Genetics inMedicine | COMMENTARY

Too much, too soon?: Commercial provision of noninvasive prenatal screening for subchromosomal abnormalities and beyond

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> I was not informed of the new micro deletion portion of [NIPS] and that it was basically experimental. I tested positive for 1p36 and chose amniocentesis to confirm or deny. The amnio was done at 15 weeks because we would have terminated for 1p36… the amnio showed normal genes… I would never do this screening again and am so frustrated that these tests are released without having them validated in a low risk population or against actual tests like amnio. The amount of trauma and stress that this brought was just horrible. (Personal correspondence, NIPS customer. Information has been edited to preserve anonymity.)

Noninvasive prenatal screening (NIPS) using cell-free fetal DNA has been commercially available in the United States since 2011 for the detection of trisomies 13 (Patau syndrome), 18 (Edwards syndrome), and 21 (Down syndrome). Five companies—Sequenom, Natera, Ariosa Diagnostics, Verinata Health, and Integrated Genetics—currently market NIPS in the United States. The perceived benefits of this technology, which include the lack of procedure-related risk associated with invasive testing while achieving higher sensitivity and specificity than serum screening, have led to rapid adoption by patients and providers, coverage by several third-party payers, and commercial success.[1,2] The state of California recently announced that it would add NIPS for aneuploidy testing to its universal prenatal screening program as a second-tier screen,[3] and some state-based testing programs and Medicaid plans now reimburse for NIPS.

Since they were introduced, NIPS panels have added fetal sex and sex chromosome aneuploidies, including XXY (Klinefelter syndrome), XYY syndrome, and monosomy X (Turner syndrome) (see for example http://www.illumina.com/clinical/reproductive-genetic-health/clinical-labs/nipt.html). Natera and Sequenom also began offering expanded test panels that claim to detect subchromosomal abnormalities (SCAs), including 22q (DiGeorge syndrome), 5p (Cri-du-chat syndrome), 15q (Prader-Willi/Angelman syndromes), and 1p36 deletion syndrome (http://www.panoramatest.com). Sequenom later added microdeletions in chromosomes 11 (Jacobsen syndrome), 8 (Langer-Giedion syndrome), and 4 (Wolf-Hirschhorn syndrome) (see https://laboratories.sequenom.com/patients/maternit21-plus/). Several companies worldwide now offer NIPS microdeletion panels (**Table 1**) because, they assert, the conditions in question are severe and the information has clinical utility. For instance, prenatal information about 22q11.2 deletions may allow physicians and families to prepare for the delivery of a child in a specialty cardiac care center.[4] But observers have argued that the clinical utility of some of the expanded content is questionable and that lumping trisomy testing and SCA testing into the same test conflates disparate clinical realities.[5]

VALIDATION

The commercial provision of NIPS for subchromosomal anomalies raises several concerns in addition to the question of clinical utility. Before offering tests for trisomies 13, 18, and 21, several companies conducted large-scale validation trials.[6–10] Peer-reviewed publications demonstrating high sensitivity (between 98.0 and 99.0%) and specificity (between 99.5% and 99.8%) were important to the uptake of NIPS by providers and payers. High specificity, in particular, is considered important in prenatal genetic testing because a reduction in false positives allows clinicians to avoid unnecessary invasive procedures that carry a small risk of miscarriage.

NIPS for SCAs has not been validated in large-scale studies, although a few reports of limited cases have been published in the peer-reviewed literature[11–13] or presented at scientific meetings.[14] Sex chromosome aneuploidies have been included in some validation studies, but researchers acknowledge that the positive predictive value of these conditions is low.[9,15,16] With rare conditions, large clinical validation studies become less feasible; the rarity of the conditions has a negative impact on the positive predictive value and negative predictive value of tests. Statistically, NIPS for SCAs and sex chromosome aneuploidies will yield more false positives than tests for more common conditions such as trisomy 21, and anecdotal accounts

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Table 1 Commercial offering of noninvasive prenatal screening for subchromosomal abnormalities

