Comparing Three Screening Strategies for Combining First- and Second-Trimester Down Syndrome Markers

Glenn E. Palomaki, Klaus Steinort, George J. Knight, PhD, and James E. Haddow, MD

OBJECTIVE: To describe the choices and tradeoffs inherent in 3 published strategies that combine first- and second-trimester markers for Down syndrome screening.

METHODS: Published marker distributions for Down syndrome and unaffected pregnancies in the first and second trimesters were combined with a maternal age distribution and age-associated Down syndrome risk in a statistical model to compare sequential, contingent, and integrated screening.

RESULTS: Sequential and contingent screening strategies are always less efficient (higher false-positive rate for a given detection rate) than integrated screening, but the reduction in efficiency is dependent on the combination of risk cutoffs chosen. At a fixed false-positive rate, sequential and contingent strategies perform better when a higher proportion of the false positives occur in the second trimester. For all 3 strategies, increasing the overall false-positive rate from 2% to 5% increases detection (from approximately 85% to 91%). Although associated with reduced screening efficiency compared with integrated screening, both sequential and contingent screening identify the majority of detected Down syndrome cases early. With contingent screening, the process is also completed in the first trimester for most women.

CONCLUSION: Integrated screening is the most efficient of the 3 strategies, but it is possible to select risk cutoffs for both sequential and contingent strategies that minimize losses in efficiency while maintaining early detection and early completion. For all of these strategies, well-designed intervention trials are needed to determine acceptability to women and providers in primary care settings and to assess real-world performance.
(Obstet Gynecol 2006;107:367–75)

LEVEL OF EVIDENCE: III

Prenatal screening for Down syndrome has improved considerably in the past 2 decades. Currently, screening is most commonly performed by using maternal age in combination with second-trimester maternal serum markers[1,2] unconjugated estriol (uE3),[3] human chorionic gonadotropin (hCG),[4] and, in some programs, dimeric inhibin-A.[5] More recently, maternal serum markers in the first trimester (pregnancy-associated plasma protein-A [PAPP-A] and hCG or its free β subunit)[6,7] have been found useful, along with ultrasound measurements of nuchal translucency thickness.[8] These first-trimester markers are now available on a limited basis at referral centers. Although there are clinical and programmatic advantages to screening in either the first or the second trimesters, the concept of combining markers from both trimesters into a single integrated interpretation provides the most accurate estimate of Down syndrome risk yet available.[9] However, the potential advantages obtained from a first-trimester diagnosis have led to a search for screening strategies that combine the high performance of integrated screening with the first-trimester detection of a high proportion of Down syndrome pregnancies.[10]

The current report focuses on the performance of 3 screening strategies: integrated screening, sequential screening, and contingent screening. All 3 strategies include nuchal translucency measurements. Integrated screening holds the first-trimester information until the second-trimester results are also available. A single risk is then provided to the woman, and a single-risk cutoff level is used to define screen-positive

From the Division of Medical Screening, Department of Pathology and Laboratory Medicine, Women & Infants Hospital, Providence, Rhode Island; and Electric Dreams, Scarborough, Maine.

Partial support for this project was provided by Genzyme Genetics, Santa Fe, New Mexico.

Corresponding author: Glenn E. Palomaki, BS, Division of Medical Screening, Women & Infants Hospital, Providence, RI 02903; e-mail: gpalomaki@ipmms.org.

ISSN: 0029-7844/05

results (eg, ≥ 1:200). Sequential screening initially offers counseling and diagnostic testing to all women with a first-trimester risk at or above an initial risk cutoff level (eg, ≥ 1:50), with the remaining women having a quadruple test (alpha-fetoprotein [AFP], uE3, hCG, and dimeric inhibin-A) in the second trimester with an "integrated" interpretation using information from both trimesters. Those with a Down syndrome risk above a final second-trimester risk cutoff level (eg, ≥ 1:270) are also offered counseling and second-trimester diagnostic testing. Contingent screening differs from sequential screening by having not only a high-risk, but also a low-risk, cutoff level defined in the first trimester (eg, ≥ 1:50 and < 1:1,500). Women with Down syndrome risks below this cutoff level are informed that they do not require further testing because they are unlikely to become screen-positive.

Given that integrated screening uses all informative markers before assigning a risk and determining who should be offered diagnostic testing, the other 2 strategies will, of necessity, be less efficient, as defined by detection and false-positive rates. This is because both sequential and contingent screening assign an interim risk and make the offer of diagnostic testing in the first trimester based on only a subset of informative markers. Thus, the early detection of some affected pregnancies and the reduced need for second-trimester screening (contingent testing) must logically be "paid for" by having less efficient screening.

