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Population-based impact of noninvasive prenatal screening on screening and diagnostic testing for fetal aneuploidy

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Purpose: To assess the population-wide impact of noninvasive prenatal screening (NIPS) on combined first-trimester screening (CFTS), early ultrasound (11–13 weeks), and invasive prenatal diagnosis in a state with over 73,000 births per year.

Methods: Analysis of population-based data from 2000 to 2015 including (i) invasive prenatal tests, (ii) CFTS uptake, and (iii) total births. Utilization of early ultrasound was analyzed before and after NIPS (2010–2015).

Results: Invasive testing decreased significantly by 39.6% from 2012 to 2015 despite steady births. More than half of all confirmed cases of trisomy 21 were ascertained by NIPS in 2015, despite NIPS comprising only 11.7% of total indications for invasive testing. CFTS uptake declined significantly from 77.5% in 2013 to 68.1% in 2015, but 11- to 13-week ultrasounds did not. In 2015, ultrasound abnormality replaced CFTS as the most common indication for invasive testing and chromosomal microarray was performed for 85.3% of all prenatal karyotypes.

Conclusion: Prenatal testing is now unequivocally in the genomic era. NIPS is now the screening test that precedes the majority of confirmed diagnoses of trisomy 21. The contributions of NIPS, early ultrasound, and chromosome microarray have led to unprecedented detection rates of major chromosome abnormalities, now found in 20% of all invasive tests.

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Key Words: combined first-trimester screening; NIPS; NIPT; noninvasive prenatal screening; prenatal diagnosis

INTRODUCTION

Voluntary screening for trisomy 21 is a standard component of prenatal care in the United States and many other countries such as the United Kingdom, Canada, Australia, China, and within the European Union. Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities, also known as cell-free DNA based screening, has been hailed as the vanguard of genomic medicine.[1] This innovative test has spread globally to over 60 countries since its introduction into clinical practice in the United States and China in 2011.[2] Based on genomic sequencing of cell-free DNA in maternal plasma, NIPS has the highest sensitivity (>99%) and specificity (>99.9%) for trisomy 21 of any prenatal screening test.[3] The importance of NIPS to current practice has led the American College of Medical Genetics and Genomics to recently update its position statement, outlining the principles of responsible implementation and importantly, endorsing NIPS as a suitable replacement for biochemical screening for trisomy 21, 18, and 13 across the maternal age spectrum.[4]

Private health insurance for this costly screening test began on a limited basis in the United States for high-risk pregnant women in 2012, and has expanded since then. The DNA sequencing technology and bioinformatics underlying NIPS are now disseminating from the private commercial sphere into the public sector. Several countries are now implementing government-funded NIPS into their national prenatal screening programs, including the United Kingdom, the Netherlands, and Denmark.[5–8]

The potential impact of NIPS on the landscape of prenatal screening is dramatic as sequencing costs decline and the use of NIPS as a primary screening test increases. Until recently, measuring the downstream effect of NIPS has been largely confined to reporting the decline in invasive testing rates in single-center or multicenter studies.[9–11] However, detailed population-based evaluation of its impact on indications for testing, diagnostic yield, and the primary methods of prenatal ascertainment of fetal aneuploidy are lacking.

We have previously reported on data from the pre-NIPS period from 1976 to 2013.[12] In this new analysis, we focus on the period during which NIPS became widely established, the "NIPS era" (2013–2015).

Our aim was to analyze population-based state data sets for (i) changes in invasive prenatal testing, including indications for testing, procedural numbers, and results; (ii) uptake of combined first-trimester screening (CFTS) and utilization of early (11–13 weeks) ultrasound; and (iii) the contributions of different screening tests to the prenatal ascertainment of trisomy 21 in the NIPS era.

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MATERIALS AND METHODS

Study population

This study analyzed prospectively collected data on prenatal screening, diagnosis, and ultrasound from the Australian state of Victoria, with approximately 73,000 births per year. In 2015, the median maternal age was 31.5 years, average fertility rate was 1.7 births per woman, and the average weekly disposable household income was AUD998 (US$744) (http://www.abs.gov.au).

