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Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues

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Abstract

Noninvasive prenatal genetic testing (NIPT) for chromosomal aneuploidy involving the analysis of cell-free fetal DNA became commercially available in 2011. The low false-positive rate of NIPT, which reduces unnecessary prenatal invasive diagnostic procedures, has led to broad clinician and patient adoption. We discuss the ethical, legal, and social issues raised by rapid and global dissemination of NIPT. The number of women using NIPT is anticipated to expand, and the number of conditions being tested for will continue to increase as well, raising concerns about the routinization of testing and negative impacts on informed decision making. Ensuring that accurate and balanced information is available to all pregnant women and that access to NIPT is equitable will require policy guidance from regulators, professional societies, and payers. Empirical evidence about stakeholders' perspectives and experiences will continue to be essential in guiding policy development so that advances in NIPT can be used effectively and appropriately to improve prenatal care.

INTRODUCTION

NIPT: noninvasive prenatal genetic testing

cffDNA: cell-free fetal DNA

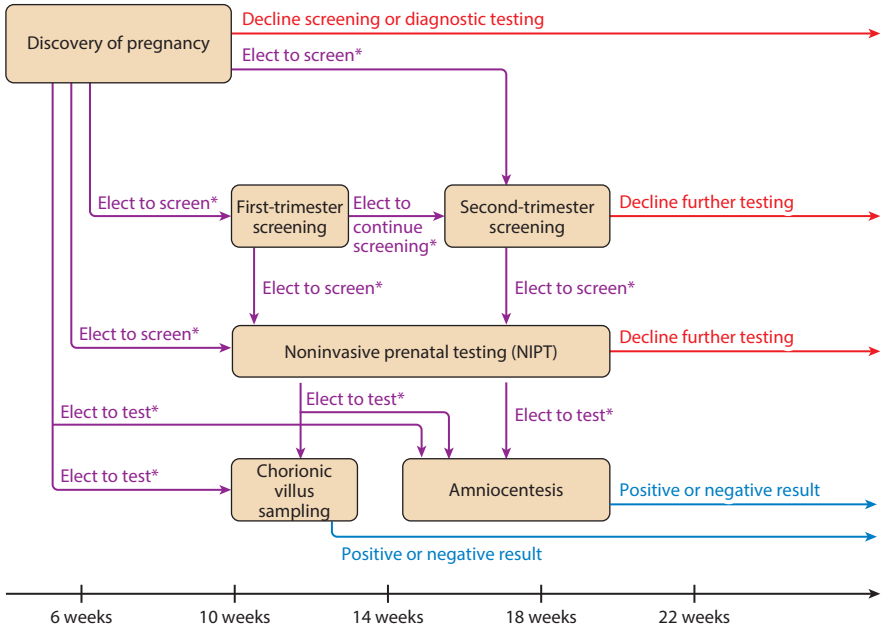
NSGC: National Society of Genetic Counselors

Prenatal genetic testing is an integral part of routine obstetrical care in the United States. Approximately 3% of live births contain a major congenital abnormality, many of which are caused by genetic factors. In addition, more than half of spontaneous miscarriages that occur in the first trimester are due to chromosomal abnormalities, such as aneuploidy (173). Prenatal testing typically begins with a screening test, which identifies women who are at high risk of carrying a fetus with a chromosomal aneuploidy, followed by an invasive diagnostic test, if warranted, to confirm the presence of an abnormality.

Screening tests typically involve a combination of ultrasounds and measurement of serum biochemical markers to calculate the risk of a fetal chromosomal aneuploidy (10, 173). These tests are offered to all pregnant women in the United States, regardless of maternal age. The screening protocol may vary by individual provider, by gestational age, or by other factors (57). First-trimester screening involves either ultrasound measurement of nuchal translucency or a combined test of nuchal translucency measurement and analysis of two serum biochemical markers. Second-trimester serum screening, which is less accurate than first-trimester screening, examines three or four biochemical markers; one of these markers, alpha-fetoprotein (AFP), can also be used to assess the presence of neural tube defects. Integrated screening, which combines the results of first- and second-trimester serum tests and nuchal translucency measurement to calculate a single aneuploidy risk score, is more accurate than first-trimester screening alone and is currently the most accurate screening test based on biochemical markers. The ultrasound and serum screening tests also provide additional information about the health of the pregnancy and the fetus beyond chromosomal aneuploidies, including birth defects (such as congenital heart anomalies) and preeclampsia risk (17). Screening tests have relatively high false-positive rates, even up to 15% depending on the test (24, 47, 173).

In contrast to screening, which calculates a risk of fetal aneuploidy, prenatal genetic diagnosis can detect the actual presence of a genetic condition. Diagnostic tests are invasive and use amniotic fluid, placental tissue, or, rarely, cord/fetal blood samples to detect whole or subchromosomal abnormalities (174). Chorionic villus sampling is typically performed at 10–13 weeks' gestation, whereas amniocentesis is performed in the second trimester, typically after 15 weeks' gestation. These procedures are associated with a small risk of pregnancy loss, approximately 1 in 300 to 1 in 500 (10), but are the only diagnostic standard for prenatal detection of aneuploidy.

In 2011, a new type of screening test became available that analyzes cell-free fragments of placental DNA found in maternal serum (119) (see **Figure 1**). This noninvasive prenatal genetic testing (NIPT) is more accurate than first- or second-trimester serum screening tests, with sensitivity and specificity reported above 99% for trisomy 21 and false-positive rates under 1% (15, 16, 31, 129, 140, 197); however, test performance varies by condition, and sensitivity is lower for all other aneuploidies (77). The lower false-positive rate for NIPT relative to first- or second-trimester serum screening tests means that fewer women who receive NIPT-based screening need invasive diagnostic testing for confirmation of results. Although NIPT claims to analyze cell-free fetal DNA (cffDNA), the cell-free DNA found in maternal serum is actually of placental origin (82). Placental and fetal DNA are frequently identical, but differences have been observed (33, 44), leading to false-positive results. Test performance is influenced by a variety of factors, including maternal body mass index, fetal fraction (the fraction of cell-free DNA that is of "fetal" origin), the presence of a vanishing twin, and singleton as opposed to multiple pregnancies (33). NIPT may be offered as early as 9–10 weeks' gestation and combines the ease of a serum screen with an information load approaching that of invasive diagnostic genetic tests. Numerous professional societies, including the National Society of Genetic Counselors (NSGC), the International Society



* Patients may elect to screen or test for many reasons, including high-risk status.

Figure 1

Prenatal screening and testing options. Following the discovery of pregnancy, a woman may elect to undergo (*purple arrows*) or decline (*red arrows*) prenatal screening and/or diagnostic testing. If she opts for screening/testing, then she is faced with a variety of decision pathways through which screening/testing can be performed, the choices of which will depend on the timing of the decision within the pregnancy, the woman's personal values, and other factors like cost and risk. Given the complexity of possible options available to pregnant women, it is important for providers to counsel women about all available options and the pros and cons of each in order to facilitate informed decision making. Screening options include the analysis of serum biochemical markers and ultrasound measurements during the first and/or second trimester as well as the sequencing of cell-free DNA in the maternal bloodstream (noninvasive prenatal genetic testing). Diagnostic testing options (amniocentesis or chorionic villus sampling) involve the use of karyotypes or chromosomal microarrays to produce or confirm a prenatal genetic diagnosis. The typical timing of different screening and testing options is presented; however, the actual timing of these options may vary in practice (e.g., amniocentesis may be performed in the third trimester). Adapted from Reference 8 with permission.

for Prenatal Diagnosis (ISPD), the Society for Maternal-Fetal Medicine (SMFM), the American Congress of Obstetricians and Gynecologists (ACOG), the American College of Medical Genetics and Genomics (ACMG), and the European Society of Human Genetics (ESHG) together with the American Society of Human Genetics (ASHG) have issued statements to guide the clinical use of NIPT (9, 21, 55, 80, 199). These guidelines stress the importance of pre- and post-test genetic counseling; clearly indicate that NIPT is a screening test, not a diagnostic test; and, with the exception of the ACMG and ESHG/ASHG guidelines, clearly specify that NIPT should be offered only to women at high risk for having a fetal aneuploidy (e.g., advanced maternal age, prior affected pregnancy, positive serum screen). In fact, some experts and members of professional societies recommend changing the NIPT abbreviation to NIPS or NIPGS (for noninvasive prenatal genetic screening) to clearly emphasize to patients and health care providers that these are screening tests.

