Trade-Offs in Prenatal Detection of Down Syndrome

Mateu Serra-Prat, MD, MPH, Pedro Gallo, MA, MSc, Albert J. Jovell, MD, DPH, PhD, Marta Aymerich, MD, and M. Dolors Estrada, MD

ABSTRACT

Objectives. This paper presents the results of different screening policies for prenatal detection of Down syndrome that would allow decision makers to make informed choices.

Methods. A decision analysis model was built to compare 8 screening policies with regard to a selected set of outcome measures. Probabilities used in the analysis were obtained from official administrative data reports in Spain and Catalonia and from data published in the medical literature. Sensitivity analyses were carried out to test the robustness of screening policies' results to changes in uptake rates, diagnostic accuracy, and resources consumed.

Results. Selected screening policies posed major trades-offs regarding detection rates, false-positive results, fetal loss, and costs of the programs. All outcome measures considered were found quite robust to changes in uptake rates. Sensitivity and specificity rates of screening tests were shown to be the most influential factors in the outcome measures considered.

Conclusions. The disclosed trade-offs emphasize the need to comprehensively inform decision makers about both positive and negative consequences of adopting one screening policy or another. (*Am J Public Health.* 1998;88:551–557)

Introduction

Several studies have shown that maternal age is clearly a risk factor for having a child with Down syndrome.[1] A prenatal screening policy for Down syndrome based exclusively on a priori risk according to maternal age has in itself a low detection rate.[2] Thus, in recent years, new noninvasive tests for prenatal screening with biochemical markers[2–7] and ultrasonography[8–10] have been developed. In any screening test for Down syndrome, a confirmatory diagnostic test for positive results has to be performed by means of a chromosomic study of amniotic liquid cells obtained by amniocentesis or chorial cells obtained by chorionic villus sampling.

However, even with the best expertise and equipment, these invasive tests are not without procedure-related risks. There is evidence that amniocentesis and chorionic villus sampling have estimated attributed risks of fetal loss of 1% and 3%, respectively.[11,12]

The aim of this study was to carry out a comparative analysis of different screening policies for prenatal detection of Down syndrome. Decision analysis has been used as a methodological tool and as a means to present and assess how the different options compare with regard to a selected set of outcomes. The criteria for choosing among the plausible screening policies for prenatal detection of Down syndrome should include not only effectiveness, equity, and efficiency measures but also the need to minimize both false-positive rates and the adverse effects of performing invasive tests. The objective of this analysis was to comprehensively present the results of different options for prenatal screening and diagnosis of Down syndrome. These results would allow decision makers, at both the provider and the consumer level, to make informed choices on the basis of effectiveness, safety, and efficiency criteria.

Methods

Decision analysis is a structured, explicit, and quantitative methodological tool that makes possible the quantification of selected outcomes associated with different courses of action in conditions of uncertainty.[13,14]

We built a decision analysis model that includes 8 screening policies or options (see Figure 1):

Option 1: Do nothing.

Option 2: Offer amniocentesis to all pregnant women but offer no previous screening (neither biochemical nor ultrasonographic).

Option 3: Offer amniocentesis to all pregnant women older than 35 and offer ultrasonographic screening (nuchal fold > 6 mm, second trimester) to all pregnant women younger than 35. If ultrasonographic screening is positive, then amniocentesis is offered.

Option 4: Offer biochemical screening to all pregnant women (triple test with alpha-

The authors are with the Catalan Agency for Health Technology Assessment, Generalitat de Catalunya, Barcelona, Spain. Pedro Gallo is also with the Department of Social Science and Administration, London School of Economics, University of London, England, and with the University of Barcelona, Spain.

Requests for reprints should be sent to Albert J. Jovell, MD, DPH, PhD, Catalan Agency for Health Technology Assessment, Travessera de les Corts 131-159, Pavelló Ave Maria, 08028 Barcelona, Spain.

This paper was accepted August 29, 1997.

