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TITLE

Population-based trends in the prenatal diagnosis of sex chromosome aneuploidy before and after non-invasive prenatal testing

SHORT RUNNING TITLE

Population-based trends in sex chromosome aneuploidy before and after NIPT

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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What's already known about this topic?

- Until recently, fetal sex chromosome abnormalities (SCAs) were usually detected incidentally in the context of a diagnostic test for an increased risk of autosomal aneuploidy.
- Non-invasive prenatal testing (NIPT) has provided new opportunities for screening for SCA.

What does this study add?

- Prenatal SCA diagnoses have not increased significantly since NIPT, but do constitute a significantly higher percentage of all prenatal diagnosis results.
- Fetal SCAs are now most commonly ascertained via high risk NIPT, rather than incidentally after testing for advanced maternal age or high risk combined screen.
- These changes in indications for testing suggest women are now more likely to be anticipating a diagnosis of SCA compared to the pre-NIPT era.

ABSTRACT

Objective

To assess the impact of non-invasive prenatal testing (NIPT) on trends in the prenatal diagnosis of sex chromosome aneuploidy (SCA) in a population with >73,000 annual births.

Method

Retrospective population-based cohort study from 1986-2016 of all women undergoing prenatal diagnosis before 25 weeks gestation in the Australian state of Victoria. Statistical significance was tested using the chi-square test for trend or proportions.

Results

There were 2,043,345 births and 842 SCA diagnoses from 1986-2016. The percentage of prenatal diagnostic tests leading to a SCA diagnosis increased significantly from 0.95% in 2010 to 2.93% in 2016 ($p < 0.001$) but due to a concurrent decline in testing, the annual prenatal diagnosis rate of SCA remained stable at 4.4/10,000 births. Among confirmed fetal SCAs the most common indication for testing in 1986 was advanced maternal age (63%); in 2016 it was high risk NIPT (49%).

Conclusion

SCAs now make up an increasing proportion of prenatal diagnostic results but due to the overall decline in diagnostic testing, the prenatal prevalence as a percentage of births remained steady. The ascertainment of fetal SCA has evolved from an incidental finding after testing for increased risk of trisomy 21, to a diagnosis obtained after suspected SCA on NIPT.

Keywords:

Prenatal screening, prenatal diagnosis, sex chromosome aneuploidy, non-invasive prenatal testing

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MAIN TEXT

Introduction

Noninvasive prenatal testing (NIPT) based on cell-free DNA (cfDNA) in maternal plasma is now well-established as the most accurate screening test for common autosomal aneuploidies such as trisomy 21 (Down syndrome), surpassing the performance of standard screening with combined first trimester screening (CFTS).[1] Until recently, fetal sex chromosome abnormalities were usually detected incidentally in the context of a diagnostic

test for an increased risk of autosomal aneuploidy.[2] However, cell-free DNA-based screening has created novel opportunities for targeted screening for sex chromosome aneuploidy (SCA).[3-7]

The most common SCAs include 45,X (monosomy X or Turner syndrome) and the sex chromosome trisomies: 47,XXY (Klinefelter syndrome), 47,XXX (triple X syndrome) and 47,XYY (XYY syndrome). Individuals with these conditions may experience impaired fertility, as well as characteristic physical features and developmental delay.[8] Despite having a combined prevalence greater than that of trisomy 21,[9] SCAs have not been traditionally included in prenatal screening programs. While some experts advocate the benefits of prenatal detection of SCA,[10] these abnormalities do not clearly fulfill the World Health Organisation criteria for disease screening[11] because of the frequently mild phenotype, coupled with uncertainty over the benefits of early treatment.[12]

A joint position paper[13] compiled by the European Society of Human Genetics and the American Society of Human Genetics recommends against routine screening for SCA with NIPT. The International Society of Prenatal Diagnosis and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists also recommend that SCA screening should be optional and only performed with informed consent.[14,15] Despite the cautious attitude of professional societies, it is apparent that many pregnant women are being screened for these conditions in their fetus. A 2016 survey conducted by UK-based external quality assessment organizations found that almost half of the 3000 laboratories performed NIPT for SCA,[16] and a single-centre study included SCA screening in 98% of NIPT assays.[17]

