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REVIEW

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Ethical issues associated with prenatal screening using non-invasive prenatal testing for sex chromosome aneuploidy

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Abstract

Prenatal screening for sex chromosome aneuploidies (SCAs) is increasingly available through expanded non-invasive prenatal testing (NIPT). NIPT for SCAs raises complex ethical issues for clinical providers, prospective parents and future children. This paper discusses the ethical issues that arise around NIPT for SCAs and current guidelines and protocols for management. The first section outlines current practice and the limitations of NIPT for SCAs. It then outlines key guidelines before discussing the ethical issues raised by this use of NIPT. We conclude that while screening for SCAs should be made available for people seeking to use NIPT, its implementation requires careful consideration of what, when and how information is provided to users.

Key points

What's already known about this area?

- It is known that expanded non-invasive prenatal testing raises significant ethical issues, especially in relation to reproductive autonomy.

What does this study add?

- This study discusses ethical issues raised specifically by screening for sex chromosome aneuploidies (SCAs), in the context of current practice and existing guidelines. It shows that providing screening for SCAs is consistent with the principle of reproductive autonomy.

1 | INTRODUCTION

Prenatal screening for sex chromosome aneuploidies (SCAs) is increasingly available through expanded non-invasive prenatal testing (NIPT). NIPT is a prenatal screening method that involves analysis of cell free foetal DNA (cffDNA) in maternal blood.[1] cffDNA can be detected from as early as 7 weeks gestation; however, it is more commonly offered from 10 weeks gestation.[2] The test became commercially available in 2011 and has since been introduced in more than 60 countries around the world.[3] The simplicity of a maternal blood test, combined with superior accuracy compared to other prenatal screening methods, such as combined first trimester screening,[4] has led to rapid and widespread uptake around the world.[5] Initially offered as a secondary screen for pregnancies with a high probability of a foetal chromosomal anomaly, NIPT is now often offered and recommended as a first-line screening test for many pregnancies, regardless of probability.[6]

While several countries have developed publicly funded screening programs using NIPT, its development, including the expanding range of conditions screened for, has been driven to a large extent by commercial interests and consumer choice. Initially, NIPT was available to screen for foetal trisomies 21 (Down syndrome), 18 (Edwards syndrome) and 13 (Patau syndrome). However, many commercial providers now offer screening for a range of other conditions, including rare autosomal aneuploidies,[7] genome-wide copy number abnormalities,[8] targeted microdeletions[9] and SCAs.[10] The accuracy of NIPT in detecting these conditions is variable. Even so, there is consumer appetite for prenatal screening for these conditions.[11–14] The increasing availability and use of these screens raises significant ethical concerns.

The purpose of this paper is to examine the ethical issues that arise around NIPT for SCAs and review current guidelines and protocols for management. There has been debate over whether SCA screening should be offered to prospective parents, in light of the variable phenotype of SCAs and still-developing accuracy of NIPT in detecting them. Internationally, guidance from professional and medical organisations varies, with no clear consensus on its ethical acceptability or clinical value. SCAs also raise complex ethical issues for clinical providers, prospective parents and future children. We begin with an overview of current practice and the limitations of NIPT for SCAs and then briefly review key guidelines before turning to a discussion of the ethical issues raised by this use of NIPT. We conclude that while screening for SCAs should be made available for people seeking to use NIPT, its implementation requires careful consideration of what, when and how information is provided to users.

2 | CURRENT PRACTICE

SCAs occur when there is an atypical number of sex chromosomes (X and Y) in a cell. SCAs are some of the most common aneuploidies and include 45,X (Turner syndrome), 47,XXY (Klinefelter syndrome), 47,XXX (triple X syndrome) and 47,XYY (Jacobs syndrome), with an estimated prevalence of approximately 1/2000 females, 1/660 males, 1/1000 females and 1/1000 males, respectively.[15–18] SCAs can be associated with a normal or mildly affected phenotype, but may also include diminished fertility, atypical stature, heart defects and other physical characteristics. SCAs are also associated with modest reductions in IQ (e.g., 47,XXX has been associated with a reduction in IQ of ~20 points[19]), which may not result in intellectual disability,[20] as well as cognitive and behavioural impacts.

