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Journal

Prenatal Diagnosis, 40(2)

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Publication Date

2020

DOI

10.1002/pd.5583

Peer reviewed

HHS Public Access

Author manuscript

Prenat Diagn. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Prenat Diagn. 2020 January ; 40(2): 185–190. doi:10.1002/pd.5583.

The utility of nuchal translucency ultrasound in identifying rare chromosomal abnormalities not detectable by cell-free DNA screening

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Abstract

Objective: To evaluate the utility of nuchal translucency (NT) screening in the detection of rare chromosomal aneuploidies in the setting of cell-free DNA (cfDNA).

Methods: A retrospective cohort study of pregnancies screened through the California Prenatal Screening Program between March 2009 and December 2012. Karyotype analysis was the primary method of chromosomal evaluation during the study period and abnormal chromosomal karyotype results were classified by whether the abnormality would be detectable by cfDNA (non-mosaic trisomy 13, 18, 21 or sex-chromosomal aneuploidy (SCA)). For those rare aneuploidies detectable by karyotype but not cfDNA, the number of cases that had an increased NT and the detection rate and positive predictive value (PPV) of increased NT for rare aneuploidies were determined.

Results: A total of 452,901 pregnant women had screening. There were 2,572 chromosomally abnormal fetuses, of which 1,922 (74.7%) had a common aneuploidy detectable by cfDNA, leaving 450,979 without T13, 18, 21. Of these, 4,181 (0.93%) had an NT ≥ 3.0mm. There were 649 rare aneuploidies not detectable by cfDNA. Of these, 108 (16.6%) had an NT ≥3.0mm. The PPV of an NT ≥3.0mm for rare aneuploidies was 2.6%. In all, 4,176 fetuses need to be screened with NT to detect a rare aneuploidy.

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CONFLICT OF INTEREST: None

DATA AVAILABILITY STATEMENT: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conclusions: The addition of NT to cfDNA screening would detect 16.6% of rare aneuploidies. Increased NT has a low PPV for rare aneuploidies and a large number of women would need NT screening to detect each affected fetus.

Introduction:

Prenatal aneuploidy screening using cell-free DNA (cfDNA) has been increasingly utilized in clinical practice since its introduction in 2011. Screening by cfDNA has a high sensitivity and specificity for the common aneuploidies, and both the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) support it as a screening method for high-risk pregnancies.[1–7] Cell-free DNA screening can detect the common aneuploidies (trisomy 13, 18, and 21) as well as many sex chromosomal abnormalities; together these comprise approximately 75–80% of all prenatal chromosomal abnormalities. However, rare non-age dependent aneuploidies that comprise the remaining 20% of all chromosomal abnormalities are generally not detectable by cfDNA.[9,10] These rare aneuploidies vary in clinical phenotype, but can have significant implications for the health of the infant and are therefore crucial to consider during counseling.

Aneuploidy screening has utilized sonographic measurement of the nuchal translucency (NT) thickness in combination with serum analytes to provide an assessment of the risk that the fetus is affected by Down syndrome.[8,11–13] While traditionally applied for aneuploidy screening, an increased NT has also been associated with single gene disorders, such as Noonan syndrome and skeletal dysplasias, as well as with a variety of structural anomalies.[14–20]A prior study of the California Prenatal Screening Program demonstrated that traditional screening utilizing serum analytes and NT has a higher detection rate for all chromosomal aneuploidy as compared to cfDNA as traditional screening will detect some rare aneuploidies. However, for women who elect cfDNA screening, it is unknown whether performing an NT measurement, without serum analytes, would allow the detection of some of the 20% of aneuploidies that are not the target of standard cfDNA screening".[17,20,21] The aim of this study was to examine the utility of NT measurement in the detection of rare chromosomal abnormalities not screened with cfDNA, considering different NT cutoffs of ≥3.0mm, ≥3.5mm, or ≥2.0 Multiples of the Median (MoM). We hypothesized that the utility of NT in detecting rare aneuploidies is of limited use in clinical practice.

