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The Benefits and Challenges of Expanding Access to Noninvasive Prenatal Testing (NIPT) Through Public Health Efforts

Maryam Farzad Hassimi, PhD

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INTRODUCTION

Noninvasive prenatal testing (NIPT) is a screening tool for pregnant women developed in 2011 to detect major chromosomal aneuploidies such as Trisomy 21 (Down Syndrome), Trisomy 18 (Edwards Syndrome), and Trisomy 13 (Patau Syndrome). In 2012, the American College of Obstetrics and Gynecology (ACOG) recommended NIPT for women considered high risk, and in August 2020 the guidelines were expanded to recommend NIPT for all pregnancies. This news was praised as a dramatic shift in ensuring broader access to the highly accurate technology early in pregnancy. NIPT is only a screening tool, but women have expressed overwhelming support for its use in prenatal care based on a low false positive rate and a reduction in the need for invasive diagnostic testing such as amniocentesis, which has a risk of miscarriage.

Robust prenatal care is a key public health effort aimed at ensuring healthy pregnancies. As a relatively new technology, NIPT has rapidly gained positive attention along with critical evaluation of what public policy framework and government intervention is appropriate. Widespread focus on NIPT has raised concerns in four major areas that will be the focus of this paper. First, NIPT is a laboratory developed test (LDT) and not an FDA-regulated *in vitro* diagnostic (IVD). As NIPT becomes a more routine component of obstetric care, it is essential that the FDA expand its role in overseeing its regulation and adoption. Second, disability advocates raise serious concerns about the widespread adoption of NIPT because of the messaging that it suggests about giving birth to and raising children with disabilities. In response, public programs and legislation can continue to support their needs through various

measures such as ensuring resources for people living with genetic disorders. Third, access to NIPT is largely determined by coverage through private insurance companies and government programs including Medicaid. Variation in coverage can exacerbate existing disparities in the social determinants of health. The benefits of the technology need to be proven to payers through studies that demonstrate the reduction of costs through fewer invasive diagnostic procedures and long-terms costs associated with disability. Lastly, as NIPT evolved within the developing field of genomics, healthcare providers such as physicians may be poorly equipped to understand the advances in genetic technology and properly advise pregnant women on NIPT results. This complicates women's abilities to make informed reproductive decisions. By adopting NIPT into routine care, physicians are also assuming a greater legal liability when missing or inaccurately diagnosing a genetic screening result. Governmental efforts to protect healthcare providers from lawsuits in this space will encourage more routine adoption and also push for more education and training in medical genetics.

BACKGROUND

There are approximately 4 million live births in the US yearly.[1] Twenty percent are considered high risk based on advanced maternal age or predisposition to certain genetic conditions.[2] Prenatal genetic testing is a key part of obstetric care for pregnant women. Approximately 3% of live births have a major congenital abnormality based on genetic factors.[3] Humans have two copies of chromosomes, and errors in cell division can lead to aneuploidies, which are the presence or absence of one or more chromosomes. The most common chromosomal aneuploidies that are screened for as part of prenatal care are Trisomy 21 (T21),

[1] Mollie A. Minear, Stephanie Alessi, Megan Allyse, Marsha Michie & Subhashini Chandrasekharan, Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues, 16 Annu. Rev. Genomics Hum. Genet. 369 (2015).
[2] *Id*.
[3] *Id*.

Trisomy 18 (T18) and Trisomy 13 (T13), and the majority of spontaneous miscarriages happen based on aneuploidies.[4] Prenatal testing enables screening during pregnancy to detect women who are at high risk, followed by the option for a diagnostic test to confirm the presence of the genetic abnormality.[5]

The origin of prenatal care in the United States began in the late 1800s as a preventative measure to decrease maternal and fetal mortality based on preeclampsia through routine measurement of blood pressure, urine and weight.[6] Guidelines for prenatal care visits were established by the American College of Obstetricians and Gynecologists (ACOG) in 1989.[7] The two types of prenatal testing are prenatal screening tests and prenatal diagnostic tests. Prenatal screening techniques are offered to all pregnant women and include serum marker screening and ultrasound imaging in the first and second trimesters to detect birth defects, including chromosomal aneuploidies.[8] The most comprehensive screening approach is integrated screening, which combines results from first and second trimester screening tests to calculate a single aneuploidy score.[9]

While prenatal screening procedures calculate a risk of fetal aneuploidy, genetic diagnostic tests actually detect the presence of whole or sub-chromosomal genetic abnormalities through invasive measurement of amniotic fluid or placental tissue.[10] Women who obtain a positive result from a screening test will be referred for diagnostic genetic testing through chorionic villus sampling (CVS) or amniocentesis.[11] CVS is generally conducted in the first

[4] Megan E. Benoy, J. Igor Iruretagoyena, Laura E. Birkeland & Elizabeth M. Petty, The impact of insurance on equitable access to noninvasive prenatal screening (NIPT): private insurance may not pay, 12 J. Community Genet. 185 (2021).
[5] *Id*.
[6] Judith A. Maloni, Ching-Yu Cheng, Cary P. Liebl & Sharp M. Jeanmarie, Transforming Prenatal Care: Reflections on the Past and Present with Implications for the Future, 25 JOGNN 17 (1996).
[7] *Id*.
[8] Minear, *supra* note 1.
[9] *Id*.
[10] *Id*.
[11] *Id*.

trimester (week 10 to 13), while amniocentesis is performed in the second trimester at week 15.[12] These invasive tests are the only diagnostic tests available for fetal aneuploidy and have a 1 in 300 to 1 in 500 risk of pregnancy loss.[13]

In 2011, based on advances in genetic technologies from the Human Genome Project, a new type of genetic screening test was introduced to the market called noninvasive prenatal testing (NIPT).[14] NIPT involves a simple maternal blood draw to measure fetal fraction, which is the amount of cell-free fragments of fetal DNA (cffDNA) circulating in the maternal bloodstream from the placenta.[15] NIPT screening is offered in the first trimester because the fetal fraction needs to be over 4 percent, which happens around the tenth week of pregnancy.[16] Compared to traditional first and second trimester screening, NIPT is more accurate with a lower false positive rate and an actual measurement (not an inferential aneuploidy risk score).[17] False positive rates for NIPT range from 0.09% to 0.13% depending on the type of aneuploidy detected.[18] The accuracy of NIPT greatly reduces the need for confirmatory follow up with invasive diagnostic testing.[19] Currently NIPT is a second-line screening that is recommended following a positive conventional screening result, but there are efforts to adopt NIPT as a first-line screening tool instead.[20]

