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The Cost Effectiveness of Prenatal Ultrasound Screening for Trisomy 21

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ABSTRACT

Objectives: To compare the cost effectiveness of opportunistic nuchal translucency ultrasound screening in pregnancy with alternative screening strategies for trisomy 21 in Australia.

Methods: A decision analytic model of various pregnancy screening strategies based on a systematic review of the literature on the effectiveness of nuchal translucency ultrasound and serum screening and costs based on current reimbursement fees. The model included the likelihood and cost of terminations following diagnostic testing and the associated risk of fetal loss. All prices are in 2001 Australian dollars

Results: With a twenty percentage point difference in detection rate the incremental cost for a combination of nuchal translucency and serum screening with age in first trimester compared to maternal serum screening in the second trimester was $105,484 per extra case detected and $374,779 per live trisomy 21 birth avoided. Serum screening in the second trimester had an incremental cost per extra case detected of between $61,700 and $117,100 per extra live birth avoided when compared with no screening.

Conclusions: The economic analysis is limited by the perspective taken and has not been able to include some of the attributes of a screening program such as reassurance and impact on the family and society of a trisomy 21 birth. Nevertheless the cost effectiveness of ultrasound screening would appear to be more attractive if it was done at the same time as current dating ultrasound. Any funding mechanism for screening should take this into account by incorporating as far as possible, provision of nuchal translucency screening into existing services provided in early pregnancy.

Key words: ultrasound; pregnancy; screening; cost effectiveness

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The Cost Effectiveness of Prenatal Ultrasound Screening for Trisomy 21

Introduction

The ultrasonographic measurement of nuchal translucency thickness in the first trimester of pregnancy is increasingly being used as a method of identifying those fetuses at risk of major genetic abnormalities, especially trisomy 21. Women who are found to have an increased risk of trisomy 21 are offered the option of invasive genetic testing, such as chorionic villus sampling (CVS) or early amniocentesis. There is evidence that screening in the first trimester of pregnancy has acceptable sensitivity and specificity compared to other screening options (MSAC, 2003). (8) Nuchal translucency screening (NTS) however is likely to be more expensive than other options. There has been some published work in the UK and the USA on the economics of prenatal screening options, but there are doubts about the generalisability of the results and the conclusions are not consistent. Gilbert et al 2001 (5) for example, conclude that for the UK a combination of NTS and maternal serum screening across trimesters is the cheapest and most effective screening alternative. Vintzileos et al (17) conclude for the USA that second trimester serum screening of pregnant women is more cost effective than 75% of women having NTS and 15% having serum screening as long as the detection rate of NTS is below 80%. The difference illustrates the problems in comparing across studies in different countries and the sensitivity of the results to the assumed detection rate and relative cost of each screening alternative. This paper presents an evaluation of the cost effectiveness of a set of prenatal screening strategies for trisomy 21 based on cost and prevalence data from Australia. It confirms a key conclusion of Vintzileos (17) that the two most critical elements determining the economic impact of potential screening strategies are the diagnostic accuracy of the first-trimester tests (combinations of age and ultrasound with or without maternal serum tests) and the cost of each ultrasound examination.

Methods

A decision analytic model was constructed to compare the cost effectiveness of four population screening strategies for a cohort of pregnant women in Australia:

1. Serum screening in second trimester followed by amniocentesis for those with a positive test
2. NTS in first trimester followed by CVS for those with a positive test;
3. NTS and maternal serum screening in the first trimester, followed by CVS for those with a positive test; and
4. NTS and maternal serum screening for high-risk women (age-related) in the first trimester, with maternal serum screening in the second trimester for other women.

Each strategy was initially compared against the next best alternative (including no screening) for a given level of uptake. Current screening practice was not used as the comparator because it proved difficult to model. Current screening practice in Australia generally consists of a mixture of ultrasound and/or serum screening with maternal age, along with diagnostic testing for some women at higher age related risk. It is unclear how much of each of these parts of screening activity is currently being done, and how much of each would be substituted by an increase in NTS. An additional set of analyses considered current practice and a number of variations in the key assumptions including uptake, detection rates, cost and the rate of substitution.

