

National data on the early clinical use of non-invasive prenatal testing in public and private healthcare in Denmark 2013-2017

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National data on the early clinical use of non-invasive prenatal testing in public and private healthcare in Denmark 2013-2017

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Conflicts of interest

None

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ABSTRACT

Introduction: In Denmark, non-invasive prenatal testing (NIPT) has been used since 2013. We aimed to evaluate the early clinical use of NIPT in Danish public and private healthcare settings before NIPT became an integrated part of the national guidelines on prenatal screening and diagnosis in 2017.

Material and Methods: NIPT data were collected between March 2013 and June 2017 from national public registries and private providers. Results from follow-up samples (chorionic villi, amniotic fluid, postnatal blood or fetal tissue) were included from The Danish Cytogenetics Central Registry and indications and outcome from The Danish Fetal Medicine Database.

Results: A total of 3,936 NIPT results were included in the study from public hospitals (n=3,463, 88.0%) and private clinics (n=473, 12.0%). The total number of prenatal tests was 19,713 during the study period: 20% was NIPT-analyses (n=3,936) and 80% invasive procedures (n=15,777).

Twenty-five per cent of NIPTs in the private clinics were performed before gestational week 11+0, whereas NIPT in public settings was used only after combined first trimester screening ($p<0.001$). Regardless of indication, the national public sensitivity was 96.9% (CI 95%: 82.0-99.8%) for trisomy (T) 21, 100%(CI95%: 46.3-100%) for trisomy 18, 100%(CI 95%: 5.5-100%) for trisomy 13 and 87.0%(CI 95%: 74.5-92.4%) for any fetal chromosomal aberration. Forty-seven true positive NIPT results included cases of common aneuploidies (trisomy 21, n=31; trisomy 18, n=5, trisomy 13, n=1), sex chromosomal aberrations (n=7) and atypical chromosomal aberrations (n=3). One false negative NIPT result occurred (trisomy 21). Twenty-one out of 47(45%) cases with a true positive NIPT result resulted in live births by choice; eleven of these children had Down and four had Edwards Syndrome.

Conclusions: The total number of NIPT analyses was low compared to the number of invasive procedures in the implementation period. In contrast to the generally high termination rate after a positive result following invasive testing in Denmark, a high proportion of true positive NIPT-results from the public setting resulted in live births. NIPT may be an important risk-free alternative to invasive testing for a minority of women in the public setting who wish to use prenatal genetic testing for information only and not for reproductive decision-making.

Key words:

Prenatal diagnosis, non-invasive prenatal testing, trisomy, chromosome aberration, DNA

Abbreviations:

NIPT, non-invasive prenatal testing;

T21, trisomy 21;

T18, trisomy 18;

T13, trisomy 13;

CVS, chorionic villus sampling;

AC, amniocentesis;

DCCR, The Danish Cytogenetics Central Registry;

cFTS, combined first trimester screening;

Key message

The number of NIPT performed in Danish public and private settings was low throughout the implementation phase. NIPT seems to be a useful alternative to couples using prenatal genetic testing for information only and in private sector prior to combined first trimester screening.

INTRODUCTION

Non-invasive prenatal testing (NIPT) uses cell-free DNA in maternal plasma to screen for fetal aneuploidy. Multiple clinical trials have documented that NIPT can be used as an accurate alternative screening tool for fetal trisomy 21, 18 and 13 (T21, T18, T13)¹⁻³. Until recently, NIPT was mainly driven by private international laboratories^{4,5}; now NIPT is being implemented in national public healthcare systems^{6,7}.

Little is known about the use of NIPT in various clinical national contexts⁷. Previous studies are limited to populations with low uptake of combined first trimester screening (cFTS)⁶. However, use of NIPT remains unclear in countries like Denmark where >96% of women participate in cFTS⁸.

NIPT can be used as either a first line test or in a contingent screening model in existing prenatal screening programmes. NIPT is superior to the cFTS for T21. Compared to invasive testing, such as chorionic villus sampling (CVS) or amniocentesis (AC), NIPT does not carry any risk of miscarriage⁹. Currently, chromosomal microarray on invasive samples is, however, superior to NIPT with respect to detection of atypical chromosomal abnormalities¹⁰⁻¹⁴. NIPT is a screening tool and false positive and false negative NIPT results occur; abnormal NIPT results must be verified by CVS or AC.