NIPT is now the most common form of prenatal screening leading to a diagnosis of an SCA and has enabled earlier and more intentional detection of foetal SCA.[21] Historically, the majority of SCA diagnoses occurred postnatally, following clinical evaluations for neurodevelopmental, medical or infertility concerns.[22] Many individuals with SCAs were never diagnosed and for those that were, this usually occurred in adulthood. Prenatal detection was uncommon since SCAs are not usually ascertained through prenatal ultrasound (with the exception of Turner syndrome). Following invasive testing for autosomal aneuploidies, SCAs were sometimes diagnosed incidentally. NIPT makes it possible for prospective parents to specifically obtain information about SCAs, in combination with diagnosis through invasive testing.[21] The earliest iterations of NIPT incorporated screening for monosomy X,[23] before expanding to include other SCAs. Loughry et al. have shown that NIPT has led to a significant increase in the rate of prenatal detection of SCAs, particularly of 47,XXY.[21]

Most commercial NIPT providers now include an opt-in consent for the analysis of SCAs. A report on the early global expansion of NIPT recorded 44 of 61 countries with SCA screening available from at least one commercial NIPT provider.[5] SCA screening is now commonly available in the USA, much of Europe and Australia.[24] In some European countries with national NIPT screening programs, including Belgium[25] and the Netherlands,[26] SCAs are not reported because of concerns over a lack of clinical utility. In the United Kingdom, the National Health Service offers publicly funded NIPT as a contingent screen following an increased chance combined or quadruple test, but this does not include an analysis for SCAs. Some Asian countries, including India and China, have legislated against reporting on foetal sex chromosomes to prevent sex selective termination of pregnancy (TOP)[27] although several research studies on NIPT in China have reported on SCAs.[28,29]

The analytical performance of NIPT for the detection of SCAs is not well defined, in part due to the nature of these conditions. While positive predictive values (PPVs) can be calculated from screen positive pregnancies undergoing diagnostic testing, NIPT test sensitivity and specificity for SCAs relies on full ascertainment of false-negative and false-positive cases. As most individuals with SCAs are undiagnosed at birth, normal newborn exams are insufficient to assign or rule out these chromosome conditions. SCA test performance is also confounded by biological causes such as high rates of confined placental mosaicism[30] and maternal sex chromosome mosaicism and aneuploidy.[31]

A large meta-analysis reported a pooled detection rate for monosomy X of 95.8% (95% CI, 70.3%–99.5%) and a false-positive rate of 0.14% (95% CI, 0.05%–0.38%). There were insufficient data to report accurately on other SCAs.[32] PPVs of 26% for monosomy X, 50% for 47,XXX and 86% for 47,XXY have been reported from NIPT referrals undergoing diagnostic testing in a large clinical laboratory; the number of cases with XYY was too small to accurately calculate a PPV.[33] The reported PPV for 45,X, which is particularly susceptible to the influence of placental and maternal mosaicism, is considerably lower than for the autosomal trisomies and other SCAs. A large retrospective analysis of SCAs reported PPVs for 45,X; 47,XXY; 47,XXX and 47,XYY as 18.14%, 58.73%, 80.29% and 71.19%, respectively.[34] In contrast, another study using a paired-end sequencing method, which can help minimise the impact of maternal SCA mosaicism on false positive results, reported higher PPVs of 85.2%, 87.5%, 83.3% and 100% for 45,X; 47,XXY; 47,XXX and 47,XYY, respectively.[35]

3 | CLINICAL GUIDELINES AND POSITION STATEMENTS FROM PROFESSIONAL BODIES

In light of complexities in SCA screening and post-test management, there is a need for recommendations from professional societies.[10] Limited guidelines specific to SCA screening have been published

internationally, and these vary in their recommendations. Some take a permissive approach that prioritises information provision and user decision-making, whereas others take a more restrictive approach, emphasising concerns about the potential harms of screening for SCAs.

