First Trimester
Interlaboratory Comparison Program

IMPORTANT NOTICE

This is the last distribution of the WIH-sponsored FT Survey

The College of American Pathologists (CAP) now has a similar product (FP1T / FP1B)

Please enroll in that survey for 2012 (www.cap.org)

See page 2 for more details

Sponsored by:
Department of Pathology and Laboratory Medicine
Women & Infants Hospital
Providence, RI

Distribution 2011 FT-C

Notice of ICP transfer to the College of American Pathologists (CAP)

The staff at Woman and Infants Hospital (WIH) has been working over the past year to transfer the Interlaboratory Comparison Program (ICP) for first trimester markers, of which you are a participant, to the College of American Pathologists (CAP). The transfer is scheduled to be completed by the end of this year, which will allow the College to offer the survey in 2012. Consequently, WIH will no longer offer the ICP in 2012.

Transferring the first trimester ICP program (now designated FP1T for hCG users and FP1B for free beta users) to CAP will complement the existing second trimester maternal screening FP survey offered by the College. This transfer will allow coordination between the two surveys that will facilitate exercises such as the Integrated Test Exercise currently offered by the ICP. As you know, CAP is the largest purveyor of External Proficiency Testing in the United States and has a significant presence outside of it. This transfer allows for the orderly growth of the program and adds needed structure and administrative support.

Drs. Glenn Palomaki and George Knight have been appointed as consultants to the Biochemical Molecular and Genetics Resource Committee, the group that advises the College on the structure and administration of proficiency testing programs for genetic testing. This includes the current FP Survey (second trimester markers) and in 2012 will include the FP1 Surveys (first trimester markers). Drs. Jack Canick and Geralyn Messerlian will continue in their current role as advisors on the operation of the program, including the supervision of the preparation and quality control of the specimens used in the survey. Our joint participation ensures continuity of the ICP program goals that have been defined and refined over the last five years.

The input and support of you, the ICP participants, has been invaluable and we thank everyone for their patience and support over these past years. We hope to continue with the collegial philosophy that proved to be so successful for the ICP program. This includes the laboratories, manufacturers and other interested parties who have collectively shared data with a view towards standardizing and improving the practice of first trimester and integrated screening.

The College will contact, or may have already contacted you, with information needed to enroll in this new first trimester PT program. Please contact us with any questions you may have about this transfer. If you know of others who may be interested, please let them know about this new CAP offering.

Thank you,

INTRODUCTION

Explanation of Data Listing and Analysis

Specimen Options: The ICP offers two choices of specimens for analysis. One specimen set is designed for those participants using intact/total hCG in their screening marker combination (**hCG sample set**). The other set is designed for those participants using the free beta subunit of hCG in their screening marker combination (**free beta sample set**). The specimens may consist of: 1) unmodified patient pools, 2) patient pools diluted with normal human serum and spiked with recombinant hCG or recombinant free beta subunit (but not both), recombinant inhibin and a PAPP-A concentrate, or 3) normal human serum spiked with recombinant hCG or recombinant free beta subunit (but not both), recombinant inhibin-A and a PAPP-A concentrate. A limited number of additional samples sets are available upon request. This allows participants switching from hCG to free beta (or vice versa) to test both sample sets.

Reading the Data Listing: The five page data listing (in a separate pdf file) contains a summary of reported results for all participants, with each page summarizing one specimen. Your laboratory identification number (ID) is listed at the beginning of the row with your results. Missing data (blanks) are likely due to participants who are manufacturers, or to participants that are not yet offering screening services. Outliers for decimal gestational age (or decimal maternal age) are identified as those outside ±0.2 weeks (or ±0.2 years) of the correct answer. For the assay results (in mass units or MoM) and Down syndrome risks, outliers are defined as being outside of ±2 standard deviations, after accounting for rounding. A revised SD is then computed. A logarithmic transformation is used for the analysis of Down syndrome risks.