Methods:

This is a retrospective cohort study of participants in the California Prenatal Screening Program between March 2009 and December 2012. The Genetic Disease Screening Program (GDSP), as part of the California Department of Public Health, directs prenatal screening in California. We included all women with singleton pregnancies who had NT measurements performed when the fetal CRL was 45.0–84.0 mm. All California NT practitioners are credentialed by the Nuchal Translucency Quality Review Program (NTQR)[22] or the Fetal Medicine Foundation (FMF),[23] and both collaborate with the GDSP to ensure proper measurements and performance of the NT. NT measurements are submitted to the California

Prenatal Screening Program as part of routine prenatal screening for chromosomal aneuploidy.

Study participants had NT measurements done by clinicians who had practitioner-specific NT medians. Wu et al.[24] previously described how practitioner-specific medians are determined. Clinicians with known practitioner-specific medians performed ultrasound examinations in which the slope of their NT measurements increased by at least 11% across gestational age. In California, these practitioner-specific medians have been demonstrated to control for less experienced practitioners whose NT measurements tended to be smaller.[24]

The California Prenatal Screening Program offers prenatal screening to all pregnant women and is comprised of first and/or second trimester serum analysis along with NT measurement. The screening program provides risk estimates for trisomies 13, 18, and 21, as well as neural tube defects and a composite adverse perinatal outcome (including Smith-Lemli-Opitz syndrome/congenital anomalies/fetal demise). MediCal (California's low-income health coverage) and the majority of all health insurers cover the cost of prenatal screening. The program provides follow up and covers the cost of services for all screen positive results, including genetic counseling, ultrasound, and diagnostic testing. Chromosomal abnormalities are diagnosed by fetal or infant karyotype, which are obtained through the GDSP California Chromosome Registry. California law mandates that physicians, cytogenetic laboratories, hospitals and prenatal diagnostic centers report chromosomal abnormalities diagnosed in the fetus or infant through one year of age to the GDSP program. Follow up of abnormal fetal chromosomal abnormalities include cases of pregnancy termination and intrauterine fetal demise. The California Prenatal Screening Program staff maintain the database and ensure that correct data are reported. Previous analyses have estimated the registry ascertainment rate to be 79.6%. [25,26]

Chromosomal microarray analysis was not in common usage for patients with positive sequential screening results during the study period and therefore only abnormal karyotype findings were examined. Abnormal karyotypes were characterized by whether they are targets of current cfDNA platforms, and therefore considered detectable, or not, by cfDNA. Although cfDNA laboratories provide varying analyses, for the purpose of the current study, detectable chromosomal abnormalities included non-mosaic trisomy 13, 18 and 21, and the sex aneuploidies (Turner syndrome, 45, X; Klinefelter syndrome, 47, XXY; 47, XXX; and 47, XYY). Chromosomal abnormalities considered detectable by karyotype but not cfDNA were rare trisomies, unbalanced rearrangements, duplications and deletions larger than 5 Mb, triploidy, and all types of mosaicism. Cases were categorized by NT measurement in MoM and millimeter units. To assess the ability of an increased NT measurement to identify chromosomal abnormalities not detected by cfDNA, cases were categorized as having an NT measurement ≥3.0 mm, ≥3.5 mm, or ≥2.0 MoM.

We determined the total number of women in the cohort who had an NT of ≥3.0mm, ≥3.5mm, and ≥2.0 MoM and had trisomy 13, 18, 21 or a sex chromosomal abnormality. We also identified those fetuses and infants who were diagnosed with a rare chromosomal aneuploidy either prenatally or in the first year of life, who similarly had sonographic NT measurements as part of prenatal screening. We calculated the proportion of chromosomally

abnormal fetuses who had had an NT of ≥3.0mm, ≥3.5mm, and ≥2.0 MoM, as well as calculated an overall detection rate for rare chromosomal abnormalities based on each of these cutoffs. In addition, we calculated the anticipated screen positive rate by determining the number of women who would have a positive test if the common aneuploidies were removed from the cohort. We then calculated the positive predictive value, or odds of being affected with a positive result, and the number of women who would need to be screened to identify each abnormality.

Results:

A total of 452, 901 women had prenatal screening, including NT, during the study period. The demographics of the cohort are displayed in Table 1. Overall, 73.6% of participants were less than 35 years of age. The majority of the participants were Hispanic (40.6%) and non-Hispanic white (30.8%).

