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Noninvasive prenatal screening (NIPS) results for participants of the eXtraordinarY babies study: Screening, counseling, diagnosis, and discordance

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Abstract

Sex chromosome aneuploidies (SCAs), including 47,XXY, 47,XXX, 47,XYY, and supernumerary variants, occur collectively in approximately one of 500 live births. Clinical phenotypes are highly variable resulting in previous ascertainment rates estimated to be only 10%–25% during a lifetime. Historically, prenatal SCA diagnoses were incidental findings, accounting for ≤10% of cases,

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CONFLIC T OF INTEREST

Susan Howell, Shanlee M. Davis, Talia Thompson, Mariah Brown, Tanea Tanda, Karen Kowal, Amanda Alston, Judith Ross, and Nicole R. Tartaglia declare that they have no conflict of interest.

HUMAN STUDIES AND INFORMED CONSENT

Approval to conduct this human subjects research was obtained by review boards: Colorado COMIRB#17–0118; and Nemours Office of Human Subjects Protection #1151006. All procedures followed were in accordance with the ethical standards of these responsible committees overseeing human subjects research and with the Helsinki Declaration of 1975, as revised in 2000. Informed written consent was obtained from all participants prior to their inclusion in the study.

ANIMAL STUDIES

No nonhuman animal studies were carried out by the authors for this article.

with the majority of diagnoses occurring postnatally during evaluations for neurodevelopmental, medical, or infertility concerns. The initiation of noninvasive prenatal screening (NIPS) in 2012 and adoption into standardized obstetric care provides a unique opportunity to significantly increase prenatal ascertainment of SCAs. However, the impact NIPS has had on ascertainment of SCAs is understudied, particularly for those who may defer diagnostic testing until after birth. This study evaluates the timing of diagnostic testing following positive NIPS in 152 infants with SCAs and potential factors influencing this decision. Eighty-seven (57%) elected to defer diagnostic testing after a positive NIPS until birth, and 8% (7/87) of those confirmed after birth were found to have discordant results on postnatal diagnostic testing, most of which would have influenced genetic counseling.

Keywords

decision-making; genetic counseling; genetic testing; noninvasive prenatal screening; prenatal diagnosis; sex chromosome aneuploidy

1 | INTRODUCTION

Sex chromosome aneuploidies (SCAs), including Klinefelter syndrome/47,XXY, Trisomy X/47,XXX, 47,XYY syndrome, and 48,XXYY syndrome, are the most prevalent supernumerary chromosomal conditions, occurring collectively in approximately one of 500 live births. Clinical phenotypes are highly variable in these conditions, often with mild dysmorphic features or neurodevelopmental involvement, resulting in only 10%–25% lifetime ascertainment (Abramsky & Chapple, 1997). Historically, prenatal SCA diagnoses accounted for 10% or less of SCA cases and were often incidental findings following CVS or amniocentesis for advanced maternal age, and the majority of SCA diagnoses occurred in the postnatal period during clinical evaluations for neurodevelopmental, medical, or infertility concerns (Bojesen et al., 2003). The initiation of cell-free fetal DNA screening, commonly referred to as noninvasive prenatal screening (NIPS), in 2012 and subsequent adoption into standardized obstetric care, has drastically changed the landscape for prenatal identification of chromosomal abnormalities. This has provided a unique opportunity to identify SCAs prenatally (Wilson et al., 2013). Beginning in 2016, and most recently updated in 2020, the American College of Obstetrics and Gynecology issued a position statement recommending that NIPS be universally offered to all pregnant women, regardless of a priori risk, as it is a superior screening test to other alternatives citing the highest level of evidence (Gregg et al., 2016; Rose et al., 2020). These guidelines also state that all patients with a positive NIPS should receive genetic counseling and be offered diagnostic testing via chorionic villus sampling or amniocentesis to confirm these screening results.

With the utilization and growing adoption of NIPS, prenatal ascertainment rates of SCAs and subsequent number of infants known to have SCAs are logically anticipated to rise. This opportunity led to the development of the eXtraordinarY Babies Study, a prospective natural history study of infants prenatally identified and subsequently diagnosed with SCA designed to examine trajectories of neurodevelopment and physical health from birth through the first few years of life as well as psychosocial factors including quality of life

and parental experiences. Funded by the National Institute of Child Health and Human Development (NICHD) and in collaboration with the American College of Medical Genetics and Genomics (ACMG) Newborn Screening Translational Research Network (NBSTRN) (ClinicalTrials.gov NCT03396562), the eXtraordinarY Babies Study enrolls infants between 2 and 12 months of age with a prenatal result (NIPS or diagnostic) of SCA, with longitudinal evaluations conducted at two sites including University of Colorado/Children's Hospital Colorado and Nemours-Dupont Hospital for Children. While the eXtraordinarY Babies Study aims to prospectively describe and compare the natural history of SCA conditions, identify predictors of outcomes in SCA, and build a rich data set linked to a biobank for future study, much has also been learned about diagnostic testing outcomes following NIPS results positive for SCA.