In Denmark, NIPT became available in the Danish public and tax-financed healthcare system before a standardised national guideline on NIPT was issued by the Danish Health Authority (January 2017). Prior to the introduction of NIPT in Denmark, all prenatal genetic results from the public clinical genetics laboratories were documented in the Danish Cytogenetics Central Registry (DCCR)¹⁵. With the introduction of NIPT, followed an irregular time period where NIPT results were not systematically registered in the DCCR, because NIPT was performed in many different clinical settings including private clinics and laboratories^{16,17}.

The primary aim of this study was to collate and describe the early clinical use of NIPT in Denmark in both public and private settings including indications, NIPT results and genetic follow-up from invasive tests and postnatal blood sampling. We also wished to evaluate pregnancy outcome to assess if women used true positive NIPT results as information only or as a basis for reproductive decision-making. Finally, we intended to estimate the extent to which NIPT changed the diagnostic rate of any fetal aberration in women opting for NIPT compared to the other national offers for invasive testing.

MATERIAL AND METHODS

Danish National Guidelines on prenatal screening and diagnosis

Since 2004, all pregnant women in Denmark have been offered tax-financed cFTS; risk assessment is performed according to the Fetal Medicine Foundation algorithm using maternal age, pregnancy-associated plasma protein A, free beta Human Chorionic Gonadotropin, and nuchal translucency measurement¹⁸. According to national guidelines, women are offered CVS at gestational weeks 11-13 or AC at 16 weeks if the calculated cFTS risk is high; defined as $\geq 1:300$ for T21 or $\geq 1:150$ for T18 or T13.

Since January 2017, revised national guidelines on prenatal screening and diagnosis have included NIPT. These guidelines are based on the guidelines from 2004 stating that NIPT should only be used in women at high risk after cFTS as an alternative to invasive testing. If malformations are detected by ultrasonography or a single outlier of the four risk parameters (maternal age ≥ 45 years, pregnancy-associated plasma protein A < 0.2 multiple of the median, free beta human chorionic gonadotropin < 0.2 or ≥ 5 multiple of the median or nuchal translucency measurement ≥ 3.5 mm) in cFTS is present, the woman will be recommended to undergo CVS or AC over NIPT.

Data collection in public settings

The clinical use of NIPT was studied retrospectively between March 2013 and June 2017. The first clinical use of a NIPT analysis occurred in March 2013; the end date of the study was chosen so the youngest children from pregnancies where NIPT was performed would be at least 15 months old when we collected data on postnatal genetic analyses. We expected that abnormal phenotypes due to serious chromosomal disorders in these children would be discovered within the first 15 months of life.

Three different sources have been used to collect NIPT data in public settings. The DCCR (Source 1) provided results from reported NIPTs, including any follow-up invasive samples or blood samples from children born to women who had undergone NIPT. Due to incomplete reporting, data were only available from two out of three of the public clinical genetic

laboratories. To obtain data from the third laboratory, we obtained approval from The Danish Patient Safety Authority (3-3013-2445/1) to supplement NIPT data through search queries in the local Astraia fetal medicine databases (Source 2), a uniform national medical record system used by all fetal medicine departments in Denmark. Finally, public clinical biochemistry laboratories performing NIPT as well as departments of obstetrics using private foreign laboratories agreed to supply NIPT reports directly for this study (Source 3). Detailed information on the various NIPT-platforms were not included from the different sources. The NIPT platforms used by Danish public laboratories were a whole genome sequencing approach including software analysis tools validated solely for T21, T18 and T13.

The Danish Fetal Medicine Database (FØTO-2017-10-12) approved inclusion of clinical data in the study. NIPT data were linked to clinical data in Danish Fetal Medicine Database using the 10-digit unique Danish civil registration number assigned to all Danish citizens. To include data from the specific pregnancy where NIPT had been performed, date of the NIPT was matched to the calculated due date determined by crown-rump-length measured by ultrasonography in the first trimester. Data added from the Danish Fetal Medicine Database were: cFETS parameters, any malformations detected by ultrasound, pregnancy outcome and civil registration number of all live born children. The latter data were used to retrieve data on any postnatal blood samples from the DCCR.

