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The Genetic Sonogram

Comparing the Use of Likelihood Ratios Versus Logistic Regression Coefficients for Down Syndrome Screening

Yan Zhong, MD, Ryan Longman, MD, Rachael Bradshaw, MS, Anthony O. Odibo, MD, MSCE

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Objectives—The purpose of this study was to compare the screening efficiency for Down syndrome using likelihood ratios versus logistic regression coefficients.

Methods—We conducted a retrospective study of women at increased risk for Down syndrome referred for a second-trimester genetic sonogram. Likelihood ratios were calculated by multiplying the risk ratio from maternal serum screening by the likelihood ratios of sonographic markers. Logistic regression coefficients were calculated using a formula derived from β coefficients generated from a multivariable logistic regression model. The screening efficiency of both methods was tested in an independent population of patients. The McNemar test was used to compare the predictive ability of the two methods.

Results—In the validation population, the use of likelihood ratios had an area under the receiver operator characteristic curve of 0.90 for Down syndrome detection, whereas the use of logistic regression coefficients had an area under the curve of 0.86. Adopting a risk cutoff point of 1/270, the sensitivity of likelihood ratios was 77.4% (95% confidence interval [CI], 58.9%–90.4%) with a false-positive rate of 17.9% (95% CI, 15.0%–21.1%), whereas the sensitivity of logistic regression coefficients was 93.5% (95% CI, 78.6%–99.2%) with a false-positive rate of 34.6% (95% CI, 30.9%–38.4%). There was significant difference in screening efficiency for Down syndrome detection between the two methods (exact McNemar χ^2, $P < .001$).

Conclusions—With a slight reduction in the Down syndrome detection rate, the use of the likelihood ratio approach was associated with a significantly lower false-positive rate compared with the logistic regression approach.

Key Words—Down syndrome; genetic sonogram; likelihood ratios; logistic regression coefficients

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Abbreviations
CI, confidence interval

Down syndrome is the most common cause of aneuploidy. It is characterized by a combination of birth defects that include cognitive impairment, dysmorphic facial features, and structural defects.[1] Caring for children with Down syndrome can place substantial emotional and financial strain on a family. Prenatal detection of fetuses affected with Down syndrome can prepare the parents for the birth of an affected child or offer them the option of pregnancy termination. Second-trimester maternal serum screening for Down syndrome is now part of routine prenatal care.[2] In addition, the genetic sonogram in the second trimester provides a noninvasive tool for identifying women whose pregnancies are at increased risk for Down syndrome and who may be candidates for invasive prenatal diagnosis.

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Both maternal serum screening and the genetic sonogram have limitations in their ability to detect Down syndrome. To improve the predictive ability, formulas based on multivariable logistic regression analysis have been suggested.[3] Although these formulas are reported to have high sensitivity, the false-positive rates are also high. For example, Vergani et al[4] reported sensitivity of 83.3% with a false-positive rate of 28.5%. Moreover, the complicated calculations of the formulas have limited their use in clinical practice. On the other hand, physicians in clinical practice tend to use a simpler method, which modifies the risk for Down syndrome by combining maternal serum screening results and likelihood ratios based on sonographic markers.[5–8]

The aim of our study was to compare the performance of likelihood ratios and logistic regression coefficients in a cohort of women at increased risk for fetal Down syndrome based on maternal serum screening.

Materials and Methods

This was a retrospective cohort study of women at increased risk for Down syndrome referred for sonographic and genetic evaluation at Washington University Medical Center from 1991 through 2006 because of abnormal second-trimester serum screening results. All referred women seen between 15 and 22 weeks' gestation were evaluated with a genetic sonogram. Multiple pregnancies and aneuploidy other than Down syndrome were excluded. Approval from the Institutional Review Board at our center was obtained.

