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Current use of noninvasive prenatal testing in Europe, Australia and the USA: A graphical presentation

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Abstract

Introduction: Noninvasive prenatal testing (NIPT) using cell-free fetal DNA has increasingly been adopted as a screening tool for fetal aneuploidies. Several studies have discussed benefits and limitations of NIPT compared with both ultrasound and invasive procedures, but in spite of some shortcomings NIPT has become extensively used within the last 5 years. This study aims to describe the current use of NIPT in Europe, Australia and the USA.

Material and methods: We conducted a survey to describe the current use of NIPT. Colleagues filled in a simple email-based questionnaire on NIPT in their own country, providing information on (a) access to NIPT, (b) NIPT's chromosomal coverage, (c) financial coverage of NIPT for the patient and (d) the proportion of women using NIPT in pregnancy. Some data are best clinical estimates, due to a lack of national data.

Results: In Europe, 14 countries have adopted NIPT into a national policy/program. Two countries (Belgium and the Netherlands) offer NIPT for all pregnant women, whereas most other European countries have implemented NIPT as an offer for higher risk women after first trimester screening. In Australia, either combined first trimester screening (cFTS) or NIPT is used as a primary prenatal screening test. In the USA, there are no national consensus policies on the use of NIPT; however, NIPT is widely implemented. In most European countries offering NIPT, the proportion of

Abbreviations: cFTS, combined first trimester screening; CMA, chromosomal microarray; NIPT, noninvasive prenatal testing; SCA, sex chromosome aneuploidies.

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women using NIPT is well below 25%. In the Netherlands, Austria, Italy, Spain and most Australian and American States, 25%-50% of women have NIPT performed and in Belgium testing is above 75%. In most countries, NIPT reports on trisomy 13, 18 and 21, and often also on sex chromosome aneuploidies. Only in Belgium, the Netherlands, Lithuania, Greece, Cyprus and Italy is NIPT offered predominantly as a genome-wide test (including some microdeletions or a whole genome coverage).

Conclusions: Noninvasive prenatal testing has been widely adopted throughout Europe, Australia and the USA, but only a few countries/states have a national policy on the use of NIPT. The variation in NIPT utilization is considerable.

KEYWORDS
cell-free fetal DNA, combined first trimester screening, noninvasive prenatal testing, prenatal genetic screening

1 | INTRODUCTION

Noninvasive prenatal testing (NIPT) screens maternal plasma for fetal aneuploidies by utilizing cell-free 'fetal' DNA (cffDNA) originating from placental apoptosis. Multiple studies have validated the clinical application of NIPT as a sensitive screening tool for the common fetal aneuploidies.[1,2] NIPT has been introduced as an alternative to traditional invasive testing procedures (chorionic villus sampling/amniocentesis) to avoid the small risk of procedure-related miscarriage.[3,4] However, NIPT is a screening tool and is limited by not being able reliably to identify the majority of 'atypical' chromosomal anomalies (ie microdeletions and miicroduplications), many of which have phenotypical importance.[5,6] Because of the false-positive results inherent in any screening test most guidelines recommend that a 'screen positive' NIPT result should be confirmed by invasive diagnostics.[7]

Noninvasive prenatal testing was introduced in 2011, initially being launched by commercial providers.[8] In recent years, NIPT has been implemented into public healthcare systems as either a first line test or a supplement to existing prenatal screening programs.[9,10] The increased use of NIPT has significantly reduced the number of invasive tests performed in many places.[11-13]

Because of the rapid development in prenatal diagnostics, there are no temporal data on the current use of NIPT in the western world. The aim of this study is to examine the current use of NIPT in Europe, Australia and the USA.

Key message

Noninvasive prenatal testing (NIPT) has been widely adopted, but only some countries/states have a national policy on the use of NIPT. If a strategy has been chosen there seems two major set-ups: An offer of NIPT-for-all or, more commonly, NIPT for women of higher risk identified at Combined First Trimester Screening or by age. When looking in greater detail, similarities cease and almost all national models are unique.