Historically, most studies evaluating outcomes following NIPS often limit follow-up to the gestational period. One report found that NIPS has not increased the prevalence of infants known to have SCAs at birth, although this study only included cases with confirmed prenatal diagnostic genetic testing (Howard-Bath et al., 2018). Given maternal pregnancy history, procedural risks inherent in prenatal diagnostic testing and other factors, women may elect to defer diagnostic testing until after birth. As such, studies evaluating the overall impact NIPS has made to increasing ascertainment of SCAs need to include both pre- and postnatal diagnostic testing results following an NIPS result positive for SCA.

Prenatal genetic counseling for SCA-positive NIPS results is challenged by relatively poor positive predictive values (PPV) for SCAs in NIPS, highly variable phenotypic outcomes, and historic peer-reviewed publications inherently biased by ascertainment (Mennuti et al., 2015; Petersen et al., 2017; Wang et al., 2020). While NIPS has been demonstrated to have high sensitivity and specificity in identification of other chromosomal conditions, such as Trisomy 21/Down syndrome, the PPV for the detection of SCAs have varied from 25% to 89% and many companies fail to include these test statistics for SCAs on their result reports entirely (Lu et al., 2021; Shi et al., 2021; Skotko et al., 2019; Zheng et al., 2020). Phenotypes among SCAs range widely from mild dysmorphisms and tall stature to increased rates of cognitive impairment, medical conditions and psychological features. Furthermore, genetic counseling for SCAs is reliant upon peer-reviewed literature publications, the majority of which include data from individuals who were postnatally ascertained due to presenting neurodevelopmental, medical or fertility problems. As such, parental decision-making for pursuing prenatal diagnostic testing at the time of an NIPS result may be overshadowed by anxiety and psychological distress balanced by decisional conflict, especially in consideration of inherent prenatal diagnostic procedural risks (Labonte et al., 2019; Lewis et al., 2016). In one retrospective study of 61 cases with positive NIPS for trisomy SCAs, only 24% elected to have prenatal diagnostic testing (Ramdaney et al., 2018). Factors affecting the decision for timing of diagnostic testing rely upon the personal history of the mother as well as information provided at the time of the result. The professional providing information and whether the identified condition was discussed prior to testing may also influence this decision (Fleddermann et al., 2019; Marteau, Nippert et al., 2002; Riggan et al., 2020; Sadlecki et al., 2018). This is especially important to consider for the SCA conditions, as most SCAs are often not discussed during pretest consent and even more

surprising due to lower public knowledge of sex chromosome trisomy (SCT) compared to Down syndrome.

Counseling for NIPS results positive for SCA are typically directed to the condition reported, yet given the complexities of interpretation in SCA NIPS, discordant abnormal diagnostic results should be considered in counseling as well (Ramdaney et al., 2018). This paper aims to report on 152 participants from the eXtraordinarY Babies Study with SCA initially identified by NIPS, the parental decisions for diagnostic testing, and parent perceptions of providers' knowledge and quantity of information presented following a positive NIPS result. We also report a series of abnormal discordant diagnostic outcomes to further inform prenatal genetic counseling for NIPS results positive for SCAs.

2 | METHODS

2.1 | Participants

Participants of this study provided informed written consent for the eXtraordinarY Babies Study (approval for human subjects research by Colorado COMIRB#17–0118 and Nemours Office of Human Subjects Protection #1151006; NIH/NICHD# R01HD42974; ClinicalTrials.gov# NCT03396562). Inclusion in the eXtraordinarY Babies Study requires prenatal identification of a supernumerary SCA, including XXY, XYY, XXX, or XXYY, either by NIPS or by diagnostic prenatal testing, with confirmatory cytogenetic testing conducted prenatally and/or postnatally if NIPS, and enrollment between 6 weeks and 13 months of age. Exclusion criteria include birth <34 weeks, presence of an additional genetic or metabolic disorder with neurodevelopmental or endocrine involvement, presence of a congenital malformation (not previously described with SCA), or neonatal complications such as hypoxic–ischemic brain injury or neonatal meningitis. This analysis includes participants of the eXtraordinarY Babies Study who were prenatally identified by NIPS with subsequent diagnostic cytogenetic testing (prenatal and/or postnatal) and who had provided reports from both tests for review. Participants were excluded from this analysis if either NIPS reports or diagnostic test results could not be obtained, or if their prenatal diagnosis was first identified by amniocentesis or CVS. A total of 152/255 participants enrolled in the eXtraordinarY Babies Study were included in this analysis.

