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The Emergence and Global Spread of Noninvasive Prenatal Testing

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Abstract

Since its introduction in 2011, noninvasive prenatal testing (NIPT) has spread rapidly around the world. It carries numerous benefits but also raises challenges, often related to sociocultural, legal, and economic contexts. This article describes the implementation of NIPT in nine countries, each with its own unique characteristics: Australia, Canada, China and Hong Kong, India, Israel, Lebanon, the Netherlands, the United Kingdom, and the United States. Themes covered for each country include the structure of the healthcare system, how NIPT is offered, counseling needs and resources, and cultural and legal context regarding disability and pregnancy

termination. Some common issues emerge, including cost as a barrier to equitable access, the complexity of decision-making about public funding, and a shortage of appropriate resources that promote informed choice. Conversely, sociocultural values that underlie the use of NIPT vary greatly among countries. The issues described will become even more challenging as NIPT evolves from a second-tier to a first-tier screening test with expanded use.

INTRODUCTION

Since its introduction in 2011, noninvasive prenatal testing (NIPT) has taken prenatal care by storm. In under 10 years, it has become available in more than 60 countries, with a global market of USD 3.9 billion in 2019, and an expected growth to USD 7.3 billion by 2024 (92) (see the sidebar titled The Global Scope of Noninvasive Prenatal Testing). It carries numerous benefits but also raises challenges, often related to cultural, social, legal, and economic contexts. To demonstrate this complexity, this article describes the implementation of NIPT in nine countries, each with its own unique characteristics: Australia, Canada, China and Hong Kong, India, Israel, Lebanon, the Netherlands, the United Kingdom, and the United States (in alphabetical order). We then go on to discuss the lessons that emerge from the global spread of NIPT and the associated challenges.

Several terms are currently used in the literature to describe NIPT: noninvasive prenatal screening, cell-free DNA screening, and cell-free fetal DNA screening. In its early days, the technology was commonly referred to as noninvasive prenatal diagnosis, but as it became clear that the method is not diagnostic, the terminology has increasingly shifted toward noninvasive prenatal screening (61). Throughout this review, however, we use the term NIPT, as it is still prevalent and employed in many countries when discussing the implementation of this technology in the prenatal screening pathway.

THE BASIC SCIENCE OF NONINVASIVE PRENATAL TESTING

In 1997, Lo et al. (87) discovered the presence of cell-free fetal DNA in maternal plasma. Ten years later, Lo et al. (88) showed that analysis of cell-free fetal DNA allowed for the detection of trisomy 21 (T21), or Down syndrome, in the fetus. Subsequent studies established that cell-free fetal DNA was of placental origin (8). The proportion of placental cell-free fetal DNA in the mother's plasma, called the fetal fraction, ranges from 3% to 30% when measured between

THE GLOBAL SCOPE OF NONINVASIVE PRENATAL TESTING

- NIPT is available in more than 60 countries (10).
- In 2018, 10 million NIPT tests were performed (138).
- The estimated global market value of NIPT varies significantly, approximately ranging from USD 3.9 billion in 2019 (92) to USD 2.83 billion in 2020 (59).
- The estimated compound annual growth rate of NIPT ranges from 10.9% (59) to 17.15% (102).
- Estimates of NIPT's future global market value vary and include USD 7.3 billion by 2024 (92), USD 13.1 billion by 2027 (102), and USD 6.5 billion by 2028 (59).
- America accounted for the largest market share in 2019–2020, followed by Europe (59, 92, 102).

weeks 10 and 20 of pregnancy (26). NIPT can be reliably performed starting in week 9, when the fetal fraction is sufficiently high to detect genetic variations. A low fetal fraction is associated with early gestational age, high maternal body mass index, smoking in the mother, and twin pregnancy (16, 148). Other factors associated with test failure are technical difficulties, such as blood sample contamination or deterioration (116).

NIPT is used primarily to screen for T21, T18 (Edwards syndrome), and T13 (Patau syndrome) and sex chromosome aneuploidies [45,X (Turner syndrome), 47,XXY (Klinefelter syndrome), 47,XYY, and 47,XXX (triple X syndrome)], as its sensitivity is high for these conditions: 99.7%, 97.9%, and 99.0% for T21, T18, and T13, respectively; 95.8% for Turner syndrome; and over 95% (some even claim 100%) for other sex chromosome aneuploidies (57). Test manufacturers offer other options (see **Table 1**), such as tests for rarer trisomies, copy number variants, and microdeletions, including 15q deletion (Prader–Willi and Angelman syndromes), 22q11.2 deletion (DiGeorge syndrome), 4p deletion (Wolf–Hirschhorn syndrome), 15p deletion (cri-du-chat syndrome), and 11q deletion (Jacobsen syndrome) (71), but the sensitivity and positive predictive value for these conditions are significantly lower (101), and there is a risk of increasing the overall false-positive rate when screening for more conditions. The most recent prenatal screening guidelines from the American College of Obstetricians and Gynecologists do not recommend using NIPT for these rarer conditions due to a lack of evidence regarding validity (13). In addition to screening for specific conditions, NIPT screening for common trisomies can be done using a targeted analysis or genome-wide sequencing–based approach, which may also reveal other aberrations.

NIPT can be performed in twin pregnancies. Although this is associated with a higher test failure rate, studies suggest that NIPT's sensitivity for T21 is similar for twin and singleton pregnancies (58). Noninvasive prenatal diagnostic tests have been developed for monogenic conditions, but they have sparked much less enthusiasm than NIPT due to technical and ethical challenges (43, 66). Furthermore, the global market for this type of test is relatively small, since it is used primarily in a diagnostic setting for the detection or exclusion of de novo dominant or recessive conditions in cases with a known family history (e.g., cystic fibrosis) or ultrasound abnormalities (e.g., achondroplasia).

AUSTRALIA

Approximately 310,000 babies are born in Australia every year (18). The Australian healthcare system, including antenatal services, operates via a mix of public and private provision. Public antenatal care is provided through a combination of a national payer system known as Medicare and state-run antenatal clinics. Certain private antenatal services are reimbursed by health insurers. Both public and private care can involve out-of-pocket costs.

Pregnant people tend to receive antenatal care under a shared model between a general practitioner and a hospital clinic, sometimes with a specialist obstetrician. While health professionals are advised to ensure that all pregnant people are informed about prenatal screening options (126), Australia has no formal prenatal screening program.

NIPT has been commercially available in Australia since late 2012 (73). Its implementation has been ad hoc, driven by test availability. All available tests screen for T21, T18, and T13, with some also offering information about sex chromosome aneuploidies, additional chromosome aneuploidies, and microdeletions despite caution from professional bodies (126). Concerns have been raised about the potential use of NIPT for sex selection, although no data are available (23, 47).

