Noninvasive Prenatal Testing and Fetal Sonographic Screening

Roundtable Discussion

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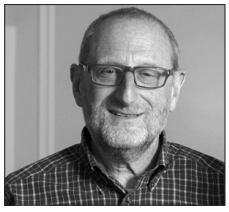

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Abbreviations

cf DNA, cell-free DNA; CMA, chromosomal microarray analysis; CVS, chorionic villus sampling; NIPT, noninvasive prenatal testing; NT, nuchal translucency

doi:10.7863/ultra.34.3.363

Supplemental material online at www.jultrasoundmed.org

Fetal cell-free DNA (cfDNA) is present in the maternal blood from the first trimester of pregnancy onward[1,2] and is rapidly cleared from the circulation after delivery.[3] For these reasons, fetal cfDNA is an important source of fetal genetic material for noninvasive prenatal testing (NIPT).[4] However, fetal cfDNA is only a small proportion of total cfDNA in the maternal blood; various methods of separating the two and quantifying the fetal portion are presently in use.[4–7] Earliest applications of NIPT focused on identifying Y-chromosome sequences not found in the mother and RhD sequences in RhD-negative mothers.[8] Advances in sequencing and computational technologies now allow quantification of the "extra" chromosome copies present in cases of fetal chromosomal trisomy, changes resulting from single gene disorders, and some recessively inherited conditions.[6,9–11] Theoretically, NIPT could also be applied for whole-genome testing of the fetus.[12]

Optimally, NIPT requires the fetal fraction of fetal cfDNA to reach 4% to 5% of the total; this level will usually occur by about 10 weeks' gestation.[9,13] Samples taken too early are at higher risk of test failure. Maternal obesity may also increase the risk of fetal cfDNA failure.[9,14,15] Other potential problems are dizygotic twin pairs, an aneuploid vanishing twin, an insufficient fetal fraction, maternal mosaicism, or malignancy.[9]

Prenatal genetic testing previously required invasive procedures with a small but real risk of miscarriage[16,17]; invasive procedures were generally performed on the advice of caregivers, after consideration of first-trimester screening results. Noninvasive prenatal testing can provide reliable answers to questions about the aneuploidy status and other genetic findings from a maternal blood specimen earlier than nuchal translucency (NT) screening.[18–21] This aspect makes NIPT attractive to many patients, although the window of opportunity for pretest counseling could be lost if patients elect to undergo NIPT without consulting their health care providers. It is incumbent on practitioners and professional societies to provide clear guidelines[13,22,23] regarding the integration of NIPT into prenatal care, including the optimal timing of NIPT, its place among other testing of the mother and her fetus, and understanding the implications of results. Among the most pressing issues for patient counseling is explaining what NIPT does not do: it does not, and cannot, ensure a "perfect baby." Although this statement will seem obvious to the practitioner, patients may glean a false sense of security from a negative NIPT result. Positive results need confirmation by invasive testing,[24] and negative results must be clarified regarding the chromosomal and structural anatomic aberrations that were not screened. False-negative results are also possible.[25,26]

Several approaches have been suggested for the integration of NIPT into existing prenatal screening programs: contingent screening would offer NIPT after other first-trimester testing in cases judged to be high risk; combined testing would insert NIPT in place of, or as a supplement to, other maternal serum analytes such as β-human chorionic gonadotropin and pregnancy-associated plasma protein A; and primary screening would enlist fetal cfDNA as a first-line screening test for aneuploidy. Considerations of cultural sensitivity, costs to public health systems, and the impact of private sector offerings are among the issues that need to be addressed by professional societies as well as regulatory agencies in each country, as the optimal approach is debated.

Ethical Considerations

Noninvasive prenatal testing is a popular option for many patients because it removes, for most women, the consideration of the small but very real risk of fetal loss from invasive testing. Indeed, changes in uptake patterns of chorionic villus sampling (CVS) and amniocentesis have already been noted[27] and will necessarily lead to a drop in the iatrogenic loss of healthy fetuses.

Theoretically, NIPT could be used to obtain whole-genome testing of the fetus. Many of these findings, however, are of unknown clinical importance. Many others may be expressed only after many years. There are potentially serious ethical issues surrounding NIPT[28–30]: among them, the provision of information that may be poorly understood and for which no answer can be provided.

Cost

Introduction of NIPT has already affected changes in the number of amniocentesis and CVS procedures performed.[27,31] The reduction in invasive procedures can offset the cost of NIPT for individuals and public health systems, which is one of its advantages.[32,33] However, as mentioned above, as more syndromes are targeted, the possibility of screen-positive results will rise, leading to an increase in invasive testing procedures for verification. This increase could lead to a resurgence of first-trimester screening as a result of this trend.

