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The implementation and impact of non-invasive prenatal testing (NIPT) for Down's syndrome into antenatal screening programmes: a systematic review and metaanalysis

Background

Non-invasive prenatal testing (NIPT) is a widely adopted, accurate maternal blood test using DNA sequencing to detect foetal chromosomal conditions, notably Down's syndrome (DS). The introduction of this test, which may have implications for important decisions made during pregnancy, requires continual monitoring and evaluation. This systematic review aims to assess the extent of NIPT introduction into national screening programs worldwide, its uptake, and impact on pregnancy outcomes.

Methods and Findings

MEDLINE, CINAHL, Scopus, and Embase for population-based studies, government guidelines, and Public Health documents from 2010 onwards. Results summarised the national policies for NIPT implementation into screening programmes geographically, along with estimated uptakes.

Meta-analyses estimated the pooled proportions of women choosing invasive prenatal diagnosis (IPD) following a high chance biochemical screening result, before and after NIPT was introduced. Additionally, we meta-analysed outcomes (termination of pregnancy and live births) amongst high chance pregnancies identified by NIPT. Results demonstrated NIPT implementation in at least 27 countries, predominantly high-income European nations. Uptake of second line NIPT varies, from 20.4% to 93.2% (n=6). Following high chance biochemical screening, the proportion of women choosing IPD decreased post-NIPT implementation from 75% (95% CI 53%, 88%, n=5) to 43% (95%CI 31%, 56%, n=5), an absolute risk reduction of 38%. A pooled estimate of 69% (95% CI 52%, 82%, n=7) of high chance pregnancies for DS after NIPT resulted in termination, while 8% (95% CI 3%, 21%, n=7) had live births of babies with DS.

NIPT has rapidly gained global acceptance, influenced by healthcare structures, historical screening practices, and cultural factors. Our findings indicate a reduction in IPD tests following NIPT implementation, but limited pre-NIPT data hinder comprehensive impact assessment. Transparent, comparable data collection is imperative for monitoring NIPT's potential consequences.

Introduction

Non-invasive prenatal testing (NIPT) was introduced as an antenatal screening test for Down's syndrome in 2011 (1), bringing with it the potential to impact existing screening pathways, reproductive choices, and medical care during pregnancy. Down's Syndrome (DS), or Trisomy 21, is the most common chromosomal condition seen in live births and results from a third (partial or complete) copy of chromosome 21 (2). Screening for DS is part of routine antenatal care in many countries (3), often based on a combination of maternal age and blood markers such as alpha-feto protein, free beta-hCG and pregnancy associated plasma protein A (4). Foetal nuchal translucency (NT) measurements from a routine first trimester ultrasound scan may also be used for women presenting for antenatal care early in pregnancy (Figure 1). This combined approach, referred to as biochemical screening, gives a chance score for the likelihood of DS and has an average detection rate (DR) of 70% and a false positive rate (FPR) of 5% (4). Subsequent diagnostic testing (genetic testing of foetal or placental cells obtained through amniocentesis or chorionic villus sampling, collectively referred to as invasive prenatal diagnosis (IPD)), is used to confirm the screening results of high chance pregnancies. IPD is, however, associated with a 0.5% procedure-related risk of miscarriage (5).

Technological advancements in DNA sequencing methods have resulted in the introduction of NIPT as an antenatal screening test for DS. NIPT can be used from 10 weeks gestation and analyses placental cell-free DNA (cfDNA) circulating in the maternal blood, utilising DNA sequencing to identify relative excess or deficit in regions of the foetal chromosomes when compared to the expected distribution (6). NIPT screening was first introduced commercially in Hong Kong and the US in 2011 and then

marketed worldwide as a privately available test. It has since been recommended for implementation into national antenatal screening programmes by various governing bodies, including the American College of Obstetricians and Gynaecologists in 2012 (7) and the UK National Screening Committee in 2015 (1) as both a contingent, or 'second line', screen for high chance pregnancies identified by 'first line' biochemical screening (8–10), or as a first line test (11). Previous reviews have reported on the widespread marketing and availability of NIPT testing (1), and on the considerable variability in population uptake of NIPT between countries - from 25-50% in the Netherlands, USA and Australia, to 75% in Belgium (12,13). However, these reviews do not focus solely on national-level implementation, and with NIPT use ever progressing, an updated understanding of the population-level impact of this test is required.

NIPT is more accurate than biochemical screening, with a DR of 99.2% and FPR of 0.09% (14). The possibility of a false positive result means that NIPT is not diagnostic, and false positives can be indicative of placental mosaicism, vanishing twin, or maternal cancer (15). Therefore, as with biochemical screening, IPD is still required for a prenatal confirmation of positive NIPT results. However, by improving the accuracy of screening tests to identify women with a high chance of having a baby with DS, it is expected that the introduction of NIPT will reduce the number of unnecessary IPD tests performed (16). Although a reduction has already been reported in some populations (12), it is important to understand if this trend is seen universally. Moreover, as the addition of this test changes the screening options and accuracy of information available to women during their pregnancy, there is potential to change the behaviours and reproductive choices following the antenatal screening pathway. It could also inform pre and postnatal care, impacting the survival of babies with DS.