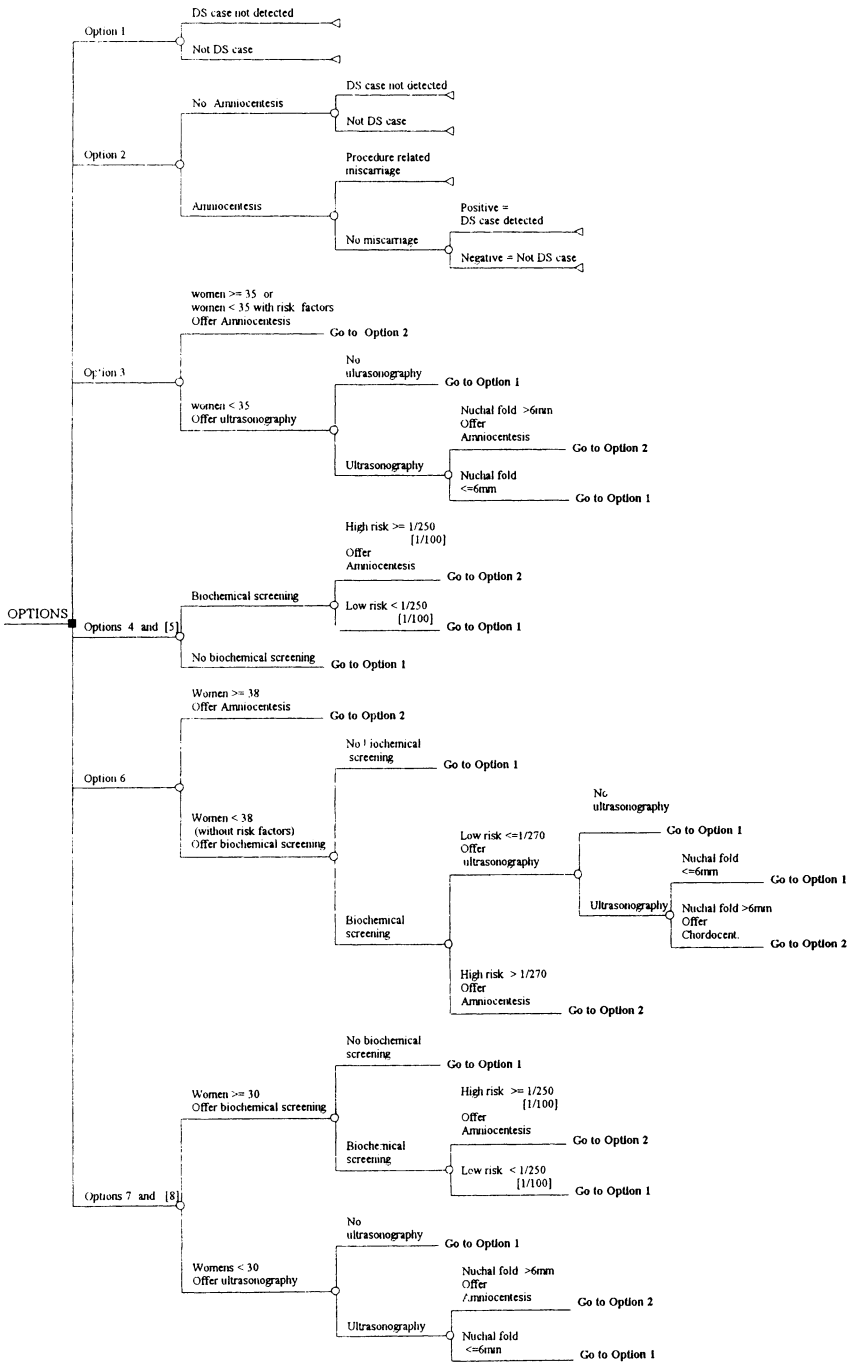

FIGURE 1—Decision analysis tree for various screening policies for Down syndrome (DS; see text for definitions of options).

fetoprotein, unconjugated estriol, and intact human chorionic gonadotrophin with cutoff point set at 1/250). Women with risk above 1/250 are considered to have high-risk pregnancies and are offered amniocentesis.

Option 5: Exactly the same as option 4 but with a biochemical screening test cutoff point set at 1/100.

Option 6: Offer amniocentesis to all pregnant women older than 38 and offer biochemical screening to those younger (triple test with the same serum markers as in options 4 and 5). Women with risk above 1/270 are offered amniocentesis. If risk is below 1/270, ultrasonographic screening is offered (nuchal fold > 6 mm, second trimester). If ultrasonographic screening results are positive, then amniocentesis or chordocentesis is offered.

Option 7: Offer biochemical screening (triple test with the same serum markers as in options 4 and 5) to all pregnant women older than 30. If risk is above 1/250, then amniocentesis is offered. Ultrasonographic screening is offered to all women younger than 30, and if positive (nuchal fold >6 mm, second trimester), then amniocentesis is offered.

Option 8: Exactly the same as option 7 but with a biochemical screening test cutoff point set at 1/100.

Options 1 and 2 are extreme screening policies and are included as reference points against which to compare the remaining policies and better estimate their impact. Option 3 is included because it had been the most widely used option in Catalonia, although ultrasonographic tests did not use nuchal fold measures, which would probably have reduced the diagnostic accuracy of the tests. Options 4 and 5, well-known screening policies in the United Kingdom,[15] add to the other options the performance of biochemical screening tests before diagnostic tests. Option 5, with a cutoff point set at 1/100, is included so as to improve the specificity of the screening test, reducing the cost and the number of procedure-related miscarriages. Option 6 was designed with the purpose of detecting not only the maximum number of Down syndrome cases but also other congenital malformations. Options 7 and 8 aim at reducing the cost of screening, and therefore improving the ratio of cost to number of Down syndrome cases detected, without performing a higher number of amniocentesis procedures than under options 4 or 5.

The decision analysis model represents, graphically and chronologically, the different events and consequences of each screening policy. The probabilities assigned to each node in the decision tree were obtained from data published in the medical literature and from official administrative data reports in both Spain and Catalonia. When no data were available, some assumptions were made that were later examined in terms of validity and robustness by means of sensitivity analyses. Whenever available, data from Catalonia were used. Table 1 lists the values used in the baseline analysis and in the sensitivity analyses for each of the parameters considered. Data sources are also shown in Table 1.

