School of Public Health

Diagnosing Fetal Aneuploidy in Australia: The Impact of Prenatal Screening and the Integration of New Technology

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Doctor of Philosophy
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DECLARATION

To the best of my knowledge this thesis contains no material previously published by any other person, except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma at any university. The published papers have co-authors who have identified and acknowledged my contribution, included in Appendix B.

Susannah Maxwell

7 August 2017

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Finally, I must express my utmost gratitude to my husband, Leigh for believing in me more than I believed in myself, and inspiring me to always aim higher. This accomplishment would not have been possible without him. Finally, to my sweet Emma, just for being there.

Susannah Maxwell

DEDICATION

This thesis is dedicated to my nephew Jai Maxwell for providing me with another perspective. I stand by my belief in the importance of providing reproductive autonomy to women and their families. However Jai has made me question if choice can ever be truly informed.

ABSTRACT

Fifty years ago it became possible to diagnose Down syndrome and other chromosomal conditions prenatally, thereby enabling women who chose to do so the opportunity to avoid the birth of a child with such a condition. However, diagnosis required the karyotyping of fetal or placental cells collected via amniocentesis or chorionic villus sampling respectively; these are invasive procedures that are associated with a small, but significant risk of miscarriage. Given the association between advancing maternal age and the incidence of fetal Down syndrome, invasive techniques were generally restricted to women of advanced maternal age. However in the mid-1980s offering invasive testing to women based on maternal age alone detected only 30% of fetal Down syndrome. By the late 1980s a screening test was available that used multiple analyte measures to provide a more refined estimate of the likelihood of fetal Down syndrome, an association recognised in the early 1980s. Screening tests have continued to evolve and prenatal screening has been routinely offered to pregnant women as part of obstetric care, regardless of age, since this time.

The primary aims of this thesis were to evaluate and analyse prenatal screening in Western Australia and provide data to inform the direction of prenatal screening policy for Down syndrome against a landscape of significant advances in screening technology. The thesis investigates the historical uptake and impact, performance and outcomes of prenatal screening for Down syndrome in Western Australia, using comprehensive Western Australian data. The thesis continues with commentary on prenatal screening policy and models the potential impact of the incorporation of the new non-invasive cell free DNA (cfDNA) test within prenatal screening pathways on costs and outcomes using these local, as well as, published data. As the remainder of the country shares similar population demographics to Western Australia and a national Health Insurance Scheme these data and results are generalisable to the Australian population.

Papers 1, 2 and 3 provide a picture of aneuploidy screening in Western Australia. Paper 1 describes trends in Down syndrome pregnancies, births and

terminations in relation to rising maternal age and the adoption of prenatal screening technology over 30 years, with a clear reduction in the expected Down syndrome live birth rate over this time. These data are complemented by an evaluation of the performance of combined First Trimester Screening (cFTS) in Papers 2 and 3, and Maternal Serum Screening (MSS) in Paper 2 as is recommended by peak bodies. The papers reveal performance in line with international standards but also widespread sociodemographic disparities in test uptake (Paper 2).

Papers 3 through 6 model the impact of adopting the most recently developed screening test, non-invasive screening (NIPT) using cfDNA, as part of a publicly funded screening program. This screening test, as applied to Down syndrome, has a performance that approaches that of invasive diagnostic testing, but the detection rate for other rare chromosomal abnormalities is lower. NIPT has been available on a user pays basis in Australia since 2011. Paper 4 explores the impact of using this test as a second tier screen on the outcomes of pregnancies with rare chromosomal abnormalities, abnormalities that would be identified by invasive diagnostic testing. The results suggest that with judicial use of NIPT and continuing use of soft markers on ultrasound to guide decisions, NIPT would have minimal impact on outcomes. Papers 5 and 6 consider the costs and outcomes of using NIPT as a second tier screen, with a clear reduction in invasive diagnostic tests and associated miscarriage, and potentially greater detection rates, at a cost per diagnosis similar to, or lower than the current screening pathway.

Paper 7 provides comment on a recent recommendation against the use of the triple test (MSS with three analytes) by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the Human Genetics Society of Australasia, concluding this to be a premature recommendation that threatens equity and access to prenatal screening in most states of Australia.

This thesis provides an assessment of the performance and uptake of cFTS (the current standard in prenatal screening) in Western Australia and the potential impact of cfDNA in prenatal screening. In summary, the successful integration of NIPT with cfDNA into publicly funded prenatal screening has the potential to

improve the detection of fetal Down syndrome, which may lead to a further decline in the live-birth rate of Down syndrome, and reduce invasive diagnostic testing and procedure related loss. The test also provides an opportunity to improve access to prenatal screening.

Significance of research

To my knowledge, this thesis provides:

- One of the largest cohorts of first trimester screened pregnancies for which pregnancy outcome data are available, globally, enabled through the use of data linkage methodology,
- The only assessment of the impact of changing prenatal screening strategies on trends in the diagnosis, termination and live birth rate of Down syndrome over the last thirty years,
- The only evaluation of the performance and uptake of prenatal screening in Western Australia and the largest study of sociodemographic disparity in the uptake of screening and diagnosis in Australia and;
- The only published data on the impact of using increasingly sensitive cFTS risk cut offs on screen positive and detection rates, and the costs and outcomes of contingent NIPT models with varied cFTS risk cut-offs in Australia, and does so using local, as well as published, data.

These data contribute to a growing body of knowledge internationally as well as to a limited body of literature in the Australian context. These data are vital for policy decisions around prenatal screening in Australia. Research output from this thesis has been cited within the most recent Royal Australian New Zealand College of Obstetrics and Gynaecology recommendations for the appropriate clinical use of NIPT[1]. Data are also being used to inform a health technology assessment submission to the Australian Government Medical Services Advisory Committee for public funding for NIPT.

LIST OF PUBLICATIONS INCLUDED IN THE THESIS

Susannah Maxwell, Carol Bower, Peter O'Leary. Impact of prenatal screening and diagnostic testing on trends in Down syndrome births and terminations in Western Australia 1980 to 2013, Prenatal Diagnosis Volume 35, Issue 13, pages 1324–1330, December 2015[2]

Susannah Maxwell, Kate Brameld, Carol Bower, Jan E Dickinson, Jack Goldblatt, Narelle Hadlow, Bev Hewitt, Ashleigh Murch, Anthony Murphy, Roseanne Stock, Peter O'Leary. Socio-demographic disparities in the uptake of prenatal screening and diagnosis in Western Australia, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 51, Issue 1, pages 9–16, February 2011[3]

Susannah Maxwell, Ian James, Jan E Dickinson, Peter O'Leary. First trimester screening cut-offs for non-invasive prenatal testing as a contingent screen: Balancing detection and screen-positive rates for trisomy 21, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 56, Issue 1, pages 29–35, February 2016[4]

Susannah Maxwell, Jan E Dickinson, Ashleigh Murch, Peter O'Leary. The potential impact of NIPT as a second-tier screen on the outcomes of high-risk pregnancies with rare chromosomal abnormalities, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 55, Issue 5, pages 420–426, October 2015[5]

Peter O'Leary, ***Susannah Maxwell,*** Ashleigh Murch, Delia Hendrie. Prenatal screening for Down syndrome in Australia: costs and benefits of current and novel screening strategies, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 53, Issue 5, pages 425–433, October 2013[6]

Susannah Maxwell, Peter O'Leary, Jan Dickinson, Graeme Suthers. Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing, Australian New Zealand Journal of Obstetrics and Gynaecology 2017 doi: 10.1111/ajo.12612[7]

Peter O'Leary, ***Susannah Maxwell,*** Michael Sinosich, Kerry DeVoss, Janice Fletcher, Enzo Ranieri, Michael P Metz. Screening for Down syndrome in the second trimester of pregnancy, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 56, Issue 1, pages 19–21, February 2016[8]

STATEMENT OF AUTHOR CONTRIBUTION

The nature and extent of the intellectual input by the candidate and co-authors has been validated by all authors and can be found in Appendix B.

Susannah Maxwell (Candidate)

Jan Dickinson (Supervisor)

Suzanne Robinson (Supervisor)

Peter O'Leary (Supervisor)

LIST OF ABBREVIATIONS AND ACRONYMS

AFP	Alpha fetoprotein
ASHG	American Society of Human Genetics
cfDNA	Cell free DNA
cffDNA	Cell free fetal DNA
DLU	Data linkage unit
DR	Detection rate
ESHG	European Society of Human Genetics
FMF	Fetal Medicine Foundation
FTS or cFTS	combined First Trimester Screening
free β-hCG	free β-human chorionic gonadotrophin
hCG	Human chorionic gonadotrophin
HGSA	Human Genetics Society of Australasia
MSS	Maternal serum screening/Second trimester screening
NIPT	Non-invasive prenatal testing
NT	Nuchal translucency
PAPP-A	Pregnancy-associated plasma protein A
RANZCOG	Royal Australian and New Zealand College of Obstetrics and Gynaecology
SCA	Sex chromosome anomalies
SPR	Screen positive rate
T21	Trisomy 21 (Down syndrome)
WARDA	Western Australian Register of Developmental Anomalies

A NOTE ON TERMINOLOGY

In 2015 Down Syndrome Tasmania lodged a complaint with the Tasmanian Anti-Discrimination Commissioner regarding language used to describe prenatal screening, specifically the use of 'risk' to describe the probability of a Down syndrome diagnosis.[9] The Anti-Discrimination Commissioner found this language to be a possible breach of the Anti-Discrimination Act 1998. This prompted a review of language used in guidelines and information pamphlets regarding prenatal testing provided by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists. The documents now use the terms 'likelihood', 'chance' and 'probability' rather than 'risk', and 'condition' rather than 'abnormality'. [9] The terminology used within the body of this thesis reflects this recent change however the published manuscripts use the traditional terms of 'risk', 'anomaly' and 'abnormality'.

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CHAPTER 1 INTRODUCTION

1.1 Prenatal diagnosis of Down syndrome

Down syndrome is the most common form of congenital intellectual disability, occurring in 1 in 1150 live births in Western Australia between 2004 and 2013,[2] and accounting for between 12 and 15 per cent of learning disability in the developed world.[10] Down syndrome occurs more frequently among children conceived by women of advancing maternal age, an association first recognised in the early 1900s.[11] Although individuals with Down syndrome share common features such as characteristic craniofacial malformation and intellectual and physical disability, the clinical presentation of the syndrome has been described as 'complex and variable'[12] with a wide range of disability and medical problems including congenital heart, gastrointestinal and thyroid defects, and a significantly increased risk of childhood leukaemia.[10, 12]

Down syndrome is caused by the presence of an extra chromosome 21 (trisomy 21 [T21]) or translocations or mosaicism of chromosome 21. Trisomy 21 was discovered shortly after confirmation in the late 1950s that the correct number of chromosomes in humans was forty-six.[13] The T21 karyotype accounts for 93-95% of Down syndrome, and is associated with poorer intellectual functioning than the mosaic karyotype (1-3% of Down syndrome cases).[10]

The life expectancy for people with Down syndrome has increased significantly over the last century from 9-12 years between 1929-1949 to 60 years in 2002.[14] Respiratory infections have historically been a major cause of mortality in individuals with Down syndrome, and as such the increase in life expectancy may be partly attributed to a reduction in infection-related mortality associated with the introduction of antibiotics in the 1950s and de-institutionalisation in the 1970s and 80s.[10] The surgical correction of heart defects and improvements in cancer care has also improved survival.[10, 15] Down syndrome is associated with accelerated ageing with a number of diseases, such as Alzheimer's occurring more frequently or earlier than seen in the general population.[10, 15]

Since the 1960s it is has been possible to diagnose Down syndrome prenatally. This technological advance, along with legal abortion, paved the way for women and couples, who chose to do so, to avoid the birth of a baby with Down syndrome.[16] Due to the contentious nature of selective abortion, publicly funded screening and diagnostic testing is commonly justified by the value placed on 'reproductive autonomy' or choice for women.[17] Other benefits to prenatal diagnosis are also cited and include providing an early opportunity for prospective parents to grieve and prepare for the birth of a child with Down syndrome.[18] In Western Australia between 1994 and 2013 the choice, for the majority of women (92.6%) given a diagnosis of fetal Down syndrome was to terminate the pregnancy.[2] This is consistent with a Victorian study in which 95% of women chose to terminate following a prenatal diagnosis of Down syndrome (1996-2004).[2, 19]

Termination rates after a diagnosis of Down syndrome vary globally, as does the median age of gestation at detection, reflecting different screening policies.[20] Between 2002 and 2004, termination rates following a diagnosis of Down syndrome ranged from 73 to 100 per cent among 10 European countries with legal termination of pregnancy for fetal anomaly.[20] A 2012 review in the United States (US) reported termination rates ranging from 67 to 85 per cent.[18] It is clear that a direct consequence of prenatal screening and diagnosis of Down syndrome is abortion. On a societal level this has the potential to decrease the live-born incidence of Down syndrome, resulting in significant long term savings for the community.[17] This societal impact of diagnosing Down syndrome prenatally cannot be ignored, and arguably provides the necessary platform upon which publicly funded prenatal screening and diagnosis programs rely despite not being the stated goal of such programs.

1.2 History of prenatal aneuploidy screening and diagnosis

In the late 1960s and 1970s there was a shift toward the legalisation of abortion. The UK Abortion Act (1967) made it legal to terminate a pregnancy where there was 'a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped'.[21] In Australia, a Victorian case in 1969 set a precedent for the legality of abortion where maternal health was at risk, and although abortion is subject to state rather than national law, this ruling was influential across the country.[22] Abortion is now legal in Western Australia on request before 20 weeks gestation and with approval from a Ministerial panel after 20 weeks where there is a severe problem affecting the woman or the fetus.[22]

The shift toward legal abortion coincided with developments in techniques to diagnose genetic disorders prenatally. In the 1960s it became possible to diagnose Down syndrome and other chromosomal anomalies prenatally through the karyotyping of fetal cells in amniotic fluid.[23-25] Amniocentesis, an invasive procedure to collect the amniotic fluid, could be done after 15 weeks of pregnancy. From the 1980s, prenatal diagnosis could be done between 11 to 14 weeks of pregnancy using a sample of chorionic villus (placental tissue) collected via another invasive technique (chorionic villus sampling).[26] As these invasive procedures are associated with a small, but significant risk of miscarriage (0.1% to 1.3%[27]) it is desirable to restrict the procedure to those women who are most likely to be carrying a fetus with Down syndrome.

The likelihood of fetal Down syndrome increases with each additional year of maternal age[28] and, in the absence of any other screening modality, advanced maternal age (>35 years) was used as the sole screening criterion for offering invasive diagnostic testing in the 1970s. However, in the mid-1980s offering testing to women based on maternal age alone detected only 30% of fetal Down syndrome, with 70% born to the 95% of women under 35 years of age.[29]

In 1984 Merkatz et al reported that a maternal concentration of alpha-fetoprotein (AFP) lower than the median was more likely among pregnancies with fetal Down syndrome.[30] In 1988, Wald et al introduced the concept of multi-analyte serum screening, using three analytes (the triple test): alpha fetoprotein (AFP), human chorionic gonadotrophin (hCG) and unconjugated oestriol, to identify pregnancies in the second trimester with a higher probability of fetal Down syndrome. By using a probability threshold of 1 in 300 at term, equivalent to the probability of fetal Down syndrome among pregnancies conceived in women >35 years, the test could identify 60% of fetal Down syndrome at a 5% false positive rate.[31]

Developments soon followed in the identification of first trimester maternal serum markers and indicators on prenatal ultrasound; in 1992 Nicolaides et al described an association between increased nuchal translucency (a fluid-filled space behind the fetal neck [NT]) in the first trimester and fetal Down syndrome.[32] By the late 1990s maternal age and NT (with crown rump length) were being combined with two first trimester maternal serum markers [pregnancy-associated plasma protein A (PAPP-A) and free β-human chorionic gonadotrophin (free β-hCG)] to provide a test with reported detection rates of between 76 and 91% at a 5% false positive rate.[3, 26] Women with pregnancies above the probability threshold of 1 in 300 were offered invasive diagnostic tests (amniocentesis or chorionic villus sampling with diagnostic karyotyping).

Techniques for fetal karyotyping also developed over this time. Advances in genomics are now providing other diagnostic options such as chromosomal microarray analysis, which are faster, cheaper and more robust.[33]

1.3 The current status of prenatal screening and diagnosis in Western Australia

Screening tests are now routinely offered in pregnancy to provide information to facilitate parental decision making about invasive diagnostic testing. Screening aims to optimise the identification of fetal Down syndrome while minimising unnecessary diagnostic procedures, reducing exposure to the risk of

procedure-related miscarriage and the high obstetric and laboratory costs of invasive procedures and karyotyping. Diagnosing Down syndrome prenatally provides women with information about their pregnancy and allows the choice to avoid or prepare for the birth of a baby with this condition.

In Western Australia cFTS, provided before 14 weeks gestation, is available in public and private ultrasound practices throughout the metropolitan area and in most large regional centres. Blood collection for second trimester MSS, available after 15 weeks gestation using three analytes occurs throughout the State. There is a Medicare rebate for the cost of the maternal serum blood tests for both cFTS and MSS, as well as for the ultrasound component of cFTS. Although cFTS accounts for the majority of screening tests,[3] MSS remains an important option for those women who attend for prenatal care later in pregnancy or for those residing outside of major centres without access to specialised first trimester screening ultrasound.[3]

Until recently cFTS was the most sensitive and specific population screening option available for assessing the probability of fetal Down syndrome. However, up to 20% of cases remain undetected in cFTS screened pregnancies and a normal karyotype is reported in the majority of those with a high probability result.[3, 34] In 2011 a new screening test became available in Australia, citing performance characteristics that approach those of invasive testing. This non-invasive prenatal test (NIPT) analyses cell free DNA (cfDNA) in maternal blood by massively parallel DNA sequencing using shotgun[35-37] or targeted DNA sequencing[38, 39] to assess the probability of fetal Down syndrome and other chromosomal conditions. The test can be done as early as 10 weeks gestation and has a sensitivity and specificity for fetal Down syndrome of 98% to 99.9%.[40, 41] NIPT has successfully identified fetal trisomy 21, 18 and 13 as well as Sex Chromosomes Anomalies (SCA), albeit with poorer performance characteristics in the latter, in both high probability pregnancies and the general obstetric populations.[35-39, 42-53] NIPT is also increasingly being used to identify microdeletions such as DiGeorge syndrome (22q11.2 deletion syndrome), but with low positive predictive values (18% for 22q11.2)[54] and significant variation in phenotype, caution has been advised in its use.[54] Since first

becoming available the price of NIPT has fallen significantly, from $1350 to $395 (as at June 2017) as multiple international providers, and the first Australian providers, have entered the market. Although NIPT does not yet attract a Medicare rebate, it is rapidly being accepted by Australian women who are willing and able to pay for the test.[55]

1.3.1 Integrating new technology – the role of NIPT with cfDNA

NIPT has the potential to increase the detection of fetal Down syndrome and reduce the number of invasive diagnostic procedures. However, the test is not yet in routine clinical use, with no public or private health funding provided in Australia, with the exception of a small number of high obstetric risk pregnancies at specialist public obstetric hospitals. The impact of NIPT in this user-pays market is already evident with a reported 51% and 37% fall in amniocentesis and CVS between the first quarter of 2013 and the last quarter of 2014 respectively.[56]

Just how this test should be integrated into a publicly funded prenatal screening program in Australia is uncertain. Any decision regarding the adoption of this, or any, new health technology requires an understanding of the landscape into which the test is entering and assessment of the potential costs and outcomes and the potential impact on equitable, informed access and clinical management. Such health technology assessment may occur as part of the development of clinical guidelines by peak bodies, regulatory bodies, or by state or federal governments considering funding new health technologies.

1.3.1.1 International experience

NIPT was first launched in Hong Kong in August 2011.[57] By 2015, the test was available from several companies in over 60 countries, on six continents.[57] As evidence has emerged, recommendations of peak international bodies have begun to endorse NIPT as a primary or contingent screening tool among both pregnancies at high probability of fetal Down syndrome and the general obstetric population.[58, 59] In 2015, Switzerland became the first national health system to fund NIPT for women at increased chance of fetal trisomy.[60] Large evaluation trials to assess the

potential for public health system support of NIPT, have been or are currently being conducted in the Netherlands (TRIDENT study),[61] United Kingdom (UK) (RAPID trial)[62] and Canada (PEGASUS trial)[63] In the UK, the National Health Service has recently accepted a submission to implement NIPT based on the results of the RAPID trial, with a plan to begin NIPT screening in 2017. In Germany, authorities will make a decision regarding public funding of NIPT for fetal trisomy in August 2019 following evaluation of the evidence and consultation with stakeholders and industry professionals.[64]

While international experience provides part of the picture, it is essential that we assess NIPT within the context of the Australian health care system and the Australian experience. This body of work provides an assessment of the performance and uptake of cFTS (the current standard in prenatal screening) in Western Australia and the potential impact of cfDNA in prenatal screening, clinical management, costs and outcomes.

1.3.2 The performance of cFTS

The performance of cFTS has been evaluated among many international programs, particularly in the early 2000s shortly after these programs began. Several of the key early studies reporting detection and false positive rates are summarised in Table 1. The largest single evaluation demonstrated a detection rate of 90% with a 5% false positive rate among 75,821 pregnancies screened at hospital clinics in the UK.[65] Variation in the reported performance between studies may reflect small sample sizes or differences in maternal age distribution. Real differences may occur due to variation in NT measurement resulting from differences in the quality of the sonographic equipment[66] and/or training and experience.[67]

Table 1 Detection and false positive rates in selected international studies

Country (year)	Pregnancies (n)	Detection rate	False positive rate
Austria (2002)[68]	4,939	86%	5.2%
France (2003)[69]	5,694	81%	4.5%
Scotland (2002)[70]	17,229	80%	5.0%
Scotland (2004)[71]	5,084	93%	5.9%
UK (2000)[72]	3,762	86%	6.7%
UK (2002)[73]	14,200	92%	6.8%
UK (2003)[66]	47,053	85%	5.0%
UK (2005)[65]	75,821	90%	5.0%
USA (2000)[74]	5223	91%	7.9%
USA (2003)[75]	8514	85%	9.4%

A pilot evaluation of cFTS in Western Australia reported a detection rate of 90% and a false positive rate of 3.6% among 10,274 pregnancies[36] screened between August 1999 and July 2001. A follow up evaluation of 22,280 screened pregnancies between 2001 and 2003 gave a detection rate of 83% with a false positive rate of 3.7%.[37] In the former study (1999-2001) the majority of scans were supervised or performed by four private obstetric sonologists, each with a minimum of ten years obstetric ultrasound experience, at nine centres, whereas the latter study (2001-2003) included 13 centres with variable obstetric ultrasound experience. Another 2010 Australian study from Victoria, reported a cFTS detection rate of 91.8% and false positive rate of 4.5% among 38,584 screened pregnancies.[76] In 2004 the Fetal Medicine Foundation's (FMF) Nuchal Translucency Ultrasound, Education and Monitoring program began an accreditation program. There were 75 accredited providers in Western Australia in 2004, which increased to 156 in 2015 (personal correspondence, Nuchal Translucency Co-ordinator, Nuchal Translucency Ultrasound, Education and Monitoring Program, East Melbourne Vic 3002, Australia). This is a typical pattern of diffusion seen in the adoption of medical technology and underpins the rationale for ongoing monitoring and evaluation.[67]

NIPT provides highly accurate risk assessment for specific fetal aneuploidies and some sex chromosome abnormalities. Other conditions such as microdeletion syndromes may be offered on the screening panel.[77] NIPT will not identify the full

range of chromosomal abnormalities that could be identified via invasive diagnostic testing. NIPT is not diagnostic. If NIPT indicates a positive result, confirmatory testing (chorionic villus sampling or amniocentesis) is recommended. For 3-5% of women the test will fail due to very low fetal DNA fractions in maternal blood which could lead to a delay in diagnosis. Factors associated with low fetal DNA include a high body mass index and early gestational age (<10 weeks). Women who experience test failures due to very low fetal DNA fractions may need to be considered at increased risk of aneuploidy. [78]

1.3.3 Access to, and uptake of prenatal screening

In 2006, O'Leary et al reported significant disparities in the provision and availability of prenatal screening services for fetal Down syndrome across Australia.[79, 80] Participation in screening ranged from 17% in the Northern Territory to 80% in South Australia. The majority of screened women had cFTS, with the exception of the Northern Territory, which did not have any accredited cFTS providers. An earlier study[81] reported similar discrepancies between Australian maternity hospitals and concluded that a woman's access to prenatal screening often depends on where she lives and the institution she is attending for prenatal care. This disparate access is also apparent in a study of Down syndrome birth rates in Queensland which reported a large fall in maternal age adjusted rates of Down syndrome births among women living in metropolitan areas but not for those in rural areas, and in mothers with private but not public obstetric care between 1990 and 2004.[82]

Prenatal screening programs aim to provide reproductive autonomy to women. Reproductive autonomy has been described as the notion that 'pregnant women should principally have equal access to effective means for preventing foreseeable severe restrictions to their individual autonomy, to their average range of opportunities'.[83] Variation in access to screening threatens this goal. Although NIPT with cfDNA could improve reproductive autonomy by providing more accurate screening test results and reducing the need for invasive diagnostic tests, it also has

the potential, particularly while it remains unfunded by the public health system, to broaden any pre-existing disparities in access to screening.

1.3.4 The role of NIPT with cfDNA and clinical care

It is not anticipated that NIPT will replace cFTS as a universal screening test among the general population in a publicly funded model in Australia, at least not in the short- to mid-term. This is due to the substantial cost and the continued value of first trimester ultrasound for determination of viability, accurate dating and the identification of structural anomalies[84] and/or multifetal pregnancies.[85] Rather, a publicly funded model could integrate NIPT as a contingent screen after identifying pregnancies that have the highest chance of fetal Down syndrome though cFTS or MSS, where results were timely enough, to enable follow up. Currently cFTS defines a pregnancy as 'high probability' for fetal Down syndrome, where the chance is greater than 1 in 300. By using a more sensitive cFTS probability threshold, such as 1 in 1000, the detection rate could be improved. Any decision to publicly fund NIPT will have to balance higher detection, and equitable access, with cost.

While the role of prenatal aneuploidy screening has traditionally been to identify fetal Down syndrome, the most commonly occurring chromosomal condition, cFTS also calculates the probability of fetal trisomy 13 and 18. However, high probability cFTS results for these conditions are also associated with other rarer birth defects and chromosomal conditions of varying severity and expression.[86] Concerns have been raised that using NIPT to inform the choice to have fetal karyotyping among pregnancies with a high probability of fetal Down syndrome would result in the diagnosis of fewer of these rare chromosomal conditions.[87-89] However, NIPT should not be provided in isolation, with early fetal anatomy survey allowing for the diagnosis of many anomalies that would not be detected by NIPT. Nevertheless, this adds to the complexity of clinical management and the counselling of women to ensure informed choice, an essential part of a prenatal screening program.

1.3.5 The cost-effectiveness of NIPT with cfDNA

Economic evaluation to determine the costs and performance of NIPT with cfDNA has been undertaken in the United States,[90-95] Canada,[96] the United Kingdom,[97, 98] the Netherlands,[99] Germany[100] and Belgium.[101] Studies have varied by perspective, screening strategy and time horizon, and include comparisons of current screening practices with universal NIPT screening, NIPT screening among high probability pregnancies, as defined by advanced maternal age, and NIPT as a contingent screen following cFTS, with some variation in the probability threshold. Studies undertaken from a public health system perspective using a horizon of the duration of pregnancy have recommended the use of NIPT as a contingent screen in the USA,[90, 93] the UK,[98] the Netherlands,[99] Belgium[101] and Canada.[96] Song et al, including lifetime cost of care, found universal screening to be a dominant screening strategy among pregnancies with a high probability of fetal Down syndrome, as defined by advanced maternal age. Benn et al used a lifetime horizon, incorporating lifetime cost of care, including trisomy 13 and 18 in the analysis and found universal screening among the general obstetric population to be cost-effective.[91]

While these studies may suggest what screening strategy could be appropriate for Australia, findings of international economic evaluations are not easily transferable. These studies were conducted within the context of different health systems and populations and may not be applicable to the Australian environment, hence the need to undertake further economic evaluation specifically for Australia, as has been done as part of this body of work in papers published in 2013 and 2016.[6] Adding to economic data for the Australian context is a paper by Ayres et al, published in 2014, which takes both a public health system perspective and a payer perspective to compare current practice with three strategies 1) universal screening, 2) NIPT for women with cFTS probability >1 in 300, 3a) NIPT for women >35 years and for women <35 with a cFTS probability > 1 in 300 and 3b) NIPT for women >40 years and for women <40 with a cFTS probability >1 in 300; the latter was found to be the most cost-effective strategy.[102]

1.4 Aims and objectives of the series of seven published works

The primary aims of this thesis were to evaluate and analyse prenatal screening in Western Australia and provide data to inform the direction of prenatal screening in Australia, in the face of advancing screening technology. The thesis explores how changes in prenatal screening policy have impacted the diagnosis, termination and livebirth rate of Down syndrome over the last thirty years, and analyses the performance of prenatal screening for Down syndrome and uptake of screening and diagnosis across different sociodemographic groups. This is enabled through the collection and analysis of comprehensive Western Australian data, generalisable to the Australian population. The thesis continues with commentary on prenatal screening policy and models the potential impact of the incorporation of the new non-invasive cfDNA test within prenatal screening pathways using these local, as well as, published data. These data add to a limited body of knowledge in the Australian context that are vital for health policy decisions on prenatal screening pathways. These data also add to a growing international body of literature on the potential impact of prenatal screening programs incorporating NIPT.