SMFM: Society for Maternal-Fetal Medicine

ACOG: American Congress of Obstetricians and Gynecologists

Many clinical practices in the United States have adopted NIPT (2). Four independent companies currently offer NIPT in the United States, and several others offer similar tests in international markets. Some laboratories and companies have signed distribution deals with these companies, whereas others have opted to license technology to be able to offer their own version or brand of NIPT. Test panels typically include the three most common autosomal aneuploidies, which are trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome); fetal sex; and sex chromosome aneuploidies, including Turner syndrome (45,X) and Klinefelter syndrome (47,XXY) (see **Table 1**). Expanded test panels may include trisomies 9, 16, and 22, which are frequently implicated in miscarriages (30, 194), and microdeletion syndromes. NIPT is considered a highly lucrative technology: The global NIPT market was estimated at US$0.22 billion in 2012 and is projected to be an estimated US$3.62 billion in 2019 (189). In this review, we examine some of the ethical, legal, and social issues associated with clinical implementation of NIPT, and discuss emerging issues as this technology continues to evolve and testing expands to include average-risk women and a broader range of medical conditions.

ETHICAL AND CLINICAL ISSUES

Informed Consent and Routinization

Many of the ethical issues raised by NIPT relate to concerns about informed decision making in prenatal testing, which may include informed consent, informed refusal, or other informed choices made before and after testing (51, 61). Such concerns have been raised repeatedly over the last few decades, as technological advances have contributed to progressively more feasible and less risky methods for detecting fetal genetic conditions (62, 65, 127, 156–158, 167). NIPT has a low false-positive rate compared with serum screening, and it can detect fetal genetic abnormalities directly rather than inferentially from serum markers or ultrasound. This is likely to enable further expansion and routinization of prenatal testing, which, observers note, frequently erodes careful attention to informed decision making (50, 63, 157). Indeed, a prospective survey of obstetricians and midwives in the United Kingdom indicated that these providers anticipated giving significantly less counseling and decision-making time for NIPT than they would for invasive testing (191). A more recent survey of genetic counselors in the United States found that nearly half believed that an offer of NIPT should include a separate informed consent form (38). Though all participants indicated that an informed consent process was in place for NIPT, most (62.2%) reported that it was solely verbal. Meanwhile, patients have emphasized the need to make considered and informed decisions about NIPT. One participant in a recent US study particularly emphasized the value of a separate informed consent document:

> [W]hen I have a consent form to sign and it says, for example, you are taking, or you agree to the NIPT, I have a chance to stop and say, "Answer this question for me" or, "Don't do the test". That option is there. Yes. I feel rushed, but I still have that option. (63, p. 625)

This statement echoes other findings suggesting that, although clinicians and patients may often view clinical consent forms as legal protection for hospitals and providers or as routine paperwork, they also frequently recognize the request to sign a consent form as a moment when patients can exercise a measure of control through shared decision making (3, 143).

NIPT poses additional challenges for an already beleaguered informed consent regime. First, informed decision making about genetic testing depends on reliable and accurate information about both the technology and the conditions it tests for. Given the speed with which NIPT has

Table 1 Commercial noninvasive prenatal genetic testing (NIPT) options

		Berry Genomics[a,b]	BGI[a]	Igenomix[a]	Illumina (Verinata)	LifeCodexx[a]	Natera	Premaitha[a]	Roche (Ariosa)	Sequenom	
Test name		Bambni	NIFTY	NACE	verifi	PrenaTest	Panorama	IONA[h]	Harmony	MaterniT21 PLUS	VisibiliT
Test price		NA	NA[c]	NA	$1,500	€595–895[f]	$1,495	NA	$795	$2,762	$790
Chromosomal aneuploidies detected	Trisomy 9			✓[d]	✓[e]						
	Trisomy 13	✓	✓	✓	✓	✓[f]	✓	✓	✓	✓	
	Trisomy 16			✓[d]	✓[e]					✓[j]	
	Trisomy 18	✓	✓	✓	✓	✓[f]	✓	✓	✓	✓	✓
	Trisomy 21	✓	✓	✓	✓	✓[f]	✓	✓	✓	✓	✓
	Trisomy 22									✓[j]	
	45,X		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	47,XXY		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	47,XXX		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	47,XYY		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	48,XXYY								✓[i]		
Microdeletions detected	Test option		NA	Opt-in[d]	Opt-in[e]		Opt-in			Opt-out	
	1p36		✓	✓[d]	✓[e]		✓			✓[j]	
	2q33.1		✓								
	4p			✓[d]	✓[e]					✓[j]	
	5p		✓	✓[d]	✓[e]		✓			✓[j]	
	8q									✓[j]	
	11q									✓[j]	
	15q			✓[d]	✓[e]		✓			✓[j]	
	22q11.2			✓[d]	✓[e]		✓			✓[j]	
Other conditions detected	Fetal sex	NA	✓	✓	✓[e]	✓	✓[g]		✓[i]	✓	✓
	Triploidy						✓				
	Vanishing twin						✓				

(*Continued*)

Table 1 (*Continued*)

		Berry Genomics[a,b]	BGI[a]	Igenomix[a]	Illumina (Verinata)	LifeCodexx[a]	Natera	Premaitha[a]	Roche (Ariosa)	Sequenom	
Additional indications	Twin pregnancies		✓	✓	✓	✓			✓	✓	
	IVF/donor egg pregnancy		✓	✓					✓	✓	
Reference(s)		75	28, 29	91	92, 93, 95	115, 116	95, 136, 137	100	11, 95	95, 101, 170	101, 171

Companies currently offering NIPT are shown along with test name, price, genetic conditions included on test panels, and additional indications for testing, such as whether the test can be used with twin or IVF/donor egg pregnancies. Only independent companies are shown; licensed providers of these companies' tests that have rebranded the tests under their own label (e.g., LabCorp's informaSeq test, which was developed using a license for Illumina's verifi test) are not shown. The microdeletions currently included on test panels are 1p36 deletion, 2q33.1 deletion, 4p− (Wolf-Hirschhorn syndrome), 5p− (cri-du-chat syndrome), 8q deletion (Langer-Giedion syndrome), 11q deletion (Jacobsen syndrome), 15q deletion (Angelman and Prader-Willi syndromes), and 22q11.2 deletion (DiGeorge syndrome or velo-cardio-facial syndrome). Abbreviations: IVF, in vitro fertilization; NA, information not available.

[a]These companies are based outside the United States, and their tests are not marketed within the United States.

[b]In March 2014, Berry Genomics suspended testing pending approval from the Chinese FDA; this approval was granted on March 31, 2015 (75).

[c]Test prices vary regionally (28).