With new countries implementing NIPT into their national antenatal screening programmes every year (8,13,17,18), continual monitoring is important for an up-to-date understanding of the extent of NIPT use in antenatal screening programmes for DS, along with its impact on IPD test uptake and pregnancy outcomes. Therefore, this systematic review will focus on two aspects 83 of NIPT introduction into antenatal screening pathways for DS. Firstly, it will investigate the extent of NIPT use in government85 implemented antenatal screening for Down's syndrome, including how NIPT has been implemented and its uptake by eligible women in these populations. Secondly, it will evaluate the impact of NIPT as a screening tool on specific reproductive choices and outcomes of pregnancies with DS in all clinical settings. This will include populations which may not have a national screening policy, exploring the proportion of IPD, termination of pregnancy and live births of babies with DS in eligible populations as key indicators of the impact of NIPT. This will provide necessary context for the future implementation of NIPT elsewhere and give insight into its potential impact on pregnancies of babies with DS.

Methods

Review questions

This systematic review aimed to address the following research questions:

A) To what extent has non-invasive prenatal testing (NIPT) been implemented as part of a national antenatal screening programme for DS globally, and what is the uptake of NIPT in these populations?

B) What impact has the use of NIPT had on the reproductive choices made and on pregnancy outcomes, in any clinical setting?

Terminology can be inconsistent; therefore, the glossary in Table 1 provides clarification and defines the terms to be used throughout this systematic review.

Search strategies and selection criteria

Searches were conducted in MEDLINE, Embase, CINAHL and Scopus from January 103 2010 to March 2023, as the first reported use of NIPT for prenatal testing was in 2011 (1). Two independent search inclusion and exclusion criteria were used to optimise screening and the identification of relevant studies for the two research questions presented.

Part A (NIPT implementation in national antenatal screening programmes for DS globally): observational studies and healthcare or governmental publications were included, from autonomous regions (countries/states/region) where NIPT had been implemented as part of national screening guidelines for DS. The specific terms used within this review are presented in the glossary. When there was evidence that a screening programme had been updated, or there were multiple papers covering the same population and period, the most recent and comprehensive study was chosen for inclusion.

Glossary

Antenatal screening programme – for the purposes of this review this corresponds to screening tests offered

to women during their pregnancy to screen for DS.
High chance pregnancy - pregnancy that meets the locally decided threshold for having a higher chance of DS (chance > 1/X pregnancies).
Biochemical testing – umbrella term for the combined use of maternal serum markers (first trimester: free beta human chorionic gonadotropin (HCG) and pregnancy associated plasma protein A (PAPP-A), second trimester: alpha-feto protein (AFP), free beta-HCG, inhibin-A and unconjugated oestriol), maternal age and nuchal translucency measurement on ultrasound to report the chance of the baby having DS. Also sometimes referred to as first trimester combined screening or traditional screening.
First line screen – a screening test that is usually offered to all pregnant women (may have inclusion/exclusion criteria) as their first test screening for the chance of the baby having DS.
Second line screen – a screening test offered to women who have already had one screening test e.g. biochemical, and have been identified as high chance. Can also be referred to as contingent screening.
Pre-NIPT vs post-NIPT – Time periods before and after NIPT was introduced into an antenatal screening programme for DS or offered in a clinical setting. For pre-NIPT, this may have been a period when biochemical screening was offered for DS, or no screening in some cases.
Autonomous Region- any country/state/geographical region with autonomy to implement health policies for its population.
Risk Threshold – the limit set by a specific antenatal screening programme to define a high chance pregnancy with DS after biochemical testing (e.g., a chance of 1 in 150 pregnancies or higher).
Table 1: Glossary of the key terms and their definitions used throughout this systematic review.
7
Studies were excluded when NIPT was not part of a national screening policy, 114 it was not being used to
115 screen for DS, no outcomes of interest were identified in the paper, or were single centre studies.
116
117 Part B (impact of antenatal NIPT screening for DS on the prevalence of specific reproductive choices
118 and pregnancy outcomes): we included observational cohort studies and healthcare or governmental
119 publications where NIPT was accessible as a screening tool, in any clinical setting, including single
120 centre studies. NIPT did not need to have been implemented as part of a national policy. We included
121 studies that provided data on the prevalence of IPD, terminations of pregnancy, and live births of
122 babies with DS. Data on these outcomes before NIPT was introduced was also extracted where
123 reported in that population.
124
125 For both parts, the search strategy (S2 Appendix) included a combination of keywords and MeSH
126 headings relating to the terms ‘non-invasive prenatal testing’, ‘Down’s syndrome’ and
127 ‘implementation’. Some studies were eligible for inclusion in both parts of this review. Reference lists
128 and citations were searched in all included studies. Where reference to a national screening
129 programme was found but the report was not in the included studies, handsearching of Google was
130 used to try and identify the grey literature or reports not formally published on the databases
131 searched. Authors of included studies were contacted if additional data were required for meta132
analysis. Screening, data extraction, and quality assessment of at least 20% of the papers were carried
133 out in duplicate by independent reviewers. No language restrictions were applied. Full details of the
134 search strategy can be found as part of the PROSPERO registered protocol (S1 Appendix). This review
135 was conducted in line with the PRISMA guidelines and checklist (19).
136
137 Quality assessment
138 After full text screening, included studies were quality assessed using the Downs and Black quality
139 checklist by one reviewer (20). Papers were scored as follows: excellent (26-28), good (20-25), fair (15-
8
19) and poor (<14), based on adaptations from evidenced-based healthcare 140 centres by Hooper et al.,
141 (21).
142
143 Data extraction and analysis
144 Study characteristics extracted for both parts, A and B, included the author and year of publication,
145 study design and aims, time period of study, country or state, primary outcome measures of the paper,
146 and declarations of interest/funding. The specific outcomes extracted for each part of the review are
147 described in Table 2. Extracted data was entered into an individual Excel spreadsheet file by each
148 independent reviewer and then merged into a central file once any discrepancies had been agreed.
Table 2: Outcomes extracted from included studies for both sections of this systematic review.

