Understanding attitudes and behaviors towards cell-free DNA-based noninvasive prenatal testing (NIPT)

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Title: Understanding attitudes and behaviors towards cell-free DNA-based noninvasive prenatal testing (NIPT): A survey of European health-care providers

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Abstract

Cell-free DNA-based noninvasive prenatal testing (cfDNA) is a relatively new screening tool that analyzes cfDNA circulating in maternal plasma to screen for aneuploidies. Since its introduction, cfDNA has been rapidly adopted by health care providers (HCPs). This rapid adoption, as well as progressive developments in the technology, requires professional societies to continuously update their guidelines to indicate the broadening scope both in terms of test indications and patient populations for whom it has become the appropriate primary test. CfDNA testing, initially applied to high-risk patients, is now largely considered an option for all patients. For HCPs, the rapid introduction of cfDNA into clinical practice has come with the requirement to stay up-to-date and accurately informed. We performed a survey to understand the current practices and views of European HCPs on the use of cfDNA. European HCPs were surveyed on several topics such as familiarity with cfDNA-based noninvasive prenatal testing (NIPT), current usage, patient counseling, test menu expansion, and future perspectives. The results of this survey demonstrate increasing usage and awareness of cfDNA-based NIPT in five European countries (UK, France, Germany, Spain and Italy). Major barriers to implementation include cost and a lack of physician education on NIPT.

Keywords

Noninvasive prenatal testing; cell-free DNA; survey; health care provider; Europe

Introduction

Cell-free DNA (cfDNA)-based noninvasive prenatal testing (NIPT) for trisomy 21 was introduced into clinical practice in October 2011 and has created a worldwide shift in the practice of prenatal screening and diagnosis. Test offerings soon expanded to include trisomies 18 and 13. A recent meta-analysis demonstrated high detection rates: 99.7% for trisomy 21, 98.2% for trisomy 18, and 99.0% for trisomy 13 (Gil et al., 2017). Screening for sex chromosome aneuploidies (SCAs) has been included in many commercial platforms but has been received with less enthusiasm because of the relatively mild and partially unpredictable phenotypes, lower detection rates, and lower positive predictive values (PPVs) (Gil et al., 2017; Mackie et al., 2017; Porreco et al., 2014).

The evolution of NIPT has continued with the introduction of "expanded panels" that include a preselected number of well-defined microdeletions, such as the 22q11.2 deletion syndrome (associated with velocardiofacial syndrome), 1p36 deletion, and 15q11.2-q13 deletions (associated with Prader-Willi and Angelman syndromes). While this has been shown to be technically feasible (Peters et al., 2011; Srinivasan et al., 2013), the prevalence of these conditions varies and there is a lack of prospective studies on clinical utility. Moreover, because of their relative rarity, expected PPVs are considerably lower than for the common trisomies (Yaron et al., 2015). An increase in the overall cfDNA NIPT false positive rate may lead to unnecessary invasive procedures.

CfDNA testing with genome-wide sequencing and analysis can provide information on rare autosomal trisomies (other than 13, 18, and 21) (Pertile et al., 2017; Van Opstal et al., 2018). If present in a non-mosaic form, these rare trisomies usually result in pregnancy loss (Goldstein et al., 2017). In mosaic form, they can be associated with congenital anomalies, developmental delay, fetal growth restriction, and intrauterine demise (Kalousek and Dill, 1983; Pertile et al., 2017; Van Opstal et al., 2018). Finally, screening for genome-wide copy

number variations (CNVs) larger than 7 to 10 Mb has also been described, with a claimed sensitivity of 97.7% and specificity of 99.9%(Lefkowitz et al., 2016). However, the clinical utility remains to be demonstrated.

Given the paucity of clinical validity and clinical utility studies, the best approach for integrating cfDNA NIPT in the prenatal screening pathway remains unclear. Discussions about its use in the all-risk population continue, albeit more on the economics. Even among those only supporting the use of cfDNA NIPT for high-risk patients, there is no consensus on the risk value cut-off for offering cfDNA NIPT. Attitudes towards cfDNA NIPT, national guidelines/regulations, and reimbursement policies vary between and within countries (Table S1). To evaluate awareness, attitudes, and current practices with respect to cfDNA NIPT, we conducted an online survey of HCPs from five European countries.

Methods

Between March 21, 2016 and April 14, 2017, we conducted a 30-minute online survey consisting of 75 multiple choice questions on clinical practice and attitudes towards cfDNA-based NIPT (Figure S1, Table S2). The survey concept originated from an Illumina, Inc Advisory Board. The original questionnaire was developed by The Link Group (http://tlg.com), a US-based clinical market research company experienced in developing and analyzing questionnaires in the healthcare arena. The questionnaire was based on interviews and consultations with a global group of prenatal-care key-opinion leaders (KOLs), including European KOLs. These KOLs gave feedback on the questions, wording, and response options, and the appropriate amendments were made. The survey was piloted by three obstetricians in the US, which resulted in the following changes: added definition of "high risk" for chromosomal aneuploidy; renamed "average risk" to "general risk"; added a full description of cfDNA NIPT and a list of different naming conventions at its first mention because it is known

by different terms globally; some text revisions and modifications of answer choices, such as the addition of a "Don't know" option for select questions. Translation was done by a market research translation company; translation reviews were performed by in-company partners.

The survey was conducted and analyzed by The Link Group. To recruit survey participants from France, Germany, Italy, Spain, and the UK they utilized a market research panel provider (M3, London, UK) experienced in developing HCP panels; survey participants received a small remuneration (< USD80) for participating and were not informated that the survey originated from an NIPT laboratory. Potential participants were asked a set of screening and role classification questions (Table S3), to confirm eligibility. All respondents were screened to ensure that they work at least 60% of the time in direct patient care and had been in practice at least 2 years. As part of the screening process, respondents provided consent to use of their anonymous responses. Because this study did not involve patients or patient data, Institutional Review Board approval and patient consent were not required.

The survey was sent to 1893 HCPs from the five most populated European countries: France, Germany, Italy, Spain, and the UK. A total of 1737 HCPs accessed the survey: 634 (36.5%) completed the survey, 655 partially completed the survey, 363 did not meet inclusion criteria, and 85 were "overquota" (ie, survey enrolment in their specific country/role was already full).

The relative contribution of each country was weighted by the annual number of live births as reported by Eurostat 2015: France 25%, UK 24%, Germany 23%, Italy 15%, and Spain 13%. For within country averages, results were weighted to the actual proportion of physicians (75%) and midwives (25%) involved in prenatal care; the exception to this was the UK, where the proportion was set at 58% physicians and 42% midwifes, to reflect the larger role of midwives in prenatal care in this country.

Results and Discussion

The survey was completed by 634 HCPs: 263 general obstetricians and gynecologists, 197 maternal fetal medicine specialists, and 174 midwives. Respondent demographics are detailed in Table 1.

Familiarity, Knowledge, Sources of information

Physicians were more likely to respond that they were very familiar with cfDNA NIPT (50%–68%) than midwives (2%–31%). Familiarity with cDNA NIPT was lowest among midwives in the UK (2%) compared with those in other countries (17%–31%). These tendencies were reflected in referral practices (Figure 1A): Physicians were more likely to offer cfDNA NIPT or refer out for it (75%–93%) than midwives (45%–82%). Consistent with the low familiarity of UK midwives, they also had the lowest referral rate (45%). Overall familiarity with testing amongst health care providers (physicians and midwives) was lowest in the UK (30% vs 49% to 58 % in the 4 other countries) but this was not reflected in the usage of expanded panels that was lowest in France and in Germany.

Of the five European countries, only French HCPs said they were not strongly influenced by guidelines. UK and German HCPs stated they were largely influenced by their respective society guidelines: 93% of UK survey respondents indicated that the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines are the most influential factor in their clinical practice; 61% of German respondents indicated that they were mainly influenced by the German Society of Ultrasound in Medicine while 36% were mostly influenced by the German Fetal Medicine Foundation Guidelines. Italian HCPs indicated they were influenced by Italian and international guidelines: 76% of respondents indicated that they follow the 2015 Ministry of Health Guidelines(2015), but up to 60% also follow the American Congress of Obstetricians and Gynecologists (ACOG) guidelines. Spanish HCPs stated that they are

primarily influenced by international guidelines: 65% follow the ACOG guidelines and 48% follow the International Society of Prenatal Diagnosis (ISPD) guidelines. American or International guidelines were not influential in France, Germany, or the UK.

With the rapid introduction of cfDNA NIPT and progressive developments in test options, continual education of HCPs is vital for them to stay current on best-practices and options for prenatal care. Here, 49% to 66% of respondents indicated that it is not easy to stay up-to-date with the ever-changing realm of cfDNA NIPT, with the highest reports of difficulty coming from the UK (66%). Except for Spain, HCPs indicated relatively little interest in information from cfDNA NIPT providers. Rather, survey results demonstrated that HCPs are more interested in, and responsive to, information from professional societies and events, Certified Medical Education programs, scientific journals, in-person meetings, national websites, webinars, and videos. Midwives were more likely to use Google or other Search Engines and product brochures.

HCPs use different resources to educate their patients: 41% to 68% of physicians and 7% to 38% of midwives reported using test provider brochures. There was considerable interest in brochures and online sources to inform patients. One notable exception was the UK, where HCPs mostly used locally developed materials, such as those provided by the Healthcare Ministry or the National Health Service.

Current cfDNA NIPT Usage

For some questions relating to current cfDNA NIPT usage, responses varied between physicians and midwives, which could reflect country-specific differences in the role of midwives in pregnancy care. In most countries, low-risk pregnancies are primarily managed by midwives.

While cfDNA NIPT had been available for over five years at the time of the survey, 50% of surveyed physicians had only been offering this test for one to two years. Spanish physicians may be considered as pioneers, with 46% of surveyed physicians having offered the test for three years or more, compared to 18% in France. HCPs generally agreed that cfDNA NIPT is beneficial for their patients (Figure 1B), indicating that it was more accurate than serum screening or combined screening, prevents most women from having to decide whether to undergo invasive prenatal diagnostic procedures, and is safe in that it lacks the risk associated with prenatal diagnostic procedures for a procedure-related miscarriage. In line with most society recommendations(Gregg et al., 2016; Salomon et al., 2017), HCPs tend to bring up cfDNA NIPT at the first visit for *a priori* high-risk patients.

The proportion of HCPs that considered NIPT as standard-of-care varied considerably between countries (Figure 2A). European HCPs generally did not conduct cfDNA NIPT as a first-line test, with the exception of Italy (Figure 2B). In Italy 67% of HCPs offer cfDNA NIPT as a primary test to everyone.

Abnormal maternal serum screening results, previous pregnancy or family history with chromosome anomaly, and advanced maternal age were indicated as the primary indications for HCPs to recommend NIPT in all countries. In the case of ultrasound anomalies or soft markers, the likelihood of recommending NIPT was 73% to 89 % in all countries but France, where it was notably lower at 65% (ultrasound anomalies) to 69% (soft markers). For twin pregnancies, 37% to 53% of respondents indicated that they would recommed NIPT. In healthy low-risk patients, 5% to 29 % of HCPs were likely to recommend NIPT; the lowest percentages were in the UK and France and the highest were in Germany and Italy

Whilst results show that 73% to 95% of European HCPs were likely to recommend cfDNA NIPT to patients with an abnormal serum screening result, only 8% to 29% of the respondents indicated that they were likely to recommend it as a primary test in healthy patients

with no indication. There was no clear consensus from respondents on what the cut-off risk for offering NIPT should be. The most frequently indicated thresholds were 1:150 and 1:200, however, HCPs in France indicated a much lower threshold (1:1000) than HCPs in the four other countries. There are now formal recommendations in the UK as well as in France to offer NIPT as a second-line test, provided there are no ultrasound anomalies (2017; Marshall, 2015; UKNSC, 2016). The cut-off risk for offering cfDNA NIPT depended on each country's policy: from 1/150 in the UK, 1/500 in Germany, to 1/1000 in France; the French policy changed after completion of this survey, with the Haute Autorité de Santé now recommending offering cfDNA NIPT as a second-line test when the serum screening risk is between 1/50 and 1/1000 (2017). The percentage of patients considered high-risk therefore varied by country and generally correlated with cfDNA NIPT usage.