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[12] *Id*.
[13] *Id*.
[14] *Id*.
[15] *Id*.
[16] *Id*.
[17] *Id*.
[18] Bin Yu, Bei-Yi Lu, Bin Zhang, Xiao-Qing Zhang, Ying-Ping Chen, Qin Zhou, Jian Jiang & Hui-Yan Wang, Overall evaluation of the clinical value of prenatal screening for fetal-free DNA in maternal blood, 96 Medicine (Baltimore) e7114 (2017).
[19] *Id*.
[20] Emilia Kostenko, Frederic Chantraine, Katleen Vandeweyer, Maximilian Schmid, Alex Lefevre, Deanna Hertz, Laura Zelle, Jose Luis Bartha & Gian Carlo Di Renzo, Clinical and Economic Impact of Adopting Noninvasive Prenatal Testing as a Primary Screening Method for Fetal Aneuploidies in the General Pregnancy Population, 45 Fetal Diagn. Ther. 413 (2019).

The NIPT global market in 2019 was valued at $2.95 billion and is expected to reach more than $10 billion by the end of 2027.[21] NIPT tests are largely developed through commercial entities. The first commercially available NIPT test was the MaterniT21 test (now MaterniT21 Plus) launched by Sequenom in 2011 to detect Trisomy 21.[22] Sequenom reports that out-of-pocket costs for the MaterniT21 Plus test will be $235 for patients covered by insurance or $1700 for those without.[23] Other commercial vendors who offer NIPT include Verinata (Verifi), Ariosa (Harmony), Natera (Panorama) and Illumina (VeriSeq).[24] The list price of these different tests ranges from $1100 to $1590, while patient out-of-pocket fees can be from $200 to $400 depending on qualifying insurance.[25]

Multiple professional associations have issued guidelines on the adoption of NIPT. These organizations include the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), the National Society of Genetic Counselors (NSGC), Stand up for Accurate Prenatal Answers (Stand up for APA) and the International Society for Prenatal Diagnosis (ISPD).[26] These associations categorize pregnancies into two groups: high risk (15%) and average risk (85%).[27] Prior to the August 2020 revised ACOG guidelines that recommended NIPT for all pregnant women, most organizations originally specified that NIPT should only be offered to women who were at high risk for fetal aneuploidies based on the following factors: maternal-age related risks, positive results on maternal serum-screening, abnormal ultrasound, or prior affected pregnancy.[28] Stand up APA advocated against age-related criteria, arguing that limiting NIPT access to women under 35 put them at higher risk

[21] Ashwin Agarwal, Lauren C. Sayres, Mildred K. Cho, Robert Cook-Deegan & Subhashini Chandrasekharan, Commercial landscape of noninvasive prenatal testing in the United States, 33 Prenat Diagn. 521 (2013).
[22] *Id*.
[23] *Id*.
[24] *Id*.
[25] Benoy, *supra* note 4.
[26] *Id*.
[27] *Id*.
[28] *Id*.

of false positive and false negative results.[29] False positive results lead to unnecessary, potentially stressful and expensive visits to specialists, while false negatives deny pregnant women the opportunity to plan and prepare accordingly.[30]

Forty commercial insurance companies covered NIPT for all pregnancies even before the expanded ACOG recommendations in 2020. But many state Medicaid programs and the two largest insurance companies – Aetna Inc. and United Healthcare (UHC) – did not cover NIPT for all pregnant women.[31] Finally in December 2020, UHC expanded NIPT coverage for all pregnancies.[32] Aetna temporarily expanded NIPT coverage to all pregnant women in response to the COVID-19 crisis but did not permanently expand access to all women until December 2020, after UHC changed its policy in response to the ACOG guidelines.[33] Despite expanded access to NIPT, clinical guidelines emphasize that NIPT is a screening tool and not a diagnostic test. Confirmatory diagnostic testing should be performed and irrevocable decisions related to pregnancy should not be made based on NIPT alone. However, the introduction of NIPT has corresponded to a reduction in diagnostic testing, which suggests that education by clinicians is critical to ensuring the accurate utilization of NIPT results.[34]

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[29] Bloomberg Press, *COVID-19: Aetna Expands NIPT Coverage for Young Pregnant Wom*en, (May 2020), https://www.bloomberg.com/press-releases/2020-05-18/covid-19-aetna-expands-nipt-coverage-for-young-pregnant-women (last visited February 6, 2021).

[30] *Id*.

[31] AISHEALTH, *To Cover or Not to Cover? Prenatal DNA Test Creates Quandary for Payers*, (January 2019), https://aishealth.com/health-plans/to-cover-or-not-to-cover-prenatal-dna-test-creates-quandary-for-payers/, (last visited February 6, 2021).

[32] PR Newswire, *Stand Up for APA Applauds Aetna Decision to Permanently Cover Noninvasive Prenatal Testing (NIPT) For All Pregnant Women*, (December 2020), https://www.prnewswire.com/news-releases/stand-up-for-apa-applauds-aetna-decision-to-permanently-cover-noninvasive-prenatal-testing-nipt-for-all-pregnant-women-301189663.html, (last visited February 6, 2021).

[33] *Id*.

[34] *Id*.