Table 1 Noninvasive prenatal testing products and what they test for

		Trisomies					Sex chromosome aneuploidies					Microdeletions								
Company	Product	21	18	13	16	22	X (Turner)	XXY (Klinefelter)	XXX (triple X)	XYY (Jacob's)	XXXY	22q (DiGeorge)	5p (cri-du-chat)	15q (Prader–Willi and Angelman)	11q (Jacobsen)	8q (Langer–Giedion)	4p (Wolf–Hirschhorn)	1p36	Others	Sex
Integrated Genetics	MaterniT 21 PLUS	Y	Y	Y	Y[a,b]	Y[a,b]	Y[a,b]	Y[a,b]	Y[a,b]	Y[a,b]	N	Y[a,b]	Y[a,b]	Y[a,b]	Y[a,b]	Y[a,b]	Y[a,b]	Y[a,b]	N	Y[b]
	MaterniT GENOME	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	All autosomal aneuploidies; gains or losses of chromosome material ≥ 7 Mb across the genome	Y
Roche	Harmony	Y	Y	Y	N	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N	N	N	N	N	N	N	Y[b]
Illumina	Verifi	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y[b]
	Verifi Plus	Y	Y	Y	Y	Y	Y[b]	Y[b]	Y[b]	Y[b]	N	Y[b]	Y[b]	Y[b]	N	N	Y[b]	Y[b]	All chromosomal aneuploidies	Y
Natera	Panorama	Y	Y	Y	N	N	Y	Y[b]	Y[b]	Y[b]	N	Y[b]	Y[b]	Y[b]	N	N	N	Y[b]	Triploidy	Y[b]
LifeCodexx	PrenaTest option 1	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y[b]
	PrenaTest option 2	Y	Y	Y	N	N	N	N	N	N	N	Y[b]	N	N	N	N	N	N	N	Y[b]
	PrenaTest option 2 *Plus*	Y	Y	Y	Y	Y	N	N	N	N	N	Y[b]	N	N	N	N	N	N	Autosomal aneuploidies	Y[b]
	PrenaTest option 3	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y[b]	N	N	N	N	N	N	N	Y[b]
	PrenaTest option 3 *Plus*	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y[b]	N	N	N	N	N	N	Autosomal aneuploidies	Y[b]

(*Continued*)

Table 1 (*Continued*)

Company	Product	Trisomies					Sex chromosome aneuploidies					Microdeletions							Others	Sex
		21	18	13	16	22	X (Turner)	XXY (Klinefelter)	XXX (triple X)	XYY (Jacob's)	XXXY	22q (DiGeorge)	5p (cri-du-chat)	15q (Prader–Willi and Angelman)	11q (Jacobsen)	8q (Langer–Giedion)	4p (Wolf–Hirschhorn)	1p36		
BGI	NIFTY	Y	Y	Y	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N	N	Y[b]	Y[b]	Y[b]	N	N	Y[b]	Trisomy 9, 2q33.1 deletion, DiGeorge II (10p14–p13 deletion), 16p12 deletion, 1q32.2 deletion (van der Woude syndrome) (all optional)	Y[b]
	NIFTY Pro	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NM	Y	NM	NM	Y	Y	Trisomy 9; more than 80 types of microdeletions and microduplications, including 7q11.23, 17p13.3, and 17p11.2	Y[b]
Igenomix	NACE	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y
	NACE 24	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y (and velocardiofacial syndrome)	Y	Y	N	N	Y	Y	All chromosome trisomies	Y
Xcelom	SafeT21-Express	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y	2q33.1	NM
Yourgene Health	IONA	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y[b]
	Sage	Y	Y	Y	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N	Y[b]	Y[b]	Y[b]	N	N	Y[b]	Y[b]	Autosomal aneuploidies	Y[b]

Table adapted and updated from Reference 104; the information was obtained from noninvasive prenatal testing providers' websites (including their brochures) on March 15, 2021, and is subject to change. Abbreviations: Y, yes; N, no; NM, not mentioned.

[a]Reported as an additional finding.

[b]Optional.

NIPT is currently being used as both a first-tier test (offered to all pregnant women) and second-tier test (offered to those already identified as high chance[1]) (53), and there is ongoing uncertainty over where it should sit in the antenatal screening pathway. The efficacy of both options has been demonstrated in audit and modeling studies (19, 85, 97, 98) and is recognized in professional guidelines (126). NIPT's increasing prevalence correlates with a decrease in invasive prenatal tests (72, 75, 85, 136). This has reduced costs to the healthcare system but has increased the costs to pregnant people, raising concerns over equity (47, 97).

There is presently no federal funding for NIPT, and it is not reimbursable through private health insurance. A test costs AUD 400–500 (USD 300–365). There is at least one local provider, and the main global companies also have a presence. Reimbursement of NIPT through Medicare in the future would require listing on the Medicare Benefits Schedule (MBS). Applications for MBS listing are considered by the national Medical Services Advisory Committee, which then makes a recommendation to the federal minister of health. There are existing MBS items for combined first-trimester screening and for invasive diagnostic testing.

Several applications for MBS listing for NIPT have been made in recent years, and it was most recently considered (as a first-tier test to detect T21, T18, and T13) in November 2019 (100). While the superiority of NIPT as a screening test was not questioned, a first-tier model was not supported for recommendation for funding, due to low incremental cost-effectiveness. Compared with combined first-trimester screening, it was determined that NIPT would detect approximately 195 extra cases of trisomy for an annual investment of AUD 100 million (approximately USD 73 million).

The Medical Services Advisory Committee's consideration of NIPT nevertheless facilitated a wide discussion, including about whether pregnant people who live in rural and remote areas—and therefore may not always have access to interventions such as ultrasound or invasive testing—should have priority access to publicly funded NIPT (99). A new application will now be needed, perhaps based on a second-tier model of implementation. If successful, it would likely cover only the cost of the test itself. There are presently no MBS items for pre- or posttest counseling.

The ad hoc implementation of NIPT, together with a devolved healthcare care system (whereby the federal government delegates responsibility for healthcare to states and territories), means that obtaining national data is difficult. No large multimodal national studies on NIPT implementation in Australia have been carried out to date. Nevertheless, several smaller studies (described below) have considered uptake, efficacy, psychological outcomes, access, and impact on rates of invasive testing.

Approximately 25–30% of pregnant people in Australia undergo NIPT (100). NIPT appears to reduce anxiety in those who receive a high-chance result on combined first-trimester screening (73, 135). The testing experience is also generally positive, although some negative experiences (such as false-positive results) have been reported (24). Disparities in uptake of NIPT have been noted, mirroring disparities in access to other forms of prenatal screening and testing (96). NIPT is taken up more widely by the 30% of pregnant people who receive private obstetric care; approximately 50–75% of people in this group are thought to choose NIPT (usually as a first-tier test), compared with 25% in the public system (53). Those who access NIPT tend to be older and to live in metropolitan areas and areas of greater socioeconomic advantage (2, 70).

[1]The more neutral term high chance is now preferred to the term high risk (which is seen as being inherently value laden and carrying negative connotations) and has been adopted by professional guidelines and in informational materials for pregnant people regarding testing in pregnancy.

The provision of NIPT in Australia is overseen by a range of regulations, guidelines, statutes, and legal precedents, most of which govern pregnancy and antenatal care more generally. Some professional guidelines specifically mention NIPT (e.g., 125–127). In addition to the points noted above, these guidelines emphasize that NIPT is a screening test and that its use by health professionals without adequate knowledge is a concern (127). They also stipulate that all pregnant people should be informed that NIPT is available but that a first-trimester ultrasound is still indicated, that various limitations of NIPT (such as unreportable results and potential unanticipated findings) should be raised, and that adequate counseling and appropriate information should be provided to facilitate informed choice (126).

In practice, there is good awareness of NIPT among target populations, although concerns remain about how the test and its current limitations may be misunderstood (95, 152). People considering NIPT can access information through an independent government-funded information portal (Lab Tests Online[AU]; **https://www.labtestsonline.org.au**), a government-funded genetics education center (31), or leaflets developed by test providers. Decision aids and supporting materials, including for low-literacy populations, have also been produced (e.g., 143).