For high-risk patients, 78% to 95% of practitioners consistently mention NIPT and 62% to 90% actively recommend it. For general-risk patients in Spain, Italy, Germany, or the UK, 54% to 74% of practitioners mention NIPT and 40% to 61% recommend it. France was a clear outlier with only 29% of surveyed HCPs indicating that they mention NIPT and 17% recommending NIPT for general-risk patients; the differences between France and the other four countries in general-risk patients were all significant at a 95% CI level. The surveyed HCPs in all countries indicated that 31% to 53% of high-risk patients and and 9% to 38% of general-risk patients request NIPT themselves.

Pre-test and post-test counseling and result delivery

HCPs generally agree that pre-test counseling for cfDNA NIPT is important. HCPs in all countries agree that it is important to discuss the possibility for false positive and false negative results and test failures during pretest counseling (Figure 3). Our survey showed that HCPs in Germany (93%–94%), the UK (73%–86%), and Spain (68-81%) placed the highest importance

on these topics, compared with Italy (47%–69%) and France (53%–63%). Explaining the concept of PPV is judged important by 59% to 71% of HCPs without significant differences between the countries. Implementation of cfDNA NIPT seems to have had little impact on the workload of most practitioners (Figure 4); however, those who offer cfDNA NIPT in their practice, as opposed to "referring out", were more likely to say it resulted in an increased work load, especially in Germany. This is consistent with the observation that German HCPs placed the most emphasis on pre-test counseling, which likely reflects the fact that according to the German Genetic Diagnostics Act "predictive genetic testing for medical purposes must be performed by a medical specialist with special qualifications"(2009).

Within the surveyed countries, cfDNA NIPT results are primarily delivered in-person (average, 71%; range, 51% [Italy] to 89% [Germany]) and patients typically are given the whole report (average, 57%; range, 41% [UK] to 77% [Italy]). The survey question on result delivery did not discern between low- and high-risk result delivery. Most likely the communication channel of result delivery differs between the two result categories.

There is agreement among professional societies that cfDNA NIPT results indicating a high likelihood of aneuploidy should be confirmed by a diagnostic follow-up test(Gregg et al., 2016; Salomon et al., 2017). Recent data suggest that chorionic villus sampling is sufficient for T21 confirmation. For cfDNA NIPT results of T13 or T18, amniocentesis is recommended in the absence of supportive ultrasound findings because of the higher likelihood for confined placental mosaicism(Grati et al., 2014). In this survey, the most commonly reported follow-up test to abnormal cfDNA NIPT results was amniocentesis, but the survey question did not differentiate between trisomies. In Germany, 54% of HCPs offer ultrasound examination as a first follow-up to abnormal cfDNA NIPT results.

For cfDNA NIPT failures, patients can choose between invasive testing, repeat cfDNA NIPT, and no further testing. Patient counseling should consider the cause of the failure: Low

fetal fraction or technical failure. Low fetal fraction is associated with increased maternal weight, testing performed too early in gestation (<10 weeks), and fetal aneuploidies that are associated with smaller placentas(Yaron, 2016). Here, recommendations for an invasive test after a failed cfDNA NIPT were highest in France (73%), followed by Germany, Italy, and Spain (all 60%), and lowest in the UK (41%) where a second blood draw is usually recommended. HCPs generally agreed that counseling a patient after a failed cfDNA NIPT test is challenging, reinforcing that this possibility should be covered in pre-test counseling.

Drivers and Barriers

An important goal of this survey was understanding HCPs motivations in offering cfDNA NIPT, and their reasons for not doing so. European HCPs stated that the primary benefits of cfDNA NIPT were the reduction in invasive procedures and the absence of risk for complications due to invasive testing. Although reimbursement policies are evolving rapidly, test cost and lack of reimbursement were the primary reported barriers to broader cfDNA NIPT uptake. When determining whether and how to offer NIPT in their practice, survey respondents indicated that cost/reimbursement constraints were considered far more important than restrictive country-specific guidelines. For example, in the UK, cost to the patient and lack of reimbursement are considered as the main drawback (38% and 45%) compared with guideline limitations (3%). However, relatively few HCPs selectively offer cfDNA NIPT to patients they think can afford it.

In Europe, public health care reimbursement decisions await evidence of cost-effectiveness of cfDNA NIPT over existing prenatal screening options. While a number of studies support that NIPT is cost effective as a contingent screen (Chitty et al., 2016; Neyt et al., 2014), studies supporting it as a primary screen are limited (Benn et al., 2015; Beulen et

al., 2014; Fairbrother et al., 2016; Walker et al., 2015) particularly in the different care systems within Europe.

As discussed above, another significant barrier is physician education on cell-free DNA-based NIPT. Physicians indicated that it is difficult to stay up to date on this rapidly evolving field, with continuous changes in test menus and technologies. All expressed an interest in access to more educational resources for themselves and their patients.

Test Menu Expansion

There has been rapid evolution in cfDNA NIPT test offerings, with most brands offering screening for SCAs, and some offering rare trisomies, select microdeletions, and CNV detection.

When HCPs were asked "What conditions are you currently using cfDNA NIPT for?", the majority responded that they are currently using the test for the common trisomies. The use of expanded cfDNA NIPT panels varied markedly by country. Respondents from Germany, Italy, and Spain reported higher testing rates for SCAs (54%, 57%, and 53%, respectively) than in the UK (41%) and France (24%). Almost half (48%) of the surveyed European HCPs stated that they had not used expanded panels. The highest reported usage of expanded panels was in Spain (62%) and the lowest in France (16%). Of those HCPs that *have* used expanded panels, most (38%) utilized microdeletion testing. The use of cfDNA NIPT for microdeletions ranged from 18%–19% in France, UK, and Germany to 37%–44% in Italy and Spain. The use of cfDNA NIPT to screen for autosomal trisomies other than 13, 18, and 21, was lowest in Germany (12%) and highest in Italy (39%). Finally, screening for genome-wide sub-chromosomal CNVs was the least utilized cfDNA NIPT approach, with the lowest rates in Germany (5%) and the highest in the UK and Italy (19%–20%). The top three reasons for use of expanded panels were as follows: Family history of condition (average, 45%; range, 27%

[Italy]–56% [Germany]); abnormal ultrasound (average 39%; range, 15% [Italy]–63% [France]); and patient request (average, 38%; range, 25% [UK]–56% [Germany]).

While survey responses suggest that the current use of expanded panels is relatively low, they indicated a strong interest in future use (Table 2). The highest interest in expanded panels was in Spain and Italy. Respondents were most interested in expanded panels for select microdeletions (such as including 22q11.2, Prader Willi-Angelman, Cri du Chat, Wolf-Hirschhorn, and 1p36), followed by whole autosome aneuploidy and, to a lesser extent, subchromosomal copy number changes at the resolution of standard karyotyping (≥7 Mb). According to the respondents the healthcare providers with most influence in deciding to use an expanded panel was obstetricians-gynecologists (27%), genetic counselors (26%), medical geneticists (14%), and maternal-fetal medicine specialists (12%). When asked who had the most influence in deciding whether to offer an expanded panel, the most common response was obstetrician gynecologist (27%) or genetic counselor (25%), followed by MFM specialist (13%) or medical geneticist (14%). However, survey respondents indicated that patients played an active role in test selection: 24% in Italy, 17% in Germany, 11% in the UK, 8% in Spain, and 1% France.

Many HCPs expressed concerns about screening for all autosome trisomies and subchromosomal copy number variations. Concerns included interpretation of results, unknown detection rates and false positive results, the need for access to genetic counselors and geneticists, variants of uncertain significance, increased patient anxiety, and unnecessary pregnancy terminations. UK respondents (83%) expressed the highest degree of concern, and Italian respondents the lowest degree of concern (39%).

We surveyed HCPs on their perceived value of "a la carte NIPT," wherein each patient can tailor her cfDNA NIPT according to personal preferences. Most HCPs saw some potential value, but relatively few felt strongly about this option. HCPs that were *very* or *extremely*

interested in "a la carte" cfDNA NIPT, gave the following reasons related to tailoring the test to the clinical scenario: Family history of condition (44.8%), abnormal ultrasound (41.8), or patient request (36.6%). For respondents that did not value an "a la carte NIPT", the following reasons were given: too complicated (33%), fear of missing something a full panel would have shown (18%), makes test panel choice more difficult (7%), and time commitment for informed consent (6%).

Importantly, concerns over whether broader adoption of cfDNA NIPT or traditional screening approaches detect more cases of fetal chromosome abnormalities(Norton et al., 2014), and about the consequences of reduced invasive testing(Evans et al., 2018; Evans et al., 2016), should largely be assuaged with broader adoption of expanded cfDNA NIPT. As cfDNA NIPT offers superior detection rates and false positive rates, adoption of expanded cfDNA NIPT inclusive of all autosomal trisomies and genome-wide CNVs should increase the yield of identified abnormalites over existing serum screening modalities at a much lower total screen positive rate. Importantly, cfDNA NIPT is not a replacement for invasive testing, and patients desiring conclusive and comprehensive evaluation of fetal chromosome status should be counselled that amniocentesis followed by chromosomal microarray is the most suitable approach.

Future Perspectives

Most HCPs reported that they anticipate the use of cfDNA NIPT to increase significantly over the next two years, with HCPs from France and Italy reporting the highest anticipated increase in use. However, only 38% of respondents across countries thought that their own practice was likely to offer cfDNA NIPT within the next two years. The lowest rate was noted in Germany (19%) and the highest rates in Spain (46%) and Italy (42%). In most countries, HCPs expect this increase to be driven primarily by high-risk patients. Patient request for cfDNA NIPT was

one of the key factors anticipated to drive the expected growth (Figure 5A). Indeed, except for Germany, 89% to 95% of physicians and 72% to 93% of midwives agreed with the statement: "*I always listen to my patients' requests for specific prenatal testing, including NIPT*". In Germany, only 58% of physicians and 38% of midwives agreed with the statement. Most HCPs (74%–82%) indicated that reduced cost and improved affordability would drive increased use of cfDNA NIPT.

HCPs typically indicated that they think cfDNA NIPT will replace maternal serum screening (MSS) and invasive testing (Figure 5B), with the highest agreement in Italy (83% and 79%, respectively) and the lowest in Germany (58% and 55%, respectively). Physicians were generally more likely than midwives to agree that cfDNA NIPT will replace MSS. Most physicians (53%–84%) and midwives (57%–69%) agreed that "*cfDNA NIPT will replace invasive procedures in the future*".

Study Limitations

While the results of this study highlight important views and practices with respect to cfDNA NIPT, it is important to note some study limitations. Similar to other survey studies with optional participation, the response rate was well below 100%. Survey participants were self-selecting, which may result in non-responder bias. Further, the restriction to a select number of European countries means that the results of this study may not be generalizable to other European countries with differing clinical practices, health care systems, or reimbursement policies.

