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National Society of Genetic Counselors

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) 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

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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.

Keywords (3-10)

Noninvasive prenatal diagnosis, aneuploidy screening, prenatal diagnosis, Down syndrome, trisomy 13, trisomy 18, trisomy 21, Position Statement, The National Society of Genetic Counselors

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.

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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 for high-risk pregnancies, which requires follow-up diagnostic testing. (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 gender 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). Other technologies for noninvasive prenatal testing for specific chromosome aneuploidies are currently being developed (Sparks et al., 2012).

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)

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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 percent, and trisomy 13 at 91.7-percent sensitivity with a false-positive rate of 0.97 percent. The overall detection rate for trisomy 13, 18, and 21 was reported as 98.9 percent sensitivity with a false-positive rate of 1.4 percent.

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 percent. They also reported NIPT's ability to detect cases of other autosomal and sex chromosome aneuploidies, as well as translocation trisomy and mosaic trisomies. These studies validate NIPT as a reliable screen for trisomies 21, 13, and 18 in high-risk pregnancies. In addition, Bianchi et al. suggest that NIPT will screen for additional chromosome abnormalities in the near future.

To date, few professional societies have statements or guidelines regarding NIPT. The International Society for Prenatal Diagnosis issued a statement accepting that, with

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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., 2011).

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., 2012). 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 *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, nondirective 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.

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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 abnormal NIPT results have a high positive predictive value, NIPT results should not be considered diagnostic at this time, 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 only 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; Palomaki et al., 2012; Bianchi et al., 2012).

3. Clinical studies show that MPS effectively detects fetal trisomy 21 (Palomaki et al., 2011; Bianchi et al., 2012), trisomy 13, and trisomy 18 (Palomaki et al., 2012; Bianchi et al., 2012). MPS has not yet been proven

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efficacious in detecting other chromosomal abnormalities or single-gene disorders, and clinical trials for other technologies have not yet been published. 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.

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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. 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. Several companies are currently administering studies to validate their laboratory-developed tests for NIPT, and many will launch competing tests in 2012. 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. low-risk women) are currently underway. As the sensitivity and specificity in the general population are better established, it is likely that NIPT will become a diagnostic test for fetal chromosomal aneuploidy for routine use in all pregnancies. 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

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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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REFERENCES:

Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, Wainscoat JS. (1997 Aug). Presence of fetal DNA in maternal plasma and serum. *Lancet, 16*;350(9076):485-7.

Chiu RW, Chan KC, Gao Y, Lau VY, Zheng W, Leung TY, Foo CH, Xie B, Tsui NB, Lun FM, Zee BC, Lau TK, Cantor CR, Lo YM. (2008 Dec 23). Noninvasive

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prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. *Proc Natl Acad Sci U S A, 105*(51):20458-63.

Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. (2008 Oct 21). *Proc Natl Acad Sci U S A, 105*(42):16266-71.

Sparks AB, Struble CA, Wang ET, Song K, Oliphant A. Noninvasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. (2012 Apr). *Am J Obstet Gynecol., 206*(4):319.e1-9. Epub 2012 Jan 26.

Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrich M, van den Boom D, Bombard AT, Deciu C, Grody WW, Nelson SF, Canick JA. (2011 Nov). DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. *Genet Med,;13*(11):913-20.

Palomaki GE, Deciu C, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrich M, van den Boom D, Bombard AT, Grody WW, Nelson SF, Canick JA. (2012 Mar). DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study. *Genet Med, 14*(3):296-305. doi: 10.1038/gim.2011.73.

Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP. (2012 May). Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing. *Obstet Gynecol, 119*(5): 1-13.

Benn P, Borrell A, Cuckle H, Dugoff L, Gross S, Johnson JA, Maymon R, Odibo A, Schielen P, Spencer K, Wright D, Yaron Y. Prenatal Detection of Down Syndrome using Massively Parallel Sequencing (MPS): a rapid response statement from a committee on behalf of the Board of the International Society for Prenatal Diagnosis, 24 October 2011. (2012 Jan). *Prenat Diagn, 32*(1):1-2. doi: 10.1002/pd.2919.

NSGC (2010). *NSGC Position Statement: Reproductive Freedom.* Retrieved from http://www.nsgc.org/Media/PositionStatements/tabid/330/Default.aspx

Disability Rights Education and Defense Fund, Generations Ahead, National Women's Health Network, Reproductive Health Technologies Project, and World Institute on Disability. (16 October 2008). *The Prenatally and Postnatally Diagnosed Conditions Awareness Act.* Retrieved from

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www.dredf.org/InfoSheetBrownbackKennedy.pdf

Benn P, Cuckle H, Pergament E. Non-invasive prenatal diagnosis for Down syndrome: the paradigm will shift, but slowly. (2012 Feb). *Ultrasound Obstet Gynecol. 39*(2):127-30. doi: 10.1002/uog.11083.

Chan K, Yam I, Leung KY, Tang M, Chan TK, Chan V. Detection of paternal alleles in maternal plasma for non-invasive prenatal diagnosis of beta-thalassemia: a feasibility study in southern Chinese. (2010 May). *Eur J Obstet Gynecol Reprod Biol, 150*(1):28-33.

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Table 1: Results from three published clinical trials that measured MPS' sensitivity and specificity in detecting common aneuploidies

	Trisomy 21		Trisomy 18		Trisomy 13	
	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)