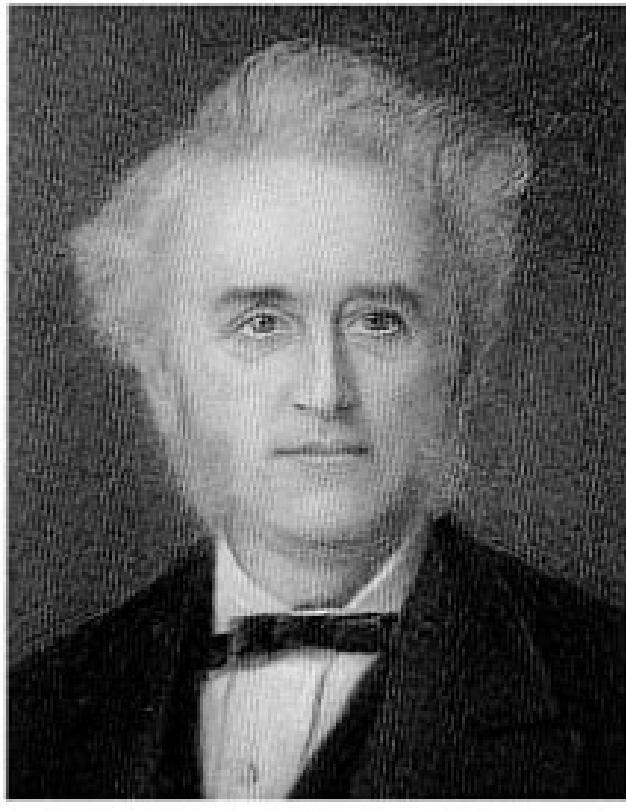


First Trimester Interlaboratory Comparison Program

Distribution 2009 FT-C



English physician John Langdon Down
(credited with first describing the condition in 1866)

Sponsored by:
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INTRODUCTION

Explanation of Data Listing and Analysis

Specimen Options: The ICP offers two choices for specimens. The first specimen set is designed for those participants using hCG in their screening marker combination (**hCG sample set**). The second 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.

The PAPP-A target concentrations in both sets are the same for all five specimens. However, participants should not test or report hCG measurements made in the free beta set, nor free beta measurements in the hCG set. This can result in spurious results for the following reasons:

- *In hCG specimen sets:* specimens spiked with recombinant hCG can yield a very high non-physiologic level of measured free beta subunit (the recombinant hCG preparation has a significant amount of free beta present).
- *In free beta specimen sets:* some free beta specimens are spiked with recombinant free beta subunit and others are made by spiking normal human serum with recombinant free beta subunit and PAPP-A concentrate. However, no recombinant hCG will have been added to either type of sample, so measurement of these specimens for hCG is not appropriate.

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 trimmed standard deviations, after accounting for rounding. A logarithmic transformation is used for the analysis of Down syndrome risks.

Conversion of reported 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 $1:1000 \times 0.74$, or 1:740. Term risks are converted to first trimester risks by multiplying by 0.57.

Down syndrome risks from participants using the free beta sample set are listed in the data sheets, but are not included in the calculation of summary statistics. 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 full decimal 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 risk 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, but 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 small numbers. However, each of these participants can review their own results by inspection of the data listing. Currently, all participants receive the free beta sample set report in term risks and these are listed in the “**Report**” column under the “**Down S Risk**” heading. **These term risks are probably not comparable to the risks listed in the “1st trim” column, even if converted to 1st trimester risks, because the free beta subunits levels are not necessarily proportional to hCG levels in the calculation of risk.**

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 appear 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 are not outliers.
- Thick lined boxes identify values that are outliers as compared to the consensus (e.g., **25.0**).

RESULTS

FT-11 and FT-11fb:

Participants were asked to calculate an NT MoM value, given a CRL of 70 mm (~ 13.1 weeks' gestation) and an NT value of 1.4 mm submitted by sonographer "FST". Participants were 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 = $10^{(-0.373+0.00613 \cdot \text{CRL})}$ using the Excel calculator supplied to participants. This equation yields an expected median NT value of 1.14 mm for a CRL of 70 mm, which results in an NT MoM value of 1.23 (1.4/1.14). The consensus NT MoM (calculated as the trimmed mean value) value is 1.21, close to the expected value. Two results (light boxes) differ from the consensus (0.80 and 0.83 MoM). Both of these participants indicate that they do not use sonographer specific medians. Rather, they use a single set of medians, which likely accounts for the difference. Overall, all laboratories can derive a median equation given sonographer NT/CRL values, and most can (or do) use those medians when providing clinical interpretations.