2.2 | Instrumentation

Data were abstracted from the eXtraordinarY Babies Study, including demographic information by a parent questionnaire (socioeconomic, race, ethnicity, state of residence to identify geographic region), family history (maternal date of birth to calculate age at delivery, maternal height and maternal prepregnancy weight to calculate prepregnancy BMI) and birth history by clinical interview with a physician (date of birth, gestational age, and birthweight). NIPS reports were reviewed and abstracted by a board certified genetic counselor (SH) to record commercial lab, date of sample collection (which was then used to calculate gestational age at the time of sample collection based on gestational age at the date of birth), date of NIPS result report, fetal fraction, and sensitivity, specificity, and positive predictive value for SCA (taken from laboratory report or if not available, calculated utilizing the perinatal quality foundation PPV calculator [https://www.perinatalquality.org/

Vendors/NSGC/NIPS/]). A one-page questionnaire was completed by 102/152 parents of participants, self-reporting date and child's age at the time of questionnaire completion and the following additional information:

- Gestational age at the time of SCA identified/diagnosed
- Type(s) of prenatal testing which identified the diagnosis
- Reason(s) prenatal testing was performed
- Medical provider's specialty who ordered prenatal screening/testing
- If the mother was informed about possible SCA diagnosis at the time of NIPS consent
- What provider(s) informed mother about the SCA diagnosis
- If the mother met with a genetic counselor after receiving results (NIPS and/or prenatal diagnostic testing)
- How and what type of information about the SCA was provided
- The perceived amount of information provided
- If the provider was perceived to be well-informed about the SCA condition
- If the diagnosis was confirmed after birth and if so, were the results the same as prenatally identified.

2.3 | Data analysis

Descriptive statistics were calculated to describe the sample and summarize the data (frequencies/proportions, means/standard deviations). Pearson's chi-square, Fisher's exact, and independent samples *t*-tests were used to analyze group differences between those who received prenatal confirmation of the diagnosis and those who deferred to postnatal diagnostic testing. All analyses were conducted in Excel and SPSS 28. Statistical significance was set for $p < 0.05$, and we did not make adjustments for multiple comparisons, as this study was meant to be exploratory and hypothesis generating.

3 | RESULTS

Demographics for the 152 infants analyzed in this cohort (104 XXY, 27 XXX, 15 XYY, and 6 XXYY) are shown in Table 1. Over half (57%) delayed diagnostic testing until after birth, of which 85% (postnatally confirmed) occurred prior to 2 months of age. We found no difference between timing of diagnostic testing based on maternal age, race, ethnicity, geographic region, self-reported indications for pursuing NIPS, maternal health history, family history, abnormal ultrasound findings, SCA karyotype result, or PPV for NIPS results. Participants earning less than $100k were less likely to pursue prenatal confirmatory testing than those in higher income brackets ($p = 0.02$). Of the 43% ($n = 65/152$) of participants who pursued prenatal diagnostic testing following NIPS, 80% elected an amniocentesis procedure. Details of elected procedures, timing of diagnostic testing,

comparisons of characteristics between those deferring to postnatal testing, and prenatal counseling experience questionnaire results are presented in Tables 2 and 3.

Eleven (7%) diagnostic results were discordant with NIPS results. Of these, two participants were found to be mosaic with a typical cell line, while nine participants had a different SCA condition altogether. Seven of these nine participants with discordant results had deferred diagnostic testing until birth. Details regarding fetal fraction on NIPS, maternal age at delivery, maternal prepregnancy BMI, and diagnostic test pursued for these 11 participants with NIPS results discordant from diagnostic results are presented in Table 4.