On the permissive side, the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis recommends that when prospective parents are offered NIPT, and SCA screening is available, they should have the option to separately accept or reject the sex chromosome analysis.[36] In the United States, the American College of Medical Genetics and Genomics (ACMG) provides explicit guidance around screening for SCAs. The ACMG notes that the use of NIPT for SCA screening has become commonplace, since there is no other screening option for these conditions. Consequently, pretest counselling must go beyond standard trisomy conditions to include information about the availability of using NIPT to screen for SCAs. This includes information about false positive rates and possible causes of these and the variable prognoses of SCAs. It also suggests that following a screen positive result, users should be referred to a trained genetic counsellor and offered diagnostic testing.[37] The American College of Obstetricians and Gynecologists takes a neutral approach to SCA screening in general but notes the additional risks of sex chromosome false positive results for patients who have previously undergone organ transplantation and the need to counsel around incidental maternal findings.[6] The National Society of Genetic Counselors does not discuss screening for SCAs specifically but concurs in the view that all pregnant patients should have access to NIPT with appropriate pretest counselling, and post-test counselling in cases of inconclusive or screen positive results.[38]

A joint committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and Human Genetics Society of Australasia takes a similar approach in its recommendations. The joint committee views NIPT as an acceptable first-line screening test for foetal chromosome abnormalities in the first trimester and recommends that all pregnant individuals be provided with information and timely access to screening tests for foetal chromosome and genetic conditions.[39] Pretest counselling should include information to support informed decision-making about testing for SCAs.[39] People should be given the choice to opt out of receiving this information[39] and in cases of 'increased chance' screening results, diagnostic testing with amniocentesis or chorionic villus sampling (CVS) should be recommended prior to definitive management decisions.[39] The committee notes the variable and generally mild phenotype of SCAs, the limited accuracy of NIPT in detecting SCAs and the likelihood of false positives.

In contrast, others have argued against NIPT for SCAs. In the United Kingdom, the Nuffield Council on Bioethics recommends against the use of NIPT to test for less significant medical conditions and impairments and nonmedical traits.[40,41] The Council specifically recommends that NIPT providers not offer sex determination of foetuses unless there is concern that the foetus may be showing signs of a significant SCA or is at risk of a sex-linked disorder.[40] This recommendation is based on concerns about the high failure, low detection and high false positive rates of NIPT for SCAs.[40] The Council notes that some of the conditions for which screening is provided have either uncertain or mild prognoses and that significant time is required to help some people consider their results and options, which is not available to all.[40]

A joint statement by the European Society of Human Genetics and the American Society of Human Genetics also recommends against reporting on SCAs in NIPT.[42] The authors note that SCA screening not only raises ethical concerns about information and counselling but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy.[42] An additional concern is that screening for SCAs by NIPT will make it impossible to avoid providing information about foetal sex to people who might want to use this for aborting female foetuses in particular sociocultural contexts.[42]

4 | ETHICAL ISSUES

Prenatal screening for SCAs raises a number of ethical issues that require careful consideration. Because SCA screening is not integrated into publicly funded programs at this time, ethical issues centre on matters pertinent to consumer choice, such as the limits of reproductive autonomy and the requirements of information provision to support autonomous decision-making and informed consent. Key issues are what prospective parents should be able to know about the foetus prenatally and what criteria are appropriate for limiting information provision. As with other prenatal tests, the information gained from NIPT can be used to inform decisions about the future of the pregnancy as well as to prepare for the birth of a child with additional support needs. Furthermore, NIPT can be sought purely for 'information only', although the ethics of using NIPT in this way have been questioned.[43] What information should be made available to prospective parents, and when, is therefore a central concern requiring further consideration.[42] These issues are not unique to NIPT for SCAs but have specific implications in this domain.

4.1 | Clinical Utility

Before discussing these issues in more detail, however, it is important to address the question of whether SCA screening with NIPT should be offered at all. As indicated above, there has been contention around this issue.[44,45] The provision of NIPT to test for a condition should accord with the principles that guide screening tests in general, such as the classic statement of such principles by Wilson and Jungner[46] or updated versions of them.[47,48] It has been controversial whether NIPT for SCAs meets these conditions, particularly around clinical utility and actionability. Some scholars have argued against the clinical implementation of NIPT for SCAs, claiming that the clinical utility has not yet been established.[49,50] SCAs detected

prenatally are generally milder than those detected postnatally.[20,51,52] Furthermore, the phenotypic diversity and variability in severity of SCAs means it can be difficult to determine future physical and psychosocial health outcomes.