Of the total cohort, 0.57% (2,572/452,901) had an abnormal karyotype, of which 1,922 (74.7%) were aneuploidies that are potentially detectable with cfDNA, while 649 (25.2%) were categorized as non-detectable. Considering the entire cohort, 0.14% had a rare aneuploidy that was in the non-detectable group.

In all, 5,105 fetuses (1.1%) had an NT ≥ 3.0mm, 2,461 (0.54%) had an NT ≥ 3.5mm, and 3,672 (0.81%) had an NT ≥2.0 MoM. There was a high rate of increased NT in the setting of trisomy 21, 18, 13 and Turner syndrome (45,X) (Table 2). For trisomy 21, 46.6%, 34.6% and 39.5% had an NT ≥3.0mm, ≥3.5mm and ≥2 MoM, respectively and slightly higher rates were noted for trisomy 18 and trisomy 13. Turner syndrome (45,X) had the highest rate of increased NT; 102 (82.9%) of fetuses with Turner syndrome had an increased NT regardless of cutoff. Other sex chromosomal abnormalities had an increased NT in 11.6% to 18.9% of cases depending on which cutoff was utilized (Table 2). Including only the 450,979 women without T13, 18, 21, or SCA, presumably detectable by cfDNA, 4,181 fetuses (0.93%) had an NT ≥ 3.0mm, 1,714 (0.38%) had an NT ≥ 3.5mm, and 2,840 (0.65%) had an NT ≥2.0 MoM.

There were 649 rare chromosomal abnormalities, considered not detectable by cfDNA, and these cases had lower rates of increased NT as compared to the common aneuploidies (Table 2). Of these abnormalities, 16.6%, 13.4%, and 16.0% had NT measurements ≥ 3.0 mm, ≥3.5 mm, and ≥2.0 MoM, respectively. Thus, among pregnancies with an NT ≥3.0 mm, 108 (16.6%) of rare aneuploidies would be detected, with a PPV of 2.6%. Among pregnancies with NT ≥3.5mm, 87 (13.4%) rare aneuploidies would be detected with a PPV of 5.1%. Finally, using an NT cutoff of ≥2.0 MoM, 104 rare aneuploidies (16.0%) would be detected with a PPV of 3.7% (Table 3). A total of 4,176 fetuses would need to be screened by NT in order to detect a rare chromosomal abnormality using a cutoff of ≥ 3.0 mm.

Mosaicism for the common aneuploidies, including mosaicism for trisomy 13, 18 and 21, made up 13% (85/649) of the rare aneuploidies and had the highest rates of increased NT with 24.7%, 20.0%, and 22.4% having NT ≥3.0 mm, ≥3.5 mm, and ≥2.0 MoM, respectively. Pregnancies with rare trisomies, such as trisomy 8, 9, and 16, had the lowest rates of

increased NT with only 6.3%, 6.3% and 8.8% having NT of ≥3.0 mm, ≥3.5 mm, and ≥2.0 MoM, respectively.

Discussion:

It has been well established that cfDNA screening is highly effective in the detection of common aneuploidies and sex chromosomal abnormalities, and that increased NT is associated with an increased risk of these more common aneuploidies.[1,2,5,8] Numerous studies have shown that these abnormalities comprise approximately 75–85% of chromosomal abberrations. However, the utility of increased NT in the detection of the more rare aneuploidies has remained unclear. In this large and diverse cohort of patients that underwent NT screening, we found that while a substantial proportion of pregnancies with common aneuploidies had an increased NT, this was the case in only 16.6% of pregnancies with rare aneuploidies not detectable by cfDNA. Specifically, the PPV of an increased NT ≥3.0 mm and ≥3.5 mm for detecting a more rare aneuploidy was only 2.6% and 5%, respectively. A total of 4,176 NT exams would need to be performed to detect one rare aneuploidy using an NT cutoff of ≥ 3.0mm.