Of the 152 total participants included for this study, 102 participants completed a one-page questionnaire self-reporting reasons for NIPS, experiences with prenatal genetic counseling and potential counseling factors influencing diagnostic testing decisions (see Table 3). The top two indications reported for pursuing NIPS were maternal age (60%) and elective/gender discovery/doctor offered (42%). The majority of participants consulted with a genetic counselor (90%) after receiving their results (NIPS and/or prenatal diagnostic test results). Those who pursued prenatal diagnostic testing were significantly more likely to have received genetic counseling compared to those who deferred to postnatal diagnostic testing ($p = 0.02$). Participants who were informed of the possibility of SCA prior to NIPS were significantly more likely to defer to postnatal diagnostic testing compared with those who were not informed of SCA as a possible finding for NIPS ($p = 0.03$). While we found no difference in diagnostic timing based on perceptions of the amount of information provided or how well-informed providers counseling were about the SCA, less than half of participants felt their provider(s) were “well-informed” about the SCA discussed and participants who endorsed their provider was “well-informed” reported receiving significantly more information than those who endorsed their provider was not well-informed ($p < 0.001$).

4 | DISCUSSION

The majority of studies on NIPS results positive for SCA focus on the analytical performance of the test limited to prenatal outcomes. In this study, we present 152 cases of NIPS results positive for SCA with their diagnostic testing results, identifying over half of these parents delayed diagnostic testing until after birth. However, 7% (11 of 152) of NIPS results positive for SCA were discordant with the diagnostic test result, with nine of these 11 results warranting different genetic counseling than what would be indicated based on the NIPS results alone (i.e., trisomy SCA versus tetrasomy SCA). Furthermore, seven of these nine discordant results elected to defer to postnatal diagnostic testing, likely based on counseling provided in conjunction with additional fetal anatomy ultrasound (Fleddermann et al., 2019). However, sex chromosome trisomies are infrequently associated with second trimester ultrasound findings, so it is unlikely that ultrasound markers to modify the PPV will be recognized (De Vigan et al., 2001). This study highlights that NIPS results positive for SCA are often deferred for diagnostic testing postnatally, that families benefit from receiving more information which results in feeling that the provider counseling is well-informed about the SCA condition being discussed, and that counseling for NIPS results

should address the possibility of discordance among NIPS and diagnostic SCA potential results.

A 2018 international population-based study concluded that while SCAs contribute to a higher percentage of confirmed prenatal diagnoses secondary to NIPS, the decline in prenatal diagnostic testing leads to a relatively steady prevalence of prenatally confirmed SCAs (Howard-Bath et al., 2018). The findings of our study demonstrate that less than 50% of pregnancies with NIPS results positive for SCA pursue prenatal diagnostic testing but the majority rather defer diagnostic testing to the postnatal period. Other studies have shown even lower percentages (25%–34%) of mothers who pursue prenatal diagnostic testing after an NIPS result positive for SCA (Ramdaney et al., 2018; Riggan et al., 2020). These high rates of deferral to postnatal diagnostic testing emphasize that estimates of the impact from NIPS on the ascertainment of SCAs should include both prenatal and postnatal diagnostic testing. As the study by Howard-Bath et al in 2018 demonstrated a steady birth prevalence of SCAs based on prenatal diagnostic testing after NIPS, based on our results and similar studies suggesting 60%–80% of those receiving positive NIPS results will have diagnostic testing shortly after birth, it can be estimated that introduction of NIPS has increased the overall SCA ascertainment in infancy by at least two-to threefold. Anecdotally, we appreciate this in our clinical practice, however, additional population-based studies are needed to confirm these assumptions.

While we collected a limited dataset of potential factors influencing the decision to defer to postnatal diagnostic testing, our study did identify a significant difference in deferral to postnatal confirmation when SCA was discussed prior to NIPS. This finding could be attributed to implicit framing effects during pre-NIPS genetic counseling, especially in context of counseling for all possible NIPS outcomes, which could precipitate post-NIPS decision-making (van der Steen et al., 2019). In addition, we also found differences in deferral to postnatal testing when mothers reported an annual household income less than $100k, which warrants further investigations. While our study did not inquire as to how or why socioeconomic factors influenced diagnostic decision-making, previous research has demonstrated socioeconomic disparities in prenatal genetic screening and informed decision-making due to limited access to care or information provided during counseling (Khoshnood et al., 2004). We did not find any differences in our results based on race or ethnicity; however, the homogeneity of our sample precludes an adequate assessment and warrants further investigations as previous research evaluating racial/ethnic groups with NIPS results positive for SCAs identified that African American women were the most likely to decline prenatal diagnostic testing, while Asian women were the most likely to elect for prenatal diagnostic testing (Ramdaney et al., 2018). These collective findings and insights highlight the need for future research further investigating disparities in prenatal genetic counseling and testing for SCAs, possible reasons for these disparities, and how to minimize them.

