Non-Invasive Prenatal Testing

Subjects: Nursing

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New technologies such as non-invasive prenatal testing (NIPT), capable of analyzing cell-free fetal DNA in the maternal bloodstream, have become increasingly widespread and available, which has in turn led to ethical and policy challenges that need addressing. NIPT is not yet a diagnostic tool, but can still provide information about fetal genetic characteristics (including sex) very early in pregnancy, and there is no denying that it offers valuable opportunities for pregnant women, particularly those at high risk of having a child with severe genetic disorders or seeking an alternative to invasive prenatal testing. Nonetheless, the ethical, legal and social implications (ELSI) include multiple aspects of informed decision-making, which can entail risks for the individual right to procreative autonomy, in addition to the potential threats posed by sex-selective termination of pregnancy (in light of the information about fetal sex within the first trimester), and the stigmatization and discrimination of disabled individuals.

Keywords: non-invasive prenatal testing ; cell-free fetal DNA ; screening ; aneuploidies ; ethical ; legal and social implications

1. Introduction

Non-invasive prenatal testing (NIPT), also referred to as cell-free DNA (cfDNA) testing and non-invasive prenatal screening (NIPS), is a highly sensitive and specific screening technique, increasingly clinically adopted to assess the risk that the fetus may carry chromosome aneuploidies and, possibly, submicroscopic copy number variations (CNVs) and other genetic conditions [1]. NIPT takes into account fetal DNA fragments resulted from placental trophoblast apoptosis, i.e., programmed cell death [2], flowing through the maternal blood and detectable from the fifth week of gestation.

As the cf-DNA in a pregnant woman is a mixture of genomic DNA fragments of maternal and placental origin (cff-DNA), the fetal fraction represents a critical and limiting factor that seems to be reliably measurable from the tenth week for clinical purposes, when it reaches a proportion of about 10% progressively increasing in the following weeks.

Given its high sensitivity and specificity, the cost-effectiveness of and the absence of risk of pregnancy loss associated with amniocentesis or chorionic villus sampling, NIPT has turned out to be a widespread screening tool for the most common fetal aneuploidy. NIPT, in fact, results in being especially effective in detecting trisomy 21 (Down's syndrome; 99% and 99.92%, respectively), trisomy 18 (Edwards syndrome; 96.8% and 99.85%, respectively), trisomy 13 (Patau syndrome 92.1% and 99.8%, respectively) and sex chromosome aneuploidies (with a lower sensitivity than the previously reported autosomal aneuploidies), with a combined false-positive rate (FPR) of 0.13% [3]. However, NIPT cannot be considered as a "prenatal diagnostic test" but, up to now, a screening tool, albeit a highly valuable one. In fact, the incidence of false-positive results, generally attributable to mosaicisms confined to placental (CPM) or, less frequently, to other conditions such as vanished twin, maternal CNVs, apoptosis of maternal cancer cells and fetal mosaicism, requires an invasive test (preferably, through an amniocentesis) to confirm a positive NIPT result [4]. Such circumstances may occur and, to date, represent the origin of possible discordant test results, failures and contraindications. However, it is expected that technological advances and the involvement of fetal medicine specialists and genetic counsellors, especially in the most complex cases, should allow current limitations to be overcome in the near future.

In the current state of our knowledge and available technical tools, the fact that the cff-DNA concentration is directly proportional to gestational age and inversely proportional to maternal body mass index (BMI) [4] represents a limitation to be kept in mind, and a reason to proceed with caution when proposing this screening method at too early a gestational age (i.e., in the first trimester) or to overweight women, potential causes for a low cff-DNA fraction and, consequently, no-call results or false negative. In that regard, studies accounting for more than 16,000 pregnancies found a low fetal fraction in maternal bloodstream to be linked to a higher risk of fetal aneuploidies [5][6].

The possibility of not having results or to obtain ambiguous results to be confirmed by other methods should be adequately clarified before applying the test, possibly in a prenatal genetic counseling setting to enable informed choices.