Serum analyte levels (α-fetoprotein, estriol, and β-human chorionic gonadotropin and dimeric inhibin A after 1996) were converted to multiples of the median after adjusting for gestational age, ethnicity, preconceptional insulin use, and body mass index, and risk ratios for Down syndrome were calculated after incorporating for maternal age. Sonographic examinations were performed by an obstetric sonographer, and the images were reviewed by maternal-fetal medicine specialist without prior knowledge of the fetal karyotype. Sonographic assessment of Down syndrome included the following sonographic soft markers: nuchal fold thickness, defined as 6 mm or greater based on the mean of 3 measurements obtained in the standard suboccipital plane from skull edge to skin edge; hyperechoic bowel, defined as bowel with echogenicity equal to or greater than the adjacent pelvic bone; echogenic intracardiac focus, defined as punctuate intracardiac echogenic areas within either or both of the cardiac ventricles with echogenicity equal to that of bone; renal pyelectasis, defined as an anteroposterior diameter of the renal pelvis of 4 mm or greater; extremity shortening, including humerus or femur shortening; and any major structural abnormalities. Nasal bone evaluation was introduced into the sonographic assessment in 2005 and was not used for this present study. Fetal karyotype information was obtained from the results of cytogenetic examinations performed at second-trimester amniocentesis or by postnatal testing when the postnatal examination was suspicious for a chromosomal abnormality.

Two methods of adjusting the risk for Down syndrome were compared in the study: likelihood ratios versus logistic regression coefficients derived for our population. The use of the likelihood ratios involved calculating the postsonographic risk for Down syndrome by multiplying the risk ratio from maternal serum screening with the likelihood ratios of sonographic markers seen during the sonographic evaluation. The likelihood ratios of the sonographic markers were derived from a previous publication by Nicolaides (Table 1).[7] For example, if the risk ratio for Down syndrome based on maternal serum screening alone was 1/100 with the sonographically detected presence of both nuchal fold thickness (positive likelihood ratio, 53.05) and an echogenic intracardiac focus (positive likelihood ratio, 6.41) but no other defects, then the final risk ratio for Down syndrome calculated by the use of likelihood ratio was $(1/100) \times 53.05 \times 6.41 \times 0.68 \times 0.62 \times 0.85 \times 0.87 \times 0.79 = 1/1.2$ (Table 1).[7] The use of logistic regression involved calculating the risk ratio for Down syndrome by a formula derived from β coefficients for Down syndrome generated from a multivariable logistic regression model. The model included the presence of sonographic markers described above. Data from 1990 through 2002 were used to generate the logistic regression formula, whereas those from 2003 through 2006 were used to validate the model and in the comparison of the predictive ability of the two methods. Patients were classified as test positive or negative using a cutoff of 1/270, which is the

Table 1. Likelihood Ratios of Second-Trimester Sonographic Markers for Down Syndrome Used in This Study

Marker	Positive LR (95% CI)	Negative LR (95% CI)
Nuchal fold	53.05 (39.37–71.26)	0.67 (0.61–0.72)
Short humerus	22.76 (18.04–28.56)	0.68 (0.62–0.73)
Short femur	7.94 (6.77–9.25)	0.62 (0.56–0.67)
Hydronephrosis	6.77 (5.16–8.80)	0.85 (5.16–8.80)
Echogenic focus	6.41 (5.15–7.90)	0.75 (0.69–0.80)
Echogenic bowel	21.17 (14.34–31.06)	0.87 (0.83–0.91)
Major defect	32.96 (23.90–43.28)	0.79 (0.74–0.83)

Data reprinted with permission from Nicolaides.[7] CI indicates confidence interval; and LR, likelihood ratio.

risk for Down syndrome for a 35-year-old woman that has been used in several previously published studies. The sensitivity and false-positive rates were calculated by comparing the predicted results from the two methods with the eventual diagnosis of Down syndrome. The McNemar test and κ statistic were used to compare the predictive ability of the two methods.

Descriptive statistics included means and SDs for continuous variables and frequency distributions for categorical variables. Comparisons between categorical variables were tested using the χ^2 test. Comparisons between continuous variables were performed using the Student *t* test for normally distributed variables and the Wilcoxon rank-sum test for variables that were not normally distributed. A multivariable logistic regression model was developed with confounders included in the model at $P < .1$ in the univariate analyses and by their biological plausibility. Stata version 10.0 software (StataCorp, College Station, TX) was used for statistical analyses.

Results

The maternal characteristics of the population from 1990 through 2002 are shown in Table 2. In the cohort of 1834 women, 46 cases were affected by Down syndrome (2.51%). Women with Down syndrome–affected fetuses were older (35 ± 5.61 years) than women without Down syndrome–affected fetuses (31 ± 5.73 years). There was no difference in gestational age at examination between the two groups. The mean risk of Down syndrome calculated by maternal serum screening alone in women with Down syndrome–affected fetuses (1/79) was significantly higher than that of women without Down syndrome–affected fetuses (1/155).