[d]NACE examines only trisomies 13, 18, and 21 and sex chromosome aneuploidies; the NACE PLUS test additionally examines trisomies 9 and 16 and six microdeletion syndromes.

[e]The basic verifi test examines trisomies 13, 18, and 21, and a wider option (at no extra charge) examines sex chromosome aneuploidies and fetal sex. An additional option examines trisomies 9 and 16 and six microdeletion syndromes.

[f]There are three PrenaTest options: Option 1 (€595) examines trisomy 21; Option 2 (€745) examines trisomies 13, 18, and 21; and Option 3 (€895) examines trisomies 13, 18, and 21 and sex chromosome aneuploidies (115). In addition, results can be expedited by paying a €100 express charge.

[g]Optional.

[h]IONA will initially screen for trisomies 13, 18, and 21 but will add sex chromosomal aneuploidies later (100).

[i]The Harmony test includes an option to examine sex chromosomes.

[j]These results are reported as an additional finding (170).

entered clinical practice worldwide (33, 41), has moved into lower-risk populations (30, 150), and has expanded to detect additional conditions (23, 114), conveying reliable and accurate information to all patients in a timely manner is virtually impossible (49, 56, 120). Second, both patients and health professionals need additional education on the possibilities and limitations of NIPT in order to facilitate informed decision making (53, 83, 85). Yet the "unprecedented" pace of clinical translation has made it difficult for provider education to keep up (33, p. 104). Finally, the rapid commercialization of NIPT has exacerbated these challenges to informed decision making, with a push to expand the scope of testing and with aggressive marketing to both providers and patients. This push has resulted in some tests being offered well before clinical validation data are available, accompanied by commercially produced educational and consent materials that do not always meet clinical and ethical standards (2, 108, 142). We discuss many of these issues in greater detail below.

Provider and Patient Information

One concern about offering NIPT on a solely for-profit basis is the strong incentive for companies to market NIPT tests aggressively to increase market share, especially in a highly competitive space (53). This incentive leads companies to highlight the advantages of testing, and of their test in particular, in ways that are not always compatible with informed decision making, contrary to best ethical practices suggested for commercial test providers [see sidebar Best Ethical Practices for Commercial Test Providers (adapted from Reference 7)]. A study of online materials about NIPT found that websites did not provide balanced or comprehensive information and were written at higher than recommended reading levels (130). Kloza et al. (108) likewise examined the patient information materials provided by companies and found that they did not meet guidelines for readability and Suitability Assessment of Materials (SAM) criteria: Reading levels ranged from 10th to 12th grade, none of the pamphlets met all SAM criteria evaluated, and none included all recommended content items. Critics observe that marketing, such as that done by direct-to-consumer testing companies (e.g., 23andMe), has increased awareness of the availability of genetic testing but has done less to educate providers about when and where such tests are appropriate (155). Meanwhile, genetic counselors have reported adverse outcomes from the provision of genetic tests by uninformed nonspecialists, including medical mismanagement, loss of trust in medical providers, unnecessary use of health care resources, and inadequate counseling (25).

Another barrier to informed decision making is providers not giving educational materials to their patients in the first place. A 2008 survey of more than 500 ACOG fellows revealed that only 29% of respondents provided educational materials to their patients following Down syndrome diagnostic testing (57). Patients in a US survey reported not receiving enough accurate and updated information about Down syndrome from their obstetricians. However, the respondents who had received printed materials reported that they were easy to read and that they incorporated the positive images and stories from the materials into their decision to continue the pregnancy (175).

The availability of more complete and accurate information about genetic conditions and their severity may also help relieve concerns that parents may choose to terminate affected pregnancies based on misinformation about raising a child with a disability (54). This is especially pertinent in the context of sex chromosome aneuploidies, which typically have milder phenotypes than other aneuploidies and are relatively common, occurring in 1 in 400 live births (134). The amount of negative information that parents are given about sex chromosome aneuploidies following a prenatal diagnosis is correlated with the decision to terminate an affected pregnancy (84). Moreover, the accuracy of the information that providers give to parents about the severity of sex chromosome aneuploidy phenotypes is highly variable. For example, the potential phenotype for trisomy X (47,XXX) has been variously described to patients as "devastating" and "stunted" or as "a normal

BEST ETHICAL PRACTICES FOR COMMERCIAL TEST PROVIDERS

Companies offering NIPT should:

1. Offer testing only through licensed clinicians and not directly to consumers.
2. Seek oversight to validate the safety and effectiveness of genetic tests from relevant regulatory agencies.
3. Do their best to comply with national and international regulations and laws regarding the results that can legally be returned to patients.
4. Implement proficiency testing procedures verified independently by a third party to ensure analytic validity, and set transparent standards for data interpretation and error rates.
5. Require verification of comprehensive informed consent from clinicians before testing is conducted. Companies may wish to provide clinicians with appropriate informed consent forms in order to facilitate this process.
6. Obtain written consent for the storage of samples and genetic data and any research conducted using samples or test results. Samples should not be used for research without explicit consent separate from consent obtained to use samples for clinical purposes, and samples should be destroyed after clinical testing unless specific consent for future use has been obtained.
7. Provide the capacity to return selected results based on the wishes of the patient.
8. Provide genetic counseling resources to assist clinicians in facilitating the informed consent process.
9. Design marketing and advertising materials to promote values-based decision making and avoid advocating for specific actions on the basis of test results.
10. Design intellectual property and licensing regimes to facilitate access to and enhance the quality of prenatal testing. To maximize equality of access and care, data from tests should be available in the public domain.

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child" (1, p. 465). In one case, a provider described Klinefelter syndrome to a couple by saying, "It wasn't Down syndrome but was another chromosome abnormality"; the couple never saw a clinical geneticist and terminated the pregnancy two days later (1, p. 464). Lalatta & Tint (111) provided a brief synopsis of the clinical phenotypes associated with sex chromosome aneuploidies and offered guidelines for counseling; however, it is unclear whether physicians or obstetrician/gynecologists are familiar with these guidelines.

Provider education is as important as patient education for quality informed decision making. A UK survey of health care providers found that few had any practical experience with Down syndrome (198). The resources providers may seek out, such as medical textbooks and peer-reviewed literature, often focus on the clinical symptoms, or negative aspects of a genetic condition; may be out of date; and may omit details about how early interventions might improve patient outcomes (198). Medical students report that they receive no clinical training about intellectual disabilities, and medical schools report that providing this training is not a high priority (183). Additionally, confounding medical issues or lack of access to health interventions may exaggerate the scope of some symptoms; for example, learning disabilities might be caused in part by untreated sensory impairments such as vision or hearing loss (198), and these comorbidities are less likely to be treated in people with special needs (183).

Getting accurate and balanced information about genetic conditions into the hands of busy providers is challenging. Compared with maternal-fetal medicine specialists, obstetrician/gynecologists were less likely to report using literature or Internet searches and journals as methods to keep updated about advances in genetic screening (57). When providers receive informational leaflets about a genetic condition, they report feeling more prepared and confident when they

deliver a diagnosis to parents (1). The question then arises of who should create these materials. Educational information developed by individual companies may be biased toward the strengths of their tests, and providers may be reluctant to read materials created by patient support or advocacy organizations because they believe such materials may paint an overly rosy picture of life with a genetic condition (198). A neutral third party, such as an academic organization or professional society, might be best suited to developing and distributing unbiased educational materials. Examples of groups that have created materials designed to be accurate and balanced include the National Center for Prenatal and Postnatal Down Syndrome Resources, run by the Human Development Institute at the University of Kentucky (**http://downsyndromediagnosis.org**); the National Coalition for Health Professional Education in Genetics (138); and the NSGC (172).

