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.


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 A11 and free β-hCG12 (or hCG13), 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,13 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.16 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 surveys18,19 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;
among those laboratories, 56% (n = 534,000) also had the AFP levels interpreted for risk of Down syndrome. 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. 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.

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 interpretation. 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>
<thead>
<tr>
<th>Table 1. Maternal Screening Proficiency Testing Survey Participation and Laboratory Screening Status in 2011 Versus 2012</th>
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</thead>
<tbody>
<tr>
<td><strong>2012 FP Survey</strong></td>
</tr>
<tr>
<td><strong>Completed</strong>, No. (%)</td>
</tr>
<tr>
<td><strong>Completed</strong></td>
</tr>
<tr>
<td><strong>Not Completed</strong></td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td><strong>All</strong></td>
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* The data from each of these laboratories for 2012 were used for their 2011 response.
† The data from each of these laboratories for 2011 were used for their 2012 response.
Table 2. Types and Annual Numbers of Down Syndrome Screening Tests Performed in US Laboratories in 2011 and 2012

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Survey 2011</th>
<th>Survey 2012</th>
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<tbody>
<tr>
<td></td>
<td>Laboratories, No. (%)</td>
<td>Screenings, Median</td>
</tr>
<tr>
<td>First trimester&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32 (24)</td>
<td>1800</td>
</tr>
<tr>
<td>Second trimester</td>
<td>130 (100)</td>
<td>2538</td>
</tr>
<tr>
<td>AFP only</td>
<td>100 (76)</td>
<td>600</td>
</tr>
<tr>
<td>Triple test</td>
<td>46 (35)</td>
<td>588</td>
</tr>
<tr>
<td>Quadraple test&lt;sup&gt;b&lt;/sup&gt;</td>
<td>123 (94)</td>
<td>2280</td>
</tr>
<tr>
<td>Integrated</td>
<td>25 (19)</td>
<td>3270</td>
</tr>
<tr>
<td>Full integrated</td>
<td>16 (12)</td>
<td>2106</td>
</tr>
<tr>
<td>Serum integrated</td>
<td>21 (16)</td>
<td>936</td>
</tr>
<tr>
<td>Sequential</td>
<td>24 (18)</td>
<td>1476</td>
</tr>
<tr>
<td>All</td>
<td>131 (100)</td>
<td>2970</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes all first-trimester tests, including those using serum measurements of total/intact human chorionic gonadotropin (hCG), free β-hCG, and inhibin-A.

<sup>b</sup> Includes tests with 5 second-trimester serum markers.

Abbreviation: AFP, α-fetoprotein.
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. 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 pregnancies21 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 overestimation 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 Gynecologists22 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 (≥25,600/yr) 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/yr) 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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References


