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Unique Challenges of NIPT for Sex Chromosome Aneuploidy

Louise Wilkins-Haug, MD,PhD [Professor],
Harvard Medical School, Brigham and Women's Hospital

Rebecca Reimers, MD/MPH [Investigator]
Rady Children's Institute for Genomic Medicine, KL2 Scholar Scripps Research Translational Institute

Abstract

Noninvasive prenatal testing (NIPT) for the sex chromosome aneuploidies (SCAs - 45,X, 47,XXY, 47,XXX and 47,XYY) differs significantly from that for the autosomal aneuploidies (trisomy 13,18, and 21). As a group, SCAs occur more commonly (1/400) than any one isolated autosomal aneuploidy, the phenotypic variation is greater, the role of mosaicism more challenging, and the positive predictive value of a high risk NIPT result is substantially lower. These considerations should be identified during pretest counseling, the inclusion of sex chromosome testing offered separately and the differences from autosomal aneuploidy NIPT clearly delineated.

Keywords

sex chromosome aneuploidies; Turner syndrome; NIPT

1. INTRODUCTION

The X and Y chromosomes are the 23rd pair of chromosomes. Like the 22 pairs of autosomes (numbers 1–22), one chromosome of the 23rd pair is inherited from the mother and the second from the father. However, unlike the autosome pairs, the genes on the X and Y play an important role in fetal gonadal development. Internal gonads, either ovaries or testes, and the hormones they produce, initiate, and support the development of external genitalia in the fetus and during puberty. Individuals with testes and male external genitalia typically possess an X and a Y chromosome (46,XY). Most often, two X chromosomes (46,XX) are present in persons with ovaries, a uterus, and female external genitalia. Alterations in the number (aneuploidy) of the X and Y chromosomes can produce variable and often subtle phenotypic alterations. Many of the changes result from the altered gonadal development and hormonal disruptions while structural anomalies are primarily associated with a single sex chromosome, in humans, the X chromosome.

Assessment of the sex chromosomes (X and Y), either as routine, opt-in, or opt out, often accompanies noninvasive prenatal testing (NIPT) for common autosomal aneuploidy

Correspondence: Louise Wilkins-Haug, MD,PhD, Brigham and Women's Hospital, Division of Maternal-Fetal Medicine, 75 Francis Street, CWN 3, Boston, MA 02115, Phone: (617) 732-5452, Fax: (617) 730-2828, lwilkinshaug@bwh.harvard.edu.

(trisomy 13,18 and 21). NIPT for the common aneuploidies has high sensitivity and specificity. Parental desire for fetal sex determination likely played a role in the inclusion of analysis for X and Y on NIPT autosomal panels. However, in a minority of countries, sex chromosomes are not routinely assessed, and in other countries, only aneuploidy of the sex chromosomes is reported. Based on large, population studies, less than 1% of NIPT tests are positive for a high-risk SCA.

Screening by NIPT for SCA differs from autosomal aneuploidy analysis in several ways and should be highlighted in pretest counseling. First, the phenotype of sex chromosome aneuploidies, whether in utero, in the child, or the adult is more subtle and with fewer medical concerns than for the autosomal aneuploidies. Secondly, SCA can occur in all studied cells (non-mosaic, such as 47,XXY) or as a combination of aneuploid and euploid cell lines known as mosaicism (examples include 46,X/46,XX; 45,X/46,XY; 45,X/46,XX/47, XXX). Compared to autosomal aneuploidy, mosaicism occurs more frequently with the X and Y chromosomes. Lastly, the positive predicate value (PPV) for a high-risk NIPT result for SCA varies between the sex chromosome conditions and is lower than the PPV for trisomy 21 NIPT. Especially for monosomy X, the PPV can be as low as 20% as compared to the 50% for trisomy 21 in women less than 35 years of age. In this manuscript, we review these three challenges to SCA NIPT screening (variable phenotypes, high rates of mosaicism and lower PPV). Additionally, we provide specific guidance for pre and post NIPT screening for SCA highlighting the areas of difference from autosomal aneuploidy NIPT counseling.

