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Noninvasive Prenatal Diagnosis: Pregnant Women's Interest and Expected Uptake

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Abstract

Objective—To investigate pregnant women's level of future interest in noninvasive prenatal diagnosis (NIPD) and what factors might affect expected uptake of this testing.

Method—Written questionnaires were administered to women in their third trimester.

Results—One hundred fourteen women returned the questionnaire (80.9% response rate). Of these, 71.9% reported interest in NIPD, 22.7% were ambivalent and 5.4% were uninterested. Safety of the fetus was the single most important factor in 75% of women's decisions. Factors associated with increased interest in NIPD included: older age ($p=0.036$), higher education ($p=0.013$), Caucasian or Asian ethnicity ($p=0.011$), and higher likelihood to terminate an affected pregnancy ($p=0.002$). Nearly 20% of women reported that they would do whatever their doctor recommended regarding NIPD, and 94.4% of women wished to meet with a genetic counselor at some point to discuss NIPD.

Conclusion—The majority of pregnant women report hypothetical interest in NIPD, primarily due to increased safety for the fetus, although a significant minority are uninterested or ambivalent. Discussions with healthcare providers regarding NIPD, and their recommendations, are likely to be an important factor in women's decisions about this testing. As such, adequate discussion of the implications of prenatal diagnostic testing will be critical.

Keywords

prenatal testing; noninvasive prenatal diagnosis; prenatal screening; chromosome abnormalities; patient decision-making

Introduction

The option of prenatal diagnostic testing for chromosome abnormalities has become a routine aspect of obstetric care, but the risk of miscarriage associated with currently available forms of diagnostic testing leads to relatively low uptake (Nakata *et al.*, 2010). ACOG recommends that all pregnant women be offered both noninvasive screening and invasive diagnostic testing (Practice Bulletin #88). Diagnostic tests appear to be undertaken primarily by women for whom the numeric risk of aneuploidy is high (due to age or screening results) or who have high levels of anxiety (Mueller *et al.*, 2005; Kobleka *et al.*, 2009), and many women at numerically higher risks decline diagnostic testing because of their concerns about the risks of an invasive test.

A noninvasive method of obtaining diagnostic information about the genetic make-up of the fetus has long been sought (Evans and Kilpatrick, 2010). Noninvasive prenatal diagnosis (NIPD) would allow fetal genetic testing through a sample of the mother's blood. The isolation of fetal cells (Herzenberg *et al.*, 1979) and later fetal cell-free DNA and RNA (Lo *et al.*, 1997; Poon *et al.*, 2000) circulating in the maternal bloodstream has made this type of testing a possibility. Ideally, NIPD would have no risk of miscarriage and could be available starting at an earlier point than current forms of diagnostic testing (De Jong *et al.*, 2010; Hall *et al.*, 2010). Earlier diagnostic testing could allow for termination of affected pregnancies (if desired by the parents) when the procedure is physically safer and less psychologically traumatic (Benn and Chapman, 2010) and might allow for earlier reassurance and bonding in normal pregnancies (Newson, 2008). Women historically prefer earlier prenatal tests (Spencer and Aitken, 2004), although there is some evidence that healthcare providers may place a higher value on earlier tests than women do (Bishop *et al.*, 2004).

The development of noninvasive forms of fetal genetic testing has been an active area of research for many years. Recent progress in cell-free fetal DNA sequencing approaches are promising (Fan *et al.*, 2008; Fan *et al.*, 2010). Several companies (including Verinata, Gene Security Network, and Sequenom) are trying to develop this technology (Verinata, 2011; Sequenom, 2011, GSN, 2011). Two large-scale validation studies published earlier this year indicate that this technology is approaching diagnostic specifications for the detection of fetal aneuploidy (Chiu *et al.*, 2011; Ehrich *et al.*, 2011) and widespread implementation of this technology is a realistic possibility within the next decade.

The broad implementation of NIPD would likely cause significant increase in the uptake of prenatal diagnostic testing due to the removal of miscarriage risk. This potential increase in uptake of diagnostic testing would lead to a larger number of affected pregnancies being identified, and terminations of affected pregnancies would almost certainly rise (Newson, 2008; Benn and Chapman, 2009). This raises concerns that if fewer affected individuals are born, this might eventually lead to less social support and acceptance of people with disabilities (Skotko, 2009; Greely, 2011). In a circular manner, decreased social acceptance of individuals with disabilities could cause pregnant women to feel undue pressure to undergo NIPD testing and terminate an affected pregnancy. In fact, a 2001 study on NIPD using fetal cells showed that nearly a third of women imagined that they would feel pressure from society, their provider, or their partner to undergo a hypothetical non-invasive diagnostic test (Zamerowski *et al.*, 2001).

The risk of miscarriage associated with amniocentesis or CVS and the invasive nature of these tests prompts healthcare professionals to have an in-depth discussion of the pros and cons of prenatal testing with their patients. For the pregnant woman, the miscarriage risk and the need to undergo a separate invasive procedure act as psychological barriers that generally prompt her to carefully consider whether she values the information provided by a

prenatal diagnostic test. When these barriers are removed, a woman may give less thoughtful consideration to her choice about diagnostic testing (Schmitz *et al.*, 2009), and healthcare professionals may provide less information about the potential ramifications of this type of testing (Van den Heuvel *et al.*, 2009; Benn and Chapman, 2010). When the risk of miscarriage is removed, a woman who does not want the information provided by a diagnostic test may also feel less justified in her decision to decline testing (Newson, 2008).

