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Detection rates and residual risk for a postnatal diagnosis of an atypical chromosome aberration following combined first-trimester screening

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Abstract

Objectives: To determine the detection rates of all types of chromosome aberrations and the residual risk for postnatal diagnosis of an atypical chromosome aberration depending on the strategy for further investigation with either noninvasive prenatal testing (NIPT) or invasive testing in pregnancies with increased risk following combined first-trimester screening (cFTS).

Methods: A review of all pregnancies examined with cFTS during 2010 to 2017.

Results: The cohort consisted of 129 493 pregnancies. There were 852 (0.7%) clinically significant chromosome aberrations, including aberrations detected later on or after birth. A total of 12% were atypical chromosome aberrations. Considering that 40% were detected due to a miscarriage/intrauterine fetal death or a malformation on ultrasound there is a 0.05% (1:2000) background risk of a postnatal diagnosis of a liveborn child with an atypical chromosome aberration if no further invasive test is performed during pregnancy. If all women with an increased risk (≥1:200) had an invasive test and NIPT was performed up to a risk of 1:1000, 95% of common trisomies/sex chromosome aberrations and 55% of atypical aberrations would be detected.

Conclusions: If NIPT was offered to all women with an increased risk following cFTS it would imply that three times as many children would be born with an atypical chromosome aberration.

1 | INTRODUCTION

The introduction of noninvasive prenatal testing (NIPT) has challenged the policies and practices for standard of care concerning prenatal screening for chromosome aberrations in the first trimester. There are different ways of implementing NIPT into clinical practice, for example, used as a second-line test for women with an increased risk following combined first-trimester screening (cFTS),[1] or as a primary screening tool for all pregnant women.[2] However, the question still remains regarding how NIPT can best be applied in an efficient and cost-effective way. There is an increasing trend that NIPT analysing the common trisomies is replacing invasive prenatal testing with an analysis of all chromosomes using either karyotype or array-CGH. One of the key questions is what we miss by using only targeted NIPT tests for trisomies 21, 18, 13 and sex chromosome aneuploidies? Studies reviewing the expected performance of primary screening using NIPT in large population-based cohorts have shown that 17%-25% of fetal chromosome aberrations are clinically significant atypical chromosome aberrations considered nondetectable by NIPT.[3-6] However, nondetectable in early pregnancy is not equivalent to the

likelihood of giving birth to a child with an atypical chromosome aberration. Other adverse pregnancy outcomes such as miscarriage/intrauterine fetal death (IUFD) and malformations detected at the second trimester scan may intervene and affect the residual risk for a postnatal diagnosis. We lack population-based studies providing information on the residual risk of giving birth to a child with an atypical chromosome aberration if prenatal screening only involves the analysis of common trisomies as the estimations published so far are based on extrapolations.[3-6] The aims of this study were to compare the residual risk of a postnatal diagnosis if either NIPT or invasive testing was used for further investigation in women with an increased risk following cFTS. Also, to estimate the detection rates for all types of chromosome aberrations depending on which strategy is used for further investigation.

What's already known about this topic?

- Studies reviewing the expected performance of primary screening using NIPT in large population-based cohorts have shown that 17%-25% of fetal chromosome aberrations are clinically significant atypical chromosome aberrations considered not detectable by NIPT. However, they were limited by the absence of information on outcome of pregnancy and did not report pregnancy complications and could not study rates of "missed" atypical abnormalities subsequently diagnosed at birth.

What does this study add?

- This is the first population-based study on residual risk for a postnatal diagnosis of an atypical chromosome aberration when miscarriages and malformations detected on ultrasound have been accounted for.
- Continuing to offer cFTS and reinstating invasive testing would allow the majority of atypical aberrations and 95% of aneuploidies to be detected.
- A total of 40% of the atypical aberrations are detected later in pregnancy due to miscarriage/IUFD or a malformation detected on ultrasound.