Definition of sex chromosome aneuploidy

When considered as a group, individuals with SCA are common (1/448 livebirths). A large study of an unselected, newborns studied by cord blood karyotype found SCAs more common than any single autosomal aneuploidy including trisomy 21.[1] Among these unselected newborns, 47,XXY (Klinefelter syndrome) was the most common SCA and occurred 3–4 times more commonly than a 45,X (Turner syndrome) (1.73/1000 vs 0.5/1000, respectively). At least two other SCAs (47,XYY, Jacobs syndrome, 1.18 /1000) and 47,XXX (Triple X syndrome, 1.06/1000) are also more common than 45,X in livebirth.[1] (Table 1) However, although 45,X is the least frequent of the SCAs, the condition is associated more often with structural maldevelopment and ovarian dysgenesis. This leads to an estimated 70% of 45,X individuals being diagnosed, most often during the newborn or childhood years.[2] For the remaining SCAs, while they occur more frequently, the individuals often remain undiagnosed even through adult life. Based on unbiased newborn surveys and registry data, excluding Turner syndrome, less than a quarter of the individuals with SCA are likely to come to medical attention (23% for 47 XXY, 7% for 47,XXX and 9 % for 47,XXY.)[2]

The origin of aneuploidy of the X and Y chromosomes also differs from that involving the autosomes. Autosomal aneuploidy (such as trisomy 21) typically occurs as a meiotic error in the gametes, typically the oocyte. In contrast, SCA typically arises in later cell divisions during early embryonic differentiation (mitotic errors). This higher rate of mitotic error in developing tissues may reflect the X and Y chromosome's unique process of pairing, replication, and gene content that differs from that in the autosomes. The "pseudoautosomal"

regions (PAR) on the Y chromosome which enable pairing with the X chromosome are significantly smaller compared to the similar pairing regions on the autosomes. Furthermore, the X chromosome is inactivated in early embryogenesis leading to only one X chromosome with active gene function in later cells regardless of the starting number. Such X-inactivation and a higher guanine-cytosine content of the X chromosome may further contribute to the instability of the sex chromosome pair. [3]

The higher rate of mitotic errors in SCA are highlighted by the lack of a maternal age association with 45,X. Most cases of 45,X are the result of loss of the paternal X. [4] While fertilization of an oocyte by a sperm without a sex chromosome has been reported, more commonly a sex chromosome is lost or gained during early cell divisions in the embryonic tissues or later. The lack of a maternal age effect for 45X is unique among the SCA as 47,XXX and 47, XXY do display associations with increasing mental age. [3]

Challenges with NIPT screening for SCA – what is the phenotype?

Perhaps spurred by pregnant persons' desire to learn the fetal sex early in pregnancy, and X or Y determination was technically possible, determination of the fetal sex is now often included with NIPT for autosomal aneuploidy. As such information was not previously available through serum screening for aneuploidy risk, this additional information was seen as desired by providers and parents. However, along with assessment fetal sex, comes the possibility of detection of a SCA – such as 45,X, 47,XXX, 47, XXY, or 47,XYY. While most countries now have guidelines for NIPT, often the determination of fetal sex, or SCAs are not addressed specifically. [5] However, inclusion of the sex chromosomes is widespread globally and practiced in most European countries, much of Australia, Israel, and Asia. [5] England, Wales, Scotland and Norway are notable exceptions to the default inclusion of the X and Y chromosome in NIPT panels. However, in these countries with formal policies to not include assessment of X and Y, private options often paired with a "bonding ultrasound" are available. [6] In the United States, > 75% of NIPT includes analysis of the sex chromosomes. Approaches of opting in or out for the inclusion of the sex chromosomes vary by country and is supported by the ACMGG. [7] Inherent in the ACMGG provision is the necessity for pretest counseling regarding the possibility of neurobehavior differences in individuals with SCA and the role of interventions. [7] In some European countries (France and Belgium), fetal sex is reported but aneuploidies of fetal sex chromosomes are not given the inherent challenges presented in this review.