Very little research has been done to explore the attitudes of women toward noninvasive prenatal diagnosis (Zamerowski *et al.*, 2001; Kooj *et al.*, 2009; Kelly and Farrimond, 2011). The aim of this study was to assess whether pregnant women are interested in NIPD and what factors would influence their interest and expected uptake. We presented NIPD as being a diagnostic test with a level of accuracy similar to that of CVS and amniocentesis, since we expect that technical progress will allow this possibility in the near future, and the implications for NIPD testing are most significant if it has diagnostic capabilities.

Methods

Pregnant women presenting for prenatal care to the outpatient Obstetrics Clinic or the Perinatal Diagnostic Center (PDC) of Lucile Packard Children's Hospital, Palo Alto, California were identified for possible enrollment. Enrollment was only offered to women who were at least 24 weeks gestation, over 18 years old, and spoke and read English. Women were approached in the waiting room and asked to complete a written survey before or after their clinic visit. English proficiency was assessed by the primary investigator (RT) prior to survey administration.

Measure

Two versions of a written survey were developed by the investigators (available by request to corresponding author). Survey questions and the related introductory material were identical with the exception of the introductory sections describing NIPD - one version contained a brief NIPD description and the other had a longer, slightly more comprehensive description of the testing (see Appendix I). In consideration of potential informed consent concerns surrounding NIPD, we chose to create the different descriptions in order to ascertain whether the amount and level of detail given would influence the hypothetical uptake of this testing. The language and ordering of information was kept as similar as possible between the two survey versions. Each woman was asked to complete only one version of the survey and was not told that there were multiple versions. The two survey types were identical in outward appearance and versions were alternated between each prospective participant.

Both versions of the survey began with an introductory section that described the background risk of having a baby with a birth defect and gave a brief overview of currently available invasive testing options, their associated risk of miscarriage and the options that are available to a woman if a chromosome abnormality is diagnosed prenatally.

NIPD was then introduced as an alternative to invasive testing that might become available in the near future. NIPD testing was described as being available earlier than invasive testing (potentially starting as early as 7–10 weeks) and having a similar level of accuracy as CVS and amniocentesis. NIPD was described as being completely safe for the fetus with no risk of miscarriage. The long version also had a more detailed discussion of NIPD that explained that the earlier timeframe would allow a woman more time to consider her options and allow more privacy in doing so, but also could identify some affected pregnancies that would have naturally ended in miscarriage, and may require an invasive test to clarify the results. The long version had a more extensive discussion of why a person might want (or not want) the

information supplied by prenatal diagnostic testing including the statement “Some reasons why people might want this information include: it would help them prepare for the birth of a child with a disability; the test results would decrease their anxiety; or they may consider terminating a pregnancy if a birth defect was found. Other people may not want this information because it would not impact how they would proceed with the pregnancy.”

After the description of NIPD was given, both versions of the survey had identical questions addressing four areas: (1) demographics (11 questions) including questions addressing previous uptake of prenatal screening and diagnosis in the current or past pregnancies, (2) eleven questions, primarily in Likert format, about the woman’s level of interest in NIPD and the various factors affecting her interest, (3) desire for genetic counseling before or after NIPD, and (4) likelihood to terminate an affected pregnancy. The survey took approximately 10 minutes to complete.

Data were analyzed using SPSS version 18. Five-point Likert scales were compressed to two or three categories to avoid small cell sizes. When inconsistencies were noted between the participant’s response to their use of prenatal screening and diagnostic testing and the results of this testing, the answers were adjusted conservatively to show consistency. (Example: If the participant marked that they did not have prenatal screening and then indicated that they had a normal result to prenatal screening, the latter response was changed to “I did not have prenatal screening.”) Data were analyzed descriptively, and comparisons were made between the responses of women who read the short NIPD description versus the long NIPD description. Chi square analysis was also used to determine the demographic factors affecting women’s level of interest in NIPD technology.

The study methodology and survey were approved by the Stanford University Institutional Review Board.

Results

We approached 141 women to complete the survey and 114 women returned completed surveys (80.9% response rate). Completion rates were slightly higher with the short description; 62 of 71 surveys with the short description and 52 of 70 surveys with the long description were returned. The vast majority of the surveys were completed by women at the outpatient obstetrics clinic (94.7%). Overall the cohort consisted of an ethnically diverse but highly educated population with a mean age of 31.6 $\pm$ 6.0 (range 19–47 years old) (Table 1). Eighty-one percent of women reported that they underwent prenatal screening in the current or a past pregnancy, and 21.4% of women had undergone an invasive diagnostic test (Table 2).