Research indicates that women have a strong preference for NIPT, including a 2018 study that found NIPT uptake was increasing in women both above and below 35 years old.[35] The key factors contributing to the support include accuracy of the results, alleviation of stress during pregnancy, and the ability to make value-based decisions without undergoing invasive diagnostic testing.[36] Yet the expanded adoption of and support for NIPT has drawn concern from disability advocates who worry that routinization of NIPT will increase pressure to test and to terminate, resulting in fewer disabled births, a corresponding reduction in social services and an increase in stigmatization.[37] For example, families with children with Down Syndrome (DS) express concern that widespread NIPT will reduce the number of DS births, thereby reducing public resources and support systems for DS families and shifting societal perceptions of children with disabilities.[38]

Advancements in the field of genetic testing and genomics (the study of all genes) enabled the development of NIPT.[39] As a genetic test, NIPT falls within the scope of public health genomics, a field defined in 2005 to oversee the "responsible and effective translation of genome-based knowledge and technologies for the benefit of the population."[40] Activities key to supporting public health include (1) enforcing laws and regulations that protect health and ensure safety, (2) developing policies and plans that support individual and community health efforts, (3) linking people to needed health services and (4) assuring a competent public and

[35] Celine Lewis, Melissa Hill & Lyn S. Chitty, Women's experiences and preferences for service delivery of noninvasive prenatal testing for aneuploidy in a public health setting: a mixed methods study. 11 PLoS ONE e0153147 (2016).
[36] Sophie Montgomery & Zaneta M. Thayer, The influence of experiential knowledge and societal perceptions on decision-making regarding noninvasive prenatal testing (NIPT), 20 BMC Pregnancy and Childbirth, 630 (2020).
[37] Alexandra Cernat, Chante De Freitas, Umair Majid, Forum Trivedi, Caroline Higgins & Meredith Vanstone, Facilitating informed choice about noninvasive prenatal testing (NIPT): a systematic review and qualitative meta-synthesis of women's experiences, 19 BMC Pregnancy and Childbirth, 27 (2019).
[38] *Id*.
[39] Minear, *supra* note 1.
[40] *Id*.

healthcare workforce.[41] To reach these aims, this paper proposes the following measures. First, expanded FDA oversight of NIPT is necessary to ensure that testing meets minimum performance standards and that marketing claims by commercial NIPT vendors are regulated. Second, as NIPT expands, public policy needs to recognize the impact on the disabled community by overseeing messaging about genetic disabilities. Third, increasing access to NIPT through expanded public insurance coverage will reduce healthcare inequities and ensure reproductive autonomy. Finally, physicians have the responsibility to inform patients of the benefits and limitations of NIPT. To minimize liability, physicians will depend on guidelines and educational resources from professional medical societies such as ACOG to ensure they are properly trained. Incorporating these essential public health services for NIPT requires a coordinated government approach to ensure the responsible and equitable adoption of the technology.

ANALYSIS

Expanded FDA oversight of NIPT is necessary to ensure that testing meets minimum performance standards and marketing claims by commercial NIPT vendors are regulated

Regulation of NIPT has sparked considerable recent debate as the adoption of the testing becomes more widespread. Clinical tests that involve the analysis of human samples such as blood or saliva are classified as either *in vitro* diagnostics (IVDs) or laboratory developed tests (LDTs).[42] IVDs are complete kits sold by manufacturers to laboratories adopting the assays, while LDTs are generally developed, marketed and run by a single laboratory for non-commercial use.[43] Since 1976, the Food and Drug Administration (FDA) has regulated IVDs

[41] *Id.*
[42] Pew Trust, *Clinical Lab Tests Need Stronger FDA Oversight to Improve Patient Safety*, (January 2021), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/01/clinical-lab-tests-need-stronger-fda-oversight-to-improve-patient-safety, (last visited February 16, 2021).
[43] *Id.*

under the Medical Device Amendments Act but has largely excluded LDTs from the stringent regulatory oversight that is required for IVDs.[44] Although LDTs are subject to FDA regulation, the agency has exercised "enforcement discretion" and chosen not to actively regulate LDTs.[45] The FDA's position is that LDTs are generally intended for limited use within a restricted environment.[46] IVDs and LDTs are also subject to oversight by the Centers for Medicare and Medicaid Services (CMS) through the 1988 Clinical Lab Improvement Amendments (CLIA), which is a federal regulatory standard that applies to clinical labs that perform basic testing on human samples.[47]

FDA oversight of IVDs consists of premarket and post market controls.[48] IVD products are classified into Class, I, II or III levels based on increasing levels of risk.[49] The risk category determines the level of regulatory control and corresponding premarket FDA process required to bring the device to market.[50] The possible premarket controls span from general controls to 510k clearance and premarket approval (PMA).[51] 510k clearance requires submitting documented evidence to the FDA that the medical device is substantially equivalent to a predicate device.[52] This evidence is evaluated by the FDA within 30 to 90 days.[53] Premarket approval (PMA) is more in-depth than 510k and is used to evaluate the safety and effectiveness of Class III devices, which are those that "those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness

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[44] Monica A. Lutgendorf, Katie A. Stoll, Dana M. Knutzen & Lisa M. Foglia, Noninvasive prenatal testing: limitations and unanswered questions, 16 Genet. Med. 281 (2014).
[45] *Id.*
[46] Hannah Mamuszka, The Neverending LDT vs IDT Debate, 6 J. Prec. Med. 1 (2019).
[47] *Id.*
[48] US. Food & Drug Admin., *Overview of IVD Regulation*, (September 2019), https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation#9, (last visited April 25, 2021).
[49] *Id.*
[50] *Id.*
[51] *Id.*
[52] Greenlight Guru, 510k v PMA, (January 2021), https://www.greenlight.guru/glossary/510k-pma, (last visited April 25, 2021).
[53] *Id.*

or injury."[54] For IVDs subject to premarket approval (PMA), the FDA requires a research phase where the investigational use of the IVD is defined, the participation and consent of research subjects is overseen by institutional review boards (IRB), and analytical and clinical validation results as well as adverse results are reported.[55] Once a PMA is submitted, the FDA has 180 days to accept or reject the application.[56]