2 | MATERIAL AND METHODS

To examine the current use of NIPT in Europe, Australia and the USA, we conducted a simple email-based survey covering four areas of interest:

- National access to NIPT, ie NIPT as a national policy,
- NIPT's chromosomal coverage (which model of coverage is most frequently used),
- NIPT's financial coverage (is NIPT publicly funded, are costs reimbursed via insurance, are costs out-of-pocket?),
- proportion of women receiving NIPT

(see Table S1 for original questionnaire).

To ensure that our results remained simple and manageable, those completing the survey were required to choose between three or four possible answers. Regarding the proportion of women receiving NIPT, we provided a 'best clinical estimate' option, to be used where national/state data were not available. We utilized our network of recognized national experts to contact colleagues whom we felt would be able to complete the survey according to NIPT use within their own country and emailed a copy of the questionnaire to confirmed participants in September 2019. We used the gradually growing study-group to collect information on colleagues in as many countries as possible.

In the USA, there are no national policies on the use of NIPT. In the USA, access to NIPT depends on individual insurance companies and State Medicaid programs, thus some questions in the questionnaire were not appropriate to describe the use of NIPT in the USA. Data

from the USA were provided as an expert statement from Professor Ron Wapner, who also conceptualized the idea behind the maps.

Data were graphically presented in maps created with Mapchart.net (https://mapchart.net/).

2.1 | Ethical approval

Surveys without patient involvement do not require approval from the Danish Research Ethics Committee System.

3 | RESULTS

3.1 | Europe

We invited 34 countries from Europe to participate in the survey. Of these, 30 filled out and returned the questionnaire (no reply from Switzerland, North Macedonia, Serbia or Montenegro). We were not able to obtain contact information on colleagues in the remaining European countries, hence they were not included in the survey (Figures 1-4, gray areas). NIPT has been adopted in all the European countries that replied to the survey but it is unevenly applied (see Figure 1). NIPT is still used by less than 25% of women in most European countries and often by less than 5%. NIPT is more widely used in Italy, Spain, Austria, the Netherlands and Belgium (Figure 2).

3.2 | Northern Europe

All Nordic European countries offer combined first trimester screening (cFTS) either to all women or to selected groups. At cFTS, a risk estimate is calculated based on maternal age, ultrasound-determined nuchal translucency and maternal blood tests. If the risk is found to be high (and definitions of 'high' vary substantially), then women are offered either invasive testing or NIPT. Some countries offer only invasive testing to women with the very highest risk (eg above 1:50 or 1:100), providing NIPT to a slightly lower-risk subset of higher risk women (eg between 1:100 and 1:1000). All prenatal screening costs are fully covered by the Nordic European national healthcare systems (see Figure 3). In Iceland, high-risk women are offered invasive testing, but if women specifically request NIPT, this is supplied, with costs being covered publicly. In the UK, Wales is the only country