2 | METHODS

There are 2.3 million people in Stockholm County with approximately 30 000 births per year. Prenatal care is free of charge, and almost all women attend. All pregnant women are routinely offered a second trimester ultrasound examination and approximately two-thirds of women undergo a cFTS test. Except for the genetic analysis performed due to an increased risk from cFTS, genetic analysis may also be undertaken later on in pregnancy as a consequence of miscarriage/IUFD, malformation detected at the time of the routine second trimester scan, or postnatally in children with a congenital birth defect. There have been changes in the strategies to offer prenatal diagnosis during the study period. Since the introduction of the cFTS test in 2005 pregnancies with increased risk on cFTS, maternal anxiety and advanced maternal age have all been indications for offering an invasive test in the form of a stand-alone QF-PCR (13, 18, 21, X, Y). This was altered to a targeted NIPT test detecting trisomy 13, 18, 21 and numerical sex chromosome aberrations (SCA) in June 2015. Karyotype/chromosomal microarray (CMA) (CMA from 2012) has been utilized if anomalies were detected on ultrasound, the nuchal translucency (NT) was >3.5 mm or cFTS risk ≥1:50 (the latter indication since 2015). All cases of IUFD after 22 weeks of gestation, as well as miscarriages detected at an ultrasound scan within our region are subject to autopsy and genetic investigation using karyotype/CMA analysis. In cases where cell culture is unsuccessful, samples are analyzed with QF-PCR for detection of common aneuploidies or if there are malformations present a CMA is performed. All abnormal karyotypes, QF-PCR and CMA results were included in the analysis, although following review of the authors some were classified as non-significant and being associated with a normal outcome, for example balanced structural rearrangement, confined placental mosaicism or inherited nonpathogenic extra structurally abnormal chromosome (ESAC). Infants with no chromosome analysis performed before 6 months of age were presumed to be euploid and not carriers of a significant chromosome aberration.

This is a retrospective review of all singleton pregnancies including in vitro fertilization examined with cFTS in the Stockholm county during an 8 year period from January 2010 through December 2017 using data from the Swedish Pregnancy Registry.[7] Mean maternal age was 32 years (14-58) with 33% of the women being ≥35 years old. The cFTS uptake among pregnant women in the region increased from 45% to 75% during the study period. Data on cFTS risk, gestational age, NT-measurement, invasive procedure, NIPT, results of chromosome analysis, miscarriage, IUFD, ultrasound examination and pregnancy outcome were collected from the Swedish Pregnancy Register. Apart from miscarriages before 22 weeks of gestation lacking a genetic diagnosis there is an expected 100% follow-up rate of the pre- and postnatal diagnosis (≤6 month) data in the Swedish pregnancy register for this cohort. Individual risk estimates were calculated using an algorithm developed by the Swedish National Quality Register for prenatal diagnosis and previously reported by our group.[8] Risk calculation at the first trimester scan involves data regarding maternal age and ethnicity, previous history of a trisomic pregnancy, ultrasonographic variables (crown-rump length, CRL), NT measurements and first trimester biochemistry markers (free β-hCG and PAPP-A). A risk calculation based on both ultrasound as well as first trimester biochemistry parameters was performed in all pregnancies. The eligibility criteria were a singleton pregnancy with a live fetus at the time of the first trimester scan. The screen-positive rates following cFTS risk assessment ≥1:50, ≥1:200, and ≥1:1000 were 1.8%, 4.5% and 14.7%, respectively. Women with a risk ≥1:200 at the time of the scan were considered screen-positive and offered further investigation. The

detection rates of trisomies 21 and 13/18 were 88% and 85%, respectively.

All genetic analyses were performed at the Department of Clinical Genetics, Karolinska University Hospital. QF-PCR was performed according to routine clinical protocol using a panel of specific short tandem repeats from chromosomes 13, 18, 21, X, and Y as previously described.[9,10] CMA was performed using an array-based comparative genomic hybridization platform, a 180 K oligonucleotide array with evenly distributed whole-genome coverage (Oxford Gene Technology). Analysis of copy number variants (CNVs) was performed using the CytoSure Interpret Software (Oxford Gene Technology). Karyotype analysis was performed with conventional G-banding using standard cytogenetic procedures.

Chromosome aberrations were classified as a common trisomy (trisomy 13, 18, 21)/numerical SCA or an atypical chromosome aberration (triploidy, deletion, duplication, unbalanced structural rearrangement, mosaicism, rare autosomal trisomy, confined placental mosaicism[CPM]). SCA mosaicism was classified as numerical SCA. Mosaicism for a rare autosomal trisomy (RAT) was classified as mosaicism, except for mosaicism confined to the placenta which was classified as CPM. CNVs detected prenatally were compared with publicly available data sets and an in-house database with ~8000 previous pre and postnatal CMA analyses and classified as benign, pathogenic, susceptibility or variants of unknown significance. Interpretation and reporting of clinically relevant CNVs, including incidental findings, were performed in line with the published national guidelines of Belgium.[11,12] The study was approved by the Swedish Ethical Review Authority (reference number 2018/2559) as well as The Swedish Pregnancy Register.