Company	Test name	Trisomies	Microdeletions	Testing option
Seqeunom	MaterniT21Plus[a,]	21, 18, 13, 16, 22	22q11.2 (DiGeorge or velocardiofacial syndrome), 1p36 deletion, 5p (Cri-du-chat syndrome), 15q11.2 (Angelman and Prader-Willi syndrome) 4p (Wolf-Hirschhorn syndrome), 8q (Langier-Gideon syndrome), 119 (Jacobsen syndrome)	Opt out
Natera	Panorama[b]	21, 18, 13	22q11.2 (Di George or velocardiofacial syndrome), 1p36 deletion, 5p (Cri-du chat syndrome), 15q11.2 (Angelman and Prader-Willi syndrome)	Opt in
BGI	NIFTY Plus[c,d,]*	21, 18, 13	5p-, 1p36, and 2q33.1 deletions	N/A
Igenomix[e]	Nace Plus[f,]*	18, 13, 21, 9, 16	22q11.2 (DiGeorge syndrome), 1p36, 15q11.2 (Angelman, Prader-Willi syndromes) 5p (Cri-du-chat syndrome), and 4p (Wolf-Hirschhorn syndrome)	N/A
Illumina	Verifi[g]	18,13, 21, 9,16	22q11.2 (DiGeorge syndrome), 1p36, 15q11.2 (Angelman, Prader-Willi syndromes) 5p (Cri-du-chat syndrome), and 4p (Wolf-Hirschhorn syndrome)	Opt in

*In these cases the tests are differentiated by name to specifically order the microdeletion testing content.

N/A, not applicable.

[a]http://laboratories.sequenom.com/maternit21plus/prenatal-test-information-for-providers. [b]http://www.panoramatest.com/en/healthcare-provider/#about. [c]http://www.niftytest.com/wp-content/uploads/2014/09/BGIDX_NIFTY_Leaflet_24.06.2014_New_Code.pdf. [d]http://www.bgilearning.com/down/NIFTY_PPT.pptx. [e]Previously Iviomics. [f]http://www.igenomix.com/wp-content/uploads/NACE-gynecologist-brochure-ENG.pdf. [g]Unpublished personal communication. See also http://progenity.com/sites/default/files/resources/GeneticCarrierPrenatal%20Req_082014-FINAL.pdf#view=Fit.

from physicians, patients, and genetic counselors concur. This leads to an increase in confirmatory invasive testing, thus eroding the benefits of NIPS in reducing unnecessary invasive procedures needed to confirm common trisomies. Without accurate information about the positive predictive value and negative predictive value of SCAs, clinicians may make uninformed decisions about ordering these tests and interpret test results inaccurately. Furthermore, patients and providers may see NIPS as a way to avoid invasive microarray testing despite the fact that invasive testing remains the gold standard for diagnosing SCAs.

The offer of NIPS is currently recommended in "high-risk" pregnancies in general: pregnancies of women with advanced maternal age, pregnancies in which an ultrasound abnormality is detected, or when there is a history of chromosomal defects. Because the risk of trisomy 21 and other chromosomal aneuploidies increases with maternal age, the validation studies of NIPS for common trisomies were carried out in high-risk pregnancies for which an invasive test was already recommended. But the target patient population for SCA screening does not correlate with that of trisomies. SCAs occur with equal frequency at all maternal ages; the relative risk of subchromosomal aberrations is therefore higher for women with a lower maternal age than those of advanced maternal age. Moreover, many SCAs are not associated with clear ultrasound abnormalities, raising questions about what constitutes a "high-risk" pregnancy for these conditions.

Data from recent clinical validation studies showed that NIPS for trisomies 13, 18, and 21 in "average-risk" women has sensitivity and specificity similar to those of high-risk women,[10,11] meaning that some providers may soon offer NIPS in all pregnancies. The impact of this shift using expanded panels may be significant, leading to a greatly expanded number of women receiving unvalidated test results for rare conditions.

