Screening for Down Syndrome in the United States

Results of Surveys in 2011 and 2012

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• ***Context.***—**Participants in a College of American Pathologists external proficiency testing program for first and second trimester Down syndrome screening.**

Objectives.—**To determine the number of women screened for Down syndrome in the United States, along with the type of test received and to compare those results to earlier surveys in 1988 and 1992.**

Design.—**Questionnaires regarding the type and number of Down syndrome tests performed per month were completed by participants in early 2011 and again in early 2012.**

Results.—**After accounting for some of the missing responses, data from up to 131 laboratories indicated that 67% (2 764 020 of 4 130 000) to 72% (2012: 2 963 592 of 4 130 000) of US pregnancies received prenatal screening for Down syndrome. Second trimester tests were most common (2012: 60%; 1 770 024 of 2 963 592), followed by integrated (2012: 21%; 627 876 of 2 963 592), and first trimester (2012: 19%; 565 692 of 2 963 592). The 6 largest laboratories tested 61% of screened pregnancies and offered the widest array of tests, while the smallest 32 tested 1% and almost always offered only second trimester tests.**

Conclusions.—**The current population estimate of 72% pregnancies screened annually is higher than estimates from 1988 (25%) and 1992 (50%). Available testing choices are also more varied, and all testing methods perform better than those methods available 10 years ago. Clinicians should ensure that women are offered tests that follow recommended best-practice testing protocols, and screening laboratories should assess whether patient needs are being met.**

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Screening programs for open neural tube defects began in the late 1970s, following documentation that elevated levels of maternal serum α-fetoprotein (AFP) in the second trimester were associated with open spina bifida and anencephaly.[1] In 1984, 2 reports identified a sufficiently strong association between fetal Down syndrome and reduced second-trimester AFP measurements to allow application as a screening test in combination with maternal age.[2,3] Test performance was relatively inefficient but was improved when additional second-trimester markers, including unconjugated estriol,[4] human chorionic gonadotropin (hCG),[5] free β-hCG,[6] and dimeric inhibin-A,[7] were identified and introduced in the late 1980s. These were incorporated into published algorithms providing patient-specific risk estimates.[8,9] Currently, the best second-trimester test is the quadruple test (AFP, unconjugated estriol, hCG [total or free β-hCG], and inhibin-A) with an 80% detection rate at a 5% false-positive rate.[10]

First-trimester maternal serum markers, including pregnancy-associated plasma protein A[11] and free β-hCG[12] (or hCG[13]), were also identified in the mid 1980s. The most-powerful first-trimester marker was the ultrasound measurement of nuchal translucency.[14] The combined test (maternal age in combination with pregnancy-associated plasma protein A, free β-hCG, and nuchal translucency measurements), which is the highest-performing first-trimester test, is roughly equivalent in performance to the second-trimester quadruple test.[10] The main advantage to first-trimester testing lies in the potential for an earlier diagnosis. The most recent innovation is to combine the best first- and second-trimester markers into the integrated test,[15] with the final interpretation provided only after all information is available in the second trimester. Using an integrated test, the detection rate is about 90% for a 2% false-positive rate.[10] Variants of the integrated test include the serum integrated test (nuchal translucency is not included)[16] and the sequential test (where some results are released in the first trimester).[17]

Maternal serum screening for Down syndrome is part of routine prenatal care in the United States and elsewhere in the world. Two surveys[18,19] have documented the changing pattern of screening in the United States over time. The first was performed in 1988 and documented that 586 000 pregnancies were screened for open neural tube defects;

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Table 1. Maternal Screening Proficiency Testing Survey Participation and Laboratory Screening Status in 2011 Versus 2012

	2011 FP Survey		
2012 FP Survey	**Completed, No. (%)**	**Not Completed**	**All**
Completed	99 total	8 screening laboratories[a] 5 new screening laboratories in 2012 13 Total	**112**
Not Completed	11 screening laboratories[b] 10 dropped out in 2012 3 stopped screening? 24 Total	15 manufacturers/other 16 screening laboratories 1 new screening laboratory 32 Total	**56**
All	**123** (73)	**45** (27)	**168**

[a] The data from each of these laboratories for 2012 were used for their 2011 response.
[b] The data from each of these laboratories for 2011 were used for their 2012 response.

