NEW YORK
state department of
HEALTH

Nirav R. Shah, M.D., M.P.H.
Commissioner

Sue Kelly
Executive Deputy Commissioner

New York State FEDM – Proficiency Testing Program

TO: Laboratory Directors

CATEGORY: Fetal Defect Markers (FEDM)

MAILOUT: May 8, 2012

FROM: Dr. G.J. Mizejewski, Director of FEDM Program

DUE DATE: May 23, 2012

Samples:
There are five (5) vials labeled **MS281** to **MS285**, each containing various predetermined amounts of alpha-fetoprotein (**AFP**), human chorionic gonadotropin (**hCG**), unconjugated estriol (**uE3**) and Dimeric **Inhibin A**. Also, five additional vials (AF 281 to AF 285) containing AFP in amniotic fluid have also been included. In addition, five extra vials **FT 281 to FT 285** containing human chorionic gonadotropin (**hCG**) and **PAPP-A** are added for ***optional*** testing. Please note that you do not have an option if you offer First Trimester and or Integrated Testing but the results of **FT 281 to FT 285** will ***not be graded***. Please analyze for all of those markers tested in your laboratory the same way as you would with a patient sample. If your lab is also measuring Amniotic fluid AFP, you are also required to measure those samples provided. Maternal serum samples are in human-derived serum base, sterile filtered and dispensed. Please **keep refrigerated** until use, but do ***not*** freeze. Before analyzing, make sure samples are mixed completely.

Reporting of Results:
All laboratories **must** submit their proficiency testing results electronically through the electronic proficiency testing reporting system (**EPTRS**) on the Department's Health Commerce System (HCS). The HCS is a secure website and requires all users to obtain an account ID in order to access the HCS and EPTRS application. The portal's URL is https://commerce.health.state.ny.us. Questions regarding the entry and submission of proficiency test results or the account application process can be directed to clepeptrs@health.state.ny.us. If your laboratory does not have an HCS account, you must request one as soon as possible before the next PT event by contacting the Clinical Laboratory Evaluation Program at 518-486-5410. Also, please **see attached May 2012 bulletin**.

For help with logins, password problems and reactivating HCS accounts, contact the Commerce Account Management Unit (CAMU) at (866) 529-1890.

Results must be reported for all 5 Maternal Sera and/or Amniotic fluid samples. Please enter your mass unit results in the spaces provided with one or two decimals accordingly. If a result exceeds your analytical range, indicate this with a "less than (<)"or "greater than (>)" sign if similar results from patient samples are reported in the same manner. If such samples are routinely retested after dilution, you may do so provided the result is identified accordingly. Select the instrument and reagent/kit used for each analyte using the drop-down menus. Please note that the risk factor and further action (not graded) for each of the samples has also been placed in the EPTRS. All applicable fields must be completed. Missing entries will result in a failing grade for the missing results.

If CLEP is contacted for permission to submit results via paper, this request may be approved under extenuating circumstances. However, the lack of active HCS accounts, the lack of submission roles, or the lack of Internet access will not excuse a laboratory from having to submit results electronically. Without such approval, mailed or faxed

proficiency test results will not be accepted. Note that such approvals will not be given on the due date! If you have any questions, please call Ms. Helen Ling at (518) 474-0036.

Special Instructions:
In order to achieve uniformity among our labs in reporting gestational age results, please report gestational week in "**decimal weeks (weeks + day/7)**" for the maternal serum samples.

Example: 18,3 weeks in the Ultrasound dating means 18 weeks + 3 days or 18.4 weeks (18 weeks + 3/7 weeks) ***not*** ~~**18.3**~~, i.e. **18.4 should be reported**

Note: We recommend the use of LMP (ultrasound dating when available) in calculating the gestational age, please note that the use of EDD is not an accepted standard of patient care.

Caution:
All human derived specimens should be handled as biohazard materials using Universal Precautions.

Only extra correspondence and/or information about **new kits** may be mailed to**:**

Fetal Defect Markers Proficiency Testing c/o Helen Ling
Wadsworth Center
Empire State Plaza, Room E610
PO BOX 509
Albany, NY 12201-0509

Please let us know immediately if you do not receive the samples in satisfactory condition by calling Ms. Helen Ling at (518) 474-0036.

DUE DATE: Results must be submitted electronically before 11:59 PM of May 23, 2012.
*Test results will not be evaluated if the results are **submitted** after the due date and a Failing Grade will be assigned.*

The next Proficiency Test mail-out for 2012 has been tentatively scheduled for:

Ship-out date	**Due date**
September 11, 2012	September 26, 2012

Second Trimester Demographic Data:

Specimen	Maternal Date of Birth	Race[1] W,B,H,A	Maternal Weight (lbs)	IDD[2] Presence	Gravida	Parity	LMP[3]	Draw Date
MS 281	**5/11/1987**	**W**	**155**	**None**	**2**	**1**	**12/30/2011**	**5/4/2012**
MS 282	5/12/1982	A	135	None	1	0	12/23/2011	5/4/2012
MS 283	**5/10/1989**	**H**	**150**	**None**	**3**	**1**	**12/9/2011**	**5/4/2012**
MS 284	5/12/1983	B	145	None	1	0	1/20/2012	5/4/2012
MS 285	**5/10/1991**	**W**	**142**	**None**	**2**	**0**	**1/6/2012**	**5/4/2012**

Specimen	GA[4]
AF 281	**18.0**
AF 282	19.0
AF 283	**20.9**
AF 284	20.0
AF 285	**17.0**

***Note: MS281, MS283 and MS285** are the serum sample matched to the amniotic fluid sample **AF281, AF283 and AF285, respectively**. (Dating by ultrasound)

[1]Race: W = White, not of Hispanic origin; B = Black, not of Hispanic origin; H = Hispanic; A = Asian

[2]IDD = Insulin-Dependent Diabetic
[3]LMP = Last Menstrual Period
[4]GA = Gestational Age in Decimal Weeks

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Fetal Defect Marker Proficiency Test Mailout[1]
May 2012

Dear Laboratory Director,
Below you will find a summary and critique of the Proficiency Testing mail-out from May 8, 2012, for Fetal Defect Markers, which included samples for first and second trimester screening, as well as amniotic fluids. Your laboratory's results and grades are printed on a separate sheet; also included are the grades from the previous two PT events. These will be mailed to you separately. Please review and sign your evaluation. Retain the signed evaluation in your files. You will need it for your next laboratory survey to demonstrate participation in the NYSPT program.

I. Graded Results Section: Table 1: Second Trimester Maternal Serum: Summary of All Lab Results

Samples *N = 27	**Sample #**	**MS 281**	**MS 282**	**MS 283**	**MS 284**	**MS 285**
	Gestational Age (weeks)	18.0	19.0	21.0	15.0	17.0
Maternal Race	Ethnic Group	White	Asian	Hispanic	Black	White
Maternal Weight	Pounds (lbs)	155	135	150	145	142
Maternal Age	Years	25	30	23	29	21
Alpha-Fetoprotein (AFP)	Mean ng/ml ± Std. Dev.	120.4 ± 10.2	66.3 ± 4.9	214.8 ± 14.5	34.4 ± 2.2	21.0 ± 1.2
	MOM ± Std. Dev.	2.74 ± 0.23	1.19 ± 0.07	3.13 ± 0.25	1.02 ± 0.07	0.52 ± 0.04
Unconjugated Estriol (uE3)	Mean ng/ml ± Std. Dev.	1.32 ± 0.07	1.46 ± 0.11	1.62 ± 0.11	0.61 ± 0.07	0.90 ± 0.09
	MOM ± Std. Dev.	1.19 ± 0.26	1.00 ± 0.20	0.75 ± 0.11	1.10 ± 0.38	0.99 ± 0.29
human Chorionic Gonadotrophin (hCG)	Mean IU/ml ± Std. Dev.	21.6 ± 2.5	18. 7 ± 2.2	17.4 ± 1.9	31.3 ± 4.3	35.4 ± 4.5
	MOM ± Std. Dev.	1.08 ± 0.10	0.95 ± 0.11	1. 07 ± 0.11	0.77 ± 0.10	1.45 ± 0.16
Dimeric Inhibin-A (DIA)	Mean pg/ml ± Std. Dev.	145.8 ± 13.8	199.8 ± 18.3	209.2 ± 19.8	141.0 ± 13.2	240.4 ± 24.8
	MOM ± Std. Dev.	0. 87 ± 0.11	1.09 ± 0.16	1. 01 ± 0.17	0.75 ± 0.10	1.39 ± 0.18
Neural Tube Screen (Positive, Negative) Percent	Pos. (+) or Neg. (-)	(+) (93%)	(-) (100%)	(+) (100%)	(-) (100%)	(-) (100%)
	Recommended Action**	G = 46% U = 29% A = 58% R = 29%	NFA	G = 54% U = 35% A = 77% R = 4%	NFA	NFA
	NTD Risk 1 in	172	4300	36	9,960	10,000
Trisomy-21 Screen (Positive, Negative) Percent 1. Triple test	Pos. (+) or Neg. (-)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)	B(+) (40%)
	Recommended Action**	NFA	NFA	NFA	NFA	G = 100% U = 50% A = 100%
	Risk Est. 1 in	10,000	5,050	6,550	5,060	398
2. Quad Test	Pos. (+) or Neg. (-)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)	B(+) (58%)
	Recommended Action **	NFA	NFA	NFA	NFA	G = 86% U = 64% A = 93%
	Risk Est. 1 in	20,000	7,395	20,000	11,950	265
Trisomy-18 Screen (Positive, Negative) Percent	Pos. (+) or Neg. (-)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)
	Recommended Action**	NFA	NFA	NFA	NFA	NFA
	Risk Est. 1 in	10,000	10,000	10,000	10,000	10,000

*N = total numbers may vary since some labs do not test all analytes. The values represent the all-lab consensus based on the arithmetic mean ± Std. Dev.
(B) = borderline positive or negative, risk reflects central tendency (Median number for NTD/Down positive or negative/borderline screen). NFA = no further action; FA = further action; G = genetic counseling; U = ultrasound, A = amniocentesis, and R = repeat.
**This percentage is normalized to labs requesting further action. ‡ Insulin Dependent Diabetic pregnancy.

[1]The use of brand and/or trade names in this report does not constitute an endorsement of the products on the part of the Wadsworth Center or the New York State Department of Health.

1) Second Trimester Maternal Serum Analytes:

A. Narrative Evaluation of Second Trimester Screening Results:

N = 27 all-lab Consensus Values.

Sample #	Summary Comments (Mock specimens):
MS 281 Wk 18.0	This specimen was obtained from a 25 year old White woman (Gravida = 2, Parity = 1) in her 18th week of gestation with a body weight of 155 lbs. She had a family (sibling) history of reproductive complications. Her sample screened positive for NTD, and her aneuploidy screens were negative for both Trisomy-18 and Trisomy-21. The MS281 sample was paired to an amniotic fluid specimen, which was elevated (AFAFP MOM = 2.88). Please see Critique for further discussion of this sample.
MS 282 Wk 19.0	This specimen was obtained from a 30 year old Asian woman (Gravida = 1, Parity = 0) in her 19th week of gestation with a body weight of 135 lbs. A race correction may be indicated. She had no personal history of pregnancy loss. Her specimen was negative for NTD and for both Trisomies and all labs were in agreement. Thus, no recommendations for further action were noted. This specimen had no amniotic fluid counterpart.
MS 283 Wk 21.0	This specimen was obtained from a 23 year old Hispanic woman (Gravida = 3, Parity = 1) in her 21st week of gestation with a body weight of 150 lbs. She had a family history of DNA repair disease complications and her specimen resulted in a positive screen for NTD with no body weight or ethnic corrections indicated. The labs were also in agreement that both Trisomy screens were negative. Specimen MS283 was paired with a non-elevated AFP amniotic fluid specimen. See critique for more discussion on this sample.
MS 284 Wk 15.0	This specimen was obtained from a 29 year old Black woman (Gravida = 1, Parity = 0) in her 15th week of gestation with a body weight of 145 lbs. She had a family history that was unremarkable. Her sample screened negative for NTD, as did her aneuploidy screen for Trisomies-21 and 18. This sample was not paired to an amniotic fluid specimen.
MS 285 Wk 17.0	This specimen was obtained from a 21 year old White woman (Gravida = 2, Parity = 0) in her 17th week of gestation with a body weight of 142 lbs. She had a family (sibling) history of pregnancy complications. Her sample screened negative for NTD; however, her aneuploidy screen was borderline positive for Trisomy-21 (58% by quad, 40% by triple) on the basis of low AFP and uE3, and moderately elevated hCG and inhibin-A levels. Recommendations for further action from labs reporting elevated T21 risks by quad screen were: genetic counseling, 86 %, ultrasound, 64 % and amniocentesis, 93 %; while by those using the triple tests were: genetic counseling, 100%; ultrasound, 50% and amniocentesis, 100%. Specimen MS285 resulted in a negative T18 screen in 100% of the participating labs. The sample was paired to an amniotic fluid specimen which had a low AFAFP level (MOM = 0.52).

Notice of Gravida/Parity Clarification for Present and Future Mail outs;

Instructional Note:

This notice regards the demographic data provided for the mock patients in the FEDM program. For the sake of this program, it will be understood that gravida indicates the pregnant status of a woman and parity is the state of having given birth to a completed term infant or infants. Thus, a gravida = n, indicates number (n) of times pregnant including the present one; a gravida = 2 indicates that the women was pregnant once before in addition to her present pregnancy. Parity = 1 indicates the patient already has one child; however, multiple birth is also considered as a single parity.

Example: A woman of gravida = 3, parity = 2 indicates that the pregnant woman has been pregnant twice before, and has two children.

2) AMNIOTIC FLUID AFP (NTD-analysis):

N=22; all-lab Consensus Values

Sample#	Values	Summary Comments:
AF 281 Wk 18.0	AFP = 27.2 ± 3.7 µg/ml MOM = 2.88 ± 0.31	The AF281 sample was targeted for an elevated AFAFP value in the routine gestational age range. Most labs called AF281 a positive screen for AFAFP specimen. The AFAFP sample was matched to maternal serum specimen MS281whose AFP was also elevated (MoM = 2.74).
AF 282 Wk 19.0	AFP = 9.4 ± 1.6 µg/ml MOM = 1.21 ± 0.13	The AF282 sample was targeted for a negative NTD screen for AFAFP in the upper-gestational screening window. All labs categorized this as an NTD screen negative specimen. This sample was not matched to a maternal serum specimen.
AF 283 Wk 20.9	AFP = 7.8 ± 1.1 µg/ml MOM = 1.40 ± 0.27	The AF283 sample was targeted for a screen negative AFAFP value in the upper gestational age screening range. All labs reported this specimen as a screen negative AFAFP value. The AF283 specimen was paired with maternal serum sample MS283, whose AFP was also elevated (MOM = 3.13). Please see critique for further discussion of samples MS283 and AF283.
AF 284 Wk 20.0	AFP = 9.9 ± 1.7 µg/ml MOM = 1.56 ± 0.18	The AF284 sample was targeted as an NTD negative screen in the upper gestational screening range. All labs categorized AF284 as a negative NTD screen specimen. This specimen had no maternal serum counterpart.
AF 285 Wk 17.0	AFP = 6.0 ± 0.8 µg/ml MOM = 0.52 ± 0.06	The AF285 sample was targeted for a low AFAFP value in the routine gestational age screening range. All labs called AF285 a non-elevated specimen for NTD. This AFAFP sample was matched to maternal serum specimen MS285, whose AFP was also low (MOM = 0.52).

II. Non-Graded Results Section:

Table 2: First Trimester Maternal Serum all-lab Results

Samples *N = 17	**Sample #**	**FT 281**	**FT 282**	**FT 283**	**FT 284**	**FT 285**
	Gestational Age (weeks)	11.2	12.0	11.5	12.5	13.0
Maternal Race	Ethnic Group	White	Asian	Hispanic	Black	White
Maternal Weight	Pounds (lbs)	120	135	130	125	120
Maternal Age	Years	28	25	23	30	21
Nuchal Translucency (NT)-Associated Measurements	Crown Rump Length (mm)	45	54	48	61	67
	NT Thickness (mm)	1.20	2.50	1.30	1.40	1.60
	NT – MOM ± Std. Dev.	1.04 ± 0.07	1.86 ± 0.11	1.07 ± 0.07	0.94 ± 0.06	0.98 ± 0.06
Human Chorionic Gonadotrophin (hCG) Total	Mean IU/mL ± Std. Dev.	80.8 ± 11.6	169.1 ± 38.6	78.0 ± 10.7	75.2 ± 8.4	70.2 ± 8.6
	MOM ± Std. Dev.	0.90 ± 0.10	2.16 ± 0.34	0.93 ± 0.09	0.97 ± 0.09	0.95 ± 0.09
Pregnancy-Associated Plasma Protein–A (PAPP-A)	Mean ng/mL*** ± Std. Dev.	678.1 ± 78.6	441.2 ± 52.0	742.5 ± 90.4	1117.8 ± 125.5	1180.6 ± 106.3
	MOM ± Std. Dev.	1.31 ± 0.72	0.65 ± 0.33	1.38 ± 0.78	1.17 ± 0.72	1.12 ± 0.65
Trisomy-21 Screen (Positive, Negative) Percent	Pos (+) or Neg. (-)	(-) (100%)	(+) (87%)	(-) (100%)	(-) (100%)	(-) (100%)
	Recommended Action **	NFA	G = 93% U = 36% A = 50% C = 57%	NFA	NFA	NFA
	Risk Estimate 1 in	8,400	13	10,000	7,500	10,000
Trisomy-18 Screen (Positive, Negative) Percent	Pos (+) or Neg. (-)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)
	Recommended Action **	NFA	NFA	NFA	NFA	NFA
	Risk Estimate 1 in	10,000	2,491	10,000	10,000	10,000

*N = total numbers may vary since some labs do not test all analytes. (B) = borderline negative or positive; NFA = no further action; G = genetic counseling; U = ultrasound; A = amniocentesis; C = chorionic villus sampling; N = number of labs participating; FT = First Trimester. **This percentage is normalized to labs requesting further action. ***Results from methods that give IU/ml were converted to ng/ml as described in section D.1 below.

1) First Trimester Maternal Sera Only:

B. Narrative Evaluation of First Trimester Screening Results:

N = 17 all-lab Consensus Values.

Sample#	Summary Comments:
FT 281 Wk 11.2	This specimen was procured from a 28 year old Asian woman of average body weight (120 lbs.). Her gestational age at the time of screening was 11.2 weeks. She had no prior history of any pregnancy complications. This FT specimen was screen negative for Trisomy-21 and all testing labs were in agreement. The FT281 risk estimate for Trisomy-21 was 1 in 8,400, and the Trisomy-18 risk was 1 in 10,000.
FT 282 Wk 12.0	This specimen was procured from a 25 year old White woman of average body weight (135 lbs.). Her gestational age at the time of screening was 12.0 weeks. She had a prior family history of pregnancy complications and adverse outcomes. This FT specimen was screen positive for Trisomy-21 and 87% of testing labs were in agreement (see Critique). The FT282 risk estimate for Trisomy-21 was 1 in 13, while the Trisomy-18 risk was 1 in 2,491 with 100% of testing labs in agreement that the T18 screen was negative.
FT 283 Wk 11.5	This specimen was obtained from a 23 year old Hispanic woman of average body weight (130 lbs.). Her gestational age at the time of screening was 11.5 weeks. She had no prior history of pregnancy complications and/or adverse outcomes. This FT specimen was screen negative with all testing labs in agreement. The FT283 risk estimate for Trisomy-21 was 1 in 10,000, and the Trisomy-18 risk was also 1 in 10,000.
FT 284 Wk 12.5	This specimen was obtained from a 30 year old Black woman with a body weight of 125 lbs. Her gestational age at the time of screening was 12.5 weeks. She had no prior history of pregnancy complications or difficulties. This FT specimen was screen negative and all testing labs were in agreement. The FT284 risk estimate for Trisomy-21 was 1 in 7,500 and the Trisomy-18 risk was 1 in 10,000.
FT 285 Wk 13.0	This specimen came from a 21 year old White woman of average body weight (120 lbs.). Her gestational age at the time of screening was 13.0 weeks. She reported no prior family history of pregnancy problems. This FT specimen was screen negative for Trisomy-21 and Trisomy-18. The Trisomy-21 risk estimate for FT285 was 1 in 10,000, and the Trisomy-18 risk was also 1 in 10,000. All labs were in agreement with both screen assessments.

III. Critique and Commentary:

A) Second Trimester Maternal Serum and Amniotic Fluid:

In general, the all-lab results were consistent with the targeted values for the NTD and the Trisomy Screens for risks and outcomes. The Caucasian maternal serum sample **MS281** was targeted as a positive specimen for NTD (Figs. 1 and 3) and was matched to the elevated **AF281** sample (Fig. 2). Most labs (93%) agreed that specimen **MS281** was screen positive for NTD and negative for both Trisomy screens. The **MS281** sample generated further action and follow-up recommendations that consisted of the following: genetic counseling, 46%; ultrasound, 29%; amniocentesis, 58%; and repeat sample, 29%. This mock patient had been referred to a tertiary care medical center for amniocentesis due to a family history of pregnancy difficulties in both close and extended family members. The present maternal serum sample was obtained prior to and on the same day of the amniocentesis; the post procedure AF specimen (untainted by color) together with the prior MS sample were subsequently analyzed. The term outcome in this mock patient revealed that level-II diagnostic ultrasound demonstrated the presence of a neural tube defect; in addition, a diagnostic Ache band was present following polyacrylamide gel electrophoresis in confirmation of an NTD.

Sample **MS285** was obtained from a white woman with a prior sibling history of pregnancy complications. Although the T21 MOM results for specimen **MS285** (MSAFP-MOM = 0.52, MSuE3-MOM = 0.99, MShCG-MOM = 1.45, DIA-MOM = 1.39) were suggestive of a T21 positive screen, a slight majority of labs (56%, 1 by triple and 14 by quad test) classified this specimen as T21 borderline positive screen and recommended further actions. Both the triple and the quad screen results failed to achieve an all-lab 80% consensus resulting in the borderline positive screen. The triple screen T21 recommended further actions for **MS285** were genetic counseling, 100%; ultrasound, 50%; and amniocentesis, 100%; while the quad test action was genetic counseling, 86%; ultrasound, 64% and

amniocentesis was 93%. The **MS285** sample produced a T21 risk of 1 in 398 by triple test and a T21 risk of 1 in 265 by quad test (Figs. 5, 6). The specimen **MS285** was designed to represent a borderline screen for Down Syndrome with a profile of both low MSAFP, low MSuE3, together with moderately elevated MShCG and MSDIA. With the addition of MS-DIA in second trimester screening, the detection rate in the literature has been reported to increase while maintaining a constant false positive rate. In the case of specimen **MS285**, the MS-DIA MOM value of 1.39 contributed to increasing the patient risk value from 1 in 398 (triple test) to a greater risk of 1 in 265 (quad test). This increased risk was reflected by more labs calling this sample screen positive and recommending "further actions". The all-lab positive screen consensus for **MS285** using the quad test was 58% compared to 40% with triple test.

Two other specimens, **MS282** and **MS284**, produced negative screens for NTD, T21, and T18, with no corrections for body weight or race being indicated.

The **MS283** specimen at 21 weeks was a special case involving discrepant levels of MSAFP and AFAFP MOMs. Sample **MS283** resulted in a positive screen for NTD, but was negative for T21 and T18. The follow-up actions recommended for **MS283** were genetic counseling, 54%; ultrasound, 35%; amniocentesis, 77%; and repeat testing, 4%. The **MS283** sample was determined to have an elevated MSAFP MOM value (3.13), but normal MShCG (MOM = 1.07), slightly low uE3 (MOM = 0.75), and normal DIA (MOM = 1.01) values. In contrast, the AFAFP measurement resulted in a non-elevated AFP MOM value. This mock patient, a 23 year old mother, was previously seen at a genetics clinic at a large university medical center to investigate the feasibility of an antenatal detection of ataxia telangiectasia (ATT). At that time, the mother was 12 weeks pregnant. Her 9 year old daughter, whose first signs of ATT were clumsiness noted at 15 months of age, had suffered progressive cerebellar motor degeneration since infancy. The family history had been negative for both leukemias and solid tumors. Consanguinity was ruled out and was unlikely as the mother was Filipino and the father was an African American. Physical examination of the affected 9 year old daughter revealed an alert, wheelchair-bound African American female. The child exhibited truncal ataxia (lack of trunk muscle coordination) and tremors, involuntary eye movement, low muscle tone, and a motor speech disorder. Multiple telangiectasias (small dilated blood vessels) were observed in the bulbar-ocular conjunctivae and on the skin of the shoulders and ears. Serum AFP had been extremely elevated in two of the postnatal samples (292 and 339 ng/ml) of the daughter, while serum immunoglobulins were normal: IgA 190 ug/ml; IgM 302 ug/ml;amd IgG 821 ug/ml. Peripheral blood lymphocyte cytogenetic studies in the 9 year old child revealed increased spontaneous chromosome breakage as well as bleomycin (BLM) hypersensitivity indicative of a DNA repair disease. Following the confirmation of ATT in the daughter, the parents requested amniocentesis (at 21 weeks' gestation) to establish the ATT status of the fetus being carried by the mother. Amniotic fluid AFP in the **AF283** specimen resulted in a normal value (MOM = 1.40) while the maternal serum AFP level of **MS283** was elevated (MOM = 3.13). A previous MSAFP at 15 weeks had resulted in borderline levels (MOM = 2.2). Due to the present elevated MSAFP value, 100% of participating labs determined that the **MS283** specimen was an NTD positive screen. Following amniocentesis of specimen **MS283**, a normal male karyotype was found, level-II ultrasound was normal, and an NTD diagnostic Ache band was not present following PAG electrophoresis. In addition, fetal amniocytes from two different normal AF were cultured together with the **AF283** amniotic fluid specimen. No differences in the frequencies of chromosome damage were observed in any of the samples. Thus, **AF283** specimen sample from the mother did not indicate a fetus at risk for ATT based on the chromosome stability analysis. Unaware of the subsequent amniocentesis and mutagenic studies, all participating labs determined **MS283** to be screen positive for NTD, which was correct in accordance with laboratory operating procedures and protocols. In retrospect, the **MS283** specimen can now be classified as a false positive NTD screen; however, the cause of the elevated MSAFP was never determined. In the biomedical literature, elevated MSAFP, low MSuE3 and normal MShCG and MSDIA usually are indicative of intrauterine growth retardation (IUGR) and ventral wall defects, both of which were absent in the **MS283** pregnancy.

The mock patient of specimen **MS283** was modeled after an ATT case report from the biomedical literature (Ref. #1). In this case, MSAFP was borderline elevated in one sample and elevated in the second MSAFP measurement (15 and 21 weeks), whereas the AFAFP was not similarly elevated. MSAFP was found to be elevated while attempting to prenatally ascertain the clinical status of a fetus at risk for ATT. The final diagnostic confirmation of ATT was obtained by cytogenetic chromosome stability studies of the fetal amniocytes. Spontaneous chromosome breakage levels were assayed in the fetal amniocytes with control cultures harvested on the same day. Induced chromosome damage was quantitated in cultures from both case and control fluids following a six-hour exposure to bleomycin, with the final four hours in the presence of colcemide. Based primarily on the chromosomal stability of the fetal fibroblast-like amniocytes, the patient was determined to be normal with no risk

for ATT. Thus, the parents elected to continue the pregnancy, which resulted in a normal infant delivered at full-term. The newborn exhibited normal birth weight, length, and head circumference with no signs of clinical ATT. Moreover, subsequent AFP serum levels of the neonate/infant were within normal limits.

