

First Trimester Interlaboratory Comparison Program

Distribution 2007 FT-A



This is not the desired outcome of sonographer and laboratory interaction

Sponsored by:
Department of Pathology and Laboratory Medicine
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DISCUSSION

Data Listing and Analysis

Reading the Data Listing: The five page data listing (attached) contains a summary of reported results for all participants; one page summarizing each of the five specimens. Your lab ID is listed at the beginning of the row with your results. Missing data (blanks) are likely due to participants being manufacturers that do not screen, or to laboratories that are not yet offering clinical services. Missing data may also result because some laboratories do not measure 'total or intact hCG' but some other marker. Outliers for gestational age or maternal age are identified as those outside +/- 0.2 weeks (or 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 trimmed standard deviations, after accounting for rounding, and after a logarithmic transformation (risk).

PAPP-A Stability: The problem of instability observed for PAPP-A in 2006 has not recurred. In particular, the dilution series yielded results that are close to expectation (see next page). Also, the overall consensus value of 2.70 mIU/mL for **FT-03** (a long-term control made up of patient sera from 12 weeks of gestation) is almost identical to the consensus values of 2.66, 2.80, and 2.67 mIU/mL obtained in the FT-A, FT-B, and FT-C distributions in 2006 for a different 12 week pool of patient sera.

Variance of Mass Unit Results: The PAPP-A analyte values for **FT-01** through **FT-04** yield CVs of 11 to 19%. In contrast, the CV for **FT-05** (a patient pool) was 30%, most likely because the consensus value is relatively low (0.60 mIU/mL). The Perkin-Elmer kit yields systematically lower values than DSL and DPC for this specimen, and it is not clear whether this is real or an artifact attributable to the sample. The CVs for hCG in all five specimens are similar (9% to 13%), suggesting that recombinant hCG reflects the specificity observed for patient samples.

Variance of MoM Results: The CVs for PAPP-A MoM values for **FT-01** through **FT-04** range from 19 to 27%, while the CV of 32% for **FT-05** is slightly higher, reflecting the higher analyte CV. The slightly higher CV for the MoM values as contrasted with the analyte values is not unexpected, since the imprecision in median values will add some additional variability. The CVs for the hCG MoM range from 6% to 13%, which is considered very good performance.

Variance of Risk Results: Almost all participants in the ICP report risks as first trimester risks. The few labs that report second trimester risks are not significantly different from those reporting first trimester risks and, consequently, all risks are analyzed collectively. The CVs of the log risk range from 8% to 21% for **FT-01** to **FT-05**.

2007 FT-A PAPP-A dilution study

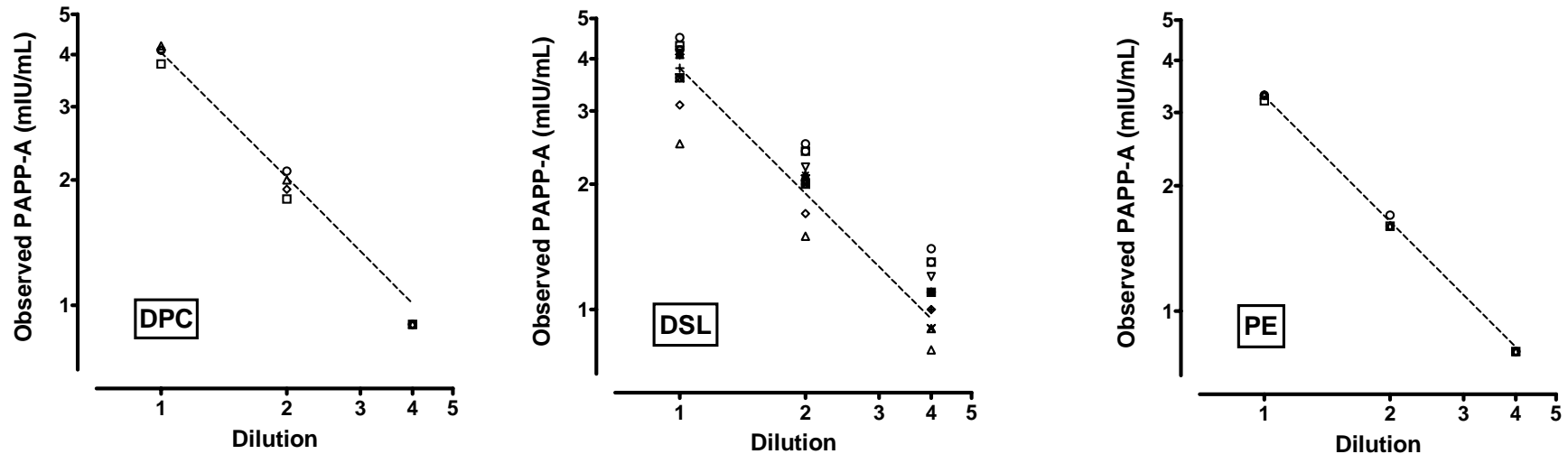


Figure 1. Dilution series for PAPP-A measurements stratified by reagent manufacturer