Outcome measure

There are a number of possible measurable consequences of a screening program. (9) The main aim of pregnancy screening is to provide women with information on fetal status. Information prior to birth may in itself be valuable to women and may also allow them to make a choice on whether or not to continue with the pregnancy. Information comes at a cost, not just in terms of the test itself but in the implications for the family and the wider society. The decision to terminate a pregnancy that would otherwise result in the birth of baby with an abnormality will have emotional, psychological and economic effects on the family as well as implications for the future extra costs of care for the rest of society. In addition, an increase in the rate of detection leads to an increase in the rate of false positive results and the risk of procedure-related miscarriage. In the absence of data on the value of information to women, the outcome measure of cases detected by a test might be regarded as a proxy for some of the information provided. This outcome measure does not capture the reassurance offered by NTS for those with a negative screen, nor the consequences of the information for the woman or the family. As a second outcome measure the analysis included the number of live births with trisomy 21. This represents a proxy measure of some of the consequences of the information. Some studies have gone further and calculated the lifetime extra cost of care for infants born with trisomy 21. (Vintzileos (17); Shackley (14)). While there are no studies of these costs for Australia, and it is not possible to take overseas results directly, it is clear that these costs are likely to be substantial. Life expectancy with trisomy 21 is now in excess of 50 years, and is usually associated with major health problems. However including only the cost of care as a negative social value of a child with trisomy 21 provides a distorted picture of the net benefits of screening. The extra cost of care needs to be balanced by the value of the benefits of having a child with trisomy 21. There are no reliable estimates of the money value of a life with or without trisomy 21, and there are conceptual difficulties in the calculation not least because of the potential for a replacement pregnancy. For these reasons the perspective of the analysis has been constrained and the full net benefits of screening have not been calculated.

NTS detects cases of trisomy 21 earlier in pregnancy. This would allow some women to have an earlier, less physically and perhaps emotionally traumatic termination. However, for others there would be an increase in unnecessary anxiety, invasive procedures and terminations of affected fetuses that would have otherwise miscarried before a second trimester serum screening was done. There is some evidence however that women have a clear preference for first trimester screening tests for trisomy 21, regardless of the rate of miscarriage between 10 and 15 weeks of gestation (11). It is less clear how to include these elements in the measurement of outcomes and the approach taken here was to calculate the number of earlier terminations as well as those that would have naturally aborted and present these alongside the main analysis.

Model

Primary analysis

The framework for the spreadsheet model is very similar in structure to Wald et al. (20) For each strategy, the model starts with a cohort of births and calculates the number of affected and unaffected births screened in a given trimester. An assumed spontaneous fetal loss rate allowed the model to calculate the number of affected and unaffected pregnancies screened. The number of trisomy 21 pregnancies detected is (the number of affected pregnancies screened) × (detection rate). The number of trisomy 21 births avoided is (the number of affected births screened) × (detection rate) × (uptake of antenatal diagnosis) × (uptake of termination). The cost of each strategy was the sum of the number of screening tests, antenatal diagnoses, terminations and miscarriages times their unit cost with the addition of the cost of counselling at each stage.

Sensitivity analysis

In order to test how robust the results are to variations in the main assumptions each key parameter was varied individually and in combination. A set of scenarios were created to consider the sensitivity of results to individual and combined variations in the key assumption of detection rates, substitution for dating ultrasound, natural foetal loss rate, and an increase in uptake of screening. (Full details of the sensitivity analysis are reported in MSAC 2002 (8)). Here we report the sensitivity of the results to variations in the key variables of cost of NTS, a comparator of current practice rather than no screening, and a simultaneous variation in detection rates for each strategy. The extent to which NTS might substitute for dating ultrasound was modelled by reducing the cost of NTS (by the excess over a dating ultrasound). In addition a comparison was made with a scenario that approximates the current approach to screening and testing of women over the age of 35. Variation in the detection rates also allowed consideration of an integrated nuchal translucency and maternal serum screening across trimesters.

Data

Prevalence of trisomy 21 pregnancy and births

There were about 260,000 births per year in Australia in 2001. It is unknown what the prevalence of trisomy 21 would be without any screening program. Data from South Australia (1) suggests that the prevalence was 1.1 per 1000 live births in 1982. Given the upward trend in maternal age since 1982 the model assumed an underlying prevalence of 1.6 per 1,000 live births. (20) This would suggest 416 trisomy 21 live births each year. Prevalence increases with age as shown in Table 1.