A CRL of 70 mm was provided for this sample, requiring each participant to calculate gestational age. Assigned gestational ages for FT-01 ranged from 12.9 to 13.6 weeks. As discussed in the 2009 FT-A report, differences most likely reflect the 'CRL to decimal weeks' equation selected for use by each laboratory.

Twelve laboratories reported using the Beckman Access or DXI for measuring PAPP-A, and values for these users are listed separately from the other methods. The CV of values for Beckman users is 6% as contrasted with 18% for all other methods combined. Between-assay imprecision is expected to be greater than within-assay impression. In addition, values in mIU/mL are reported with only one significant figure might further inflate the PAPP-A CV, compared to three or four significant figures for those reporting ng/mL. The CVs of MoM levels is relatively high (22%) as compared to the CV of values, as is typically observed. The consensus value for hCG is 367 IU/mL, and the CV is 23%. This CV is much higher than that calculated for specimens with values around 100 IU/mL, indicating that hCG methods may be more variable at high values than at lower values. The CV of 41% for the consensus log risk of 1:5 is very high, as is commonly observed for very elevated risks. This reflects the fact that the PAPP-A trimmed mean MoM of 0.14 is very low and the corresponding hCG MoM of 6.29 is very high, falling at the extreme of the population distribution of values. Small differences in MoM values can yield relatively large differences in the likelihood ratios that are used in the risk calculation. All laboratories called the specimen screen positive.

FT-12 and FT-12fb:

This specimen is a pool of sera from 12 week pregnancies, and may, therefore, more accurately reflect actual between-lab and between-kit differences than manufactured samples. The CVs for PAPP-A mass values are low for both the Beckman assay and all other methods combined (3% and 7%, respectively). The CV for the PAPP-A MoM is distinctly higher (28%). The CVs for the hCG value and MoM values are typically low (10% and 12%, respectively). It is noteworthy that the CV for the hCG MoM is almost as low as for the values themselves, suggesting that laboratories

have reliable hCG median values. The trimmed mean risk was low (1:640), and all but one participant reported it as screen negative.

FT-13 and FT-13fb:

The CVs for PAPP-A values are relatively low for both the Beckman assay and all other methods combined (5% and 11%, respectively). The CV for the PAPP-A MoM is much higher (28%), as is typically observed. The CVs for hCG values and MoM are 15% and 10%, respectively. The consensus first trimester risk is 1:350, lower than typical first trimester screening cut-offs used by ICP participants (approximate range 1:150 to 1:290, see answers to Q2/Q3 below). When the risks are close to screening cut-off levels, the expectation is that some laboratories will interpret their risk as screen positive while others will not. In fact, 33% call it screen positive while the rest call it screen negative. The 2 to 1 ratio of screen negative to screen positive is consistent with the consensus risk being lower than screening cut-offs.

FT-14 and FT-14fb:

The CVs for PAPP-A values are relatively low for both the Beckman assay and all other methods combined (4% and 9%, respectively). As is observed for almost all other specimens the CV of the PAPP-A MoM levels is much higher than the values themselves. The CVs for both hCG values and MoM levels were typically low (10% and 12%, respectively). The consensus risk for this woman was low (1:500), and all but one participant considered it screen negative.

FT-15 and FT-15fb:

The CVs for PAPP-A values are relatively low for both the Beckman assay and all other methods combined (4% and 11%, respectively). Also, the CV of the PAPP-A MoM is again much higher (23%) than for the PAPP-A values. The CVs for both hCG values and MoM levels are typically low (11% and 8%, respectively). The trimmed mean risk was 1:1900 and all participants called the specimen screen negative.

Sample dilution challenge:

In this distribution sample FT-13 was created to specifications, and an aliquot of that sample was diluted 1:1 in normal human sera to create sample FT-15. It can be safely assumed that virtually no PAPP-A, hCG or inhibin-a was present in the diluent. Thus, the expectation is that the ratio of sample FT-15 to sample FT-13 should be about 0.5. Table 1 shows the reported results for all participants. The results are sorted by PAPP-A values so that the table is easier to read. Overall, the consensus ratios for PAPP-A, hCG, inhibin-a and the free beta subunit of hCG are 0.51, 0.52, 0.50 and 0.50, respectively.