Counseling and Results

The rapidly changing nature of prenatal testing has exacerbated the need for effective counseling and education of both prenatal care providers and patients. A survey of 141 American women who had received a prenatal diagnosis of Down syndrome and opted to continue their pregnancies found that women wanted to receive the diagnosis in person and with their partner present, as opposed to alone via an unscheduled phone call (175). Respondents, who reported feeling anxious after receiving test results, strongly favored nondirective counseling about pregnancy options. Skotko et al. (177) used these survey data and other literature to develop evidence-based recommendations for providers on how to best deliver a prenatal diagnosis of Down syndrome. They recommended that the difference between a screening and a diagnostic test be clearly explained; that the person who delivers the diagnosis undergo special training to deliver a sensitive, accurate, and up-to-date diagnosis; and that this person offer contact information for local support groups, if warranted (177).

There is evidence that, at least in the United States, providers are increasingly supportive of parents who elect to continue an affected pregnancy (175). Although several studies have pointed out an implicit bias among providers toward termination of an affected pregnancy (59, 117), others have suggested that this bias may be diminishing (175). This potential attitude shift coincides with decreasing rates of pregnancy termination in the United States following a prenatal diagnosis of Down syndrome (139), although no clear relationship between these two trends has been established. Additionally, some activists have suggested that genetic counselors may harbor bias against disability communities (64, 121, 132); a US survey of women's experiences with genetic counselors after a prenatal diagnosis found that the genetic counselors largely failed to give information about quality-of-life issues (162). Data also suggest that clinicians' reported bias might vary by condition (81), so further empirical data on the experiences of women and parents receiving a variety of prenatal diagnoses should be gathered in order to inform best practice guidelines on how to deliver prenatal diagnoses for a variety of conditions—a skill that will be increasingly required as NIPT use expands.

Health care providers themselves are aware that the way in which they present information about Down syndrome may affect the decisions made by their patients; as a UK provider in one study observed, they have "an incredible amount of power in that relationship" (198, p. 233). In spite of this self-awareness, a survey of health care providers who delivered diagnoses of Down syndrome revealed that providers varied widely in counseling women about termination decisions, on a spectrum from actively urging termination to actively urging continuation (196). The Accreditation Council for Genetic Counseling, which oversees all genetic counseling graduate programs, does not include clear guidelines on how to train genetic counselors to address disabilities in clinical practice (164). Such findings point to the need for education and best practice guidelines on prenatal test counseling, not only for trained genetic counselors and

BEST ETHICAL PRACTICES FOR CLINICIANS

Medical providers offering NIPT should:

1. Offer all women the opportunity to receive reliable, medically relevant prenatal tests that have demonstrated safety and effectiveness in their demographic.
2. Where possible, work with third-party payers to help all patients access NIPT, if medically appropriate.
3. Structure the informed consent process so that it is comprehensive, interactive, and sensitive to the need to understand the subjective experience of disease and disability.
4. Ensure that patients are offered genetic counseling both before and after testing.
5. Give patients clear opportunities to decline testing, both in general and for specific disorders, and never pressure patients to undergo testing.
6. Encourage patients to make clear choices about which results they wish to receive, including paternity and sex testing, before testing is undergone.

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clinical geneticists but also for any primary care providers involved in prenatal care [for examples, see sidebar Best Ethical Practices for Clinicians (adapted from Reference 7)]. This is especially important in light of surveys showing that many practitioners do not feel comfortable counseling patients on genetic test results. A 2009 survey of ACOG fellows reported that 85% of respondents personally counsel their patients about Down syndrome risk and screening tests, but only 36% felt their residency training made them "well qualified" to provide counseling for patients who screened positive (57). In a review of perceived barriers to the integration of genetic testing into the health care system, Mikat-Stevens et al. (131, p. 172) found that "providers expressed concerns about feeling unqualified to provide genetic counseling to patients and making the correct management decisions," and many also reported that "the location of the nearest genetic center was too inconvenient" for their patients. This access barrier is not restricted to rural or remote areas. According to *Scientific American*, as of 2014, there are fewer medical students specializing in genetics than there were 30 years ago; as a result, there are no medical geneticists in Alaska or Idaho, while Maine, Georgia, and Tennessee have only three each (126). Given the increasing complexity of DNA-based prenatal testing, the scarcity of medical geneticists is concerning.

Research shows that comprehensive counseling with a qualified genetic counselor results in lower anxiety levels, more accurate risk perception, and better knowledge outcomes (97, 144, 187). When surveyed by Horsting et al. (88), 98% of a sample of genetic counselors agreed with the statement "pretest counseling is necessary for cffDNA testing," and 92.3% agreed with the statement "the physicians I work with believe patients should have genetic counseling before offering cffDNA testing." Bernhardt et al. (26) found that although 80% of genetic counselors were comfortable with helping patients understand most prenatal findings, including possible mosaicism, only 43% were confident of their ability to counsel patients through an uncertain prenatal microarray result, which might be obtained from an invasive procedure such as amniocentesis or chorionic villus sampling, if termination was an option. Because prenatal microarrays look at copy-number variation (CNV) and other chromosomal abnormalities with a higher resolution than is possible with traditional karyotype analysis, the possibility of uncertain or unknown findings is greatly elevated (195). Furthermore, as more individuals undergo testing for sex chromosome disorders, the potential for incidental findings relevant to maternal health increases; these findings may include previously undetected maternal sex chromosome trisomy or

CNV: copy-number variation

maternal malignancy (i.e., cancer) (32, 113, 145, 182, 200). This development raises the specter of what Bernhardt et al. (26) call "toxic knowledge" (p. 139): information about the pregnant woman's genome, or that of her partner, that they were unwilling and/or unprepared to know. Negotiating these questions only emphasizes the need for trained pre- and post-test counseling.

PPV: positive predictive value

Unfortunately, the high demand for genetic counseling has not translated to routine integration of such counseling into clinical practice. Most insurance companies in the United States do not reimburse for prenatal genetic counseling. A survey of genetic counselors reported that although 69% of respondents billed for their services, more than 85% of these were billing under a physician's name and billing code, and only 8% were billing the patient directly (86). Although prenatal genetic counselors were reportedly more likely to bill than those working in pediatrics, the percentages remain low. This has led some observers to argue that alternate funding models should be found. Swanson et al. (186) argue that

> [t]he increased need for genetic counselors in this role, coupled with the time required and a limited number of trained and available counselors presents a challenge to current models for making genetic testing available to patients and their healthcare providers effectively and efficiently. The employment of genetic counselors at genetic/genomic laboratories is one model to expand the resources for providing this service. (p. 647)

Indeed, there are now genetic counselors employed at all US NIPT companies. However, some argue that providing counseling through counselors paid by genetic testing companies creates an inherent conflict of interest. One critic observed, "Is it ethical for genetic counselors, who advise patients on whether to undergo testing, to be paid by the companies that perform the tests?" (154). Moreover, these counselors contribute primarily to post-test counseling, not pre-test counseling.