3 | RESULTS

The cohort consisted of 129 493 pregnancies examined with cFTS at 10 ultrasound units in the Stockholm county. There were 870 (0.7%) chromosome aberrations in the whole cohort, also including chromosome aberrations found later in pregnancy, following miscarriages/IUFD or after birth. Eighteen atypical aberrations were considered not clinically significant and excluded from further analyses resulting in 852 clinically significant aberrations in the cohort. Common trisomies (13, 18, 21, and) or SCAs constituted 88% (754) of these, in our study presumed to be possible to detect by NIPT analysis, and 12% (98) were atypical chromosome aberrations not detectable by targeted NIPT (Table 1). The proportion of chromosome aberrations in each cFTS risk group is seen in Figure 1. A screen-positive result was defined as an increased risk for either trisomy 21 or trisomy 13/18. We could observe a three times increased risk for an atypical aberration in the group of women with a risk ≥1:200 for trisomy 13/18 compared to increased risk for trisomy 21 (2.1% vs 0.7%) and in the women with a risk >1:50 this factor was 2.5 (4% vs 1.6%). Twenty-nine of the 98 (30%) clinically significant atypical chromosome aberrations in the cohort had an abnormal ultrasound (US)-scan at 18-20 weeks' gestation and 10% (10/98) resulted in miscarriage/IUFD, both indications for further genetic analysis. Thus, 39 out of the 98 (40%) clinically significant atypical chromosome aberration cases were detected due to miscarriage/IUFD or a malformation at the following US-scan (Figure 2 and Table 2). Eighteen of the 98 (18%) had an increased NT >3.5 mm usually implicating an increased risk at the cFTS. In our cohort with 129 493 pregnancies examined with cFTS the background prevalence of a pregnancy with a clinically significant atypical chromosome aberration was 0.1% (98/129 493). As 40% were detected due to either a miscarriage/IUFD or a malformation on ultrasound there is a 0.05% (1:2000) background risk of a postnatal diagnosis of a liveborn child with an atypical chromosome aberration if no further invasive test is performed during the pregnancy.

Out of the 98 clinically significant atypical chromosome aberrations 24 (24%) were liveborn. However, four of the 24 liveborn presented with high cFTS risk. In three cases an atypical chromosome aberration was detected after invasive prenatal testing and the pregnancy was continued following genetic counseling. In one case only QF-PCR was offered according to the local guidelines at that time and

TABLE 1 Distribution of clinically significant chromosome aberrations in the cohort

	Clinically significant aberrations	Comments
Common trisomies or sex chromosome aberrations	754 (88%)	Presumably detectable by targeted NIPT
T21	499	
T13	49	
T18	137	
X0	55	
XXY	10	
XXX	4	
Atypical chromosome aberrations	98 (12%)	Not detectable by targeted NIPT
Triploidy	28	
Rare autosomal trisomy	3	T9, T16, T22
Deletion	38	Including twelve del(22)(q11.21)
Duplication	12	
Unbalanced translocation	9	
Mosaicism	7	T16, T22, +i(8)(p10), T2, monosomy 22, del(12)(p13.32)/dup(12)(p13.31p13.32), del(18)(q21.31)
Other	1	XX-male (*SRY* Xp-Yp translocation)
All aberrations	852 (100%)	

Abbreviation: NIPT, noninvasive prenatal testing.