NIPT is now the main source of diagnoses of T21 in Australia (72), with high rates of subsequent termination. The potential that people may be terminating on the basis of NIPT alone, despite professional guidelines stating that confirmatory diagnostic testing should be undertaken prior to termination (126), has been raised. One study showed that approximately 50% of people who receive a positive NIPT result do not go on to have an invasive test (72). Termination of pregnancy is permitted in Australia, but it is not always publicly funded and may involve complex access pathways.

CANADA

Approximately 370,000 babies are born in Canada every year (145). Healthcare is a provincial and territorial jurisdiction, meaning that there are 13 publicly funded healthcare systems. All Canadian provinces and territories have a publicly funded prenatal screening program, offering maternal serum screening in the first and/or second trimester, with or without nuchal translucency, and diagnostic testing in case of a high-chance result.

Each province and territory can decide whether to include NIPT in its prenatal screening program. To date, NIPT has been implemented as a second-tier publicly funded test for T21, T18, and T13 in three provinces (Ontario, British Columbia, and Quebec) and one territory (Yukon). Ontario also covers testing for sex chromosome aneuploidies free of charge. However, NIPT is available across Canada and for an out-of-pocket cost of approximately CAD 500–550 (USD 380–420) (122).

A national study called Personalized Genomics for Prenatal Abnormalities Screening Using Maternal Blood (PEGASUS) (2013–2017) validated NIPT's utility and performance in provincial genetic laboratories and suggested that its adoption as a second-tier test would decrease the number of amniocenteses, offsetting its cost and making it cost-neutral (111). A follow-up project, PEGASUS-2, began in 2018 to evaluate NIPT's utility and cost-effectiveness as a first-tier test and for the screening of an expanded number of conditions. Both projects also studied the ethical, social, and legal aspects of the implementation of NIPT in Canada (118).

The most recent guidelines from the Society of Obstetricians and Gynaecologists of Canada emphasize that NIPT is not diagnostic but state that healthcare professionals (HCPs) should offer it based on a high-chance result, even if the healthcare system does not cover it (17). A 2018 study showed women indeed think HCPs should always mention NIPT as a screening option, regardless of coverage (164). Additionally, HCPs could be legally liable for failing to offer NIPT

or incorrectly informing their patients about its risks (153). Overlooking NIPT could even lead to wrongful birth claims, where patients proceed with legal action against their HCP because they would have terminated the pregnancy had they been aware of the testing option (106).

Qualitative and quantitative Canadian studies show that women would prefer that NIPT be covered as a first-tier test for all pregnancies (21, 63, 164). By contrast, only a minority of surveyed HCPs thought NIPT should be offered as a first-tier test, possibly reflecting their greater awareness of NIPT's technical limitations and the healthcare system's economic constraints (21). In a qualitative study of Quebec HCPs, they expressed concerns about economic constraints and about cost barriers promoting access inequalities (64). A Canadian Delphi study involving HCPs, academic researchers, and patient advocates showed support for public funding of NIPT for conditions characterized by severe pain or early death but not for nonmedical conditions (49). A qualitative study showed that Ontarian women have mixed opinions—balancing the desire to use NIPT as they wish, while acknowledging a need to restrict its use for conditions of limited or nonmedical severity (164).

In a survey of 882 Canadian pregnant people and 395 partners, just over half said they would consider terminating a pregnancy if the fetus were diagnosed with T21 (21). In Canada, no legal barrier exists regarding termination, regardless of the pregnancy stage, although access can be limited by geographic barriers. Most terminations, however, occur before 24 weeks (64). Termination of pregnancy is much less politicized in Canada than it is in the United States.

MAINLAND CHINA AND HONG KONG

NIPT was first introduced in mainland China and Hong Kong as an out-of-pocket test in 2011. Mainland China and Hong Kong have distinct healthcare systems, and the implementation of NIPT in the two regions therefore varies.

Mainland China

In mainland China, approximately 15 million babies are born every year (146). The current NIPT cost is approximately RMB 860–2,600 (USD 130–380), and coverage (i.e., government funding) varies based on region. For example, in Zhengzhou (a middle-income central region), NIPT is not covered and is paid for privately or through private health insurance. In Shenzhen (a high-income eastern region), where NIPT is mostly covered by medical insurance, users pay two-fifths of the price. NIPT is still expensive, particularly for individuals from lower-income households (176). Since 2016, some regions have been piloting a model of offering NIPT free of charge to eligible pregnant people (170).

The Chinese Food and Drug Administration regulates medical devices and reagents, and the National Health and Family Planning Commission oversees the operation of medical institutions and the medical services industry. Regulations governing NIPT in mainland China were generally absent during early implementation between 2011 and 2014 (124), and many tests were performed direct-to-consumer without involving healthcare providers. The absence of proper oversight or genetic counseling led to controversial uses of NIPT, such as sex selection and paternity testing. It also raised ethical concerns, such as failure to obtain informed consent.

In early 2014, the Chinese Food and Drug Administration ruled that any application of DNA sequencing technology moving from laboratory research to clinical service should be registered with the Chinese Food and Drug Administration and approved by the National Health and Family Planning Commission. NIPT services thus came to a temporary halt. In 2015, the commission resumed NIPT pilots at 108 designated hospitals, and in 2016 it granted official permission for

clinical use of NIPT nationwide. The commission published clinical guidelines for NIPT practice, recommending its offering as a second-tier screen between 12 and 22 gestational weeks. A Chinese research team recently proposed to implement NIPT as a first-tier screening test (86).

In 2016, the central government abolished the one-child population control policy that had been in place for 36 years. The current policy allows families to have two children, and many women of advanced maternal age wish to have a second child, expanding the use of prenatal screening and diagnosis.

NIPT is anticipated to spread across the country in the next five years, coinciding with emerging biotechnological development and the national plan for disability prevention. This plan lists "strengthen[ing] prenatal screening and diagnosis" as one way of achieving "effective control of disability caused by birth defects and developmental disorders" (35) and suggests granting state permits before allowing families to have a baby (175).

The Chinese family planning policy encourages patriotic Chinese parents to adopt a utilitarian approach that ensures the quality of the population. Disability is seen as an impediment to national industrialization (175) and to the social goal of improving national competitiveness. Birth defects are depicted as associated with poor quality of life, and parents see avoidance of suffering for the future child as a part of their parental responsibility (109). Parenting a disabled child can thus be associated with shame, blame, and damage to "moral reputations" (68, p. 4).

Some believe that raising a child with a disability will be a less rewarding experience than raising an able-bodied child (109). Having a disabled child can be considered a disruption to the "natural order" (68, p. 4) or a burden on the family and can raise concerns about financial security (84, 109). It can also be seen as a failure to meet cultural expectations related to parental obligations (68) or to meet social norms related to being a good mother (7, 68). The stigmatization of children with genetic conditions and the low social acceptance of disability thus promote the use of prenatal screening (79, 84, 172), while emerging technologies allow increased medicalization of pregnancy (124).