Currently, the more than 40 NIPT solutions available on the market fall under the category of LDTs and not IVDs.[57] The LDT classification means that NIPT manufacturers are not required to submit evidence of clinical validity to the FDA.[58] They also avoid supervision of their marketing claims.[59] The classification of NIPT as an LDT is insufficient oversight to tackle the possibility of false negative or false positive results. Disability advocates such as the National Down Syndrome Society have questioned why the FDA does not provide more stringent oversight over NIPT, which is now being used routinely to make significant decisions about a pregnancy.[60] NIPT is most appropriately used to screen for Down, Edwards and Patau syndromes and has been expanded in scope to identify extra or missing copies of the X and Y sex chromosomes.[61] Yet the accuracy of NIPT depends on the type of chromosomal disorder that is being detected, and the technology is evolving to look at additional chromosomal

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[54] US. Food & Drug Admin., *Premarket Approval (PMA)*, (May 2019), https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma, (last visited April 12, 2021).
[55] *Id*.
[56] *Id*.
[57] Jean Gakas, Sylvie Langlois, Vardit Ravitsky, Francois Audibert, David Gradus van der Berg, Hazarg Haidar & Francois Rousseau, Noninvasive prenatal testing for fetal chromosome abnormalities: review of clinical and ethical issues, 9 Appl Clin Genet 15 (2016).
[58] *Id*.
[59] *Id*.

[60] National Down Syndrome Society, *Noninvasive Prenatal Tests (NIPTs)*, (January 2021), https://www.ndss.org/programs/ndss-legislative-agenda/healthcare-research/noninvasive-prenatal-tests-nipts, (last visited April 25, 2021).
[61] Medline Plus, *What is noninvasive prenatal testing (NIPT) and what disorders can it screen for?* (November 2020), https://medlineplus.gov/genetics/understanding/testing/nipt/, (last visited April 25, 2021).

disorders that are based on variations in smaller regions of genetic material, such as changes in single genes or pieces of chromosomes.[62]

Furthermore, NIPT was originally developed as a screening tool for high-risk pregnancies. As its adoption spreads to the general pregnancy population, where the prevalence of trisomy is less than that for high-risk pregnancies, more studies and data need to be collected to evaluate the false positive and negative rate of the testing for average risk women. A recent study found that the use of NIPT in the general population could return false positive results up to 20% of the time for Down syndrome and even higher rates for the detection of Edwards and Patau syndromes.[63] From a policy perspective, sub-group analysis is critical as the accuracy of NIPT testing has been shown to be higher in high-risk pregnancies and more accurate for T21 than T18 or T13.[64]

There is evidence that some women consider NIPT diagnostic and do not realize it is a screening tool that precedes confirmatory diagnostic testing by CVS or amniocentesis.[65] The concern is that pregnant women will make decisions about whether to continue a pregnancy based on incomplete results, or that they will be unprepared to raise a child with a chromosomal abnormality if they are faced with a false negative result. This is where FDA oversight could lead to the development of standards that require test developers to define the target population, specify the intended use of the technology and demonstrate the analytical and clinical validity of the test, leading to a reduction in false positive and negative results.[66] A recent survey of ACOG members reported that half of them favored more oversight of NIPT.[67]

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[62] *Id*.
[63] Sian Taylor-Phillips, Karoline Freeman, Julia Geppert, Adeola Agbebiyi, Olalekan A. Uthman, Jason Madan, Angus Clarke, Siobhan Quenby & Aileen Clarke, Accuracy of noninvasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis, 6 BMJ Open 1 (2016).
[64] *Id*.
[65] Pew Trust, *supra* note 42.
[66] *Id*.
[67] Minear, *supra* note 1.

There have also been calls for the FDA to regulate marketing and product use labels of NIPT by requiring claims about the tests to be truthful, non-misleading and scientifically robust.[68] Advertisements may exaggerate the accuracy of the results and also promote the unapproved use of NIPT to screen for a broader range of chromosomal disorders, such as microdeletions underlying Cri-du-Chat or sex chromosome aneuploidies.[69] Both individuals and their healthcare providers may lack sufficient information to understand the physical and cognitive characteristics associated with these genetic conditions. They may disproportionately rely on content from commercial NIPT websites, who are in the business of marketing and selling the tests, and the concern is that the industry has paved the narrative about NIPT.[70] The major concern with the misleading advertising is that women may be choosing to abort pregnancies based exclusively on NIPT results alone without pursuing diagnostic confirmatory testing or considering the potential false positive rates.

In 2010, the FDA expressed a need for greater regulation of LDTs, and in 2014 it published two guidance documents describing potential efforts to enhance oversight.[71] The proposals included a framework to Congress describing how the FDA would regulate LDTs, and they were eventually incorporated into the Diagnostic Accuracy and Innovation Act (DAIA).[72] This legislation evolved based on FDA revisions into the bipartisan Verifying Accurate Leading-edge IVCT Development Act of 2020 (the VALID Act).[73] The VALID Act includes multiple provisions aimed at increasing the stringency of LDT regulation by incorporating procedures

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[68] *Id*.
[69] National Council on Disability, *Genetic Testing and the Rush to Perfection: Part of the Bioethics and Disability Series*, (October 2019), https://ncd.gov/sites/default/files/NCD_Genetic_Testing_Report_508.pdf, (last visited April 25, 2021).
[70] *Id*.
[71] *Potential Impact of the VALID Act on IVD Manufacturers*, (March 2021), https://www.thejournalofprecisionmedicine.com/the-journal-of-precision-medicine/potential-impact-of-the-valid-act-on-ivd-manufacturers/, (last visited April 25, 2021).
[72] *Id*.
[73] *Id*.

required through the IVD regulation process, such as ensuring the analytical and clinical validity of the tests.[74] The goal is for the FDA to oversee a unified set of standards as it does with IVDs and to require evidence-based, truthful representation of product claims by testing manufacturers.[75]

Specifically, the legislation includes a precertification requirement where one test within a test group would be subject to premarket approval (PMA) as is required for high-risk IVDs.[76] When applied to NIPT tests, the additional required documentation is key to establishing a record of efficacy about false positive and negative rates and to specifying the types of chromosomal disorders measured and reported.[77] The challenge with the expanded process though is that it is time-consuming and costly and may be prohibitive for the smaller labs who can establish NIPT testing through the LDT route but may face obstacles of time and cost through the IVD PMA requirements. The FDA does provide provisional approvals for IVDs which is a streamlined path for small labs to obtain PMA, but the provisional path was not included in the VALID Act for LDTs.[78] Since the PMA approval is lengthy, a more viable alternative is to require NIPT manufacturers to apply for 510k clearance, which is currently required for Class II medical devices.[79] Through this process, the NIPT companies demonstrate to the FDA that their low risk device is substantially equivalent (as safe and effective) as a device that is already on the market.[80] The application and review process is less extensive and shorter than that required for PMA approval. This approach may be a more reasonable step since NIPT vendors have not been subject to any FDA oversight. A transitional, gradual level of

[74] *Id.*
[75] *Id.*
[76] *Id.*
[77] *Id.*
[78] *Id.*
[79] *Id.*
[80] *Id.*

oversight will address concerns while simultaneously supporting the rapid pace of innovation and adoption of NIPT.