As noted initially, except for 45,X which is the least frequent of the SCAs, most individuals with SCA aneuploidy are unlikely to require medical attention during their lifetime. And even among fetuses identified as true positives after a high risk for monosomy X by NIPT, there is more variation in the expected outcomes than occurs for the autosomal aneuploidies diagnosed in utero. 45,X is unique among the SCA with an association with structural anomalies including cystic hygroma in the first trimester, cardiac anomalies, and renal anomalies. Chronic medical conditions such as hypothyroidism, hypertension, and hearing loss have also been noted. With bilateral ovarian dysgenesis, small stature is expected as well as amenorrhea and infertility. Advances in pubertal induction and hormone replacement have been actively pursued in girls with a prepubertal diagnosis of 45,X. [8] The "typical"

phenotype of 45,X is variable and has generally been based on individuals evaluated as children or adults who presented with one of the classic findings. When assessed from a fetal standpoint, even further variability in the phenotype for X chromosome disorders is noted. With a high-risk monosomy X NIPT result, and the presence of a cystic hygroma or anomaly, the likelihood of a true positive 45,X is higher (98% PPV). However, with a normal ultrasound, the PPV is lowered but the NIPT may still reflect a fetal 46,XX/45,X mosaic or a X chromosome variant. While mosaicism is generally considered to be associated with lessor impact on overall phenotype, the ability to predict for an individual fetus is limited. [9] The individual with a mosaic 45,X may have less risk of a cardiac anomaly but their risks of various health issues including hypertension, hypothyroidism, bicuspid aortic valve and short stature remain.[10–13]

Notably, and with impact on the phenotype, SCA mosaicism involves not only the combinations of 45,X, 47,XXX with 46,XX but also cell lines with an X chromosome structural variants such as a ring X chromosome, isochromosome of X, deletions of X or X/autosome translocations. These mosaic SCA combinations are noted among newborns and children with SCA as well as when high risk monosomy X NIPT results lead to a diagnostic procedure. In one recent study, among the true positive results, half (52%) were 45,X while the other half (48%) were either mosaic or had a X chromosome variant.[14] These findings are similar to a literature review of the true positive monosomy X following high-risk NIPT which found fetal chromosome compositions were 45,X in 67%, mosaics 45,X/46,XX in 20%, mosaic 45,X/46,XY in 10%, and X chromosome rearrangements in 3%. [15] This is not dissimilar to the distribution of 45,X, 45,X/46,XX and X chromosome variants detected among girls with clincial Turner phenotypes. [13]

For 47,XXY, a fetal phenotype is also emerging which includes increased first trimester nuchal translucency (> 3.0 mm) noted in 6/26 (23.1%) and second trimester anomalies (CNS, cardiac, echogenic bowel and limb abnormalities) in 7/24 (29.2%). [16] Of note, the degree of maldevelopment of the systems is variable with CNS findings ranging from mild ventriculomegaly to holoprosencephaly and the skeletal findings including a unilateral clubfoot to shortened long bones. [16] Further work is needed to develop the 47,XXY fetal phenotype as these observations are from a cohort of 41 fetuses. While children with 47,XXY have higher incidences of developmental delay, learning disability, and behavioral issues, and in the adult the effects of gonadal dysgenesis include infertility and osteoporosis, structural anomalies have not been associated with the overall phenotype. If structural maldevelopment and the potential need for medical or surgical corrections are developed as part of the 47,XXY fetal phenotype, this information should further inform the prenatal counseling. Of note, prenatally diagnosed 47,XXY people have milder neurodevelopmental differences than their postnatally diagnosed peers potentially reflecting early treatment modalities and intervention. [17] For the remainder of the sex chromosome trisomies, an increased nuchal translucency (> 99.0%) has been noted in as many as 40% of SCA on ultrasounds.[18] For the majority of fetuses with a SCA, prenatal ultrasound findings are not identified, and the majority will not come to medical attention.