Paper 1

Susannah **Maxwell**, Carol Bower, Peter O'Leary. Impact of prenatal screening and diagnostic testing on trends in Down syndrome births and terminations in Western Australia 1980 to 2013, Prenatal Diagnosis Volume 35, Issue 13, pages 1324–1330, December 2015

Objective: To assess how prenatal screening and diagnostic testing have impacted the diagnosis, termination and birth prevalence of Down syndrome in Western Australia (1980-2013)

Paper 2

Susannah **Maxwell**, Kate Brameld, Carol Bower, Jan E Dickinson, Jack Goldblatt, Narelle Hadlow, Bev Hewitt, Ashleigh Murch, Anthony Murphy, Roseanne Stock,

Peter O'Leary. Socio-demographic disparities in the uptake of prenatal screening and diagnosis in Western Australia, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 51, Issue 1, pages 9–16, February 2011

Objective: To assess the performance of prenatal screening in Western Australia and identify sociodemographic disparities in the uptake of prenatal screening

Paper 3

Susannah **Maxwell**, Ian James, Jan E Dickinson, Peter O'Leary. First trimester screening cut-offs for non-invasive prenatal testing as a contingent screen: Balancing detection and screen-positive rates for trisomy 21, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 56, Issue 1, pages 29–35, February 2016

Objective: To analyse the impact of using more sensitive cFTS risk cut offs and maternal age to define women as high risk for fetal Down syndrome, on screen positive and detection rates

Paper 4

Susannah **Maxwell**, Jan E Dickinson, Ashleigh Murch, Peter O'Leary. The potential impact of NIPT as a second-tier screen on the outcomes of high-risk pregnancies with rare chromosomal abnormalities, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 55, Issue 5, pages 420–426, October 2015

Objective: Estimate the proportion of chromosomal abnormalities that would go undetected if NIPT was introduced as a second-tier test for pregnancies identified at risk by FTS.

Paper 5

Peter O'Leary, Susannah **Maxwell**, Ashleigh Murch, Delia Hendrie. Prenatal screening for Down syndrome in Australia: costs and benefits of current and novel screening strategies, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 53, Issue 5, pages 425–433, October 2013

Objective: To analyse the cost-effectiveness and performance of non-invasive prenatal testing (NIPT) for high-risk pregnancies following first-trimester screening compared with current practice

Paper 6

Susannah **Maxwell**, Peter O'Leary, Jan Dickinson, Graeme Suthers. Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing, Australian New Zealand Journal of Obstetrics and Gynaecology 2017 doi: 10.1111/ajo.12612

Objective: To describe the diagnostic and economic performance of prenatal screening models for trisomy 21 that use non-invasive prenatal testing as a contingent screen across a range of increasingly sensitive combined first trimester screening risk cut-offs

Paper 7

Peter O'Leary, **Susannah Maxwell,** Michael Sinosich, Kerry DeVoss, Janice Fletcher, Enzo Ranieri, Michael P Metz. Screening for Down syndrome in the second trimester of pregnancy, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 56, Issue 1, pages 19–21, February 2016

Objective: To evaluate the decision to recommend against the use of the triple test for second-trimester screening for fetal T21 in recent guidelines issued by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the Human Genetics Society of Australasia

1.5 Methods

This body of work involves;

- The analysis of historical aggregated data on Down syndrome pregnancies, births and terminations in Western Australia between 1980 and 2013;
- The collection and analysis of an observational cohort of screened and unscreened pregnancies between 2005 and 2009; and

- The modelling of hypothetical scenarios to assess the potential performance and outcomes of incorporating NIPT within prenatal screening pathways.

These are described briefly below. More detailed methodology is described within each manuscript.

1.5.1 Historical aggregated data (1980-2013) – Paper 1

Historical aggregated data (1980 to 2013) on reportable conditions were obtained from the Western Australian Register of Developmental Anomalies (WARDA). WARDA is a government-funded body, providing detailed information on birth defects for live births, stillbirths and terminations of pregnancy for fetal anomaly before 20 weeks gestation in Western Australia. The registry has multiple sources of case ascertainment including obstetricians, hospital, ultrasound practices, all cytogenetics, perinatal pathology and genetic services for the State and has high ascertainment of cases of chromosomal conditions.[103]

WARDA data were modelled with miscarriage rates in fetal Down syndrome to determine the impact that Down syndrome screening, diagnosis and termination have had over this time, and in relation to changes in screening policy.

1.5.2 Observational cohort of screened and unscreened pregnancies (2005-2009) – Papers 2-4

Data were collected from each of the ultrasound and pathology laboratories providing first and second trimester screening in Western Australia between 2005 and 2006 (Stage 1) and 2007 and 2009 (Stage 2). All accredited cFTS ultrasound centres in Western Australia participated. Identified data were extracted using a customised query from each centre's Fetal Medicine Foundation patient database. Data collected included all information required for cFTS including ultrasound measurements and biochemistry. Stage 1 also included the analysis of second trimester screening data which were provided by the PathWest Antenatal Screening Program at Princess Margaret Hospital and Western Diagnostic Pathology. The remaining two providers of second trimester screening in WA did not participate

owing to concerns about privacy but indicated how many screens they had completed. Fetal karyotyping records were also collected for these time periods from the Cytogenetic Laboratory at Women's and Children's Health Service and Western Diagnostic Pathology.

Screening and diagnostic data were linked via the Department of Health Western Australia's Data Linkage Unit (DLU) to data from the Western Australian Register of Developmental Anomalies, Hospital Morbidity and Mortality databases and the Midwives Notification System, which records all births reaching 20 weeks gestation. Health datasets also provided data on unscreened pregnancies to allow for the analysis of the uptake of prenatal screening. In order to ensure privacy, data collection and linkage was a multi-step process through the Department of Health's DLU (APPENDIX A). The DLU follows internationally accepted privacy-sensitive protocols.

A final composite dataset, restricted to singleton pregnancies, provided a cohort of screened (2005-2009) and unscreened (2005-2006) pregnancies and their outcomes. Data were analysed to determine sensitivity and specificity of screening (performance) and sociodemographic disparities (Stage 1) in screening and diagnostic test uptake. These data allowed us to map the screening pathway including uptake of diagnostic testing following screen positive or negative results.

Linked data had previously been used for analysis of the performance of maternal serum screening for trisomy 21 and neural tube defects in a Victorian study and was found to be an efficient method for ascertainment of pregnancy outcomes.[104] The Victorian program also followed up with an analysis of the performance of cFTS using linked data (n=16153 pregnancies), published in 2007[105], and the performance, uptake and diagnostic testing pathways among women having MSS (n=19022) and cFTS (n=41663) published in 2010.[76]

1.5.3 Modelling the impact of new screening technology - Papers 3-6

A series of hypothetical scenarios are presented within four papers to determine what impact incorporating cfDNA into the screening pathway may have

on costs and outcomes (Papers 5 and 6), the diagnosis of rare chromosomal anomalies (Paper 4) and the detection rate of fetal Down syndrome where probability thresholds for cFTS are modified in a contingent screening model (Paper 3).

In Paper 5 a decision analytic model is populated with data from the cohort of screened pregnancies to report on the expected costs and outcomes of incorporating cfDNA into the current screening pathway. In Paper 4, cases in which a rare chromosomal condition have been diagnosed within the cohort of screened pregnancies were reviewed by a fetal medicine specialist and clinical geneticist to determine which cases may have been missed by a screening protocol using NIPT as a second tier test and how this may have changed the outcomes of these pregnancies. Paper 3 considers how variation in the sensitivity and specificity of cFTS impacts the screen positive and detection rates of the screening protocol, where NIPT is used as a second tier screen dependent on the results of cFTS. Paper 6 models these data to determine the potential costs and outcomes of using NIPT as a contingent screen dependent on incrementally sensitive cFTS probability thresholds.

CHAPTER 2 PAPER 1

IMPACT OF PRENATAL SCREENING AND DIAGNOSTIC TESTING ON TRENDS IN DOWN SYNDROME BIRTHS AND TERMINATIONS IN WESTERN AUSTRALIA 1980 TO 2013

Susannah **Maxwell**, Carol Bower, Peter O'Leary. Impact of prenatal screening and diagnostic testing on trends in Down syndrome births and terminations in Western Australia 1980 to 2013, Prenatal Diagnosis Volume 35, Issue 13, pages 1324–1330, December 2015

ORIGINAL ARTICLE

Impact of prenatal screening and diagnostic testing on trends in Down syndrome births and terminations in Western Australia 1980 to 2013

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ABSTRACT

Objective To assess how prenatal screening and diagnostic testing have impacted the diagnosis, termination and birth prevalence of Down syndrome in Western Australia (1980–2013).

Method We analysed trends in termination rates and birth prevalence of Down syndrome using aggregated data (1980–2013). We modelled the expected live-birth rate and prevalence of Down syndrome and compared different eras of screening and diagnosis with respect to the impact on live-birth rate and prevalence of Down syndrome.

Results Between 1980 and 2013, the rate of Down syndrome pregnancies increased, corresponding to a greater proportion of babies born to older women. Following the introduction of screening in 1994, the rate of live-born infants with Down syndrome reduced significantly ($p = 0.001$). The rate of terminations of pregnancy for Down syndrome remained stable over this period. In the absence of termination, the Down syndrome live-birth rate would have risen from 1.1 per 1000 to 2.17 per 1000 between 1980 and 2013.

Conclusion Prenatal testing in Western Australia has reduced the birth prevalence of Down syndrome despite an increased rate of Down syndrome pregnancies. Most women for whom a prenatal diagnosis of fetal Down syndrome is made, chose to terminate the pregnancy (93%), and this proportion has not changed over the study period. © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION

Invasive diagnostic tests for fetal chromosomal abnormalities [such as Down syndrome (DS)] have been available since the 1970s.[1] These tests can detect the presence of a chromosomal abnormality via the karyotyping of fetal DNA within a sample of amniotic fluid (amniocentesis) or the placenta (chorionic villus sampling). As these tests carry a small but significant risk of miscarriage (0.6%–1.0%), their use has been generally recommended only among women with pregnancies considered to be at high risk for chromosomal abnormality.[2,3]

As the risk of chromosomal abnormality increases with advancing maternal age, invasive diagnostic tests were initially recommended only for women at high risk based on advanced maternal age (over 35 years of age), a threshold risk of 1 : 300, which was considered to balance the procedure related miscarriage risk with that of having a live-born infant with DS.[2] In the late 1980s, a screening test, based on the measurements of three maternal serum analytes at 15 to 18 weeks of pregnancy [maternal serum screening (MSS)], became available.[4] This offered a more refined risk assessment for fetal DS as well as Edwards and Patau syndromes. First-trimester combined screening (FTS) using two serum markers in combination with an ultrasound measurement of the nuchal fold in the fetal neck provided a yet more accurate test in the late 1990s and was available at an earlier stage of pregnancy (9–13 weeks). Until recently, this was the best option for the assessment of risk for fetal Down syndrome, with a detection rate of 86% at a false positive rate of 5%.[5] However, since 2012, a screening test has become available with a performance that approaches that of invasive testing, identifying pregnancies at high risk of fetal DS with a sensitivity and specificity of 98% to 99%.[6,7] In Australia, prenatal screening for fetal anomalies is offered to pregnant women through general practitioners and obstetric specialists, supported by a universal health insurance scheme for diagnostic

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Table 1 Data sources

Data by year (1980–2013)	Source
Live-births, stillbirths and terminations of Down syndrome	WARDA [unpublished data]
Maternal age distribution among pregnancies with fetal Down syndrome	WARDA [unpublished data]
All births	WARDA[12]
Maternal age in all births (% over 35 years)	Western Australian Midwives Notification System,[13] Australian Bureau of Statistics[14]
Down syndrome fetal loss rate	Literature[27]
The number of benefits paid (and cost) by the AIHC for prenatal screening and diagnosis (1994–2013)	Australian Health Insurance Commission[18]
MSS (MBS Item 66321, 66740, 66751)	—
FTS bloods (MBS Item 66750)	—
FTS ultrasound (MBS Item 55707)	—
Amniocentesis (MBS Item 16600)	—
Chorionic Villus Sampling (MBS Item 16603)	—

WARDA, Western Australian Register of Developmental Anomalies; MSS, maternal serum screening; FTS, first trimester test; MBS, Medicare Benefits Schedule.

and therapeutic services. Government health services provide health professionals and individuals a range of genetic paediatric, obstetric and general genetic services, including counselling services for prenatal diagnosis, carrier detection, predictive testing and newborns. Regardless of their choice regarding screening or diagnostic testing, families can access free or subsidised health and support services for children with disabilities.

Non-invasive prenatal testing (NIPT) uses cell-free fetal DNA circulating within maternal blood to assess the risk of fetal DS and several other chromosomal abnormalities. Throughout this period of development in prenatal testing, there have been significant changes in maternal age distribution, with a growing percentage of babies born to women over the age of 35 years.[8] With this shift has come an increased prevalence of fetal chromosomal abnormality.[8]

Non-invasive prenatal testing is not yet in routine clinical use, with no public or health care funding for the test in Australia at this time. With recent discussion around the role of NIPT within the screening pathway and the potential impact of the introduction of this yet more accurate screening test,[9–11] it is timely to review the history of prenatal screening and diagnostic testing and births and terminations of Down syndrome in Western Australia over the last 30 years. This will allow us to assess the impact that these tests may have had on diagnosis and termination rates and the birth prevalence of DS in the Western Australian community.

METHODS

We used aggregated unpublished data from the Western Australian Register of Developmental Anomalies (WARDA)[12] and reports from the Western Australian Midwives Notification System[13] and Australian Bureau of Statistics[14] to analyse trends in termination rates and the birth prevalence of DS between 1980 and 2013. We provide data and analysis on three different eras of prenatal testing defined by when advances in prenatal testing occurred, specifically when the wide-spread use of maternal serum screening (from 1994 in Western Australia),[4] and first trimester screening (from 2004 in Western Australia). We also compare the pre and post screening periods (1980–1994 and 1995–2013). NIPT became available in Western Australia in late 2012 on a user-pays basis; however, its use is not expected to have yet been widespread enough to be able to report on the impact of this technology. WARDA data relate to all notified cases of Down syndrome (ICD9-BPA codes 75800–75809) born and terminated in Western Australia over this time. The Registry has been shown to have a high level of case ascertainment.[15] Of note, is that prenatally diagnosed DS that resulted in spontaneous miscarriage prior to 20 weeks are not recorded on the registry.

Using these data and assuming all terminations occurred following a confirmed diagnosis, we modelled the expected live-birth rate and live-birth prevalence of Down syndrome in the absence of prenatal diagnosis over this time, accounting for the expected miscarriage rate in fetal DS. Savva *et al.* showed that the loss rate for fetal DS between chorionic villus sampling (considered to be <16 weeks) and amniocentesis (considered to be >16 weeks) and full term pregnancy varied by maternal age, with older women having higher rates of loss.[16] To account for this variation, we calculated the expected fetal loss among terminations for each year based on the proportion terminated before and after 16 weeks and the median maternal age for these terminations using the fetal-loss rates reported by Savva *et al.*[16] The upper and lower confidence interval limits were also used to provide less and more conservative estimates of fetal loss, shown as error bars in figures. Data on the distribution of maternal age among pregnancies and among those pregnancies with fetal DS are also presented. We used piecewise linear (segmented) regression[17] to compare the live-born rates of DS and the percentage of DS terminated over the different eras of prenatal diagnosis (1980–1993, 1994–2003, 2004+) allowing possibly different line segment slopes and intercepts within each of these three periods. Analysis was done in Excel (Microsoft Corporation, Redmond, WA, USA) and TIBCO Spotfire S+ version 8.2 (TIBCO Spotfire, Boston, MA, USA).

To provide a picture of trends in the uptake and costs of prenatal screening, we also sourced data from the Australian Health Insurance Commission (AHIC), available from 1994 onwards. These data include the absolute number of, and

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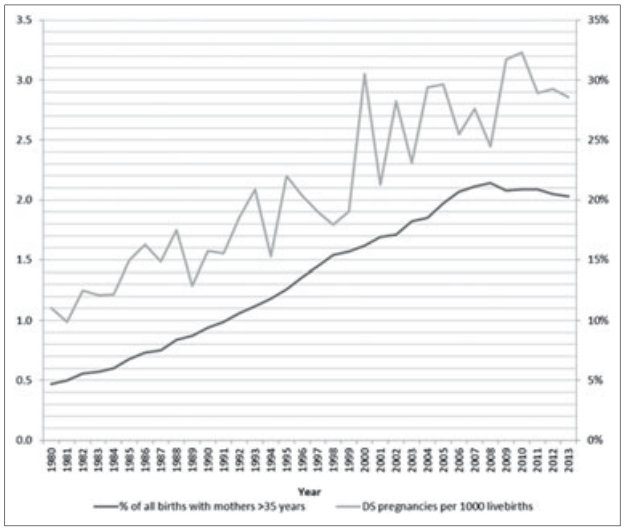

Figure 1 Down syndrome pregnancies per 1000 live births and % of babies born to women over the age of 35 years

* one case of fetal DS that was terminated following the prenatal diagnosis of other anomalies but diagnosed with fetal DS post mortem has been removed from this chart to prevent possible identification of the case.

Figure 2 Down syndrome pregnancies diagnosed prenatally and percent of Down syndrome pregnancies terminated

benefits paid by the AHIC via Medicare for first trimester and maternal serum screening between 1994 and 2013.[18] All women qualify for a rebate for MSS and FTS blood tests; however, some centres do not consider all women to qualify for the FTS ultrasound because of differences in the interpretation of the Medicare item number. We therefore used the number of FTS blood tests to quantify the number of FTS combined screens. We also report the number of invasive prenatal tests (amniocentesis and chorionic villus sampling); however, the data are not specific to the use of these tests for the diagnosis of Down syndrome. Item numbers used are shown in Table 1. Additional data used to develop the models are provided in Appendix 1.

RESULTS

Between 1980 and 2013, there were 1918 cases of fetal DS (including those terminated, stillborn and live-born) in Western Australia and 892908 births (2.1 cases of fetal DS per 1000 births). Fifty six percent of fetal DS (1082/1918) were diagnosed prenatally, and 52% of all cases (1006/1918) were terminated. Of the 48% of cases which were not terminated, 868 were live-born, and 44 were stillborn. There was no significant difference ($p = 0.69$) between the percentage of pregnancies terminated following prenatal diagnosis of DS in the period 1980 to 1994 (94.9%) compared with the period 1994 to 2013 (92.6%).

The rate of Down syndrome pregnancies (including terminations) per 1000 births increased from 1.1 in 1980 to 2.9 in 2013 (Figure 1), consistent with the steady increase in the percentage of babies born to women of advanced maternal age (>35 years; Figure 1). Over the same time period, the percentage of DS diagnosed prenatally and termination rates for fetal DS also increased (Figure 2).

The birth prevalence rate of Down syndrome per 1000 live-born infants fluctuated from year to year with a gradual downward trend. In the absence of prenatal diagnosis and termination, taking into account the percentage of fetal DS that would have been lost by term based on the median maternal age among terminations (Table 2), the birth rate for DS would have risen steadily from 1.1 per 1000 in 1980 to 2.17 per 1000 in 2013 (Figure 3). Using a more conservative estimate of DS fetal loss, the birth rate would have been 2.27 per 1000 in 2013, while the less conservative estimate gave a birth rate of 2.05 per 1000.

Table 2 Births, Down syndrome and prenatal diagnosis and termination rates by prenatal testing era

	1980–1993	1994–2003	2004 onwards	Overall
Observed data	—	—	—	—
All births in women >35 years (%)	8	15	20	14
Fetal DS per 1000 births	1.48	2.16	2.87	2.15
Live-born DS per 1000 births	1.11	0.91	0.87	0.97
Fetal DS terminated (%)	22	55	68	52
DS diagnosed prenatally (%)	24	60	73	56
Modelled data	—	—	—	—
Reduction in live-born DS (%) (range)	18 (16,19)	49 (47,50)	59 (57,61)	45 (43,47)

DS, Down syndrome.

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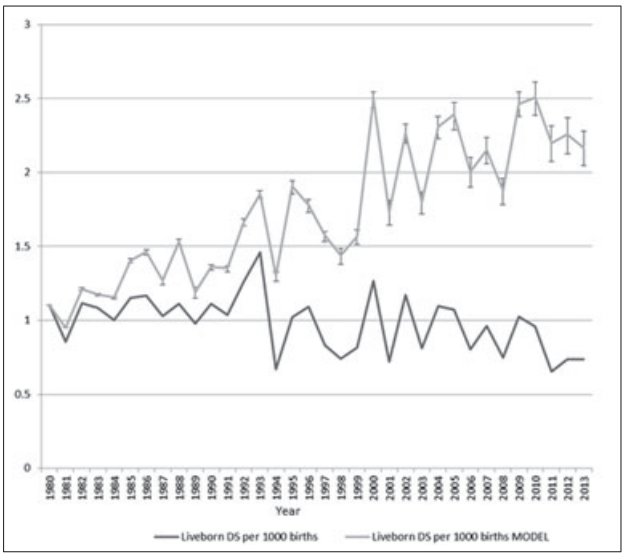


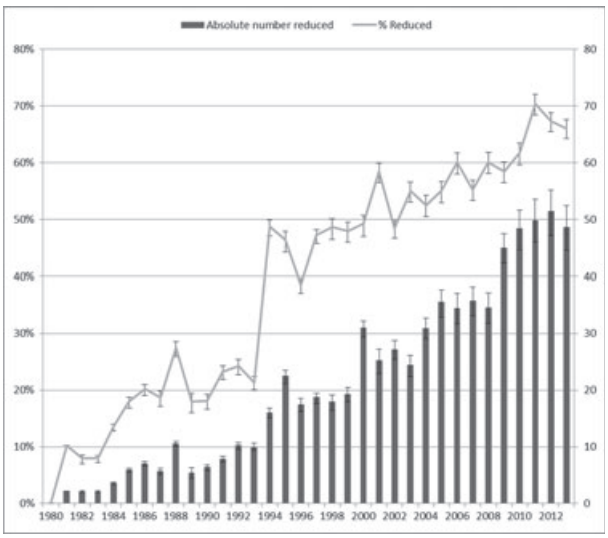
* Error bars denote the potential rate range with low and high estimates of fetal loss for pregnancies with Down syndrome for women aged 38.

Figure 3 Live-born Down syndrome per 1000 births and the modelled rate for live-born Down syndrome per 1000 births in the absence of prenatal diagnosis and termination

In absolute terms prenatal diagnosis and termination resulted in a reduction in the number of babies that would have been born with DS by 714 (657–762 with high and low fetal loss rates) or 45% (43%–47% with high and low fetal loss rates; Figure 4).

Results by era

The majority of Down syndrome cases identified and terminated (386) occurred from 2003 onwards, following the introduction of FTS, a period in which 73% of fetal Down syndrome were diagnosed prenatally, compared to 60% between 1994 and 2003 and 24% prior to 1994 when the use of MSS became widespread (Table 2). The rate of live-born DS per 1000 births was relatively steady in the pre screening period (1980–1993) and also in the post screening period to 2003 (Figure 3; Table 2), but the rate was lower by an estimated 0.19 from 1994 to 2003 ($p = 0.01$). From 2004 to 2013, the rate of live-born DS decreased significantly (−0.037/year, $p = 0.04$; Figure 3). There was no difference in the rate of increase in the percentage of DS terminations for DS pregnancies between 1980 and 1993 and the rate after 1994 (Figure 4; $p = 0.58$). However, there was a slight jump (0.16%) between 1993 and 1994 ($p < 0.00005$) corresponding to the introduction of MSS.



* Error bars denote the potential rate range with low and high estimates of fetal loss for pregnancies with Down syndrome for women aged 38.

Figure 4 The impact of termination on the number of live-born babies with Down syndrome (% reduction and absolute numbers)

The number of benefits paid by the AHIC via Medicare increased steadily between 1994 and 2013. While initially dominated by MSS the focus transitioned to first-trimester combined screening between 2002 and 2005 (Figure 5a). The total number of screening tests (MSS and FTS, as determined by the number of blood tests) increased by 135% over this time, while the number of live births (and therefore, we assume, pregnancies) increased by 33%. The total cost of screening and diagnostic tests including karyotyping to Medicare was $30.9 million (Figure 5b; $38.2 million when converted to 2013 Australian dollars).[19] However, the karyotype data are not specific to screening and diagnosis of Down syndrome and therefore must be interpreted with caution. The number of invasive prenatal diagnostic tests over this same-time period, as percentage of births, showed a steady downward trend, from 6.13% of all births in 1994 to 3.59% of all births in 2013 [data not shown].

DISCUSSION

Steadily increasing maternal age over the last 30 years, in the absence of prenatal testing and termination for fetal Down syndrome, would have resulted in an annual increase in the birth rate of Down syndrome, with a live-birth rate in 2013 estimated to be twice that of 1980. Rather, as a result of increasing prenatal diagnosis and subsequent termination, the live-birth rate decreased between the pre and post screening eras (<1993, >1993; $p = 0.001$). Overall prenatal diagnosis resulted in the births of around 45% fewer children with Down syndrome (701) than would have been expected over the 33-year period. However, because of the increase in births overall, the absolute number of children born with DS has remained relatively stable. In Australia, UK and Denmark, the uptake of Down syndrome screening is 56% to 84%, and the proportion of screen positive women who proceed to invasive diagnostic testing is >75%.[20–22] The rate of pregnancy termination following prenatal screening for Down syndrome in Canada, USA, The Netherlands, Scotland and Taiwan in the 1990s varied between 70% and 100%[23]; while in Europe, the overall rate of pregnancy termination for fetal anomalies was 83%.[24] The rates of screening, diagnostic testing and terminations of pregnancy in the current study are consistent with the data reported from other countries.

The increase in the percentage of fetal DS diagnosed prenatally is likely to be a result of improving prenatal screening tests as well as increasing uptake of testing among pregnant women. At the same time, invasive prenatal diagnostic tests as a percentage of live births declined. In the absence of MSS or FTS, this percentage –and the number of procedure related miscarriages– is likely to have increased because of advanced maternal age, with 20% of babies born to mothers over 35 years of age in 2013 compared with 12% in 1994 and 4.7% in 1980.[4]

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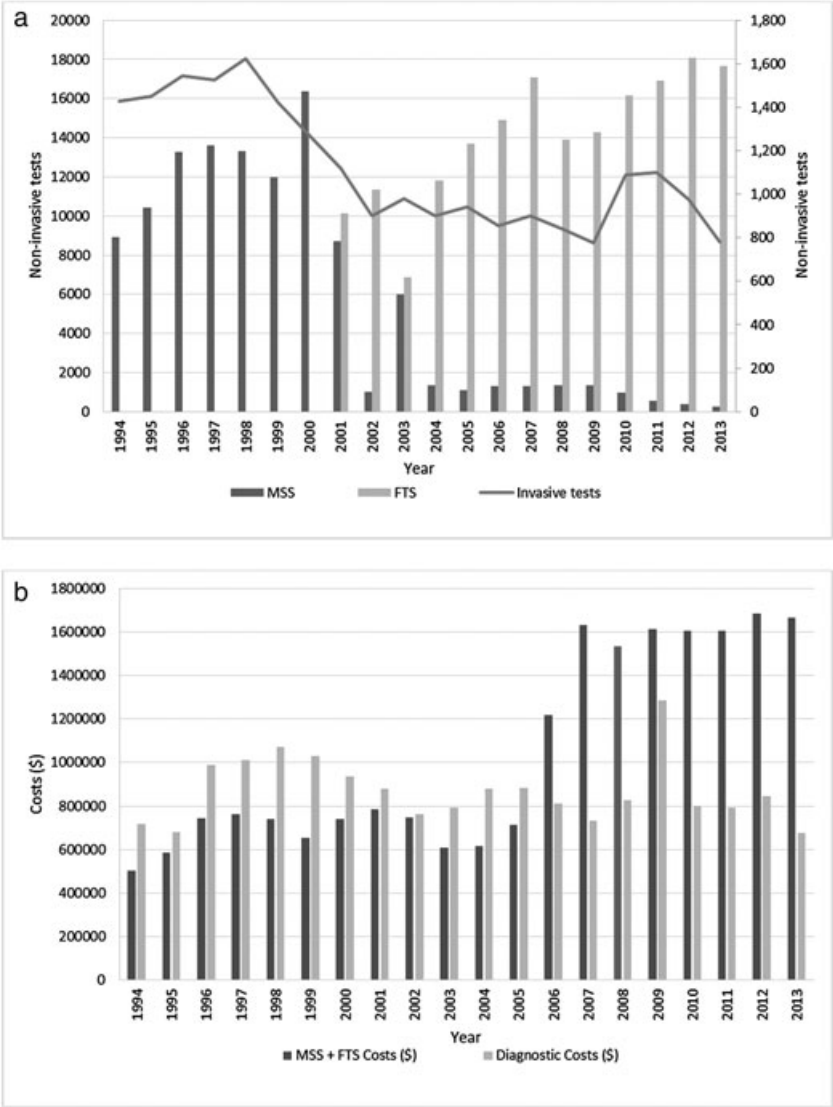

Figure 5 a) Numbers of non-invasive maternal serum screening and first trimester test and invasive tests performed (1994–2013); b) Medicare benefits paid (1994–2013) for screening and diagnostic tests including karyotyping (1994–2013)

The Medicare data demonstrate a clear pattern in the use of prenatal screening in Western Australia. MSS uptake rose steadily from 1994, with the introduction of this test having a significant impact on the percentage of terminated DS. MSS decreased from 2001, as FTS became more commonly used. Although available in Western Australia from around 2000, it was not until late 2004 that the ultrasound nuchal translucency measurement was officially funded by Medicare. We are unsure about the uptake of FTS during this transition time but expect that some women may have been self-funding the test and/or that other Medicare item numbers non-specific to FTS could have been used by providers during this time.