As NIPT expands, public policy needs to recognize the impact on the disabled community of messaging about genetic disabilities

As prenatal genetic testing becomes more widespread, disability advocates have raised concerns that the growing adoption of NIPT reflects a negative valuation of individuals with disabilities.[81] A major argument is that by simply offering prenatal screening, society is communicating an implicit bias against fetuses with genetic conditions.[82] Yet advocacy for NIPT screening can coexist with support for the disabled. Prenatal screening is not aimed at eliminating the birth of individuals with disabilities but instead assisting expecting families to make informed reproductive decisions.[83] Nonetheless, the disabled community may understandably reject the notion that NIPT screening, and more significantly, the potential termination of pregnancies as a result, does not negatively impact the perception of those genetic conditions. It is therefore important to recognize the position of these communities and ensure that their concerns are heard and addressed while simultaneously encouraging the responsible routinization of NIPT screening.

A key concern raised about NIPT by disability advocates is that the number of Down Syndrome related pregnancies will decrease based on NIPT results as women choose to terminate the pregnancies.[84] Older data from 1990 to 2010 showed that approximately 5300 Down Syndrome babies were born annually from 2006-2010 and that the termination rate of

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[81] *Id*.
[82] Minear, *supra* note 1.
[83] Eline M. Bunnik, Adriana Kater-Kuipers, Robert H. Galjaard & Inez D. de Beaufort, Should pregnant women be charged for noninvasive prenatal screening? Implications for reproductive autonomy and equal access, 46 J. Med. Ethics 194 (2020).
[84] Melissa Hill, Angela Barrett, Mahesh Choolani, Celine Lewis, Jane Fisher & Lyn S. Chitty, Has noninvasive prenatal testing impacted termination of pregnancy and live birth rates of infants with Down syndrome?, 37 Prenat. Diagn. 1281 (2017).

Down Syndrome pregnancies was estimated at thirty percent.[85] This study though predates the introduction of NIPT in 2011. There is a need for continued examination of the impact of NIPT on elective terminations to ascertain what the actual outcome is on the birth of individuals with disabilities. Critics of NIPT point to countries such as Iceland where almost 100% of women who receive a positive Down Syndrome result from prenatal screening choose to have abortions. The headlines read "Inside the country where Down Syndrome is Disappearing"[86] and "A World Without Down Syndrome"[87] and paint a picture that a pattern of requesting abortion on demand exists and that the birth of a child with Down Syndrome is devalued.

Research indicates that women have a strong preference for NIPT.[88] Since support for NIPT is high, public policies need to be adopted that establish a framework where resources for the disabled community continue to be available and prioritized. The National Council on Disability (NCD) issued a 2019 report titled "Genetic Testing and the Rush to Perfection" with recommendations for Congress and federal authorities that are "aimed at greater federal and state oversight and quality control of genetic tests and improving genetic counselor education on disability.[89] Genetic counselors can have a significant impact by understanding and presenting accurate information to expecting families. In the 1980s, the life expectancy of a child born with Down Syndrome was 25 years, but it is now closer to 60-70 years.[90] Specifically, the NCD recommended that the FDA end enforcement discretion and regulate NIPT.[91] The NCD report stated that:

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[85] Gert de Graaf, Frank Buckley & Brian G. Skotko, Estimates of the Live Births, Natural Losses, and Elective Terminations with Down Syndrome in the United States, 167 Am. J Med. Gen. 756 (2015).
[86] Julian Quinones & Arijeta Lajka, *What kind of society do you want to live in? Inside the country where Down syndrome is disappearing*, (August 2017), https://www.cbsnews.com/news/down-syndrome-iceland/, (last visited March 18, 2021).
[87] Alison Gee, *A world without Down's syndrome?* (September 2016) https://www.bbc.com/news/magazine-37500189, (last visited March 18, 2021).
[88] Lewis, *supra* note 35.
[89] National Council on Disability, *supra* note 69.
[90] *Id.*
[91] *Id.*

> The FDA has identified problems with a number of LDTs, including claims that are not adequately supported by evidence, lack of appropriate controls yielding erroneous results, and in a few cases, falsification of data. These problems demonstrated a need for greater FDA oversight to assure both analytical and clinical validity of LDTs relied on by physicians and patients.[92]

Furthermore, there is a call by the NCD for the Federal Trade Commission (FTC) to regulate the marketing claims and business practices of the genetic testing companies.[93] For example, the FTC regulates the content of consumer advice on direct-to-consumer (DTC) genetic testing webpages, and the NCD's position is that this oversight should be extended to prenatal genetic testing companies as well.[94] Lastly, it is critical to have abundant resources available highlighting the meaningful life experiences of individuals with disabilities. The federal PPDCAA (Prenatally and Postnatally Diagnosed Conditions Awareness Act) was a first step that was signed into law in October 2008 but has been largely unfunded.[95] The aim of the legislation was to provide information to healthcare providers and families about living with genetic conditions and obtaining support, and nineteen states have adopted similar legislation.[96] But the scope of the outreach varies state by state and efforts to collect data on rollout and efficacy are limited.[97]

Increasing access to NIPT through expanded private and public insurance coverage will reduce healthcare inequities and ensure reproductive autonomy

In the United States, health insurance coverage is predominantly available through commercial insurance providers and publicly funded insurance for those who meet certain criteria.[98] Private insurance is the predominant source of health insurance coverage in the United

[92] *Id*.
[93] *Id*.
[94] *Id*.
[95] Center for Dignity in Healthcare for People with Disabilities, *Healthcare Discrimination and Inequities Facing People with Disabilities*, (January 2020), https://www.ucucedd.org/center-for-dignity-in-healthcare-for-people-with-disabilities/, (last visited April 25, 2021).
[96] *Id*.
[97] *Id*.
[98] Benoy, *supra* note 4.