Also the study was not designed to address the question whether NIPT should be used as a primary or as a contingent screen, nor the opinions on how cost-effectiveness of cfDNA NIPT versus traditional screening drives or should drive prenatal care practice. These are

important topics, particularly given the recent introduction of reimbursement for NIPT in select European countries, and could be the topic of future research in this area.

Conclusions

European HCPs expect that the use of cfDNA NIPT will continue to increase, more so in countries where introduction has lagged. In most countries, HCPs expect the increased usage to be primarily driven by the patients. The key perceived benefits of cfDNA NIPT are the higher detection rates, and the reduction in invasive procedures compared with traditional screening. The main perceived barriers to widespread use of cfDNA NIPT are the cost to the patient, in the absence of reimbursement and the expected lack of counseling capacity. This aligns with conclusions of other studies that called for guides on pre-test counseling and improvement of practices, as well as public funding of NIPT (Brewer et al., 2017; Filoche et al., 2017; Huang et al., 2018). Significant differences between clinicians have been shown in patients' uptake of NIPT versus invasive testing indicating that clinician's different approaches affect the choices patients make (van der Steen et al., 2018). New models for counselling could be explored that focus less on conveying detailed information and more on expecting parent(s)' attitudes and values, hence limiting information to generic information about potential test outcomes (Kater-Kuipers et al., 2018). As there was a significant interest in resources for physicians to educate patients, the development of more online educational materials and app-based educational tools (Five minutes Ltd., 2018) may be warranted. A pioneer randomized trial conducted in California between 2010 and 2013 showed that in the absence of financial barriers, a computerized, interactive decision-support guide led to more informed choices and less test use. It will be worthwile testing such models in other populations (Kuppermann et al., 2014).

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Figure Legends

Figure 1. Current cfDNA-based NIPT offering practices and perceived value to patients.

(A) Current offering practices of surveyed physicians (P) and midwives (M) for cfDNA NIPT by country. (B) Survey responses when asked "How beneficial is NIPT to patients?".

Figure 2. How cfDNA-based NIPT is incorporated into clinical practice.

(A) Survey respondents were asked to indicate on a scale ranging from "one of several options" to "standard of care" how they viewed cfDNA NIPT. (B) Survey respondents were asked for their high-risk patients receiving cfDNA NIPT, what percent received cfDNA NIPT as a first-line versus second-line test.

Figure 3. Important topics for pre-test counseling.

Figure 4. Perceived impact of the introduction of cfDNA-based NIPT on HCP workload.

Most respondents thought that cfDNA NIPT does not change their workload.

Figure 5. Future use of cfDNA-based NIPT.

(A) The top reasons listed for the anticipated future increase in use of cfDNA NIPT. (B) Health care providers anticipate that cfDNA NIPT will eventually replace serum screening and invasive procedures.

Table 1. Demographics of survey respondents.

Demographic	HCP Role*	France	UK	Germany	Italy	Spain
Current role, n						
General OB/GYN	P	58	41	72	51	41
MFM	P	37	29	30	44	57
Midwife	M	30	51	29	32	32
Gender, n (%)						
Female	P	27 (28%)	32 (46%)	39 (38%)	39 (41%)	42 (43%)
Male	P	68 (72%)	38 (54%)	63 (62%)	56 (59%)	56 (57%)
Female	M	30 (100%)	51 (100%)	22 (76%)	26 (81%)	28 (88%)
Male	M	0 (0%)	0 (0%)	7 (24%)	6 (19%)	4 (13%)
Years in practice/current role, mean						
	P	23	19	19	19	19
	M	10	18	18	12	15
Practice Setting, n (%)						
University Hospital	P	16 (17%)	33 (47%)	15 (15%)	28 (29%)	47 (48%)
Regional Hospital	P	42 (44%)	35 (50%)	20 (20%)	32 (34%)	18 (18%)
Midwife Practice	P	0 (0%)	0 (0%)	0 (0%)	15 (16%)	0 (0%)
General Practitioner	P	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)
Center for Prenatal Ultrasound	P	4 (4%)	0 (0%)	12 (12%)	9 (9%)	4 (4%)

Other	P	33 (35%)	1 (1%)	55 (54%)	10 (11%)	28 (29%)
University Hospital	M	4 (13%)	18 (35%)	2 (7%)	6 (19%)	20 (63%)
Regional Hospital	M	7 (23%)	10 (20%)	18 (62%)	6 (19%)	3 (9%)
Midwife Practice	M	16 (53%)	18 (35%)	5 (17%)	9 (28%)	8 (25%)
General Practitioner	M	0 (0%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)
Center for Prenatal Ultrasound	M	0 (0%)	0 (0%)	2 (7%)	1 (3%)	0 (0%)
Other	M	3 (10%)	3 (6%)	2 (7%)	10 (31%)	1 (3%)
# Prenatal patients per month, median						
	P	120	75	78	60	100
	M	40	50	30	20	60
# Prenatal screening/diagnosis consultations per month						
	P	48	20	38	41	57
	M	12	12	15	20	20

* P, physician; M, midwife.

Table 2. The proportion of European HCPs with a strong interest in pursuing expanded cfDNA-based NIPT panels in the future.

Expanded panel type	France (n = 74)	UK (n = 37)	Germany (n = 83)	Italy (n = 51)	Spain (n = 72)
Microdeletion panel†	72%	65%	74%	73%	78%
Sex chromosomes	51%	49%	63%	75%	78%
Select trisomies (9, 16, 22)	50%	46%	60%	69%	64%
All autosome chromosomal copy number changes (chromosomes 1-22)	58%	54%	66%	76%	79%
All chromosome chromosomal copy number changes and sub-chromosome deletions/duplications ≥ 7 Mb	57%	43%	58%	69%	72%

† 22q11.2 deletion [DiGeorge], 15q11 [Prader-Willi syndrome/Angelman syndrome], 5p- [cri-du-chat syndrome], 4p- [Wolf-Hirschhorn], 1p36 deletion

References

2009. The German Genetic Diagnostics Act (GenDG). http://www.drze.de/in-focus/predictive-genetic-testing/legal-aspects).

2015. Italian Ministry of Health: Higher Health Council. Guidelines DNA-based Non-Invasive Prenatal Testing – NIPT http://www.salute.gov.it/imgs/C_17_pubblicazioni_2438_allegato.pdf.

2017. Haute Autorité de Santé Place des tests ADN libre circulant dans le sang maternel dans le dépistage de la trisomie 21 foetale: Synthèse de l'argumentaire et recommandations.

Benn, P., Curnow, K.J., Chapman, S., Michalopoulos, S.N., Hornberger, J., Rabinowitz, M., 2015. An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population. PLoS One 10(7), e0132313.

Beulen, L., Grutters, J.P., Faas, B.H., Feenstra, I., van Vugt, J.M., Bekker, M.N., 2014. The consequences of implementing non-invasive prenatal testing in Dutch national health care: a cost-effectiveness analysis. Eur. J. Obstet. Gynecol. Reprod. Biol. 182, 53-61.

Brewer, J., Demers, L., Musci, T., 2017. Survey of US obstetrician opinions regarding NIPT use in general practice: implementation and barriers. Journal of Maternal-Fetal and Neonatal Medicine.

Chitty, L.S., Wright, D., Hill, M., Verhoef, T.I., Daley, R., Lewis, C., Mason, S., McKay, F., Jenkins, L., Howarth, A., Cameron, L., McEwan, A., Fisher, J., Kroese, M., Morris, S., 2016. Uptake, outcomes, and costs of implementing non-invasive prenatal testing for Down's syndrome into NHS maternity care: prospective cohort study in eight diverse maternity units. BMJ 354, i3426.

Evans, M.I., Evans, S.M., Bennett, T.A., Wapner, R.J., 2018. The price of abandoning diagnostic testing for cell-free fetal DNA screening. Prenat. Diagn. 38(4), 243-245.

Evans, M.I., Wapner, R.J., Berkowitz, R.L., 2016. Noninvasive prenatal screening or advanced diagnostic testing: caveat emptor. Am. J. Obstet. Gynecol. 215(3), 298-305.

Fairbrother, G., Burigo, J., Sharon, T., Song, K., 2016. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. J. Matern. Fetal Neonatal Med. 29(7), 1160-1164.

Filoche, S.K., Lawton, B., Beard, A., Stone, P., 2017. Views of the obstetric profession on non-invasive prenatal testing in Aotearoa New Zealand: A national survey. Aust. N. Z. J. Obstet. Gynaecol. 57(6), 617-623.

Author, 2018. NIPT Insights. https://itunes.apple.com/hr/app/nipt-insights/id1408704012?mt=8.

Gil, M.M., Accurti, V., Santacruz, B., Plana, M.N., Nicolaides, K.H., 2017. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet. Gynecol. 50(3), 302-314.

Goldstein, M., Svirsky, R., Reches, A., Yaron, Y., 2017. Does the number of previous miscarriages influence the incidence of chromosomal aberrations in spontaneous pregnancy loss? J Matern Fetal Neonatal Med, 1-5.

Grati, F.R., Malvestiti, F., Ferreira, J.C., Bajaj, K., Gaetani, E., Agrati, C., Grimi, B., Dulcetti, F., Ruggeri, A.M., De Toffol, S., Maggi, F., Wapner, R., Gross, S., Simoni, G., 2014. Fetoplacental mosaicism: potential implications for false-positive and false-negative noninvasive prenatal screening results. Genet. Med. 16(8), 620-624.

Gregg, A.R., Skotko, B.G., Benkendorf, J.L., Monaghan, K.G., Bajaj, K., Best, R.G., Klugman, S., Watson, M.S., 2016. Noninvasive prenatal screening for fetal

aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med.

Huang, T., Dougan, S., Walker, M., Armour, C.M., Okun, N., 2018. Trends in the use of prenatal testing services for fetal aneuploidy in Ontario: a descriptive study. CMAJ open 6(4), E436-e444.

Kalousek, D.K., Dill, F.J., 1983. Chromosomal mosaicism confined to the placenta in human conceptions. Science 221(4611), 665-667.

Kater-Kuipers, A., Bunnik, E.M., de Beaufort, I.D., Galjaard, R.J.H., 2018. Limits to the scope of non-invasive prenatal testing (NIPT): an analysis of the international ethical framework for prenatal screening and an interview study with Dutch professionals. BMC Pregnancy Childbirth 18(1), 409.

Kuppermann, M., Pena, S., Bishop, J.T., Nakagawa, S., Gregorich, S.E., Sit, A., Vargas, J., Caughey, A.B., Sykes, S., Pierce, L., Norton, M.E., 2014. Effect of enhanced information, values clarification, and removal of financial barriers on use of prenatal genetic testing: a randomized clinical trial. JAMA 312(12), 1210-1217.

Lefkowitz, R.B., Tynan, J.A., Liu, T., Wu, Y., Mazloom, A.R., Almasri, E., Hogg, G., Angkachatchai, V., Zhao, C., Grosu, D.S., McLennan, G., Ehrich, M., 2016. Clinical validation of a noninvasive prenatal test for genomewide detection of fetal copy number variants. Am J Obstet Gynecol 215(2), 227 e221-227 e216.

Mackie, F.L., Hemming, K., Allen, S., Morris, R.K., Kilby, M.D., 2017. The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis. BJOG 124(1), 32-46.

Marshall, J., 2015. Evidence update: new consultation on non-invasive prenatal testing and latest UK NSC recommendations.

https://phescreening.blog.gov.uk/2015/08/13/evidence-update-new-consultation-on-non-invasive-prenatal-testing-and-latest-uk-nsc-recommendations/.