Views toward NIPD are shown in Table 3. The majority of women surveyed indicated that they would be interested in having NIPD testing if it were available (71.9%), although a significant minority expressed that they were ambivalent (22.7%) or uninterested (5.4%) in this type of testing. When asked to identify a single factor which was the most important for their decision about NIPD, women overwhelmingly indicated that the elimination of miscarriage risk was most important (75%), followed distantly by accuracy of the results (13%). More than 10% of women chose multiple answers to this question, and among these, the majority indicated the elimination of miscarriage risk as one of the factors that they chose.

Respondents indicated that they would want to have NIPD either in place of (~30%) or in addition to (~40%) current screening and diagnostic testing (Table 3). Nearly 20% of respondents indicated that they would do whatever their doctor recommended regarding NIPD. The vast majority of women indicated interest in talking to a genetic counselor about

NIPD (94.6%), but they were split about the ideal time when this should occur: before undergoing NIPD testing (32.4%), after results were received (47.8%), or both (14.4%).

Women's level of interest in NIPD testing did not significantly differ based on the amount of detail given in the description of NIPD at the start of the survey (74.1% interested with the brief description vs 69.2% interested with the detailed description; $\chi^2=0.326$; $p=0.568$). However, women who indicated that they were less likely to terminate an affected pregnancy were more likely to be ambivalent or uninterested in NIPD ($\chi^2=12.014$; $p=0.002$). Level of interest in NIPD was also significantly associated with older age ($\chi^2=4.405$; $p=0.036$), higher education level ($\chi^2=6.149$; $p=0.013$), and ethnicity ($\chi^2=6.526$; $p=0.011$) such that women who reported their ethnicity as Caucasian or Asian were more likely to indicate interest in NIPD (Table 4).

Women who received the detailed versus brief NIPD descriptions were significantly less likely to prefer NIPD as a replacement for currently available diagnostic tests (19.6% vs 40.7%; $\chi^2=5.687$; $p=0.017$). There also seemed to be a trend that women who received the detailed description were more likely to want to follow-up a positive NIPD result with invasive testing for confirmation (41.2%) as compared to women who received the brief description (27.1%; $\chi^2=2.422$; $p=0.12$). Women whose prenatal screening results indicated that they were at high risk for a chromosome abnormality or neural tube defect also appeared to be more likely to prefer NIPD over screening (7 of 10) as compared to women whose prenatal screen showed a low or average risk (20 of 75), although the numbers of individuals in each category prohibited us from running a valid statistical analysis.

Discussion

This study is one of the first to assess pregnant women's hypothetical views toward noninvasive prenatal diagnosis. Demographic factors and attitudes toward termination influenced women's level of interest in NIPD. Many women reported that they would follow their doctor's recommendations about NIPD, suggesting that informed consent for this testing is a critical issue.

Demographic factors which were associated with higher level of interest in NIPD included older age, higher education level, and Caucasian or Asian ethnicity. These findings are generally consistent with previous research on women's approaches to invasive prenatal testing. Uptake of prenatal diagnostic testing is higher in older women (Nakata *et al.*, 2010; Van Landingham *et al.*, 2011) and among those who are more educated (Saucier *et al.*, 2005). Uptake and attitudes toward invasive prenatal testing also differ between ethnicities (Kupperman *et al.*, 1996; Learman *et al.*, 2003; Saucier *et al.*, 2005), with Caucasian and Asian women being more likely to undergo invasive testing. Likelihood to terminate an affected pregnancy was the most predictive factor in a woman's interest in NIPD. Again this is consistent with previous research showing that willingness to terminate a pregnancy is predictive of a woman's attitudes about prenatal screening and invasive testing (Lumley *et al.*, 2006). Interestingly, self-reported religiosity was not significantly associated with interest in NIPD, although it was highly associated with a woman's likelihood to terminate an affected pregnancy ($\chi^2=19.976$; $p=0.001$). This suggests that although religiosity may play a role in a woman's views about termination, disability, and the value of prenatal testing (White, 2009; Teman *et al.*, 2010) it cannot be used to predict her attitudes toward NIPD.

Although there was a slight difference in interest level based on which NIPD description was given, this difference was not statistically significant. It is likely that our limited sample size would not have sufficient power to pick up small to moderate differences between the

two survey versions. It is also possible that the level of detail or the specific areas that were lengthened, which mainly expanded on the pros and cons of NIPD testing, truly did not affect a woman's interest level. It is notable, however, that the women who read the longer description were less likely to consider NIPD to be a replacement for invasive prenatal diagnosis, but rather to think of it as a first step in their prenatal decision making.

When asked if they would prefer NIPD over current screening or diagnostic testing, 1 in 5 women reported that they would do whatever their doctor recommended. This indicates that for a significant portion of women a discussion with their healthcare provider, as well as the professional recommendation of their physician, would be crucial to their choice about the test. This discussion between the patient and healthcare provider surrounding NIPD has the potential to significantly affect a woman's views toward this type of testing. Considering the gravity of the information that can be obtained through NIPD and the potential difficult decisions that this testing could lead to, it is critical that women make a thoughtful and informed decision regarding this testing, which requires a comprehensive discussion about appropriate informed consent for NIPD testing.