MATERIALS AND METHODS

The parameters and truncation limits necessary for modeling are taken from the Serum, Urine, and Ultrasound Screening Study (SURUSS).[11,12] These data were derived from pregnancies (both Down syndrome and unaffected) that were still viable in the second trimester and include the logarithmic means, standard deviations, pair-wise correlation coefficients, and truncation limits. Our modeling assumes a fixed number of second-trimester Down syndrome cases that may be detected (or missed) in either the first or second trimester. If a case is detected in the first trimester, it is not eligible for detection in the second trimester. All of the marker parameters vary between 11 and 13 weeks of gestation, and this report uses the parameters at 12 weeks of gestation as a compromise. The maternal age distribution is that for the United States in 2000, where the median age is 27 years and 13% of the women are age 35 years or older.[13] The age-specific term risk for Down syndrome is based on a published equation.[14] The assigned Down syndrome risks and risk cutoff levels have been adjusted for an estimated 43% spontaneous loss in Down syndrome pregnancies between the late first trimester and term and a 23% loss between the early second trimester and term.[15]

The modeling program relies on Monte Carlo simulation to generate maternal age and the associated 7 markers (PAPP-A, hCG, and nuchal translucency in the first trimester, and AFP, uE3, hCG, and dimeric inhibin-A in the second trimester) for over a million hypothetical cases of Down syndrome and for the same number of unaffected pregnancies. These data are drawn from a 7-dimensional Gaussian distribution defined by published parameters.[11,12] For each of the hypothetical pregnancies, 2 risks are assigned: 1) a first-trimester risk based on maternal age and first-trimester measurements of nuchal translucency, PAPP-A, and hCG, and 2) a second trimester integrated risk based on maternal age, first-trimester measurements of nuchal translucency, and PAPP-A, and second-trimester measurements of AFP, uE3, hCG, and dimeric inhibin-A. Among the group of unaffected pregnancies, false-positive rates are computed in the first trimester using cutoff levels associated with specific false-positive rates (eg, 1%, 2%, 3%). The second-trimester false-positive rates are also set to specific levels and computed so that the 2 rates can be directly added together to obtain the overall false-positive rate. Among the group of Down syndrome pregnancies, the detection rate is computed for those detected in the first trimester, those negative in the first trimester but detected in the second trimester, and the overall rate for those detected in the first or second trimester. These detection rates are computed using the risk cutoff levels chosen earlier to attain selected false-positive rates. The basic modeling program has been used in earlier publications[5,16] and is validated by comparing the results to other independent models whose performance estimates have been reported in the literature. We have assumed complete adherence to all protocols as part of the modeling (ie, no women drop out, all women with a positive first-trimester test undergo diagnostic testing, and no women classified as having a high first-trimester risk requests second-trimester testing). This study received review exemption from the Institutional Review Board of Women & Infants Hospital.

RESULTS

Figure 1 shows a schematic representation of sequential screening in a hypothetical cohort of 600,000 women. Initially, the pregnancies are stratified into the 1,000 women with a Down syndrome pregnancy along with the 599,000 women with unaffected pregnancies (step 1). In the first trimester, all 600,000