Some Chinese women regard having a baby with T21 as a remarkably negative event, compared with having a procedure-related pregnancy loss (32). They would accept a miscarriage risk of up to 0.5% as a trade-off for obtaining more rather than less information when making a reproductive decision (33). Interestingly, women expressed a decreased interest in NIPT and an increased preference for invasive testing (with a chromosomal microarray for obtaining more definitive genetic results) when they were counseled that the procedure-related fetal loss rate of the invasive test was 0.1–0.2% (34, 108).

Termination of pregnancy for medical reasons is common and seen as less morally complex than it is in the Western context (84, 109). In both China and Hong Kong, terminations of pregnancies diagnosed with abnormal chromosomal aneuploidies are common (81, 171). Elective terminations for oral clefts have been reported (79) even though this malformation can be corrected after birth. Chinese families are primed to see birth defects as catastrophes, and some children with special medical or developmental needs are sent to an orphanage to await adoption. This context helps clarify the high uptake of pregnancy termination. Structural reform in family planning, social, and public policies is pivotal to embrace the inclusion of disabled individuals in communities (175).

Hong Kong

In Hong Kong, approximately 53,000 babies are born every year (28). The public healthcare system provides universal prenatal and postnatal services for all pregnant people, while the private system—paid for out of pocket—provides similar yet faster service. Women may choose to supplement their public system prenatal care with private services. Since July 2011, Hong Kong's

public system has offered free-of-charge routine prenatal screening for T21 for all pregnancies, irrespective of maternal age.

In the early phase, starting in 2011, when NIPT was marketed as an out-of-pocket test, the price ranged from approximately HKD 6,000 to HKD 8,000 (USD 770–1,000). The test was promoted through the media, consumer websites and forums, news outlets, and academic institutions as easy and simple. It later rapidly spread in private clinical settings, even before guidelines were issued by regional or international professional societies.

In December 2019, NIPT started being rolled out as a second-tier screening for T21, T18, and T13 in the publicly funded pathway (69) (users can also obtain additional information via private providers). Following a positive test result from conventional serum screening, women are given a choice between NIPT and the traditional approach of either invasive diagnosis or standard care (i.e., pregnancy follow-up without genetic testing). The two-tiered screening model is speculated to improve detection rate and be more cost-effective (137).

Local research confirmed pregnant people's preference for NIPT (173). The uptake rate among users with a high-chance first-tier screening result gradually increased, ranging from 20% to 90% (108). Both women and healthcare providers perceived NIPT as beneficial in improving prenatal care. The high cost, however, was considered a major ethical concern, hindering equal access to the test among those with less means (173, 174).

Genetic counseling services are rapidly evolving globally (1), and mainland China and Hong Kong are also committed to expanding local capacity for such services (38, 149). In studies conducted in mainland China and Hong Kong, women had limited knowledge of NIPT and in some cases made incorrect assumptions. They were sometimes unaware of test limitations, such as false-negative results or lower sensitivity or specificity for atypical autosomal anomalies, and unaware of the possibility of detection of maternal disease (78).

INDIA

More than 24 million babies were born in India in 2019 (77). Most healthcare services are "heavily dependent on out-of-pocket expenditure and private health care" (132, p. 760), and no public prenatal screening program exists (90, 120). NIPT is therefore mostly paid for out of pocket (120). It was commercially introduced in India in 2012, mainly in large cities (166), probably because it is not well known to obstetricians who practice outside urban settings and due to the test's prohibitive cost for most pregnant people (167).

Initially, blood samples were sent out of the country for analysis (94), and the test could cost up to INR 50,000–60,000 (USD 700–800). However, many laboratories now offer the test and perform the analysis domestically, significantly reducing NIPT's cost to approximately INR 10,000–12,000 (USD 130–160). In some privileged contexts, only approximately 5% of patients refuse NIPT because of its cost. Still, this cost represents up to 10% of the Indian average annual income per capita, which was the equivalent of USD 1,735 in 2018 (169). In rural areas, only people of higher socioeconomic status can afford NIPT (I. Verma, personal communication). Since developing and implementing a national prenatal screening program are not currently governmental priorities (94), NIPT will probably continue to be available only out of pocket, and hence poorly accessible, for the foreseeable future.

Prenatal screening and diagnosis are regulated under the Pre-Conception and Pre-Natal Diagnostic Techniques (PCPNDT) Act of 1994 (6). The PCPNDT, which aims primarily to eliminate sex-selective abortions, prohibits fetal sex determination and disclosure to parents (94). NIPT can be used to screen for sex chromosome aneuploidies, but the fetal sex cannot be reported to the

future parents if no such aneuploidy is detected (144, 165). NIPT can be used to test for T21, T18, and T13 and for certain microdeletions (166).

Some have argued that NIPT should be used as a second-tier test in India, because of its high cost (90, 165). However, the Medical Termination of Pregnancy Act of 1974 allows pregnancy termination up to 20 weeks' gestation (6, 119), which means that first-tier NIPT could shorten the time to diagnosis and allow time for decision-making regarding pregnancy continuation.

A study of NIPT's effectiveness conducted in India with 516 pregnant people at an intermediate (1:1,000 to 1:250) to high (greater than 1:250) chance of T21 showed a lower positive predictive value for T21 compared with other studies (168). However, the overall positive predictive value for T21, T18, T13, and monosomy X was similar to that of other studies.

The PCPNDT requires that women receive pre- and posttest counseling, and genetic counseling is seen as an "important component of medical genetic services in India" (6, p. 163). However, if the uptake of NIPT increases, the shortage of genetic counselors and of obstetricians who are trained to offer NIPT could become a barrier to women's informed decision-making. Given India's population size of more than 1.3 billion, some authors recommend alternative counseling modes, such as distance counseling (telemedicine) or group counseling (94).

The PCPNDT may have contributed to NIPT's slow adoption in India (167). Some have suggested that by allowing fetal sex determination earlier in pregnancy, NIPT may facilitate sex-selective abortion (23). Sex selection due to a cultural preference for boys is a critical issue in India. The introduction of amniocentesis in the 1970s was followed by a decline in the ratio of girls to boys, which was accentuated in the 1980s with the advent of ultrasound, allowing fetal sex to be determined easily and inexpensively (89).

Overall, the introduction of prenatal screening and diagnostic technologies has been strongly associated with a persistent skewed sex ratio, although "excess child mortality of girls and female infanticide" (89, p. 425) also explain this. In 2011, at the time of the most recent census, the sex ratio for ages 0–6 stood at 914 girls to 1,000 boys (and even below 900 to 1,000 in some states), well below the average of approximately 952 girls to 1,000 boys in most countries (89).

An estimated 37.3 million women are missing in India, which has been associated with higher rates of rape, kidnapping, and trafficking (89). Under the PCPNDT, penalties for fetal sex determination exist for both patients and HCPs. Couples face a jail sentence of up to five years and a fine of INR 50,000 (USD 670), depending on whether the offense has been repeated. HCPs' names can be removed from the state council for five years, or permanently in the case of a repeat offense (46). However, some have argued that the law is poorly enforced (107, 123).

Cultural context may also explain NIPT's relatively low uptake in India. Most pregnant people who have access to prenatal care prefer undergoing amniocentesis, because it is diagnostic and can completely rule out the tested chromosomal abnormalities, whereas NIPT is a screening test. This preference may also be explained by the geographical context: For those living in periurban or rural areas, amniocentesis has the advantage of not requiring them to return to the clinic in case of a high-chance or no-call result (167). However, access to invasive testing is also difficult because of limited numbers of trained medical staff (40).