Expansion of Test Content

Effective counseling will become not only more necessary but also more difficult as new conditions are added to NIPT panels. When NIPT was initially launched, it was limited to pregnancies screened as high risk for the three most common trisomies (trisomies 13, 18, and 21)—the same conditions, with the exception of trisomy 13, detected by the standard integrated serum screen used in many areas of the United States (173). Given the incidence of trisomy 21 in the United States, the positive predictive value (PPV) of NIPT for a 35-year-old patient with no other risk factors ranges from approximately 28% to approximately 80% (20). Given the comparative rarity of trisomies 13 and 18, the PPV for these conditions is lower—approximately 10% for a 35-year-old pregnant woman with no other risk factors (20). However, in a recent study, pregnant women expressed reservations about the predictive value of NIPT and how it impacts prenatal decision making, worrying that incorrect results could lead women either to "the wrong decision" or to a lifetime of worrying when "there was nothing wrong" (63, p. 621).

Despite some reservations about the PPV of NIPT, data from the first few years of implementation suggest that NIPT for these conditions showed clinical utility in reducing the uptake of follow-on diagnostic testing. In North Carolina, Beamon et al. (19) reported a reduction in invasive diagnostic procedures from 11.8% before the introduction of NIPT to 8.8% after. In California, Chetty et al. (43) also found that NIPT was associated with a decreased use of invasive prenatal diagnosis, from 47.2% in the year before the introduction of NIPT to 39.2% after. Some observers have even expressed concern that reduced demand for diagnostic procedures will negatively affect the ability to train future providers and give them the technical proficiency needed to keep procedural pregnancy loss rates low (163). The introduction of NIPT also significantly decreased the

likelihood that a patient would decline further testing (from 52.8% before the introduction of NIPT to 21.2% after) (43), suggesting that patients have greater confidence in the accuracy of NIPT.

In 2013, commercial NIPT companies began expanding their test offerings. All US-based NIPT companies now offer testing for sex chromosome aneuploidies and determination of fetal sex. Sex chromosome aneuploidies have highly variable phenotypes, including phenotypic expressions that are so mild that some individuals are largely asymptomatic and are never diagnosed. One genetic counselor explained her reaction to a prenatal finding of 47,XYY:

> You don't have to tell anybody about this. . .because every time he falls over or doesn't say a word right, you're already going to think, "Is this because he has an extra Y chromosome?" Do you want your parents thinking that too, or his siblings?. . .If you never had this test, you may never have known this because he may not have any of that stuff. (125, p. 313)

Such concerns are unaddressed in patient education materials from testing companies.

Following the addition of sex chromosome aneuploidies, some NIPT companies further expanded their test panels to include microdeletions and additional trisomies. As an example, as of fall 2014, Sequenom's MaterniT21 PLUS test included trisomies 16 and 22 as well as eight microdeletion syndromes: 22q11.2 deletion (DiGeorge syndrome or velo-cardio-facial syndrome), 1p36 deletion, 5p– (cri-du-chat syndrome), Angelman and Prader-Willi syndromes on chromosome 15q11.2, 4p– (Wolf-Hirschhorn syndrome), 8q deletion (Langer-Giedion syndrome), and 11q deletion (Jacobsen syndrome) (169). Verinata/Illumina and Natera likewise offer microdeletion testing, although as of fall 2014, their panels included only five microdeletion syndromes (136) (see **Table 1**). Although it is not known how NIPT companies decided on which subchromosomal abnormalities to add to their test panels, prenatal diagnosis for some of these microdeletions has clear clinical utility. Almost 60% of patients with Jacobsen syndrome (11q deletion) have congenital heart defects that may be life threatening and require surgery at birth or in the neonatal period (128). In addition, almost all Jacobsen syndrome patients have a rare platelet disorder called Paris-Trousseau syndrome, which means that patients may require whole-blood transfusion and/or prophylactic platelets before, during, and/or after corrective heart surgery. Clinician awareness of the bleeding disorder in advance of the child's birth may be life saving (58). Nevertheless, given the rarity of subchromosomal abnormalities, the predicted PPV for the most common microdeletion, 22q11.2, is 2–4%; for 1p36 deletion, it is less than 1% (20). The high potential for false-positive results with these rare microdeletions means that additional testing will be needed to verify NIPT results, thus eroding the advantage of using NIPT to reduce invasive diagnostic procedures. Although all companies recommend test counseling, the lack of clinical data on test performance and PPV for microdeletions hinders the ability of prenatal providers to offer complete and accurate information to their patients to facilitate informed decisions regarding whether to undergo testing for microdeletions (5, 142, 193). Giving providers accurate knowledge about genetic conditions will prove especially important for these microdeletion syndromes because most will never encounter a patient with one of these conditions.

Equity in Access

One of the most distinctive features of NIPT has been its introduction as a strictly commercial product; all the companies that offer it are for-profit businesses, and at least one is publicly traded. This has raised questions about whether commercial incentives can be aligned with equitable use of NIPT. In the United States, a complicated network of private insurance, public insurance/health

care programs, and government health plans funds health care, and each of these entities makes its own decision about coverage of NIPT. Meanwhile, several countries, such as Canada, the Netherlands, and the United Kingdom, are conducting publicly funded studies to evaluate the implementation of NIPT in a national health system. As an emerging technology, NIPT must prove its value to payers either by reducing costs incurred from invasive procedures or by lowering long-term care costs associated with disability; cost-effectiveness studies performed to date differ in their conclusions on whether NIPT can reduce costs as a population screen (46, 60, 181).

Until this debate is resolved, some women will access NIPT only by paying out of pocket. The cost of NIPT tests varies widely. In 2014, Ariosa's Harmony test cost US$795, whereas Sequenom's MaterniT21 PLUS cost US$2,762 (53, 95). Sequenom had initially promised that out-of-pocket costs would not exceed US$230, regardless of insurance coverage; this cap was later removed, and in 2013 a Sequenom shareholder sued Sequenom, saying that this "capping scheme" was not in shareholders' best interest (71). Although many states have statewide prenatal screening programs or have made allowances to cover serum screening in their state Medicaid programs (see 39), not all state Medicaid programs currently cover NIPT.

These cost and reimbursement issues add another layer of complication to decisions about whether to undergo prenatal testing and which test to use. In a 2012 study, Allyse et al. (6) surveyed the public about their views on NIPT and whether it should be used. While an increase in accuracy was the factor cited as most important, the second-most-discussed feature was cost. Horsting et al. (88) found that, in addition to the actual decision to test, "insurance coverage, billing policies, reimbursement, and price of NIPT surfaced multiple times as issues genetic counselors were concerned with in regard to offering cffDNA testing" (p. 398). Many counselors also reported that concerns about cost or lack of insurance coverage caused patients to decline testing. Meanwhile, Vahanian et al. (190) reported that, after controlling for race, patients with public insurance were 83% less likely to accept NIPT than those with private insurance. These findings suggest that even if cost-benefit analyses, such as those by Song et al. (181), find an objective benefit to the introduction of NIPT into prenatal care, the reality is that widely varying financial elements influence how much actual testing is done and who receives the tests. Furthermore, as Stoll et al. (185) have pointed out, these analyses are predicated on an assumption that many affected pregnancies are terminated, an assumption that is neither in line with the principle of nondirective counseling nor applicable in all patient populations.

SOCIAL ISSUES

Trends in Prenatal Screening and Termination of Affected Pregnancies

The lower false-positive rates associated with NIPT address one concern raised by women who decline prenatal screening, namely that receiving an incorrect assignment of high risk caused by a false-positive result would direct them toward unnecessary invasive diagnostic testing, which carries the risk of miscarriage. Women who might otherwise decline biochemical marker screening might now opt for NIPT (99), thus increasing the volume of women undergoing prenatal genetic testing.