To check the robustness of the baseline analysis results to changes in sensitivity and specificity rates of screening tests, and in uptake rates of the different tests, we performed 3 different sensitivity analyses. The first considered only changes in uptake rates, that is, patients' acceptance of tests when offered, maintaining the rest of the parameters unchanged. A second sensitivity analysis considered only variations in sensi-

tivity and specificity rates of screening tests. Finally, a multiple-way sensitivity analysis was performed in which the worst scenario was defined as the one with the lowest uptake rate, the lowest sensitivity and specificity rates for screening tests, and the highest fetal loss rate attributed to invasive procedures, and the best scenario was defined as the one with the highest uptake, sensitivity, and specificity rates and the lowest fetal loss rate.

We have included an analysis of resources consumed by the different screening policies from the public financing perspective. The type of resources considered includes the number of biochemical screening tests and the number of invasive procedures carried out. To translate resources consumed into monetary units, we applied reimbursement rates provided by the Catalan Health Service in 1994 and still in use (Table 1).

The analyses were performed with Decision Analysis by TreeAge (DATA for Windows) (TreeAge Software Inc, Williamstown, Mass).

TABLE 1—Values Used in the Baseline and Sensitivity Analyses of Various Screening Policies for Down Syndrome

Variable	Value	Most Probable Range	Reference
Amniocentesis			
Sensitivity	100%	....	
Specificity	100%	....	
Biochemical test			
Sensitivity, 1/270	60%	47%–90%	2–7, 16–20
Specificity, 1/270	93%	86%–95%	2–7, 16–20
Sensitivity, 1/250	58%	45%–89%	2–7, 16–20
Specificity, 1/250	95%	89%–96%	2–7, 16–20
Sensitivity, 1/100	44%	31%–75%	2–7, 16–20
Specificity, 1/100	98.3%	92%-99%	2–7, 16–20
Ultrasonography screening test			
Sensitivity	45%	25%–65%	8, 21–28
Specificity	95%	90%–99%	8, 21–28
Probability of miscarriage			
After amniocentesis	1%	0.5%–2%	11
After chordocentesis	2%	1%–3%	Assumed to be average of other invasive procedures
Proportion of pregnancies			
Women < 30 y	57.15%	...	29
Women < 35 y	88.59%	...	29
Women < 38 y	97.33%	...	29
Down syndrome risk			
Women < 30 y	0.0007986	...	1
Women 30+ y	0.0025117	...	1
Women < 35 y	0.001029	...	1
Women 35+ y	0.0054231	...	1
Women < 38 y	0.0011961	...	1
Women 38+ y	0.0096389	...	1
Second trimester (age-standardized)	0.00154	...	1, 29
Uptake			
Screening test	80%	60%–98%	3, 7, 30, 31
Amniocentesis			
All women	50%	35%–65%	31–33
Women 35+ y	80%	70%–90%	31–33
Women 38+ y	85%	70%–95%	31–33
Diagnostic test after positive screening test	95%	80%–99%	3, 7, 30–33
Catalan Health Service rate			
Biochemical screening test, 1996 pesetas	1 450	...	Catalan Health Service, 1994
Amniocentesis, 1996 pesetas	30 000	...	Catalan Health Service, 1994
Chordocentesis, 1996 pesetas	35 000	...	Catalan Health Service, 1994
No. pregnancies, Catalonia, 1992	68 474	...	1, 29

Results

The results of the baseline analysis are shown in Table 2 and Figure 2. Option 6 resulted in the highest detection rate and the lowest number of false-negative cases. At the same time, with the exception of option 2, option 6 had the highest number of procedure-related miscarriages, the highest total program cost, and the highest ratio of cost to number of Down syndrome cases detected. Option 7 resulted in detection of slightly more than 40% of the Down syndrome cases as well as a higher number of false-negative cases. On the other hand, it had the lowest ratio of cost to number of Down syndrome cases detected and consumed the fewest resources among the options considered.

The results of the multiple-way sensitivity analysis are also shown in Table 2 and Figure 2. The robustness of the results of the different options to changes in uptake rates, of both screening and diagnostic tests, are displayed in Table 3. The relative positions of the different options for each of the outcome measures considered in the analysis remained practically unchanged when variations in uptake rates took place. The results from the sensitivity analysis for changes in specificity and sensitivity rates of screening tests are also shown in Table 3. Apart from option 2, in which biochemical screening tests were not performed, the options presented different degrees of sensitivity to changes in the diagnostic accuracy of biochemical tests.