Currently, the informed consent process for prenatal screening differs significantly from the consent procedure for invasive diagnostic testing (Benn and Chapman, 2010). The consent process for invasive prenatal diagnostic testing is often quite rigorous; the patient generally meets with a healthcare professional to discuss the pros and cons of testing and the full implications of the information being obtained, and then again briefly discusses testing with the doctor who will perform the procedure before providing written consent. The consent process for prenatal screening is often much less thorough. Patient consent for maternal serum screening has historically been problematic (Benn and Chapman, 2009) with many women reporting unawareness in whether they underwent screening, and confusion regarding what the test is able to determine. Many women who undergo maternal serum screening seem to be passively involved in the decision to undergo the testing (Seror *et al.*, 2006) or appear not to make an informed choice (Van den Berg *et al.*, 2005). Although this situation is less than ideal, an opportunity for providing more information and guidance occurs if the woman is found to be at high risk. This two-step process allows women at high risk to receive thorough counseling without alarming low-risk women and saves time for the healthcare providers (Benn and Chapman, 2010). When considering NIPD testing, it is unclear whether the consent process will follow the model of prenatal screening or invasive diagnostic testing.

Since NIPD would have no physical risks and would be logistically convenient, informed consent for NIPD may follow the model of prenatal screening, and several authors have expressed concern over this possibility (Wright and Chitty, 2009; Benn and Chapman, 2010; Deans and Newson, 2010). Women undergo a multitude of blood tests during pregnancy and the similarity of this diagnostic test to other pregnancy blood draws might mask its implications and ramifications. NIPD testing could be performed virtually anywhere and could be ordered by a patient's obstetrician or primary care physician, eliminating the need for referral to a specialty center. Due to the noninvasive nature and the lack of miscarriage risk, obstetricians may be less likely to approach the consent process as rigorously for NIPD as they currently do for invasive diagnostic testing (Van den Heuvel *et al.*, 2009). While the elimination of physical risk removes one important aspect of the informed consent discussion for diagnostic testing, the information obtainable from this testing and the consequences of knowing this information, including the potential decisions that may arise if a fetus is diagnosed with aneuploidy, should also be a major focus of the consent process (Benn and Chapman, 2010; Deans and Newson, 2010).

In our study over a quarter of women were hesitant about NIPD testing. Considering this, we suggest that an in-depth discussion about the potential results and ramifications of this testing (such as an ultimate decision of whether to terminate the pregnancy) should occur before NIPD is undertaken. It is unclear who will be responsible for having this discussion with patients. The discussion could occur through the obstetrician or through referral to a genetic counselor. In our study, half of the respondents expressed interest in pre-test genetic counseling and 94.6% were interested in discussing NIPD results with a genetic counselor at some point. Considering the limited number and distribution of genetic counselors nationwide, it will likely not be possible for counselors to be the sole, or even primary facilitators of informed consent for NIPD. Prenatal genetic counseling practice will need to develop approaches to work with obstetrical practices to ensure that appropriate information is provided to women to facilitate informed decisions at the point when NIPD becomes routinely available to all pregnant women.

Study Limitations

This study was limited by its relatively small sample size, which although unusually diverse in ethnic background, had an over-representation of highly educated and older women. Nationwide, approximately 15% of pregnant women are 35 or older, compared to 33% in our sample (CDC National Vital Statistics System, 2008 data). Due to the older age of this sample population, these women were at baseline higher risk to have a baby with a chromosomal abnormality than the general population, as indicated by the higher screen positive rate seen in our sample of 11% compared to the California average of 4.8% (California Dept of Public Health, PDC Manual). Thirty-one percent of pregnant women have a college degree or higher nationwide, compared to 71% in our sample (CDC, 2008 data). Since older women and highly educated women are more likely to demonstrate interest in prenatal diagnosis, this may have biased our results in favor of NIPD. Future studies with larger sample sizes and different populations would be useful to further determine women's attitudes toward NIPD. It is important to remember that women's current attitudes toward NIPD may not predict future uptake. Additional research into the best ways to provide informed choice to women regarding NIPD testing is also needed.

Conclusions

Pregnant women were generally interested in NIPD, although over a quarter reported that they were ambivalent or uninterested in this type of testing. Sufficient discussion between healthcare providers and patients about NIPD testing will likely be crucial to allow women to make an informed choice regarding NIPD.

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References

- American College of Obstetrics and Gynecology Practice Bulletin No. 88. Invasive prenatal testing for aneuploidy. *Obstet Gynecol.* December; 2007 110(6):1459–1467. [PubMed: 18055749]
- Benn PA, Chapman AR. Ethical challenges in providing noninvasive prenatal diagnosis. *Curr Opin Obstet Gynecol.* 2010; 22:128–134. [PubMed: 20098325]
- Benn PA, Chapman AR. Practical and Ethical Considerations of Noninvasive Prenatal Diagnosis. *JAMA.* 2009; 301(20):2154–2156. [PubMed: 19470991]
- Bishop AJ, Marteau TM, Armstrong D, et al. Women and health care professionals' preferences for Down's syndrome screening tests: a conjoint analysis. *BJOG.* 2004; 111:775–779. [PubMed: 15270923]