Table 2. Maternal Characteristics in the Population From 1990 Through 2002

Characteristic	Down Syndrome	Non–Down Syndrome	*P*
Patients	46 (2.5)	1788 (97.5)	
Age, y	35 ± 5.6	31 ± 5.7	<.001
Gestational age, wk	19 ± 1.9	19.1 ± 1.8	.86
Race			.03
White	42 (91.3)	1379 (77.1)	
Black	1 (2.2)	312 (17.5)	
Hispanic	1 (2.2)	14 (0.8)	
Asian	0 (0)	46 (2.6)	
Other	2 (4.4)	37 (2.1)	
Median risk for Down syndrome by maternal serum screening	1/79	1/155	.006

Data are number (percent) and mean ± SD. CI indicates confidence interval; and LR, likelihood ratio.

The univariate comparison for the association between sonographic markers and Down syndrome is displayed in Table 3. Nuchal fold thickness (odds ratio, 30.9; 95% confidence interval [CI], 13.6–70.3) and the presence of any major abnormality (odds ratio, 24.2; 95% CI, 12.0–48.9) showed the strongest association with Down syndrome. An echogenic intracardiac focus, a renal pelvis, a short femur, and a hyperechoic bowel were also associated with Down syndrome, although the association with a short femur was of borderline significance (Table 3). A short humerus was not significantly associated with Down syndrome.

When maternal age, race, and associated sonographic markers were combined in a multivariable model, maternal race, a short femur, and a dilated renal pelvis were excluded from the final prediction model due to nonsignificance. The interaction between nuchal fold thickness and any major abnormalities was found to be significant. The parameter estimates of the final model are displayed in Table 4.

Using the parameter estimates in Table 4, the following formula was generated to calculate a woman's adjusted risk of carrying a fetus with Down syndrome: probability of having a fetus with Down syndrome = $1 - \{1/(1 + \exp(-9.05 + [0.1 \times \text{maternal age}] + [3.8 \times \text{nuchal fold thickness} \geq 6 \text{ mm}] + [3.6 \times \text{hyperechoic bowel}] + [3.4 \times \text{any major abnormalities}] + [-2.2 \times \text{nuchal fold thickness} \geq 6 \text{ mm} \times \text{any major abnormalities}]))\}$.

Among those seen from 2003 through 2006, there were 673 women with abnormal serum screening results, of which 31 fetuses with Down syndrome were detected (4.6%). The mean maternal ages were 35.3 ± 6.0 years for women with Down syndrome–affected fetuses and 30.9 ± 5.9 years for women without Down syndrome–affected fetuses. The mean gestational age at sonography for this cohort was 19.4 ± 1.7 weeks. When using this population for validation of the two methods of risk adjustment, the use of likelihood ratios had an area under the receiver operating characteristic curve of 0.90 for Down syndrome detection, whereas the use of logistic regression coefficients had an area under the curve of 0.86 (Figure 1). Adopting a risk cutoff point of 1/270, the sensitivity of the use of likelihood ratios was 77.4% (95% CI, 58.9%–90.4) with a false-positive rate of 17.9% (95% CI, 15.0%–21.1%), whereas the sensitivity of the use of logistic regression coefficients was 93.5% (95% CI, 78.6%–99.2%) with a false-positive rate of 34.6% (95% CI, 30.9%–38.4%). There was a significant difference in the screening efficiency between the two methods for Down syndrome detection (positive results by both methods, 106; negative results by both methods,

389; positive results by likelihood ratios and negative results by logistic regression, 106; positive results by logistic regression and negative results by likelihood ratios, 33; exact McNemar χ^2, $P < .001$). The agreement between the two methods was fair ($\kappa = 0.38$; SE = 0.04; agreement, 73.6%; expected agreement, 57.5%).

Discussion

We compared the diagnostic accuracy of using likelihood ratios versus logistic regression coefficients for Down syndrome screening at 15 to 22 weeks in a high-risk population. With a risk cutoff point of 1/270, there was a significant difference in the screening efficiency for Down syndrome between the two methods. Using likelihood ratios had a lower false-positive rate but also a lower detection rate, whereas using logistic regression coefficients had a higher detection rate but a higher false-positive rate.