Neyt, M., Hulstaert, F., Gyselaers, W., 2014. Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis. BMJ open 4(11), e005922.

Norton, M.E., Jelliffe-Pawlowski, L.L., Currier, R.J., 2014. Chromosome abnormalities detected by current prenatal screening and noninvasive prenatal testing. Obstet. Gynecol. 124(5), 979-986.

Pertile, M.D., Halks-Miller, M., Flowers, N., Barbacioru, C., Kinnings, S.L., Vavrek, D., Seltzer, W.K., Bianchi, D.W., 2017. Rare autosomal trisomies, revealed by maternal plasma DNA sequencing, suggest increased risk of feto-placental disease. Sci. Transl. Med. 9(405).

Peters, D., Chu, T., Yatsenko, S.A., Hendrix, N., Hogge, W.A., Surti, U., Bunce, K., Dunkel, M., Shaw, P., Rajkovic, A., 2011. Noninvasive prenatal diagnosis of a fetal microdeletion syndrome. N. Engl. J. Med. 365(19), 1847-1848.

Porreco, R.P., Garite, T.J., Maurel, K., Marusiak, B., Ehrich, M., van den Boom, D., Deciu, C., Bombard, A., 2014. Noninvasive prenatal screening for fetal trisomies 21, 18, 13 and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA. Am J Obstet Gynecol 211(4), 365 e361-312.

Salomon, L.J., Alfirevic, Z., Audibert, F., Kagan, K.O., Paladini, D., Yeo, G., Raine-Fenning, N., 2017. ISUOG updated consensus statement on the impact of cfDNA aneuploidy testing on screening policies and prenatal ultrasound practice. Ultrasound Obstet. Gynecol. 49(6), 815-816.

Srinivasan, A., Bianchi, D.W., Huang, H., Sehnert, A.J., Rava, R.P., 2013. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. Am. J. Hum. Genet. 92(2), 167-176.

UKNSC, T.U.n.s.c., 2016. The UK NSC recommendation on Fetal anomaly screening in pregnancy. https://legacyscreening.phe.org.uk/fetalanomalies.

van der Steen, S.L., Houtman, D., Bakkeren, I.M., Galjaard, R.H., Polak, M.G., Busschbach, J.J., Tibben, A., Riedijk, S.R., 2018. Offering a choice between NIPT and invasive PND in prenatal genetic counseling: the impact of clinician characteristics on patients' test uptake. Eur. J. Hum. Genet.

Van Opstal, D., van Maarle, M.C., Lichtenbelt, K., Weiss, M.M., Schuring-Blom, H., Bhola, S.L., Hoffer, M.J.V., Huijsdens-van Amsterdam, K., Macville, M.V., Kooper, A.J.A., Faas, B.H.W., Govaerts, L., Tan-Sindhunata, G.M., den Hollander, N., Feenstra, I., Galjaard, R.H., Oepkes, D., Ghesquiere, S., Brouwer, R.W.W., Beulen, L., Bollen, S., Elferink, M.G., Straver, R., Henneman, L., Page-Christiaens, G.C., Sistermans, E.A., 2018. Origin and clinical relevance of chromosomal aberrations other than the common trisomies detected by genome-wide NIPS: results of the TRIDENT study. Genet. Med. 20(5), 480-485.

Walker, B.S., Nelson, R.E., Jackson, B.R., Grenache, D.G., Ashwood, E.R., Schmidt, R.L., 2015. A Cost-Effectiveness Analysis of First Trimester Non-Invasive Prenatal Screening for Fetal Trisomies in the United States. PLoS One 10(7), e0131402.

Yaron, Y., 2016. The implications of non-invasive prenatal testing failures: a review of an under-discussed phenomenon. Prenat. Diagn. 36(5), 391-396.

Yaron, Y., Jani, J., Schmid, M., Oepkes, D., 2015. Current Status of Testing for Microdeletion Syndromes and Rare Autosomal Trisomies Using Cell-Free DNA Technology. Obstet. Gynecol. 126(5), 1095-1099.

Supplemental data

Supplementary Table 1. Summary of the current state of cfDNA NIPT for each of the five surveyed countries according to local industry experts.

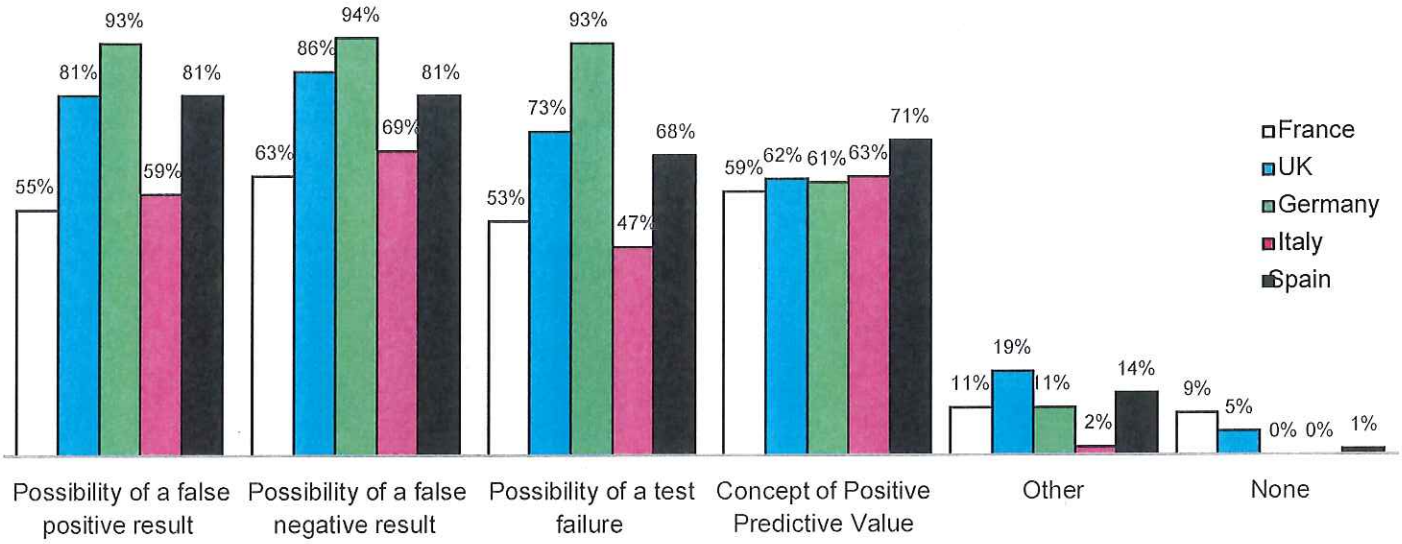
* In country testing indicates that blood samples drawn in the indicated European country can be sent to a laboratory within the same country for cfDNA-based NIPT. Overseas testing indicates that blood samples drawn in the indicated European country can be sent to a testing laboratory located in a different country for cfDNA-based NIPT.

Supplementary Table 2. Survey questions.

* Indicates answer order is randomized for each participant.

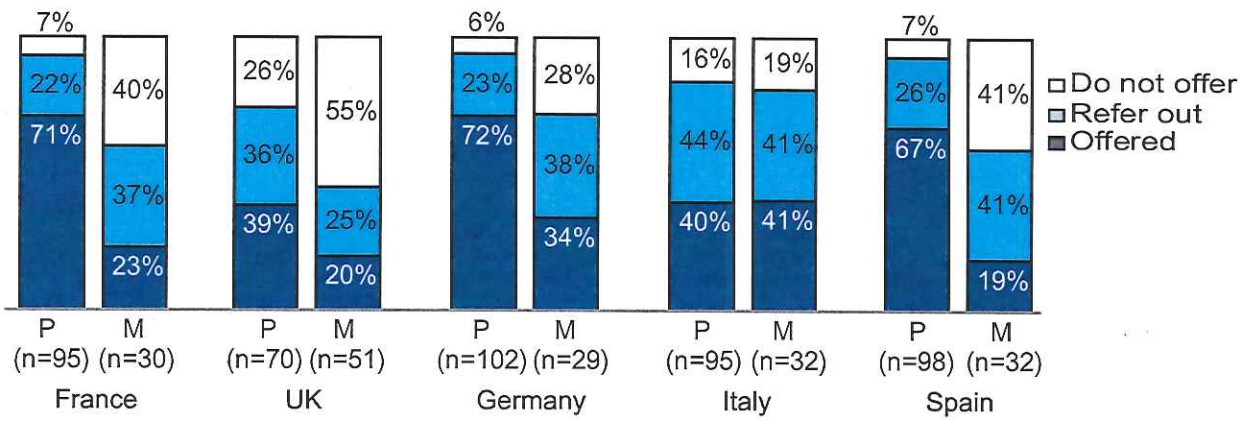
SupplementaryTable 3. Screening and role classification questions.

Supplementary Figure 1. Survey flow overview.



Importance of Pre-test Counseling Topics

A


7%
22%
71%
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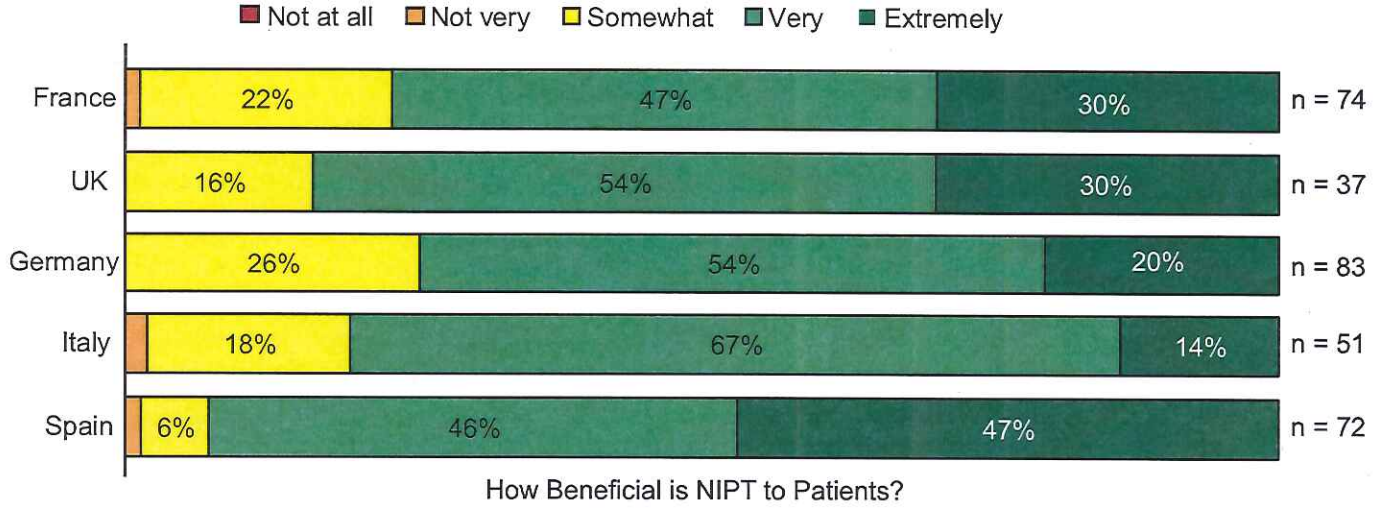
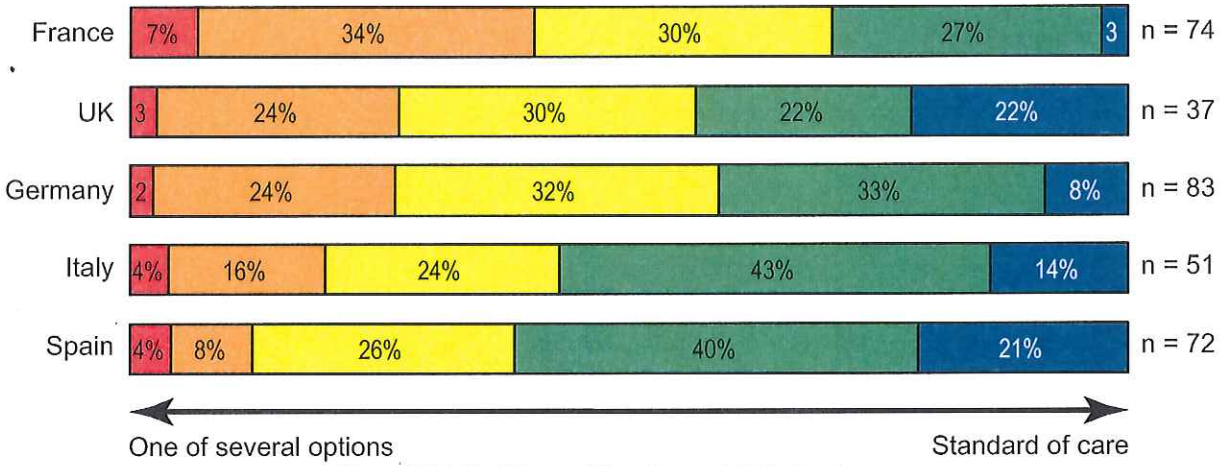
37%
23%
26%
36%
39%
55%
25%
20%
6%
23%
72%
28%
38%
34%
16%
44%
40%
19%
41%
41%
7%
26%
67%
41%
41%
19%
Do not offer
Refer out
Offered
P (n=95)
M (n=30)
France
P (n=70)
M (n=51)
UK
P (n=102)
M (n=29)
Germany
P (n=95)
M (n=32)
Italy
P (n=98)
M (n=32)
Spain