534 000 of these (91%) also had the AFP levels interpreted for risk of Down syndrome.[18] Taking into account laboratories not responding to the survey or not enrolled in the quality assessment program, the overall estimate for the United States was 1 000 000 pregnancies tested annually. That translates into about a 25% screening-uptake rate. A second US survey, in 1992, aimed at documenting the introduction of multiple second-trimester serum markers for Down syndrome.[19] That more-complete survey used data from 2 external proficiency testing programs and documented that 242 of the 301 US participants (80%) provided Down syndrome screening for 1 924 000 pregnancies. Among those laboratories, 56% (n = 169) offered AFP alone; 30% (n = 90) offered AFP, unconjugated estriol, and hCG (the triple test); and 14% (n = 42) offered AFP and hCG (the double test). Overall, nearly one-quarter of the screened pregnancies had multiple analytes tested, and about one-half of all US pregnancies were screened.

The current survey documents the current extent of Down syndrome screening in the United States and examines the introduction of combined testing during the first trimester and various forms of integrated testing during the past decade. No information was collected regarding screening for open neural tube defects.

MATERIALS AND METHODS

The College of American Pathologists (CAP) currently offers the Maternal Screening Proficiency Testing Survey (FP) to participants that either directly perform maternal serum screening for open neural tube defects and Down syndrome (http://www.cap.org, accessed August 22, 2012), or are commercial suppliers of relevant reagents and/or platforms. Five manufactured specimens that simulate early second-trimester, maternal serum samples are distributed 3 times each year. Each specimen has targeted amounts of AFP, unconjugated estriol, hCG, and inhibin-A, and participants are asked to report the assay results in mass (or international) units; interpretive units (multiples of the median); computed, patient-specific Down-syndrome risk; and the laboratory's suggested follow-up, if any. A separate and independent Interlaboratory Comparison Program provided similar assessment for laboratories performing first-trimester combined and integrated testing between 2005 and 2010.[20] In 2011, that program was incorporated into the CAP Maternal Screening Survey, designated FP1. Nearly all laboratories offering serum screening for Down syndrome will participate in one or both of the FP survey offerings.

In the first distribution of the 2011 FP survey, all participants were asked to respond to a 1-page questionnaire regarding the type of Down syndrome tests offered and the number of women tested in the previous month. The questionnaire was repeated in the first distribution of the 2012 FP survey. No individual laboratory information was available outside of the CAP. Participants were assigned a unique identification number (not their CAP identification number) to allow their responses to the 2 surveys to be linked. Each participant was identified as having a mailing address inside the United States or outside of the United States. The deidentified results were made available only to members of the Molecular and Biochemical Genetics Resource Committee, which oversees the FP surveys (G.E.P., G.J.K.). Raw summaries of the survey results were reported to FP survey participants as part of their summary report.

Before the analysis, key decisions were made regarding adjustments that might need to be applied to the reported results. We anticipated that some laboratories may report yearly rather than monthly results. We emphasized this potential for error as part of the second questionnaire and attempted to identify such errors by comparing reported results from the 2 questionnaires for each participant. It was also anticipated that some participants would respond to one questionnaire but not the other or to neither. In an attempt to determine whether a nonresponder did or did not offer screening for Down syndrome, we examined the data reported as part of the FP survey. Usually, manufacturers or nonscreening laboratories report only the analyte values and not the associated multiples of the median or Down syndrome risk estimates. In this way, we attempted to distinguish between those participants that did not report but do screen women in the United States and those that did not need to report because they do not offer a clinical service.

Two sets of analyses were performed. The first set documented the total pregnancies screened by each test in 2011 and 2012. Thus, any laboratory reporting results in 2011 or 2012 would be included. The second set examined the difference in testing patterns in 2011 versus 2012, and it relied only on the subset of laboratories that reported results for both 2011 and 2012.