Voluntary screening for fetal chromosome and structural abnormalities is offered as a standard component of prenatal care in Australia.[13] Government rebates are provided for CFTS, second-trimester serum screening ("quadruple test") (STSS), and the midtrimester morphology scan (performed at 18–22 weeks), but most tests involve a variable out-of-pocket cost to the pregnant woman. Invasive testing (amniocentesis and chorionic villus sampling (CVS)) are fully government-funded if performed in a public hospital or partially government-funded if performed in the private sector. NIPS does not currently attract any government or private health insurance subsidy and the total cost is borne by the patient. NIPS became clinically available in Victoria via overseas laboratories in 2013 at a price exceeding AUD 1000 (US$746) and a 10-day turnaround time. By 2015, the average price had fallen to about AUD 500 (US$373) and turnaround time for the locally established laboratories was 3–5 days.

Ethics approvals for this study were provided by the Human Research Ethics Committees of the Royal Children's Hospital (ref. no. 3115A) and Monash Health (ref. no. 12063B).

Data sources

Victorian Prenatal Diagnosis Database

Prenatal diagnosis data from 2000 to 2015 were obtained from the Victorian Prenatal Diagnosis Database. This period was selected to span the period of the CFTS program, which commenced in 2000, and the first 3 years of NIPS availability (2013–2015). This database included all prenatal diagnostic testing (amniocentesis and CVS) in the state, contributed by the four Victorian cytogenetic laboratories. All amniocentesis and CVS results performed prior to 25 weeks gestation on women resident in Victoria by postcode were included in the study. This gestational age limit was chosen to capture invasive testing performed after routine screening for chromosome and fetal structural abnormalities.

The data fields collected for each woman included maternal age and gestation at the time of testing, test date, type of diagnostic test, indication for test, karyotype result, and singleton or multiple pregnancy. A single record was created for twin pregnancies or women who required repeat testing in the same pregnancy.

Clinical indications for testing was based on information provided to the laboratories by the referring clinician. The indications for testing and their definitions are listed here:

1. CFTS: maternal serum levels of pregnancy-associated plasma protein-A and total human chorionic gonadotropin (sampled at 9–13^{+6} weeks gestation) in conjunction with a measurement of the nuchal translucency (NT) (11 to 13^{+6} weeks). CFTS was considered positive if the trisomy 21 risk was ≥ 1 in 300 or the trisomy 18/trisomy 13 risk was ≥ 1 in 150.

2. Ultrasound abnormalities: fetal structural abnormality (including fetal death, intrauterine growth restriction, soft ultrasound markers of aneuploidy), placental or amniotic fluid abnormalities, NT ≥ 3.5 mm if nominated by the clinician as the sole indication and not a part of high-risk CFTS result.

3. Advanced maternal age: maternal age at estimated due date > 36 years, coded as such only in the absence of other indications.

4. STSS for trisomy 21 and trisomy 18 with the quadruple test: laboratory risk reporting thresholds were ≥ 1 in 250 for trisomy 21, and ≥ 1 in 200 for trisomy 18.

5. NIPS: including any test performed for "high risk" or "failed NIPS" result.

6. Maternal history: family or personal history of a previous pregnancy with a known chromosome or genetic condition, and/or known parental chromosome rearrangement carrier status.

7. Other: women undergoing an invasive test with no increased screening risk result, no prior history of a pregnancy with a known chromosome abnormality, and not meeting the criteria for advanced maternal age. This includes women having chromosome analysis performed following an invasive test for other miscellaneous conditions including suspected congenital infection and fetal blood group testing (in the absence of an ultrasound abnormality).

8. Single-gene testing: women who underwent invasive testing due to a risk of a specific monogenic disorder.

In women with more than one indication for invasive testing (e.g., high-risk NIPS result and fetal structural abnormality) both indications were coded. The total number of indications thus exceeds that of the number of women undergoing invasive testing.

The types of genetic testing performed included G-banded karyotype, fluorescent in situ hybridization, chromosomal microarray (CMA), and DNA testing for single-gene disorders (e.g., cystic fibrosis, fragile X, thalassemia). All CMAs were performed by a central laboratory using the Affymetrix Cytoscan 750K array (Santa Clara, CA, USA; genomic resolution of 0.2 Mb). The results of fluorescent in situ hybridization and single-gene testing are not reported in this paper. Chromosome analysis performed on fetal blood samples was rare and was also excluded. Multiple tests performed in the same pregnancy (for multiple pregnancies or repeat testing) were combined into a single report.