B


Not at all
Not very
Somewhat
Very
Extremely
France
22%
47%
30%
n = 74
UK
16%
54%
30%
n = 37
Germany
26%
54%
20%
n = 83
Italy
18%
67%
14%
n = 51
Spain
6%
46%
47%
n = 72
How Beneficial is NIPT to Patients?

A



How NIPT is Viewed for Prenatal Patients

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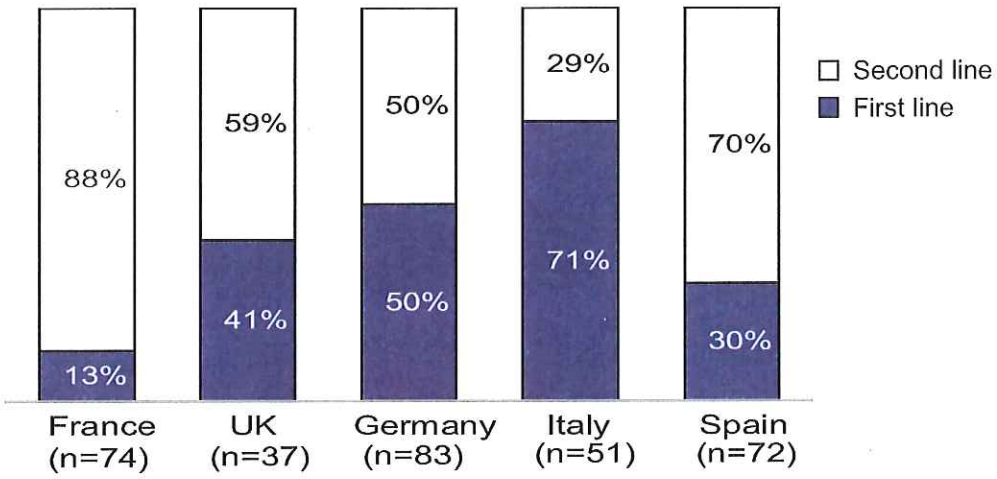
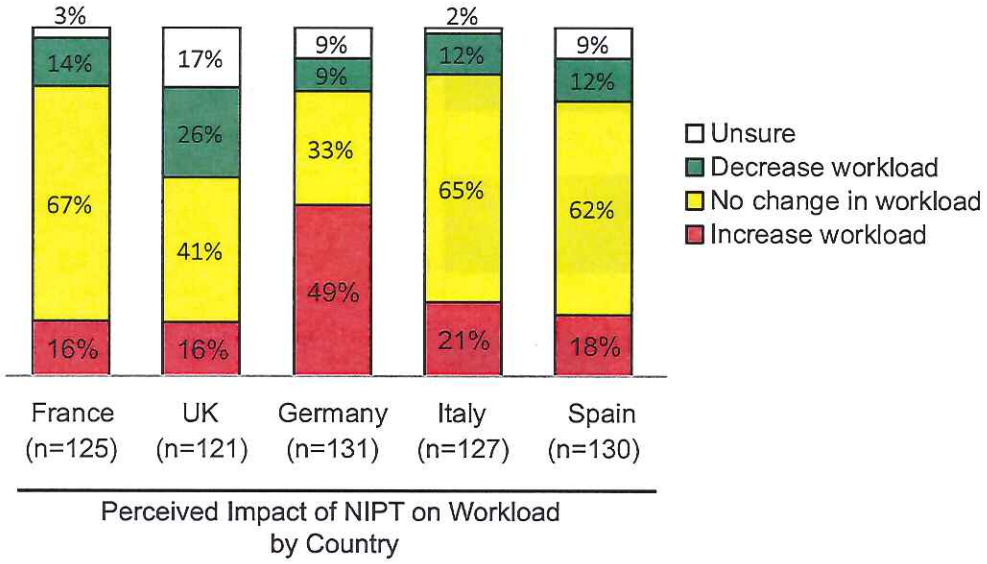
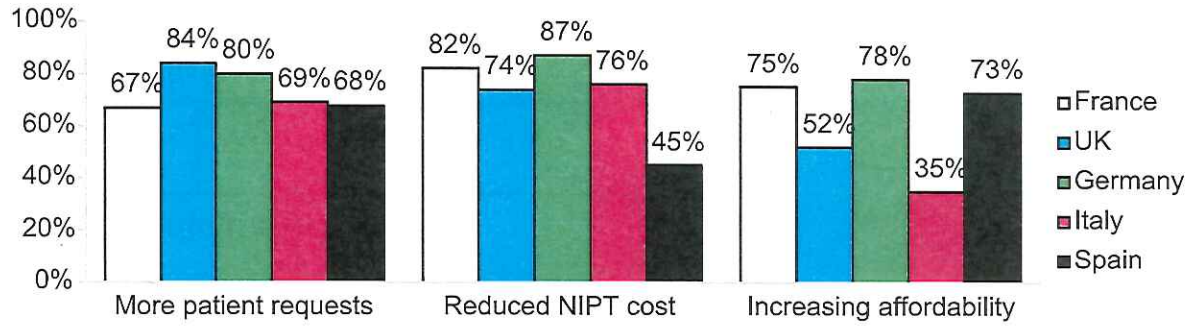




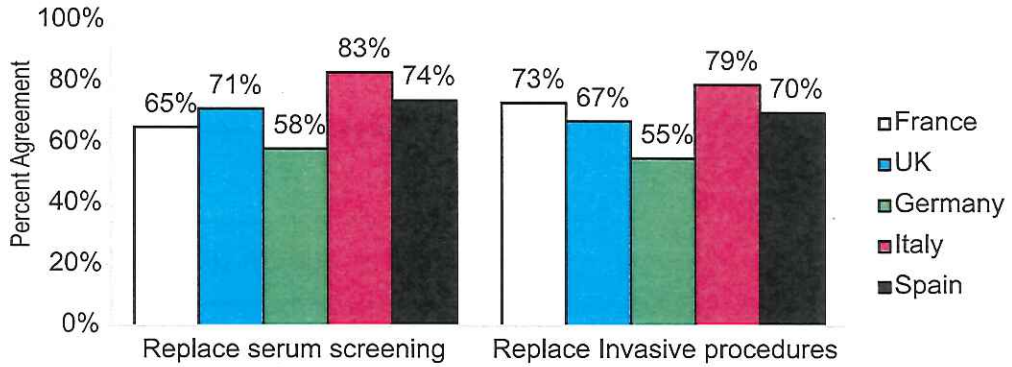
Perceived Impact of NIPT on Workload by Country

A

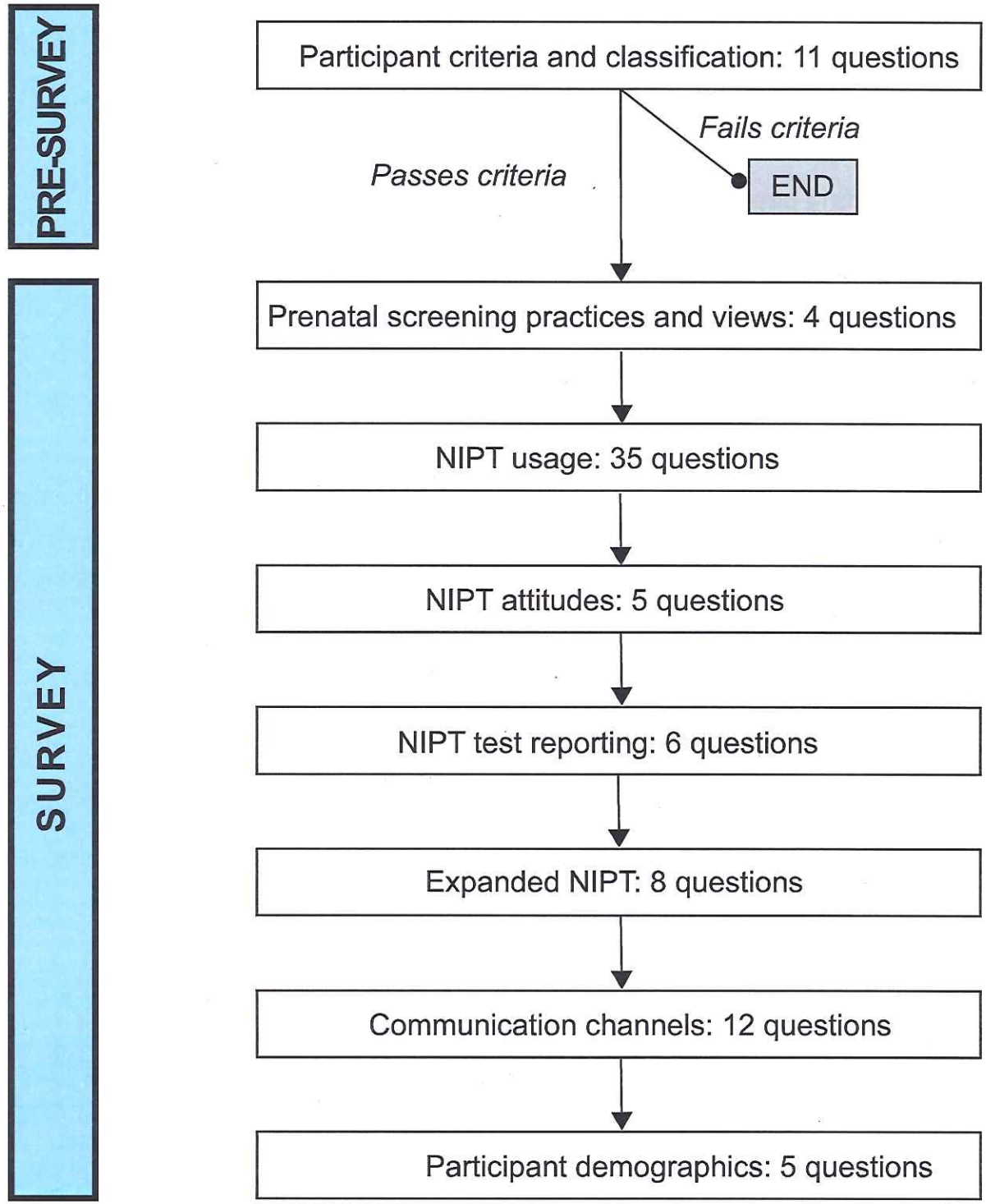


Top Reasons for Anticipated Increase in NIPT Use in the Future

B



Anticipated Future Utilization of NIPT


PRE-SURVEY
SURVEY
Participant criteria and classification: 11 questions
Fails criteria
Passes criteria
END
Prenatal screening practices and views: 4 questions
NIPT usage: 35 questions
NIPT attitudes: 5 questions
NIPT test reporting: 6 questions
Expanded NIPT: 8 questions
Communication channels: 12 questions
Participant demographics: 5 questions

Supplementary Table 1. Summary of the current state of cfDNA NIPT for each of the five surveyed countries according to local industry experts.

