Role of Second-Trimester Genetic Sonography After Down Syndrome Screening

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Abstract

OBJECTIVE—To estimate the effectiveness of second-trimester genetic sonography in modifying Down syndrome screening test results.

METHODS—The First and Second Trimester Evaluation of Risk (FASTER) aneuploidy screening trial participants were studied from 13 centers where a 15- to 23-week genetic sonogram was performed in the same center. Midtrimester Down syndrome risks were estimated for five screening test policies: first-trimester combined, second-trimester quadruple, and testing sequentially by integrated, stepwise, or contingent protocols. The maternal age-specific risk and the screening test risk were modified using likelihood ratios derived from the ultrasound findings. Separate likelihood ratios were obtained for the presence or absence of at least one major fetal structural malformation and for each “soft” sonographic marker statistically significant at the P<.005 level. Detection and false-positive rate were calculated for the genetic sonogram alone and for each test before and after risk modification.

RESULTS—A total of 7,842 pregnancies were studied, including 59 with Down syndrome. Major malformations and 8 of the 18 soft markers evaluated were highly significant. The detection rate for a 5% false-positive rate for the genetic sonogram alone was 69%; the detection rate...
increased from 81% to 90% with the combined test, from 81% to 90% with the quadruple test, from 93% to 98% with the integrated test, from 97% to 98% with the stepwise test, and from 95% to 97% with the contingent test. The stepwise and contingent use of the genetic sonogram after first-trimester screening both yielded a 90% detection rate.

CONCLUSION—Genetic sonography can increase detection rates substantially for combined and quadruple tests and more modestly for sequential protocols. Substituting sonography for quadruple markers in sequential screening was not useful.

Multiple-marker screening for Down syndrome is an established part of routine prenatal care in most countries. Most centers use at least three second-trimester maternal serum markers, many use first-trimester serum markers together with concurrent ultrasound nuchal translucency measurement, and some have adopted sequential policies using both first- and second-trimester markers.

An ultrasound anatomic survey of the fetus (genetic sonogram or anomaly scan) has also become widely used in the second trimester. In pregnancies at high risk of Down syndrome because of advanced maternal age, family history, or abnormal Down syndrome screening, findings from the genetic sonogram are often used to inform choice. Absence of any major structural abnormality or minor “soft” marker is assumed as reassuring, and invasive prenatal diagnosis might be avoided. Conversely, in low-risk women, the presence of these signs is sometimes taken as sufficient grounds for invasive testing. However, there are a number of inherent limitations to genetic sonograms that have limited widespread implementation in clinical practice. To minimize false reassurance and unnecessary intervention, a more formal approach to the interpretation of the sonogram is needed.

Algorithms that allow post hoc risk calculation have been published. Essentially, the risk obtained by Down syndrome screening is modified by likelihood ratios (LRs) derived from the scan. When used routinely either on all screened women or selectively, depending on the screening result, this could substantially increase Down syndrome detection.

The First and Second Trimester Evaluation of Risk (FASTER) trial is in a unique position to estimate the increase in detection of Down syndrome fetuses with the addition of genetic sonography. The trial involved prospective screening in both the first and the second trimesters where intervention was delayed until the second trimester. For a large proportion of pregnancies, intervention was further delayed until a genetic sonogram was performed, either at a FASTER center or elsewhere. In the current article, we evaluated the role of genetic sonography as an adjunct to other first- and second-trimester screening tests.

MATERIALS AND METHODS

The detailed protocol for the FASTER trial has been published elsewhere. Briefly, 15 centers in the United States enrolled women who underwent a first-trimester nuchal translucency scan concurrently with the first-trimester maternal serum markers pregnancy-associated plasma protein A (PAPP-A) and free β-hCG, and in the second trimester α-fetoprotein, unconjugated estriol, free β-hCG and inhibin-A. Not all women completed the process; in particular, those found on nuchal translucency scan to have a septated cystic
hygroma were offered immediate invasive pre-natal diagnosis. Those who completed the planned testing were offered prenatal diagnosis if the risk based on either the first- or the second-trimester components of the testing was high.