States, consisting of the group market (employer-sponsored insurance) and individual markets.[99] Public insurance programs include Medicaid, a joint federal-state program that finances medical services for low-income individuals, Medicare and TRICARE for military families.[100] Obstetricians have noted that the cost of NIPT is interfering with its incorporation into prenatal care.[101]

The 2020 ACOG guidelines recommend unrestricted access to NIPT for low and high-risk women.[102] Prior to the update, forty commercial insurance companies covered NIPT for all pregnancies, but the two largest insurance companies, Aetna Inc. and United Healthcare (UHC), only covered high-risk pregnancies.[103] In May 2020, Aetna temporarily expanded NIPT coverage to all pregnant women in response to the COVID-19 crisis but did not permanently expand access to all women until December 2020, after UHC changed its policy in response to the 2020 ACOG guidelines.[104] Aetna and UHC joined Anthem, Cigna and other commercial insurance providers in efforts to ensure that NIPT coverage is provided for all expectant mothers, thereby enabling more than 90 percent of all women covered by private insurance to access NIPT.[105] Despite the expansion of coverage, women who are covered by private insurance may still bear financial burdens associated with deductibles, co-pays or lack of coverage for certain genetic indications.[106] NIPT is a better test than older screening methods for the detection of the

[99] Ryan J. Ross, U.S. Health Care Coverage and Spending, CRS Report IF10830 (2021).
[100] *Id*.
[101] *Id*.
[102] The American Society of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM), Screening for Fetal Chromosomal Abnormalities, 226 Practice Bulletin 1 (2020).
[103] AIS Health, To Cover or Not to Cover? Prenatal DNA Test Creates Quandary for Payers, (January 2019), https://aishealth.com/health-plans/to-cover-or-not-to-cover-prenatal-dna-test-creates-quandary-for-payers/, (last visited April 15, 2021).
[104] PR Newswire, *supra* note 32.
[105] *Id*.
[106] Benoy, *supra* note 4.

three major aneuploidies, but insufficient data are available about its reliability to capture rarer genetic conditions.[107]

The United States does not have a national policy about what types of services government insurance programs must provide to pregnant women beyond inpatient and outpatient hospital care.[108] The absence of formal federal guidance leaves discretion to the states.[109] State Medicaid programs are the leading source of financing for births and are required to provide coverage of inpatient and outpatient hospital services for eligible women.[110] But they have broad discretion on funding for broader categories of pregnancy-related services.[111] Developing a public policy framework for NIPT though is not neutral.[112] If the government establishes policies to provide NIPT for free, governments may be seen as endorsing the screening, while copayment requirements may be viewed as discouraging the procedure.[113] There is evidence demonstrating the benefit of enabling women the choice to access NIPT by removing a payment barrier which diminishes the impact of external influences on a woman's decision to pursue NIPT.[114]

Interestingly, a recent study showed that low-risk women with government insurance are 3.43 times more likely to obtain NIPT than equivalent risk woman covered by commercial insurance providers.[115] Healthcare disparities are more apparent in low-income families, but when NIPT is covered for free by public insurance, women are more likely to utilize the

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[107] *Id*.
[108] Kathy Gifford & Jenna Walls, *Medicaid Coverage of Pregnancy and Perinatal Benefits: Results from a State Survey*, (April 2017), http://files.kff.org/attachment/Report-Medicaid-Coverage-of-Pregnancy-and-Perinatal-Benefits, (last visited April 15, 2021).
[109] *Id*.
[110] *Id*.
[111] *Id*.
[112] Bunnik, *supra* note 83.
[113] *Id*.
[114] *Id*.
[115] Benoy, *supra* note 4.

screening.[116] On the other hand, women with private insurance are more influenced by cost when considering NIPT.[117] It is interesting that women who do not face the same socioeconomic challenges are nonetheless experiencing inequity of NIPT adoption based on the cost. This underscores the importance of promoting public funding of NIPT and influencing commercial companies to reduce the associated cost.

While more than 90 percent of all women who are covered by private insurance can now access NIPT, the proportion of women who are covered for NIPT by public insurance through Medicaid is highly variable state by state. Under state Medicaid programs, payment for laboratory tests is limited to those classified as medically necessary under each state's medical assistance (MA) program.[118] Therefore, advocacy for inclusion of NIPT as a medically necessary test will drive the rollout of availability for women. Seven state Medicaid programs (AZ, ID, NE, NV, NM, RI, UT) and DC Medicaid have no coverage for NIPT, while twelve state Medicaid programs cover NIPT for all pregnancies (FL, IL, KY, MD, MN, ND, NJ, OH, OR, PA, VA, WA). The remaining 31 states cover NIPT for high-risk pregnancies only. Yet the state Medicaid programs are not the only target for test expansion. To reduce administrative costs, Medicaid programs contract with managed care organizations (MCOs), and 69% of Medicaid beneficiaries are enrolled in a managed care plan.[119] Reaching these organizations to expand NIPT coverage is also a critical step in increasing adoption, as MCO guidelines vary across different organizations. MCOs may defer to state Medicaid guidelines or may establish their own parameters for covering NIPT, and this variability widens the coverage gap for women based on their state program's enrollment.[120] For example, Maryland Physicians Care is an

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[116] *Id*.
[117] *Id*.
[118] New York Codes, Rules and Regulations, *Laboratory Services*, NYCRR §505.7 (2002).
[119] Elizabeth Hinton, Robin Rudowitz, Lina Stolyar & Natalie Singer, 10 Things to Know about Medicaid Managed Care, 9343 Issue Brief 1 (2020).
[120] *Id*.