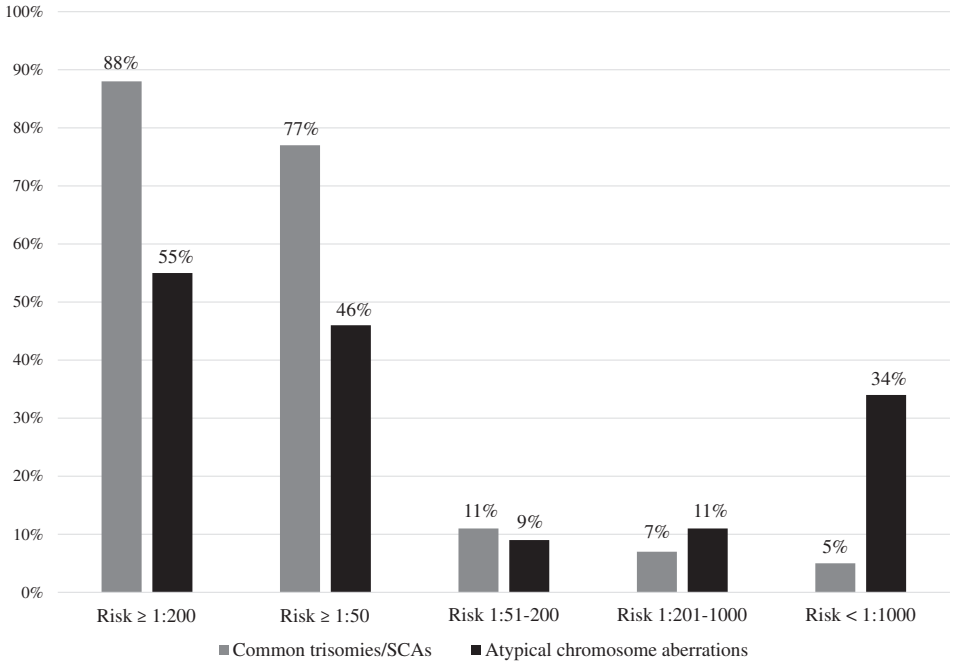

FIGURE 1 Proportion of chromosome aberrations in each cFTS risk group. A total of 852 clinically significant aberrations in the cohort, 754 common trisomy or SCA, and 98 atypical chromosome aberrations. cFTS, combined first-trimester screening; SCA, sex chromosome aneuploidies

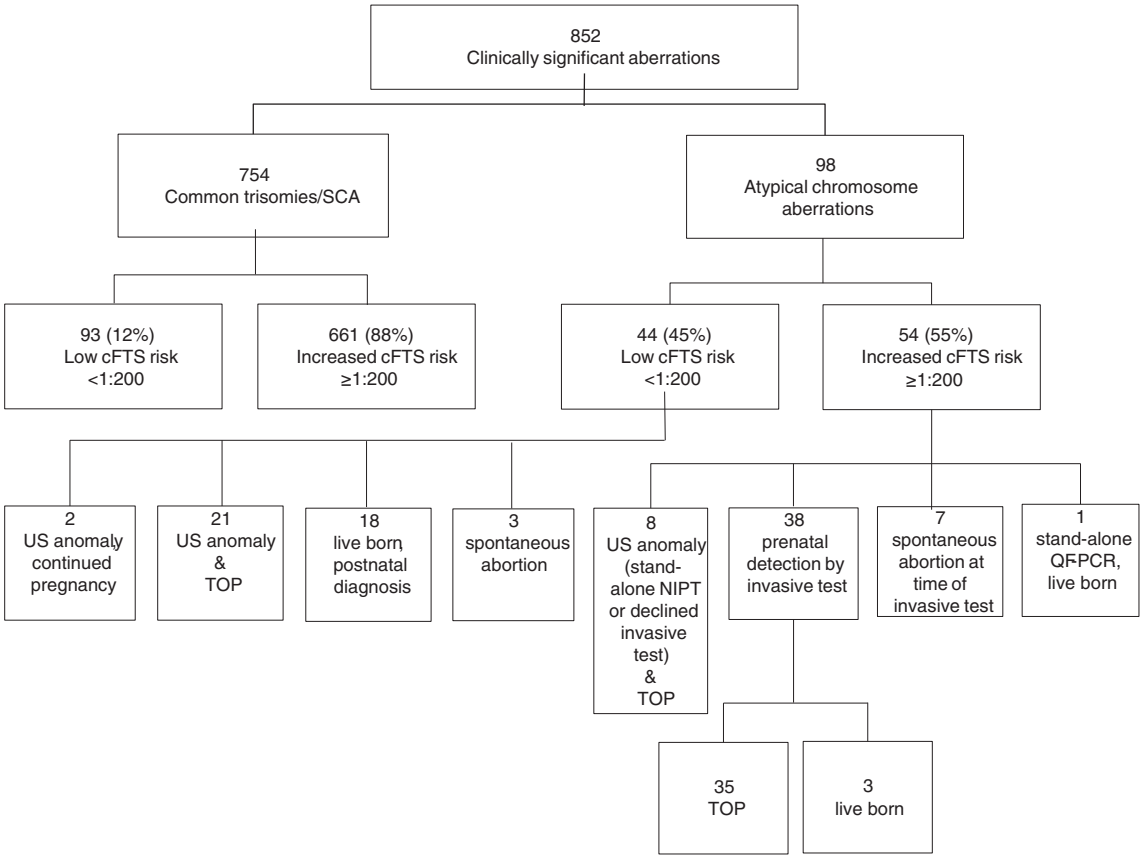

FIGURE 2 Flowchart of the original cohort with outcomes after cFTS and subsequent investigations. cFTS, combined first-trimester screening; QF-PCR, quantitative fluorescent-polymerase chain reaction; SCA, sex chromosome aberration; TOP, termination of pregnancy; US, ultrasound