A unique aspect of prenatal genetic counseling following a NIPS result positive for SCA is the presentation, interpretation and often calculation of the positive predictive value (PPV). The PPV for NIPS results regarding SCAs is inherently variable among laboratories with published values ranging from 20% to 86% (Lu et al., 2021; Petersen et al., 2017;

Ramdaney et al., 2018; Shi et al., 2021). A 2019 review of 10 NIPS laboratory reporting methods concluded recommendations that laboratory reports visibly and clearly state the detection rate (DR), specificity (SPEC), positive predictive value (PPV), and negative predictive value (NPV) for all conditions being screened in order to assist patients and providers in making decisions and interpreting results (Skotko et al., 2019). As noted in the review, no commercial laboratories published their PPV on the respective reports (at that time). While some improvements have been made to various lab reports since this 2019 publication, there continues to be significant variability in what information is disclosed on NIPS result reports industrywide and many omit PPV values, which could be contributed to the relatively low prevalence of the condition, such as XXYY, and respective validation challenges (Sorensen et al., 1978). Recognizing the importance of these variables for clinical interpretation and informed counseling, a task-force was established, including members of the National Society of Genetic Counselors and the Perinatal Quality Foundation, to review the medical literature and build consensus regarding best estimates to develop algorithms and ultimately the publication of the NIPS/cffDNA Predictive Value Calculator (https://www.perinatalquality.org/Vendors/NSGC/NIPS/). When estimates of sensitivity and specificity are not provided on the laboratory report, this calculator utilizes estimates based on a meta-analysis of available studies (Gil et al., 2015). Today, the NIPS/cffDNA Predictive Value Calculator published by the PerinatalQuality Foundation and the National Society of Genetic Counselors (NSGC; www.perinatalquality.org) provides genetic counselors with a tool to estimate the PPV when faced with an NIPS result positive for SCA. While this calculator is intended to facilitate informed decision-making, counseling for SCAs commonly results in setting expectations of a false positive if PPV is below 50%, in which mothers perceive diagnostic lab outcomes more likely to be normal. While we did not find any difference in timing of diagnostic testing based on PPV (provided by the lab or calculated online), further studies evaluating mothers' expectations based on presented PPV may be useful to improve genetic counseling when NIPS results are positive for SCA given the relatively poor PPVs.

While consent for NIPS may be influenced by various factors ranging from desire of early fetal gender identification to experiences of previous pregnancy outcomes, NIPS results positive for SCA may have a pivotal psychological impact on the expectant mother. In a 2013 study by Lalatta et al., the importance of utilizing a framework in genetic counseling, including the potential findings for SCAs, prior to prenatal diagnosis was supported to help reduce the emotional devastation with unexpected results of SCA given the relatively high incidence of these conditions compared to other aneuploidies (Lalatta & Tint, 2013; Riggan et al., 2020). While women who receive a NIPS result positive for SCA are recommended to receive genetic counseling regarding diagnostic testing options, the approach to prenatal genetic counseling for SCAs still continues to be far from standardized (Gregg et al., 2016). In a 2019 study surveying 176 genetic counselors to evaluate genetic counseling practices throughout the United States following an NIPS result positive for SCA, significant discrepancies were identified that highlighted the need to establish professional guidelines in order to provide consistencies in care for NIPS results positive for SCA (Fleddermann et al., 2019).

Effective prenatal genetic counseling is fundamental in providing accurate, unbiased, and updated information alongside nondirective psychological support for families faced with an at-risk or confirmed prenatal genetic diagnosis. As such, it is imperative to evaluate the prenatal genetic counseling experiences and diagnostic timing decisions in parents who continued pregnancies following NIPS results positive for SCAs. The majority of participants in our study reported that they met with a genetic counselor after receiving results (NIPS or diagnostic), yet less than 50% of participants felt their provider was "well-informed" about SCAs. We found no difference in decisions in timing of diagnostic testing based on the amount of information provided about the SCA. Our study results did demonstrate that consultation with a genetic counselor after results were received was associated with higher likelihood of prenatal diagnostic testing, and the amount of information provided during genetic counseling was positively and significantly associated with mothers' perceptions that providers were well-informed. These findings are consistent with previous publications reporting that even genetic providers feel poorly equipped to provide adequate support at the time of SCA counseling based on limited time during appointments, lack of knowledge regarding SCAs and few educational resources available (Farrell et al., 2016; Riggan et al., 2020). Our study promotes future comprehensive education programs regarding SCA for genetic counselors and the importance of extensive information regarding SCA be provided to mothers at the time of counseling in order to appropriately support informed decision-making.