Part A Part B
9
 Year of NIPT implementation.
 NIPT inclusion/exclusion criteria.
 When in the screening pathway NIPT is offered.
 How NIPT is funded (public/patient/both).
 Size of eligible population (n).
 Uptake of NIPT (% of eligible women who opt for NIPT).
 How NIPT is funded (public/patient//both)
 Average maternal age accessing NIPT.
 When NIPT is offered (first/second line screening)
 Number of high chance results after biochemical screening (when NIPT is offered as second line)
 High chance women after NIPT screening (first and/or second line)
 Number of IPD following high chance result from biochemical and/or NIPT screening.
 Number of terminations following high chance biochemical and/or NIPT screening.
 Number of live births of babies with Down's syndrome following high chance biochemical and/or NIPT screening.
 NIPT detection rate for DS and performance of NIPT in the screening pathway (sensitivity/specificity).
 Pre-NIPT implementation data on all variables above.

The data extracted for part A was summarised using appropriate 149 graphical and descriptive analysis. A 150 map of the regions that have implemented NIPT into a national screening programme was produced 151 using Mapchart.net. Narrative synthesis was used to compare the implementation methods between 152 regions. Uptake was compared between regions as a percentage or narratively, depending on whether 153 studies used comparable measures.

154 For part B, data was summarised using frequencies and percentages. Denominator data was the 155 number of eligible women in the population for each stage of the pathway (e.g. population eligible for 156 screening). Data before NIPT was implemented (pre-NIPT) was used to provide comparison data 157 where available.

158 Der Simonian and Laird random effects meta-analyses (22) were used to calculate pooled proportions 159 with respective 95% CI and pooled odds ratios (OR), when there were at least three studies reporting 160 an outcome in part B. Risk ratio and absolute risk difference was also calculated for clearer 161 interpretation of the results. Where there was evidence of moderate heterogeneity ($I^2 > 40\%$), 162 subgroup analyses, as defined a priori, and meta-regressions were used to assess heterogeneity163 inducing factors, including risk threshold for NIPT, whether NIPT was accessed as first or second line screening, uptake of NIPT and whether it was a national im 164 plementation (for studies included in both 165 parts A and B). Publication bias was investigated using funnel plots. Not all papers reported both 166 termination of pregnancy and live birth outcomes. Therefore, a sensitivity analysis was performed on 167 the subgroup of papers that reported both outcomes to investigate whether this influenced the 168 estimated proportion. Further sensitivity analyses, where each included study was omitted one by 169 one, was performed for each of the meta-analyses, to identify the influence of individual studies on 170 the pooled effect size and between-study heterogeneity. Meta-analyses results were displayed using 171 forest plots. All analyses were conducted in R v4.1.3.

172 Results

173 Study Selection

174 Database, citation and grey literature searching returned 1724 records after de-duplication, of which 175 167 studies underwent full text screening for inclusion in parts A, B, or both. The initial search looked 176 for publications from 2010 to 10th May 2022, and was updated 29th March 2023. In total, 42 studies or 177 reports were selected for inclusion in parts A and/or B. The stages of screening, and reasons for study 178 exclusion at the full text screening stage are summarised in the PRISMA diagram in Figure 2. PRISMA 179 checklist for systematic review reporting is provided in S3 Appendix. The characteristics of the 42 180 included studies, including the quality assessment Downs and Black score, are described in detail in 181 Table S2 Appendix.

Part A – The implementation and uptake of NIPT in national antenatal screening programmes for Down's syndrome

Twenty-one manuscripts met the inclusion criteria for part A, reporting on 27 countries, states or autonomous regions in Europe, North America and Asia that implemented NIPT as part of a recommended antenatal screening policy for DS between 2011 and 2023 (Figure 3). Eight were retrospective cohort studies of population-based data (8,10,12,17,18,23–25), evaluating the

Figure 2: PRISMA diagram showing the flow of screening stages in the systematic review. Figure includes details from both the initial search up to 10th May 2022, and the updated search on 29th March 2023.

implementation of NIPT into their screening programmes for DS, and four 189 were prospective cohort studies (11,26–28). Also included were eight official government documents describing the implementation of NIPT (9,29–35) and one study that undertook a survey of clinical experts worldwide, providing data on multiple countries (13). Survey estimates of NIPT uptake from this study were not extracted as it relied on best clinical estimates and was not based on population data.