Given this variable phenotype and the potential for milder outcomes following a prenatal diagnosis, the utility of NIPT for SCA has been questioned. [19] Inherent in offering

SCA NIPT is the appreciation not only of the variable phenotypes within and between the SCAs conditions but also the potential utility of the diagnosis for the pregnant individual. Such utility includes whether parental knowledge provides information that will alter the pregnancy outcome, both the option of not continuing a pregnancy based on the pregnant individuals' preference and also whether alterations in pregnancy care would be made based on the knowledge of a SCA. For the latter, for all except 45,X, the fetus with a SCA is anticipated to do well during pregnancy with normal growth and would not require specialized newborn care. 45,X, however, is the exception with a higher rate of structural anomalies of various systems including the cardiac system. These concerns may be significant enough to be life threatening at birth (hypoplastic left heart syndrome) and may alter the delivery site of care. Additionally, pregnancies with 45,X are at higher rates of stillbirth throughout pregnancy, even in the absence of cardiac or other structural anomalies. However, pregnancy interventions, such as fetal surveillance and delivery by term have not been investigated as pathways to address the higher stillbirth rate as has been shown for trisomy 21. [20]

Increasingly, there is support for the approach that knowledge of a SCA prior to birth may alter neurodevelopmental care in the early childhood period. As these children would not be routinely tested for SCA as newborns, the prenatal determination of their SCA may be an influencing factor in their future health and developmental care. In the child with 47,XXY, health concerns such as androgen insufficiency and neurodevelopmental issues can be addressed preemptively. Some authors have noted that testosterone supplementation even at 1–2 years of age may influence neurodevelopmental differences, though this is still an area of investigation. [21] In children with 47,XXX, monitoring and addressing early hypotonia, developmental milestones, and monitoring for seizures is suggested. [22] From the parents' perspective, the early knowledge of a SCA, which would not have been detected by physical exam in the newborn, was a benefit and provided a means for earlier intervention. [21] For 45,X, if structural anomalies to promote a diagnostic evaluation are not present in the newborn, concern remains about delayed diagnosis and the potential missed opportunities for early intervention including pubertal induction and hormonal support. Fetal diagnosis for 45,X (or from cord blood prompted by a high risk NIPT for SCA) opens avenues for earlier intervention. This extends to the recent work and success in both early oocyte freezing and ovarian tissue freezing for future fertility in the 45,X individual without underlying cardiac concerns. [8]

Challenges with NIPT screening for SCA – higher rates of mosaicism

For SCAs as a group, and 45,X in particular, there are higher rates of mosaicism at preimplantation genetic testing, in the fetus, the newborn and in the child when compared to autosomal aneuploidy. Also, when compared to autosomal aneuploidy, the sex chromosomes are more likely to be involved in mosaicism confined to the placenta (CPM). This higher rate reflects the above-described mechanism of mitotic errors in later developing issues rather than meiotic errors in the gamete. Mosaicism adds complexity to NIPT for SCA with challenges to the expected phenotype as noted previously, in the interpretation of high risk NIPT results, and the appropriate diagnostic test to offer.

For instance, high risk NIPT results for a SCA are more likely to be influenced by unrecognized maternal SCA mosaicism than occurs for high-risk autosomal aneuploidy results. A SCA in the mother, and not the fetus, is now a recognized contributor to “false positive” SCA NIPT results in as many as 6–24% of instances. (Roberts AW, Abstract 93, SMFM 2/2023) [23, 24] [25] This speaks directly to the variable phenotypes and undiagnosed presentations of SCA in these pregnant people. Especially among people with mosaic 45X/46,XX, infertility is not universal given approximately 5% conceive spontaneously. [13] Among a small sample of pregnant persons who underwent maternal karyotypes following high risk NIPT for SCA (N=47), there were individuals with 45,X (N=3) and with 45,X mosaics (N=13) were compared to the karyotypically normal pregnant persons, (N=31). Among those with newly diagnosed SCA, significantly higher rates of short stature, hearing loss and prior growth hormone treatment were noted. Neither infertility nor maternal chronic disease reached significant levels between the groups. (Roberts AW, Abstract 93, SMFM 2/2023)