Ataxia telangiectiasia is an autosomal recessive gene disorder comprising one of the chromosome instability disorders (1, 2). It is characterized by progressive cerebellar ataxia, cutaneous telangiectasia, impaired immunocompetence, increased cell radiosensitivity, and a propensity for the development of lymphorecticular cancers (2, 3). The ATT syndrome further manifests a profound immunodeficiency exhibiting sinopulmonary microbial infections, degeneration of the thymus gland, and multiple chromosomal aberrations observed in patients' lymphocytes and fibroblasts (4, 5, 6). The chromosomal breakages encompassed gaps, breaks, dicentrics, and multi-radial configurations. ATT is a neuromotor degenerative disorder with an incidence ranging from 40,000 to 100,000 (6, 7) with a major mutation mapped to a defective gene on chromosome 11q22-23. Such patients display high AFP serum levels (liver-derived) (8, 9, 10) that can range from 30 to 400 ng/ml and these levels increase with age in most cases (11, 12, 13). Lymphocytes and other cells of ATT patients show increased sensitivity to ionizing radiation and radiomimetic chemicals, displaying aberrant cell cycle checkpoints that allow continuation through the cell cycle oblivious to DNA breaks that require repair prior to the next replication phase (14, 15). This phenomenon is referred to as radio-resistant DNA synthesis (RDS) and is, in fact, a basis for one of the phenotypic designations of ATT patients (16, 17).

One of the major contributing factors of ATT is a gene mutation located on chromosome position 11q22-23, which involves the ataxia telangiectasia mutated (ATm) gene (18, 19). Mutations in this gene have been found in more than 90% of the ATT patients examined (20, 21); however, to date, more than 400 different mutations have been documented extending over 66 exons of the gene (22-25). Once cloned, ATm was found to share sequence homology with RAD-3, a kinase that regulates passage through the cell cycle following DNA damage and involves the high molecular weight phosphoinosital kinase-3 (PI3-kinase) signal transduction pathway (26-28). These genes also share homology with kinases that regulate cell cycle checkpoints following DNA damage, chromosomal abnormalities, and sensitivity to UV, X-ray, and chemical mutagens (29). The accompanying PI3 kinase has been cloned and mapped to chromosome 3q22-q24 being named the Ataxia Telangiectasia related (ATr) kinase; both ATm and ATr were also found to form part of the synaptonemal complexes during gamete cell division (30). The ATm kinase activates p53 when cells are subjected to DNA damaging agents such as UV and ionizing radiations; ATm can also phosphorylate c-abl, a protein kinase implicated in the growth arrest response to DNA damage (31, 32). Other ATm targets include BRCA1, p95, mdm2, Mre11, and IKB alpha (NF-KB related), all of which are implicated in various stress and apoptotic responses (31-36). Overall, ATm appears to be involved in regulating numerous cell cycle checkpoints and apoptotic events in response to DNA damage. The non-mutated normal AT gene senses the presence of double-stranded DNA damage and mediates a subsequent response. In contrast, the ATm mutated gene is blinded and lacks the ability to process double-strand DNA break repairs correctly, which could account for aberrant cell divisions, T-cell receptor deficits, and abnormal gene rearrangements in immunoglobulins and somatic recombinations. Similar deficits are observed in cells responding to DNA damaging agents in mouse models of ATT(4).

Neurodegeneration in the human brain in ATT involves the loss of Purkinje cells by apoptosis in the cerebellum (38). However, the neural damage can occur throughout the brain being found in the amygdala, caudate, corpus callosum, thalamic nuclei, and the hippocampus regions (34). The neurodegenerative processes have not been observed in the cerebral cortex, and the full-fledged cerebellar cell damage attributed to the ATm does not occur until well after birth with an onset reported from 2 to 6 years of age (35). Although ATT is a rare disorder, it is widely distributed through the world in countries such as Turkey, Norway, Costa Rica, Iran, Saudi Arabia, North African, South African, and the USA (36). Typically, the clinical appearance of ATT involves the following: a) an occurrence of ocular and various telangiectasias, b) growth retardation, c) progressive cerebellar ataxia, d) DNA repair disruption and, e) highly elevated serum levels of AFP (37, 38). It is these clinical manifestations that distinguish ATT from the other chromosomal instability disorders such as Nijmegen Breakage Syndrome, Fanconi Anemia, Bloom Syndrome, Xeroderma Pigmentosium, and Cockayne Syndrome (39, 40).

Previously, physicians relied mostly on the clinical physical appearances of patients with ATT before a diagnosis was made. The use of serum AFP levels and other severe immune deficiency biomarkers have aided in the diagnostic workup for the early onset of this disorder. Elevated serum AFP is found in over 90% of young children bearing the ATT disorder and AFP levels are known to increase with age (41, 42). One third of ATT patients also have a severe immune deficiency characterized by absent or decreased levels of immunoglobulin

including IgA and IgG2 accompanied by an absence of thymic tissue and a decreased responsiveness to skin antigenic stimulation (43, 44, 45). The most serious consequence of patients with ATT, however, is their propensity to develop cancer later in life. The lifetime occurrence of cancer in patients is 1 in 20 in ATT patients developing one or more malignancies (46, 47, 48). Lymphoreticular (T-cells) and leukemic cancers predominate in the first 2 decades, and solid tumors thereafter. Unfortunately, the radiation sensitivity of ATT reduces the clinical therapy options available to these afflicted patients.

A subtype of ATT, referred to as ataxia with ocularmotor apraxia (AOA), also exhibits raised levels of AFP. Apraxia itself is a disorder characterized by loss of learned voluntary motor movements despite having the ability to do so. Apraxia is due to damage to areas of the cerebrum and differs from ataxia, which is a lack of coordination of motor movements. Apraxia can affect various areas of the body including the face (mouth, lips, and ears), hands and fingers, arms and legs, larynx, and eye muscles (oculomotor). Unlike ATT, patients having ataxia with oculomotor apraxia (AOA) show no increased sensitivity to ionizing radiation; however, similar to ATT, the AOA disorder is associated with highly elevated serum levels of AFP. The gene mutation responsible for AOA resides in the helicase domain of the Senataxin (SETX) molecule (51). AOA is an autosomal recessive inherited disorder with onset over an age range of 4 to 14 years in children. The childhood appearance of AOA is characterized by progressive cerebellar ataxia, oculomotor apraxia, and developing motor peripheral neuropathy. Cases of AOA have been reported worldwide occurring in countries such as Portugal, Japan, French Canada, Italy, France, and the U.S.

Although postnatal levels of serum AFP are highly elevated in almost all ATT patients, the concentrations of AFP in the amniotic fluid of most affected fetuses has remained largely unreported to date. The omission of AFP measurement in such published reports can only be explained by oversight or lack of experiences and/or educational training in the clinicians treating such patients and the practitioners performing the chromosomal damage testing. In the case history- modeled in sample MS283, the negative ATT prenatal determinations were deduced from three different results, namely a) non-elevated AFAFP, b) the absence of mutagenic factors in the amniotic fluid, and c) the lack of spontaneous and bleomycin-induced chromosomal damage in fetal amniocytes. Following birth of the infant, a negative ATT diagnosis was confirmed by both normal serum AFP levels and chromosome breakage assays, with and without bleomycin-induced stress. In contrast, the older sibling (9 yr old girl) of the newborn had demonstrated elevated AFP values following birth, increased levels of spontaneous chromosome instability, and proven bleomycin responsiveness; she was then diagnosed with ATT (1). At present, multiple pregnancies at risk for ATT have been studied by various prenatal diagnostic approaches indicating that prenatal screening and diagnosis has great value. Such techniques include a) direct mutational analysis; b) gene deletion by PCR analysis; c) rate and frequency of chromosomal aberration; and d) radio-resistant DNA synthesis. Although the prenatal diagnosis of ATT has been employed and been available since 1993 (49, 50), combining the measurement of MSAFP and AFAFP with these chromosome instability assays have not been practiced and reported in the published investigations.

B) <u>Assay Kit Performance</u>:

The performances of the various kits for maternal serum analytes (AFP, uE3, hCG, and Inhibin A) are presented in a bar-graph format (Figs. 7- 9B, 10). As shown in Figs. 7A and 8A, AFP and uE3 mass measurements in serum among the individual kits mostly agreed. In contrast, when the kit specific uE3 MOMs were compared, values from Siemens Immulite 2000/2500 ranged from 40 to 60% higher than those from Beckman (Fig. 8B). Regarding the hCG kits (Fig. 10), the Beckman UNICEL instrument results that were 10% higher than those from Beckman Access 2, while the Siemens Immulite/2000 results were 10% lower than those from the other assay platforms. Finally, the method comparison for Inhibin-A displayed in Fig. 9A shows that the results from the Beckman Access/2 or UNICEL were similar and that of the Diagnostic Systems Lab (DSL) assay platform were 20-25% lower; in contrast the Inhibin MOM values (Fig. 9B) from DSL were 20% higher than the others.

Interestingly, when the AFP mass measurements in **amniotic fluid** were compared, the differences among the various methods appeared somewhat larger (Fig. 7B), while AFAFP MOM values (Fig.7D) were invariant throughout. In particular, mass value results from the Abbott Axsym were 15-20% higher, whereas those from the Beckman UNICEL instrument were about 10-15% lower, with the results from the other instruments somewhere in between. Since these specimens are derived from actual AF samples, these levels would be comparable to real patient testing**.**

C) Second Trimester Screening Software Utilized:

The alpha and Benetech software packages were each used by 29% and 22%, of the labs, respectively; Robert Maciel (RMA) software was employed by 30%; and in-house and "other" softwares comprised 15%. Labs using programs classified as "other" are presumably proprietary software packages.

D) First Trimester Screen:

Five first trimester maternal serum mock samples were provided in the present mailout. All laboratories that are **validation-approved** and presently perform first trimester Down syndrome screening are **REQUIRED** to test and report screen results; however, the laboratory results will **not** be graded at this time. Those laboratories not presently offering the test, nor planning to implement the test, can request that no further samples be sent to them. The FT sample (FT = first trimester) information provided to participating labs included maternal age, nuchal translucency (NT) in millimeters, last menstrual period (LMP), crown-rump length (CRL) in millimeters, race, maternal body weight, and date of blood draw.

As shown in Table 2 for the **FT281** Asian specimen, the gestational age all-lab mean was reported as 11.2 weeks. Assay measurements resulted in an all-lab total hCG mass measurement of 80.8 $\pm$ 11.6 IU/ml (MOM = 0.90 $\pm$ 0.10); the all-lab PAPP-A mass measurement was 678.1 ± 78.6 ng/ml (MOM = 1.31 $\pm$ 0.72). The all-lab T21 screen consensus for **FT281** was negative with a risk assessment of 1 in 8,400 (Fig. 13). No further actions were recommended by the labs. Finally, the **FT281** specimen also screened negative for T18 (1 in 10,000 Fig. 14).

The all lab measurement of the 12.0 week Caucasian **FT282** specimen for total hCG resulted in a mass mean of 169.1 $\pm$ 38.6 IU/ml, with a MOM of 2.16 $\pm$ 0.34; the all-lab mass mean for PAPP-A was 441.2 $\pm$ 52.0 ng/ml with a MOM of 0.65 $\pm$ 0.33. As a result, the all-lab T21 risk assessment for **FT282** was 1 in 13 (Fig. 13). The **FT282** sample displayed an 87% consensus T21 positive screen assessment. Further action was indicated which included genetic counseling, 93%, ultrasound, 36%, amniocentesis, 50%, and chorionic villus sampling, 57%. The labs that did not interpret this sample as screen positive may want to re-examine their risk assessment. Finally, 100 % of labs considered the **FT282** specimen screen negative for T18 (1 in 10,000) using a cutoff of 1 in 100 (Fig.14).

As demonstrated in Section II, Table 2, the all lab measurement of the 11.5 week Hispanic **FT283** specimen for total hCG resulted in a mass mean of 78.0 IU/ml $\pm$ 10.7, with a MOM of 0.93 $\pm$ 0.09. Furthermore, the all-lab mass mean for PAPP-A was 742.5 $\pm$ 90.4 ng/ml with a MOM of 1.38 $\pm$ 0.78. This resulted in an all-lab T21 risk assessment of 1 in 10,000 for the **FT283** specimen and is a negative screen (Fig. 13) and also a negative T18 risk assessment of 1 in 10,000 (Fig. 14).

In the **FT284** African American specimen, the gestational age all-lab mean was reported as 12.5 weeks. Assay measurements for **FT284** resulted in an all-lab total hCG mass measurement of 75.2 $\pm$ 8.4 IU/ml (MOM = 0.97 $\pm$ 0.09), while the all-lab PAPP-A mass assessment was 1117.8 $\pm$ 125.5 ng/ml (MOM = 1.17 $\pm$ 0.72). All labs agreed that the **FT284** sample was screen negative for T21 with a risk of 1 in 7,500 (Fig. 13), and negative for T18 with a risk assessment of 1 in 10,000 (Fig. 14).

For the Caucasian **FT285** specimen, the gestational age all-lab mean was reported as 13.0 weeks. Assay measurements resulted in an all-lab total hCG concentration of 70.2 $\pm$ 8.6 IU/ml (MOM = 0.95 $\pm$ 0.09) while the all-lab PAPP-A concentration was 1180.6 $\pm$ 106.3 ng/ml (MOM = 1.12 $\pm$ 0.65). The all-lab FT T21 risk assessment was 1 in 10,000 and all labs agreed that the **FT285** sample was negative for T21 (Fig. 13). Similarly, the **FT285** specimen was also screen negative for T18 with an all-lab risk assessment of 1 in 10,000 (Fig.14).

D. 1.) First Trimester Assay Kit Performance:

In order to compare the Beckman UNICEL assays (53% users) for PAPP-A with those of the older Siemens Immulite and DSL assay platforms, a conversion factor was calculated from participating labs using data from the last five PT mailouts (Note: this conversion factor may not be applicable to real patient samples because of potential matrix effects in the PT samples). Hence, Beckman Access 2/ UNICEL (y-axis) data for PAPP-A in ug/ml were plotted versus Siemens Immulite 2000 (x-axis) data in mIU/ml yielding a linear correlation with an R^2 value of 0.9654, a slope of 0.1413 and a Y intercept of essentially 0 (Fig. 15A). In Fig. 15B, Beckmann Access 2/ UNICEL

PAPP-A values (y-axis) were plotted against DSL PAPP-A values (x-axis) yielding a second degree polynomial correlation with an R^2 value of 0.9881. Using the respective correlation equation allowed us to convert mIU/ml values into ng/ml and to directly compare Beckman UNICEL PAPP-A mass units of ng/ml to the mIU/mL mass units generated by Siemens Immulite and DSL (Fig. 12A). However, for grading purposes, each lab's results were compared to their own peer group without conversion.

The performance of the kits used for first trimester maternal serum analytes (hCG and PAPP-A) are presented in Figs. 11, and 12A for the five FT samples. As shown in Fig 11, FT hCG measurements by Beckman Access/2 were ~10% higher than those by Beckman UNICEL, while the Siemens Immulite instruments measured approximately 15-20% below the Beckman Access 2/UNICEL instruments. Thus, the results from the three PAPP-A kits, when converted to the same mass units, were relatively consistent among each other. In contrast, when the PAPP-A kit MOMs were compared, Siemens Immulite were more than double those from DSL and Beckman (Fig. 12B).

E) First Trimester Screening Software Utilized:

The alpha and Benetech software packages were each used by 31% and 19% of the labs, respectively; Robert Maciel (RMA) software was employed by 31%; and in-house software comprised 19%. None of the labs used programs classified as "other" which are proprietary software packages.

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Section-II. Adverse Pregnancy Complications/Outcomes Related to HAFP Levels:

Even though AFP was thought to be the "gold standard" biomarker for neural tube defects, elevated AFP levels had been used since 1976 as an indicator for additional perinatal distress conditions such as bilateral renal agensis, fetomaternal transfusion, pre-eclampsia, intra-uterine growth retardation (IUGR), and fetal demise [1-3] (Table-3). In many instances, AFP accumulates in a biological compartment (such as amniotic fluid) by: 1) leakage from fetal serum and cerebrospinal fluid (NTD) 2) exposure of blood vessels in extruding viscera leading to transudation of AFP (exopthalmos); 3) expedited protein filtration and passage into urea (congenital nephrosis); 4) impaired fetal swallowing or digestion in amniotic fluid (GI anomaly) and 5) altered or obstructed transplacental passage such as in placenta accreta (Table-3). The early developmental malformations reported in the literature were structural in nature and late pregnancy complications were directly life threatening to the fetus and oftentimes the mother. Such conditions included severe pre-eclampsia, premature labor, intrauterine and/or perinatal death, preterm birth, fetal wastage, and trophoblast abnormalities including placental previa and disruption [4-8]. Non-pathological elevations of AFP in pregnancy can be the result of physiological or procedural phenomena such as twining or multiple pregnancy, low birth weight, prematurity, or incorrect gestational age dating [9-12]. Fetal defects and malformations can also be parsed by classifying them according to high or low levels of AFP in biological fluids (Table-3). Elevated serum and amniotic fluid (AF)-AFP levels are usually indicative of the presence of an anatomical lesion such as observed in NTD, anencephaly, ventral wall defects, gastrointestinal atresia, renal anomalies, poly-and oligohyramnios, cystic hygromas with fetal hydrops, teratomas, blastomas, and disruption of placental barriers [13-19].

At the opposite extreme, low AFP levels signify the presence of chromosomal abnormalities (aneuploides) such as trisomies, as well as fetal loss, hydatidiform mole, hydrocephalus, diaphragmatic

hernias, Turner's syndrome, choroid plexus cyst, duodermal atresia, renal pyelectasis, and fetal growth restriction [20-24]. Again, the fetal malformation and adverse conditions can be classified according to the calculated multiple of a population AFP median (MOM) compared to the patient's AFP median value. Low AFP disorders categorized by various investigators have included low birth weight, multiple pregnancies, fetal wastage, perinatal death, spontaneous abortions, stillbirths, and neonatal deaths [25-27]. An association was also found between second trimester low HAFP levels and subsequent Sudden Infant Death Syndrome (SIDS). The investigators in this latter study suggested that the risk of SIDS might be mediated in part through impaired fetal growth and occurrence of adverse preterm birth events [28]. Finally, the measurement of MSAFP together with the introduction of computer-assisted Doppler measurement, which is indicative of absent or altered diastolic arterial flow in critical tissue areas, has been a major advancement in prenatal monitoring technologies.

The application of Doppler velocimetry as an adjunct to perinatal screening programs has recently increased in clinical usage. Elevated MSAFP has now been correlated with reduced uteroplacental blood flow observed in the uterine artery [29]. A study for second trimester screening for pre-eclampsia was recently reported which showed that higher MS levels of HCG, Inhibin-A, Activin-A and AFP were accompanied by increased rates of the Doppler pre-diastolic notch and the derived uterine artery resistance index [30]. Even though a test sensitivity of 70 to 93% and a specificity of 87-98% was achieved, the addition of Doppler velocimetry only slightly improved the predictive efficiency of the total biomarkers when used alone. The measurement of fetal middle-cerebral artery Doppler velocity has also been employed, together with MSAFP and fetal hemoglobin as biomarkers to predict the risk of fetal anemia [31]. Investigators have indeed found significant correlations between MSAFP and both Doppler arterial measurement ($r = 0.56$) and fetal hemoglobin ($r = 0.71$) levels. In cases of alloimmunised pregnancies with fetal anemia, measured MSAFP elevations preceded the presence of increased Doppler velocity by nearly 3 weeks. In contrast to the previous report, another group reported that both first and second-trimester biochemical markers of trisomies had no relationship to maternal hemoglobin concentrations; however, Doppler velocity measurements were not done in this instance [32]. Finally, the

application of Doppler methodology to the analysis of factors predicting antepartum stillbirth was studied in conjuction with MSAFP and pregnancy-associated plasma protein-A (PAPP-A) levels [33]. Antepartum stillbirth, the single most common cause of perinatal death, has been previously associated with fetal abnormalities, congenital infections, Rh-isoimmunisation, and pregnancy complications such as IUGR, pre-eclampsia, and placental abruption [34]. Both MSAFP and PAPP-A measurement used in conjunction with Doppler indices of resistance to flow were found predictive of antepartum stillbirth. Both MSAFP and PAPP-A levels are involved in placental passage and functional dynamics because the risk of stillbirth in late pregnancy may be a result of a placental dysfunction of the placenta in early pregnancy. The invasion of the trophoblast into the uterine vessels is associated with decreased resistance to flow in the uterus and impaired placentation is reflected in high resistance Doppler flow velocity waveforms recorded from the utero-placental circulation [35].

The increased usage of uterine artery Doppler and placental ultrasound has aided in the elucidation of unexplained discordant levels of MSAFP in the perinatal period of pregnancy. However, in the third trimester, the root cause of an AFP-associated pregnancy disorder can often be attributed to some form of placental disfunction. Pregnancy complications related to placental disease include: a) pre-eclampsia b) intrauterine growth restriction c) placental abruption; d) fetal death; and e) spontaneous preterm labor/birth [10]. Both AFP and hCG alone or in combination with other analytes can increase these associations and their subsequent risks [36, 37] (Table-2 and 4). Premature labor and subsequent preterm delivery constitute some of the major contributors of perinatal death in the world [35]. Adverse perinatal complications such as fetal death or preterm delivery are often attributable to chronic uteroplacental vascular insufficiency and placental infarction. Elevated MSAFP levels are frequently found to be associated with reduced uteroplacental blood flow detected by uterine artery Doppler measurements [30]. Moreover, abnormalities such as placental shape and/or texture, in conjunction with elevated MSAFP have been correlated with poor pregnancy outcome.

In a recent Canadian study, combined elevations of AFP and hCG were employed to predict severe placental complications using uterine artery Doppler (UAD), ultrasound, and placental

morphology at the 19-23 week period [36] (Table-4). Relative risk data from this combined analyte study revealed the presence of abnormalities in studies using both placental ultrasound and UAD correlated with multiple perinatal complications such as preterm delivery, IUGR, intrauterine fetal death, and pre-eclamptic pathology. Their clinical results showed a 10-fold increase in abnormal UAD scans underscored by a high rate of underlying chronic placental vascular pathology that limited the maternal blood supply and damaged the nutrient exchanging placental villi. These investigators further reported instances of cases displaying severe pre-elcampsia in addition to patients exhibiting the HELP (Hemolysis, Elevated liver enzymes, and Low Platelets) syndrome. The authors stated that their test may be able to identify the majority of women destined to either lose their fetus or deliver a preterm baby due to uteroplacental vascular insufficiency.

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Table - 3: Pregnancy Stages/Conditions with Abnormal Levels (High/Low) of Human Alpha-fetoprotein (HAFP)

I. Stage Specific Disorders:

First and Second Trimester Pregnancy	Third Trimester Pregnancy
1. Oligohydraminos	1. Severe Pre-eclampsia
2. Renal Agenesis	2. Intrauterine growth retardation
3. Gastrointestinal Defects	3. Premature labor
4. Fetal Growth Restriction	4. Perinatal loss
5. Cystic Hygroma	5. Fetal Demise
6. Fetal-Maternal Bleed	6. Placental Previa
7. Placental Obstructions	7. Placental Acrecia
8. Multiple Gestation	8. Placental Abruption
9. Incorrect Gestational Age Levels	9. Prematurity

II. Fetal Defect Associated:

High AFP Levels	Low AFP Levels
1. Spina Bifida	1. Blighted ova
2. Anencephaly	2. Polyhydraminos
3. Duodemal	3. Insulin-dependent diabetes
4. Omphalocoele	4. Diapharmatic Hernia
5. Gastroschissis	5. Trisomy-21
6. Congenital Nephrosis	6. Turner's syndrome/hydrops
7. Neuroblastoma, hepatablastoma	7. Intra-uterine growth retardation
8. Tyrosinemia	8. Hydrocephalus
9. Germ Cell Tumors	9. Trisomy-18

III. Pregnancy Condition Associated

High HAFP Levels	Low HAFP Levels
1. Stillbirth	1. Trisomies/aneuploides
2. Premature Labor	2. Stillbirth fetus
3. Neonatal Death	3. Hydadiform mole
4. Fetal Wastage	4. Long Standing Fetal Demise
5. Multiple Pregnancy (twins)	5. Non-pregnancy
6. Low Birth Weight	6. Fetal Death
7. Open spinal defect	7. Overestimated Gestational Age
8. Toxemia of pregnancy	8. HIV infection
9. Rh – isoimmunization	9. Spontaneous abortion

* Data was extracted and compiled from the following References:

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ABSTRACTS

A) Screening Abstract "Picks-of-the-Month":

(1) Title: First-trimester screening for neural tube defects using alpha-fetoprotein

Source: Fetal Diagn Ther, 2012. **31**(2): p. 109-14.

Authors: Bredaki FE, Poon LC, Birdir C, Escalante D, Nicolaides KH.

Abstract: Objective: To assess the potential value of maternal serum alpha-fetoprotein (AFP) at 11-13 weeks' gestation in early screening for fetal neural tube defects (NTDs). Methods: Maternal serum AFP at 11-13 weeks' gestation was measured in 32 cases of fetal NTDs, including 18 cases of acrania and 14 cases of spina bifida, and 1,500 unaffected controls. The measured serum AFP was converted into multiple of the expected median (MoM) after adjustment for gestational age and maternal characteristics and Mann-Whitney test was used to determine the significance of difference in the mean MoM of serum AFP in the NTD group to that in the controls. Results: The mean AFP MoM in the NTD group (1.76, 95% CI 1.39-2.23) was significantly higher than in the controls ($p < 0.0001$). The mean AFP MoM was not significantly different between the cases of acrania and cases of spina bifida (1.78 vs. 1.75; $p = 0.722$). The detection rates of NTD in screening by serum AFP were 50.0% (95% CI 31.9-68.1) and 37.5% (95% CI 21.1-56.3) at fixed false-positive rates of 10 and 5%, respectively. Conclusion: Measurement of maternal serum AFP at 11-13 weeks' gestation may be useful in screening for fetal NTDs.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22377693

(2) Title: Autism spectrum disorders and maternal serum alpha-fetoprotein levels during pregnancy

Source: Can J Psychiatry, 2011. **56**(12): p. 727-34.

Authors: Abdallah MW, Grove J, Hougaard DM, Norgaard-Pedersen B, Ibrahimov F, Mortensen EL.

Abstract: Objective: Numerous studies have been trying to disentangle the complex pathophysiology of autism spectrum disorders (ASD). In our study, we explored the potential role of maternal serum (MS) alpha-fetoprotein (AFP) in the prediction and the pathophysiology of ASD. Methods: A total of 112 patients with ASD and 243 control subjects were included in a case-control study, using a historic birth cohort maintained at Statens Serum Institute. Measurements of MS-AFP were obtained from a multicentre screening program, whereas clinical data were obtained from nationwide registers. Association between MS-AFP and ASD status was analyzed using logistic regression models and nonparametric tests. Results: Crude, but not adjusted, estimates showed that MS-AFP levels were slightly, but significantly, higher in mothers of children with ASD, compared with their control subject counterparts. People with ASD had an odds ratio of 2.33, with 95% confidence intervals of 1.00 to 5.39, to have MS-AFP above 2.5 multiple of median. Excluding subjects with congenital malformation comorbidities did not alter the direction of our estimates (OR 2.60; 95% CI 1.04 to 6.51, $P = 0.04$). Conclusion: Biologic plausibility of its role in the pathophysiology of ASD makes AFP a good candidate for further larger-scale studies to confirm such an association and to determine whether this pattern is unique to ASD or related to other psychiatric disorders as well.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22152641

(3) Title: Effect of mild hepatic or renal impairment on maternal serum screening biochemical measures

Source: J Obstet Gynaecol Can, 2011. **33**(12): p. 1218-22.