Likelihood ratios of sonographic markers have been developed to modify a priori baseline risk estimates using the Bayes theorem. Prior risk is based on either the maternal age risk or second-trimester serum screening risk. Several authors have calculated likelihood ratios for sonographic markers.[5–8] DeVore[8] examined cardiovascular and noncardiovascular prenatal sonographic markers and used logistic regression to identify which combination of markers significantly contributed to the identification of fetuses with Down syndrome. In that study, the likelihood ratio for each significant marker was computed from the logarithmic transformation of the corresponding coefficient. The study considered varying skills of the physicians for diagnosing cardiovascular anomalies and examined models of different combinations, including using both cardiovascular and noncardiovascular markers, using noncardiovascular markers only, and using selective real-time sonography markers. That approach allowed the physicians to choose makers according to their diagnostic skills. Using the computing strategy described in that study, physicians can compute the risk for Down syndrome on the basis of the sonographic results. That is a very useful study, providing likelihood ratios for positive and negative findings on a second-trimester anomaly scan. However, the study did not provide likelihood ratios for some of the markers included in our study, such as an echogenic intracardiac focus, a short femur, and a short humerus; therefore, we were unable to use their data as reference.[8] However, in this study, we used a similar approach as DeVore's study[8] for computing likelihood ratios and individual risk factors for Down syndrome.

On the other hand, Nyberg et al[5] calculated overall and isolated likelihood ratios for 6 sonographic markers of Down syndrome (nuchal fold thickness, a hyperechoic bowel, a short humerus, a short femur, an echogenic intracardiac focus, and pyelectasis). Bromley et al[6] further evaluated the 6 markers with the addition of major structural anomalies. Finally, Nicolaides[7] combined data from the studies by Nyberg et al[5] and Bromley et al[6] and provided positive and negative likelihood ratios for sonographic makers of Down syndrome, which we used as referential likelihood ratios for our study.

The findings from this study regarding the efficiency of the likelihood ratio approach are similar to those from other reports. For example, Nyberg et al[9] also performed an age-adjusted sonographic risk assessment for Down syndrome, which multiplied a priori risk based on maternal age with likelihood ratios calculated on the basis of the presence or absence of specific sonographic findings for each patient. Using an age-adjusted sonographic risk assessment and a threshold of 1/200, they reported sensitivity of 74% at a false-positive rate of 14.7%. Bahado-Singh et al[10] developed a comprehensive midtrimester test based on multiple urine, serum, and sonographic markers and used a multivariable gaussian algorithm plus age to derive the patient-specific Down syndrome risk. The comprehensive midtrimester test finally consisted of the urine human chorionic gonadotropin level, β-core fragment, and

Table 3. Associations Between Sonographic Markers and Down Syndrome in the Population From 1990 Through 2002

Characteristic	Down Syndrome	Non–Down Syndrome	Unadjusted OR (95% CI)	*P*
Patients	46 (2.5)	1788 (97.5)		
Nuchal fold thickness ≥6 mm	11 (23.9)	18 (1.0)	30.9 (13.6–70.3)	<.001
Hyperechoic bowel	3 (6.5)	6 (0.3)	20.7 (5.0–85.5)	<.001
Short femur	3 (6.7)	37 (2.1)	3.3 (1.0–11.0)	.057
Short humerus	4 (11.1)	95 (6.4)	1.8 (0.6–5.3)	.258
Echogenic intracardiac focus	9 (19.6)	55 (3.1)	7.7 (3.5–16.7)	<.001
Renal pelvis	11 (23.9)	24 (1.3)	23.1 (10.5–50.8)	<.001
Any major abnormalities	15 (32.6)	35 (2.0)	24.2 (12.0–48.9)	<.001

Data are number (percent). CI indicates confidence interval; and OR, odds ratio.

nuchal fold thickness and showed sensitivity of 93.7% at a 5% false-positive rate for the overall population. In the validation population of our study, the use of likelihood ratios generated sensitivity of 87.1% (95% CI, 70.2%–96.4%) with a false-positive rate of 36.5% (95% CI, 32.7%–40.3%) with a risk cutoff point of 1/270. The difference in diagnostic accuracy between studies may result from different study populations, different likelihood ratios used, different approaches to calculating the likelihood ratios, and different cutoff points used to define a screen-positive case. In this study, we used a cutoff of 1/270, which is the risk for Down syndrome for a 35-year-old woman that has been used in several previously published studies. The high false-positive rate for our population suggests that a higher cutoff may be preferable. A higher rate, however, would result in lower sensitivity. Thus, standardization is needed to improve the performance of screening.