The commonly stated aim of prenatal screening is to provide information that will enable women and their partners to make autonomous reproductive choices. However, within the context of a public health prenatal screening programme, participants encounter two apparently contradictory messages: first, the screening programme's clinical effectiveness is determined by the proportion of affected cases detected, and secondly, the utility depends on the proportions of those who choose to continue or terminate an affected pregnancy. The recommendations of the European and American Societies of Human Genetics are especially pertinent in this context: Prenatal screening should inform the trade-offs between meaningful reproductive choices, the balance of benefits and burdens to the individuals, and the goals and values that are acceptable to society.[25]

Although we can quantify the impact of prenatal diagnosis and termination on rates of live-born Down syndrome, it is more difficult to analyse the impact of prenatal diagnosis on women and their families. The number of women who have been faced with a diagnosis of fetal DS and therefore a decision regarding the continuation of their pregnancy rose from 0 in 1980 to 75 in 2013. Overall, 1082 women were faced with this decision, and of these, 1006 chose to terminate. In two Dutch surveys of women who terminated their pregnancy following the diagnosis of a fetal anomaly, Korenromp *et al.* described the decision to terminate a wanted pregnancy as a 'profoundly difficult decision' and a 'major life event' with emotions

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encompassing grief for the 'chosen' loss of a child, relief and doubt arising from guilt about ending a life, partner disagreement and uncertainty about how DS would have manifested in their child,[20] as well as sustained pathological morbidity.[21] Assuming diagnosis occurred before 20 weeks and the option of termination was available, 76 of these 1082 women made the decision to carry their baby to term. For these women, the value of having this information before birth may have been the opportunity to resolve their grief before the birth of their child with DS.[22]

Our data have some limitations and aspects of these data must be interpreted with caution. The data clearly show an increase in the prevalence of fetal DS. While this, in the absence of other risk factors, can largely be attributed to the increase in maternal age, some of the rise is likely to be an artefact of prenatal diagnosis itself, as in the absence of prenatal diagnosis and termination cases of DS lost before 20 weeks would not have been identified. Another limitation is that the WARDA data do not include fetal DS cases diagnosed but spontaneously lost before 20 weeks. This may result in an underestimate of diagnosis and an over-estimate of the termination rate following prenatal diagnosis. It may also result in an over-estimate of the number of cases of fetal DS lost by term within our model of DS live-birth rates in the absence of prenatal testing, if most loss occurs by 20 weeks. Furthermore, while the Medicare data demonstrate the trend in prenatal testing, they only account for reimbursements for government-subsidised services and will not include services charged directly to women by private practitioners or the small proportion (<2%) of public inpatient services. We cannot be sure what percentage of screening and diagnosis occurs without Medicare rebate because the overall uptake of screening varies between 39% and 80% of pregnancies in different regions.[26] However, it is likely that data on 95% of pregnancies would have been captured.

CONCLUSION

Prenatal screening and diagnosis has reduced the birth prevalence of DS in the Western Australian community. Proportionately, fewer invasive diagnostic tests are being performed while a larger percentage of fetal DS is being diagnosed. Many women and their families have been faced with a diagnosis of fetal DS and decisions about the continuation of their pregnancy. With the introduction of another more accurate screening test, efforts to ensure informed choice for all women and information and support for women following a prenatal diagnosis of fetal DS must continue. The need for support and services for children with Down syndrome and their families remains.

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- There have been many advances in screening to assess the risk of fetal aneuploidy 39 over the last 30 years, with the most recent development being use of cell-free 40 DNA (non-invasive prenatal testing).

WHAT DOES THIS STUDY ADD?

- The availability of prenatal tests for fetal aneuploidy over the last 30 years has significantly reduced the live-birth prevalence of Down syndrome in Western Australia. This is despite of an increasing rate of fetal Down syndrome.
- Without prenatal diagnosis and termination, the rate of live-born infants with Down syndrome would have doubled between 1980 and 2013.

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APPENDIX 1

Table A1 **Median maternal age among terminations by year and gestation at time of termination**

Year	Age at TOP <16 weeks	Age at TOP >16 weeks
1980	NA	NA
1981	NA	39
1982	NA	39
1983	NA	39
1984	NA	39
1985	NA	37
1986	NA	40.5
1987	NA	39
1988	40	39
1989	38	40
1990	40	34.5
1991	38.5	38
1992	38	36
1993	36	39
1994	40	35
1995	NA	36
1996	NA	45
1997	40	37
1998	41	36
1999	38	38
2000	34.5	34
2001	34	36
2003	37.5	36
2004	35	37
2005	37	36
2006	37.5	36
2007	37	36
2008	36.5	36
2009	37	37
2010	37	36
2011	37	38
2012	37	36
2013	37	35

Table A2 **Fetal loss rates in pregnancies with fetal DS as reported by Savva *et al*[16]**

	Fetal loss rate (%)	
Maternal age at EDD (years)	CVS (<16 weeks) to term (95% CI)	Amniocentesis (>16 weeks) to term(95% CI)
25	23 (16–31)	19 (14–27)
26	24 (17–32)	20 (14–28)
27	24 (18–32)	20 (15–28)
28	25 (19–32)	21 (16–28)
29	26 (20–32)	21 (17–28)
30	27 (21–33)	22 (17–28)
31	28 (22–34)	23 (18–29)
32	29 (23–35)	23 (19–29)
33	30 (24–36)	24 (20–29)
34	31 (26–36)	24 (20–30)
35	32 (27–38)	25 (21–31)
36	33 (27–39)	26 (22–31)
37	34 (28–40)	26 (22–32)
38	35 (29–42)	27 (23–33)
39	36 (30–43)	28 (23–35)
40	38 (31–45)	29 (24–36)
41	39 (31–47)	30 (24–37)
42	40 (32–49)	30 (25–39)
43	41 (32–51)	31 (25–41)
44	43 (33–53)	32 (25–43)
45	44 (33–56)	33 (26–45)
Average	32 (27–38)	25 (21–30)

EDD, estimated due date; NA, not available.

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CHAPTER 3 PAPER 2

SOCIO-DEMOGRAPHIC DISPARITIES IN THE UPTAKE OF PRENATAL SCREENING AND DIAGNOSIS IN WESTERN AUSTRALIA

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Original Article

Socio-demographic disparities in the uptake of prenatal screening and diagnosis in Western Australia

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Introduction: Since the early 1980s, prenatal screening using ultrasound and biochemical markers has been used to refine the risk of Down syndrome and other fetal anomalies prior to considering fetal karyotyping. The performance of prenatal screening is subject to ongoing monitoring in Western Australia. The collection of these data can also assist in the identification of any potential inequities of access to prenatal screening within the state-wide programme.
Methods: Prenatal screening data (2005–2006) were collected from accredited ultrasound and pathology laboratories in Western Australia. Screening data were linked to diagnostic and pregnancy outcome data. Performance characteristics of screening and uptake by socio-demographic characteristics were analysed.
Results: Complete screening data were collected for 35,142 of the estimated 38,081 women screened during 2005 and 2006. There were 59,999 births related to this screening period. The lowest uptake of screening was among women who were Aboriginal (14.9%), living in remote areas (38.0%), under the age of 25 (40.2%), in the lowest quintile of the SEIFA index (41.6%) and with three or more children (48.4%). Logistic regression analysis showed all socio-demographic factors to be strongly associated with screening behaviour, with adjustment for ethnicity, socio-economic status, age, parity and area of residence.
Discussion: Our results have important implications for the delivery of prenatal screening services in Western Australia. While the screening programme meets international and national performance standards, the disparities in screening uptake suggest inequity in access to services, particularly for Aboriginal, remote and socio-economically disadvantaged women.

Key words: aneuploidy, prenatal diagnosis, screening, socio-demographics.

Introduction

Over 100 years ago, an association was reported between advancing maternal age and the chance of having a fetus with Down syndrome (trisomy 21).[1] Following the development of fetal karyotyping with amniocentesis and chorionic villus sampling (CVS) in the 1960s, it became standard practice to offer diagnostic testing on the basis of maternal age–related risk. However, diagnostic intervention based on maternal age alone detected only 30% of Down syndrome pregnancies (in

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1984), with 70% of cases born to the 95% of women under 35 years of age.[2] Since the early 1980s, screening programmes involving ultrasound and biochemical markers have been used to refine the risk of Down syndrome and other fetal anomalies prior to considering fetal karyotyping,[2,3] and offering initial multiparameter screening to women of all ages is now the established standard of care.[4]

Aneuploidy screening may be undertaken in either the first or second trimester. The former involves a combination of ultrasound and maternal serum testing at 10–13 weeks gestation (first-trimester combined screening; first-trimester screening, FTS), and the latter maternal serum testing alone, at 15–18 weeks (second-trimester screening; maternal serum screening, MSS).[5] In Western Australia, FTS is available in public and private ultrasound practices throughout the metropolitan area and in most large regional centres. There is a Medicare rebate for the cost of the maternal serum blood tests for both FTS and MSS and also for the ultrasound component of FTS. Blood collection for MSS occurs throughout the state.

Professional guidelines recommend the ongoing monitoring of prenatal screening programmes, allowing benchmarking of programme performance within Australia and internationally.[6] The performance characteristics of FTS in Western Australia have previously been evaluated through the linkage of data from screening providers with pregnancy outcome information from Department of Health datasets, Birth Defects Registry, the Midwives Notification System, the WA Mortality Register and the WA Morbidity Database.[4,5,7] The current data linkage study, part of the ongoing monitoring of screening performance, also incorporated second-trimester screening and diagnostic data.

In addition to measuring performance characteristics, the collection of screening data can also assist in the identification of any potential inequities of access to prenatal screening within the state-wide screening programme.[8] While in principle, prenatal screening is available for all women, socio-demographic factors are known to influence the use of health services, including prenatal testing.[9–11] Our large cohort of pregnancies provides an ideal opportunity to investigate screening uptake in Western Australia by area of residence, age, parity, ethnicity and socio-economic status. Western Australia has a population of 2.24 million, the majority of whom live in metropolitan areas (72%) or large regional centres (13%).[12] The provision of health services is challenging by virtue of the vast size of the state, covering an area of 2.5 million square km (half the size of Western Europe),[13] a multicultural population and longstanding difficulties in meeting the health needs of the Aboriginal population.[14] The aim of this study was to investigate socio-demographic characteristics in the uptake of prenatal aneuploidy screening in Western Australia to identify potential barriers to screening access.

Methods

Data were collected from each of the accredited ultrasound and pathology laboratories providing first- and second-trimester screening services in Western Australia during 2005 and 2006. FTS data included fetal nuchal translucency, free beta-hCG and PAPP-A, and risk estimates. Second-trimester screening data included biochemical measurements of alpha-fetoprotein, free beta-hCG and unconjugated estriol, and risk estimates. Diagnostic data were collected from cytogenetic laboratories. Overall, screening and pregnancy outcome data were available on 35,142 women, 92.3% of those who undertook screening tests.

All ultrasound providers contributed data to the project; however, data were not available for those providers who had ceased operating prior to the time of data collection. First-trimester biochemistry data for women screened by these providers during this time period (n = 1477) were made available from the two main pathology laboratories. Additionally, biochemistry data were incomplete for 483 FTS records. These incomplete data did not provide a combined risk estimate. Second-trimester MSS data were not available from two of four providers owing to concerns about privacy issues but the total number of cases screened by these two providers during the study period (n = 981) were made available.

Screening data were linked to Western Australian diagnostic data, hospital morbidity and mortality data (2005–2007), midwives notification data (2005–2007), and the Birth Defects Registry data (2005–April 2009) through the Department of Health Western Australia's Data Linkage Branch.[15] Defects reported to the Birth Defects Registry include structural or functional abnormalities present at conception or before the end of the pregnancy and diagnosed before the age of 6 years.[16] Birth defects data were included to April 2009, at that time the children from the screening dataset would have been aged between 22 and 46 months. As birth defects can be reported to 6 years of age, more children may still be diagnosed. However, 89% of birth defects are diagnosed by 1 year of age.[17] The Birth Defects Registry has been shown to have a high level of case ascertainment and includes terminations of pregnancy as a result of fetal abnormality.[18] Data on births that were not screened during the same time period as the screened cohort were also obtained from the Midwives Notification Database.

Records removed prior to analysis included multiple screens for the same pregnancy (n = 64) and those for multiple births (n = 1270). The data were analysed to determine the uptake, outcomes and performance of first- and second-trimester screening and diagnostic testing, socio-demographic characteristics of screened and unscreened women, and uptake of diagnostic testing in different socio-demographic groups. Midwives Notification Data were used in the calculation of uptake of screening. This was restricted to only those pregnancies that reached 20 weeks of gestation.

Logistic regression analysis was performed to identify differences between the screened and nonscreened population in terms of age, parity, ethnicity, socio-economic status and area of residence. Ethnic groups were Caucasian, Aboriginal or "other", which included Indian, Asian, Polynesian, Maori and African/Negroid. Socio-economic

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status using the Australian Bureau of Statistics (ABS) 2006 Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage[19] was assigned based on the mother's census collection district. Each census collection district in Australia has a SEIFA score, which represents the level of disadvantage experienced in comparison with other areas. This SEIFA score is derived from Census data on income, education, employment and dwellings without a motor vehicle.[19] Each record was assigned to a SEIFA quintile based on the SEIFA score, with quintiles ranging from most disadvantaged to least disadvantaged. For the purpose of the logistic regression, the top two quintiles (those representing the least disadvantaged) were combined because of small numbers of people in these quintiles living in remote areas or whose ethnic status was Aboriginal. Area of residence was classified using the 2006 Accessibility Remote Index of Australia (ARIA) Remoteness Area Classification, a measure based on road accessibility to services.[20] This is made possible through the geo-coding of the midwives database.[15] Records were assigned to three categories by collapsing the five categories in the Remoteness Structure of the 2001 Australian Standard Geographical Classification (ASGC) into metro, regional and remote.

The study received ethics approval from the King Edward Memorial Hospital and the Department of Health Western Australia (formerly CHIC) Health Research Ethics Committees.

Results

The quality and performance of FTS and MSS are shown in Table 1. FTS accounted for 90.4% of prenatal screening undertaken in WA. Using a risk cut-off of 1 in 300, we found screen-positive rates of 3.6% and 5.1% and false-positive rates of 3.4% and 5.1% for FTS and MSS, respectively. FTS had a sensitivity of 80.9%, failing to identify 18 cases of Down syndrome among 94, while MSS failed to identify one case of three. Overall at a false-positive rate of 5%, the detection rates were 86% and 66% for FTS and MSS, respectively. The positive and negative predictive values were 6.5 and 1 for FTS and 1.5 and 1 for MSS.

Complete screening data were collected for 35,142 of the estimated 38 083 women screened. Based on the number of births for the period matching the screening period (n = 59 999), it was estimated that 58% of pregnant women undertook either first- or second-trimester screening (Table 2). This estimate includes the 981 screened women for whom we do not have socio-demographic data. Screening uptake, including data with socio-demographic characteristics, is shown in Tables 2 and 3. The groups with the lowest uptake of screening were Aboriginal women (14.9% screened), women living in remote areas (38.0%), those under the age of 25 (40.2%), those in the lowest

Table 1 Quality, performance and outcomes of first-trimester screening (FTS) and second-trimester screening (MSS)

	FTS	MSS
Women screened	34 438	3645
Number of complete screening records†	32 478	2664
Detection rate for DS, %	80.9	67
Screen-positive rate, %	3.6	5.1
False-positive rate, %	3.4	5.1
Positive predictive value, %	6.5	1.5
Uptake of diagnostic testing in increased-risk category, %	75.3	56.9
Outcome of diagnostic testing in increased-risk category, % DS	7.8	2.6
Number of cases with DS identified as increased risk	76	2
Number of cases with DS identified as low risk	18	1
Total number of cases with DS	94	3

DS, Down syndrome.
†Records with a complete risk score (for FTS, this is a combined risk).

Table 2 Demographic characteristics of screened and unscreened pregnancies†

	Screened				
	FTS	MSS	Total	Unscreened	All women
Number of women	31 508	2446‡	33 954‡	26 045	59 999
Maternal age [median years (range)]	31 (14–48)	28 (15–47)	31 (14–48)	28 (12–49)	30 (12–49)
Aged 35 or over (%)	24.3	12.5	23.5	16.2	20.3
Outside the Perth metropolitan area (%)§	26.3	51.5	27.4	32.3	29.9
Aboriginal (%)	1.1	8.7	1.6	12.3	6.3
SES					
Most disadvantaged quintile (%)§	13.1	33.1	14.5	27.6	20.2
Least disadvantaged quintile (%)§	24.1	8.0	22.3	16.1	20.0

DS, Down syndrome; SES, socio-economic status.
†Only includes data on births reported to the Midwives Notification System. This does not include pregnancies that did not reach 20 weeks of gestation.
‡Does not include 981 missing MSS records. Screening uptake calculation (339 54 + 981)/59 999.
§Data on area of residence/SES missing for 1499 records.

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Table 3 Percentage of subgroup screened (FTS and MSS) and adjusted odds ratios†

	Total births (59 999)	Subgroup screened (%)	Odds ratio $P < 0.0001$	95% CI
Age				
<25 years	12 900	40.2	1.0	
25–29 years	15 914	56.9	1.81	1.72, 1.91
30–34 years	19 003	66.8	2.69	2.55, 2.83
35 years+	12 182	69.1	3.24	3.05, 3.44
Area of residence‡				
Major city	40 999	61.1	1.0	
Regional	12 530	60.4	1.15	1.11, 1.21
Remote	4971	38.0	0.61	0.57, 0.66
Socio-economic status‡				
Advantaged & most advantaged	23 614	68.1	1.0	
Average	10 808	61.4	0.85	0.81, 0.89
Disadvantaged	12 282	55.9	0.77	0.73, 0.81
Extreme disadvantaged	11 796	41.6	0.59	0.56, 0.62
Ethnicity				
Caucasian	49 464	63.7	1.0	
Aboriginal	3771	14.9	0.22	0.20, 0.25
Other	6764	48.1	0.54	0.51, 0.57
Indian	515	59.0	–	–
Asian	3250	55.7	–	–
Polynesian	57	42.1	–	–
Maori	506	28.5	–	–
African/Negroid	620	26.9	–	–
All others	1816	44.1	–	–
Parity				
First child	18 206	62.0	1.0	
1 previous child	18 331	62.7	0.87	0.83, 0.91
2 previous children	11 272	59.1	0.69	0.66, 0.73
3+ previous children	12 190	48.4	0.46	0.43, 0.48

†Based on births reported to the Midwives Notification System that does not include pregnancies that did not reach 20 weeks of gestation. Estimates of missing screening data are not included.
‡Data relating to area of residence and therefore socio-economic status were missing for 1499 births.

quintile of the SEIFA index (41.6%) and women with three of more children (48.4%). Screening uptake was highest in women over the age of 35 (69.1%), for those in the two highest SEIFA quintiles (69.1%) and for Caucasian women (63.7%).

Seventy-three per cent of women with increased-risk screening results had subsequent diagnostic testing. Uptake varied from 60.3% in ethnic minority groups to 79.4% in women aged 25–29 years (Table 4). As with screening, diagnostic test uptake was highest in women in the top SEIFA quintile (78.6%), in Caucasian women (74.9%) and lowest in women under 25 (61.6%). There was little variation in uptake by area of residence (66.7%–76.0%) or between Caucasian (74.9%) and Aboriginal (70.5%) women. No logistic regression was undertaken for diagnostic test uptake because of the small sample size of subcategories.

Logistic regression analysis showed all socio-demographic factors to be strongly associated with screening behaviour (Table 3). All variables remained significant with adjustment for ethnicity, socio-economic status, age, parity and area of residence. Screening was significantly lower for Aboriginal women (OR = 0.22), and this was compounded for those in remote areas and with low socio-economic status ($P < 0.0001$). Women living in regional areas were more likely to be screened than those living in the Perth metropolitan area (OR = 1.15), while those in remote areas were least likely to undertake screening (OR = 0.61). Women under 25 years of age were least likely to undertake screening, as were women with three or more children compared to those who had not previously given birth (OR = 0.46). The likelihood of undertaking screening increased significantly as socio-economic status increased ($P = 0.0096$) (Table 3).

Discussion

The performance characteristics of the WA prenatal screening programme are consistent with previous evaluations and remain comparable with international and national standards.[5,21] Despite this achievement, we have clearly shown that there are significant socio-demographic disparities in the uptake of prenatal screening across Western

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Table 4 Percentage of those at high risk having diagnostic testing by socio-demographic subgroups

	Total increased-risk screens (1137)	Subgroup diagnostic testing (%)
Age		
<25 years	73	61.6
25–29 years	126	79.4
30–34 years	310	78.4
35 years+	628	70.5
Area of residence†		
Major city	586	76.0
Regional	261	66.7
Remote	70	71.4
Socio-economic status†		
Advantaged & most advantaged	504	78.6
Average	235	72.3
Disadvantaged	191	67.0
Extreme disadvantaged	172	67.4
Ethnicity		
Caucasian	979	74.9
Aboriginal	17	70.5
Other	141	60.3

†Data relating to area of residence and therefore socio-economic status were missing for 35 births.

Australia by ethnicity, socio-economic status, area of residence, age and parity.

Our screening uptake results support the findings of several Australian and international studies.[8,11,22–31] A previous Australian study on the uptake of prenatal diagnostic testing in the absence of a screening programme reported lower uptake in rural women, women with three or more children and among Asian women. Higher uptake was observed for those women who gave birth in private hospitals, a surrogate indicator of higher socio-economic status.[26] Similar socio-economic disparities have also been reported in the UK.[22,25] In our study, Aboriginal Australians and other ethnic minority groups were also less likely to access screening compared to Caucasian Australians. Disparity in prenatal testing uptake for different ethnic groups has also been shown in the UK[23,25] and USA.[29] Additionally, lower uptake rates for other screening programs, such as breast and cervical cancer have previously been reported for Aboriginal Australians and those of lower socio-economic status.[32,33] Our results are consistent with the findings of a study of population-based trends in Queensland, Australia, which showed a significant fall in Down syndrome birth rates between 2000 and 2004 for metropolitan women and those receiving care from a private obstetrician. Similar trends were not seen for mothers in rural areas or those receiving prenatal care in a public hospital.[34]

The uptake of diagnostic testing by women with an increased risk screening result (60–79%) showed less variation than uptake of screening (14–69%) when analysed by socio-demographic criteria. The variation in diagnostic test uptake was smallest for area of residence (metropolitan 76%, regional 67%, remote 71%), despite diagnostic testing only being available in metropolitan areas. It may be that the offer and uptake of screening is influenced by the perceived accessibility of diagnostic testing or that women who entered the screening pathway were provided with continuity of care. Our results differed from those of Muggli *et al.*[11] who described significantly less prenatal diagnostic testing in women identified as high risk through screening in some of Victoria's most remote areas. Interpretation of our results is limited as we have not adjusted for socio-demographic variables.

In principle, prenatal testing for Down syndrome is a choice, rather than a routine test, so we cannot determine from our data if disparities in screening uptake reflect differences in women's attitudes towards prenatal testing, the perceived value of testing, barriers to undertaking screening or a combination of these. However, this has been extensively explored in other studies.[25,28,35,36] Dormandy *et al.*[25] found maternal age to be the only significant indicator of attitude to prenatal screening in a diverse group of women in the UK, and separate studies of Muslim and Vietnamese Australians suggested positive attitudes towards prenatal screening and testing in these groups.[35,36] In contrast, disparate prenatal testing uptake rates in a group of ethnically and socio-economically diverse women in the USA could be explained by attitudinal factors and the perceived risk and value of information.[28] We are unaware of any published studies regarding the attitudes of Aboriginal Australians towards prenatal screening. The lower rates of screening in women with more children in our study could reflect attitudinal differences, perhaps associated with lower perceived risk or higher acceptance of the possibility of having an affected child.[23,26]

With the exception of associations with maternal age and parity, attitudes towards prenatal testing may not vary greatly by socio-demographic criteria. As with other health services, it may be that barriers, rather than attitudes, to screening explain more of the variation in screening uptake. Barriers to prenatal screening include not being offered prenatal screening by the attendant health professional, late initiation of prenatal care resulting in missed opportunities for screening, access, suboptimal communication and poor understanding of screening tests leading to lack of informed choice. These barriers are inter-related.

Internationally, there are no consistent conclusions about disparities in the offer of prenatal testing based on age, ethnicity and socio-economic status.[27,31] Where screening is not offered, possible reasons include ethnic stereotyping by health professionals as to cultural or religious beliefs, and assumptions about intentions to terminate.[8,31] There is some anecdotal evidence that, in Australia, health professionals have a belief that Australian Aboriginal women do not want screening, and therefore they are not offered screening.[37] Additionally, it may be that for some subgroups, such as Aboriginal Australians, who are more likely to present with risk factors in pregnancy such as diabetes, smoking and inadequate nutrition, prenatal screening may not be

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considered as a high priority in prenatal health care and as a result may not be offered.[14]

Failure to offer screening may also be related to health professionals feeling less able to ensure informed choice for women with lower levels of education, or language barriers. Knowledge of screening and levels of informed choice have been shown to be higher in white, socio-economically advantaged women.[23,25,27] While greater screening knowledge is also associated with a higher uptake of screening,[23] it has been suggested that this may reflect a greater level of interest and therefore information-seeking behaviour.[24,38]

Prenatal care and referral for screening must be undertaken within 10–13 weeks gestation for FTS and 15–18 weeks for MSS. Socio-demographic factors have been shown to be associated with late initiation of prenatal care within Australia and internationally.[31] In Australia, Aboriginal women are more likely than Caucasian women to initiate prenatal care later in pregnancy and attend fewer prenatal care appointments[37] In the UK, Rowe et al. found that Black women (Black African, Caribbean or Black other) were six times more likely than Caucasian women to book late and women born outside the UK were most likely to attend for prenatal care late in pregnancy.[31] As prenatal care is accepted as being effective in reducing adverse outcomes for women and babies,[39] it is acknowledged that the implications of late initiation of prenatal care go beyond lack of informed choice for prenatal screening.

Situational, psychosocial and system-related barriers may prevent timely access to screening and/or prenatal care in general.[40] Situational barriers that often reflect socio-economic disadvantage include access to transport, child-care and having time away from work.[24,30,31,40] Psychosocial barriers include being unaware of the pregnancy, lack of knowledge of available services, negative attitudes to health professionals, depression and personal or family problems.[40] System-related barriers include cost, physical access to providers, discrimination and cultural and language barriers.[31,40,41] In Western Australia, FTS providers are generally located in high socio-economic areas and there are few in regional and remote areas. Where FTS is not available MSS should be offered as an alternative. However, in some remote areas, women may still need to travel long distances to access this service. Compared to FTS, the lower sensitivity of MSS may also be interpreted as an inferior screening test. This view would be unfortunate as it would discriminate against those who only have access to MSS because of remoteness or because they present later for antenatal care. In addition to the issue of remoteness, many of the aforementioned barriers are apparent within Australian Aboriginal communities and may explain some of the variation in screening uptake.[14,42]

Our study was limited by the incomplete ascertainment of all screening data for the specified time period. However, this represented only 6% of the FTS data and is not expected to have compromised our calculation of screening performance. The MSS data were 75% complete; however, the small numbers of Down syndrome cases ($n = 3$) raises some doubt about the reliability of these results. It is unlikely that those groups found to have lower odds of screening in our study (disadvantaged, remote, Aboriginal) would have been over-represented within the group of women for whom MSS data were missing. A further limitation is that we only have socio-demographic data on women whose pregnancies reached 20 weeks of gestation. Screened pregnancies may have been over-represented in pregnancies not reaching 20 weeks of gestation as they are more likely to undertake diagnostic testing with a risk of miscarriage and choose to terminate a pregnancy based on a diagnosis of a fetal anomaly.

Conclusion

Our results have important implications for the delivery of prenatal screening services in Western Australia. While the screening programme meets international and national standards in terms of performance, the disparities in screening uptake suggest inequity in access to services, particularly for Aboriginal, remote and socio-economically disadvantaged women. To ensure equity and autonomy in reproductive decision making,[11] barriers to informed choice in accessing screening need to be addressed. While we can hypothesise the reasons behind the lower uptake of screening in certain subgroups of the population, further research is essential to determine the reasons and to identify potential solutions that will improve access and equity. Additionally, disparities in prenatal fetal anomaly screening must be considered within the broader context of the provision of all prenatal care.

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CHAPTER 4 PAPER 3

FIRST TRIMESTER SCREENING CUT-OFFS FOR NON-INVASIVE PRENATAL TESTING AS A CONTINGENT SCREEN: BALANCING DETECTION AND SCREEN-POSITIVE RATES FOR TRISOMY 21

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Original Article

First trimester screening cut-offs for noninvasive prenatal testing as a contingent screen: Balancing detection and screen-positive rates for trisomy 21

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Objective: To provide data on how screen-positive and detection rates of first trimester prenatal screening for fetal Down syndrome vary with changes in the risk cut-off and maternal age to inform contingency criteria for publicly funded noninvasive prenatal testing.

Materials and Methods: First trimester screening and diagnostic data were collected for all women attending for first trimester fetal aneuploidy screening in Western Australia between 2005 and 2009. Prenatal screening and diagnostic data were linked to pregnancy outcomes, including data from the Midwives' Notification System and the Western Australian Registry of Developmental Anomalies. The prevalence of Down syndrome and performance of screening by risk cut-off and/or for women >35 years were analysed.

Results: The current screening risk cut-off of 1:300 has screen-positive and detection rates of 3.5% and 82%. The screen-positive rate increases by 0.7–0.8% for each 100 point change in risk, up to 19.2% at 1:2500 (96% detection rate). Including all women >35 years as screen positive would increase the screen-positive rate and detection rates to 30.2% and 97.2%.

Conclusion: Variation in screening risk cut-off and the use of maternal age to assess eligibility for noninvasive testing could significantly impact the demand for, and cost of, the test. A contingent first trimester screening approach for risk assessment is superior to the use of a combination of screening and maternal age alone. These data will inform decisions regarding the criteria used to determine eligibility for publicly funded noninvasive prenatal testing.

Key words: first trimester screening, noninvasive prenatal testing, policy, prenatal screening.