Despite evidence suggesting a downward trend in pregnancy termination for Down syndrome, Natoli et al. (139) found that rates for these terminations remain high in the United States, ranging from 50% to 85% depending on the study. Data for 2005–2007 from the California state screening program show that termination rates vary by condition. Termination rates for conditions associated with high early mortality ranged from 60% to 70%, whereas those for sex chromosome aneuploidies were much lower, ranging from 39% to 43%; the rate for Down syndrome was

61% (103). By contrast, termination rates for Down syndrome appear to be higher worldwide than in the United States (122, 176). The effects of NIPT on rates of elective termination are unclear. However, as more women choose NIPT, pressure to undergo screening—and therefore face decisions about termination for genetic conditions—may increase for women.

Perspectives Regarding Disabilities

Much has been written about the tension between prenatal genetic testing and disability rights (for examples, see 4, 12–14, 34, 35, 106, 147, 149, 165, 184). One of the arguments of the disability rights movement is that the mere presence of prenatal screening and diagnostic testing shows a societal bias against those with disabilities and implies that the life of a fetus with a disability is not valued as much as that of a "healthy" fetus (35, 99, 147, 149). However, others have found that support for prenatal testing does not necessarily conflict with support for people born with disabilities (160, 161). Although some observers predict that NIPT will lead to increased use of prenatal testing, it remains to be seen what impact NIPT will have, if any, on advancing the discussion regarding the value that society places on its disabled members.

There are scant empirical data regarding public opinions about Down syndrome (79); however, a study in the United Kingdom found that public perceptions were complex and conflicted (37). Public misconceptions about the nature of disability may factor into some prenatal testing and termination decisions. Although survey data show that people with Down syndrome overwhelmingly report being happy with their lives (179), a survey of Dutch women who opted to terminate a pregnancy affected by Down syndrome found that most believed that Down syndrome, when combined with low societal respect for those with disabilities, would lead to an excessively burdensome life for the child (109). Likewise, 64% of women in the Dutch survey felt that raising an affected child would be a burden (109). However, parents of children with Down syndrome reported feeling love and pride in their child, and only 4% expressed regret over having that child (178).

Several studies have examined the attitudes of parents who have children with Down syndrome or intellectual disability toward prenatal genetic testing and its impact on the disability community (104, 110, 112). These studies found that women who have a child with Down syndrome tend to support the availability of prenatal genetic testing to all women. However, they expressed concern that if the number of people born with disabilities drops as a result of increased prenatal testing, it may lead to a decrease in the availability of social support services, such as physical therapy or school programs, for those living with disability. Many mothers of children with Down syndrome nonetheless reported that they would consider using prenatal testing (including NIPT) in future pregnancies, regardless of whether they would consider termination. These results align with previous studies of prenatal testing that found that many parents value prenatal information about potential health problems and having time to prepare for the birth of an affected child (89).

LEGAL ISSUES

Intellectual Property

All the technology underlying NIPT products in the United States has been patented. The NIPT patent landscape in the United States is therefore quite complex—featuring at least 100 patents and applications (2)—and the first four companies to enter the US market have been embroiled in patent litigation since 2011 (2). These legal challenges and appeals, as well as patent interference and reexamination cases at the US Patent and Trademark Office, are ongoing. Recent US Supreme Court decisions (*Association for Molecular Pathology v. Myriad Genetics, Inc.* and *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*) regarding the patent eligibility of naturally occurring

gene sequences and genetic diagnostic methods have helped address much of the concern surrounding the potential for monopolies in the NIPT market (40). But it is clear that the legal issues will take considerable time and judicial attention to resolve, as seen in disputes over *BRCA1* and *BRCA2* gene patents (78).

Patent litigation and US Patent and Trademark Office decisions may have created freedom for new test providers to operate and helped mitigate concerns raised about monopolies limiting patient access (166); for example, Sequenom recently granted its first license for NIPT to Quest Diagnostics in the United States. Sequenom and Verinata/Illumina have also settled their NIPT litigation out of court and have agreed to pool their patents (74). However, patent litigation and opposition are expensive, and this raises concerns that companies may maintain high prices to recoup litigation costs. Concerns also surround proprietary databases that NIPT companies may use for market advantage and how they may affect clinical implementation of NIPT. Indeed, clinicians and patient advocates have raised concerns over proprietary databases that some companies, such as Myriad Genetics, maintain on clinical phenotypes of genetic variants that may impede independent clinical interpretation of genetic test results and quality of care (45).

The international patent landscape for NIPT has not been mapped extensively, and patent claims likely vary by jurisdiction. It is also not clear whether or how recent US court decisions on gene patenting will affect patent eligibility assessments made in other countries. BGI recently received patent protection, valid in 15 European countries, for technology underlying the NIFTY (Noninvasive Fetal Trisomy) test (27). On the other hand, many European countries are developing NIPT as part of their public health sector and have anecdotally expressed concern about patents impeding their ability to offer those tests as a clinical service, even though companies have historically been unsuccessful in enforcing patents against single-payer health systems, such as those of Canada, the United Kingdom, and Australia (192). In recent developments, Illumina has sued UK-based Premaitha Health for patent infringement; Premaitha Health recently launched an in vitro diagnostic for NIPT and has a contract with the UK National Health Service (76). Although intellectual property issues do present some uncertainty for new test developers, whether they will affect the affordability and availability of NIPT remains to be seen.

LDT: laboratory-developed test

FDA: Food and Drug Administration

Regulatory Oversight

All four US companies market NIPT as a laboratory-developed test (LDT), and their laboratories are regulated by the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA) act. The US Food and Drug Administration (FDA) has thus far exercised its discretionary power not to regulate LDTs. However, in 2012, the FDA suggested that it was considering extending oversight over NIPT because of the "high risk" associated with these tests (159). The FDA recently issued draft LDT regulation (66), and the idea of FDA regulation of LDTs in general has met with mixed response. However, one recent study indicated that nearly half of ACOG fellows favor FDA oversight of NIPT specifically (22). Some US companies have announced plans to seek premarket approval from the FDA for NIPT test kits. Other test developers may also choose to develop kits, which would then be regulated as devices. In the future, test developers may benefit from clarity about whether the FDA will choose to regulate NIPT offered as LDTs and whether it will be considered a high-risk test. There is currently no clear consensus in the United States about the regulation of NIPT given that several prenatal tests, such as commercially offered prenatal chromosomal microarray tests, are not regulated by the FDA and have been offered as LDTs.

Because much of the NIPT currently offered globally is performed in laboratories based in the United States, China, or Europe, only the laboratory accreditation/oversight mechanisms

in the United States, China, and/or Europe apply. Although genetic testing in most developing countries generally occurs without national regulatory oversight, recent events in China highlight how regulatory issues can affect clinical implementation (42, 72, 73). The regulatory framework for NIPT will also depend on how business models evolve; as an example, Premaitha Health launched its IONA test as an in vitro diagnostic in early 2015 with CE marking in Europe, and will also seek US FDA approval (100). Nevertheless, regulatory agencies are likely to continue monitoring the impact of NIPT, especially data regarding pregnancy terminations based on false-positive findings, to inform future oversight decisions.

Abortion

Varying state laws in the United States that restrict abortion, particularly gestational limits for legal abortion, may affect implementation of NIPT, as with other prenatal technologies. Because NIPT can be performed as early as 9–10 weeks' gestation, it allows families to obtain relatively accurate information earlier in the pregnancy and potentially terminate an affected pregnancy within the legal gestational limit.

