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Inclusion of sex chromosomes in noninvasive prenatal testing in Asia, Australia, Europe and the USA: A survey study

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Abstract

Objective: To examine the extent to which sex chromosomes are included in current noninvasive prenatal testing (NIPT) and the reporting practices with respect to fetal chromosomal sex and sex chromosome aberrations (SCAs), in addition to an update on the general implementation of NIPT.

Method: A questionnaire addressing the research objectives was distributed by email to fetal medicine and clinical genetics experts in Asia, Australia, Europe and the USA.

Results: Guidelines on NIPT are available in the majority of the included countries. Not all existing guidelines address reporting of fetal chromosomal sex and SCAs. In most settings, NIPT frequently includes sex chromosomes (five Australian states, China, Hong Kong, Israel, Singapore, Thailand, USA and 23 of 31 European countries). This occurs most often by default or when parents wish to know fetal sex. In most settings, a potential SCA is reported by stating the risk hereof as "low" or "high" and/or by naming the SCA. Less than 50% of all pregnant women receive NIPT according to respondents from three Australian states, China, Israel, Singapore, Thailand and 24 of 31 European countries. However, this percentage, the genomic coverage of NIPT and its application as primary or secondary screening vary by setting.

Conclusion: In most of the studied countries/states, NIPT commonly includes sex chromosomes. The reporting practices concerning fetal chromosomal sex and SCAs are diverse and most commonly not addressed by guidelines. In general, NIPT is variably implemented across countries/states.

Key points

What is already known about this topic?

- Noninvasive prenatal testing (NIPT) has been widely adopted in many countries.
- NIPT allows screening for sex chromosomes including sex chromosome aberrations (SCAs); however, positive predictive values are lower than for trisomies 13, 18 and 21.

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What does this study add?

- In 30 out of 38 countries surveyed, NIPT commonly includes sex chromosomes, either automatically or based on a parental wish to know fetal sex.
- Reporting practices concerning fetal chromosomal sex and SCAs based on NIPT are diverse and often not founded in guidelines.
- In most countries studied, less than 50% of pregnant women receive NIPT; however, this proportion varies substantially between settings.

1 | INTRODUCTION

Noninvasive prenatal testing (NIPT) is rapidly evolving as a prenatal genetic screening strategy. Initially established as a highly sensitive screening tool for trisomies 13, 18 and 21, NIPT has been developed to include a much broader range of genetic conditions. NIPT also allows analysis of the sex chromosomes[1] and thereby information on fetal chromosomal sex and sex chromosome aberrations (SCAs).[2] However, the positive predictive values of screening for SCAs using NIPT are lower than for the common trisomies. A recent study found a positive predictive value of 29.0% (95% confidence interval [CI] 18.2–42.9) for NIPT showing monosomy X and 57.5% (95% CI 40.9–73.0) for NIPT showing 47, XXY.[3] Yet, interpreting these positive predictive values is not straight forward because they vary by the sample used for confirmation (chorionic villus sampling, amniocentesis, or blood from newborn)[3] and depend on the population frequency which for SCAs may be unknown. In addition, the variable and potentially mild phenotype of SCAs has been raised as an important issue in discussions about the clinical utility of screening for SCAs using NIPT.[1,4–6] Nevertheless, screening by NIPT leading to early diagnosis may enable greater parental preparedness and promote timely interventions to improve outcomes. For example, an early diagnosis of Turner syndrome allows timely screening for cardiovascular disease and early start of growth hormone therapy in line with recommendations.[7,8] In a recent survey, parents of children with SCAs expressed a positive view on using NIPT for these conditions.[9]

In addition to detecting SCAs, including sex chromosomes in NIPT may provide information on fetal chromosomal sex with high accuracy in early gestation. A systematic review reported the sensitivity and specificity of NIPT for fetal chromosomal sex in singleton pregnancies to be 0.989 (95% CI 0.980–0.994) and 0.996 (95% CI 0.989–0.998), respectively.[10] In recent studies, pregnant women and partners have expressed an interest in applying NIPT to determine the sex of the fetus[11,12]; yet, such knowledge may have potential ethical implications.[11]

Taken together, these perspectives on prenatal screening for fetal SCA and fetal chromosomal sex using NIPT reflect challenges faced in clinical practice. The perspectives and clinical challenges further points to the relevance of investigating the real-world implementation of this new technology.

We have previously investigated the use of NIPT in Australia, Europe and the USA.[13] Although we reported variability within and between countries in NIPT implementation, two general strategies were identified in countries having NIPT as a national, prenatal offer: (1) using NIPT for all pregnant women as a primary screening tool or, more commonly, (2) using NIPT for those pregnant women who were identified as at-risk on first-trimester combined screening or by age. We also reported that as of 2019, the extent to which NIPT included testing for SCAs was variable between countries and, in Australia and the USA, between states. For example, out of 30 European countries, NIPT included fetal SCA screening in addition to the common trisomies in 13 countries (in four of these as an option). In contrast, in seven countries, NIPT included the common trisomies only.

However, as NIPT continues to evolve, this picture may change. In the course of implementing prenatal screening and diagnostic technologies, experiences and practices from other settings may be of value for the international community of clinicians and researchers. This is particularly the case when those technologies pose clinical challenges such as NIPT screening for fetal SCA and fetal chromosomal sex. Therefore, the aim of this international survey study was to describe (1) the inclusion of sex chromosomes in the current typical use of NIPT as well as the reporting practices concerning fetal chromosomal sex and SCAs and (2) the general use of NIPT in Australia, the USA, and countries in Europe and Asia.