4.1 | Practice implications

Importantly, our study presents a series of 11 participants (7% of our total sample) in which NIPS SCA results were discordant with the final SCA diagnosis, of which nine participants were diagnosed with a different condition and could have been counseled inaccurately if counseled based solely upon the NIPS trisomy result condition alone. While NIPS results may be indeterminate in cases of reduced fetal fraction, including cases of maternal obesity that are associated with reduced fetal fraction, discordance between NIPS result and fetal karyotype has also been well established to be attributed by various factors including, but not limited to, confined placental mosaicism, maternal copy number variation (CNVs), maternal X chromosome aneuploidy and/or mosaicsm, maternal malignancy, vanishing twin, and technical, bioin-formatics, or human errors (Hartwig et al., 2017; Shree et al., 2021). For these and other reasons, NIPS remains classified as a screening, nondiagnostic test with standard recommendations that any positive NIPS result be followed by confirmatory diagnostic testing (Devers et al., 2013; Hartwig et al., 2017). However, five of our nine discordant results showed an NIPS result for a sex chromosome trisomy (XXY or XYY) and parents elected to defer to postnatal diagnostic testing, which subsequently resulted in an unexpected diagnosis of a tetrasomy, 48,XXYY. Similarly, a retrospective study of 27 NIPS screens positive for XXY had discordant results with other SCAs (XYY, XXYY, and XXXXY) upon diagnostic testing, also demonstrating NIPS more likely to result as trisomic, possibly attributed to relative incidence compared to tetrasomies (Ramdaney et al., 2018). While postnatal recall of prenatal counseling experiences has inherent limitations and biases, routine counseling for NIPS results of XXY or XYY does not routinely provide in-depth information regarding a possible diagnosis of 48,XXYY (or other tetrasomy outcomes) to facilitate informed decision-making. Traditionally, genetic counseling for NIPS results is

based upon the presenting NIPS laboratory report. These five discordant results represent the imperative need for prenatal genetic counseling on NIPS results positive for SCAs to also include the possibility for an SCA diagnosis that is abnormal but discordant with the NIPS laboratory result. In a recent study, this concern is articulated specific to NIPS results positive for 47,XXY, with the authors underlining the importance of a definitive diagnosis not only for excluding a false positive but also excluding other chromosomal variations which may have a different and more severe phenotype (Ronzoni et al., 2021). Our study findings reinforce the importance of counseling regarding possible other SCAs as there are significant phenotypic differences associated with higher risks of medical complexity and neurodevelopmental involvement when comparing sex chromosome trisomies vs. tetrasomies, such as 48,XXYY (Raznahan et al., 2018; Skuse et al., 2018; Tartaglia et al., 2011, 2012).

4.2 | Study limitations

Although this study represents the largest sample to date that investigates factors contributing to timing of diagnostic testing following NIPS positive for supernumerary SCAs, we were underpowered to detect small differences between groups that may exist (effect sizes <0.30 for chi squared analyses and <0.46 for *t*-tests), and even larger effect sizes were needed with the outcomes we analyzed from survey responses given the smaller number of participants for which data were available. In addition, the study sample was relatively homogenous with predominately older, non-Hispanic white mothers with XXY infants, all of whom chose to enroll in a longitudinal natural history study, therefore generalizing these results to all women with a positive NIPS result may be inappropriate. Another potential limitation is the retrospective nature for survey collection, which is prone to intentional or unintentional recall bias.

In consideration of future areas of research, investigation of possible reasons for disparities in prenatal genetic testing in SCA and how to minimize these disparities is warranted. Additionally, studies are needed to better inform genetic counselors about SCA and potential discordant outcomes when NIPS results are positive. Recognizing the phenomenon of some mothers pursuing prenatal diagnostic testing, while other mothers defer testing to after birth, results in a two-tier ascertainment impact from NIPS screening in SCA. Future areas of research could further investigate whether the postnatal outcomes in the children or if the parental experiences, such as attachment, differ significantly among these two cohorts. Additional areas for future research could include investigation into the long-term emotional health of parents raising a child with an SCA initially identified by NIPS, including discordant results, and prenatal genetic counseling factors that impacted these parental outcomes.