ISRAEL

Approximately 177,000 babies were born in Israel in 2019 (30). A publicly funded screening program for T21 involving biochemical tests is well established, and the uptake rates of these tests are high (177). A growing number of commercial providers have marketed NIPT in Israel since 2013. Costs vary, depending on the provider and the tested conditions. Basic panels test for the

common aneuploidies (i.e., T21, T18, and T13, with or without sex chromosome aneuploidies). More extensive panels include additional trisomies and microdeletions.

In Israel, a committee convened by the minister of health and minister of finance is responsible for the inclusion of new technologies in the annual update of the national list of health services. In 2019, NIPT was submitted to the committee to be considered for public funding, where it competed against other technologies and drugs in the context of a limited budget. Following evaluation of all submitted items, funding for NIPT was rejected. Consequently, NIPT has not been adopted by statutory health insurance and is not publicly funded.

Women are offered NIPT privately (or semiprivately, as many complementary and private health insurance plans cover at least some of the costs). The test is performed mostly in a private setting and analyzed in private labs, either in Israel or abroad. Some public genetics institutes offer the test, such as one that belongs to a governmental hospital and provides counseling, blood draw, and lab analysis.

Both the Department of Laboratories and the Department of Community Genetics in the Ministry of Health are the regulators overseeing NIPT providers. However, since the Ministry of Health is not responsible for laboratories operating in foreign countries, it requires that the laboratory meet the regulatory standards in that country.

According to a 2018 position paper by the Israeli Society of Obstetrics and Gynecology, women should be informed by their attending obstetrician–gynecologist regarding available prenatal tests, including NIPT, preferably at the beginning of their pregnancy. Failing to inform women of the test could therefore have medicolegal implications. However, this paper does not specify the content of the information that should be provided.

The Israeli Society of Medical Genetics issued its latest position paper on NIPT in 2018. The paper details the information that should be provided to women regarding the test, both benefits and limitations. It also recommends replacing the current publicly funded biochemical T21 screening tests with NIPT as a first-tier screening for T21, T18, and T13 in all pregnancies.

As a genetic test, NIPT is subject to the Genetic Information Law of 2000 (56), although the law does not mention prenatal genetic testing explicitly, other than regarding testing for kinship. The law also does not explicitly regulate direct-to-consumer genetic testing. However, it does require obtaining informed consent and providing explanations by an authorized medical figure, thereby prohibiting the classic route for direct-to-consumer genetic testing. Yet this leaves room for women to receive such services from private test providers, who employ HCPs with potential bias, rather than the services of health professionals from the public system.

As opposed to some other countries, where the introduction of NIPT into the market or its implementation with public funding has provoked public debate and opposition from diverse stakeholders, the test was not publicly contested in Israel. Indeed, Israelis have long been considered eager adopters of medical technologies, including those that are controversial elsewhere (121). Reproductive and genetic technologies, in particular, receive substantial support from the state, professionals, and the public (65, 131).

The lack of Israeli opposition to NIPT is perhaps most striking when looking at disability advocacy, and specifically T21 organizations. Whereas such organizations play a central role in the opposition to NIPT elsewhere (151), the only statement in Israel concerning NIPT, issued by a T21 advocacy organization, was a supportive one. It protested the test's high cost and stressed the importance of the test being accessible to all women. This is in line with other supportive views of NIPT, as well as other prenatal tests, held by disability advocates, including representatives of T21 organizations and parents of children with T21. Such advocates and parents emphasized their twofold view of disability: the wish to prevent it (in order to prevent suffering) on the one hand and the responsibility to support those already born with special needs on the other (110, 130).

As NIPT tests for currently incurable conditions, it also interrelates with the Israeli abortion law (119), which authorized pregnancy termination in cases of embryopathy. According to the Central Bureau of Statistics, 19% of the requests for pregnancy termination in 2018 were due to "risk of physical or mental disability of the fetus" (29). Willingness to terminate affected pregnancies (e.g., due to intellectual disability) is common in Israel (45, 60) and goes hand in hand with the high uptake of prenatal testing (140, 141), which is perceived as a necessary aspect of responsible parenthood (134).

In practice (178), studies have reported an approximately 50% live birth rate of pregnancies diagnosed with T21 in the Jewish population, compared with approximately 81% in the Muslim population. However, the numbers are much lower in the secular population (25%), where "the quest for the perfect baby" (134, p. 21) is prevalent. This tendency is supported by high rates of invasive testing due to self-requests by women (i.e., without medical indication) (147). The preference to maximize detection of abnormalities is further supported by current professional guidelines. Since 2019, all invasive tests in Israel have been coupled with chromosomal microarray analysis, which has a higher detection rate than standard karyotyping (48). Moreover, in its position paper, the Israeli Society of Medical Genetics stressed the superiority of chromosomal microarray analysis over NIPT.

LEBANON

Approximately 80,000 babies are born in Lebanon every year (22). The Lebanese healthcare system is characterized by a hybrid structure, with some services covered publicly and the majority offered through the private sector (14). Prenatal tests, such as maternal serum screening and amniocentesis, either are publicly funded or may be covered by private health insurance (64).

In Lebanon, NIPT is offered mainly as a second-tier screening test to detect fetal aneuploidies, such as T21, T18, and T13 and sex chromosome anomalies, for women who have been identified as having a high-chance pregnancy due to maternal age, medical history with previous pregnancies, or maternal serum screening. Some physicians offer it as a first-tier screen, replacing current tests. Currently, there is no regulatory oversight for NIPT implementation, and the test must be ordered by a physician.

NIPT is only available privately and costs approximately USD 800. This may be a barrier to access since the minimum monthly wage is LBP 675,000 (which is currently, following the economic meltdown, equivalent to approximately USD 100) (39). At the same time, since having to pay for care out of pocket is common in Lebanon, patients may not expect NIPT to be covered. This was one of the findings of a qualitative study, where the majority of interviewed Lebanese pregnant people and couples stated that cost had relatively little influence over their decision to use NIPT, especially if they have a high chance of having a child with a genetic condition (63). Nevertheless, participants in this study were enthusiastic about public funding, although they thought it could create subtle pressure on pregnant people to use NIPT (63).

In another qualitative study with Lebanese HCPs, cost was seen as potentially increasing disparities in access to prenatal testing (since only those of higher socioeconomic status would benefit from private coverage) and hence limiting NIPT's ethical implementation (64). Another issue was the potential use of NIPT for sex-selective terminations, either because of a preference for boys or for family balancing, which are culturally important in some regions of Lebanon (64).

In Lebanon, physicians are highly regarded, and patients generally have a preference for firm recommendations (4). Hence, physicians' recommendations of NIPT are an important decision-making factor for pregnant people and couples. Contrary to the Western paradigm, directive counseling is not regarded as an intrusion on autonomous decision-making (63). Moreover, since the

family occupies a significant place in Lebanese culture, it is often involved in decision-making, notably in healthcare. Several interviewed couples said they wanted to decide on the use of NIPT together and achieve a consensus (63).

Under the Lebanese Penal Code, termination of pregnancy is prohibited unless the pregnant person's life is in danger (67). However, abortions are sought on the black market and are performed clandestinely and regularly up to 24 weeks of pregnancy (15). Moreover, the cost of an abortion may be prohibitive [depending on, among other factors, the location of the procedure (a clinic or an operating room) and gestational stage], ranging from USD 300 to USD 5,000 (52, 63). This means that while NIPT increases people's access to information, it does not necessarily expand their choices regarding pregnancy management.