Introduction

In 2003, the Australian public health system began funding first trimester screening (FTS), a test undertaken between 11 and 14 weeks of pregnancy using combined ultrasound and biochemistry markers to assess the risk of Down syndrome (DS) and trisomy 13 (T13) and 18 (T18).[1] The test provided an earlier option to maternal serum screening (14–18 weeks), and a more accurate risk assessment than that based on maternal age alone, with the potential to reduce the number of invasive diagnostic tests – and associated procedure-related miscarriage – and improve the detection of DS during pregnancy.[2] Until recently, this was the best option for screening available, with an 86% detection rate at a 5% false-positive rate in Western Australia.[3]

However, noninvasive prenatal testing (NIPT) now allows for the assessment of cell-free fetal DNA circulating within maternal blood as early as 10-week gestation to provide a risk of DS with a sensitivity and specificity of 98% to >99%.[4,5] In late 2012, this screening test became available privately in Australia as a user-pays option. The cost of the test has dropped significantly since this time, from $1350 to as low as $420 (as at February 2015), and is rapidly being adopted by Australian women. Just how NIPT should be integrated into a publicly funded prenatal screening program is uncertain.[5–8] Despite the superior performance of NIPT, and emerging evidence of high performance in both high- and low-risk pregnancies,[9] it is not anticipated that it will replace FTS as a universal screening test, at least in the short- to mid-term, due to

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the substantial cost and the continued value of first trimester ultrasound for determination of viability, accurate dating and the identification of structural anomalies[10] and/or multifetal pregnancies.[5] Rather, in a publicly funded model, NIPT has been proposed as a screen for high-risk women based on advanced maternal age (35 years or older (AMA)) alone and/or as a second tier screen with access contingent upon the result of FTS.[5–8]

In addition to the high detection and low false-positive rates of NIPT, the safety of the test (using only a maternal blood sample) provides the opportunity to increase the detection of fetal DS (using a more sensitive FTS risk cut-off) without increasing the uptake of invasive diagnostic procedures and exposure to the risk of procedure-related miscarriage. For women with high-risk pregnancies, the choice to have an invasive diagnostic test to confirm or exclude DS or other chromosomal abnormality must be balanced against the risk of procedure-related miscarriage. When FTS was introduced to identify highest risk pregnancies, a risk cut-off of 1 in 300 at the time of screening provided the balance between the identification rate of fetal DS and the procedure-related miscarriage risk of an invasive diagnostic procedure (0.6–1.0%).[11] In a screening model incorporating NIPT, which has a substantially lower miscarriage risk, it is timely to reassess the benefits of adjusting the risk cut-off. Changing the criteria for a screen-positive FTS result by lowering the FTS risk cut-off will increase the detection rate (DR) of fetal DS. Consequently, there will also be an increase in the number of women offered further testing (screen-positive rate (SPR)) and therefore cost.

With publically funded universal screening being cost prohibitive, how do we decide which pregnancies should be eligible for funded NIPT? This decision will have to balance equitable access and higher detection with cost. Published Australian economic evaluations of NIPT have reported results for universal screening, contingent screening using the current FTS risk cut-off (1:300) and/or screening based on maternal age to determine eligibility, but have not considered how variation in the FTS risk cut-off impacts outcomes.[7,12] This study uses a cohort of screened pregnancies to demonstrate how variation in the criteria used to determine eligibility for publicly funded NIPT is likely to impact DRs and SPRs, and the potential absolute cost of NIPT. In addition to looking at variation in the FTS risk cut-off, we have also considered an approach in which all women of AMA would be eligible for NIPT. Although it is well established that FTS is superior to the use of AMA for the detection of fetal DS, it is valuable to include this approach in our analysis given the evidence that invasive diagnostic testing has still been offered and undertaken on the indication of AMA, despite the availability of FTS[13] and recent discussion of the use of AMA as an indicator for NIPT.[7] These data will inform further health economic modelling of NIPT screening in Australia.

Materials and Methods

Between 2005 and 2009, 115 648 live births and stillbirths of 20-week gestation or more were registered in Western Australia (WA).[14] We collected FTS data for all women who underwent screening during this period from FMF-accredited ultrasound practices in WA (n = 90 352); data were not available for any providers who had ceased operating prior to the time of collection. The FTS risk algorithm (Astraia FMF software, FMF Foundation, UK) incorporated the biochemical biomarkers, PAPP-A, free βhCG and nuchal translucency measurement. Screening data were linked to prenatal cytogenetic karyotyping data collected from the two main pathology laboratories in WA and pregnancy outcome data. Outcome data included hospital morbidity and mortality, the Midwives Notification System and the WA Register of Developmental Anomalies (WARDA). Defects reported to WARDA include 'a structural or functional anomaly, which is present at conception or occurs before the end of pregnancy and is diagnosed during pregnancy, or after stillbirth or termination of pregnancy, or after live birth'.[14] Linkage was enabled through the Department of Health Western Australia's Data Linkage Branch.[15] The data collection and linkage was done over two periods, as part of two separate evaluation phases, 2005–2006 and 2007–2009. The 2005–2006 data collection and analysis has been previously described and is consistent with the methodology used for the 2007–2009 data.[3]

The final data set of singleton pregnancies excludes incomplete screening tests (missing at least one of the following: maternal bloods (PAPP-A, free βhCG), nuchal translucency, maternal age, adjusted risk) and pregnancies for which data on the presence of chromosomal abnormalities were unknown (ie no midwives record, birth defect record or diagnostic test record). Where a screened pregnancy had more than one diagnostic test, the second result was retained. The population characteristics describing maternal age and risk parameters are summarised in Table 1.

The data were analysed to determine the characteristics of the screened cohort, the prevalence of fetal DS, and the screen-positive and detection rates of FTS by risk cut-off. We present these data for:

1 The use of FTS alone, and;
2 An approach in which all women of advanced maternal age are considered to be screen positive in addition to all women <35 years with a screen-positive FTS result (defined as: FTS/AMA). Age was determined using the age variable recorded in the FTS data which takes into account the use of IVF and donor eggs/embryos.

Uptake rates of diagnostic testing by FTS risk cut-off are also presented. Where the approach is not specified (ie FTS/AMA), the data reported are for FTS only.

The study received ethics approval from the King Edward Memorial Hospital, Curtin University and the Department of Health Western Australia (formerly CHIC)

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Table 1 Characteristics of the FTS screened population presented by maternal age – median (IQR)

	Age <35	Age 35+	Total	Lost to follow-up
N	65 078	18 314	83 392	2452
Age distribution (years)	29 (26–32)	37 (35–38)	30 (27–34)	30 (26–34)
Risk result, 1 in *n*	11 024 (6371–16 528)	2508 (1191–3845)	8327 (3410–14 918)	8043 (3158–14 767)
CRL (mm)	63 (58–69)	64 (59–69)	63 (58–69)	63 (57–68)
NT (mm)	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.5 (1.3–1.8)
PAPP-A (MoM)	1.04 (0.7–1.5)	1.0 (0.7–1.5)	1.0 (0.7–1.5)	1.0 (0.7–1.4)
Free βhCG (MoM)	0.96 (0.6–1.4)	0.97 (0.7–1.4)	0.96 (0.6–1.4)	0.95 (0.6–1.5)

CRL, crown rump length; FTS, first trimester screening; NT, nuchal translucency measurement.

Health Research Ethics Committees, which exempted the study from requiring individual patient consent.

Results

Ninety five per cent (85 844) of the 90 352 singleton screens had a complete screening record, with biochemistry, nuchal translucency, maternal age and a combined risk result. Of these, 97% (83 392) had follow-up data in the form of midwives data, birth defect data and/or diagnostic test data (Table 2).

The prevalence of fetal DS in this cohort was 1 in 334, the majority (155/250) of which occurred in the 22% of pregnancies of AMA (Table 3). The screen-positive, detection and false-positive rates (FPR) for the current FTS risk cut-off of 1:300 were 3.5%, 82% and 3.2%, respectively. At a 5% FPR, the DR was 88% (risk cut-off 1:531). The positive and negative predictive values (PPV and NPV) were 7.1% and 99.9%. In this cohort in the absence of FTS, that is using only AMA to identify high-risk pregnancies, 22% of pregnancies would be considered screen positive with a detection rate of 62% (Fig. 1).

Screen-positive and detection rates for the range of risk cut-offs from 1:2 to 1:2500 are shown in Figure 1. The figure also shows the screen-positive and detection rates for the alternate FTS/AMA approach.

According to the FTS-only model, the SPR increased from 3.5% to 19.2% between the risks of 1:300 and 1:2500, while the DR increased from 82% to 96%. In the FTS/AMA approach, the SPR increased from 23.6% to 30.2%, with AMA contributing the majority (22%) of screen-positive pregnancies across all risk cut-offs. At a SPR of 23.6%, the DR of FTS/AMA is 90.4%, considerably lower than the DR of 96.8% at the same SPR using FTS only. The FTS SPR of 23.6% is equivalent to a risk cut-off of 1:3182 (data not shown).

The SPR for FTS rises approximately linearly (Fig. 1), with an increase of 0.7–0.8%, or about 600 pregnancies for every 100 point change in risk cut-off below 1:300 (Table 3), with the number of screen-positive women doubling from 3.5% at the 1 in 300 risk cut-off to 7% at 1 in 762. The majority (67%) of fetal DS cases occur in pregnancies with a risk of >1:50, with a further 15% between 1:50 and 1:300. Another 14% of cases occur between a risk of 1:300 and 1:2500. As 22% of the cohort is of advanced AMA, in the FTS/AMA approach, most screen-positive cases are identified immediately, with an average 0.3–0.4% increase in the SPR for each 100 point change in the risk cut-off. The NPVs at a risk cut-off ranging from 1:300 to 1:2500 are 99.94% to 99.98% and 99.96% to 99.99% for FTS and FTS/AMA, respectively (Fig. 2). The PPVs range from 7.09% to 1.49% and 1.15% to 0.96% (Fig. 2) over the same risk categories. The total potential cost of NIPT and variation by fee assuming 100% uptake of NIPT in eligible women is shown for the FTS-only approach in Table 4. This table does not include those screened women who were lost to follow-up. The uptake of invasive diagnostic testing (amniocentesis or chorionic villus sampling) among women within different risk brackets is shown in Figure 3.

Of the women who had a risk <1:300, 1.9% had an invasive diagnostic test.

Discussion

In our cohort of screened pregnancies in Western Australia, FTS had a DR of 82% at a 3.2% FPR. At a 5% FPR, the DR would be 88%, within the 76–91% range reported within the literature.[16–20] Variation in the FTS risk cut-off used and the use of AMA alone to assess eligibility for publicly funded NIPT could significantly impact the potential demand for, and cost of, this test.

Table 2 Outcomes for first trimester screening (FTS) screened pregnancies presented by maternal age

	Age <35, *n* (%)	Age 35+, *n* (%)	Total, *n* (%)
Screens	65 078 (78)	18 314 (22)	83 392
Screen-positive (risk ≥1:300)	1394 (2.1)	1506 (8.2)	2900 (3.5)
Down syndrome	95 (38)	155 (62)	250 (205 FTS risk > 300)
Prevalence rate	1:685	1:118	1:334

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Table 3 Screen-positive rates (SPR) and detection rates (DR) within different first trimester screening (FTS) risk brackets (data are not cumulative†)

	FTS‡			FTS/AMA§		
Risk bracket	Fetal Down syndrome, *n* (DR)	Screen Positive, *n* (SPR)	Cumulative SPR, %	Fetal Down syndrome, *n* (DR)	Screen positive, *n* (SPR)	Cumulative SPR, %
1:2–1:50	167 (66.8)	892 (1.1)	1.1	203 (81.2)	18 678 (22.4)	22.4
1:51–1:300	38 (15.2)	2008 (2.4)	3.5	23 (9.2)	1030 (1.2)	23.6
1:301–1:400	7 (2.8)	653 (0.8)	4.3	3 (1.2)	320 (0.4)	24.0
1:401–1:500	7 (2.8)	632 (0.7)	5.0	4 (1.6)	280 (0.3)	24.3
1:501–1:600	4 (1.6)	638 (0.8)	5.8	1 (0.4)	302 (0.4)	24.7
1:601–1:700	2 (0.8)	624 (0.7)	6.5	0 (0.0)	275 (0.3)	25.0
1:701–1:800	0 (0.0)	622 (0.8)	7.3	0 (0.0)	264 (0.3)	25.3
1:801–1:900	1 (0.4)	583 (0.7)	8.0	0 (0.0)	270 (0.3)	25.6
1:901–1:1000	1 (0.4)	607 (0.7)	8.7	1 (0.4)	280 (0.3)	25.9
1:1001–1:1500	10 (4.0)	3017 (3.6)	12.3	4 (1.6)	1276 (1.5)	27.4
1:1501–1:2000	2 (0.8)	2957 (3.6)	15.9	4 (1.6)	1170 (1.4)	28.8
1:2001–1:2500	1 (0.4)	2774 (3.3)	19.2	0 (0.0)	1049 (1.3)	30.1
<1:2500	10 (4.0)	67 386 (80.8)		7 (2.8)	58 199 (69.8)	
All	250	83 392		250	83 392	

†The table shows the data for each risk bracket, not cumulative numbers. Cumulative figures are shown in Figures 1 and 2.
‡FTS refers to an approach in which NIPT is offered only to women with an FTS risk cut-off as shown.
§FTS/AMA refers to an approach in which NIPT is offered to women with an FTS risk cut-off as shown, in addition to any woman of advanced maternal age.

Changing the FTS risk cut-off to increase the DR to 96% from 82% (baseline) would come with a 5.5-fold increase in screen-positive pregnancies.

Our data clearly demonstrate that offering NIPT to all women of AMA and women with a high-risk FTS result is less effective than using FTS alone to determine eligibility for all women, with much higher screen-positive rates required to identify the same number of cases of fetal DS. Although some women of AMA may decide to self-fund NIPT based on their maternal age, this should not be considered in the targeting of a publicly funded screening model. Within the FTS approach, as expected, each increase in the screen-positive rate comes with a progressively smaller increase in the detection rate. This will translate to a reduction in the cost-effectiveness of screening with every increase in the FTS risk cut-off. To demonstrate with a simple calculation, in this cohort assuming 100% uptake of NIPT in eligible women at $400 per test, a risk cut-off of 1:300 would identify 205 (82%) cases of fetal DS at an NIPT cost of $1.2 million ($5700/case) compared to 240 (96%) cases at an NIPT cost of $6.4 million at a risk cut-off of 1 in 2500 ($27 000/case). These costs demonstrate a concept only, with a full economic evaluation incorporating all outcomes, costs and cost savings along the screening pathway, and comparison of screening models, necessary to inform policy.[21]

A decision regarding where the balance lies between detection and screen-positive rates – and therefore cost – will be impacted by the methodology of economic evaluations, such as the inclusion of downstream costs (ie the lifetime cost of care for an individual with DS) and the perspective taken (ie societal or health system), as well as the value placed on nonhealth outcomes[22] such as the provision of information and choice for families, the psychosocial impact of a false-negative result and equity of access. Understanding is also needed of the potential uptake of NIPT among eligible women and the overall budget impact of providing NIPT.

The uptake of invasive diagnostic testing in our cohort suggests that some women are making the decision to have further testing following FTS based on their individual risk assessment. This is consistent with the level and patterns of invasive testing uptake following FTS in Victoria during 2003/2004, as reported by Jaques *et al.*[23] The uptake of invasive testing among low-risk pregnancies, 1.9% is also similar to the 2.5% reported by Jaques *et al.* One of the limitations of our study is that we have incomplete ascertainment of all pregnancy outcomes associated with screening. It is possible that clinical features of the pregnancy could prompt further diagnostic tests without formal screening risk assessment. Our data also suggest that some women are taking into account the categorisation of 'high' and 'low' risk as determined by the FTS risk cut-off, demonstrated by the accelerated reduction in invasive testing after the risk falls <1:300. We have shown previously that for women identified as high risk by FTS, NIPT could significantly reduce the number of diagnostic tests and procedure-related miscarriages.[12] What our data cannot tell us is how women will make decisions about further testing following a screen-positive FTS result – when that test is NIPT – given there is no immediate risk of miscarriage, and the out-of-pocket costs for private patients may be lower than those for an invasive test. In addition to these factors, as our data

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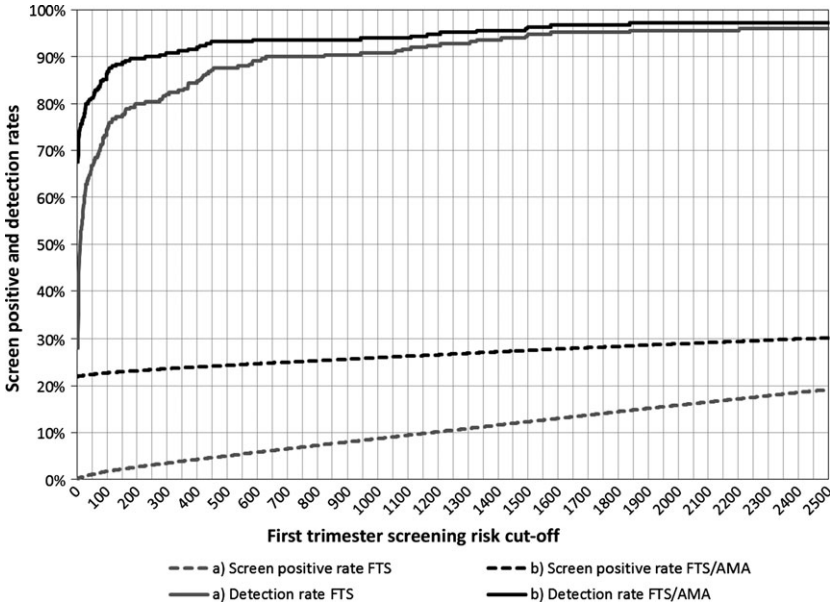

Figure 1 Detection and screen-positive rates by FTS risk cut-off for (a) FTS only (FTS refers to an approach in which NIPT is offered only to women with an FTS risk cut-off as shown.) and (b) FTS/AMA. (FTS/AMA refers to an approach in which NIPT is offered to women with an FTS risk cut-off as shown, in addition to any woman of advanced maternal age). - - -, screen-positive rate FTS; - - -, screen-positive rate FTS/AMA; ——, detection rate FTS; ——, detection rate FTS/AMA.

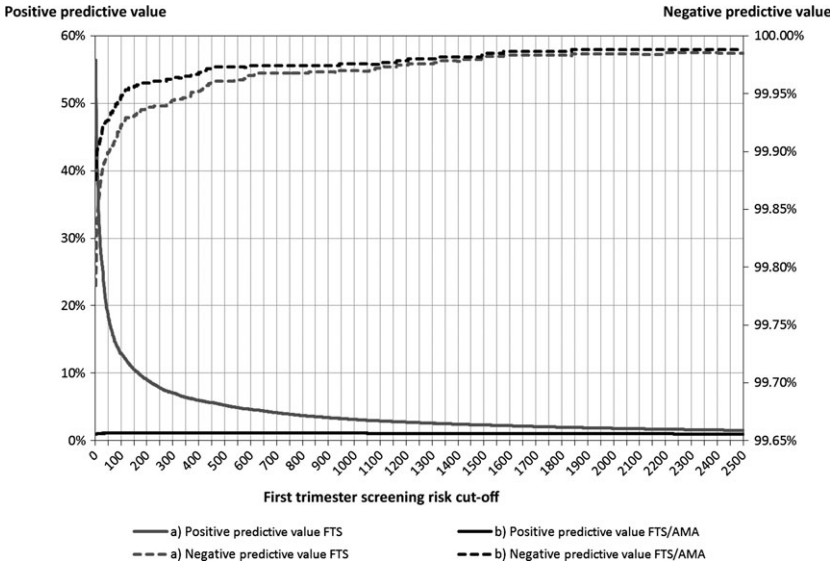

Figure 2 Positive and negative predictive values (PPV and NPV) by FTS risk cut-off for (a) FTS only (FTS refers to an approach in which NIPT is offered only to women with an FTS risk cut-off as shown.) and (b) FTS/AMA. (FTS/AMA refers to an approach in which NIPT is offered to women with an FTS risk cut-off as shown, in addition to any woman of advanced maternal age.) ——, positive predictive value FTS; ——, positive predictive value FTS/AMA; - - -, negative predictive value FTS; - - -, negative predictive value FTS/AMA.

suggest women place gravitas on the categorisation of 'high'- and 'low'-risk, moving these categories is also likely to increase uptake in those pregnancies which would migrate to 'high' risk with a more sensitive risk cut-off. The increased percentage of CVS over amniocentesis in women with a risk of >1:50 is also consistent with the literature.[23] This may reflect the desire to have a result earlier, and/or acceptance of a higher risk procedure in the presence of a very high-risk FTS result, or the potential for clinicians to provide preferential access to invasive procedures at short notice for these very high-risk pregnancies. It may also be due to a higher rate of

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Table 4 Total potential cost of NIPT† by first trimester screening (FTS) risk cut-off for 2005–2009 cohort (83 392 FTS screened pregnancies) and NIPT fee‡

	NIPT Fee				
FTS risk cut-off	$200	$300	$400	$500	Detection rate (%)
1:300 (*n* = 2900)	$580 000	$870 000	$1 160 000	$1 450 000	82.0
1:500 (*n* = 4185)	$837 000	$1 255 500	$1 674 000	$2 092 500	87.6
1:1000 (*n* = 7259)	$1 451 800	$2 177 700	$2 903 600	$3 629 500	90.8
1:1500 (*n* = 10 276)	$2 055 200	$3 082 800	$4 110 400	$5 138 000	94.8
1:2000 (*n* = 13 233)	$2 646 600	$3 969 900	$5 293 200	$6 616 500	95.6
1:2500 (*n* = 16 006)	$3 201 400	$4 802 100	$6 402 400	$8 003 500	96.0

†This is not an economic evaluation, and it merely provides an idea of how the FTS risk cut-off and therefore screen-positive rate will impact the potential number of tests and cost of NIPT overall.
‡Assumes 100% uptake of NIPT in eligible women (cohort of screened pregnancies = 83 392). This does not include those lost to follow-up (2.8%). Assuming a similar risk profile, this could add a further 2.8% to the cost.

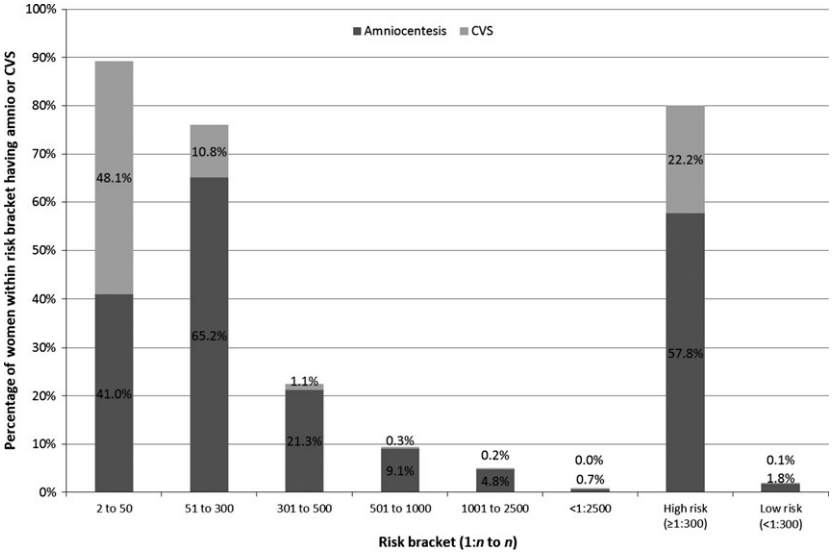

Figure 3 Uptake of amniocentesis, chorionic villus sampling (CVS) and amniocentesis or CVS by FTS risk cut-off (this figure shows the uptake of diagnostic testing for the risk cut-off). ■, amniocentesis; ■, CVS.

miscarriage in these very high-risk pregnancies, with some women miscarrying before having the opportunity to have an amniocentesis.

The most significant limitation of our study is that the FTS screening algorithm used between 2005 and 2009 in Western Australia did not incorporate nasal bone, tricuspid flow or ductus venosus, additional markers that can now, with further certification, be included in the screening algorithm. With the inclusion of these sonographic markers, Nicolaides *et al.* demonstrated an increase in the detection rate of FTS from 85–95% to 93–96%, with a 50% reduction in the false-positive rate from 5% to 2.5%.[24] We are unsure to what extent these are being used in clinical practice across Australia, but understand that use may be restricted. Our study was also limited by the incomplete ascertainment of outcomes for all screened pregnancies; however, we believe this would not have impacted the results as those lost to follow-up only represented 3% of all complete screens, the characteristics of which were similar to those for which we had follow-up. The generalisability of these results will depend on the age distribution of screened women, with cohorts with older women expecting higher SPRs. The proportion of women of AMA in our cohort (22%) mirrors that of births in Australia (18.8% in 2003, 22.4% in 2012).[25] The strength of our data is that it reflects screening performance across a range of service providers and an entire pregnant population over five years.

Given the recommendation for first trimester ultrasound prior to NIPT, the DRs of FTS and the prohibitive cost of universal NIPT screening at this time, we propose that women, regardless of age, have their eligibility for publicly funded NIPT assessed using FTS. Where FTS is not available, maternal serum screening (MSS) for the assessment of risk in the second trimester (15–18 weeks) could be used to assess eligibility, but must be undertaken

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as early as possible to allow time for MSS and NIPT results and invasive diagnostic testing where indicated. Further economic evaluation considering the impact of variation in FTS and MSS risk cut-offs, and total budget impact, is required, but will demand more robust data on the uptake of NIPT in screen-positive women. This would be best informed by a pilot program into publicly funded NIPT in which women's choices to have NIPT and/or invasive testing can be observed. Research into the value of nonhealth outcomes of NIPT such as information and choice and equity of access could also provide insight into the role of prenatal screening in Australia.

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CHAPTER 5 PAPER 4

THE POTENTIAL IMPACT OF NIPT AS A SECOND-TIER SCREEN ON THE OUTCOMES OF HIGH-RISK PREGNANCIES WITH RARE CHROMOSOMAL ABNORMALITIES

Susannah Maxwell, Jan E Dickinson, Ashleigh Murch, Peter O'Leary. The potential impact of NIPT as a second-tier screen on the outcomes of high-risk pregnancies with rare chromosomal abnormalities, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 55, Issue 5, pages 420–426, October 2015

Original Article

The potential impact of NIPT as a second-tier screen on the outcomes of high-risk pregnancies with rare chromosomal abnormalities

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Aim: To describe the potential impact of using noninvasive prenatal testing (NIPT) as a second-tier test, on the diagnosis and outcomes of pregnancies identified as high risk through first trimester screening (FTS) in a cohort of real pregnancies.

Materials and Methods: Western Australian FTS and diagnostic data (2007–2009) were linked to pregnancy outcomes. Karyotype results from invasive prenatal testing in high-risk women were analysed. The outcomes of abnormal results that would not be detected by NIPT, assuming a panel of trisomy 21/18/13 and sex chromosome aneuploidies, and the likelihood of diagnosis in a screening model using NIPT as a second-tier test are described.

Results: Abnormal karyotype results were reported in 224 of 1488 (15%) women with high-risk pregnancies having invasive diagnostic testing. NIPT potentially would have identified 85%. The 33 abnormalities unidentifiable by NIPT were triploidies ($n = 7$, 21%), balanced ($n = 8$, 24%) and unbalanced rearrangements ($n = 10$, 30%) and level III mosaicisms ($n = 8$, 24%). For conditions not identifiable by NIPT, fetal sonographic appearance was likely to have led to invasive testing for 10 of 17 (59%) pathogenic abnormalities. If a policy was adopted recommending invasive testing for FTS risk >1:50 and/or ultrasound detected abnormality, the residual risk of an unidentified pathogenic chromosomal abnormality in those without a diagnosis would have been 0.33% (95% CI 0.01–0.65%).

Conclusions: A screening model with NIPT as a second-tier for high-risk pregnancies would be unlikely to have changed the outcome for the majority of pregnancies. Optimising the diagnosis of rare pathogenic abnormalities requires clear indicators for invasive testing over NIPT.

Key words: abnormal karyotype, prenatal diagnosis, prenatal screening, ultrasonography.

Introduction

Over the last forty years, the use of invasive diagnostic testing for fetal aneuploidies has been targeted to pregnancies most at risk, reducing exposure to the associated risk of miscarriage[1] but also to the cost of the test for women, insurers and public health systems. In the 1970s, risk assessment was based on maternal age alone; however, by the turn of the century, this risk could be further refined using first (FTS) or second trimester screening algorithms incorporating maternal serum analyte levels[2] and measurements from fetal ultrasound (FTS).[3] These tests are now routinely offered in pregnancy; however, almost 20% of Down syndrome pregnancies still go undetected in women screened and the majority of invasive procedures in high-risk pregnancies identify normal karyotype fetuses.[4,5] Furthermore, the biomarker profile is a poor predictor of other rare fetal chromosomal abnormalities such as polyploidies, balanced and unbalanced rearrangements and mosaicisms.[6,7]

In 2012, novel noninvasive prenatal testing (NIPT) technologies that analyse cell-free fetal DNA present in the plasma of maternal blood became available commercially in Australia through international companies.[8] NIPT has been shown to be highly sensitive and specific as a screening test for the detection of the common fetal aneuploidies in high-risk populations,[9–11] with superior performance to those of current screening strategies. NIPT detection rates for trisomy 21, 18 and 13 have been reported at 99%, 97% and 90%, respectively[12,13] with

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false-positive rates of ≤0.2%.[14] Other fetal aneuploidies such as sex chromosome abnormalities can also be detected. Evidence is also accumulating validating the use of NIPT in low- and average-risk populations.[15] However, until further validation studies in these populations are published and the costs fall, NIPT is likely to be limited by public health systems and insurers to that of a second-tier test in high-risk pregnancies, an approach currently supported by clinical groups.[16,17]

Before policymakers can recommend and fund the routine use of NIPT as part of the screening pathway in pregnancy, an understanding is required of the potential impact of the test on clinical management and outcomes, costs and benefits. One such question concerns the effect of incorporating NIPT into prenatal screening in terms of the detection of other rare chromosomal abnormalities.[18–20] The purpose of this study was to estimate the proportion of chromosomal abnormalities that would go undetected if NIPT was introduced as a second-tier test for pregnancies identified at increased risk by FTS.

Materials and Methods

Using population data collected for the routine evaluation of FTS in Western Australia (WA),[5,21] we have modelled the types and number of abnormalities that would not be identified by NIPT in a cohort of high-risk women having invasive diagnostic testing and, based on the real outcomes of these pregnancies, report on the potential impact of introducing NIPT as a second-tier test.

