FINAL REPORT

Cost-effectiveness of offering ultrasound scan to pregnant women at 18 to 20 weeks for the detection of non-chromosomal abnormalities

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THE CENTRE FOR INTERNATIONAL ECONOMICS
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Summary

The routine offering of a fetal development and anatomy ultrasound scan to pregnant women between 18 and 20 weeks gestation is current practice in Australia, although there is no previously published cost-effectiveness evidence to support this.

International studies are of limited significance to Australia and economic modelling has required various assumptions to be made, which are supported by the evidence that exists.

The results of this economic evaluation is that screening for congenital abnormalities at 18-20 weeks is moderately cost-effective, without generating significant risks, although without driving substantive benefits. Costs are estimated at $100.7 million annually (approximately $46 000 – $68 000 per fetal abnormality detected depending on severity) with benefits (avoided costs) of $172.4 million. Hence benefits exceed costs by 1.71:1.

This excludes the positive psychological value of the information, which may be associated with improvements in fetal wellbeing, and benefits from the detection of placental problems and confirmation of gestational age, making these estimates fairly conservative.

Purpose of this study

Module 2 of the Australian Clinical Practice Guidelines for Antenatal Care (currently in development) recommends routine offering of a fetal development and anatomy ultrasound scan to pregnant women between 18 and 20 weeks gestation. The scan is primarily recommended for the detection of structural abnormalities.

This screen is already current practice in Australia and in many advanced economies, reflecting the fact that ultrasound screening for structural abnormalities at 18-20 weeks is clinically effective and sufficiently early to enable women to choose to terminate their pregnancy following the detection of a lethal or severe congenital abnormality. While popular with women, its cost-effectiveness has not been comprehensively appraised in an Australian context.

In this report, the cost-effectiveness of the universal offering of the scan is assessed, with respect to a theoretical alternative to not offer screening at 18-20 weeks. A risk-based approach to screening for structural abnormalities has not been used due to the lack of clinically identifiable risk factors. This review assesses the validity/transferability of findings and data from the international literature, and develops a probabilistic model of clinical outcomes and associated costs and benefits that flow from the information provided through screening.

Clinical outcomes from routine screening limited to reduced perinatal mortality

Prenatal detection of congenital abnormalities is only rarely associated with improved *survival*, such as for a small number of cases of babies with congenital heart disease (Yates, 2004). There is also insufficient evidence that routine screening at 18-20 weeks improves outcomes for babies or leads to less health service use by mothers and babies (Whitworth et al, 2010).

Romano and Waitzman (1998) found that the cost-effectiveness of screening was driven by the specificity of ultrasound (rate of true negative) and the women's willingness to pay for reassurance of a normal scan. A comprehensive review of women's views of pregnancy by Garcia et al (2002) highlighted the positive impact of second trimester scanning through the reassurance that mothers experience.. The 18-20 week scan may provide stress and anxiety relief through providing visual confirmation of fetal development, which may improve maternal-fetal bonding (Garcia et al, 2002), and through confirmation from the sonographer of normal fetal structure. This may have the effect of reducing stress, anxiety and depression during pregnancy, providing a further important benefit given the linkages between untreated anxiety and depression in pregnancy and risks to fetal wellbeing (see, for example, Pearlstein, 2008).

More recent analysis by DiPietro (2010) found that dispositional levels of maternal stress and anxiety are modestly associated with aspects of fetal heart rate and motor activity.

However, it is acknowledged in the literature (see Davalos, D., Yadon, C., and Tregellas, H., 2012) that prepartum depression and negative outcomes in offspring are understudied compared to empirical papers on the effects of postpartum depression (after birth). This has produced ongoing debate on the effects of prenatal depression on a developing fetus and later in infancy and early childhood.

Due to the paucity of data/estimates on the utility or value of reassurance from the routine scan, including in terms of psychological wellbeing, these benefits are not well integrated into cost-effectiveness studies.

The literature does show that screening leads to a significant reduction in additional lifetime medical and developmental costs associated with morbidity resulting only from an increase in the rate of pregnancy termination for fetuses with lethal or severe abnormalities.

Hence, this economic evaluation is limited to assessing the potential benefits of routine screening through the inclusion of the potential avoided costs of care associated with higher rates of termination of fetuses with lethal or severe congenital abnormalities.

It also does not take into account other clinical pathways and benefits of screening at 18-20 weeks from the detection of placental problems such as low-lying placenta which is diagnosed at the 18-20 week scan.

Transferability of international literature is limited

Eleven economic studies were included in the literature review, although their transferability to an Australian context is generally limited. Two of the cost-effectiveness studies identified were randomised control trials.

- The Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) trial – where due to the low detection rates of major malformations and therefore minimal impact on perinatal mortality, the RADIUS trial did not strongly support the cost-effectiveness of routine screening, as did the Helsinki trial (Whitworth et al, 2012).
- The Helsinki trial – which demonstrated routine screening improved the detection of fetal abnormalities, resulting in an increase in the termination of pregnancies.

Roberts et al (1998), Bricker et al (2000), and Ritchie et al (2005) focus on the value of second trimester screening for congenital abnormalities, with respect to screening at other stages. The literature supports the conclusion that screening at the second trimester is the preferred strategy for screening for structural abnormalities.

Several studies identify the cost of screening relative to the avoided cost of care:

- Long and Sprigg (1998) conclude that the financial benefit of pregnancies, due to the avoided cost of caring for malformed fetuses, exceed the cost of routine screening
- Vintzileos et al (2000) suggest that the benefit cost ratio is dependent on the rate of detection, with a negative benefit cost ratio found when applying detection rates achieved in non-tertiary centres which are associated with poor rates of sensitivity
- Waitzman and Romano (1998) conclude that the sensitivity of ultrasound in detecting congenital abnormalities would need to be at least 0.5 to make routine screening viable.

Caution should be applied in transferring the results of these studies to the Australian context. The rates of ultrasound sensitivity and underpinning cost assumptions determine cost-effectiveness outcomes when measured in terms of the cost per anomaly detected or in terms of avoided costs through termination, and need to be relevant to the Australian context.

Modelling results

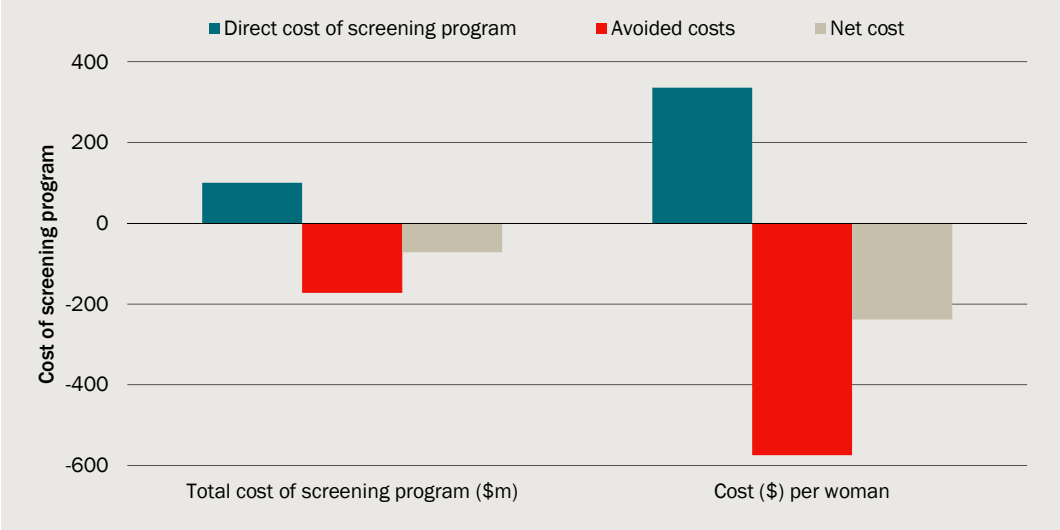
Due to the limitations in the transferability of data from the literature, particularly on the cost side, it is desirable to use localised data in the appraisal of the cost-effectiveness of routine screening in Australia.

However, the availability of Australian data is poor, particularly around the cost of care associated with severe or lethal congenital abnormalities, and several assumptions have been required to be made.

Notwithstanding data limitations, the results of modelling undertaken for this review show that ultrasound screening at 18-20 weeks for the detection of fetal congenital abnormalities is cost-effective under a range of assumptions.

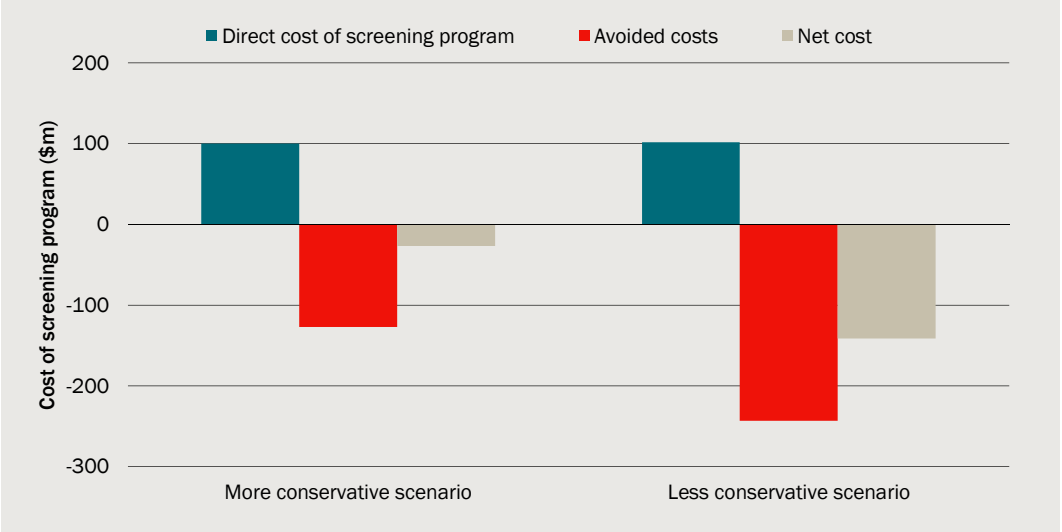
- **Avoided costs (benefits) associated with the scan exceed costs by 2.4 to 1.3 (see chart 1), demonstrating a small positive result overall. The cost per anomaly detected is estimated to be approximately $46 619 per anomaly, or $68 389 per major anomaly.**
- **Additional unquantified outcomes include from the utility or psychological value of the information and benefits from the detection of placental problems and confirmation of gestational age.**
  - **Importantly, reassurance is received in approximately 98.2 per cent of cases where the fetus is scanned and correctly diagnosed as normal(or for the parents of around 285 624 fetuses each year).**
- **A scenario analysis to test variance in results based on variation in the rate of prevalence, rate of detection and probability of termination shows that the ratio of avoided costs to costs from screening for congenital abnormalities at 18-20 weeks ranges from 1.27:1 to 2.39:1 (see chart 2). Hence, using the more conservative (but plausible) assumptions, benefits exceed costs by a small amount, and using more bullish assumptions, benefits exceed costs but still by a relatively modest amount.**
- **Ultimately, the results of the economic evaluation is that screening for congenital abnormalities at 18-20 weeks is most likely to be moderately cost-effective, but without generating substantive risks or benefits.**
- **There are additional, unquantified impacts from the positive psychological value of the information particularly for mothers, which may be associated with improvements in fetal wellbeing, and benefits from the detection of placental problems and confirmation of gestational age.**

1 Estimated costs of screening program in Australia



Data source: The CIE.

2 Scenario testing – more and less conservative scenarios



Data source: The CIE.

1 Background

The CIE was commissioned by the Department of Health and Ageing to review the cost-effectiveness implications of several recommendations in the draft Clinical Practice Guidelines for Antenatal Care – Module 2.

One of these is the recommendation to routinely offer a fetal development and anatomy scan to pregnant women between 18 and 20 weeks gestation.

It is already current practice, in Australia and in many advanced economies, however the cost-effectiveness of the ultrasound scan and associated clinical outcomes has not been comprehensively appraised in an Australian context.

Antenatal screening for fetal abnormalities in Australia

It is common practice in Australia to offer a scan to assess fetal structure and development between 18 and 20 weeks, regardless of maternal age. Routine offering of the second trimester ultrasound scan for fetal abnormalities and location of the placenta is also recommended in the United Kingdom via the 2008 National Institute for Health and Clinical Excellence guidelines, in the United States via the 2009 MedSolutions Ultrasound Imaging Guidelines and Canada through the Society of Obstetricians and Gynaecologists of Canada Clinical Practice Guideline of 2009.

The current principle of the Royal Australian and New Zealand College of Gynaecologists (RANZCOG) is that 'all women, irrespective of their geographical location, resources or chosen model of antenatal care, are entitled to informed prenatal screening and diagnostic testing for fetal abnormalities'.

Module 2 of the Australian Clinical Practice Guidelines for Antenatal Care in its draft form recommends that all women be offered a fetal development and anatomy ultrasound scan between 18 and 20 weeks gestation to detect structural abnormalities and to estimate gestational age where this has not already been determined. Repeat ultrasound is not recommended unless clinically indicated, as it may increase the cost to women such as through elevating anxiety levels.

Objective of this study

It is common for women to accept the offer for a second trimester ultrasound scan for fetal anatomy and development, in Australia and abroad, suggesting that women value the scan and the information it can provide. While Australia is a wealthy, developed country, there are nonetheless tradeoffs in the allocation of individual and government

resources to health care and other goods and services. There is a need to appraise the cost of obtaining information, with respect to the appearance or absence of fetal congenital anomalies, and the flow of benefits and costs associated with this information. The objective of this study is to assess the cost-effectiveness of routinely offering a fetal development and anomaly scan at 18 to 20 weeks.

The primary emphasis of the study is the detection of fetal congenital anomalies. However, it is important to acknowledge that there are additional purposes of this scan. In particular, the scan may also be utilised to detect gestational age where this has not already been identified, and to assess placental location such as to identify a low-lying placenta (placenta praevia).

Theoretical alternatives to routine offering of scan

Given that it is common practice to offer a routine scan, and women have become accustomed to having access to this health service, it may be difficult in practice to discontinue the practice of offering the second trimester scan. Despite its theoretical nature, however, it is most appropriate to analyse the cost-effectiveness of routinely offering the 18-20 week scan with respect to the case where the ultrasound scan is not routinely offered. That is, we assume that women do not undergo a second trimester screen under the 'counterfactual' or alternative scenario.

