First Trimester
Interlaboratory Comparison Program

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

Distribution 2010 FT-A

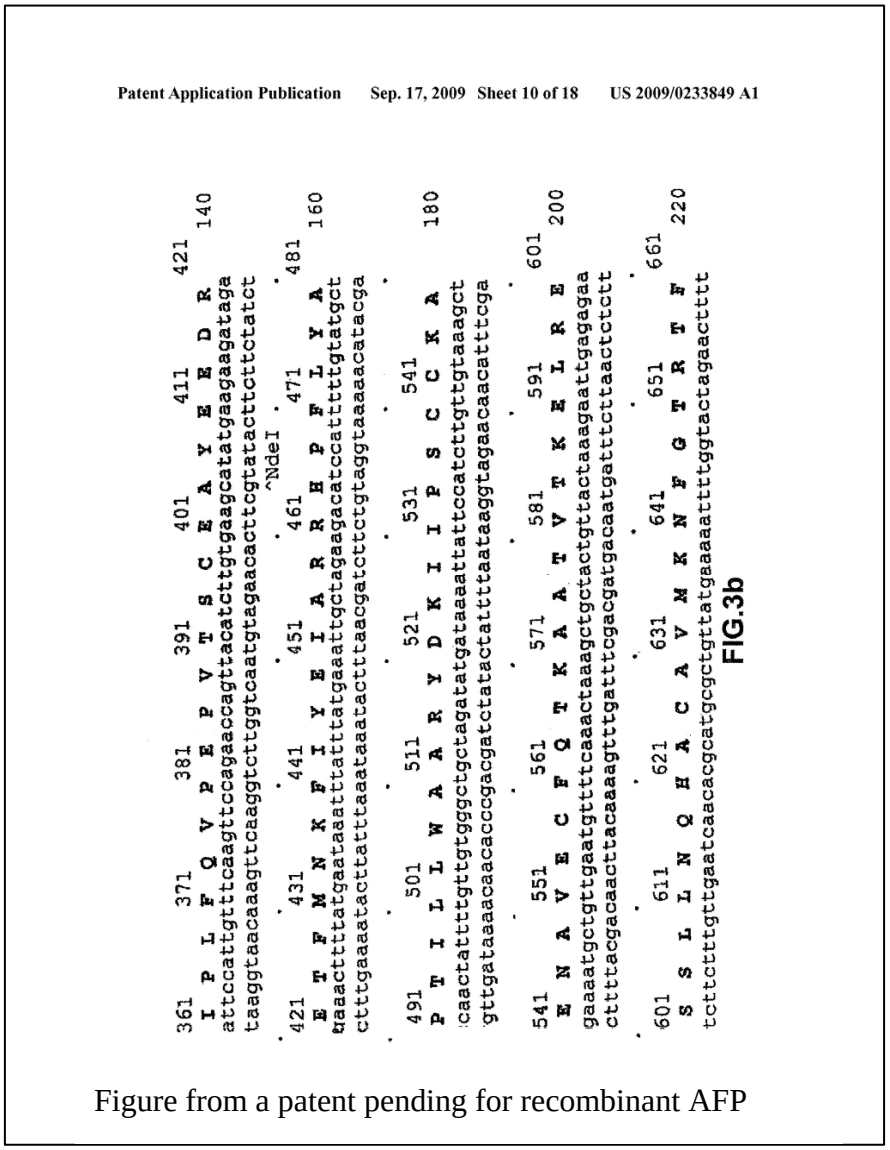

Figure from a patent pending for recombinant AFP

INTRODUCTION

Explanation of Data Listing and Analysis

Specimen Options: The ICP offers two choices for specimens for analysis. One specimen set is designed for those participants using hCG in their screening marker combination (**hCG sample set**). The other set is designed for those participants using free beta subunit 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 PAPP-A concentrate.

A limited number of additional samples sets are available upon request (free of charge) so that laboratories considering switching from hCG or vice versa can receive both the hCG and the free beta 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 rather than screening labs, or to laboratories that are not yet offering screening services. Outliers for gestational age (or 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 logarithmic transformation is used for the analysis of Down syndrome risks.

Conversion of Reported Down Syndrome Risks to First Trimester Risks: Most laboratories report first trimester risks, but some laboratories report second trimester or term risks. 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 by a single statistic, 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 (43% 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 to first trimester risks by multiplying by 1/0.57.