Laws on abortion vary widely around the world (67) in their limitations on both the grounds for abortion and gestational age (68). In recent years, a trend toward the liberalization of abortion laws has been observed (67), but this trend has not been universal; for example, both El Salvador and Nicaragua removed all exceptions to the prohibition of abortion in 1998 and 2006, respectively (36). However, in practice (68), women often seek illegal abortions for unplanned/unwanted pregnancies in countries that restrict abortion (168). In jurisdictions where abortion is restricted, women may also travel outside the country to obtain abortion services, often at a high financial and social cost (69, 146). NIPT facilitates access to early and accurate prenatal genetic information and may help reduce mortality from unsafe abortions by allowing women to seek abortion legally in areas where gestational limits are set at less than 20 weeks. Even if abortion is sought illegally, earlier termination may reduce procedural complications and be safer, thus helping reduce abortion-related maternal mortality.

Reproductive Rights and the Return of Genetic Disability and Fetal Sex Information

The rapid growth of NIPT creates a tension between reproductive rights, on the one hand, and sex equality and respect for persons with disabilities, on the other, especially because NIPT offers women the option of early accurate information and earlier termination (152). There is some concern that this tension may be politicized as a tool to limit women's reproductive rights. King (105) warned that limiting the availability of abortion in response to NIPT could harm both women and children, and that regulators must be aware of this tension as they develop guidelines for NIPT. The increasing numbers of US state laws seeking to prohibit abortion for reasons of genetic disability or fetal sex provide evidence of this politicization (105).

Sex-selective abortion is common in parts of Asia, where the practice has resulted in severely skewed sex ratios caused by poorly enforced laws regulating the return of fetal sex information (48, 70, 87, 90, 94, 102, 133, 135, 141, 151, 153). Additionally, some evidence suggests that Asian immigrants in the United States may also practice sex-selective abortion (18). Given that NIPT can accurately detect fetal sex as early as 7 weeks' gestation, before most ultrasounds are performed (52), observers are concerned that NIPT may further exacerbate sex-selective abortions in places such as China and India. Companies marketing NIPT in these countries state that they are compliant with national laws, but additional monitoring is needed to assess whether fetal sex information is ordered/reported and whether current laws adequately protect against the use of

NIPT for determining fetal sex. More information and guidance is also needed about how prenatal diagnosis of sex chromosome aneuploidies is provided, given their unavoidable relationship to fetal sex.

Although fetal sex determination for family balancing is generally accepted in the developed world, the legality of sex-selective abortion is changing in some US states. It has been argued, especially in the eight states where laws have been passed (or proposed) banning sex-selective abortion, that these measures will deter the practice of sex selection. Others have argued that these laws are not based on empirical evidence of the existence of sex-selective abortion in the United States and that they serve only to restrict women's reproductive rights (18, 98). In addition, a law passed in North Dakota and a similar one being considered in Missouri expressly prohibit abortion even when a genetic disorder is diagnosed (98). Health care providers and test developers need to be cognizant of these laws in the United States as they offer NIPT, given that fetal sex and sex chromosome aneuploidy reporting is available from all US-based NIPT providers.

Physician Liability

The geographic and technological expansion of NIPT also raises concerns about legal liability, as providers are increasingly tasked with integrating NIPT into clinical care. Liability for medical negligence may arise if a physician does not meet the professional standard of care for prenatal genetic testing, resulting in a missed or inaccurate diagnosis of a genetic condition. These claims may be based on inadequate disclosure of a heightened genetic risk or appropriate testing options; failure to interpret test results accurately; or failure to meet the duty of informed consent by not thoroughly describing the risks, benefits, and alternatives for each test—including full disclosure of NIPT's limitations (53, 188). In some cases, physicians may also have a duty to refer patients to appropriate resources, such as genetic counseling, for further information (123).

Claims for prenatal medical negligence are typically brought as wrongful birth or wrongful life lawsuits, in which the parents of a genetically disabled child allege that they would have terminated their pregnancy but for the physician's negligence in failing to diagnose the genetic condition (53, 188). Although these are controversial claims and are expressly prohibited on public policy grounds in a number of jurisdictions (188), in some cases families have recovered millions of dollars in economic damages to compensate for the cost of raising a child with a disability (e.g., *Levy v. Legacy Health System*). To date, there has not been a successful US lawsuit based on negligent administration of NIPT, but the history of litigation surrounding amniocentesis and chorionic villus sampling suggests that such a case is likely to occur. As with many new medical technologies, experts expect to see more litigation as this technology becomes increasingly widespread (124).

For many physicians, especially those who have not had thorough training in medical genetics, this raises questions about their exact legal obligations to their patients (124). Although practice guidelines such as the 2012 ACOG Committee Opinion (9) offer evidence of the standard of care, that standard continues to evolve as NIPT advances and becomes more routine (53). In a survey of practicing obstetricians, more than 80% of respondents expressed a desire for ACOG to continue developing guidelines to identify best practices and proper scope for NIPT (23). In the meantime, however, physicians must take care to ensure that their patients are thoroughly informed about NIPT, its limitations and alternatives, and the implications of any results in order to avoid legal liability.

Legislation Mandating Awareness of Prenatally Diagnosed Genetic Conditions

In light of the disparate and sometimes inaccurate information given to patients when they receive a diagnosis of a genetic condition, some federal and state lawmakers have sought to close the

information gap to ensure informed decision making. In 2008, the bipartisan Prenatally and Postnatally Diagnosed Conditions Awareness Act [Pub. L. No. 110–374, 122 Stat. 4051, 4053 (2008)] went into effect, with the goal of providing "up-to-date, evidence-based, written information" and "contact information regarding support services" for prenatal care providers to give to patients who receive a diagnosis of Down syndrome. However, this federal law remains unfunded, so several state legislatures are considering or have recently passed similar legislation. Nine states have passed such laws [Va. Code 54.1-2403.01.B (2008), Mass. H.3825 (2012), Ky. S.B.34 (2013), Mo. Rev. Stat. 191.923 (2013), Del. H.B.214 (2014), La. H.B.1058 (2014), Md. S.B.654 (2014), Ohio H.B.552 (2014), and Pa. H.B.2111/S.B.1339 (2014)], and two are considering them (N.J. A3233, Okla. S.B.586). Most of these state laws require clinicians to provide women who receive a prenatal diagnosis of Down syndrome with state-approved information and access to support services, although some states have changed the model language. Most notably, the Maryland law only authorizes—rather than requires—the provision of information, and the Louisiana law expressly forbids discussion of termination "as a neutral or acceptable option." Similar state-level efforts can be expected to continue as NIPT use increases and expands to include additional conditions. However, it remains to be seen how variations in these laws will affect patients and clinicians.

WGS/WES: whole-genome/exome sequencing

THE FUTURE OF NONINVASIVE PRENATAL GENETIC TESTING

NIPT is a dynamic field where research, commercialization, and clinical translation continue at a rapid pace. The business models of NIPT companies continue to diversify, and new entries into the marketplace will likely accelerate test availability, especially given the lucrative nature of the global prenatal testing market. Similarly, technology platforms are expected to expand, as illustrated by recent reports that NIPT can be performed using microarray technology with similar accuracy and cost as using massively parallel DNA sequencing (96). The applications of NIPT in prenatal care will also continue to expand, as observed with the introduction of testing for subchromosomal abnormalities such as microdeletion syndromes. Some observers predict that, in the near future, NIPT may analyze genome-wide CNVs. Noninvasive testing for single-gene disorders will also become available as new techniques for detecting point mutations in cffDNA are developed (114). Finally, whole-genome/exome sequencing (WGS/WES) of cffDNA has been demonstrated and may eventually be used in clinical settings (107, 118). It is therefore possible that alternative prenatal testing options/algorithms will emerge in parallel with basic testing that includes only chromosomal aneuploidies followed by additional tiers of testing for panels of CNVs, single-gene disorders, and possibly the whole fetal genome/exome. These test options can be expected to come with different pricing structures and coverage policies, and will present additional challenges for informed decision making and genetic counseling.