There are currently limited data in the literature on the utility of NT in screening for rare chromosomal abnormalities. Our findings are consistent with a few previous reports showing that rare chromosomal aneuploidies are associated with relatively low rates of increased NT. In a Danish cohort, Christiansen et al.[17] demonstrated that NT measurements of pregnancies affected by rare chromosomal aneuploidies are similar to those of normal pregnancies, suggesting that NT is not a useful screening tool for these rare conditions. Torring et al[21] likewise found the MoM for NT to be approximately 1.0 for rare trisomies. Conversely, a few studies have reported that unbalanced chromosomal translocations may be associated with an increased NT.[7,27] However, these were smaller studies showing a minimal increase in the NT measurement in the pregnancies with unbalanced chromosomal translocations. While the mean NT was somewhat increased, the majority of these affected pregnancies had an NT less than 3.0mm or <2.0 MoM, and would not be considered high risk through standard screening.

In our cohort, rare aneuploidies comprised 25% of all chromosomal abnormalities, consistent with previous reports. [9,10] These rare aneuploidies should be considered in prenatal testing, as they can be associated with significant morbidity. Although some non-mosaic rare aneuploidies are lethal, early diagnosis of these abnormalities allows ample time for patient counseling and appropriate decision-making regarding the pregnancy. While most screening methods do not target rare aneuploidies, prior studies utilizing the California Prenatal Screening Program database have shown that integrated screening, including serum analytes and NT measurement, will detect some of these abnormalities while standard cfDNA, which is more specific for the common aneuploidies, does not[8,28] Based on the results of our study, it appears that the addition of NT to cfDNA screening would not substantially increase the detection of these rare aneuploidies.

While the actual measurement of the NT may not be superior or provide additional yield for aneuploidy risk screening in the setting of cfDNA, the NT measurement and first trimester

ultrasound have the potential to provide other useful information. Increased NT has been associated with major structural anomalies including cardiac and gastrointestinal malformations [29–33] First trimester ultrasound may aid in the earlier diagnosis of major structural anomalies, confirming viability of a pregnancy and assessing chorionicity of multiple gestations, Further research will be important to clarify the incremental yield of the NT measurement and first trimester anatomy evaluations over the baseline yield with available genetic screening methods.[34]

Strengths of our study are that it is based on a large and diverse state-wide cohort, and it answers an important question about the utility of NT which has been difficult to answer with prior smaller studies. However, it is not without limitations. Our study was limited to women who participated in the screening program, and abnormal karyotype information was based on results obtained prenatally or within the first year of life. It is possible that due to the incomplete ascertainment of the California Chromosome registry, which has been estimated to be 79% in prior studies, some abnormal karyotypes were not captured and some diagnoses were made at a later time. [26] Our findings are based on potential detection by cfDNA and are not based on actual testing. For the purpose of this analysis, we assumed that all common aneuploidies would be detected by cfDNA, however, it is likely that some true cases would be missed. Further, some cfDNA tests have the potential to detect some rare chromosomal abnormalities, such as triploidy, mosaicism, or rare trisomies, [35,36] although validation data for these are lacking. Importantly, our study did not capture copy number variants (CNVs) that may be associated with an increased NT, but are only detectable by chromosomal microarray analysis (CMA). Thus, it is possible that the 16% detection rate of NT for rare chromosomal aneuploidies in our study is an underestimate of its true detection capabilities For example, CNVs such as 22q11 deletion are important to consider for prenatal diagnosis, and increased NT measurements have been associated with single gene disorders such as Noonan Syndrome and skeletal dysplasias.[14,15,37] While the use of CMA in the setting of an enlarged NT may identify more chromosomal abnormalities[37], karyotype analysis continues to be widely utilized due to various reasons such as limited CMA availability and patients electing karyotype in order to avoid potential variant of unknown significance (VUS) on CMA.

Rare chromosomal aneuploidies are important to consider in prenatal screening, in addition to the more common trisomies that are the focus of most current screening methods. While first trimester ultrasound may serve an important role in early assessment of fetal anatomy, the NT measurement is of relatively low yield in screening for chromosomal aneuploidies that are not addressed by cfDNA but that would be detectable with karyotype. Further studies are needed to assess overall utility of NT in diagnosing other fetal structural abnormalities and CNVs detectable with CMA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS:

We would like to acknowledge the California Prenatal Screening Program Coordinator staff, whose work and efforts were critical in ensuring the quality of the data collected.