The relatively high likelihood of false positive results undermines clinical value and may have negative outcomes for prospective parents. PPV, one measure of clinical utility, varies between providers and SCAs but can be as low as 26% for monosomy X. While this value is higher than what was previously accepted in conventional screening for the common autosomal aneuploidies,[53,54] it still translates to around three quarters of positive monosomy X screens resulting in a false positive. Although the literature on this is limited, the experience of a false positive result can be emotionally challenging.[55,56] Furthermore, among other things, false positives may be attributed to maternal factors such as mosaicism or copy number variation,[10,11,32,57] meaning SCA screening could reveal a previously unknown maternal genetic anomaly.

Nevertheless, prenatal investigations for SCAs may have clinical benefits, particularly given that any positive NIPT result will generally be followed up by a diagnostic test such as CVS. The phenotype of some SCAs, including 47,XXX and 47,XYY, may be relatively mild and options for clinical intervention are minimal; for others, such as 45,X and 47,XXY, which are more commonly associated with distinct phenotypic profiles, early detection can be more beneficial. Early detection gives prospective parents the opportunity to access emotional and educational support and enables the management of endocrine problems.[49] Prenatal detection may also improve perinatal care of those foetuses with cardiac or renal anomalies, which may be associated with monosomy X.[58] These benefits have been supported by parents who learnt of a suspected SCA through NIPT.[59] However, others argue that these benefits do not justify *prenatal* diagnosis per se, since there are no prenatal or perinatal treatments.[49] Consequently, these benefits may work best to justify newborn screening. However, limiting SCA detection to the postnatal period denies people the possibility of TOP. Furthermore, as we discuss below, respect for autonomy is likely to mean that prospective parents ought to be supported to make their own decisions in conditions of uncertainty.

4.2 | Reproductive autonomy and parental rights to information

The principle of reproductive autonomy has been widely discussed in relation to NIPT and may justify claims to a right of prospective parents to screen for foetal SCAs.[45,60,61] Prenatal screening, including for SCAs, increases the reproductive options available to prospective parents, including but not limited to the decision of whether to continue or terminate a pregnancy. The moral primacy of reproductive autonomy in prenatal care helps to establish a right of prospective parents to information about their foetus and pregnancy where the technology is available to provide that information. This may be bolstered further if, as has been argued, the gestational parent has a special claim to information obtained using NIPT because it is shared information, rather than simply information about the foetus.[62] This argument is based on the prior claim advanced by philosophers of pregnancy (e.g., Kingma[63,64]) that the foetus is *part of* the gestational parent, not simply contained by them.[62] Given this relationship between reproductive autonomy and a right to information, the ethical onus lies on justifying the application of constraints or limits to what information is made available to users of NIPT.

At least three such limits have been proposed. First, autonomy claims have been challenged on the basis that the extent of information that is potentially available to users of NIPT may actually undermine autonomy. One version of this argument is that there is potentially so much information available that it may overwhelm prospective parents with information and the need to make sense of complex genetic results (e.g., Johnston et al.[65]). Another version, made more specifically in relation to SCAs, is that there may be insufficient information available about SCA phenotypes to support parents to make an autonomous choice.[45] Consequently, some scholars argue that it is not unreasonable that the information and choices made available to parents may be limited if screening would result in significant harms, including moral harms, such as undermining autonomy.[60,66] These concerns, however, may be allayed by considering *how* and *when* information is provided to NIPT users and ensuring this is done in a way that supports rather than undermines autonomy. We discuss this point further in what follows.

The second potential limit on parental rights to know arises from countervailing concerns about the welfare and interests of the future child. Some authors have argued for a general 'right not to know' in genetic testing, a right that may be extended to the future child.[61,67,68] Along these lines, Hens has argued that testing for conditions such as 47,XXY or 47,XYY for the purpose of 'information only' violates the future child's genetic privacy and their right not to have knowledge of their genetic information.[45] Given that SCAs are associated with variable phenotypes, and there is no consensus on therapeutic benefits due to presymptomatic detection, Hens contends that the rights of the future child to genetic privacy outweighs the parental right to know.[45] More generally, concerns exist regarding the impact of SCA diagnosis on the self-esteem and potential for stigmatisation of the child[42,69] and the parent–child relationship.[42,45,61] Such arguments rest on the presumption that there will be a child in the future. However, if test results contribute to a decision to terminate a pregnancy, then concerns for the future child will not be relevant.