Down syndrome risks from participants using the free beta sample set are listed in the data sheets, and may be included in the calculation of summary statistics if the target levels are similar to those for hCG. Otherwise, the risks are listed 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 risk is small for most ages, use of decimal age rather than completed years can be important for an older woman, especially one whose age falls close to a whole year (*e.g.*, 34.1 versus 34.9 years). Each of these women would be considered to be 34 completed years, even though they are almost one year different. Laboratories 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 better precision. Almost all labs in the ICP report decimal age. Currently, the lab(s) that report integer maternal ages are listed separately on the data summary results. In the future, such results will be listed along with decimal ages but will not be included in the calculations.

NT MoM Reporting: The ICP provides a target NT MoM for most challenges. Participants need to generate the MoM values provided in the histories by trial and error, usually by entering various combinations of CRL/NT/GA values. 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 could reproduce the targeted MoM value. Almost all participants report NT MoM values that closely match the targeted value. If participants are having difficulty generating a reliable MoM, we can provide assistance.

The ICP also includes at least one challenge that provides a patient CRL and NT value (in mm), along with a set of NT and CRL values from the submitting 'hypothetical' sonographer (identified by initials) who provided those measurements. Participants can then use that set of sonographer-specific NT/CRL values to generate NT medians for use in converting the NT values (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 also provide an Excel spreadsheet that can be used to calculate the CRL/NT median equation with accompanying quality assurance parameters (e.g. slope and log standard deviation).

Labs that do not use the MoM for interpretation of NT 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.

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

Currently, all participants receiving the free beta sample set report risks as term risks, and these are listed in the "Report" column under the "Down S Risk" heading. Term risks are converted to first trimester risks and listed in the 1st trim column next to each free beta user's reported term risk. 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 term to first trimester risks). 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 are approximately 50% to 60% of the absolute values of hCG for patient specimens, 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 are not included in the risk summary statistics. Note also that the impact of hCG and free beta MoM values on the final risk may differ even for identical MoM values because the parameters used in the risk calculation differ for the two analytes.

PAPP-A Values: Many laboratories are now using the Beckman assay for measuring PAPP-A. The Beckman assay is calibrated in ng/mL, which gives absolute values that are approximately 300 higher than those reported in mIU/mL. Beckman results are now listed separately in the data sheets for each specimen. Also, some laboratories using the Beckman assay clinically report out PAPP-A results in ug/mL (ng/mL divided by 1000). These results are converted to ng/mL to avoid introducing further complexity in the report. Finally, most laboratories using the PerkinElmer assay report results in mIU/mL, but some report in mIU/L, which yields values 1000 times higher than those reported in mIU/mL. These values are converted to mIU/mL by dividing by 1000 in the report, again to avoid complexity.

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

- 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). For example, a group of laboratories appears to use only a single set of median NT values (rather than sonographer-specific reference ranges) for calculating MoM values. These differ significantly from the results reported by participants using sonographer-specific medians, but cannot be considered as outliers.
- Thick lined boxes identify values that are outliers as compared to the consensus (e.g., 25.0).

RESULTS

PAPP-A and MoM values (All specimens):

Values. Among the 28 participants, about half report in mIU/mL and half in ng/mL. There is no constant conversion between these units (see earlier reports) so separate analyses are performed for each group. The CVs for the 15 participants reporting in mIU/mL are generally higher (14 to 37%) than for the 13 participants reporting in ng/mL (4 to 6%). This is most likely due to the fact that three separate manufacturers' reagents are used to report in mIU/mL, while only a single assay reports in ng/mL. Therefore, between method differences are the likely reason for the high CVs seen for participants reporting in mIU/mL. Medians should account for these differences, and it should be expected that there are smaller differences between the CVs in these two groups after results are reported in MoM (see below).

MoM. The CV of MoM values for PAPP-A in this distribution range from 24% to 41%, with higher CVs for lower values. The CV of PAPP-A MoM values have historically always been relatively high for ICP results as compared to mass and MoM values for hCG, and this reflects the relatively high between-assay CV described above. This may change as the newer methods with better precision come on line, assuming laboratories have generated reliable kit-specific and population-specific median values. However, differences in between-kit mass values need to be proportional over the entire range of values, (*e.g.* differences in values attributable only to calibration differences) for MoM values to be comparable. In practice, this is not always the case, and methods may still show systematic differences in MoM results even if median values have been carefully determined. For samples FT-04 and FT-05, we stratified the MoM results by PAPP-A units (mIU/mL or ng/mL) and found the corresponding CV of the MoM levels to be about 26% and 10% respectively. This indicates that after conversion to MoM levels, there is a smaller difference in variability between the groups.

hCG mass and MoM values (All specimens):

Values. The all method CVs for the hCG values are typically low as compared to PAPP-A, and this distribution is no different (range 11% to 14%). Systematic between-kit differences may exist, but are likely to be small.