Conversion of Reported Down Syndrome Risks to First Trimester Risks: Most participants report risk relevant for the first trimester, but some report risk for the second trimester or at term. If the reported risks are not first trimester, these risks are displayed in the column labeled “Report” under the “Down S Risk (1:n)” heading. To allow all risks to be evaluated together, second trimester risks are converted to first trimester risks using the factor 0.74. This accounts for fetal loss between the first and second trimesters (46% from first trimester to term and 23% from second trimester to term). For example, if the second trimester risk is 1:1000, the first trimester risk is 1:[1000 x 0.74], or 1:740. Term risks are converted by multiplying by 0.54 in a similar manner.

Down syndrome risks (and interpretations) from participants using the free beta sample set are listed, and may be included in the calculation of summary statistics, if the free beta MoM levels are similar to those for hCG. Otherwise, the risks are listed in the “Report” column but not included in the analysis. When sufficient numbers are available, a separate analysis will be performed.

Maternal Age Reporting: Maternal age can be reported either as a decimal or as completed years (integer). Although the difference in Down syndrome risk is small for most ages, use of decimal age can be important for women age 35 and older, especially one whose age falls close to a whole year (*e.g.*, 36.1 versus 36.9 years). Each of these women would be considered to be 36 completed years, even though they are almost one year apart. Participants commonly calculate risk using a maternal age equation rather than a table of risks, and it is straightforward to use the more accurate age to obtain a more accurate risk. Almost all participants in the ICP report decimal age. Currently, the lab(s) that report integer maternal ages are listed separately. In the future, such results will be listed along with decimal ages but will not be included in the calculations.

NT MoM Reporting: For most challenges, the ICP only provides a target NT MoM. Participants need to generate these NT MoM values by trial and error, usually by entering various combinations of CRL/NT/GA combinations. Approximate CRL values (in mm) and GA values (in weeks and

days) are provided as an aid. Participants are asked to report the MoM value that they actually obtained to serve as a check on how reliably they can reproduce the targeted MoM value. Almost all participants report NT MoM values that closely match the targeted value. If participants are having difficulty generating these target NT MoM levels, we can provide assistance.

The ICP also includes at least one challenge each distribution that provides only a patient CRL and NT value (in mm), along with a set of NT and CRL values from the submitting 'hypothetical' sonographer (identified by three initials) who provided those measurements. Participants can then use that set of NT/CRL values to generate sonographer-specific NT medians. Those medians can then be used to convert the reported patient NT value (in mm) to MoM. That NT MoM is then used along with maternal age and the chemistry results to calculate the patient-specific Down syndrome risk. We have provided an Excel spreadsheet that can be used to calculate the CRL/NT median equation with two accompanying quality assurance parameters (*e.g.,* slope and log SD). Participants that do not use NT MoM for interpretation will only be evaluated for analyte values.

Greater Than and Less Than Risks: Risks that are reported as less than (<) or greater than (>) are displayed in the "Report" column under the "Down S Risk (1:n)" column. These risks are listed as the actual numeric risk in the "1st trim" column and may be included in the final calculation of the consensus risk. For example, >1:10 indicates a risk that is higher than 1:10.

Free Beta Subunit Results: The data listings include the analyte and MoM values for the free beta measurements for those participants using the free beta specimen set. A median is reported, but a comprehensive analysis is not currently performed, due to the limited number of participants. However, each of these participants can review their own results by inspection of the data listing.

If the consensus MoM for free beta is similar to the hCG MoM, the reported risks for free beta users are included in the summary statistics (after converting risks to the first trimester). A close approximation in MoM values is possible for most manufactured specimens (but not all) because advantage is taken of the high correlation between hCG and free beta values (r values of ~0.8). Roughly, absolute free beta values in mg/mL are approximately 40% to 80% of the absolute values of hCG for patient specimens in IU/mL (*e.g.*, 100 IU/mL hCG will typically have a free beta value of 50-60 ng/mL). For some specimens, the relationship for manufactured specimens does not hold, and these would be excluded from the risk summary statistics. Even if the hCG and free beta MoM values are similar, the risks may differ because the referent parameters differ for the two analytes.