The current study was restricted to women with singleton pregnancies who had screening tests both at 11–13 weeks and at 15–18 weeks of gestation and had a genetic sonogram at 15–23 weeks in the same FASTER center in which they were enrolled. Women included for analysis in our current study had a genetic sonogram completed at 15–23 weeks, with the majority completing the test from 17 to 21 completed weeks of gestation. In total, among the 33,546 trial participants with complete first- and second-trimester data, 8,533 also underwent genetic sonography at a FASTER center. However, because we sought to estimate the benefits of genetic sonography in modifying Down syndrome screening tests using all current methods of screening (combined, quadruple, integrated, stepwise, and contingent), our analysis was restricted to the 7,842 pregnancies from 13 centers out of 28,198 with complete screening test results at those centers (28%). There were 84 pregnancies with Down syndrome at those centers, and 59 of 84 (70%) underwent genetic sonography and had complete screening.

Six of the 13 centers performed the majority of genetic sonograms, and at those centers the proportions of screened participants who had a genetic sonogram were 53% (83%, 76%, 74%, 29%, 29%, and 29% at each center). The incidence of Down syndrome at these centers was 4.7 in 1,000, compared with 2.6 in 1,000 (87 in 33,546) in FASTER as a whole. The remaining 7 centers only provided 191 genetic sonograms (1.4% of those screened), and the Down syndrome incidence was 120 in 1,000. These remaining 7 centers were therefore considered separately in the analysis because of potential surveillance bias.

Midtrimester Down syndrome risks were calculated for five standard screening tests using published parameters derived from the FASTER trial. The tests are defined as first trimester combined (11- to 13-week PAPP-A, free β-hCG, and nuchal translucency), second-trimester quadruple (15- to 18-week α-fetoprotein, unconjugated estriol, free β-hCG, and inhibin), and the following sequential protocols: integrated (PAPP-A, nuchal translucency, and quadruple markers), stepwise (combined markers and, unless the risk exceeds 1 in 30, quadruple markers), and contingent (combined markers and, if the risk is 1 in 30–1,500, quadruple markers). For those having the quadruple markers in the stepwise and contingent tests, the risk is calculated from all seven markers.

Each center conducted the fetal anatomic survey according to the practice guideline of the American Institute of Ultrasound in Medicine. Measurements were obtained for the biparietal diameter, head and abdominal circumferences, and femoral and humeral lengths. Reduced long bones are markers of Down syndrome, and these measurements were expressed in multiples of the gestation-specific median (MoM) in unaffected pregnancies using regression. After previous practice, a femur length less than 0.91 MoM or humerus length less than 0.89 MoM was regarded as reduced. A structured report form was used to record at the time of the sonogram the presence or absence of the following potential soft markers: nuchal skin-fold 6 mm or more, choroid plexus cyst, enlarged cisterna magna over 10 mm, ventriculomegaly 10 mm or more, echogenic intracardiac focus, pericardial effusion,
hydrops, echogenic bowel (with echogenicity equal to adjacent bone), liver calcification, pyelectasis of 3 mm or more, two-vessel umbilical cord, polydactyly, clinodactyly, sandal gap, and club foot. The presence of any putative major structural abnormality was recorded—diaphragmatic hernia, spinal, cardiac, other thoracic, abdominal, and extremities—as well as a description of the abnormality. General observations made by the person performing the scan were also recorded. The descriptions of abnormalities and general observations were reviewed without knowledge of fetal karyotype and were classified as major or not.

In our analysis, we distinguish between nuchal translucency and nuchal fold in the following fashion. In accordance with the parent trial and current standard sonographic procedures, nuchal translucency describes the translucent nuchal space as viewed in the midsagittal plane during the first trimester (11 to 13 and 6/7 weeks). The nuchal fold assessment is distinct from the assessment of nuchal translucency because it is obtained in the midtrimester and taken in the axial plane, where the measurement is attained from the outer edge of the occipital bone to the outer margin of the skin.