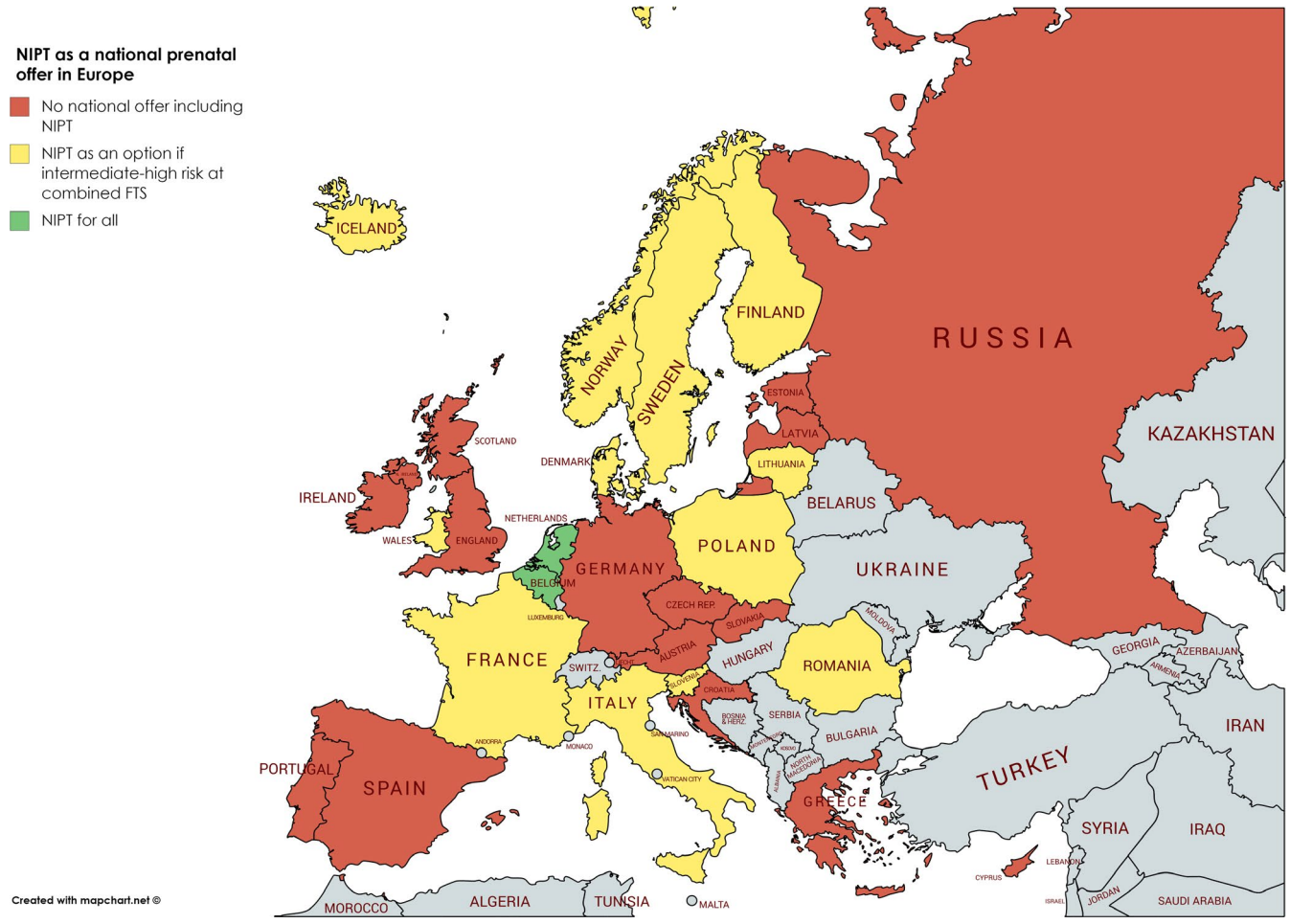

FIGURE 1 Noninvasive prenatal testing (NIPT) as a national prenatal offer in Europe

FIGURE 2 Proportion of women receiving noninvasive prenatal testing (NIPT) in Europe. Best clinical guess: A, CZ, ES, HR, IT, PL, RO, RU, SE, SK, WAL

to have integrated NIPT in public prenatal screening, offering NIPT as a financially covered alternative to invasive testing in high-risk women after cFTS. NIPT is not currently offered as a commissioned test within the Antenatal Screening pathway in England, Scotland or Ireland. This is anticipated to change in 2020. In Latvia and Estonia, there is no national policy including NIPT; however, in Estonia, NIPT providers are negotiating with health insurance companies about provision for high-risk patients. Lithuania offers self-financed NIPT to high- and intermediate-risk women after cFTS.

3.3 | Eastern Europe

In Slovakia, Russia and the Czech Republic, there are no publicly funded offers of NIPT; NIPT is self-financed through private clinics. Poland and Romania offer only invasive testing after cFTS to women at very highest risk (above 1:100), and then NIPT to higher risk women (1:100-1:1000). NIPT is self-financed.