NIPT data from research projects, validation samples collected after abnormal results of invasive tests, cases without information on NIPT result or cases where civil registration number was missing were excluded from the study. NIPT results from twin pregnancies have also been included.

Data collection in private settings

NIPT results from private clinics were collected by contacting all known clinics offering NIPT. Six out of eleven private clinics offering NIPT to women agreed to forward data for this study; some of the clinics not participating explain that the great majority of their patients were not Danish citizens. Private clinics in Denmark are not currently obliged to document data in national registries. Data were collected anonymously and only maternal age at NIPT, gestational age at NIPT and NIPT results were included. NIPT results on women who were not Danish citizens were excluded. Results from follow-up samples such as CVS or AC were reported by the clinic.

Data management and statistics

Data were collected and managed using the REDCap electronic data capture tools hosted at Aarhus University, Denmark. Stata version 15 was used for all statistical analyses. The Chi-squared or Fisher's exact tests were used for comparison of proportions, the two-sample Wilcoxon rank sum test and the unpaired sample t-test were used for continuous outcomes. The Danish Data Protection Agency approved the study (1-16-02-656-16).

RESULTS

Clinical settings, pregnancy and test characteristics

A total of 3,936 NIPT results from public hospitals (n=3,463, 88.0%) and private clinics (n=473, 12.0%) were included in the study. The five regions in Denmark commenced using NIPT at different times and for different indications. Two public departments of obstetrics in two regions were the first to implement NIPT in March 2013 using foreign international private laboratories. Next, private clinics followed in 2013-2014. In all regions, departments of obstetrics began to offer NIPT provided through public clinical genetics and biochemistry laboratories in 2015-2016. All included NIPT analyses from private clinics were performed at commercial foreign laboratories. In the public setting, NIPT was additionally offered to a group at intermediate risk (defined as 1:300-1:700 or 1:300-1:1000 for T21 depending on geographical region) by two out of five Danish regions for a limited period. The total number of prenatal tests was 19,713 during the study period: 20% was NIPT analyses (n=3,936) and 80% invasive procedures (n=15,777). (Figure 1).

Twenty-five per cent of NIPTs in private clinics were performed before gestational week 11+0, whereas NIPT in public settings was used only after cFTS ($p<0.001$). Women seeking NIPT in private clinics were older than women obtaining NIPT through public healthcare (median age in years: 37 versus 33, $p<0.0001$) (Table 1). The failure rate or proportion of inconclusive results was lower in private than in public settings (1.7% versus 6.1%, $p<0.001$).

Public sector NIPT results and outcome

Overall, 76 out of 3,463 (2.2%) had an abnormal NIPT result of which 64 (84.2%) were followed by invasive or postnatal testing (Figure 2). Twelve cases were with no pre- nor postnatal follow-up. Among the 64 pregnancies with follow-up of a positive NIPT result 47 were true positive

NIPT results and 17 cases were false positives. One false negative NIPT result occurred (46,XX,+21,rob) (Table 2).

Indications for obtaining NIPT were high risk (54.4%, n=1,883) or intermediate risk (27.0%, n=902 risk of 1:300-1:700 and n=33 risk of 1:701-1:1000) after cFTS or "other indication" (18.6%, n=645) (Table 2). Independent of indication, sensitivities were 96.9% (CI95%: 82.0-99.8%) for T21, 100% (CI95%: 46.3-100%) for T18 and 100% (CI95%: 5.5-100%) for T13. The false positive rate was <0.2% for all chromosomal aberrations. The positive predictive values ranged between 20.0 and 88.6%; T13 was lowest and T21 was highest (Supporting Information Table S1).

A total of 21 out of 47 (45%, CI95%: 30.5-59.8) true positive cases resulted in live births by choice; Down syndrome (n=11) (Figure 3), Edwards syndrome (n=4) and children with sex chromosomal aberrations (Monosomy X, n=2; XXY, n=3; XXX, n=1). Three women with true positive NIPT results experienced a miscarriage and 19 women chose termination of pregnancy after the positive NIPT result had been confirmed; 4 pregnancies were lost to follow-up.