Confined placental mosaicism (CPM) refers to the presence of a karyotypically normal and an abnormal cell line within the placenta. CPM for autosomes is noted in approximately 1–2 % of CVS samples and the majority are associated with a normal fetal karyotype. Conversely, for SCA mosaicism identified by CVS, while CPM can occur, the majority of fetuses were found to have either true fetal SCA or a SCA mosaicism. From a large study of SCA mosaicism by CVS (N=522), CPM was confirmed in 23% (normal fetal karyotype), 8% were true fetal mosaics, and 68% were non-mosaic SCA fetuses.[26] For those ascertained by NIPT, these ratios are greatly influenced by whether there are ultrasound anomalies (inclusive of nuchal lucency > 3.0 mm). [27] This is an important consideration for care as NIPT and CVS both examine placental DNA. Direct CVS preparations can yield results without time-consuming cell culture; however, this type of examination looks at the same tissue that yields NIPT results - the cytotrophoblasts on the exterior of the chorionic villus. Culture of chorionic villi preferentially examines the core of the villus which is more likely to reflect the fetal population of cells.

Challenges with NIPT screening for SCA – low positive predictive value

NIPT provides an extremely sensitive and specific approach to screening for autosomal aneuploidy and reasonable but lower levels for sex chromosome aneuploidy. For the common autosomal trisomies, sensitivity is high ranging from 95.85–99.7% with specificities at 99.1%. For the SCA, however, sensitivity is lower and variable within the group; sensitivities from 83.4%–93.9% for monosomy X and 76.3%–93.0% for XXY, XYY and XXX. [22]

Most strikingly, and clinically relevant, however, are the lower and variable positive predictive values (PPV) of the SCAs assessed. The PPV provides the most helpful clincial information to the pregnant person as it details the chances that for their pregnancy, the NIPT results reflect a true fetal positive. PPV is influenced by several factors which become important especially when 45,X is considered. These include the frequency of the condition, the influence (or not) of the maternal age, the technical aspects of the test, the likelihood of placental mosaicism and the possibility that a maternal rather than a fetal condition

is present. The last two have been discussed previously. For the autosomal aneuploidies, numerous studies have established that for trisomy 13,18,21, the PPV can range from over 90% (in a pregnant person over 40 years old) to less than 20% (for a pregnant person less than 20 years for the rarer condition of trisomy 13). A recent meta-analysis highlights a lower PPV for SCA as a group around 50% and for X monosomy alone, as low as 15%. [22] This data replicates earlier findings of lower and variable PPVs across the categories of SCAs. (Table 2)

Reported population prevalence of a condition is included in the PPV and is more consistent for autosomal aneuploidy which is often diagnosed at birth. For the sex chromosome disorders, however, the majority may go undiagnosed or not identified until adulthood. A 2023 metanalysis utilizing varying published population frequencies for each SCA showed a notable impact of the PPV reported. As much as a fivefold difference in published population prevalence of the various SCA resulted in wide ranges of PPV. [22](Table 3)

The studies excluded indications such as ultrasound anomaly and in at least one large study abnormal biochemical findings. The variation in prevalence may be influenced by the gestational age at testing (first trimester CVS having the highest prevalence), as well as by maternal age for all but the 45,X results. Of note, among a cytogenetics registry, even when ultrasound anomalies are removed from the analysis, the determination of 45,X by CVS and by amniocentesis was 13 times and 6 times higher than from individuals sampled at livebirth. [28] This reflects the increased pregnancy loss rate of 45,X between first trimester CVS and 2nd trimester amniocentesis and then second trimester to term.