The three figures above show the dilution series for DPC (4 users), DSL (12 users) and PE (4 users) reagents. Sample **FT-01** was a pool of patient serum (neat), sample **FT-02** was manufactured by adding 1 part of **FT-01** to 1 part off-clot serum (1 to 2 dilution), and **FT-04** was 1 part **FT-01** to 3 parts off-clot serum (1 to 4 dilution). The PAPP-A results in mIU/mL observed by participating laboratories were plotted on the logarithmic Y-axis with the dilution plotted on the logarithmic X-axis. The mean PAPP-A value for the neat sample (**FT-01**) was calculated for each kit, and that value divided by two and by four is plotted as the dotted line on the graph. Overall, these data provide evidence that the dilutions are reasonably linear, although there is some additional spread in the DSL data (note, however, that the DSL users that began below the line remain below the line in a linear fashion). It is important not to overanalyze these data given the artificial nature of the samples used in this exercise.

Dimeric inhibin-A: DIA measurements were reported by three participants (Table 1). All reported using the same method (Di-01 or DSL). The following table provides the reported DIA values and MoM levels for all three samples. Included also is the likelihood ratio for DIA in the context of the other two markers. Overall, the laboratories report DIA values, MoM levels and changes in Down syndrome risk that are very consistent. This is true also for very high levels of DIA found in **FT-05** that would require dilution.

Table 1. Dimeric inhibin-A measurements for FT-A, 2007

Sample Number	Laboratory	Value	MoM	DS Risk (1:n)	DIA LR¹
FT-01	A	246.0	0.87	310	0.45
	B	238.0	1.08	1820	0.34
	C	262.0	1.19	467	0.45
FT-02	A	590.0	2.02	10	
	B	666.0	2.72	12	
	C	614.0	2.36	7	
FT-03	A	615	2.61	82	2.56
	B	657	2.94	35	5.60
	C	565	2.62	98	4.43
FT-04	A	391.0	1.50	560	0.93
	B	382.0	1.56	2400	0.92
	C	389.0	1.53	938	0.88
FT-05	A	6730.0	22.06	10	
	B	5830.0	22.00	6	
	C	5969.0	20.19	4	

¹ For each participant, the increase/decrease in risk from the combination of NT, PAPP-A and hCG, divided by the risk that includes DIA measurements. Blanks indicate that the likelihood ratio cannot be reliably determined, usually because both reported risks are very high (e.g., 1:10 and 1:10).

Supplemental Questions – Evaluating NT measurements from New Sonographers

Question 1: Of the 20 participating laboratories, 17 reported that they routinely convert NT measurements (in mm) to multiples of the median as part of clinical service. The three other non-clinical laboratories are manufacturers. Analysis will be restricted to the 17 clinical service laboratories.

Question 2: Of the 17 participating clinical laboratories, four (24%) always used a single set of medians, seven (41%) sometimes used sonographer- or center-specific medians, and six (35%) nearly always used sonographer- or center-specific medians. **Comment:** Optimal performance would require sonographer-specific medians for all NT measurements interpreted by the laboratory. However, laboratories must balance the possibility of unreliable sonographer-specific medians if few samples have been submitted, versus more reliable, but possibly inappropriate center- or published sets of medians.

Question 3: Of the 13 participating clinical laboratories that use sonographer- or center-specific medians for some observations, all provided an answer as to how those medians are computed for clinical use, seven (54%) reported that the computation needs to be performed off-line and then entered into the clinical software, and one (8%) reported using a third party for computation.

Question 4: Of the 17 participating clinical laboratories, 15 (88%) completed the assessment of the three sonographer datasets (NT in mm and CRL in mm). The following table summarizes the very consistent findings. Two of the 15 sonographers reported the slope rather than the percent increase, but the reported slope would have converted into the correct percent increase per week. **Comment:** Our question was poorly worded in requesting the “slope per week” where more correctly it should have been the “percent increase per week”. The slope will, of course, differ depending on whether the regression is on CRL (in mm) or on gestational age (in days, decimal weeks or completed week). There was wide variation in the number of significant digits reported. As a way to become more consistent, we suggest that increase per week be reported as an integer (e.g., 16, 5, 50), median MoM be reported to two decimal places (e.g., 0.99, 1.00, 1.02) and log standard deviation to three (or four) places (e.g., 0.124, 0.087, 0.180).