Diagnostic rate of any fetal aberration after NIPT in public settings

Three cases of atypical chromosomal aberrations (duplication on chromosome 2, T2 and T16) were detected by NIPT (Table 2). Among the normal NIPT results, six cases of *clinically significant* atypical chromosomal aberrations were detected later in pregnancy (n=1) or postnatally (n=5). These six cases could not be expected to be detected by NIPT (not common aneuploidies) as they included 69,XXX (n=1), 47,XX,i(18)(p10) (n=1) and subchromosomal aberrations (n=4). To estimate the diagnostic rate of *any* fetal aberration after NIPT (47 true positive NIPTs + missed cases T21, n=1; significant atypical chromosomal aberrations, n=6), a fictive pooled sensitivity was calculated (excluding failed and inconclusive results): 47/54=87.0% (CI 95%: 74.5-92.4%). Pooled sensitivities differed between the two risk categories after the cFTS; high and intermediate risk, respectively (92.3% vs 42.9%, $p=0.006$; Table 2 and Supporting Information Table S2).

Private sector NIPT results

Private sector NIPT results were abnormal in 1.7 % (T21, n=4; T18, n=2; sex chromosomal aberrations, n=2). Fifty per cent were true positive (T21, n=3) and 50% were false

positive (high risk for T21, n=1, high risk for sex chromosomal aberrations, n=2). Information was not available for the two cases with NIPT results indicating high risk for T18. None of the clinics were aware that they had experienced false negative NIPT results.

DISCUSSION

Initially, NIPT in the Danish public health care setting (2013-2017) was unevenly distributed between geographical regions in terms of commencement and indication until the revised national prenatal guideline appeared in 2017. NIPT was introduced early through the private sector; this was unprecedented in Denmark because it became possible to conduct private prenatal genetic testing without any national registry practice or formal counselling. The irregular use of NIPT in Denmark is similar to other countries where NIPT has also been introduced through commercial companies, the private sector and/or public regional set-ups⁷. However, compared to countries such as the US and Australia^{19,20}, where the number of invasive procedures has declined after the introduction of NIPT, the situation is different in Denmark. The number of NIPTs performed in Danish healthcare is low compared to the number of invasive tests (Figure 1). The number of NIPT analyses would have been markedly higher if NIPT had been used as a first-tier test as in the Netherlands⁶. Contrary, NIPT has primarily been used as an offer after cFTS in the public setting owing to a general acceptance of cFTS among Danish fetal medicine experts and Danish pregnant women. The general high rate of invasive tests in Denmark may be explained by Danish women's and health professionals' preference for comprehensive genetic information²¹, and the low risk of miscarriage following invasive testing⁹. Questionnaire studies have shown that generally many Danish pregnant women are positive towards NIPT²¹⁻²². The reason for the actual low NIPT uptake from our data may be that comprehensive genetic information is prioritized over no miscarriage risk when pregnant women are facing an actual high-risk screening result and undergo pre-test counselling by a health professional.

In our study, the sensitivity of NIPT for T21 was 96.9% and reflects the actual start-up phase of the clinical implementation of NIPT in prenatal care and may not be comparable to a controlled clinical set-up or trial as in other studies. Our numbers are small and just the one de novo isochromosome (21), that are known to be overrepresented among false negative NIPT results, can markedly decrease sensitivity²³.

Our aim was also to estimate how NIPT changed the diagnostic rate of *any* fetal

aberration in women opting for NIPT compared to the other national offers of invasive testing. The overall fictive pooled sensitivity was 87.0%; this was, as expected, lower than the normally reported NIPT sensitivities for common aneuploidies. The fictive pooled sensitivities differed between the two risk groups after cFTS and performed better among the high risk compared to the intermediate risk group (92.3% versus 42.9%, $p=0.006$). This result indicates that NIPT may not be the right choice for women with an intermediate risk after cFTS if the woman also wants to get genetic information on other chromosomal abnormalities than T21. We acknowledge that NIPTs described here cannot detect atypical chromosomal abnormalities yet and therefore the calculated fictive pooled sensitivities should be interpreted with caution. However, in line with our data, previous studies have demonstrated that 45% of atypical chromosomal aberrations can be found in the risk-group 1:1000-1:200 after cFTS¹⁴. Future research is needed in order to study how women in the intermediate risk group can be cared for as these pregnancies seem to have a high proportion of atypical chromosomal abnormalities²⁴.