Table 4 shows the results of options 4 through 8 when the diagnostic accuracy of biochemical screening tests is kept unchanged and when it is variable across maternal age groups. Table 5 shows the ratio of cost to Down syndrome cases detected from the baseline, best-scenario, and worst-scenario analyses and with the use of a range of costs for both screening and diagnostic tests. According to these results, option 3 would shift from having the highest ratio of cost to Down syndrome cases detected under the Catalan Health Service rates to having the lowest ratio as costs increase, especially costs for biochemical screening. It should also be mentioned that an increase in costs would keep options 7 and 8 as the ones with the lowest ratio of cost to Down syndrome cases detected, except when compared with option 3, while options 4, 5, and 6 would maintain their intermediate positions.

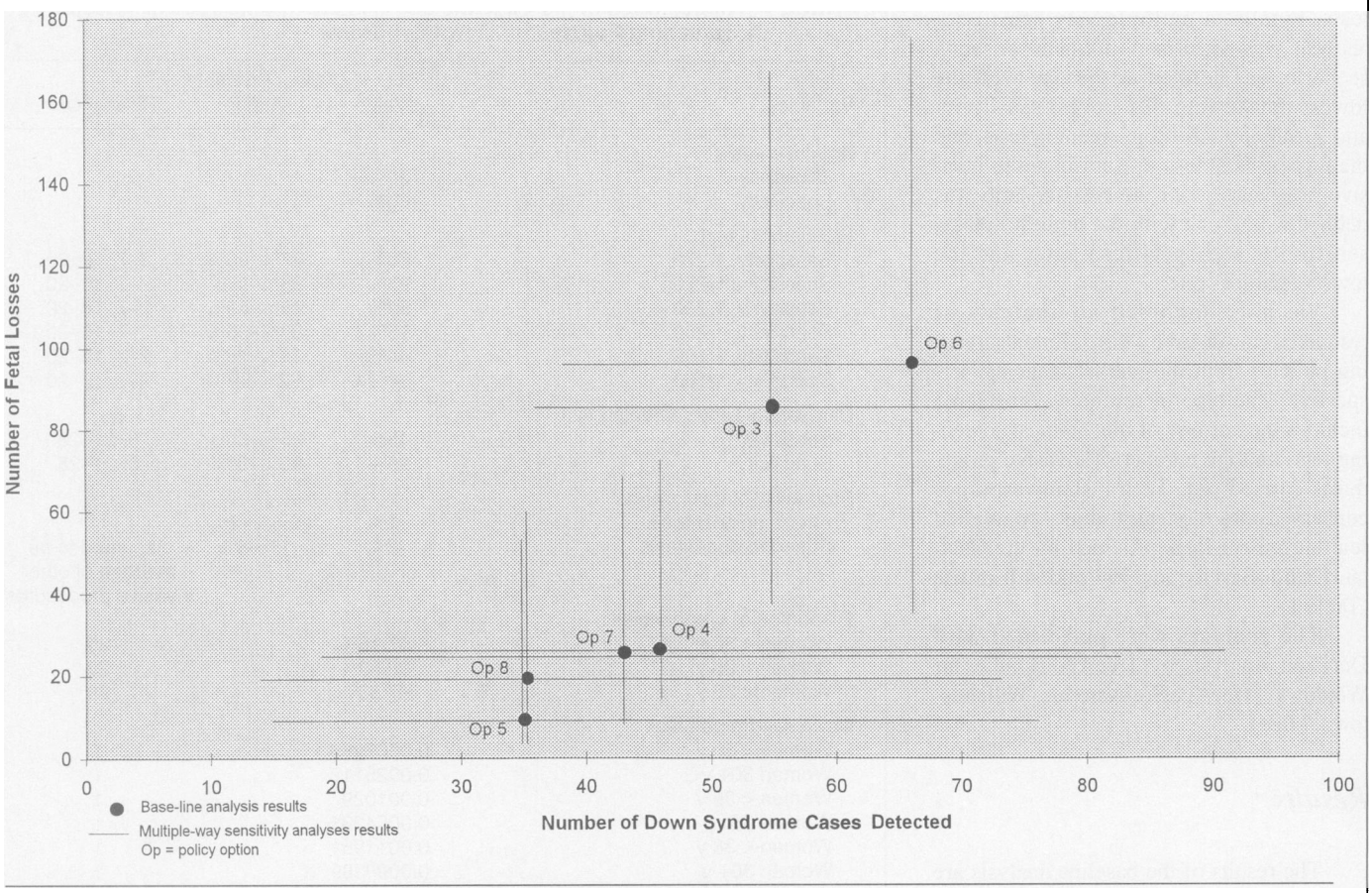

FIGURE 2—Down syndrome detection rates and fetal loss rates across policy options.

Discussion

The selection of these outcome measures responded to the initial objective of this research, which was to comprehensively present the results of each screening policy. Baseline analysis showed a close positive relationship between detection rates, procedure-related miscarriages, and resource consumption. This relationship was also observed in the subsequent sensitivity analyses, proving that improvement in one outcome measure might result in the worsening of another.

If the goal of any prenatal detection program for Down syndrome is to achieve the best possible detection rate at the minimum cost and with the minimum number of procedure-related miscarriages, we should carry out amniocentesis tests selectively, that is, only in those pregnancies with the highest probability of having an affected fetus. To accomplish this goal it becomes necessary to use a screening test with maximum diagnostic accuracy, that is to say, with the maximum capacity to discriminate whether or not a pregnancy is affected.