PAPP-A Values: Many participants are now using the Beckman DxI assay for measuring PAPP-A. The Beckman assays are calibrated in ng/mL (rather than mIU/mL), which gives absolute values that are approximately 300-350 times larger. PAPP-A results in ng/mL are now listed separately from those in mIU/mL. Some participants report PAPP-A results in ug/mL (ng/mL divided by 1000) or in ug/dL (ng/mL divided by 10). The ICP converts these results back to ng/mL as a way to avoid introducing further complexity in the report. Also, most participants using the PerkinElmer assay report results in mIU/mL, but some report in mIU/L. These values have also been converted to mIU/mL by dividing by 1000 in the report.

Values in Boxes: The ICP uses two types of highlighted boxes in the individual data listings:

- Thick lined boxes identify values that are outliers as compared to the consensus (*e.g.*, 25.0).
- Thin lined boxes are used to call attention to values that are significantly different from the consensus but are not considered outliers (*e.g.*, 1.07). The most common reason is that they are now outside of ±2 trimmed SDs, but were initially within ±2 untrimmed SDs.

RESULTS

PAPP-A mass and MoM values (All specimens):

Values. Among the 29 participants, 16 report results in ng/mL (or equivalent) and 11 report in mIU/mL (or equivalent). Two participants did not report PAPP-A results. Over time, the relationship between these units has ranged from 300 to 350. The conversion factors for the five current specimens are reasonably consistent (332, 322, 326, 327 and 301 respectively (*i.e.,* factor * mIU/mL equals ng/mL). Separate analyses are performed for each of the groups. The CVs for the participants reporting in mIU/mL are higher (20% to 22%) than for those reporting in ng/mL (5% to 7%). This difference is in large part attributable to the fact that laboratories reporting in ng/mL are using a single manufacturer's reagents, while multiple manufacturers' reagents are included in participants reporting in mIU/mL. Although data are insufficient to allow a separate analysis by method for the mIU/mL data, visual inspection suggests that within-kit precision is better than that calculated using the all method CV.

MoM. Medians should, at least in part, normalize for the differences observed for PAPP-A values and does account for the differences in units. The CV of MoM values for PAPP-A in this distribution range from 13% to 24%. The CV of PAPP-A MoM values have been relatively high historically, as compared to corresponding values observed for hCG. This relationship is changing, however, as the new, higher precision methods begin to dominate. This assumes that participants generate their own reliable median values.

hCG mass and MoM values (All specimens):

Values: The all-method CVs for the hCG values are typically low, and this distribution is no exception (range 8% to 10%). If systematic between-kit differences exist, they appear to be small.

MoM: The all-method CVs for MoM values range from 11% to 15% for the five specimens in this distribution. This is almost as precise as the mass values, indicating that participants have developed reliable kit-specific population-specific medians.

Free beta mass and MoM values (All specimens):

Values: The number of participants using free beta subunit measurements (all use the PerkinElmer assays) is too few to allow a separate analysis (mean, SD, CV). However, from visual inspection of the data, it is evident that the between-participant agreement is high.

MoM: As is true for free beta mass values, the number of participants using free beta subunit measurements is insufficient to allow a separate analysis (mean, SD, CV). However, the limited data suggests that the between-participant agreement is also high.

Down Syndrome Risk (All specimens):

The consensus trimmed risks for the five specimens in this distribution, ranked from highest to lowest are 1:120 (FT-11), 1:240 (FT-14), 1:330 (FT-12), 1:1400 (FT-15), and 1:1500(FT-13). The CVs of the log risk for these ranked risks are 14%, 13%, 10%, 5%, and 10%, respectively. The CVs decrease monotonically across the range of risks with the exception of FT-13.

Free beta results: Down syndrome risks for free beta subunit users were included in the risk analysis for specimens FT-14 and FT-15. For the remaining three specimens, the values are listed for inspection.