Establishing qualitative knowledge on women's preferences for different prenatal testing methods is beyond the scope of this study. However, in the present study, an unexpected high proportion (45%) of couples in the public setting chose to continue the pregnancy after a true positive NIPT result; this is in contrast to the generally high termination rate (>95%) after a positive result following invasive testing in Denmark¹⁵. This tendency was also described in two other studies^{22, 25}. Furthermore, the numbers of invasive tests performed between 2013-2017 have not changed in Denmark and equal the years before the introduction of NIPT in 2013¹⁵ (Figure 1). Therefore, it seems that women at high risk after cFTS who chose NIPT over invasive testing may have chosen not to proceed with any further testing if NIPT had not been an option to them. Two Danish studies have reported that the rate of follow-up testing after a high risk cFTS screening result increased when NIPT was an alternative to invasive testing^{16, 22}. In the private setting, NIPT seems to be of particular value to older women and women at an early gestational age. The main users of NIPT in Denmark in the study period seem to be women of age (private sector, prior to cFTS) and women uninterested in reproductive choices for T21 (public sector, after cFTS).

A limitation to this study might be the incomplete data collection; especially from the private sector where data were anonymous and systematic follow-up not available. Concerning public NIPT data, it was not possible to get all data from the DCCR or directly from the laboratories. With input from the local Astraia fetal medicine databases, we estimated having collected more than 96% of all public NIPT analyses in the study period. In a study like this,

including all national NIPT data from three different public sources, it is inevitable not to experience data loss.

The strengths of this study are that we have included results from follow up samples and outcome through public national registries on the vast majority of the included pregnancies. In this way, the sensitivity of NIPT for any fetal chromosomal aberration could be calculated and women's decision-making concerning further testing after receiving a NIPT result could be evaluated.

The present study mainly evaluated national NIPT data prior to the implementation of revised Danish guidelines on prenatal screening and diagnosis in January 2017. Future studies focusing on the implementation of NIPT after 2017 in Denmark will show whether NIPT will lead to a change in screening procedures and outcome, though not indicated by the results from present study.

CONCLUSION

NIPT was introduced unevenly into Danish healthcare during 2013-2017 in terms of initiation and indication. At least 12% of all NIPTs performed in Danish women were performed in the private sector. The total number of NIPT analyses has been low compared to the number of invasive tests for this implementation period.

The study of NIPT has extended our knowledge of NIPT sensitivities in an actual clinical start-up phase in a country with low NIPT uptake. The sensitivity for T21 (~97%) was lower than in previous studies and the sensitivity for any fetal chromosomal aberration, including common aneuploidies and chromosomal aberrations that NIPT is not validated for, was overall ~87%.

Forty-five per cent of women in the public setting with a true positive NIPT result chose to continue the pregnancy, which is an unusually high rate in Denmark. NIPT used after cFTS in the public system seems to be a good alternative in the minority of Danish pregnant couples who wish to use prenatal genetic testing for information only and not for reproductive decision-making. Contrary, in the private sector NIPT is mainly used by older women at an early gestational age likely with reproductive choices in mind.

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Legends

Table 1. Pregnancy and test characteristics in the public and private settings. NIPT data for singleton and twin pregnancies (<2.4%) are shown. The percentages do not add up to 100% due to missing data. In public, 37 women (1.1%) underwent NIPT in two or more different pregnancies during the study period.

Table 2. NIPT results, fictive pooled sensitivity and indication in the public setting. Only cases with genetic follow-up are included. Fictive pooled sensitivity includes *any* fetal chromosomal aberration. Other indications included prior pregnancy with T21, T18 or T13, abnormal fetal ultrasonography or no indication was specified.

