

Noninvasive Prenatal Testing/Noninvasive Prenatal Diagnosis: the Position of the National Society of Genetic Counselors

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Abstract The 1997 discovery of free fetal DNA in maternal plasma launched clinical researchers' efforts to establish a reliable method for non-invasive prenatal testing for fetal genetic conditions. Various methods, including, but not limited to, massively parallel sequencing (MPS) and selective analysis of cell-free fetal DNA in maternal plasma, have recently been developed as highly sensitive and specific noninvasive screening tools for common fetal chromosome aneuploidies.

Incorporating these new noninvasive technologies into clinical practice will impact the current prenatal screening paradigm for fetal aneuploidy, in which genetic counseling plays an integral role. The National Society of Genetic Counselors (NSGC) currently supports Noninvasive Prenatal Testing/Noninvasive Prenatal Diagnosis (NIPT/NIPD) as an option for patients whose pregnancies are considered to be at an increased risk for certain chromosome abnormalities. NSGC urges that NIPT/NIPD only be offered in the context of informed consent, education, and counseling by a qualified provider, such as a certified genetic counselor. Patients whose NIPT/NIPD results are abnormal, or who have other factors suggestive of a chromosome abnormality, should receive genetic counseling and be given the option of standard confirmatory diagnostic testing.

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Introduction

The National Society of Genetic Counselors (NSGC) releases position statements that are intended to convey to the public the Society's unique views and opinions on issues of relevance to the practice of genetic counseling. The NSGC Public Policy Committee (PPC) leads the creation of new statements or revision of existing statements based on emerging data or issues. This paper highlights the background data that informed the task force members' discussions and shaped the statement on noninvasive prenatal testing put forward to the NSGC membership and Board of Directors for comments and approval.

Background

Noninvasive prenatal testing (NIPT) uses fetal genetic material obtained from a maternal blood sample to detect certain genetic conditions during pregnancy. Current literature often refers to NIPT as noninvasive prenatal diagnosis (NIPD). This terminology may be misleading given that, at the time of this writing, the technology is recommended only as a highly specific screening measure, which requires follow-up diagnostic testing (www.ariosadx.com, www.sequenomcmm.com, www.verinata.com). While beyond the scope of NSGC's position statement, it is important to note that NIPT is clinically available for fetal sex determination and fetal RhD genotyping, and several companies offer non-invasive paternity testing directly to the consumer.

In 1997, Lo et al. first discovered cell-free fetal DNA in the plasma of pregnant women. In 2008, two research groups used massively parallel sequencing (MPS) of maternal plasma to detect an overrepresentation of material from chromosome 21 in pregnancies affected with trisomy 21 (Chiu et al. 2008; Fan et al. 2008).

Three published clinical trials validated MPS to detect common aneuploidies with a high sensitivity and specificity (see Table 1). This led to the clinical availability of NIPT in high-risk pregnancies in the United States, beginning in late 2011. Palomaki et al. (2011) demonstrated the ability of MPS of maternal plasma to detect fetal trisomy 21 with a near 99-percent sensitivity and specificity in high-risk pregnancies, defined by maternal age, family history, or positive serum and/or sonographic screening tests. The group then published an analysis from the same study (Palomaki et al. 2012) demonstrating the detection of trisomy 18 at 100-percent sensitivity with a false-positive rate of 0.28 %, and trisomy 13 at 91.7-percent sensitivity with a false-positive rate of 0.97 %. The overall detection rate for trisomy 13, 18, and 21 was reported as 98.9 % sensitivity with a false-positive rate of 1.4 %.

Bianchi et al. (2012) also examined the use of MPS in maternal serum of high-risk pregnancies, using a slightly different algorithm for analysis. In this study, NIPT detected trisomy 21 with 100-percent sensitivity, trisomy 18 with 97.2-percent sensitivity, and trisomy 13 with 78.6-percent sensitivity – all with a specificity of 100 %. They also reported NIPT's ability to detect cases of other autosomal and sex chromosome aneuploidies, as well as translocation trisomy and mosaic trisomies. Specifically, they reported monosomy X detection with 93.8 % sensitivity and 99.8 % specificity. In addition, Bianchi et al. suggest that NIPT will screen for additional chromosome abnormalities in the near future.

Selective analysis, in which cell-free DNA from maternal plasma is sequenced for selected loci from specific chromosomes of interest, has been proposed as a more efficient and potentially less expensive option for NIPT (Sparks et al.