- California Department of Public Health. [Accessed 18 April 2011] Prenatal Diagnosis Center Manual. 2009. http://www.cdph.ca.gov/programs/pns/Documents/PDCManualFinal_3-26-09.pdf
- Center for Disease Control and Prevention, National Vital Statistics System. [Accessed 31 March 2011]. Birth Data-Characteristics of Mother. 2008. <http://www.cdc.gov/nchs/nvss.htm>
- Chiu RWK, Lo YMD. Non-invasive prenatal diagnosis by fetal nucleic acid analysis in maternal plasma: the coming of age. *Semin Fetal Neonatal Med.* 2010; 16(2):88–93. [PubMed: 21075065]
- Chiu RWK, Akolekar R, Zheng YWL, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ.* 2011; 342:c7401. [PubMed: 21224326]
- De Jong A, Dondorp WJ, de Die-Smulders CEM, et al. Non-invasive prenatal testing: ethical issues explored. *Eur J Hum Genet.* 2010; 18:272–277. [PubMed: 19953123]
- Deans Z, Newson A. Should Non-Invasiveness Change Informed Consent Procedures for Prenatal Diagnosis? *Health Care Anal.* 2010; 1007/s10728-010-0146-8
- Ehrich M, Deciu C, Zwiefelhofer T, et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. *Am J Obstet Gynecol.* 2011; 204:205.e1–11. [PubMed: 21310373]
- Evans MI, Kilpatrick M. Noninvasive Prenatal Diagnosis: 2010. *Clin Lab Med.* 2010; 30:655–665. [PubMed: 20638579]
- Fan HK, Blumenfeld YJ, Chitkara U, et al. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *PNAS.* 2008; 105(42):16266–16271. [PubMed: 18838674]
- Fan HK, Quake SR. Sensitivity of Noninvasive Prenatal Detection of Fetal Aneuploidy from Maternal Plasma Using Shotgun Sequencing Is Limited Only by Counting Statistics. *PLoS ONE.* 2010; 5(5):e10439. [10.1371/journal.pone.0010439](https://doi.org/10.1371/journal.pone.0010439) [PubMed: 20454671]
- Gene Security Network. [Accessed June 1, 2011] Non-invasive Prenatal Diagnosis [Online]. 2011. Available at: <http://www.genesecurity.net/other-testing/nipd/>
- Greely HT. Get ready for the flood of fetal gene screening. *Nature.* 2011; 469:289–291. [PubMed: 21248817]
- Hahn S, Jackson LG, Kolla V, et al. Noninvasive prenatal diagnosis of fetal aneuploidies and Mendelian disorders: new innovative strategies. *Expert Rev Mol Diagn.* 2009; 9(6):613–621. [PubMed: 19732005]
- Hall A, Bostanci A, Wright CF. Non-Invasive Prenatal Diagnosis Using Cell-Free Fetal DNA Technology: Applications and Implications. *Public Health Genomics.* 2010; 13:246–255. [PubMed: 20395693]
- Herzenberg LA, Bianchi DW, Schroeder J, et al. Fetal cells in the blood of pregnant women: detection and enrichment by fluorescence-activated cell sorting. *Proc Natl Acad Sci.* 1979; 76:1453–1455. [PubMed: 286330]
- Kelly SE, Farrimond HR. Non-invasive prenatal diagnosis: A study of public attitudes. *Public Health Genomics.* 2011 in press.
- Kobleka C, Mattman A, Langlois S. An evaluation of the decision-making process regarding amniocentesis following a screen-positive maternal serum screen result. *Prenat Diagn.* 2009; 29:514–519. [PubMed: 19242922]
- Kooj L, Tymstra T, van den Verg P. The attitudes of women toward current and future possibilities of diagnostic testing in maternal blood using fetal DNA. *Prenat Diagn.* 2009; 29:164–168. [PubMed: 19180577]
- Kuppermann M, Gates E, Washington A. Racial-ethnic differences in prenatal diagnostic test use and outcomes: Preferences, socioeconomic, or patient knowledge. *Obstet Gynecol.* 1996; 87:675–682. [PubMed: 8677066]
- Learman LA, Kuppermann M, Gates E, et al. Social and familial context of prenatal genetic testing decisions: Are there racial/ethnic differences? *Am J Med Genet.* 2003; 119C(1):19–26. [PubMed: 12704634]
- Lo YMD, Corbetta N, Chamberlain PF. Presence of fetal DNA in maternal plasma and serum. *Lancet.* 1997; 360:485–487. [PubMed: 9274585]