In addition, religious factors may be crucial regarding a decision to terminate a pregnancy (63). According to Muslim teachings, the acceptability of abortion is generally tied to a point in time known as ensoulment, in which the fetus is bestowed the moral status of a human being; this occurs between 40 and 120 days after conception, and abortion is more acceptable before ensoulment than it is later in the pregnancy (74). NIPT (if performed as a first-tier test) thus holds the potential to test at a time that allows a decision about pregnancy management prior to ensoulment (62).

THE NETHERLANDS

Approximately 170,000 babies are born in the Netherlands every year (27). Prenatal care is well organized on a national level. Prenatal screening programs are coordinated and monitored by the National Institute of Public Health and the Environment's Centre for Population Screening under the auspices of the Ministry of Health, Welfare, and Sport.

The Netherlands was one of the first countries to implement NIPT as part of a publicly funded fetal aneuploidy screening program. Since April 2014, NIPT has been offered in the context of a national study, the Trial by Dutch Laboratories for Evaluation of Non-Invasive Prenatal Testing (TRIDENT-1) study, to women with an increased chance of having a fetus with T21, T18, or T13 based on the first-trimester combined test (risk cutoff 1:200) or because they have a previous child with a trisomy (114). Since April 2017, NIPT has been offered to all pregnant people irrespective of their risk status in the context of the TRIDENT-2 study (160). Women can still choose the first-trimester combined test first, with NIPT as a second-tier test. To avoid unequal access, each first-tier screening test (NIPT and the first-trimester combined test) is offered at a comparable out-of-pocket cost of approximately EUR 175 (USD 205). The additional costs of NIPT are paid by the Dutch government.

Currently, prenatal NIPT screens for the three common trisomies using a whole-genome sequencing approach (160). Women can choose whether they wish to have the other autosomes reported for aberrations (10–20-Mb size resolution) at no additional cost. Sex chromosomes are not analyzed.

Prenatal screening for fetal conditions is subject to a governmental license under the Dutch Population Screening Act (161), which was established in 1996 to protect people against potentially harmful screening. Consequently, there are no commercial laboratories or providers that offer NIPT outside of the Dutch healthcare system, although women can obtain private testing abroad. Public demand was an important driving force for making NIPT available. When the license for NIPT was not yet available, many pregnant people went abroad to be tested (163).

Eventually, licenses were obtained in 2014 and 2017 by the Dutch NIPT Consortium for the TRIDENT-1 and TRIDENT-2 studies, respectively. This consortium was formed in 2011 and comprises all institutions, organizations, and professionals involved in prenatal screening, enabling

the integration of the perspectives of different stakeholders (163). The two TRIDENT studies aim to evaluate all aspects of implementation of NIPT, including practical and logistical issues, test uptake and outcome, and perspectives of both the women and providers. Findings from the studies will be used to shape future policy on the responsible implementation of NIPT in the Netherlands.

To enhance autonomous decision-making in fetal aneuploidy screening, pregnant people and their partners are offered a 30-minute pretest counseling session by a certified provider, typically a primary care midwife (160). Counseling is supported by a leaflet in five languages and online information, including at the TRIDENT study website (**https://meerovernipt.nl**). To ensure uniformity, the Centre for Population Screening coordinates and produces the information for both professionals and the general public. Training programs with blended learning activities for counselors are developed and organized together with the eight regional centers for prenatal screening.

In the Netherlands, the introduction and expansion of prenatal screening have generated substantial political and public debate (161). Similar to what was seen in other countries, the introduction of NIPT raised concerns, particularly regarding the possible routinization of prenatal screening, undermining women's informed decision-making. Others—for example, parents of children with T21—feared that fewer people with T21 would be born as a result of advances in prenatal screening tests, which might reduce the acceptance and care of children with T21 and leave women with no choice but to have screening (162).

The uptake of prenatal screening for fetal aneuploidy is relatively low in the Netherlands compared with other European countries. Several reasons have been proposed for this, including out-of-pocket costs and the emphasis on the right not to know about the option of screening (i.e., women are first explicitly asked whether they want to receive information about the screening) (37).

From a cultural and historical perspective, the rather positive attitudes toward having a child with T21 and the negative attitudes toward pregnancy termination may be factors explaining the low uptake (20, 37). Before the introduction of NIPT, a stable or slightly decreased live birth rate of babies with T21 was demonstrated in the Netherlands, estimated at approximately 13 in 10,000 (42), which is higher than the estimated rate in most European countries (41).

Since the start of the national prenatal screening program with the introduction of the first-trimester combined test in 2007, the uptake of screening has gradually increased to approximately 36% in 2016. After the introduction of first-tier NIPT in 2017, first-trimester combined test rates showed a steep decline, while NIPT rates stabilized at 46% in the second year (159). It is expected that in April 2023, NIPT will be fully implemented, outside a study context, as a first-tier screening test for fetal aneuploidy.

THE UNITED KINGDOM

Approximately 730,000 babies were born in the United Kingdom in 2018 (115). The UK National Screening Committee (UK NSC) advises government ministers and the National Health Service in the four UK countries on all matters related to screening (157). The committee advises on the introduction of new screening programs, significant changes to established ones, and the cessation of some.

Frameworks to guide implementation and management are developed at the national level in the individual countries to ensure a programmatic approach to screening. These frameworks include the arrangements for data collection and monitoring, quality assurance, education and training for professionals, and information for the public. The National Health Service is responsible for commissioning and delivering the screening program within these frameworks.

The UK NSC recommended the use of NIPT as a second-tier test for T21, T18, and T13 in November 2015, referred to in the UK context by their full names: Down's syndrome, Edwards' syndrome, and Patau's syndrome, respectively (155; see also the Related Documents section in 156). The recommendation is that women who chose to take up the initial screening offer and have a higher-chance combined test result in the first trimester or in the second-trimester quadruple test (using a threshold of 1:150 from either) are eligible for the offer of NIPT. The UK NSC recommendation was implemented in Wales in April 2018 and in Scotland in September 2020. NIPT will be available in England starting in May 2021. The UK NSC–recommended screening programs are publicly funded and free at the point of delivery, and this applies to NIPT for women who are eligible for the test. Women can also access the test privately.

The UK NSC recommended that NIPT be rolled out within an evaluative framework. The preparations for rollout were informed by the considerations reported below.

The evidence supporting the UK NSC recommendation on NIPT came from several sources. A systematic review explored the published literature on the accuracy of NIPT in the general obstetric population and in women offered NIPT contingently, based on a primary screening test (150). The analysis in this latter group was supported by a more substantial evidence base than the analysis for the general population. From the studies that make up this evidence base, the review estimated positive predictive values of 91%, 84%, and 87% for T21, T18, and T13, respectively. Despite high sensitivity and specificity, NIPT could therefore not be considered a diagnostic test, and invasive testing remains necessary to confirm the presence of a trisomy.

A cost–consequence analysis estimated that offering NIPT in a population with a 1:150 chance of T21, T18, or T13 would reduce the number of invasive tests, would broadly maintain the trisomy detection rate of combined test screening, and would remain cost-neutral (155, 156). The systematic review identified several uncertainties in the evidence (150). In particular, there was limited information on the test failure rate and on test performance in multiple pregnancies or for T18 and T13. There was little information on the way in which the introduction of NIPT affected the uptake of screening or women's choices at different points of the screening and diagnostic pathway.