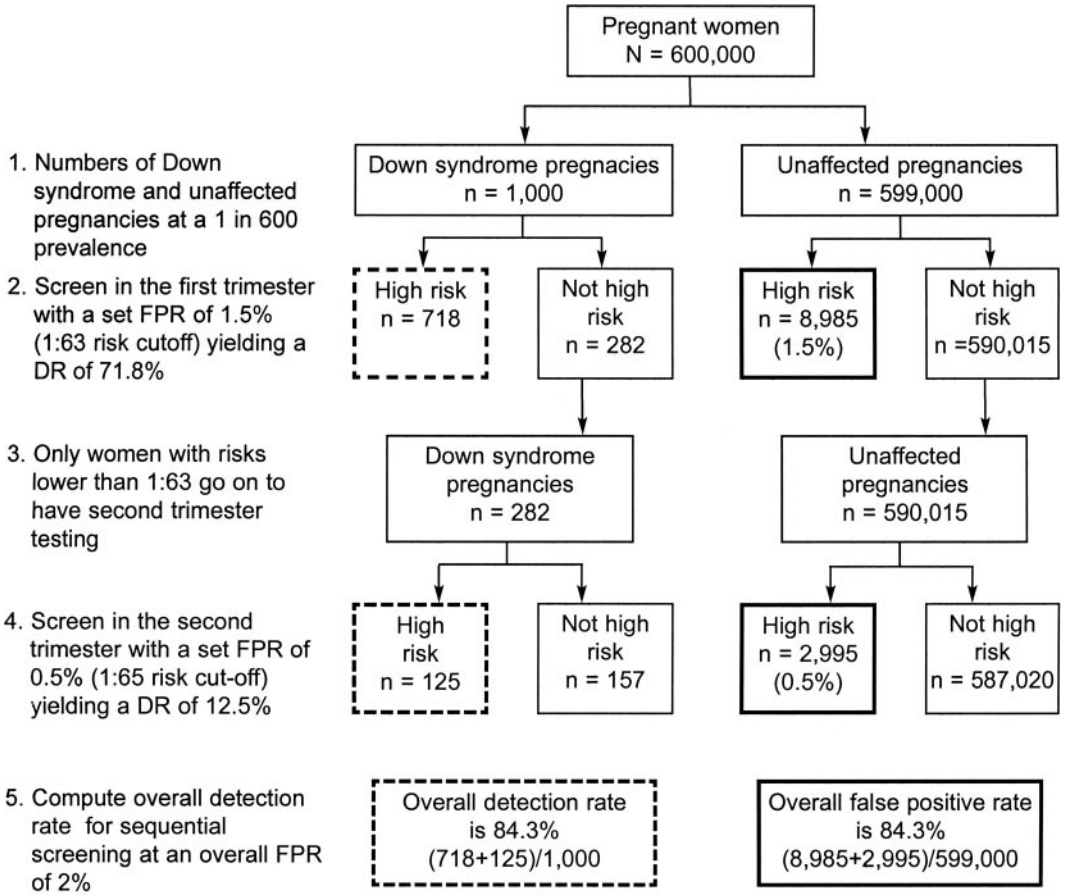

Fig. 1. A schematic flow diagram showing an example of the testing pathway for the sequential screening strategy for Down syndrome in a hypothetical cohort of 600,000 pregnant women. The diagram is read from top to bottom and shows what testing is offered, and to whom, in the first and second trimester. The text on the left side describes each step. The upper two dashed boxes are used to compute the detection rate in the lower dashed box. The upper two bolded boxes are used to compute the false-positive rate in the lower bolded box. DR, detection rate; FPR, false-positive rate.

Palomaki. Comparing Down Syndrome Screening Strategies. Obstet Gynecol 2006.

women undergo testing at 12 weeks of gestation and are provided a first-trimester Down syndrome risk based on maternal age, nuchal translucency measurements, and serum measurements of PAPP-A and hCG. In this example, we have chosen to examine screening performance when the overall false-positive rate is 2.0% (1.5% in the first trimester and 0.5% in the second trimester). Based on modeling, 1.5% of the 599,000 women with unaffected pregnancies will have first-trimester interim risks of 1:63 or higher. Using the 1:63 risk as a cutoff level, the associated detection rate is 71.8% (718 of the 1,000 Down syndrome pregnancies) (step 2). The remaining 282 Down syndrome pregnancies and 590,015 unaffected pregnancies will undergo additional screening in the second trimester (step 3). A new serum sample is obtained for quadruple testing and the results combined with the first-trimester nuchal translucency and PAPP-A measurements to provide a second-trimester integrated risk. Step 4 shows that 0.5% of women with unaffected pregnancies have an integrated risk of 1:65 or higher, along with 12.5% of all Down syndrome pregnancies. Step 5 shows that the overall detection rate is 84.3% (71.8% + 12.5%) at the predetermined overall false-positive rate of 2.0% (1.5% + 0.5%). As a comparison, integrated screening would require fewer false positives (using a second-trimester integrated risk cutoff of 1:100) to detect the same 84.3% of Down syndrome pregnancies: 7,188 women (1.2%) rather than the 11,980 women (2%) shown in Figure 1. The 4,792 fewer women undergoing amniocentesis represent a 0.8% reduction in absolute terms and a 40% reduction in relative terms. This reduction in the false-positive rate translates into 24 fewer unaffected pregnancies lost due to procedure-related complications (using a loss rate of 1:200).

Table 1, row 2 (bolded entries), provides a summary of the computations shown in Figure 1. The overall false-positive rate (2%) and associated detection rate (84.3%) are shown in the first 2 columns. The next 6 columns contain the corresponding Down syndrome risk cutoff levels, along with false-positive and detection rates for the first trimester (1:63, 1.5%, 71.8%, respectively) and the second trimester (1:65, 0.5%, 12.5%, respectively). The last 4 columns show the integrated risk cutoff level and false-positive rate (1:100, 1.2%, respectively) that will be associated with the same detection rate found for sequential screening (84.3%), along with the reduction in the false-positive rate achieved by integrated screening. The reduction is shown in both absolute (0.8%) and relative (40%) terms.

The first group of 5 risk cutoff combinations (rows 1 through 5) in Table 1 shows the same information for other combinations of first- and second-trimester false-positive rates that add up to 2%. The first row uses all 2% of the allowed false positives in the first trimester; no women would be tested in the second trimester (indicated by the lack of a risk cutoff and by having the detection and false-positive rates set to zero). In this row, the last 4 entries provide a lower limit to sequential screening performance and can be viewed as a comparison of stand-alone first-trimester screening versus integrated screening. In the last row

Table 1. Comparison of Sequential and Integrated Screening at Fixed False-Positive Rates in the General Population of Pregnant Women