Authors: Ying I, Wyatt PR, Nisenbaum R, Ray JG.

Abstract: BACKGROUND: Integrated maternal serum screening (MSS) is commonly used to screen for fetal trisomies and neural tube defects in early pregnancy. The kidney and liver each play an important role in hormone metabolism, and anecdotal data suggest that MSS biochemical measures may vary with a mother's health status. We examined the correlations between kidney and liver function parameters and MSS markers and the possible association of mild renal or hepatic impairment with MSS measures. METHODS: We completed a prospective cross-sectional study of 257 consecutive women who underwent integrated MSS at a single hospital. Serum analytes (pregnancy associated plasma protein A [PAPP-A], hCG, creatinine [Cr], and alanine aminotransferase [ALT]) were drawn at approximately 12 weeks' gestation, and alpha-fetoprotein and unconjugated estriol were drawn at 16 weeks' gestation. Creatinine clearance was calculated using the Cockcroft-Gault formula. Abnormally elevated serum Cr and ALT were each defined as >/= 90th percentile among all women. A low creatinine clearance (CrCl) was set at </= 10th percentile. RESULTS: Serum hCG, PAPP-A, and alpha-fetoprotein were negatively correlated with CrCl, but not after correction for maternal age, weight, and ethnicity. No association between MSS and serum ALT was observed. The median serum concentrations of both PAPP-A (P = 0.04) and alpha-fetoprotein (P = 0.02) were significantly higher among those whose CrCl was </= 10th percentile. At the more extreme concentrations of PAPP-A and alpha-fetoprotein, no significant association with a low CrCl or an elevated serum ALT was seen. CONCLUSIONS: Among a group of apparently healthy pregnant women, mild renal or hepatic impairment had little or no significant correlation with individual MSS markers. Further work should focus on the effect of more severe renal or hepatic dysfunction on MSS measures.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22166275

(4) Title: Maternal serum alpha-fetoprotein in normal pregnancy at 11-13 weeks' gestation

Source: Fetal Diagn Ther, 2011. **30**(4): p. 274-9.

Authors: Bredaki FE, Wright D, Akolekar R, Cruz G, Nicolaides KH.

Abstract: OBJECTIVE: To establish a reference distribution of maternal serum alpha-fetoprotein (AFP) at 11-13 weeks' gestation and define the contribution of maternal variables that influence the measured concentration of AFP. METHODS: Serum concentration of AFP at 11-13 weeks was measured in 1,500 singleton pregnancies which were not complicated by hypertensive disorders or diabetes mellitus and resulted in the live birth at or after 37 weeks of phenotypically normal neonates with birth weights above the 5th and below the 95th percentile. Multiple regression analysis was used to account for maternal characteristics that influence the measured concentration of AFP and a distribution of log multiples of the median (MoM) values was fitted. RESULTS: Log(10) AFP increased with gestational age, decreased with maternal weight and was significantly affected by maternal racial origin, smoking status and method of conception. Compared with values in Caucasian women who were non-smokers and conceived spontaneously, AFP MoM was on average 23% higher in Afro-Caribbeans and 8% lower in East Asians, 11% higher in smokers and 10% higher in those conceiving by in vitro fertilization. CONCLUSION: In normal pregnancies at 11-13 weeks, serum AFP increases with gestational age and is affected by maternal race, weight, smoking status and method of conception.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22156386

B) Case History Screening "Picks-of-the-Month":

(1) Title: Prenatal screening for fetal aneuploidy in singleton pregnancies

Source: J Obstet Gynaecol Can, 2011. **33**(7): p. 736-50.

Authors: Chitayat D, Langlois S, Wilson RD.

Abstract: OBJECTIVE: To develop a Canadian consensus document on maternal screening for fetal aneuploidy (e.g., Down syndrome and trisomy 18) in singleton pregnancies. OPTIONS: Pregnancy screening for fetal aneuploidy started in the mid 1960s, using maternal age as the screening test. New developments in maternal serum and ultrasound screening have made it possible to offer all pregnant patients a non-invasive screening test to assess their risk of having a fetus with aneuploidy to determine whether invasive prenatal diagnostic testing is necessary. This document reviews the options available for non-invasive screening and makes recommendations for Canadian patients and health care workers. OUTCOMES: To offer non-invasive screening for fetal aneuploidy (trisomy 13, 18, 21) to all pregnant women. Invasive prenatal diagnosis would be offered to women who screen above a set risk cut-off level on non-invasive screening or to pregnant women whose personal, obstetrical, or family history places them at increased risk. Currently available non-invasive screening options include maternal age combined with one of the following: (1) first trimester screening (nuchal translucency, maternal age, and maternal serum biochemical markers), (2) second trimester serum screening (maternal age and maternal serum biochemical markers), or (3) 2-step integrated screening, which includes first and second trimester serum screening with or without nuchal translucency (integrated prenatal screen, serum integrated prenatal screening, contingent, and sequential). These options are reviewed, and recommendations are made. EVIDENCE: Studies published between 1982 and 2009 were retrieved through searches of PubMed or Medline and CINAHL and the Cochrane Library, using appropriate controlled vocabulary and key words (aneuploidy, Down syndrome, trisomy, prenatal screening, genetic health risk, genetic health surveillance, prenatal diagnosis). Results were restricted to systematic reviews, randomized controlled trials, and relevant observational studies. There were no language restrictions. Searches were updated on a regular basis and incorporated in the guideline to August 2010. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies. The previous Society of Obstetricians and Gynaecologists of Canada guidelines regarding prenatal screening were also reviewed in developing this clinical practice guideline. VALUES: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care. BENEFITS, HARMS, AND COSTS: This guideline is intended to reduce the number of prenatal invasive procedures done when maternal age is the only indication. This will have the benefit of reducing the numbers of normal pregnancies lost because of complications of invasive procedures. Any screening test has an inherent false-positive rate, which may result in undue anxiety. It is not possible at this time to undertake a detailed cost-benefit analysis of the implementation of this guideline, since this would require health surveillance and research and health resources not presently available; however, these factors need to be evaluated in a prospective approach by provincial and territorial initiatives. RECOMMENDATIONS 1. All pregnant women in Canada, regardless of age, should be offered, through an informed counselling process, the option of a prenatal screening test for the most common clinically significant fetal aneuploidies in addition to a second trimester ultrasound for dating, assessment of fetal anatomy, and detection of multiples. (I-A) 2. Counselling must be non-directive and must respect a woman's right to accept or decline any or all of the testing or options offered at any point in the process. (III-A) 3. Maternal age alone is a poor minimum standard for prenatal screening for aneuploidy, and it should not be used a basis for recommending invasive testing when non-invasive prenatal screening for aneuploidy is available. (II-2A) 4. Invasive prenatal diagnosis for cytogenetic analysis should not be performed without multiple marker screening results except for women who are at increased risk of fetal aneuploidy (a) because of ultrasound findings, (b) because the pregnancy was conceived by in vitro fertilization with intracytoplasmic sperm injection, or (c) because the woman or her partner has a history of a

previous child or fetus with a chromosomal abnormality or is a carrier of a chromosome rearrangement that increases the risk of having a fetus with a chromosomal abnormality. (II-2E) 5. At minimum, any prenatal screen offered to Canadian women who present for care in the first trimester should have a detection rate of 75% with no more than a 3% false-positive rate. The performance of the screen should be substantiated by annual audit. (III-B) 6. The minimum standard for women presenting in the second trimester should be a screen that has a detection rate of 75% with no more than a 5% false-positive rate. The performance of the screen should be substantiated by annual audit. (III-B) 7. First trimester nuchal translucency should be interpreted for risk assessment only when measured by sonographers or sonologists trained and accredited for this service and when there is ongoing quality assurance (II-2A), and it should not be offered as a screen without biochemical markers in singleton pregnancies. (I-E) 8. Evaluation of the fetal nasal bone in the first trimester should not be incorporated as a screen unless it is performed by sonographers or sonologists trained and accredited for this service and there is ongoing quality assurance. (II-2E) 9. For women who undertake first trimester screening, second trimester serum alpha fetoprotein screening and/or ultrasound examination is recommended to screen for open neural tube defects. (II-1A) 10. Timely referral and access is critical for women and should be facilitated to ensure women are able to undergo the type of screening test they have chosen as first trimester screening. The first steps of integrated screening (with or without nuchal translucency), contingent, or sequential screening are performed in an early and relatively narrow time window. (II-1A) 11. Ultrasound dating should be performed if menstrual or conception dating is unreliable. For any abnormal serum screen calculated on the basis of menstrual dating, an ultrasound should be done to confirm gestational age. (II-1A) 12. The presence or absence of soft markers or anomalies in the 18- to 20-week ultrasound can be used to modify the a priori risk of aneuploidy established by age or prior screening. (II-2B) 13. Information such as gestational dating, maternal weight, ethnicity, insulin-dependent diabetes mellitus, and use of assisted reproduction technologies should be provided to the laboratory to improve accuracy of testing. (II-2A) 14. Health care providers should be aware of the screening modalities available in their province or territory. (III-B) 15. A reliable system needs to be in place ensuring timely reporting of results. (III-C) 16. Screening programs should be implemented with resources that support audited screening and diagnostic laboratory services, ultrasound, genetic counselling services, patient and health care provider education, and high quality diagnostic testing, as well as resources for administration, annual clinical audit, and data management. In addition, there must be the flexibility and funding to adjust the program to new technology and protocols. (II-3B).

URL:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21749752

(2) Title: Biochemical screening of fetal aneuploidies and neural tube defects by "double-test" in Croatia: a 10 years' experience

Source: Coll Antropol, 2011. **35**(3): p. 957-62.

Authors: Tislaric-Medenjak D, Kosec V, Tonkovic-Durisevic I, Zec I, Sabolovic-Rudman S, Kuna K, Herman R, Ivicevic-Bakulic T, Soljacic-Vranes H, Tuckar N, Muzinic D, Butorac D, Bolanca I, Kosec A, Stipoljev F.

Abstract: The aim of the study is to investigate the efficiency of the second-trimester biochemical screening, with maternal serum alpha-fetoprotein (MS-AFP) and free beta-subunit of human chorionic gonadotropin (free beta-hCG), during the ten-year period. The study included 11,292 of pregnant women between the 15th and 18th gestational week, who underwent screening from November 1996 to December 2006. The risk for trisomy 21 and trisomy 18 were calculated by computer software, based on a model which generated the final risk for fetal aneuploidies from the pregnant woman's a priori age risk and the likelihood ratio of the distribution of the biochemical markers, according to the second-trimester gestation. With the cut-off value of the final risk > or = 1:250,

the detection rate for trisomy 21 was 75% (21/28). In women less than or equal to 35, the detection was 57.1% (8/14) and 92.9% (13/14) in those over 35 years, respectively. The detection rate of trisomy 18 was 50% (2/4). The results confirmed that the implementation of double-test, as non-invasive screening for fetal aneuploidies, should be accepted as a complementary method of antenatal care.

URL:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22053587

(3) Title: Alphafetoprotein in the Dutch External Quality Assurance programme: a need for improvement

Source: Ann Clin Biochem, 2012.

Authors: Houwert AC, Lock MT, Lentjes EG,

Abstract: BACKGROUND: Elevated alphafetoprotein (AFP) concentrations may result from a variety of clinical conditions, but their role as an important tumour marker has been well established. There may be differences in AFP values due to laboratories using different methods, even though most methods have been calibrated with the same international standard (WHO IS 72/225). Therefore it is important to know the analytical performance of the various methods in relation to the analytical requirements for AFP measurement. METHODS: Annually, from January 2005 to July 2010, the results were analysed from the 65-75 laboratories that took part in the AFP survey of the External Quality Assurance programme of the Foundation Quality Control Medical Laboratories (the SKML/Binding Analysis) in the Netherlands. RESULTS: The Elecsys/Modular (36%) and the Immulite 2000/2500 (29%) are the methods used most. The methods show, on average, up to 15% positive and 12% negative bias, compared with the all-laboratory trimmed mean. Of the laboratories using the Immulite or the Elecsys/Modular analyser, over 70% show sufficient analytical performance to meet the Fraser criterion for method imprecision. Of the laboratories using a different method, over 50% do not meet this criterion. CONCLUSIONS: AFP immunoassays suffer from method bias, even though all methods have been calibrated with the same international standard. Some of the methods used show insufficient performance.

URL:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22454543

(4) Title: The reliability of maternal serum triple test in prenatal diagnosis of fetal chromosomal abnormalities of pregnant Turkish women

Source: Genet Test Mol Biomarkers, 2011. **15**(10): p. 701-7.

Authors: Demirhan O, Pazarbasi A, Guzel AI, Tastemir D, Yilmaz B, Kasap M, Ozgunen FT, Evruke C, Demir C, Tunc E, Kocaturk-Sel S, Onatoglu-Arikan D, Koc S, Ozer O, Inandiklioglu N,

Abstract: AIM: The purpose of this article was to evaluate the reliability of maternal serum triple marker screening of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol for the prenatal diagnosis of fetal chromosomal abnormalities in Turkish pregnant women. METHOD: Medical records were used to analyze indications of amniocentesis and quantitative fluorescent-polymerase chain reaction. Anomaly screening was performed for all patients between 13 and 22 weeks of pregnancy. A total of 1725 pregnancies with chromosomal abnormality risk according to triple test screening were accepted for fetal chromosome analysis and quantitative fluorescent-polymerase chain reaction. RESULTS: Chromosomal aberrations were observed in 56 (3.2%) cases. About 44.6% of the abnormalities detected were numerical aberrations; however, 55.3% of the abnormalities were structural aberrations. Abnormalities detected were inversion of

chromosome 9 in 20 cases, trisomy 21 in 14 cases, 46,XX/47,XX, +21 in 1 case, trisomy 18 in 2 cases, trisomy 13 in 1 case, 47,XXY, in 1 case, 45,X, in 1 case, structural abnormalities in 12 cases, and mosaic or tetraploidy in 6 cases. CONCLUSION: Second trimester triple test is an effective screening tool for detecting fetal Down syndrome in Turkish women.

URL:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21699408

C) News of Note: Abstracts of New Markers:

(1) Title: Combinations of maternal serum markers to predict preeclampsia, small for gestational age, and stillbirth: a systematic review

Source: J Obstet Gynaecol Can, 2012. **34**(2): p. 142-53.

Authors: Hui D, Okun N, Murphy K, Kingdom J, Uleryk E, Shah PS.

Abstract: OBJECTIVE: Abnormal serum screening markers have been associated with adverse pregnancy outcomes. We sought to review the performance of combined abnormal first and/or second trimester maternal serum markers used in prenatal screening for aneuploidy and open neural tube defects for predicting preeclampsia (PET), small for gestational age (SGA), and stillbirth beyond 24 weeks' gestation. DATA SOURCES AND STUDY SELECTION: Medline, EMBASE, and Cochrane Library databases were searched for studies from 1970 to May 2010 that analyzed predictive abilities of combined serum markers for defined outcomes. DATA EXTRACTION AND SYNTHESIS: Data were extracted independently by two authors, and 15 studies were included. Eight studies of 115,290 pregnancies, 11 studies of 144 853 pregnancies, and seven studies of 80 274 pregnancies examined PET, SGA, and stillbirth respectively. Because of the heterogeneity of marker combinations and thresholds, outcome definitions, and analytic methods, limited meta-analysis was possible for the outcomes of PET and SGA only. Three relatively homogeneous studies on prediction of PET, and two on prediction of SGA were meta-analyzed. Several single studies demonstrated utility in combining markers to predict adverse outcome; however, this effect was not confirmed after meta-analysis. The most common combination of markers evaluated was alpha fetoprotein and human chorionic gonadotrophin for all outcomes. The highest positive likelihood ratios for predicting PET (5.68; 95% CI 0.73 to 43.97) and SGA (6.18; 95% CI 1.84 to 20.85) were seen with combined alpha fetoprotein and human chorionic gonadotrophin (> 2.5 multiples of the median). CONCLUSIONS: Currently, no identifiable combination of serum markers performs well as a screening test for preeclampsia, small for gestational age, and stillbirth beyond 24 weeks. Large cohort studies with standardized screening test parameters and outcomes are needed.

URL:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22340063

(2) Title: Management of abnormal serum markers in the absence of aneuploidy or neural tube defects

Source: J Matern Fetal Neonatal Med, 2012.

Authors: Schnettler WT, Hacker MR, Barber RE, Rana S.

Abstract: Objective: Few guidelines address the management of pregnancies complicated by abnormal maternal serum analytes (MSAs) in the absence of aneuploidy or neural tube defects (NTDs). Our objective was to gather preliminary data regarding current opinions and management strategies among perinatologists in the US. Methods: This survey of Maternal Fetal Medicine (MFM)

physicians and fellows used a secure electronic web-based data capture tool. Results: A total of 545 potential participants were contacted, and 136 (25%) responded. The majority were experienced academic physicians with robust practices. Nearly all (97.7%) respondents reported a belief in an association between abnormal MSAs and adverse pregnancy outcomes other than aneuploidy or NTDs. Plasma protein A (PAPP-A) and alpha-fetoprotein (AFP) were most often chosen as markers demonstrating a strong association with adverse outcomes. Most (86.9%) respondents acknowledged that abnormal MSAs influenced their counseling approach, and the majority (80.1%) offered additional ultrasound examinations. Nearly half started at 28 weeks and almost one-third at 32 weeks. Respondents acknowledging a relevant protocol in their hospital or practice were more likely to offer additional antenatal testing ($p = 0.01$). Conclusions: Although most perinatologists were in agreement regarding the association of MSAs with adverse pregnancy outcomes, a lack of consensus exists regarding management strategies.

URL:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22372385

(3) Title: Stability of inhibin A and unconjugated oestriol in the second trimester of pregnancy

Source: Ann Clin Biochem, 2011. **48**(Pt 1): p. 72-4.

Authors: Brown LF, Shearing CH, Tydeman G.

Abstract: BACKGROUND: The introduction of a second trimester quadruple test for fetal Down's syndrome adds the measurement of serum inhibin A (InhA) and unconjugated oestriol (UE3) to the existing repertoire of alphafetoprotein and intact human chorionic gonadotrophin. The aim of this study was to assess the stability of InhA and UE3 in whole blood and serum. METHODS: To determine whole blood stability, five extra blood specimens were obtained from each of 10 women attending an antenatal clinic. Samples were stored at room temperature for either two hours, one, three, five or seven days and centrifuged prior to analysis. Serum stability was studied by the analysis of surplus serum from 14 routine second trimester screening samples: seven stored at room temperature and seven stored at 4 degrees C. An aliquot from each specimen was analysed two hours, one, three, five or seven days post centrifugation. Specimens were analysed for InhA and UE3 using the Beckman Access 2((R)) Immunoassay analyser. RESULTS: No significant difference ($P > 0.05$) was shown in InhA or UE3 concentrations between the initial time point on the day of venepuncture and each of the subsequent analyses at one, three, five and seven days following collection for either whole blood or serum. CONCLUSIONS: InhA and UE3 are stable in whole blood and serum for seven days.

URL:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21115569

D) News of Note: Abstracts of New Testing Agents/Methods:

(1) Title: Evaluation of the UniCel DxI 800 Immunoassay Analyzer in Measuring Five Tumor Markers

Source: Yonsei Med J, 2012. **53**(3): p. 557-64.

Authors: Park Y, Park J, Kim HS.

Abstract: Purpose: Tumor marker concentrations in a given specimen measured by different analyzers vary according to assay methods, epitopes for antibodies used, and reagent specificities. Although great effort in quality assessment has been instituted, discrepancies among results from different analyzers are still present. We evaluated the assay performance of the UniCel DxI 800 automated

analyzer in measuring the alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, CA 15-3 and CA 19-9 tumor markers. Materials and Methods: The linearity and precision performance of the five tumor marker assays were evaluated, and concentrations of the respective markers as measured by DxI were compared to those measured by other conventional analyzers (ADVIA Centaur and Vitros ECi) using 200 specimens collected from 100 healthy persons and 100 patients with respective cancers. Results: The linear fits for all five tumor markers were statistically acceptable (F=4648 for AFP, F=15846 for CEA, F=6445 for CA 125, F=2285 for CA 15-3, F=7459 for CA 19-9; p<0.0001 for all). The imprecision of each tumor marker assay was less than 5% coefficient of variation, except for low and high concentrations of AFP. The results from UniCel DxI 800 were highly correlated with those from other analyzers. Conclusion: Our results demonstrate that UniCel DxI 800 has good linearity and precision performance for the tumor markers assayed in this study. However, there were discrepancies between assaying methods. Efforts to standardize tumor marker assays should be undertaken, and the redetermination of cut-off levels is necessary when developing methods of analyzing tumor markers.

URL:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22477000

(2) Title: Interference in the autoDELFIA(R) hAFP immunoassay and effect on second-trimester Down's syndrome screening

Source: Ann Clin Biochem, 2011. **48**(Pt 5): p. 438-40.

Authors: Mannings L, Trow S, Newman J, Nix B, Evans C.

Abstract: BACKGROUND: Falsely decreased serum alphafetoprotein (AFP) concentrations are reported in the autoDELFIA((R)) hAFP immunoassay due to interference by complement. AFP is measured, using this assay, as part of second-trimester and integrated Down's syndrome screening tests. Decreased AFP concentrations increase the calculated risk of Down's syndrome; therefore falsely low AFP, due to assay interference, may artificially increase a patient's risk, and have the potential to cause false screen positive results. It was our aim to assess whether negative interference in the autoDELFIA((R)) hAFP assay was a cause of very low AFP concentrations, and to examine the effect of falsely decreased concentrations on the calculated risk of Down's syndrome. METHODS: Three hundred and twenty-three sequential Down's screening serum samples with very low serum AFP concentration (<15 KU/L) using the autoDELFIA((R)) hAFP immunoassay were selected and AFP re-measured using the E170 AFP immunoassay. RESULTS: Interference was detected in nine samples (from eight patients) on the basis of discordant AFP concentrations. The interference decreased following storage of samples at 4 degrees C to deplete complement. Use of the falsely low AFP concentrations to calculate risk of Down's syndrome resulted in significantly increased calculated risk compared with complement depleted results. CONCLUSIONS: Laboratories should be aware that falsely low AFP concentrations due to complement interference may be obtained using the autoDELFIA((R)) hAFP immunoassay. We have shown that falsely low AFP concentrations increase the calculated risk of Down's syndrome. This is a potential cause of false Down's syndrome screen positive results.

URL:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21795408

(3) Title: Microchip Device with 64-site Electrode Array for Multiplexed Immunoassay of Cell Surface Antigens based on Electrochemiluminescence Resonance Energy Transfer

Source: Anal Chem, 2012.

Authors: Wu MS, Shi HW, He LJ, Xu JJ, Chen HY.

Abstract: This paper describes a novel on-chip microarray platform based on electrochemiluminescence resonance energy transfer (ECL-RET) strategy for rapid assay of cancer cell surface biomarkers. This platform consists of 64 antigen-decorated CdS nanorods spots with the diameter of 1.0 cm uniformly distributed on 16 Indium tin oxide (ITO) strips, which is coated with a multi-channel decorated PDMS slice to realize multiplexed determination of antigens. To shorten the immune reaction time in the microchannels and simplify the device, magnetic stirring and four-channel universal serial bus (USB) ports to realize plug-and-play were used. Ru(bpy)32+ labeled antibodies were selectively captured by the corresponding antigens on CdS nanorods array, and then ECL-RET from CdS nanorods (donor) by cathodic emission in the presence of K2S2O8 to Ru(bpy)32+ (acceptor) occurred. By the signal amplification of Ru(bpy)32+ and competitive immunoassay, embryonic antigen (CEA), alpha-fetoprotein (AFP) and prostate specific antigen (PSA) as models were detected on this microfluidic device via recording the increased ECL-RET signals on electrode surfaces. Furthermore, this multiplexed competitive immunoassay was successfully employed to determine cancer cell surface antigens via the specific antibody-cell interactions and used to cell counting via cell surface receptors and antigens on CdS nanorods surface. Experimental results revealed that this on-chip ECL competitive assay enabled the rapid, sensitive and high-throughput identification and quantification of cell surface antigens. This platform provides a simple and sensitive approach with L-level sample volume and holds great promise for multiplexed detection of antigens and antigen-specific cells.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22494075

(4) Title: Analysis of Polarized Secretion of Fucosylated Alpha-Fetoprotein in HepG2 Cells

Source: J Proteome Res, 2012.

Authors: Nakagawa T, Moriwaki K, Terao N, Miyamoto Y, Kamada Y, Miyoshi E.

Abstract: Fucosylated alpha-fetoprotein (AFP) is a more specific biomarker for hepatocellular carcinoma (HCC) than AFP. However, the mechanisms underlying the increase in fucosylated AFP in sera of HCC patients remain largely unknown. Recently, we reported that fucosylation is a possible signal for the secretion of hepatic glycoproteins into bile and that the fucosylation-based sorting machinery might be disrupted in the liver bearing HCC. In this study, we investigated the selective secretion of fucosylated AFP into bile canaliculus (BC) structures of the human hepatoma cell line HepG2. The proportion of fucosylated AFP in BC structures was higher than that in the medium, as judged by lectin affinity electrophoresis. Suppression of fucosylation by the double knock-down of GDP-mannose-4,6-dehydratase and the human homologue of GDP-4-keto-6-deoxymannose-3,5-epimerase-4-reductase, which contribute to the synthesis of GDP-fucose, a donor substrate for fucosyltransferases, did not decrease the proportion of fucosylated AFP in BC structures but decreased this proportion in conditioned medium. Furthermore, increased AFP fucosylation was observed in medium, but not in BC structures, upon adding free fucose. These results suggest that saturation of fucosylated AFP in BC structures is accompanied by its increase in conditioned medium, probably leading to increased fucosylated AFP in sera of HCC patients.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22483194

E) Special Abstract Selection:

(1) Title: Defining hepatoblastoma responsiveness to induction therapy as measured by tumor volume and serum alpha-fetoprotein kinetics

Source: J Pediatr Surg, 2010. **45**(1): p. 121-8; discussion 129.

Authors: Lovvorn HN 3rd, Ayers D, Zhao Z, Hilmes M, Prasad P, Shinall MC Jr, Berch B, Neblett WW 3rd, O'Neill JA Jr.

Abstract: PURPOSE: Hepatoblastoma is commonly unresectable at presentation, necessitating induction chemotherapy before definitive resection. To refine the paradigm for timing of resection, we questioned whether a plateau in hepatoblastoma responsiveness to neoadjuvant therapy could be detected by calculating tumor volume (TV) and serum alpha-fetoprotein (sAFP) kinetics. METHODS: To calculate TV and sAFP as measures of treatment responsiveness over time, infants having initially unresectable epithelial-type hepatoblastomas were identified at a single institution (1996-2008). Effects of therapy type, therapy duration, and lobe of liver involvement on TV, sAFP, margin status, and toxicity were analyzed. RESULTS: Of 24 infants treated for epithelial-type hepatoblastoma during this interval, 5 were resected primarily, and 15 had complete digital films for kinetics analysis. Both TV and sAFP decreased dramatically over time ($P < .0001$). No statistically significant difference in mean TV or sAFP was detected after chemotherapy cycle 2. Left lobe tumors had greater presenting levels of and significantly slower decay in sAFP compared with right lobe tumors ($P = .005$), although no statistically significant differences in TV existed between liver lobes. Resection margins did not change with therapy duration. CONCLUSIONS: Measuring TV and sAFP kinetics accurately reflects hepatoblastoma responsiveness to induction therapy. Treatment toxicities may be reduced by earlier resection and tailoring of chemotherapeutic regimens.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20105591

(2) Title: Avoiding Harmful Procedures in Patients With Elevated alpha-Fetoprotein Concentrations: Hereditary Persistence of alpha-Fetoprotein is an Important and Benign Differential Diagnosis!