In our analysis, option 6 was the one that detected the most cases, since it was the only option in which ultrasonography was offered as a second screening test to women with negative results from a previous biochemical screening test (1/270). This second screening test aimed at reclassifying those false-negative cases resulting from biochemical screening. Option 6, moreover, had a lower cutoff point than other options (1/270), which increased the probability of classifying a pregnancy as positive for Down syndrome. In short, this option rewarded sensitivity over specificity, which translated into a higher detection rate but, at the same time, into a higher number of false-positive cases that would lead to amniocentesis, resulting in a higher number of related miscarriages and higher resource consumption. In contrast, options 5 and 8 were those that detected fewer cases, rewarding specificity over sensitivity. These two options set the cutoff point for high risk at 1/100 and did not reclassify pregnancies with a previous negative test result. Furthermore, options 5 and 8 had lower positive and false-positive rates, which produced fewer amniocentesis tests, resulting in a lower cost and fewer related miscarriages. Options 7 and 8 seemed to have the lowest ratio of cost to Down syndrome cases detected, benefiting from the diagnostic accuracy of ultrasonographic tests, which did not represent an important additional cost.

The ultrasonographic screening test considered required trained ultrasonographers and high-resolution equipment, and it probably added some extra time to patients' visits. It has been assumed that this test is used on a routine basis in prenatal visits during the second trimester. In our analysis, we considered that the additional cost of ultrasonographic screening was zero or minimal, although this assumption may not be entirely true. If we take the cost of this procedure to be 1000 pesetas more than routine ultrasonographic monitoring tests in the second trimester, which require the measurement of the nuchal fold, only the options that include ultrasonographic screening (3, 6, 7, and 8) will undergo an increase in the ratio of cost to Down syndrome cases detected. Nevertheless, options 7 and 8 still had the

TABLE 2—Results of Baseline and Multiple-Way Sensitivity Analyses of Various Screening Policies for Down Syndrome

Screening Policy	Outcome Measure and Scenario											
	Detection Rate, %			Ratio of Procedure-Related Miscarriages to Cases Detected			Ratio of Cost[a] to Cases Detected			Total Cost[a] of Program		
	Baseline	Best	Worst	Baseline	Best	Worst	Baseline	Best	Worst	Baseline	Best	Worst
Option 2	49.4	64.8	34.3	6.56	3.27	13.30	19.75	19.64	19.97	1 027.1	1 335.2	719.0
Option 3	52.1	73.3	34.3	1.57	0.50	4.67	4.62	2.98	6.99	257.2	229.8	251.5
Option 4	43.8	86.7	20.9	0.57	0.15	3.30	3.45	1.97	7.66	158.8	179.6	168.6
Option 5	33.3	72.4	14.3	0.26	0.05	3.52	3.06	1.57	9.25	107.0	119.5	138.8
Option 6	62.9	93.3	36.2	1.45	0.36	4.64	4.80	2.96	8.01	316.9	289.7	304.4
Option 7	40.7	79.0	18.1	0.62	0.10	3.62	2.63	1.08	6.78	113.3	89.6	128.8
Option 8	33.3	69.5	13.5	0.54	0.05	4.30	2.68	0.87	8.28	94.0	64.7	116.0

Note. See text for definitions of screening policies and scenarios.
[a]In millions of pesetas, using Catalan Health Service rates (see Table 1).

TABLE 3—Results of Sensitivity Analyses of Various Screening Policies for Down Syndrome, by Differences in Uptake Rates[a] and Accuracy of Screening Tests

Screening Policy[b]	Outcome Measures, Uptake, and Accuracy											
	Detection Rate, %				Ratio of Procedure-Related Miscarriages to Cases Detected				Ratio of Cost[c] to Cases Detected			
	Best Uptake	Worst Uptake	Best Accuracy	Worst Accuracy	Best Uptake	Worst Uptake	Best Accuracy	Worst Accuracy	Best Uptake	Worst Uptake	Best Accuracy	Worst Accuracy
Option 2	64.6	35.2	49.5	49.5	6.56	6.48	6.56	6.56	19.63	19.43	19.75	19.75
Option 3	59.7	40.9	61.9	43.8	1.59	1.61	1.03	2.36	4.69	4.84	3.11	7.09
Option 4	55.9	27.6	67.6	34.3	0.57	0.58	0.30	1.60	3.37	3.78	2.03	7.00
Option 5	42.4	20.9	57.1	23.8	0.26	0.26	0.10	1.67	2.94	3.50	1.61	8.19
Option 6	79.0	42.9	75.2	53.3	1.56	1.31	0.71	2.89	4.87	4.84	2.98	8.51
Option 7	51.9	25.7	61.9	29.5	0.62	0.62	0.20	1.76	2.60	2.80	1.10	6.37
Option 8	42.5	21.9	54.3	21.9	0.54	0.52	0.10	2.07	2.54	2.65	0.90	7.71

[a]Patients' acceptance of tests when offered.
[b]See text for definitions.
[c]In millions of pesetas, using Catalan Health Service rates (see Table 1).

lowest ratio of cost to Down syndrome cases detected when these changes took place.