In many areas of health economics, it is possible to identify risk factors or risk preferences that may 'trigger' the practitioner to offer the intervention (in this case, the ultrasound scan). While risk factors are identifiable for chromosomal abnormalities such as Down syndrome, according to Long and Sprigg (1998), 90 per cent of infants with congenital malformations are born to women with no clinically identifiable risk factors. A risk factor based approach for the 18-20 week scan is not possible or appropriate. Indeed this appears to be acknowledged in the literature with only one study able to be identified that compares the cost-effectiveness of a risk-based approach with routine screening (see Long and Sprigg, 1998).

Furthermore, the question of this study is not one of whether the second trimester scan should be offered in place of earlier screening for chromosomal abnormalities. While a low share of chromosomal abnormalities may be detected at the second trimester screen, through utilising 'soft markers' whereby some markers in the second trimester ultrasound occur more frequently in fetuses with chromosomal abnormalities, it is more clinically effective to screen for chromosomal abnormalities earlier in pregnancy. It is also more accurate to estimate gestational age earlier in the pregnancy.

It is, however, more clinically effective to screen for structural abnormalities between 18 to 20 weeks. Therefore, we assume that the current practice of routinely offering screening for chromosomal abnormalities between 11 and 14 weeks, as well as the dating scan, remains.

This report

The CIE undertakes a literature review, utilising a documented research strategy and appropriate internal/external validity criteria, to appraise the findings and transferability of these findings on the cost-effectiveness of routine offering of ultrasound screening to pregnant women at 18 to 20 weeks to the Australian context.

Due to the limitations on the transferability of the international literature with respect to the Australian context, the CIE reviews clinical and cost data where possible from Australia (or with regard to the Australian context) to model the potential cost-effectiveness of routinely offering the 18 to 20 week scan. The model parameters are discussed in chapter 2, and results are presented in chapter 3.

Overview of the economic literature

A review of the literature identified 11 cost-effectiveness studies on the use of antenatal ultrasound screening at 18-20 weeks for an unselected or low risk population. There is a lack of clinical data on the effectiveness of ultrasound screening in many contexts which results in many studies extrapolating sensitivity or detection rates from studies undertaken in other countries.

While sensitivity rates drive the rate of fetal anomalies that are detected, and the potential utility derived from the detection of abnormalities, the international literature broadly fails to provide an integrated assessment of the benefits derived from other outcomes, namely the value of reassurance from a normal scan result.

A full assessment of the economic literature and the search strategy are provided in Appendix A.

By way of overview, the findings of the literature review include the following:

- Ultrasound screening in the second trimester is clinically effective in detecting structural abnormalities, and sufficiently early to enable clinical intervention.
  - A review by the Cochrane Collaboration (Whitworth et al, 2010) into routine compared with selective ultrasound screening in early pregnancy (< 24 weeks) found that there is insufficient evidence that routine scans reduce adverse outcomes for babies or lead to less health service use by mothers and babies.
  - The CIE's review of the literature suggests that second trimester ultrasound screening is associated with a reduction in additional lifetime medical and developmental costs related to morbidity, resulting only from an increase in the rate of pregnancy termination for fetuses with a lethal or severe abnormality.

This indicates that a significant factor in the cost-effectiveness of routine ultrasound screening is the acceptability of terminations in instances of the detection of lethal and severe congenital abnormalities (Bricker et al, 2000).

Some research suggests improved neonatal outcomes in selective, small populations. Yates (2004) concludes that while 'there appears to be little survival advantage associated with prenatal diagnosis' for structural congenital heart disease, more selective studies

mostly involving only a small number of cases, show improved survival and reduced morbidity in prenatally diagnosed infants presenting to cardiac intensive care units.

Romano and Waitzman (1998), using a utility-based approach to evaluating the value of second trimester screening outcomes, found that the cost-effectiveness of screening was driven by the specificity of ultrasound (rate of true negative) and the women's willingness to pay for the reassurance of a normal scan.

A comprehensive review of women's views of pregnancy by Garcia et al (2002) highlighted the positive impact of second trimester scanning through the sense of reassurance experienced by mothers. The authors reviewed a broad range of studies in terms of their design and context, and found that ultrasound screening is very attractive to women and their families, including in providing reassurance (thereby reducing stress and anxiety) associated with a normal fetus and a visual image of their baby (Garcia et al, 2002). It may also promote maternal wellbeing through strengthened maternal-fetal bonding (Garcia et al, 2002). Garcia et al (2002) also identified a clear need for all staff, women and partners to be well informed about the specific purposes of the ultrasounds, as well as what they can and cannot achieve (Garcia et al, 2002).

With research suggesting that untreated anxiety and depression in pregnancy may reduce fetal wellbeing in a range of ways (see, for example, Pearlstein, 2008), reassurance to the mother may result in increased fetal wellbeing. An article in the Journal of Psychiatry and Neuroscience (Pearlstein, 2008) identifies a range of risks to fetal wellbeing and childhood development from untreated prenatal stress and depression from published research, including:

- adverse obstetric complications including miscarriage, preeclampsia, low Apgar scores, neonatal complications and high neonatal cortisol levels at birth
- elevated cortisol levels, language and cognitive impairment, impulsivity, attention-deficit disorder, and behavioural dyscontrol in offspring during childhood and sleep problems between 18 and 30 months of age
- the risks associated with harmful prenatal health behaviours that may develop from prenatal depression and anxiety such as poor nutrition, poor prenatal medical care, and substance abuse.

More recent analysis by DiPietro (2010) found that dispositional levels of maternal stress and anxiety are modestly associated with aspects of fetal heart rate and motor activity. Both induced maternal arousal and relaxation generate fairly immediate alterations to fetal neurobehaviours — the most consistently observed fetal response to changes in maternal psychological state involves suppression of motor activity. The study also found evidence that fetal behaviours elicit maternal physiological responses. The study found some support for fetal imaging and maternal-fetal attachment, pointing to improved attachment and an increase in the percentage of infants at the age of 12 months who are securely attached.[1]

[1] Di Pietro, J. A. (2010), 'Psychological and psychophysiological considerations regarding the maternal-fetal relationship', *Infant and Childhood Development,* 19 (1): pp. 27-38.

However, it is acknowledged in the literature that prepartum depression and negative outcomes in offspring are understudied compared to empirical papers on the effects of postpartum depression (after birth). Furthermore, the disparate empirical findings have produced ongoing debate regarding the effects of prenatal depression on a developing fetus and later in infancy and early childhood.[2]

Due to the paucity of data and difficulty with estimating the 'value' of reassurance from the routine scan, utility or psychological impacts from screening are usually omitted from cost-effectiveness analyses.

Two large randomised control trials have been undertaken to examine the cost-effectiveness of detecting fetal abnormalities through a second trimester ultrasound scan. These studies identify the value of screening in terms of the rate of sensitivity, and associated clinical outcomes (rate of termination), as opposed to utility.

- The low detection rate of major fetal malformations in the RADIUS trial, of 17 per cent, implies unsatisfactory performance (Whitworth et al, 2012). Due to the low detection rates of major malformations and therefore minimal impact on perinatal mortality, the RADIUS trial did not strongly support the cost-effectiveness of routine screening, as did the Helsinki trial (Whitworth et al, 2012).
- The Helsinki trial demonstrated routine screening improved detection of fetal abnormalities, resulting in an increase in the termination of pregnancies.

However, the findings of the Helsinki trial, which are based on lower inpatient and outpatient days and fewer ultrasounds, are potentially unstable (University of York, 2013). The cost-effectiveness evaluation of the Helsinki trial by Leivo et al (1996) is therefore not transferable to Australia. The study also does not incorporate the longer term medical and developmental costs associated with malformed fetuses.

There are a range of other studies that review or identify the potential clinical effectiveness of routine ultrasound screening in the country of focus, and attempt to provide localised cost data. The extent to which these studies are transferable to Australia varies, but is generally limited. The key findings of the included studies and the CIE's appraisal of the transferability of their findings, as well as any cost or clinical effectiveness data is provided in table 1.1.

[2] Davalos, D., Yadon, C., and Tregellas, H. (2012), 'Untreated prenatal maternal depression and the potential risks to offspring: a review', *Archives of Women's Mental Health*, February 2012, Volume 15, Issue 1, pp. 1-14.

1.1 CIE appraisal of the transferability of literature findings and cost and clinical effectiveness data

	Findings cost-effectiveness)	Transferability of general findings	Transferability of cost data	Transferability of clinical data
Bricker et al, 2000	▪ Second trimester anomaly scan associated with lowest cost for lethal and less severe anomalies, compared to first and third trimester scans ▪ For 'severe' (long term morbidity) anomalies, and overall, third trimester scan is lowest cost per case detected, but does not leave option for termination.	▪ Should not use to assess cost-effectiveness of including first trimester screen ▪ Could use the cost per anomaly detected from second trimester scan	▪ Uncertain transferability- Primary study and comprehensive review of international data, but relatively low costs	▪ Transferable
Leivo et al, 1996	▪ Ultrasound screening resulted in 'lower perinatal mortality' (higher terminations) in screened group ▪ Longer ultrasounds and more numerous advanced examinations lead to fewer perinatal deaths i.e. higher rates of termination (75 per cent versus 35 per cent), better cost-effectiveness ratio ▪ One-stage second trimester ultrasound screening is cost-effective when all significant costs and effects are taken into account (inpatient and outpatient days, ultrasound scans)	▪ Study takes a short term perspective and results may not be stable	▪ Unit costs could be transferable– contains direct and indirect costs from screening ultrasound, potentially low ▪ Probability of clinical pathways may be different (costs take into account probability) ▪ Negative costs should not be relied on	▪ Detection rate may be used for comparison
Long and Sprigg, 1998	▪ Financial benefit, due to avoided cost of caring for malformed fetuses, exceed the cost of routine screening	▪ Uncertain, due to unclear transferability of cost information and potentially conservative rate of detection	▪ Costs unlikely to be transferable ▪ Average cost of care provides a useful comparison, however the year of data is unclear	▪ Potentially conservative detection rate: authors note mixed experience of sonographers
Ritchie et al, 2005	▪ Preferred strategy is first and second trimester combined ultrasound. First trimester screening for chromosomal abnormalities is more expensive, but associated with fewer	▪ Uncertain validity/transferability of clinical effectiveness assumptions and cost information, therefore unclear about robustness of findings	▪ Unlikely to be transferable	▪ Not transferable (no primary data)

	Findings cost-effectiveness)	Transferability of general findings	Transferability of cost data	Transferability of clinical data
	iatrogenic losses. ▪ Strategies which include second trimester ultrasound result in higher detection of abnormalities, lower cost per anomaly detected			
Roberts et al, 1998	▪ Lack of data and uncertainty around estimates means it is not possible to make defensible decisions about which practice should be preferred	▪ Cannot be guaranteed due to limitations in data as acknowledged by authors and insufficient information on which costs are included	▪ No transferable data	▪ No transferable data
Romano and Waitzman, 1998	▪ Routine ultrasound screening is the preferred strategy for most women	▪ Potentially, as key drivers of outcome unlikely to vary significantly between country contexts, but transferability cannot be guaranteed due to uncertainty of transferability of key assumptions	▪ No transferable data	▪ Provides estimates of probability of termination and estimates of sensitivity and specificity from meta-analysis which may be used for comparison. Note: rate of termination in literature tends to be higher than Australian statistics suggest is the case
Vanara et al, 2004	▪ Introducing an organised program in Italy was expected to reduce costs and increase the detection rate, resulting in a reduction in the cost per malformed fetus diagnosed by routine second trimester screening	▪ Not transferable	▪ Unlikely to be transferable	▪ Not transferable (no primary data)
Vintzileos et al, 2000	▪ The benefit cost ratio is dependent on the rate of detection assumed with a negative BCR found when applying detection rates achieved in non-tertiary centres	▪ BCR's may be lowered by the more limited scope of abnormalities incorporated in the estimates of averted savings (on the conservative side), but not directly transferable due to the inclusion of benefits from averted preterm and post-term labour and indirect ('productivity') savings from averting morbidity	▪ May be used for comparison	▪ Transferability unclear - Wide variation in sensitivity rates between tertiary and non-tertiary centres
Waitzman and Romano, 1998	▪ Only under 'favourable' assumptions does the preliminary analysis demonstrate that the	▪ Unclear, as incorporates 'indirect' costs associated with lost productivity which are not	▪ Cost of care per anomaly (only direct costs should be utilised)	▪ Not transferable (no primary data)

	Findings cost-effectiveness)	Transferability of general findings	Transferability of cost data	Transferability of clinical data
	costs associated with routine ultrasound policy exceed benefits ▪ Probability of the detection (sensitivity) of congenital abnormalities would need to be at least 0.5 to make it variable	applicable to this study		
Whitlow et al, 1999	▪ Majority of fetal structural and chromosomal abnormalities can be detected by sonographic screening at 11-14 weeks, but the second trimester scan should not be abandoned	▪ Findings not of direct relevance to issue of cost-effectiveness of second trimester ultrasound screening	▪ Insufficient data	▪ Unlikely to be transferable

Source: The CIE.

2 Australian data and model assumptions

Due to the limitations in the transferability of data from the literature, particularly on the cost side, it is desirable to use localised data in our appraisal of the cost-effectiveness of routine screening in Australia.

In this chapter, we discuss data availability and input parameters for our model which include rates of prevalence, sensitivity, rates of termination, the cost of screening and associated clinical pathways and costs averted through termination. Generally, data availability in the Australian context is poor which leads to a reliance on a range of assumptions. The greatest uncertainty is the costs avoided through the termination of a fetus diagnosed with a severe or lethal abnormality.

Use of screening for the detection of fetal congenital abnormalities

The CIE expects that at least 90-95 per cent of pregnant women in Australia currently receive a second trimester scan for the assessment of fetal development and presence of fetal anomalies. The Australian Handbook for General Practitioners (2007) suggests that approximately 97 per cent of women may accept the second trimester scan. Screening data from the Queensland Perinatal Data Collection indicated that 96 per cent of women selected an ultrasound scan at 19-20 weeks in 2009-10 (Endo et al, 2011).

The same data set from Queensland showed that the use of ultrasound screening at 19-20 weeks did not decrease for women in the 'less advantaged' socioeconomic categories. Relative to women in major cities, the use of the anomaly scan did not reduce for women in inner or outer regional or remote areas. However, the use of the scan was reduced for 'very remote' women and Indigenous women.