Calculation of gestational age and NT MoM Exercise (FT-15 and FT-15FB):

Participants were asked to calculate an NT MoM value, given a CRL of 59 mm (about 12.3 weeks' gestation) and an NT value of 1.7 mm. Results were submitted by sonographer identified as "GNG". Participants were provided with a set of 150 NT/CRL measurements for sonographer GNG (participants may have already calculated sonographer-specific medians for this sonographer in a previous exercise). However, participants may or may not have used those medians to calculate their MoM value, depending on their own laboratory protocols. The expectation is that the resulting MoM values reported by participants that use sonographer-specific medians should be similar, while those using a single fixed set of NT medians might be different. We calculated the median equation for sonographer GNG to be:

$$\text{median NT} = 10^{(-0.239+0.00724*\text{CRL})}$$

using the ICP Excel calculator provided to all subscribers. This equation yields an expected median NT value of 1.54 mm for a CRL of 59 mm, which results in a NT MoM value of 1.10 (1.7/1.54). The trimmed mean NT MoM value is 1.10; identical to the expected value. One participant reported a value of 1.21 that was an outlier on the first SD pass, and two labs with values of 1.00 and 1.17 were outliers on the second SD pass

The two laboratories with outlying values of 1.17 and 1.21 indicate that they use a single set of median values. These two laboratories were also outliers for sample FT-10 in the FT-B distribution; a similar exercise. The use of a single set of medians is a possible explanation of why they had outlying NT MoM results compared to the consensus. We specifically designed data for sonographer GNG to allow for agreement between all participants in NT MoM so that the focus would primarily be on the serum measurements. GNG's measurements yield median values advocated by the Fetal Medicine Foundation. That group strives to have all credentialed sonographers achieve the same NT measurements for any given woman (within statistical limits). Although a laudable goal, it may not always be achieved in practice. The use of sonographer-specific medians could be viewed as an interim step in for practitioners who have not yet met this goal.

Using the CRL of 59 mm, all participants reported a gestational age of either 12.3 or 12.4 weeks (one participant reported an outlying value of 12.1 weeks). These small differences are likely attributable to the use of different conversion equations (see the 2009 FT-A report that includes an analysis of the 'CRL to decimal weeks' equation reported by each participant).

Dimeric inhibin-A (DIA)

First trimester DIA measurements were reported by four participants (Table 1). DIA mass values show excellent between-laboratory agreement, but MoM levels were more variable. Included in Table 1 are the DIA likelihood ratios (LR), in the context of the other markers.

Table 1. Dimeric Inhibin-A results and comparison of DS risks including, and omitting DIA

Sample No.	Lab	Method	Value[1]	MoM	DS Risk (1:n) including DIA	DS Risk (1:n) omitting DIA[2]	DIA LR[3]
FT-11	A	Beckman DxI	291	1.26	120	70	0.58
	B	Beckman DxI	331	1.32	130	95	0.73
	C	Beckman DxI	272	0.98	336	300	0.89
	D	Beckman DxI	290	0.79	319	183	0.57
FT-12	A	Beckman DxI	199	0.98	300	220	0.73
	B	Beckman DxI	214	0.96	300	170	0.57
	C	Beckman DxI	192	0.75	647	455	0.70
	D	Beckman DxI	198	0.58	778	374	0.48
FT-13	A	Beckman DxI	187	0.73	630	500	0.79
	B	Beckman DxI	221	0.80	1900	450	0.24
	C	Beckman DxI	171	0.69	16200	3990	0.25
	D	Beckman DxI	190	0.76	12800	6860	0.54
FT-14	A	Beckman DxI	250	1.17	200	140	0.70
	B	Beckman DxI	291	1.25	110	78	0.71
	C	Beckman DxI	229	0.87	657	418	0.64
	D	Beckman DxI	247	0.73	452	216	0.48
FT-15	A	Beckman DxI	295	1.37	1000	1100	1.10
	B	Beckman DxI	324	1.40	930	730	0.78
	C	Beckman DxI	294	1.18	3520	2300	0.65
	D	Beckman DxI	282	0.94	4600	2480	0.54

1 Rounded value in ng/mL

2 DS risk reported for NT, PAPP-A, and hCG

3 For each participant, the DIA likelihood ratio (LR) is computed by dividing the reported risk for NT, PAPP-A and hCG by the risk that also includes DIA measurements. If blank, the LR cannot be reliably determined, usually because one (or both) of the risks are very high (*e.g.,* >1:10) or very low (*e.g.,* <1:10,000).

Interpretative Questions:

The aim of this interpretative question was to determine sources of variability in the reported integrated risks, and determine whether recommendation to select participants might reduce the overall variability is assigned Down syndrome risks. Twenty-one participants provided sufficient responses to be included in the analysis. Their responses are summarized below.