2 | METHODS

We developed a questionnaire addressing the inclusion of sex chromosomes in the typical use of NIPT and the reporting practices with respect to fetal chromosomal sex and SCAs. We aimed to distinguish between the analysis performed (that is, if testing included sex chromosomes) and what would or would not be reported (i.e., potential SCAs and/or fetal chromosomal sex) based on such an analysis. Therefore, to address the analysis performed, questions used the phrases "NIPT most commonly covers/includes […] sex chromosomes" and "NIPT includes testing for sex chromosomes", while we used the phrase "If NIPT is indicative of sex chromosomal aberrations (SCA) how is this reported?" to address reporting. The questionnaire was an add-on to our previous study[13] and, as such, also contained questions regarding the general use of NIPT (complete questionnaire in Supporting Information S1). All questions were presented as multiple choice with the option of adding open-end comments.

The present study sought to update our prior findings[13] and relied on our scientific network. In addition, we intended to include selected countries in Asia based on population size and perceived

international interest in their use of NIPT. Hence, the questionnaire was distributed by email to experts in fetal medicine and/or clinical genetics from the *NIPT-map Study Group* of our previous publication[13] and their professional networks, as well as members of the International Faculty List of the International Society of Ultrasound in Obstetrics and Gynecology. Experts in Australia, China, Hong Kong, India, Israel, Japan, Singapore, Thailand, the USA and 42 European countries were invited during May–July 2022 to complete the questionnaire. One expert was invited to answer the survey for each of these 51 countries except for Australia, where one expert was invited for each state. In line with our prior work,[13] we sought to obtain data from individual states in Australia and the USA where the organization of health care provision may vary between states. Responders were contacted by follow-up email for clarification of specific questions when needed. When no national data existed (such as the number of pregnant women receiving NIPT), an educated guess by contributors was accepted.

Data were compiled in a spreadsheet, and MapChart (https://www.mapchart.net/) was used for graphical presentation of results. No results from Asia are presented graphically due to the limited number of countries included from this continent. As such, only selected findings are presented in figures, while all results are provided in tables and Supporting Information S1.

Survey studies do not require ethical approval according to Danish law; thus, this was not obtained.

3 | RESULTS

We received survey responses from 38 out of 51 countries (China, Hong Kong, Israel, Singapore, Thailand, the USA (covering all states), 31 European countries and Australia). From Australia, responses are from Queensland, South Australia, Tasmania, Victoria and Western Australia.

3.1 | NIPT including sex chromosomes

Current practices with respect to inclusion of sex chromosomes in NIPT may be shaped by national guidelines. Of the 38 countries surveyed, 22 have national guidelines on NIPT. However, not all guidelines address the reporting of fetal sex and SCAs and when they do, recommendations vary (Table 1). For example, guidelines approve reporting fetal chromosomal sex but disapprove reporting of SCAs in Belgium and Italy. In Denmark, Estonia and the USA, reporting of both results is approved. In contrast, reporting of fetal chromosomal sex is not approved by guidelines in China. In Australia, guidelines address the poorer accuracy of NIPT analysis for sex chromosomes as compared to autosomes but they do not explicitly discuss *reporting* of fetal chromosomal sex or SCAs.[14] However, the Australian guideline recommends that women are counseled and able to opt out of receiving this information. In England, Scotland and Wales, guidelines do not address reporting of fetal chromosomal sex or SCAs

TABLE 1 Existing guidelines on the use of noninvasive prenatal testing (NIPT) and their recommendations regarding the reporting of fetal chromosomal sex and/or sex chromosome aberrations (SCA) based on NIPT.

No national guidelines exist[a]	National guidelines exist	
Albania	Guidelines approve reporting of fetal chromosomal sex	Belgium
Belarus		Denmark[b]
Croatia		Estonia
Cyprus		Germany[b]
Finland[c]		Italy
Greece		Thailand
Hong Kong		USA
Iceland	Guidelines disapprove reporting of fetal chromosomal sex	China
Latvia		
Montenegro		
Norway	Guidelines approve reporting of SCA	Denmark
Portugal		Estonia
Russia		Hungary
Serbia		USA
Singapore	Guidelines disapprove/ recommend against reporting of SCA	Austria
Slovakia		Belgium
		France
		Italy
	Guidelines do not address reporting of both fetal chromosomal sex and of SCA	Czech Republic
		England
		Israel
		Lithuania
		The Netherlands[d]
		Queensland
		Scotland
		South Australia
		Spain
		Sweden
		Switzerland
		Tasmania
		Victoria
		Wales
		Western Australia

[a]Guidelines are currently (Spring 2022) under development in Norway, Portugal and Iceland.

[b]Reporting of fetal chromosomal sex is only allowed/recommended after 14 + 0 weeks of gestation (Germany) or 11 + 6 weeks of gestation (Denmark).

[c]No actual guidelines exist; however, recommendations are in place.

[d]Testing for fetal chromosomal sex and SCAs is not allowed by law. Hence, this is not a subject of the guidelines.

in accordance with current practices of not including sex chromosomes in NIPT. In The Netherlands, testing for fetal chromosomal sex or SCAs is prohibited and, consequently, the Dutch guidelines do not address reporting hereof.