Chromosome test results were categorized as normal or abnormal. The abnormal results were further divided into "major" and "minor" chromosome abnormalities. Major chromosome abnormalities included all cases of autosomal and sex chromosome aneuploidy, polyploidy, unbalanced rearrangements, level III mosaics, and pathogenic copy-number variants (CNVs). Minor chromosome abnormalities

included balanced rearrangements, confined placental mosaicisms, and CNVs of uncertain or unknown significance (VUS).

We defined "diagnostic yield" as the percentage of diagnostic tests that detected a major chromosome abnormality. The total abnormality rate was the total major and minor chromosome abnormalities as a percentage of the total number of invasive tests.

The total numbers of CFTS and STSS were obtained from the state central screening laboratory. This lab performs the serum biomarker testing and the aneuploidy risk calculation for all CFTS and STSS referrals in the state, using NT measurements supplied by the referring doctor. The total number of women accessing NIPS was not obtainable due to the lack of systematic data collection for this testing.

Victorian births

Annual and quarterly statistics on Victorian live births were obtained from the website of the Australian Bureau of Statistics (http://stat.data.abs.gov.au/Index.aspx?QueryId=505) to estimate uptake rates of screening and invasive testing. Australian Bureau of Statistics data do not include stillbirths or terminations of pregnancy, and have previously been calculated to underestimate total confinements by $<1\%$.[14]

Ultrasound scans

Ultrasound scan numbers in Victoria were estimated from billing statistics from the Medicare Australia Medical Benefits Scheme database (http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp) using item number 55707 ("pregnancy ultrasound at 11–13 weeks gestation where NT measurement is performed to assess risk of fetal abnormality"). These billing numbers do not include services provided by hospital doctors to public patients in public hospitals, which comprise a minority of prenatal screening services. While the Medical Benefits Scheme figures consistently underestimate the annual number of 11- to 13-week scans by a median of 31% when compared to total number of CFTS tests (data not shown), they are an accepted measure of general trends in community practice in prenatal testing.[15,16]

Statistical analysis

Statistical analysis was performed with PRISM 6 Version 6.0h (San Diego, CA, USA). We performed two-tailed chi-squared tests for comparison of two proportions, or chi-squared tests for trend where appropriate, with a P value of <0.05 being considered significant.

RESULTS

Annual prenatal diagnostic procedures

The total number of diagnostic procedures performed <25 weeks gestation during the 16-year study period was 62,536. The annual number of diagnostic tests declined steadily after the introduction of CFTS in 2000 (**Figure 1a**). Steeper reductions in annual tests occurred following the gradual incorporation of nasal bone assessment from 2011, which had the effect of reducing the screen-positive rate of