Source: J Pediatr Hematol Oncol, 2012.

Authors: Bonfig W, Hempel M, Teichert-von Luttichau I, Liptay S, Burdach S.

Abstract: BACKGROUND:: Hereditary persistence of alpha-fetoprotein (AFP) is a rare but benign condition. OBSERVATION:: A 13-year-old girl presented with dysmenorrhoic complaints and irregular cycles. Diagnostic workup revealed a cystic lesion of the ovary and elevated AFP; beta-human chorionic gonadotrophin was negative. Right-sided ovarectomy was performed. Postsurgery AFP concentration did not decline. The patient underwent further diagnostic workup with negative results. Histology revealed follicular cysts but no tumor. Finally, hereditary persistence of AFP was suspected and AFP testing was performed in the family. CONCLUSIONS:: It is important to include hereditary persistence of AFP in the differential diagnosis of elevated AFP concentrations to avoid harmful procedures.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22430587

(3) Title: Risk of bronchopulmonary dysplasia by second-trimester maternal serum levels of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol

Source: Pediatr Res, 2012. **71**(4 Pt 1): p. 399-406.

Authors: Jelliffe-Pawlowski LL, Shaw GM, Stevenson DK, Oehlert JW, Quaintance C, Santos AJ, Baer RJ, Currier RJ, O'Brodovich HM, Gould JB.

Abstract: INTRODUCTION: Although maternal serum alpha-fetoprotein (AFP), human chorionic gonandotropin (hCG), and estriol play important roles in immunomodulation and immunoregulation during pregnancy, their relationship with the development of bronchopulmonary dysplasia (BPD) in young infants is unknown despite BPD being associated with pre- and postnatal inflammatory factors. RESULTS: We found that these serum biomarkers were associated with an increased risk of BPD. Risks were especially high when AFP and/or hCG levels were above the 95th percentile and/or when unconjugated estriol (uE3) levels were below the 5th percentile (relative risks (RRs) 3.1-6.7). Risks increased substantially when two or more biomarker risks were present (RRs 9.9-75.9). DISCUSSION: Data suggested that pregnancies that had a biomarker risk and yielded an offspring with BPD were more likely to have other factors present that suggested early intrauterine fetal adaptation to stress, including maternal hypertension and asymmetric growth restriction. METHODS: The objective of this population-based study was to examine whether second-trimester levels of AFP, hCG, and uE3 were associated with an increased risk of BPD.

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22391642

VI. Potentially helpful website connections/locations:

1) http://health.allrefer.com/health/alpha-fetoprotein-info.html

2) www.healthopedia.com/alpha-fetoprotein

3) http://pregnancy.about.com/cs/afp/a/afptesting.htm

4) http://www.webmd.com/baby/alpha-fetoprotein-afp-in-blood

5) http://pregnancy.about.com/od/afp/Alphafetoprotein_Testing.htm

6) http://www.americanpregnancy.org/prenataltesting/afpplus.html

Figure 1

Maternal Sera AFP MoM

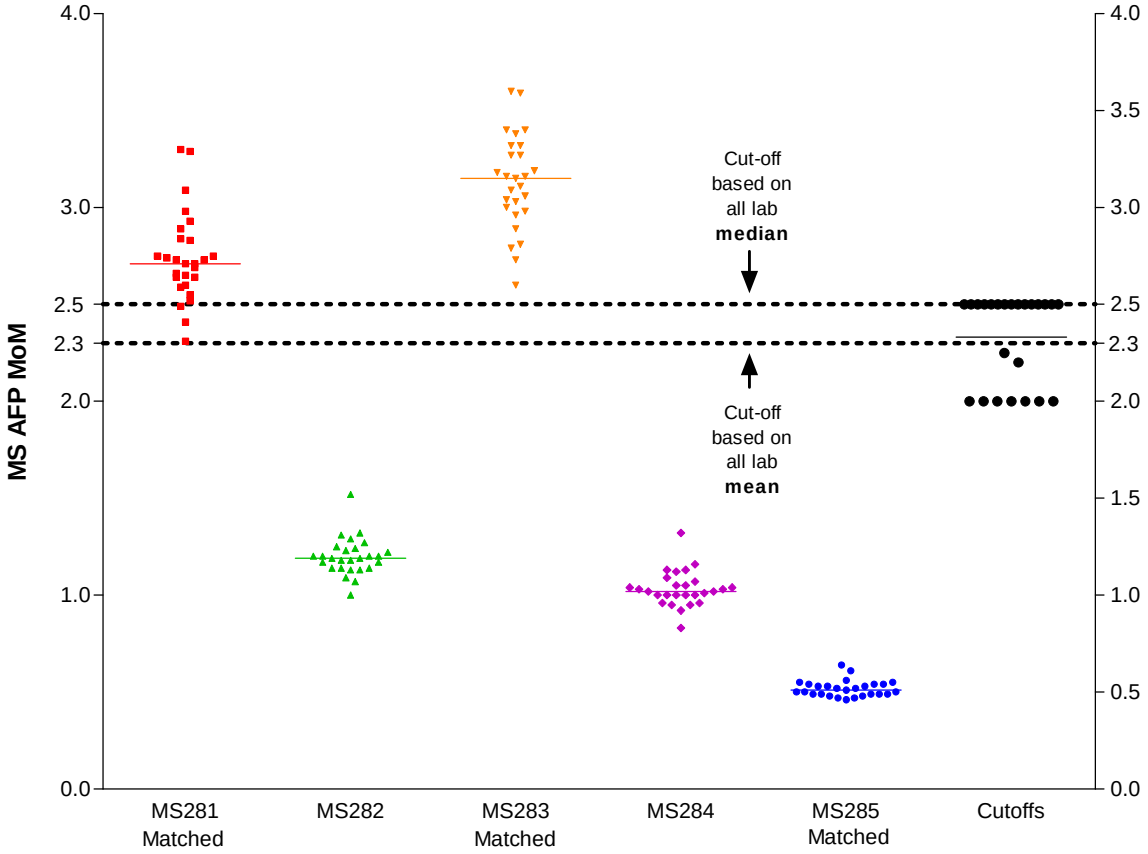

Figure 2

Amniotic Fluid AFP MoM

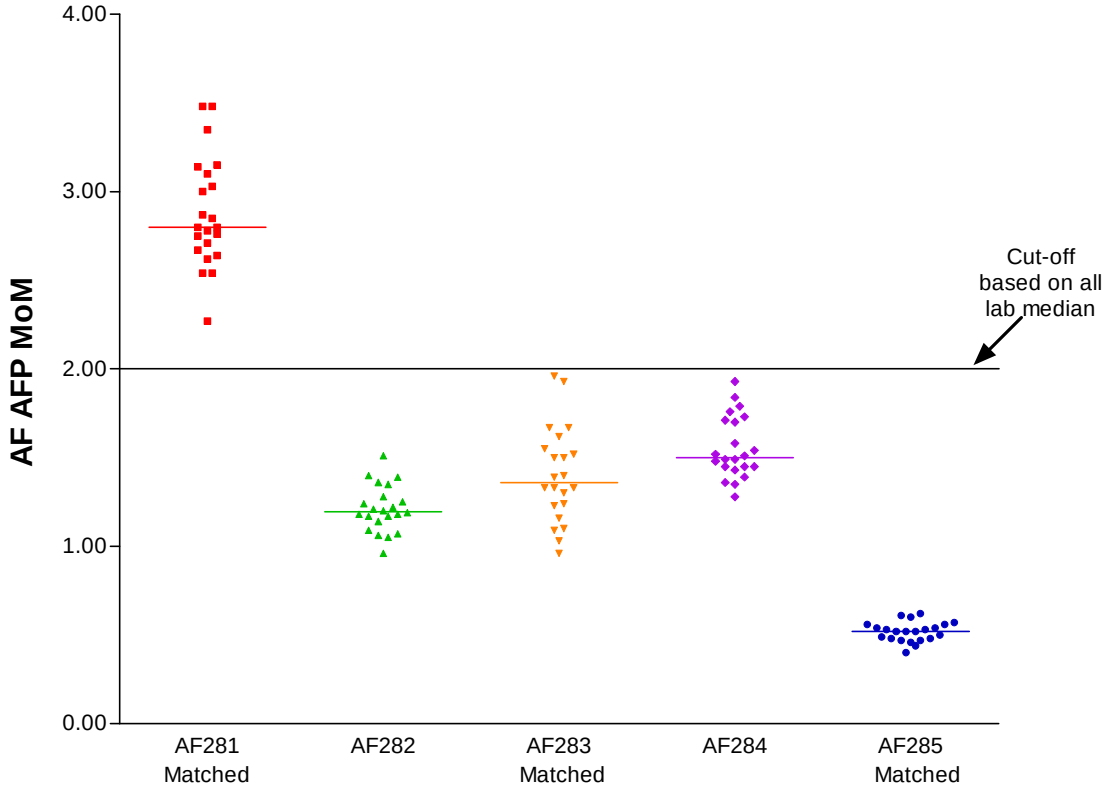

Figure 3

Graphic Distribution of Second Trimester Neural Tube Defect Risk Estimates

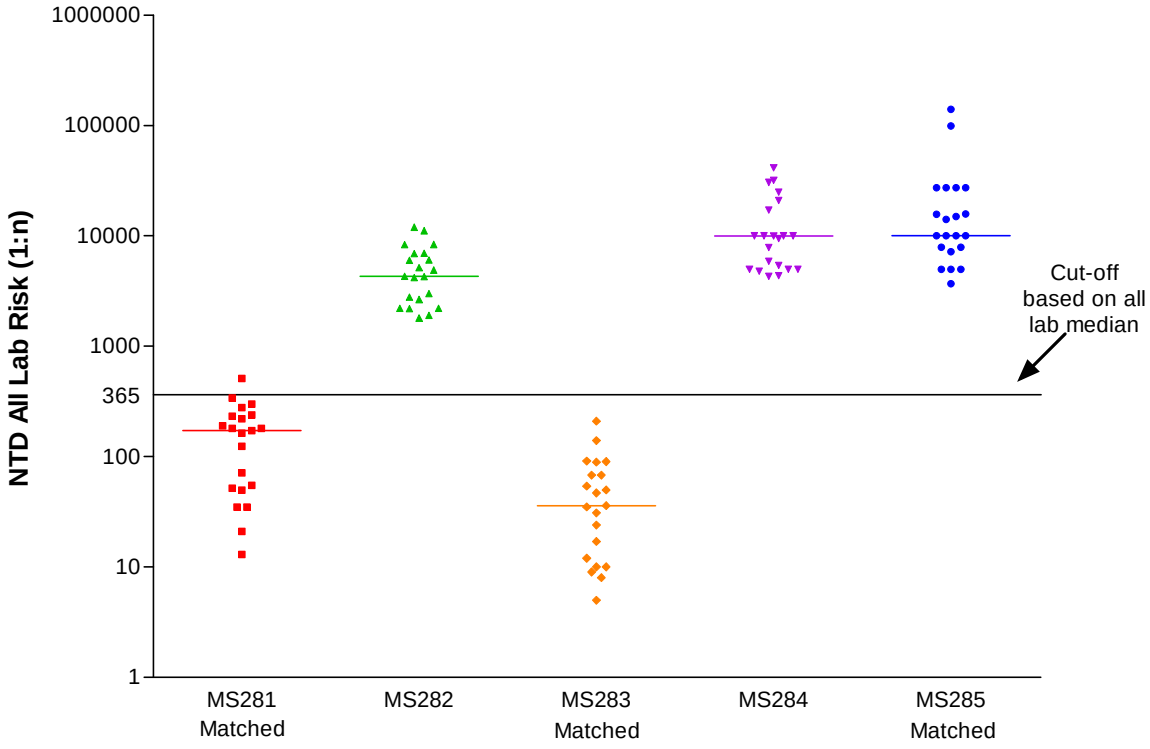

Figure 4

Graphic Distribution of Second Trimester Trisomy 18 Risk Estimates

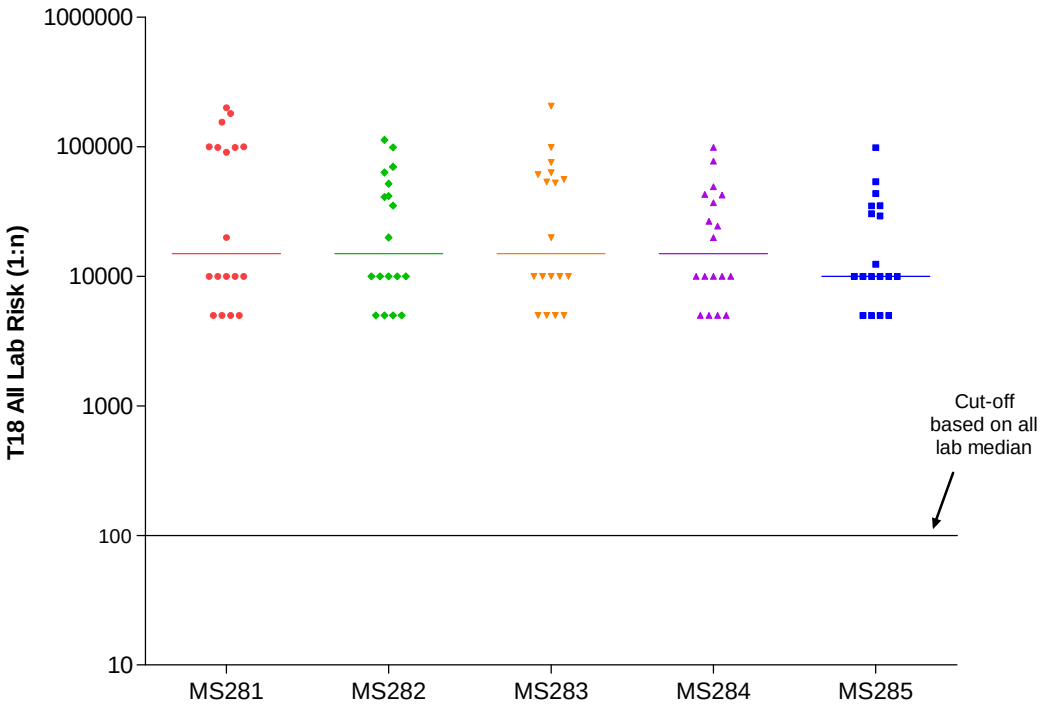

Figure 5

Graphic Distribution of Second Trimester Trisomy 21 Triple Risk Estimates

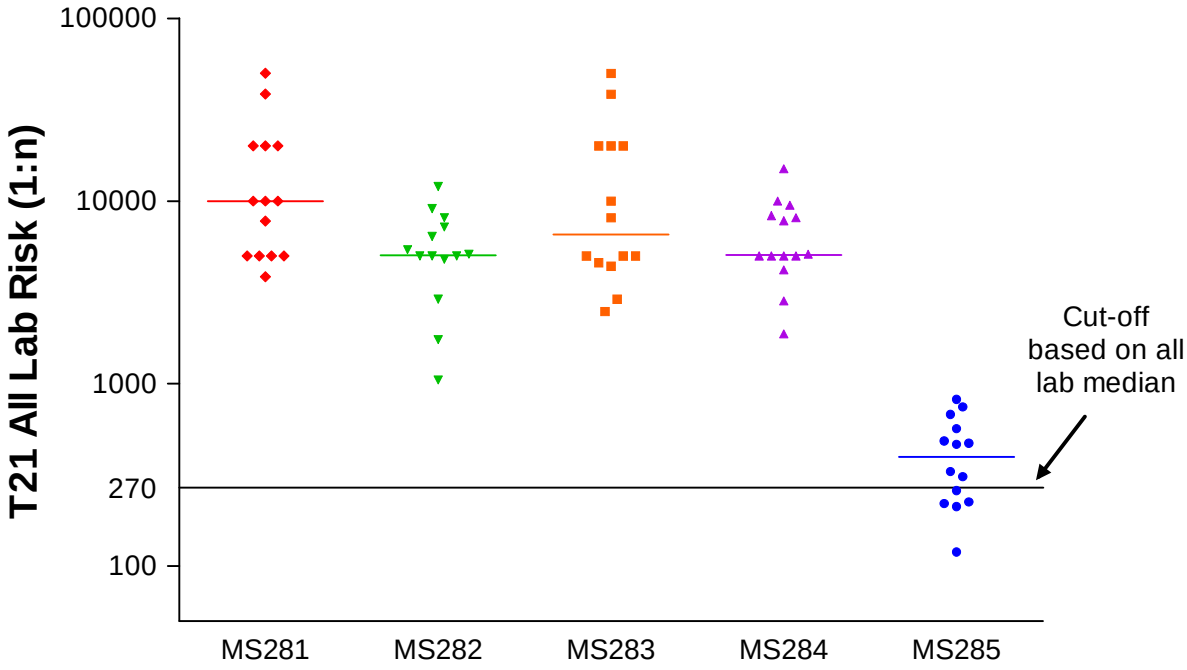

Figure 6

Graphic Distribution of Second Trimester Trisomy 21 Quadruple Risk Estimates

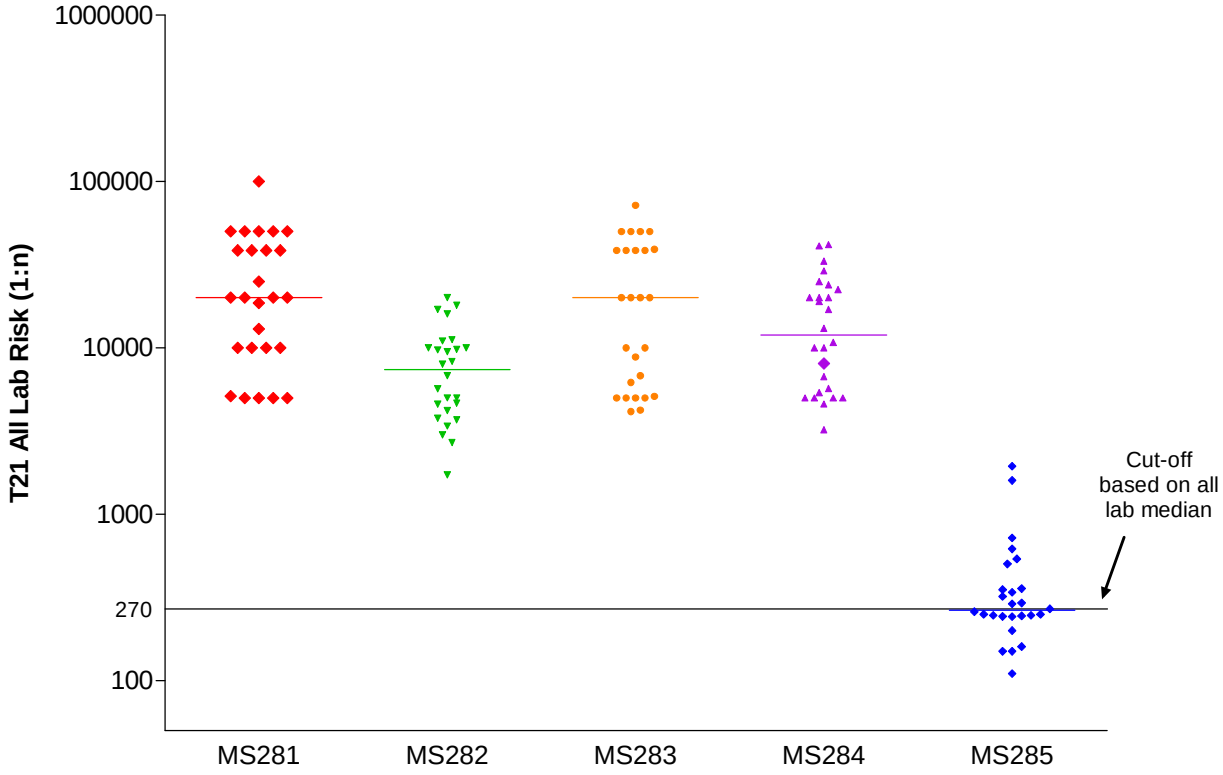

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Figure 7A

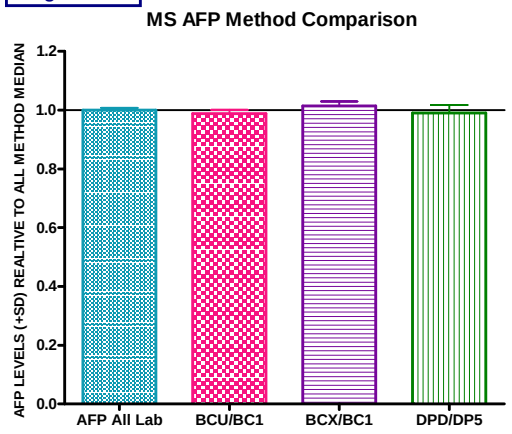


Figure 7C

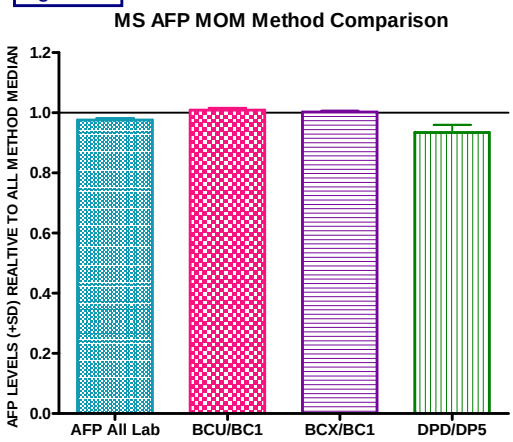


Figure 8A

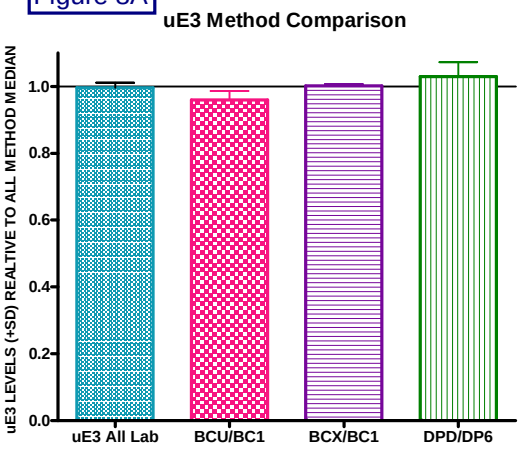


Figure 8B

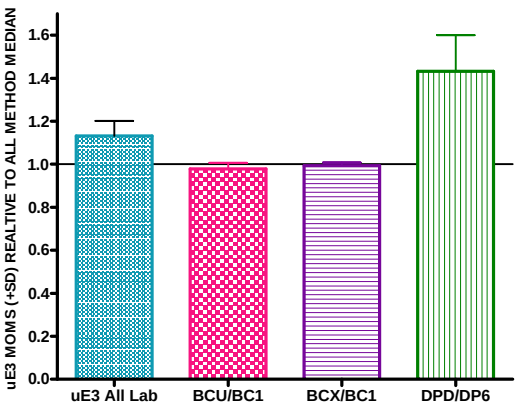


Figure 9A

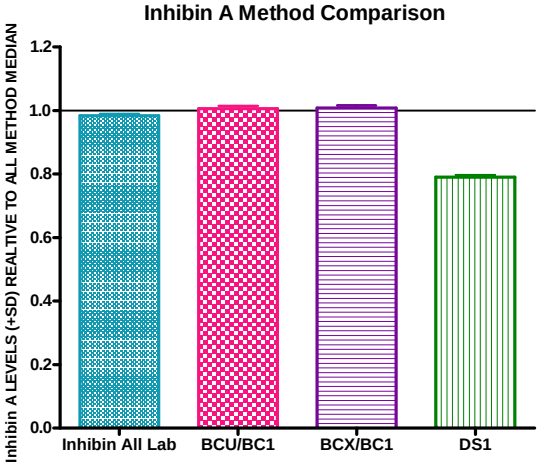
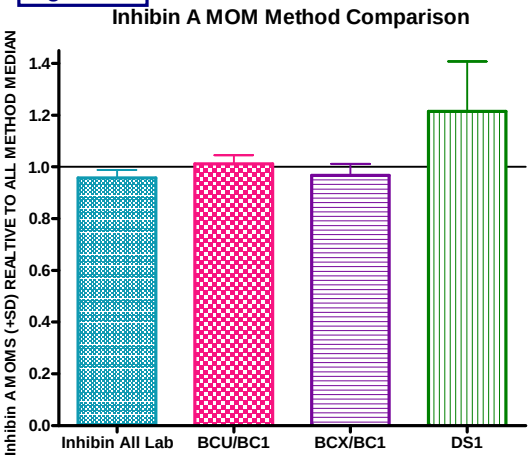


Figure 9B



BCX/BC1 = Beckman Access/2
BCU/BC1 = Beckman Unicel
DPD/DP5 = Siemens Immulite 2000
DS1 = Diagnostic Systems Labs

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Figure 7B

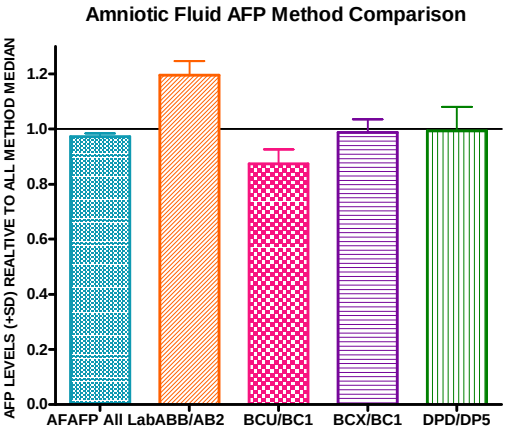


Figure 7D

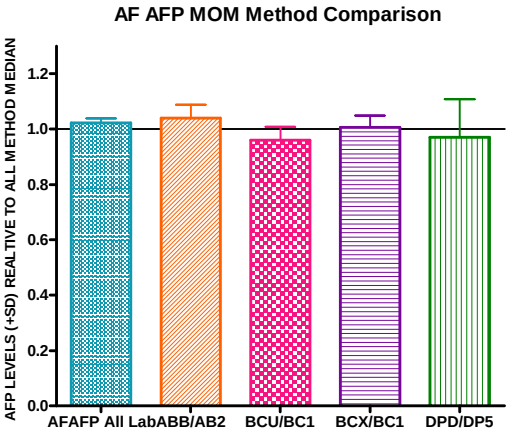


Figure 10

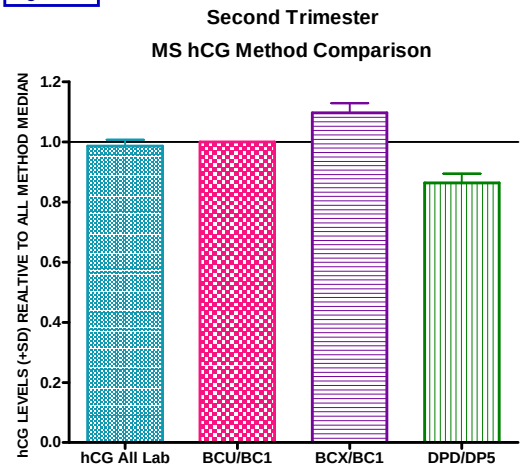


Figure 11 FT hCG Method Comparison

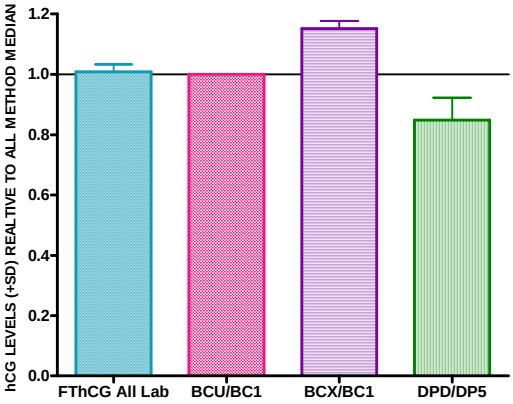


Figure 12A FT PAPP-A Method Comparison

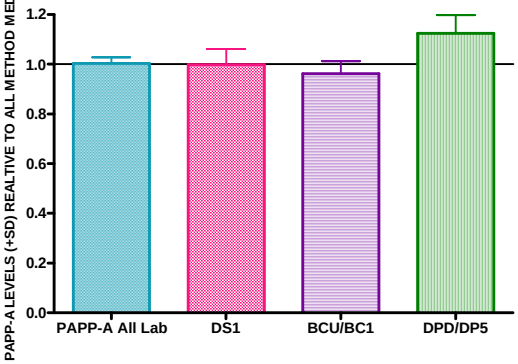
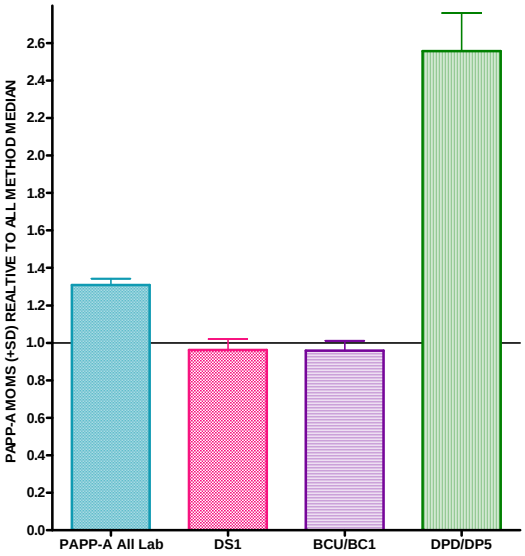