postnatal array-CGH analysis due to seizures in the new-born baby detected a ≈ 150 kb del(20)(q13.33) inherited from the mother causing familiar benign seizures. In addition there were two cases where a malformation was detected on US and the pregnancy was continued after counseling. One case with a de novo 1,46 Mb del(22)(q11.21q11.22) causing distal 22q11 deletion syndrome detected as

TABLE 2 The number of atypical aberrations, miscarriage/IUFD, and malformations detected by ultrasound depending on cFTS risk group category

	No. of atypical aberrations	Risk >1:200	Risk > 1:50	Risk 1:51-1:200	Risk 1:201-1:1000	Risk >1:1000	Risk <1:1000
No. of atypical aberrations	98	54	45	9	11	65	33
US anomalies at 18-20 weeks' gestation	29/98 (30%)	8/54 (15%)	3/45 (7%)	5/9 (56%)	6/11 (55%)	14/65 (22%)	15/33 (45%)
Miscarriage/IUFD	10/98 (10%)	7/54 (13%)	7/45 (16%)	0 (0%)	0 (0%)	7/65 (11%)	3/33 (9%)
Undetected	59/98 (60%)	39/54 (72%)	35/45 (78%)	4/9 (44%)	5/11 (45%)	44/65 68%	15/33 (45%)

Abbreviations: cFTS, combined first-trimester screening; IUFD, intrauterine fetal death; US, ultrasound.

TABLE 3 Comparison of detection rates and residual risk for a postnatal diagnosis of an atypical chromosome aberration depending on different strategies for further investigation following an increased risk after cFTS, including proportion of cases with miscarriage/IUFD or malformations detected by ultrasound

Strategy	Detection rate per screening strategy n (%)	Additional cases detected by second trim ultrasound n (%)	Additional cases detected by the analysis of miscarriage/IUFD n (%)	Undetected n (%)
1. Combined invasive/NIPT I cFTS ≥1:50→CMA cFTS 1:51-1:200→NIPT	45 (46%)	26 (26%)	3 (3%)	24 (24%)
2. Combined invasive/NIPT II cFTS ≥1:50→CMA cFTS 1:51-1:1000→NIPT	45 (46%)	26 (26%)	3 (3%)	24 (24%)
3. Targeted NIPT only (Trisomy/SCA) cFTS ≥1:200→NIPT	0 (0%)	29 (30%)	10 (10%)	59 (60%)
4. Strategy 4 (Expanded invasive and NIPT) cFTS ≥1:200→CMA cFTS 1:201–1:1000→NIPT	54 (55%)	21 (21%)	3 (3%)	20 (20%)

Note: Based on the 98 clinically significant atypical chromosome aberration cases in our cohort of 129 493 pregnancies examined with cFTS.
Abbreviations: cFTS, combined first-trimester screening; CMA, chromosomal microarray; IUFD, intrauterine fetal death; NIPT, noninvasive prenatal testing; SCA, sex chromosome aberrations.

an incidental finding when an invasive test was performed due to a suspected malformation on US. The other case was a de novo 134 kb del(8)(p23.1) including the GATA4-gene causing a heart malformation detected on US in g.w. 20 + 4. In the remaining 18 liveborn cases the atypical aberration was detected in a live born child postnatally following a pregnancy with a low cFTS risk and lacking US anomalies. Among the liveborn cases 78% (14/18) of the pregnant women were <35 years of age as compared to 67% in the entire cohort.

The detection rates of various types of chromosome aberrations and residual risks of a postnatal diagnosis of an atypical chromosome aberration were stratified according to cFTS risk using four different models (Table 3).