Although NIPT is already commercially available to average-risk women, especially those who can pay for it out of pocket, its use has been limited largely to high-risk pregnancies in the United States. This is partly because the initial clinical validation studies were performed only with high-risk women, and as a result payers have supported reimbursement only for high-risk patients. After reviewing some of the early studies comparing NIPT performance in high- and average-risk populations, the SMFM stated that the findings were not sufficient to warrant a change in their official guidelines; therefore, the SMFM and ACOG still recommend restricted offering of NIPT to high-risk women (180). However, recent studies from commercial providers suggest that the tests have similar specificity and sensitivity in average-risk pregnancies as in high-risk pregnancies (31), although more data are needed on test failure rates and PPVs in average-risk populations. Provider-offered NIPT is expected to expand to average-risk pregnant women and may eventually be routinely used in prenatal screening, perhaps replacing first-trimester

screening or serving as a second-tier screen contingent on a woman's first-trimester screening risk. The availability of testing in average-risk women may allow better detection of subchromosomal changes in younger women, because these changes are not known to be associated with advanced maternal age. However, large-scale clinical validation studies are needed to ascertain false-positive and false-negative rates before NIPT testing for CNV detection is offered broadly, let alone offered to average-risk women.

The expansion of NIPT to average-risk women also raises questions about coverage and reimbursement because the current patchwork coverage policies in the United States may lead to greater disparities in access to prenatal genetic services; this will be especially true if state payers, such as Medicaid programs, do not cover NIPT for average-risk women. However, the cost of NIPT is predicted to decrease as a result of future technological innovations, which may make coverage more feasible for payers. The use of NIPT in the entire population of pregnant women also raises concerns surrounding the erosion of informed consent by routinization of NIPT if, for example, NIPT were included in a battery of tests performed during a blood draw at the first prenatal visit. Most stakeholders agree that there will not be sufficient numbers of genetic counselors to meet the dramatically increased need for pre- and post-test genetic counseling. Health care providers will increasingly be required to perform this counseling on their own so that families can make informed reproductive decisions. In the absence of robust education of patients and providers, the wider availability of NIPT and the expanding range of test options will further exacerbate existing challenges of informed decision making. Increased use of NIPT further raises the possibility of more medical malpractice lawsuits surrounding wrongful birth/life, with resulting implications for physician malpractice insurance. It also raises the possibility of increased termination of pregnancies for fetuses with genetic abnormalities, leading to more concern from activists and patient advocates about stigmatization of genetic conditions and reduced social support for children born with genetic abnormalities.

The clinical use of cffDNA WGS/WES will initially be limited because of cost. However, as DNA sequencing costs continue to drop and innovations in testing methods continue, the use of noninvasive cffDNA WGS/WES is expected to broaden, potentially to reporting a set of genetic conditions that are clinically relevant for reproductive decision making, pregnancy management, and neonatal interventions. More women may choose WGS/WES NIPT options in the future simply because it will be convenient. This will likely present additional genetic counseling challenges related to returning information and incidental findings, as well as concerns about the expansion of the conditions tested to include adult-onset conditions and behavioral disorders of varying severity. If used as the basis of pregnancy termination, testing for these conditions would raise moral and philosophical concerns about eugenics. WGS/WES also poses important ethical questions about the future autonomy of the child and the role of genetic determinism in influencing parental decisions about pregnancy termination. Although the ethical challenges surrounding the use of prenatal genetic testing are not entirely unique to NIPT, the increase in the volume of such testing resulting from the wider acceptance of NIPT could increase the magnitude of the problem.

POLICY CONSIDERATIONS

As technologies for NIPT continue to evolve and testing becomes more common worldwide, it will be important for professional societies to monitor NIPT offerings and expediently provide guidelines for appropriate clinical practice. Clear and transparent guidelines on what payers will cover and how they assess clinical utility and validity to make coverage decisions, especially from state-based payers, will be important to ensure that disparities in access to prenatal genetic testing are not exacerbated. In countries where NIPT is offered entirely through the private

sector, including the United States, public support for clinical studies comparing emerging NIPT technologies with standards of care and evaluating their cost effectiveness will facilitate appropriate implementation. Clear guidance on regulatory oversight of NIPT and establishment of proficiency testing will help ensure the quality of testing as both the number of providers and types of platforms increase. Patient and provider education resources developed collaboratively by stakeholders (clinicians, patients, industry, disease advocates, and disability rights advocates) to provide accurate and balanced information are essential to foster informed decision making. Innovative approaches to deliver genetic counseling, patient decision-making tools, and provider education will be required. Careful monitoring of nonmedical uses of NIPT (such as for fetal sex selection) by professional societies and national/international agencies is also warranted. Addressing this long list of policy issues requires empirical data on the experiences and perspectives of a wide group of stakeholders in the United States and internationally, where data gaps are even more critical. Concerted engagement among stakeholders is essential to ensure that NIPT technologies are used ethically and effectively, maximizing benefits for women and families worldwide.

SUMMARY POINTS

1. Noninvasive prenatal genetic testing (NIPT) combines the ease of a serum screen with higher test accuracy and may lead to broad adoption and routinization of prenatal genetic testing for chromosomal abnormalities.
2. Expansion of NIPT to average-risk women will exacerbate existing (and frequently unmet) needs for effective pre-test counseling and could further erode informed consent.
3. The introduction of NIPT as an exclusively commercial product raises questions regarding cost effectiveness, equal access, and the impact of marketing strategies on patient and provider education and informed decision making.
4. NIPT may increase acceptance of prenatal genetic testing, which will allow many parents to prepare for the birth of a child with a genetic condition; however, it may also lead to increased pressure to test and an increase in terminations of affected pregnancies.
5. The rapid expansion of NIPT panels to include sex chromosomes, rare aneuploidies, and selected microdeletions has raised new concerns regarding clinical utility, lack of clinical validation data, lack of up-to-date and balanced education for providers, and appropriate pre- and post-test counseling for patients.
6. Laws restricting the grounds for abortion (e.g., for genetic conditions or fetal sex) affect implementation of NIPT in the United States and abroad; however, in contexts where abortion is restricted or illegal, early information may reduce abortion-related maternal mortality from late-term or unsafe illegal terminations.

FUTURE ISSUES

1. Regulatory oversight of NIPT is likely to evolve, especially as the US Food and Drug Administration reconsiders policies for regulating laboratory-developed tests. Oversight of laboratory accreditation, including proficiency testing, will also be essential in ensuring the quality of NIPT as the number of platforms and commercial providers continues to increase.

2. Future use of NIPT for single-gene disorders, genome-wide copy-number variations (CNVs), and whole-genome/exome sequencing (all already proven in principle) will increase the magnitude of ethical challenges surrounding prenatal genetic testing, including informed decision making, cost effectiveness, equal access, and protection of the future child's autonomy.
3. The likely expansion of NIPT into routine screening for average-risk pregnancies will allow better screening for CNVs in younger women but will exacerbate concerns about false positives and negatives, informed decision making, equal access, and decreased support for people with disabilities.
4. Up-to-date clinical guidelines from professional societies and clear guidelines from governments about uses of NIPT for sex selection will help ensure ethically and socially responsive clinical implementation of NIPT.
5. Effective informed decision making for NIPT will require collaborative efforts by a variety of stakeholders to develop accurate and balanced educational materials and innovative approaches to provider education and patient counseling.

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