3.4 | Southern Europe

In Spain, there is no national policy on the use of NIPT. Some regions, such as Madrid province, have decided to offer NIPT to high-risk patients. In other regions without official programs, different hospitals have incorporated NIPT according to their needs and budget, and in these cases NIPT is publicly financed. Due to extensive use of NIPT in the private sector, the proportion of women receiving NIPT in Spain is high (25%-50%, see Figure 2). In Portugal, a public guideline on NIPT is under preparation, but such as Spain, some public clinics already offer NIPT to high-risk patients. In Italy, there are official guidelines supporting the use of NIPT to women of high risk, but only two regions currently reimburse the test (Toscana and province of Bolzano). Italy has a high use of NIPT (25%-50%) through private clinics. In Greece and Cyprus, there are no national guidelines/policies of NIPT, but NIPT is available as a self-financed service. In Slovenia, there is only an offer of NIPT if invasive testing is contraindicated by maternal factors, and in such cases NIPT is publicly financed.

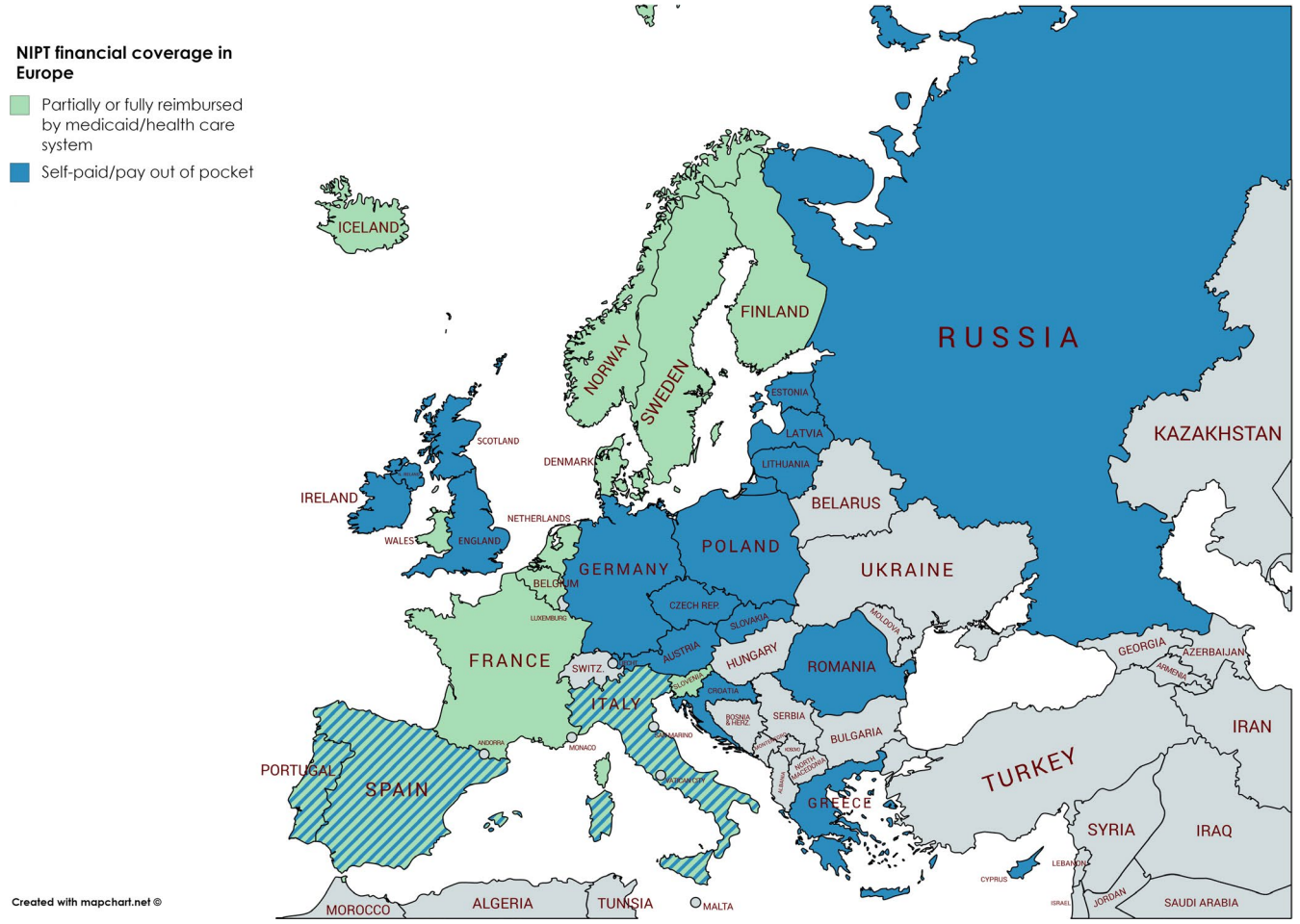

FIGURE 3 Noninvasive prenatal testing (NIPT) financial coverage in Europe. Stripes indicates two possible options within the same country. See text for details

3.5 | Western Europe

France offers NIPT to high-risk women after cFTS free of charge. However, women receive results on trisomy 21 only, and not for trisomy 13 or 18 with NIPT. In Germany, a national decision on the use of NIPT is pending, and NIPT will most likely be offered for high-risk women and with public reimbursement. Since 2017, NIPT has been available to all pregnant women in the Netherlands (as a result of the TRIDENT-2 study, a nationwide study which allows for all pregnant women to have NIPT performed) as a first line screening test, but less than 42% of women opt for NIPT.[14] NIPT is partially self-paid and partially reimbursed. In Belgium, NIPT is offered to all pregnant women in addition to ultrasound (excluding biomarkers and thus cFTS) and is reimbursed by insurance. The proportion of women opting for NIPT is very high (>75%). In Austria, there is no national policy on the use of NIPT; however, the estimated use of NIPT is considerable (25%-50%).

3.6 | NIPT chromosomal coverage in Europe