NIPT commonly includes testing of sex chromosomes in 30 out of 38 countries surveyed (Figures 1 and 2 and Table 2). In contrast, NIPT most commonly does *not* include sex chromosomes but *only* chromosomes 13, 18 and 21 in a minority of European countries (Austria, England, France, Norway, Scotland, Slovakia and Wales) (Figure 1 and Table 2). As shown in Figures 1 and 2 and Table 3, the proportion of all pregnant women receiving NIPT that includes sex chromosomes varies between settings from <10% (e.g., in France and Norway where NIPT only very rarely includes sex chromosomes or the Netherlands where no women have NIPT for sex chromosomes based on current legislation) to >75% in Belgium and Hong Kong. In most settings, the proportion of all the pregnant women having NIPT that includes sex chromosomes matches the proportion of all pregnant women having NIPT regardless of the coverage confirming that NIPT as it is applied today most frequently includes testing for sex chromosomes (Figures 1 and 2, Tables 2 and 3). In the USA, an estimated >75% of all NIPT performed includes sex chromosomes. The proportions of all pregnant women receiving NIPT that includes sex chromosomes are based on an educated guess in Austria, Czech Republic, England, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Portugal, Queensland, Russia, Scotland, Serbia, Singapore, Slovakia, Spain, Switzerland, Tasmania, Victoria and Western Australia.

When sex chromosomes are included in NIPT, this is done automatically (i.e., by default) in a number of countries (Table 4). However, the pregnant woman and partner may opt out of being informed about fetal chromosomal sex (this is the case in Finland, Estonia, Hong Kong, Latvia and Serbia). Conversely, parents in other settings, including Australia, Thailand and Singapore, may opt for sex chromosomes to be included in NIPT based on a wish to know fetal sex. Some responders (e.g., Finland, Italy, Sweden, Tasmania and

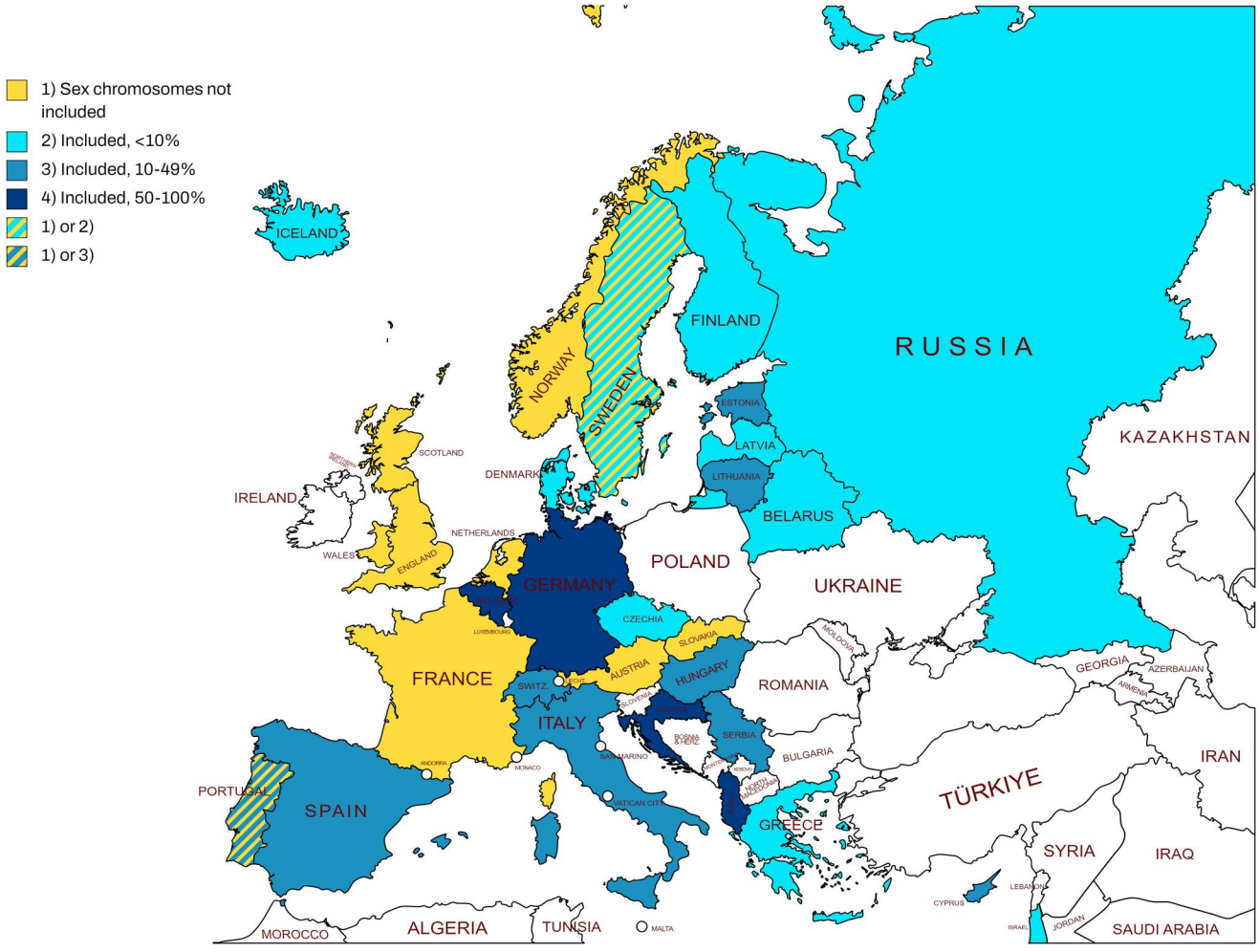

FIGURE 1 Inclusion of sex chromosomes in common uses of noninvasive prenatal testing (NIPT) and proportions of all pregnant women having NIPT that includes sex chromosomes in European countries. To enhance the graphical presentation, reporting categories have been collapsed as compared to Table 3. In Austria, inclusion of sex chromosomes is available on demand. Reported proportions are based on an educated guess: Austria, Czech Republic, England, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Portugal, Russia, Scotland, Serbia, Singapore, Slovakia, Spain and Switzerland. [Colour figure can be viewed at wileyonlinelibrary.com]