Wide variations in the prenatal detection of SCA have been reported across European congenital anomaly registries, reflecting national differences in prenatal screening approaches, as well as organization and cultural factors.[18] In the pre-NIPT era, less than 50% of expected SCA were diagnosed during pregnancy.[19,20] Assessing trends in the prenatal diagnosis of SCA is important from a public health perspective because there may be implications for clinical practice and genetic counselling services, as well as for allocation of resources for obstetric and paediatric care. Our epidemiological study aimed to assess state-wide trends in the prenatal diagnosis of SCA through amniocentesis or chorionic villus sampling, particularly focusing on the years before and after the introduction of NIPT in 2013. We hypothesized that the annual prevalence rate of prenatal SCA would have increased after 2013 due to the widespread availability of X and Y chromosome assessment with NIPT.

Methods

This was a retrospective study including all women undergoing amniocentesis or chorionic villus sampling < 25 weeks gestation from 1986-2016 in the Australian state of Victoria. The Victorian Prenatal Diagnosis Database collects cytogenetic data from four laboratories in Victoria: Victorian Clinical Genetics Services, Monash Medical Centre, Australian Clinical Laboratories and Melbourne Pathology. This dataset has been described in detail elsewhere.[21] The data obtained for each record included postcode, date of test, gestational age, maternal age, indications for testing, type of diagnostic procedure, karyotype or microarray result, singleton or multiple pregnancy. Chromosome analysis was performed either by G-banded karyotype or increasingly from 2013 onwards, chromosomal microarray. Tests involving a multiple pregnancy or repeat test during the same pregnancy were condensed into a single record.

Data on total numbers of tests performed per year and total major chromosome abnormalities were extracted. Major chromosome abnormalities were defined as: autosomal trisomies, autosomal monosomies, SCA, polyploidies, unbalanced rearrangements, level III mosaics and pathogenic copy number variants (CNVs). Pathogenic CNVs have previously been defined as those that encompass a region implicated in a well-described abnormal phenotype.[22] Minor chromosome abnormalities were balanced rearrangements and CNVs of uncertain or unknown significance (VOUS).[23]

Records relating to abnormalities involving one or both sex chromosomes were examined in detail. Whole chromosome SCAs (including those with co-existent autosomal abnormalities) were used to calculate the rate of prenatally diagnosed SCAs amongst total live births, total prenatal diagnostic tests, and total chromosome abnormalities. Means for maternal age, gestational age and numbers of amniocentesis and CVS were also calculated for whole chromosome SCA results. Other abnormalities involving sex chromosomes including Level III mosaics, CNVs, structural chromosome rearrangements, and confined placental mosaicism were tabulated separately and not included in statistical analysis.

Indications for diagnostic testing for women with a confirmed diagnosis of whole chromosome SCA were analyzed to assess trends in ascertainment of SCA. Indications were provided by the clinical referrer and included: advanced maternal age (AMA) ($\geq$37 years old), abnormal ultrasound findings, combined first trimester screening result (CFTS), non-invasive prenatal testing result (NIPT), second trimester serum screening result (STS, also known as the 'quadruple test'), and 'other' indication (history of a chromosomal abnormality in a parent or

previous child, single gene test, history of a neural tube defect, suspected uniparental disomy, any other indication), and 'unknown'. Indications were reported for the entire study period as well as the individual years of 1986, 1996, 2006 and 2016 to give representative cross-sections of the different eras of prenatal screening.

Data on individual SCA karyotypes were also analyzed, including the indications for different types of SCA. Median numbers of individual karyotypes as a percentage of all prenatal SCA diagnoses were calculated.

Annual numbers of Victorian births were obtained from the Australian Bureau of Statistics and used to calculate the rate of prenatal SCA diagnoses per 10,000 live births.

Descriptive analyses were performed using Stata 14.2 (StataCorp. 2017. *Stata Statistical Software:* Release 14.2. College Station, TX: StataCorp LP). To highlight long-term trends in graphical display, each data point was calculated as a three year moving average, by obtaining the mean number of SCA for the data point for each year and the two subsequent years.

Trends were analyzed across the entire 31-year study period, as well as the period from 2010-16. This contemporary era was selected for two reasons: (1) It represents the immediate years before and after NIPT was introduced into clinical practice, and (2), the population uptake of all forms of aneuploidy screening amongst pregnant women was comparatively stable (over 70%). PRISM 6 Version 6.0h was used to determine statistical significance using the χ^2 test for trend, and defined as a p value <0.05.