There is likely to be a reasonable degree of variation in the percentage of women accepting scans across regional Australia, with the rates of acceptance expected to be considerably lower across the remote areas of the Northern Territory, the Kimberley region of north Western Australia and Cape York Peninsula of far north Queensland. For instance, in the Northern Territory approximately one in four births is attributed to women living very remotely.

The potential for wide variation in the acceptance rate should be recognised, as there are significant barriers for a relatively small number of women living very remotely, such as the cost and time associated with transportation and the anxiety involved in travelling far from home to receive screening tests – particularly if the purpose of screening is not well understood. However, at an aggregate level the costs of screening are entirely variable in the modelling exercise and as such, the assumed of acceptance rate does not affect the results of the modelling (the benefit cost ratio).

Prevalence and detection of congenital abnormalities

While prevalence is reasonably well established for congenital abnormalities, the rate of detection of congenital abnormalities appears to vary widely. However, the variation in the sensitivity of ultrasound screening at 18 to 20 weeks may in part be explained by the scope of the abnormalities that are included in determining this rate. Only one large randomised study from the Australian context could be identified (see Wong et al, 2004), such that it is necessary to draw on the international literature to determine an appropriate sensitivity rate for the detection of congenital abnormalities.

International literature

Bricker et al (2000) conducted a comprehensive review of cost and clinical effectiveness studies of a second trimester ultrasound scan offered in unselected or low risk populations. This review distinguished prevalence and the rate of detection by the degree of severity of the anomaly: lethal anomalies; anomalies where survival is possible with long term morbidity (we refer to as 'severe') and anomalies associated with possible short term morbidity (we refer to as 'less severe'). Based on studies included in the review, the rate of detection by group was:

- 76 per cent for lethal anomalies
- 39 per cent for severe anomalies
- 21 per cent for less severe anomalies.

The combined sensitivity or detection rate[3] for both lethal and severe anomalies, weighted by the relative prevalence of anomalies, is 45 per cent. The prevalence of lethal and severe anomalies in the Bricker et al (2000) literature review is 0.2 per cent and 0.9 per cent, respectively. The prevalence of less severe anomalies is around 0.5 per cent (Bricker et al, 2000). This indicates that 1.6 per cent of fetuses may have congenital anomalies, with 1.1 per cent having lethal or severe anomalies.

However, the types of anomalies identified cover many but not all possible anomalies such that the total prevalence of anomalies by each level of severity is likely to be higher. The average share of fetuses with an anomaly reported across the studies was 1.9 per cent (Bricker et al, 2000).

Two large randomised trials were undertaken to establish the clinical effectiveness of ultrasound screening: the Helsinki trial undertaken in Finland from 1986 to 1987 and the RADIUS trial undertaken from 1987 to 1991. The sensitivity of the RADIUS study varied considerably between the tertiary and non-tertiary settings. In the Helsinki trial, the average sensitivity was 40 per cent (Wong et al, 2004) while the average sensitivity achieved in the RADIUS trial was only 16.5 per cent (Wong et al, 2004). Both trials included tertiary and non-tertiary settings whereby the sensitivity rate varied accordingly. In both trials, minor abnormalities were included, resulting in a lower degree of sensitivity (Wong et al, 2004).

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[3] The rate of sensitivity is utilised interchangeably with the detection rate.

2.1 Summary of Bricker et al review of clinical effectiveness 18-20 week ultrasound

Anomaly	Potential intervention	Prevalence per 1000	Sensitivity (out of 1)
Lethal anomalies		**2.03**	**0.76**
Anencephaly	TOP	0.58	0.97
Trisomy 18	K, TOP	0.33	0.67
Trisomy 13	K, TOP	0.14	0.50
Hypoplastic left heart	TOP	0.35	0.56
Bilateral renal agenesis	TOP	0.38	1.0
Lethal musculoskeletal disorders	TOP	0.39	0.20
Possible survival and long term morbidity		**8.84**	**0.39**
Spina bifida	TOP	0.56	0.67
Hydrocephalus	K, TOP	0.71	0.56
Encephalocoele	TOP	0.17	1.00
Holoprosencephaly	TOP	0.19	0.57
Down syndrome	K, TOP	1.88	0.15
Complex cardiac malformations	K, TOP	1.71	0.23
AVSD	TOP	0.45	0.08
Anterior abdominal wall defects			
Gastroschisis		0.21	1.00
Exomphalos	K	0.17	1.00
CDH	K, TOP	0.33	0.45
Tracheo-oesophagael atresia		0.33	0.13
Small bowel obstruction/atresia		0.25	0.13
CAML		0.25	1.00
Renal dysplasia		0.31	0.60
Multiple abnormality/syndrome	K, TOP	1.32	0.79
Total lethal and severe anomalies		**10.9**	**0.45**
All listed anomalies (including less severe)		**15.6**	**0.36**

Source: Bricker et al, 2000.

Australian literature

The CIE was able to identify just one study undertaken in Australia to assess the transferability of these results. The study by Wong et al (2004) utilises data from the Mater Mothers' Hospital over the period December 1993 to December 1998. Anomalies were recorded according to whether they were major or minor, as defined by the National Perinatal Statistics Unit of the Australian Institute of Health and Welfare (AIHW). The AIHW defines major congenital malformations as those which are either lethal or significantly affect the child's function and/or appearance.

The study reported that major anomalies were detected in 1.01 per cent of fetuses, although 1.39 per cent of fetuses had a major anomaly.

- **The diagnostic sensitivity for major anomalies from the Brisbane hospital was 72.8 per cent, with 123 major anomalies detected from 169 major anomalies present.**

While the study was undertaken in a tertiary centre, the ultrasound machines utilised were considered 'medium range' at the time and operators had varying degrees of experience.[4] In addition, Wong et al (2004) identifies a range of other large series whereby the sensitivity rate for major abnormalities varied between 44 and 85 per cent. Therefore, using the average rate of detection for major abnormalities identified by Bricker et al, of 45 per cent, may be conservative.

Impact of previous screening on prevalence and sensitivity

The majority of women that receive the 18-20 week scan have previously received screening for chromosomal abnormalities such as Down syndrome. Victorian and Queensland data suggests that at least 50 per cent of women participate in Nuchal Translucency (NT) screening at 10-12 weeks gestation. In addition, in place of the first trimester screening for chromosomal abnormalities, it is estimated that around 10 per cent of women receive second trimester maternal serum screening from 14 to 20 weeks. A small portion of women will undergo invasive testing procedures without NT or maternal serum screening.

As a result, there is likely to be a lower rate of prevalence/detection of *previously undiagnosed* fetal anomalies in women that have previously been screened. However, chromosomal abnormalities represent only a portion of all lethal and severe congenital abnormalities that may be detected at the 18-20 week scan. Conditions that may be detected at earlier screening, including chromosomal abnormalities and to a lesser extent spina bifida, represent roughly one quarter of lethal and severe fetal congenital anomalies. Bricker et al (2000) suggest that approximately 0.29 per cent of all fetuses may have a chromosomal abnormality from 1.1 per cent of fetuses with severe and lethal congenital abnormalities.

The prevalence or detection of new chromosomal abnormalities at the 18-20 week scan is assumed to reduce by the proportion that is detected at earlier screening – with spina bifida having the lowest sensitivity of approximately 9 per cent (see Saltvedt et al, 2006) and chromosomal abnormalities having a high sensitivity of approximately 78 per cent (see Whitlow et al, 1999).

The prevalence of *previously undetected* chromosomal abnormalities is reduced from 0.29 per cent to 0.10 per cent for those previously screened – across 60-65 per cent of women receiving the 18-20 week scan. As such, the prevalence of undetected structural abnormalities that are either lethal or severe (chromosomal or non-chromosomal) is adjusted to approximately **1.0 per cent** (from 1.1 per cent)**.**

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[4] Ultrasound scans were performed at 18-22 weeks gestation utilising a Toshiba SSA-250 and ATL-3000. The scans were performed by five general obstetricians with special interest in ultrasound, three maternal and fetal medicine subspecialists and three qualified sonographers.

Chromosomal abnormalities generally have a low rate of detection at the 18-20 week scan. To account for this, the CIE adjusted the rate of prevalence used in Bricker et al (2000) of undetected chromosomal abnormalities at the 18-20 week scan, thereby altering their representation in the total mix of undetected anomalies at the 18-20 week scan. The average sensitivity for major abnormalities (lethal and severe), increases from approximately 45 per cent to **52 per cent**.

Rate of termination

The rate of termination is a product of the rate of detection and the rate of termination once an abnormality is detected. Some groups of conditions, such as central nervous system (CNS) anomalies and urinary tract anomalies, have relatively high rates of detection at the 18 to 20 week scan. The literature review by Bricker et al (2000) suggested that the rate of detection for CNS anomalies was approximately 76 per cent and for urinary tract abnormalities, 67 per cent.[5] The average detection rate of cardiac anomalies in the Bricker et al study was only 17 per cent, although there is an expectation that this has increased over the past decade.

The decision to terminate a pregnancy as a result of detection of severe or lethal fetal malformation may vary significantly between each country depending on the sum of the cultural and religious beliefs of the individuals. As such, it would be desirable to use rates of termination from the Australian context.

One source of data identified is the Queensland Government's perinatal data collection on congenital abnormalities from July 2007 to June 2010 (Howell et al, 2011). Data for this period includes live births, fetal deaths and terminations, earlier than 20 weeks gestation, for major congenital abnormality.

The CIE conducted a concordance of the rates of termination in the Queensland Perinatal Data Collection with the congenital anomalies identified in the Bricker et al review (2000). For several conditions that were not reported in Queensland data[6] it was necessary to utilise European Surveillance of Congenital Anomalies (EUROCAT) data which provides a record of the prevalence of and outcomes (births, deaths and terminations) for congenital anomalies in 21 European countries. The data accessed was for a five year period, from 2007 to 2011.

In addition, the CIE completed the same process of concordance of the rates of termination in the EUROCAT data with the congenital anomalies identified in Bricker et al. This provided a basis for comparison, and indicated that the rates of termination identified in Queensland were significantly lower across many anomalies.

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5 Skeletal abnormalities had a detection rate of just 24 per cent, while gastrointestinal and pulmonary anomalies had higher detection rates of 42 per cent and 50 per cent, respectively.

6 Including complex cardiac malformations, bilateral renal agenesis, atrioventricular septal defect, cystic adenomatoid malformation of the lung, atrial septal defect, renal dysplasia, multiple abnormality/syndrome, teratogenic syndromes with malformations, non-lethal dwarfism.

There are many factors indicating that the rates of termination due to diagnosis of major fetal abnormality sourced from the Queensland data may not be representative of the rates of termination in other states. Laws vary between states in relation to pregnancy termination and while it is generally lawful for mental and physical health reasons, the accessibility to termination can vary between states and locations within states. In Queensland, the common law provides that abortion is lawful where a woman's mental or physical health is in danger (Women's Health Victoria, 2010), however it is possible that lingering uncertainty in Queensland around termination laws have reduced access to terminations particularly over the data period.

Furthermore, the Queensland data includes terminations carried out up to 20 weeks of gestation whereas terminations may occur after 20 weeks in cases where the fetus has a severe congenital abnormality.

The CIE was unable to identify alternative sources of data for other states and as such, utilises EUROCAT data in the model as an indicator of rates of termination in Australia due to fetal abnormality.

Methodology for estimating terminations due to 18-20 week scan

It was necessary to adjust the rates of termination for chromosomal abnormalities and spina bifida by the expected share of terminations occurring because of the second trimester ultrasound scan. The expected share of terminations occurring from earlier screening is a product of the share of women receiving earlier screening (approximately 60-65 per cent), the rate of prevalence and the rate of detection. Overall, these adjustments are significant, reducing the percentage of terminations by approximately 40 per cent to reflect those attributed to the 18-20 week scan.

The rate of termination resulting from Trisomy 13, 18 and 21, and spina bifida is relatively high. However, chromosomal abnormalities (Trisomy 13, 18 and 21) are most commonly detected at the earlier stage of screening. As such, only 19 per cent of terminations from Trisomy 13 were attributed to the second trimester screening, only 23 per cent for Trisomy 13 and 7 per cent for Down syndrome. Spina bifida is not frequently detected at the earlier screening (which only a portion of women receives); while detection is expected to be approximately 67 per cent at the 18-20 week scan. Therefore, 91 per cent of terminations for spina bifida were attributed to the second trimester screening. It is assumed that 100 per cent of terminations across other abnormalities were associated with the 18-20 week scan.

Estimates of terminations

Table 2.2 shows two series of estimates of the rate of termination. The first column is derived from Queensland data (supplementing EUROCAT data, as necessary). The second column is derived solely from 2007-2011 EUROCAT data.

For less severe anomalies, it is likely that those terminations were associated with the presence of more severe abnormalities. For this reason, we use the data from terminations associated with lethal and severe anomalies only.

Table 2.2 shows that in many cases the rate of termination prior to 20 weeks in Queensland is significantly below the rate of termination in the EUROCAT data. For instance, the rate of termination for cases of hypoplastic left heart is indicated to be 9.3 per cent in Queensland compared to 35.7 per cent in Europe. It is also significantly different for anencephaly, bilateral renal agenesis, spina bifida, hydrocephalus and others.