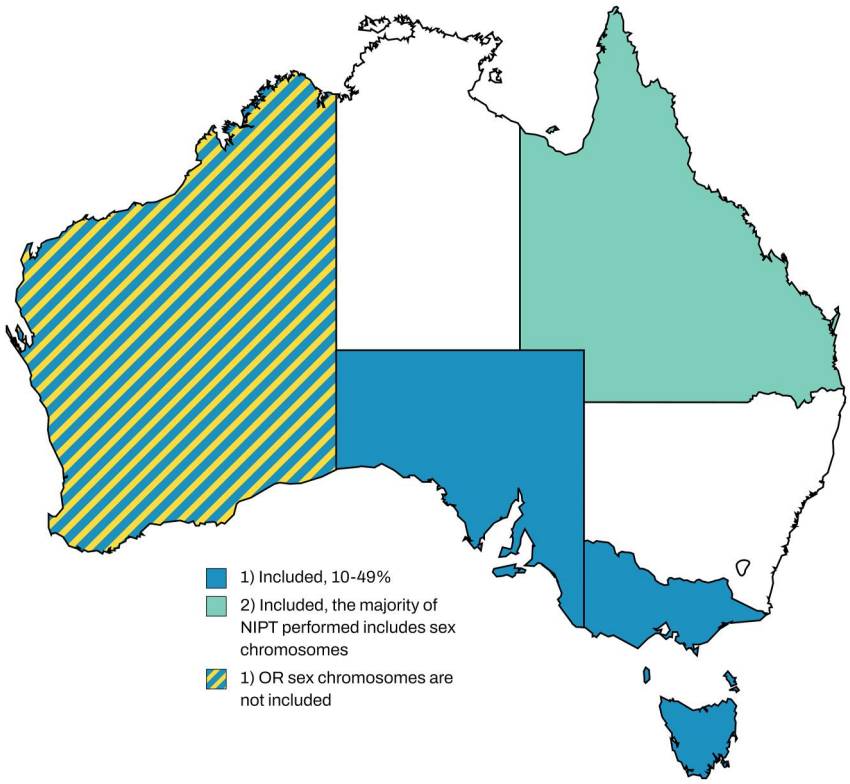

FIGURE 2 Inclusion of sex chromosomes in common uses of noninvasive prenatal testing (NIPT) and proportions of all pregnant women having NIPT that includes sex chromosomes in Australian states. To enhance the graphical presentation, reporting categories have been collapsed as compared to Table 3. Reported proportions are based on an educated guess: Queensland, Victoria and Western Australia. [Colour figure can be viewed at wileyonlinelibrary.com]

Victoria) noted that the practice of including sex chromosomes in NIPT depends on the provider (e.g., variation between different companies or between public and private providers). In the USA, testing for fetal chromosomal sex and/or SCAs is decided based on shared decision-making between pregnant women/partners and clinicians.

If NIPT indicates SCA, various reporting practices are used (Table 5). In a majority of the included countries/states, results would be reported by naming the potential SCA and/or stating the probability for the potential SCA as "low" or "high" (e.g., "high probability of Turner syndrome"). A number of respondents noted that reporting practices vary by provider (e.g., Lithuania, Italy, Slovakia, the USA and Victoria).

3.2 | General use of NIPT

In most of the studied settings, NIPT is applied as a secondary test in case of increased risk during first-line screening such as first-trimester combined screening (Table S1). In contrast, NIPT is used mainly as primary screening in Albania, Belgium, Italy, Montenegro, the Netherlands and Thailand (regardless of history or risk factors) and in Germany, Norway and Victoria (in case of a pregnancy with increased a priori risk [such as age >35 years]). In some countries/states, NIPT is used both as primary *and* secondary screening. For example, this choice is at the discretion of the pregnant woman in Hungary, while it depends on the region/hospital in China, Singapore and Spain. In Queensland, Tasmania and Western Australia, use of NIPT as primary or secondary screening varies by socioeconomic position/affordability. In the USA, patient and provider preference and insurance coverage determine the application as primary or secondary screening.

In most of the studied countries, the proportion of all pregnant women receiving NIPT (regardless of its coverage) is <50% (Table 3 and Figure S1). These proportions are based on an educated guess in Austria, England, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Portugal, Queensland, Russia, Scotland, Serbia, Singapore, Slovakia, Spain, Switzerland, Tasmania, Victoria and Western Australia. However, the proportion of all pregnant women having NIPT varies across Europe and Asia from <10% to >75%. In Australia, the proportion of all pregnant women receiving NIPT ranges from 30% to 35% in Western Australia to about 50% in Victoria. Respondents from Australia, Thailand and the USA noted that adoption of NIPT varies between socioeconomic groups and/or depends on affordability.