Country	Estimated annual births	In country testing*	Overseas testing*	Reimbursement by State	Risk categories recommended for by local professional societies and/or government
France	800.000	Yes	Yes	High-risk (End 2018)	High-risk (1/50-1/1000)
Germany	800.000	Yes	Yes	No	High-risk (1/50-1/1000) and all risk categories
Italy	450.000	Yes	Yes	No	All risk categories
UK	636.401	Yes	Yes	From October 2018	High Risk (as part of contingent screening program)
Spain	410.000	Yes	Yes	Depends on the region	Depends on the region

* In country testing indicates that blood samples drawn in the indicated European country can be sent to a laboratory within the same country for cfDNA-based NIPT. Overseas testing indicates that blood samples drawn in the indicated European country can be sent to a testing laboratory located in a different country for cfDNA-based NIPT.

Supplementary Table 2. Survey questions.
* Indicates answer order is randomized for each participant.

Section 1: General Prenatal Screening Questions				
1*	Which of the following personnel/resources does your practice or health system/integrated delivery network have? *Please select all that apply.*			
	Genetic Counselor			
	Medical Geneticist			
	Molecular Pathologist			
	Bioinformatician			
	Cytogeneticist			
	Midwife *[Option hidden for respondents identified as a Midwife by screening questions]*			
	Nurse			
	None of these			
	I don't know			
2	Of the [INSERT RESPONSE FROM SCREENER] prenatal patients that [you see/your practice sees] in an average month, what percent of these patients are considered a high a priori risk for fetal aneuploidy? By high a priori risk, we mean they have at least one of the following characteristics: • Advanced Maternal Age (35 or older) • Previous pregnancy with a chromosome abnormality			
	Free text entry of numeric value between 0 and 100.			
3	How many consultations per month do you personally have with patients seeking information or testing related to prenatal screening/diagnosis? Please enter your best estimate below.			
	Free text entry of numeric value.			
4*	Which of the following prenatal testing options does your practice offer? *One answer per row.*			
		We **do not** offer this testing	We **refer out** to another practice for this testing	We **offer** this testing to our patients
	Maternal serum screening (such as the quad screen, first trimester combined screen)	☐	☐	☐
	Non-invasive prenatal testing (NIPT). This is a newer screening test that analyzes cell-free fetal DNA circulating in maternal blood, and may also be referred to as NIPS (non-invasive prenatal screening), cfDNA (cell-free DNA) screening or cffDNA (cell-free fetal DNA) screening.	☐	☐	☐
	CVS	☐	☐	☐
	Amniocentesis	☐	☐	☐
	Ultrasound	☐	☐	☐

Section 2: NIPT Usage						
5	The "NIPT" test can go by various names. Please read the description below, and select which name you use most frequently to refer to the test described. *Please select one response.*					
	Non-invasive prenatal testing					
	Prenatal Cell-free DNA screening					
	Other, please specify:					
6	For our purposes today, to be consistent, we will refer to this testing as "Non-invasive Prenatal Testing" or NIPT. How would you describe your familiarity with Non-Invasive Prenatal Testing (NIPT). *Please select one response.*					
	Not at all familiar					
	Not very familiar					
	Somewhat familiar					
	Very familiar					
	Extremely familiar					
7	*If Question 2 answer was Physician, show question otherwise skip to Question 19.* For how many years [have you / has your practice] been utilizing Non-invasive Prenatal Testing (NIPT)? *Please select one.*					
	Less than 1 year					
	1 – 2 years					
	3+ years					
	I'm not sure / don't know					
8	To what percent of each of the following patient types [do you/does your practice] typically mention that NIPT (Non-invasive Prenatal Testing) is available as an option for genetic screening? *Please type a number between 0 and 100 for each.*					
	High risk patients (high risk for fetal aneuploidy)	*Free text entry of numerical value*				
	General / all other risk patients	*Free text entry of numerical value*				
9	To what percent of each of the following patient types [do you/does your practice] typically recommend NIPT? *Please type a number between 0 and 100 for each.*					
	High risk patients (high risk for fetal aneuploidy)	*Free text entry of numerical value*				
	General / all other risk patients	*Free text entry of numerical value*				
10	What percent of each of the following patient types specifically request NIPT (prior to being offered it by the practice)? *Please type a number between 0 and 100 for each.*					
	High risk patients (high risk for fetal aneuploidy)	*Free text entry of numerical value*				
	General / all other risk patients	*Free text entry of numerical value*				
11	Where would you place [yourself/your practice] on the scale below, relative to how you view NIPT for your prenatal patients? *Please select the point on the scale that best fits your viewpoint.*					
	5 point slider scale: 1 indicates "NIPT is one of several options for prenatal testing"; 5 indicates "NIPT is standard of care for my prenatal patients"					
12*	What impact do each of the following patient characteristics have on [your/your practice's] likelihood to recommend NIPT to a patient? *Please select one response for each row.*					
		Much less likely	Somewhat less likely	No impact	Somewhat more likely	Much more likely
	Advanced maternal age (≥35 years old at delivery)					
	Abnormal ultrasound findings (such as heart defect, cystic hygroma, etc)					
	Soft marker(s) on ultrasound (such as echogenic					

	intracardiac focus, etc.)					
	Abnormal maternal serum screening					
	Previous pregnancy with a chromosome abnormality					
	Family history of chromosome abnormalities					
	Family history of hereditary and/or rare disease(s)					
	Twin pregnancy					
	Healthy patients with no indications					
	Obese patients					
	Exposure to environmental factors (e.g. radiation, chemicals)					
	History of alcohol abuse					

13	*If Question 12 answer for "Abnormal maternal serum screening" was "somewhat more likely" or "much more likely", show question otherwise skip to next question.* You indicated that you are more likely to offer NIPT to a patient who has an abnormal serum screen. What should the cut-off risk be for offering NIPT? *Please select one.*	
	1:150	
	1:200	
	1:500	
	1:750	
	1:1,000	
	1:1,500	
	1:2,500	
	1:5,000	
	Other (please specify):	
14	What percent of [your/your practice's] patients actually receive the following during their pregnancy? *Please type a number between 0 and 100 for each. Your responses DO NOT need to add up to 100%.*	
	Maternal serum screening	*Free text entry of numerical value*
	NIPT	*Free text entry of numerical value*
	CVS	*Free text entry of numerical value*
	Amniocentesis	*Free text entry of numerical value*
	Ultrasound	*Free text entry of numerical value*

15	*If Question 14 answer for "NIPT" was >0, show question otherwise skip to Question 18.* When do you typically first talk about NIPT with patients? *Please select one response per column*		
		High Risk Patients	General / Average Risk Patients
	At the first prenatal visit (before any testing)		
	After received results of conventional screening tests (such as combined first trimester screening)		
	Only if the patient asks about it		

16	For the patients that receive NIPT during their pregnancy, what percent fall into each of the scenarios below? *Please type a number between 0 and 100 for each. Your responses should add up to 100%.*	
	NIPT done 1st line (i.e. before or at the same time as any other prenatal testing)	*Free text entry of numerical value*
	NIPT done as a reflex test after a positive result on another screening test	*Free text entry of numerical value*
17	*If Question 16 answer for NIPT as a reflex test was >0, show question otherwise skip to next*	

	question. For those patients who receive NIPT second line (following another test), what testing did they have done first? *Please type a number between 0 and 100 for each. Your responses can add up to greater than 100%, if your patients had multiple tests done prior to NIPT.*	
	Ultrasound	*Free text entry of numerical value*
	Maternal serum screen	*Free text entry of numerical value*

18	What conditions are you currently using NIPT for? *Please select all that apply.*						
	Trisomy 18, 13, and 21						
	Microdeletions						
	Sub chromosomal abnormalities						
	Other autosomal trisomies						
	Fetal sex						
	Sex chromosome aneuploidies						
19	How often are you, personally, involved in each of the following discussions around NIPT? *Please select one response per row.*						
		Never	Rarely	Occasionally	Usually	Always	
	Offer/Recommend NIPT to patients						
	Educate patients about NIPT (including benefits and limitations)						
	Discuss pricing of NIPT with patients						
	Share positive (abnormal) results from NIPT with patients						
	Share negative (normal) results from NIPT with patients						
	Counsel patients if they receive positive results from their NIPT						
20	Who is primarily involved in each of these discussions. *Please select one response per row.*						
		General OB/GYN	Nurse	MFM Specialist	Genetic Counselor	Midwife	Other Office Staff	Not discussed
	Offer/Recommend NIPT to patients							
	Educate patients about NIPT (including benefits and limitations)							
	Discuss pricing of NIPT with patients							
21	Which of the following are important to discuss in pre-test counselling for NIPT? *Please select all that apply*						
	Possibility of a false positive result						
	Possibility of a false negative result						
	Possibility of a test failure						
	The concept of "Positive Predictive Value"						
	Other, please specify:						
	None of the above						
22	Overall, how beneficial do you think NIPT is for [your/your practice's] patients? *Please select one response.*						
	Not at all beneficial						

	Not very beneficial
	Somewhat beneficial
	Very beneficial
	Extremely beneficial
23	Why do you think NIPT is "[insert response from Question 22]" for [your/your practice's] prenatal patients? *Please be specific.*
	Open-ended free text entry
24	How do you anticipate [your/your practice's] use of NIPT changing in the next 2 years? I expect that it will… *Please select one response.*
	Decrease significantly
	Decrease slightly
	Stay the same
	Increase slightly
	Increase significantly
	Don't know
25	*If Question 24 answer was not "Don't know", show question otherwise skip to Question 31.* You said you anticipate NIPT use will [insert response from Question 24] in the next 2 years. How do you think use will change for each of these specific patient types in the next 2 years? *Please select one response per row.*

	Decrease significantly	Decrease slightly	Stay the same	Increase slightly	Increase significantly	Don't know
High risk patients (high risk for fetal aneuploidy)						
General / all other risk patients						