Table 2. Median (range) of reported QA parameters for three ‘artificial’ sonographers

Sonographer Initials	Number of samples	Increase/wk (%)	Median NT MoM	Log standard deviation (SD)
HFW	60 (60 - 60)	16 (16 – 16)	0.99 (0.99 – 0.99)	0.124 (0.12 – 0.124)
DAB	77 (77 - 77)	5 (5 – 5)	1.00 (1.00 – 1.00)	0.087 (0.086 – 0.09)
GGU	76 (75 - 77)	40 (38 – 40)	1.02 (1.01 – 1.02)	0.180 (0.1787 – 0.18)

Question 5: Of the 15 laboratories reporting results for Table 2, all responded to this question.

Question 5A: “Which, if any, of the QA parameters would raise your concern, and why?” One laboratory (7%) reported that none of the parameters are concerning. Another two laboratories (13%) didn’t know or don’t evaluate such parameters, and the results from the remaining 12 laboratories are shown in Table 3. Correctly, none found problems with the median NT MoM. There was good agreement that sonographer HFW was fine, sonographer DAB has only a small increase per week and GGU had a rather high increase per week. Although all laboratories

found the log SD acceptable for HFW, four (33%) found the log SD too tight (low) for DAB, and six (50%) found the SD too broad (high) for GGU.

Table 3. Interpretation of reported NT quality assessment parameters for three ‘artificial’ sonographers

Sonographer	Increase/wk (%)			Log SD		
	0/Low	12/OK	0/High	0/Low	12/OK	0/High
HFW	0/Low	12/OK	0/High	0/Low	12/OK	0/High
DAB	12/Low	0/OK	0/High	4/Low	8/OK	0/High
GGU	0/Low	1/OK	11/High	0/Low	6/OK	6/High

Question 5B: “Do you have ‘target’ values for any/all of these QA parameters, and if so, what are they?”

Three laboratories reported having no targets, and two others did not know. Table 4 summarizes the responses of the remaining 11 clinical laboratories. The target for the percent increase per week was 15 to 25 or 10 to 30 for eight laboratories (73%). There was less consensus for the log SD targets, with most having a lower limit of 0.09 to 0.11 and an upper limit of between 0.13 and 0.15. **Comment:** NTQR has proposed a range for the increase per week of 15 to 25%, a target MoM of 1.00 (with no fixed limits) and a range of log standard deviation from 0.11 to 0.15 (<https://www.ntqr.org/SM/Provider/wfProviderInformation.aspx#report>). The Fetal Medicine Foundation will recertify a sonographer if between 40% and 60% of the NT values are above the median (on 30 or more observations) or, if the submitted NT images are of good quality. Setting reasonable limits for the laboratories to identify sonographers with outlying QA parameters is an evolving area. Interestingly, none of the laboratories mentioned statistical significance or number of samples needed for an evaluation.

Table 4. Target values for NT quality assessment parameters

Parameter	Range	Number
Increase/wk (%)	15 to 25	5
	10 to 30	3
	None	3
Log SD	0.09 to 0.14	1
	< 0.15	1
	0.10 to 0.15	1
	0.11 to 0.15	1
	0.09 to 0.13	1
	0.09 to 0.14	1
	None	5
Median NT MoM	Target 1.00	2
	0.90 to 1.10	4
	None	5

Question 6: Write a short narrative that describes your laboratory's methods of determining what is needed for a 'new' sonographer. All clinical laboratories responded to the query. The following are transcribed from the comments received with only minor edits for clarity. Text in brackets (e.g., [commercial software]) indicates editors' remarks.

Evidence of at least some training, type not specified. At least 20 data points (paired CRL/NT) requested. Require log SD of MoM about 0.10 and slope about 20%, or consistency with center equation if part of a center that already exists. We have noticed that centers sometimes do not alert us to new sonography staff members.

NT licensure required (FMF or US and data to NTQR).

We require that a sonographer's certificate of competence from one of the certifying agencies (FMF, MFMF, NTQR) be received at the organization before any report is issued. We do not require any NT/CRL measurements prior to beginning. Sonographer-specific medians are calculated as soon as enough data have been collected. A graphic representation of the medians (including QA parameters) of all of a specific site's sonographers (de-identified) is periodically sent to each center. Graphs of individual sonographers are also available. We are still discussing the role of this organization in improving the performance of those sonographers whose medians are borderline or unacceptable. NT/CRL measurements are periodically transferred to the appropriate certifying agency.