The reimbursement rates used in these analyses might have underestimated the real costs derived from screening and diagnostic tests. Studies in other countries have estimated these costs to be higher than the one considered in our baseline analysis.[3,15,34] The consequences of using alternative cost data are described in Table 5. The observed improvement in the ratio of cost to Down syndrome cases detected of option 3 is explained by the fact that this option did not include biochemical screening. Option 7 presented the lowest ratio of cost to Down syndrome cases detected under baseline, best, and worst conditions when changes in costs took place.

The outcome measures considered were more robust to changes in uptake rates than to variations in specificity and sensitivity rates of screening tests. It was expected that both the ratio of cost to Down syndrome cases detected and the ratio of procedure-related miscarriages to cases detected would be very sensitive to changes in diagnostic accuracy, since an improvement in sensitivity and specificity of screening tests not only decreased the numerator but simultaneously increased the denominator. Although all options involving biochemical or ultrasonographic screening tests moved in the same direction in response to changes in the accuracy of these tests, not all of them did so to the same degree. The explanation lies in the different maternal age and/or cutoff point selection criteria and in the different indication each screening policy makes of ultrasonographic screening.

Since age is positively correlated with the probability of a positive result on screening tests,[16–20] increases in sensitivity and decreases in specificity of biochemical screening tests according to maternal age raise the detection rate and, at the same time, the total number of amniocentesis procedures performed. Therefore, the ratio of procedure-related miscarriages to detected Down syndrome cases increased slightly as a result of the number of miscarriages[7] being higher than the increase in the number of Down syndrome cases detected. The ratio of cost to detected Down syndrome cases experienced no important changes, because the increase in cost owing to the performance of more invasive procedures was compensated by a similar increase in the number of Down syndrome cases detected.

The distribution pattern of pregnancies along maternal age used in this study was based on data for births in Catalonia in 1992 published by the Spanish Institute of Statistics in 1995.[29] The use of these data implies 2 important limitations. First, we assumed that the pattern of pregnancies followed the pattern of births along maternal ages, which is not necessarily true, since voluntary interruptions of pregnancies may not be distributed homogeneously throughout maternal age groups.[35] Second, the data used refer to 1992, and the distribution of

TABLE 4—Outcome Measures of Various Screening Policies for Down Syndrome, with Accuracy of Biochemical Screening Tests across Maternal Age Groups Unchanged and Variable (Baseline Conditions)

Screening Policy[a]	No. Cases Detected	No. Procedure-Related Miscarriages	Ratio of Miscarriages to Cases Detected	Ratio of Cost[b] to Cases Detected
Specificity and sensitivity unchanged across maternal age groups[c]				
Option 4	46	26	0.57	3.45
Option 5	35	9	0.26	3.06
Option 6	66	96	1.45	4.80
Option 7	43	26	0.62	2.63
Option 8	35	19	0.54	2.68
Specificity and sensitivity variable across maternal age groups[c]				
Option 4	57	39	0.68	3.47
Option 5	47	21	0.45	3.05
Option 6	70	104	1.49	4.87
Option 7	54	39	0.72	2.82
Option 8	47	31	0 .66	2.77

[a]See text for definitions.
[b]In millions of pesetas, using Catalan Health Service rates (see Table 1).
[c]Baseline specificity and sensitivity rates of screening tests (see Table 1).
[d]The following specificity and sensitivity rates have been assumed:
Cutoff point 1/250; women < 35 y, sensitivity 58% and specificity 95%; women ≥ 35 y, sensitivity 95% and specificity 70%.
Cutoff point 1/100; women < 35 y, sensitivity 44% and specificity 98.3%; women ≥ 35 y, sensitivity 85% and specificity 75%.
Cutoff point 1/270; women < 35 y, sensitivity 60% and specificity 93%; women ≥ 35 y, sensitivity 97% and specificity 68%.

TABLE 5—Ratio of Cost to Down Syndrome Cases Detected by Various Screening Policies, by Scenario and with Varying Costs of Testing

	Testing Costs[a] and Scenario														
	1 450 PTA[b] 30 000 PTA[b] 35 000[b] PTA[b]			2 000 PTA 18 000 PTA 18 000 PTA			4 000 PTA 34 000 PTA 34 000 PTA			7 000 PTA 34 000 PTA 34 000 PTA			12 000 PTA 50 000 PTA 50 000 PTA		
Screening Policy	Baseline	Best	Worst	Baseline	Best	Worst	Baseline	Best	Worst	Baseline	Best	Worst	Baseline	Best	Worst
Option 2	19.75	19.64	19.97	11 85	13.10	11.98	22.38	22.25	22.65	22.38	22.25	22.65	32.92	32.72	33.38
Option 3	4.68	2.98	6.99	2.80	1.79	4.19	5.30	3.38	7.92	5.30	3.38	7.92	7.79	4.97	11.64
Option 4	3.45	1.97	7.66	3.41	2.01	6.70	6.71	3.97	13.08	10.23	7.31	18.68	17.16	10.35	30.66
Option 5	3.06	1.57	9.25	3.60	1.94	8.64	7.15	3.86	16.94	11.84	6.51	25.16	20.09	11.08	58.11
Option 6	4.80	2.96	8 01	3.69	2 49	5.85	7.29	4.86	11.28	9.55	6.83	14.39	15.40	11.17	22.94
Option 7	2.63	1.08	6.78	2.19	1.03	5.11	4.27	2.04	9.86	5.91	3 02	12.64	9.62	5.11	20.17
Option 8	2.68	0.87	8.28	2.31	0.97	6.39	4.52	1.92	12.35	6.54	3.10	16.12	10.76	5.23	25.85