Figure 12B FT PAPP-A MOM Method Comparison



ABB/AB1 = Abbott Asxym
BCX/BC1 = Beckman Access/2
BCU/BC1 = Beckman Unicel
DPD/DP5 = Siemens Immulite 2000
DS1 = Diagnostic Systems Labs

Figure 13

Graphic Distribution of First Trimester
Trisomy 21 Risk Estimates

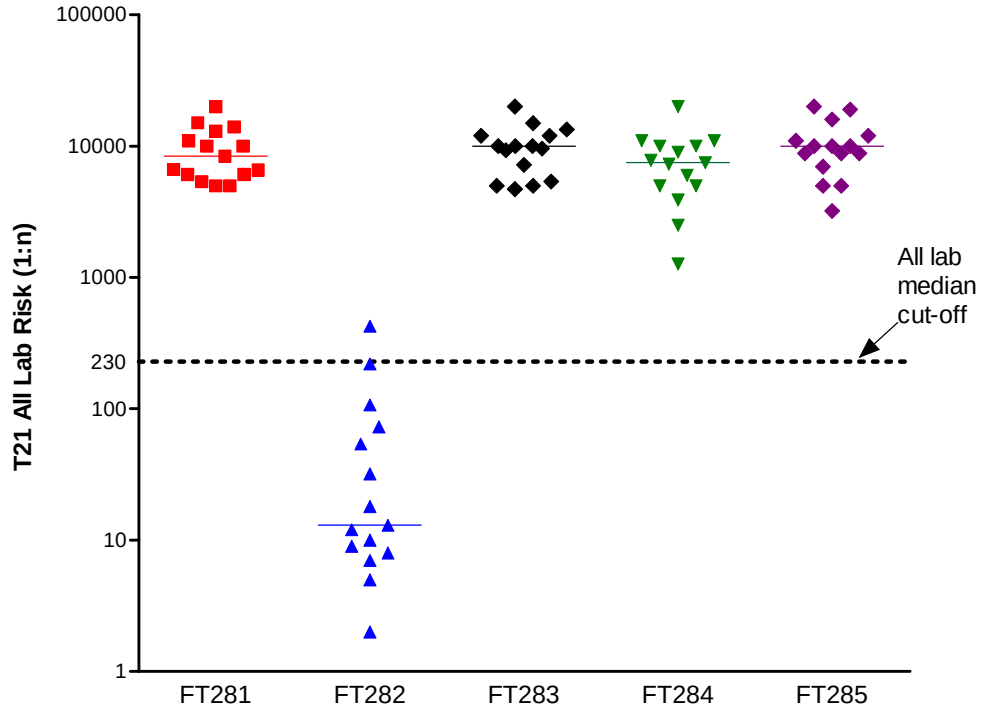


Figure 14

Graphic Distribution of First Trimester
Trisomy 18 Risk Estimates

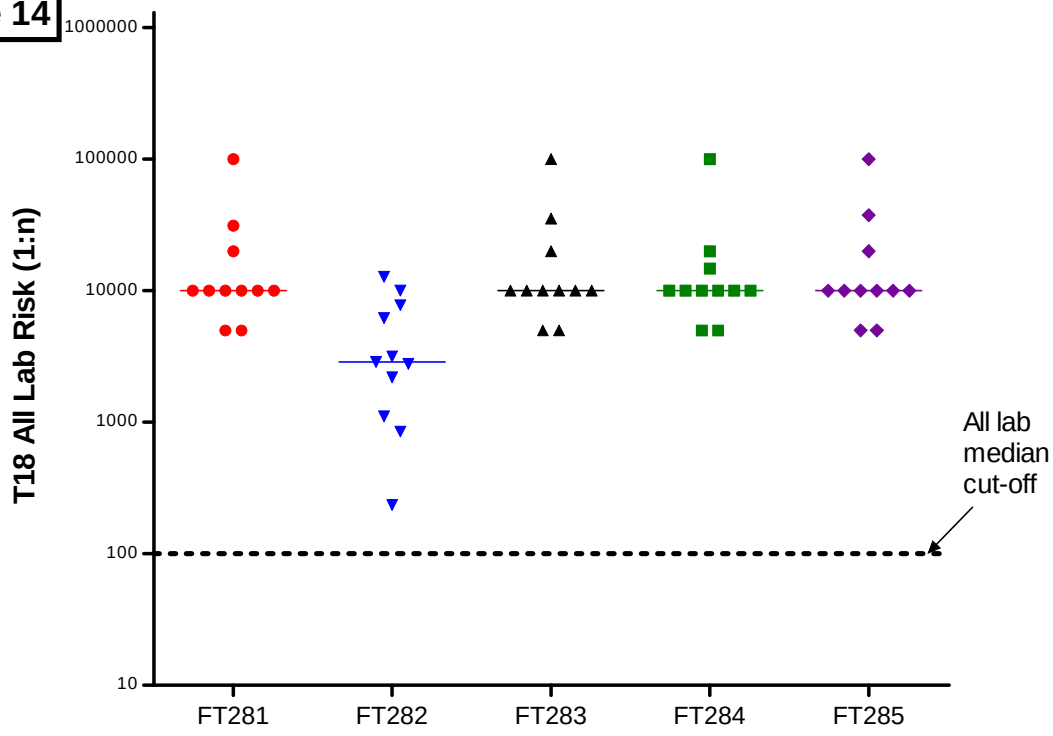


Fig. 15A

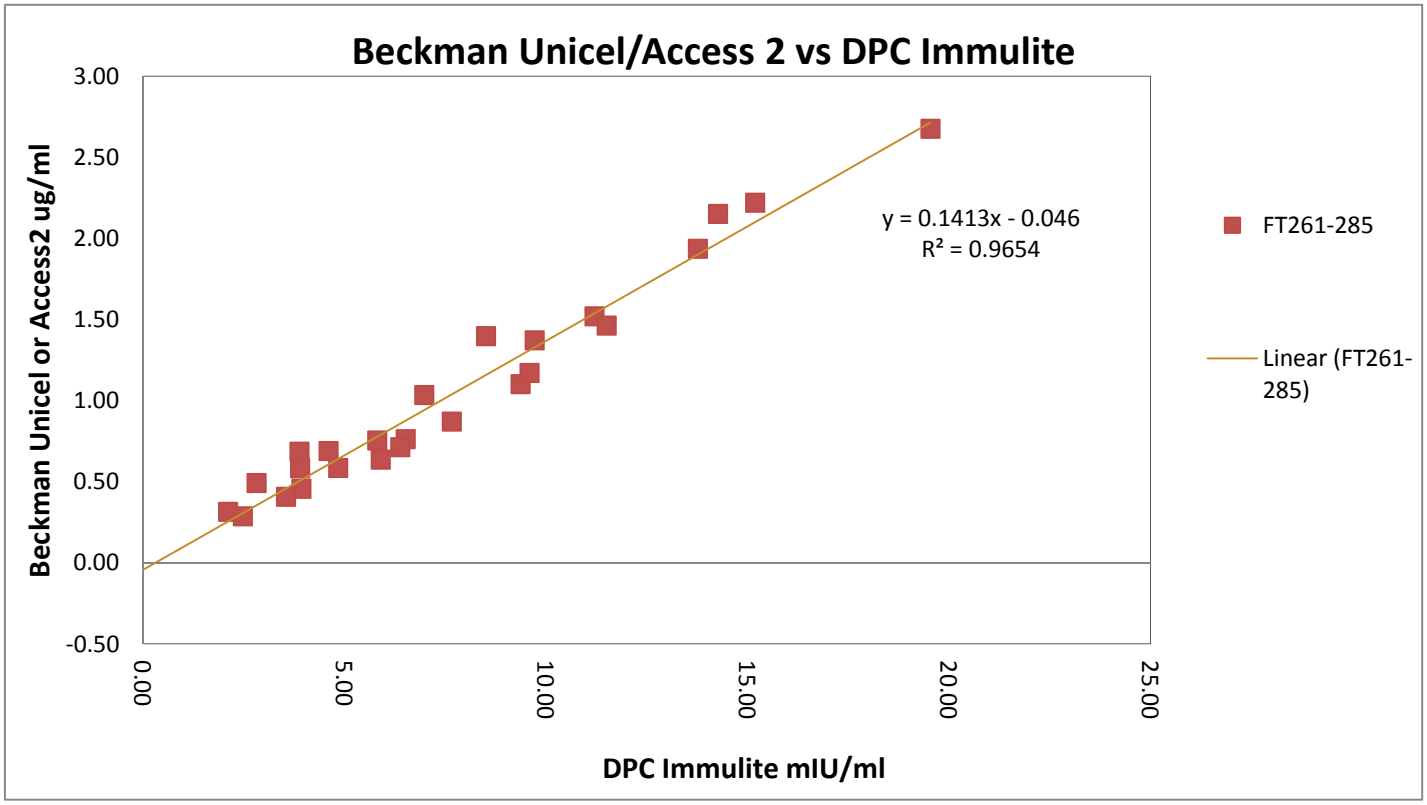
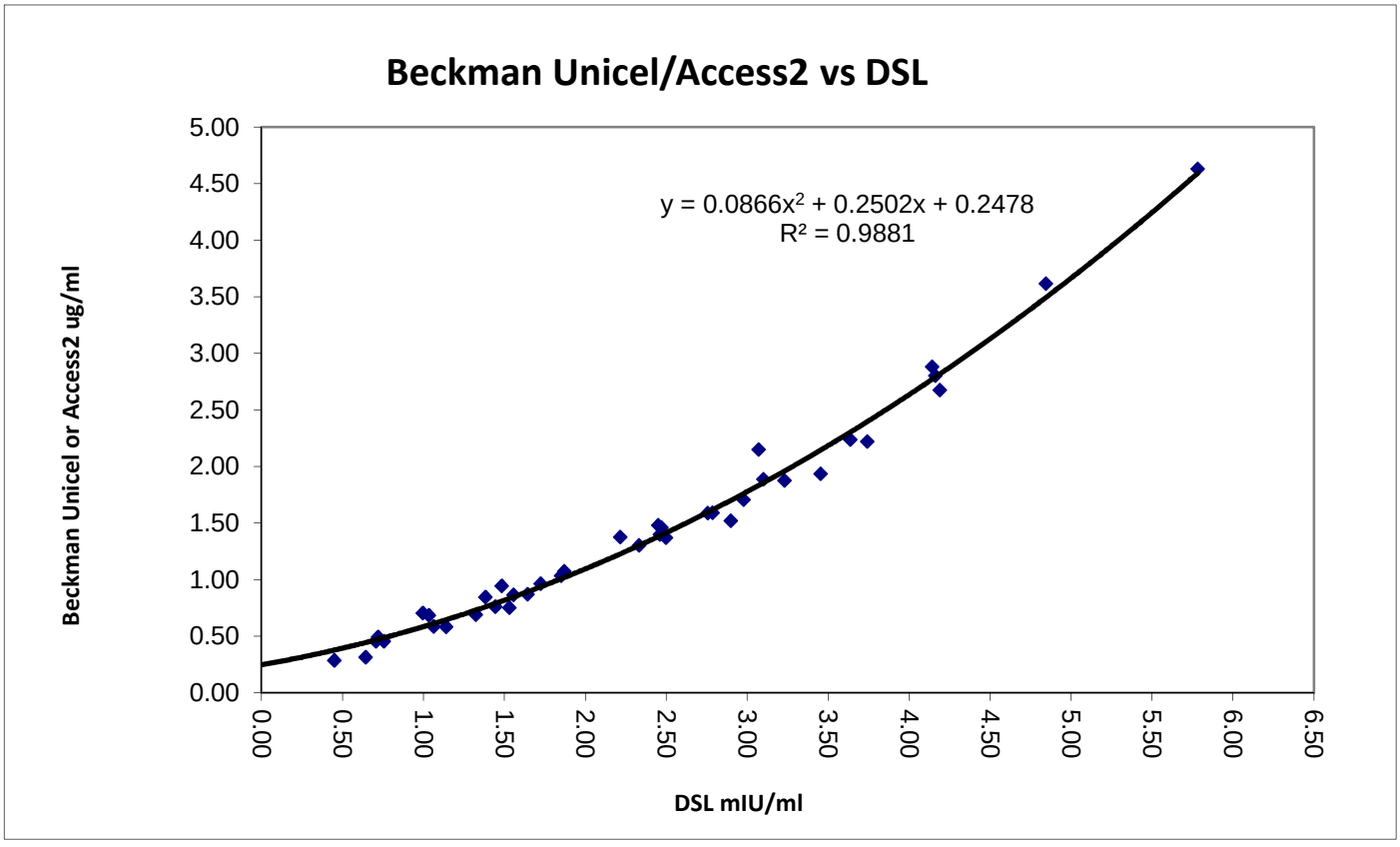


Fig. 15B



New York State Fetal Defect Markers Proficiency Test,
May 2012
Summary of Results

	MS 281	MS 282	MS 283	MS 284	MS 285
Gestational Age All Lab Mean:					
Mean	18.0	19.0	21.0	15.0	17.0
SD	0.00	0.00	0.06	0.00	0.00
%CV	0.0%	0.0%	0.3%	0.0%	0.0%
mean+3*SD	18.0	19.0	21.2	15.0	17.0
mean-3*SD	18.0	19.0	20.8	15.0	17.0
N	27	27	27	27	27

	MS 281	MS 282	MS 283	MS 284	MS 285
MS AFP All Lab Mean:					
mean	120.4	66.3	214.8	34.4	21.0
SD	10.2	4.9	14.5	2.2	1.2
%CV	8.5%	7.4%	6.7%	6.4%	5.7%
mean+3SD	151.0	81.1	258.3	41.0	24.6
mean-3SD	89.8	51.6	171.4	27.8	17.4
N	27	27	27	27	26
median	121	66.5	215.5	34.2	20.65
mean/all kit median	1.01	1.00	1.00	1.00	0.99
MS AFP Beckman Unicel (BCU/BC1) mean:					
Mean	119.6	65.1	209.2	34.0	21.4
SD	6.6	4.9	17.2	2.4	1.0
%CV	5.5%	7.6%	8.2%	6.9%	4.6%
mean + 3SD	139.5	79.9	260.8	41.1	24.4
mean - 3SD	99.8	50.3	157.5	26.9	18.5
N	9	9	9	9	8
Median	122.3	64.4	212.3	34.5	21.3
mean/All kit median	1.00	0.98	0.97	0.99	1.00
MS AFP Beckman Access/2 (BCX/BC1) mean:					
mean	123.1	66.3	221.9	34.8	21.3
SD	17.3	6.4	16.3	3.1	1.6
%CV	14.0%	9.7%	7.3%	8.9%	7.6%
mean+3SD	174.9	85.6	270.7	44.0	26.2
mean-3SD	71.3	47.0	173.0	25.5	16.4
N	8	8	8	8	8
median	120.3	65.4	219.5	34.4	20.7
mean/all kit median	1.03	1.00	1.03	1.01	1.00
MS AFP DPC Immulite 2000 (DPD/DP5) mean:					
mean	117.6	67.5	214.6	34.3	20.2
SD	4.1	4.0	8.3	1.1	0.6
%CV	3.5%	5.9%	3.8%	3.1%	2.8%
mean+3SD	130.0	79.5	239.4	37.5	21.9
mean-3SD	105.2	55.5	189.8	31.1	18.6
N	8	8	8	8	8
median	118.0	68.4	212.5	34.2	20.4
mean/all kit median	0.98	1.02	1.00	1.00	0.95
MS AFP kit average:					
mean	120.1	66.3	215.2	34.4	21.0
SD	2.8	1.2	6.4	0.4	0.7
all kit median	119.6	66.3	214.6	34.3	21.3

	MS 281	MS 282	MS 283	MS 284	MS 285
MS AFP MoM All Lab Mean:					
mean	2.74	1.19	3.13	1.02	0.52
SD	0.23	0.07	0.25	0.07	0.04
%CV	8.4%	6.1%	7.9%	7.0%	8.0%
mean+3SD	3.44	1.41	3.87	1.24	0.64
mean-3SD	2.05	0.97	2.39	0.81	0.39
N	27	26	27	26	27
All Median	2.71	1.19	3.15	1.02	0.51
mean/all kit median	0.98	0.98	0.97	0.98	0.97
MS AFP MoM Beckman Unicel (BCU/BC1) mean:					
Mean	2.83	1.23	3.22	1.05	0.54
SD	0.22	0.12	0.27	0.06	0.05
%CV	7.7%	9.9%	8.5%	5.9%	8.5%
mean + 3SD	3.49	1.60	4.04	1.23	0.68
mean - 3SD	2.18	0.86	2.39	0.86	0.40
N	8	8	8	8	8
Median	2.78	1.20	3.16	1.05	0.53
mean/all kit median	1.01	1.02	1.00	1.00	1.01
MS AFP MoM Beckman Access/2 (BCX/BC1) mean:					
Mean	2.79	1.21	3.22	1.06	0.53
SD	0.30	0.10	0.20	0.14	0.04
%CV	10.7%	8.5%	6.1%	13.0%	7.1%
mean + 3SD	3.69	1.52	3.81	1.47	0.65
mean - 3SD	1.90	0.90	2.63	0.64	0.42
N	9	9	9	9	9
Median	2.75	1.20	3.27	1.03	0.54
mean/all kit median	1.00	1.00	1.00	1.01	1.00
MS AFP MoM DPC Immulite 2000 (DPD/DP5) mean:					
Mean	2.60	1.16	2.98	1.00	0.48
SD	0.12	0.06	0.23	0.05	0.01
%CV	4.7%	5.2%	7.6%	5.2%	3.1%
mean + 3SD	2.97	1.34	3.66	1.16	0.53
mean - 3SD	2.24	0.98	2.29	0.85	0.44
N	8	8	8	8	8
Median	2.62	1.18	3.01	1.00	0.49
mean/all kit median	0.93	0.96	0.92	0.96	0.90
MS AFP MoM kit average:					
mean	2.74	1.20	3.14	1.04	0.52
SD	0.12	0.04	0.14	0.03	0.03
all kit median	2.79	1.21	3.22	1.05	0.53

New York State Fetal Defect Markers Proficiency Test,
May 2012
Summary of Results

	MS 281	MS 282	MS 283	MS 284	MS 285
MS uE3 All Lab Mean:					
mean	1.32	1.46	1.62	0.61	0.90
SD	0.07	0.11	0.11	0.07	0.09
%CV	5.5%	7.9%	7.1%	11.2%	10.5%
mean+3SD	1.54	1.80	1.96	0.81	1.18
mean-3SD	1.10	1.11	1.28	0.40	0.62
N	26	26	26	26	26
mean/all kit median	0.98	0.98	1.00	1.01	1.01
MS uE3 Beckman Unicel (BCU/BC1) mean:					
Mean	1.26	1.41	1.62	0.57	0.87
SD	0.05	0.08	0.11	0.04	0.05
%CV	4.4%	5.5%	6.9%	7.2%	5.7%
mean+3SD	1.42	1.64	1.95	0.69	1.01
mean-3SD	1.09	1.17	1.28	0.45	0.72
N	9	9	9	9	9
mean/all kit median	0.93	0.95	1.00	0.95	0.97
MS uE3 Beckman Access/2 (BCX/BC1) mean:					
mean	1.35	1.48	1.64	0.60	0.89
SD	0.05	0.07	0.08	0.03	0.05
%CV	3.7%	4.9%	4.6%	4.5%	6.0%
mean+3SD	1.50	1.70	1.86	0.68	1.05
mean-3SD	1.20	1.27	1.41	0.52	0.73
N	8	8	8	8	8
mean/all kit median	1.00	1.00	1.01	1.00	1.00
MS uE3 DPC Immulite/2000 (DPD/DP6) mean:					
Mean	1.35	1.49	1.61	0.65	0.94
SD	0.07	0.16	0.15	0.09	0.14
%CV	5.0%	10.8%	9.5%	14.0%	14.8%
mean+3SD	1.56	1.97	2.06	0.92	1.36
mean-3SD	1.15	1.00	1.15	0.38	0.53
N	9	9	9	9	9
mean/all Kit Median	1.00	1.00	1.00	1.09	1.06
MS uE3 kit average:					
mean	1.32	1.46	1.62	0.61	0.90
SD	0.06	0.05	0.02	0.04	0.04
all kit median	1.35	1.48	1.62	0.60	0.89

	MS 281	MS 282	MS 283	MS 284	MS 285
MS uE3 MoM All Lab Mean:					
Mean	1.19	1.00	0.75	1.10	0.99
SD	0.26	0.20	0.11	0.38	0.29
%CV	21.6%	19.5%	14.2%	34.2%	28.7%
mean+3SD	1.95	1.59	1.06	2.23	1.85
mean-3SD	0.42	0.41	0.43	-0.03	0.14
N	26	26	25	26	26
mean/all kit Median	1.10	1.10	1.06	1.24	1.16
MS uE3 MoM Beckman Unicel (BCU/BC1) Mean:					
Mean	1.00	0.89	0.70	0.88	0.84
SD	0.08	0.09	0.07	0.12	0.08
%CV	7.7%	9.8%	10.1%	13.0%	9.5%
mean+3SD	1.23	1.15	0.92	1.23	1.07
mean-3SD	0.77	0.63	0.49	0.54	0.60
N	9	9	9	9	9
mean/all kit Median	0.93	0.98	1.00	1.00	0.98
MS uE3 MoM Beckman Access/2 (BCX/BC1) Mean:					
Mean	1.07	0.91	0.68	0.89	0.86
SD	0.09	0.08	0.06	0.09	0.09
%CV	8.1%	9.3%	8.7%	10.3%	10.7%
mean+3SD	1.33	1.16	0.86	1.16	1.13
mean-3SD	0.81	0.65	0.51	0.61	0.58
N	8	8	8	8	8
mean/all kit Median	1.00	1.00	0.97	1.00	1.00
MS uE3 MoM DPC Immulite/2000 (DPD/DP6) Mean:					
Mean	1.47	1.20	0.90	1.50	1.27
SD	0.23	0.20	0.16	0.37	0.32
%CV	15.7%	16.7%	17.4%	24.7%	25.4%
mean+3SD	2.16	1.79	1.37	2.62	2.24
mean-3SD	0.77	0.60	0.43	0.39	0.30
N	9	9	9	9	9
mean/all kit Median	1.37	1.32	1.28	1.70	1.49
MS uE3 MoM kit average:					
mean	1.18	1.00	0.76	1.09	0.99
SD	0.25	0.17	0.12	0.36	0.25
all kit median	1.07	0.91	0.70	0.89	0.86

New York State Fetal Defect Markers Proficiency Test,
May 2012
Summary of Results

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG All Lab mean:					
mean	21.6	18.7	17.4	31.3	35.4
SD	2.5	2.2	1.9	4.3	4.5
%CV	11.4%	11.7%	11.1%	13.7%	12.6%
mean+3SD	28.9	25.3	23.2	44.2	48.8
mean-3SD	14.2	12.1	11.6	18.4	22.0
N	27	27	27	27	27
mean/all kit median	1.01	0.97	0.99	0.96	1.00

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG Beckman Access/2 (BCX/BC1) mean:					
mean	24.0	20.2	19.2	34.9	40.1
SD	1.4	1.2	1.4	2.3	2.3
%CV	5.7%	5.8%	7.2%	6.5%	5.8%
mean+3SD	28.1	23.7	23.4	41.8	47.1
mean-3SD	19.9	16.7	15.1	28.1	33.2
N	8	8	8	8	8
median	24.1	20.3	19.2	35.8	39.8
mean/all kit median	1.12	1.05	1.10	1.08	1.13

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG Beckman Unicel (BCU/BC1) mean:					
mean	21.4	19.3	17.5	32.5	35.4
SD	1.6	2.1	1.4	3.3	2.6
%CV	7.5%	11.0%	7.8%	10.3%	7.2%
mean+3SD	26.20	25.72	21.60	42.46	43.09
mean-3SD	16.60	12.93	13.38	22.47	27.78
N	9	9	9	9	9
median	21.60	19.40	17.10	33.10	34.30
mean/All kit median	1.00	1.00	1.00	1.00	1.00

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG DPC Immulite 2000 (DPD/DP5) mean:					
mean	19.2	16.4	15.5	26.7	30.8
SD	1.9	1.2	1.1	2.2	2.8
%CV	9.9%	7.2%	7.4%	8.2%	9.0%
mean+3SD	24.9	20.0	18.9	33.2	39.1
mean-3SD	13.5	12.9	12.0	20.1	22.5
N	8	8	8	8	8
median	18.8	16.4	15.9	27.3	30.0
mean/all kit median	0.90	0.85	0.88	0.82	0.87

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG MoMs All Lab Mean:					
mean	1.08	0.95	1.07	0.77	1.45
SD	0.10	0.11	0.11	0.10	0.16
%CV	9.5%	11.3%	10.3%	13.0%	11.0%
mean+3SD	1.39	1.28	1.41	1.08	1.93
N	26	26	26	26	26

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG kit average:					
mean	21.5	18.6	17.4	31.4	35.4
SD	2.4	2.0	1.9	4.2	4.7
all kit median	21.4	19.3	17.5	32.5	35.4

New York State Fetal Defect Markers Proficiency Test,
May 2012
Summary of Results