Sonographic scanning of fetal anatomy will continue to play an essential role in prenatal surveillance, although its focus may shift away from identification of the various "markers for Down syndrome" to comprehensive anatomic scans. The optimal timing and scope of sonographic investigation of the fetus are still the subjects of some debate and may vary from country to country.

Noninvasive prenatal testing has perhaps raised more questions than it has provided answers.[5] We approached 5 experts in the field of prenatal diagnosis to participate in an online roundtable discussion. We asked them the 10 most pressing questions surrounding NIPT, concerning integration of the testing into existing screening programs, ethical considerations of primary genetic screening, and how they envision prenatal testing (in particular, first-trimester screening) 10 years from now.

The panelists shared their thoughts on each of the 10 questions, and all responses were then sent to all of the participants for a rebuttal round. The expert opinions and consensus from the first and second rounds are summarized below. The full responses of all panelists and their rebuttals to their colleagues' responses are available in the online Appendix.

Questions Posed to the Panel

There is a growing body of evidence that NIPT will soon replace, in one way or another, other screening programs for prenatal diagnosis of chromosomal aberrations. In light of this rapidly developing alternative, please discuss the following:

1. How do you see now, and in the near future, NIPT: as a screening test or as a diagnostic test?

2. If you see NIPT as a screening test, what other screening tests would you recommend be performed in combination with it?

3. Is such an approach worthwhile, or will pairing or grouping NIPT with other screening tests (with lower sensitivity) only detract from its very high sensitivity and specificity? (Its sensitivity now approaches 100%.)

4. What range of gestational ages do you believe is optimal for screening: 11 to 13 or 13 to 15 weeks?

5. Will the current cost of NIPT make such an approach affordable in a public health system?

6. Apart from trisomies, this approach could eventually assess many other genetic abnormalities and associated risks. What are the potential ethical implications?

7. Ethical concepts must also be debated in view of the marketing and "cross-border" shopping that can happen much more easily with these technologies. Do you have any other ethical concerns for using NIPT in view of widespread marketing and consumer expectations that are often encountered in daily practice?

8. Please describe your vision for screening genetic and pregnancy complications 10 years from now.

9. First-trimester screening in the "NT window" includes a sonographic assessment of other complications of pregnancy, such as cervical length for preterm labor, uterine artery Doppler measurements for preeclampsia, fetal biometric measurements for growth restriction, and early fetal anatomic surveys. Do you see them as important features of early pregnancy screening, and will the integration of NIPT into this mix change the order and timing of these screening tests?

10. Will NT measurement alone remain an important part of prenatal screening? Does it have a place in an early screening program that includes NIPT for the most common chromosomal aberrations? Does it have a place as an early second-trimester screening test, if a technically acceptable complete anatomic survey is performed at the same time?

Summary of Responses

1. How do you see now, and in the near future, NIPT: as a screening test or as a diagnostic test?

Summary

Discussants unanimously agreed that NIPT is a screening test and will remain so for the foreseeable future.

2. If you see NIPT as a screening test, what other screening tests would you recommend be performed in combination with it?

Summary

Respondents presented several viewpoints on this question, based both on cost considerations and other added values of first-trimester screening. If cost were not an issue, NIPT could be offered to all patients; one respondent suggested that all patients should be offered all options (CVS, chromosomal microarray analysis [CMA], etc), and NIPT should be offered for those who decline invasive testing after first-trimester screening. Most suggested that NIPT should be implemented as part of a contingent protocol that would retain the advantages of first-trimester screening for triage and other obstetric complications.

Rebuttal

Prof Van den Veyver rebutted that it is essential to offer all options in a nondirective way, detailing all of the risks and benefits of each test. Although costs are high, the costs of missed diagnoses should be taken into account. Prof Wapner rebutted that although a contingent approach is attractive, cutoff values for invasive testing need to be adjusted compared to those presently used to keep costs at a reasonable level and maintain high detection rates of trisomy 21, as well as identify the most common chromosomal anomalies not detected by NIPT.

3. Is such an approach worthwhile, or will pairing or grouping NIPT with other screening tests (with lower sensitivity) only detract from its very high sensitivity and specificity? (Its sensitivity now approaches 100%.)