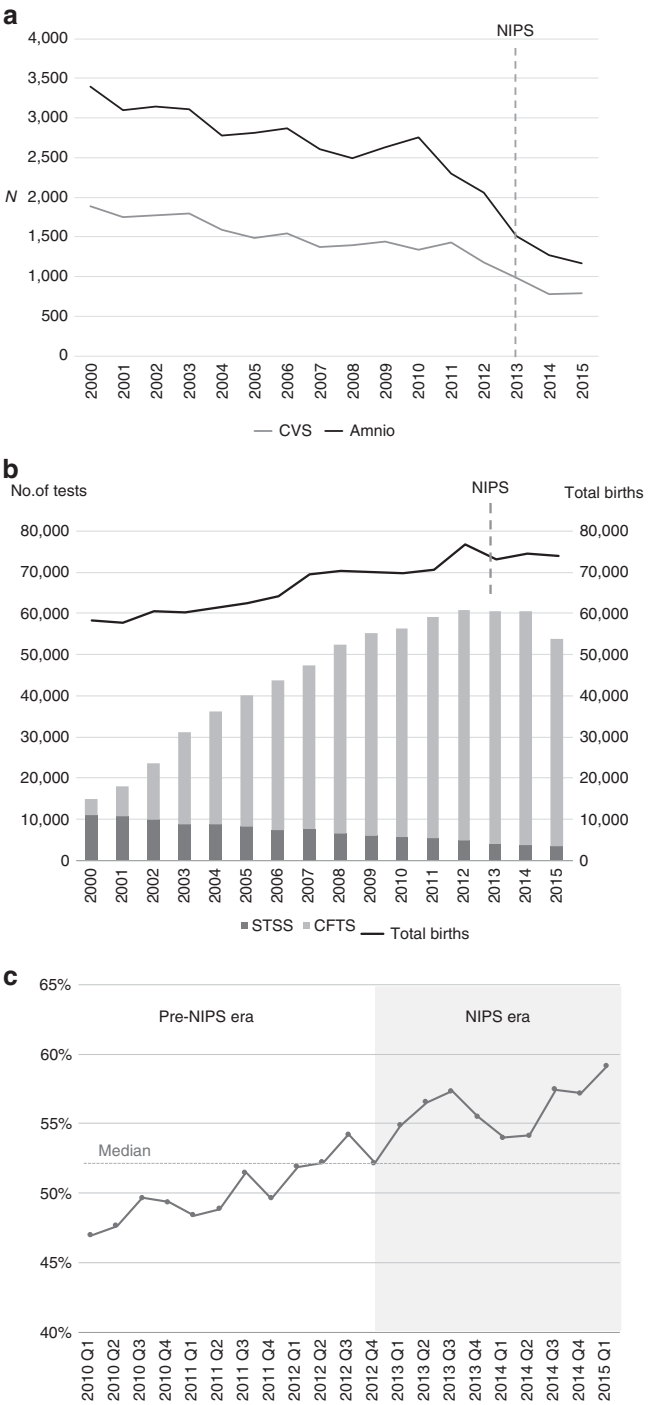

Figure 1 Trends in diagnostic procedures, serum screening, and 11–13 week ultrasounds. (**a**) Annual numbers of prenatal diagnostic tests performed <25 weeks gestation in Victoria (2000–2015). (**b**) Uptake of combined first- and second-trimester serum screening and annual births for 2000–2015. (**c**) Run chart of statewide trends in 11- to 13-week ultrasounds: government billings as a proportion of total births. Medicare billings for item 55707 underestimate total scans performed for combined first-trimester screening by approximately 31% (data not shown). Births are taken from the period two quarters subsequent to the time of the 11- to 13-week scan to correspond to expected due date. Amnio, amniocentesis; CFTS, combined first-trimester screening; CVS, chorionic villus sampling; NIPS, noninvasive prenatal screening; STSS, second-trimester serum screening.

CFTS. The steepest annual decline of 22.9% was observed in 2013, the year that NIPS became available. From 2012 to 2015 there was a 39.6% reduction in invasive tests and by 2015, only 1,957 (794 CVS, 1,165 amniocenteses) were performed.

Uptake of CFTS and early ultrasound (11–13 weeks) from 2012 to 2015

The population uptake of CFTS increased annually during the first 10 years of clinical implementation and plateaued between 70.4% and 76.6% from 2009 to 2012 (**Figure 1b**). During the NIPS era the annual uptake rate of CFTS declined significantly for the first time, falling from 77.5% in 2013 to 68.1% in 2015 (χ^2 test for trend = 2,276, $P < 0.0001$). Meanwhile, quarterly numbers in government billing for NT ultrasounds as a percentage of births showed a steady increase in the proportion of women having an 11- to 13-week ultrasound (χ^2 for trend = 1,923.9, $P < 0.0001$) (**Figure 1c**).

The overall uptake of STSS continued its long-standing gradual decline and was used by <5% of women in 2015.

Indications for diagnostic testing

There were major changes in the ranking of common indications for testing in 2015 (**Figure 2a**). In 2015, an ultrasound abnormality was present in 35.0% (685/1,957) of all women undergoing an invasive test, replacing CFTS as the most common indication for prenatal diagnosis. An increased risk CFTS result was the indication for 31.1% (608/1,957) of invasive tests.

Of the invasive tests performed for an ultrasound abnormality in 2014–2015, 41.6% (532/1,282) were performed prior to 18 weeks gestation. NT ≥3.5 mm as a stand-alone indication (without a CFTS risk) comprised 41.0% (218/532) of indications for testing <18 weeks.