1. **What is your source of age-associated risk for down syndrome used to compute your second trimester quadruple risk?**

   Table 2 summarizes the responses to the question. One participant did not respond. Most participants did not choose one of the listed responses (Morris 2003, Cuckle 1987 and Heckt and Hook 1996). This confusion is likely due to the number of times Morris and colleagues presented the same equation in different settings. The same data can be referred to as Morris 2002 (*J Med Screen*), Morris 2003 (*Prenat Diagn*) and Morris 2005 (*Prenat Diagn*). A correction to the Morris equation was published in 2007 (*J Med Screen*).

   The reference to the Alpha software by one participant is likely the Morris equation. The SURUSS report in 2003 used the Morris equation. The response of 'Wald', with no specified year, is also likely to be Morris. The Bray reference from 1998 is a meta-analysis and is likely to be reliable.

   In summary, the Morris equation is the most common source for age-related risks for Down syndrome. Most likely, 15 of the 20 responders (75%) use it for clinical reporting. If one uses this equation, it should include the refinement mentioned in the 2007 correction (*J Med Screen* 2005;12:202). Other participants should consider changing to this equation for consistency. In addition, Morris has the only publication with age-associated risks for trisomy 18 and trisomy 13.

   Table 2. Sources of age-associated risk equations

Source		N (%)
Morris et al., 2002, 2003, 2005, 2007		12 (52)
Cuckle et al., 1987		3 (14)
Not Reported		1 (5)
Hecht and Hook 1996		1 (5)
Other		4 (24)
Alpha	1 (Morris?)	
SURUSS 2003	1 (Morris?)	
Bray et al., 1998	1	
Wald	1 (Morris?)	
		21(100)

2. **Fill in the follow information about the second trimester sample FP-15**
   All but one participant reported the maternal age and four analyte levels in MoM for sample FP-15. The following analyses summarize the results of the responses
   a. All laboratories reported a maternal age of 34.7, except one that used truncated years.
   b. The median AFP, uE3, hCG and DIA MoM results were 0.97, 0.53, 1.17 and 0.61, respectively.
   c. The median reported risk was 1:1100. Participants were asked to report their quad risk both as part of this query and as part of the integrated supplemental questions. Two

participants reported different risks (1:316 vs 1:845 and 1:870 vs 1:530). Although not used in the analysis, these discrepancies should be checked.

d. Fifteen of the 21 participants reported second trimester risks, while the remaining six used term risks.
e. Fifteen of the 21 participants reported using LMP parameters for assigning quadruple risks, while the remaining six used US parameters. The six are not the same six that used term risks.

3. **When combining the second trimester markers with the first trimester markers, how are the two hCG measurements handled?**
   Nineteen of the 21 (90%) chose to use only the second trimester hCG measurement. Two participants use both measurements. Given that the two measurements are highly correlated, there can be problems including both in a multivariate algorithm. Such 'repeated measurements' have a checkered past, with some studies finding theoretical or actual improvement in screening performance, while others have not confirmed these findings. If possible the two participants using repeated measurements screening should review their program to determine if the correlation between the first and second trimester hCG measurements are being taken into account in the risk calculation.

4. **What is the trimester of risk for the integrated test?**
   Of interest, all but one participant reported using the same trimester of risk for both the integrated and quadruple test. The one exception reported 2nd trimester risks for quad testing, but term risks for integrated testing. If this is true, it may cause confusion among practices served by this program, as Down syndrome risks reported in the second trimester vary by trimester, depending on the test ordered.

5. **How do you account for the gestational age based on LMP in the second trimester, but via ultrasound (CRL) in the first trimester?**
   All but one participant reported that the US parameter set should be used for interpreting integrated test results. This is correct. The use of LMP parameters is inappropriate, given that a CRL measurement is required to calculate an NT MoM. Even if the second trimester sample has only LMP information reported, the US parameters should be used for calculating Down syndrome risk. However, that gestational age might be reported using LMP. Some professionals recommend that if an LMP date is confirmed by US, then the LMP information is considered the most reliable estimate of gestational age. However, the parameter set used for calculation of Down syndrome risk is more of a choice between an estimated GA (LMP parameters) and a known/confirmed GA (US parameters).