RESULTS

The FP survey questionnaire was completed by 242 participants in 2011 and/or 2012. Of these, 74 participants (31%) were located outside the United States and were not included in the analyses. Among the remaining 168 participants, 99 (59%) completed the questionnaire regarding tests offered and corresponding numbers of samples tested for both years (Table 1). An additional 24 participants (14%) completed the questionnaire in 2011 but not in 2012 (lower left corner of Table 1). Eleven of these 24 laboratories (46%) still offered screening (as evidenced by their responses to the 2012 challenges), 10 (42%) did not report any results for the 2012 FP challenges, and 3 (13%) apparently stopped offering Down syndrome interpretations. Another 13 participants (8%) reported in 2012, but not in 2011 (upper right corner of Table 1), but 8 of these 13 (62%) did offer screening in 2011. The remaining 5 (38%) did not report any results in 2011. Lastly, 32 participants

Table 2. Types and Annual Numbers of Down Syndrome Screening Tests Performed in US Laboratories in 2011 and 2012

Type of Test	Survey 2011			Survey 2012		
	Laboratories, No. (%)	Screenings, Median	Screening, No. (%)	Laboratories, No. (%)	Screenings, Median	Screening, No. (%)
First trimester[a]	**32** (24)	**1800**	459 876 (17)	**34** (28)	**3000**	**565 692** (19)
Second trimester	**130** (100)	**2538**	**1 741 932** (63)	**122** (99)	**2838**	**1 770 024** (60)
AFP only	100 (76)	600	218 808 (8)	85 (69)	720	235 992 (8)
Triple test	46 (35)	588	106 284 (4)	44 (36)	402	90 132 (3)
Quadruple test[b]	123 (94)	2280	1 416 840 (51)	118 (96)	2400	1 443 900 (49)
Integrated	**25** (19)	**3270**	**562 212** (20)	**30** (24)	**4176**	**627 876** (21)
Full integrated	16 (12)	2106	72 396 (3)	22 (18)	2136	102 972 (3)
Serum integrated	21 (16)	936	130 956 (5)	21 (17)	888	119 760 (4)
Sequential	24 (18)	1476	358 860 (13)	24 (20)	2436	405 144 (14)
All	**131** (100)	**2970**	**2 764 020** (100)	**123** (100)	**3660**	**2 963 592** (100)

[a] Includes all first-trimester tests, including those using serum measurements of total/intact human chorionic gonadotropin (hCG), free β-hCG, and inhibin-A.
[b] Includes tests with 5 second-trimester serum markers.

Abbreviation: AFP, α-fetoprotein.

(19%) did not report results for either of the 2 questionnaires. Of these, 15 (47%) are likely manufacturers or nonscreening laboratories (multiples of the median and risks not provided for any challenges) and the remaining 17 (53%) are likely screening laboratories (1 of these was new in 2012). Thus, the raw 2011 response rate (*laboratories reporting/all screening laboratories*) was 84% (123/[123 + 8 + 16]), and for 2012 was 80% (112/[112 + 11 + 16]). For a subset of the screening laboratories in the off-diagonal (Table 1), a good estimate of their test offerings can be gained by using their results from the year they did report. For example, a screening laboratory might report in 2011, but not in 2012. Rather than assume no tests were performed in 2012, it would be more appropriate to use their reported numbers from 2011. If that adjustment was made, the adjusted response rates would increase to 89% for both years. It is not possible to reliably estimate any information for the remaining 16 screening laboratories that did not report in either period.

Table 2 shows the number of laboratories offering each type of test (first trimester, second trimester, and integrated) along with the estimated numbers of samples tested annually. If more than one specific test was included in the questionnaire (eg, triple test, quadruple test under second trimester), those subtotals are also presented. In 2011 and 2012, approximately 2.8 and 3.0 million pregnancies were screened for Down syndrome in the United States, an increase of 7.2%. In both years, most of the screened pregnancies (63% [1 741 932 of 2 764 020] and 60% [1 770 024 of 2 963 592], respectively) received second-trimester serum screening, with the quadruple test being most common. All reporting laboratories offered some form of second-trimester screening. Integrated testing was the next-most-common mode of screening, representing 21% (562 212 of 2 764 020 and 627 876 of 2 963 592) of the population for each of the 2 years. Sequential screening was the most common form of integrated testing. First-trimester combined testing increased from 7% (459 876 of 2 764 020) in 2011 to 19% (565 692 of 2 963 592) of all tests performed in 2012.

