies and therefore, as stated in [20], NIPT should not be offered in twin pregnancies; see Table 4 – Example 11.

Challenge 13: Physicians should be aware that in twin pregnancies NIPT maybe not as reliable as in singletons, and advise couples accordingly.

2.3.4 Why Proper Counselling Is Really Important for NIPT Testing

As demonstrated by the points and examples previously enumerated, it can consistently be concluded that well-informed counseling for NIPT is important—see also [36]. Certainly, most test users will receive a negative result and feel relieved afterward. However, some of them may experience a rude awakening if a disabled child is born. It is imperative that the treating physician explicitly articulate which diseases can be tested for in the individual NIPT and which are ultimately tested for. In addition, 9.8-84.5% of positive cases are false positives, which must also be conveyed. Furthermore, the latter cases require special attention from the treating physician; see Table 4 – Example 12.

Challenge 14: NIPT can cause relief or anxiety in pregnant women—both of which can mean more work for MDs. This is mainly because the NIPT has not yet become an established part of prenatal care.

2.4 Ethical Issues

NIPT and the aforementioned lack of knowledge about options, abbreviations, potential problems, and technical, biological, and medical challenges already raise numerous ethical questions. In particular, it seems questionable that a test that is clearly not really understood, not only by the general public, consumers, and professional providers, is being used on such a large scale universally. Misunderstandings regarding reliability (keyword: use of the misleading PPV instead of the false positive rate) are just one ethically questionable aspect here. Sadly, NIPT-related publications tend to present the test in the most positive light. The omission of information, such as the fact that a PPV of 0.99 only applies to tests for trisomy 21 and certain groups of pregnant women, is unfortunately found not only in commercials for NIPT but also in scientific articles. In 2019, D'Ambrosio et al. [37] wrote: "NIPT has revolutionized the approach to prenatal diagnosis and remains the superior screening method for common autosomal aneuploidies". If anything, this only applies to the detection of trisomy 21. Yang et al. expressed a similar view in [38]: "Our results suggest that the use of NIPT is becoming increasingly widespread both as a first-line screening tool in the general obstetric population and for screening for sex chromosome abnormalities and copy number variations." As we asked before: "Is this really ethically justified when the false positive rates are between >50 and 95%" [14]? In conclusion, ethical problems associated with the use of a test like NIPT, which is not yet fully developed and not well understood by the general public, raise additional ethical issues, as outlined below.

2.4.1 How Reliable Is the Signed Informed Consent?

All of the above points also raise the question of the extent to which valid informed consent can actually be obtained. This was summarized before [39] like this: "Respect for autonomy requires that informed consent be obtained. From a medical-legal perspective, consent must be voluntary. The person must also be adequately informed about a test or procedure, including the associated risks and benefits. The required scope of information provision is generally determined by what information a reasonable person would expect in that person's situation. From an ethical perspective, however, it is important that the information is understood, not just that a person has received the information required by law. Given the complexity of expanded panels and WGS-NIPT, ensuring understanding means that a lot of time must be invested. (...) It is tempting to respect autonomy by not being paternalistic or directive in counseling and by providing parents with all information from prenatal testing, regardless of its nature. However, this shifts the burden of uncertain results and the resulting fears to the parents. Qualitative and quantitative studies show that parents whose results revealed abnormalities of uncertain significance are more likely to regret their decision. At least some parents would not have consented to the test if they had known what it would mean. The uncertainty of doctors about what these results might actually mean for a future child increased the burden on parents."

2.4.2 Considerations About the Rights of the Unborn

Every prenatal examination raises ethical dilemmas. The unborn child's right to live, as long as biology and health allow this, is considered to be not as important as the mother's right to decide

which child she wants to give birth to [40-42]. This means the fundamental right to life of an unborn child is superseded by other values.

2.4.3 How to Consider Selective Reproduction?

NIPT enables the determination of the gender of the unborn child already at 10-11 weeks of gestation. Since in many countries the birth of a boy is traditionally preferred over the birth of a girl, most countries have introduced legal restrictions to make sex selection more difficult [2, 43]. Nevertheless, the use of NIPT has alarmed organizations dedicated to the promotion of disability rights, as this test could reinforce the trend toward (i) performing selective reproduction, (ii) devaluing the lives of people with Down syndrome, or even (iii) eugenics [40]. These concerns are further exacerbated by publications that conclude NIPT is the most cost-effective strategy for a society to avoid babies with Down syndrome [44, 45]. Others [41] suggest NIPT could be just a first entry point for later testing of unborn children, newborns, and all adults for any diseases. However, this does not appear to be a realistic threat given the problems, limitations, and shortcomings of NIPT and the techniques on which it is based [2]. Some interesting thoughts can be found in a paper by Rehmann-Sutter [46].

2.4.4 What About Social Pressure?

Even before the introduction of NIPT, parents of a child with Down syndrome experienced attacks such as: Could this (the affected child) not have been avoided [47] NIPT and the high expectations of the public regarding its reliability have been shown to increase this social pressure. The pressure to undergo appropriate testing, even with the use of NIPT, and, in the event of a positive test result, the pressure to terminate the pregnancy, is subjectively increasing for “a large minority of pregnant women” [45].

2.4.5 The Issue of Accessibility of NIPT

Based on the (questionable) assumption that NIPT can replace all traditional prenatal care scenarios, there are also “ethical concerns” regarding fairness and inequality in access to this test. While there has been no such debate about funding the first trimester screening program e.g. in Germany [2], there is suddenly great concern that poorer families may not have access to NIPT and that only wealthier families will be able to have the test done; therefore, some people argue that there is an urgent need for government funding of NIPT testing [48-50]. The real ethical issue is not the funding of NIPT by society, but that such a problematic test is administered so frequently and uncritically.

3. Conclusions

It must be noted that in connection with NIPT, there are more technical, biological, and medical challenges than ethical issues. As we have already written in [2]: “The theoretical possibilities of NIPT are promising. However, the problems and limitations must also be taken into account. Overall, NIPT results are not well understood, and the reliability of the data obtained is not well communicated, at least to the physicians ordering the test and the pregnant women undergoing it”. The lack of knowledge on cell-free placental DNA has also been highlighted recently by Yuen et al.

[51]. As Hessel and Henn [52] recently noted: “The fact is that NIPT is considered by many pregnant women to be a standard measure for pregnant women and is performed without question.” This attitude (...) can lead to a rude awakening. Therefore, adequate training and continuing education for physicians who offer NIPT counseling are urgently needed. As discussed elsewhere [8], this can only be achieved through unbiased continuing education programs—not by NIPT providers, but by medical associations or independent researchers.

Author Contributions

Review was drafted and written by TL.

Competing Interests

The author has declared that no competing interests exist.

Data Availability Statement

All data is included in this paper and corresponding references.

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