	MS 281	MS 282	MS 283	MS 284	MS 285
MS Inhibin A all lab mean:					
Mean	145.8	199.8	209.2	141.0	240.4
SD	13.8	18.3	19.8	13.2	24.8
%CV	9.5%	9.1%	9.5%	9.4%	10.3%
mean + 3SD	187.2	254.7	268.6	180.6	314.8
mean- 3SD	104.3	145.0	149.7	101.3	166.0
N	26	26	26	26	26
All Lab Median	150.0	202.5	213.0	142.5	247.9
mean/all kit median	0.99	0.98	0.98	0.98	0.99
MS Inhibin A Beckman Unicel (BCU/BC1) mean:					
Mean	151.0	204.3	215.3	143.5	244.1
SD	10.5	12.9	11.9	9.8	20.6
%CV	6.9%	6.3%	5.5%	6.8%	8.4%
mean + 3SD	182.5	242.9	251.0	172.9	305.9
mean- 3SD	119.5	165.8	179.6	114.1	182.3
N	11	11	11	11	11
kit median	150.3	200.4	212.5	142.0	242.2
mean/all kit median	1.02	1.00	1.01	1.00	1.00
MS Inhibin A Beckman Access/2 (BCX/BC1) mean:					
Mean	147.9	205.4	214.2	145.4	249.2
SD	8.2	11.7	11.9	8.0	14.0
%CV	5.5%	5.7%	5.6%	5.5%	5.6%
mean + 3SD	172.4	240.4	250.0	169.5	291.3
mean- 3SD	123.4	170.4	178.4	121.3	207.1
N	12	12	12	12	12
kit median	150.4	208.8	216.7	147.5	253.1
mean/All kit median	1.00	1.01	1.00	1.01	1.02
MS Inhibin A Diagnostic System Labs (DS1) mean:					
Mean	118.1	161.1	166.6	113.8	191.9
SD	11.9	7.6	18.3	9.5	20.3
%CV	10.1%	4.7%	11.0%	8.3%	10.6%
mean + 3SD	153.8	184.1	221.5	142.1	252.7
mean- 3SD	82.3	138.2	111.7	85.4	131.1
N	3	3	3	3	3
kit median	116.5	160.2	167.2	111.0	185.0
mean/all kit median	0.80	0.79	0.78	0.79	0.79
MS Inhibin A kit average:					
mean	139.0	190.3	198.7	134.2	228.4
SD	18.2	25.3	27.8	17.7	31.7
all kit median	147.9	204.3	214.2	143.5	244.1

	MS 281	MS 282	MS 283	MS 284	MS 285
MS Inhibin A MoM All Lab mean:					
mean	0.87	1.09	1.01	0.75	1.39
SD	0.11	0.16	0.17	0.10	0.18
%CV	12.6%	14.8%	17.2%	14.0%	12.8%
mean+3SD	1.20	1.57	1.53	1.07	1.92
mean-3SD	0.54	0.61	0.49	0.44	0.86
N	26	26	26	26	26
mean/all kit median	1.00	0.94	0.92	0.96	0.97
MS Inhibin A MoM Beckman Unicel (BCU/BC1) mean:					
Mean	0.93	1.16	1.09	0.77	1.43
SD	0.10	0.16	0.17	0.09	0.17
%CV	10.7%	14.1%	15.4%	12.0%	12.1%
mean + 3SD	1.22	1.65	1.60	1.05	1.95
mean- 3SD	0.63	0.67	0.59	0.49	0.91
N	11	11	11	11	11
Kit Median	0.87	1.09	1.03	0.76	1.37
mean/all kit median	1.07	1.00	1.00	0.99	1.00
MS Inhibin A MoM Beckman Access (BCX/BC1) mean:					
Mean	0.86	1.09	0.99	0.78	1.43
SD	0.06	0.09	0.11	0.08	0.11
%CV	6.7%	8.6%	11.2%	10.2%	8.0%
mean + 3SD	1.04	1.36	1.32	1.02	1.77
mean- 3SD	0.69	0.81	0.66	0.54	1.08
N	12	12	12	12	12
Kit Median	0.89	1.09	1.04	0.77	1.43
mean/all kit median	1.00	0.93	0.91	1.00	1.00
MS Inhibin A MoM Diagnostic System Labs (DS1) mean:					
Mean	0.81	1.70	1.32	1.01	1.67
SD	0.19	0.47	0.33	0.20	0.48
%CV	23.0%	27.4%	24.8%	19.8%	29.1%
mean + 3SD	1.36	3.10	2.30	1.61	3.12
mean- 3SD	0.25	0.30	0.34	0.41	0.21
N	3	3	3	3	3
Kit Median	0.72	1.56	1.27	1.00	1.51
mean/all kit median	0.93	1.46	1.21	1.30	1.17
MS Inhibin A MoM kit average:					
mean	0.87	1.32	1.13	0.85	1.51
SD	0.06	0.34	0.17	0.14	0.14
all kit median	0.86	1.16	1.09	0.78	1.43

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	AF 281	AF 282	AF 283	AF 284	AF 285
AF AFP All Lab mean :					
mean	27.2	9.4	7.8	9.9	6.0
SD	3.7	1.6	1.1	1.7	0.8
%CV	13.6%	16.8%	14.5%	16.8%	12.9%
mean+3SD	38.3	14.1	11.2	14.8	8.3
mean-3SD	16.2	4.6	4.4	4.9	3.7
N	22	22	22	22	22
All kit median	27.5	9.8	8.0	10.2	6.2
mean/all kit mean	0.99	0.96	0.98	0.97	0.96
AF AFP Beckman Unicel (BCU/BC1) mean:					
Mean	25.6	8.1	7.4	8.5	5.3
SD	4.2	1.1	0.7	0.7	0.5
%CV	16.4%	14.0%	9.5%	8.1%	8.5%
X+3SD	38.0	13.5	12.1	14.2	8.0
X-3SD	16.0	5.2	5.1	5.6	4.0
N	8	8	8	8	8
median	23.8	7.6	7.2	8.5	5.2
mean/all kit median	0.93	0.83	0.93	0.83	0.85
AF AFP Beckman Access/2 (BCX/BC1) mean:					
mean	27.0	9.4	8.6	9.9	6.0
SD	3.7	1.4	1.2	1.4	0.7
%CV	13.5%	14.8%	13.5%	14.5%	11.1%
mean+3SD	38.0	13.5	12.1	14.2	8.0
mean-3SD	16.0	5.2	5.1	5.6	4.0
N	6	6	6	6	6
median	25.9	9.15	8.1	9.55	5.8
mean/all kit median	0.98	0.96	1.07	0.97	0.96
AF AFP DPC Immulite 2000 (DPD/DP5) mean:					
mean	28.0	10.2	6.7	10.5	6.4
SD	1.9	0.8	0.3	0.8	0.3
%CV	6.7%	7.7%	4.5%	7.6%	5.3%
mean+3SD	33.7	12.6	7.7	12.8	7.5
mean-3SD	22.3	7.9	5.8	8.1	5.4
N	5	5	5	5	5
median	27.6	10.3	6.7	10.1	6.3
mean/all kit median	1.02	1.04	0.84	1.03	1.04
AF AFP Abbott Axsym (ABB/AB2) mean:					
mean	32.2	11.9	9.3	13.1	7.2
N	2	2	2	2	2
mean/all kit median	1.17	1.21	1.16	1.28	1.16
AF AFP kit average:					
mean	28.2	9.9	8.0	10.5	6.2
SD	2.8	1.6	1.2	1.9	0.8
all kit median	27.5	9.8	8.0	10.2	6.2

	AF 281	AF 282	AF 283	AF 284	AF 285
AF AFP MoM All Lab Mean:					
mean	2.88	1.21	1.40	1.56	0.52
SD	0.31	0.13	0.27	0.18	0.06
%CV	10.8%	10.8%	19.1%	11.3%	10.7%
mean+3SD	3.81	1.61	2.20	2.08	0.69
mean-3SD	1.95	0.82	0.60	1.03	0.35
N	22	22	22	22	22
All median	2.80	1.20	1.36	1.50	0.52
mean/all kit median	1.03	1.01	1.03	1.04	1.00
AF AFP MoM Beckman Unicel(BCU/BC1) mean:					
Mean	2.94	1.15	1.41	1.45	0.50
SD	0.38	0.13	0.17	0.07	0.04
%CV	13.0%	11.1%	12.0%	4.9%	8.8%
X+3SD	4.09	1.53	1.92	1.66	0.63
X-3SD	1.80	0.77	0.90	1.23	0.37
N	8	8	8	8	8
median	2.83	1.14	1.36	1.47	0.51
mean/all kit median	1.03	0.92	0.96	0.91	0.98
AF AFP MoM Beckman Access (BCX/BC1) mean:					
Mean	2.82	1.20	1.58	1.56	0.51
SD	0.36	0.16	0.29	0.25	0.08
%CV	12.6%	13.1%	18.5%	15.7%	15.3%
X+3SD	3.89	1.68	2.46	2.30	0.74
X-3SD	1.75	0.73	0.70	0.82	0.28
N	6	6	6	6	6
median	2.77	1.17	1.46	1.47	0.50
mean/all kit median	0.99	0.97	1.08	0.99	1.00
AF AFP MoM DPC Immulite 2000 (DPD/DP5) mean:					
Mean	2.86	1.28	1.07	1.60	0.55
SD	0.25	0.09	0.08	0.13	0.05
%CV	8.8%	7.2%	7.1%	7.9%	9.4%
X+3SD	3.61	1.56	1.30	1.98	0.71
X-3SD	2.11	1.01	0.84	1.22	0.40
N	5	5	5	5	5
median	2.80	1.28	1.09	1.58	0.54
mean/all kit median	1.00	1.03	0.73	1.01	1.08
AF AFP MoM Abbott Axsym (ABB/AB2) mean:					
Mean	2.84	1.30	1.53	1.78	0.51
N	2	2	2	2	2
mean/all kit median	1.00	1.04	1.04	1.12	1.00
AF AFP MoM kit average:					
mean	2.87	1.23	1.40	1.60	0.52
SD	0.05	0.07	0.23	0.14	0.02
all kit median	2.85	1.24	1.47	1.58	0.51

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	FT281	FT282	FT283	FT284	FT285
FT Gestational Age All Lab Mean:					
Mean	11.2	12.0	11.5	12.5	13.0
SD	0.13	0.04	0.12	0.10	0.05
%CV	1.2%	0.4%	1.1%	0.8%	0.4%
mean+3*SD	11.6	12.1	11.9	12.8	13.1
mean-3*SD	10.8	11.8	11.1	12.2	12.8
N	17	17	17	17	17

	FT281	FT282	FT283	FT284	FT285
FT NT MoM All Lab Mean:					
Mean	1.04	1.86	1.07	0.94	0.98
SD	0.07	0.11	0.07	0.06	0.06
%CV	7.0%	6.2%	6.7%	6.8%	5.7%
mean+3SD	1.26	2.20	1.29	1.13	1.15
mean- 3SD	0.83	1.51	0.85	0.75	0.81
N	16	16	16	16	16
All Median	1.04	1.86	1.07	0.94	0.99

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	FT281	FT282	FT283	FT284	FT285
FT hCG All Lab Mean:					
mean	80.8	169.1	78.0	75.2	70.2
SD	11.6	38.6	10.7	8.4	8.6
%CV	14.4%	22.8%	13.7%	11.2%	12.3%
mean+3SD	115.6	284.9	110.0	100.4	96.0
mean- 3SD	46.0	53.3	45.9	49.9	44.4
N	16	16	16	16	16
mean/All kit median	1.00	0.97	1.03	1.01	1.03

	FT281	FT282	FT283	FT284	FT285
FT hCG DPC Immulite 2000(DPD/DP5) mean:					
mean	68.9	125.5	66.5	66.3	61.2
SD	5.6	15.7	2.4	5.1	5.1
%CV	8.1%	12.5%	3.6%	7.7%	8.3%
mean+3SD	85.7	172.6	73.7	81.6	76.4
mean- 3SD	52.1	78.4	59.3	51.1	46.0
N	5	5	5	5	5
median	67.5	118.6	67.5	68.5	61.8
mean/All kit median	0.85	0.72	0.88	0.90	0.89

	FT281	FT282	FT283	FT284	FT285
FT hCG MoM All Lab Mean:					
Mean	0.90	2.16	0.93	0.97	0.95
SD	0.10	0.34	0.09	0.09	0.09
%CV	10.9%	15.8%	10.1%	9.6%	9.4%
mean+3*SD	1.20	3.18	1.21	1.25	1.22
mean - 3*SD	0.60	1.13	0.65	0.69	0.68
N	15	15	15	15	15
All Median	0.92	2.09	0.93	0.98	0.96

	FT281	FT282	FT283	FT284	FT285
FT hCG Beckman Unicel (BCU/BC1) mean:					
mean	80.7	174.7	75.4	74.1	68.5
SD	11.5	24.8	4.7	5.0	3.0
%CV	14.3%	14.2%	6.2%	6.8%	4.4%
mean+3SD	100.4	277.2	102.3	93.2	90.4
mean- 3SD	81.1	124.3	77.0	73.6	67.9
N	5	5	5	5	5
median	75.4	176.8	76.0	72.7	67.8
mean/All kit median	1.00	1.00	1.00	1.00	1.00

	FT281	FT282	FT283	FT284	FT285
FT hCG Beckman Access (BCX/BC1) mean:					
mean	90.8	200.8	89.7	83.4	79.2
SD	3.2	25.5	4.2	3.3	3.7
%CV	3.5%	12.7%	4.7%	3.9%	4.7%
mean+3SD	100.4	277.2	102.3	93.2	90.4
mean- 3SD	81.1	124.3	77.0	73.6	67.9
N	6	6	6	6	6
median	91.0	191.4	91.1	82.9	79.6
mean/All kit median	1.13	1.15	1.19	1.13	1.16

	FT281	FT282	FT283	FT284	FT285
FT hCG kit average:					
mean	80.1	167.0	77.2	74.6	69.6
SD	11.0	38.2	11.7	8.6	9.0
all kit median	80.7	174.7	75.4	74.1	68.5

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	FT281	FT282	FT283	FT284	FT285
FT PAPP-A All Lab Mean:					
Mean	678.1	441.2	742.5	1117.8	1180.6
SD	78.6	52.0	90.4	125.5	106.3
%CV	11.6%	11.8%	12.2%	11.2%	9.0%
mean + 3SD	914.0	597.3	1013.7	1494.2	1499.4
mean- 3SD	442.2	285.0	471.2	741.4	861.8
N	15	15	15	15	15
All Lab Median	654.6	444.4	706.8	1137.0	1159.0
mean/All kit median	0.99	0.97	1.03	1.02	1.01

	FT281	FT282	FT283	FT284	FT285
* **FT PAPP-A DPC Immullite 2000 (DPD/DP5) Mean:**					
Mean	787.2	455.1	855.5	1278.0	1308.6
SD	86.1	37.4	105.6	12.6	56.3
%CV	10.9%	8.2%	12.3%	1.0%	4.3%
mean + 3SD	1045.5	567.5	1172.2	1315.7	1477.6
mean - 3SD	528.9	342.8	538.8	1240.3	1139.5
N	3	3	3	3	3
Kit Median	739.6	466.9	820.2	1273.7	1317.5
mean/All kit median	1.15	1.00	1.19	1.16	1.12

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A Beckman Unicel(BCU/BC1) Mean:					
Mean	634.7	406.0	712.3	1101.1	1168.9
SD	40.2	29.4	54.4	101.5	70.3
%CV	6.3%	7.2%	7.6%	9.2%	6.0%
mean + 3SD	755.4	494.1	875.5	1405.6	1379.9
mean - 3SD	514.0	317.8	549.0	796.6	958.0
N	8	8	8	8	8
Kit Median	627.5	394.4	696.4	1090.1	1149.4
mean/All kit median	0.93	0.89	0.99	1.00	1.00

	FT281	FT282	FT283	FT284	FT285
***FT PAPP-A Diagnostic Systems Lab (DS1) Mean:**					
Mean	682.9	501.1	718.2	1031.1	1107.8
SD	56.4	37.4	88.4	113.5	123.4
%CV	8.3%	7.5%	12.3%	11.0%	11.1%
mean + 3SD	1.6	1.1	1.9	2.5	2.6
mean - 3SD	0.9	0.5	0.7	1.3	1.4
N	4	4	4	4	4
Kit Median	684.6	503.8	732.3	1022.5	1120.1
mean/All kit median	1.00	1.10	1.00	0.94	0.95

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A kit average:					
mean	701.6	454.1	762.0	1136.7	1195.1
SD	77.9	47.6	81.1	127.3	102.9
all kit median	682.9	455.1	718.2	1101.1	1168.9

***Note: The above 2 tables contain converted values (mIU/ml->ng/ml) from equations obtained based on in house correlation data.**
(see critique)

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	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM All Lab Mean:					
Mean	1.31	0.65	1.38	1.17	1.12
SD	0.72	0.33	0.78	0.72	0.65
%CV	55.3%	51.0%	56.3%	61.9%	58.0%
mean + 3SD	3.49	1.66	3.71	3.34	3.07
mean- 3SD	-0.86	-0.35	-0.95	-1.00	-0.83
N	15	15	15	15	15
All Lab Median	1.01	0.55	1.14	0.94	0.83
mean/ All kit median	1.36	1.29	1.30	1.32	1.27

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM DPC Immulite 2000 (DPD/DP5) Mean:					
Mean	2.63	1.27	2.82	2.50	2.31
SD	0.30	0.18	0.36	0.33	0.35
%CV	11.4%	13.9%	12.9%	13.1%	15.3%
mean + 3SD	3.53	1.80	3.90	3.48	3.37
mean - 3SD	1.73	0.74	1.73	1.52	1.25
N	3	3	3	3	3
mean/All kit median	2.38	2.33	2.65	2.82	2.61

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM Beckman Unicel(BCU/BC1) Mean:					
Mean	0.97	0.51	1.06	0.89	0.89
SD	0.20	0.07	0.17	0.13	0.14
%CV	20.3%	12.8%	16.2%	15.1%	15.7%
mean + 3SD	1.55	0.70	1.58	1.29	1.30
mean - 3SD	0.38	0.31	0.54	0.49	0.47
N	8	8	8	8	8
Kit Median	0.94	0.49	1.02	0.94	0.84
mean/All kit median	0.87	0.94	1.00	1.00	1.00

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM Diagnostic System Labs (DS1) Mean:					
Mean	1.11	0.54	1.01	0.86	0.77
SD	0.37	0.12	0.27	0.23	0.09
%CV	33.7%	21.3%	26.5%	27.1%	12.1%
mean + 3SD	2.23	0.89	1.81	1.55	1.05
mean - 3SD	-0.01	0.20	0.21	0.16	0.49
N	3	3	3	3	3
Kit Median	1.16	0.61	1.14	0.97	0.81
mean/ All kit median	1.00	1.00	0.95	0.97	0.87

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM kit average:					
mean	1.57	0.77	1.63	1.41	1.32
SD	0.92	0.43	1.03	0.94	0.86
all kit median	1.11	0.54	1.06	0.89	0.89