Additionally, as shown in table 3, when aneuploidy of the X chromosome alone is involved, the PPV is the lowest and most variable in prediction of a true positive suggesting other factors are also involved. Technical challenges of X chromosome sequencing due to its high CG content are recognized and lead to variability in detection between laboratories and technology utilized. A newer approach of the Oxford nanopore, a third-generation sequencing platform, may resolve some of these variations in detection of the X chromosome. Able to provide sequencing without PCR amplification, a recent publication [29] of the application of Oxford nanopore to cfDNA (nanoNIPT) provided a proof of principle in converting the technology from detection of long reads to short needed for noninvasive testing. Advances in technology are likely to increase the interest in nanoNIPT as a lower cost approach to sequencing even for short segments as in cfDNA. The noted improvements in detection of the X chromosome await further confirmation.

Diagnostic testing challenges

For high-risk NIPT for SCA, the decision for modality of diagnostic testing is more nuanced than for an autosomal high-risk NIPT. With a high-risk trisomy 18 or 21 NIPT result, diagnostic testing can be offered early in the pregnancy with a CVS allowing time for additional consultation and pregnancy options. If there are ultrasound findings, trisomy 13 should also be offered CVS while in the absence of ultrasound findings, amniocentesis should be considered. [30] Mosaicism of the autosomes, either placental or fetal, is uncommon and CVS results provide a definitive diagnosis. By contrast, with the higher

rates of mosaicism with SCA disorders as previously described, a CVS will resample the same cells depicted by the NIPT result.

For SCA, consideration of the appropriate diagnostic test can be informed by a first trimester US for nuchal lucency as well as an early fetal survey. A cystic hygroma or a major cardiac anomaly in conjunction with an elevated risk NIPT for a SCA can support offering CVS. Alternatively with a normal first trimester US, further diagnostics for the elevated risk SCA are best reserved for an amniocentesis and additionally, a maternal karyotype. A recent large study confirmed this pathway with a cystic hygroma having a 99% PPV for a true fetal SCA and a small risk (1.8%) of a fetal mosaicism. In contrast, a CVS for an elevated risk SCA in the setting of a normal US will more likely detect mosaicism confined to the placenta (66.6%) with only a minority (16%) having true fetal SCA. [27].With a normal first trimester US and positive NIPT for monosomy X, an amniocentesis would best characterize the fetal composition with the fewest diagnostic procedures. A note of caution, this extensive rate of placental mosaicism of 45,X/46,XX is not true for the other SCA. For positive NIPT for XXX, XXY, XYY, the NIPT result reflects the fetus in over 90% of cases meaning that CVS results will most often detect a non-mosaic result reflective of the fetus.

Summary - pre and posttest counseling

The unique characteristics of SCA NIPT warrant further discussion if these conditions are to be reported when the intent of X and Y determination is for fetal sex determination. For autosomal aneuploidy, both pre and post-test counseling are now delineated in greater detail in the literature[31] [7, 32]. Clearly differentiating pretest counseling surrounding SCA from that provided for autosomal aneuploidy may help decrease the anxiety surrounding sex chromosome conditions which can continue throughout the pregnancy.[19, 33].

This current review highlights the unique areas of pretest counseling for the SCA. First, as compared to autosomal aneuploidy, the developmental impact on the fetus, child and adult with a SCA is considerably variable and may involve gonadal dysfunction with infertility. Less commonly, neurodevelopmental concerns may be present but increasingly may be approachable by intervention and hormone replacement. As a by-product of the more subtle phenotypes, screening for SCA carries a greater risk for identification of a medical condition in the birth person. While multi-autosome aneuploidy NIPT can be associated with a current maternal cancer, though this is rare. [34] An elevated risk of SCA disorder during pregnancy has a greater chance of uncovering a maternal SCA which may impact maternal care. These individuals' subsequent management remains undefined. Secondly, the higher presence of mosaicism (placental and fetal) for the sex chromosomes as compared to the autosomes impacts pretest counseling in several fashions. The issues of subtle phenotypes, mosaicism and the technical challenges of X chromosome sequencing all contribute to a lower PPV for SCA. As such, CVS is warranted only in the setting in which a fetal malformation is identified in the early US as sampling of the placenta will often recapitulate the SCA identified in NIPT. These considerations are challenging for individuals to assimilate especially if the overall counseling focuses on autosomal aneuploidy. We would advocate that SCA NIPT pretest counseling should be specifically differentiated from NIPT for

common trisomies (13,18,21) and highlight the greater variability in phenotype, potential for detection of maternal condition and a lower PPV. (Table 4)