MCO managing 216 thousand Medicaid lives but only covering NIPT for T21 for high-risk pregnancies.[121] Molina Healthcare is a California-based MCO that also covers NIPT for high-risk pregnancies but includes all aneuploidies.[122] To address inequities in access to NIPT, ACOG has established a payment advocacy and policy portal where patients can submit tickets related to non-coverage, prior authorizations or payment issues.[123] Conversion of state policies from no or specific coverage to unrestricted access will impact the ability of all expectant mothers to include NIPT in their prenatal care routine.

California leads state public health efforts to accelerate availability of NIPT for expectant mothers. In 2021, California's Department of Public Health (CDPH) requested additional funding in its budget proposal to incorporate NIPT as a first-line instead of second-line screening for all pregnancies by 2022 through its CDPH Genetic Disease Screening Program (GDSP.)[124] The GDSP serves the people of California by providing programs to reduce the emotional and financial burden of disability and death caused by genetic and congenital disorders, and the proposal is intended to support:

> CDPH's mission to advance the health and well-being of California's diverse people and communities by optimizing the use of science and technology to improve health and by increasing health equity through universal access to the highest quality of care.[125]

The CDPH recognizes that the use of NIPT has become more widely requested by pregnant patients and that it is more reliable with respect to false positive and detection rates.[126] The proposal states that the follow up care managed by the Prenatal Screening Program (PNS) will be

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[121] *Id.*
[122] Molina Healthcare, Noninvasive Prenatal Testing (NIPT), MCP-157 (2017).
[123] ACOG, *Payment Advocacy & Policy Portal*, https://acogcoding.freshdesk.com/support/login, (last visited March 15, 2021).
[124] State of California, *Budget Change Proposal, Revision to Consolidated Leg BCP,* 5225-420-BCP-2019-MR (2020) DF-46.
[125] *Id.*
[126] *Id.*

reduced by 90% due to the lower false positive rate associated with NIPT, resulting in overall budget savings.[127] If more states follow the California approach, then healthcare inequities for maternal care will be significantly reduced and families will be more informed and prepared to make reproductive decisions that are emotionally and financially manageable.

Physicians have the responsibility to inform patients of the benefits and limitations of NIPT, but to minimize liability, physicians must also have guidelines and resources from professional medical societies such as ACOG to ensure they are properly trained on interpreting and communicating NIPT results to patients

As more medical professionals incorporate genetic data into the scope of their practices and patient treatment plans, important questions are raised about how prepared they are to inform patients of benefits and potential risks associated with NIPT results. Proponents of NIPT strive to make it the genetic screening standard of care for all pregnancies because it is a noninvasive accurate approach that reduces additional invasive testing associated with risks of fetal loss.[128] Physicians may face liability issues though if they fail to inform patients of the availability of NIPT or fail to communicate effectively the limitations in the results.[129] For example, advances in NIPT technology will increase the types of genetic variation that can be detected early in a pregnancy. Yet, the corresponding medical impact of those genetic variations will not match the pace of measurement. This delay in clinical knowledge is a challenge for physicians who are not fully trained to analyze genetic data but are expected to interpret data and advise their patients. It is critical that physicians have reliable, independent information about the limitations and impact

[127] *Id*.
[128] Maeghan Toews & Timothy Caulfield, Physician Liability and Noninvasive Prenatal Testing, 36 JOGC 907 (2014).
[129] *Id*.

of NIPT testing so that they can effectively communicate the benefits and drawbacks to their patients.[130]

Physicians have a legal obligation to treat their patients with the same reasonable care as other similarly situated physicians.[131] Questions about the legal duties of physicians handling genetic data have recently been explored.[132] The standard of care in prenatal surveillance is key to protecting physicians from liability. To date, amniocentesis has been a gold standard in prenatal testing based on its high accuracy rate. Physicians have a duty to disclose the risks and benefits of amniocentesis. If a pregnant woman miscarries from this invasive testing, the physician would be protected for recommending a procedure that is consistent with the standard of care.[133] With respect to NIPT, a physician could demonstrate that it is a reasonable medical practice in prenatal care - medical professional societies recommend the test and insurance companies cover its costs for all pregnanies. NIPT is emerging as a standard of care, which is key to protecting physicians from liability. However, if NIPT completely replaces amniocentesis and CVS as the standard of care, then physicians could be found negligent if they recommend invasive diagnostic tests that result in fetal loss.[134] As standards of care change based on advancements in the fields of medicine and genetic testing, the liability landscape for physicians will change as well, since "it is the standard in place at the time the alleged negligence occurs that will be used to judge the physician's conduct."[135]

Claims against physicians for prenatal medical negligence include wrongful birth claims where a risk was undetected because genetic testing was not performed.[136] These are actions

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[130] *Id*.
[131] *Id*.
[132] Jessica L. Roberts & Alexandra L. Foulkes, Genetic Duties, 62 William & Mary Law Review 143 (2020).
[133] Paola Frati, Vittorio Fineschi, Mariantonia Di Sanzo, Raffaele La Russa, Matteo Scopetti, Filiberto M. Severi & Emanuela Turillazz, Preimplantation and prenatal diagnosis, wrongful birth and wrongful life: a global view of bioethical and legal controversies, 23 Hum. Reprod. Update 338 (2017).
[134] Toews & Caulfield, *supra* note 128.
[135] *Id*.
[136] *Id*.

brought by families of a child with a congenital disease against the treating doctor. The claim is that the doctor failed to warn that the child might be born with a serious genetic condition and that the family lost the opportunity to determine whether to terminate the pregnancy.[137] Currently 28 states recognize wrongful birth claims and 12 states prohibit them.[138] To date there have not been any successful US lawsuits based on negligent administration of NIPT, but there have been for other screening methods.[139] Recent wrongful birth actions include a NJ suit where a pregnant mother's 21-week ultrasound was read as inconclusive but the child was born with Beckwith-Wiedemann syndrome.[140] The mother claimed that she was deprived an option for an abortion because her physician failed to inform her of the possibility that the child might be born with a genetic disorder.[141] The settlement awarded was $1,080,000.[142] Another large settlement was approved in a recent medical malpractice suit involving prenatal screening.[143] In this case, the plaintiff underwent a routine ultrasound and a "Quad Screen" test during her pregnancy that both reported normal results.[144] She ended up giving birth to a child with Down Syndrome and brought suit against her physician.[145] The plaintiff claimed that her physician violated the standard of care because she only communicated the normal results and failed to advise her on potential age-related risks or false negative results.[146] Without additional guidance and context,