MoM: The all-method CVs for MoM values range from 10% to 14% for the five specimens in this distribution, which are almost as precise as the mass values themselves. This indicates that collectively, laboratories 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 PerkinElmer assays) is insufficient to allow a separate analysis (mean, SD, CV). However, from visual inspection of the data it is evident that the between-lab agreement is very good for this analyte.

MoM. As is true for free beta mass values, the number of participants using free beta subunit measurements (all use PerkinElmer assays) is insufficient to allow a separate analysis (mean, SD, CV). However, the limited data suggest that the between-lab agreement is also good.

Down Syndrome Risk (All specimens):

The consensus risks for the five specimens in this distribution, ranked from highest to lowest are **1:29** (FT-01), **1:105** (FT-02), **1:170** FT-04), **1:720** (FT-03), and **1:1400** (FT-05). The CVs of the log risk for these ranked risks are **30%, 19%, 18%, 10%, and 7%,** respectively. The CVs tend to decrease as risks get lower. The atypically very high CV of 30% for FT-01 likely reflects the fact that the PAPP-A trimmed mean MoM of 0.27 is very low and the corresponding hCG MoM of 5.43 is very high, falling at the extremes of the population distributions of MoM values. Small differences in MoM values can yield relatively large differences in the likelihood ratios that are used in the risk calculation. In addition, different laboratories may employ algorithms that use different truncation limits for calculating risks. Correlation coefficients used in the algorithms become quite important in these outlying regions.

Free beta results: The agreement in both the MoM values and the final risk is good for free beta versus for samples FT-01, FT-02, FT-3, and FT-04. These results are therefore included in the summary statistics for risk (after converting term risks to first trimester risks). The free beta MoM values for FT-05 are significantly different from the hCG MoM values and are not included in the summary statistics.

Calculation of gestational age and NT MoM Exercise (FT-01 and FT-01fb):

Participants were asked to calculate an NT MoM value, given a CRL of 48 mm (~ 11.6 weeks' gestation) and an NT value of 0.9 mm submitted by sonographer "FST". Participants were previously provided with a set of 150 NT/CRL measurements for FST and may have already calculated a sonographer-specific median equation (sent again in this distribution for those who may need to recompute the median equation). 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 laboratories 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 FST to be: median NT = $10^{(-0.373+0.00613*CRL)}$ using the Excel calculator supplied to participants. This equation yields an expected median NT value of 0.83 mm for a CRL of 48 mm, which results in a NT MoM value of 1.08 (0.9/0.83). The consensus NT MoM (calculated as the trimmed mean value) value is 1.08, equal to the expected value. Four of these results (light boxes) differ from the consensus (0.69, 0.77, 0.82 and 0.71 MoM), but have not been identified as outliers. Two of these four laboratories indicate that they do not use sonographer-specific medians (0.69, 0.77), but instead use a single set of medians, which likely accounts for the differences in reported NT MoM. The remaining two labs indicate that they do not know the source of their median values (0.82, 0.71). The lab with a MoM value of 0.62 has been identified as an outlier because they say that they use sonographer specific medians. Overall, previous exercises have shown that all laboratories can derive a median equation, given a set of sonographer-specific paired CRL/NT measurements. This exercise shows that most laboratories can (or do) use those medians for calculating a NT MoM for providing clinical interpretations.

A CRL of 48 mm was provided for this sample, requiring each participant to calculate gestational age. All but four labs reported a gestational age of 11.6 weeks; two reported 11.3 weeks and two reported 11.4 weeks. This is most likely due to the use of different conversion equations. For more information, see the 2009 FT-A report that includes an analysis of the 'CRL to decimal weeks' equation reported by each laboratory.

.

Dimeric inhibin-A (DIA)

First trimester DIA measurements were reported by four participants. Table 1 lists the reported DIA values and MoM levels for each sample. DIA values show reasonable between-method and between-lab agreement. MoM levels are more variable. Included in the table are the DIA likelihood ratios (LR) in the context of the other markers.