2.2 Estimates of termination rate due to abnormality detected at 18-20 week scan

	Likelihood of termination due to detection at 18-20 weeks, if a fetus has a congenital abnormality		Per cent of all fetuses terminated due to detection at 18-20 week scan	
CIE estimates utilising	Queensland data	EUROCAT data	Queensland data	EUROCAT data
Lethal anomalies			**0.077**	**0.098**
Anencephaly	63.5	82.9	0.037	0.048
Trisomy 18	13.7 (59.0)	16.9 (72.8)	0.005	0.006
Trisomy 13	15.1 (81.7)	13.4 (72.1)	0.002	0.002
Hypoplastic left heart	9.3	35.7	0.003	0.013
Bilateral renal agenesis	62.3	62.3	0.024	0.024
Musculoskeletal disorders	16.8	16.8	0.007	0.007
Possible survival and long term morbidity			**0.104**	**0.169**
Spina bifida	23.2 (25.4)	55.1 (60.3)	0.013	0.031
Hydrocephalus	2.4	35.9	0.002	0.026
Encephalocoele	58.3	60.3	0.010	0.010
Holoprosencephaly	43.6	64.0	0.008	0.012
Down syndrome	3.3 (49.7)	3.0 (45.6)	0.006	0.006
Complex cardiac malformations	14.9	14.9	0.025	0.025
AVSD	18.4	18.4	0.008	0.008
Non-lethal dwarfism	0	47.3	0.000	0.000
Gastroschisis	2.8	12.9	0.001	0.003
Exomphalos	35.4	33.5	0.006	0.006
CDH	7.3	17.4	0.002	0.006
Tracheo-oesophagael atresia	0.0	5.8	0.000	0.002
Small bowel obstruction/atresia	0.0	0.0	0.000	0.000
CAML	9.8	9.8	0.002	0.002
Renal dysplasia	21.0	21.0	0.007	0.019
Multiple abnormality/syndrome	10.0	10.0	0.013	0.013
Total across all anomalies	**10**	**15**	**0.181**	**0.267**

Note: Shown in brackets is the percentage of terminations associated with chromosomal abnormalities and spina bifida (from early screening AND the 18-20 week scan).

Source: Howell et al, 2011, and EUROCAT, 2013.

It is unclear whether the rates of termination in the Queensland data are applicable to the rest of Australia. It is possible that the more conservative rates of termination reflect the way that the Queensland data is reported and specific contextual factors stemming from

Queensland legislation on abortion (particularly over the data period) and associated impediments to the access of terminations.

South Australian data suggests that, in 2010, 157 pregnancies were terminated due to the detection of congenital abnormalities, from 20 002 births. This included 91 terminations of fetuses with non-chromosomal abnormalities (SA Health, 2012). A minority of the other 66 fetuses terminated due to chromosomal abnormalities may have been associated with the 18-20 week ultrasound.

Utilising a conservative approach to attributing the detection of anomalies to the second trimester screening suggests that around 0.480 per cent of fetuses were terminated in South Australia in 2010 due to the detection of abnormalities at the 18-20 week scan. By comparison, based on Queensland data the rate of fetuses terminated (prior to 20 weeks) may be in the order of 0.181 per cent. This suggests that using estimates based on data for Queensland as a proxy for the whole of Australia would not be appropriate.

Due to the uncertain transferability of the Queensland data, we utilise EUROCAT data for the central case estimate of the share of anomalous fetuses terminated in Australia following detection. Using the CIE estimates of termination rates based on EUROCAT data presented in table 2.2, we derive rates of termination for anomalies *detected* at the 18-20 week ultrasound scan of:

- 72 per cent for lethal anomalies
- 45 per cent for severe anomalies
- **53 per cent**, when averaged across all lethal and severe anomalies.

Comparison with broader literature

Comparison with the broader literature suggests using estimates from EUROCAT data to represent the 'average' rate of termination due to major fetal abnormality would be reasonable. Bricker et al (2000) review the rates of fetal termination due to screening for congenital abnormalities across a range of studies (see table 2.3). We understand these refer to anomalies detected at the second trimester screening only and therefore results may not be directly transferable to the Australian context, where detection at earlier screening is associated with a significant share of terminations (estimated to be approximately 40 per cent).

2.3 Rate of terminations of all pregnancies

Study	Screening program	Prevalence anomalous fetuses	Sensitivity before 24 weeks	Share of pregnancies terminated due to detection of anomaly(ies)	Share of anomalous fetuses terminated
		Per cent	Per cent	Per cent	Per cent
Chitty et al, 1991	18-20 weeks	1.5	71.5	**0.60**	40
Shirley et al, 1991	19 weeks	1.4	57.3	**0.45**	32
Luck, 1992	12-14 weeks, 19 weeks[a]	1.9[b]	85.3	**0.21**	11
Crane et al 1994	15-22 weeks, 31-35 weeks	2.3	16.6	**0.12**	5
Skupski et al, 1996	18-20 weeks	2.3[c]	15.0	**0.23**	10
Magriples and Copel, 1998	16-20 weeks	3.07	71.4	**0.67**	22
Lee et al, 1998	18-20 weeks, 32-34 weeks	0.76	13.5	**0.09**	12
Van Dorsten et al 1998	15-22 weeks	1.30	47.6	**0.25**	19
Boyd et al, 1998	18-22 weeks	2.17	41.1	**0.51**	24
Average		**2.09**	**41.3**	**0.41**	**21.5**

[a] Results are for 19 weeks scan [b] Prevalence of anomalies, rather than anomalous fetuses [c] Corrected an error in Bricker et al (2000) or an original source which indicated prevalence was just 1.15 per cent.

Note: The rate of prevalence may be influenced by the scope of the anomalies (ranging from lethal to non-severe) incorporated

Source: Bricker et al (2000).

As the table shows, termination rates vary widely. They reflect a combination of the rate of prevalence, the sensitivity rates and belief systems at large. Where estimates are close to the estimates calculated from the Queensland data, the rate of sensitivity or prevalence is very low.

Table 2.4 shows the implied rate of termination from the international literature presented in table 2.3. It suggests that, on average, 47.5 per cent of fetuses diagnosed with major malformations at the second trimester ultrasound scan may be terminated. The estimates derived from EUROCAT data – whereby **53 per cent** of fetuses with a major anomaly detected are terminated – therefore appear to be reasonable for use in the central case of our model.

However, we utilise scenario analysis to examine the potential impact of a significantly more conservative rate of termination in chapter 4.

2.4 International literature – portion of fetuses with anomaly detected and share terminated

	Implied share of fetuses with a major anomaly detected before 24 weeks	Implied share of anomalous fetuses that were terminated
	Per cent	Per cent
Chitty et al, 1991	1.07	55.9
Shirley et al, 1991	0.80	56.1
Luck, 1992	1.62	13.0
Crane et al 1994	0.38	31.4
Skupski et al, 1996	0.35	66.7
Magriples and Copel, 1998	2.19	30.6
Lee et al, 1998	0.10	87.7
Van Dorsten et al 1998	0.62	40.4
Boyd et al, 1998	0.89	57.2
Average	**0.86**	**47.5**

Source: Derived from Bricker et al (2000)

Cost of ultrasound screening

In Australia, approximately 70 per cent of mothers give birth through the public hospital system. The Medicare Benefits Schedule provides a standard reimbursement for ultrasound screening of $100 per ultrasound, plus $86 for an obstetric consultation. However, it is expected that the cost to the public system if all fixed and variable costs are taken into account would be similar to the private health care system. We therefore look to the private health care system for a measure of the resources involved in screening across both the public and private system.

It should be acknowledged, however, that there is likely to be considerable variation in the resources required for ultrasound screening across both the public and private health care systems. In some cases, for instance, the CIE understands that an ultrasonologist/specialist would be paid a sessional rate for the scan and follow up consultations may be performed by less specialised personnel including midwives, nurses and Aboriginal and Torres Strait Islander health practitioners resulting in lower costs.

However, due to the paucity of data on the cost side it is not appropriate to suggest a potential range in costs and as such, estimates used in the model of the cost of screening which draw on private health care system costs may be conservative (high).

The NIB Health Funds guide for private health insurance customers on the cost of having a baby indicates that in January 2010 the cost per ultrasound may be have been approximately $150 plus between $50-$400 for a follow up consultation with a doctor or specialist. We assume that all women having an ultrasound scan also require a doctor or obstetrician to review their results. In total, the CIE assumes that the cost per ultrasound is $300 in 2010 terms, which is scaled to approximately $329 to reflect current prices. This appears to be higher than in other countries, due to the inclusion of the obstetric

consultation, where the average cost per ultrasound scan was estimated to be $170 in 2012 terms (see Bricker et al, 2000).

The Expert Advisory Committee for this cost-effectiveness review expects that in Australia only a small percentage of patients would require a repeat scan due to the fetal positioning. We assume that 5 per cent of those accepting the scan will require a repeat scan.

Cost of follow up procedures

In Australia, women that receive a 'positive' test for fetal abnormalities are expected to be referred to an obstetrician and be referred for genetic counselling. A minority of women with a positive result, particularly those that have not previously been screened for chromosomal abnormalities may choose to have amniocentesis, which may require a patient to be in hospital for approximately two hours[7]. In addition, women that have a fetus with a lethal or severe abnormality may choose to terminate their pregnancy.

A termination following the 18 to 20 week scan involves inducing the woman into labour and is therefore a procedure that is comparable in resource intensity to a woman giving birth at 40 weeks. It is expected to require between two and three hospital days. The NIB guide indicates that the average cost for a woman to give birth in January 2010 was approximately $2027.65. The cost of a genetic counselling session is based on the Medicare Benefits Schedule due to the absence of other information.

The cost assumptions, which are based on the costs provided in the NIB publication, are provided in table2.5. Costs have been scaled by the quarterly wage price index movements for health care and social assistance from the March quarter of 2010 to the December quarter of 2012.

2.5 Cost of follow up procedures and consultations in the case of 'positive' test

Procedure	Cost assumptions
	A$
Cost of obstetric consultation following 'positive' test	164.6
Amniocentesis (medicare schedule fee, doctor or specialist costs related to procedure and additional obstetric visit)	1081.9 (67.0+850.3+164.6)
Cost of genetic counselling	75.1
Cost of termination	2224.6

Note: Costs sourced from NIB have been scaled using the wage price index for health care and social assistance to reflect potential price increases from January 2010 to December 2012.

Source: Derived using NIB, 2013.Medicare Benefits Schedule Book Category 5 (December 2012).

Women diagnosed with placenta praevia would require a further scan in the third trimester. However, the cost of follow up consultations for placenta praevia at the second

[7] The cost of amniocentesis has not been derived from this indicative estimate of the procedural time.

trimester scan has not been incorporated, as the associated benefits are not quantified in this study.

Avoided cost of care

Table 2.6 provides a breakdown of the assumptions utilised in the model to estimate the cost of care for fetuses born with lethal and severe congenital abnormalities. Our estimate of the average avoided costs of care, associated with termination, is $221 439. This is reasonably similar to the estimate by Long and Sprigg (1998) of the lifetime care savings of infants born with congenital abnormalities within the context of their study of A$172 681 (2012 terms)[8].

2.6 Estimated direct cost of care for babies born with congenital abnormalities

	Approximate cost	Share of terminations
	$A	Per cent
Lethal anomalies	23 713	40
Severe anomalies associated with possible survival and long term morbidity	351 269	60
Average	**221 439**	

Source: The CIE.

Avoided cost of care – severe congenital abnormalities

In the literature, studies predominantly refer to work undertaken by Waitzman et al in 1994[9] and 1996[10] in relation to the direct costs avoided from pregnancy termination associated with the detection of (a) severe congenital condition(s). The CIE identified estimates from the US Environmental Protection Agency (EPA) on the cost of congenital anomalies, which were based on Waitzman et al (1996). The CIE uses the EPA estimates scaled to 2012 terms and converted to Australian dollars.

The costs include the incremental costs beyond what would have been incurred by an individual without the congenital condition. They take into consideration the costs at each stage of life, and the life expectancy of a person with the associated anomaly. The costs include direct medical costs, such as inpatient and outpatient care, pharmaceuticals, laboratory tests, X-rays and long term care. Non-medical direct costs associated with developmental services and special education are also estimated. Together, direct medical and non-medical costs represent an estimate of the total per-capita costs incurred by society in the care of individuals with the associated abnormality. Costs are discounted at a rate of 5 per cent.

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8 The original estimate was £145 078, we assume that original estimates are in 1993 terms.

9 Waitzman, N., Romano, P., and Scheffler, R. 1994. Estimates of the economic costs of birth defects. Inquiry 31: 188-205

10 Waitzman, N., Scheffler, R, and Romano, P. 1996. The cost of birth defects: The value of prevention. University Press of America. Lanham, MD.

Table 2.7 shows the original estimates published by the EPA in 2002 (in 1996 dollars), and scaled estimates, across the range of congenital abnormalities available. The CIE used the RBA inflation calculator to convert 1996 dollars to 2012 dollars while the exchange rate used to convert US dollars to Australian dollars represents an average of monthly exchange rate data for 2012 sourced from the RBA.

2.7 Direct medical and non-medical costs of care – severe congenital abnormalities

	$US 1996	$A 2012
Down syndrome	235 617	407 843
Spina bifida	202 933	351 269
Cleft lip and palate	22 626	39 165
Limb reductions	77 686	134 471
Cardiac anomalies		
Truncus arteriosus	346 339	599 498
Transposition/DORV	117 085	202 669
Tetralogy of Fallot	183 887	318 301
Single ventricle	165 674	286 775

Source: The CIE.

It would be meaningless to utilise a simple average of the costs listed in the table, which represent just a sample of lethal and severe abnormalities and include lower order conditions (cleft lip and palate and limb reductions). Therefore, we utilise the cost of care for spina bifida as a proxy for the broader range of severe (but not 'lethal' category of) congenital abnormalities for which parents may seek a termination.

Due to significant uncertainties and gaps in the literature around the cost of care for congenital abnormalities, it is not appropriate to identify a confidence interval around the estimate. There remains significant uncertainty around the transferability of these costs to the Australian context. It is also unclear how representative these costs are of the broader range of conditions for which parents may seek a termination. In particular, spina bifida is a condition which is amenable to longer term survival and may be utilised only as a proxy for other conditions amenable to survival.

Avoided cost of care –lethal congenital abnormalities

Only around 20-25 per cent of congenital abnormalities prevalent at the 18-20 week scan are categorised as 'lethal' conditions. However, due to the higher rate of detection and termination of lethal conditions, the prevalence of lethal abnormalities among terminations may be higher at around 35 to 40 per cent. The life expectancy for lethal conditions may be as low as several days indicating that it would not be appropriate to utilise spina bifida, which is associated with considerably longer life expectancy, as a proxy for the cost of lethal congenital conditions.

A study in Denmark by Goldstein and Neilson (2008) of data[11] from 1977-1986 found that the median rate of survival for trisomy 13 was 2.5 days, while the same figure for trisomy 18 was 6.0 days. Similarly, babies born with bilateral renal agenesis have a very short life span.

Cardiac transplantation has become a possibility for infants with hypoplastic left heart syndrome. According to Fruitman (2000), this has changed the outlook for children in the United States and Canada from an expected mortality of 95 per cent by one month of age without treatment to an approximate actuarial survival of 58 per cent at five years after staged surgical palliation intervention, and 55-60 per cent at seven years after cardiac transplantation. However, many parents remain unprepared to put their children through multiple operations with uncertain outcomes (Fruitman, 2000).