Overall, the strategies for implementation of NIPT in antenatal DS screening have varied between populations – as both a first and second line screening test, publicly and privately funded, along with differing risk thresholds and criteria used to define high chance pregnancies for DS (Table 3).

Risk of bias

The Downs and Black quality scores are presented in Table S2. The studies that could be quality assessed were 'good' (n=9) or 'fair' (n=3). The government guidelines included in this review were not able to undergo risk of bias assessment as they did not follow the format of a scientific study.

NIPT implementation

The ways in which NIPT has been implemented as part of a prenatal screening policy for DS reported in our included studies are summarised in Table 3. NIPT has been implemented as a first (n=7) or second (n=15) line screening test. In Ontario (Canada) and Japan the option of either pathway is offered. Figure 4 depicts the first and second line screening pathways, as well as describing how the option of both is offered in some regions. Information on when NIPT is offered in the screening pathway was not available for Lithuania, Finland or Slovenia (13). For second line NIPT screening, the risk threshold for NIPT access after a biochemical screening result varies considerably in the included studies; ranging from a chance over 1:1000 in France, Switzerland and Sweden, to a chance over 1:100

Figure 3: Autonomous regions that have implemented NIPT into antenatal screening guidelines for Down's syndrome. Including data from Gadsboll et al.,(13) and NIPT offered under Medicaid cover in the USA but where no other formal offer of NIPT in an antenatal screening programme has been found. Created using Mapchart.net. NIPT = non-invasive prenatal testing.

in Moscow. This threshold dictates the number of women eligible for NIPT and in turn determines the sensitivity, specificity, and overall cost-effectiveness of the screening programme.

Twelve of the 27 regions implementing NIPT reported that they provide NIPT at least partly funded by public health care or insurance plans, and four provide NIPT at full cost to the patient. The UK nations, except Northern Ireland, which has no DS antenatal screening programme, have implemented NIPT as a second line screening test for women with a high chance of having a baby with DS (8,9,32).

Some countries updated their guidelines for implementation and access to NIPT in prenatal screening programmes throughout the period searched. The Netherlands pilot roll-out of NIPT in 2014 (named TRIDENT-1) offered funded NIPT as a second line screen for those pregnant women who had undergone first trimester combined testing (FCT) and were high chance for DS or had a positive medical history (36). The guidelines were updated in 2017, with TRIDENT-2, an evaluative roll-out which offered NIPT to all pregnant women in the Netherlands as a first line screening test at a cost of 175 Euros (11). This was then again updated with the end of the evaluation phase and the full launch of the programme in 2023.

Poland, Romania, Lithuania, Finland, and Slovenia are reported by Gadsboll et al (13) to have implemented NIPT. However, handsearching for relevant documents did not find any information on their screening programmes.

Country / state / province

Year of NIPT implementation When is NIPT offered in the pathway? Funding Risk threshold for NIPT eligibility Study ID
Hong Kong 2011 Second line screen Patient funded >=1: 250 Kou et al., 2016(25)
Japan 2013 First and second line screen - depending on indications
Not reported >1:300 classed as high risk – guidelines do not rely on this for access to NIPT
Samura et al., 2017(37)
Victoria, Australia 2013 First line screen Patient funded N/A Lindquist et al., 2019(18)
Switzerland 2015 Second line screen Publicly funded (insurance)
>1:1000 Swiss public health insurance guidelines, 2015 (33)
Taiwan 2015 First line screen Patient funded N/A Hsiao et al., 2022(24)
Ontario, Canada 2016 First and second line screen
Publicly funded (insurance)
After first trimester screening >=1:350 or second trimester screening >= 1:200
Dougan et al., 2021(23)
Sweden 2016 Second line screen Not reported 1:51 – 1:1000 SFOG guidelines 2016 (35)
Belgium 2017 First line screen Publicly funded (insurance)
N/A Van den Bogaert et al., 2021(12)
Denmark 2017
Danish national guidelines for NIPT introduced in 2017, has been publicly available (funded) since 2013 in some regions of Denmark.
Second line screen Public and patient funded – regional variations
Public setting – >=1:300, some regions offer to intermediate risk: 1:300 – 1:700 or 1:1000.
Lund et al., 2020(17)
South Spain – Andalucía
2017 Second line screen Not reported >=1:280 Torres Aguilar et al., 2021(27)
The Netherlands 2017 First line screen (opt for either NIPT or FCT at similar price)
Subsidised (cost of 175 Euros unless previous history of DS)
N/A Van der Meij, 2019 (11)

Table 3: The implementation methods of NIPT reported in the included studies of part A, when NIPT has been implemented as part of a national screening programme for Down's syndrome.