Table 1 Prevalence of trisomy 21 per 1,000 live births by age

Maternal age (years)	<30	<35	>30	>35
Prevalence of trisomy 21 births	0.6	0.9	2.6	3.2

Source: Jane Halliday, Manager, Victorian Perinatal Data Collection Unit, Department of Human Services, Victoria, personal communication, 2000

There is a high spontaneous rate of miscarriage of trisomy 21. Between the first trimester and term, the rate is reported to be 40–48 per cent (16), and between the second trimester and term, 23–30 per cent (3). These data are not precise and do not accord exactly with the dates of NTS and serum screening. For the purposes of the primary modelled analysis the assumption was a 40% rate of spontaneous miscarriage of trisomy 21 between the time when NTS would be performed in the first trimester and term. The rate of foetal loss between the time when a second trimester serum screen would be done and term was assumed to be 23%

Current practice

The number of women screened, the test used type and the timing of screening varies across Australia. In some States, NTS in the first trimester is part of current practice. Anecdotal evidence is that this might be as high as 25% of pregnant women. However, common practice, and the one that is publicly funded by Medicare, is a combination of maternal age and serum marker screening in the second trimester. In the state of Victoria some 30% of pregnant women had a serum screen in 2001 (22) while South Australia has reported rates of serum screening in excess of 80%.

Serum screening

A systematic review of the literature (MSAC report 2002 Table 21 (8)) suggested that the detection rate for triple marker serum screening in the second trimester (AFP, total hCG, inhibin A) was no more than 64 per cent with a 5% false positive rate. CVS or amniocentesis is offered to those who have a risk in excess of 1:250 in second trimester and 1:300 in first trimester either determined through screening or because of the risk associated with maternal age. Amniocentesis has been reported to have a procedure-related foetal loss rate of 0.9 per cent (95% CI=1.2% to 0.6%) in the second trimester of pregnancy. (20) The current uptake of amniocentesis among women with a positive screen has been reported as 85 per cent. (13) The vast majority of women whose fetuses are diagnosed as having trisomy 21 seek elective terminations of the pregnancy (4), (18), (6), (10) and 90% was assumed in this analysis.

Nuchal translucency screening

Yates et al (23) estimated in 1991 and 1992 that 97% of pregnant women had at least one ultrasound scan, and that 46% had two or more. NTS may substitute for the current use of ultrasound in the first trimester, with considerable implications for the cost-effectiveness of ultrasound screening. If we take the current Medicare fee for genetic defect screening ultrasound at 17–22 weeks ($100) as indicative of the likely cost of a first trimester NTS then the *extra* cost of NTS over a current ultrasound examination at less than 16 weeks ($60-70) would be only $30–40. The primary analysis assumes that there will be no substitution for current first trimester ultrasound, but the sensitivity analysis considers an 80 per cent substitution in the first trimester at a marginal cost of $40. This approach is in contrast to Gilbert et al (5) who, based on the cost structure of the UK, assume a very low marginal cost for NTS.

Evidence from Snijders et al (15) suggests that with a false positive rate of 5 per cent, the sensitivity of NTS for trisomy 21 was 77 per cent (95% CI=72%, 82%). A combination of NTS, double serum markers and age were assumed to raise the detection rate to 86.4 per cent. Women who screen positive would be offered CVS or amniocentesis. The uptake of diagnostic testing following a positive screen was assumed to be 85% with a 100 per cent detection rate and a procedure-related rate of foetal loss of 0.9 per cent irrespective of the test. The sensitivity analysis considered alternative assumptions about the detection rate and target risk group. The underlying assumptions about the natural history of trisomy 21 pregnancies and the characteristics of screening assumed in primary analysis are summarised in Table 2 and Table 3.