To estimate the cost of care for infants with lethal congenital abnormalities, which are estimated to represent around 35-45 per cent of terminations, we use Australian data on the cost of an infant with severe neonatal morbidity. Lain et al (2013) provide an analysis of the New South Wales Perinatal Data Collection for 599 753 live born infants from 2001-2007. Based on an average number of in-hospital days for infants with neonatal morbidity of 23.4 days, the cost per birth admission of an infant with neonatal morbidity may be approximately $26 143 (Lain et al, 2013). This compares to an average cost of birth admissions for infants without severe neonatal morbidity of $2403 (Lain et al, 2013).

- This amounts to an additional $23 713 per live birth of an infant with severe neonatal morbidity, which equates to an additional $1013 per day. This differential is used as a rough proxy of the additional cost of care associated with an infant with a lethal congenital abnormality.

The CIE acknowledges that this estimate relates to the broader range of causes of neonatal morbidity, of which congenital abnormalities represents just a small share. A significant share of infants born with lethal congenital abnormalities would not live to 23.4 days, leaving some uncertainty around whether the average length of stay following birth is transferable to this context. On the other hand, there may be additional costs for infants with lethal congenital abnormalities such as the cost of surgical intervention that are not proportionately reflected in these average cost assumptions. We also do not account for the rate of miscarriage among women carrying fetuses with lethal congenital conditions.

Long and Sprigg (1998) utilise estimates from the Royal College of Gynaecologists (1984) and Trent Regional Health Authority (1986) for the estimated lifetime care savings of fetuses terminated (or with the potential to have been) for major congenital abnormalities present in fetuses across routine screening and risk based screening groups. The estimates corresponding to 'lethal' conditions classified in Bricker et al included £5000 for Trisomy 18 and £41 250 for hypoplastic left heart. Although the exact year of the estimates is unclear, we assume they refer to the context of the study (1993), such that

[11] Data was ascertained through The Danish Central Cytogenetic Register, all cytogenetic laboratories in Denmark, pediatric departments throughout the country, The Medical Birth Register and The Register of Causes of Death in Denmark.

the cost in Australian dollars in today's terms may be approximately A$5 951 for Trisomy 18 and A$49 098 for hypoplastic left heart. This suggests that our estimate of the average cost of lethal conditions of $23 713 may be reasonable.

Indirect costs

The costs associated with lost pay and lost leisure for women attending the scan and adults accompanying them, travel costs and the cost of childcare in Bricker et al (2000) provide a measure of the opportunity costs and indirect costs of attending an ultrasound scan. However, due to the limitations of the study, making it difficult to transfer these costs to the Australian context, as well as the low order of magnitude of opportunity costs relative to direct medical costs we have excluded indirect costs from the model. Potential additional costs not incorporated in the central case assumptions are broadly addressed through the scenario analysis.

As shown in table 2.8, the indirect costs estimated in the Bricker et al (2000) study were very small, just £9.37 in 1997 terms or $10.22 in 2012 Australian dollars. However, in Bricker et al (2000) this represented close to 8 per cent of the average cost of a scan. If scaled by 8 per cent of the estimated cost of a routine scan in Australia then the cost would be $26.30. Nonetheless, the indirect costs are still very small and not expected to be an important driver of cost-effectiveness in aggregate.

- **However, indirect costs may be substantive for women that live remotely, in terms of both transportation costs and time.**

There is a range of issues with the transferability/validity of the study for use in the Australian context. It appears that only a subset of women reported losing pay or leisure time, 10 per cent in total, such that there is no measure of opportunity cost for the remaining 90 per cent of women. The majority of women were not in paid employment, which also suggests that the context of the study is different to Australia where a high percentage of pregnant women would be expected to be in paid employment. In addition, the average hourly wage in that context was only £5.37, which is equivalent to approximately $5.90 in 2012, Australian dollars.

2.8 Indirect costs associated with attending 18-20 week scan

	Share of women affected	Mean cost per woman affected	Cost averaged over all women	Cost averaged over all women
	Per cent	£ 1997	£ 1997	$A 2012
Lost pay	5.7	6.76	0.39	0.42
Lost leisure	3.8	2.7	0.10	0.11
Accompanying adults off work	42.8	8.38	3.59	3.91
Accompanying adults not in paid employment	37.4	5.03	1.88	2.05
Travel				
Car	74.5	1.4	1.04	1.14
Public transport	15.1	5.48	0.83	0.90
Taxi	8.5	8.46	0.72	0.78
Parking fees	21.9	0.53	0.12	0.13
Childcare				
Paid	2.8	17	0.48	0.52
Time off work	2.8	8.38	0.23	0.26

Source: Bricker et al (2000) and CIE adjustments.

3 Model of options for Australia

The CIE finds that ultrasound screening at 18-20 weeks for the detection of fetal congenital abnormalities is cost-effective under a range of assumptions.

Under the central case assumptions, we could expect the avoided costs (benefits) derived from the scan to exceed costs by 1.71 to 1. This incorporates generous assumptions on the cost of screening, while excluding the utility value and benefits from the detection of placental problems and confirmation of gestational age.

A scenario analysis suggests that the ratio of avoided costs to costs from screening for congenital abnormalities at 18-20 weeks could range from 1.27:1 and 2.39:1.

Clinical pathways

To evaluate cost-effectiveness, the CIE utilised a probabilistic model to generate benefit and cost flows from the recommendation to offer ultrasound screening to pregnant women at 18-20 weeks gestation in Australia, compared to the case where a scan is not offered. The probabilities of each outcome reflect the level of prevalence, sensitivity, and specificity upon diagnosis – these are important inputs to our model and were discussed in the previous chapter (see table 3.1).

3.1 Formula used to derive probability of outcomes

	Actual presence of congenital abnormality	
Test accuracy	Positive	Negative
True	True positive *prevalence × sensitivity*	True negative *(1-prevalence)×specificity*
False	False negative *prevalence × (1- sensitivity)*	False positive *(1-prevalence) × (1- specificity)*
Total	**Actual positive** **prevalence**	**Actual negative** **1 – prevalence**

Note: Sensitivity refers to the rate of detection if an anomaly is present.

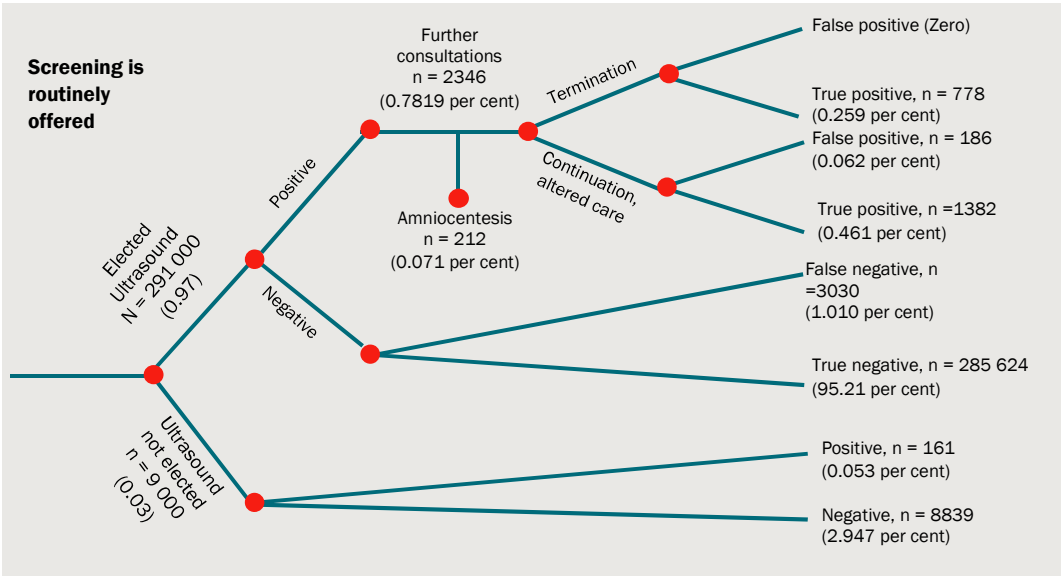
Source: The CIE

Chart 3.2 identifies the clinical pathways associated with screening for congenital abnormalities at 18-20 weeks. The number of cases for each outcome reflects the probability of the outcome multiplied by the number of births in a given year. In recent years, the birth rate in Australia has been around 300 000.

The probabilities shown in chart 3.2 provide a basis for estimating costs associated with screening:

- 97 per cent of women are assumed to accept screening, at a cost of approximately $329 per pregnancy (including an ultrasound scan and obstetric visit)
  - plus an additional cost for rescreening for approximately 5 per cent of pregnancies where the fetus was not well positioned at the initial screening, at an additional cost of $165
- for 0.7819 per cent of all women or for 100 per cent of women receiving a true or false positive test, further consultations are required including consultation with a specialist obstetrician and genetic counsellor. From these women:
  - approximately 9 per cent choose to undertake amniocentesis (0.071 per cent of pregnancies), at an approximate cost of $1082 each
  - approximately 33 per cent choose to have a second trimester termination (0.259 per cent of pregnancies), at an average cost of approximately $2225.

3.2 Probabilistic framework and screening outcomes underpinning model



Data source: The CIE.

Termination of pregnancy as a result of the detection of an anomaly at the 18-20 week scan has an attached probability (in our model, of 0.259 per cent or 778 fetuses per year). This represents 53 per cent of pregnancies where a lethal or severe anomaly has been detected, or 36 per cent of all fetuses that are *correctly* diagnosed with an abnormality of any level of severity. This pathway is associated with avoided direct medical and non-medical costs, estimated to be in the order of $221 439 per fetus.

Importantly, although difficult to quantify, there are a range of other outcomes that should be acknowledged:

- reassurance is received in approximately 95.21 per cent of cases (or for the parents of around 285 624 fetuses each year) where the fetus is correctly diagnosed as normal. This translates to 98.2 per cent of cases where a mother accepts a scan.
- false reassurance is given in approximately 1.01 per cent of cases (or for around 3030 pregnancies each year) that receive a false negative result

- false alarm in approximately 0.0619 per cent of cases or around 186 pregnancies where there is a false positive diagnosis
- there would be uncertain psychological impacts in approximately 1382 pregnancies (0.461 per cent) that receive a true positive test and continue their pregnancy. Earlier notification may make the pregnancy more stressful for some, however it may also provide an opportunity for the parents to be better prepared to manage the arrival of their baby.

Review of the literature suggests that the probability of a termination resulting from an inaccurate diagnosis of fetal abnormality is extremely low. There is only one documented case of this occurring in the literature reviewed by CIE. False positive diagnoses are generally associated with less severe abnormalities, which are harder to detect, and medical practitioners take considerable care in diagnosing major fetal abnormalities. The rate of specificity (99.94 per cent) is based on the Bricker et al (2000) literature review.

4 Key findings

Ultimately, the result of the economic evaluation is that screening for congenital abnormalities at 18-20 weeks is most likely to be moderately cost-effective, but without generating substantive risks or benefits.

Avoided costs (benefits) associated with the scan to exceed costs by 1.71:1, demonstrating a relatively modest positive result overall. The cost per anomaly detected is estimated to be approximately $46 619 per anomaly, or $68 389 per major anomaly.

Additional unquantified outcomes include from the utility or psychological value of the information, which may be associated with improvements in fetal wellbeing, and benefits from the detection of placental problems and confirmation of gestational age.

A scenario analysis to test variance in results based on variation in the rate of prevalence, sensitivity and probability of termination shows that the ratio of avoided costs to costs from screening for congenital abnormalities at 18-20 weeks ranges from1.27:1 to 2.39:1. Hence, using the most conservative (but plausible) assumptions, benefits exceed costs by a small amount, and using more bullish assumptions, benefits exceed costs but still by a relatively modest amount.

Costs and cost-effectiveness

Under the central assumptions identified in chapter 2, we estimate that the cost of the 18-20 week ultrasound screening program may be approximately $46 619 per fetal abnormality diagnosed. The total cost of screening women for fetal abnormalities at 18 to 20 weeks may be around $100.7 million.

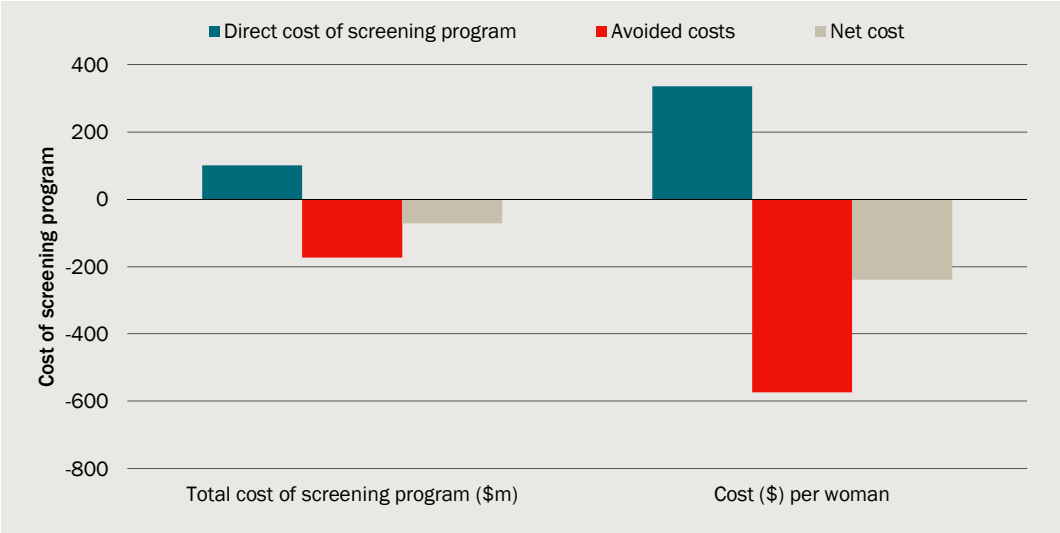
From 291 000 women assumed to accept the offer for a routine scan, approximately 2 160 are expected to receive a true positive diagnosis of fetal abnormality including 1 472 with lethal or severe abnormality detected. The cost per major anomaly detected is estimated to be approximately $68 389.