Table 1. Diluted sample challenge (FT-15 is FT-13 diluted 1:1 with normal human sera)

Sample FT-13 (A)				Sample FT-15 (B)				B/A			
PAPP-A	hCG	DIA	Free β	PAPP-A	hCG	DIA	Free β	PAPP-A	hCG	DIA	Free β
1.5 IU/mL	125.1			0.8	72.5			0.53	0.58		
1.6	103.0			0.8	60.4			0.50	0.59		
1.7	151.0	359		0.9	69.9	184		0.53	0.46		
1.8	157.9			1.0	71.7			0.56	0.45		
1.9	142.7	337		1.1	77.5	164		0.58	0.54	0.49	
1.9	146.5			0.9	76.3			0.47	0.52		
1.9	138.7			1.0	73.6			0.53	0.53		
1.9				0.9				0.47			
2.0			18.8	1.0			9.0	0.50			0.48
2.1	153.8			1.1	78.7			0.52	0.51		
2.1	112.0			1.2	67.4			0.57	0.60		
2.1			17.9	1.0			9.3	0.48			0.52
2.2	291.6			1.0	152.6			0.45	0.52		
2.2			18.4	1.0			9.4	0.45			0.51
540.0 ng/mL	132.0	342		270.0	72.9	182		0.50	0.55	0.53	
554.4	144.3			305.2	79.4			0.55	0.55		
555.0	169.0			302.8	84.5			0.55	0.50		
564.2	161.7			287.4	73.0			0.51	0.45		
569.0	163.0			290.0	77.8			0.51	0.48		
587.0	179.9			300.0	82.5			0.51	0.46		
590.0	180.6			300.0	90.9			0.51	0.50		
593.0	175.2			299.0	89.4			0.50	0.51		
600.0	153.5	354		290.0	77.4	171		0.48	0.50	0.48	
607.7	146.6			310.1	73.6			0.51	0.50		
626.6	182.7			308.3	94.9			0.49	0.52		
641.6	151.3			317.3	75.6			0.49	0.50		
	118.6				62.2				0.52		
Consensus ratio								0.51	0.52	0.50	0.50
CV of the ratio								6.4%	7.9%	5.5%	4.3%

Dimeric inhibin-A (DIA)

First trimester DIA measurements were reported by four participants. Table 2 lists the reported DIA values and MoM levels for each of the five samples. DIA values show reasonable between-method and between-lab agreement. MoM levels are more variable, but show good between-lab agreement. Included in the table are the DIA likelihood ratios (LR) in the context of the other markers.

Table 2. Dimeric Inhibin-A results for FT-C 2008

Sample No.	Lab	Method	Value ¹	MoM	DS Risk (1:n)	DIA LR ²
FT-11	A	Beckman Dxl	781	3.64	10	1.00
	B	Beckman Dxl	803	3.57	8	3.25
	C	Beckman Dxl	813	3.42	4	1.00
	D	Beckman Access	785	2.97	5	1.00
FT-12	A	Beckman Dxl	278	1.02	140	0.79
	B	Beckman Dxl	262	1.31	1300	0.69
	C	Beckman Dxl	310	1.37	1250	0.78
	D	Beckman Access	296	1.24	1380	1.26
FT-13	A	Beckman Dxl	342	1.28	280	0.79
	B	Beckman Dxl	337	1.15	1300	0.70
	C	Beckman Dxl	359	0.97	766	0.82
	D	Beckman Access	354	0.99	488	0.69
FT-14	A	Beckman Dxl	289	1.01	180	0.83
	B	Beckman Dxl	261	1.24	740	0.65
	C	Beckman Dxl	285	1.17	1370	0.65
	D	Beckman Access	286	1.14	1150	1.27
FT-15	A	Beckman Dxl	182	0.72	1500	0.65
	B	Beckman Dxl	164	0.57	>10000	-
	C	Beckman Dxl	184	0.52	11400	0.42
	D	Beckman Access	171	0.49	6850	0.36

¹ Rounded value

² For each participant, the DIA 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 likelihood ratio 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).