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[137] *Id*.
[138] Roxana Hegeman, *Kansas court hears arguments over "wrongful birth" law*, (September 2020), www.washingtonpost.com/health/kansas-court-hears-arguments-over-wrongful-birth-law/2020/09/16/507ea2e2-f867-11ea-85f7-5941188a98cd_story.html, (last visited February 20, 2021).
[139] Toews & Caulfield, *supra* note 128.
[140] David Gialanella & Charles Toutant, $1.08 Million Settlement Approved in Bergen County Wrongful Birth Case, (February 2020), https://www.law.com/njlawjournal/2020/02/04/1-08-million-settlement-approved-in-bergen-county-wrongful-birth-case/, (last visited March 15, 2021).
[141] *Id*.
[142] *Id*.
[143] David Gialanella, $1.7 Million Settlement of Fetal Failure-to-Diagnose Case Approved in Union County, (June 2019), https://www.law.com/njlawjournal/2019/06/07/1-7-million-settlement-of-fetal-failure-to-diagnose-case-approved-in-union-county/, (last visited March 15, 2021).
[144] *Id*.
[145] *Id*.
[146] *Id*.

the plaintiff argued that she was denied the option for an abortion.[147] The case was settlement awarded was $1,700,000.[148] The settlements demonstrate the challenge of sending these cases through litigation because of the complexity of demonstrating that physicians failed their legal obligations to their patients and the challenge of quantifying the impact on the families.

Based on these settlements for wrongful birth claims, it is likely that litigation in the NIPT space will emerge as the testing becomes more widespread. Physicians who offer NIPT screening will have a duty to inform patients of the risks and benefits of the recommended interventions. The associated risks are the possibility of false negative as well as false positive results. It is currently unclear how liability in cases where a pregnancy is terminated based on false positive NIPT results will be handled and this will likely be an area of future consideration and debate. The key to enforcing the duty of care is requiring physicians to obtain informed consent from patients when offering NIPT and to "disclose the material, special or unusual risks that a reasonable person in the patient's position would want to know."[149]

The first published report of a false negative NIPT outcome was for a fetus that was postnatally diagnosed with Down Syndrome despite a negative NIPT result for Trisomy 21.[150] The pregnant mother chose NIPT over invasive diagnostic testing through amniocentesis, and received a negative result by the Verifi test for all three Trisomies tested (13, 18 and 21).[151] NIPT is not a diagnostic test. Advertisements by NIPT vendors that that convey greater than 99% specificity and sensitivity may confuse patients into thinking that the results are completely accurate, even though NIPT is only a screening tool. This report emphasized that medical

[147] *Id*.
[148] *Id*.
[149] *Id*.
[150] Meagan Smith, Kimberly M. Lewis, Alexandrea Holmes & Jeannie Visootsak, A Case of False Negative NIPT for Down-Syndrome-Lessons Learned, 2014 Case Rep. Genet. 1 (2014).
[151] *Id*.

professionals need to be properly trained to knowledgably convey the utility of NIPT and to provide anticipatory guidance regarding possible outcomes.[152]

Variable training in medical genetics and advances in testing and technology creates challenges for physicians who want to adopt NIPT as part of the prenatal standard of care. Eighty percent of obstetricians questioned about NIPT in a recent study expressed their desire that ACOG continue to develop guidelines and best practices for incorporating NIPT into routine care.[153] When physicians are properly trained to understand the limitations and recommendations for NIPT, they can properly communicate those to their patients.

> As the medical community continues to embrace new technologies and incorporate them into daily clinical practice, it is imperative to ensure that the appropriate level of education is occurring for the provider ordering the test and the patient being offered the test. When knowledgeable medical professionals properly discuss the utility of NIPT and provide patients with anticipatory guidance regarding the possible outcomes, they enable the patient to make a more informed decision regarding the role of NIPT in their pregnancy.[154]

Women prefer to learn about NIPT from their healthcare providers.[155] It has been shown that even brief trainings on NIPT can have a positive impact on physician knowledge. In 2017, a United Kingdom study was conducted to determine physician confidence regarding NIPT after a 40-minute training session.[156] The results indicated a statistically significant increase in the number of participants who reported being more comfortable discussing NIPT with their patients.[157] However, 65% of the respondents still missed key technical points about NIPT, including false positive rates and the source of DNA for the test. The study authors concluded that a variety of educational formats are important to ensure reinforcement of the science and preparation for discussions of informed consent and genetic counseling.[158]

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[152] *Id*.
[153] *Id*.
[154] *Id*.
[155] Cernat, *supra* note 37.
[156] *Id*.
[157] *Id*.
[158] *Id*.

CONCLUSION

The development and adoption of NIPT as an accurate, noninvasive test early in pregnancy has expanded prenatal care by providing pregnant women the opportunity to screen for genetic disorders and make informed reproductive decisions early in their pregnancy. Yet as a newer technology, NIPT requires a closer examination and evolving guidelines with respect to FDA regulation, messaging about disabilities, access through insurance and physician liability. Expanded FDA oversight of NIPT is necessary to ensure that testing meets minimum performance standards and marketing claims by commercial NIPT vendors are regulated. As NIPT expands, public policy needs to recognize the impact on the disabled community and the messaging about genetic disabilities. Increasing access to NIPT through expanded private and public insurance coverage will reduce healthcare inequities and ensure reproductive autonomy. Lastly, as NIPT is now part of the prenatal standard of care, physicians have the responsibility to inform patients of the benefits and limitations of the screening. To do this effectively, healthcare professionals will need proper training to understand the technical basics and evolving scientific applications of NIPT and the impact on pregnancy decisions.