5 | CONCLUSIONS

In conclusion, our study supports that the majority of NIPS results positive for supernumerary SCA are confirmed postnatally, that NIPS has increased the ascertainment of SCAs two- to threefold when accounting for both prenatal and postnatal diagnostic tests, and that prenatal counseling for NIPS results positive for SCA should include providing

extensive information regarding the SCA and discussion regarding possible abnormal but discordant diagnostic outcomes in order for mothers to feel well-informed and able to make an informed decision regarding diagnostic testing.

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DATA AVAIL ABILIT Y STATEMENT

Deidentified data that support the findings of this study are available from the corresponding author upon reasonable request.

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What is known about this topic

Prenatal ascertainment of sex chromosome aneuploidies (SCA) is increasing with the adoption of noninvasive prenatal screening (NIPS), although diagnostic confirmation may be delayed until the postnatal period. The positive predictive value of NIPS for SCA is relatively poor.

What this paper adds to this topic

The majority (57%) of parents with a NIPS result positive for SCA defer diagnostic confirmation until birth; however, diagnostic results can be discordant with NIPS results, which may impact genetic counseling.

TABLE 1

Subject demographics

	Total *N* = 152
Race	*N* (%)
White	139 (91)
Asian	11 (7)
Native American	3 (2)
African American	2 (1)
Ethnicity	
Non-Hispanic	134 (88)
Hispanic	18 (12)
Annual household income	
<$100k	42 (28)
$100–$150k	36 (24)
$150–$250k	39 (26)
>$250k	23 (15)
Unreported	12 (8)
Gestational age at NIPT (wks)	13 ± 5.4
Fetal fraction on NIPT (%)	9.2 ± 3.9
Maternal prepregnancy BMI, M ± SD (kg/cm^2)	26 ± 6.0
Prenatal diagnostic testing (CVS or amniocentesis)	65 (43)
Final karyotype result	
47,XXY	104 (68)
47,XXX	27 (18)
47,XYY	15 (10)
48,XXYY	6 (4)
Birthweight (kg)	3.25 ± 0.7
Gestational age at delivery (wks)	38.7 ± 1.4
Maternal age at delivery (years)	35.3 ± 4.8
Geographic region[a]	
Northeast	31 (20)
Midwest	24 (16)
South	42 (28)
West	53 (35)
International	2 (1)

Note: Data are mean ± standard deviation (SD) or *n* (%).

Abbreviations: BMI, body mass index; CVS, chorionic villus sampling; NIPT, noninvasive prenatal testing.

[a]US Geographic Regions as designated by the US Census BureauNortheast: CT, MA, ME, NH, NJ, NY, PA, RI, VT; Midwest: IA, IL, IN, KS, MI, MN, MO, NE, ND, OH, SD, WI; South: AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; West: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA WY.

TABLE 2

Karyotypes stratified by timing of diagnostic testing

Diagnostic karyotype	Full cohort of NIPT Positive for SCA[a] (*n* = 152)	CVS prenatal diagnostic testing (*n* = 13)	Amnio prenatal diagnostic testing (*n* = 52)	Deferred to postnatal diagnostic testing (*n* = 87)[b]
47,XXY	104 (68%)	10 (10%)	37 (36%)	57 (55%)[a]
47,XXX	27 (18%)	1 (4%)	11 (41%)[a]	15 (56%)
47,XYY	15 (10%)	2 (13%)	3 (20%)	10 (67%)
48,XXYY	6 (4%)	-	1 (17%)[a]	5 (83%)[a]
All SCAs	152 (100%)	13 (9%)	52 (34%)	87 (57%)

Abbreviations: amnio, amniocentesis; CVS, chorionic villus sampling; NIPT, noninvasive prenatal testing.

[a]Includes Discordant NIPT versus Diagnostic Results, see Table 4.

[b]85% of all diagnostic confirmations deferred to postnatal were conducted prior to 2 months of age and were confirmed in cord blood or peripheral blood.