Supplemental analysis: PAPP-A units comparison

As reported in the 2009 FP-B distribution, the PAPP-A results from the new Beckman assay (Be-01) are quite different from the other assays currently in use, primarily due to the use of different units. We now separate these results prior to analysis, but continue to analyze the resulting MoM levels regardless of the kit/reagents used. This allows for a relatively simple comparison between the methods. In this distribution, the ratios were (from lowest to highest PAPP-A result) FP-15, 304 ng/IU, FP-13, 305 ng/IU, FP-11, 318 ng/IU, FP-14, 357 ng/IU; and FP-12, 367 ng/IU. The median conversion factor for these five challenges is 330 ng/IU, with all but one below the median of 362 ng/IU derived in the last distribution. These challenges highlight the changing nature of the conversion between ng/mL and IU/mL and reinforce our recommendation that participants not use any conversion factors in reporting PAPP-A results. For a more complete discussion of this issue, see the FP-B 2009 summary report (available on-line at www.ipmms.org).

Interpretative 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). This exercise has pointed out the desirability of having a consistent parameter set to use for generating all sets of risks reported from your laboratory. In this distribution, the serum and full integrated risks are analyzed in the same way as the first trimester combined risks (see data listing).

In the following analysis the consensus second trimester estimate for the quad test for specimen FP-19 is 1:480. The consensus PAPP-A MoM is 0.55 and the NT MoM is 1.60 for specimen FT-12. Table 3 shows the results of this analysis from the 17 participants reporting integrated risks. Twelve participants report second trimester integrated risks, while five report term risks (for comparison, these latter risks are multiplied by 0.74 to convert them to second trimester risks). Four laboratories use a triple marker rather than quad marker. However, the FP-19 inhibin consensus value was 1.81 MoM, indicating that integrated risks calculated using quad markers are reasonably similar to those calculated using triple markers. Therefore, we combined the triple and quad 'integrated' test results together for analysis. The CVs of the risks for serum integrated and full integrated are **9%** and **13%** for consensus estimates of 1:230 and 1:98, respectively. To put the results in perspective, there have been three challenges in 2009 for the first trimester combined test that have had consensus values between 1:50 and 1:500 (the range in which these two risks fall). They are: FTB-08, risk of 1:120, **12%** CV; FTB-10, risk of 1:68, **15%** CV; FTC-13, a risk of 1:350, **13%** CV. The outlier rate of 3 out of 34 reported risks for the serum and full integrated risks in the current exercise (**9%**, 95% CI 2% to 24%) is higher than the corresponding 3 out of 65 (**5%**, 95% CI 1% to 13%) for the first trimester combined test, but not significantly so ($p=0.4$). Participants with outlying values (or those near to the upper/lower limit, might want to check their MoM levels and algorithm.

Table 3. Analysis of Reported Integrated risks for 2009, FP-C

	Serum Integrated Risk (1:n)		Full Integrated Risk (1:n)	
	Term	2 nd trimester	Term	2 nd trimester
		170		65
		175		69
		280		140
		180		75
		700		100
		202		94
		83		33
		1700		260
		153		62
		190		80
		25		10
		190		70
	300	213	110	78
	470	334	200	142
	440	312	190	135
	290	206	140	99
	700	497	530	376
data trimmed		25, 1700		10
trim mean		230		98
trim sd		0.22		0.25
CV		9%		13%
mean-2sd		84		31
obs. low		83		33
obs. high		700		376
mean+2sd		617		310

Supplemental Questions: Epidemiological Monitoring for First Trimester Combined Testing

Q1. Does your laboratory provide clinical results? Of the 27 respondents in this distribution, 24 report providing clinical results for first trimester Down syndrome screening. The remaining analyses are restricted to these 24 participants.

Q2/Q3. What is your first trimester risk cut-off? / trimester of risk? Overall, 16 of the 24 participants (66%) reported the cut-off as first trimester risks, three (13%) in second trimester, and five (21%) at term. To allow more direct comparisons, the cut-off levels for those using second trimester or term risks were multiplied by 0.74 and 0.57, respectively. After conversion of all responses to first trimester risks, the cut-off levels ranged from a high of 1:114 (a 1:200 term risk) to 1:270 (reported as a first trimester risk). The results are shown in Table 4.

Q4. What percent of women are screen positive? A total of 19 participants reported the proportion of women with screen positive test results. The results ranged from 2.2% to 18.5% (median 7.5%). The results are shown in Table 4.

Q5. What percent of your population is age 35 or older at EDC? The same 19 participants reported the proportion of their population age 35 or older (1 additional participant reported 12.5%, but did not report the corresponding screen positive rate and was excluded from further analyses). The proportion ranged from 6% to 63.9% (median 25.8%). The results are shown in Table 4.