High-risk (or failed) NIPS result was the third most common indication for testing in 2015 (11.7% of all tests), showing a steep increase from 29 cases in 2013 to 229 in 2015 (**Figure 2a**). After many decades as the leading indication for invasive testing, advanced maternal age alone is no longer ranked among the top three indications for prenatal diagnosis, forming the sole indication in only 4.7% of tests.

Abnormal results and diagnostic yield in the NIPS era

Trisomy 21 remained the most common condition detected on prenatal diagnosis in the NIPS era (**Table 1**). The year 2015 was notable for the highest number of confirmed trisomy 21 cases ever recorded in Victoria ($n = 204$). Of these, cases, 105 (51.5%) had a high-risk NIPS as an indication for diagnostic testing (**Figure 2b**).

The diagnostic yield of testing by indication for 2013–2015 is presented in **Table 2**. High-risk NIPS result, parental translocation carrier, and ultrasound abnormality were the indications most likely to result in a confirmed diagnosis of a major chromosome abnormality. Of the 229 women in 2015 who had a diagnostic test following high-risk or failed NIPS result, 148 had a major abnormality confirmed, resulting in an overall positive value of 64.6%. Of these

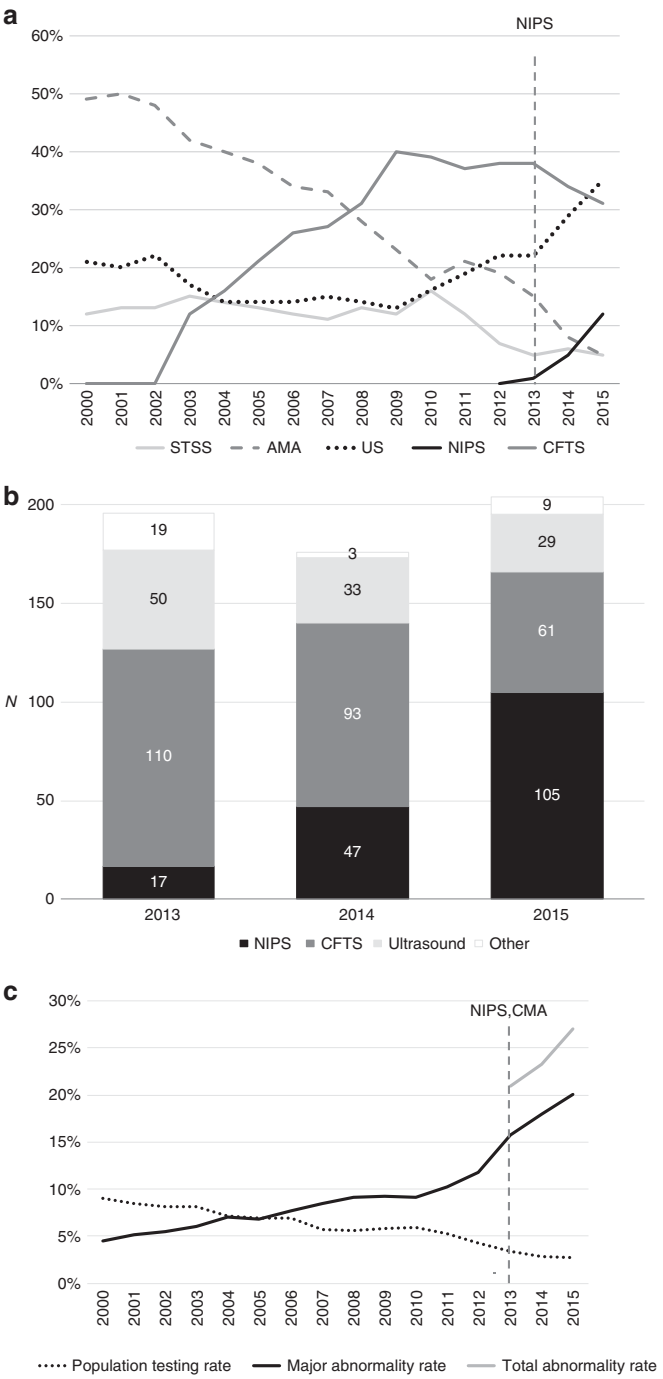

Figure 2 Trends in indications for diagnostic testing, testing rates and diagnostic yield. (**a**) Indications for invasive prenatal testing as % of all tests. (**b**) Indications for testing in confirmed cases of trisomy 21 in the noninvasive prenatal screening era (2013–2015). (**c**) Statewide trends in prenatal testing and chromosome abnormality detection rates (2000–2015). Population testing rate = total number of invasive prenatal tests <25 weeks gestation/live births. Major abnormality rate = number of major chromosome abnormalities (excluding benign variants, variants of unknown/uncertain significance)/number of diagnostic tests. Total abnormality rate = total number of chromosome abnormalities/number of diagnostic tests. AMA, advanced maternal age; CFTS, combined first-trimester screening; CMA, chromosome microarray; NIPS, noninvasive prenatal screening; STSS, second-trimester serum screening; US, ultrasound.

Table 1 Results of all prenatal chromosome tests by year (2013–2015)

Karyotype result	2013	2014	2015
Total tests	2,500	2,046	1,957
Normal karyotype	1,969	1,548	1,427
Major chromosome abnormalities	395 (15.8%)	369 (18.0%)	394 (20.1%)
Trisomy 21	198	176	204