The majority of costs are expected to be associated with the initial scan, with the overwhelming majority of women (approximately 96.22 per cent) receiving a true or false negative result. The direct medical costs of offering routine screening to all women, based on 300 000 births each year, is approximately $98.2 million. The cost of follow up consultations is estimated to be a more modest $2.5 million.

In comparison, the avoided cost of care for the 778 fetuses terminated due to the presence of a lethal or severe anomaly may be in the order of $172.4 million each year. On balance, we would expect that the avoided costs associated with terminated pregnancies

would exceed the direct costs from the screening program (see chart 4.1). The avoided costs are only a partial measure of the utility derived from screening for congenital abnormalities, with a significant component of the benefit expected to be the value of reassurance (see Romano and Waitzman, 1998) in terms of its utility and the association between maternal psychological wellbeing and fetal wellbeing.

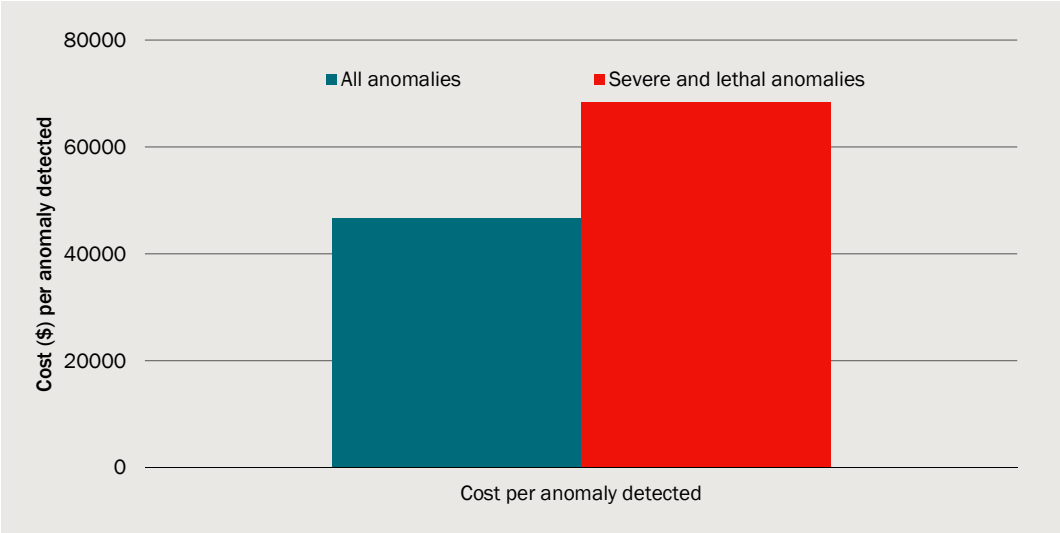
4.1 Estimated costs of screening program in Australia



Data source: The CIE.

The cost-effectiveness in terms of the cost per anomaly detected, and the cost per major anomaly detected is shown in chart 4.2.

4.2 Cost-effectiveness in terms of the cost per anomaly detected



Data source: The CIE.

Scenario analysis

The analysis presented above suggests that routinely offering screening to women in Australia, compared to not offering screening, is cost-effective. The robustness of this conclusion can be tested through scenario analysis, in which the degree of change in cost-effectiveness indicators associated with more or less conservative assumptions is assessed. It should be noted, however, that we have sought to be conservative under the central case and that the less conservative scenario outlined below is not improbable.

The CIE has been generous in accounting for the potential costs associated with an ultrasound screening program. While there is some uncertainty around whether all costs have been accounted for, such as the additional cost of monitoring resulting from routine screening, much of the uncertainty is expected to come from the input probabilities. These include:

- the rate of prevalence of anomalies, including lethal and severe anomalies
- the average rate of sensitivity
- the probability of termination once an anomaly has been detected at the 18-20 week scan.

In addition, the rate of acceptance of the scan alters the overall cost per woman (offered screening) but does not change the cost-effectiveness. This is because there is no change to the rate of prevalence and detection associated with screening more or less women.

As noted earlier, there is also considerable uncertainty around the direct medical and non-medical cost of care over the lifetime of a child born with a lethal or severe congenital abnormality.

In table 4.5, we show the range in parameters that are tested through scenario analysis. The 'more conservative scenario' reflects more conservative assumptions of the prevalence of congenital abnormalities, sensitivity rate and the preference for termination. The less conservative assumptions together present a more optimistic scenario with respect to the value of the 18-20 week ultrasound scan.

For prevalence rates, the lower bound reflects the average because there is confidence that the average is already very conservative. The less conservative scenario whereby 2.1 per cent of fetuses have congenital abnormalities is based on EUROCAT data on the rate of prevalence from registries in 21 European countries from 2007 to 2011. The range used of 1.9 to 2.1 per cent is consistent with data from New South Wales from 2003 to 2008 which indicated that between 1.8 per cent and 2.1 per cent of infants were reported as having congenital conditions (NSW Government, 2011). The prevalence of anomalies is scaled proportionately.

The sensitivity of testing for major anomalies in the more conservative scenario is based on the average performance of screening for congenital abnormalities from a literature review of screening at 18-20 weeks undertaken by Bricker et al (2000). The result is lower than the central case because in the central case we adjust the rate of prevalence of undetected chromosomal abnormalities (which typically have low detection rates at the second trimester scan) as well as spina bifida reflecting the fact that the majority of women are screened for these conditions prior to the 18-20 week scan. This adjustment

increases the rate of detection, while decreasing the rate of prevalence, due to the lower share of chromosomal abnormalities across all congenital conditions that undetected prior to the 18-20 week scan.

The sensitivity assumptions for the less conservative scenario are based on the sensitivity rate achieved by the Queensland Mater hospital of 72.8 per cent for the detection of major abnormalities, which is similar to the rate achieved in other large studies (Wong et al, 2004). The overall rate of sensitivity, which drives the number of anomalies detected and cost of follow up consultations, was adjusted proportionately.

In the central case and less conservative scenario, the rate of pregnancy termination following the detection of lethal or severe abnormality is based on EUROCAT data. The more conservative scenario is based on both the international (EUROCAT) and Queensland rates of termination. The more conservative assumption of 43.7 per cent is lower than the average rate of termination sourced from international literature of 47.5 per cent (see table 2.4).

4.3 Sensitivity testing on probabilities used in model

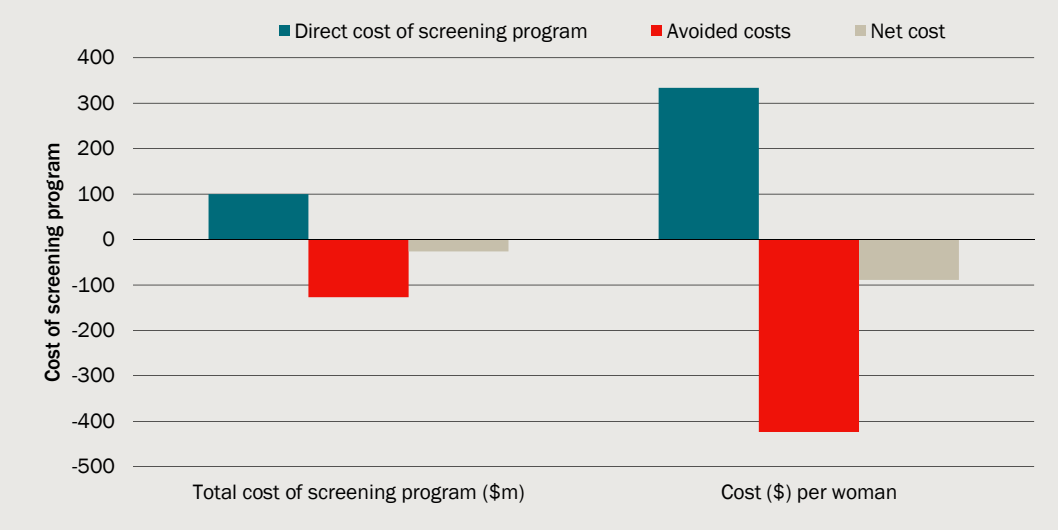
	Central case	More conservative scenario	Less conservative scenario
	Per cent	Per cent	Per cent
Prevalence of lethal or non-serious anomalies for women at the 2nd week scan	1.0	1.0	1.1
Prevalence of all anomalies (brackets refers to anomalies not previously detected)	1.9 (1.8)	1.9 (1.8)	2.1 (2.0)
Sensitivity - lethal and severe anomalies only	51.5	45.3	72.8
Sensitivity - all anomalies	41.6	36.6	58.8
Average probability of terminating a pregnancy following detection of lethal and severe anomalies at 18-20 weeks	52.9	43.7	52.9

Source: The CIE.

Utilising a combination of conservative assumptions indicates that the cost-effectiveness of routinely offering scanning is much lower or the cost per anomaly detected higher. When considering the benefits of the scan, in terms of the avoided cost of care associated with termination, screening appears to be relatively cost neutral. The net direct benefits of screening may be $26.79 million (see chart 4.4).

This estimate does not take into account women's willingness to pay for the information associated with a normal or abnormal result. It also does not take into account other clinical pathways and benefits of screening at 18-20 weeks from the detection of placental problems such as low-lying placenta which is diagnosed at the 18-20 week scan as well as the promotion of improved maternal (and therefore fetal) wellbeing via the reassurance or utility the scan may provide.

4.4 Cost of screening program – more conservative assumptions

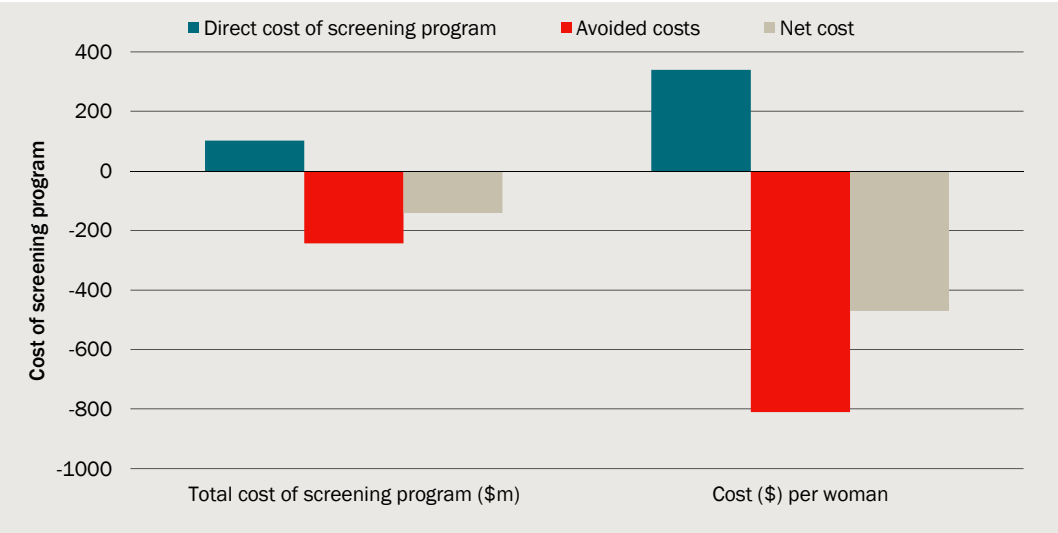


Data source: The CIE.

As shown in chart 4.5, more optimistic assumptions around the sensitivity of screening at 18-20 weeks, and less conservative assumptions around the rate of prevalence and terminations following the detection of lethal and severe anomalies results in larger avoided costs.

Using less conservative assumptions increases the cost of screening only marginally, which is associated with higher rates of detection, but almost doubles the costs avoided as a result of screening (and associated terminations) compared to the more conservative scenario.

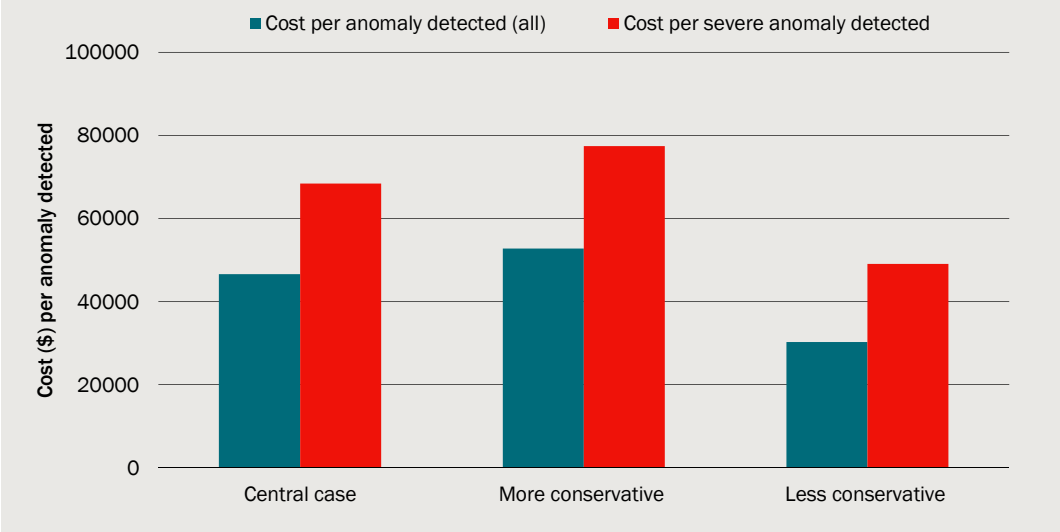
4.5 Cost of screening program – less conservative assumptions



Data source: The CIE.

The range of estimates of the cost per anomaly detected is presented in chart 4.6.

4.6 Cost per anomaly detected across central case and alternative scenarios



Data source: The CIE

Implications for improving access to services

While there is largely universal access to ultrasound screening for the detection of fetal congenital abnormalities at 18 to 20 weeks, women in very remote areas have poorer access to health care services due to the distance from services. According to the National Perinatal Data Collection, women in remote areas accounted for approximately 1.7 per cent of births in 2007 while women in very remote areas comprised approximately 1.1 per cent of births. That is, it is likely that between 1.1 per cent of women and 2.8 per cent of women have more limited access to ultrasound screening, associated with between approximately 3000 and 8000 births each year.