Sequential Screening								Integrated Screening*			
Overall		1st-Trimester Interpretation†			2nd-Trimester Interpretation‡			@ DR (c + d)		FPR Reduction (%)§	
FPR (a + b)	DR (c + d)	Cutoff	FPR (a)	DR (c)	Cutoff	FPR (b)	DR (d)	Cutoff	FPR	Absolute	Relative
2	74.5	1:81	2	74.5	None	0	0	1:25	0.3	1.7	85
2	**84.3**	**1:63**	**1.5**	**71.8**	**1:65**	**0.5**	**12.5**	**1:100**	**1.2**	**0.8**	**40**
2	86.1	1:41	1	67.7	1:110	1	18.4	1:135	1.6	0.4	20
2	87.0	1:22	0.5	60.8	1:145	1.5	26.2	1:160	1.9	0.1	5
2	87.4	None	0	0	1:170	2	87.4	1:170	2.0	0.0	0
3	78.3	1:121	3	78.3	None	0	0	1: 40	0.5	2.5	83
3	86.2	1:100	2.5	76.7	1:5	0.5	9.5	1:135	1.6	1.4	47
3	87.8	1:81	2	74.5	1:130	1	13.3	1:180	2.1	0.9	30
3	88.6	1:63	1.5	71.8	1:175	1.5	16.8	1:210	2.4	0.6	20
3	89.2	1:41	1	67.7	1:210	2	21.5	1:240	2.7	0.3	10
3	89.8	None	0	0	1:270	3	89.2	1:270	3.0	0.0	0
4	81.0	1:168	4	81.0	None	0	0	1:60	0.8	3.2	80
4	89.0	1:121	3	78.3	1:145	1	10.7	1:230	2.6	1.4	35
4	90.3	1:81	2	74.5	1:245	2	15.8	1:300	3.3	0.7	17
4	91.1	1:41	1	67.7	1:330	3	23.4	1:355	3.8	0.2	5
4	91.4	None	0	0	1:380	4	91.4	1:380	4.0	0.0	0
5	83.0	1:205	5	83.0	None	0	0	1:80	1.0	4.0	80
5	89.9	1:168	4	81.0	1:165	1	8.9	1:275	3.1	1.9	38
5	91.2	1:121	3	78.3	1:275	2	12.9	1:365	3.9	1.1	22
5	91.9	1:81	2	74.5	1:370	3	17.4	1:425	4.4	0.6	12
5	92.3	1:41	1	67.7	1:450	4	24.6	1:470	4.8	0.2	4
5	92.5	None	0	0	1:495	5	92.5	1:495	5.0	0.0	0

FPR, false positive rate; DR, detection rate; @ DR (c + d), the performance of integrated screening at the same DR shown for sequential screening.

The bolded row contains the information derived in Figure 1. Cutoff indicates the Down syndrome risk level (specific to the trimester of interpretation) used for determining screen-positive status.

* The FPR and cutoff are set so that the detection rate for full integrated screening is equivalent to that found overall for sequential screening, (column 2).

† First-trimester Down syndrome risk generated using maternal age in combination with nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), and human chorionic gonadotropin (hCG). Those women with risks at or above the cutoff level (positive) would be offered diagnostic testing and not tested in the second trimester.

‡ Among those women with "negative" first-trimester risks, an integrated second-trimester risk based on maternal age in combination with first-trimester nuchal translucency and PAPP-A, and second-trimester alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and dimeric inhibin-A (DIA).

§ The absolute reduction is the integrated FPR–the overall sequential FPR (column 1). The relative reduction is the absolute reduction divided by the overall sequential FPR × 100.

of the group, no women are identified as being screen positive in the first trimester. This row provides an upper limit to sequential screening performance at an overall 2% false-positive rate and corresponds to integrated screening. The 3 middle rows provide intermediate combinations between the upper and lower limits. Based on the last 2 columns that compare sequential and integrated performance, the lower the first-trimester false-positive rate, the closer the performance is to integrated screening. Using a high first-trimester risk cutoff of 1:22 (row 4), 60.8% of Down syndrome pregnancies can be identified early, with a 0.5% false-positive rate. This sequential screening protocol is nearly as efficient as integrated screening, which yields an absolute reduction of 0.1% (relative reduction of 5%).

The remainder of Table 1 shows similar patterns with higher overall detection rates, as the overall false-positive rates increase from 3% to 5%. As expected, at each of the 4 false-positive rates, and for all combinations of sequential risk cutoff levels, sequential screening is associated with higher false-positive rates than integrated screening (at the same detection rate). The difference is smallest when the overall false-positive rates are high (ie, 5%), and when fewer of the positive results occur in the first trimester. At an overall 4% false-positive rate, for example, one combination of sequential cutoff levels (1:41 in the first and 1:330 in the second trimester) yields false-positive rates of 1% and 3% and is associated with a detection rate of 91.1%. Performing integrated screening at the same detection rate is only slightly more efficient, with an absolute reduction in the false-positive rate of 0.2% (a 5% relative reduction). Using such a combination would identify 67.7% of the Down syndrome pregnancies in the first trimester. Increasing the false-positive rate from 2% to 5% is associated with increases in detection from about 85% to 91%, a 6% absolute increase in detection. Alternatively, this can be viewed as the proportion of false-negative results being reduced from 15% to 9%.