Figure 1. Timeline of the use of NIPT and invasive procedures in Denmark 2013-2017 shown in six-month intervals. Y-axis shows total number of tests and X-axis time by six-month intervals. Abbreviations: CVS, chorionic villus sampling; AC, amniocentesis

Figure 2. Flow diagram of public NIPT results and genetic follow-up. The flow diagram shows public NIPT results and includes all available information from follow-up analyses in The Danish Central Cytogenetics Registry. Prenatal genetic follow-up are invasive samples and postnatal genetic follow-up are both blood samples from children and fetal tissue samples. Abbreviations: FN, false negative; FP, false positive; LB, live born; na, follow-up not available; other, atypical chromosomal aberration beyond common trisomy or sex chromosomal aberrations; SCA, sex chromosomal aberration; T21, trisomy 21; T18, trisomy 18; T13, trisomy 13; TN, true negative; TOP, termination of pregnancy; TP, true positive.

Figure 3. Total number of positive NIPTs for T21 (false positives excluded) and outcome. The number of cases is shown on the y-axis and the different outcomes on the x-axis. The striped bar illustrates that outcome was not available in six cases and two of those had no genetic follow-up. Abbreviations: LB, live born; TOP, termination of pregnancy; na, not available; T, trisomy; DS, Down syndrome; FP, false positive.

Supporting Information legends

Table S1. Sensitivities, specificities and predictive values for common trisomies and sex and chromosomal aberrations independent of indication.

Table S2. Pooled sensitivity for any fetal chromosomal abnormality.

Table 1. Pregnancy and test characteristics in the public and private settings. NIPT data for singleton and twin pregnancies (<2.4%) are shown. The percentages do not add up to 100% due to missing data. In public, 37 women (1.1%) underwent NIPT in two or more different

	Public, n=3,463	Private, n=473	Difference
Maternal age			
Median Age, years (IQR)	33 (28.5;37)	37 (34;40)	$p<0.001^{**}$
Age ≥ 45 years n (%)	31 (0.1%)	10 (2.1%)	$p<0.001^{**}$
Gestational age			
Median weeks+days (IQR)	13 ⁺² (12 ⁺⁵ ; 14 ⁺¹)	12 ⁺³ (10 ⁺⁶ ;13 ⁺⁶)	$p<0.001^{**}$
NIPT test characteristics			
Median TAT, days (IQR)	8 (6;9)	5 (4;6)	$p<0.001^{**}$
Median FF % (IQR)	10.5 (8;13.3)	8.8 (7.2;11.5)	
Failed or inconclusive test n (%)	211 ^a (6.1%)	8 (1.7%)	$p<0.001^{**}$

pregnancies during the study period.

Abbreviations: NIPT, non-invasive prenatal testing; IQR, interquartile range; TAT, turn-around-time; FF, fetal fraction.

^aOne laboratory later changed their method of analyses to improve diagnostic rate.

Table 2. NIPT results, fictive pooled sensitivity and indication in the public setting. Only cases with genetic follow-up are included. Fictive pooled sensitivity includes any fetal chromosomal aberration. Other indications included prior pregnancy with T21, T18 or T13, abnormal fetal ultrasonography or no indication was specified.

	NIPT with genetic follow-up				
NIPT results, n=3,463 (Genetic follow-up, n=3,451)		Indication for NIPT			True positives
		High risk after cFTS, n=1,879	Intermediate risk after cFTS, n=900	Other or unknown indication, n=672	
NIPT Positive n=76	All, n=64 (84.2%):				n=47 (73.4%)
	T21, n=35	n=27 TP, n=24; FP, n=3	n=2 TP, n=2	n=6 TP, n=5; FP, n=1	
	T18, n=7	n=7 TP, n=5; FP, n=2	n=0	n=0	
	T13, n=5	n=4 TP, n=1; FP, n=3	n=0	n=1 FP, n=1	
	Sex chromosomal aberrations, n=13	n=6 TP, n=4; FP, n=2	n=3 TP, n=1; FP, n=2	n=4 TP, n=2; FP, n=2	
	Other chromosomal aberrations, n=4	n=2 TP, n=2 ^a	n=0	n=2 TP, n=1 ^b ; FP, n=1 ^c	
NIPT Normal n=3,176	All, n=131 (4.1%)	n=3, (other chr. abn. ^d)	n=1, 46,XX,+21,rob(21;21)(q10;q10) n=3, (other chr. abn. ^e)	n=0	n=7 (5.3%)