The chromosomal/genomic coverage of NIPT is limited to chromosomes 13, 18, and 21 in a minority of the studied settings, while in a majority of settings, this coverage is extended by the inclusion of sex chromosomes and further, in some countries, a few microdeletions (Table 1). NIPT having genomic coverage is commonly used in eight settings (Belgium, Hungary, South Australia, Switzerland, Tasmania, the USA, Victoria and Western Australia). Two or more NIPT options having differing chromosomal/genomic coverage are available and commonly used in China, the Netherlands, Portugal, Sweden, Switzerland, Victoria, the USA and Western Australia (Table 1).

The costs of NIPT are most often either self-paid or reimbursed by the healthcare system in the included countries/states (Figures 3 and 4 and Table S2). In many settings where NIPT is fully or partially

TABLE 2 Common chromosomal/genomic coverage of noninvasive prenatal testing (NIPT).

Coverage	Country/state	
Chromosomes 13, 18 and 21 only	Austria[a]	Portugal
	China	Scotland[b]
	England[b]	Slovakia
	France	Sweden
	The Netherlands	Wales[b]
	Norway	Western Australia
Chromosomes 13, 18, 21 ***and*** sex chromosomes	Czech Republic	Portugal
	Denmark	Queensland
	Estonia	Spain
	Finland	Sweden
	Germany	Switzerland
	Iceland	Tasmania
	Israel	Thailand
	Italy[c]	USA
	Latvia	Victoria
	Montenegro	Western Australia
Chromosomes 13, 18, 21 and a few microdeletions	Western Australia	
Chromosomes 13, 18, 21, a few microdeletions ***and*** sex chromosomes	Albania	Russia
	Belarus	Serbia
	China	Singapore
	Croatia	Spain
	Cyprus	Switzerland
	Greece	USA
	Hong Kong	Western Australia
	Lithuania	
Chromosomes 13, 18, 21, genome-wide coverage, but ***not*** sex chromosomes	The Netherlands	
Chromosomes 13, 18, 21, genome-wide coverage ***and*** sex chromosomes	Belgium	Tasmania
	Hungary	USA
	South Australia	Victoria
	Switzerland	Western Australia

Note: Please note that for some countries/states, more than one common use of NIPT is listed.

[a]Sex chromosomes are available upon request.

[b]Private/self-funded NIPT may include sex chromosomes. Data on uptake are extremely limited.

[c]Chromosomes 13, 18, 21, genome-wide coverage ***and*** sex chromosomes may be a choice for pregnant women in some regions.

reimbursed by a publicly funded healthcare system or health insurance, it is also available self-paid in a private setting (Denmark, England, Finland, Hong Kong, Iceland, Italy, Norway, Portugal, Scotland, Slovakia, Spain and Wales). In these countries, NIPT is often reimbursed when performed as a second-line test, while NIPT as primary screening is self-paid (e.g., Denmark, England, Hong Kong, Iceland, Italy, Scotland, Wales and in part in Spain). In Australia, NIPT is self-paid in all of the states studied, while in the USA, coverage varies between states depending on local legislation and health insurance providers.

4 | DISCUSSION

This survey study mapped the inclusion of sex chromosomes in the current use of NIPT in European and Asian countries as well as the USA and Australia. We report that not all countries have guidelines on NIPT; when they do, these do not always address the reporting of fetal chromosomal sex and SCAs. In most of the studied countries/states, sex chromosomes are commonly included when NIPT is performed. This may be the default or may be an option when pregnant women and their partners wish to know fetal sex; the inclusion of sex chromosomes is rarely because of clinical findings indicating SCAs. The proportion of all pregnant women receiving NIPT (regardless of its genomic coverage) is less than 50% in most of the included countries. However, this proportion varies between and within nations. The adoption of NIPT in terms of chromosomal/genomic coverage and application as primary or secondary screening depends not only on the country or state of residence but in some settings also follows from the individual's health insurance and/or socioeconomic conditions in combination with the available financial coverage of NIPT.

Previous studies that investigated screening for SCAs by NIPT reported similar results. For example, in a 2016–2017 survey, 24% of responding midwives and physicians from France reported testing for SCAs, while that number in Germany, Italy and Spain ranged from 53% to 57%.[15] This corresponds to our finding that testing commonly does not include sex chromosomes in France. In addition, a number of countries reported to include fetal SCA screening in NIPT in our 2019 survey and to include sex chromosomes in the present study (Croatia, Cyprus, Czech Republic, Denmark, Estonia, Germany, Iceland, Latvia, Lithuania and the USA), while countries which in 2019 did not screen for SCAs (Norway, Austria, Slovakia and Wales) continue not to include sex chromosomes in the majority of NIPT performed. The consistent practice of commonly screening for SCAs by NIPT in the USA has recently been underlined by American College of Medical Genetics and Genomics guidelines strongly recommending such screening.[16] These consistencies across time—albeit only a few years—may indicate that cultural practices around whether NIPT includes sex chromosomes have generally persisted since the introduction of NIPT in these settings.

TABLE 3 Proportion of all pregnant women receiving noninvasive prenatal testing (NIPT) (regardless of chromosomal/genomic coverage) and proportion of all pregnant women receiving NIPT for sex chromosomes.