Trisomy 18	61	49	42
Trisomy 13	30	21	15
Other autosomal aneuploidy, polyploidy	18	22	21
Sex chromosome aneuploidy	31	33	28
Pathogenic copy-number variation	25	39	39
Other major abnormalities[a]	32	29	45
Minor chromosome abnormalities[b]	136 (5.4%)	129 (6.3%)	136 (6.9%)

[a]Includes level III mosaic, unbalanced translocation/rearrangement, and uniparental disomy. [b]Includes balanced translocations, variations of unknown/uncertain significance, and confined placental mosaicism.

Table 2 Diagnostic yield for major chromosome abnormalities by indication for testing (2013–2015)

	2013	2014	2015	Combined rate 2013–15
High-risk NIPS	82.8% (24/29)	64.3% (72/112)	64.6% (148/229)	65.9% (244/370)
Known parental rearrangement	7.9% (3/38)	37.8% (14/37)	34.9% (15/43)	27.1% (32/118)
Ultrasound abnormalities	20.9% (116/554)	22.9% (137/597)	19.0% (130/685)	20.9% (383/1,836)
High-risk CFTS	21.3% (203/954)	20.5% (160/781)	18.9% (115/608)	20.4% (478/2,343)
Prior pregnancy with chromosomal abnormality	2.8% (2/71)	5.6% (3/53)	8.1%% (4/49)	5.2% (9/173)
High-risk second-trimester screening	6.1% (7/115)	2.9% (4/139)	5.2% (5/96)	4.6% (16/350)
Advanced maternal age alone	6.8% (26/382)	1.1% (2/175)	3.3% (3/92)	4.8% (31/649)
Other	0.9% (1/112)	5.7% (5/88)	3.3% (3/91)	3.1% (9/291)

CFTS, combined first-trimester screening; NIPS, noninvasive prenatal screening.
Some cases had more than one indication coded; hence, column totals may not sum to total number of tests performed by year. Testing for single-gene disorders is not included in this table.

confirmed abnormalities, there were 105 cases of trisomy 21, 18 of trisomy 18 or 13, and 10 of a sex chromosome aneuploidy (**Table 3**).

Among women who had an invasive test for an ultrasound abnormality in 2014–2015, diagnostic testing prior to 18 weeks gestation was associated with a significantly higher rate of major chromosome abnormality (32.6%, 173/532), compared with testing at 18–24 weeks gestation (12.5%, 94/750) ($\chi^2 = 75.4$, $P < 0.0001$).

The NIPS era has coincided with increasing utilization of chromosome microarrays for prenatal diagnostic testing. The percentage of all tests that were submitted for CMA analysis increased from 14.2% in 2012 to 85.3% in 2015. This was accompanied by a significant increase in pathogenic CNVs as a proportion of all tests, from 1.0% in 2013 to 2.0% in 2015 ($\chi^2 = 7.6$, $P = 0.006$), but this gain was associated with an increase in the numbers of VUS from 3.9% to 6.4% over the same period.