Strategy 1 (Combined invasive/NIPT I). cFTS followed by an offer of an invasive test to women with a risk ≥1:50 and NIPT to those with a risk between 1:51 and 1:200. Using this contingent testing model 83% (706/852) of all clinically significant and 46% (45/98) of the atypical chromosome aberrations would be detected respectively (Tables 3 and 4).

Strategy 2 (Combined invasive/NIPT II). cFTS followed by an offer of an invasive test to women with a risk ≥1:50 and NIPT to between 1:51 and 1:1000. With this model 89% (762/852) of all clinically significant and 46% (45/98) of the atypical chromosome aberrations would be detected respectively. The proportion of undetected cases with a postnatal diagnosis following cFTS would be 24% (24/98) with both strategies 1 and 2.

Strategy 3 (Targeted NIPT only). cFTS followed by an offer of a targeted NIPT (Trisomy/SCA) to women with a risk ≥1:200. Using this model 78% (661/852) of all clinically significant and 0% (0/98) of the atypical chromosome aberrations would be detected respectively. Thus, if only analysis for common trisomies and SCA is offered to women with an increased cFTS risk ≥1:200, the proportion of undetected cases with a postnatal diagnosis would be 60% (59/98). The absolute risk of a postnatal diagnosis for a pregnancy with an atypical chromosome aberration in women with a risk ≥1:200 is 1.0% (59/5779).

Strategy 4 (Expanded invasive and NIPT). cFTS followed by an offer of an invasive test and CMA analysis to women with a risk ≥1:200 and NIPT if the risk was between 1:201 and 1:1000. Using this testing model 90% (771/852) of all clinically significant and 55%

TABLE 4 Comparison of detection rates for the two categories of chromosome aberrations (n = 852) depending on different strategies for further investigation in women with an increased risk following cFTS

Strategy	Detection rate		
	Common trisomies and sex chromosome aberrations	Atypical chromosome aberrations	All significant chromosome aberrations
1. Combined invasive/NIPT I cFTS ≥1:50→CMA cFTS 1:51–1:200→NIPT	661/754 (88%)	45/98 (46%)	706/852 (83%)
2. Combined invasive/NIPT II cFTS ≥1:50→CMA cFTS 1:51–1:1000→NIPT	717/754 (95%)	45/98 (46%)	762/852 (89%)
3. Targeted NIPT only (Trisomy/SCA) cFTS ≥1:200→NIPT	661/754 (88%)	0/98 (0%)	661/852 (78%)
4. Strategy 4 (Expanded invasive and NIPT) cFTS ≥1:200→CMA cFTS 1:201–1:1000→NIPT	717/754 (95%)	54/98 (55%)	771/852 (90%)

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

TABLE 5 Atypical chromosome aberrations in 2323 pregnancies with an increased cFTS risk ≥1:50

	Atypical chromosome aberrations nondetectable by NIPT
cFTS risk ≥1:50 (N = 2323)	45/2323 (1.9%)
No. of cases detected due to miscarriage/IUFD/US anomaly	10/2323 (0.4%)
Residual risk for a postnatal diagnosis if only NIPT analysis is offered	35/2323 (1.5%)

Abbreviations: cFTS, combined first-trimester screening; IUFD, intrauterine fetal death; NIPT, noninvasive prenatal testing; US, ultrasound.

(54/98) of the atypical chromosome aberrations would be detected respectively (Tables 3 and 4). The proportion of undetected cases with a postnatal diagnosis following cFTS would be 20/98 (20%).

Investigating the 2323 (1.8%) women with the highest risk (≥1:50) after cFTS, 27% (623/2323) had a chromosome aberration, 93% (578/623) of the detected chromosome aberrations are common trisomies and SCA detectable with NIPT. 1.9% (45/2323) had an atypical aberration requiring an invasive test for diagnosis and eliminating the cases detected due to a miscarriage/IUFD or US anomaly, the residual risk for an atypical aberration to go undetected following a NIPT analysis restricted to only common trisomies and SCA is 1.5% (35/2323) (Tables 2 and 5).