		Proportion of all pregnant women receiving NIPT				
		<10%	10%–24%	25%–49%	50%–75%	>75%
Proportion of all pregnant women receiving NIPT *for sex chromosomes*	<10%	Czech Republic Denmark England Finland Iceland Israel Latvia Russia Scotland Slovakia Sweden Wales[a]	Belarus France[a] Greece Norway[a]	The Netherlands[d]		
	10%–24%		Cyprus Estonia Hungary Lithuania Portugal Switzerland Thailand	China Tasmania		
	25%–49%			Serbia Singapore South Australia Spain[b] Western Australia	Italy	
	50%–75%				Albania Croatia Germany Victoria[c]	
	>75%					Belgium Hong Kong

Note: In Austria, 25%–49% of all pregnant women receive NIPT. Inclusion of sex chromosomes is available on demand. In Queensland (missing response on proportion of all pregnant women receiving NIPT), >75% of NIPT performed includes sex chromosomes. Reported proportions are based on an educated guess: Austria, Czech Republic, England, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Portugal, Queensland, Russia, Scotland, Serbia, Singapore, Slovakia, Spain, Switzerland, Tasmania, Victoria and Western Australia.

[a]NIPT never or only very rarely includes testing for sex chromosomes.

[b]The proportion may be lower (i.e., 10%–24%) in some regions of the country.

[c]About 50% of all pregnant women receive NIPT.

[d]The proportion of all pregnant women receiving NIPT for sex chromosomes is 0% since this is prohibited by law.

With widespread utilization of NIPT, testing for sex chromosomes follows the possibility of increasing numbers of SCAs diagnosed prenatally. Indeed, in Victoria, Australia, a prenatal diagnosis of SCA based on amniocentesis or chorionic villus sampling occurred in 5.8 per 10,000 births in 2005 increasing to 8.7 per 10,000 births in 2020 following the introduction of NIPT.[17] In 2020, 91% of 47, XXY

TABLE 4 Indications for including sex chromosomes in noninvasive prenatal testing (NIPT).

Testing for sex chromosomes is automatically included (i.e., by default)		Testing for sex chromosomes can be included based on a parental wish to know fetal sex		Testing for sex chromosomes can be included based on clinical findings suspicious of sex chromosome aberrations
Albania	Latvia[a]	Belgium	Singapore	Germany
Belarus	Montenegro	Croatia	Slovakia	Lithuania
China	Portugal Russia	Cyprus	South Australia	USA
Denmark	Serbia[a]	Czech Republic	Switzerland	
Estonia[a]	Spain	Germany	Tasmania[b]	
Finland[a]	Sweden	Hungary	Thailand	
Greece	Tasmania[b]	Israel	USA	
Hong Kong[a]	Victoria[b]	Italy[a]	Victoria[b]	
Iceland	Western Australia[b]	Lithuania	Western Australia[b]	
Italy[c]		Queensland		

Note: Settings where NIPT never or only very rarely includes sex chromosomes are excluded. Please note that countries/states may be listed more than once.

[a]The pregnant woman may opt out of being informed about fetal chromosomal sex.

[b]Depending on provider.

[c]NIPT performed by private operators mostly includes sex chromosomes by default, whereas in the public healthcare system this relies on pre-test counseling.

TABLE 5 Reporting of a noninvasive prenatal screening result indicative of a sex chromosome aberration (SCA).

Reporting phrase	Country/state	
"Normal" or "abnormal" with respect to sex chromosomes	Italy	
	Thailand	
	USA	
"Low probability" or "high probability" with respect to SCA	Albania	Portugal
	Belarus	Queensland
	Cyprus	Serbia
	Denmark	Singapore
	Estonia	South Australia
	Finland	Spain
	Hong Kong	Tasmania
	Israel	USA
	Italy	Western Australia
	Lithuania	
The amount/number of chromosomes Y and X material detected is reported	China	Lithuania
	Denmark	Portugal
	Germany	Sweden
The specific, potential SCA is named	Croatia	Serbia
	Cyprus	Singapore
	Czech Republic	South Australia
	Greece	Switzerland
	Hungary	Tasmania
	Latvia	Western Australia
	Russia	

Note: Please note that countries/states may be listed more than once.

cases had been detected through NIPT.[17] Similar trends are likely in those countries studied here where a high proportion of pregnant women have NIPT, sex chromosomes are commonly included in NIPT and potential SCAs are reported. However, our findings show that although sex chromosomes in some settings are commonly (and sometimes per default) included in NIPT, this does not necessarily mean that potential SCAs are reported. Examples include Belgium and Finland, where NIPT performed in the public sector usually includes assessment for fetal chromosomal sex but not for SCAs. Thus, diverse reporting practices mean that findings such as those reported from Victoria[17] may not necessarily be extrapolated to other settings.

Likewise, including sex chromosomes in NIPT does not necessarily mean reporting fetal chromosomal sex. In many settings, parents may opt out of knowing fetal chromosomal sex, while in other settings reporting fetal sex is prohibited (China) or restricted until a certain gestational age is reached in accordance with guidelines (Denmark) or the law (Germany).[18] This exemplifies how the ethical considerations about testing for fetal chromosomal sex using NIPT are translated into real world practices. Concerns have been raised that introducing NIPT could facilitate sex selective termination of pregnancy.[11,12] A skewed sex ratio at birth toward more males has previously been reported (e.g., in China) as a result of increased availability of prenatal ultrasound in the 1980s[19] with a continued rise after 2000.[20] However, a recent study found that the male-female ratio at birth declined in China from 2010 to 2020.[21] Nevertheless, more research is needed to investigate the potential impact of NIPT utilization on sex-selection. Such investigations rely on high quality census data available for researchers to follow trends in sex ratio at birth—particularly in countries where fetal chromosomal sex determination by NIPT is accessible.