As a way of verifying these results, we used each laboratory's quad MoM results in the calculation of a full integrated risk, and then cross-checked this computed risk versus each participants reported full integrated risk. The next section provides more detail on the methodology and the results of that analysis.

Figure 1 displays a comparison of the full integrated Down syndrome risks, reported by participants, versus a risk computed based on their reported MoM levels and maternal age. To compute this 'expected' risk, we used the SURUSS[1] parameters for US dated pregnancies. The four filled circles indicate participants who appear to be using SURUSS parameters relevant for LMP-dated pregnancies, rather than for US-dated pregnancies. The age-associated risk[2] was set to the trimester of risk reported by each participant. If all participants used this exact set of parameters to compute their risk, one would expect the two estimates to fall on the dashed line (Y=X). In general, most observations do fall near this line of equality. Minor differences can occur due to the use of different age-associated risk equations, rates of fetal loss from trimester to

trimester or different published parameter sets. The maternal age of 34.7 years is in a region where most maternal age associated risk equations agree, so variability due to his factor is likely to be small for this example. Participants most often report using the SURUSS parameter set and this is why it was chosen to compute expected risks. The r-squared value is 0.50, indicating that about half of the variability in reported risks can be explained by the variation in MoM levels.

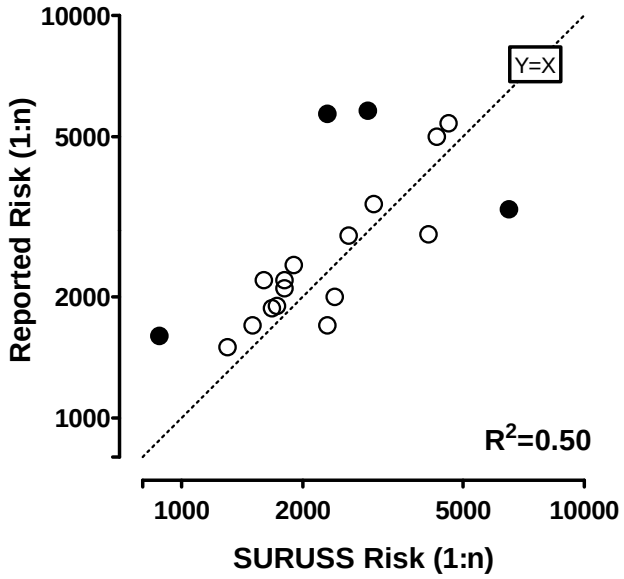

Figure 1. Scatterplot of computed and reported Down syndrome risks for the full integrated screening test. The x-axis shows the computed Down syndrome risk using the SURUSS parameters and each participant's reported maternal age and analyte levels in MoM. The y-axis shows each participant's reported risk. The paired risk values are for the same trimester.

Four participants (filled circles) reported risks that are reasonably different from expectation. We attempted to find an explanation for these differences by choosing varying parameter sets. Although it is difficult to be certain, it appears that all four of these participants are using the SURUSS parameters that are appropriate for LMP-dated pregnancies. If true, this is inappropriate practice, as all full integrated tests include NT and CRL measurements, and use of the CRL measurement for calculating gestational age rather than LMP is recommended. This discrepancy may be due to the unique nature of our challenge, as the quadruple test was first interpreted by FP maternal screening survey participants using LMP dating, as provided in the CAP history. Our ICP challenge (FT-15) arrives later with the US information (CRL), the reverse of what would occur in actual practice. However, participants should check their protocols to ensure that all full integrated risks are computed using US-based parameters. We recomputed a revised reported risk using the CRL provided for sample FT-15 for these four participants and all four revised estimates placed the points near the line of identity (not shown). The revised r-squared value was 0.86, indicating that if this is true, then nearly 90% of the variability is due to variation in the MoM, and the choice of parameter set, age-associated risk and other factors contributes to the remaining 10% of the variability.

[1] Wald NJ, *et. al*. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine, and Ultrasound Screening (SURUSS). *J Med Screen,* 2003;10(2):56-104.

[2] Morris JK, *et.al*. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. *J Med Screen,* 2002;9(1):2-6.