NIPT Failed or inconclusive, n=211	All, n=80 (37.9%)	n=2 (T21; T18) n=4 (other chr. abn. ^f)		n=0	n=6 (7.5%)
Fictive pooled sensitivity - TP/(TP+FN) (failed and inconclusive results are not included)		High risk 36/39=92.3% (CI95%: 78.0- 98.0 %)	Intermediate risk 3/7=42.9% (CI95%: 11.8-79.8%)	Other indication 8/8=100%	
	All indications 47/54=87.0% (CI95%: 74.5-94.2%)				

^{a)} T16 and >60 Mb duplication on chromosome 2

^{b)} T2

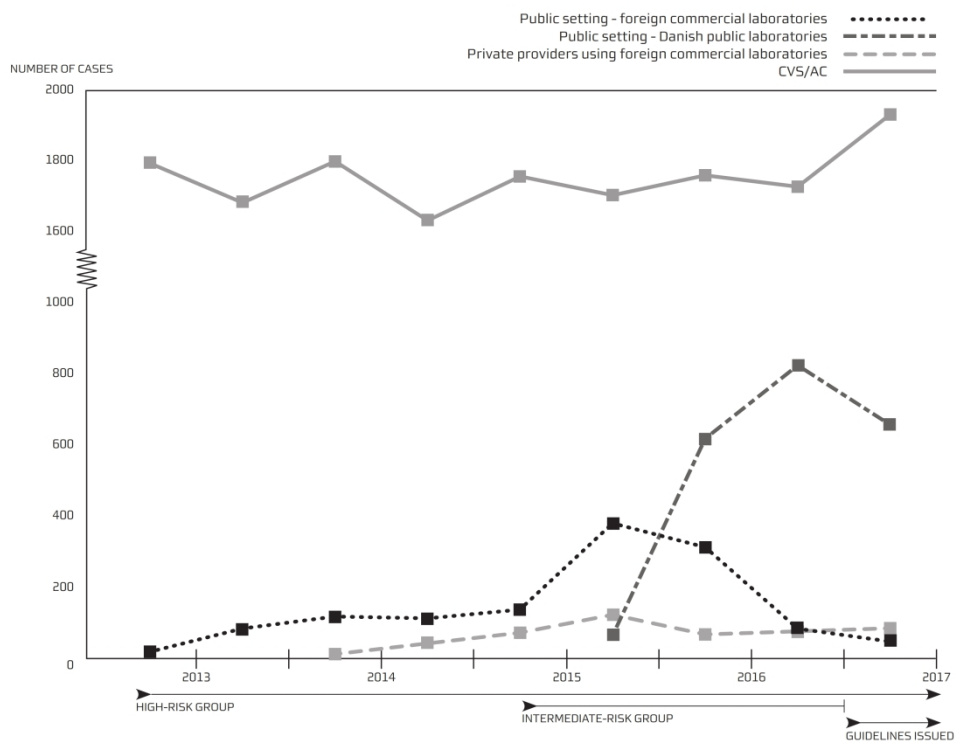
^{c)} Deletion on chromosome 20

^{d)} 47,XX,i(18)(p10), 69,XXX and arr[GRCh37] 10q22.1q22.2(72985755-75416855)x3

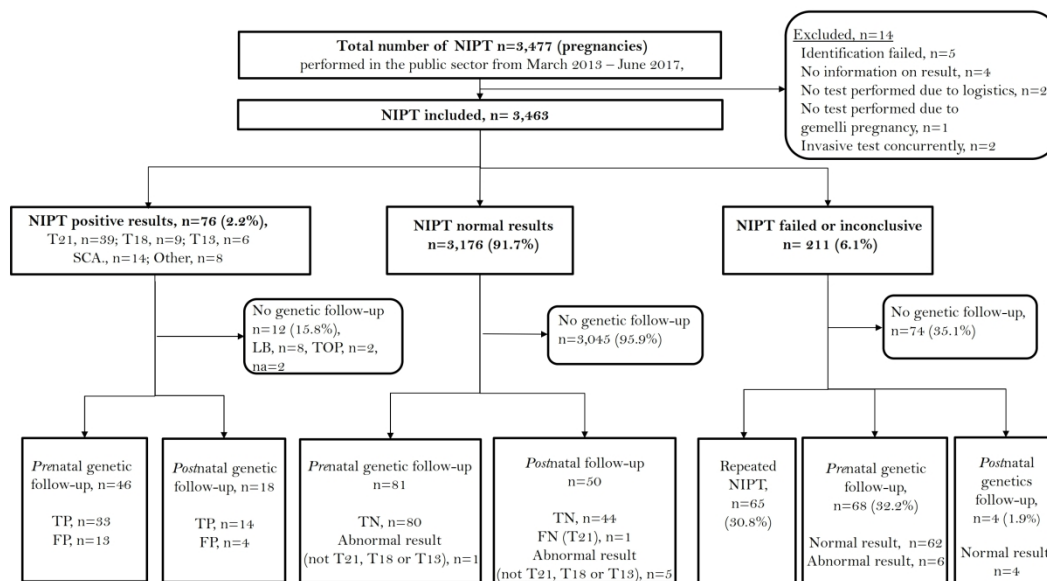