This study was approved by the Royal Children's Hospital Human Research Ethics Committee (Reference No. 31135B) and the Monash Health Human Research Ethics Committee (Reference No. 12063B).

Results

There were 2,043,345 births, 116,613 prenatal diagnostic tests and 842 prenatal SCA diagnoses during the 31-year study period (Table 1). Overall, the annual number of prenatal SCA diagnoses increased over the study period (median 29), plateauing after 2006 (n = 41) before peaking again in 2016 (n = 43) (Figure 1a).

The annual number of total prenatal diagnostic tests increased during the first half of the study period up until 1998, before falling to the lowest number in 2016 (Figure 1a). The percentage of diagnostic tests resulting in a prenatal SCA diagnosis increased significantly over the 31-year period (χ^2 trend = 90.4, p <0.001). The steepest increase occurred from 2010-2016, when SCAs as a proportion of all procedures rose from 0.95% to 2.93% (χ^2 trend = 32.83, p <0.001) (Figure 1b).

The annual rate of SCA per 10,000 births increased over the 31-year study period in line with trends in absolute numbers (χ^2 trend = 31.95, p <0.001) but remained steady between 2010 and 2016 at 4.4 SCA per 10,000 births (1 in 2381 births) (χ^2 trend = 0.06, p = 0.80) (Figure 2).

Overall, the number of SCAs as a percentage of total major chromosomal abnormalities (Supplemental Figure 1) decreased significantly over the study period (χ^2 = 49.28, p <0.001) and from 2010-16, the percentage remained steady (χ^2 = 0.20, p = 0.65). Since 2011, SCA has made up less than 12% of all major chromosomal abnormalities each year.

Primary indications for diagnostic testing in confirmed cases of prenatal SCA (Figure 3) changed over the 31-year study period. The most common indication for testing in 1986 was AMA (63%), followed by 'other indication' (25%) and abnormal ultrasound findings (13%). In both 1996 and 2006, the most common indication for testing was ultrasound abnormality. NIPT as a percentage of indications for diagnostic testing in SCA cases increased sharply following its introduction in 2013. By 2016 NIPT was the most common indication, responsible for almost half of SCA diagnoses (49%), despite only making up 17% of indications for total tests in that year. Ultrasound abnormality was the second most common indication (37%), followed by CFTS (9%).

45,X was the most common SCA diagnosis across the study period (median 53%), followed by 47,XXY (median 23%), 47,XXX (median 15%) and 47,XYY (median 10%). These percentages remained stable after the introduction of NIPT. Annual diagnoses of individual SCA karyotypes are presented in Supplemental Figure 2.

For the total study period, 45,X as a percentage of all SCAs by procedure type was 67.3% (303/450) of all CVS, and 38.3% (150/391) of all amniocentesis. When the pre-NIPT vs NIPT periods were compared, there was no significant difference in 45,X as a percentage of all SCAs by procedure type (78.6% of SCA abnormalities on CVS in the pre-NIPT era vs 84.7%

during the NIPT era, p = 0.34). The median age of women with a prenatal diagnosis of 45,X was 31 years (range 16-47) and for all other SCAs was 38 years (range 18-50).

Discussion

Our study represents the first population-based study assessing the impact of NIPT on the prenatal diagnosis of SCA. We had access to a unique and comprehensive data set containing all cytogenetic data collected in the state since 1976. Like other authors[24] we predicted the annual number of prenatal SCA diagnoses would increase in the NIPT era, however this was not confirmed in our study. What we did find was that SCAs now make up a significantly greater proportion of all diagnostic tests performed, though the contemporary rate of detection remains steady at 4.4 per 10,000 births. These findings are explained by the declining number of diagnostic tests being performed each year and the associated decline in SCA cases ascertained incidentally after high risk CFTS or for advanced maternal age.