TABLE 3

Participant characteristics stratified by timing of confirmatory diagnostic testing ($N = 152$)

	Pursued prenatal $N = 65$ (43%)	**Deferred to postnatal $N = 87$ (57%)**	***p*-value**
Demographics			
Maternal age (years): M ±SD	35.14 ± 4.40	35.4 ± 5.05	0.74
Annual Household Income			0.02 *
<$100k	12 (18.5)	33 (38)	
$100–$150k	15 (23.1)	23 (26.4)	
$150–$250k	22 (33.8)	20 (23)	
>$250k	15 (23.1)	10 (11.5)	
Race/Ethnicity: *N*(%)			
Racial Minority (non-White)	6 (9)	7 (8)	0.99
Hispanic	7 (11)	10 (11.5)	0.99
Underrepresented Minority (combined race and ethnicity)	12 (18.5)	16 (18.4)	0.99
Geographic region[a]			0.64
Northeast	15 (23.1)	16 (18.4)	
Midwest	14 (22)	10 (11.5)	
South	15 (23.1)	27 (31)	
West	19 (29.2)	34 (39.1)	
SCA result on NIPT report			0.68
47,XXY	46 (70.8)	58 (66.7)	
47,XXX	11 (17)	16 (18.4)	
47,XYY	6 (9.2)	12 (13.8)	
Calculated PPV[b] M ± SD	49.52 ± 23.19	50.88 ± 25.45	0.73
Prenatal experience questionnaire results stratified by timing of confirmatory diagnostic testing ($N = 102$)			
	Pursued prenatal $N = 49$ (48%)	**Deferred to postnatal $N = 53$ (52%)**	***p*-value**
Self-Reported Indications for NIPT			
Maternal age $N = 61(60)$	29 (59.2)	32 (60.4)	0.90
Abnormal ultrasound findings $N = 4(4)$	1 (2.0)	3 (5.7)	0.62
Gender discovery/Elective/Doctor offered $N = 43(42)$	21 (42.9)	22 (41.5)	0.99
Other (family history, prior pregnancy loss) $N = 17(16)$	7 (14.3)	10 (18.9)	0.60

Counseling experience			
Informed about possibility of SCA prior to NIPT (“yes,” %) *N* = 29(28.4)	9 (18.4)	20 (37.7)	**0.03** *
Consulted with a genetic counselor after receiving NIPT results (“yes,” %) *N* = 92(90.2)	48 (98.0)	44 (83.0)	**0.02** *
Impression that providers were well-informed about condition (“yes,”%) *N* = 42(41.2)	21 (42.9)	21 (39.6)	0.56
Perceived Amount of Information Provided (scale:0–100) M ± SD Total = 52.75 ± 26.12	58.4 ± 27.98	47.74 ±23.5	0.29

Note: Data are mean ± standard deviation (SD) or *n* (%).

Abbreviations: NIPT, noninvasive prenatal testing; PPV, positive predictive value.

The bold indicates significant findings *p* value <0.05.

* $p < 0.05$.

[a] US Geographic Regions as designated by the US Census Bureau: Northeast: CT, MA, ME, NH, NJ, NY, PA, RI, VT; Midwest: IA, IL, IN, KS, MI, MN, MO, NE, ND, OH, SD, WI; South: AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; West: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA WY.

[b] PPV calculations were taken from report or if not available, calculated utilizing the perinatal quality foundation PPV calculator (https://www.perinatalquality.org/Vendors/NSGC/NIPT/).

TABLE 4

Discordant results between NIPT and diagnostic karyotype

NIPT result	Fetal fraction per NIPT report (%)	Maternal age range at delivery (years)	Maternal prepregnancy BMI (kg/cm^2)	Diagnostic test pursued	Diagnostic test result
45,X	NR	35–39	23.9	Amnio	47,XXX
47,XXX	10.7	35–39	29.4	Amnio	47,XXX[6]/46,XX[9]
47,XYY	6.3	35–39	21.2	Postnatal	47,XXY
Increased risk for trisomy 13/18/triploidy	3.2	30–34	29.8	Postnatal	47,XXY
Inconclusive	6	30–34	36.5	Amnio	47,XXY
47,XXY	6.9	20–24	29.4	Amnio	47,XXY[91%]/46,XX[9%]
47,XXY	6	30–34	20.5	Postnatal	48,XXYY
47,XXY	NR	20–24	22.3	Amnio	48,XXYY
47,XYY	11.8	30–34	24	Postnatal	48,XXYY
47,XXY	7	30–34	26.4	Postnatal	48,XXYY
47,XYY	6.1	35–39	30.2	Postnatal	48,XXYY
47,XXY	4	35–39	36.6	Postnatal	48,XXYY

Abbreviations: BMI, body mass index; NIPT, noninvasive prenatal testing; NR, not reported.