Figure 1

Maternal Sera AFP MoM

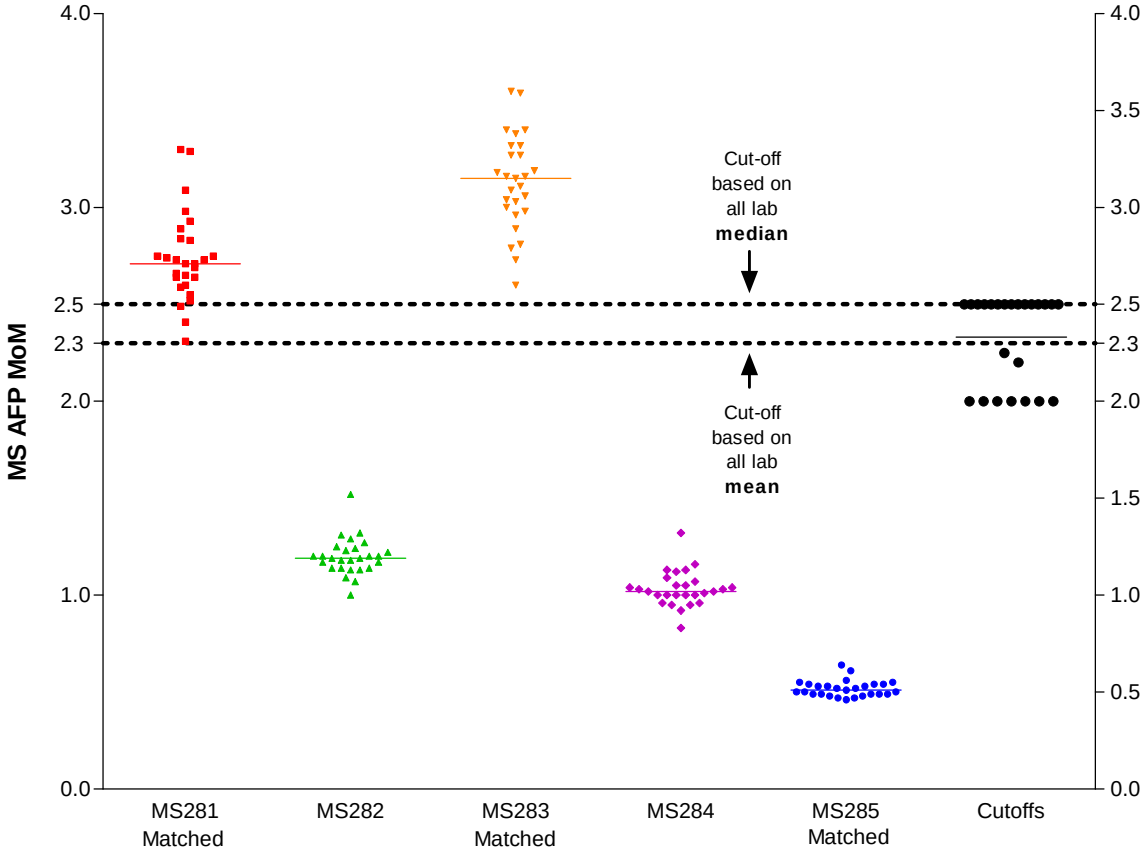

Figure 2

Amniotic Fluid AFP MoM

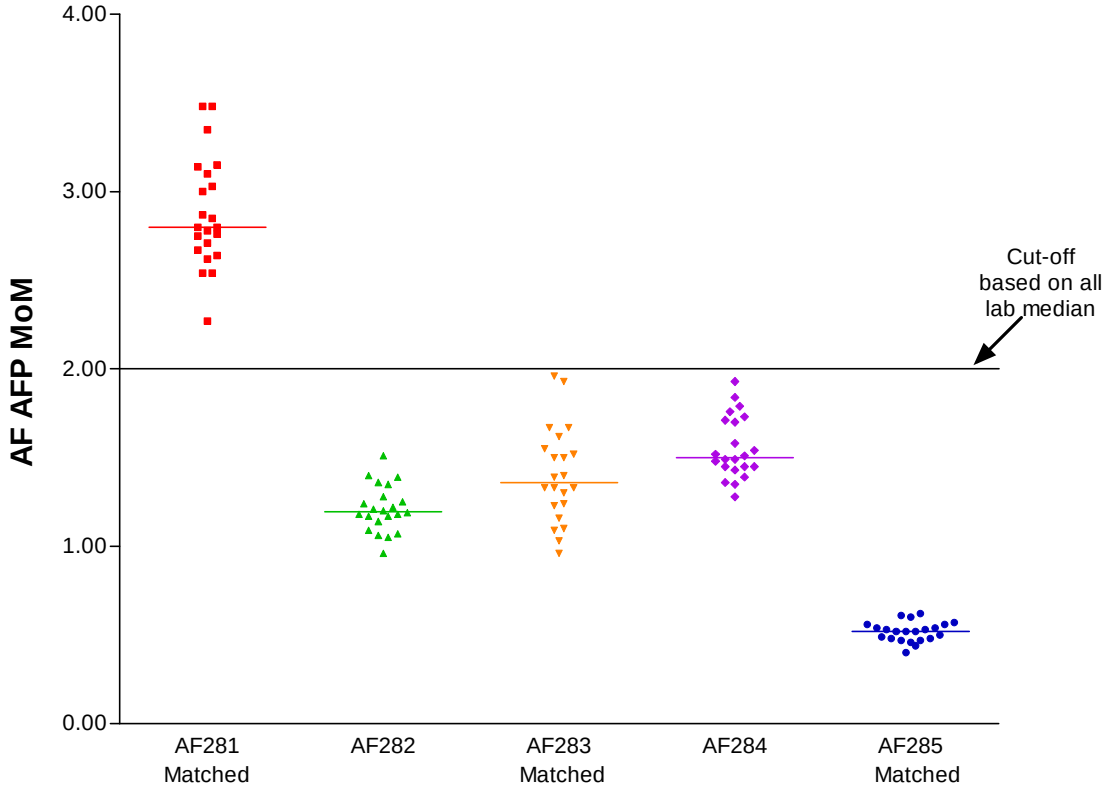

Figure 3

Graphic Distribution of Second Trimester Neural Tube Defect Risk Estimates

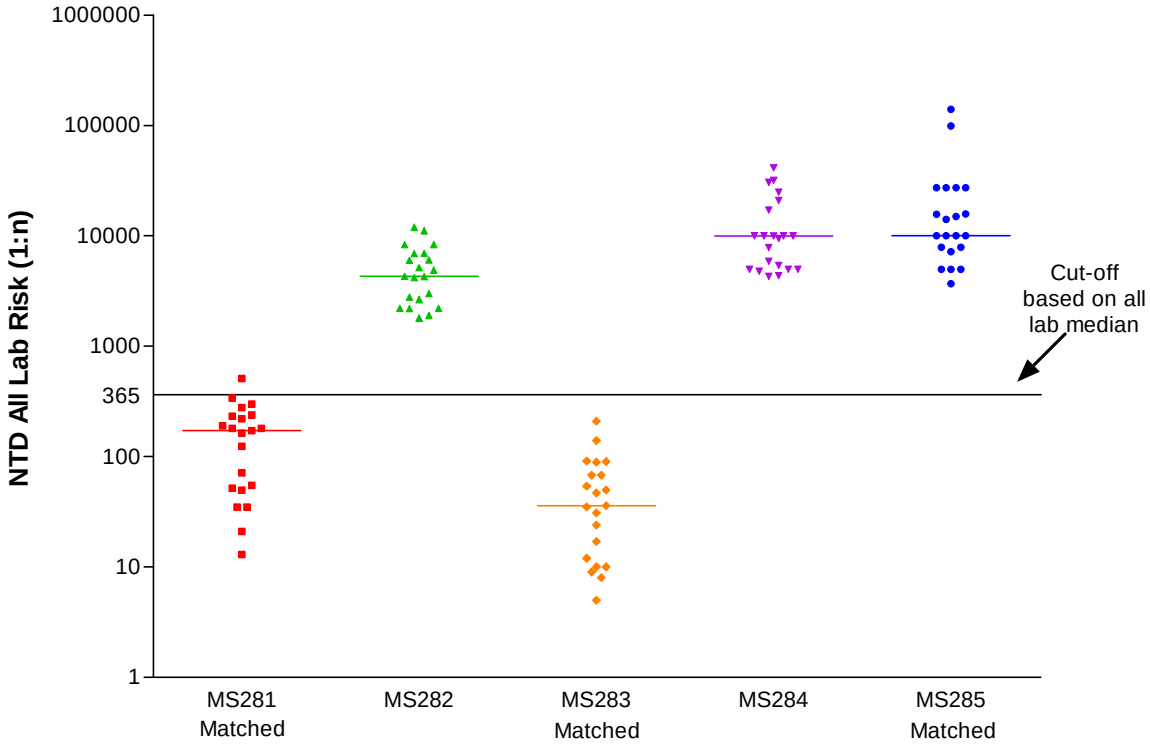

Figure 4

Graphic Distribution of Second Trimester Trisomy 18 Risk Estimates

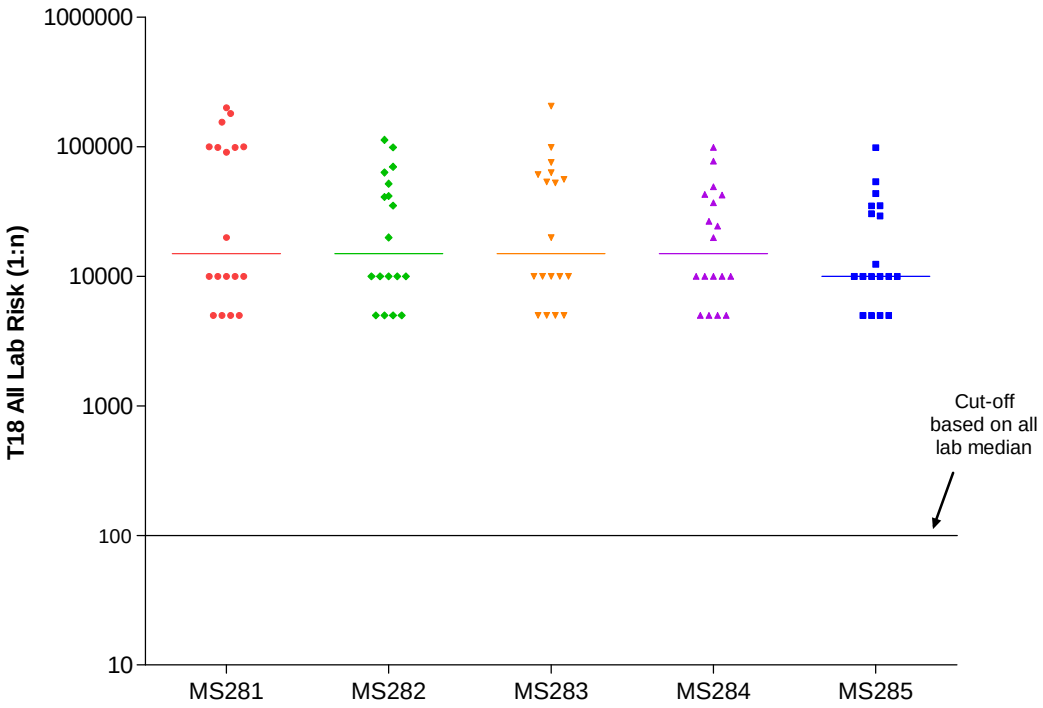

Figure 5

Graphic Distribution of Second Trimester Trisomy 21 Triple Risk Estimates

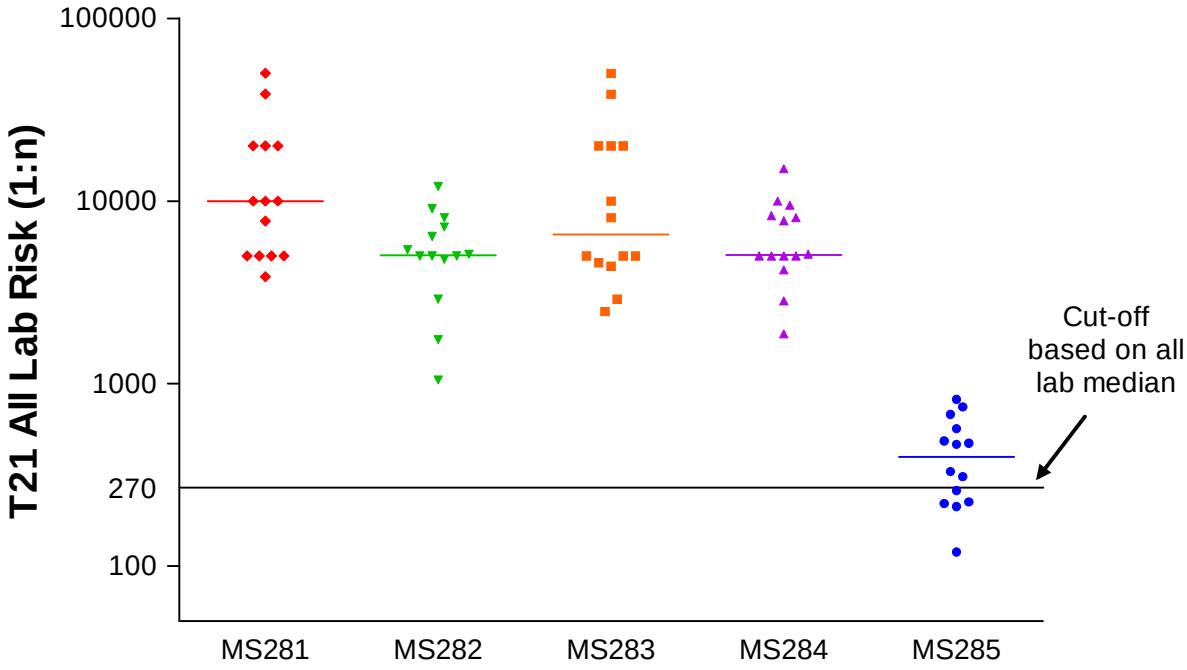

Figure 6

Graphic Distribution of Second Trimester Trisomy 21 Quadruple Risk Estimates

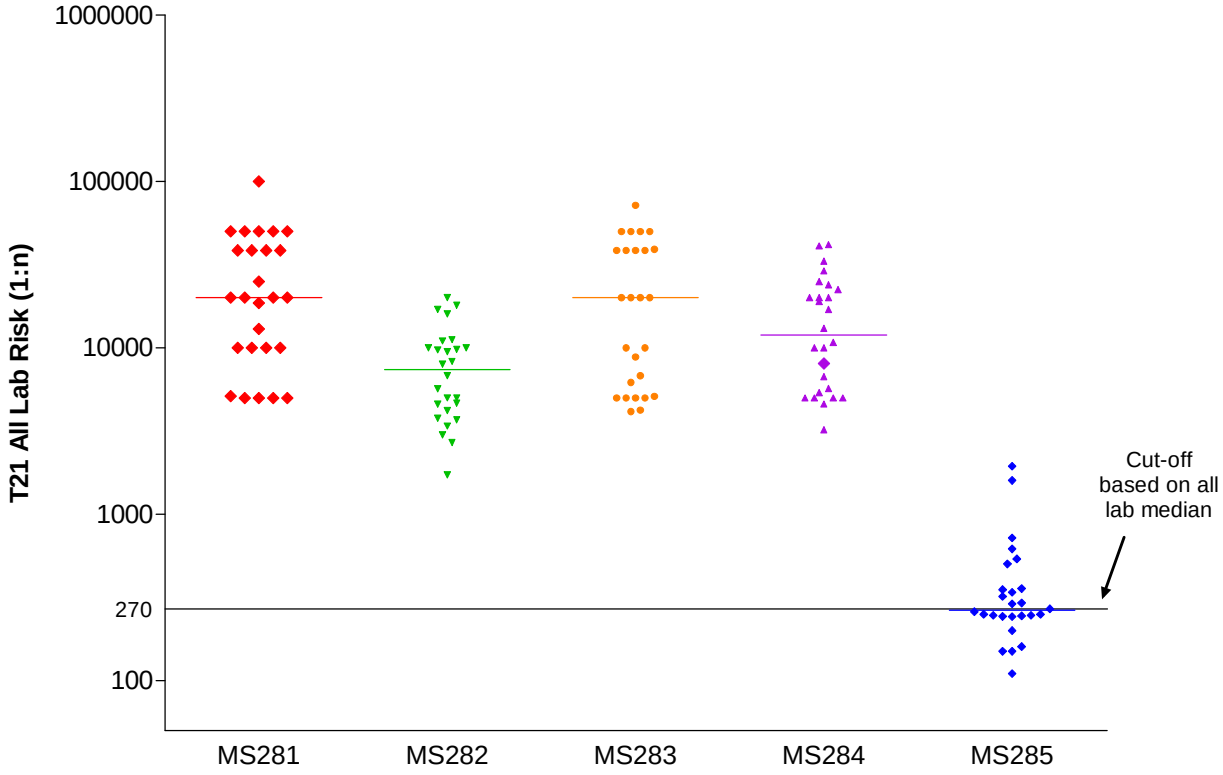

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Figure 7A

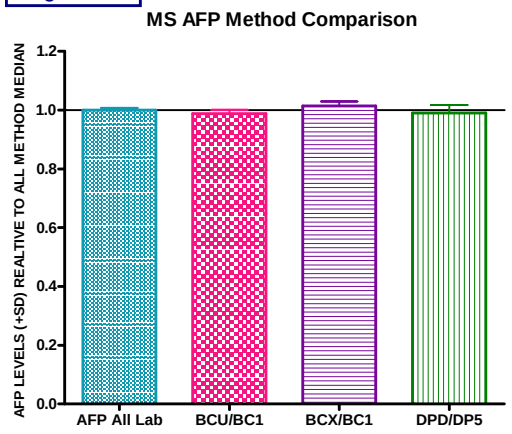


Figure 7C

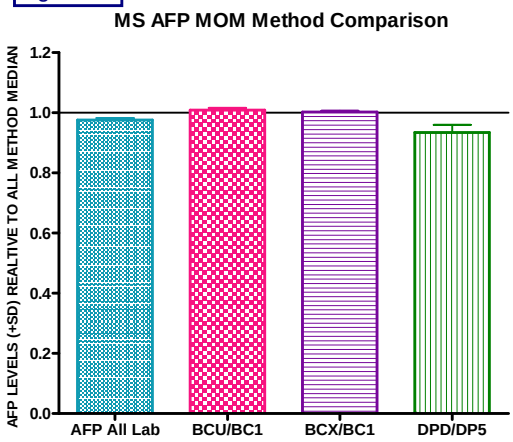


Figure 8A

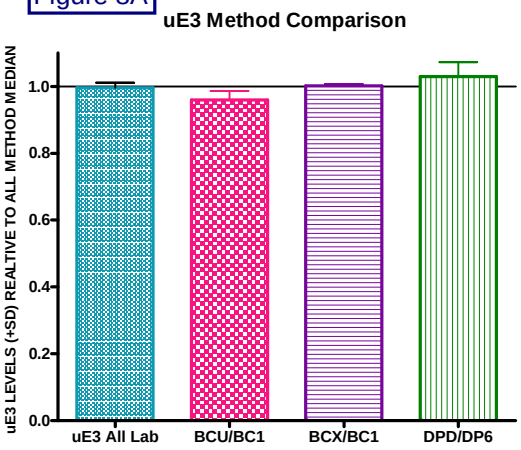


Figure 8B

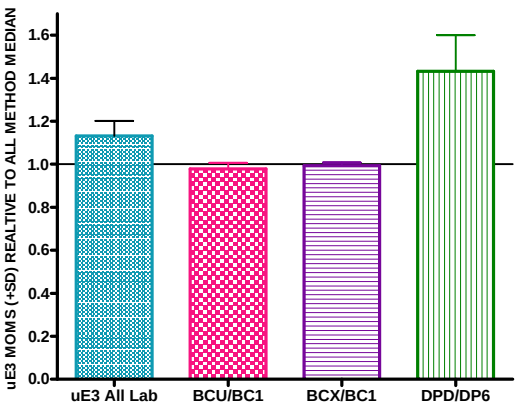


Figure 9A

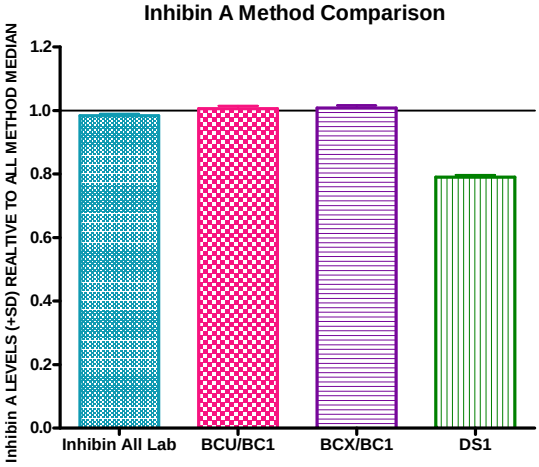
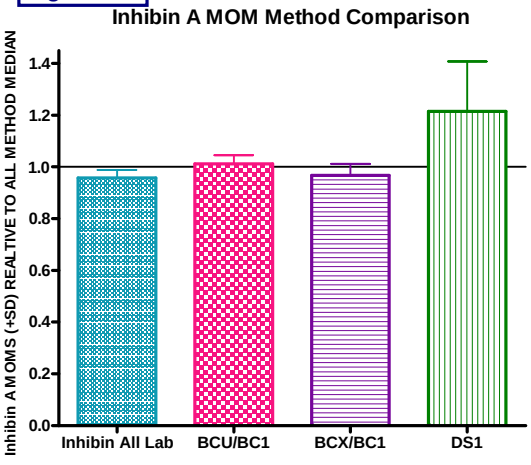


Figure 9B



BCX/BC1 = Beckman Access/2
BCU/BC1 = Beckman Unicel
DPD/DP5 = Siemens Immulite 2000
DS1 = Diagnostic Systems Labs

NYS FEDM PT 5/12

Figure 7B

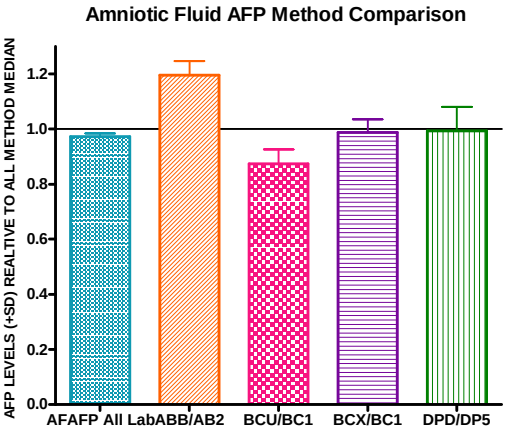


Figure 7D

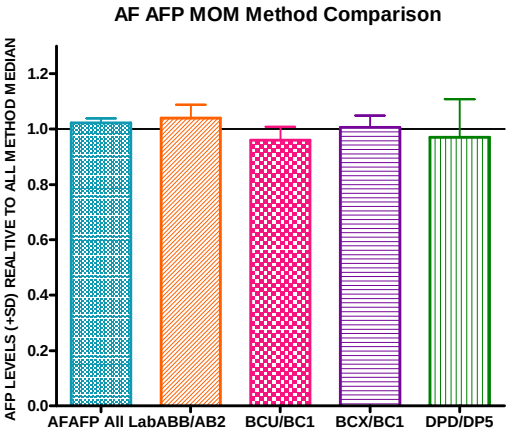


Figure 10

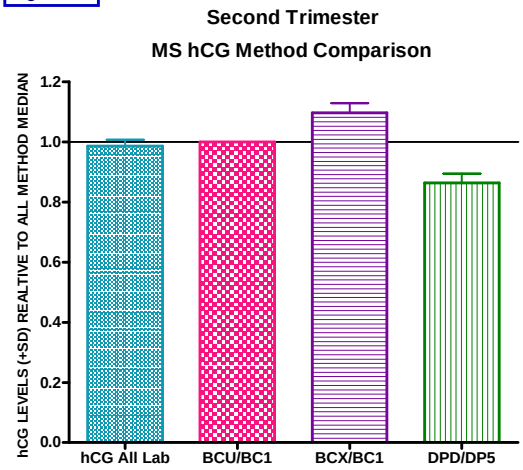


Figure 11 FT hCG Method Comparison

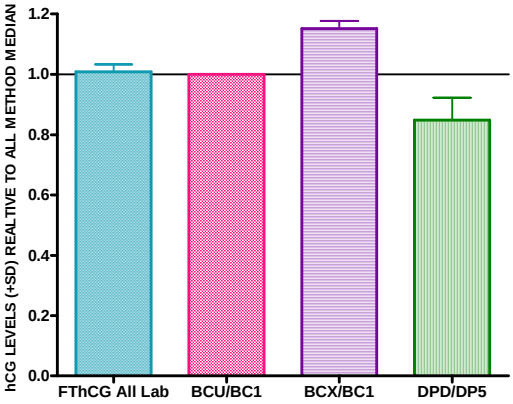


Figure 12A FT PAPP-A Method Comparison

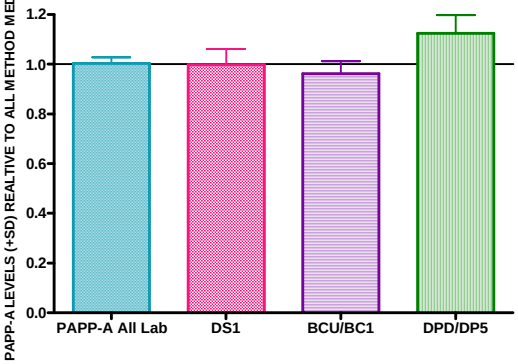
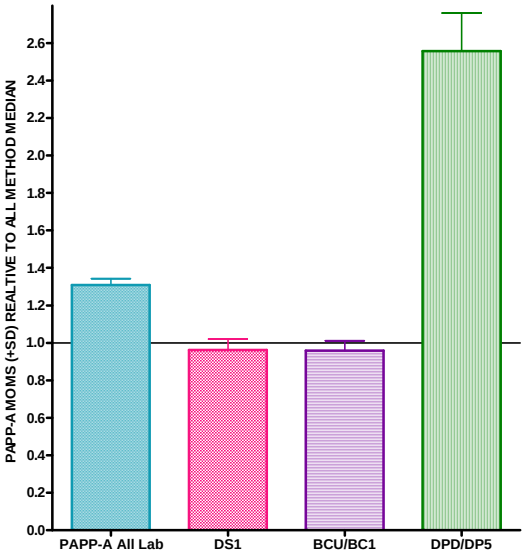


Figure 12B FT PAPP-A MOM Method Comparison



ABB/AB1 = Abbott Asxym
BCX/BC1 = Beckman Access/2
BCU/BC1 = Beckman Unicel
DPD/DP5 = Siemens Immulite 2000
DS1 = Diagnostic Systems Labs

Figure 13

Graphic Distribution of First Trimester
Trisomy 21 Risk Estimates

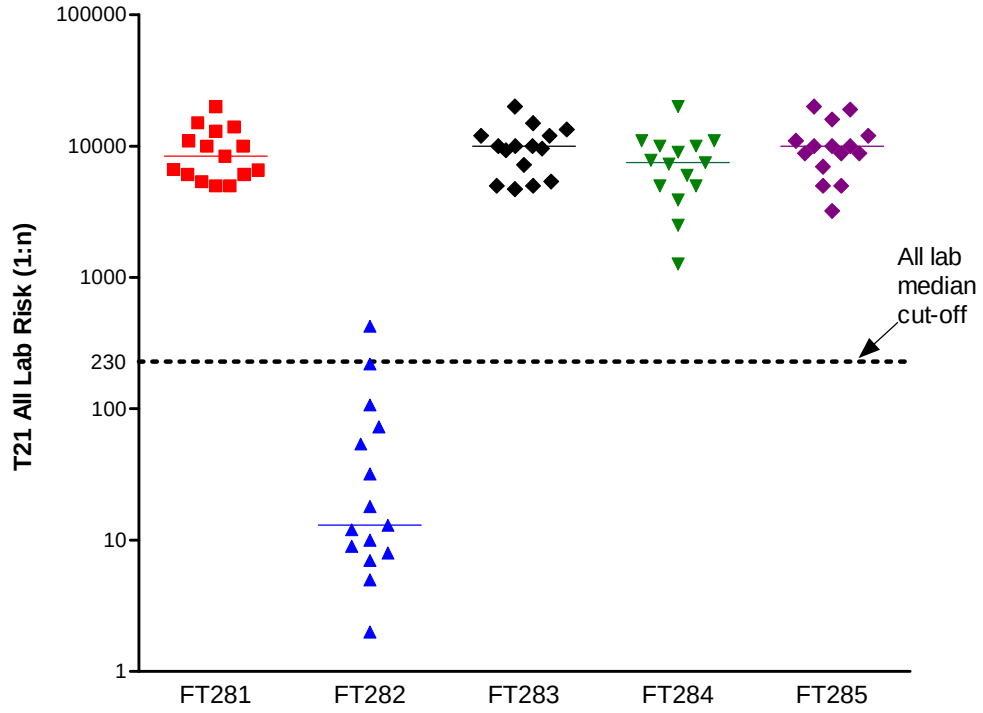


Figure 14

Graphic Distribution of First Trimester
Trisomy 18 Risk Estimates

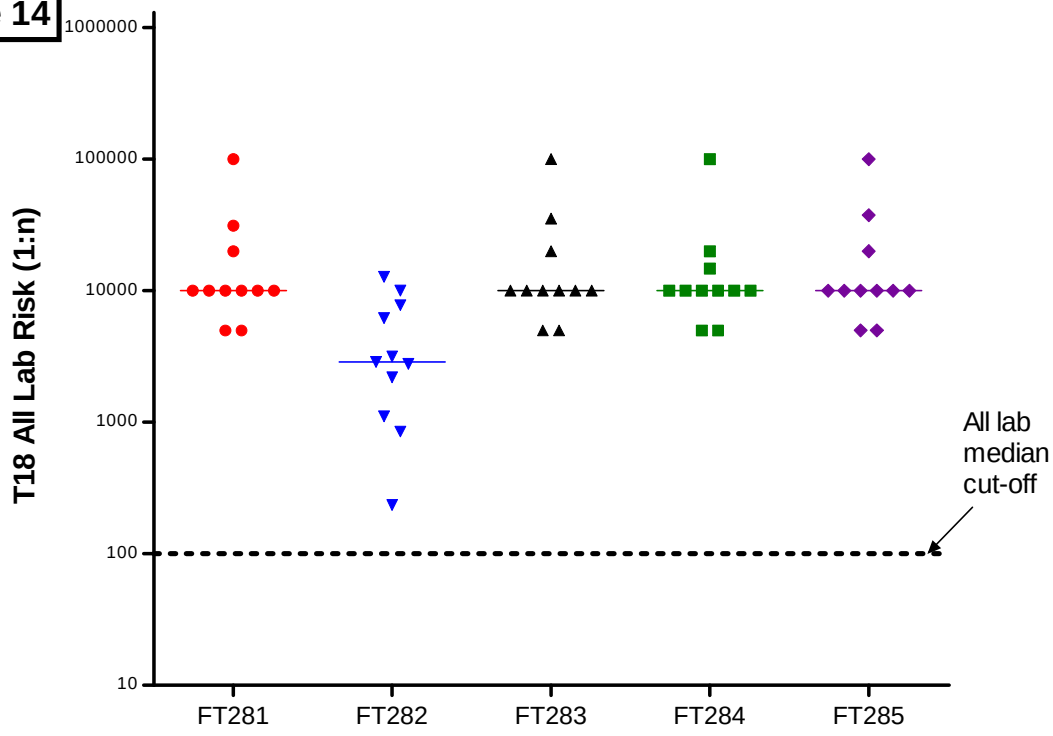


Fig. 15A

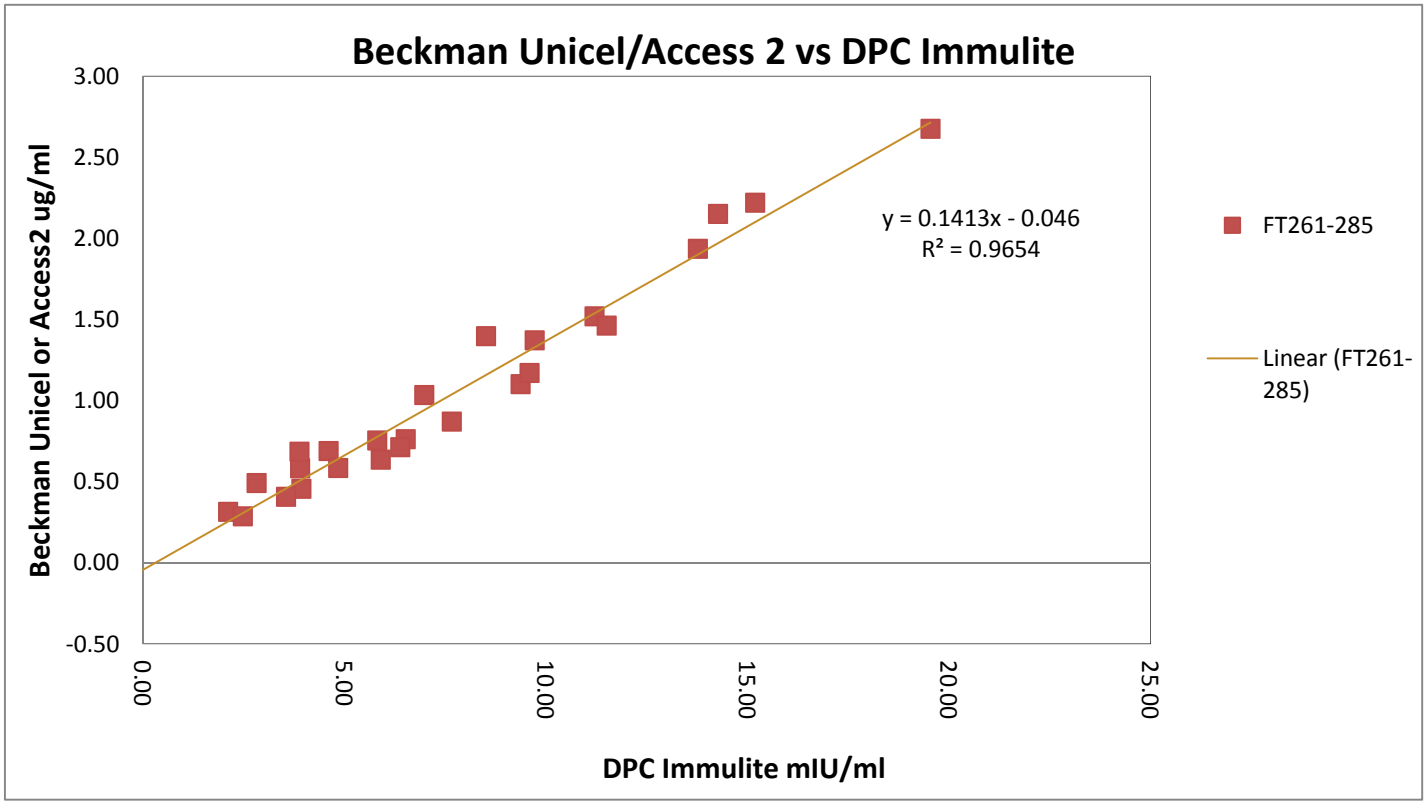
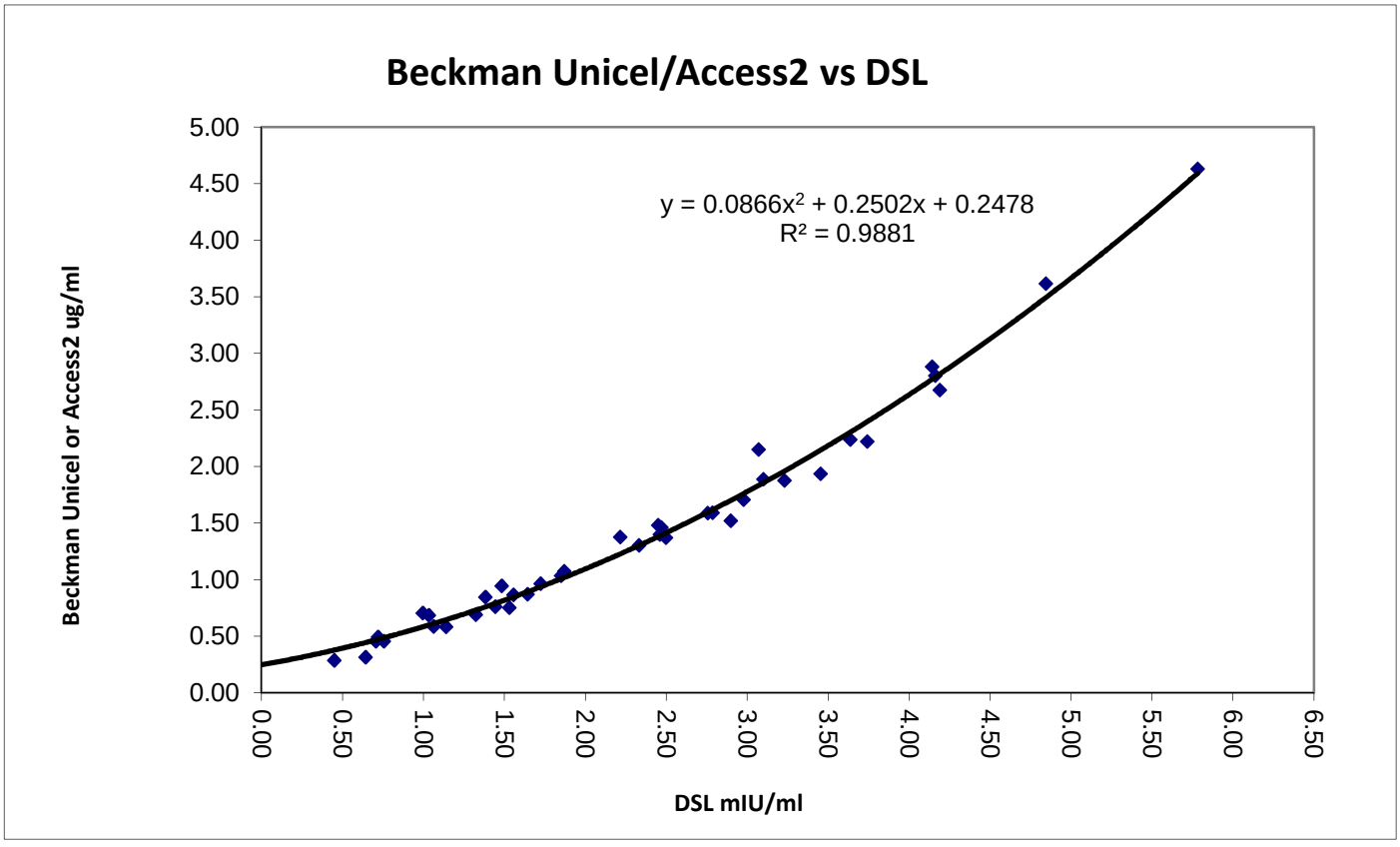


Fig. 15B



NEW YORK
state department of
HEALTH

Nirav R. Shah, M.D., M.P.H.
Commissioner

Sue Kelly
Executive Deputy Commissioner

Electronic Proficiency Test Reporting System Bulletin
May 2012

Laboratories participating in the May 2012 proficiency testing events in the categories listed below are required to submit results through the Electronic Proficiency Test Reporting System (EPTRS) system.