- **The incidence of births comprised by women living very remotely is significantly higher in the Northern Territory, at more than 26 per cent in 2007 or 945 births each year (AIHW, 2009).**
- **The portion of births attributed to women living very remotely is also expected to be high in the Kimberly region of north Western Australia and in the Cape York peninsula of Queensland.**

The analysis presented above indicates that there may be net benefits of routine screening of around $239 per woman; however, this could range between $89 and $471 per woman. In total, the screening program across Australia may be expected to generate savings in the order of $71.7 million, across approximately 300 000 pregnancies each year. Furthermore, additional benefits from screening at 18-20 weeks may include the diagnosis of placental problems such as placenta praevia and the benefit of the information regarding the fetal development of their child.

The cost-effectiveness of the fetal anatomy and development scan at 18-20 week scan gestation suggests that equity could be improved to women living very remotely,

particularly in the Northern Territory where access to services may be limited for around one in four women.

A Collection and appraisal of the economic literature

Approach

The search terms and databases searched for this project are listed in table A.1.

A.1 Search strategy

	Strategy
Databases	Medline, CINAHL, The Cochrane Library, Embase, EconLit and Science Direct
Search terms	Cost-effectiveness, cost, economic, evaluation, pregnancy, screen, scan, ultrasound, structural abnormalities, 18 to 20 weeks, anomaly

Source: The CIE.

The CIE established an inclusion and exclusion criteria to determine the appropriateness of the studies identified (shown in table A.2). To be included the studies needed to appraise screening at 18 to 20 weeks gestation, relative to no second trimester screening or a risk-based screening approach, including or excluding earlier screening for chromosomal abnormalities. We were reasonably generous with regard to the gestational date of screening, with several studies examining second trimester ultrasound screening from around 16 weeks up to 22 weeks gestation.

Many studies focus on the effectiveness of ultrasound screening with respect to a subset of congenital anomalies, such as Down syndrome, however we are interested in all fetal congenital anomalies. While evaluating the cost-effectiveness of ultrasound screening requires an assessment of the change in obstetric outcomes, resulting from the detection of congenital anomalies, many studies simply identify the cost per case detected. These studies were incorporated if they contained potentially useful information about costs and clinical effectiveness.

A.2 Inclusion and exclusion criteria for the cost-effectiveness of offering ultrasound at 18-20 weeks gestation

Group	Inclusion criteria	Example reasons for exclusion
Types of studies	Economic evaluations or cost-effectiveness studies	No relevant or useable data on cost or consequences. Data should discuss both cost and consequences.
Participants	Pregnant women at 18-20 weeks gestation (unselected population)	Very specific patient group
Intervention	Screening at 18 to 20 weeks for the detection of structural (non-chromosomal) abnormalities (Note: some allowance is made if study includes scanning at these weeks as well as weeks preceding these)	▪ Inappropriate intervention: – testing at a different time point – testing focuses on chromosomal abnormality
Comparison	Study may identify: ▪ Routine scanning compared to selective scanning based on presence of indications for the detection of structural (non-chromosomal) abnormalities ▪ Routine scanning compared to no second trimester anomaly scan The context may be either screening in the second trimester for all congenital abnormalities, after no first trimester anomaly scan AND/OR screening in the second trimester after a first trimester scan for chromosomal abnormalities	▪ Inappropriate comparator: – Another form of intervention that is not considered or not targeted towards the detection of non-chromosomal abnormalities: e.g. maternal serum alpha-fetoprotein screening program
Outcome measures	Cost per obstetric outcome. ▪ In many cases, information provided is cost per detection. ▪ Where possible, it is desirable for outcomes (benefits and costs) associated with detection of anomalies to be provided	Cost information is provided with no reference to obstetric outcome (not a cost-effectiveness study)

Source: The CIE

Search results

From the literature search, the CIE identified 20 studies with the potential to provide cost data and information on cost-effectiveness. These studies originated predominantly from the United Kingdom, the United States and, to a lesser extent, other European countries (Finland, Italy and France). The studies were predominantly from the 1990s, although several studies that are more recent were identified but excluded.

Excluded studies

The CIE rejected nine of the studies on the basis that they did not meet the criteria for inclusion outlined in table A.2. The principle reasons for exclusion were that upon review, no cost data was identified, or cost data was provided without information on clinical outcomes, the study involved an irrelevant comparator and/or the screening

focused on the detection of chromosomal abnormalities. A list of excluded studies, and the reasons for their exclusion, is provided in table A.3.

A.3 Studies excluded from appraisal

Author	Title	Date	Country	Reason(s) for exclusion
DeVore, G.	The routine antenatal diagnostic imaging with ultrasound study (RADIUS): another perspective	1994	US	Scan at 15-20 weeks, irrelevant comparator (maternal serum alpha-fetoprotein).
DeVore, G.	Is genetic ultrasound cost-effective?	2003	US	Study examines risk of Trisomy 21 only (chromosomal), comparator is universal amniocentesis
El-Sayed, M., Mohamed, S,. Jones, M.	Cost-effectiveness of ultrasound use by on-call registrars in an acute gynaecology setting	2011	UK	Patient group is women with gynaecological problems
Harris, A.	The cost-effectiveness of prenatal ultrasound screening for trisomy 21	2004	Australia	Screening for Trisomy 21 only (chromosomal abnormality)
Henderson, J., Bricker, L, Roberts, T., Mugford, M, Garcia, J., Neilson, J.	British National Health Service's and women's costs of antenatal ultrasound screening and follow-up tests	2002	UK	Not a cost-effectiveness study or evaluation: Contains costs per scan type and cost to women.
Kott, B., Dubinsky, T.	Cost-effectiveness model for first-trimester versus second-trimester ultrasound screening for Down syndrome	2004	US	Screening for Down syndrome only (chromosomal abnormality)
Luck, C.	Value of routine ultrasound scanning at 19 weeks: a four year study of 8849 deliveries	1992	UK	Not a cost-effectiveness study. Provides clinical outcomes data useful for consideration. Note, however the clinical pathway differs from the Australian context (dating scan plus α-fetoprotein measurements plus 19 week scan)
Rozenberg, P., Bussières, L., Chevret, S., Bernard, J-P., Malagrida, L., Cuckle, H., Chabry, C., Durand-Zaleski, I., Bidat, L., Lacroix, I., Moulis, M., Roger, M., Jacquemot, MC., Bault, JP., Boukobza, P., Boccara, P., Vialat, F., Giudicelli, Y., Ville, Y.	Screening for Down syndrome using first-trimester combined screening followed by second trimester ultrasound examination in an unselected population	2007	France	Chromosomal screening only, screening at 20-22 weeks
Seffah, J,. Adanu, R.	Obstetric ultrasonography in low-income countries	2009	Ghana	No outcomes data. Discussion paper, rather than review or primary data.

Source: The CIE.

Relevant or included studies

Listed in table A.4 are the remaining 11 studies that met the inclusion criteria. They vary in terms of the primary outcome measure/s identified, their methodology in accounting for costs and benefits and in terms of their relevance to the Australian context. These issues are appraised in the next section.

A.4 Cost-effectiveness studies to be included

Author	Title	Year	Country
Bricker, L., Garcia, J., Henderson, J., Mugford, M., Neilson, J., Roberts, T., Martin, M-A.	Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views	2000	UK
Leivo, T., Tuominen, R., Saari-Kemppainen, A., Ylostalo, P., Karjalainen, O., Heinonen, O.	Cost-effectiveness of one-stage ultrasound screening in pregnancy: a report from the Helsinki ultrasound trial	1996	Finland
Long, G., Sprigg, A.	A comparative study of routine versus selective fetal anomaly ultrasound scanning	1998	UK
Ritchie, K., Bradbury, I., Slattery, J., Wright, D., Iqbal, K., Penney, G.	Economic modelling of antenatal screening and ultrasound scanning programmes for identification of fetal abnormalities	2005	UK
Roberts, T., Mugford, M., Piercy J.	Choosing options for ultrasound screening in pregnancy and comparing cost-effectiveness: a decision analysis approach	1998	UK
Roberts. T., Henderson, J., Mugford, M., Bricker, L., Neilson, J., Garcia, J	Antenatal ultrasound screening for fetal abnormalities: a systematic review of studies of cost and cost-effectiveness	2002	UK
Romano, P., Waitzman, N.	Can decision analysis help us decide whether ultrasound screening for fetal anomalies is worth it?	1998	US
Vanara, F., Bergeretti, F., Gaglioti, P., Todros, T.	Economic evaluation of ultrasound screening options for structural fetal malformations	2004	Italy
Vintzileos, A., Ananth, C., Smulian, J., Beazoglou, T., Knuppel, R.	Routine second-trimester ultrasonography in the United States: A cost-benefit analysis	2000	US
Waitzman, N., Romano, P.	Reduced costs of congenital anomalies from fetal ultrasound: Are they sufficient to justify routine screening in the United States?	1998	US
Whitlow, B., Chatzipapas, I., Lazanakis, M., Kadir, R., Economides, D.	The value of sonography in early pregnancy of fetal abnormalities in an unselected population	1999	UK

Source: The CIE

Overview of internal and external validity

All studies listed in table 2.4 were considered in further detail to determine their generalisability or the capacity to utilise the studies to inform the cost-effectiveness of second trimester fetal development and anatomy screening in Australia. The first component of this assessment is the internal validity assessment, which the Cochrane Collaboration (2013) defines as 'the extent to which the design and conduct of a study are likely to have prevented bias'. This is important to assess as variation in quality can explain the variation between the results of studies included in a systematic review

(Cochrane Collaboration, 2013). The second requirement is to assess the extent to which results provide a correct basis for generalisations to other circumstances which is known as the external validity (Cochrane Collaboration, 2013).

There is a lack of clinical data on the effectiveness of ultrasound screening in many contexts which results in many studies extrapolating sensitivity or detection rates from studies undertaken in other countries. This is an important limitation, with the sensitivity rate having been shown to be an important determinant of cost-effectiveness when measured in terms of the cost per anomaly detected.

With all of the cost or cost-effectiveness studies identified being from the international context (rather than Australia) and from the 1990s or earlier, in transfering findings to the Australian context we need to consider a range of potential variables associated with time and context. Previous large randomised trials, the Helsinki and RADIUS trials, among others suggest the benefits of ultrasound screening to detect fetal anomalies may vary according to the quality of the ultrasound, in particular the level of experience/skill of ultrasonographers which drives the rate of detection (Romano and Waitzman, 1998). The Helsinki trial identified significant variation in the malformation detection rate between the two hospitals involved in the study (75 per cent in one hospital and 35 per cent in the other), reflecting differences in skill and experience. In Australia, there is debate around the homogeneity of sonographers' skills such that it is difficult to assert whether results from studies in a 'tertiary' or 'non-tertiary' context are most applicable to Australia.

The most significant technological change since the late 1980s in ultrasound screening has been the introduction of three-dimensional (3D) ultrasound screening. According to Taddei et al (2007), sections reconstructed from the 3D ultrasound are easier to obtain but far less defined than those obtained by 2D ultrasound.

- **Two-dimensional ultrasound 'remains the gold standard for diagnosis for fetal abnormalities' (Taddei et al, 2007). Therefore, studies that utilise 2D scans are not outdated or irrelevant to the current context. However, it requires an experienced operator while 3D imaging can be more easily used by less skilled operators (Taddei et al, 2007).**[12]

There may be variation between contexts in the value of the information and personal decision making subsequent to receiving that information. For instance, the literature shows that screened women terminate pregnancies more frequently than unscreened women. However, the increase in terminations in the Helsinki and RADIUS trials resulting from screening was statistically significant in only the Helsinki trial (Romano and Waitzman, 1998). The rates of termination may vary considerably across populations although this partially reflects how malformations are defined (Romano and Waitzman, 1998).

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12 The 3D ultrasound has the advantage of providing reconstructed planes which can be utilised for rapid assessment of normal anatomy and are not impeded by fetal movements. In the evaluation of abnormal cases, the data can be sent to specialised centres for further examination.

The benefits of screening depend on termination being an acceptable option; this remains the only change in clinical outcomes that has been shown to be significant (see, for example, Whitworth et al, 2010). In theory, there may be improvements to clinical outcomes for neonates and their mothers from the detection of fetal anomalies that are derived from better information such as the capacity to improve the timeliness of interventions and improvement in fetal wellbeing resulting from reduced maternal anxiety from greater reassurance. However, such improvements to neonatal outcomes resulting from screening are yet to be proven (Whitworth et al, 2010) and would be difficult to attribute back to the scan.

In some cases, the transferability of a study to the Australian context is questionable because the study is premised on routine screening causing a reduction in resource use (reduced scans). In the Australian context, we would not expect the number of ultrasounds to reduce, relative to the counterfactual. In addition, some studies take a very short term view, leading to the association between ultrasound screening and lower inpatient and outpatient days. That is, lower patient days may be associated with the termination of pregnancies, but we would expect that these would be largely offset by parents seeking to have another child after some time.

Validity assessment

Internal and external validity appears on a spectrum. In some cases, conclusions may not be transferable to the Australian context, but the study may contain data that may be used or used to validate data for modelling the question of cost-effectiveness of ultrasound screening in Australia. Factors considered in the internal and external validity assessment are provided in box A.5.

A.5 Internal and external validity assessment

Factors considered in the internal validity assessment include whether:

- the study question was well defined and health care options clearly described
- cost estimates related to the baseline population risk
- the relevant costs and consequences were identified for each health care option
- costs and consequences were measured accurately and credibly
- incremental analysis was performed or able to be performed
- a sensitivity analysis was performed
- modelling was logical, clear and reasonable.

In appraising external validity, factors considered included:

- the patient group and the implications for resource consumption
- the health system setting, such as the institutional size or type, the constraints in Australia which may limit its transferability, or differences in incentive structures of health care professionals, institutions or patients
- the health care options, including the treatment options available or time spent as an inpatient
- the resource costs and how readily and appropriately these may be transferred to the Australian setting. In practice, these factors are difficult to assess in this instance and we would expect that the resource allocation identified in most other settings (countries and time periods) are not transferable to Australia.

A summary of our assessment of each of the 11 studies is provided in table 2.6. Each was rated by:

- a tick – which indicates that the criteria was met satisfactorily
- a question mark – indicating that there is some doubt that the criteria was met and factors should be considered when transferring the findings of the study to the Australian context
- a cross that indicates that reliability of the study cannot be guaranteed, for instance, due to limitations in the data used in the study.