Table 2 is constructed similarly to Table 1 but shows a comparison between contingent and integrated screening. The table entries are computed

Table 2. Comparison of Contingent Screening With Integrated Screening at Fixed False-Positive Rates Using a First-Trimester Low-Risk Cutoff Level of 1:1,500

Contingent Screening*								Integrated Screening†			
Overall		1st-Trimester Interpretation‡			2nd-Trimester Interpretation§			@ DR (c + d)		FPR Reduction (%)‖	
FPR (a + b)	DR (c + d)	Cutoff	FPR (a)	DR (c)	Cutoff	FPR (b)	DR (d)	Cutoff	FPR	Absolute	Relative
2	84.1	1:63	1.5	71.8	1:70	0.5	12.3	1:95	1.2	0.8	40
2	85.8	1:41	1	67.7	1:120	1	18.1	1:130	1.6	0.4	20
2	86.6	1:22	0.5	60.8	1:160	1.5	25.8	1:150	1.9	0.1	5
3	87.3	1:81	2	74.5	1:145	1	12.8	1:170	2.0	1.0	33
3	88.1	1:63	1.5	71.8	1:200	1.5	16.3	1:195	2.3	0.7	23
3	88.7	1:41	1	67.7	1:250	2	21.0	1:215	2.5	0.5	17
4	89.8	1:81	2	74.5	1:295	2	15.3	1:270	3.0	1.0	25
4	90.3	1:41	1	67.7	1:405	3	22.6	1:300	3.3	0.7	17
5	89.5	1:168	4	81.0	1:195	1	8.5	1:250	2.8	2.1	42
5	90.5	1:121	3	78.3	1:345	2	12.2	1:310	3.4	1.6	32
5	91.1	1:81	2	74.5	1:480	3	16.6	1:355	3.8	1.2	24
5	91.5	1:41	1	67.7	1:595	4	23.9	1:390	4.1	0.9	18

FPR, false-positive rate; DR, detection rate; @ DR (c + d), the performance of integrated screening at the same DR shown for sequential screening.

* Using a first-trimester low risk cut-off level of 1:1500, 5% of Down syndrome and 76% of unaffected pregnancies have risks less than this level, and testing is completed in the first trimester. No offer of second-trimester testing is made. Cutoff indicates the Down syndrome risk level (specific to the trimester of interpretation) used for determining screen-positive status.

† The FPR and cutoff are set so that the detection rate for full integrated screening is equivalent to that found overall for contingent screening (column 2).

‡ First-trimester Down syndrome risk generated using maternal age in combination with nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), and human chorionic gonadotropin (hCG). Those women with risks at or above the cutoff level (positive) would be offered diagnostic testing and not tested in the second trimester.

§ Among those women with risks between the first-trimester risk cutoff level and 1:1,500, an integrated second-trimester risk based on maternal age in combination with first-trimester NT and PAPP-A, and second-trimester alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and dimeric inhibin-A (DIA).

‖ The absolute reduction is the integrated FPR–the overall contingent FPR (column 1). The relative reduction is the absolute reduction divided by the overall contingent FPR × 100.

assuming that women with a first-trimester risk of 1:1,500 or lower are not tested in the second trimester. This low risk group includes 76% of unaffected pregnancies, as well as 5% of all Down syndrome pregnancies. For these women, screening is considered to be complete in the first trimester. The risk cutoff of 1:1500 is arbitrary and is chosen with the thought that women with low risks in the first trimester are unlikely to be screen-positive if testing were to be performed in the second trimester. For each of the false-positive rate groups in Table 2, there are no rows showing the results of screening in only one trimester because they are no longer appropriate for comparison. The first 2 columns provide the overall detection rates for contingent screening at the same 4 overall false-positive rates. The next 3 columns summarizing the first-trimester screening performance are unchanged from Table 1 because at this point there is no difference in performance between sequential and contingent screening. The next 3 columns summarizing second trimester performance are slightly different from Table 1 because nearly three fourths of the unaffected pregnancies and 5% of the Down syndrome pregnancies are not considered for second-trimester testing because their first-trimester interim risks were 1:1500 or lower. The overall detection rate for contingent screening is slightly lower because a small proportion of the Down syndrome pregnancies in the low-risk group would have been detected if they had gone on for second-trimester testing. As a consequence, integrated screening can match the contingent detection rate at an even lower false-positive rate than was found for sequential screening. At an overall 4% false-positive rate, the middle row of Table 2 can be compared with the corresponding row from Table 1. The last 2 columns indicate that, when integrated screening is compared with contingent screening (Table 2), the reduction in the false-positive rate is 1.0% (relative reduction of 25%). When sequential screening is compared in the same way (Table 1), the reduction is 0.7% (relative reduction of 17%). The tradeoff in the false-positive rate for contingent screening is that three fourths of the women have completed testing in the first trimester.

Table 3 also shows a comparison between contingent and integrated screening, but the low-risk cutoff level in the first trimester is set to 1:3,250. Included in this low-risk group are 2.5% of all Down syndrome pregnancies and 60% of unaffected pregnancies. Because of this lower-risk cutoff level, the performance of contingent screening in Table 3 is closer to integrated screening than the contingent example shown in Table 2.