- Lumley MA, Zamerowski SA, Jackson L, et al. Psychosocial correlates of pregnant women's attitudes toward prenatal maternal serum screening and invasive diagnostic testing: Beyond traditional risk status. *Genetic Testing*. 2006; 10(2):131–138. [PubMed: 16792517]
- Mueller VM, Huang T, Summers AM, Winsor SHM. The influence of risk estimates obtained from maternal serum screening on amniocentesis rates. *Prenat Diagn*. 2005; 25:1253–1257. [PubMed: 16353274]
- Nakata N, Wang Y, Bhatt S. Trends in prenatal screening and diagnostic testing among women referred for advanced maternal age. *Prenat Diagn*. 2010; 30:198–206. [PubMed: 20063323]
- Newson AJ. Ethical aspects arising from non-invasive fetal diagnosis. *Semin Fetal Neonatal Med*. 2008; 13:103–108. [PubMed: 18243828]
- Poon LLM, Leung TN, Lau TK, Lo YM. Presence of fetal RNA in maternal plasma. *Clin Chem*. 2000; 46:1832–1824. [PubMed: 11067820]
- Saucier JB, Johnston D, Wicklund CA, et al. Racial-ethnic differences in genetic amniocentesis uptake. *J Genetic Counseling*. 2005; 14(3):189–195.
- Schmitz D, Henn W, Netzer C. No risk, no objections? Ethical pitfalls of cell-free fetal DNA and RNA testing. *BMJ*. 2009; 339:165.
- Sequenom Inc. [Accessed June 1, 2011] Professor Dennis Lo Trisomy 21 Clinical Validation Study Published in British Medical Journal [Online]. 2011. Available at: <http://www.sequenom.com/home/media/news/>
- Seror V, Ville Y. Prenatal screening for Down syndrome: women's involvement in decision-making and their attitudes to screening. *Prenat Diagn*. 2009; 29:120–128. [PubMed: 19123253]
- Skotko BG. With new prenatal testing, will babies with Down syndrome slowly disappear? *Arch Dis Child*. 2009; 94(11):823–826. [PubMed: 19531527]
- Spencer K, Aitken D. Factors affecting women's preference for type of prenatal screening test for chromosomal anomalies. *Ultrasound Obstet Gynecol*. 2004; 24:735–739. [PubMed: 15505874]
- Teman E, Ivry T, Bernhardt B. Pregnancy as a Proclamation of Faith: Ultra-Orthodox Jewish Women Navigating the Uncertainty of Pregnancy and Prenatal Diagnosis. *Am J Med Genet, Part A*. 2010; 155:69–80.
- Van de Heuvel A, Chitty L, Dormandy E, et al. Will the Introduction of Non-Invasive Prenatal Diagnostic Testing Erode Informed Choices? An Experimental Study of Health Care Professionals. *Patient Education and Counseling*. 2009; 78:24–28. [PubMed: 19560305]
- Van den Berg M, Timmermans DRM, ten Kate LP, et al. Are pregnant women making informed choices about prenatal screening? *Genetics in Medicine*. 2005; 7(5):332–338. [PubMed: 15915085]
- Van Landingham S, Bienstock J, Wood Denne E, Hueppchen N. Beyond first trimester screen: Can we predict who will choose invasive testing? *Genetics in Medicine*. 2011 epub ahead of print. 10.1097/GIM.0b013e31820a7701
- Verinata Health. [Accessed June 1, 2011] Maternal and Fetal Health [Online]. 2011. Available at: <http://www.mdv.com/our-companies/verinata-health>
- White M. Making Sense of Genetic Uncertainty: The Role of Religion and Spirituality. *Am J Med Genet*. 2009; 151C:68–76. [PubMed: 19170081]
- Wright CF, Chitty LS. Cell-Free Fetal DNA and RNA in Maternal Blood: Implications for Safer Antenatal Testing. *BMJ*. 2009; 339:161–165.
- Zamerowski ST, Lumley MA, Arreola RA, et al. Favorable attitudes toward testing for chromosomal abnormalities via analysis of fetal cells in maternal blood. *Genetics in Medicine*. 2001; 3(4):301–309. [PubMed: 11478531]

Appendix I: NIPD Descriptions

Brief NIPD description

Every pregnant woman has a chance to have a baby with a birth defect. There are some types of birth defects, called chromosome abnormalities, that we can learn about before the baby is born. Examples of chromosome abnormalities are Down syndrome and Trisomy 18

and there is no cure for these conditions. The risk for having a child with one of these conditions increases as a woman gets older, although it can happen to a woman of any age. The current tests that are available to diagnose chromosome abnormalities before birth are amniocentesis and chorionic villus sampling (CVS). These tests are very accurate but they are invasive tests and they have a small risk of causing a miscarriage (less than 1%). CVS can be done between 10–12 weeks of pregnancy and amniocentesis is available after 15 weeks of pregnancy.

If a chromosome abnormality is diagnosed prenatally, the available options are to continue the pregnancy and either keep the baby or give it up for adoption, or terminate the pregnancy. When deciding whether to have a diagnostic test for chromosome abnormalities, you should consider whether you would want to have this information about your developing baby and if you might do anything differently on the basis of the results.

A new test, called **Non-Invasive Prenatal Diagnosis (NIPD)**, may soon be available that could diagnose chromosome abnormalities earlier in pregnancy (between 7–10 weeks). This test uses a sample of mom's blood and is completely safe for the unborn child. This test does NOT have a risk of miscarriage and we expect that it will have a similar level of accuracy as CVS and amniocentesis.