Table 1. Dimeric Inhibin-A results for FT-A 2010

Sample No.	Lab	Method	Value[1]	MoM	DS Risk (1:n)	DIA LR[2]
FT-01	A	Beckman Dxl	814	3.67	18	1.89
	B	Beckman Dxl	742	2.63	21	1.33
	C	Beckman Dxl	914	2.68	193	1.08
	D	Beckman Dxl	819	2.35	19	1.11
FT-02	A	Beckman Dxl	412	1.74	91	0.76
	B	Beckman Dxl	360	1.41	58	0.55
	C	Beckman Dxl	409	1.37	878	0.58
	D	Beckman Dxl	406	1.35	214	0.57
FT-03	A	Beckman Dxl	227	0.91	840	0.89
	B	Beckman Dxl	203	0.71	830	0.52
	C	Beckman Dxl	234	0.63	3740	0.52
	D	Beckman Dxl	223	0.62	1840	0.48
FT-04	A	Beckman Dxl	97	0.50	16	0.75
	B	Beckman Dxl	97	0.43	770	0.08
	C	Beckman Dxl	104	0.47	8360	0.15
	D	Beckman Dxl	98	0.40	3230	0.09
FT-05	A	Beckman Dxl	209	1.16	1800	0.72
	B	Beckman Dxl	179	0.81	5000	0.17
	C	Beckman Dxl	219	1.04	8180	0.29
	D	Beckman Dxl	202	0.85	9170	0.20

[1] Rounded value

[2] 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).

Interpretive Questions: First trimester screening for trisomy 18

Q1/Q2. Does your laboratory provide clinical results for trisomy 18 in the first trimester? All analyses are restricted to the 26 participants responding "Yes". Manufacturers were not included.

Q3. What markers do you use?
All 26 participants (100%) used NT measurements and all 26 also used PAPP-A measurements. Table 2 provides a listing of the various combinations used to provide a trisomy 18 risk.

Table 2

Combination (maternal age and)	**N (%)**
NT + PAPP-A	6 (23)
NT + PAPP-A + hCG	17 (65)
NT + PAPP-A + free beta	3 (12)
Any	26 (100)

Q4. How do you interpret results for trisomy 18?
All 26 participants provided information on how they report trisomy 18 interpretations (screen positive/screen negative) and the actual patient-specific risk. Table 3 summarizes those findings.

Table 3

Reporting methods	**N (%)**
Interpretation (+/-) on all reports	0 ( )
Interpretation and risk on all reports	16 (62)
Interpretation on pos only	5 (19)
Interpretation and risk on pos only	2 (8)
Interpretation on all, risk on pos only	3 (11)
Any	26 (100)

Before going on to the next question, we need to discuss the change in trisomy 18 risks by maternal age and by gestational age.

Age associated risk for trisomy 18: Most commonly, the estimated term risk for trisomy 18 is computed by dividing the age-associated Down syndrome risk by a factor of 10 (*e.g.* a 35 year old has a 1:385 term risk for DS and a 1:3850 term risk for trisomy 18). Recently, a large series of trisomy 18 diagnoses in the UK has allowed for an age-specific curve to be fitted (Savva et al., 2010). The form is as follows with age in completed years:

$$\text{Trisomy 18 probability} = \frac{1}{(1 + \exp(9.11 - (4.27 / (1 + \exp(-0.324(\text{age} - 38.9)))))))}$$

Using this equation, a 35 year old would have a term risk of 1:3530, similar to the abbreviated method described above. For 20, 25, 30, 35, 40 and 45 year old women, the corresponding risks would be about 1:8960, 1:8630, 1:7210, 1:3530, 1:734 and 1:213.

Trisomy 18 loss rates: The fetal loss rate for trisomy 18 is higher than for Down syndrome. Several years ago, a large collaborative study of fetal loss after diagnosis was reported (Morris & Savva 2008) that provided the best evidence now available. From the late first trimester to term, 72% of

trisomy 18 fetuses would be lost, with 65% of cases lost between the early second trimester and term. Thus, for every 100 trisomy 18 fetuses at birth, there would be 286 at the time of amniocentesis (100/(1-.65)) and 357 at the time of CVS (100/(1-.72)). To convert term risks to second trimester or first trimester risks, you should multiply the odds by 0.35 and 0.28, respectively. For example, the 37 year old with a term risk of 1:3530 has a second trimester risk of 1:1236 (0.35 x 3530) and a first trimester risk of 1:988 (0.28 x 3530). To convert a second trimester to first trimester risk, use the factor 0.8, i.e., 1:988 (0.8 x 1236).