The proportion of all pregnant women receiving NIPT appears to be stable in most European countries compared with results from our

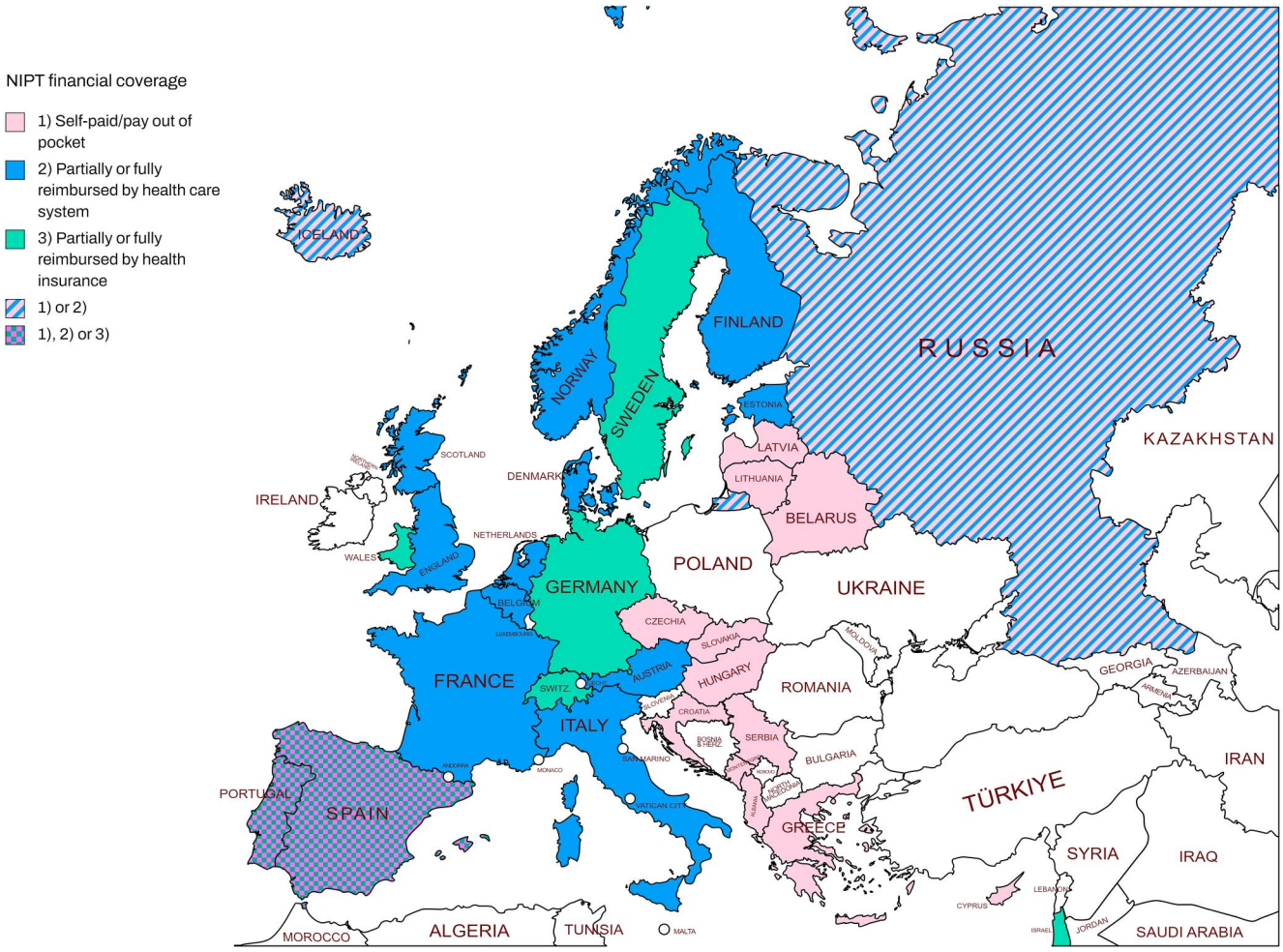

FIGURE 3 Financial coverage of noninvasive prenatal testing (NIPT) in European countries. For Australia, China, Hong Kong, Singapore and Thailand: see text and Table S2. [Colour figure can be viewed at wileyonlinelibrary.com]

2019 survey.[13] Exceptions are Croatia and Germany where proportions increased from <25% to 50%–75% in both countries. However, care should be taken when interpreting these findings, since the estimation of the percentage of women receiving NIPT is uncertain in many settings and because of answers provided as intervals. Further, the present study confirms our prior finding that when NIPT is performed within a public health care setting, this is often as a second tier test for pregnant women at high risk after first-trimester combined screening for the common trisomies or based on age[13] (China, Denmark, England, Finland, France, Hong Kong, Iceland, parts of Italy, Norway, Scotland, South Australia, parts of Singapore, parts of Spain, Sweden, Tasmania and Wales). In many of these countries/states, NIPT is additionally available in a private setting for pregnant women paying out-of-pocket and here, more often used as primary screening. However, information on this use of NIPT and on the percentage of women accessing NIPT privately is limited. In contrast to this trend, more state Medicaid programs in the USA now cover NIPT as primary screening compared with 2019[13] (21 vs. six).