NIPT first introduced as TRIDENT-1 pilot scheme in 2014, updated

in 2017 with TRIDENT-2
Yukon, Canada 2017 Second line screen (other
indications e.g. twins /
over 35 years offered
NIPT as well)
Publicly funded
(insurance)
Not reported Health and social services
Yukon, 2019 (30)
Wales, UK 2018 Second line screen Publicly funded (NHS) >=1:150 Bowden et al., 2022 (8)
Poissy Saint-
Germain, France
2019
Available under guidelines since
2015, fully funded from 2019
Second line screen Publicly funded (as of
2019)
1:51- 1:1000 Duvillier et al., 2021 (10)
Poland, Romania,
Iceland, Lithuania,
Italy, Finland,
Slovenia, USA
Tuscany, Italy - 2019 Poland and Romania -
second line screen
High chance women can
access NIPT in Iceland
Medicaid coverage
described for NIPT in many
USA states.
Not reported Gadsboll et al 2020* (13)
Korea 2020 Second line screen Not reported >=1:270 Choe et al., 2021 (29)
Moscow, Russia 2020 Second line screen Not reported >=1:100, or 1:101 – 1:2500 Olenev et al., 2021 (28)
Scotland 2020 Second line screen Publicly funded (NHS) >=1:150 Scottish Government - Chief
Medical officer Directorate
2020 (32)
England 2021 Second line screen Publicly funded (NHS) >=1:150 Public Health England,
2021(9)
California, USA 2022 First line screen Publicly funded
(insurance)
N/A The California prenatal
screening programme (34)
Shah et al., 2014(26)
Norway 2022
Updated guideline offering
universal NIPT for women over
35yrs.
First line screen Publicly funded
(insurance)
N/A Norwegian Health
Directorate - national
professional guidelines (31)
228
15
229 Uptake of NIPT
230 The proportion of eligible women opting for NIPT was extracted from eight studies included in part A
231 (Table 4).
232 The uptake of NIPT is highly variable between countries for both first and second line screening. First
233 line NIPT is taken up by 1.54% of the women booking for antenatal care in Ontario, compared to 42%

234 in The Netherlands, although this may be influenced by women having the choice of either first or
235 second line screening in Ontario. Uptake of NIPT as a second line screen among women meeting the
236 local risk threshold after biochemical screening ranges from 20.4% uptake in Hong Kong, to 93.2% in
237 Andalucía, Spain.

Country / state / province	Uptake (%) of NIPT among eligible pregnancies		Reference
	First line	Second line	
Andalucía, Spain		93.2	(27)
Belgium	78.7*		(12)
California, USA		30.86	(26)
Denmark	1.1*		(17)
Hong Kong		20.4	(25)
Ontario, Canada	1.54	73.9	(23)
The Netherlands		42	(11)
Wales, UK		84.3	(8)

Part B – The impact of NIPT on IPD, termination 238 of pregnancy and live births of babies
239 with DS.
240 Thirty-one articles were included for data extraction in part B, ten of which were also included in part
241 A (Table S2 Appendix). Quality assessment classified the included studies into poor (n=5), fair (n=11)
242 and good (n=14). Data was extracted regarding pregnancy choices and outcomes (IPD, termination of
243 pregnancy and live births with DS) from both single centres and populations where NIPT screening
244 had been introduced.
245 Invasive prenatal diagnosis (IPD) following a high chance result for Down's syndrome
246 after biochemical and NIPT screening
247 Twelve studies reported the proportion of women with a high chance pregnancy for DS that had IPD
248 in the period post-NIPT implementation, although only five of these reported outcome data for the
249 pre-NIPT implementation as well.
250 IPD uptake pre-NIPT implementation period vs post-NIPT implementation period
251 Data was extracted from five studies reporting the proportion of women opting for IPD pre-NIPT and
252 post-NIPT implementation.
253 In the pre-NIPT period, between 48% and 93% of women who had a high chance biochemical
254 screening result for DS, opted for IPD. A meta-analysis of proportions was conducted to produce a
255 random effects pooled estimate for the proportion of women with a high chance pregnancy opting
256 for IPD (Figure 5A) indicating a pooled proportion of 75% (95% CI 53%, 88%, I2 = 97%) of women that
257 underwent IPD in the period before NIPT was introduced.
Figure 5: Forest plots for meta-analyses of proportions of IPDs chosen by higher chance pregnancies after biochemical screening for DS. A) pre-NIPT implementation B) post-NIPT implementation. C) Odds ratio metaanalysis, comparing the pre and post NIPT implementation time periods for the odds of having an IPD procedure in higher chance women.