4 | DISCUSSION

In previous studies describing the residual risk for an atypical chromosome aberration, the pregnant women with an increased risk after cFTS have been offered a full karyotype or CMA analysis prenatally.[3-6] Hence, the majority of pregnancies where an atypical aberration was detected presumably had a termination and it will be difficult to predict if the fetus would have survived to term or not. To address this question, we undertook an extensive analysis of 129 493 pregnancies examined with cFTS and are able to present detection rates as well as the residual risk of giving birth to a child with an atypical chromosome aberration depending on which strategy is used for further investigation in women with an increased risk. To the best of our knowledge this is the first large population-based study presenting data on actual numbers of cases with a postnatal diagnosis when also miscarriages and anomalies detected on ultrasound have been accounted for instead of just using estimations. In our setting, following a positive cFTS the majority of the pregnant women have been offered a stand-alone QF-PCR or NIPT test which has allowed us to assess how many pregnancies that would have ultrasound anomalies or suffer a miscarriage. This study shows that a majority (55%) of atypical chromosome aberrations display an increased risk at the cFTS examination but will only be detected if an invasive test is performed. The residual risk for a postnatal diagnosis would be three times greater (60% vs 20%) if NIPT was undertaken rather than an invasive test in women with a risk ≥1:200 (Table 3). Currently, in our region 2/3 pregnancies with a risk ≥1:200 are investigated with NIPT and the policy is to offer an invasive test only to women with a risk ≥1:50 due to that many common aneuploidies are present in this group as well as a large part of the atypical aberrations. Yet 23% of women in this risk group still elect to have NIPT, most often due to fear of suffering a procedure-related complication. Our study shows that the actual risk of an atypical aberration in this group is only 1.9% but includes 45% of all atypical aberrations. In the end, health economic rather than medical factors will determine how prenatal diagnosis is offered in the first trimester. However, we believe that in most institutions, parents are not counseled and aware of detection rates, residual risks and the clinical consequences of an atypical

chromosome aberration when they undergo cFTS. The results of this study may help in overall decision making.

The NIPT-analysis performance is improving continuously and when CNV detection based on cfDNA is comparable to CMA performance, the need for an invasive test will dissolve. Detection of segmental imbalances as well as submicroscopic CNVs has been reported and is feasible for some NIPT platforms.[13-25] Yet, the resolution of CNV detection based on cfDNA analysis is today not comparable to CMA and a large part of the atypical chromosome aberrations in our cohort would have been missed.

We also investigated the detection rates of all types of chromosome aberrations according to different strategies for offering population-based prenatal diagnosis if either NIPT or CMA was used for further investigation in pregnancies with an increased risk following cFTS. Of the strategies studied the one offering an invasive test with CMA analysis with risk ≥1:200 (4.5%) and NIPT if risk 1:201-1:1000 (10.2%) achieves the best detection rate; 95% of the common trisomy/SCA cases and 55% of the atypical chromosome aberrations. Also, the residual risk of giving birth to a child with an atypical chromosome aberration would be only 1/7000. In first trimester screening, the paradigm is shifting rapidly from screening only for trisomies using the cFTS test to also identifying a majority of major malformations as well as screening for preeclampsia (PE) combined with an offer of low-dose aspirin to women at high-risk and thereby reducing the risk of preterm PE.[26] It seems apparent that first trimester biochemistry is here to stay for the near future and also that the procedure-related risk following invasive testing is considerably lower than previously believed.[27-30]

Increased NT seems to have a stronger association with fetal abnormalities and genetic syndromes in general rather than to be associated with atypical chromosome aberrations.[31] It has also been proposed that the presence of pathogenic CNVs in association with high fetal NT are due to the presence of other malformations rather than to the high fetal NT per se.[32] In a large population-based study of 1.3 million pregnant women the investigators found that 17% of chromosome aberrations were not detectable by noninvasive testing and that 35% of atypical aberrations had an increased risk (>1:100) following cFTS which is consistent with our results with increased NT >3.5 mm in 18% of pathogenic CNVs, and 55% of atypical aberrations having an increased risk (>1:200).[4] Clearly, the combined first trimester test including biochemical markers, seems more sensitive in terms of detecting the more uncommon atypical chromosome aberrations compared to only using a NT above 3.5 mm as an indication for further investigation.

Limitations to our study is that malformations were not recorded at the time of the first trimester scan and that miscarriages before 22 weeks may have occurred without receiving a genetic diagnosis. The fact that strategies to offer prenatal diagnosis varied during the study period and that CMA was used first after 2012 is not believed to have affected results as postnatal follow-up of children was virtually complete through the Swedish Pregnancy Registry.

In conclusion, our data in this study support that we should keep the cFTS examination and use it as a window of opportunity to not only detect common aneuploidies but also atypical chromosome aberrations. These are more uncommon but often cause more morbidity compared to Down syndrome.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to the sensitivity of clinical data.

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