Informed choice and reproductive autonomy have been the primary goals of fetal anomaly screening since its establishment as a UK NSC–approved program in 2001 (early statements on informed choice as the aim of the program can be found in 44, 154). An independent public engagement exercise on NIPT was undertaken by the Nuffield Council on Bioethics. The council concluded that accurate, coproduced information for the public; education and training for health professionals; and sufficient time to discuss concerns were essential elements to support the ethical delivery of NIPT within the Fetal Anomaly Screening Programme (113, 128).

The Reliable Accurate Prenatal Non-Invasive Diagnosis (RAPID) study (36, 83) contributed evidence on this important issue from eight UK maternity units. This study reported that a high rate of informed choice could be achieved if the elements described by the Nuffield Council were in place. It also suggested that a significant proportion of women accept the offer of screening only to gain information about the pregnancy, not necessarily with the intention of terminating an affected pregnancy. A subsequent study, which reported a lower rate of informed choice, highlighted the challenge of maintaining the level of informed choice outside a strict research environment (82).

The UK screening programs have produced information for the public, and educational resources for health professionals have been produced in cooperation with organizations representing people with T21, T18, and T13. The test is offered as an optional second screening test, and an opportunity to discuss it is offered following a high-chance result from the combined or

quadruple test. Evaluations are accompanying the rollout of the test and will inform future developments within the screening programs.

The human rights of disabled people and their equality under the law are addressed by the Equality Act of 2010 (50), which followed the UK government's 2009 ratification of the UN Convention on the Rights of Persons with Disabilities (158). Termination of pregnancy on grounds of fetal anomaly is lawful within the terms of the 1967 Abortion Act in England, Scotland, and Wales (3).

A public stakeholder consultation on the UK NSC recommendation focused attention on the cultural context in which NIPT was being considered in the UK (155, 156). Thirty stakeholders responded to the consultation, many of whom were supportive of the recommendation. Within this group of responses, there was some interest in expanding the eligibility of NIPT and in simplifying the screening pathway to increase the trisomy detection rate.

The responses that were not supportive of the recommendation came from organizations with distinct, but overlapping, perspectives on disability rights and termination of pregnancy. For these stakeholders, the use of NIPT would exacerbate concerns that they consider intrinsic to antenatal screening, where termination of pregnancy is offered as an option. These concerns centered on the potential for NIPT to routinize the screening process and to institutionalize the choice of not proceeding to term with a fetus identified as having T21, T18, or T13 (129). Most stakeholders who were supportive of the UK NSC's recommendation wished to implement NIPT in a way that addresses these concerns.

THE UNITED STATES

There were 3.79 million births in the United States in 2018 (93). Prenatal screening for T21 is part of routine prenatal care (117), and the United States was one of the first countries to introduce NIPT in 2011. Marketed as a laboratory-developed test, it is regulated by the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments of 1988 (10). As early as 2012, the US Food and Drug Administration raised the possibility of regulating NIPT, notably because of its aggressive marketing, including direct-to-consumer advertising, by companies and lack of "comprehensive validation" (12, p. 3124). To date, this regulation has not materialized.

Still, according to some authors, institutional actors, and nonprofit organizations, the Food and Drug Administration's regulation of NIPT is critical, given the sensitivity of the decisions that are made in the prenatal context (76). According to King (76), the Food and Drug Administration should impose a threshold of accuracy for the marketing of new screening tests using NIPT and raise awareness among HCPs, patients, and the public.

In the absence of direct regulation of genetic testing and a centralized healthcare system, NIPT's implementation in the United States has been influenced by the commercial sector, medical professional associations, and private insurers (12). The result is a patchwork of state Medicaid and private medical insurance coverage, where the majority of state Medicaid programs cover NIPT for high-chance pregnancies, six Medicaid programs cover it for average-chance pregnancies, and nine do not cover it at all (53).

It is estimated that 25–50% of pregnant people in the United States use NIPT (53), so far mostly as a second-tier test. The most recent prenatal screening guidelines from the American College of Obstetricians and Gynecologists recommend offering NIPT to all pregnant people regardless of their risk level (13). Given the significant influence of professional associations on NIPT's adoption in the United States, it is reasonable to expect that these new recommendations will increase NIPT's coverage and, consequently, expand its use. NIPT's coverage by Medicaid

or private insurance is a critical factor in women's decision-making. In a cost–benefit reasoning where amniocentesis is covered in most US states and the result is diagnostic, NIPT's cost may not seem worthwhile for many women (11, 51).

NIPT's expanded coverage would enhance access and hence reproductive autonomy, but it would also raise certain issues, especially if offered for an expanded range of conditions. People generally support using NIPT to detect a broader range of severe genetic conditions, although they acknowledge the complexities it would raise for decision-making and the possible exacerbation of the information overload associated with prenatal testing, which may reduce the capacity for informed choice (5, 51).

Prenatal care providers find it challenging to keep up with NIPT's developments, express the need for more training, and report a lack of time to counsel their patients (55). The shortage of genetic counselors and physicians certified in genetics makes it difficult to support an increasing number of NIPT users (10, 51), and patient advocacy groups have limited resources to respond to questions (101). Appropriate resources for HCP training and funding for patient advocacy groups are thus imperative to mitigate these issues.

Marketing materials and consent documents for NIPT produced by the companies that offer the test fail to mention risks, such as the anxiety it may generate (101). Moreover, the websites of many US NIPT companies emphasize its "99% statistical accuracy," but approximately a quarter of the consent documents do not specify that NIPT is not diagnostic (54, 142). This may lead people to make critical pregnancy decisions without undergoing prenatal diagnosis (103). HCPs are thus reluctant to use biased materials to counsel their patients (9). Moreover, some have expressed concern that even information provided by HCPs themselves is biased, as it focuses primarily on health risks associated with T21 and not on the positive lived experiences of families (103, 139). Multiple US states have adopted a Down Syndrome Information Act, which requires HCPs to provide complete and balanced information regarding T21 but does not specify what this means (80).

Abortion is a highly politicized and divisive issue in the United States, and since prenatal testing detects mostly conditions for which there is no treatment, it becomes entangled in this debate (129). As NIPT detects an expanding range of conditions, it could increase the number of selective abortions, which makes it a target for pro-life lobbies. Moreover, since NIPT is available from week 9 of pregnancy, it allows earlier detection, which is an important consideration because termination of pregnancy is legal until the 24th week in most US states (76). Despite concerns that pro-life laws may limit access to NIPT, this has not been the case to date. However, Indiana, Louisiana, and North Dakota prohibit termination if the fetus is diagnosed with a genetic condition, including T21, and Ohio prohibits termination if the fetus has T21 specifically. Although Indiana's law was declared unconstitutional and Louisiana's law is under litigation, the ban is in effect in North Dakota (133). Such limits on access to termination can impact the use of NIPT for those who test with the intent of terminating an affected pregnancy.