Note. See text for definitions of screening policies and scenarios.
[a]In millions of pesetas (PTA); costs given are for (top to bottom) biochemical tests, amniocentesis, and chordocentesis.
[b]Catalan Health Service rates.

cases along maternal age groups may have changed slightly since then. An aging in the distribution of pregnancies would bring options 7 and 8 closer to options 4 and 5. An expected increase in the proportion of pregnancies among women aged 30 through 35 at the expense of younger age groups would barely influence the final results in option 6, since this option screens by age, setting the cutoff point at 38 years. An increase in the number of pregnancies among women aged 38 years or older would increase detection rates at the expense of a higher total cost and a worsening of the ratio of cost to Down syndrome cases detected.

In conclusion, sensitivity and specificity rates of screening tests have emerged as the variables that most influence the final results. Bearing in mind the trade-off between the two, the only way to simultaneously improve all outcome measures is through the amelioration of both sensitivity and specificity rates. This may be possible by looking into combinations of existing serum and ultrasonography markers, or by searching for new ones. Future research should explore along these lines.

Finally, the analyses we performed disclosed significant trade-offs among the outcome measures. This fact emphasizes the need to comprehensively inform decision makers about both positive and negative consequences of adopting one screening policy or another. This information should include effectiveness, equity, quality, safety, and efficiency considerations that might be useful in overcoming the ethical implications associated with the important trade-offs between the effectiveness and the risk of prenatal screening policies. Therefore, societal and individual values should be taken into account in the design and implementation of screening policies for Down syndrome. In view of the results of this study, there is no single strategy that simultaneously optimizes all outcome measures. Policymakers may thus be willing to provide two different strategies, one that would maximize detection rates and a second one that would minimize the number of procedure-related miscarriages, letting pregnant women choose according to their values and preferences. □

Acknowledgments

The authors would like to thank the persons and institutions that provided the necessary information and support for carrying out this study, especially Marta Solé and Marga Amat for their technical and administrative support, Angela Boland for her ideas, and the Catalan Health Service and the Catalan Agency for Health Technology Assessment.