The presence of at least one major abnormality and each of the 18 potential soft markers separately in Down syndrome and unaffected pregnancies was assessed by a $\chi^2$ test. Only those where there was a statistically significant ($P<.005$) difference were included in further analyses. Likelihood ratios for the presence and absence of a major abnormality or soft marker were computed, as well as the LR for the absence of any abnormality or marker. For the long bone measurements, LRs were also computed for each MoM value using log gaussian frequency distributions with the observed means and standard deviations in Down syndrome and unaffected pregnancies.

For each woman in the study, an overall LR was calculated from the product of the individual LR in turn corresponding to the presence and absence of an abnormality or marker. When none were present, the overall LR was the directly computed value. The Down syndrome risk based on maternal age alone and each of the screening tests, respectively, was modified by multiplying the odds by the overall LR. To do this, the risk was first expressed as an odds, which was then multiplied by the LR and reexpressed in terms of risk, as described by Royston and Thompson. In general, the LR for the presence of a useful marker is greater than 2, and that for absence will be somewhat less than 1 but not markedly so. Thus, the presence of even a single isolated marker is likely to increase the Down syndrome risk. However, if that marker is relatively weak, it may be considerably offset by the absence of other stronger markers when multiplied together.

For the genetic sonogram alone, the 92nd–99th percentiles of risk were computed, and the detection rate was calculated using these as the cutoff risks. This detection rate for a fixed 5% false-positive rate was similarly calculated for the five screening tests before and after risk was modified by the genetic sonogram results. In addition, the detection rates were calculated for policies of substituting the genetic sonogram for biochemistry as the second stage of stepwise and contingent tests. Detection and false-positive rates were also calculated using a fixed 1 in 270 midtrimester risk cutoff. Pearson correlation coefficients were calculated, after logarithmic transformation, between each of the seven Down syndrome screening markers, in MoMs, and the overall LR. Pearson correlation coefficients were also...
calculated between femur and humerus length, in MoMs, after logarithmic transformation. To avoid the influence of extreme outliers, results exceeding three standard deviations from the mean were excluded.

During the trial, patients who remained at their original FASTER site for genetic sonography were counseled about any soft markers based on accepted clinical practice and policies in place at the time of study initiation. The LRs cited herein were not available to clinicians and hence were not used to inform decision making or choice.

RESULTS

The mean (±SD) maternal age in the study was 30.6±6.1 years, consistent with recent U.S. estimates on the mean maternal age distribution approximating 28 years. Table 1 compares the patient characteristics of those who had a genetic sonogram at one of the 13 participating FASTER centers compared with those who were not scanned there. The cohort who received a genetic sonogram at a FASTER center did not differ from the index study population by virtue of mean maternal age (30.6±6.1 compared with 30.1±5.8 years), advanced maternal age, body mass index (25.1±5.2 compared with 25.1±5.3 kg/m²), or obesity (body mass index 30 kg/m² or greater) (Table 1). The cohort receiving a genetic sonogram had a higher a priori risk of Down syndrome, but not markedly so (Table 1). A significantly greater proportion of women self-identifying as of Hispanic origin underwent genetic sonography because the FASTER center contributing the largest number of sonographic examinations had a 68% Hispanic population (Table 1).

Major malformations and 8 of the 18 soft markers evaluated were highly significantly associated with Down syndrome (Table 2). The proportions of Down syndrome and unaffected pregnancies with the presence of a malformation or soft marker is shown are Table 2, together with the LRs for presence and absence. The LR for findings in isolation are also represented in Table 2 and, as expected, are appreciably lower than when considered in combination. Table 2 also shows the LR for sonograms where none of the highly significant factors are present (no markers present). The value of 0.41 is higher than that obtained by multiplying together the LRs for absence of each factor separately (0.32), because of some degree of correlation between the factors.

Femur and humerus length MoM values were highly correlated in the 25 Down syndrome pregnancies with both measurements (r=0.57) and the 3,777 unaffected pregnancies (r=0.76). For this reason and because humerus length was not recorded in approximately half the pregnancies, only the femur length MoMs were used in the calculation of risk. The means and log_{10} standard deviations of femur length were 0.94 and 0.034 MoM in Down syndrome and 1.00 and 0.030 MoM in unaffected pregnancies.