DISCUSSION

This review of the implementation of NIPT in various countries reveals some striking similarities and differences (for a summary, see the sidebar titled Similarities and Differences Among Countries). Overall, issues related to cost as a barrier to equitable access, to decision-making about public funding and cost-effectiveness, and to a shortage of appropriate resources that promote informed choice are common and seem to represent global challenges. Conversely, sociocultural values that underlie the use of NIPT vary greatly among countries. These values include—among others—different attitudes toward disability, pregnancy termination, and the importance of

SIMILARITIES AND DIFFERENCES AMONG COUNTRIES

Similarities Among Countries

- *Cost as a barrier to equitable access*: Cost is still perceived as a barrier in countries that do not offer public funding, raising concerns about justice and inequitable access.
- *Public funding and cost-effectiveness*: Public funding of NIPT is endorsed by users and is key to promoting equitable access and reducing use of invasive tests. However, in some countries, funding is challenging due to limited resources, and decisions surrounding cost-effectiveness can be complex.
- *Shortage of appropriate resources that promote informed choice*: Although many professional guidelines emphasize the need for appropriate counseling regarding NIPT, a shortage of trained professionals and of comprehensive, balanced, neutral informational materials seems to be an issue in many countries. As the number of conditions NIPT can test increases, creative and innovative counseling mechanisms will be required.
- *Protection of disability rights*: The implementation of NIPT in all countries should be accompanied by measures to support and guarantee care for people with disabilities in a way that allows pregnant people's choices to be truly free and uncoerced.

Differences Among Countries

- *Attitudes toward pregnancy termination*: The political context surrounding abortion varies greatly across countries. The availability of legal and safe abortion is relevant to the implementation of NIPT for those who might consider terminating a pregnancy based on a diagnosed condition in the fetus.
- *Attitudes toward disability*: Attitudes toward disability vary greatly across countries and are not necessarily associated with the status of NIPT implementation. In countries with advanced implementation of NIPT (e.g., the Netherlands and the United Kingdom), this implementation has provoked strong reactions. In countries where NIPT is only partially covered or not covered at all (e.g., Israel and China), NIPT has raised no disability rights concerns.

informed and free choice regarding prenatal testing. In this discussion, we illustrate these issues by exploring what we have learned from this review.

Cost and Funding

Although the cost of NIPT has significantly decreased since its introduction in 2011, it is still perceived as a barrier in countries that do not offer public funding, which raises concerns about inequitable access for those who cannot afford to pay. In the United States, for example, coverage by private insurers or Medicare is a determining access factor, and in countries such as India, China, and Lebanon, NIPT's cost is prohibitive for most of the population. In India, for example, it represents up to 10% of the average annual income per capita. In countries where diagnostic testing is covered but NIPT is not—as is the case in Australia, for example—justice concerns are raised regarding pregnant people choosing an invasive test with an associated risk of fetal loss over a safer test that could have reassured them.

Public funding of NIPT is thus highly desirable to promote equitable access and to reduce the use of invasive tests. However, funding in lower- and middle-income countries may be difficult or impossible due to limited resources (25), and in high-income countries decisions surrounding coverage of NIPT are complex. Most cost-effectiveness studies show that NIPT is not yet

cost-effective as a first-tier test but could be cost-neutral or cost-effective as a second-tier test. The analysis of most studies on cost-effectiveness is based on considerations such as money saved through the reduction in invasive tests, or on the investment needed to detect the same number of cases with NIPT compared with existing alternatives. Some studies also include the reduction in costs of caring for individuals with the conditions tested by NIPT, i.e., savings to society through the prevention of certain births (112). Quantifying the cost of care of individuals with disabilities can translate into an evaluation of the value of their lives, raising acute ethical concerns regarding disability rights and eugenic social attitudes (129).

Counseling

Professional guidelines published by relevant medical organizations in several countries emphasize the need for appropriate counseling regarding NIPT, to enable and promote autonomous and informed decision-making. In countries with close oversight over the implementation of NIPT (e.g., as part of a national research project, as in the Netherlands) or extensive public consultation (as in the United Kingdom), counseling appears to be better organized and funded. However, a shortage of trained HCPs and of comprehensive, balanced, neutral informational materials seems to be an issue in many countries, especially those where NIPT is offered mainly or exclusively in the private sector. For example, despite legislation in some US states to ensure that pregnant people receive complete information regarding prenatal testing, the number of medical geneticists and genetic counselors is insufficient, and informational resources are not optimal. This is also the case in India and Australia, where the number of appropriately trained HCPs is insufficient.

Many countries have developed online informational resources and decision aids, which represents what seems to be an inevitable move from one-on-one in-person counseling toward adaptive and innovative models of counseling that rely to a lesser degree on trained HCPs. As the number of conditions that NIPT can test for increases, possibly to include nonmedical uses, creative counseling mechanisms will be required to help people critically reflect on their decision whether to have NIPT (and if so, to detect what) and to mitigate harms from information overload. Since a growing number of individuals rely on the internet and social media to search for information about NIPT, it may be effective for HCPs to use online platforms to engage with the target population (91).

Attitudes Toward Disability and Pregnancy Termination

Attitudes toward disability and pregnancy termination are highly variable among different countries, and the political context surrounding the abortion debate also varies greatly. Termination is legal at any pregnancy stage in some countries, such as Canada and China; it is legal but subject to limits in some other countries, such as the United States, Australia, and the Netherlands; and it is completely banned in others, such as Lebanon. The availability of legal and safe termination is relevant to the implementation of NIPT for those who test not only to prepare for the birth of their baby, but also because they may consider terminating the pregnancy if they discover a severe medical condition in the fetus.

Attitudes toward disability also vary greatly. In the Netherlands and the United Kingdom, for example, the implementation of NIPT provoked strong reactions, particularly from families of individuals with T21 and patient advocacy organizations. Interestingly, these are among the countries where NIPT implementation is most advanced. By contrast, in Israel and China, for example, NIPT raised no disability rights concerns. In China, NIPT coincides with a national plan for disability prevention, and in Israel, disability advocates support it. Here again, attitudes toward

disability are not necessarily associated with the status of NIPT implementation. For example, in the Netherlands, although attitudes toward disability are rather positive, NIPT is implemented in the publicly funded national screening program as a first-tier screening test (with women having to pay only a part of the cost), but in Israel, where termination of pregnancies with T21 is common, women have to pay the full cost of NIPT out of pocket.

Despite these stark sociocultural differences, the implementation of NIPT should be accompanied by measures to support and guarantee care for people with disabilities in a way that allows pregnant people's choices to be truly free and uncoerced and by an opportunity to receive full and balanced information, including about the lived experiences of those raising children with the tested conditions. These are important considerations for an ethically appropriate implementation of NIPT worldwide (105).

CONCLUSION

NIPT is one of the fastest-spreading genetic technologies globally, and while this review presents some illuminating case studies, other countries (not surveyed here) have also provided valuable insights into its global implementation. NIPT is characterized by a commercial implementation in the private sector, prior to an adoption—in some countries—by the public health system. It carries many benefits and is overall well regarded by pregnant people and HCPs. Its implementation and uptake are influenced by many local and national factors, such as the structure of the healthcare system; the existence or absence of a prenatal testing program and of public funding; and sociocultural, legal, and political contexts. These factors are interwoven, making the implementation of NIPT intricately complex.

The issues described in this article will become even more challenging in the coming years, as NIPT evolves from a second-tier to a first-tier screening test, substantially increasing the target population. Additional challenges will emerge from the gradual expanded use of NIPT to generate an increasing amount of genetic information, potentially toward less severe conditions and even nonmedical characteristics. Nuanced and contextualized discussion of socioethical implications is indispensable as countries cope with decisions regarding what uses of NIPT they wish to allow or fund.

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