Detailed NIPD description

Every pregnant woman has a chance to have a baby with a birth defect. There are some types of birth defects, called chromosome abnormalities, that we can learn about before the baby is born. Examples of chromosome abnormalities are Down syndrome and Trisomy 18 and there is no cure for these conditions. The risk for having a child with one of these conditions increases as a woman gets older, although it can happen to a woman of any age. The current tests that are available to diagnose chromosome abnormalities before birth are amniocentesis and chorionic villus sampling (CVS). These tests are very accurate but they are invasive tests and they have a small risk of causing a miscarriage (less than 1%). CVS can be done between 10–12 weeks of pregnancy and amniocentesis is available after 15 weeks of pregnancy.

If a chromosome abnormality is diagnosed prenatally, the available options are to continue the pregnancy and either keep the baby or give it up for adoption, or terminate the pregnancy. When deciding whether to have a diagnostic test for chromosome abnormalities, you should consider whether you would want to have this information about your developing baby. Some reasons why people might want this information include: it would help them prepare for the birth of a child with a disability; the test results would decrease their anxiety; or they may consider terminating a pregnancy if a birth defect was found. Other people may not want this information because it would not impact how they would proceed with the pregnancy.

A new test, called **Non-Invasive Prenatal Diagnosis (NIPD)**, may soon be available that could diagnose chromosome abnormalities earlier in pregnancy. This test uses a sample of mom's blood and is completely safe for the unborn child. This test does NOT have a risk of miscarriage and we expect that it will have a similar level of accuracy as CVS and amniocentesis. Since NIPD testing can be performed very early in pregnancy (between 7–10 weeks), it could give a woman more time to consider her options regarding termination or continuation of the pregnancy. These test results would also be available to a woman before her pregnancy is physically visible to other people, allowing for a more private decision if she chose to terminate the pregnancy. It is important to realize that many pregnancies where the fetus has a chromosome abnormality will naturally end in a miscarriage and because this

test is performed so early, it could identify a chromosome abnormality in a pregnancy that would naturally end in miscarriage. There is also some chance that NIPD testing could give an unclear result and an invasive test (CVS or amniocentesis) would be offered later in the pregnancy to clarify the results.

What's already known about this topic?

- Pregnant women report hypothetical interest in NIPD in two previous studies.
- Healthcare providers may treat the consent process for NIPD differently than for invasive diagnostic testing

What does this study add?

- Age, ethnicity, education level, and likelihood to terminate an affected pregnancy are associated with level of interest in NIPD.
- Many women will look to their doctor's recommendations when making a decision about NIPD.
- Women are interested in seeing a genetic counselor to discuss NIPD.

Table 1

Demographic characteristics of the sample according to which NIPD description was received

	Total n (%)	Brief n (%)	Detailed n (%)
Age			
< 35	76 (66.7%)	43 (69.4%)	33 (63.5%)
≥ 35	38 (33.3%)	19 (30.6%)	19 (36.5%)
Education			
High school or less	10 (8.8%)	6 (9.7%)	4 (7.7%)
Some college	23 (20.2%)	12 (19.4%)	11 (21.2%)
College degree	34 (29.8%)	21 (33.9%)	13 (25.0%)
Graduate/Post-Graduate	47 (41.2%)	23 (37.1%)	24 (46.2%)
Ethnicity			
White, non-Hispanic	34 (29.8%)	18 (29.0%)	16 (30.8%)
African-American	10 (8.8%)	5 (8.1%)	5 (9.6%)
Hispanic	24 (21.1%)	17 (27.4%)	7 (13.5%)
Asian-Pacific Islander	35 (30.7%)	17 (27.4%)	18 (34.6%)
Middle Eastern	2 (1.8%)	0 (0%)	2 (3.8%)
Other	2 (1.8%)	1 (1.6%)	1 (1.9%)
Multiracial	7 (6.1%)	4 (6.5%)	3 (5.8%)
Religion			
Christian	64 (57.1%)	34 (55.7%)	30 (58.8%)
Jewish	2 (1.8%)	1 (1.6%)	1 (2.0%)
Muslim	5 (4.5%)	3 (4.9%)	2 (3.9%)
Hindu	6 (5.4%)	3 (4.9%)	3 (5.9%)
Buddhist	3 (2.7%)	2 (3.3%)	1 (2.0%)
Other	8 (7.1%)	6 (9.8%)	2 (3.9%)
None	24 (21.4%)	12 (19.7%)	12 (23.5%)
Religiosity			
High	42 (38.5%)	17 (29.3%)	25 (49.0%)
Medium	34 (31.2%)	25 (43.1%)	9 (17.6%)
Low	33 (30.2%)	16 (27.6%)	17 (33.3%)

Table 2

Previous use of prenatal screening and diagnostic tests

	n (%)
Had prenatal screening in current or past pregnancy?	
Yes	91 (81.3%)
No	19 (17.9%)
Unsure	1 (0.9%)
Results of prenatal screening *	
High risk for trisomy	10 (11.0%)
High risk for NTDs	1 (1.1%)
Low or average risk	75 (82.4%)
Unsure	6 (6.6%)
Had CVS or amniocentesis in current or previous pregnancy?	
Yes	24 (21.4%)
No	87 (77.7%)
Unsure	1 (0.9%)
Results of CVS or amniocentesis †	
Diagnosis of a genetic condition	3 (12.5%)
Other problem	2 (8.3%)
Normal result	19 (79.2%)

* This data represents only women who underwent prenatal screening (n=91).