The detection rates of the genetic sonogram alone, for a fixed 1–8% false-positive rate, were 39% (23/59), 49% (29/59), 59% (35/59), 66% (39/59), 69% (41/59), 75% (44/59), 80% (47/59), and 83% (49/59). The detection and false-positive rates for a 1 in 270 midtrimester risk cutoff were 83% (49/59) and 12% (922/7,783).
There was some evidence of biased interpretation of the genetic sonogram in the minor centers where the prior risk of Down syndrome was considerably increased. The overall LR was a little larger: a median of 0.36, compared with 0.30 in the major centers (P<.05). However, this did not seem to alter the results markedly. The false-positive rate was higher (23% compared with 12%), but this was largely due to more advanced maternal age, with medians of 34.8 and 31.7 years among unaffected pregnancies in the two groups, respectively. Moreover, the detection rate was lower (74% compared with 89%), although this was not statistically significant (P=.23).

Two-thirds of genetic sonograms (65%) were performed at 17–20 weeks of gestation, with 18% at 15–16 weeks and 17% at 21–23 weeks. The detection and false-positive rates for a 1 in 270 midtrimester risk cutoff were similar at the modal time (83% and 10%) to earlier or later (83% and 14%).

None of the seven Down syndrome screening markers were highly correlated with the overall LR from the genetic sonogram. In unaffected pregnancies, the r values ranged between −0.04 and 0.03; in Down syndrome pregnancies, the values were higher, ranging from −0.10 to 0.24, but did not reach statistical significance. Hence, any underlying associations are likely to be too small to invalidate the use of the overall LR to modify Down syndrome risk regardless of the screening marker profile.

Table 3 shows the detection rate for 5% false-positive rate for the five standard Down syndrome screening tests before and after the genetic sonogram. There was a 9–11% increase in detection for the first- and second-trimester tests, a 5% increase for the integrated test, and a 1–2% increase for the other sequential screening tests. The increases in detection after a genetic sonogram were statistically significant for the first- and second-trimester tests and the integrated test (P<.05, McNemar test, one-tailed). Table 3 also shows that the stepwise and contingent use of the genetic sonogram after first-trimester screening yielded the same detection rate as for routine use. However, the detection rates were lower than for standard stepwise and contingent tests that use the quadruple markers. Table 4 shows the detection and false-positive rates for all the screening options using a fixed 1 in 270 risk cutoff.

DISCUSSION

We have demonstrated in a large prospective study that the use of the genetic sonogram to modify Down syndrome risk after a second-trimester quadruple test can substantially increase the detection rate. Our analysis further establishes that the first-trimester combined test results can be substantially improved even when only women with borderline risks have the procedure. In contrast, the sequential screening results were only modestly improved with the addition of the genetic sonogram. Although Smith-Bindman et al1,7 have studied a large number of women who underwent genetic sonogram after being determined to be at high risk of aneuploidy after Down syndrome screening, our current study is the only large-scale prospective investigation that has directly compared the effect of using the genetic sonogram routinely after different Down syndrome screening tests.

Obstet Gynecol. Author manuscript; available in PMC 2016 April 07.
A clear limitation of our study is that only 28% of FASTER pregnancies in the 13 contributing centers had a genetic sonogram in that center; others would have had genetic sonograms elsewhere (non-FASTER site) or not at all. The incidence of Down syndrome in the overall FASTER cohort was 2.6 in 1,000. By comparison, in these centers contributing genetic sonography data, the Down syndrome incidence was 4.7 in 1,000. Although this raises the possibility of ascertainment bias in our study population, we believe that this is not likely to be significant for several reasons. First, we included all patients who remained at their FASTER site of enrollment for their antenatal care and received a genetic sonogram at that site. These were therefore unselected patients at each site, rather than patients specifically referred because of abnormal screening or sonographic abnormalities. Second, the genetic sonogram results in the study as a whole were largely uncorrelated with screening marker levels.