Table 2 Natural history of trisomy 21 pregnancy and screening characteristics assumed in primary analysis

Factor in analysis	Occurrence (range used)
Rate of trisomy 21 births	0.016[c]
Spontaneous loss of foetus from time of NTS to term	0.4[d]
Spontaneous loss of foetus from time of second trimester serum screen to term	0.23[e]
NTS detection rate	0.77 (0.72- 0.82)[b]
NTS false positive rate	0.05
Second trimester serum screening detection rate	0.64 (0.63 –0.80)[c]
Serum testing false positive rate	0.05
Combined NTS and first trimester serum screening detection rate	0.86 (0.71 – 0.88) [a]

NTS = nuchal translucency screening
a. point estimate and 95% CI from Cuckle and van Lith (2)
b. Snijders et al (16)suggest that with an FPR of 5 per cent, the sensitivity of NTS for trisomy 21 was 77 per cent (95% CI=72%, 82%).
c. Wald (21)
e. Cuckle (3)
d. Pandya et al (12)

Table 3 Uptake of screening and foetal losses assumed in primary analysis

Uptake or loss	Rate of occurrence
Uptake of antenatal diagnostic test	0.85
Amniocentesis procedure-induced foetal loss rate	0.009
CVS procedure-induced foetal loss rate	0.009
Termination of affected pregnancy	0.9
Screening coverage with serum markers	1
Screening coverage with ultrasound	1

CVS = chorionic villus sampling

Costs

Cost items included and the unit cost data are shown in Table 4. The cost of pre-test information and counselling, including any dating ultrasound scan, was assumed to be the same in each screening modality in the primary analysis and was excluded. However for those who have a positive screen, an additional cost of counselling was added and for those who went on to have a diagnostic test there was an additional ultrasound scan. NTS may involve post-test counselling at the time of the screen for women who screen positive, given the immediacy of the results. Serum screening would probably involve an additional visit to discuss the results. Nevertheless, it may be that there is little difference in the actual time spent counselling, and these cost differences have been ignored. Given the comparatively small number of positive cases, this is unlikely to make any significant impact on the economic analysis. Those who decline further diagnosis are likely to receive additional counselling, and a cost has been included for this. For those who accept the diagnostic test, there is the risk of loss of an unaffected foetus.

Table 4 Unit cost assumptions in primary analysis

Resource type	Unit cost	Source
Serum screening cost per woman (first or second trimester)	$54.50	MBS item 66740 schedule fee for second trimester serum test
NTS cost per woman	$100.00	Assumed equivalent to 2nd trimester ultrasound MBS item 55706 schedule fee
Antenatal diagnosis cost first trimester CVS	$683.00	MBS costs of procedure including ultrasound and karyotyping
Antenatal diagnosis cost second trimester amniocentesis	$782.90	MBS costs of procedure including ultrasound and karyotyping
Additional counselling for positive screens who do not have a diagnostic procedure	$20.00	Estimate based on expert opinion
Dating first trimester ultrasound	$60.00	MBS 55700 schedule fee first trimester ultrasound
Cost of termination	$1,016.00	DRG based costs from National Hospital Cost Database
Cost of procedure-induced foetal loss	$905.00	DRG based costs from National Hospital Cost Database

CVS = chorionic villus sampling; DRG = diagnostic related group; MBS = Medical Benefits Schedule; NTS = nuchal translucency screening. All prices are in 2001 Australian dollars

Results

Primary analysis

Table 5 illustrates the basic structure of the model and results with respect to NTS. Parallel calculations for serum screening in second trimester and a combination of first trimester serum screening and ultrasound were developed with the differences screening characteristics shown in Table 2 and amniocentesis substituted for CVS.

Table 6 shows the number of cased detected, live trisomy 21 births, and the cost of each strategy ranked in order of cases detected and live births avoided. In the absence of screening or diagnosis in a cohort of 260,000 live births there were 693 trisomy 21 pregnancies at 11 weeks, 540 trisomy 21 foetuses at 16 weeks and 416 live trisomy 21 births. Serum screening detected 346 cases of trisomy 21 per year at a cost of $21.3 million and had 208 live births. NTS in the first trimester added an additional $12.5 million but detected a further 188 cases while avoiding a further 35 live births. NTS combined with serum screening in the first trimester, had an additional cost of $14.3 million but 65 additional cases detected. NTS combined with first trimester serum screening compared with serum screening in the second trimester, had an extra cost of $26.7 million but an extra 253 cases detected and 71 live births avoided.

The combination of NTS and serum screening in the first trimester when compared with serum screening in the second trimester, resulted in 155 less traumatic terminations, but also 44 additional terminations that would have otherwise resulted in a foetal loss before 16 weeks.