We collected FTS data for all women screened in WA between 2007 and 2009 from ultrasound practices certified by the Nuchal Translucency Ultrasound, Education and Monitoring Program. Screening records (n = 58146) were linked to prenatal cytogenetic karyotyping data collected from the two main pathology laboratories in WA and pregnancy outcome data (hospital morbidity and mortality data, Midwives' Notification System and the WA Register of Developmental Anomalies) through the Department of Health Western Australia's Data Linkage Branch.[22] Defects reported to the WA Registry of Developmental Anomalies (WARDA) include 'a structural or functional anomaly, which is present at conception or occurs before the end of pregnancy and is diagnosed during pregnancy, or after stillbirth or termination of pregnancy, or after live birth, but before six years of age'.[23]

We removed multifetal pregnancies and duplicate screening records (n = 2353), incomplete screening tests (no maternal biochemistry and/or no nuchal translucency measurement) (n = 1260) and women who had failed to link with other data records (n = 1240) prior to the analysis. Outcome data were available for 98 per cent (52058/53293) of the remaining cohort. The sensitivity and specificity of first trimester screening for trisomy 21 and trisomy 13 and 18 using a risk cut-off of 1:300 and 1:150, respectively, as per clinical practice,[24] were calculated, based on the 52058 pregnancies with outcome information. Where a screened pregnancy had more than one diagnostic test, the second result was retained. Women who had invasive diagnostic testing (amniocentesis or chorionic villus sampling) following a high-risk screening result (>1:300 for trisomy 21 and/or >1:150 for trisomy 13/18) were identified. Our data capture all cases of termination following diagnosis of fetal chromosomal abnormality.

We flagged diagnostic test results as normal or abnormal and categorised abnormal results as trisomy 21, 13 or 18, sex chromosome aneuploidy, polyploidy (including triploidy), unbalanced rearrangement, balanced rearrangement or level III mosaicism. No microarrays were in use during this study period. We assumed that the NIPT panel had the potential to detect trisomy 13, 18, 21 and sex aneuploidies, as is available through a number of commercial providers.[16]

A clinical cytogeneticist (AM) assessed the pathogenicity of the abnormal karyotype based on cytogenetic karyotyping, birth defect data and clinical experience, categorising the abnormality as 'benign', 'mild and/or likely normal', or 'pathogenic'. Cases with mild intellectual handicap and/or minor dysmorphic features are defined as 'mild'. 'Likely normal' refers to cases with balanced chromosome rearrangements and some unbalanced ones which are most commonly associated with a normal phenotype. A small proportion of patients with apparently balanced rearrangements at the cytogenetic level are unbalanced when investigated molecularly or the rearrangement disrupts and inactivates a significant gene, thus resulting in an abnormal phenotype. A specialist in fetal maternal medicine (JED) assessed the probability of the abnormality being indicated on ultrasound for further invasive testing based on FTS data, cytogenetic karyotyping, birth defect description and clinical experience. Ultrasound images were not available for this study and the assessment was not restricted to anomalies detectable at the FTS examination but encompassed those detectable at the time of the mid-trimester fetal morphology ultrasound. Categories for the indication by ultrasound were 'yes', 'probably', 'possibly' or 'no'. Where there was a clear abnormality indicated on a birth defect record (such as single cardiac ventricle or holoprosencephaly), the case was classified as 'yes'. Triploidies in the absence of a birth defect record with clear abnormality were classified as 'probably'.

The study received ethics approval from the Curtin University Health Research Ethics Committee (Number: HR98/2014).

Results

Of 53293 FTS singleton tests performed in WA between January 2007 and December 2009, 3.6% (n = 1943) had a high-risk screening result for trisomy 21 (>1:300) and/or trisomy 13/18 (>1:150). The performance of these screening tests and the characteristics of the screened population are shown in Table 1 and 2, respectively. Of

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Table 1 Performance (i.e sensitivity and specificity) of FTS for the detection of trisomies 21 and 13 and 18 (2007–2009)*

Screens	Trisomy 21	Trisomy 13/18
All screens, *n*	53293	53293
Screen positive, *n* (%)	1858 (3.49)	457 (0.86)
Screens with outcome data, *n*	52058	52058
Screen positive, *n* (%)	1781 (3.42)	423 (0.81)
True positive, *n*	130	54
False negative, *n*	27	12
True negative, *n*	50250	51623
False positive, *n*	1651	369
Sensitivity (95% CI)	82.8 (76.0 – 88.3)	81.2 (70.4 – 90.2)
Specificity (95% CI)	96.8 (96.7 – 97.0)	99.3 (99.2 – 99.4)
Positive predictive value (95% CI)	7.30 (6.13 – 8.61)	12.77 (9.74 – 16.33)
Negative predictive value (95% CI)	99.95 (99.92 – 99.96)	99.98 (99.96 – 99.99)

*These results are for the performance of FTS alone. Indication on ultrasound as part of FTS may also lead to a recommendation for invasive diagnostic testing despite a low-risk FTS screening result.

Table 2 Characteristics of the screened population*, by outcome–median (interquartile range)

Characteristic	Trisomy 21 (*n* = 157)	Trisomy 18 (*n* = 43)	Trisomy 13 (*n* = 23)	Unaffected/Other (*n* = 51835)
Maternal age (yrs)	36 (32, 39)	36 (33, 40)	36 (33, 40)	30 (27–34)
Maternal weight (kg)	68 (60, 78)	67 (58, 76)	65 (57, 75)	66 (58, 76)
Crown rump length (mm)	64 (59, 70)	53 (49, 60)	57 (53, 62)	63 (58, 69)
Nuchal translucency (mm)	2.9 (2.0, 4.4)	3.6 (1.7, 6.2)	4.5 (2.4, 6.2)	1.5 (1.3, 1.8)
Serum PAPP-A (MoM)	0.4 (0.3, 0.7)	0.3 (0.2, 0.6)	0.4 (0.3, 0.5)	1.0 (0.7, 1.5)
Serum-free β-hCG (MoM)	1.8 (1.3, 2.5)	0.2 (0.2, 0.3)	0.3 (0.2, 0.4)	1.0 (0.7, 1.4)

*These characteristics relate to the screened population for which we had outcome data (*n* = 52058).

the women with a high-risk FTS result, 1488 (76.6%) women had invasive diagnostic testing.

With the exception of Tables 1 and 2, results relate only to high-risk women who had an invasive test. Abnormal karyotype was reported in 15% (*n* = 224) of high-risk women having invasive diagnostic testing. NIPT, with a panel of trisomy 13, 18, 21 and sex chromosome abnormalities, would be expected to have identified up to 85.3% of these abnormalities (Table 3a). This is the highest potential detection rate, with the possibility that some of these aneuploidies may have had false-negative NIPT results. Table 3b shows the types of chromosomal anomalies that would not have been detected by NIPT.

Of those conditions that would not have been identified by NIPT, the fetal sonographic appearance was likely to have led to a recommendation for an invasive test ('yes' and 'likely') for 10 of the 17 (59%) pathogenic abnormalities and would 'possibly' have led to a recommendation for six (35%). One pathogenic level III mosaicism was unlikely to have been identified (Table 4). Of the terminated cases, 71% (10/14) were considered likely to have had invasive testing recommended, with a further 21% (3/14) possibly recommended (Table 4).

Of the high-risk pregnancies having invasive diagnostic testing, 1338/1488 (90%) had an FTS risk of <1:50. In this group, there were 132 chromosomal abnormalities, and four of the pathogenic abnormalities would not have been identified by NIPT and were unlikely to be recommended for invasive testing based on ultrasound appearance. Women with an FTS risk <1/50 and a negative NIPT result therefore had a residual risk of an

Table 3 Chromosomal abnormalities (a) potentially detectable (b) not detectable by NIPT

Chromosomal abnormality	*n*	% of all abnormalities (*n* = 224)
(a)		
Trisomy 21	119	53.1
Trisomy 18	31	13.8
Trisomy 13	17	7.6
Sex chromosome	24	10.7
Total	191	85.3
(b)		
Other polyploidy	7	3.1
Unbalanced rearrangement	10	4.5
Balanced rearrangement	8	3.6
Level III mosaicism	8	3.6
Total	33	14.7

These data only reflect cases of trisomy 21, 13 and 18 among high-risk pregnancies which had invasive diagnostic testing. The number of cases of trisomy 21 and trisomy 13 or 18 in all women identified as high risk by FTS is shown in Table 1.

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Table 4 Pregnancy outcomes for NIPT undetectable cases

Ultrasound indication for invasive test over NIPT	Pathogenic	Mild/likely normal	Benign	Total (%)
Yes	Unbalanced (16,171) Polyploidy (569, 107) Polyploidy (2, 71)	**Level III mos (74, 6978)**	Balanced (75, 252)	5 (15.2)
Likely	Polyploidy (559, 108) *Unbalanced (353, 106)* Unbalanced (100, 1095) Polyploidy (489, 136) Polyploidy (2032, 113) Polyploidy (401, 86) Polyploidy (201, 45)			7 (21.2)
Possibly	Level III mos (16, 576) Unbalanced (267, 1441) *Unbalanced (65, 200)* Unbalanced (89, 525) Unbalanced (40, 289) *Unbalanced (372, 116)*	**Level III mos (11, 11)** **Level III mos (248, 1863)** *Level III mos (504, 62)*		9 (27.3)
No	Level III mos (38, 116)	**Unbalanced (219, 19923)** **Level III mos (51, 85)** **Balanced (142, 717)** **Level III mos (32, 4166)** **Balanced (69, 24756)**	**Balanced (259, 1949)** **Balanced (12, 378)** **Balanced (501, 118)** **Unbalanced (215, 4144)** **Balanced (108, 2343)** **Balanced (64, 229)**	12 (36.4)
Total *n* (%)	17 (51.5)	9 (27.3)	7 (21.2)	33 (100)

*The numbers in brackets following each case refer to the first trimester risk result for trisomy 21 and trisomy 13/18, respectively.
Level III mos refers to Level III mosaicism.
Unbalanced refers to unbalanced rearrangements.
Balanced refers to balanced rearrangements.
Pregnancy outcomes are depicted as liveborn (bolded, n=15), stillborn (italicised, n=4), terminated (n=14).

undiagnosed pathogenic karyotypic abnormality of 0.33% (95% CI 0.01–0.65%). Forty-one per cent of all chromosomal abnormalities and 27% of those not identified by NIPT occurred in those with a risk >1:50.

Discussion

Noninvasive prenatal testing provides the opportunity to reduce the use of invasive diagnostic testing and associated procedure-related miscarriage in women with pregnancies identified as high risk through FTS. However, the implications of using NIPT as a screen prior to fetal karyotyping in high-risk women must be understood. In our cohort of high-risk women undergoing invasive diagnostic testing, fetal karyotyping showed an abnormal result for 15%, the majority (75%) of which were trisomy 21, 18 and 13, consistent with data reported by Syngelaki *et al.*[6] This assumes a 100% detection rate for these trisomies. Assuming NIPT could also detect sex aneuploidies, NIPT could identify up to 85% of chromosomal abnormalities currently reported through fetal karyotyping, potentially leaving a small, but not insignificant number of rare chromosomal abnormalities undetected. This observation is consistent with data reported by Susman and Norton.[18,19] If NIPT were also capable of detecting triploidy, as reported recently[25], this figure could increase to 88%. A strength of our study is that we witnessed how women used this information, evident in their decision to terminate or to continue with the pregnancy. Our results suggest that for the majority of our cohort of high-risk pregnancies, the inclusion of NIPT as a second-tier test would have been unlikely to have changed the pregnancy outcome. Over half (58%) of the fetuses with rare chromosomal anomalies detected by invasive testing but undetectable by NIPT were live-born at full term or stillborn. Additionally, for the 42% of the fetuses with undetectable conditions that were terminated, it was considered likely that structural defects on ultrasound would have led to a recommendation for an invasive test in up to 71% of cases, providing women with the opportunity to make this choice in their pregnancy.

Of the pathogenic chromosome abnormalities in this cohort, the majority were likely to have been recognised by prenatal ultrasound with structural malformations or severe early onset growth restriction, prompting a diagnostic test. Typically, triploid fetuses surviving the first trimester present with abnormal ultrasound appearances such as early onset asymmetrical growth

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restriction, abnormal placental appearances and a range of structural anomalies.[26,27] There is a substantial spontaneous attrition rate for triploid fetuses with increasing gestation in the second trimester[28], and given the lethality of this condition, there is arguably not a strong imperative for prenatal detection, apart from providing the opportunity for termination.[29] The potential for failure of diagnosis of some significant anomalies does place an increased diligence on those performing prenatal ultrasound, as many, although not all, cases could potentially be recognised by ultrasound. Six of the pathogenic chromosome abnormalities (18.2%) may not have been recognised prior to birth. If a policy was adopted recommending invasive testing for FTS risk >1:50 and/or ultrasound detected abnormality, the residual risk of an unidentified pathogenic chromosomal abnormality in those without a diagnosis would have been 0.33% (1/302).

The clinical significance of the conditions that would not be detected by NIPT varies with the nature of the abnormality. While it is believed that 1–3% of conceptions are triploid, 99.99% miscarry by the end of the second trimester.[30] *De novo* unbalanced rearrangements include a wide range of abnormalities, some of which, such as small acrocentric derived dicentric chromosomes, will be phenotypically benign, but most will be associated with phenotypic abnormality of varying severity.[31] Inherited balanced rearrangements are likely to be benign as are *de novo* balanced rearrangements with no associated ultrasound abnormality; however, those associated with abnormality on ultrasound carry a significant risk of pathogenicity.[31] Level III mosaicisms make up a mixed group of cytogenetic abnormalities, with those detected in CVS samples most likely to be confined to the placenta and benign[32], whereas those seen in amniotic fluid will represent true fetal mosaicism and the likely pathogenicity will be related to specific abnormality detected. The uncertainty of the significance of many of these abnormalities presents significant challenges for counselling and may cause unnecessary anxiety for women.[33]

In the interpretation of our results, consideration must be given to the likely increased uptake of NIPT, as compared to invasive diagnostic testing, due to the increased simplicity and safety of the test. On a population level, increased uptake of NIPT (compared to invasive testing) could result in an increase in the identification of severe abnormalities prenatally, despite decreasing identification on an individual level. The increased uptake also has implications for our results. The rate of Down syndrome in the 23% of pregnancies who did not choose to have invasive testing was lower (1:48) than in the 77% who did (1:12), suggesting different risk profiles and characteristics in these two groups of women.[17] It may be that the rates of rare chromosomal abnormalities in this group would also differ. Our study was limited to those who chose to have invasive diagnostic testing to ensure full karyotype data.

The generalisability of our results is limited by the small number of cases and should be supplemented by other data. Also, importantly, we did not have access to ultrasound images and therefore relied on the experience of a fetal medicine specialist in assessing the likelihood the condition would be identified through indication on ultrasound leading to invasive testing. As the ability to identify anomalies on ultrasound depends on the skill and expertise of the sonographer, there is potential for wide variation in the identification of these anomalies across clinical practice.

Despite these limitations, the results do suggest a number of implications for clinical practice and support the informed introduction of NIPT as a second-tier screen. NIPT is just one part of a first trimester screening model that exists within the context of ongoing prenatal care and investigation for fetal anomaly and adverse outcomes. Reducing the use of invasive testing will place greater importance on the role of sonography and require clear indications for the use of invasive testing over NIPT, with the potential for increased demand for screening at specialist centres. The International Society of Ultrasound in Obstetrics and Gynecology consensus statement provides guidelines on the appropriate use of NIPT and recommends that NIPT should not replace invasive testing in women identified as very high risk (>1:10) by FTS.[34] Petersen et al.[35] report on the diagnostic consequences of NIPT in a large Danish cohort, with consideration given to the use of varying FTS risk cut-offs and other risk markers (such as maternal age, abnormal biochemistry or increased fetal nuchal translucency) to direct recommendations for invasive testing. Consideration of individual components of FTS for the assessment of risk of atypical karyotypic abnormalities was outside the scope of the current study, but warrants further investigation.

These results must be interpreted within the context of a rapidly changing landscape. The literature describing NIPT is growing, with validation studies now being published in low- and average-risk populations, falling prices and continuing advances in the capability of NIPT.[25,36] Expanded testing has recently also become available for some microdeletion syndromes and trisomies 16 and 22,[20] although caution has been advised.[20] Parallel to these developments is the evolution of microarray testing as, potentially, a first-tier invasive diagnostic test, increasing, once again, the number and types of abnormalities that can be detected by invasive testing. These advances will continue to impact the results of comparisons of different screening pathways and add complexity to the counselling of women.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Ultrasound indicating invasive testing according to pathogenicity and karyotype.

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CHAPTER 6 PAPER 5

PRENATAL SCREENING FOR DOWN SYNDROME IN AUSTRALIA: COSTS AND BENEFITS OF CURRENT AND NOVEL SCREENING STRATEGIES

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Original Article

Prenatal screening for Down syndrome in Australia: Costs and benefits of current and novel screening strategies

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Objective: To analyse the cost-effectiveness and performance of noninvasive prenatal testing (NIPT) for high-risk pregnancies following first-trimester screening compared with current practice.

Methods: A decision tree analysis was used to compare the costs and benefits of current practice of first-trimester screening with a testing pathway incorporating NIPT. We applied the model to 32 478 singleton pregnancies screened between January 2005 and December 2006, adding Medicare rebate data as a measure of public health system costs. The analyses reflect the actual uptake of screening and diagnostic testing and pregnancy outcomes in this cohort.

Results: The introduction of NIPT would reduce the number of invasive diagnostic procedures and procedure-related fetal losses in high-risk women by 88%. If NIPT was adopted by all women identified as high risk by first-trimester combined screening, up to 7 additional Down syndrome fetuses could be confirmed. The cost per trisomy 21 case confirmed, including NIPT was 9.7% higher ($56 360) than the current prenatal testing strategy ($51 372) at a total cost of $3.91 million compared with $3.57 million over 2 years.

Conclusion: Based on the uptake of screening and diagnostic testing in a retrospective cohort of first-trimester screening in Western Australia, the implementation of NIPT would reduce the number of invasive diagnostic tests and the number of procedure-related fetal losses and increase the cost by 9.7% over two years. Policy planning and guidelines are urgently required to manage the funding and demand for NIPT services in Australia.

Key words: antenatal screening, Down syndrome, noninvasive prenatal testing, economic analysis, policy.

Introduction

Prenatal screening strategies have used biochemical assays of maternal serum PAPP-A and free hCGβ and ultrasound measurements of fetal nuchal translucency (NT) in first-trimester screening (FTS) to identify 85% of Down syndrome pregnancies with a 5% screen positive rate.[1,2] Subsequent diagnostic tests of fetal karyotype require invasive tests such as chorionic villus sampling or amniocentesis, but the collection of these samples carries a small risk of miscarriage.[3] While any woman may choose to have a diagnostic test, the majority are at high risk based on their age or screening risk result.[4]

Novel technologies involving noninvasive prenatal testing (NIPT) and assays of cell-free fetal DNA (cffDNA) in maternal blood by massively parallel sequencing using shotgun [5–7] or targeted DNA sequencing [8,9] offer significantly improved detection with low false-positive rates. These techniques are set to challenge the current policies and practices for standard of care.[10] Commencing in 2008, massively parallel sequencing (MPS) technology has been applied to the analysis of cell-free DNA in maternal plasma for trisomy 21.[11,12] NIPT in both high-risk and low-risk pregnancies has successfully identified fetal trisomy 21, 18 and 13[5–9,12–23] without risk of invasive procedural-related losses.[19] The American College of Obstetricians and Gynecologists Committee on Genetics and the Society for Maternal Fetal Medicine Publications Committee have endorsed NIPT as an option for a primary screening test in women identified at high risk of aneuploidy,[24] based on the published high detection rates and low false-positive rates for trisomy 21 and trisomy 18 using cffDNA analyses. The International Society for Prenatal Diagnosis has issued guidelines endorsing the use of cffDNA in maternal blood for women classified at high risk on traditional criteria or those who choose to personally finance their testing.[25]

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In 2012, NIPT for trisomy 21 by sequencing of maternal plasma DNA was offered on a clinical and commercial basis in the United States and China at costs ranging from US$795 to US$1900, depending on the patient's insurance.[10,26,27] In Australia, several centres have begun to offer NIPT to women who can afford to access the technology. The majority of reports have evaluated NIPT as a second tier screening test for women identified at high risk of fetal aneuploidy by current first-trimester screening before proceeding to an invasive diagnostic test for fetal karyotyping.[28] Although NIPT poses no direct risk of harm to mother or fetus as it is not invasive, false-positive results could lead to unnecessary invasive procedures, procedure-related fetal losses and increased costs. So far, most studies have reported on the use of NIPT in selected high-risk populations with higher prevalence, where the false-positive rate would be expected to be lower and positive predictive value, higher than in the general population.[28]

The cost-effectiveness of combined first-trimester screening has been the subject of several studies in the context of the healthcare systems in the USA [29] and Canada.[30] Recent published studies comparing current first-trimester screening with NIPT indicate that the performance of NIPT can be less costly,[31] deliver higher detection rates, lower false-positive rates and reduce the number of invasive diagnostic tests with fewer procedural losses of fetuses.[6,9,15,16,31] However, these studies were conducted within the context of the different health systems and may not be applicable to the Australian healthcare environment.

The objectives of this study are to analyse the costs and benefits of NIPT for high-risk pregnancies following first-trimester screening (combined PAPP-A, free hCGβ and nuchal translucency measurements). While NIPT may be suitable as a primary screening strategy in certain circumstances,[24] our approach has been to consider the NIPT only as an intermediary step to reduce the number of invasive diagnostic tests. The primary outcomes are the costs of introducing NIPT and the benefits in terms of reduced numbers of invasive diagnostic tests and fetal-procedural losses. We estimated the relevant costs of current first-trimester screening and NIPT by re-evaluating our data from the 2005–2006 audit of West Australian prenatal screening data.[2]

Materials and Methods

Data were collected from all accredited ultrasound and pathology laboratories providing first-trimester screening services in Western Australia during 2005 and 2006. First-trimester screening data included fetal nuchal translucency, free β-hCG and PAPP-A, and risk estimates. Screening data were linked to Western Australian diagnostic data, hospital morbidity and mortality data, midwives notification data, and the Birth Defects Registry data through the Department of Health Western Australia's Data Linkage Branch. Data on births that were not screened during the same time period as the screened cohort were also obtained from the Midwives Notification Database. The data were analysed to determine the uptake, outcomes and performance of first-trimester screening and diagnostic testing, and uptake of diagnostic testing. Midwives Notification Data were used in the calculation of uptake of screening and were restricted to only those pregnancies that reached 20 weeks of gestation. Logistic regression analysis was performed to identify differences between the screened and nonscreened population in terms of age, parity and ethnicity. The current analysis was undertaken from a public health sector perspective.

Simulation model

Using modelling software (TreeAge Software Pro 2013, Williamstown, Massachusetts), we generated a decision tree to compare the costs and benefits of current first-trimester (11–14 weeks gestation) screening practice (model 1) in Australia with a prenatal testing pathway incorporating NIPT (model 2) in a cohort of 32 478 women in the first trimester of their pregnancy (Fig. 1). In model 1, women found to be at high risk of having a Down syndrome pregnancy via first-trimester screening (>1:300) are offered invasive prenatal diagnostic testing. Women can access invasive chorionic villus sampling between 11 and 14 weeks or amniocentesis between 15 and 20 weeks gestation. In model 2, high-risk women are offered NIPT as an intermediary step, with blood samples sent to an international NIPT provider, and those identified with a high risk of a Down syndrome pregnancy through NIPT are then offered confirmatory invasive

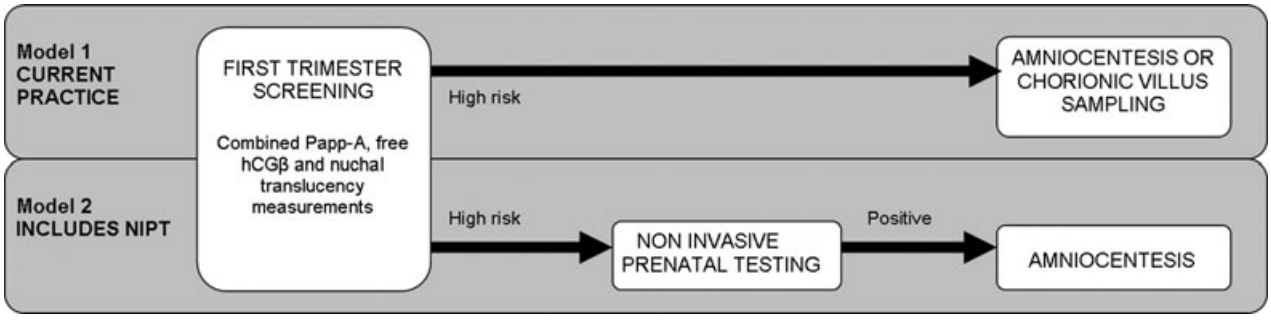

Figure 1 Models of current prenatal screening and proposed NIPT practice.

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diagnostic testing via amniocentesis. Although NIPT has been reported to demonstrate high sensitivity (99.9%, CI: 99.7–99.9) and specificity (99.8%, CI: 99.6–100) for trisomy 21,[5,7,9,12,15–22,32] the positive predictive value and false-positive rate in a high-risk population are not known. Therefore, confirmatory diagnosis is recommended for all positive results.[24,25] The model requires that only women identified as 'at high risk' by first-trimester combined screening (risk > 1:300) are able to access publicly funded NIPT. Those found to be not at high risk are assumed to undergo invasive diagnostic testing at the same rate to those in the 2005–2006 cohort.

Costs and benefits reported include the cost of each model and the numbers of 'high-risk' pregnancies with a confirmed diagnosis of Down syndrome, invasive diagnostic tests and procedure-related miscarriages. The cost per Down syndrome pregnancy confirmed is also presented. Sensitivity analysis determined the impact of variation in model parameters on costs and benefits.

The study was approved by the Department of Health (Western Australia) Health Research Ethics Committee.

Model parameters

The decision model uses real data for a cohort of 32 478 singleton pregnancies in Western Australia who completed first-trimester screening (blood test and ultrasound) between January 2005 and December 2006 (Fig. 2). These data reflect the actual uptake of screening and diagnostic testing as well as numbers of Down syndrome pregnancies in women identified 'at high risk' and 'not at high risk'. Within this cohort, 94 women had a Down syndrome pregnancy (prevalence 1:345). Seventy-six (81%) of these were identified through first-trimester screening (Table 1).

Although the risks are described as 'at high risk' or 'not at high risk', in practice, women are provided with an absolute risk. Accordingly, women who choose to have diagnostic testing following a high-risk result are more likely to have a Down syndrome pregnancy than those who choose not to have a diagnostic test following a high-risk result. The risk of having a Down syndrome pregnancy following a 'not at high-risk' result also varied by uptake of

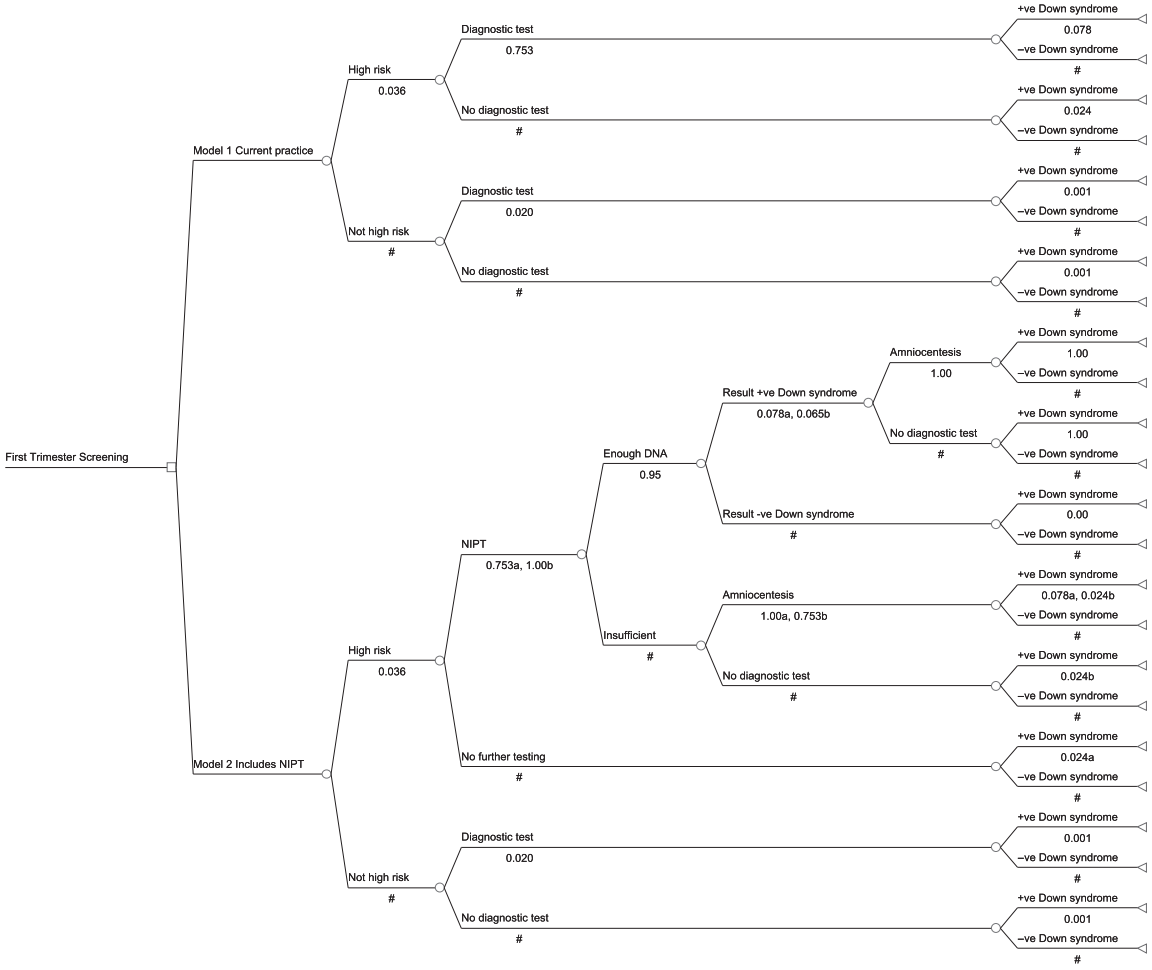

Figure 2 Decision tree of the current prenatal screening model (1) and alternate NIPT model (2) with baseline parameters.