2012). A recently published multicenter cohort study evaluated the performance of chromosome-selective sequencing on chromosomes 21 and 18 in a population of women undergoing CVS or amniocentesis for any indication (Norton et al. 2012) (See Table 1). Sequencing was performed using the Digital ANalysis of Selected Regions (DANSR) method and risk analysis was performed with the Fetal-fraction Optimized Risk of Trisomy Evaluation (FORTE) algorithm. Using a predefined cut-off value of 1 in 100 (1 %) for classifying a sample as High Risk versus Low Risk, the sensitivity and specificity for trisomy 21 were 100 % and 99.97 %. The sensitivity and specificity for trisomy 18 were 97.4 % and 99.93 %. A subsequent publication (Ashoor et al. 2012) reported 80 % sensitivity and 99.95 % specificity for trisomy 13, using the DANSR and FORTE methods in a retrospective, case-control study.

These studies validate NIPT as a reliable screen for trisomies 21, 13, and 18 and monosomy X in high-risk pregnancies. In addition, preliminary evidence indicates NIPT should have similar sensitivity and specificity in an average risk population (Nicolaidis et al. 2012), suggesting that expansion to average-risk women may be possible with further experience (Norton et al. 2012).

To date, few professional societies have statements or guidelines regarding NIPT. The International Society for Prenatal Diagnosis issued a statement accepting that, with suitable genetic counseling, MPS for aneuploidy screening can be helpful for women determined to be high-risk by other screening methods, maternal age, or family history (Benn et al. 2012a).

NIPT's introduction into clinical practice has the potential to significantly shift the paradigm of prenatal diagnosis and screening for all women. The importance of comprehensive genetic counseling should not be underestimated and NIPT only increases the need for genetic counseling (Benn et al. 2012b). NSGC firmly believes that reproductive decisions should be made in the context of unbiased and comprehensive information, free from discrimination or coercion (NSGC Position Statement: Reproductive Freedom 2010). The National Coalition for Health Professional Education in Genetics, in conjunction with NSGC, created a Non-Invasive Prenatal Testing Fact Sheet (NCHPEG 2012) designed to help health professionals apply NIPT appropriately in the prenatal screening/testing paradigm, critically evaluate NIPT tests and laboratories, counsel women about options and results, and anticipate future directions of this technology.

The *Prenatally and Postnatally Diagnosed Conditions Awareness Act* (2008) was enacted to increase the provision of scientifically sound information and support services to patients receiving a positive-test diagnosis for Down syndrome or other prenatally and postnatally diagnosed conditions. Both NSGC and disability advocacy groups deem it essential that pregnant women receive unbiased, value

Table 1 Results from four published clinical trials that measured NIPT's sensitivity and specificity in detecting common aneuploidies

	Trisomy 21		Trisomy 18		Trisomy 13		Monosomy X	
	Sensitivity (95 % CI)	Specificity (95 % CI)	Sensitivity (95 % CI)	Specificity (95 % CI)	Sensitivity (95 % CI)	Specificity (95 % CI)	Sensitivity (95 % CI)	Specificity (95 % CI)
Palomaki et al. 2011	98.6 % (95.9 - 99.7)	99.8 % (99.4 - 99.9)	—	—	—	—	—	—
Palomaki et al. 2012	—	—	100 % (93.9 -100)	99.7 % (99.3 - 99.9)	91.7 % (61-99)	99.1 % (98.5 - 99.5)	—	—
Bianchi et al. 2012	100 % (95.9 - 100)	100 % (99.1 - 100)	97.2 % (85.5 - 99.9)	100 % (99.2 - 100)	78.6 % (49.2 - 99.9)	100 % (99.2 - 100)	93.8 % (69.8-99.8)	99.8 % (98.7->99.9)
Norton et al. 2012	100 % (95.5-100)	99.97 % (99.8 -99.99)	97.4 % (86.5-99.9)	99.93 % (99.75 - 99.98)	—	—	—	—
Ashoor et al. 2012	—	—	—	—	80 % (49-94.3)	99.95 % (99.71-99.99)	—	—

neutral information regarding prenatal genetic conditions. This information and support enables a pregnant woman and her family to determine an outcome that fits within their personal, cultural, religious, and social context (DEDFR et al. 2008). Genetic counselors play an integral role in this process.