The results shown in Table 2 have been adjusted for screening laboratories reporting for only one of the questionnaires (Table 1). During the process of creating this table, 9 sets of results (5%) were identified as having a ratio of pregnancies screened in 2012 versus 2011 that were quite different from the expected ratio result of about 1. Several ratios were close to 12 (or the reciprocal 1/12), likely indicating a report of annual rather than monthly number of samples tested for one distribution. After review (G.E.P., G.J.K., J.E.H.), 4 sets of responses (2%) had 2011 results divided by 12 to be consistent with 2012 results, and 2 (1%) had 2012 results divided by 12. Three (2%) with ratios much closer to 1 were left unchanged. Another 8 sets of results (5%) had large increases (or decreases) between the 2 surveys for only 1 or 2 types of testing. In one of these cases, both responses were yearly, rather than monthly, and both responses were divided by 12. In the other, a new test offering was considered so large an increase that it was assumed to have been a yearly response and was divided by 12. The remaining 6 results (4%) were left unchanged because the changes were plausible.

Table 3 stratifies 2012 survey results of testing by the total number of pregnancies screened by each laboratory. Laboratories are grouped by size, with the first group screening more than 100 000 pregnancies per year. For each group, the proportion of all first-trimester, second-trimester, and integrated testing is summarized, along with the total proportion of women tested. The 6 largest laboratories are responsible for 61% (1 798 956 of 2 963 592) of the Down syndrome screening in the United States, whereas the 32 smallest laboratories (<1500 per year) screen only 1% (29 760 of 2 963 592) of the total. The largest laboratories are also responsible for 83% (518 364 of 627 876) of all integrated screening being performed.

Table 4 focuses on the 99 laboratories that reported results for both surveys. In this subset, the results are stratified into fewer groups, with the largest laboratories now defined as screening 50 000 pregnancies or more per year. The 2 largest groupings (>50 000 and 12 000–49 900) both showed large increases in first-trimester screening. Only 3 of the 99 (3%), all relatively small laboratories, reported the same results for both surveys, indicating that laboratories did not just copy earlier responses. Only the smallest laboratories showed an overall decrease (–12%) in the numbers of women tested. Overall, there was a 5.4% increase in the number of women screened.

Table 5 displays the types of Down syndrome testing offered at each laboratory (ie, first trimester, second

Table 3. Numbers and Types of Down Syndrome Testing Performed, Stratified by the Annual Number of Pregnancies Screened in 2012

Laboratories, No. (%)	Pregnancies, No.	Down Syndrome Test Performed, No. (%)			
		First Trimester[a]	Second Trimester[b]	Integrated[c]	Any
6 (5)	>100 000	431 760 (76)	848 832 (48)	518 364 (83)	1 798 956 (61)
6 (5)	50 000–99 900	78 324 (14)	298 920 (17)	45 528 (7)	422 772 (14)
6 (5)	25 000–49 900	13 848 (2)	209 364 (12)	8424 (1)	231 636 (8)
10 (8)	12 000–24 900	23 412 (4)	113 676 (6)	32 520 (5)	169 608 (6)
21 (17)	6000–11 900	12 480 (2)	164 952 (9)	11 076 (2)	188 508 (6)
19 (15)	3000–5900	3240 (1)	60 888 (3)	11 052 (2)	75 180 (3)
23 (19)	1500–2900	2628 (4)	43 776 (2)	768 (<1)	47 172 (2)
32 (26)	<1500	0 (0)	29 616 (2)	144 (<1)	29 760 (1)
123 (100)	All	565 692 (100)	1 770 024 (100)	627 876 (100)	2 963 592 (100)

[a] First trimester testing includes maternal age and, most commonly, pregnancy-associated plasma protein A and total human chorionic gonadotropin (hCG) or the free b subunit of hCG.
[b] Second trimester testing is most commonly the quadruple test (maternal age in combination with α-fetoprotein, unconjugated estriol, human chorionic gonadotropin, and inhibin-A) but also includes 1, 2, 3, or 5 serum markers.
[c] Integrated testing includes both first- and second-trimester markers.