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Table 1 Model inputs used in the decision tree analysis

Variable	Baseline probability (range)
First-trimester screening – 'high-risk' result	0.036*
Down syndrome pregnancy when 'not high risk'	<0.001*
Having a Down syndrome pregnancy when 'high risk'	0.065
Amniocentesis-related miscarriage	0.006[33] (0.005, 0.007)
Chorionic villus sampling-related miscarriage	0.007[33] (0.003, 0.014)
Proportion of diagnostic tests that are amniocentesis following NOT high-risk result†	0.96*
Model 1 – Current practice FTS with invasive diagnosis	
Having a diagnostic test	
After a 'high-risk' result >1:300	0.753*
After a 'not high-risk' result <1:300	0.020*
Having a Down syndrome pregnancy if 'high risk'	
For women who have a diagnostic test	0.078*
For women who do not have a diagnostic test	0.024*
Proportion of diagnostic tests following a 'high-risk' result that are amniocentesis†	0.71*
Model 2 – First-trimester screening with NIPT	
Having NIPT	
After a 'high-risk' result	0.753*(0.753a, 1.00b)‡
After a 'not high-risk' result	0 – unavailable
Having a diagnostic test	
After a 'not high-risk' result <1:300	0.020*
Sufficient blood for NIPT (feasibility)	0.95[17] (0.95,1.00)
Diagnostic testing following insufficient blood for NIPT	1.00 (0.753b, 1.00a)‡
NIPT sensitivity	1.00 (0.98-1.00)[6,15,17,28]
NIPT specificity	1.00 (0.97-1.00)[6,15,17,28]
Diagnostic testing following a positive NIPT	1.00 (0,1.00)
Proportion of diagnostic tests following a high-risk result that are amniocentesis	1.00

*Data from cohort of 32478 women having FTS in WA 2005–2006[2]

†Chorionic villus sampling accounted for the remainder of diagnostic tests

‡The uptake of NIPT impacts the uptake of diagnostic testing following an insufficient blood sample, and paired probabilities are indicated by 'a' and 'b'.

diagnostic testing; however, as this number is so small (<0.001), we used an average probability in our model.

The model includes the cost of first-trimester screening (blood test and ultrasounds) and diagnostic testing (amniocentesis, chorionic villus sampling and NIPT) which, with the exception of NIPT, were based on Australian Medicare rebates (85% of the schedule fee)[33] (Table 2). The baseline cost of $743 for NIPT reflects the lowest published cost of US$795[31] converted to Australian dollars using the average exchange rates over the 6 months, September 2012 to March 2013 (US $1 = A$0.93) as reported by the Australian Tax Office.[34] Variation in cost was considered in a threshold analysis with upper limits matching published prices.[26,27] We assumed that NIPT tests initiated but not completed due to insufficient bloods are not charged. Downstream costs such as termination and the lifetime cost of care for an individual with Down syndrome have not been included. All costs are in 2013 Australian dollars.

Sensitivity analysis considered the impact of variation in a number of model parameters, including the cost and uptake of NIPT following a high-risk result and the rate of successful NIPT (ie sufficient DNA). Our baseline model assumed a 75.3% uptake (consistent with the uptake of invasive testing in the cohort). However, with the relative ease of a simple blood test and no risk of miscarriage, NIPT has the potential to drive a significant increase in uptake of this test following a high-risk FTS result. As the probability of Down syndrome varied by the choice to have invasive diagnostic testing in the original cohort, to maintain the same rate of Down syndrome, we were restricted to an NIPT uptake of either 75.3% or 100%. Unlike other parameters varied in sensitivity analysis, changing the uptake of NIPT required some downstream probabilities to be adjusted. We assumed that if the uptake of NIPT was 100%, diagnostic testing following insufficient bloods for NIPT would be 75.3%, reflecting

Table 2 Cost data for components of screening and diagnostic tests

Medicare cost[29]	85% schedule fee	MBS item
First-trimester screening		
Blood test	33.80	66750
Ultrasound	59.50	55707
Total	93.30	
Second-trimester screening	47.00	66751
Amniocentesis		
Procedure	146.75	16600
Karyotyping	196.35	55054
Total	343.10	73293
Chorionic villus sampling		
Procedure	196.35	16603
Karyotyping	196.35	55054
Total	392.70	73293
Published international commercial cost		
NIPT[33]	743	–

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the same behaviour shown in the original cohort when only invasive diagnostic testing was available. A break even analysis determined at what price point NIPT would become less costly than current practice for both 75.3% and 100% uptake.

Although we assumed 100% sensitivity and specificity for cffDNA,[5,9,15,17,22],[7,8] a two-way sensitivity analysis was also undertaken for NIPT using 98% sensitivity and 97% specificity [6,15,28] as a worst-case scenario (Tables 3 and 4).

The rates of procedure-related pregnancy loss for invasive diagnostic testing were also varied. Rates reported in the literature are inconsistent, reflecting the difficulty in establishing background risk and differences in the time frame used to define procedure-related loss. The amniocentesis and chorionic villus sampling miscarriage rates of 0.6% and 0.7% used in our baseline model were based on a pooled rate for pregnancy loss within 14 days following the procedure as calculated by a 2007 systematic review.[35] The figures used in the sensitivity analysis reflect the confidence intervals of this pooled analysis [35] and the ratio of amniocentesis to chorionic villus sampling on each pathway (Table 1).

Table 3 Comparison of outcomes of current model (FTS with invasive diagnostic testing) and FTS with NIPT

Outcomes	Current model*	FTS with NIPT Baseline (sensitivity analysis)*	
Diagnostic/NIPT test uptake	0.753	0.753	1.00
	n	*n*	*n*
FTS – at high-risk result	1176	1176	1176
FTS – not at high-risk result	31 302	31 302	31 302
1117NIPT tests (sufficient DNA)	–	842	1117
Invasive diagnostic tests			
After high-risk result	885	110 (132)	116 (146)
After not at high-risk result	634	634	634
Total	1519	744 (765)	750 (780)
Procedure-related miscarriages			
After high-risk result	6	<1	<1
After not at high-risk result	4	4	4
Total	10	<5	<5
High risk confirmed T21	69	69 (68)	75–76 (74)

*Baseline results were calculated using 100% sensitivity and specificity for NIPT; Sensitivity analysis refers to the results of a two-way sensitivity analysis assuming a worst-case scenario with NIPT sensitivity 98% and specificity 97%, based on published data.[6,15] Sensitivity analysis results are not shown where baseline and sensitivity analysis results are the same.

Results

Base case

The costs and benefits of the two prenatal screening and diagnosis models are presented in Tables 3 and 4. Variation in the uptake of NIPT following a high-risk result has been included. There were 51% and 88% fewer invasive diagnostic tests and procedure-related miscarriages in all women and high-risk women, respectively, in the FTS/NIPT screening model compared with current practice. If the uptake of NIPT were to reach 100% in women identified at high risk by first-trimester screening, an additional 6-7 Down syndrome pregnancies would be confirmed. Under baseline assumptions, using NIPT as an intermediary step before offering invasive diagnostic testing would have increased the cost of prenatal testing by $345 700 (9.7%) over two years from $3.56 million to $3.91 million. If NIPT uptake reached 100%, the cost would have increased by $553 500 (15.5%). This translates to an additional cost of between $69 000 and $111 000 per averted procedure-related loss. First-trimester screening to identify women at high-risk accounts for 85%, 77% and 74% of the total cost of prenatal testing in model 1, model 2 (75.3% NIPT uptake) and model 2 (100% NIPT uptake), respectively.

Sensitivity analysis

If the cost of NIPT were to drop to $330 and $550 for 75% and 100% uptake, respectively, FTS/NIPT would become less costly in confirming Down syndrome pregnancies than current practice. The model incorporating NIPT is the same cost to the health system where the cost of NIPT is $330 (current uptake) and $248 (where uptake is 100%).

Two-way sensitivity analysis of NIPT with lower sensitivity (98%) and specificity (97%) [6,15,28] still reduced the number of invasive tests by about 50% and did not significantly change the number of confirmed Down syndrome cases compared with baseline assumptions (Table 3). The number of procedure-related pregnancy losses and the cost of diagnostic testing increased by a little less than 3% (Tables 3 and 4).

Variation in the uptake of confirmatory invasive diagnostic testing and feasibility (sufficient DNA) of NIPT made negligible difference to the cost-effectiveness of confirming a Down syndrome pregnancy (data not shown). Procedure-related miscarriages increased proportionately to the increase in risk, with 8 procedure-related miscarriages following a high-risk result in model 1, and 1 procedure-related miscarriage for high-risk women in the NIPT model using base-line figures when assuming a high miscarriage rate (Table 5).

Discussion

The cost per Down syndrome case confirmed in the NIPT model was 9.7% higher ($56 360) than the current

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Table 4 Costs and cost-effectiveness ratios of alternative screening and diagnosis models

Costs/cost-effectiveness	Current practice*	FTS with NIPT *Baseline (sensitivity analysis)	
Diagnostic test uptake	0.753	0.753	1.00
Total cost of testing pathway	3 565 542	3,911,278 (3 919 262)	4 119 025 (4 129 486)
Cost of screening	3 030 197	3 030 197	3,030,197
Cost of invasive diagnostic testing†	535 344	256,481 (264,015)	258 749 (269 010)
Cost of NIPT	–	625 050	830 079
Cost per T21 case confirmed*	51 372	56 360 (57 557)	54 186 (55 373)
ICER‡		NA	83 724 (109 108)

*Baseline results were calculated using 100% sensitivity and specificity for NIPT; Sensitivity analysis refers to the results of a two-way sensitivity analysis assuming a worst-case scenario with NIPT sensitivity 98% and specificity 97%, based on published data.[6,15]
†Includes all Down syndrome cases confirmed through diagnostic testing, regardless of screening test result
‡ICER: (incremental cost-effectiveness ratio) is the ratio of the change in costs to incremental benefits of NIPT.[44]

prenatal screening and diagnosis strategy using invasive diagnostic testing ($51 372) at a total cost of $3.91 million compared with $3.57 million over two years in Western Australia. The higher cost of a model with NIPT following a high-risk result is inconsistent with that reported in the United States by Garfield *et al.*[36] While not directly comparable to our study, Song *et al.*, whose model included women over 35 years as 'high risk' and incorporated termination and lifetime cost of care for Down syndrome, also differed from our results, with NIPT shown to be less costly and more cost-effective than current first-trimester screening.[31] These differences are largely explained by the lower cost of invasive diagnostic testing in our model compared with those reported in the United States and the inclusion of lifetime costs.

The costs and cost-effectiveness of prenatal screening and diagnosis using NIPT are highly variable, ranging from $3.45 to $5.75 million over a two-year period depending on the price and uptake of NIPT. While NIPT is likely to become cheaper over time with improved technology, competition internationally and economies of scale, the real price of sourcing NIPT from international providers will remain susceptible to exchange rates. With NIPT accounting for between 16% and 20% of the total cost of the model, a decrease in the value of the Australian dollar by 10% would increase the cost of prenatal testing by 1.6 to 2% or $62 000 to $83 000 over 2 years.

Table 5 The predicted number of procedure-related miscarriages in the cohort under different assumptions

	Miscarriage rate	Current	NIPT 75%	NIPT 100%
Not at high risk	Baseline	3.83	3.83	3.83
	Low	3.12	3.12	3.12
	High	4.62	4.62	4.62
High risk	Baseline	5.57	0.66	0.70
	Low	3.91	0.55	0.58
	High	7.99	0.77	0.81

Baseline, low and high miscarriage rate calculated from the range of risks for amniocentesis and CVS provided in Table 1 and the ratio of amniocentesis to CVS in each pathway (high risk 71% amniocentesis, not at high risk 96% amniocentesis)

The purchasing behaviour of women seeking prenatal testing is also of interest with the availability of NIPT having further potential to impact public health service uptake and associated costs. Depending on the way in which NIPT is funded, the simplicity of the test and the reduced miscarriage risk may have a flow on effect by increasing the overall uptake of prenatal screening in Western Australia (currently around 60%).[37] In the absence of Medicare funding for NIPT, high-risk women may seek out public hospitals that decide to provide the test, potentially shifting costs from Federal to State governments. Additionally, with the reported out of pocket costs of invasive diagnostic procedures in the private system reaching almost a thousand dollars at some centres,[38] even in the absence of public funding, some women may soon find NIPT to be a cheaper option with the effect of reducing the number of publicly funded invasive tests. Although not included in our model pathway, it is possible that some women, who previously would have declined screening or diagnostic testing, could choose NIPT.

While our analysis provides us with a clear comparison of the cost of the two prenatal testing models assuming the same uptake of NIPT as currently seen with diagnostic testing, when we consider a higher uptake of testing with NIPT, the results are more difficult to interpret. If the uptake of NIPT included all women identified at high risk by first-trimester combined screening, an extra 6–7 Down syndrome pregnancies (2 per 10 000 women) would be confirmed at an additional cost of $553 500 ($83 700 per additional case). Of the additional Down syndrome pregnancies confirmed with 100% NIPT uptake, it is estimated that about 50% of these pregnancies (3–4) would have miscarried spontaneously.[39] Some of these may have been lost prior to receiving test results (estimated to take 3 weeks), others after confirmation. Taking miscarriage into account, in our original cohort, the 6–7 additional Down syndrome pregnancies confirmed could have averted up to 4 Down syndrome births, assuming women choose to terminate affected fetuses.

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A clear benefit of NIPT is the 88% reduction in invasive diagnostic procedures and associated miscarriage, comparable to the 84% reduction predicted by Susman *et al.*[40] NIPT has the potential to improve the clinical experience by offering a result with higher sensitivity and specificity than FTS alone.[40] Reducing the need to weigh the risk of procedure-related miscarriage against that of having a Down syndrome pregnancy may reduce anxiety for women and their families. While it is not clear why 25% of the women in our cohort identified 'at high risk' chose not to have invasive diagnostic testing – although some are likely to have miscarried prior to having the opportunity – previous studies have suggested that miscarriage risk plays a significant role in this decision.[41,42] In the current model of care, there was a 75% uptake of diagnostic invasive testing by women identified at high risk by first-trimester screening. We speculate that there would be greater uptake of NIPT as an intermediate screening step because it provides greater sensitivity and specificity than FTS and may avoid the need for invasive diagnostic testing and the risk of procedural loss.

Although the majority of published studies have reported sensitivity and specificity for NIPT at 100%[5,8,9,12,15,17,18,20–23] (our baseline assumption), these studies used samples with a very high prevalence of Down syndrome; therefore, we also considered the impact of lower sensitivity (98%) and specificity (97%)[6,15] for NIPT in a two-way sensitivity analysis. As several validation studies have shown that NIPT will detect more than 99% of trisomy 21 with false-positive rates of less than 0.1%, we considered this to be the worst-case scenario. Lower specificity led to a small increase in invasive procedures and associated costs and procedure-related miscarriage.

Our study had a number of limitations. Although NIPT can also detect trisomy 13 and 18 and sometimes the sex chromosome abnormalities, we have only included Down syndrome in this analysis. False-positive NIPT results for trisomy 18 and 13 could increase the number and cost of unnecessary invasive tests and procedure-related fetal losses. In NIPT validation studies where there is a high prevalence of Down syndrome, NIPT has been shown to have a false-positive rate of 0.2% and 0.1% for trisomy 13 and 18, respectively[9,13,16,18,199]; however, this remains lower than the false-positive rates for trisomy 13 and 18 for first-trimester screening alone.[43] We have also not considered the current inability for NIPT to diagnose other chromosomal abnormalities that would be diagnosed through traditional karyotyping. Susman *et al.* demonstrated that the introduction of NIPT (with diagnosis of trisomies 21, 18 and 13) could result in the diagnosis of 17% fewer chromosomal abnormalities with varying severity. Some of these may be identified by amniocentesis following the detection of fetal abnormality on ultrasound, but the data on this are limited.[40] In our analysis, we have not considered that some women may choose to have invasive testing over NIPT for this reason. Additionally, due to a lack of data, we could not include the number of high-risk women in our cohort who would have had amniocentesis had they not miscarried. In the hypothetical model, some of these women may have had NIPT purely because it was available earlier (from 14 weeks) than amniocentesis (16 weeks), thus increasing costs.

Our analysis looks only at the use of NIPT as a tool to reduce the number of invasive diagnostic procedures following a screening test result that is 'at high risk' according to current guidelines. This reflects current evidence for the use of NIPT,[24] but also the need to constrain costs, with the use of NIPT as a stand-alone screening tool coming at a significant price. As more women at high risk choose to have NIPT testing, the number of Down syndrome cases identified during pregnancy would increase, however, the rate of false negatives in FTS means that there would still be a number of Down syndrome pregnancies that would not be identified. In our cohort, 19% of cases of Down syndrome were missed by FTS. If NIPT were to become more widely adopted as a secondary screening tool, it would be worth considering how variation in the risk cut-off of FTS (currently 1:300) could improve detection of Down syndrome and how this would impact costs.

Noninvasive prenatal testing has the potential to reduce procedure-related miscarriage, improve the mother's experience of prenatal testing and detect more cases of Down syndrome compared with current practice, at an increased, but variable cost. As NIPT becomes more widely adopted, it will certainly challenge the current model of care in Australia and raise questions about equity, access and funding. In this rapidly developing area, Australian experts and policymakers will need to formulate guidelines and a regulatory framework for this new technology ensuring, among other things, that women receive the most accurate information available regarding the performance of NIPT. This should include the positive predictive value of the test as well as sensitivity and specificity. The potential benefits, increased awareness of women and availability of NIPT through clinical and pathology providers, present an urgent need to define how these screening technologies will be supported, monitored and evaluated.

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CHAPTER 7 PAPER 6

DIAGNOSTIC PERFORMANCE AND COSTS OF CONTINGENT SCREENING MODELS FOR TRISOMY 21 INCORPORATING NON-INVASIVE PRENATAL TESTING

Susannah Maxwell, Peter O'Leary, Jan Dickinson, Graeme Suthers. Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing, Australian New Zealand Journal of Obstetrics and Gynaecology 2017 doi: 10.1111/ajo.12612

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ORIGINAL ARTICLE

Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing

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Conflicts of interest: GK Suthers is an employee and shareholder of Sonic Healthcare, and is involved in the provision of non-invasive prenatal testing in Australia. Sonic Healthcare had no other interest in designing, funding or approving the study and manuscript. JD, POL and SM have no conflicts of interest to declare.

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Background: Contingent screening for trisomy 21 using non-invasive prenatal testing has the potential to reduce invasive diagnostic testing and increase the detection of trisomy 21.

Aim: To describe the diagnostic and economic performance of prenatal screening models for trisomy 21 that use non-invasive prenatal testing as a contingent screen across a range of combined first trimester screening risk cut-offs from a public health system perspective.

Methods: Using a hypothetical cohort of 300 000 pregnancies, we modelled the outcomes of 25 contingent non-invasive prenatal testing screening models and compared these to conventional screening, offering women with a high-risk (1 > 300) combined first trimester screening result an invasive test. The 25 models used a range of risk cut-offs. High-risk women were offered invasive testing. Intermediate-risk women were offered non-invasive prenatal testing. We report the cost of each model, detection rate, costs per diagnosis, invasive tests per diagnosis and the number of fetal losses per diagnosis.

Results: The cost per prenatal diagnosis of trisomy 21 using the conventional model was $51 876 compared to the contingent models which varied from $49 309–66 686. The number of diagnoses and cost per diagnosis increased as the intermediate-risk threshold was lowered. Results were sensitive to trisomy 21 incidence, uptake of testing and cost of non-invasive prenatal testing.

Conclusion: Contingent non-invasive prenatal testing models using more sensitive combined first trimester screening risk cut-offs than conventional screening improved the detection rate of trisomy 21, reduced procedure-related fetal loss and could potentially be provided at a lower cost per diagnosis than conventional screening.

KEYWORDS

cost-effectiveness, policy, prenatal diagnosis, prenatal screening, trisomy 21

INTRODUCTION

The diagnosis of Down syndrome (trisomy 21, T21) prenatally requires the analysis of DNA collected via amniocentesis or chorionic villus sampling. As these invasive tests carry a small but significant risk of miscarriage, their use tends to be recommended only for pregnancies considered to be at high risk as determined by prenatal aneuploidy screening. First trimester

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screening (cFTS) using combined ultrasound and biochemistry biomarkers to assess aneuploidy risk at 11–14 weeks gestation has been publicly funded in Australia since 2003. Using a risk cut-off of one in 300, this test can identify 82% of fetal T21 at a 3.5% false positive rate.[1] While cFTS has reduced the number of invasive diagnostic tests, almost 20% of fetal T21 remains undiagnosed.[1,2]

Recent advances in prenatal screening technology now provide the opportunity to improve the detection of fetal T21 and reduce the number of invasive diagnostic procedures and associated miscarriage rates.[3] Non-invasive prenatal testing (NIPT) involves the extraction and analysis of feto-placental DNA circulating within maternal blood to provide a risk of fetal T21 with a sensitivity of 99.2% and specificity of 99.91%. The test can be done from 10 weeks gestation.[4] Despite its superior performance, it is not anticipated that NIPT will replace cFTS as part of a publicly funded, population-wide first-line screening test in the short- to mid-term due to cost and to the ill-defined benefit of cFTS in detecting other chromosomal abnormalities.[5,6]

There is also the option to use NIPT as a second-tier screen, contingent upon the result of cFTS, as is being internationally considered.[7,8] Contingent screening has the potential to reduce false positive rates and invasive diagnostic testing, and to increase the detection of T21, depending on the cFTS risk cut-off.[1,9] Previously we reported on the costs and outcomes of NIPT in Australia as a second-tier screen with the currently accepted cFTS screen-positive risk cut-off (one in 300), demonstrating that such a strategy would reduce procedure-related miscarriages but would not improve the detection rate of fetal T21.[3] Another Australian study considered NIPT as a second-tier screen for women identified as high risk by cFTS as well as for women of advanced maternal age (>35 and >40 years).[10] In this paper we describe the diagnostic and economic performance of contingent NIPT screening models using a range of increasingly sensitive cFTS risk cut-offs compared to conventional screening from the perspective of the Australian public health system.

MATERIALS AND METHODS

Using Microsoft Excel, we developed a decision model of the costs and outcomes of two first trimester screening strategies.

1 Conventional screening: women with a cFTS test risk of >1:300 were offered invasive prenatal diagnostic testing.
2 Contingent screening incorporating NIPT: cFTS results were classified as high, intermediate and low. Women with a high risk were offered invasive diagnostic testing only, while women with an intermediate risk were offered NIPT; women at low risk were not offered further testing. Those women with a positive NIPT result were offered an invasive diagnostic test. Our analysis considered 25 contingent models using different risk cut-offs to define high and intermediate risk. High-risk cut-offs were one in five, 10, 20, 30 and 50. Intermediate-risk cut-offs used were one in 300, 600, 1000, 1500 and 2500.

We present costs and outcomes for a hypothetical cohort of 300 000 screened pregnancies, representing the approximate number of live births annually in Australia.[11] Costs and outcomes include the overall cost of each screening model, the detection rate of fetal T21, the cost per diagnosis, invasive diagnostic tests per diagnosis and the biological cost, that is the number of fetal losses per diagnosis (reported as fetal losses per 1000 diagnoses). Downstream costs and outcomes following screening and diagnosis were not considered. Sensitivity analyses determined the impact of variation in model parameters on the incremental cost per diagnosis.

Model parameters

Base case values and ranges used in one-way sensitivity analyses are shown in Table 1. The decision model used data from a

TABLE 1 Base case values and ranges used in one-way sensitivity analyses

Parameter	Base case (sensitivity analysis)
T21 at 16 weeks	0.00299 (0.002–0.004)[1]
Procedure-related fetal loss rate	0.006 (0.001–0.013)[23]
Data for cFTS risk cut offs	Figure 1[1]
Conventional model	
cFTS risk cut off (1 in *x*)	300
Uptake of invasive testing	100% (80–100%)[1]
Contingent models	25 models
cFTS intermediate-risk cut off	300/600/1000/1500/2500
cFTS high-risk cut off	5/10/20/30/50
NIPT	
Sensitivity	0.990 (0.98–0.999)[26]
Specificity	0.9992 (0.995–0.9999)[26]
Unreportable	1.0% (0.1–4%)[24]
Uptake of NIPT – intermediate-risk	100% (85–100%)
Uptake of invasive testing	
High-risk cFTS	100%
After unreportable NIPT	100% (80–100%)[1]
After positive NIPT	100% (85–100%)[25]
Costs	
cFTS	$102.95[10]
GP consultation	$36.30[10]
NIPT	$400 ($300–500)
Invasive test (including consultations)	$697.05[10]

cFTS, first trimester screening using combined ultrasound and biochemistry biomarkers; GP, general practitioner; NIPT, non-invasive prenatal testing.

comprehensive retrospective audit of 83 392 singleton pregnancies in Western Australia (January 2005 to December 2009) in which there was a completed cFTS as previously reported.[1] These pregnancies represented 97% of all singleton screens with compete screening data (83 392/85 844), with the remaining 3% lost to follow up. A further 4508 singleton screens did not have complete screening data and were not included in the screened cohort. Over this same time period there were 143 245 singleton births in Western Australia.[12] Within this screened cohort, 250 women had a T21 pregnancy (prevalence 1:334) with 205 (82%) identified through cFTS.

Applying the pathway probabilities from this cohort to the larger hypothetical cohort allows us to estimate total costs and total numbers Australia-wide over a one year time period. This cohort provided data on the prevalence of T21 within the screened population and detection, screen- and false-positive rates at different cFTS risk cut-offs. Figure 1 shows the proportion of this cohort with a cFTS risk above these risk cut-offs, and the corresponding proportion of pregnancies identified with fetal T21. This cohort study received ethics approval from the King Edward Memorial Hospital, Curtin University and the Department of Health Western Australia (formerly CHIC) Health Research Ethics Committees, which exempted the study from requiring individual patient consent. Further ethics approval was not sought for the modelling study presented here.

Our base case analysis assumed 100% uptake in all women who are offered cFTS, NIPT or an invasive diagnostic test. We used 100% uptake due to the uncertainty surrounding the uptake of NIPT and invasive diagnostic testing at different risk cut-offs, and the complexity of varying these figures for screening models with different high- and intermediate-risk cut-offs. These rates also allowed us to report the potential performance and cost of these screening models. The impact of variation in the uptake of invasive testing and NIPT was considered with sensitivity analysis.

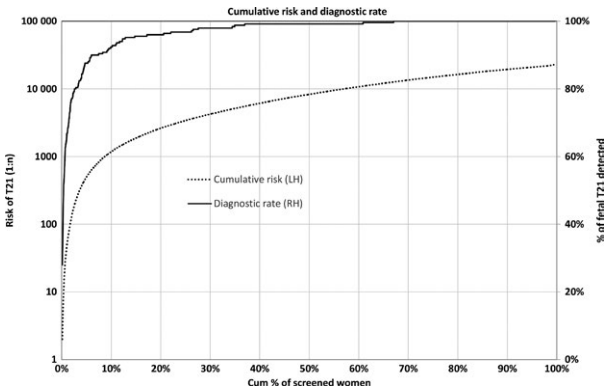

FIGURE 1 Cumulative risk distribution at first trimester screening (cFTS) (left axis) and cumulative diagnostic rate (right axis) in the unselected cohort used as the basis for the analysis.

The sensitivity and specificity of NIPT for detecting T21 were taken to be 0.99 and 0.9992, respectively[4] (Table 1). It was assumed that 1% of NIPTs could not be reported. In the absence of consensus regarding the management of a woman at intermediate risk with an unreportable NIPT, we assumed such a woman would be offered invasive diagnostic testing if her cFTS risk was >1:300.

With one exception, we used the lowest cost estimates described in a 2014 Australian NIPT cost analysis[10] as these represent the cost of services that are subsidised by the Australian Government under Medicare, presented in 2014 Australian dollars. The exception was NIPT which is not covered by Medicare and for which the cost had fallen rapidly since that publication. We assumed a cost of $400, reflecting the lowest cost among available commercial tests in Australia at June 2016. We included the cost of cFTS despite it being universal to estimate the overall costs of models with different risk cut-offs. We included the cost of a general medical consultation following a screen-positive cFTS and a positive NIPT result, and the cost of an initial and consequent consultation with an obstetrician where a woman had invasive diagnostic testing.

Sensitivity analysis

We based our sensitivity analysis on the contingent model which had the closest equivalent cost per diagnosis to the conventional screening model under baseline assumptions. One-way sensitivity analyses determined the relative impact of variation in NIPT performance parameters, cost and uptake on the incremental cost per diagnosis. Variation in procedural fetal loss rate was considered across all 25 contingent models. We also performed a threshold analysis to determine the price point for NIPT at which contingent models would have a total public health system cost equivalent to that of the conventional model.

RESULTS

Base case

The costs and outcomes of conventional screening and the 25 contingent screening models under baseline assumptions are presented in Tables 2 and 3. In the conventional model, 3.5% of women had a cFTS risk of >1:300 and were offered invasive testing (Table 2). In the contingent models, 0.3–1.1% of women were at high risk (and were offered invasive testing), with 2.4–18.9% of women being at intermediate risk (and offered NIPT) (Table 3). The sensitivity of the contingent models varied from 81.3 to 95.5% (730–856/897 cases of fetal T21) compared to 82% (736/897 cases of fetal T21) for the conventional model.

