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Non-invasive prenatal testing (NIPT): a call for change in reporting practices

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ABSTRACT

The use of non-invasive prenatal testing (NIPT) technology has revolutionized the practice of prenatal screening. The assay's validity and reliability have been demonstrated in both low- and high-risk pregnancies. Despite its excellent screening parameters, its reliability is often overestimated due to confusing and incorrect terminology that appears in private NIPT reports. Herein, we provide a brief explanation of the potential implications at two different levels: patient and provider. We conclude with a call to redesign the way in which information is presented on NIPT reports to avoid stressing patients, enhance transparency in clinical counselling, and perhaps most critically, to prevent medical decisions that may not be warranted solely based on the NIPT results.

KEYWORDS
NIPT, aneuploidy, screening, age-adjusted PPV, reporting practices

1 | INTRODUCTION

The use of non-invasive prenatal testing (NIPT) technology, which detects the presence of cell free fetal DNA (cfDNA) in maternal blood, has revolutionized the practice of prenatal screening and modern obstetrics. (1) Though originally reserved for primarily high-risk pregnancies, its validity and reliability have been demonstrated in both low- and high-risk pregnancies as well. (2) Not surprisingly, NIPT now represents the primary method used for prenatal screening in North America. Despite its excellent screening parameters, with sensitivity and specificity estimates over 90-99% for most conditions tested, its reliability is often overestimated due to confusing and incorrect terminology that appears in private NIPT reports.

2 | THE ISSUE

In these authors' experience, most NIPT reports include a table that lists each tested condition with an estimate of risk or probability. Often, this risk or probability is reported as either inferior to 1/10,000 (0.01%) when the test is negative, and depending on the condition, as greater than 99/100 (99%) "probability" when the test is positive. This estimate is considered as a high-risk result and flagged for subsequent diagnostic testing. The diagnostic test in this case is amniocentesis or chorionic villous sampling (CVS), and both procedures carry the risk of serious complications.

What is a layperson to make of the word "probability" in the context of a positive NIPT result? The word translates colloquially to a chance of greater than 99% for carrying an affected pregnancy. Yet, this assumption is incorrect. A brief explanation follows.

3 | SENSITIVITY AND POSITIVE PREDICTIVE VALUE

The NIPT test is marketed as the best and most accurate method to screen for fetal aneuploidy during pregnancy. Statements like "over 99% accurate" often figure in the marketing of these assays. While the superior performance of NIPT over the maternal serum screen (MSS, nuchal translucency) is undisputed, all screens are faced with the obstacle that is Bayes' theorem.

Bayes' theorem dictates that prevalence (or pre-test probability in an individual) influences the positive predictive value (PPV) obtained. Put simply: the more common a condition is, the more reliable a screen for it is, and hence, PPV is higher with increasing prevalence (and vice versa). The prevalence of trisomies is low in the population, so even among individuals considered to be at highest risk of Trisomy 21 (Down syndrome), the PPV will always be lower than the sensitivity. Sensitivity is defined as our ability to detect true positive results and answers this question, "among patients with a disease, how many will have a positive test?" Therefore, the 99% "probability" reflects the sensitivity, and not the PPV. The PPV asks the more important question in this context which is: "among the positive screening tests, how many will end up having the condition?"

4 | THE PATIENT

Many expecting parents are eager to discover fetal sex and to ascertain fetal health early in pregnancy. Patients may resort to private companies for NIPT screening because the assay is not typically covered by the public healthcare system in most North American jurisdictions. Most of these companies provide a copy of results to the patient regardless of its findings. While access to health information is fundamental, the way in which the information is presented can have a significant impact on how it is received. The nature of private NIPT means that many individuals will access this assay as a first line test. Pre-test probability is low; therefore, many parents are subjecting their pregnancies to overscreening. Moreover, Canadian prenatal screening programs usually reserve NIPT as the follow-up test for an abnormal result from a less specific screen, and this practice is endorsed by the Society of Obstetricians and Gynaecologists of Canada. (1) Often, patients will receive the abnormal screening result without explanation and are directed to diagnostic testing. This process can be unnecessarily anxiety-inducing and render the experience of pregnancy more stressful. Little to no research has studied parental anxiety in the interval between a positive NIPT screen and subsequent diagnostic testing. (3) In addition to psychological distress, the clinical risks of overscreening include false positive results and the medical complications inherent to the diagnostic testing. The latter include premature rupture of membranes, clubbed feet, placental hemorrhage, and fetal demise.

5 | THE PROVIDER

A basic understanding of sensitivity and PPV is critical when engaging in clinical counselling with patients. We must be mindful that the NIPT is not intended to be a diagnostic test. The NIPT has an excellent negative

predictive value of over 99%. (2) Yet, PPV values may fall below 50%. The NIPT technology yields a significant number of false positives because the low prevalence of trisomic conditions falls well below the prevalence threshold. (4) The prevalence threshold varies by test and is defined as the "prevalence level below which the PPV declines most sharply relative to disease prevalence." The prevalence threshold for NIPT is 7% and trisomic conditions have a prevalence of 0.2%. (5)

When facing a patient with a positive result, the provider can use a clinical tool to calculate age adjusted PPV such as the NIPT/Cell Free DNA Screening Predictive Value Calculator (6) provided by the [American] National Society of Genetic Counselors and the Prenatal Quality Foundation. Some of these calculations have been simulated and are presented in Table 1 for reference. Subsequently, for all expecting parents with an abnormal result, the provider should refer the patient on to local genetic counsellors and possible diagnostic testing.

6 | CONCLUSION

In the context of screening, words like "risk" and "probability" as they appear on NIPT reports may be misleading to the lay public and carry significant undue stress for patients. Because NIPT reports are often made directly available to consumers, these authors propose that laboratories offering direct-to-consumer prenatal screening by cfDNA (i) clearly indicate these tests are meant for screening and not for diagnostic purposes and (ii) report age-adjusted PPV and NPV as the "probability" of results in lieu of sensitivity to provide a more accurate calculation of true risk. When a healthcare provider is confronted with one of these reports, these values can be simply calculated using a medical calculator as presented. (6) We hope that, ultimately, these changes would reduce parental anxiety and the medical and economic impacts of overtesting following NIPT.

	Sensitivity	Specificity	Age 25		Age 30		Age 35		Age 40	
			PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)
Trisomy 21	99.2	99.91	51	99	61	99	79	99	93	99
Trisomy 18	96.3	99.87	15	99	21	99	39	99	69	99
Trisomy 13	91	99.87	7	99	10	99	21	99	50	99

PPV = positive predictive value; NPV = negative predictive value.

These values were calculated using the tool available at: https://www.perinatalquality.org/Vendors/NSGC/NIPT. (5)

TABLE 1 PPV of NIPT by condition as a function of maternal age

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