† This data represents only women who underwent CVS or amniocentesis (n=24).

Table 3

Attitudes of women toward NIPD and termination of an affected pregnancy based on which NIPD description they received

	Total n (%)	Brief n (%)	Detailed n (%)
Interest in NIPD			
Very interested	62 (56.4%)	32 (55.2%)	30 (57.7%)
Somewhat interested	17 (15.5%)	11 (19.0%)	6 (11.5%)
Neutral	25 (22.7%)	13 (22.4%)	12 (23.1%)
Less interested	4 (3.6%)	1 (1.7%)	3 (5.8%)
Not at all interested	2 (1.8%)	1 (1.7%)	1 (1.9%)
Single most important factor in decision about NIPD			
Safety for fetus	75 (75%)	43 (75.4%)	32 (74.4%)
Accuracy of the results	13 (13%)	7 (12.3%)	6 (14.0%)
Results available earlier	7 (7%)	5 (8.8%)	2 (4.7%)
Specific conditions tested for	5 (5%)	2 (3.5%)	3 (7.0%)
Safety for mother	0 (0%)	0 (0%)	0 (0%)
Convenience	0 (0%)	0 (0%)	0 (0%)
Preference for NIPD or current form of prenatal screening			
Prefer NIPD	34 (30.6%)	20 (32.8%)	14 (28.0%)
Prefer current screening	4 (3.6%)	2 (3.3%)	2 (4.0%)
Prefer to have both	46 (41.4%)	26 (42.6%)	20 (40.0%)
Would do whatever doctor recommends	22 (19.8%)	10 (16.4%)	12 (24.0%)
Unsure	5 (4.5%)	3 (4.9%)	2 (4.0%)
Preference for NIPD or current diagnostic tests			
Prefer NIPD and would use for decisions about pregnancy	34 (30.9%)	24 (40.7%)	10 (19.6%)
Prefer NIPD but follow-up positive results with CVS/amnio	37 (33.6%)	16 (27.1%)	21 (41.2%)
Prefer both NIPD and CVS/amnio	7 (6.4%)	3 (5.1%)	4 (7.8%)
Prefer CVS/amnio only	4 (3.6%)	4 (6.8%)	0 (0%)
Would do what doctor recommends	20 (18.2%)	8 (13.6%)	12 (24.0%)
Unsure	8 (7.3%)	4 (6.8%)	4 (7.8%)
Would like to meet with a genetic counselor regarding NIPD *			
Before testing	55 (49.5%)	29 (47.5%)	26 (52.0%)
After testing regardless of results	36 (32.4%)	21 (34.4%)	15 (30.0%)
After testing, only if results were bad	33 (29.7%)	19 (31.1%)	14 (28.0%)
Prefer not to meet with a genetic counselor	6 (5.4%)	4 (6.6%)	2 (4.0%)
Likelihood to terminate an affected pregnancy			
Likely	38 (33.9%)	19 (31.7%)	19 (36.5%)
Unsure	37 (33.0%)	23 (38.3%)	14 (26.9%)
Not likely	37 (33.0%)	18 (30.0%)	19 (36.5%)

* Participants could select multiple responses so percentages do not add to 100%

Table 4

Level of interest in NIPD compared to demographic and other factors

	Low or neutral interest n (%)	High interest n (%)	p-value
Age			
< 35	25 (34.7%)	47 (65.3%)	0.036
≥ 35	6 (15.8%)	32 (8.4%)	
Education			
Less than college degree	14 (45.2%)	17 (54.8%)	0.013
College degree or higher	17 (21.5%)	62 (78.5%)	
Ethnicity			
Caucasian or Asian	13 (19.4%)	54 (80.6%)	0.011
All other categories	18 (41.9%)	25 (58.1%)	
Self-reported Religiosity			
Low	9 (27.3%)	24 (72.7%)	0.940
Medium	10 (31.3%)	22 (68.8%)	
High	12 (29.3%)	29 (70.7%)	
Self-reported Likelihood to terminate an affected pregnancy			
Low	17 (48.6%)	18 (51.4%)	0.002
Medium	8 (22.9%)	27 (77.1%)	
High	5 (13.2%)	33 (86.8%)	
Description given			
Brief	15 (25.9%)	43 (74.1%)	0.568
Detailed	16 (30.8%)	36 (69.2%)	
Previous use of prenatal screening			
Yes	22 (24.7%)	67 (75.3%)	0.167
No	8 (40.0%)	12 (60.0%)	
Outcome of previous prenatal screening			
High risk	4 (36.4%)	7 (63.6%)	N/A
Low or average risk	15 (16.5%)	76 (83.5%)	
Previous use of diagnostic testing			
Yes	6 (25.0%)	18 (75.0%)	0.792
No	23 (27.7%)	60 (72.3%)	
Outcome of diagnostic testing			
Abnormal Prenatal Diagnosis	1 (20.0%)	4 (80.0%)	N/A
Normal result	5 (25.0%)	15 (75.0%)	

* N/A indicates that p values could not be calculated due to there being cell sizes of <5.