References

1. Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol.* 1987;94:387–402.
2. Wald NJ, Cuckle HS, Densem JW, et al. Maternal screening for Down's syndrome in early pregnancy. *BMJ.* 1988;297:883–887.
3. Wald NJ, Kennard A, Densem JW, Cuckle HS, Chard T, Butler I. Antenatal maternal serum screening for Down's syndrome: results of a demonstration project. *BMJ.* 1992;305:391–394.
4. Spencer K, Coombes EJ, Mallard A, Ward AM. Free beta human choriogonadotropin in Down's syndrome screening: a multicentre study of its role compared with other biochemical markers. *Ann Clin Biochem.* 1992;29:506–518.
5. MacDonald ML, Wagner RM, Slotnick RN. Sensitivity and specificity of screening for Down syndrome with alpha-fetoprotein, hCG, unconjugated estriol and maternal age. *Obstet Gynecol.* 1991;77:63–68.
6. Phillips OP, Elias S, Shulman LP, Andersen RN, Morgan CD, Simpson JL. Maternal serum screening for fetal Down syndrome in women less than 35 years of age using alpha-fetoprotein, hCG and unconjugated oestriol: a prospective 2-year study. *Obstet Gynecol.* 1992;80:353–358.
7. Haddow JE, Palomaki GE, Knight GJ, et al. Prenatal screening for Down's syndrome with use of maternal serum markers. *N Engl J Med.* 1992;327:588–593.
8. Benacerraf BR, Gelman R, Frigoletto FD. Sonographic identification of second-trimester fetuses with Down's syndrome. *N Engl J Med.*1987;317:1371–1376.
9. Lockwood C, Benacerraf B, Krinsky A, et al. A sonographic screening method for Down syndrome. *Am J Obstet Gynecol.* 1987;157:803–808.
10. Vintzileos AM, Egan FX. Adjusting the risk for trisomy 21 on the basis of second trimester ultrasonography. *Am J Obstet Gynecol.* 1995;172:837–844.
11. Tabor A, Philip J, Madsen M, Bang J, Obel EB, Norgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet.* 1986;i:1287–1293.
12. Meade TW, Ammälä P, Aynsley-Green A, et al. Medical Research Council European Trial of chorion villus sampling. *Lancet.*1991;337:1491–1499.
13. Weinstein MC, Fineberg HV, Elstein AS, et al. *Clinical Decision Analysis.* Philadelphia, Pa: WB Saunders Co; 1980.
14. Sonnenberg FA, Hagerty CG, Kulinowski CA. An architecture for knowledge-based construction of decision models. *Med Decis Making.* 1994;14(1):27–39.
15. Fletcher J, Hicks NR, Kay JDS, Boyd PA. Using decision analysis to compare policies for antenatal screening for Down's syndrome. *BMJ.* 1995;311:351–356.
16. Goodburn SF, Yates JRW, Raggatt PR, et al. Second-trimester maternal serum screening using alpha-fetoprotein, human chorionic gonadotrophin, and unconjugated oestriol: experience of a regional programme. *Prenat Diagn.* 1994;14:391–402.
17. Cheng EY, Luthy DA, Zebelman AM, Williams MA, Lieppman RE, Hickok DE. A prospective evaluation of a second-trimester screening test for Down syndrome using maternal serum alpha-fetoprotein, hCG, and unconjugated estriol. *Obstet Gynecol.* 1993;81:72–77.
18. Burton BK, Prins GS, Verp MS. A prospective trial of prenatal screening for Down syndrome by means of maternal serum alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol. *Am J Obstet Gynecol.* 1993;169:526–530.
19. Haddow JE, Palomaki GE, Knight GJ, Cunningham GC, Lustig LS, Boyd PA. Reducing the need for amniocentesis in women 35 years of age or older with serum markers for screening. *N Engl J Med.* 1994;330:1114–1118.
20. Mancini G, Perona M, Dall'Amico D, et al. Maternal serum markers. Estimation of the risk of Down's syndrome: a prospective study. *Int J Clin Lab Res.* 1994;24:49–53.
21. Perrella R, Duerinckx AJ, Grant EG, Tessler F, Tabsh K, Crandall BF. Second-trimester sonographic diagnosis of Down syndrome: role of femur-length shortening and nuchal-fold thickening. *Am J Roentgenol.* 1988;151:981–985.
22. Lynch L, Berkowitz GS, Chitkara U, Wilkins IA, Mehalek KE, Berkowitz RL. Ultrasound detection of Down syndrome: is it really possible? *Obstet Gynecol.* 1989;73:267–270.
23. Ginsberg N, Cadkin A, Pergament E, Verlinsky Y. Ultrasonographic detection of the second-trimester fetus with trisomy 18 and trisomy 21. *Am J Obstet Gynecol.* 1990;63:1186–1190.
24. Crane J, Gray DL. Sonographically measured nuchal skinfold thickness as screening tool for Down syndrome: result of prospective clinical trial. *Obstet Gynecol.* 1991;77:533–539.
25. Donnenfeld AE, Carlson DE, Palomaki GE, Libruzzi RJ, Weiner S, Platt LD. Prospective multicentre study of second-trimester nuchal skinfold thickness in unaffected and Down syndrome pregnancies. *Obstet Gynecol.* 1994;84:844–884.
26. Gray DL, Crane JP. Optimal nuchal skin-fold thresholds based on gestational age for prenatal detection of Down syndrome. *Am J Obstet Gynecol.* 1994;171:1282–1286.
27. Borrell A, Martínez JM, Delgado RD, et al. Validez del pliegue nucal fetal como marcador ecográfico del síndrome de Down. *Gac San.* 1995;50(9):61.
28. Grandjean H, Sarramon MF, Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant Study Group. Sonographic measurement of nuchal skinfold thickness for detection of Down syndrome in the second-trimester fetus: a multicentre prospective study. *Obstet Gynecol.* 1995;85:103–105.
29. Movimiento Natural de la Población Española 1992. Tomo II. Resultados por Comunidades Autónomas. Madrid, España: Instituto Nacional de Estadística; Cataluna. 1995.
30. Wishart JG. Prenatal screening for Down's syndrome. *BMJ.* 1991;303:468–469.
31. Murray D, Tennison B. Decision analysis and screening for Down's syndrome. Estimate of uptake of amniocentesis is overoptimistic. *BMJ.* 1995;311:1371.
32. Spencer K, Carpenter P. Risk of Down's syndrome and amniocentesis rate. *BMJ.* 1992;304:640.
33. Halliday J, Lumley J, Watson L. Comparison of women who do and do not have amniocentesis or chorionic villus sampling. *Lancet.* 1995;345:704–709.
34. Shackley P, McGuire A, Boyd PA, et al. An economic appraisal of alternative pre-natal screening programmes for Down's syndrome. *J Public Health Med.* 1993;15(2):175–184.
35. Registre d'interrupcions voluntàries de l'embaràs, avortament legal a Catalunya, 1992. Barcelona, Spain: Unitat d'Estadistiques Sanitàries, Direcció General de Recursos Sanitaris, Departament de Sanitat i Seguretat Social, Generalitat de Catalunya; 1993.