The approach of refining risk by multiplying sonographic likelihood ratios is based on the assumption that there is no significant correlation between sonographic and serum markers. Some authors argue that such assumptions are not always accurate because different screening findings are not necessarily independent.[3,7,8] Therefore, the use of logistic regression coefficients from a predictive formula has been proposed to facilitate an accurate understanding of prenatal Down syndrome risk. DeVore[8] examined noncardiac markers (including central nervous system malformations, choroid plexus cysts, nuchal translucency, a hyperechoic bowel, and pyelectasis) and cardiac markers (including ventricular septal defects, right-to-left chamber disproportion, pericardial effusion, and outflow tract abnormalities). In that study, all but 3 markers (choroid plexus cysts, mitral regurgitation, and outflow tract abnormalities) contributed significantly to the identification of 91% of fetuses with Down syndrome, with a false-positive rate of 14%. The logistic coefficients were 4.2 for nuchal fold thickness, 1.7 for a hyperechoic bowel, and 1.5 for pyelectasis. Interactions were found between nuchal fold thickness and right-to-left chamber disproportion, with coefficients of –3.5. When only noncardiovascular markers were examined, all markers but choroid plexus cysts contributed to the identification of 60% of fetuses with Down syndrome, with a false-positive rate of 5.9%. Schluter and Pritchard[3] generated a formula based on multivariable analysis of sonographic markers that adjusted the maternal age– and gestational age–derived risk for Down syndrome in a prospective group of unselected pregnant women. They found that a thickened nuchal fold, a short humerus, an echogenic bowel, renal pelvic dilatation, and aneuploidy-associated anomalies were significantly associated with Down syndrome. They also found an interaction between gestational age and a thickened nuchal fold thickness and between a short humerus and aneuploidy-associated anomalies. They suggested that risk estimates should be derived from appropriate multivariable models because of the relationship between sonographic findings.

Vergani et al[4] developed a multivariable sonographic model adjusted for gestational and maternal age in a population at high risk because of a maternal age of 35 years or older. They found a nuchal fold thickness of 5 mm or greater, renal pelvic dilatation, absence of a mid phalanx of the fifth digit, noncardiac malformations, and isolated heart defects to be significantly associated with Down syndrome, with coefficients of 15.2, 2.9, 3.4, 3.0, and 4.1, respectively. They also found a significant interaction between gestational age and nuchal fold thickness of 5 mm or greater and heart defects, with coefficients of –0.80 and –3.6, respectively. With the exception of maternal age, which was used as a categorical variable in that study, the coefficients for the other markers were similar to those reported in our study. Using this model and a risk cutoff point of 1/270, they reported sensitivity of 83.3% with a false-positive rate of 28.5% in their validation population. In our final parsimonious model, nuchal fold thickness of 6 mm or greater, a hyperechoic bowel, an echogenic intracardiac focus, and major abnormalities were associated with Down syn-

Table 4. Parameter Estimates for the Formula Generated for the Population From 1990 Through 2002

Characteristic	Logistic Regression Parameter Estimate		Adjusted OR (95% CI)
	β	SE	
Maternal age	0.1	0.04	1.1 (1.1–1.2)
Nuchal fold thickness ≥6 mm	3.8	0.51	44 (16.0–121.3)
Hyperechoic bowel	3.6	0.87	35.4 (6.4–196.7)
Echogenic intracardiac focus	2.2	0.49	8.6 (3.3–22.7)
Any major abnormalities	3.1	0.44	22.4 (9.4–53.6)
Any major abnormalities × nuchal fold thickness ≥6 mm	–2.2	1.17	0.1 (0.01–1.1)

CI indicates confidence interval; and OR, odds ratio.

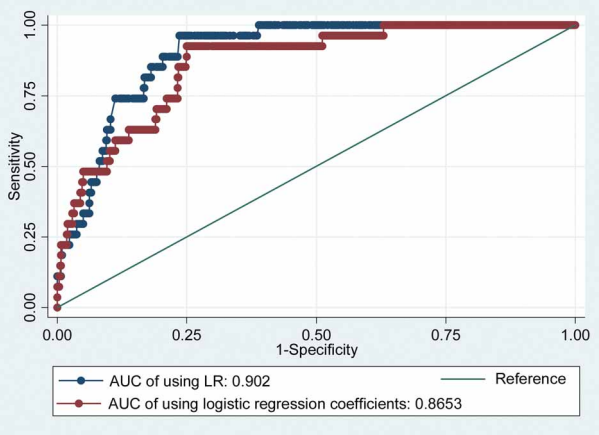

Figure 1. Comparison of the areas under the receiver operating characteristic curve (AUC) between the use of likelihood ratios (LRs) and the logistic regression coefficients in the population from 2003 through 2006. The use of likelihood ratios showed an area under the curve of 0.902, whereas the use of logistic regression coefficients showed an area under the curve of 0.8653.