DISCUSSION

To confirm the accuracy of our modeling, we compared detection and false-positive rates at selected risk cutoff levels with the results of the SURUSS study.[11] Minor differences in screening performance might be due to the inclusion of hCG rather than the free β subunit, as well as to slight differences in the underlying maternal age distribution and the use of a priori risk equations that differ somewhat in the small proportion of women over age 45.[14,17] In spite of these factors, our detection and false-positive rates for integrated screening are nearly identical to those reported in SURUSS[11] and provide support that the analytic methodology is correct. Our modeling does not include replacing hCG measurements with the free β subunit of hCG. Screening strategies that include this measurement might have slightly different individual estimates of screening performance, but the overall trends and conclusions will be the same. We also did not compare marker combinations that include measurements of both hCG and the free β subunit in different trimesters. When strategies are being compared, markers used in the various combinations need to be held constant.

Choosing a screening strategy for Down syndrome is complicated by the need to consider ancillary issues, such as timing and availability of diagnostic tests, adherence to risk cutoff levels, concern about holding first-trimester test results until the second trimester to improve efficiency, acceptability of a given strategy to women and health providers, financial costs, medical costs, and second-trimester serum testing for open neural tube defects.

Proponents of reporting first-trimester screening results[8,18–20] (including stand-alone first-trimester, sequential, and contingent screening strategies) argue that women desire an earlier diagnosis because of social considerations, along with safer and less-invasive first-trimester termination. Two studies indicate that women prefer testing in the first trimester.[21,22] However, the women in these studies were not made aware that a first-trimester test is less efficient than integrated testing. One study from the United Kingdom found that health care professionals were more likely than pregnant women to favor earlier testing for Down syndrome.[23] The authors believed that this attitude could favor the adoption of earlier screening tests compared with tests with lower miscarriage rates and higher detection rates that might be performed later in pregnancy. In one first-trimester intervention study from chorionic villus sampling (CVS) centers in the United States, it was possible to determine

whether women diagnosed early had a first-trimester termination. In that study, 25 of the 40 women (63%) choosing termination of a Down syndrome pregnancy did not do so until the second trimester,[20] thereby negating one of the perceived advantages of first-trimester interpretations. This would argue that the additional information available from second-trimester serum testing should be included as part of the risk assessment provided to these women.

Most intervention trials have used risk cutoff levels roughly equal to the risk of 35-year-old women (1:270 in the second trimester). Even though some reports of intervention trials have included the use of second-trimester risk cutoff levels of 1:190 or even 1:100,[24,25] there is little or no documentation of women's behavior when their risks are high, but not high enough to be considered screen-positive (eg, 1:50). One report suggests offering CVS only to women with a first-trimester risk of 1:7.8 or higher.[10] Women with risks of 1:10 or 1:20 would be asked to wait until the second trimester to receive more accurate risks. Many of these women with borderline interim risks (or their physicians) might request diagnostic testing, and the predicted screening performance would not be achieved. For this reason, it would be important to subject strategies with high-risk cutoff levels to intervention trials before introducing them into routine practice. Neither contingent nor sequential screening have yet been formally tested in real world settings.

One way to improve adherence to protocols and avoid confusion would be to not report the interim risks for women whose risks fall below the first-trimester cutoff level. They would receive only the integrated risk in the second trimester. It is difficult to "take back" an initial risk estimate. If sequential screening were to be viewed as integrated screening, with the exception that about 2% of women are reported as high risk in the first trimester, then not reporting the risks in the remaining women until all information is available in the second trimester would

Table 3. Comparison of Contingent Screening With Integrated Screening at Fixed False-Positive Rates Using a First-Trimester Low-Risk Cutoff Level of 1:3,250

Contingent Screening*								Full Integrated Screening†			
Overall		1st-Trimester Interpretation‡			2nd-Trimester Interpretation§			@ DR (c + d)		FPR Reduction (%)‖	
FPR (a + b)	DR (c + d)	Cutoff	FPR (a)	DR (c)	Cutoff	FPR (b)	DR (d)	Cutoff	FPR	Absolute	Relative
2	84.2	1:63	1.5	71.8	1:65	0.5	12.4	1:98	1.2	0.8	40
2	85.9	1:41	1	67.7	1:110	1	18.2	1:130	1.6	0.4	20
2	86.9	1:22	0.5	60.8	1:150	1.5	26.1	1:155	1.8	0.2	5
3	86.3	1:100	2.5	76.7	1:80	0.5	9.6	1:140	1.7	1.3	43
3	87.6	1:81	2	74.5	1:130	1	13.1	1:180	2.1	0.9	30
3	88.4	1:63	1.5	71.8	1:180	1.5	16.6	1:205	2.4	0.6	20
3	89.1	1:41	1	67.7	1:225	2	21.4	1:235	2.7	0.3	10
4	88.8	1:121	3	78.3	1:150	1	10.5	1:220	2.5	1.5	37
4	90.2	1:81	2	74.5	1:260	2	15.7	1:290	3.2	0.8	20
4	90.9	1:41	1	67.7	1:350	3	23.2	1:340	3.7	0.3	7
5	89.8	1:168	4	81.0	1:170	1	8.8	1:270	3.0	2.0	40
5	91.0	1:121	3	78.3	1:295	2	12.7	1:350	3.8	1.2	25
5	91.7	1:81	2	74.5	1:400	3	17.2	1:410	4.3	0.7	14
5	92.1	1:41	1	67.7	1:490	4	24.4	1:450	4.6	0.4	8