In five European countries, NIPT primarily covers chromosome 13, 18, and 21 only. In nine countries, NIPT also covers sex chromosome aneuploidies, and four countries offer a choice between these two options. The Netherlands, Belgium, Lithuania, Italy, Cyprus and Greece primarily offer NIPT for 13, 18, 21, sex chromosome aneuploidy, microdeletions and/or whole-genome coverage (ie NIPT including some microdeletions, with or without SCA or whole genome coverage) (Figure 4).

3.7 | Australia

We received responses from clinicians working in seven of the eight states and territories (no data were available from the Northern Territory). The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) states that either cFTS or NIPT are acceptable primary prenatal screening tests.

In Australia, cFTS is partially government financed, whereas NIPT is self-funded. There is a difference in uptake of NIPT according to model of care, with >50% to 75% of women in private obstetric care utilizing NIPT as a primary screen, compared with <25% of public patients. As private obstetric care accounts for approximately 30% of births in Australia, it is estimated that 25%-50% of the total pregnant population self-fund NIPT as first line screening test in Victoria, Australian Capital Territory, Queensland and South Australia. In New South Wales, Tasmania and

FIGURE 4 Noninvasive prenatal testing (NIPT) chromosomal coverage in Europe. Stripes indicate that two options exist and are used fairly evenly. In France, NIPT only reports on chromosome 21

Western Australia, it was estimated that less than 25% of the total pregnant population have NIPT performed (Figure 5). NIPT genome coverage in Australia generally varies by provider more than by state.

3.8 | The USA

In the USA, nearly all commercial insurance companies cover NIPT for high-risk patients (ie >35 years, positive cFTS, etc.), as do most state-sponsored Medicaid programs. In six states, Medicaid programs also cover NIPT for average risk women. In nine states, Medicaid programs do not cover NIPT at all (Figure 6). It is estimated that 25%-50% of all pregnant women receive NIPT. NIPT covering chromosome 13, 18, 21 and sex chromosome aneuploidies is the most frequently used, although screening for rare aneuploidies, triploidy and some microdeletions is available but not recommended.