We have calculated risk using an overall LR obtained from the product of the individual LRs for the presence or absence of a serious abnormality and for each soft marker in turn. Another approach is to multiply the appropriate LR for abnormality by LRs corresponding to the number of soft markers observed. The LRs for zero, one, two, and three or more soft markers were 0.46, 3.1, 21, and 170. Using this method, the detection rate for a 5% false-positive rate was 63%, which is lower than the 69% we obtained using the LR product method for the same false-positive rate.

Some genetic sonogram studies have also provided LRs for the presence of each soft marker when it is an isolated finding. We do not advocate such an approach because even in the largest series the LR will necessarily be based on small numbers of cases. For example, in our study isolated echogenic bowel was found in only one Down syndrome and 28 unaffected pregnancies, so the observed LR of 4.7 is subject to considerable imprecision. The value obtained from Table 2 by multiplying LR+ for echogenic bowel and each LR− for the remaining markers is 10. This is a statistically more robust estimate for risk calculation.

Although the direct comparison between the five standard tests with and without the genetic sonogram is a simple means of assessing the gain in detection achieved by the sonogram, it does not provide a reliable estimate of detection rates for any of them. The rates are underestimated because some early detected cases, particularly those with cystic hygromas, were excluded. Conversely, there will be overestimation due to the viability bias inherent in intervention studies arising from the termination of nonviable Down syndrome pregnancies. Furthermore, any individual study of routine Down syndrome screening has insufficient statistical power to precisely estimate detection rates because of the relatively low incidence of the disorder. Our study included just 59 cases, and with these numbers, e.g., an observed 95% detection rate would have a 95% confidence interval of 86–99%.

Increased nuchal fold was the strongest soft marker studied. The FASTER trial was conducted in a period when the practice was to interpret nuchal fold dichotomously, with an increase defined against a fixed cutoff in millimeters. Subsequently, it has been shown that nuchal fold, like nuchal translucency, is best expressed in MoMs and LRs calculated continuously from a log gaussian distribution.14,15 Had the actual nuchal fold measurements...
been recorded in this study, it is likely that higher detection rates would have been demonstrated for policies using the genetic sonogram.

A major structural malformation was observed in 8.5% of Down syndrome pregnancies, a much lower rate than in other studies. This may be due to the diagnosis of such malformations earlier in pregnancy after the nuchal translucency scan performed in FASTER. For example, in the genetic sonogram study of Nyberg et al,\textsuperscript{2} the structural malformation rate was 17% (31/186), but half (16) had a cystic hygroma or hydrops, conditions likely to have been detected earlier in FASTER. Another reason for differences in the observed rate is the definition of a major malformation. For example, Bromley et al\textsuperscript{3} observed a rate of 27% (44/164), but one-third (16) had ventriculomegaly, which we define as a marker rather than a malformation.

It is usual practice to define echogenic bowel only when the echogenicity is as bright as adjacent bone. However, in our study we classified this as marked echogenic bowel and also recorded whether there was more moderate echogenicity. There was a highly statistically significantly association with Down syndrome for both marked and moderate echogenic bowel. Also, unexpectedly, the two LR\textsubscript{s} were almost identical, rather than that for marked echogenic bowel being greater than for moderate. One explanation is that sonographers had difficulty distinguishing the extent of brightness compared with bone, which is consistent with the reported frequency of these markers. Among unaffected pregnancies, 0.51% were reported as having either marked or moderate echogenic bowel, a similar frequency to that for echogenic bowel in three large studies combined: 0.57% (102/17,934).\textsuperscript{1,2,7} We therefore combined the markers when estimating Down syndrome risk.

We found little correlation between Down syndrome screening markers and the LR from the genetic sonogram. Because nuchal fold was a major contributor to LR, some degree of correlation with nuchal translucency might be expected. However, three studies have directly compared nuchal translucency and nuchal fold and found that they can be considered independent determinants of Down syndrome risk.\textsuperscript{16–18}

Two newer biometric markers of the fetal face, nasal bone length and prenasal translucency, not included in the study, have great potential in Down syndrome risk assessment. Statistical modeling indicated that they together with nuchal fold can achieve very high detection rates even when a full genetic sonogram is not performed.\textsuperscript{19,20} A third new facial marker, frontal maxillary angle,\textsuperscript{21} may improve this further.