The steady increase in the annual numbers of abnormal karyotypes identified on diagnostic testing and the decline in invasive tests have intersected to produce a historically high diagnostic yield of 20.1% in 2015. The total abnormality rate including VUS was 27.0%. Overall, the proportion of all births in Victoria undergoing prenatal diagnosis prior to 25 weeks was 2.7% (**Figure 2c**).

DISCUSSION

This study is the first to comprehensively analyze the profound impact of NIPS on prenatal screening and diagnosis on a population-wide basis. We observed a 39.6% reduction in total invasive tests in the first three years of NIPS availability, consistent with the global experience.[6–11] While CFTS was still used by the majority of women in 2015, uptake in that year significantly declined for the first time since its introduction in 2002. We attribute this decline to the increasing use of NIPS as a primary screening test, rather than an overall reduction in screening uptake. This statement is based on the observations that (i) invasive testing for NIPS increased from 29 women in 2013 to 229 in 2015, (ii) 2015 had a record number of confirmed trisomy 21 cases, and (iii) NIPS has now displaced CFTS as the most common screening test preceding a confirmed diagnosis of trisomy 21.

Importantly, there was no evidence of a trend to fewer 11- to 13-week scans in 2015. This indicates that the significant decline in CFTS uptake and the introduction of NIPS has not been accompanied by a decline in opportunities

Table 3 Results of diagnostic tests performed for noninvasive prenatal screening results

	2013	2014	2015
Total diagnostic tests for NIPS[a]	29	112	229
Karyotype results			
Normal	4 (13.8%)	37 (33.0%)	75 (32.8%)
Total major abnormalities	24 (82.8%)	72 (64.3%)	148 (64.6%)
Trisomy 21	18 (62.1%)	46 (42.0%)	105 (45.9%)
Trisomy 18	3 (10.3%)	4 (3.6%)	13(5.7%)
Trisomy 13	1	3	5
Other autosomal aneuploidy	0	0	3
Sex chromosome aneuploidy	2	12	10
Level III mosaic	0	5	12
Pathogenic CNV	0	2	2
Minor abnormalities[b]	1	3	6

CNV, copy-number variant; NIPS, noninvasive prenatal screening.
[a]Includes 15 tests performed after "no call" NIPS result. [b]Includes confined placental mosaicism and variations of unknown significance.

for early structural assessment of the fetus prior to the routine midtrimester morphology scan. In fact, ultrasound abnormality is now the most common indication for invasive testing, with 41% of these procedures in 2014–2015 being performed prior to 18 weeks. This suggests that practitioners who are using NIPS as a primary aneuploidy screening test still recognize the value of an early ultrasound for a fetal structural survey. Furthermore, we observed a high diagnostic yield for invasive testing for ultrasound abnormalities prior to 18 weeks (32.6%), supporting the clinical utility of this practice.

The high sensitivity and specificity of NIPS has contributed to the overall increase in the numbers of major chromosome abnormalities detected and the decline in invasive testing to the lowest level in 30 years.[12] Over the same period, we also observed the impact of the routine adoption of CMA in a significant trend to higher detection of pathogenic CNVs. Working in parallel, these two developments in prenatal screening and diagnosis have produced historic diagnostic yields for prenatal testing, with one in five invasive tests now leading to a diagnosis of a major chromosome abnormality.

Implications for practice

These results have important implications for clinical practice. The 11- to 13-week ultrasound examination became incorporated into routine prenatal care about 15 years ago for the purpose of trisomy 21 screening. The initial role of the examination was to measure the NT thickness and crown rump length and combine these measurements with maternal serum biochemical markers for individualized aneuploidy risk assessment. However, advances in the performance of the 11- to 13-week ultrasound have seen it evolve into a detailed structural morphology survey, able to detect up to 50% of all major structural abnormalities including cardiac defects.[17] The option of using NIPS as a primary screening test for aneuploidy in the first trimester has caused the profession to reexamine the value of retaining the 11- to 13-week scan. Opinion leaders have argued that first-trimester ultrasound continues to have an important role in the NIPS era for the detection of fetal structural anomalies and prediction of obstetric complications.[18,19] Several retrospective studies examining the additional information provided by the early ultrasound in the NIPS era have emphasized its important role for accurate pregnancy dating, and diagnosis of fetal demise, multiple gestation, fetal structural anomalies, and placental and maternal pathology.[20,21] From a public health perspective, early diagnosis of fetal abnormalities may not change final pregnancy outcomes as most would be detected at the midtrimester morphology scan. However, from a patient perspective, early diagnosis of a major fetal abnormality would have substantial medical, social, and psychological benefits.