26	*If Question 24 answer was "Increase slightly" or "Increase significantly", show question otherwise skip to next question.* Why do you anticipate [your/your practice's] use of NIPT to [insert response from Question 24] over the next 2 years? *Please select all that apply*
	Improvements in the technology
	Increased physician comfort level
	Increased staff comfort level
	Increased patient comfort level
	More patients requesting NIPT
	Better data supporting use of NIPT
	Positive experiences in the practice using NIPT
	Better accuracy of results compared to other screening methods
	Reduced cost of offering NIPT
	More educated on the benefits of NIPT
	Changes in the society guidelines on who is an appropriate patient for NIPT
	It is becoming more affordable for my patients
	NIPT is being used to screen for more conditions
	Increased payer reimbursement for average risk pregnancies
	Increased insurance coverage in general
	Other, please specify:
27	*If Question 24 answer was "Decrease slightly" or "Decrease significantly", show question otherwise skip to Question 31.* Why do you anticipate [your/your practice's] use of NIPT to [insert response from Question 24]

	over the next 2 years? *Please select all that apply*
	Bad past experiences using NIPT
	Fewer patients requesting
	It is not cost effective for us to offer NIPT
	It is too difficult logistically for us to offer NIPT
	Accuracy of NIPT has not been as good as we hoped
	It is too expensive for my patients
	[I/We] have concerns about the results from NIPT
	NIPT is too limited in what it screens for
	It is too expensive for patients
	We don't have enough staff to educate / counsel patients on NIPT
	We experience too many inconclusive results
	Referring NIPT to a different care provider
	Fewer referrals from other providers to do NIPT (i.e. they are handling it themselves)
	Other, please specify:
28	*If Question 27 answer was "Bad experiences using NIPT", show question otherwise skip to next question.* Please explain why you had a bad past experience using NIPT. *Please be specific.*
	Open-ended free text entry
29	*If Question 27 answer was "We experience too many inclusive results", show question otherwise skip to Question 31.* For NIPT, what percent of the time do you experience inconclusive results. *Please be specific.*
	Open-ended free text entry
30	*If Question 4 answer for NIPT was "We do not offer this testing" or "We refer out to another practice for this testing", show question otherwise skip to Question 32.* How likely do you think your practice is to offer Non-invasive Prenatal Testing (NIPT) in the next 2 years? *Please select one response only.*
	Not at all likely
	Not very likely
	Somewhat likely
	Very likely
	Extremely likely
31	What are the primary reasons [you do/your practice does] not currently offer NIPT? *Please be specific.*
	Open-ended free text entry
32*	How strongly do you agree or disagree that the following are benefits of NIPT? *Please select one response for each row.*

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
It is less costly to patient than other testing options					
It is more accurate/lower chance of a false positive than maternal serum screening					
It is easier for the practice to conduct than other types of testing					
It is easier for the patient than other types of testing					

	Results are easy to interpret / understand					
	Results come back faster than maternal serum screening					
	Can be conducted earlier in the pregnancy than other testing options					
	Prevents some women from having invasive prenatal diagnostic procedures					
	Lower risk than invasive diagnostic procedures (amniocentesis/CVS)					

33	What do you think is the biggest benefit of NIPT? *Please select one response.*
	[Insert responses for which "Agree" or "Strongly Agree" was indicated in Question 32]
	Other, please specify:
*34	*If Question 4 answer for NIPT was "We do not offer this testing" or "We refer out to another practice for this testing" show question otherwise skip to Question 36.* How strongly do you agree or disagree that the following are barriers to [Insert "offering NIPT" if "*We do not offer this testing*" was selected in Question 4; insert "recommending NIPT to patients" if "*We refer out to another practice for this testing*" was selected in Question 4]? *Please select one response for each row.*

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
Cost to the patient					
Access to blood draw					
Concern over inaccurate test results					
Availability of appropriate health care providers to educate patients and/or discuss results with patients					
Not enough education on NIPT available for healthcare providers					
Difficulty interpreting test results					
Lack of reimbursement for NIPT					
Practice staff not knowledgeable on NIPT					
NIPT is too limited in terms of what it screens for					
Offering NIPT requires too much staff time in terms of pre-test and post-test counseling					
Lack of data available in certain patient populations					
Concern over false positives					
Concern over false negatives					
Current guidelines (such as those provided by ISPD)					
NIPT is not as accurate for more rare disorders					
Turnaround time is too long compared to maternal serum screening					
Quality of NIPT lab services (e.g. customer service)					
Access to NIPT lab services					

35	*If at least one row was rated as "Agree" or "Strongly Agree" in Question 34, show question otherwise skip to next question.* Which of these would you consider to be the biggest barrier to [Insert "offering NIPT" if "*We do not offer this testing*" was selected in Question 4; insert "recommending NIPT to more patients" if "*We refer out to another practice for this testing*" was selected in Question 4]? *Please select*

	one response.
	[Insert responses for which "Agree" or "Strongly Agree" was indicated in Question 34]
	Other, please specify:
36	What impact do you believe NIPT [would have / has had] on your workload as a healthcare provider? *Please select one response only.*
	Increase workload
	Decrease workload
	No change in workload
	Unsure
37	Does your country/region provide reimbursement for NIPT? *Please select one*
	Yes
	Partial
	No
	I don't know
38	If NIPT is to be reimbursed in your country/region, in your opinion, who should be reimbursed? *Please select one*
	All pregnant women
	All pregnant women who had conventional screening for aneuploidy regardless of result (first trimester combined ultrasound and/or serum, markers)
	Only women at high risk for aneuploidy based on conventional screening
	No one should receive reimbursement.
39	*If answer to Question 37 was "Partial" or "No" AND respondent classification in screening questions (Supplemental Table 1) was "Physician" or "Midwife", show question otherwise skip to next question.* How does reimbursement policy in your country / region influence your decision whether to offer a screening test to your patients or not? *Please select one*
	I only offer a screening test to patients who, in my opinion, can afford to pay for it themselves
	I would not offer a screening test unless it is reimbursed by the government/National Health Service or a private insurance
	I inform patients on the availability of a screening test even if it is not reimbursed and let them decide.

Section 3: NIPT Attitudes

40* How influential are guidelines from each of the following in terms of your practice? *Please select one response for each row.*

	Not at all influential	Not very influential	Somewhat influential	Very influential	Extremely influential
ACOG (The American Congress of Obstetricians and Gynecologists)					
ACMG (American College of Medical Genetics and Genomics)					
SMFM (Society for Maternal-Fetal Medicine)					
ISPD (International Society for Prenatal Diagnosis)					
[Insert for Germany] German Society of Ultrasound in Medicine					
[Insert for Germany] Fetal Medicine Foundation Germany					
[Insert for Italy] Ministry of Health – Higher Health Council of Italy					
ESHG (European Society of Human Genetics)					
ASHG (American Society of Human Genetics)					
[Insert for the UK] RCOG (Royal College of Obstetricians and Gynaecologists)					

41 If an NIPT brand received CE-IVD approval, what impact would that have on each of the following. *Please select one response per row.*

	Not at all impactful	Not very impactful	Somewhat impactful	Very impactful	Extremely impactful	Don't Know
Likelihood to recommend NIPT, in general, to patients						
Likelihood to recommend that specific NIPT brand over other brands that do not have CE-IVD approval						

42 You indicated that an NIPT brand receiving CE-IVD approval would be [Insert response from Question 41 for Row 1] on your likelihood to recommend NIPT, in general. Why is that?

Open-ended free text entry

43 You indicated that an NIPT brand receiving CE-IVD approval would be [Insert response from Question 41 for Row 2] on your likelihood to recommend that specific NIPT brand over other brands that do not have CE-IVD approval. Why is that?

Open-ended free text entry

*44 How much do you agree or disagree with the following statements regarding NIPT, specifically. *Please select one response for each item*

	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

	NIPT will replace invasive procedures in the future	1	2	3	4	5
	More studies are needed to establish the clinical validity and utility of NIPT					
	NIPT will replace serum screening in the future					
	I believe NIPT is beneficial for all of my patients, regardless of their risk level					
	It's very important for me to know my patient's specific beliefs before offering or recommending specific prenatal testing, including NIPT					
	I always listen to my patients' requests for specific prenatal testing, including NIPT					

Section 5: NIPT reporting and NIPT selection	
45	How do patients receive their NIPT results? *Please select all that apply*
	Over the phone
	Online through the patient portal provided by the testing company
	Online through our practice's own patient portal
	Through email
	In person
46	What specifically is being communicated/provided to the patient from NIPT? *Please select all that apply*
	They are given the whole test report
	They are given a summary of the test results
	They are told only the relevant information from the test results
	They do not receive any information from the test results, only what the recommendation is for next steps.
	Other, please specify
	I do not know [MUTUALLY EXCLUSIVE]
47	What should be the follow-up for an abnormal NIPT test result? *Please select all that apply.*
	Chorionic villus sampling (CVS)
	Amniocentesis
	Ultrasound examination
	Termination of pregnancy after confirmation by invasive testing
48	What do you recommend to a patient following an NIPT test failure? *Please select all that apply.*
	Redraw a blood sample and perform a second NIPT
	Invasive procedure
	Ultrasound
	Genetic counselling
	Nothing
49	To what extent do you agree or disagree with this statement "It is very challenging to consult with patients after a failed NIPT test"? *Please select one*
	Strongly disagree
	Somewhat disagree
	Neither agree nor disagree
	Somewhat agree
	Strongly agree

50	Should the laboratory providing the NIPT result be informed of clinical outcomes? *Please select one.*
	Yes, always
	Yes, but only in abnormal pregnancy outcomes
	Yes, but only if discordant (false positive/false negative)
	Yes, but only upon request from the lab
	No, I prefer not to share follow-up information from the lab
	No, because of patient privacy
	No, it is time consuming
	No, it is not important

Section 6: Expanded NIPT	
51	*If identified as a physician in screening questions, show question otherwise skip to Question 57.* Which of these expanded panels for NIPT [have you/has your practice] ever used? *Please select all that apply.*
	Testing for microdeletions
	The ability to test and get information on the aneuploidy status of all chromosomes
	A Copy Number Variant (CNV) screen for sub chromosomal abnormalities across the genome
	None of the above [MUTUALLY EXCLUSIVE]
52*	*If respondent indicated experience with expanded panels in Question 51, show question otherwise skip to next question.* What are the reasons [you have/your practice has] pursued expanded panels in NIPT (including microdeletions, all autosomes and genome-wide subchromosomal abnormalities)? *Please select all that apply.*
	There was an abnormal ultrasound
	It was used as a first line screen
	Patient anxiety
	Patient request
	Did not realize it was part of the test (received the results, though hadn't specified)
	Received additional information for the same/similar cost
	History of pregnancy loss
	Family history of condition
	Other, please specify:
53*	The following are either currently being offered with NIPT or will be in the near future. Please indicate your interest level in each being added to the scope of NIPT. *Please select one response for each item.*

	Not at all interested	Not very interested	Somewhat interested	Very interested	Extremely interested	Don't Know
Sex chromosomes (X&Y)						
Microdeletion syndromes (22q11.2/DiGeorge, Prader-Willi / Angelman, Cri du Chat, Wolf-Hirschhorn, 1p36)						
Select trisomies (9, 16, 22)						
All autosomal chromosomal copy number changes (chromosomes 1-22)						