FUNDING STATEMENT:

Dr. Norton receives research support from Natera. However, no funding was received for the purposes of this study. She is also a clinical advisor for Invitae.

Dr. Sparks is supported by grant 5K12HD001262-18 from the National Institutes of Health (NIH). The contents of the publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Dr. Sparks is also supported by a grant from the Fetal Health Foundation.

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WHAT IS KNOWN ABOUT THIS TOPIC?

- Increased nuchal translucency (NT) thickness is associated with an increased risk of Down syndrome
- Cell-free DNA screening has a high sensitivity and specificity for Down syndrome and common aneuploidy

WHAT DOES THIS STUDY ADD?

- Our study addresses the role of NT measurement in the setting of cell-free DNA. In our study, the addition of an NT measurement to cell-free DNA screening is of low utility and would detect 16% of rare aneuploidy detectable on karyotype analysis
- A total of 4,176 would need to be screened by NT to detect a rare chromosomal aneuploidy

Table 1:

Maternal Characteristics of the 452,901 Women Screened

Maternal Characteristic	Number of Women screened (%)
Maternal age at expected date of delivery	
<35 years	333,189 (73.6)
≥35 years	119,712 (26.4)
Maternal race or ethnicity	
Hispanic	184,078 (40.6)
White	139,537 (30.8)
Asian	64,418 (14.2)
Black	19,142 (4.2)
Other	29,002 (6.4)
Multi-racial	16,724 (3.7)

Table 2:

Detection Rates of Common Aneuploidy and Rare Aneuploidy by NT range

		NT ≥3.0mm	NT ≥3.5mm	NT ≥2.0MoM
	All (N)	**N (%)**	**N (%)**	**N (%)**
Total women screened	**452,901**	**5,105**	**2,461**	**3,672**
Common aneuploidies				
Trisomy 21	1251	583 (46.6)	433 (34.6)	494 (39.5)
Trisomy 18	323	163 (50.5)	150 (46.4)	164 (50.8)
Trisomy 13	130	58 (44.6)	51 (39.2)	58 (44.6)
Turner syndrome (45X)	123	102 (82.9)	102 (82.9)	102 (82.9)
Other SCA [*]	95	18 (18.9)	11 (11.6)	14 (14.7)
Aneuploid by cf(DNA)	1922	924 (48.1)	747 (38.8)	832 (43.2)
Total normal by cf(DNA)	**450,979**	**4,181**	**1,714**	**2,840**
Common aneuploidy Mosaicism [†]	85	21 (24.7)	17 (20.0)	19 (22.4)
Other trisomies [‡]	79	5 (6.3)	5 (6.3)	7 (8.8)
Unbalanced	414	71 (17.1)	58 (14.0)	69 (16.7)
rearrangements [§] Triploidy	71	11 (15.5)	7 (9.8)	9 (12.7)
Total rare aneuploidies	**649**	**108**	**87**	**104**

Data are in Row %

Bold indicates category total

cf(DNA), cell free DNA

[*] Includes Klinefelter syndrome (n=36), XYY (n=18) XXX (n=32) other sex chromosome abnormalities (n=9)

[†] Includes trisomy 21 (n=24), trisomy 18 (n=10), trisomy 13 (n=13), Turner syndrome 45X (n= 38)

[‡] See supplementary table

[§] Includes other robertsonian translocations (n=33), insertions and/or deletions (n= 117), Marker (n= 34), and “other abnormalities” including monosomy, nontrisomy 18 mosaicism, other translocations, additions, duplications, inversions, rings, fragile, dicentric isochromosome, other (n= 230)

Table 3:

Screening performance by NT for rare aneuploidies

	N	NT ≥3.0mm	NT ≥3.5mm	NT ≥2.0MoM
Total normal by cf(DNA)	**450,979**	**4,181**	**1,714**	**2,840**
Total rare aneuploidies not detected by cf(DNA)	649	108	87	104
Screen positive rate (%)		0.93%	0.38%	0.65%
Odds of affected with a positive result		1/39	1/20	1/35
Detection rate of increased NT (%)		16.6%	13.4%	16.0%
PPV of NT for detection of rare aneuploidy (%)		2.6%	5.1%	3.7%

cf(DNA), cell free DNA. PPV, positive predictive value.