Our study also confirms the need for confirmatory diagnostic testing after a high-risk NIPS result, and demonstrates the decline in the positive predictive value of NIPS with its expansion to the general pregnant population. In the first year of availability, when Australian practitioners were predominately using NIPS in high-risk women, the rate of confirmed aneuploidy after diagnostic testing for a high-risk NIPS result was 82.9%.[22] As the offer of self-funded NIPS expanded to general-risk women, accordingly lower rates of confirmed abnormalities were observed in 2014 and 2015 (**Table 2**).

The impact of routine utilization of CMA for prenatal diagnosis is also evident in our study. Offering genome-wide diagnostic testing is now standard practice for pregnancies with fetal structural abnormalities[23] including NT measurements ≥ 3.5 mm.[24,25] Even in the presence of normal ultrasound and karyotype, there is ~1% background rate of clinically significant CNVs.[26] Recently, the Society for Maternal Fetal Medicine and the American Congress of Obstetricians and Gynecologists have supported offering the option of CMA analysis to all women undergoing prenatal diagnostic testing.[27] Our results show that expanding the use of CMA does result in significantly more diagnoses of pathogenic CNVs, but with an accompanying increase in the detection of VUS. The relatively high rate of VUS in our study may be related to the use of a high-resolution, whole-genome single-nucleotide polymorphism array, rather than a targeted prenatal array, and highlights the growing demand for genetic counseling and database annotation of genetic variants.

Strengths of the study

This is the first study to demonstrate the significant impact of NIPS on prenatal screening and diagnosis for an entire population. We had complete prenatal ascertainment of CFTS, STSS, and prenatal diagnostic tests for Victoria because of a unique long-standing collaboration with all cytogenetic laboratories in the state.[12] Prior multicenter studies of NIPS have usually been based on maternity units[6] or laboratory

services.[11] The advantages of a population-based approach are large sample sizes, and the avoidance of potential selection biases caused by tertiary referral populations, a single NIPS provider, or individual clinical practice patterns.

Limitations

We were not able to obtain data for women who had NIPS without diagnostic testing due to the fragmented nature of NIPS provision among private and nonprofit providers. We therefore cannot ascertain the total number of women who accessed NIPS during pregnancy but had to confine our analysis to the women who underwent prenatal diagnosis as a result of high-risk NIPS result. An estimate of the total numbers of women accessing NIPS in 2015 can be calculated using figures from a recent study of over 5,000 Australian women using NIPS as a primary or secondary screening test.[28] Adopting the 2.2% screen-positive rate and 73.4% invasive testing rate from this study, we estimated that 14,181 women would have used NIPS in order to lead to 229 invasive tests in 2015. This figure represents 19% of all Victorian births, which is in keeping with our impressions of local clinical practice. We were also not able to identify which women with a high-risk NIPS result had utilized this as a primary or secondary screening test.

Other limitations of our study are that we could not perform linkage to pregnancy outcomes, and hence were unable to ascertain false-negative screening results, termination of pregnancy rates, or follow-up clinical outcomes from false-positive NIPS results. Past studies on prenatal screening suggest significant differences in access according to the geographical location and maternal demographics in our population.[29] This was beyond the scope of this study, but further analysis is planned to determine whether there is any association between geographical and social disadvantage on prenatal screening and indications for invasive testing.

Conclusion

Our population-based study demonstrates the rapidly emerging importance of NIPS and the declining influence of CFTS in the genomic era—an experience with relevance for other countries adapting to NIPS from a preexisting paradigm of CFTS. The willingness of women to self-fund NIPS has led to a dramatic reduction in invasive testing over 3 years, accompanied by the highest diagnostic yield ever recorded. NIPS is now the single biggest contributor to prenatal ascertainment of T21 in our population. Ultrasound-detected abnormalities have become the most common indication for diagnostic testing, highlighting the continued importance of early ultrasound and high-resolution genomic testing in the NIPS era.

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DISCLOSURE

The authors declare no conflict of interest.

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