Table 4. Change in Numbers and Types of Down Syndrome Tests Performed Among Laboratories Reporting in Both 2011 and 2012, Stratified by the Annual Number of Pregnancies Screened in 2012

Laboratories, No. (%)	Pregnancies, No.	Average of Down Syndrome Tests Performed, No. (% Increase)							
		First Trimester[a]		Second Trimester[b]		Integrated[c]		Any	
		2011, No.	2012, No. (% Increase)	2011, No.	2012, No. (% Increase)	2011, No.	2012, No. (% Increase)	2011, No.	2012, No. (% Increase)
9 (9)	>50 000	42 860	54 220 (27)	121 776	116 053 (−4.7)	51 822	54 873 (5.9)	202 954	212 252 (4.6)
13 (13)	12 000–49 900	1248	2408 (93)	17 886	20 032 (12)	2604	2799 (7.5)	22 139	25 239 (14)
32 (32)	3000–11 900	515	491 (−4.6)	4846	5137 (6.0)	713	691 (−3.1)	6076	6319 (4.0)
45 (45)	<3000	77	58 (−25)	1616	1406 (−13)	7	20 (192)	1686	1484 (−12)
99 (100)	All	4264	5430 (27)	14 630	14 454 (−1.2)	5285	5589 (5.7)	24 040	25 327 (5.4)

[a] First trimester testing includes maternal age and, most commonly, pregnancy-associated plasma protein A and total human chorionic gonadotropin (hCG) or the free β subunit of hCG.
[b] Second trimester testing is most commonly the quadruple test (maternal age in combination with α-fetoprotein, unconjugated estriol, human chorionic gonadotropin, and inhibin-A) but also includes 1, 2, 3, or 5 serum markers.
[c] Integrated testing includes both first- and second-trimester markers.

Table 5. Types of Down Syndrome Testing Offered by Each Laboratory, Stratified by Their Total Annual Number of Pregnancies Screened in 2012

Pregnancies, No.	Types of Down Syndrome Testing Offered, No. (Row %)				
	Second Trimester[b] Only	First Trimester,[a] Second Trimester,[b] and Integrated[c]	First Trimester[a] and Second Trimester[b]	Second Trimester[b] and Integrated[c]	Total Laboratories
>50K	0 (0)	8 (67)	2 (17)	2 (17)	12 (100)
12–49.9K	7 (44)	7 (44)	2 (12)	0 (0)	16 (100)
3–11.9K	25 (63)	8 (20)	5 (12)	2 (5)	40 (100)
<3K	52 (95)	2 (4)	0 (0)	1 (2)	55 (100)
All	**84** (68)	**25** (20)	**9** (7)	**5** (4)	**123** (100)

[a] First trimester testing includes maternal age and, most commonly, pregnancy-associated plasma protein A and total human chorionic gonadotropin (hCG) or the free β subunit of hCG.
[b] Second trimester testing is most commonly the quadruple test (maternal age in combination with α-fetoprotein, unconjugated estriol, human chorionic gonadotropin, and inhibin-A) but also includes 1, 2, 3, or 5 serum markers.
[c] Integrated testing includes both first- and second-trimester markers.

trimester, or integrated), stratified by numbers of pregnancies screened in 2012. Only 4 combinations of testing types were reported by participants, the most common being the offer of only second-trimester testing. The remaining combinations were: all 3 types, first trimester and second trimester testing, and second trimester and integrated testing, in decreasing order of laboratory usage. Laboratories with fewer pregnancies screened per year relied heavily on second-trimester testing (95%), whereas larger laboratories more often offered all 3 types (67%).

COMMENT

It has been 20 years since the last comprehensive survey of Down syndrome screening in the United States.[19] At that time, many screening laboratories had not yet begun offering a Down syndrome interpretive risk, and first

trimester or integrated screening were almost unknown. The current survey provides documentation that approximately 72% of the 4.13 million pregnancies in the United States received Down syndrome screening in 2011 and 2012. For comparison, during a recent 2-year period, the state-run program in California tested more than 752 000 pregnancies[21] out of approximately 1 104 000 births, yielding a screening uptake rate of 68% (2009 births: http://www.cdc.gov/nchs/data_access/vitalstats/VitalStats_Births.htm, accessed August 10, 2012). Most of the testing in the United States (61%; 1 798 956 of 2 963 592) was performed by a limited number of high-throughput laboratories offering a wide array of testing options. About 6 in 10 pregnancies (60%) that receive screening, however, are still screened in the second trimester, most often with the quadruple markers. Growing numbers of pregnancies are being screened by both first trimester and various forms of integrated testing.