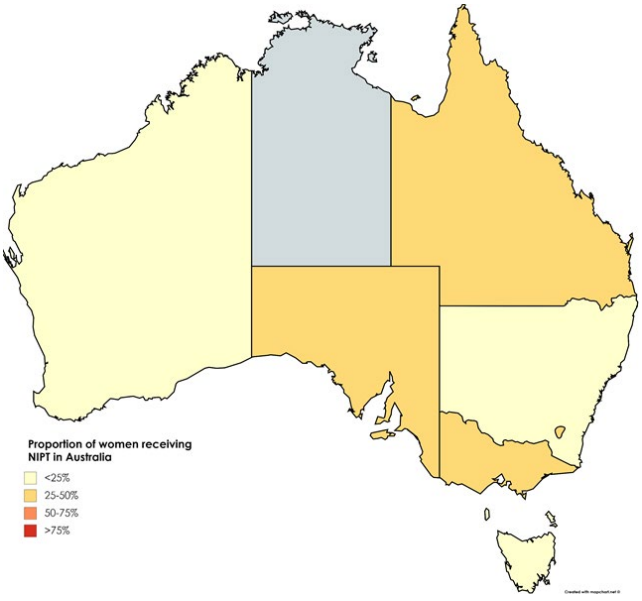

FIGURE 5 Proportion of women receiving noninvasive prenatal testing (NIPT) in Australia (self-funded). Best clinical guesses

4 | DISCUSSION

Here, we present data on the current use of NIPT in Europe, Australia and the USA. All countries that replied to the survey have NIPT in use