Q5. What is the trisomy 18 screening cut-off level?
Among the 26 participants, 25 reported the trimester of risk which they report. Of these, 14 (56%) provide first trimester risks, six (24%) provide second trimester risks, and five provide term risks. We assumed that the participant who did not respond used first trimester risks. By far, the most common cut-off level among those reporting risks in the first or second trimester was 1:100 (19 of 21, or 90%). This may be related to the 1:100 risk cut-off that is commonly used for trisomy 18 screening during the second trimester. We standardized all of the risk cutoffs to the first trimester by adjusting the second trimester and term risks as described in Q4. Table 4 contains the results of that analysis.

Table 4

Trisomy 18 risk cut-off level (1:n)	N (%)
< 1:50	2 (18)
1:50 - 1:99	13 (50)
1:100	11 (42)
Total	26 (100)

Q6. What is the source of your algorithm?
Three labs reported developing an in-house algorithm, 20 reported using commercial software, and three reported other sources. Among the 20 reporting commercial software, 12 used LMS Alpha, four used Benetech PRA, three used SMS Maciel and one used PerkinElmer life cycle software.

Q7/Q8. What is the reported risk and interpretation?
Overall, 18 of the participants (73%) reported a 'screen positive' interpretation, with adjusted risks (after accounting for trimester) ranging between 1:2 and 1:92. The remaining eight participants (27%) either reported a screen negative (seven participants), or reported 'Other' for the interpretation, but assigned a low risk. The range of adjusted risks in this group was 1:108 to 1:2000.

Further Analyses: In order to gain more insight into how laboratories create their risk estimates and the associated variability in risk, we attempted to 'recompute' each laboratory's risk using their reported MoM levels and combination of markers (consensus NT, PAPP-A and hCG (or free beta) MoM levels were 1.7, 0.23 and 0.50, respectively). The woman was 39.5 years old, with the sample collected at 13.6 weeks' gestation. In this analysis, the reported risks are exactly as reported (i.e., not adjusted for trimester). Two participants with screen negative results were not able to obtain risk estimates from their software and a third did not report the necessary hCG MoM value. Besides age-associated birth prevalences and loss rates, the analysis also requires parameters for each of the markers (log means, SD, correlations and truncation limits) listed in Table 5. These are from a 2004 analysis, published in abstract form (Palomaki et al., 2004, available upon request). NT measurements have been adjusted for bias of ascertainment. The correlations between PAPP-A, hCG and free beta are 0.005, 0.004 in unaffected pregnancies; 0.449 and 0.420 in affected pregnancies, respectively.

Table 5.

Analyte	Log mean (log standard deviation) Unaffected	Trisomy 18	Truncation Limits
PAPP-A	0,000 (0.3127)	-0.5541 (0.2309)	0.2 – 0.7
hCG	0.000 (0.2127)	-0.4290 (0.3259)	0.3 – 1.0
Free beta hCG	0.000 (0.2978)	-0.6293 (0.3142)	0.2 – 1.0
NT	0.000 (0.1325)	0.2997 (0.2942)	0.8 – 2.2

Figure 1 shows a scatter plot of the reported trisomy 18 risks versus our 'recomputed' risks for the 23 participants with sufficient data. Although there is scatter around the expected Y=X line (indication that the risks agree), the values correlate reasonably well. The R^2 value indicates that 77% of the variability is explained by the varying biochemistry MoM levels and trimester of risk. Remaining unexplained variability includes: parameters, assignment of prior risk, and accounting for gestational age-related fetal losses. It might be possible to at least standardize the age-associated risks and loss rates, as those are published. In addition, hCG or free beta hCG measurements should be included in risk calculations. This addition would result in considerable improvement. This exercise did not include variability contributed by variations in the interpretation of NT, as all laboratories used a value of 1.70 MoM in their calculations.