Table 4. Summary of first trimester risk cut-off levels, proportion age 35 and older, and screen positive rate for participants providing clinical Down syndrome screening services

Risk cut-off (1:n)¹		Proportion \geq age 35		Screen positive rate (%)	
Range	N (%)	Range	N (%)	Range	N (%)
< 150	1 (4)	<10%	1 (4)	2.0-3.9%	2 (8)
150-199	6 (25)	10-19%	3 (13)	4.0-5.9%	4 (17)
200-249	14 (58)	20-29%	9 (37)	6.0-7.9%	5 (21)
250-299	3 (13)	30-39%	5 (21)	8.0-9.9%	4 (17)
		40-49%	1 (4)	10-11.9%	3 (13)
		\geq 50%	1 (4)	12-13.9%	0 (0)
		missing	4 (17)	\geq 14%	1 (4)
				missing	4 (17)
All	24 (100)		24 (100)		24 (100)

¹ after converting reported cut-offs in 2nd or term risks (multiplied by 0.74 and 0.57, respectively)

Q6. Do you monitor median MoM levels? All 24 participants report that they monitor their median MoM levels. However, only 19 participants (79%) actually reported levels for both analytes.

Q7. If yes, provide the recent median MoM levels for each analyte (and time interval, if available). Although all 24 reported monitoring their median MoM levels, two laboratories provided no data, and one lab reported no value for hCG. Also, we erred in allowing for only 1 decimal point. However, many participants reported the median MoM to 2 decimal places.

- a. PAPP-A. A total of 22 participants reported median PAPP-A levels. We assume the remaining two laboratories also measure PAPP-A, but didn't report results. The MoM levels ranged from 0.90 to 1.10, with 15 of the 22 participants (68%) between 0.95 and 1.05. It is recommended that laboratories take action when the median MoM falls outside the range of 0.90 to 1.10 (+/- 10%); 22 of 24 participants reported results within these limits (92%). However, because we did not allow for two decimal places, it is possible that values reported with only one decimal point might actually fall outside these limits (e.g., 0.88 might be reported as 0.9). Nine laboratories reported results from 1 month's data (possibly indicating that medians are monitored monthly). The remaining laboratories reported median MoMs calculated using between 2 and 10.5 months of data (evenly distributed over that time period). This latter group might also monitor monthly, but provided the most recent 'window' of data.
- b. hCG (or free beta). A total of 20 participants reported median hCG or free beta MoM levels. The MoM levels ranged from 0.9 to 1.2, with 12 of the 20 (60%) between 0.95 and 1.05. The distribution of number of months included was similar to that found for PAPP-A.
- c. Inhibin A. Four participants reported inhibin-A median levels. They ranged from 0.94 to 1.1 with included months similar to results for the other markers.

Discussion

Participants report a wide range of screen positive results (2% to 18.5%) for first trimester combined testing. At least some of this variability is likely due to the risk cut-off level chosen (first trimester risks ranging from 1:114 to 1:270) and the maternal age distribution of the screened population (proportion age 35 and older ranging from 6% to 64%). Other factors that may also be involved include the median MoM level for each of the analytes and what analytes are included (e.g., inhibin-A). In order to explore these relationships further, we performed a stepwise linear multivariate analysis of these five covariates to predict the screen positive rate. The results for two participants (one with an outlying screen positive rate and another with an outlying proportion age 35 and older) were excluded from analysis, leaving results from 17 participants for analysis. In two instances median MoM levels were not reported, and we assumed a result of 1.0. The one laboratory reporting integrated risks using free beta hCG measurements was grouped with those reporting hCG measurements. This was possible because the FT sample chosen had reasonably similar hCG and free beta hCG MoM levels (1.09 and 1.51, respectively). Finally, use of inhibin-A measurements was taken as a 'yes/no' rather than a median MoM level as only four participants reported using this analyte.

The strongest predictor is the proportion of women age 35 and older. It is responsible for 52% of the variability ($r^2=0.52$) in the reported screen positive rates. The next most important predictor is the hCG median level, which explains another 19% of the variability. The remaining three variables (PAPP-A median MoM level, screening cut-off level and whether inhibin-A was included) did not enter the model. PAPP-A probably did not provide predictive value because all median MoM levels were within +/- 0.1, and 68% were within +/- 0.05. It is not clear why the screening cut-off level was not an important predictive factor, but it was probably due to the relatively small range of reported cut-off levels. Overall, these findings are somewhat surprising, and we would like to repeat the question in the near future. If there is a reason your group was unable to provide a screen positive rate for first trimester combined testing, perhaps steps could be implemented so that this rate is available for future analyses.

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