Despite the tendencies described above, we found variability in the utilization and availability of NIPT across countries as previously reported.[13,15,22] This heterogeneity exists both within (e.g., Australia, Italy, Spain, Sweden and the USA) and between countries when it comes to chromosomal/genomic coverage of NIPT, proportions of pregnant women receiving NIPT, application of NIPT as primary or secondary screening, reporting practices and financial coverage of testing. One contributor to this heterogeneity is provider variability when different private companies operate in a country and/or both private and public offers co-exist. As reported previously,[23–25] socioeconomic status is another contributor to prenatal screening and testing heterogeneity. This may especially be true when the adoption of NIPT depends on non-universal health insurance and/or payment out-of-pocket, as commented by some respondents in the present survey. As noted in a recent review, potential inequity of access adds to the list of ethical issues surrounding NIPT for SCAs.[6] However, not only external factors influence the use of NIPT, since this is also a matter of personal attitude.[26]

4.1 | Strengths and limitations

This study is limited by national data not being routinely collected or available in all settings, leaving some of the replies based on an

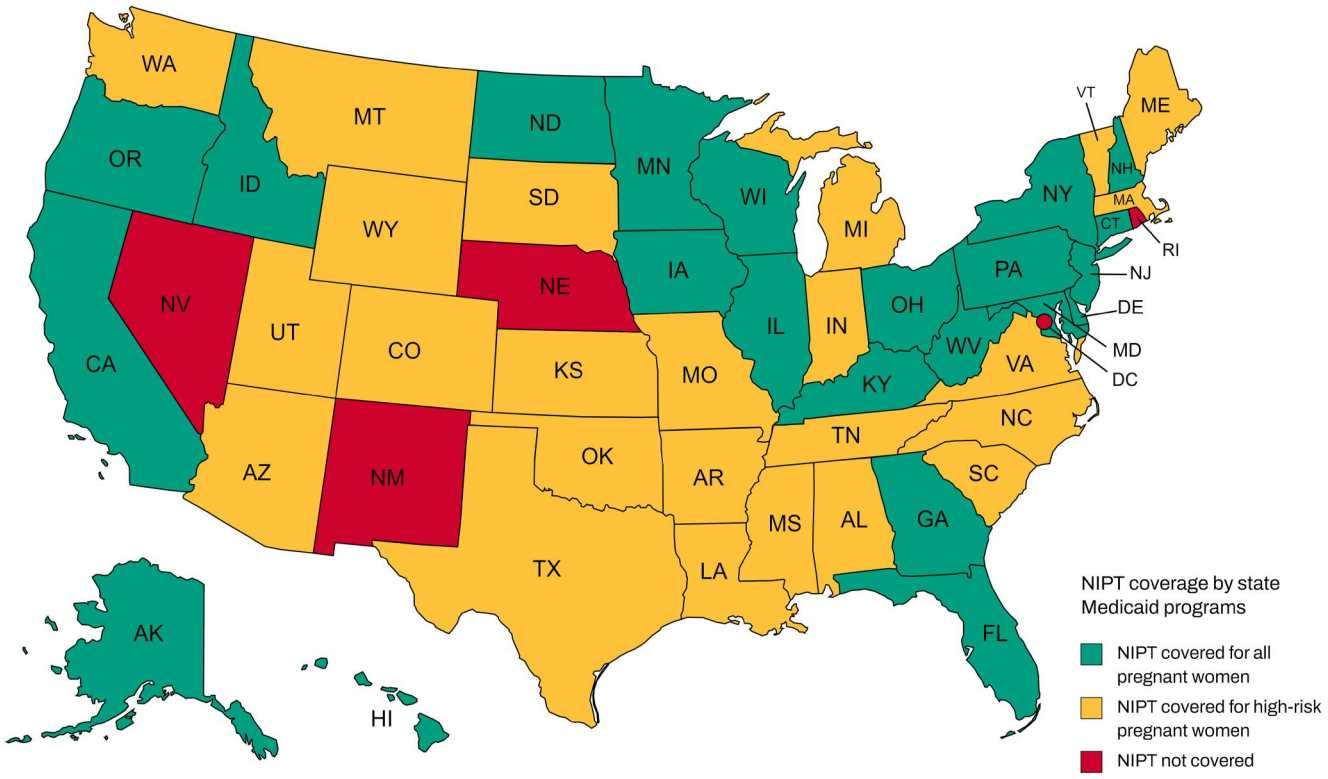

FIGURE 4 Financial coverage of noninvasive prenatal testing (NIPT) by state Medicaid programs in the USA. In three states (LA, TX and LA) coverage for all pregnant women is currently under consideration. [Colour figure can be viewed at wileyonlinelibrary.com]

educated guess (for example, the proportion of pregnant women receiving NIPT). This may particularly be the case for countries where NIPT is mostly available in a private setting.

Further, replies to the survey were obtained mainly through our scientific network, thereby limiting the geographical scope of the study. Nevertheless, we acknowledge the importance of studying the current use of NIPT not only in the countries/states included in this work, and we encourage such research worldwide.

Finally, given the study's simple design and its aim of obtaining information on the most common adoptions of NIPT, details and nuances of the current practice could not be completely covered in this publication.

5 | CONCLUSION

We found that across countries in Asia and Europe and states in Australia and the USA, NIPT commonly includes testing for sex chromosomes and this is often done either by default or based on a parental wish to know fetal sex. Yet, only a subset of countries has national guidelines on the reporting of SCAs and fetal chromosomal sex and the reporting practices in case NIPT is suggestive of SCA are variable. In most of the studied settings, an estimated <50% of pregnant women have NIPT; however, utilization of NIPT varies. This variation may be related to, for example, the availability of a national/regional prenatal screening offer and the pregnant woman's/couple's ability to pay for private testing.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest in relation to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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