Following a positive NIPT for SCA, referral to a genetic counselor or other individuals knowledgeable in SCA can be helpful to understand the nuances of the screening, the utility of a CVS or amniocentesis and the natural history of the SCAs. Even with a confirmed diagnosis of fetal Turner syndrome, limitations to prognostication are important including the presence of mosaicism especially if other X chromosome variants are present, potential epigenetic influences and role of interventions. [35, 36] Explorations from the pregnant individual's perspective indicate greater challenges in appreciating the diagnosis without US findings as well as identifying key areas to be addressed (Table 5) [6]. Post-test counseling with inclusion of genetic and pediatric specialists knowledgeable in the care of children and adults with SCA is beneficial when weighing timing of a diagnostic procedure.

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Table 1:

The incidence of sex chromosome aneuploidy (SCA) at livebirth in a cohort of newborns in Denmark. (data from Nielsen, 1991 and Berglund, 2020)

Type of SCA	Incidence at livebirth	Clinical diagnosis during lifetime
47,XXY and mosaicism	1.73 per 1,000	23%
47,XYY	1.18 per 1,000	NA
47,XXX	1.06 per 1,000	7%
45,X	0.53 per 1,000	70%
Other SCA	0.09 per 1,000	NA

Table 2:

Positive predictive value (PPV) of NIPT for Sex Chromosome Aneuploidy (SCA)

SCA	PPV	Number of SCA cases
45,X	23%	78
47,XXY	50%	63
47,XYY	36%	26
47,XXX	27%	62

- adapted from Luo et al 2021

Table 3

PPV and NPV rates of a high-risk NIPT for SCA incorporating varied prevalence rates (modified from Shear 2020[22])

	Estimated prevalence (per 1000)	PPV	95% range	NPV	95% Confidence interval range
45,X	0.30 – 1.8	4.8 – 22.9%	2.2 – 57.6%	99.9–100%	99.9–100%
47,XXX	0.54 – 1.8	32.4 – 61.6%	15.3 – 95.4%	same	same
47,XXY	0.91 – 2.4	94.1 – 97.7%	58.2 – 100%	same	same
47,XYY	0.32 – 0.75	100%	58.5 – 76.5%	same	same

Table 4

[6]

What do expectant parents find helpful?
- Accurate information about the medical condition, while acknowledging the uncertainties
- Being listened to, and being given space and time to process information and ask questions
- Signposting to reputable online sources of information
- Opportunities to learn more about lived experience of the SCA
- Acknowledgement of the importance of individual life circumstances in how a prenatal diagnosis is received
- Prognostic information that provides a picture of what ‘real life’ with a child with an SCA would be like with a normal fetal ultrasound.

Table 5

Pretest Counseling – Comparison of Important Aspects between Sex Chromosome and Autosomal Aneuploidy

	Chance of a high-risk NIPT result	**PPV**	**Maternal Condition**	**Mosaicism at CVS and true fetal aneuploidy**	**Phenotype of true positive**	**Prenatal diagnostic modality**
SCA	0.3 – 0.6%	20 – 50%	Maternal unrecognized SCA = 6 – 24%	45,X - 16%	Majority undiagnosed during life Exception – 45,X - 70%	CVS- if NT > 3.0, or anomalies Amniocentesis – normal first trimester US
Autosomal aneuploidy	1.0 – 5.0%	Trisomy 21 - 50% (< 35 yo) - 80% (> 35 yo)	Maternal cancer = 1/1,800	T21 – 2% T18 – 4% T13 – 22%	Majority, if not all, diagnosed as a newborn	CVS or amniocentesis