The overall decline in amniocentesis and CVS observed over the past decade in our population has been reported in detail previously.[23] A major contributing factor to this decline in diagnostic testing is the increasing uptake of NIPT and the subsequent reduction in false positive trisomy 21 screening results. Despite the inclusion of SCA in the majority of NIPT panels offered in Victoria, SCAs made up a smaller proportion of total chromosomal abnormalities diagnosed via invasive testing in the NIPT era compared with previously. This was due to the concurrent rise in the detection of autosomal aneuploidies and pathogenic copy number variants over the same period.[23]

It has been previously established that the prevalence of prenatally diagnosed SCA is higher in countries with high prenatal detection rates of trisomy 21.[18] Of particular interest in our study were the changing indications for diagnostic testing in confirmed cases of SCA. In our population, advanced maternal age was the predominant indication for the ascertainment of prenatal SCA in the late 1980s, with abnormal ultrasound finding becoming the main indication from the 1990s and CFTS in the late 2000s. Importantly, none of these screening methods specifically test for SCA, except where an ultrasound finding of cystic hygroma may raise suspicion of 45,X. Although maternal age is known to be associated with the sex chromosome trisomies[25] – also confirmed in our results – detection of trisomy 21 is the primary rationale for offering diagnostic testing for advanced maternal age. Therefore, traditional pre-test counselling prior to diagnostic testing would have been unlikely to provide information about SCAs. By 2016, almost one half of women had diagnostic testing because

of a high risk SCA result on NIPT, meaning that the diagnosis is increasingly anticipated, rather than being an "incidental" finding after trisomy 21 screening.

Not surprisingly, NIPT played a more important role in the diagnosis of the sex chromosome trisomies than for 45,X. Ultrasound abnormality has remained the main indication for diagnostic testing in fetuses with 45,X due to its well-recognised association with cystic hygroma, fetal hydrops and enlarged nuchal translucency. In contrast, NIPT detected the majority of 47,XXY cases from 2014 onwards (5/10 in 2014, 5/7 in 2015, 7/8 in 2016). 47,XXY is not associated with a specific prenatal or newborn phenotype and it is estimated that approximately 50% of males with this condition go undiagnosed in Victoria.[20] Current recommendations for the care of children with a prenatal diagnosis of 47,XXY are that they undergo comprehensive developmental assessments at 9-15 months, 18-24 months and 30-36 months.[26] Therefore, prenatal screening for 47,XXY opens up new possibilities for early intervention and anticipatory care as well as challenges for individuals, families and health professionals that require careful consideration.[27]

The findings of this population-based study have important implications for clinical practice. A dramatic shift has occurred in the group of women receiving a diagnosis of fetal SCA, with subsequent changes in pre-test genetic counselling requirements. Patient knowledge of the possible physical, cognitive and behavioural issues related to SCA, when compared to autosomal conditions such as trisomy 21, is limited.[28] Moreover, a high proportion of women are uncertain whether they would have diagnostic confirmation after a high risk NIPT result.[29] Ensuring timely access to suitably-qualified health professionals after a high risk NIPT result for a SCA is crucial to the ethical provision of prenatal screening services, as the quality of information is known to influence parental decisions to continue with a pregnancy or terminate.[30]

One important limitation of our study is the incomplete data on women undergoing NIPT. This is due to the lack of a central data collection for NIPT, which has multiple commercial and non-profit providers in our population. Due to the fragmented nature of this data we were unable to assess the uptake of screening for SCA using NIPT or the proportion of women with a high risk NIPT result that proceeded to diagnostic testing. We were also unable to obtain individual pregnancy outcomes in our study population, and therefore could not determine the perinatal outcomes and termination of pregnancy rates. While these missing data would have added valuable insights into the use of NIPT for SCA screening in our population, it was not

feasible to obtain these data for our study period due to restrictions in data sharing and ethics approval.

Conclusion

Prenatal detection of SCA is an increasingly important consideration for health professionals and women electing to have prenatal diagnoses in the NIPT era. Although the annual rate of prenatal SCA diagnoses has remained steady in recent years, SCAs now make up a greater proportion of outcomes from all diagnostic tests. A prenatal diagnosis of SCA is now less likely to be an incidental finding after diagnostic testing for increased risk of autosomal aneuploidy, but most commonly an anticipated outcome based on NIPT result. This has important implications for genetic counselling and clinician education.

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FIGURE LEGENDS

Figure 1a. State-wide annual numbers of total diagnostic tests and confirmed sex chromosome aneuploidies (1986-2016).

For graphical display, annual numbers of sex chromosome aneuploidies are presented as 3-year moving averages.
SCA, sex chromosome aneuploidy

Figure 1b. Percentage of all diagnostic tests resulting in sex chromosome aneuploidy (1986-2016).