Third, the information provided to parents may be limited in order to prevent broader social harms. For example, information about SCAs may be limited because of concerns about the wider issue of sex selective TOP. Cell-free DNA in maternal plasma can accurately diagnose foetal sex as early as 7 weeks gestation.[70] Sex determination has been described as both a secondary finding from SCA investigations[12,49,71] as well as the primary reason for screening the sex chromosomes.[72] Sex determination is frequently stated as a primary motive for undergoing NIPT.[13,73,74] While there appears to

be considerable interest in using NIPT to learn foetal sex, there are numerous ethical issues associated with sex determination, including concerns that it could facilitate sex selective TOP.[27,42,75,76] In light of these issues amongst others, the UK Nuffield Council for Bioethics recommended that outside the context of managing serious sex-linked conditions, NIPT for sex determination should not be available.[40] However, if an SCA is suspected through NIPT, it is not possible to convey the results *and* withhold the sex of the foetus.

Prospective parents may seek to use foetal SCA screening for several reasons. In practice, it may be difficult to determine the motivations of parents in testing, and the test results may influence decision-making. Procedures that support autonomous decision-making throughout the testing process will best enable prospective parents to navigate the difficulties presented by both extensive and inconclusive information about SCAs. This points to the importance of robust pre and post-test counselling.

5 | PRETEST DECISION-MAKING

Including SCA screening in NIPT poses challenges but is important to support autonomous decision-making. Pretest genetic counselling is advocated as a means of supporting parents' consideration of whether to screen for SCAs.[76] Counselling should include material information including the clinical variability of the conditions being screened for,[12,36,56] possible test results[36,77] and subsequent implications, including possible intervention and care options.[36,56,78,79] The importance of pretest counselling is particularly potent given that some parents experience regret at having learnt about a suspected SCA prenatally.[56]

Despite this support for comprehensive pretest genetic counselling around SCAs, a recent study by Riggan et al. that explored the experience of parents following prenatal diagnosis of SCA found that most parents (43/46; 93.5%) were unaware of the possibility of an SCA result.[80] This may be because the variable phenotype of common SCAs can complicate genetic counselling[75,81–83] or because of the inadvertent screening of SCAs alongside autosomal aneuploidies.[84] The lack of explicit discussion of SCAs prior to NIPT may leave parents feeling unprepared, thus impacting the decision-making process.[72,78]

Informed consent is a core ethical concept in pretest genetic counselling and is frequently understood as a means of supporting parents' reproductive autonomy. As an ethical concept, informed consent is generally seen as requiring that sufficient information is provided, that the information is comprehensible and that the agent receiving the information (the patient or consumer) has the capacity to make treatment decisions and voluntary choices. We note here that the information requirements for a valid consent are different to the legal standard imposed on doctors in relation to their duty to inform patients under the law of negligence. However, we are not able to explore the details of legal requirements for consent, and how these may differ from the broader ethical concept, here.

In the context of NIPT, informed consent requires parents to competently and voluntarily authorise their healthcare providers to perform the test following the provision and understanding of material information. While there are possible challenges in ensuring that parents *understand* all material information provided prior to consenting,[85] there are strategies that may be implemented to support decision-making in this context. Educational tools or decision aids via technological platforms could be used to support both parents and clinicians.[12,85] This may involve informing prospective parents about the scope and potential implications of the test through an online medium, supplementary to discussions with healthcare providers, as well as assisting parents to consider NIPT in relation to their personal values and beliefs. Providing parents with sufficient time to consider the information prior to deciding whether to proceed with SCA screening is also significant in supporting their reproductive autonomy.[79] Information about NIPT and provision of the test itself should occur in separate appointments to facilitate sufficient consideration.

6 | POST-TEST DECISION-MAKING

The importance of comprehensive post-test counselling in relation to NIPT has been emphasised numerous times.[49,86,87] This is in part due to the recognition that NIPT involves complex decision-making following the return of positive results.[49,50,81] Since NIPT is a screening test, diagnostic testing is recommended to confirm a positive screen. However, diagnostic testing does entail a small risk of miscarriage.[88]