In the current practice, the clinical application of NIPT is limited to the screening of the most common fetal aneuploidy and the associated risk assessment. However, in light of the considerable technological advancements in the field and progressively greater affordability of such techniques, NIPT has also begun to be used to test for single-gene disorders [7], as well as for additional and more rare chromosomal disorders [8] and sub-microscopic CNVs [9]. Although further research and validation are needed in order to determine the accuracy in detection rates and false positive and negative rates for these technical and clinical implementations, it is reasonable to predict that in the next few years NIPT will gradually become more applicable and widely adopted to the screening of several more genetic anomalies, including CNVs and single-gene disorders [10].

The suitability of advanced technical tools will involve further changes in clinical practice and, at the same time, will require an equally rapid ability to reflect on the ethical and legal aspects they open up.

2. Non-Invasive Prenatal Testing (NIPT) Ethical, Legal and Social Implications: Maybe Advancing Reproductive Autonomy, But at What Cost?

First introduced in 2011, NIPT was at first offered by private health care providers, and has in recent years been integrated among public healthcare services. In Italy, the NIPT test was introduced in Tuscany in 2019 as a public healthcare tool in the birth path [11].

The increased use of NIPT has significantly reduced the number of invasive tests carried out in many of the nations where it is commonly used. As of today, NIPT is used in less than 25% of pregnancies in most European countries, and as low as 5% in some countries. The highest levels of NIPT use in European Countries have been recorded in Belgium (>75% of pregnancies) and the Netherlands, Italy, Spain and Austria (generally ranging between 25% and 50% of pregnancies) [12]. In the USA, NIPT for high-risk patients (i.e., >35 years, positive cFTS, etc.) is covered by most healthcare insurance companies and most state-sponsored Medicaid programs (in all but nine states). Overall, at the national level, 25–50% of all pregnant women undergo NIPT, which mostly screens for chromosome 13, 18, 21 and sex chromosome aneuploidies. On the other hand, the ever lower costs of new molecular technologies and the non-invasiveness of the diagnostic method could allow for greater diffusion and availability, particularly in low-income developing countries.

Screening for other triploidies, rare aneuploidies and some microdeletions is also available, albeit rather rarely used, and not recommended.

Nonetheless, in terms of ethical, legal and social implications, NIPT has a broad range of complexities that need exploring. Prenatal screening for fetal abnormalities is a morally sensitive practice, since it could lead, or at least contribute, to a decision to terminate one’s pregnancy in case of positive results.

Although population screening programs are mostly directed towards the purpose of reducing morbidity and mortality rates, linked to diseases or disorders, in the population at large, two major ethical issues arise as a result of that objective, as far as prenatal screening is concerned. First and foremost, if the success of the program is deemed to rest upon the termination rate of fetuses with detected abnormalities, confirmed by follow-up testing, that interpretation might well generate a certain degree of pressure on women to seek to terminate their pregnancies if fetal genetic conditions are detected. Some fear the risk of turning the personal choice to voluntarily terminate one’s pregnancy into a “public health instrument” [13]. Secondly, the main objective of prenatal screening techniques makes the practice disputable according to the “disability rights” or “expressivist” critique. Such a philosophical stance denounces that a discriminatory message may be sent by the mainstream use of prenatal screening about the inherent worth of human life, and particularly the lives of those suffering from severe disabling conditions [14]. The considerable discrepancies that are still unsolved between the various assessments of NIPT’s potential benefits and risks, in addition to the ethical values to which they relate, are bound to engender challenges and conflicts that public policy-makers need to address.

Three core principles have been laid out in a recent, wide-ranging analysis by the Nuffield Council on Bioethics [15], which may be summarized as follows:

- The societal context and environment in which NIPT screening is developed and provided ought to be taken into account when devising and undertaking NIPT policy-making initiatives.
- Access to NIPT should be guaranteed to women and couples under conditions and in an environment that prioritizes autonomous, informed choices.
- Potential, significant risks posed by the growing use and development of NIPT ought to be dealt with and minimized through concerted, multilayered efforts, involving all stakeholders and elected officials.

Such major ethical concerns have also been addressed and countered in policy positions issued by various societies in several countries (such as France [16], the United Kingdom [17], Denmark [18], and the Netherlands [19]). In their analyses, said institutions stressed that the fundamental purpose of prenatal screening is not to prevent children with specific abnormalities from being born, but rather to foster reproductive awareness and uphold reproductive rights by enabling pregnant women and their partners to exercise their full autonomy through informed decisions.