In the conventional model, the number of invasive diagnostic tests required to make one diagnosis of T21 in a fetus was 14.2, whereas 1.6–4.7 invasive diagnostic tests were required to make a

TABLE 2 Costs and outcomes for conventional screening

Outcome	Conventional model
High-risk (%)	3.5%
DR for T21 (%)	82.0%
Cost/diagnosis ($)	51 876
IDT/diagnosis (*n*)	14.18
Fetal loss/1000 diagnoses	85.1
Total cost ($million)	38.16

DR, detection rate; IDT, invasive diagnostic test.

diagnosis of T21 in the contingent models (Tables 2,3). This number was predominantly driven by the proportion of women in the high-risk category. The rate of fetal losses per 1000 diagnoses was 85.1 in the conventional model and ranged from 3.8 to 22.0 in the contingent models, with the lowest biological cost per diagnosis in the contingent model with risk cut-offs of 1:1500 (intermediate) and 1:5 (high). Reducing the high-risk cut-off from 1:5 to 1:10 in this model increased the rate of fetal loss by 60%, as did the next step (from 1:10 to 1:20). In terms of fetal loss, the contingent screening models were 4–22 times less costly when compared to the conventional model.

The overall cost of screening and diagnostic testing in the cohort of 300 000 women was $38.2M in the conventional model and ranged from $36.0M to $57.1M in the contingent models (Tables 2,3). As expected, the lowest overall cost corresponded to the contingent model with the smallest proportion of women having NIPT or invasive testing, that is risk cut-offs of 1:300 (intermediate) and 1:5 (high); however, this model failed to reach the diagnostic performance of the conventional model (81.3% compared to 82%).

The cost per diagnosis of the conventional model was $51 876 compared to the contingent models which varied from $49 201 to $66 686 (Tables 2,3), with the number of diagnoses and cost per diagnosis increasing as the intermediate-risk threshold was lowered. At an intermediate-risk cut-off of 1:1000 the cost per diagnosis was closest to that of the conventional model (Table 2) but with a sensitivity of >90% (compared to 82%), representing an additional 73 diagnoses of fetal T21 in a population of 300 000 screened women. Incremental costs and diagnoses of the 25 contingent models compared to conventional screening are shown in Figure 2. While the intermediate-risk cut-off used in the contingent models had an impact on overall cost and effectiveness, the high-risk cut-off did not. Contingent screening using the same risk cut-off as conventional screening (1:300) was both less costly and marginally less effective (due to the <100% sensitivity of NIPT). The high-risk cut-off had a significant impact on the biological cost per diagnosis (Table 3).

Sensitivity analyses

A contingent model with an intermediate-risk cut-off of 1:1000 and a high-risk cut-off of 1:10 was used for the sensitivity analyses. This model had a cost per diagnosis almost equivalent to the conventional model in the base case analysis. The incremental cost per diagnosis was relatively insensitive to variation in the performance parameters of NIPT, but was sensitive to the incidence of T21 in the population, changes in the uptake of invasive testing and NIPT, and the cost of NIPT (Fig. 3). If the frequency of procedure-related fetal loss was reduced from 0.6% (base case) to 0.1%, the rate of fetal loss per 1000 diagnoses was 14.2 for the conventional model, and between 0.6 and 3.7 for the contingent models. If the frequency of procedure-related fetal loss was higher (1.3%), the rate of fetal loss rose to 1844 for the conventional model and was between 82 and 477 for the contingent models. There was little impact on the relative difference in rate of fetal loss between the various contingent models (data not shown). The NIPT price points for each contingent model which resulted in a total cost to the public health system equal to that of the conventional model ranged from $52 to $640 (Table 4).

DISCUSSION

Our results show that contingent NIPT models using more sensitive cFTS risk cut-offs than conventional screening, improve the detection rate of fetal T21 and reduce procedure-related fetal loss, and could be provided at a lower cost per diagnosis than conventional screening. Conventional screening had a cost per diagnosis of $51 876, while the cost per diagnosis of our contingent models ranged from just under $50 000 at an 81.3% detection rate (cut-offs 1:10 and 1:300) to almost $67 000 (cut-offs 1:50 and 1:2500) at a 95.5% detection rate. It is not particularly helpful to compare economic evaluations modelled on different healthcare systems, costs and assumptions; however, our finding that contingent screening offers a cost-effective alternative national health model to conventional screening is consistent with international studies in Belgium,[13,14] the Netherlands[15] and the UK.[16] In a Flemish study the introduction of NIPT predicted a reduction in procedure-related miscarriages without increasing the short-term screening costs,[14] while another showed lowering the risk from 1:300 to 1:600 would increase costs by a maximum of 3%.[13]

Given the intangible benefits of prenatal screening in providing information and facilitating informed reproductive choice, and the reluctance to make assumptions about termination and averted lifetime costs of care for those with disability, the cost-effectiveness of prenatal screening programs can be difficult to determine. However, if we consider that conventional screening represents a cost-effective model, there are a number of potential comparators for the assessment of contingent screening models. A contingent model with an intermediate-risk cut-off of 1:1000 costs ~$1300 more per diagnosis than the conventional model, but delivers an 8% increase in sensitivity (90.1%), while a model with a risk cut-off of 1:600 costs as much as $2500 less per diagnosis with a 6% increase in sensitivity (88.4%). These contingent models (with a high-risk cut-off of 1:10) achieve these outcomes with up to 12-fold fewer fetal losses per diagnosis than in

TABLE 3 Costs and outcomes for the 25 contingent models

	High-risk cut-off				
Intermediate-risk cut-off	**1/5**	**1/10**	**1/20**	**1/30**	**1/50**
1/300†	‡				
Inter/high-risk (%)	3.2%/0.3%	3.1%/0.4%	2.9%/0.6%	2.7%/0.8%	2.4%/1.1%
DR for T21 (%)	81.3%	81.5%	81.6%	81.7%	81.7%
Cost/diagnosis ($)	49 309	49 281	49 367	49 434	49 685
IDT/diagnosis (*n*)	1.70	2.13	2.87	3.45	4.67
Fetal loss/1000 diagnoses	4.2	6.8	11.2	14.7	22.0
Cost ($million)	35.97	36.01	36.12	36.21	36.42
1/600					
Inter/high-risk (%)	5.5%/0.3%	5.4%/0.4%	5.2%/0.6%	5.%/0.8%	4.7%/1.1%
DR for T21 (%)	88.4%	88.5%	88.6%	88.7%	88.8%
Cost/diagnosis ($)	49 222	49 201	49 283	49 347	49 580
ICER ($)	15 297	15 662	17 269	18 512	21 843
IDT/diagnosis (*n*)	1.65	2.04	2.73	3.26	4.38
Fetal loss/1000 diagnoses	3.9	6.3	10.4	13.6	20.3
Cost ($million)	39.04	39.08	39.19	39.27	39.49
1/1000		§			
Inter/high-risk (%)	8.5%/0.3%	8.3%/0.4%	8.1%/0.6%	7.9%/0.8%	7.6%/1.1%
DR for T21 (%)	90.0%	90.1%	90.2%	90.3%	90.4%
Cost/diagnosis ($)	53 115	53 090	53 167	53 227	53 453
ICER ($)	65 834	65 361	66 051	66 579	68 927
IDT/diagnosis (*n*)	1.65	2.03	2.70	3.23	4.33
Fetal loss/1000 diagnoses	3.9	6.2	10.2	13.4	20.0
Cost ($million)	42.88	42.91	43.02	43.11	43.33
1/1500					
Inter/high-risk (%)	12.1%/0.3%	11.9%/0.4%	11.7%/0.6%	11.6%/0.8%	11.3%/1.1%
DR for T21 (%)	93.9%	94.0%	94.1%	94.2%	94.3%
Cost/diagnosis ($)	56 545	56 519	56 591	56 647	56 863
ICER ($)	88 645	88 123	88 423	88 648	90 145
IDT/diagnosis (*n*)	1.63	2.00	2.64	3.15	4.20
Fetal loss/1000 diagnoses	3.8	6.0	9.9	12.9	19.2
Cost ($million)	47.64	47.68	47.79	47.88	48.09
1/2500					¶
Inter/high-risk (%)	18.9%/0.3%	18.8%/0.4%	18.6%/0.6%	18.4%/0.8%	18.1%/1.1%
DR for T21 (%)	95.1%	95.2%	95.3%	95.4%	95.5%
Cost/diagnosis ($)	66 407	66 370	66 431	66 478	66 686
ICER ($)	157 301	156 221	156 004	155 815	156 884
IDT/diagnosis (*n*)	1.64	2.01	2.64	3.14	4.18
Fetal loss/1000 diagnoses	3.8	6.0	9.9	12.8	19.1
Cost ($million)	56.65	56.69	56.80	56.89	57.10

DR, detection rate; ICER, incremental cost per diagnosis; IDT, invasive diagnostic test; Inter, intermediate-risk.
†ICERs for this model are negative and are therefore not reported.
‡Lowest detection rate, lowest cost per diagnosis and lowest cost overall.
§Higher detection rate than conventional model with closest cost per diagnosis to the conventional model ($1214 more per diagnosis).
¶Highest detection rate, highest cost per diagnosis and highest cost overall.

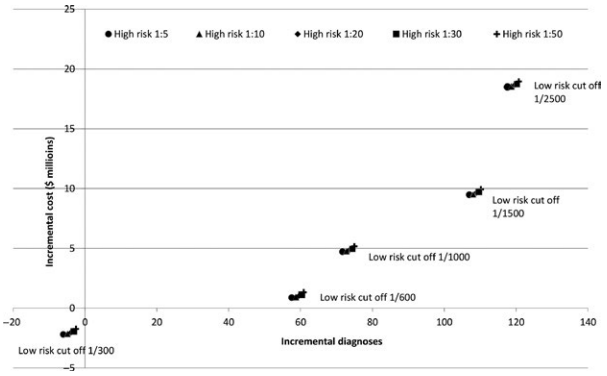

FIGURE 2 Incremental total costs and diagnostic performance for detecting fetal T21 of the 25 contingent models compared to conventional screening.

the conventional model. The cost-effectiveness of improving the detection rate further is less clear. An intermediate-risk cut-off of 1:1500 achieves a detection rate of 94% at a cost per diagnosis of approximately $56 000, that is an incremental improvement in detection rate of 3.1% at an incremental cost per additional diagnosis of approximately $88 000.

The high-risk cut-off (directing women toward invasive testing) has negligible impact on the overall cost of screening but a significant impact on biological cost, supporting a model that places fewer women in the high-risk category. A high-risk cut-off of 1:10 may represent a reasonable balance between the benefit of identifying other rare chromosomal abnormalities in women with a high cFTS risk and the risk of fetal loss, but data remain limited. Susman *et al.* and Norton *et al.* reported that 88 and 83% of all chromosomal abnormalities among high-risk pregnancies were accounted for by those conditions commonly detected by NIPT (trisomy 21, 18, 13 and sex chromosome abnormalities). Some of the remaining rarer conditions may still be diagnosed where sonographic fetal appearance suggests invasive testing. A retrospective analysis of 224 high-risk pregnancies with a chromosomal anomaly identified by invasive testing, demonstrated that if invasive testing, and not NIPT, were recommended for cFTS risk >1:50 and/or ultrasound-detected abnormality, the residual risk of an unidentified pathogenic chromosomal abnormality would have been 0.33%.[6] The choice to have invasive diagnostic testing or NIPT among high-risk women will ultimately depend on the individual and her circumstances, attitudes and values. The finding that the high-risk cut-off has negligible impact on the overall cost and cost per diagnosis supports such patient autonomy.

The cost-effectiveness of these models is sensitive to variation in uptake in invasive testing and NIPT. The majority of the costs of the screening program is accounted for by cFTS, so a reduction in the uptake of invasive testing following a positive NIPT result will result in a higher cost per diagnosis as the number of cases diagnosed has decreased. Where the sensitivity analysis considers

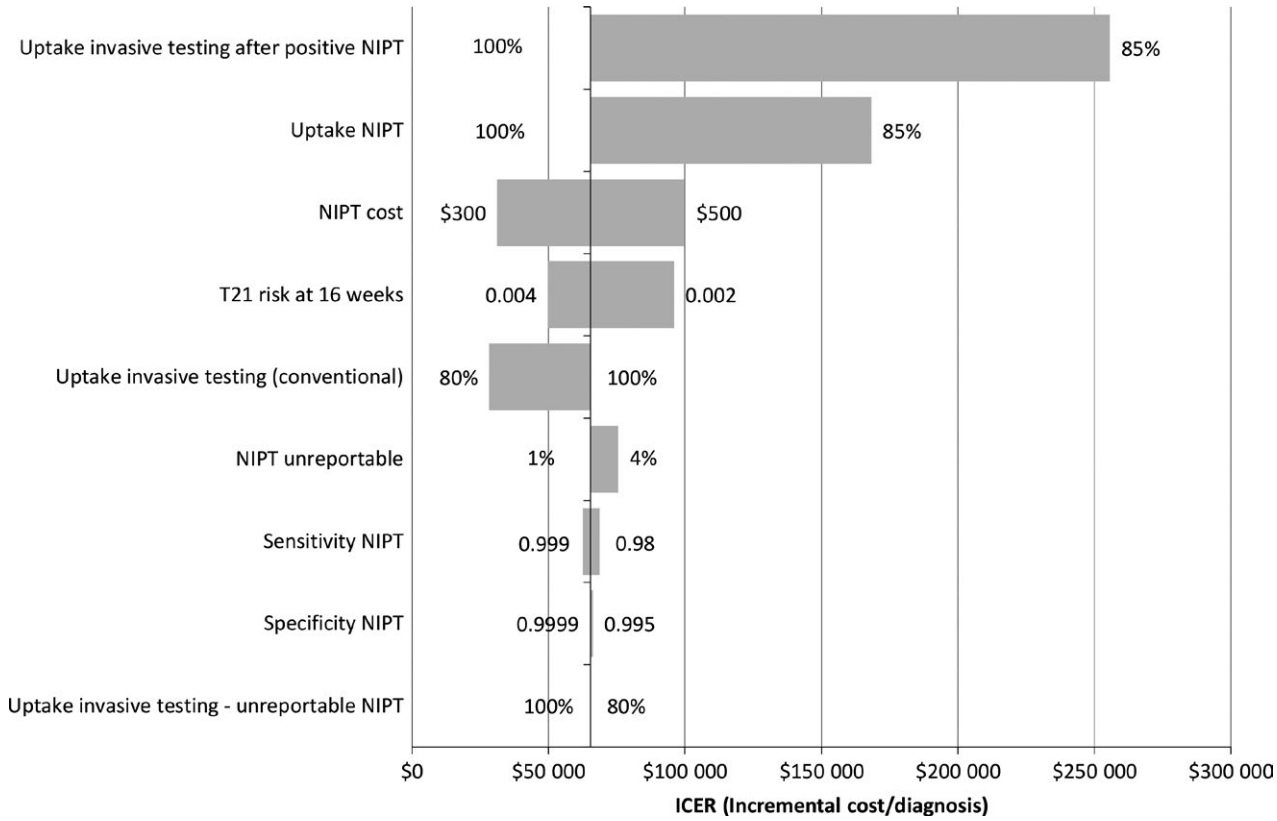

FIGURE 3 Tornado diagram showing the relative impact of variation in input parameters on the ICER (incremental cost per diagnosis) for a contingent model with first trimester screening using combined ultrasound and biochemistry biomarkers (cFTS) risk cut-off of 1:10 (high risk) and 1:1000 (intermediate risk). The high and low parameter estimates are shown by each bar.

TABLE 4 Threshold analysis: non-invasive prenatal testing cost that provides a total public health system cost equal to that of the conventional model for each of the 25 contingent models

	High risk				
Intermediate risk	**1/5**	**1/10**	**1/20**	**1/30**	**1/50**
1/300	$626	$632	$636	$639	$640
1/600	$347	$343	$334	$326	$306
1/1000	$214	$209	$200	$192	$174
1/1500	$138	$134	$126	$120	$106
1/2500	$75	$71	$66	$61	$52

a reduction in the uptake of invasive testing in the conventional model, the incremental cost per diagnosis for the contingent model is less expensive. This occurs because the contingent model is now leading to the diagnosis of even more cases of fetal T21 compared to the conventional model, making it incrementally less expensive to diagnose each case. This uncertainty is a significant limitation of our study. It is difficult to predict how NIPT might impact a woman's decision to participate in prenatal screening and to have further testing following a high- or intermediate-risk result. Uptake is likely to vary with out-of-pocket costs, knowledge and attitudes and risk.[17,18] Chitty *et al.*[8] reported NIPT uptake at eight National Health Service hospitals in the UK. In women with a risk >1:150, 74% had NIPT and 17.8% had invasive diagnostic testing, and the uptake of NIPT in those with a risk between 1:150 and 1:1000 was similar (80%). Other studies report uptake between 28 and 91.5%.[17,19]

While international experience provides some insight, it is very difficult to forecast how the availability and accessibility of NIPT will affect behaviour in Australia, particularly across models with varied definitions of high and intermediate risk. For this reason, we chose to model the highest possible uptake across all contingent screening models to determine the potential of the program. Our study assumed 100% uptake to demonstrate the potential costs and outcomes of screening, and may overestimate the actual costs and benefits. Medicare data from 2005 to 2015 suggest that only 54% of pregnant women had either cFTS or second trimester screening; this rate was unchanged from a 2006 report.[20] This may be an underestimate as not all screens are captured by the Medicare data. However, our study of screening in Western Australia had a complete ascertainment documented uptake of only 58%.[2] If NIPT were to become more accessible it may attract more women to cFTS with an overall increase in the cost of screening to the health system. While a government decision to subsidise NIPT would be made based on a price or subsidy agreement, the budgetary cost to the public health system of including NIPT will remain unclear until a program is underway.

Our analysis was limited to a public health system perspective across the duration of screening and diagnosis. The analysis is of the screening and diagnostic components of prenatal screening, with the effectiveness of the program measured by diagnosis and averted fetal loss following invasive procedures. We have not attempted to assign a cost to the loss of a fetus, nor have we assigned costs or made assumptions about the consequences of diagnosing or failing to diagnose T21 prenatally, such as the termination of pregnancy or lifetime cost of care for a person with T21. The birth of fewer children with T21 as a measure of effectiveness would be inconsistent with the goal of prenatal screening to provide supported, autonomous choice,[21] and would not capture the value or challenges of a prenatal diagnosis of T21. Furthermore, we cannot assume that the identification of more cases of fetal T21 using NIPT will result in similar termination rates, as NIPT may be undertaken among women who would not consider having invasive testing or termination.[21] However, we acknowledge that the inclusion of these downstream outcomes may support lowering the intermediate-risk cut-off further. As our analysis took a public health system perspective, out-of-pocket costs to patients were not considered. An analysis from a broader perspective may also provide support to a further lowering of the intermediate-risk cut-off and/or a higher acceptable NIPT price. NIPT screening panels also include trisomies 13 and 18, and can also include sex chromosome anomalies and, increasingly, microdeletion syndromes (for which screening performance data are limited). We limited our analysis to T21 as it is the most common trisomy, the basis upon which fetal aneuploidy screening was introduced, and the only condition for which we had high-quality risk distribution and outcomes data.

CONCLUSION

There are no national data on the utilisation of NIPT across Australia. Nonetheless, the decline in the rate of invasive diagnostic testing across Australia[22] indicates the impact of NIPT on prenatal screening practices. While this trend will benefit the public health system by reducing costs, the shift of the cost of testing from Medicare to the individual patient raises an issue of equity. Given the comparative safety and cost of NIPT, consideration should be given to subsidising the test in a public health system. We propose that reasonable models for a contingent screening program would have high-risk cut-offs of 1:10 or 1:20 and intermediate-risk cut-offs of 1:1000 or 1:1500. We recognise that other thresholds would also be defensible. We also appreciate that modelling cannot capture the nuances of caring for individual patients and communities. Our analysis is the starting point, rather than the end, of discussions that can lead to good practice.

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CHAPTER 8 PAPER 7

SCREENING FOR DOWN SYNDROME IN THE SECOND TRIMESTER OF PREGNANCY

Peter O'Leary, Susannah Maxwell, Michael Sinosich, Kerry DeVoss, Janice Fletcher, Enzo Ranieri, Michael P Metz. Screening for Down syndrome in the second trimester of pregnancy, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 56, Issue 1, pages 19–21, February 2016

CHAPTER 3 PAPER 2

SOCIO-DEMOGRAPHIC DISPARITIES IN THE UPTAKE OF PRENATAL SCREENING AND DIAGNOSIS IN WESTERN AUSTRALIA

Susannah Maxwell, Kate Brameld, Carol Bower, Jan E Dickinson, Jack Goldblatt, Narelle Hadlow, Bev Hewitt, Ashleigh Murch, Anthony Murphy, Roseanne Stock, Peter O'Leary. Socio-demographic disparities in the uptake of prenatal screening and diagnosis in Western Australia, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 51, Issue 1, pages 9–16, February 2011

Opinion

Screening for Down syndrome in the second trimester of pregnancy

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Antenatal screening for fetal anomalies has provided women and their partners with information to make reproductive choices based on the risk of serious chromosomal or structural defects since the 1990s. Alternative tests include first-trimester screening (combined ultrasound and maternal serum markers), second-trimester maternal serum markers and noninvasive cell-free DNA testing. The recent recommendations by the Royal Australian and New Zealand College of Obstetrics and Gynaecology and the Human Genetics Society of Australasia against second-trimester triple testing are based on unsound performance criteria, raise several contestable issues around access and equity and challenge the principles of governments providing affordable options.

Key words: antenatal screening, Down syndrome, triple test.

Background

Over the past 25 years, important improvements have occurred in antenatal screening for Down syndrome and other fetal structural and genetic anomalies. Beginning with maternal age as a primary screening tool, we have witnessed developments in maternal serum screening[1] and ultrasound[2] and newer genetic testing methods to refine risk estimates. Screening has been available to women in the second trimester of pregnancy – via maternal serum screening (the triple or quadruple test) – since the early 1990s, and in the first trimester – via combined first-trimester screening (cFTS) – since the early 2000s. More recently, noninvasive prenatal testing using cell-free DNA (cfDNA NIPT) has become available, offering those able to pay the opportunity to screen for Down syndrome, trisomies 13, 18 and sex-chromosomal anomalies.[3]

During the 1990s, the triple test was the dominant screening moiety in all Australian states[4,5] except for one laboratory in Victoria offering second-trimester quadruple screening tests.[6] Then, from around 2000, cFTS largely replaced second-trimester maternal serum screening as the preferred screening method, as it provided an earlier screening option with higher detection and lower false-positive rates for fetal Down syndrome and enabled the identification of additional structural abnormalities via ultrasound.[7–9] Nevertheless, laboratories have retained second-trimester maternal serum screening principally to provide a service to those women who cannot access NT ultrasound providers due to barriers such as cost and physical location, and for those who present for antenatal care after the first trimester. These are generally our most vulnerable pregnant women.

Recent guidelines issued by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and the Human Genetics Society of Australasia (HGSA) no longer recommend the use of the triple test for second-trimester screening. Guideline 3.2 states women in the second trimester may be offered maternal serum screening with the quadruple test (15–20 weeks) or cfDNA testing (any gestation after 10 weeks) but advise against use of the triple test for trisomy 21 based on performance criteria (sensitivity <75%/specificity <95%) (http://www.ranzcog.edu.au/component/docman/doc_download/938-prenatal-screening-and-diagnosis-of-chromosomal-and-genetic-abnormalities-in-the-fetus-in-pregnancy-c-obs-59.html?Itemid=946).

This recommendation is based on limited evidence, is not supported by a Cochrane review and has implications for service providers, referral pathways and the provision of second-trimester screening to Australian women.

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Comparing the triple test to the quadruple test

The statistical evidence that quadruple tests are superior to triple tests is controversial.[10] In 2003, based on evidence from the Serum, Urine and Ultrasound Screening Study (SURUSS) multicentre evaluation of first- and second-trimester screening markers in more than 47 500 pregnancies, Wald *et al.* proposed that the evidence did not support continued use of the triple test.[11]

However, a more recent 2012 Cochrane review concluded that 'tests involving two or more markers in combination with maternal age are significantly more sensitive than those involving one marker' but that 'the value of combining four or more tests (including inhibin) has not been proven to show statistically significant improvement.[10] In a recent review of the performance of second-trimester screening protocols in the UK, Kevin Spencer reported the detection rate of triple test screening (67%) to be slightly lower than quadruple tests (72%).[12] Although the sample sizes are small, Australian data published by Jacques et al[13] on the Victorian quadruple test indicate detection rate of 72% (24/33) which is similar to the South Australian triple test 74% (50/67) data.[14] However, in both reports, the false-positive rates exceeded 7%. Clearly, detection rates can be improved by increasing the screen-positive rate, but at a conventional 5% false-positive rate, the performance will be less than reported above. Without a national audit to assess antenatal screening test characteristics, it is implausible that performance standards can be imposed without evidence that the standards can be achieved or maintained.

Despite the recommendation of the NHS Fetal Anomaly Screening Program in the UK that only quadruple tests be offered in the second trimester (http://www.fetalanomaly.screening.nhs.uk/publications), 64 of 137 laboratories (47%) participating in the NEQAS quality assurance program report triple test results in comparison with 34 of 137 (25%) reporting quadruple test results or a combination of AFP and hCG (25%). In the American College of Pathologists CAP survey, 27% of participating laboratories provide triple tests (44/118).[15]

Impact of new policy guidelines

Currently, the triple test is the only second-trimester maternal serum screening test available in Western Australia, South Australia, New South Wales, Queensland and the Northern Territory. The test may be provided to public patients through State funded health laboratories, or to private patients at private laboratories, with some private laboratories referring the tests to government laboratories. Public patient testing is funded by state governments, while private patients receive a Medicare rebate.

To comply with the new guidelines, laboratories that currently do the triple test would have to expand the screening panel to include inhibin A or no longer provide second-trimester screening. However, the 2012 Cochrane systematic review of second-trimester screening tests recommended against introducing quadruple tests into wider clinical practice without careful consideration of cost.[10] We estimate that adding inhibin A into the screening panel would increase the cost of maternal serum screening threefold. For public patients, the entire cost would be borne by the state government, whereas for private patients, a Medicare rebate would apply. However, the standard Medicare rebate is identical for both triple and quadruple tests. The additional cost to state governments (in the case of public patients) and private laboratories or women (in the case of private patients) is not justified by the potential marginal increase in detection.

If laboratories were to cease offering second-trimester screening, women presenting in the second trimester or unable to access FTS would have the option to have cfDNA NIPT, as referred to in the guidelines. Offering a much improved detection rate (>99% for Down syndrome) with a reduced number of invasive diagnostic tests,[16] cfDNA NIPT has been adopted enthusiastically by clinicians and pregnant women.[17–19] For private patients, in the absence of Medicare or private health funding for cfDNA NIPT, this would, for the first time in Australia, represent a shift into a user-pays model for second-trimester antenatal screening. With the exception of women in Victoria, it may be difficult for women to access affordable screening. Furthermore, within the state public system, the cost of providing cfDNA NIPT to patients would be disproportionate to that of providing the triple test and would initiate a publicly funded population NIPT program that would be difficult to manage in terms of demand access and equity. A further option to ensure access to second-trimester screening may be to have all second-trimester blood samples sent to the Victorian laboratory that provides quadruple tests. However, this would require agreement among public and private laboratories and is likely to increase costs for women and/or referring laboratories.

Conclusion

The stated aims of prenatal screening for fetal anomalies have always emphasised the provision of choice, specifically reproductive choice, over the detection and termination of fetuses with abnormalities such as Down syndrome. Choice is informed by the evidence about the performance of screening tests, the balance of risks involved with diagnostic invasive tests and the individual's personal decisions about having a child with a disability. There is also a public policy and health dimension that determines what resources should be invested in meeting public demands and expectations, and equality of access. A likely consequence of the current RANZCOG and the HGSA Guidelines against continued use of the triple test will be to increase health service inequality. These are complex issues and beyond the scope of this commentary, but they frame the current consensus about what are

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reasonable screening tests to make available to pregnant women and their partners to inform their reproductive choices.

With these developments, it is reasonable to ask what antenatal screening options should be provided to pregnant women and their partners in Australia. Our health system provides a safe system that is accessible and equitable and generally meets the expectations of health consumers. In the absence of clear evidence as to the superiority of the quadruple test and a lack of robust evaluation of the triple and quadruple tests in Australia, the recommendation against the triple test is premature and threatens access to affordable second-trimester screening for women. The retention of both the triple and quadruple tests (in Victoria) appears warranted.

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CHAPTER 9 DISCUSSION

The aim of this thesis was to evaluate and analyse prenatal aneuploidy screening in Western Australia to inform policy for Down syndrome screening against a landscape of significant advances in screening technology. To my knowledge, this thesis includes one of the largest cohorts of first trimester screened pregnancies for which pregnancy outcome data are available, globally, and the only assessment of the historical impact, performance and uptake of prenatal screening in WA. The thesis also provides the only published data on the impact of using increasingly sensitive cFTS risk cut offs on screen positive and detection rates, and the costs and outcomes of contingent NIPT models with varied cFTS risk cut-offs in the Australian context.

Paper 1 clearly showed that prenatal screening and diagnostic testing for fetal Down syndrome has had a significant impact on Down syndrome births and terminations in Western Australia, with a 45% reduction in the expected number of babies born with Down syndrome between 1980 and 2013.[2] The paper showed an almost threefold increase in the rate of Down syndrome pregnancies, attributable to rising maternal age, with 4.7% and 20% of babies born to mothers over 35 years of age in 1980 and 2013 respectively. Despite this, invasive prenatal diagnostic tests as a percentage of live births declined and the live-born rate fell from 1.1 per 1000 in the pre-screening period (pre 1994) to 0.87 per 1000 in the period following the introduction of cFTS (2004 onwards) enabled by improvements in contemporary screening methods compared with maternal age screening. We predicted that in the absence of prenatal testing and termination the live-born rate of Down syndrome would have otherwise doubled over this time.

Paper 2 reported both on the performance parameters of available screening strategies in Western Australia (MSS and cFTS) and the uptake of prenatal screening and diagnostic testing according to sociodemographic characteristics, providing a surrogate measure of access to screening. MSS and cFTS performance parameters were consistent with international performance standards with detection rates of 86 and 66 per cent at a 5% false positive rate respectively. Using a

cFTS probability cut off of 1 in 300, 3.6% of women screened positive and 80.9% (76/94) of fetal Down syndrome cases were detected. Eighteen women carrying a child with Down syndrome were falsely reassured with a low risk result. Fifty eight per cent of women with singleton pregnancies had prenatal screening (2005-2006), with cFTS accounting for 90.4% of tests performed.[3] Seventy five per cent of women with a high probability cFTS result had an invasive diagnostic test, and 93% of those with a diagnosis of fetal Down syndrome chose to terminate.