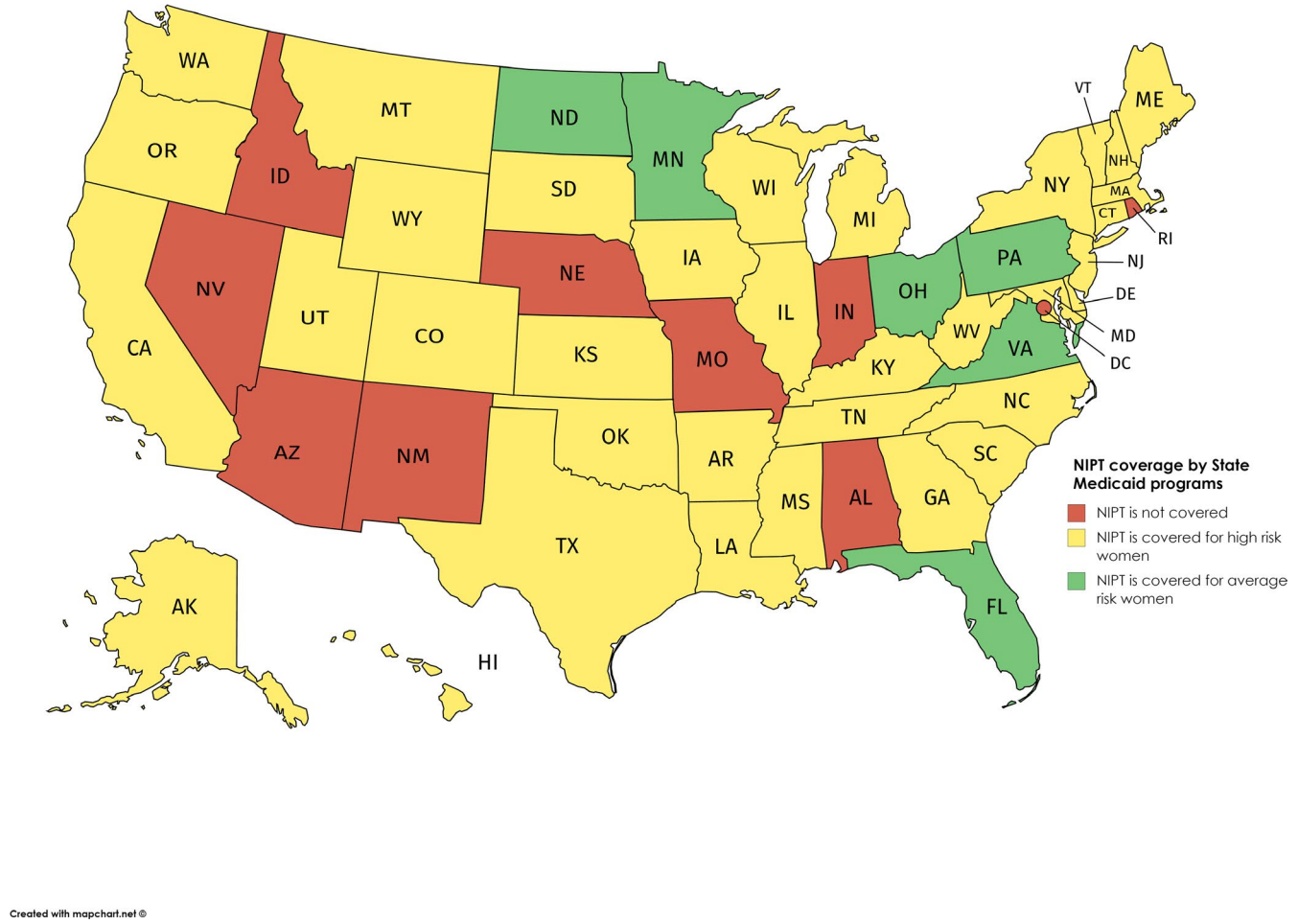

FIGURE 6 Noninvasive prenatal testing (NIPT) coverage by State Medicaid programs

(private or public), and many countries/states have guidelines or policies (present or currently being planned/drafted) and/or laws regulating its use. There appear to be two main strategies for the implementation of NIPT: offering NIPT after high-risk cFTS or offering NIPT as the first line test for all. The current uptake of NIPT varies greatly. Although less than 25% of women in most European countries currently use NIPT, uptake is higher within the Netherlands, Italy, Spain and Austria, where 25%-50% of women use NIPT, and in Belgium, where the uptake is still higher (>75%). In most American and Australian states, 25%-50% of the pregnant population have NIPT performed.

We found much variation in the way in which NIPT is used worldwide, as well as between the different European countries. In some countries, recommendations regarding NIPT even vary from region to region. The simplicity of this survey, and thus the final graphics produced, means we are unlikely to have demonstrated the full range and depth of this diversity.

Figure 1 presents a seemingly homogeneous picture of NIPT in the Nordic European countries, where all countries have implemented NIPT after cFTS. However, the ways in which NIPT is practiced are very different. Norway offers cFTS only to women above 38 years of age or after a previously complicated pregnancy.[10] Therefore, only around 10% of all pregnant women are offered cFTS. Of these, 10% (1% of pregnant women) are at high risk following cFTS and are offered NIPT. Other differences, not adequately covered by our data/figures, relate to the effect of NIPT on invasive-testing rates. In Denmark, the introduction of NIPT has not affected invasive rates, which are even increasing,[15] whereas in Finland, invasive rates were halved by the introduction of NIPT (data from Professor Vedran Stefanovic, no reference). In Denmark, women are offered chromosomal microarray after invasive testing. In Finland, women are offered trisomy PCR; thus the diagnostic gain of invasive testing compared with NIPT is greater in Denmark.

France appears to be relatively comparable to the Nordic European countries in offering NIPT after cFTS. An interesting resemblance is found between France and Norway, as both countries have laws to restrict the use of NIPT to some groups (Norway) or to some disorders (France). In Norway, it is illegal to offer cFTS or NIPT to women under the age of 38.[10] In France, all blood-based prenatal screening is subjected to laboratory authorization by national authority. For NIPT specifically, a law was only recently passed to make testing for trisomy 21 available for authorization, and authorization for trisomy 13 and 18 is not yet available. Thus, there seems to have been

an additional need, above that which was contained within existing national policies on prenatal screening, to regulate the use of NIPT.