A new sonographer must be certified by NTQR and have an active registration number. In addition, a physician who is also certified by NTQR and has an active registration number must review all NT scans. We send all NT results to NTQR monthly and use their referent group as expected performance. New sonographers are then assigned to our center specific "all sonographer" median equation as an interim solution. Their performance is reviewed every three months and discussed with the reviewing physician, if in a small group. A [commercial software] "Median NT by crown-rump length" report is printed quarterly and the following parameters are examined: Median NT -- median NT must not be statistically significantly different from 1.00; 10th and 90th centiles – these are compared to the center specific "all sonographer" results and are interpreted along with the regression equation and % increase in median NT per week; Regression equation – coefficient A should be 0.6 ± 0.1 and coefficient B should be 1.014 ± 0.002 ; % increase in median NT per week – should be 15-25%. If the above criteria are met and the sonographer has completed 200 scans a sonographer specific median equation is assigned. Quarterly monitoring is continuous.

So far we have kept our data [from one center] together as one center. We should probably track them individually, but haven't so far. If we receive a request from an office/ultrasonographer outside [that center], we have requested the following:

- Evidence of attendance at an approved course (Nicolaides [FMF])
- Ideally, CRL measurements with an associated NT from 40-50 different patients with GA 11 weeks to 13 weeks, 6 days.
- We do have data for 2 other ultrasonographers but have not used them because they are not using our lab.
- COMMENT: we have requested NT data from a couple of offices that have wanted to send us samples – they are generally upset by the request because [a national laboratory] doesn't request this information.

We require new sonographers to be credentialed by the FMF or NTQR and require that they submit their sonographer number from these organizations. We do not require a minimum number of NT/CRL measurements. Credentialed sonographers are accepted regardless of performance as long as they maintain their credentials. As this time we are leaving assessment of performance to the credentialing organization.

Minimum of 100 NT and CRL measurements with slope per week, median, and log SD of NT MoM within the “target” values and certification (including certification # for cross-checking against registry of certified sonographers) by either NTQR or FMF NT certifying organizations. Sonographers from a specific center are NEVER considered acceptable regardless of performance – performance must ALWAYS be validated as meeting quality metrics criteria.

Sonographers and clinicians must be NTQR (US) or FMF (UK) credentialed. Proof is required. No additional requirements for new sonographers.

A new sonographer must provide documentation of certification of training in measurement of NT. We request a set of measurements with which to evaluate their NT medians, and to ensure that the QA parameters are within acceptable limits. We will provide feedback to sonographers concerning their medians, by reporting their QA parameters (with desired range) and plotting their measurement distribution and regression superimposed over a “reference” distribution.

If a sonographer has attended one of the classes run by either NTQR or FMF, and has not received their credentials yet, we will require at least 20 images (CRL and NT) to be reviewed. If their images are found to be of high quality, they will be allowed to have their measurements incorporated with our biochemical markers. Those sonographers who do not submit acceptable images will be asked for 10 additional images and will receive our help sheet which gives pointers on the acquisition of NT. Sonographers who have yet to be approved may continue to submit their images for review and evaluation with regard to slope, log SD and median based on our standard equation, however, their patients will only be allowed to have the serum integrated test until they are approved.

We request 50 cases with CRL = gestational age and NT. These values are entered into [a commercial software program] to calculate a median for this sonographer. We also request proof of NT certification. We monitor the NT median MoM on a monthly basis.

Sonographer certification for NT measurements is required. A copy of the certification is retained on file in the laboratory. No minimum number of measurements is required. The laboratory will submit sonographic-specific NT measurement data to NTQR to monitor and provide feedback.

Require proof that sonographer has passed FMF and/or FMI courses. Minimum number NT-CRL to start = 15.

We require certification through NTQR or FMF. We ask for a copy of sonographers' certificate prior to using their nuchal translucency values. Once certified, we ask for the measurements they turned in for certification and store them in a sonographer-specific file, and add more measurements that come in with samples. We have overall medians based on the scans from all the certified sonographers that we use for new sonographers.

Once we have many measurements from the same sonographer (about 50 from a variety of gestational ages), we send the data to [a commercial software program] who performs a regression analysis to create sonographer-specific medians. [the commercial software program] tells us verbally if the data looks "in line with other centers", but we do not currently compare the data to specific QA parameters ourselves. Samples from that sonographer will then use his or her own medians, and their measurements will continue to be included in the overall medians used for sonographers who do not have individual medians yet. Sonographers' medians are monitored monthly. If their median MoM rises above 1.1 or below 0.9 for several months in a row, the coefficients of the regression for that sonographer's medians are recalculated by the software.

Sonographer needs to have succeeded theoretical and practical courses (provided by FMF, FMI, or equivalent). No certificate is required. Minimum of NT/CRL to establish user-specific curve: 15. Review of % increase NT per week: needs to fall between 5 and 50%. Sonographers could be asked to provide additional NT/CRL when the shape of the curve does not meet the expected increase. All sonographers would have to undertake the training and pass the initial performance criteria.

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