Several factors might have led to overestimation or underestimation of the numbers of screened pregnancies. First, 37 participants (22%) in the FP survey who appear to offer Down syndrome screening completed the questionnaire only once. The effect of this underestimation factor was partially mitigated by taking advantage of a subset of 19 of the 37 laboratories (51%) that participated in both surveys but only completed the questionnaire in one. For those laboratories, the number of screened pregnancies reported in 1 year was repeated for the missing year's results. Among all participants not responding to either questionnaire, we assumed that 30 could have, but did not, report their results. If these laboratories screened the median number of pregnancies per year (3660; Table 2, 2012 results), their inclusion would raise the 2012 screening rate only modestly (from 63% to 66%). The median rather than the mean was used because we believe that most large-volume laboratories have reported and that nonresponding laboratories would screen fewer pregnancies than responding laboratories. Another factor that could lead to underestimation is for screening laboratories to only participate in the New York State proficiency testing program (http://www.wadsworth.org, accessed August 10, 2012). However, in the 1992 survey,[19] only 6 of 307 laboratories (2%) responding to the survey were not enrolled in the CAP survey but were enrolled in the New York State program. Even if they were relatively large, their inclusion would lead to only a slight increase in the overall screening rate.

There are also factors that would tend to cause overestimating of the screening rate. The questionnaire asked for laboratories to report the number of pregnancies screened per month. It is clear from the 2 years' matched results that some reported yearly estimates. We attempted to identify and correct for that, but such errors may not be easily identified (eg, a laboratory reported yearly totals for both questionnaires). Hypothetically, were 5 laboratories to report an annual rate of 5000 pregnancies screened that was incorrectly interpreted as 5000 per month, correcting that mistake would have the overall effect of reducing the screening rate from 63% to 62%. Some laboratories may have reported a single pregnancy's testing twice. That might occur when a first-trimester combined test is followed by a second-trimester AFP test designed only for the detection of open neural tube defects. In some instances, the woman's first and second trimester sample may be incorrectly counted as 2 tests, when the correct interpretation is a single integrated test. These latter types of errors are likely to be less common and sporadic with, at most, a minimal effect on the reported results.

Guidelines from the American College of Obstetricians and Gynecologists[22] recommend that women having prenatal visits in the first trimester be offered some form of integrated screening or, if early diagnosis is highly valued, first-trimester screening. Quadruple screening should be offered if the woman has her first visit after 13 completed weeks' gestation. An estimated 68% of women in the United States have their first prenatal visit in the first trimester, 20% in the second trimester, and 5% in the third trimester. An additional 2% have no prenatal care, and 5% did not report the information (using data from the 26 states reporting the month prenatal care began) (http://205.207.175.93/Vitalstats/TableViewer/tableView.aspx?ReportId=42524, accessed August 10, 2012). Based on these data, most of the screening laboratories are not directly offering Down syndrome screening tests that meet the needs of the prenatal care community. Some may be sending out such testing to other laboratories and our survey would not capture such activity. However, it may also represent a more-limited choice of test offerings for some women, even though all tests are available throughout the United States. Limited test offering may be one contributor to the current domination of prenatal screening by larger laboratories. For example, the 11 largest laboratories ($\geq$25 600/y) offering Down syndrome screening in 1992 tested about 9% of all screened pregnancies, as opposed to 61% of all screened pregnancies currently being accounted for by the 6 largest laboratories ($>$100 000/y) in 2012.

These data suggest that national Down syndrome screening participation rates of 67% to 72% may be the upper limit, indicating that patient-centered decision-making is present in current programs. They also provide guidance to screening laboratories about the types of testing that are both acceptable and desirable from a patient's viewpoint. Taken together, these findings provide a solid baseline to examine future trends in prenatal screening for Down syndrome that might include tests using circulating cell-free DNA.

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