drome, with coefficients of 3.8, 3.6, 2.2, and 3.1, respectively. We found a significant interaction between nuchal fold thickness of 6 mm or greater and major structural abnormalities, with a coefficient of –2.2. This finding was similar to DeVore's finding of a significant interaction between an increased nuchal skin fold and cardiac malformations.[8]

With a risk cutoff point of 1/270, the sensitivity of using logistic regression coefficients was higher than that reported by DeVore[8] and Vergani et al[4] (93.5%), but the false-positive rate was also higher (34.6%). Moreover, a comparison of the screening efficiency showed a significant difference between the use of likelihood ratios versus logistic regression coefficients. Among the 4 studies using the logistic regression approach, the sonographic markers in the final models and the coefficients included in the final equations were different. The studies by DeVore[8] and Vergani et al[4] and our study used high-risk populations, whereas Schluter and Pritchard[3] used an unselected population. All of these results suggest that the formulas from multivariable logistic models vary between different populations and different centers.

Our study was not without limitations. For example, recent data suggest that second-trimester nasal bone absence or hypoplasia has the potential to improve Down syndrome detection. Cicero et al[11] reported that the likelihood ratios of a hypoplastic nasal bone for Down syndrome were 132.1 (95% CI, 49.1–351.9) for white patients and 8.5 (95% CI, 2.7–20.1) for African Caribbean patients, and the respective values for a present nasal bone were 0.39 (95% CI, 0.24–0.58) and 0.27 (95% CI, 0.05–0.77). Odibo et al[12] reported that combining the nasal bone with other proven markers for Down syndrome (nuchal fold thickness, femur and humerus lengths, choroid plexus cysts, and an echogenic bowel) increased the sensitivity from 59% to 82% and the specificity from 74% to 87%. In another study,[13] they showed that absence of a nasal bone was a more efficient marker of Down syndrome than nuchal fold thickness of greater than 6 mm. In our study, we did not incorporate the nasal bone into our models because this marker was only introduced routinely into our practice in recent years and would have limited our sample size. However, we hope that future studies incorporating the nasal bone and other second-trimester sonographic markers of fetal aneuploidy would improve Down syndrome detection and decrease false-positive rates using either approach.

In our study, we included major abnormalities as a single variable and did not classify them into detailed subtypes, which may have overestimated the contribution of this marker to our models or missed the associations between specific subtypes and Down syndrome. However, we expect the impact of this limitation on our results to have been small because the Down syndrome detection rates of specific subtypes of major abnormalities (apart from cardiac) are small.[4,5] Previous studies also included all of the subtypes as a single variable.[4,5]

Finally, as the use of first-trimester screening for Down syndrome increases, its influence on second-trimester assessment of Down syndrome will become increasingly important.[14] Our study could not address the impact of first-trimester screening on the performance of genetic sonography because of a similar limitation as for the nasal bone mentioned above. In addition, because of the relatively large number of variables associated with Down syndrome and the small number of Down syndrome cases, our study may not have had enough power to detect small but possibly important differences in screening efficiency between the use of likelihood ratios and logistic regression coefficients. Therefore, our failure to show a significant difference between the two methods does not equate to the likelihood ratio method's being superior to the logistic regression method.

Finally, our study may be criticized for using published likelihood ratios for one set of comparisons and using coeffeicients derived from our population for the logistic regression approach. We chose to use the published likelihood ratios because they came from 2 robust data sets.[5,6] Although it would have been attractive to use only data from our center for comparing both methods, the ap-

proach would have limited the generalizability of the findings to other populations.

In conclusion, we found a significant difference in diagnostic accuracy for Down syndrome between the use of likelihood ratios and logistic regression coefficients. The use of likelihood ratios resulted in a lower false-positive rate but also a lower detection rate, whereas the use of logistic regression coefficients resulted in a higher detection rate but also a higher false-positive rate. Given the ease of using the likelihood ratio method and the familiarity of clinicians with that approach, the findings suggest that the continuing use of the likelihood ratio approach is reasonable, especially when the goal is to reduce the false-positive rate. Our results indicate that future studies on the genetic sonogram should aim to identify variables that could result in improvement in diagnostic accuracy, and standardization of markers included in such studies is desirable.

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