Discussion

Important Considerations

1. NSGC recognizes NIPT as an option for aneuploidy assessment in pregnancy: Peer-reviewed data currently supports NIPT only as a screening tool for select populations (Benn et al. 2012). While NIPT has proven effective in detecting fetuses with aneuploidy, in light of potential false positive results, NIPT results should not be considered diagnostic, and any abnormal results should be confirmed through a conventional prenatal diagnostic procedure, such as chorionic villus sampling or amniocentesis.
2. NSGC does not currently support NIPT as a routine, first-tier aneuploidy screening test in low-risk populations: To date, these technologies have been validated primarily in pregnancies considered to be at an increased risk for fetal aneuploidy, based on maternal age, family history, or positive serum and/or sonographic screening tests (Palomaki et al. 2011, 2012; Bianchi et al. 2012) or in pregnancies in which invasive testing is being performed (Norton et al. 2012), which is not truly representative of an average-risk population. Although one study has suggested that NIPT in screening for trisomy 21 and trisomy 18 in an average risk population would be effective (Ashoor et al. 2012), further studies are needed before NIPT can replace current aneuploidy screening programs.
3. Clinical studies show that MPS effectively detects fetal trisomy 21 (Palomaki et al. 2011; Bianchi et al. 2012), trisomy 13, trisomy 18 (Palomaki et al. 2012; Bianchi et al. 2012), and monosomy X (Bianchi et al. 2012) and that DANSR effectively detects trisomy 21, trisomy 18 (Norton et al. 2012), and trisomy 13 (Ashoor et al. 2012). NIPT has not yet been proven efficacious in detecting other chromosomal abnormalities or single-gene disorders. NSGC recommends that pretest counseling for NIPT include information about the disorders that it may detect, its limitations in detecting these conditions, and its unproven role in detecting other conditions.
4. Pre- and post-NIPT genetic counseling: As with any prenatal testing, patients must have accurate, up-to-date information regarding the test, the possible results,

and the available follow-up in order to make an informed choice when considering NIPT. Given NIPT's vastly superior sensitivity and specificity compared to other available aneuploidy screening – such as, first-trimester nuchal translucency and/or biochemical screening and second-trimester quad screening – it is imperative that patients understand the significant implications of a positive result prior to undergoing NIPT. NSGC recognizes that, due to limited resources, it may not be feasible for all women seeking NIPT to receive pretest counseling from a genetic counselor. But a qualified healthcare provider should provide nondirective pretest counseling for all women considering NIPT. NSGC recommends that any patient with abnormal NIPT results should receive genetic counseling with a certified genetic counselor and be given the option of conventional confirmatory diagnostic testing.

5. NSGC recommends that patients who have other factors suggestive of a chromosome abnormality should receive genetic counseling and have the option of conventional confirmatory diagnostic testing, regardless of NIPT results: Because NIPT does not screen for all chromosomal or genetic conditions, it does not replace standard risk assessment and prenatal diagnosis. Indications for genetic counseling, regardless of NIPT results, include the presence of ultrasound abnormalities, family or personal history of a chromosome anomaly, and a history of recurrent pregnancy loss. Patients who are of advanced maternal age and/or have had a positive screening test may also benefit from detailed genetic counseling, regardless of NIPT results. In addition, patients who have an increased risk for genetic conditions that are beyond NIPT's scope should receive genetic counseling to discuss appropriate testing options.
6. Future Considerations: NIPT's landscape is rapidly changing. Additional companies are currently administering studies to validate their laboratory-developed tests for NIPT, and are expected to launch competing tests in the near future. NIPT will likely expand to include additional chromosomal abnormalities and/or microarray analysis as future studies support the clinical validity of such results. Studies to assess clinical validity in the general population (e.g. average-risk women) are currently underway. As the sensitivity and specificity in the general population are better established, NIPT has the potential to function with the sensitivity and specificity similar to currently available diagnostic tests. Single-gene testing will also be possible, as this is an area of ongoing research (Chan et al. 2010). As this technology evolves, NSGC will reassess its recommendations to reflect these changes.

Conclusion

With this in mind, the NSGC's position statement on NIPT is as follows:

The National Society of Genetic Counselors currently supports Noninvasive Prenatal Testing/Noninvasive Prenatal Diagnosis (NIPT/NIPD) as an option for patients whose pregnancies are considered to be at an increased risk for certain chromosome abnormalities. NSGC urges that NIPT/NIPD only be offered in the context of informed consent, education, and counseling by a qualified provider, such as a certified genetic counselor. Patients whose NIPT/NIPD results are abnormal, or who have other factors suggestive of a chromosome abnormality, should receive genetic counseling and be given the option of standard confirmatory diagnostic testing. (Adopted February 18, 2012)

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