FPR, false-positive rate; DR, detection rate; @ DR (c + d), the performance of integrated screening at the same DR shown for sequential screening.

* Using a first-trimester low-risk cutoff level of 1:3,250, 2.5% of Down syndrome and 60% of unaffected pregnancies have risks less than this level, and testing is completed in the first trimester. No offer of second trimester testing is made. Cutoff indicates the Down syndrome risk level (specific to the trimester of interpretation) used for determining screen-positive status.

† The FPR and cutoff are set so that the detection rate for full integrated screening is equivalent to that found overall for contingent screening (column 2).

‡ First-trimester Down syndrome risk generated using maternal age in combination with nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), and human chorionic gonadotropin (hCG). Those women with risks at or above the cutoff level (positive) would be offered diagnostic testing and not tested in the second trimester.

§ Among those women with risks between the first-trimester risk cutoff level and 1:3,250, an integrated second-trimester risk based on maternal age in combination with first-trimester NT and PAPP-A, and second-trimester alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and dimeric inhibin-A (DIA).

‖ The absolute reduction is the integrated FPR–the overall contingent FPR (column 1). The relative reduction is the absolute reduction divided by the overall contingent FPR × 100.

be justifiable. However, if sequential screening were to be viewed as first-trimester screening that also includes a standard second-trimester quadruple test for those not initially screen-positive, then not reporting the risks in 98% of the women might not be justifiable. Integrated screening avoids these problems by providing only a single risk estimate when all information is available in the second trimester.

Reliable cost analyses in the context of the United States health care system will only be possible once intervention trials provide information about uptake rates, adherence to protocols, and patient decision making. Contingent screening might appear to be the least costly, because the costs of testing two thirds to three fourths of women in the second trimester would be avoided. However, the costs associated with even a small decrease in detection could offset much of these savings. Also, some women with negative first-trimester risks will opt for second-trimester serum testing for Down syndrome in conjunction with screening for open neural tube defects. Maternal serum AFP testing in the second trimester is likely to remain commonplace as a screening test for open neural tube defects and will need to be accounted for in cost analyses associated with contingent screening. It will also oblige the physician (and laboratory) to work harder to determine whether the appropriate test or sequence of tests has been ordered.

Medical costs, including the procedure-related loss of unaffected pregnancies, also need to be considered. One measure of medical costs is the number of Down syndrome cases detected for every procedure-related loss. The bolded second row of Table 1 shows one sequential protocol with an 84.3% detection rate. Assuming a second-trimester prevalence of 1:600, the ratio of Down syndrome cases detected per unaffected pregnancy lost is 14:1. However, that same detection rate can be achieved with integrated screening with a ratio of 23:1. If higher false-positive rates are chosen (ie, Table 1, second line of the 5% false-positive group) these ratios are less favorable at 6:1 and 9.5:1.

The following is an example of how the information in this paper might be used to derive an effective Down syndrome screening policy based on 1 of these 3 strategies. First, a policy group decides that contingent screening is impractical to implement (eg, multiple screening cutoff levels, open neural tube defect screening) and chooses a sequential strategy. A 90% detection rate is selected as a target, and it is decided that a second-trimester risk equivalent to a 35-year-old woman (1:270) should be maintained. The policy group judges that too high a first-trimester cutoff level (eg, 1:20) might result in low adherence to the protocol. Based on the data from Table 1, the group agrees to aim for an overall false-positive rate below 5% and for a false-positive rate in the second trimester that is 2 or 3 times higher than in the first trimester. Given these constraints, the closest set of risk cutoff levels in Table 1 is 1:41 and 1:330. The policy group chooses to use risk cutoff levels of 1:50 in the first trimester and 1:270 in the second trimester. Further modeling shows the corresponding overall detection and false-positive rates to be 90.4% and 3.7%, respectively. An estimated 69.7% of Down syndrome pregnancies will be identified in the first trimester with a 1.2% false-positive rate. At this same detection rate, integrated screening would require a false-positive rate of 3.3%, an absolute reduction of 0.4% (relative reduction of 11%).

Selecting and implementing a multistep screening strategy is a complicated decision-making process for laboratories, health care providers, and women. Before any strategy can be recommended or rejected, it is important to subject it to both statistical evaluations and to appropriately designed intervention trials. At that point, policy makers will have sufficient information to recommend a comprehensive program that will meet the needs of pregnant women while limiting the number of choices and tradeoffs that could occur if each laboratory/screening program were to make its own decisions.