Summary

Most responded that some sort of cost-effective combination would be the most sensible approach. Combining NIPT with current first-trimester screening might decrease its specificity, although first-trimester screening has other added values. The minority opinion was that

CVS and CMA should be offered to all women and NIPT reserved for cases interested in specific chromosomal abnormalities. It is imperative to consider the issue of fetal loss in addition to the economic cost. Performing CMA for all will lead to many false-positive results and much greater fetal loss.

Rebuttal

Prof Van den Veyver rebutted that the issue of comparative sensitivities must be considered. Prof Wapner reiterated that counseling is key, and that patients can make their own risk/benefit assessment: "There is no balance of sensitivity and specificity that is right for all patients."

4. What range of gestational ages do you believe is optimal for screening: 11 to 13 or 13 to 15 weeks?

Summary

There was no consensus on this issue; viewpoints varied across several possible approaches, from performing screening as early as possible to suggested algorithms that encompassed both the earlier and later windows. Recommendations for the integration of NIPT into existing screening programs should consider the advantages and disadvantages of both windows in addition to cost factors. Screening for NT and maternal serum analytes at 11 to 13 weeks is feasible and allows performance of CVS in suspected cases. However, the addition of NIPT only after receipt of the analysis may introduce a delay that moves invasive testing beyond the CVS window. It may be more desirable to use transvaginal sonography if fetal anatomic screening is a major goal of first-trimester screening during early pregnancy. However, the practice of routine transvaginal sonography is not uniformly accepted among different countries, and its routine implementation could be limited by economic limitations.

Rebuttal

Prof Cuckle reiterated that screening at 13 to 15 weeks would obviate the problem of placental mosaicism raised by Prof Kagan: since the source of fetal cfDNA is the placenta,[34] some test-positive results may represent placental mosaicism with a normal fetus. Chorionic villus sampling might inadvertently repeat this false-positive result. Amniocentesis, however, would avoid this pitfall by sampling fetal, as opposed to placental, cells.

5. Will the current cost of NIPT make such an approach affordable in a public health system?

Summary

Since costs will vary from place to place, this factor is difficult to determine for all practice sites. However, the question can be addressed again as the cost of NIPT decreases. Many factors must be taken into consideration, including the savings in avoided invasive procedures, the cost of missed diagnoses, and the human cost of fetal loss from invasive testing. The consensus is that at today's prices, NIPT is not affordable in a public health system.

6. Apart from trisomies, this approach could eventually assess many other genetic abnormalities and associated risks. What are the potential ethical implications?

Summary

Respondents viewed this question very differently. Since genomic investigation is already available clinically, two argued that extending this technology to fetuses would not raise a new issue; rather, the rules that are already in place would apply in this case as well. Issues surrounding the cumulative false-positive rates and lower positive predictive values, and subsequent invasive testing for trivial findings, were raised, as was the issue of cultural differences. The small risk of invasive testing imposed some restraints on "unlimited" fetal genomic testing. The magnitude of testing will change as genetic materials become more accessible. Many findings may be of questionable importance at best because they may become relevant only very late (eg, *BRCA*). However, prenatal knowledge of some findings may confer an advantage in improved postnatal outcomes through appropriate intervention and management.

Rebuttal

Prof Wapner stressed that well-counseled and -informed patients can understand the implications of genomic findings, whether collected invasively or noninvasively. As experience with CMA has increased, our knowledge of the clinical relevance of findings has improved so that findings of uncertain clinical relevance now occur in only 1% of cases.

7. Ethical concepts must also be debated in view of the marketing and "cross-border" shopping that can happen much more easily with these technologies. Do you have any other ethical concerns for using NIPT in view of widespread marketing and consumer expectations that are often encountered in daily practice?

Summary

All respondents agreed to some degree that there is a need for patient counseling, caregiver education, and regulation

of laboratories providing the services. Although local authorities must devise informed consent and information materials, monitoring the observance of guidelines will be difficult. If testing is offered in the framework of a public health service, that provider will be able to control what is examined and require provision of counseling. This process can help limit overuse and the increase in false-positive results and unnecessary invasive testing.

Rebuttal
Prof Wapner stressed that in a public health service setting, the provider can control the breadth of testing and require counseling, thereby limiting overuse and increased false-positive results and invasive testing.

8. Please describe your vision for screening genetic and pregnancy complications 10 years from now.

Summary
Respondents varied widely in their vision for the future, from integrating NIPT into existing practice to a complete change in approach, with comprehensive genetic analysis for all. Please see question 9 below, in which they were asked to describe a practical approach to first-trimester screening that integrated the sonographic scan with NIPT.