For graphical display, all percentages are presented as 3-year moving averages.
SCA, sex chromosome aneuploidy
NIPT, non-invasive prenatal testing

Figure 2. Annual rate of prenatal sex chromosome aneuploidies per 10,000 births (1986-2016).

For graphical display, all rates are presented as 3-year moving averages.
SCA, sex chromosome aneuploidy
NIPT, non-invasive prenatal testing

Figure 3. Primary indications for diagnostic testing as a percentage of total tests among confirmed prenatal sex chromosome aneuploidies (1986-2016).

For graphical display, all indications except NIPT are presented as 3-year moving averages.
SCA, sex chromosome aneuploidy
NIPT, non-invasive prenatal testing
CFTS, combined first trimester screening
US, ultrasound
AMA, advanced maternal age (≥37 years)

† "Second trimester serum screening" and "unknown" indications constituted <10% of all indications annually throughout the study period and are not depicted in this figure.

SUPPLEMENTAL DATA

Supplemental Figure 1. Prenatal sex chromosome aneuploidies as a percentage of total major chromosomal abnormalities (1986-2016).

SCA, sex chromosome aneuploidy
NIPT, non-invasive prenatal testing

Supplemental Figure 2. Annual prenatal sex chromosome aneuploidies as individual karyotypes (1986-2016).

For graphical display, all annual diagnoses are presented as 3-year moving averages.
SCA, sex chromosome aneuploidy

Table 1. Summary statistics of all fetal sex chromosome abnormalities diagnosed in Victoria from 1986-2016.

Whole sex chromosome aneuploidy		
Total diagnoses (n)		842
Maternal age in years (mean)		34
Gestational age in weeks (mean, range)		14 (9,24)
Total diagnostic tests for confirmed fetal SCA† (n, %)	Chorionic villus sampling	450 (53.4%)
	Amniocentesis	391 (46.4%)
Karyotype for confirmed fetal SCA (n, %)	45XO‡	454 (53.9%)
	47XXY§	189 (22.5%)
	47XXX	129 (15.3%)
	47XYY	65 (7.7%)
	Other	3 (0.4%)
	Unspecified sex chromosome aneuploidy	2 (0.2%)
Indications (% total tests for confirmed fetal SCA) ‖	Ultrasound findings	47%
	Advanced maternal age (≥37 years old)	21%
	Combined first trimester screening	16%
	Other	8%
	Second trimester screening	3%
	Non-invasive prenatal testing	5%
Confirmed fetal SCA with co-existent autosomal abnormality (n)	Major abnormality	28
	Minor abnormality	15
Other sex chromosome abnormalities		
Confined placental mosaicism (n)		42
Level III mosaic¶ (n)		285
Other abnormalities (n)		127

† There was 1 unknown procedure (0.12%).

‡ In twin pregnancies where SCA was diagnosed in both fetuses this was coded as one SCA diagnosis (the more prevalent SCA e.g. 45XO).

§ 48XXXY karyotype was coded as 47XXY karyotype due to the similar phenotype.

‖ There were 2 unknown indications (0.24%).

¶ There was 1 twin pregnancy where a LIII mosaic was diagnosed in both fetuses. This was coded as a single LIII mosaic diagnosis.