Some small cohort studies report high uptake of diagnostic testing following a positive SCA screen.[11,56,89] This is supported by recent population studies demonstrating that prenatal diagnostic investigations for SCAs, as well as subsequent diagnoses, have significantly increased following the clinical introduction of NIPT.[21,84] However, not all prospective parents are interested in prenatal diagnostic testing; instead, some postpone further investigations till after birth or even decline testing completely.[80,90,91] It could be that some prospective parents do not consider SCAs a reasonable ground for pregnancy termination or perceive the procedural risks and associated anxiety of invasive testing to outweigh the benefits of prenatal diagnosis.[56,90]

For those who do decide to proceed with invasive diagnostic testing, if the suspected SCA is confirmed, prospective parents face a complex decision regarding the future of the pregnancy. The uncertainty of the phenotypic profile and severity of SCAs is likely to complicate this decision. Rates of termination following prenatal diagnosis vary between 55% and 80%, but seem to be decreasing over time.[86,90,92–96] A 2012 systematic review of decision-making following an SCA diagnosis found that a number of factors influence the decision to terminate or continue the pregnancy: the type of SCA, gestational age at diagnosis, parental age, number of (desired) children and the genetic expertise of the healthcare provider managing the pregnancy.[97]

Of particular influence is the way results are conveyed and managed.[72,94,95,97–99] Variation in parental decision-making has been

associated with the clinical specialty of the person providing genetic counselling. If counselling was performed by a healthcare professional without genetic expertise, individuals were more likely to terminate the pregnancy, whereas those who received counselling from a genetic specialist were more likely to continue the pregnancy.[97] Further, the mode, delivery and explanation of the results can influence decision-making, particularly if the prospective parents perceive the results to be conveyed negatively.[72,81,93,99] The influence the provider can have on decision-making highlights the importance of ensuring comprehensive and balanced counselling at the time of diagnosis so that prospective parents are supported, but do not feel directed to act in a certain way.

A further complexity in post-test decision-making is the possible, albeit rare, chance of discordance between the results of diagnostic testing and the original NIPT result. For example, Ramdaney et al. reported 3 cases of a positive NIPT for 47,XXY, which were postnatally confirmed as 47,XYY, 48,XXYY and 49,XXXXY.[90] The implications of this means prospective parents may prepare for the possible diagnosis of one condition, only to receive a diagnosis of another, likely causing confusion and distress. The possibility of a discordant result creates further challenges for genetic counselling.

Genetic counselling following the return of a positive screen is critical to help prospective parents navigate the meaning of the result as well as discuss options for intervention and management. However, a 2019 study investigating the opinions of genetic counsellors on counselling for SCAs found that there were inconsistencies between management of patients following a positive screen.[100] While diagnostic testing and ultrasound were frequently offered, there was considerable variability between how often or in what situations other clinical tests such as chromosomal microarray analysis, maternal karyotype, echocardiogram and postnatal evaluations were discussed. Given that intervention and/or targeted surveillance for some SCAs has been demonstrated to be of clinical benefit, the variability in post-test care may mean the benefits of early detection are lost.

7 | CONCLUSION

The development and expansion of NIPT has in large part been driven by commercial interests and consumer demand. Public health considerations have played a reduced role, though they come into effect in the implementation of publicly funded national screening programs, such as for trisomy conditions. NIPT for SCAs is now widely available through commercial providers but is not yet included in publicly funded programs. This raises questions about equity of access, but prior to that is the ethical question of whether prospective parents should be able to access NIPT for SCAs. In regard to this question, issues centre on concerns about the extent of reproductive autonomy, and how autonomy is best supported through information provision procedures such as pre and post-test counselling. While acknowledging the challenges and disparities in the provision of pre and post-test counselling, we conclude that NIPT for SCAs should be available for users. These challenges and disparities do not justify limiting reproductive autonomy but instead place an onus on providers to ensure that counselling procedures are sufficient. Critical consideration needs to be paid to appropriate information delivery procedures, including what, how and when information is provided to users to best support reproductive autonomy. Undertaking that examination, and a correlative analysis of previously proposed solutions, is outside the scope of this discussion. Similarly, whether SCAs should be included in publicly funded schemes requires further examination, especially with reference to public health considerations.

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CONFLICT OF INTEREST

Martin B. Delatycki is the Clinical Director of the Victorian Clinical Genetics Services, a not-for-profit organisation that provides the percept NIPT. Mark D. Pertile is Head of the Division of Reproductive Genetics at the Victorian Clinical Genetics Services.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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