Other authors have provided estimates of detection and false-positive rates with incorporation of genetic sonogram by statistical modeling using data from published studies to model the effectiveness of second-trimester sonography. Krantz et al\textsuperscript{22} performed statistical modeling to predict the effect of stepwise sequential and contingent use of the genetic sonogram after a combined test. There was a predicted 6% increase in detection with a 1.2% increased false-positive rate for the stepwise policy and 5% and 0.7%, respectively, for the contingent approach. We found a smaller 2% increase in detection for both policies but a reduction in the false-positive rate. Benn and Egan\textsuperscript{23} used modeling to predict the use of the genetic sonogram in combination with second-trimester triple and quadruple tests.
They predicted an increase in the detection rate for a 5% false-positive rate by 5% and 4% for the two tests, respectively. This is a much smaller gain for the quadruple test than the 11% we observed. Finally, Weisz et al.\textsuperscript{24} conducted a small prospective study of the integrated test followed by the genetic sonogram. There were 2,332 screened pregnancies, including 12 with Down syndrome. The use of LRs from the genetic sonogram reduced the detection rate by 8% and the false-positive rate by 0.7–1.2%, depending on the risk cutoff. We found an increased detection rate for this test and an even greater reduction in the false-positive rate.

Although practitioners and patients may wish to use data derived from studies such as ours to provide threshold values where invasive testing may be warranted, we would caution against use of our data in such a manner. Decisions pertaining to further invasive testing are ultimately highly individualized and value laden. It is our desire that the LRs reported herein be used in guiding discussions among providers and patients to optimize individualized assessment of risk.

In conclusion, using our unique population of prospectively collected first- and second-trimester serum and sonographic screening data, we have demonstrated that genetic sonography can substantially increase the Down syndrome detection rates for the first-trimester combined and second-trimester quadruple tests. We have also shown more modest improvements in the detection rates for sequential tests when genetic sonography is added. These results support the continued use of genetic sonography in antenatal care with two provisos. First, the sonogram should be performed in centers with sufficient experience of the techniques. Second, the results of the sonogram should be used in combination with prior screening data to provide each patient with an individual risk assessment.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**References**


Table 1
Patient Characteristics According to Whether a Genetic Sonogram Was Performed in the Same Center

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Genetic Sonogram Performed in Same FASTER Center</th>
<th>Genetic Sonogram Not Performed in This FASTER Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age 35 y or older</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>Combined test risk 1 or more in 270</td>
<td>9.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Quadruple test risk 1 or more in 270</td>
<td>12</td>
<td>9.1</td>
</tr>
<tr>
<td>BMI 30 kg/m² or greater</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Smoker</td>
<td>3.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td>Hispanic</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>Black</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Asian</td>
<td>5.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Other</td>
<td>0.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

FASTER, First and Second Trimester Evaluation of Risk; BMI, body mass index.

Data are %.

*Obstet Gynecol.* Author manuscript; available in PMC 2016 April 07.
Table 2
Genetic Sonogram: Statistically Significant \(^*\) Associations With Down Syndrome