Taking account of changes to current practice

The primary analysis did not take account of the current level of testing in those 35 or over. Taking a conservative estimate that a third of women aged 35 years or more have an amniocentesis in the second trimester solely as a consequence of the risk associated with their age, the model predicted 56 cases detected at a cost in excess of $9 million. Screening is less expensive than amniocentesis, but with a lower detection rate. If done earlier in pregnancy it could however detect a higher absolute number of cases of trisomy 21 (a proportion of which would have resulted in spontaneous abortion). As a consequence as long as the take up of screening is greater than 43 per cent, and the detection rate is at least 86 per cent, the combination NTS and serum screening would dominate current testing with amniocentesis. In other words screening 43% of all pregnant women with a combination of NTS and serum screening in the first trimester would save money and detect more cases compared to testing a third of women aged over 35 with amniocentesis. Taking account of a reduction in the current rate of amniocentesis therefore would improve the overall cost effectiveness of NTS. It needs to be said, however, that the rate of amniocentesis and CVS has already fallen (in part as a consequence of increased levels of serum screening) and it is not known if a greater use of NTS will lead to a further reduction in these tests in women aged over 35. NTS may offer greater direct visual re-assurance to women, but it may be that those at higher risk of an abnormal pregnancy may prefer to have the certainty of amniocentesis or CVS and may not be willing to accept the results of ultrasound and serum screening tests. If that is a common view, there might be little substitution in this age group.

Table 5 Nuchal translucency ultrasound screening for trisomy 21 for all pregnant women (260,000 live births)

	Trisomy 21 pregnancies									
			No. of women	Cost per woman	Total cost	Unaffected pregnancies		No. of women	Cost per woman	Total cost
NTS	12 weeks		693	$100	$69,333			259,584	$100	$25,958,400
	Detection rate	77%	534			FPR	5%			
CVS	Decline	15%	80	$20	$1,602	Decline	15%	1,947	$20	$38,938
	Accept	85%	454	$626	$283,980	Accept	85%		$626	$6,904,026
Termination		90%	408	$905	$369,609	Foetal loss	0.9%	99	$905	$89,858
Spontaneous miscarriage		40%	114	$905	$103,143					
Live trisomy 21 births			171							
Total cost					$827,667					$32,991,222
Total cost of screening										$33,818,889

CVS = chorionic villus sampling; FPR = false positive rate; NTS = nuchal translucency screening

Table 6 **Primary cost-effectiveness analysis of pregnancy screening strategies for trisomy 21 in 260,000 pregnancies compared with next best strategy: cost per trisomy 21 case detected and birth avoided**

Option		Cases detected	Live trisomy 21 births	Total cost ($million)	Cost per case detected ($'000)	Cost per live trisomy 21 birth avoided ($'000)	Incremental cost per extra case detected ($,000)[a]	Incremental cost per extra live trisomy 21 birth avoided ($'000)[a]	Comparison
A	No screening	0	416	-					
B	Serum screening T2	346	212	21.3	61.7	117.1	61.7	104.8	A
C	NTS	534	171	33.8	63.3	201.7	66.3	301.4	B
		599	141	48.1	80.2	345.5	218.6	476.3	C
D	NTS + serum testing T1						105.5	374.8	B

NTS = nuchal translucency screening T1 = first trimester T2 = second trimester
[a] Extra refers to the increment compared to the next most effective option

Sensitivity analysis

The results were sensitive only to the assumed detection rate for NTS and the extent of substitution for dating ultrasound. The latter is important because of the potential cost saving. With 100% substitution, the incremental cost per extra case detected and trisomy 21 birth averted for the combination of NTS and serum screening in first trimester compared to serum screening in the second trimester was less than 50% of the primary results.

The sensitivity of the cost effectiveness to variation in the detection rates for the 3 screening modalities was assessed in a probabilistic sensitivity (Monte Carlo) analysis. This assumed a uniform probability distribution for each of the detection rates shown in Table 2 and sampled from that distribution 1000 times to produce a distribution of mean incremental cost per case detected. The uniform distribution chosen was conservative in that it assumed more uncertainty than the literature suggests. The result was an incremental cost per extra case detected for the second trimester NTS and serum screening combination compared to serum screening alone of $121,554 (95% CI $104,109 $141,664). This compares with the $105,484 per extra case detected in the primary analysis.