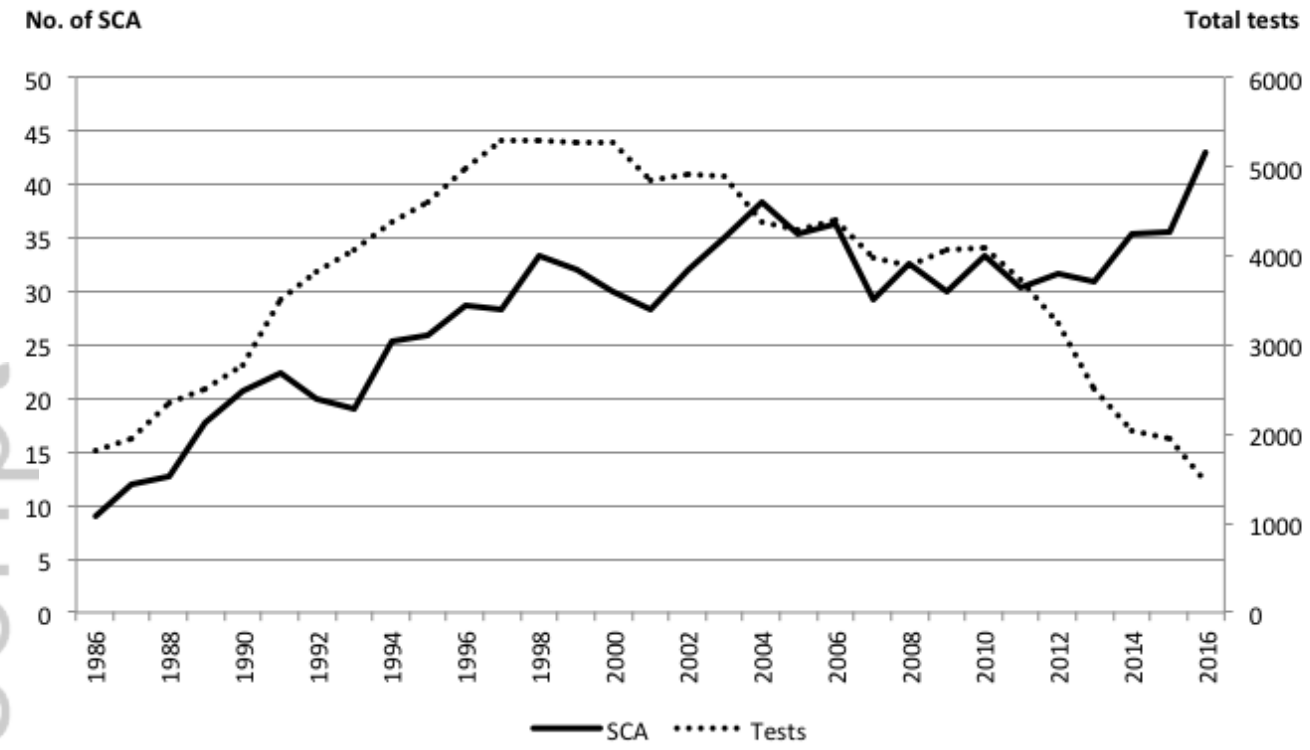

Figure 1a

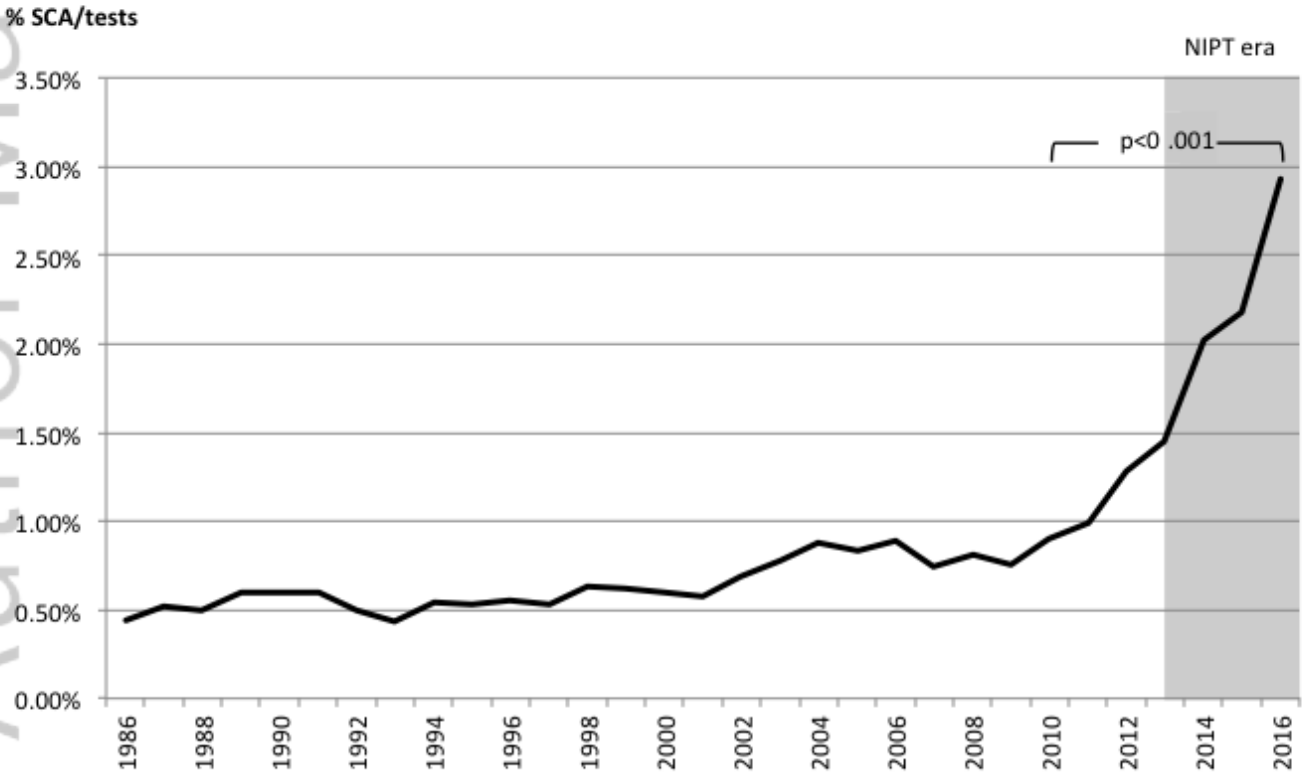

Figure 1b

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Figure 2