REFERENCES

1. Merkatz IR, Nitowsky HM, Macri JN, Johnson WE. An association between low maternal serum alpha-fetoprotein and fetal chromosomal abnormalities. Am J Obstet Gynecol 1984; 148:886–94.
2. Combining maternal serum alpha-fetoprotein measurements and age to screen for Down syndrome in pregnant women under age 35. New England Regional Genetics Group Prenatal Collaborative Study of Down Syndrome Screening. Am J Obstet Gynecol 1989;160:575–81.
3. Canick JA, Knight GJ, Palomaki GE, Haddow JE, Cuckle HS, Wald NJ. Low second trimester maternal serum unconjugated oestriol in pregnancies with Down's syndrome. Br J Obstet Gynaecol 1988;95:330–3.
4. Wald NJ, Cuckle HS, Densem JW, Nanchahal K, Royston P, Chard T, et al. Maternal serum screening for Down's syndrome in early pregnancy [published erratum appears in BMJ 1988;297:1029]. BMJ 1988;297:883–7.
5. Haddow JE, Palomaki GE, Knight GJ, Foster DL, Neveux LM. Second trimester screening for Down's syndrome using maternal serum dimeric inhibin A. J Med Screen 1998;5:115–9.
6. Ozturk M, Milunsky A, Brambati B, Sachs ES, Miller SL, Wands JR. Abnormal maternal serum levels of human chorionic gonadotropin free subunits in trisomy 18. Am J Med Genet 1990;36:480–3.
7. Wald N, Stone R, Cuckle HS, Grudzinskas JG, Barkai G, Brambati B, et al. First trimester concentrations of pregnancy

associated plasma protein A and placental protein 14 in Down's syndrome. BMJ 1992;305:28.

8. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet 1998;352:343–6.
9. Wald NJ, Watt HC, Hackshaw AK. Integrated screening for Down's syndrome on the basis of tests performed during the first and second trimesters. N Engl J Med 1999;341:461–7.
10. Wright D, Bradbury I, Benn P, Cuckle H, Ritchie K. Contingent screening for Down syndrome is an efficient alternative to non-disclosure sequential screening. Prenat Diagn 2004;24: 762–6.
11. Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). J Med Screen 2003; 10:56–104.
12. Wald NJ, Rodeck C, Hackshaw AK, Rudnicka A. SURUSS in perspective. BJOG 2004;111:521–31.
13. National Center for Health Statistics. 2000 natality data set. Vital and health statistics, CD-ROM Series 21, No. 14. Hyattsville (MD): Department of Health and Human Services, Centers for Disease Control and Prevention; 2002.
14. Hecht CA, Hook EB. Rates of Down syndrome at livebirth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin: a proposed revised rate schedule for use in genetic and prenatal screening. Am J Med Genet 1996;62:376–85.
15. Morris JK, Wald NJ, Watt HC. Fetal loss in Down syndrome pregnancies. Prenat Diagn 1999;19:142–5.
16. Palomaki GE, Neveux LM, Knight GJ, Haddow JE, Pandian R. Maternal serum invasive trophoblast antigen (hyperglycosylated hCG) as a screening marker for Down syndrome during the second trimester. Clin Chem 2004;50:1804–8.
17. Morris JK, Mutton DE, Alberman E. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. J Med Screen 2002;9:2–6.
18. Copel JA, Bahado-Singh RO. Prenatal screening for Down's syndrome–a search for the family's values. N Engl J Med 1999;341:521–2.
19. Cuckle HS. Growing complexity in the choice of Down's syndrome screening policy. Ultrasound Obstet Gynecol 2002; 19:323–6.
20. Wapner R, Thom E, Simpson JL, Pergament E, Silver R, Filkins K, et al. First-trimester screening for trisomies 21 and 18. N Engl J Med 2003;349:1405–13.
21. Kornman LH, Wortelboer MJ, Beekhuis JR, Morssink LP, Mantingh A. Women's opinions and the implications of first- versus second-trimester screening for fetal Down's syndrome. Prenat Diagn 1997;17:1011–8.
22. Mulvey S, Wallace EM. Women's knowledge of and attitudes to first and second trimester screening for Down's syndrome. BJOG 2000;107:1302–5.
23. Bishop AJ, Marteau TM, Armstrong D, Chitty LS, Longworth L, Buxton MJ, et al. Women and health care professionals' preferences for Down's Syndrome screening tests: a conjoint analysis study. BJOG 2004;111:775–9.
24. Haddow JE, Palomaki GE, Knight GJ, Williams J, Pulkkinen A, Canick JA, et al. Prenatal screening for Down's syndrome with use of maternal serum markers. N Engl J Med 1992;327: 588–93.
25. Palomaki GE, Kloza EM, Haddow JE, Williams J, Knight GJ. Patient and health professional acceptance of integrated serum screening for Down syndrome. Semin Perinatol 2005;29:247–51.