9. First-trimester screening in the "NT window" includes a sonographic assessment of other complications of pregnancy, such as cervical length for preterm labor, uterine artery Doppler measurements for preeclampsia, fetal biometric measurements for growth restriction, and early fetal anatomic surveys. Do you see them as important features of early pregnancy screening, and will the integration of NIPT into this mix change the order and timing of these screening tests?

Summary
All respondents recognized the importance of sonographic anatomic screening as well as sonographic and maternal serum screening for other obstetric complications.

10. Will NT measurement alone remain an important part of prenatal screening? Does it have a place in an early screening program that includes NIPT for the most common chromosomal aberrations? Does it have a place as an early second-trimester screening test, if a technically acceptable complete anatomic survey is performed at the same time?

Summary
The consensus was that NT measurement will continue to be a useful part of first-trimester screening.

Second-Round Questions

At the end of the first round, the panelists' full responses were sent to all other participants with summaries of the consensus and dissenting opinions, as well as moderators' comments. Discussants were invited to rebut their colleagues' responses and to answer the 3 following questions, which arose during the process of collation:

1. None of the respondents considered the question of fetal loss that would result from the algorithm they suggest. I would ask: How would your suggested integration of NIPT into first-trimester screening impact fetal loss rates?

Summary
All respondents agreed that as false-positive rates are reduced and fewer invasive procedures are performed, loss rates will also drop. However, as testing expands to include more anomalies, false-positive rates will rise. Two related issues were raised: that of the true loss rate from invasive testing, which has been shown to be lower than what is usually quoted,[16,35] and the approach to counseling for invasive testing. The acceptable level of risk, of both missing an affected pregnancy and losing a healthy fetus, will vary among patients. Counseling enables fully informed and empowered patients to decide regarding NIPT and invasive testing.

2. Broadening the scope of NIPT will lead to increased false-positive rates and possibly to increased (instead of decreased) invasive testing. How would you envision regulation to prevent this, to prevent increases in fetal loss: on the level of national professional organizational guidelines, international professional guidelines, or national legislation?

Summary
There was no consensus on this question, as respondents considered various aspects of the issue. Regulation might contain costs in public health services, and national registries may assist in validation of testing. The importance of comprehensive patient counseling was stressed again.

3. If one of our goals in first-trimester screening is to provide an early anatomic screen, it should be performed

in the best way possible. Nuchal translucency scanning can be performed at 13 weeks as part of a full anatomic scan, if anatomic scanning is performed by transvaginal sonography. Should we maximize the anatomic survey during the first trimester by performing transvaginal scanning to increase detection rates of anatomic anomalies?

Summary

There was no consensus on this question. Respondents differed regarding the feasibility of integrating full anatomic scanning into existing systems, from considerations of cost as well as quality control compared to existing first-trimester screening, and whether the incremental added value of the earlier examination would justify the investment. Where 13-week anatomic scanning is performed, the extent should be carefully defined, but the approach might be left to the discretion of the operator.

Moderator's Closing Remarks

I would like to thank the panelists for their thoughtful responses to our roundtable discussion. This was an enlightening opportunity for experts of various disciplines to exchange and debate their impressions of the present and future of prenatal genetic testing.

Questions fell roughly into 3 domains: practical design of first-trimester screening, including provision and timing of NIPT, NT measurement, and fetal anatomic scanning; ethical considerations of patient autonomy and beneficence; and regulatory and cost/benefit issues. There is considerable overlap among the domains, as would be expected in any health service debate: eg, cost will impact accessibility to services, and some regulation will be instituted if NIPT is provided in a public health service setting.

There were some areas of consensus. For the time being, NIPT will continue to be considered a screening, as opposed to diagnostic, test. Nuchal translucency will continue to have a place in first-trimester screening. An overarching theme for all panelists was the imperative of respecting patient autonomy while maintaining the balance between beneficence and nonmaleficence. Panelists agreed that thorough and effective counseling is key to achieving these aims.

Various algorithms for the integration of NIPT into first-trimester screening were broached. Local adoption of any screening algorithm will depend on the cost of the test and whether it will be underwritten by patients, insurers, or a public health system. The feasibility and timing of complete first-trimester anatomic scanning will also vary, depending on the cost and availability of trained personnel, among other constraints. The final configuration of first-trimester screening in any locale will necessarily be influenced by local cultural differences and many other practical factors.

Many issues are still subjects of controversy: the breadth of testing that should be offered, whether regulation is desirable or even possible, and the issue of fetal risk from referral to invasive testing were points of difference. Although educated and empowered patients can understand the risk of tests they undergo, it is incumbent on practitioners to inform their decisions to mitigate avoidable risk.

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