After NIPT was available in these populations, 30% to 62% 258 opted for IPD after a high chance
259 biochemical screening result, and the pooled proportion was 43% (95%CI 31%, 56%; I2 = 95%,
260 suggesting that the proportion of women opting for IPD following a high chance biochemical
261 screening is reduced after NIPT is implemented as a second line screening test in the same
262 population.
263 The pooled odds ratio (Figure 5C) suggests a significant reduction in the odds of opting for an IPD
264 following a high chance biochemical screening result in the post-NIPT period compared to the odds
265 of the pre-NIPT period (OR = 0.25;95% CI 0.1, 0.61; p = 0.0024; I2 = 89%). This reduction represented
266 a risk ratio of 0.62 (95% CI 0.55 – 0.70), and an absolute risk reduction of 38% (S3).
267 IPD uptake among pregnant women with a high chance biochemical screening result after NIPT
268 implementation as a second line screening test
269 To obtain a more robust estimate of the pooled proportion of women with a high chance pregnancy
270 for DS after biochemical screening that chose IPD in the post-NIPT period, a meta-analysis was
271 conducted using data from all studies (n=12, Figure 6). The resulting pooled proportion showed that
272 27% (95% CI 15%, 43%; I2 = 99%) of high chance pregnancies opted for IPD, when NIPT is available as
273 a second line screening test.
274 Uptake of IPD among pregnant women with a high chance NIPT result for DS, after NIPT was
275 available as a first or second line screen
276 The combined pooled proportion of women opting for IPD following a high chance NIPT result, when

277 offered either as a first or second line screen (n = 21), is 87% (95% CI 80%, 92%; I2 = 94%) (S3
278 Appendix). The pooled proportions of IPDs opted for after a high chance NIPT result, when NIPT was
Figure 6: Forest plot of the pooled estimate for proportion of higher chance pregnancies (resulting from biochemical screening) that went on to have an invasive prenatal diagnosis (IPD) after NIPT was implemented as a second line screen.
18
introduced as either a first or second line screening test were also 279 calculated separately (Figures 7A
280 and 7B).
281 The pooled proportion of those opting for IPD following a high chance NIPT result is higher when
282 NIPT is introduced as a first line screening test versus second line introduction - 89% (95% CI 80%,
283 94%; I2 = 94%) of pregnancies, compared to 80% (95% CI 69%, 88%; I2 = 90%) - however there is
284 substantial overlap of the respective CIs. Meta-regression to adjust for first or second line offering of
285 NIPT did not demonstrate any significant difference in IPD uptake between the groups (n=21,
286 p=0.36).
287 Subgroup and meta-regression analyses – factors influencing IPD uptake
288 Subgroup and meta-regression analyses were used to explore the influence of specific variables on
289 the heterogeneity present in the above meta-analyses investigating IPD uptake (Table 5). No
290 significant difference was found between those studies where the biochemical screening threshold
291 to determine high chance pregnancies for DS (and subsequent access to NIPT) was more than 1:149
292 compared to less than 1:150 (p=0.22). When repeated for high chance pregnancies identified by NIPT
293 testing, there did seem to be a significant difference in IPD uptake between the biochemical risk
294 threshold groups and no threshold being in place (first line NIPT) (p<0.0001). Whether NIPT is
295 offered first, second line or as either, does not seem to have a significant effect on the proportion of
296 women choosing to have an IPD after a high chance result from NIPT; subgroup analysis showed 90%
297 (n=8), 81% (n=11) and 91% (n=2) of high chance pregnancies went on to choose IPD when NIPT was
298 implemented as a first, second or as both first- and second-line screening respectively (p = 0.28).
299 Moreover, there was no evidence for NIPT being implemented as part of a national guideline
300 influencing the proportion of women going on to have IPD.
Figure 7: A) Forest plot of pooled proportion of women with a high chance NIPT result that opt for an IPD procedure (NIPT available as a first line screening test); B) Forest plot of pooled proportion women with high chance NIPT result that opt for an IPD (NIPT available as a second line screening test).
19
Meta-regression analysis adjusting for percentage uptake 301 of NIPT when offered as a second line
302 screen, after biochemical screening, showed a significant decrease of NIPT uptake on IPD use
303 (p=0.0002). The regression coefficient (-0.044(-0.067, -0.021)) suggests that for every 1% increase in
304 uptake of NIPT, the uptake of IPD decreases by -0.044. The uptake of first line NIPT screening was
305 not shown to be a significant factor influencing the proportion of IPDs (p=0.60) (Table 5).

Subgroup analyses Predictor variables	Proportion opting for IPD (95% CI) random effects	Test for subgroup differences (pvalue)
Risk threshold for access to NIPT testing (% opting for IPD out of women with a high chance biochemical screening result): - Chance higher than 1:149 (n = 3) - Chance equal to or lower than 1:150 (n = 5)	0.45(0.17,0.77) 0.19(0.06,0.48)	0.22
Risk threshold for access to NIPT testing (% opting for IPD out of women with a positive NIPT result): - Biochemical chance higher than 1:149 (n = 2) - Biochemical chance equal to or lower than 1:150 (n = 6) - No threshold for access (first line NIPT) (n=9)		
i.e. did the risk threshold for NIPT access after biochemical screening (or no threshold for first line NIPT) change the proportion of women opting for IPD?	0.94(0.60,0.99)	