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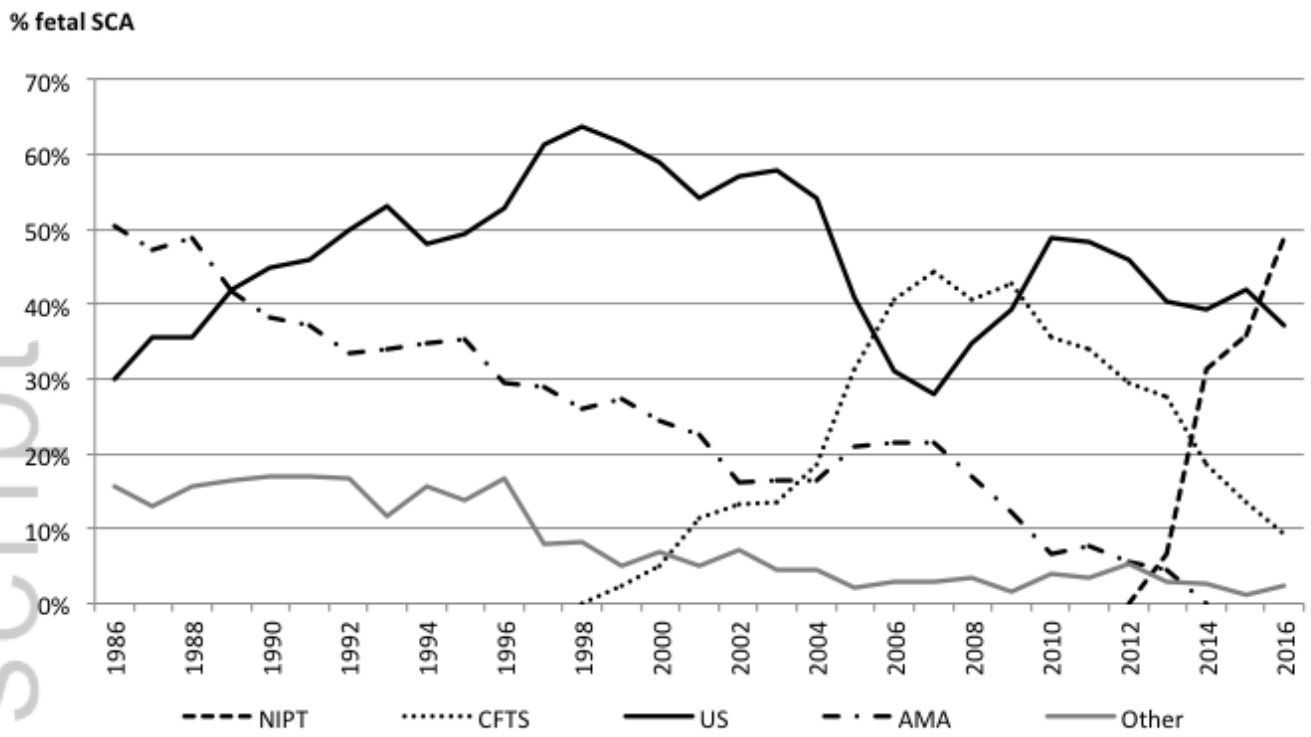

Figure 3

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