3. High Medicolegal Standards Must Be Met in Order to Avoid Negligence and Malpractice Allegations

Most litigation instances involving prenatal testing arise from negligence allegations, i.e., the breach of legal duty that resulted in “unreasonable risk” [20], which is common in virtually all medical malpractice-related litigation. Healthcare operators are typically charged with failing to provide services that meet the standards of reasonable professional practice governing the healthcare provider’s profession or specialty in force when the intervention was rendered. Plaintiff patients often allege that as a direct result of such non-compliance, damage was caused that would not otherwise have happened.

Lawsuits centered around allegations of malpractice in the provision of prenatal genetic testing may arise under several circumstances. Physicians or genetic counselors may be accused of negligence in the provision of genetic counseling, e.g. withholding information from patients as to the potential reproductive risk based on carrier status or age, denying requests to carry out invasive procedures or neglect informing the patient about the need or availability of such procedures. As an integral part of the informed consent process, doctors are professionally bound to disclose and discuss risks, benefits, and possible alternatives to a procedure and may, therefore, have a duty to disclose the availability of NIPT. Explaining and discussing possible alternatives constitutes a fundamental element of the disclosure process; patients, in fact, are often in no position to assess the risk in abstract terms and, therefore, need to be provided with a frame of comparison, so that they can arrive at an informed decision [21]. Non-invasive screening options ought to be disclosed to patients prior to the implementation of an invasive procedure, especially when the non-invasive tests could give information that could help patients decide whether or not to consent to the procedure [22]. Patterns may also develop involving laboratory negligence charges or genetic counseling based on misinterpreted laboratory results which lead the patients to make choices that they would not have made, had they had correct information, including the choice to bring the pregnancy to term. These are usually referred to as “wrongful birth” or “wrongful life” instances. Laboratory negligence or genetic counseling based on incomplete or misinterpreted laboratory results may also lead to claims in which the plaintiffs argue that they would not have aborted a fetus had they been correctly diagnosed or properly counseled about the risks of terminating a pregnancy without further confirmatory test results. Such cases have been termed “wrongful abortion” lawsuits. Wrongful birth claims are ethically contentious: if in fact a pregnancy is terminated because of predicted anomalies, a conflict may come into being between the reproductive rights of women and the respect for the disabled [23]. Such conflict is further amplified if physicians can be held legally accountable for failing to recommend prenatal screening to their patients, and if a child is eventually born with a genetic condition that could have been foreseen. For that reason, prenatal screening and lawsuits centered around the notion of wrongful birth are criticized by several ethicists [24] and advocates for the rights of disabled people [25]; wrongful birth claims, they contend, demean or ignore the multiple unique traits and values of personhood that every newborn child brings into the world [26], including children suffering from genetic abnormalities resulting in disabilities.

Ultimately, it is safe to say that in order to ensure an ethically sound implementation of NIPT, and likely Non-Invasive Prenatal Diagnosis (NIPD) in the near future, and to avoid a dangerous downslide towards selective reproductive technologies (SRTs) and eugenics, such issues need to be dealt with and discussed through the involvement of all stakeholders and the public at large, in a concerted, multidisciplinary and highly coordinated approach. The number of women availing themselves of NIPT screening is likely to gradually rise in the foreseeable future, as will the number of conditions being tested. That is certain to afford to prospective mothers a great opportunity to make informed reproductive decisions, but it also poses issues and concerns about the routinization of testing and negative impacts on informed consent and decision making at its core. In order to make sure that each step towards greater control over human reproduction is suitably confronted, and to stave off any potential inconsistency and conflict with bioethical and social values, specific issues have to be addressed, while keeping an eye on the diversity in cultural contexts at all times. After all, medically-assisted reproduction (MAP) techniques, which also entail legal and ethical challenges, have followed similar dynamics as they have developed over the years. Eventually, legislative frameworks have been enacted, at the national level, to govern MAP, with suitably varying and adjustable degrees of restrictions [27]. With that in mind, newly updated frameworks ought to be devised and developed, aimed at serving as guidance towards an ethically sustainable implementation of NIPT. Moreover, NIPT counseling must be provided in a way that prioritizes and upholds the rights and

best interests of fetuses, pregnant women and couples, while at the same time avoiding paternalistic or directive initiatives by counselors, in keeping with the best traditional approaches of genetic counseling. In that regard, healthcare professional training, education and practice are of critical importance.

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