Paper 2 showed significant disparities in the uptake of screening, with lower uptake among Aboriginal, remote and socio-economically disadvantaged women. Screening is in principle a choice, and not a routine test, and therefore variation in screening could reflect differences in attitudes towards prenatal testing and the perceived value of testing. However, as with other health services, it is likely that barriers to accessing the service explain more of the variation in screening uptake. Possible barriers to prenatal screening include not being offered screening by the attendant health professional, late initiation of prenatal care resulting in missed opportunities, difficult physical access and suboptimal communication and understanding of screening tests resulting in lack of informed choice and cost. Further research is essential to determine the reasons and to identify potential solutions that will improve access and equity. Additionally, disparities in prenatal fetal anomaly screening must be considered within the broader context of the provision of all prenatal care.

The thesis papers thus far provide an overview of prenatal screening in Western Australia. It is evident that Western Australia has a screening program that meets international and national performance standards, that cFTS is the preferred screening test and that the availability of screening has impacted the live-birth rate of Down syndrome in Western Australia. However despite the performance achievements, we also showed significant disparities in the uptake of, and potentially access to, screening. Furthermore, cFTS falsely reassures some women, failing to identify up to 20% of cases of fetal Down syndrome and creates

unnecessary anxiety and risk for others, with the majority of invasive diagnostic procedures in high probability pregnancies revealing normal karyotype.

With the recent availability of NIPT with cfDNA come great expectations. NIPT's performance characteristics -approaching that of diagnostic testing- has the potential to improve the performance of prenatal aneuploidy screening, above and beyond that of the current screening strategy. NIPT with cfDNA represents yet another opportunity to improve the detection rate of fetal Down syndrome, giving more women who chose to do so, the option to avoid the birth of a child with Down syndrome, while also reducing unnecessary invasive diagnostic testing and associated miscarriages.

Papers 3 to 6 present and use data from our cohort to model hypothetical scenarios that explore the potential costs and outcomes of incorporating NIPT with cfDNA into the prenatal screening pathway. Using a larger cohort of pregnancies having cFTS (2005-2009) Paper 3 provided a more detailed assessment of the performance of cFTS, exploring the impact of increasingly sensitive probability thresholds on screen positive rates (SPR) and detection rates (DR) for the purpose of determining eligibility for NIPT with cfDNA in a contingent screening model. There was a 0.7-0.8% increase in SPR for each 100 point change in probability threshold used in cFTS, up to a 19.2% SPR at a threshold of 1 in 2500 (DR 96%). These data confirmed that an approach in which all women, regardless of age, have cFTS to refine the estimated probability of fetal Down syndrome is superior to an approach in which only women <35 years of age have cFTS with women of advanced maternal age automatically considered to be high probability. The results also demonstrated the potential superior performance of a screening strategy that offers NIPT contingent on the results of cFTS.

Paper 4 described the potential impact of using NIPT as a contingent test on the diagnosis and outcomes of pregnancies identified through cFTS as having a high probability of fetal Down syndrome using data from the 2007-2009 cohort. The key finding was that if the screening program had used NIPT as a second-tier test for pregnancies identified by cFTS, the outcome for the majority of these pregnancies

would have most likely been the same. An abnormal karyotype result was reported in 15% of women with cFTS results indicating high probability of fetal Down syndrome who had invasive diagnostic testing. NIPT would have potentially identified 85% of these. For conditions not identifiable by NIPT, fetal sonographic appearance was likely to have led to invasive testing for 59% of pathogenic conditions. If a policy was adopted recommending invasive testing for cFTS with a probability of fetal Down syndrome >1 in 50 and/or an ultrasound detected, the residual probability of an unidentified pathogenic chromosomal condition in those without a diagnosis would have been just 0.33%. With consideration given to the role of ultrasound in screening, NIPT could be incorporated in prenatal screening programs with minimal impact on the diagnosis of rare chromosomal conditions. These findings are consistent with other Australian data.[87]

Paper 5 used data from the 2005-2006 cohort of screened pregnancies to model the cost-effectiveness and performance of NIPT for the detection of fetal Down syndrome among pregnancies with a high probability cFTS result compared to conventional practice (high probability cFTS followed by invasive diagnostic testing). The key findings were that the introduction of NIPT would reduce the number of invasive diagnostic procedures and procedure-related fetal losses in high probability pregnancies by 88%, with a DR of 82%. If NIPT was adopted by all women identified with a high probability of carrying a Down syndrome fetus by cFTS, up to 7 additional cases (from 69 to 75-76 cases) of fetal Down syndrome could be confirmed in Western Australia over two years. The cost per fetal Down syndrome case confirmed, including NIPT was 9.7% higher than the conventional prenatal testing strategy, but is based on the 2013 cost of NIPT at $743 per test. The test is now available for $400. This paper was highlighted within a Flemish Health Technology Assessment of NIPT as being the only economic evaluation of NIPT for fetal Down syndrome where the authors did not have any explicit conflict of interest.[101] A limitation of this study is that diagnostic testing was performed by cytogenetic rather than molecular genomic methods. Therefore, it is likely that the results under-represent the true prevalence of rare chromosomal abnormalities and possibly overestimate the performance of NIPT.

Paper 6 provided a more recent cost-effectiveness analysis and considered a range of contingent NIPT models using increasingly sensitive cFTS probability thresholds using data from the 2005-2009 cohort and an NIPT cost of $400. This analysis showed that contingent screening with NIPT offers a cost-effective alternative national health model to conventional screening. This conclusion is consistent with international studies in Belgium,[101, 106] the Netherlands[99] and the UK.[98] Our study found that increasing the cFTS probability threshold from 1 in 300 to 1 in 1000 would increase the detection rate by 8% to 90% at a similar cost per diagnosis to conventional screening.

In addition to reducing invasive diagnostic tests and improving the detection rate of fetal Down syndrome, the successful and equitable integration of NIPT into the screening pathway may also provide an opportunity to improve disparities witnessed in the uptake of screening (Paper 5).[3] This issue of disparate access was raised, once again in Paper 7 which comments on the recent guidelines issued by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the Human Genetics Society of Australasia which no longer recommends the use of the triple test, but endorses the quadruple test, for second trimester screening.[1] While cFTS accounts for the majority of Australian prenatal screening tests for aneuploidy (Papers 1, 5), in most states (Queensland, Western Australia, South Australia, New South Wales and the Northern Territory) second trimester screening using the triple test remains an important option for women who cannot access cFTS. The statistical evidence for the superiority of the quadruple test over the triple test is controversial and with no suitable alternative screening pathway for those women who cannot access cFTS in these States, we proposed that the recommendation against the triple test was discriminatory, not evidence-based and premature. NIPT may provide an alternate screening pathway option although challenges remain in determining how to manage access to publicly funded NIPT for women who present too late for cFTS or for those in areas where cFTS is unavailable.[8] Without public funding, the availability of this superior screening technology will benefit only those who can afford to pay, potentially broadening pre-existing disparities in the accessibility of screening.

9.1 Significance of research

This thesis includes the only work undertaken to monitor the performance of cFTS (Papers 2 and 3) across all service providers in Western Australia thus far, as is recommended by peak bodies, and, to my knowledge, the only analysis of the historical experience and impact of changes in prenatal screening policy in Western Australia. These data provide the contextual base upon which policy decisions regarding the provision of prenatal screening and introduction of new screening technologies should be made.

The main contribution of this body of work is the use of comprehensive local data. This includes over 30 years of fetal anomaly data to enable analysis of the historical experience of prenatal screening in Western Australia (Paper 1). Although the notification of birth defects was not mandatory until 2011, the Registry's Down syndrome case ascertainment has been shown to be high, and provides valuable data on Down syndrome pregnancies, diagnoses and terminations.[107] These data span the time over which prenatal screening developed, allowing for observation of trends. The paper provides, to my knowledge, the only study that explores the relationship between changing prenatal screening policy to trends in the diagnosis, termination and live birth rates of Down syndrome along with estimates of expected birth prevalence over this time frame. This provides some insight into the potential impact of introducing another, yet more accurate screening test.

We also analysed five years of prenatal screening and diagnostic data, accessed from Western Australia providers (Papers 2 through 6), beginning in 2005, shortly after cFTS became publicly funded and ultrasound NT providers were able to be accredited through the FMF (2004). These screening and diagnostic data were linked by the Western Australian Data Linkage Branch to State-wide health datasets to create a comprehensive composite dataset which included screening and diagnostic results, sociodemographic information, hospital morbidity and mortality data, pregnancy outcomes, terminations and birth defects for both screened (2005-2009) and unscreened pregnancies (2005-2006).

These data represented the real clinical experiences of over 80,000 women attending for prenatal screening and/or diagnosis in Western Australia across a range of public and private service providers in urban, rural and remote areas, with cFTS data collected from all active screening providers. All data were de-identified for analysis. Ethics approval was granted with a waiver of consent to enable complete ascertainment of screens and outcomes. Complete ascertainment of these data is particularly important for calculating the sensitivity and specificity of screening programs with rare outcomes. Additionally the size of the composite dataset of combined first trimester screens with pregnancy outcome data, enabled by the data linkage methodology is one of largest reported previously internationally. While Nicolaides reported the results of 75,000 screens in 2005,[65] most previous evaluations have been limited to fewer than 20,000 pregnancies.[68-71, 73-75] This dataset provided performance characteristics of screening for an established screening program over a large geographic area, but also enabled analysis of the sociodemographic characteristics of women having prenatal screening and diagnosis.

This comprehensive dataset also provides value to the second half of the thesis. Papers 5 and 6 model the potential costs and outcomes of publicly funded NIPT in Western Australia and Australia respectively using these extensive local data to inform probabilities for screening pathways and outcomes. Although the data are sourced from Western Australia, the results are generalisable to the remainder of the country, which shares similar population demographics and a national Health Insurance Scheme. The data cover metropolitan, regional and remote populations, and include women from different ethnic and socio-economic groups and of different ages.

Research output from this thesis has been cited within the most recent Royal Australian New Zealand College of Obstetrics and Gynaecology recommendations for the appropriate clinical use of NIPT[1] and data are being used to inform a health technology assessment submission to the Australian Government Medical Services Advisory Committee for public funding for NIPT.

9.2 Limitations

The thesis has a number of limitations, described within each manuscript, and some results should be interpreted with caution. We showed an increase in the prevalence of fetal Down syndrome over time in Paper 1 which we attributed to the increase in maternal age; however it is likely that some of this increase is an artefact of prenatal diagnosis itself, as in the absence of prenatal diagnosis and termination cases of Down syndrome lost before 20 weeks would not have been identified. Also, WARDA data do not include fetal Down syndrome cases diagnosed but spontaneously lost before 20 weeks, which could lead to an underestimate of diagnosis and an over-estimate of the termination rate following prenatal diagnosis and/or an over-estimate of cases of fetal Down syndrome which would have been lost by term. However, these impacts are likely to have been minimal and general trends stand.

Paper 2, which describes the performance and socio-demographic disparities of prenatal screening may have been limited by the incomplete ascertainment of all Western Australian screening data for the specified time period. For cFTS, this represented only 6% of screens and is unlikely to have compromised our performance results. However, the MSS data were only 75% complete with a small numbers of Down syndrome cases (n = 3), as such there is some doubt about the reliability of these performance results. With regards to socio-demographic disparities we believe it is unlikely that those groups found to have lower uptake of screening would have been over-represented within the group of women for whom screening data were missing. Paper 3 was limited by the incomplete ascertainment of outcomes for all screened pregnancies; however, we do not believe this would have impacted the results as those lost to follow-up only represented 3% of all complete screens, the characteristics of which were similar to those with follow-up data.

The use of the screened cohort (2007-2009) to investigate what NIPT would have missed among this screened population had NIPT been offered rather than invasive testing (Paper 4), has a number of limitations. The nature of the study,

considering rare chromosomal conditions, meant there were only a small number of cases. Unfortunately the data collected for the 2005-2006 cohort of screened pregnancies did not include details on rare chromosomal conditions, which would have increased the number of conditions assessed. Despite this limitation, the results are consistent with other larger studies.[87, 108] Additionally, we did not have access to ultrasound images and therefore relied on the experience of a fetal medicine specialist to retrospectively assess the likelihood that the condition would have been identified through indication on ultrasound and to a recommendation for invasive testing. Furthermore, as the ability to identify anomalies on ultrasound depends on the skill and expertise of the sonographer, there is potential for wide variation in the identification of these anomalies across clinical practice.

A further limitation of the cFTS dataset (2005-2009) relates to its use to inform the modelling of screening in Papers 5 and 6. The cFTS screening algorithm used between 2005 and 2009 in Western Australia (and reported in Papers 2 and 3) did not incorporate nasal bone, tricuspid flow or ductus venosus, additional markers that can now, with further certification, be included in the screening algorithm. With the inclusion of these sonographic markers, Nicolaides et al. demonstrated an increase in the detection rate of cFTS from 85–95% to 93– 96%, with a 50% reduction in the false-positive rate from 5% to 2.5%.[109] While this limitation does not impact the results reported in Papers 2 and 3, when using these data to inform the potential outcome of changing cFTS probability thresholds, as we have done in Papers 5 and 6, we have to be aware that the performance of cFTS itself may have changed as a result of changing practice. We are unsure to what extent these additional markers are being used in clinical practice across Australia, but understand that use may be limited. Furthermore, the generalisability of the cFTS results for future cohorts of women (as hypothesised in Papers 5 and 6) will depend on the age distribution of screened women, with cohorts with older women expecting higher screen positive rates. The proportion of women of advanced maternal age (>35 years) has increased over time. In our cohort 22% were of advanced maternal age, reflecting that of births in Australia (18.8% in 2003, 22.4%

in 2012).[110] Any changes to this age distribution among future cohorts of screened pregnancies may impact the results of cFT screening.

Possibly the most significant limitation of Papers 5 and 6 is the uncertainty surrounding how the availability of publicly funded NIPT will impact women's choices regarding screening, diagnosis and termination, and the affect this will have on costs and outcomes. Uptake of screening overall is likely to vary along with out of pocket cost, knowledge and attitudes and risk factors, for which we have little to no information in Australia currently. Inaccuracy of the test and the risk of miscarriage associated with invasive diagnostic procedures have been cited as key reasons for declining cFTS,[111-114] suggesting an increase in the uptake of screening overall with NIPT. In a 2013 Dutch study of 149 women, 57% (n=35) of the 61 women who had declined cFTS indicated they would have NIPT in a subsequent pregnancy if it were available.[114] Another 2016 Dutch study found that 23% (77/239) of women who had previously declined cFTS intended to have NIPT in a current or subsequent pregnancy while 39% (93/239) would not have NIPT. [115] The reasons behind declining cFTS were more likely to be related to cFTS test itself in the former group, and attitudes towards Down syndrome or termination in the latter. The remaining 29% (69/239) of women were unsure.[115]

International experience (discussed in Paper 6), such as that gained in the RAPID trial (UK), PEGASUS (Canada) and TRIDENT (Netherlands), may provide some insight, however uptake rates of conventional screening vary internationally, and NIPT is likely to be no different. In 2009 the uptake of conventional screening was just 26% in the Netherlands and in 2010, 61% and 84% in England and France respectively.[116] Differences in screening policy and the health system in which screening is implemented have been shown to affect the way in which health professionals interact with women during consultation, in turn impacting decisions to accept or decline screening.[116]

Given this international variation, it is very difficult, in the absence of a large local trial, to forecast how the availability and accessibility (i.e. out of pocket cost) of NIPT will affect behaviour in Australia, particularly across models with varied

probability thresholds to define high and intermediate probability categories. For this reason we modelled the highest possible uptake of screening across all models to determine the potential of the program (Paper 6). While we can hypothesise about women's behaviour and consider different scenarios, these analyses remain hypothetical.

To explore this uncertainty, NIPT and diagnostic test uptake were varied in sensitivity analysis, with high and low uptake scenarios in Paper 5 and one way sensitivity analysis for one of the twenty five models in Paper 6. The cost-effectiveness of these models is sensitive to variation in uptake in invasive testing and NIPT. The majority of the cost of the screening program is accounted for by cFTS, so lower uptake of invasive testing following a positive NIPT leads to fewer cases diagnosed and a higher cost per diagnosis. Variation in screening uptake overall was not considered. Screening rates have been estimated to be between 54 and 58% in WA. Any increase in screening uptake would be likely to increase the overall costs of screening commensurately. Furthermore, as discussed in Papers 5 and 6, our analysis has not considered termination rates. Between 2005 and 2006, 75% of women with a high probability result had invasive testing and 93% of these women with a diagnosis of fetal Down syndrome chose to terminate.[3] We cannot assume that invasive testing, and therefore diagnostic rates, or termination rates would be consistent in an NIPT screening program, as NIPT may attract a greater proportion of women who would choose to have screening to gain knowledge and would not consider invasive testing or termination.[115, 117, 118]

Furthermore, although NIPT can also detect trisomy 18 and 13 and SCAs, we only included Down syndrome in our modelling of the impact of NIPT (Papers 5 and 6). False-positive NIPT results for trisomy 18 and 13 and SCAs could increase the number and cost of unnecessary invasive tests and procedure-related fetal losses. We have also not considered the current inability for NIPT to diagnose other chromosomal conditions that would be diagnosed through traditional karyotyping, as has been discussed in Paper 4.

There are also other less tangible outcomes which were outside the scope of the analyses undertaken in Papers 5 and 6. While we have outlined the financial costs and the performance characteristics of a contingent screening program with NIPT we have not considered how NIPT could impact women's experiences of screening. The superior performance characteristics of NIPT, and reduced need for invasive diagnostic testing may result in an improved screening experience.[119, 120] Certainly, women's preferences for screening tests that are safe and accurate,[121] and reasons given for declining conventional screening based on test characteristics,[113-115] support this notion. In the UK RAPID trial women were found to be 'overwhelmingly positive' towards NIPT, valuing 'the opportunity to have a test that was procedurally safe, accurate, reduced the need for invasive testing and identified cases of Down syndrome that might otherwise have been missed.'[119] The study found that 30% of those women who accepted NIPT, particularly those in the medium probability group, stated reassurance as the main motivator for having the test.[119] Conversely, concerns have been raised about anxiety resulting from an extended contingent screening process[120] and the potential lack of informed choice and possible routinisation of screening with NIPT.[120] The TRIDENT study which provided a controlled environment for the education and counselling of women, achieved informed choice for 78% of women. Among these women anxiety and decisional regret were significantly lower.[120] Maximising the utility of a screening program will require a coordinated program that ensures informed choice.

9.3 Future directions

This thesis demonstrates the significant impact of evolving prenatal screening and diagnostic practices on Down syndrome in Western Australia and describes the performance characteristics of current screening programs as well as the potential impact of new screening technology. The analyses validate the incorporation of NIPT into prenatal screening pathways and provide support for public funding for this new technology. However, as has been recommended in a joint statement of the American Society of Human Genetics (ASHG) and the European Society of Human Genetics (ESHG),[17] 'where prenatal screening is offered

as a public health program, governments and public health authorities should adopt an active role to ensure the responsible innovation of prenatal screening on the basis of ethical principles.' The statement describes crucial elements of responsible innovation as the quality of the entire screening process including the provision of information, education and counselling and the evaluation of all aspects of screening, as well as accountability to all those who are impacted by screening programs and promotion of equitable access.[17] As it currently stands, the rapid acceptance of NIPT by Australian women on a user pays basis has led to a loss of control by the health care system. There are currently no data on the volume of tests in Australia, test performance in the field, the no-call result rates, nor are there data on outcomes, including the choices women are making based on their results. The collection and analysis of these data is essential for the ongoing integrity of prenatal screening programs and the quality of patient care. Further work is warranted to ensure the delivery of an equitable, effective prenatal screening program in line with the ASHG/ESHG recommendations.[17]

9.3.1 Prenatal screening access and equity

Choice is a fundamental component of 'reproductive autonomy' and should be available to all women, not just those in privileged socio-demographic groups. We still do not have a clear understanding of the reasons for socio-demographic disparities in prenatal screening in Western Australia. Further research is warranted to confirm why these exist, and where this is due to a lack of access, rather than personal choice, solutions should be identified. Publicly funded new technology, such as NIPT, may provide some of that solution. Without public funding new technologies threaten to magnify pre-existing disparities, as only those women who can afford to access testing will do so. Barriers to access must be considered within the broader context of the provision of all prenatal care.

9.3.2 Integration of publicly funded NIPT

Without robust Australian data on the uptake of screening, NIPT and invasive diagnostic testing the total budget impact of funding NIPT will remain

unclear. A pilot NIPT program, similar to those conducted in the UK, Canada and the Netherlands, in which women's choices to have NIPT and/or invasive testing could be observed would provide greater certainty around Australian women's behaviour. Despite the current lack of data, at the time of writing, an application had been submitted to the Medical Benefits Schedule committee for funding for NIPT. It is anticipated that public funding will be achieved eventually, particularly as the cost of this test continues to fall. However, without further research, it is likely that the budget impact will not be realised until the program is well underway.

9.3.3 Monitoring and evaluation of prenatal screening and policy

Ongoing monitoring and evaluation of prenatal screening is essential, both to understand the performance and impact of current screening strategies but also to inform the direction of screening policy. With the inevitable public adoption of NIPT, monitoring of screening should include the performance of prenatal screening pathways in the diagnosis of rare chromosomal conditions, in addition to the trisomies, SCAs, and micro-deletions. The impact of these tests on screening pathways should also be monitored. The declining numbers of invasive diagnostic tests has raised concerns about expertise and training in the procedure.[56, 122-124] Concerns have also been raised that as the number and types of conditions that can be tested for continues to expand, ensuring informed choice will become increasingly difficult, and that safer tests (compared to invasive diagnostic testing) may not be subject to as rigorous decision making.

Furthermore, technology, emerging evidence on current strategies and costs should be monitored to ensure that screening policy remains appropriate. Should the cost of NIPT continue to fall, a move to universal NIPT screening may be appropriate. However, this will require further evidence on the role of cFTS in pregnancy management outside of risk assessment for fetal trisomy.

The introduction of a new, more accurate screening test is likely to once again accelerate the decline in the birth rate of children with Down syndrome (or other conditions identified prenatally), as was seen with the introduction of cFTS.

Programs should be designed and monitored to ensure that women receiving a diagnosis of fetal Down syndrome make subsequent decisions based on balanced information, an important component of reproductive autonomy.

9.4 The contribution of this thesis

This thesis provides an assessment of the performance and uptake of cFTS (the current standard in prenatal screening) in Western Australia and the potential impact of cfDNA in prenatal screening. To my knowledge, this thesis includes one of the largest cohorts of first trimester screened pregnancies for which pregnancy outcome data are available, globally. These data represent an established screening program, and includes women from metropolitan, regional and remote areas and across a range of sociodemographic and ethnic groups and of different ages. It also provides the only assessment of the impact of changing prenatal screening strategies on trends in the diagnosis, termination and livebirth rate of Down syndrome over a thirty year time frame, and represents the only evaluation undertaken on the performance and uptake of prenatal screening and diagnosis in WA. The thesis also provides the only published data on the impact of using increasingly sensitive cFTS risk cut offs on screen positive and detection rates, and the costs and outcomes of contingent NIPT models with varied cFTS risk cut-offs in Australia. Research output from this thesis has been cited within the most recent Royal Australian New Zealand College of Obstetrics and Gynaecology recommendations for the appropriate clinical use of NIPT[1] and data are being used to inform a health technology assessment submission to the Australian Government Medical Services Advisory Committee for public funding for NIPT.

9.5 Conclusion

This thesis reveals a current prenatal screening program using cFTS that meets international performance standards, but for which significant socio-demographic disparities exist. Using these data to model hypothetical scenarios, the thesis validates the incorporation of NIPT with cfDNA into prenatal screening pathways and provides support for public funding for this new technology.

However, consideration must be given to equity of access and the appropriate use of NIPT within prenatal screening and clinical management. A pilot program with funding for NIPT to explore women's choices and behaviour and the effective integration of the test would be a valuable extension of this research. NIPT, as a superior screening test, has the potential to improve access and accelerate downward trends in the rate of Down syndrome births, as we saw with the introduction of cFTS in 2004. Ongoing monitoring and evaluation will be essential to ensure the equitable and effective integration of NIPT, and other tests, into the prenatal screening pathway to ensure quality patient care. Prenatal screening programs should continue to endeavour to provide equitable access and informed and supported choice throughout pregnancy and beyond.

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APPENDIX A: COHORT STUDY DATA COLLECTION PROTOCOL

Collection of cFTS data:

Step 1: A customised query was used to extract data from the FMF patient database at each accredited cFTS ultrasound centre. The data included identifying data (patient names, addresses and dates-of-birth) and screening data. All data was encrypted before transit.

Step 2: The data was de-identified by providing a personal identifying number (PIN) for each case. Postcodes were retained with clinical data for analysis of regions.

Step 3: The PIN with the identified data (patient name, address, date of birth) was provided to the Data Linkage Unit (DLU), with no clinical details.

Step 4: The DLU linked the PIN with outcome data from the Midwives Notification System, Birth Defects Registry, WA Morbidity Database and WA Mortality Register.

Step 5: The DLU provided the clinical data with a PIN to Susannah Maxwell

Step 6: The outcome data was linked to the screening/diagnostic data using PIN. The composite dataset did not have any identifying information.

Collection of second trimester screening and diagnostic data

Some providers indicated a preference to provide data de-identified from the outset, which was enabled by the following protocol.

Step 1: Pathology laboratories provided databases of patient names, addresses and dates-of-birth to the DLU. These data included an internal patient number (different from the laboratories' numbering system), but did not include any clinical details. All data was encrypted before transit.

Step 2: The DLU linked the pathology identifying data to their database of patient identifiers and provided an encrypted personal identifying number (PIN) together with the original internal patient number back to the pathology laboratories.

Step 3: The laboratories attached the PIN to the clinical data using the internal patient number and provided the clinical data and DLU PIN to Susannah Maxwell for analysis.

Step 4: The DLU provided Susannah Maxwell with the encrypted PINs and clinical data from the Midwives Notification System, Birth Defects Registry, WA Morbidity Database and WA Mortality Register.

APPENDIX B: AUTHOR CONTRIBUTION LETTERS

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To Whom It May Concern

I, Susannah Maxwell, was a major contributor to the conceptualisation, coordination, and implementation of the research which resulted in the following paper:

> ***Susannah Maxwell,*** Carol Bower, Peter O'Leary, Impact of prenatal screening and diagnostic testing on trends in Down syndrome births and terminations in Western Australia 1980 to 2013, Prenatal Diagnosis Volume 35, Issue 13, pages 1324–1330, December 2015

I contributed to a significant extent, to the conceptualisation, drafting, writing and editing of the paper above which is used for my PhD thesis. Accordingly I am lead author on this publication (Paper 1).

Susannah Maxwell

I, as co-author, endorse that this level of contribution by the candidate indicated above is appropriate.

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I, Susannah Maxwell, was a major contributor to the coordination, and implementation of the research which resulted in the following paper:

Susannah Maxwell, Kate Brameld, Carol Bower, Jan E Dickinson, Jack Goldblatt, Narelle Hadlow, Bev Hewitt, Ashleigh Murch, Anthony Murphy, Roseanne Stock, Peter O'Leary, Socio-demographic disparities in the uptake of prenatal screening and diagnosis in Western Australia, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 51, Issue 1, pages 9–16, February 2011

I contributed to a significant extent, to the conceptualisation, drafting, writing and editing of the paper above which is used for my PhD thesis. Accordingly I am lead author on this publication (Paper 2).

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I, as co-author, endorse that this level of contribution by the candidate indicated above is appropriate.

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I, Susannah Maxwell, was a major contributor to the conceptualisation, coordination, and implementation of the research which resulted in the following paper:

Susannah Maxwell, Ian James, Jan E Dickinson, Peter O'Leary, First trimester screening cut-offs for non-invasive prenatal testing as a contingent screen: Balancing detection and screen-positive rates for trisomy 21, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 56, Issue 1, pages 29–35, February 2016

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The potential impact of NIPT as a second-tier screen on the outcomes of high-risk pregnancies with rare chromosomal abnormalities, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 55, Issue 5, pages 420–426, October 2015

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I, Susannah Maxwell, was a major contributor to the conceptualisation, coordination, and implementation of the research which resulted in the following paper:

Peter O'Leary, ***Susannah Maxwell,*** Ashleigh Murch, Delia Hendrie, Prenatal screening for Down syndrome in Australia: costs and benefits of current and novel screening strategies, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 53, Issue 5, pages 425–433, October 2013

I contributed to a significant extent, to the conceptualisation, drafting, writing and editing of the paper above which is used for my PhD thesis. Accordingly I am a co-author on this publication (Paper 5).

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To Whom It May Concern

I, Susannah Maxwell, was a major contributor to the coordination, and implementation of the research which resulted in the following paper:

Susannah Maxwell, Peter O'Leary, Jan Dickinson, Graeme Suthers, Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing. Australian New Zealand Journal of Obstetrics and Gynaecology 2017 doi: 10.1111/ajo.12612

I contributed to a significant extent, to the conceptualisation, drafting, writing and editing of the paper above which is used for my PhD thesis. Accordingly I am lead author on this publication (Paper 6).

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To Whom It May Concern

I, Susannah Maxwell, was a major contributor to the following paper:

Peter O'Leary, ***Susannah Maxwell,*** Michael Sinosich, Kerry DeVoss, Janice Fletcher, Enzo Ranieri, Michael P Metz
Screening for Down syndrome in the second trimester of pregnancy, Australian and New Zealand Journal of Obstetrics and Gynaecology Volume 56, Issue 1, pages 19–21, February 2016

I contributed to the drafting and editing of the paper above which is used for my PhD thesis. Accordingly I am a co-author on this publication (Paper 7).

Susannah Maxwell _____ Maxwell _____

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Michael Sinosich _____ 19/10/16.

Kerry DeVoss _____ Kerry DeVoss 25.10.16.

Janice Fletcher _____ 20 March 2017

Enzo Ranieri _____ 20/3/2017

Michael P Metz _____ 24/10/2016

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