Interpretive question: Integrated screening

Twenty-one participants reported integrated risks using first trimester marker results (FT-15) in combination with their second trimester quadruple markers results (CAP FP survey, sample FP-15). Seven participants (including several manufacturers) do not perform integrated testing and one other did not respond. All of the 21 participants report integrated risks using second trimester quadruple markers; a subset also report integrated risks using a second trimester triple test. Only the integrated quadruple risk is analyzed. Seventeen participants report risks in the second trimester; five report risks at term. Term risks are adjusted to the second trimester using a 0.74 survival coefficient (*e.g.*, a term risk of 1:1000 equals a second trimester risk of 1:740). Table 2 lists these Down syndrome risks (1:n), along with the trimester of risk. The last column in each category contains the risk (rounded to two significant figures) after adjustment to the second trimester. Two participants using the free beta subunit are included in the summary statistics (last two entries in Table 2). One participant's full integrated risk was identified as an outlier.

Table 2. Summary of Integrated Down Syndrome Risks

Trimester of Risk	Quad Risk (FP-15) Reported	Quad Risk (FP-15) Adjusted	Serum Integrated Risk Reported	Serum Integrated Risk Adjusted	Full Integrated Risk Reported	Full Integrated Risk Adjusted
2	1100	1100	780	780	1500	1500
2	470	470	1500	1500	2400	2400
2	1300	1300	1800	1800	3400	3400
2	1900	1900	910	910	1700	1700
2	845	850	1100	1100	2000	2000
3[1]	2700	2700	1019	1020	2839	2100
2	1400	1400	1200	1200	2200	2200
2	586	586	1487	1490	2860	2900
2	940	940	1100	1100	490	490
2	907	910	1830	1800	1700	1700
2	460	460	NR	NR	1600	1600
2	990	990	930	930	2100	2100
2	220	220	900	900	5800	5800
2	440	440	1100	1100	3400	3400
2	375	380	3300	3300	5800	5800
3	1900	1400	2600	1900	3400	2500
2	1300	1300	1300	1800	1900	1900
3	2200	1600	2400	1800	5000	3700
3	1700	1300	2400	500	5700	4200
3	2600[2]	1900[2]	2700[2]	2000[2]	5400[2]	4000[2]
3	2900[2]	2100[2]	3400[2]	2500[2]	3300[2]	2400[2]
Trimmed		220		3300		490
Geo Mean risk		1040		1400		2430
CV(log risk)		8%		5%		6%
Mean-2SD		340		650		1100
Low		380		900		1600
High		2700		3300		5800
Mean+2SD		3200		3000		6000

[1] Quad and serum integrated risks second trimester; full integrated risk at term
[2] Participants using free beta subunit rather than total/intact hCG measurements

The trimmed geometric mean risk for the second trimester quadruple test for ICP participants is 1:1040. This is close to the consensus risk of 1:1300 for FP-15 reported by the CAP FP-C participant summary report for all participants in that survey. The trimmed mean PAPP-A MoM value for specimen FT-15 is 0.92. The crossover point for PAPP-A is 0.6 MoM (defined as the MoM value where the heights of the unaffected and affected distributions are equal resulting in a likelihood ratio of 1.0). PAPP-A values higher than 0.6 MoM would therefore be expected to lower the serum integrated risk.

- Serum integrated risk: As predicted, the geometric mean for the serum integrated risk for ICP participants is1:1400, lower than the quad risk of 1:1040.
- Full integrated risk: The trimmed mean NT MoM value calculated by ICP participants for FT-15 is 1.10. The crossover point for the affected and unaffected distributions of NT MoM is approximately 1.45 MoM. The expectation is, therefore, that the risk for the full integrated test would decrease as compared to the serum integrated test. The reduced geometric mean risk of 1:2430 versus 1:1400 for the serum integrated test meets expectation (LR of 0.58).

George J. Knight, Ph.D.	Glenn E. Palomaki, Ph.D.	(207) 894-6610
Jacob A. Canick, Ph.D.	Geralyn M. Messerlian, Ph.D.	(401) 453-7650

Department of Pathology and Laboratory Medicine
Women & Infants Hospital
Providence, Rhode Island