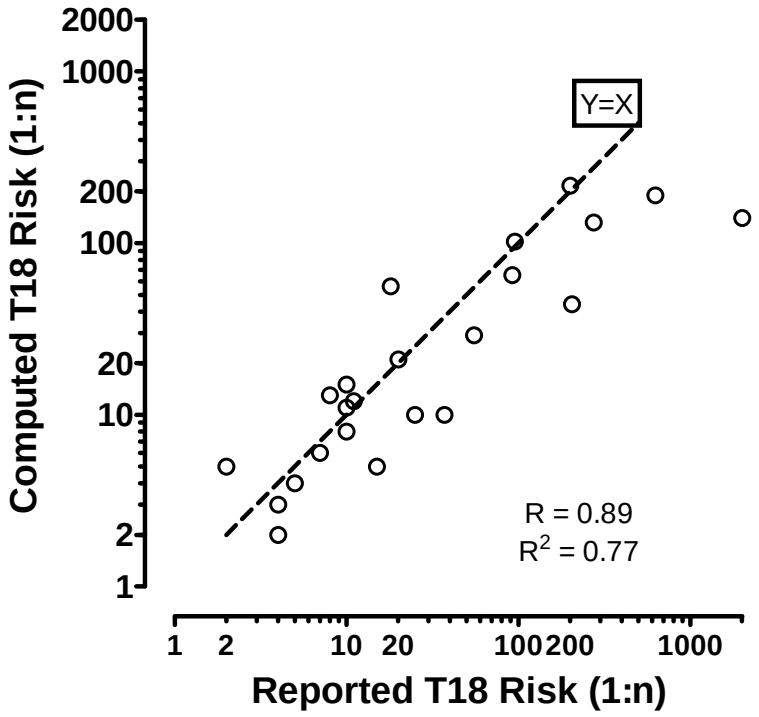

Figure 1. Scatterplot of reported trisomy 18 risks versus 'computed' risks using a standardized algorithm

References

Savva GM, Walker K, Morris JK. The maternal age-specific live birth prevalence of trisomies 13 and 18 compared to trisomy 21 (Down syndrome). *Prenat Diagn* 2010;**30**:57-64.

Morris JK, Savva GM. The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. *Am J Med Genet* 2008;146A:827-832.

Interpretive question: Integrated screening

Over the past three years, we have focused our integrated screening analysis on computing likelihood ratios showing the progression of risk from quad (or triple) to serum integrated (adding PAPP-A) to full integrated (adding NT). The serum and full integrated risks are now analyzed in the same way as the first trimester combined risks. Fourteen participants calculate integrated risks using first trimester markers (FT-02) in combination with the second trimester quadruple test (FP-04). All but one provided risks in the second trimester (that lab reports term risks). Table 6 lists these risks, along with the trimester of risk. The last column contains the risk after adjustment to the second trimester (for purposes of comparison). Only one outlier was identified. Similar results were found for serum integrated testing (last two columns). Four additional laboratories report integrated risks using first trimester markers in combination with the triple test. It is evident that these risks are, on average, considerably lower. These cannot be combined with the fourteen earlier estimates because there were no FP-A survey samples with inhibin-A MoM levels that could have been selected that would have yielded a likelihood ratio of 1.0.

Table 6

	Full Integrated Risk (with 2nd trimester quad)		**Serum Integrated Risk** (with 2nd trimester quad)	
Trimester of Risk	**Reported**	**Adjusted**	**Reported**	**Adjusted**
2	960	960	980	980
2	5,600	5,600	3,400	3,400
2	20	20	16	16
2	790	790	530	530
2	360	360	260	260
2	536	536	343	343
2	270	270	210	210
2	1,600	1,600	1,068	1,068
2	2,780	2,780	2,440	2,440
2	1,300	1,300	890	890
2	1,200	1,200	900	900
2	290	290	210	210
2	130	130	110	110
3	4,100	3,157	3,000	2,250
Data trimmed		20		16
Geo mean		**876**		**649**
CV		**16%**		**16%**
Mean - 2 SD		**99**		**77**
Low (obs)		**130**		**110**
High (osb)		**5,600**		**3,400**
Mean + 2 SD		**7,800**		**5,500**
	(with 2nd trimester triple)		(with 2nd trimester triple)	
3	17,000	13,090	8,500	6,375
3	15,000	11,550	7,700	5,775
3	5,600	4,312	2,800	2,100
3	14,000	10,780	8,300	6,225

For our ICP participants, the consensus second trimester estimate for the quadruple test is 1:875 (CAP specimen FP-04). The consensus PAPP-A MoM for specimen FT-02 is 0.49. The cross over point (likelihood ratio of 1.0) for the affected and unaffected PAPP-A distributions is approximately 0.6 MoM. Thus, the expectation for the PAPP-A MoM of 0.49 is for an increased risk for the serum integrated risk compared to the quadruple risk. The reported serum integrated risk of 1:649 meets this expectation. The NT MoM provided in the ICP history is 1.30. The cross over point for the affected and unaffected disruptions for NT MoM is approximately 1.4 MoM. The expectation is, therefore, that combining the NT MoM value of 1.3 with the serum integrated test would slightly lower the Down syndrome risk. The reported full integrated risk of 1:876 also meets expectation.

George J. Knight, Ph.D.	Glenn E. Palomaki, B.S.	(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