<table>
<thead>
<tr>
<th>Finding</th>
<th>Down Syndrome</th>
<th>Unaffected Pregnancies</th>
<th>LR(^+)</th>
<th>LR(^−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major malformation</td>
<td>5/59 (8.5%)</td>
<td>38/7,783 (0.49%)</td>
<td>17</td>
<td>0.92</td>
</tr>
<tr>
<td>Nuchal skinfold (6 mm or greater)</td>
<td>6/33 (18%)</td>
<td>24/6,473 (0.37%)</td>
<td>49</td>
<td>0.82</td>
</tr>
<tr>
<td>Femur length (less than 0.91 MoM)</td>
<td>16/56 (29%)</td>
<td>514/7,761 (6.6%)</td>
<td>4.6</td>
<td>0.73</td>
</tr>
<tr>
<td>Humerus length (less than 0.89 MoM)</td>
<td>3/26 (12%)</td>
<td>89/3,840 (2.3%)</td>
<td>5.0</td>
<td>0.90</td>
</tr>
<tr>
<td>Echogenic intracardiac focus (either ventricle)</td>
<td>15/53 (28%)</td>
<td>345/7,725 (4.5%)</td>
<td>6.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Pyelectasis (3 mm or greater)</td>
<td>4/55 (7.3%)</td>
<td>103/7,777 (1.3%)</td>
<td>5.5</td>
<td>0.94</td>
</tr>
<tr>
<td>Marked echogenic bowel (bright as bone)</td>
<td>2/55 (3.6%)</td>
<td>12/7,778 (0.15%)</td>
<td>24(^†)</td>
<td>0.96(^†)</td>
</tr>
<tr>
<td>Moderate echogenic bowel</td>
<td>6/55 (11%)</td>
<td>28/7,777 (0.36%)</td>
<td>30(^†)</td>
<td>0.89(^†)</td>
</tr>
<tr>
<td>Ventriculomegaly (10 mm or greater)</td>
<td>3/54 (5.6%)</td>
<td>17/7,767 (0.22%)</td>
<td>25</td>
<td>0.95</td>
</tr>
<tr>
<td>No markers present(^‡)</td>
<td>21/59 (36%)</td>
<td>6,775/7,783 (87%)</td>
<td>—</td>
<td>0.41</td>
</tr>
</tbody>
</table>

LR, likelihood ratio; MoM, multiples of the median.

\(^*\) \(P<.005\), \(\chi^2\) test.

\(^†\) For either marked or moderate echogenic bowel, LR\(^+\) is 28 and LR\(^−\) is 0.86.

\(^‡\) Excluding humerus length.
Table 3
Detection Rate for a 5% False-Positive Rate With Standard Screening Policies and With Risk Modified by Genetic Sonogram Result

<table>
<thead>
<tr>
<th>Policy</th>
<th>Standard</th>
<th>After Sonogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>81</td>
<td>90*</td>
</tr>
<tr>
<td>Quadruple</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>Integrated</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>Stepwise</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Contingent</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>Stepwise sonogram†</td>
<td>—</td>
<td>90</td>
</tr>
<tr>
<td>Contingent sonogram†</td>
<td>—</td>
<td>90</td>
</tr>
</tbody>
</table>

Data are %.

* Not interpreting the test until the sonogram is complete.
† Replacing the second-stage quadruple markers with the sonogram.
### Table 4
Detection and False-Positive Rate for Standard Screening Policies and With Risk Modified by Genetic Sonogram Result

<table>
<thead>
<tr>
<th>Policy*</th>
<th>Standard Detection Rate</th>
<th>Standard False-Positive Rate</th>
<th>After Sonogram Detection Rate</th>
<th>After Sonogram False-Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>88</td>
<td>8.7</td>
<td>95†</td>
<td>6.2†</td>
</tr>
<tr>
<td>Quadruple</td>
<td>86</td>
<td>12</td>
<td>93</td>
<td>7.4</td>
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<tr>
<td>Integrated</td>
<td>93</td>
<td>7.1</td>
<td>98</td>
<td>5.2</td>
</tr>
<tr>
<td>Stepwise</td>
<td>97</td>
<td>7.2</td>
<td>98</td>
<td>5.6</td>
</tr>
<tr>
<td>Contingent</td>
<td>95</td>
<td>6.6</td>
<td>97</td>
<td>5.0</td>
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<tr>
<td>Stepwise sonogram‡</td>
<td>—</td>
<td>—</td>
<td>95</td>
<td>6.2</td>
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<tr>
<td>Contingent sonogram‡</td>
<td>—</td>
<td>—</td>
<td>93</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Data are %.

* Cutoff based on midtrimester risk: 1 in 270 for final results, 1 in 30 and 1 in 1,500 for the first-stage high and low cutoffs in contingent and stepwise policies.

† Not interpreting the test until the sonogram is complete.

‡ Replacing the second-stage quadruple markers with the sonogram.

*Obstet Gynecol. Author manuscript; available in PMC 2016 April 07.*