With a high level of substitution of NT ultrasound screening for dating ultrasound in pregnancy, and a consequent reduction in the total amount of serum screening, it is possible that there would be a resource saving. If at least one third of NTS replaced a current ultrasound test, with an extra cost of less than $40, the effect is to reduce the overall cost of NT ultrasound screening below that of serum screening in the second trimester.

Integrated test

A combined assessment of results from tests conducted in the first two trimesters of pregnancy has been considered by some to offer a higher detection rate. (19) While potentially attractive in terms of comparative cost and effectiveness, there have been suggestions that an “integrated test” like this would introduce an unacceptable delay. In addition the combination of NTS and maternal serum screening has not been assessed in a single large group of pregnant women. (7) The practicality of this option is in some doubt in Australia and so it has not been considered here as a primary comparison. If we accept that such an approach would increase the detection rate to 95% (5) *ceteris paribus* the estimated cost per extra trisomy birth averted compared to second trimester serum screening alone was $271,382.

Discussion

The cost effectiveness analysis is based on a simplified model of pregnancy screening in Australia. With a difference in the detection rate of 20 percentage points, the cost of NTS combined with serum screening was an extra $26.7 million per year, with 253 more trisomy 21 cases detected and 71 fewer trisomy births. The incremental costs were $105,484 per extra case detected and $374,779 per live birth avoided. If screening was restricted to women aged 30 years or over, then the cost per case detected was one-third less. If screening was restricted to women aged 35 years or over, then the cost per case detected was halved. Provided NTS was a direct substitute for existing ultrasound tests in the first trimester, and the additional cost was no more than $40, it was cost saving with more cases detected and live trisomy 21 births avoided. A limitation of these results is that the true cost of these tests are not known but have been estimated from current public insurance reimbursement rate for private services in Australia. This means that the cost effectiveness analysis was based on a subsidised screening test without consideration of the costs or outcomes of a coordinated population screening program with either maternal serum testing or ultrasonography and does not fully take into account the range of current screening practices in Australia. The charge for NTS has been assumed to be the same as a mid trimester ultrasound at $100. Many patients are currently pay an out of pocket charge of at least $50. However the fact that the $100 represents the opportunity cost of a scan to government does make the fee the relevant cost from the perspective of the major funder of services. In contrast a recent estimate by Gilbert et al (5) of the cost of NTS in the UK has a cost of only 4 pounds ($10). In that study the cost of serum screening was 2.5 times the cost of the NTS whereas the reimbursement in Australia for serum screening about half the cost of a mid trimester ultrasound. Clearly these differences could reflect the nature of medical practice, medical incomes and the system of reimbursement and limits the generalisability of these studies across countries. On the other hand the cost of amniocentesis and CVS is very similar across the two countries using current exchange rates. This illustrates that the cost effectiveness of NTS is likely to depend critically on the extent to which it can be administered as an adjunct to the existing regime of ultrasound in pregnancy. If NTS can be added on in a few minutes to a first trimester dating ultrasound with no additional overhead or capital costs, as Gilbert et al (5) assume, then it has a very low additional cost. On the other hand if NTS involves an extra visit to a specialist practice that attributes some additional doctor time, overheads and capital charges to the ultrasound the cost is likely to be considerably higher.

Policy implications

The analysis here confirms that if a combined test can achieve a detection rate of over 85% at a low additional cost over serum screening then the incremental cost per live trisomy 21 birth avoided could be low. In May 2002 the Medical Services Advisory Committee (MSAC) recommended that consideration should be given to public funding of nuchal translucency screening or nuchal translucency screening in conjunction with first trimester maternal serum screening by incorporating as far as possible, provision of the services into existing services provided in early pregnancy. This appears to reflect in part a desire to get the benefits of a potentially higher detection rate from NTS without an unnecessary increase in the overall number of ultrasound scans.

If however there was little substitution of NTS for dating scans, then the extra cost of almost $375,000 per trisomy 21 birth avoided needs to be compared with the social willingness to pay for the benefits of such detection and prevention. Whether health care decision makers are willing to pay for the net benefits that include reassurance, the emotional and psychological effects on the family of a disabled child, and the savings from the care of a disabled child, depends on both the long term costs of care and the prevailing social ethics.

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