	All chromosomal copy number changes and sub-chromosomal deletions/duplications at a resolution of ≥7 Mb (resolution of a standard karyotype)						
54*	*If respondent responded that they were at least "somewhat interested" in Question 53, show question otherwise skip to next question.* How would you use these expanded panels for NIPT? *Please select all that apply.*						
	After an abnormal ultrasound						
	As a first line screen						
	History of pregnancy loss						
	Patient request						
	Family history of condition						
	Patient anxiety						
	None of these						
55	*If respondent responded that they were at least "somewhat interested" in expanded panels for all autosomes or large copy cumber changes in Question 53, show question otherwise skip to next question.* What concerns, if any, would you have around genetic counseling if NIPT included all chromosomal copy number changes?						
	Open-ended free text entry						
56*	Who has (or would have) the most influence in deciding to use an expanded panel (i.e. testing for microdeletions or testing chromosomes outside of 21,18, and 13)? *Please select one.*						
	OB/GYN						
	Nurse						
	MFM Specialist						
	Patient						
	Genetic Counselor						
	Midwife						
	[Insert answers from Question 1]						
	I don't know						
	Other, specify						
57	To what extent would you find an "a la carte NIPT," where every option can be selected individually, valuable or not valuable? *For example, Chromosome 21 only, Chromosome 18 and 22q11 only, 3 selected micro-deletions only, Chromosome 16 only, etc. Please select one.*						
	Definitely would NOT be valuable						
	Probably would NOT valuable						
	Might or might not be valuable						
	Probably would be valuable						
	Definitely would be valuable						
58	What makes you say an "a la carte NIPT" [Insert response from Question 57]? *Please be specific.*						
	Open-ended free text entry						

Section 7: Communication Channels						
59*	How much do you agree or disagree with the following statements about finding information about NIPT? *Please select one response for each item*					
		Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
	I am able to find all of the information I am interested in around NIPT					
	It is easy for me to stay up to date on the latest advancements in NIPT					
	It is important for me to stay up to date on the latest advancements in NIPT					
60*	Through which of these channels have you obtained information about NIPT in the past? *Please select all that apply.*					
	Social media (LinkedIn, Twitter, Facebook, etc)					
	Professional conferences, Congresses, Peer to Peer programs					
	Continuing medical information (CME)					
	3rd party websites (e.g. WebMD)					
	Reference lab websites					
	NIPT laboratory websites					
	Professional Societies					
	Sales representatives					
	Blogs					
	Google or other search engine					
	Wikipedia					
	Podcasts					
	Scientific/medical journals- print					
	Scientific/medical journals- online					
	Online discussion forums					
	Online videos					
	Reviews in popular scientific magazines (Scientific American, Time, etc)					
	Other websites, please specify:					
	Other, please specify:					
	None. I have not obtained any information on NIPT.					
61	*If "3rd party websites", "Reference lab websites", or "NIPT laboratory websites" was selected in Question 60, show question otherwise skip to next question.* What websites, specifically, do you go to for information about NIPT? *Please be specific.*					
	Open-ended free text entry					
62	*If "Scientific/medical journals (print or online)", or "Reviews in popular scientific magazines" was selected in Question 60, show question otherwise skip to next question.* What scientific journals/magazines do you go to for information about NIPT? *Please be specific.*					
	Open-ended free text entry					
63	*If "Podcasts" was selected in Question 60, show question otherwise skip to next question.* What podcasts do you listen to for information about NIPT? *Please be specific.*					
	Open-ended free text entry					
64*	*If "Social media" was selected in Question 60, show question otherwise skip to next question.*					

	Through which specific social media sources have you obtained information about NIPT? *Please select all that apply.*
	LinkedIn peer profiles
	LinkedIn Groups
	Twitter
	Facebook
	YouTube
	Google+
	Forums for mothers and babies
	Other, please specify:
65*	*If "*Professional Societies*" was selected in Question 60, show question otherwise skip to next question.* In which of these ways have you received information from professional societies about NIPT? *Please select all that apply.*
	Society website
	Society congresses
	Society webinars
	Society guidelines
	Other, please specify:
66*	*If multiple items were selected in Question 60, show question otherwise skip to next question.* Which source of information did you find to be most useful for information regarding NIPT? *Please select one.*
	[Insert all answers selected in Question 60]
67*	How interested would you be in information about NIPT if it came from each of the following sources? *Please select one response for each row.*

	Not at all interested	Not very interested	Somewhat interested	Very interested	Extremely interested
A specific NIPT company					
Medical Society					

68*	How helpful would you find each of the following resources for your own learning about NIPT? *Please select one response for each row.*

	Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
Brochures or informational package					
Webinars (Live or Recorded)					
Online videos					
Blogs					
Podcasts					
Commercial website					
3rd party website					
National website (such as NHS, etc.)					
Social Media					
In-person meeting or course					

	A folder of all recent publications about NIPT
69*	Which educational materials on NIPT do you currently utilize for patients? *Please select all that apply.*
	Brochures (provided by the specific NIPT brand)
	Brochures / leaflets (created by you or someone in your practice)
	Online videos
	Commercial website
	3rd party website
	National website (such as NHS in the UK, etc.)
	Online Genetic Counselling Service; Please specify name of service:
	App (provided commercially, from an NIPT brand)
	App (created by your practice)
	National information folder put together by your health care ministry (i.e. NHS in the UK, etc.)
	Other, please specify:
	None. We do not utilize any educational materials on NIPT.

70* How helpful do you find each of the following type of resources for patients to learn about NIPT? *Please select one response for each row.*

	Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
Brochures					
Online video					
Website					

Section 8: Demographics	
71	In which of the following locations/regions/states do you practice? *Please select all that apply.*
For respondents from the UK	Scotland
	England
	South East
	London
	North West
	East of England
	West Midlands
	South West
	Yorkshire and the Humber
	East Midlands
	North East
	Wales
	Northern Ireland
For respondents from France	Grand-Est
	Nouvelle-Aquitaine
	Auvergne-Rhône-Alpes
	Bourgogne-Franche-Comté
	Occitanie
	Hauts-de-France
	Normandie

	Bretagne
	Corse
	Centre
	Île-de-France
	Pays de la Loire
	Provence-Alpes-Côte d'Azur
For respondents from Germany	Baden-Württemberg
	Freistaat Bayern
	Berlin
	Brandenburg
	Freie Hansestadt Bremen
	Freie und Hansestadt Hamburg
	Hessen
	Niedersachsen
	Mecklenburg-Vorpommern
	Nordrhein-Westfalen
	Rheinland-Pfalz
	Saarland
	Freistaat Sachsen
	Sachsen-Anhalt
	Schleswig-Holstein
	Freistaat Thüringen
For respondents from Spain	Andalucia
	Aragon
	Asturias
	Balearic Islands
	Basque Country
	Canary Islands
	Cantabria
	Castilla La Mancha
	Castilla y Léon
	Catalonia
	Extremadura
	Galicia
	La Rioja
	Madrid
	Murcia
	Navarra
	Valencia
For respondents from Italy	Abruzzo
	Valle d'Aosta
	Basilicata
	Calabria
	Campania
	Emilia-Romagna
	Friuli-Venezia Giulia
	Lazio
	Liguria
	Lombardy (Lombardia)

	Marche
	Molise
	Piemonte
	Puglia
	Sardegna
	Sicilia
	Toscana
	Trentino-Alto Adige
	Umbria
	Veneto
72	Please select your gender.
	Male
	Female
73	How long have you been working for your current practice?
	Free text entry of numerical value
74	Which of the following best describes your practice setting? *Please select one.*
	University Hospital
	Regional Hospital
	Midwife Practice
	General Practitioner
	Centre for Prenatal Ultrasound
	Genetic institute
	Other, please specify:
75	Which of the following would best describe your practice location? If you work at multiple locations, please select all that apply. *Click on all that apply.*
	Urban
	Suburban
	Rural

Supplementary Table 3. Screening and role classification questions.

#	Question and Answer Options	Screening Result
0	Before we begin the survey, we would like to ask you to please read and agree to the following terms and conditions: I understand that the information collected by The Link Group and its client(s) will be used for research purposes only. All information will be analyzed with responses from others and no personally identifying information will be reported. I also agree to carefully read and answer each question. I understand that if it is shown I sped through and/or did not carefully read the questions, I may lose my opportunity to complete the survey.	
	I understand and give my consent to these uses and conditions	
	I do NOT give my consent	Disqualified
1	Do you or any members of your immediate family work for any of the following types of companies? *Please select all that apply*	
	Market Research Company	Disqualified
	Public Relations Firm	Disqualified
	Advertising Agency	Disqualified
	Pharmaceutical Company	Disqualified
	Medical Device Company	Disqualified
	None of the Above	Continue to Question 2
2	Which of the following best describes your role? *Please select one*	
	Nurse Practitioner (NP)	Disqualified
	Physician Assistant (PA)	Disqualified
	Physician	Continue to Question 3
	Medical Assistant (MA)	Disqualified
	Registered Nurse (RN) / Licensed Practical Nurse (LPN)	Continue to Question 6
	Genetic Counselor	Disqualified
	Office Manager / Practice Manager / Administrator / Receptionist	Disqualified
	Midwife	Continue to Question 5
	Other	Disqualified
3	*If Question 2 answer was Physician.* What is your primary medical specialty? By primary, we mean that it is your focus of practice. *Please select one*	
	Family Medicine/ Family Practice	Disqualified
	General Practice	Disqualified
	Internal Medicine	Disqualified
	Maternal-Fetal Medicine (MFM)	Classify as MFM
	Obstetrics and Gynecology	Continue to Question 4
	Pediatrics	Disqualified
	Urology	Disqualified
	Other (Please Specify):	Disqualified
4	*If Question 3 answer was Obstetrics and Gynecology.* Within Obstetrics and Gynecology, are you board certified or board eligible in any of the following sub specialties?	
	Maternal-fetal medicine/perinatology	Classify as MFM
	Reproductive endocrinology and infertility	Classify as General OB/GYN
	Gynecological oncology	Disqualified
	Female pelvic medicine and reconstructive surgery	Disqualified
	Other, please specify:	Classify as General OB/GYN
	None of the above	Classify as General OB/GYN

5	*If Question 2 answer was Midwife.* Do you currently have the authority to write prescriptions and order tests for patients?	
	Yes	
	No	Disqualified
6	*If Question 2 answer was Registered Nurse (RN) / Licensed Practical Nurse (LPN)* In which of the following specialties do you work on a regular basis? *Please select a response. If you work in multiple specialties regularly, please select all that apply.*	
	Primary Care / Internal Medicine / General Practice / Family Practice	
	Cardiology	
	Orthopedics	
	Obstetrics and/or Gynecology	Disqualify if NOT selected
	Rheumatology	
	Other (please specify:)	
7	*If Question 2 answer was Registered Nurse (RN) / Licensed Practical Nurse (LPN) and not disqualified in Question 6.* What percent of your time is devoted to Obstetrics and/or Gynecology?	
	Free text entry	Disqualify if <50%
8	*If Question 2 answer was Physician OR Registered Nurse (RN) / Licensed Practical Nurse (LPN) AND not classified as MFM in Question 3 or 4* Which of the following best describes the focus of your practice? *Please select one response only*	
	Gynecology only	Disqualified
	Obstetrics only	
	Both Gynecology and Obstetrics	
9	What percent of your time do you spend in each of the following settings? *Enter a percent for each. If you do not spend time in a particular capacity, enter "0" for that row. Your responses must sum to 100%.*	
	Clinical practice/Direct Patient Care	Disqualify if <60%
	Research and/or teaching	
	Other professional duties (e.g. hospital/ practice administration not connected to direct patient care)	
10	How many years have you been in [practice/your current role]? *Round to the nearest year.*	
	Free text entry	Disqualify if <2 OR >35 years
11	How many prenatal patients [do you/does your practice] see in an average month? *Please enter your best estimate below.*	
	Free text entry	Disqualify if <10 patients