COUNSELING AND CONSENT

This expansion raises difficult issues in the context of genetic counseling. Screening for trisomy 21 and, to a lesser extent, trisomies 13 and 18 has been in place for many years. There are numerous educational resources, patient support groups, guidelines on returning results, and expert scholarship on the psychology of interpreting and delivering a Down syndrome diagnosis.[17–19] Even in the majority of obstetric/family practices that do not include genetic counselors, most clinicians have a working knowledge of the physical and social profile of Down syndrome and can counsel potential parents on their options. By contrast, data from clinical experiences with NIPS demonstrate that interpretation and counseling in the context of screening for sex chromosome aneuploidies, in particular X chromosome aneuploidies, is more complicated[20–25]; NIPS for sex chromosome aneuploidies is increasingly uncovering incidental findings in the pregnant woman rather than the fetus.[26] This complicates the already problematic process of counseling for sex chromosome abnormalities and requires additional resources to help families understand the clinical significance of these incidental findings.

This is even truer of SCAs. Even if testing is restricted to clinically actionable conditions, whether most clinicians are well versed in the advances in NIPS or the clinical management of rare conditions is not clear.[27,28] Prenatal genetic counseling is rarely considered a reimbursable expense by third-party payers, meaning that the number of practices that can afford to support prenatal counseling services will remain limited. While some testing companies offer telephone counseling services as part of their business model, whether this will be sufficient to address the rising need is far from clear, and there are concerns about conflicts of interest.[29,30] For the most part, physicians or other care providers who order these tests will have to counsel patients themselves.[31]

The panel of subchromosomal conditions currently offered is significantly smaller than those included in prenatal chromosomal microarrays, which are increasingly used in invasive prenatal testing. However, recent research demonstrates that NIPS may be used to detect genome-wide variations in chromosomal copy number,[32] and companies are likely to report more SCAs in the future. This expansion of NIPS will further increase false-positive rates, possibly leading to more anxiety and more follow-up invasive procedures. Equally concerning is the possibility of higher number of false negatives, which may lead to false reassurance, especially if there are no ultrasound abnormalities detected at 9–11 weeks' gestation, when NIPS is frequently ordered.

Some companies also include an expanded panel of SCAs as an opt-out test on the test requisition form. This approach not only fails to acknowledge the clinical differences between testing for trisomies versus SCAs, but failing to check the "opt-out" box may result in a failure of informed consent, leading families to receive information they do not want.[33] On the other hand, while an "opt-in" model may encourage explicit discussions about potential outcomes, physicians may be concerned that a failure to recommend expanded testing will lead to wrongful birth lawsuits.[34,35]

CONCLUSION

The expansion in NIPS is driven, at least in part, by for-profit companies striving to differentiate themselves in a highly competitive market. The field remains litigious, creating uncertainty and pressure to secure market share.[36] While noninvasive SCA testing is a potentially beneficial development for some pregnancies, test menus and how they are offered should be actively monitored to identify ethical and clinical concerns. For instance, testing companies frequently advertise high sensitivity and sensitivity for NIPS. When testing for SCAs, however, providers should provide greater transparency about the actual positive predictive value and negative predictive value of these panels. Extra attention should be given to the consent process so that patients do not "accidentally" opt in to SCA testing. Similarly, payers should monitor how microdeletion tests are ordered and subsequent testing outcomes, especially to identify costs of unnecessary follow-up testing as a result of false positives. They should continue to systematically evaluate NIPS for coverage decisions, especially as the number of women receiving NIPS expands.

Professional and academic communities have begun to systematically gather and analyze real-world data for NIPS for chromosomal aneuploidies, providing insight into the performance of these tests. Beginning to collect data on the performance of NIPS for SCAs is equally important. Professional societies have not provided explicit guidance on the use of NIPS for microdeletion testing and should do so quickly because test menus continue to expand. Companies should also consider voluntarily reporting aggregate data about SCAs to public databases, especially for variants of unknown significance. As NIPS platforms continue to evolve, head-to-head comparisons between approaches (i.e., array versus massively parallel sequencing) and current gold-standard methods should be conducted to inform clinical practice guidelines. These strategies may assist all stakeholders in ensuring ethical and beneficial translation of NIPS as it moves toward genome-wide analysis.

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DISCLOSURE

The authors declare no conflict of interest.

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