^{e)} arr[GRCh37] 16p11.2(28824794-29042118)x1, arr[GRCh37] 15q11.2(22765628-23208901)x1 and
arr [GRCh37] Xp22.31(6489877-8131810)x3

^{f)} 69, XXX; arr[GRCh37] 16p11.2(29428531-30350748)x1; arr[GRCh37] 7q21.11(77742,651-
83261523)x1;
arr[GRCh37] 15q11.2q26.3(22770,421-102429,040)x2~3

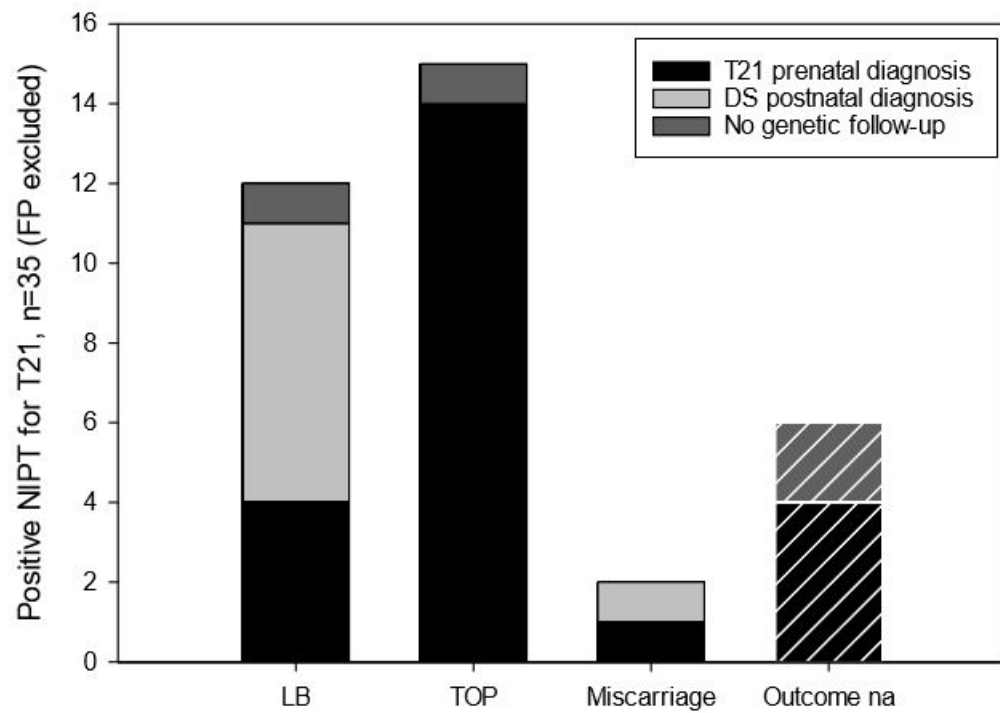
Abbreviations: NIPT, Non-Invasive Prenatal Testing; cFTS, combined first trimester screening; T21, trisomy 21; T18, trisomy 18; FP, false positive; other chr. abn., other/atypical chromosomal abnormality; TP, true positive.



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