0.65(0.61,0.69)
0.90(0.86,0.93)
<0.0001
When NIPT is offered in the pathway (% opting for IPD out of women with a high chance NIPT result):
- First (n = 8)
- Second (n = 11)
- First or Second (n = 2)
0.90(0.85,0.93)
0.82(0.68,0.90)
0.91(0.25,0.99)
0.28
Meta-regression analyses
Predictor variable Regression coefficient
P-value
Uptake of NIPT as a second line test (%) (n = 9)
Uptake of NIPT as a first line test (%) (n = 4)
-0.0441(-0.067, -0.021)
0.0085(-0.024,0.04)
0.0002
0.60
NIPT implemented as a national guideline (yes) -0.377(-1.3,0.55) 0.42
20
In summary, these analyses demonstrate that the uptake of IPD by 306 high chance pregnant women can 307 be explained in part by how NIPT is implemented (the risk threshold used and when it is offered in a 308 pathway). However, none of these analyses explained a considerable proportion of the 309 heterogeneity.
310 Termination of pregnancies following a high chance screening result for Down's 311 syndrome
312 Only one study provided data reporting the proportion of terminations of pregnancy for babies with 313 DS pre-NIPT implementation. Bjerregaard et al.(38) reports 10 (3.95%) terminations of pregnancy 314 (TOP) for DS after 253 high chance biochemical screening results.
315 Two studies provided data post-NIPT implementation on TOP for DS, after a high chance biochemical 316 screening result, reporting proportions of 4.96% and 10.2% (38,39). Meta-analysis of data (n=7) for 317 pregnant women opting for TOP after a high chance NIPT result (first or second line) provides a 318 pooled proportion of 69% (95% CI 52%, 82%; I2 = 88%) (Figure 8).
319 Live births following a high chance NIPT result for Down's syndrome
320 None of the included studies reported the proportion of live births of babies with DS following a high 321 chance biochemical screening test pre-NIPT implementation.
322 In the post-NIPT period, Dap et al., 2022 reported two live births of babies with DS following a high 323 chance biochemical screening result, out of 98 higher chance women identified by biochemical 324 screening. After a high chance NIPT result, seven studies reported the live births of babies with DS 325 (Figure 9).
21
The proportion of live births of babies with DS after high chance NIPT 326 ranged between 0% and 28%, 327 with a pooled proportion of 8% (95% CI 3%, 21%; I2 = 87%).
328 Only four of the studies included in the TOP and live birth analysis reported data on both outcomes, 329 allowing a comparison of these estimates in the same population. The pooled proportions of 330 terminations of pregnancy and live births were 72% (95% CI 50%, 87%; I2 = 91%) and 10% (95%CI 3% 331 to 28%; I2=90%) respectively. There is some discrepancy between the values for live births and 332 terminations of pregnancies, where we do not have an outcome for each pregnancy reported in 333 some included papers. The remainder of pregnancies will have ended in spontaneous pregnancy loss 334 or will have been lost to follow up within the study period.
335 Sensitivity analyses
336 Funnel plots of each meta-analysis demonstrated some asymmetry, which could be due to 337 publication bias, or true heterogeneity within the data (S4 Appendix). Sensitivity analyses were run

on each meta-analysis to explore heterogeneity, whereby one study was omitted at a time. None of the studies in the meta-analyses exploring IPD uptake showed significant influence over the estimated proportion or heterogeneity of the analysis. This was also found in the TOP meta-analyses, however, for the live birth meta-analysis omitting Samura et al. was seen to reduce the heterogeneity to 64% (from 87%) and gave a pooled estimate of 11% (95% CI 4%, 28%). S3 Appendix provides the results of each sensitivity analysis.

Discussion

Summary of findings:

Overall, part A demonstrates a huge variation in NIPT implementation and its uptake between eligible populations. NIPT has been implemented throughout the period of the search (2011 – 2023) as a first and second line screen in 27 autonomous regions, both funded by governments and

privately. The differences in NIPT implementation could partially explain the heterogeneity in uptake. However, differences between healthcare systems, access to medical and social care resources, and societal attitudes towards termination of pregnancy (TOP) and other aspects of prenatal screening will also play a role in the acceptability of NIPT to the general public.

The overall proportion of IPD procedures after biochemical screening seems to have reduced after the introduction of NIPT as a second line screen. Moreover, pooled results showed that, overall, 89% of pregnant women opted for IPD after a high chance NIPT result, 69% chose to have a TOP, and 8% of high chance pregnancies after NIPT ended in live births of babies with DS, although with a high level of heterogeneity. When it was possible to do so, adjusting for different aspects of NIPT implementation using subgroup analysis and meta-regression accounted for some heterogeneity in the results looking at the uptake of IPD, namely the uptake of NIPT as a second line test and the risk threshold used for NIPT access. Other factors analysed didn't seem to account for this heterogeneity. Pooled estimates of key outcome measures of NIPT impact in populations around the world were provided, an important starting point for the continual monitoring of NIPT impact.

Strengths:

This systematic review followed focussed review questions, with inclusion and exclusion criteria selected a priori and published on the PROSPERO register. It utilised an exhaustive search strategy on multiple databases, using sources that will deliver both published materials and grey literature. A standardised risk of bias assessment tool was used, with appropriate subgroup, meta-regression and sensitivity analyses to explore sources of heterogeneity and bias in the included studies. The screening of manuscripts was undertaken by two independent reviewers, and discussion taken to a third reviewer for settling disagreements.

Limitations:

Not every study included in part A provided details of NIPT implementation or uptake values for their population, limiting the available evidence for comparison between screening programmes. Uptake data was also limited by the level of detail provided, for example with some articles not providing the denominator data for NIPT uptake.