The Netherlands and Belgium offer NIPT as a first line test for all women, but their specific models of use differ significantly. In the Netherlands, the proportion of women using NIPT is low (<42%), mirroring the historical uptake for cFTS, which was also low prior to the introduction of NIPT.[14] NIPT is currently offered without cFTS, and it is uncertain whether this offer will remain the same once the national TRIDENT study is complete.[14] In Belgium, NIPT is offered to all pregnant women alongside first trimester ultrasound with nuchal translucency measurement, but without biomarkers. Here, uptake is much higher than in the Netherlands. One potential explanation for this difference could be that NIPT is fully reimbursed in Belgium, whereas in the Netherlands reimbursement is only partial. Both countries have implemented genome-wide NIPT (whole genome coverage with a resolution of potentially 10-20 Mb). The exact role of genome-wide NIPT, however, is a topic of considerable professional disagreement[16] and has likely not yet found its final form or place in prenatal screening.

It is difficult to compare the use of NIPT in Europe with the use in Australia and the USA because of the major differences in the structure of the respective healthcare systems. In the USA, the use of NIPT depends primarily on insurance company and State Medicaid policy. Within their most recent recommendations (2016), the American College of Obstetricians and Gynecologists suggests that NIPT is a valid alternative to invasive testing in patients identified as high risk after first trimester screening.[7] Medicaid programs, which provide health coverage to millions of Americans, cover NIPT for high-risk patients. However, NIPT is not covered in nine states or in Washington, DC (Figure 6). NIPT is covered by insurers for at least 114 million women with average-risk singleton pregnancies. However, more than 70 million women are insured by providers who do not currently cover/reimburse NIPT for average-risk women. In Australia, NIPT can be used as an alternative to cFTS for primary screening. An application for government NIPT subsidy is currently under revision, with two models being proposed: universal screening with NIPT or NIPT after high-risk cFTS. These two models are also the most commonly used strategies around Europe.

Our findings are limited by the simplicity of the questionnaire and the resulting data provided by our colleagues. We were not able to obtain information from all European countries, and 'missing' data were prevalent in the south-eastern part of Europe. Thus, the use of NIPT in this part of Europe remains uncertain. Some data are provided as 'best clinical esimates', where national data were not available (see figures). Much of the detail and complexity relating to NIPT use within and across countries is thus not addressed here. NIPT continues to develop rapidly in terms of resolution, price and implementation, and our comparison may thus have a short time-window of relevance. We did not investigate whether NIPT had increased or decreased the total number of fetal chromosomal aberrations detected in each country, nor did we focus on the price of NIPT in each country, which may greatly influence the number of women receiving NIPT. In a study from 2015, Minear et al found that the price of NIPT varied from 350USD (Australia) to 2900USD (USA).8 The overall price has likely decreased in recent years, which may have affected uptake. The price of testing also differs greatly within Europe. In central Europe, NIPT may be offered for free (eg being covered by the national healthcare system), or prices may range from 150 to 300€. Within southern Europe, the price of the same test from the same companies, may be >1000€.[17] Specific national economic, social and cultural contexts are likely to affect the extent to which NIPT is offered and accepted. Further, in most countries, NIPT is also available as a self-paid service through the private sector, the uptake and outcomes of which may be more difficult to monitor.

5 | CONCLUSION

Noninvasive prenatal testing is implemented in all countries studied. Some countries have national policies and many more policies are in the pipeline. Where a specific strategy has been chosen, there appear to be two popular models of provision: An offer of NIPT-for-all or an offer of NIPT for women identified as at risk at cFTS. Some countries have enacted specific legislation on the use of prenatal screening and/or NIPT. In most European countries, less than 25% of women have NIPT performed. In the USA and Australia, NIPT is more widely used. When looked at in greater detail, similarities cease and almost all models are unique.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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