Most studies were deemed, on balance, to be internally valid. The CIE has indicated that, on balance, eight out of the 11 studies broadly met the internal validity criteria. However, many had a question mark with respect to the relevance or completeness of costs and consequences identified for each option, and/or the accuracy of the measurement or valuation of costs. It is difficult to know whether this was a product of the limited data available (likely) or the context in which the study was undertaken (or both).

A review of the validity and transferability of each study to the Australian context is provided further in table A.6.

A.6 CIE appraisal of internal and external validity of included studies

	Bricker et al, 2000	Leivo et al, 1996	Long and Sprigg, 1998	Ritchie et al 2005	Roberts et al 1998	Romano and Waitzman, 1998	Vanara et al 2004	Vintzileos et al 2000	Waitzman and Romano, 1998	Whitlow et al, 1999
Study question well defined and appropriate health care options chosen	√	√	√	√	√	√	√	√	√	√
Cost estimates related to baseline population	√	√	√	√	√	√	√	√	√	√
Other estimates related to baseline population	√	√	√	?	?	√	?	√	?	√
Relevant costs and consequences were identified for each health care option	√	√	√	?	?	√	√	?	√	?
Costs and consequences were measured accurately and valued credibly	√	?	√	?	?	?	√	√	?	?
Incremental analysis	√	√	√	√	×	√	√	√	√	×
Sensitivity analysis	√	√	×	?	?	√	√	√	√	×
Clear, logical modelling/methodology	√	√	√	?	√	√	?	√	√	?
Appraisal of internal validity	√	?	√	?	×	√	?	√	√	×
Patient group	√	√	√	√		√	√	√	√	
Health system setting	√	?	?	?		?	×	√	√	
Health care options	?	√	√	√		√	×	√	?	
Resource costs	√	?	?	?		?	×	?	?	
Other issues relating to guideline		yes								
Appraisal of external validity	?	?	?	?	n.a.	?	×	?	?	n.a.

Note: Roberts et al 2002 present a literature review only of costs and cost-effectiveness. The studies included in the cost and cost-effectiveness review were subjected to robust quality assessment criteria to assess internal consistency. It is deemed internally valid for use in this evaluation.

Source: The CIE

Roberts et al (1998)

One of the two studies for which internal validity cannot be guaranteed is *Choosing options for ultrasound screening in pregnancy and comparing cost-effectiveness: a decision analysis approach* (Roberts et al, 1998). The main limitation of the study is that, as acknowledged by the authors, there is insufficient information on the methodology and types of costs that are included in the cost information, which is obtained from a literature review. The study does not take into account the rate or cost of termination and other procedures that may be associated with a 'positive' scan. A lower order issue is that it also excludes indirect costs such as travel and time off work, as well as counselling.

Expert clinical opinion is used in cases where the extensive literature review does not provide robust information such as for the clinical effectiveness of routine screening for a range of important congenital anomalies. The authors conclude that due to the lack of data and uncertainty around the estimates employed, it was not possible to make defensible decisions about which ultrasound practice should be used. In particular, there was insufficient data with respect to the clinical effectiveness of the first trimester anomaly screen which underpinned the rationale for the exclusion of first trimester screening from the Bricker et al (2000) comprehensive study of the cost-effectiveness of routine ultrasound screening. Bricker et al (2000) indicate that the rate of detection in international literature was lower than assumed by experts in their original modelling published in Roberts et al (1998).

Whitlow et al (1999)

The second study for which the internal validity is not guaranteed is *The value of sonography in early pregnancy of fetal abnormalities in an unselected population (*Whitlow et al, 1999). While the study concludes that the second trimester scan should not be abandoned, the conclusion is based on clinical information only. The study does not include the cost of the second trimester scan or detail the clinical pathways (and associated costs) such as from false positive and false negative results. In addition, where costs are provided for the first trimester scan, there is inadequate detail regarding how these have been measured or sourced.

The Whitlow et al (1999) study provides clinical effectiveness data for a tertiary setting. The study indicates that 59 per cent of structural abnormalities are detected in 'early' pregnancy (11 to 14 weeks) while 81 per cent were detected with both the first and second trimester scans. In Australia, the focus of the first trimester Nuchal Translucency (NT) ultrasound and blood test is the detection of chromosomal abnormalities, rather than structural abnormalities. Therefore, the detection rate of first and second trimester screening in Australia would differ from that identified in the study.

Ritchie et al (2005)

There were several possible issues identified making it difficult to confirm the internal validity of the Ritchie et al 2005 study: *Economic modelling of antenatal screening and ultrasound scanning programmes for identification of fetal abnormalities*.

The purpose of the Ritchie et al (2005) study was to determine the most clinically effective and cost-effective policy on screening for fetal abnormalities in early pregnancy. It concluded that strategies which include a second trimester ultrasound scan result in the detection of more abnormalities and have lower costs per anomaly detected, when compared to the same screening strategy without a second trimester scan.

The study identifies strategies including first trimester NT screening and blood test screening for markers, and/or screening for markers in the second trimester, with or without a second trimester scan. Two of the six scenarios are applicable to this evaluation (scenarios 1 and 2), while a further two scenarios are potentially applicable (scenarios 5 and 6), which include a double rather than quadruple maternal serum screening process.

However, there are a couple of potential weaknesses in the methodology, raising questions around the transferability of the findings of this study. Importantly, the detection rate assumed for second trimester anomaly screening of 75 per cent for major abnormalities is based on what should be achieved, as advised in the NICE guidelines, and not necessarily applicable to the population. Furthermore, the CIE is unable to follow how the incremental effectiveness ratio calculations have been derived (in table 6) suggesting some possible miscalculations in the tables, although the overall conclusion appears to be appropriate for the data outputs provided.

With respect to the transferability of cost data provided by Ritchie et al (2005), some of the costs appear too low to be consistent with the Australian context while others appear comparable. The year of the data is assumed to be 2004, although this is not made explicit.

Leivo et al (1996)

The Leivo et al (1996) study found that ultrasound screening resulted in lower perinatal mortality in screened group, due to induced abortions. In Leivo et al (1996), the cost of inpatient days is found to have a significant impact on the cost-effectiveness ratio.

- **The difference between inpatient days of the control and intervention groups is likely the result of chance, which leads a Cochrane review to consider these findings 'unstable' (University of York, 2013).**
- **Furthermore, the CIE finds it is potentially problematic that inpatient and outpatient days, as well as fewer ultrasounds, are associated with routine ultrasound screening.**

The implication is that screening results in terminations, which reduces the use of health services per patient. While this may be true in the short term, with the trial conducted over a short time period (1986 to 1988) it may not hold over the longer term as women that terminate their pregnancy proceed to try for another child.

Vanara et al (2004)

Vanara et al (2004) study the potential cost-effectiveness of routine screening for fetal malformations at 19-21 weeks. The study is based on the theory that a routine screening program will both reduce the average number of scans per woman, where three scans are commonly offered, and therefore decrease cost, and will increase the accuracy of scans from the use of better machines, training and organisation.

The results of the study reflect the input assumption that sensitivity rates will increase following the introduction of a routine screening program, drawing on the results from a UK study by Boyd et al (1998). This appears acceptable, however, given the central case assumptions are relatively conservative and therefore, potentially appropriate in relation to the Italian context. However, parameters used in scenario testing indicate a high degree of uncertainty around the assumptions for the current sensitivity rates ranging from 16.6 per cent to 71.5 per cent but confidence in the sensitivity rates that may be achieved following the program ranging between 61.4 per cent and 79.2 per cent. The wide variation in estimates indicates considerable uncertainty with respect to model inputs.

This results in considerable uncertainty around cost-effectiveness estimates, ranging from 52 710 to 175 034 euros per anomalous fetus detected under the conditions in Italy at the time of the study, and from 33 244 euros to 84 108 euros after the implementation of routine screening.

Vanara et al (2004) provide estimates of unit costs from the National Health Service based on the national tariff, on an average cost basis.

- Some of the unit costs may be utilised to benchmark costs in Australia although the cost per ultrasound appears low when compared against Australian data.
- The context in Italy in 2004 varies significantly from the current situation in Australia, indicating that it would be inappropriate to conclude that the cost per anomaly detected was similar to Australia.

While the organised screening program assumes one ultrasound per woman, there are some differences between the clinical pathways assumed for Italy and the current Australian context:

- amniocentesis appears to be routinely used following a positive scan
- a diagnostic scan is (always) used to confirm the presence of malformations
- four further period examinations are incorporated in the cost per scan.

Waitzman and Romano (1998)

The Waitzman and Romano (1998) study is based in the United States. The Waitzman and Romano (1998) estimates of costs averted through termination includes both the avoided increase in medical and developmental costs and the indirect costs from the assumed reduction in the average productivity of a human with congenital abnormalities compared with one without congenital abnormalities.

The authors indicate that these productivity impacts would be conditional on the parents having another child within one year of the termination. This is an important issue to consider given that the indirect cost component estimates are large. The CIE does not consider it relevant, particularly in the Australian context, to assume a requirement for a replacement child. In Australia, we can 'import' adults and their children to increase the population. It is also potentially inappropriate to incorporate a reduction in productivity, compared to the hypothetical alternative which is reflected by the 'average' working capacity of the population. Due to the scale of these 'indirect' costs incorporated in this study, the findings of this study may not be transferable to this study.

Estimates generally relate to the baseline population, however with limited data on the rates of termination in the United States the study relies on international data and makes an adjustment downwards to accommodate the more conservative cultural context. The authors also state that the percentage of fetuses that were terminated, but would have died prior to birth, is not taken into consideration due to the paucity of data. This is a common problem across studies.

Vintzileos et al (2000)

Vintzileos et al (2000) provide a cost benefit analysis of screening at less than 24 weeks, utilising the detection rate identified in the Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) trial. The study is guided by the unsatisfactory performance of ultrasonography in non-tertiary centres through the RADIUS trial. The study finds that the ratio of savings to cost was between 1.35 and 1.70 if ultrasonography is performed in tertiary centres, and below 1.0 when performed in non-tertiary centres. This leads the authors to conclude that ultrasonography may only be satisfactory if performed in tertiary centres, a finding which is unlikely to be transferable to the Australian context.

A few other noteworthy factors underpinning the results of this study are listed.

- Averted costs, based on Waitzman et al (1994, 1995), incorporate indirect costs from lost productivity resulting from early death or disability. These are not incorporated in our study.
  - However, the scope of the conditions included in estimating averted costs (through termination) associated with morbidity is conservative – with a combined prevalence of only 0.6 per cent. This represents a significant share of severe congenital conditions, but excludes all lethal conditions.
- Benefits include the averted use of treatment for preterm labour and postdate treatment resulting from the second trimester ultrasound. In the Australian context, most women are expected to receive a dating scan at 11-14 weeks gestation, such that the benefits from averted preterm labour and postdate treatment are usually attributable to this scan.

Long and Sprigg (1998)

Long and Sprigg (1998) evaluate the costs and benefits from moving from selective screening (risk-based) to routine screening in the United Kingdom. The study compares actual hospital data 12 months prior to the introduction of routine screening, when the

practice was selective screening, with data from the 12 months following the introduction of routine screening. The study identified an increase in the number of terminations of pregnancies where there were severe/lethal congenital abnormalities detected and provides estimates of the average lifetime care costs associated with these abnormalities. The study also identified congenital abnormalities that were not screened for but present in the selective screening group, which might have been detected through routine screening.

Costs reflect the incremental cost of moving from selective to routine screening, and include capital and maintenance of this capital (machines), labour, materials and counselling. The rent for the building was excluded, which may have been considered a sunk cost (a cost already incurred and not avoided if screening was not routine). The total cost per woman of routine screening was 16 pounds, in 1994, which is equivalent to $18.60 in today's terms which is clearly very low.

Long and Sprigg (1998) note that the sonographers in their study included technicians, obstetricians and midwives, with varying levels of experience. There is some question as to whether the 34.8 per cent sensitivity rate for the detection of fetuses with at least one major anomaly found by the study would be transferable to the Australian context.

Romano and Waitzman (1998)

Romano and Waitzman (1998) examine the value of routine screening for fetal anomalies in the second trimester through a utility analysis. The advantage of the approach is that it considers the utility or value of information, for both true and false positive and negative screening results. The authors conclude that the preferred option is for routine screening, and the choice is most sensitive to the specificity of ultrasound (rate of true negative) and the women's willingness to pay for reassurance of a normal scan.

Various willingness-to-pay parameters are obtained from other studies, and rescaled for comparability, and in several cases the probability of certain outcomes or utilities needed to be estimated. The authors acknowledge that this means 'the results are tentative'. Furthermore, it is difficult to know how these estimates would be transferable to Australia.

- **The authors acknowledge that 'key probability and utility estimates are essentially unknown and likely to vary considerably from woman to woman and from nation to nation'. However, the results of the decision analysis are 'insensitive to the parameters most likely to vary by site: the sensitivity of the ultrasound, the proportion of anomalous fetuses electively aborted, and the disutility of false negative and false positive findings'.**

While we find this study meets our internal validity criteria, transferability of findings to the Australian context is unclear. Due to wide-ranging assumptions underpinning the study, it is essentially difficult to determine the transferability of the study to the Australian context.

Bricker et al (2000)

The Bricker et al (2000) study meets internal and external validity criteria. However, the comparison between the first and second or third trimester screening cost-effectiveness should be interpreted with caution. The authors do not incorporate first trimester screening for fetal abnormalities, and the first trimester ultrasound is essentially a dating scan. The authors assume approximately 10 per cent of lethal and severe congenital abnormalities are detected at this scan, but they acknowledge the lack of robust evidence for this. This may be reasonable if we consider that one quarter of lethal and severe anomalies are chromosomal, and the combined detection of these is at least 50 per cent in early screening. While this is achievable through the screening procedures for chromosomal abnormalities (NT screening or maternal serum screening), the CIE understands the dating scan is not generally utilised for detecting abnormalities on its own. Furthermore, the costs of the dating scan, as opposed to the NT screening and blood test, is built in to the cost of first trimester screening.

As such, when interpreting the scenarios utilised in Bricker et al (2000) it is not appropriate to conclude that second trimester screening is preferable over combined screening at both the first and second trimester.

However, Bricker et al (2000) provides comprehensive data from a review of the average rate of sensitivity for key conditions, grouped by severity, as well as a primary cost study. The quality of the study and context of the primary cost study gives us the confidence to utilise sensitivity and prevalence data in our model.

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