This review is restricted to published material and grey literature referenced in included studies, and as government guidelines or recommendations may not be always made publicly available or published this will have limited the number of countries included in our results. National policies on NIPT implementation that are not mentioned in peer reviewed literature will have been omitted.

The studies included in this review are mostly observational cohort studies. These are difficult to assess for quality, as many elements of the data collection are not able to be controlled. The Downs and Black scoring system has been used. However, as none of these studies are randomised cohort trials there will inherently be bias in these studies.

Many studies do not report the data necessary to analyse the outcomes of interest (missing data, lost to follow up, not enough data to estimate raw frequencies). Where data is reported, often the sample sizes were small and confidence intervals very wide. Pre-NIPT implementation data was not separately searched for, which means we have limited data to compare to available post-NIPT implementation data. Data on high chance women after biochemical screening was extracted so that it would be comparable between pre and post NIPT periods, where biochemical screening was used in both, but the raw data for women undergoing each type of screening was not often reported or available.

The meta-analyses showed high heterogeneity overall. Random effect models were used to adjust for statistical heterogeneity, and sensitivity and subgroup analyses to explore its possible sources.

Comparison with existing literature:

This review sought to provide an updated understanding of where and how NIPT has been implemented as part of a national screening programme. The results demonstrate that NIPT is available globally, although mostly among European and high-income countries. Changes and updates to the provision of NIPT were identified and may be due to the initial cost of the test gradually decreasing with the more common use and availability of this technology, which has meant many countries have been able to introduce this test as a first line screen (40).

The infrastructure and provision of healthcare resources, including cost and access, differ greatly between countries and will influence the acceptability of a new screening test or process such as NIPT. A comparative study of NIPT use in Quebec (Canada) and Lebanon highlighted the barriers to access and ethical considerations presented in each population. This included the cost of screening tests, coverage by insurance, lobbying by disability rights activists in Quebec, and the attitudes towards termination of pregnancy (41). Similarly, the contrast between NIPT implementation in Germany and Israel has been discussed by Raz et al., 2021 (42). These aspects were not able to be accounted for in analyses and could inevitably be influencing the variation seen in the results.

Overall, vast heterogeneity in the healthcare systems and cultural differences between populations and regions will strongly influence the use and uptake of NIPT. What is clear is that each country has implemented NIPT in a different way, depending on several factors that might include the pre-existing infrastructure for a screening programme; how the healthcare system runs; expected cost of healthcare; the cultural and societal expectations on pregnancy screening and acceptability of disability in these populations.

Implications for clinical practice / policy:

Numerous professional bodies have recommended the implementation of NIPT into screening programmes (43,44) citing benefits such as cost effectiveness, improved accuracy for detecting trisomies, and a potential reduction in the number of invasive procedures performed. When considering the methods of implementation and eligibility criteria for access to NIPT there seems to be no consensus in how best to achieve this, instead pre-existing healthcare and societal aspects play significant roles.

Since first marketed in 2011, NIPT has expanded rapidly from the commercial to public sectors. As argued by Dougan et al. (23), the highly commercialised and marketed nature of the introduction of NIPT resulted in the quick, and unstandardised implementation of this test into the public sector. It is therefore important to understand the extent of availability and the impact this has had on the choices made by women and on the outcomes of babies with DS, warranting ongoing examination at a population level.

There is a lack of comprehensive data on the uptake of NIPT in populations, presented for a few countries included in this review. Moreover, there will be an inevitable lag between the implementation of a new technology and the publishing of any evaluation data, as well as many countries not having the resources to collect the required data to present these statistics. Consequently, data from those areas where NIPT has been more recently implemented will be unavailable, and subsequently the reported list of countries or states implementing NIPT will not be exhaustive, and the outcome data included in the meta-analyses limited.

The data analysed in this systematic review, and lack of completeness, emphasizes the requirement for further population-based data to be published, which should allow for comparison between a more diverse set of countries and possibly start to demonstrate associations between population characteristics and uptake of NIPT.

Being a particularly sensitive topic, many countries may be reluctant to publicly endorse pregnancy screening for DS or publish their guidelines; suggested as one of the reasons behind countries such as Germany not introducing a nation-wide policy on NIPT (42).

Ultimately, policy decisions impact on the choices made during pregnancy, and careful consideration should be given to the way these changes are implemented. Transparent and publicly available data is essential for a global approach to monitoring such impactful changes to screening programmes for DS.

In conclusion, NIPT has been implemented as an antenatal screening test in national DS screening programmes in many countries, and in a variety of ways, depending on the pre-existing healthcare structure and resources of that country. The uptake of NIPT is seen to differ greatly between

449 populations, with no clear association with how NIPT has been implemented. There is evidence that
450 the number of pregnancies undergoing invasive prenatal diagnosis has reduced after second line
451 NIPT screening was implemented. The impact of NIPT on terminations of pregnancy and live births of
452 babies with DS cannot be examined in this review as comparable data for pre-NIPT period is not
453 available. Further studies using comparative pre and post NIPT data in the same populations are
454 required to understand its impact on these outcomes.

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