Clinical Chemistry
Diagnostic Immunology (Diagnostic and Donor)
Endocrinology
Fetal Defect Markers
Human Immunodeficiency Virus
Mycology (Antifungal Susceptibility, Identification, Identification - Yeast Only)
Oncology Soluble Tumor Markers
Parasitology (Antigen Detection, Blood Smears, Comprehensive)
Therapeutic Substance Monitoring
Quantitative Toxicology
Toxicology Blood Lead
Trace Elements (Serum, Urine and Whole Blood)
Virology (Comprehensive, HSV Testing and Influenza, Rotavirus and RSV Direct Detection)

The Health Commerce System (HCS) Portal URL is https://commerce.health.state.ny.us
After logging into the Portal, 'My Applications' is listed on the left side of the page. If you have access to EPTRS, the acronym 'EPTRS' will be listed under the heading 'My Applications'. Click on 'EPTRS' to access the homepage. If you do not see the acronym 'EPTRS', please send an email to clepeptrs@health.state.ny.us

Important Phone Numbers:

1. Technical Assistance with EPTRS - Monday through Friday between **8am and 4pm** by calling 518-486-5410.
2. Commerce Accounts Management Unit - for account information and passwords - Monday through Friday between 8am and 5 pm by calling 866-529-1890.

HCS Accounts – every user accessing EPTRS must have their own account for the HCS. It is a violation of the security and use agreement to share an account User ID and password with someone else. Sharing your account information with someone else will result in the suspension of your account. Please email clepeptrs@health.state.ny.us for assistance with requesting accounts for additional users.

EPTRS Webpage:

- Event Menu Page - Please review the laboratory's persistent data (instruments, reagents, methods, contact, email, etc). It is the responsibility of each laboratory to verify the data and make any required changes.
- Summary Page
    - Results submission - When you are ready to submit, navigate to the bottom of the Summary Page and click on the Submit/Attest button. **Saving or validating without submitting results will result in a failure for non-participation.** If you do not see the "Submit/Attest" button on the EPTRS Summary Page or if you have questions concerning result entry, please contact the Clinical Laboratory Evaluation Program at clepeptrs@health.state.ny.us.
    - Attestation statement - must be printed and signed by the laboratory director or responsible assistant director, the delegated submitter and the analyst prior to submission of the proficiency test results. The signed document must be kept on file in the laboratory for review by the laboratory surveyor during the next onsite survey.

If you experience any difficulty accessing EPTRS, please contact clepeptrs@health.state.ny.us

New York State Fetal Defect Markers Proficiency Test, FEDM PT, May 2012

PFI __ __ __ __ (1) **Lab Name and address** _____

Date samples obtained __ __ /__ __ /__ __ **Analyzed** __ __ / __ __ / __ __ (2) _____

Due Date: **May 23, 2012** _____

_____

Analyte Second Trimester Maternal Serum	**Analytical results**					Instrument code*	Reagent code*
	Vial **MS281**	Vial **MS282**	Vial **MS283**	Vial **MS284**	Vial **MS285**		
Gestational Age (weeks)	__ __.__ (3)	__ __.__ (4)	__ __.__ (5)	__ __.__ (6)	__ __.__ (7)		
MS AFP (ng/ml)	__ __ __.__ (8)	__ __ __.__ (9)	__ __ __.__ (10)	__ __ __.__ (11)	__ __ __.__ (12)	__ __ __ (13)	__ __ __ (14)
MS AFP MoM	__ __.__ __ (15)	__ __.__ __ (16)	__ __.__ __ (17)	__ __.__ __ (18)	__ __.__ __ (19)		
MS uE3 (ng/ml)	__ __.__ __ (20)	__ __.__ __ (21)	__ __.__ __ (22)	__ __.__ __ (23)	__ __.__ __ (24)	__ __ __ (25)	__ __ __ (26)
MS uE3 MoM	__ __.__ __ (27)	__ __.__ __ (28)	__ __.__ __ (29)	__ __.__ __ (30)	__ __.__ __ (31)		
MS hCG Please Check: _Total(IU/ml)/ _freeβ (mIU/ml)	__ __ __.__ (32)	__ __ __.__ (33)	__ __ __.__ (34)	__ __ __.__ (35)	__ __ __.__ (36)	__ __ __ (37)	__ __ __ (38)
MS hCG Total or Freeβ MoM	__ __.__ __ (39)	__ __.__ __ (40)	__ __.__ __ (41)	__ __.__ __ (42)	__ __.__ __ (43)		
MS Dimeric Inhibin A (pg/ml)	__ __ __.__ (44)	__ __ __.__ (45)	__ __ __.__ (46)	__ __ __.__ (47)	__ __ __.__ (48)	__ __ __ (49)	__ __ __ (50)
MS Dimeric Inhibin A MoM	__ __.__ __ (51)	__ __.__ __ (52)	__ __.__ __ (53)	__ __.__ __ (54)	__ __.__ __ (55)		
Neural Tube Screen 1 = positive, 0 = negative	__ (56)	__ (57)	__ (58)	__ (59)	__ (60)	NTD Based on: ❑ MoM cut-off ❑ Risk cut-off	←
Trisomy 21 Screen 1 = positive, 0 = negative	__ (61)	__ (62)	__ (63)	__ (64)	__ (65)	Based on: ❑ Quad ❑ Triple	←
Trisomy 18 Screen 1 = positive, 0 = negative	__ (66)	__ (67)	__ (68)	__ (69)	__ (70)		

New York State Fetal Defect Markers Proficiency Test, FEDM PT, May 2012

Amniotic Fluid	Vial **AF281**	Vial **AF282**	Vial **AF283**	Vial **AF284**	Vial **AF285**	Instrument code*	Reagent code*
AF AFP (μg/ml)	__ __.__ 71	__ __.__ 72	__ __.__ 73	__ __.__ 74	__ __.__ 75	__ __ __ 76	__ __ __ 77
AF AFP MoM	__.__ 78	__.__ 79	__.__ 80	__.__ 81	__.__ 82		
Interpretation **1 = elevated w/ Ache indicated 0 =Normal**	83	84	85	86	87	Please indicate the Cut-off → MoM value used for interpretation	_____

***codes are on P. 4**

Risk Assessment Ratio (1:n) and Further Action	**MS281**	**MS282**	**MS283**	**MS284**	**MS285**	**Risk (MoM) Cut-off (white, Black, IDDM)**
NTD Risk (or MoM)						**White**_____ **Black**_____
R=Repeat, U=Ultrasound, A=Amnio NFA=NoFurtherAction, G=Genetic Counseling						**IDDM white**_____ **IDDM black**_____
Trisomy 21 Risk by Quad						**White**_____
R=Repeat, U=Ultrasound, A=Amnio NFA=NoFurtherAction, G=Genetic Counseling						**Black**_____ **IDDM**_____
Trisomy 21 Risk by Triple						**White**_____
R=Repeat, U=Ultrasound, A=Amnio NFA=NoFurtherAction, G=Genetic Counseling						**Black**_____ **IDDM**_____
Trisomy 18 Risk						**White**_____
R=Repeat, U=Ultrasound, A=Amnio NFA=NoFurtherAction, G=Genetic Counseling						**Black**_____ **IDDM**_____
Indicate software company used to calculate risk	_ αlpha	_ Benetech PRA		_ RMA	_other_____	

We, the undersigned, attest that the findings provided were produced in this laboratory from the analysis of proficiency test samples which were introduced into the routine workflow of the laboratory and analyzed using protocols and procedures which are (or which will be) routinely applied to **clinical** specimens. We further attest that the laboratory did not engage in any form of communication with individuals outside of our laboratory regarding the proficiency test and/or results obtained therefrom. **The laboratory director or the authorized assistant director who holds a CQ in Fetal Defect Markers must sign this form (stamps are not acceptable). If the director does not hold a CQ in this category, then the assistant director holding the appropriate CQ must sign. Do not forget to add your CQ codes; these are required for proper tracking of your results. Forms without all the required information will be returned. Failure to submit the required signatures will result in a score of zero.**

Analyst _____ **Laboratory director** _____ **CQ code**__ __ __ __ __ __

Analyst _____ **Assistant director** _____ **CQ code**__ __ __ __ __ __

(Please print and sign your names)

New York State Fetal Defect Markers Proficiency Test, FEDM PT, May 2012

First Trimester Demographic Data:

Sample	Date of Birth	Race (B,W,H)	NT[1] (mm)	M. Wt (lbs)	LMP[3]	**CRL[4] (mm)**	US[2]/ Draw Date
FT 281	1/1/1984	A	1.20	120	2/17/2012	**45**	5/4/2012
FT 282	1/1/1987	W	2.50	135	2/10/2012	**54**	5/4/2012
FT 283	1/1/1989	H	1.30	130	2/13/2012	**48**	5/4/2012
FT 284	1/1/1982	B	1.40	125	2/6/2012	**61**	5/4/2012
FT 285	1/1/1991	W	1.60	120	2/3/2012	**67**	5/4/2012

[1]NT = Nuchal Translucency [2]US = Ultrasound [3]LMP = Last Menstrual Period [4]CRL = Crown Rump Length

First Trimester Maternal Serum	Vial **FT 281**	Vial **FT 282**	Vial **FT 283**	Vial **FT 284**	Vial **FT 285**	Instrument code*	Reagent code*
FT Gestational Age (weeks)	__ __.__ 88	__ __.__ 89	__ __.__ 90	__ __.__ 91	__ __.__ 92		
FT NT MoM	__.__ __ 93	__.__ __ 94	__.__ __ 95	__.__ __ 96	__.__ __ 97		
FT hCG Please Check: _Total(IU/ml)/ _freeβ (mIU/ml)	__ __ __.__ 98	__ __ __.__ 99	__ __ __.__ 100	__ __ __.__ 101	__ __ __.__ 102	__ __ __ 103	__ __ __ 104
FT hCG Total or Freeβ MoM	__ __.__ __ 105	__ __.__ __ 106	__ __.__ __ 107	__ __.__ __ 108	__ __.__ __ 109		
FT PAPP-A Please Check: _ mIU/ml _ng/ml	__ __.__ __ 110	__ __.__ __ 111	__ __.__ __ 112	__ __.__ __ 113	__ __.__ __ 114	__ __ __ 115	__ __ __ 116
FT PAPP-A MoM	__ __.__ __ 117	__ __.__ __ 118	__ __.__ __ 119	__ __.__ __ 120	__ __.__ __ 121		
FT Trisomy 21 Screen 1 = positive, 0 = negative	__ 122	__ 123	__ 124	__ 125	__ 126		
FT Trisomy 18 Screen 1 = positive, 0 = negative	__ 127	__ 128	__ 129	__ 130	__ 131		

Results will *not* be graded. Information will be used for future possible implementation.

Risk Assessment Ratio (1:n)and Further Action	**FT281**	**FT282**	**FT283**	**FT284**	**FT285**	**Risk Cut-off (white, Black, IDDM)**
Trisomy 21 Risk by First Trimester						**White**_____ **Black**_____ **IDDM**_____
R=Repeat, U=Ultrasound, A=Amnio, G=Genetic Counseling, C=CVS NFA=NoFurtherAction						
Trisomy 18 Risk by First Trimester						**White**_____ **Black**_____ **IDDM**_____
R=Repeat, U=Ultrasound, A=Amnio, G=Genetic Counseling NFA=NoFurtherAction						
Indicate software company used to calculate risk	_ αlpha	_ Benetech PRA		_ RMA	_other_____	

Instrument codes:

Abbott AxSym	ABB
Abbott Architect	ABH
Automatic (Robotic) Pipetting Station with or and Microplate Reader	APM
Bayer/Siemens Technicon Immuno-1	TNM
Siemens (Chiron) ACS-180	COS
Siemens ADVIA-Centaur	COB
Beckman Access/2	BCX
Beckman Unicel Dxl	BCU
Beckman Array	BCA
Siemens Diagnostic Dimension Rxl	DUD
Siemens Diagnostic MARK V with or and Microplate Reader	DPC
Qiagen Plato 3000 with or and Microplate Reader	QPM
Siemens Diagnostic Products Immulite	DPB
Siemens Diagnostic Products Immulite 2000	DPD
Siemens Diagnostic Products Immulite 2500	DPF
Trinity Biotech Nexgen	TBN
(DSL ELISA) with Microplate Reader	MPR
DSL Ario	DSA
DSL DSX with or and Microplate Reader	DSX
DSL Plato	DSP
UV/Vis Spectrophotometer	UVA
Gamma Counter	GAA
Rocket Immuno-Electrophoresis	RCE
P E Wallac Delfia	WAD
Analyzer/Instrument not shown, **specify on form**	ZZZ

Reagent/kit codes:

Abbott AFP Mono/Poly	AB1
Abbott AFP Mono/Mono	AB2
Abbott hCG	AB3
Abbott βhCG	AB4
Siemens (formerly Bayer)	BA1
Siemens (formerly Chiron)	CO1
Beckman Coulter	BC1
Siemens Diagnostic (Dade Behring)	DA1
Beckman Coulter, DSL ELISA (formerly Diagnostic Systems Lab EIA)	DS1
Diagnostic Systems Lab liquid RIA	DS2
Diagnostic Systems Lab solid RIA	DS3
DiaSorin-Clinical Assays	DC1
Siemens Diagnostic (DPC) Coat-A-Count	DP1
Siemens DPC Immulite, Immulite 2000 or Immulite 2500	DP5
New Siemens DPC Immulite, Immulite 2000 or Immulite 2500 for **uE3 only**	**DP6**
In-House	IH1
P E Wallac Delfia kit	PE1
Reagent/Kit not listed, **specify on form**	ZZZ

If an instrument and/or reagent you are using are not listed please provide us with the information, so that we can include it in the future. If you do not perform an assay leave the fields empty. No special codes are needed to indicate that an assay is not performed.

New York State Fetal Defect Markers Proficiency Test,
May 2012
Summary of Results

	MS 281	MS 282	MS 283	MS 284	MS 285
Gestational Age All Lab Mean:					
Mean	18.0	19.0	21.0	15.0	17.0
SD	0.00	0.00	0.06	0.00	0.00
%CV	0.0%	0.0%	0.3%	0.0%	0.0%
mean+3*SD	18.0	19.0	21.2	15.0	17.0
mean-3*SD	18.0	19.0	20.8	15.0	17.0
N	27	27	27	27	27

	MS 281	MS 282	MS 283	MS 284	MS 285
MS AFP All Lab Mean:					
mean	120.4	66.3	214.8	34.4	21.0
SD	10.2	4.9	14.5	2.2	1.2
%CV	8.5%	7.4%	6.7%	6.4%	5.7%
mean+3SD	151.0	81.1	258.3	41.0	24.6
mean-3SD	89.8	51.6	171.4	27.8	17.4
N	27	27	27	27	26
median	121	66.5	215.5	34.2	20.65
mean/all kit median	1.01	1.00	1.00	1.00	0.99
MS AFP Beckman Unicel (BCU/BC1) mean:					
Mean	119.6	65.1	209.2	34.0	21.4
SD	6.6	4.9	17.2	2.4	1.0
%CV	5.5%	7.6%	8.2%	6.9%	4.6%
mean + 3SD	139.5	79.9	260.8	41.1	24.4
mean - 3SD	99.8	50.3	157.5	26.9	18.5
N	9	9	9	9	8
Median	122.3	64.4	212.3	34.5	21.3
mean/All kit median	1.00	0.98	0.97	0.99	1.00
MS AFP Beckman Access/2 (BCX/BC1) mean:					
mean	123.1	66.3	221.9	34.8	21.3
SD	17.3	6.4	16.3	3.1	1.6
%CV	14.0%	9.7%	7.3%	8.9%	7.6%
mean+3SD	174.9	85.6	270.7	44.0	26.2
mean-3SD	71.3	47.0	173.0	25.5	16.4
N	8	8	8	8	8
median	120.3	65.4	219.5	34.4	20.7
mean/all kit median	1.03	1.00	1.03	1.01	1.00
MS AFP DPC Immulite 2000 (DPD/DP5) mean:					
mean	117.6	67.5	214.6	34.3	20.2
SD	4.1	4.0	8.3	1.1	0.6
%CV	3.5%	5.9%	3.8%	3.1%	2.8%
mean+3SD	130.0	79.5	239.4	37.5	21.9
mean-3SD	105.2	55.5	189.8	31.1	18.6
N	8	8	8	8	8
median	118.0	68.4	212.5	34.2	20.4
mean/all kit median	0.98	1.02	1.00	1.00	0.95
MS AFP kit average:					
mean	120.1	66.3	215.2	34.4	21.0
SD	2.8	1.2	6.4	0.4	0.7
all kit median	119.6	66.3	214.6	34.3	21.3

	MS 281	MS 282	MS 283	MS 284	MS 285
MS AFP MoM All Lab Mean:					
mean	2.74	1.19	3.13	1.02	0.52
SD	0.23	0.07	0.25	0.07	0.04
%CV	8.4%	6.1%	7.9%	7.0%	8.0%
mean+3SD	3.44	1.41	3.87	1.24	0.64
mean-3SD	2.05	0.97	2.39	0.81	0.39
N	27	26	27	26	27
All Median	2.71	1.19	3.15	1.02	0.51
mean/all kit median	0.98	0.98	0.97	0.98	0.97
MS AFP MoM Beckman Unicel (BCU/BC1) mean:					
Mean	2.83	1.23	3.22	1.05	0.54
SD	0.22	0.12	0.27	0.06	0.05
%CV	7.7%	9.9%	8.5%	5.9%	8.5%
mean + 3SD	3.49	1.60	4.04	1.23	0.68
mean - 3SD	2.18	0.86	2.39	0.86	0.40
N	8	8	8	8	8
Median	2.78	1.20	3.16	1.05	0.53
mean/all kit median	1.01	1.02	1.00	1.00	1.01
MS AFP MoM Beckman Access/2 (BCX/BC1) mean:					
Mean	2.79	1.21	3.22	1.06	0.53
SD	0.30	0.10	0.20	0.14	0.04
%CV	10.7%	8.5%	6.1%	13.0%	7.1%
mean + 3SD	3.69	1.52	3.81	1.47	0.65
mean - 3SD	1.90	0.90	2.63	0.64	0.42
N	9	9	9	9	9
Median	2.75	1.20	3.27	1.03	0.54
mean/all kit median	1.00	1.00	1.00	1.01	1.00
MS AFP MoM DPC Immulite 2000 (DPD/DP5) mean:					
Mean	2.60	1.16	2.98	1.00	0.48
SD	0.12	0.06	0.23	0.05	0.01
%CV	4.7%	5.2%	7.6%	5.2%	3.1%
mean + 3SD	2.97	1.34	3.66	1.16	0.53
mean - 3SD	2.24	0.98	2.29	0.85	0.44
N	8	8	8	8	8
Median	2.62	1.18	3.01	1.00	0.49
mean/all kit median	0.93	0.96	0.92	0.96	0.90
MS AFP MoM kit average:					
mean	2.74	1.20	3.14	1.04	0.52
SD	0.12	0.04	0.14	0.03	0.03
all kit median	2.79	1.21	3.22	1.05	0.53

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	MS 281	MS 282	MS 283	MS 284	MS 285
MS uE3 All Lab Mean:					
mean	1.32	1.46	1.62	0.61	0.90
SD	0.07	0.11	0.11	0.07	0.09
%CV	5.5%	7.9%	7.1%	11.2%	10.5%
mean+3SD	1.54	1.80	1.96	0.81	1.18
mean-3SD	1.10	1.11	1.28	0.40	0.62
N	26	26	26	26	26
mean/all kit median	0.98	0.98	1.00	1.01	1.01
MS uE3 Beckman Unicel (BCU/BC1) mean:					
Mean	1.26	1.41	1.62	0.57	0.87
SD	0.05	0.08	0.11	0.04	0.05
%CV	4.4%	5.5%	6.9%	7.2%	5.7%
mean+3SD	1.42	1.64	1.95	0.69	1.01
mean-3SD	1.09	1.17	1.28	0.45	0.72
N	9	9	9	9	9
mean/all kit median	0.93	0.95	1.00	0.95	0.97
MS uE3 Beckman Access/2 (BCX/BC1) mean:					
mean	1.35	1.48	1.64	0.60	0.89
SD	0.05	0.07	0.08	0.03	0.05
%CV	3.7%	4.9%	4.6%	4.5%	6.0%
mean+3SD	1.50	1.70	1.86	0.68	1.05
mean-3SD	1.20	1.27	1.41	0.52	0.73
N	8	8	8	8	8
mean/all kit median	1.00	1.00	1.01	1.00	1.00
MS uE3 DPC Immulite/2000 (DPD/DP6) mean:					
Mean	1.35	1.49	1.61	0.65	0.94
SD	0.07	0.16	0.15	0.09	0.14
%CV	5.0%	10.8%	9.5%	14.0%	14.8%
mean+3SD	1.56	1.97	2.06	0.92	1.36
mean-3SD	1.15	1.00	1.15	0.38	0.53
N	9	9	9	9	9
mean/all Kit Median	1.00	1.00	1.00	1.09	1.06
MS uE3 kit average:					
mean	1.32	1.46	1.62	0.61	0.90
SD	0.06	0.05	0.02	0.04	0.04
all kit median	1.35	1.48	1.62	0.60	0.89

	MS 281	MS 282	MS 283	MS 284	MS 285
MS uE3 MoM All Lab Mean:					
Mean	1.19	1.00	0.75	1.10	0.99
SD	0.26	0.20	0.11	0.38	0.29
%CV	21.6%	19.5%	14.2%	34.2%	28.7%
mean+3SD	1.95	1.59	1.06	2.23	1.85
mean-3SD	0.42	0.41	0.43	-0.03	0.14
N	26	26	25	26	26
mean/all kit Median	1.10	1.10	1.06	1.24	1.16
MS uE3 MoM Beckman Unicel (BCU/BC1) Mean:					
Mean	1.00	0.89	0.70	0.88	0.84
SD	0.08	0.09	0.07	0.12	0.08
%CV	7.7%	9.8%	10.1%	13.0%	9.5%
mean+3SD	1.23	1.15	0.92	1.23	1.07
mean-3SD	0.77	0.63	0.49	0.54	0.60
N	9	9	9	9	9
mean/all kit Median	0.93	0.98	1.00	1.00	0.98
MS uE3 MoM Beckman Access/2 (BCX/BC1) Mean:					
Mean	1.07	0.91	0.68	0.89	0.86
SD	0.09	0.08	0.06	0.09	0.09
%CV	8.1%	9.3%	8.7%	10.3%	10.7%
mean+3SD	1.33	1.16	0.86	1.16	1.13
mean-3SD	0.81	0.65	0.51	0.61	0.58
N	8	8	8	8	8
mean/all kit Median	1.00	1.00	0.97	1.00	1.00
MS uE3 MoM DPC Immulite/2000 (DPD/DP6) Mean:					
Mean	1.47	1.20	0.90	1.50	1.27
SD	0.23	0.20	0.16	0.37	0.32
%CV	15.7%	16.7%	17.4%	24.7%	25.4%
mean+3SD	2.16	1.79	1.37	2.62	2.24
mean-3SD	0.77	0.60	0.43	0.39	0.30
N	9	9	9	9	9
mean/all kit Median	1.37	1.32	1.28	1.70	1.49
MS uE3 MoM kit average:					
mean	1.18	1.00	0.76	1.09	0.99
SD	0.25	0.17	0.12	0.36	0.25
all kit median	1.07	0.91	0.70	0.89	0.86

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	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG All Lab mean:					
mean	21.6	18.7	17.4	31.3	35.4
SD	2.5	2.2	1.9	4.3	4.5
%CV	11.4%	11.7%	11.1%	13.7%	12.6%
mean+3SD	28.9	25.3	23.2	44.2	48.8
mean-3SD	14.2	12.1	11.6	18.4	22.0
N	27	27	27	27	27
mean/all kit median	1.01	0.97	0.99	0.96	1.00

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG Beckman Access/2 (BCX/BC1) mean:					
mean	24.0	20.2	19.2	34.9	40.1
SD	1.4	1.2	1.4	2.3	2.3
%CV	5.7%	5.8%	7.2%	6.5%	5.8%
mean+3SD	28.1	23.7	23.4	41.8	47.1
mean-3SD	19.9	16.7	15.1	28.1	33.2
N	8	8	8	8	8
median	24.1	20.3	19.2	35.8	39.8
mean/all kit median	1.12	1.05	1.10	1.08	1.13

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG Beckman Unicel (BCU/BC1) mean:					
mean	21.4	19.3	17.5	32.5	35.4
SD	1.6	2.1	1.4	3.3	2.6
%CV	7.5%	11.0%	7.8%	10.3%	7.2%
mean+3SD	26.20	25.72	21.60	42.46	43.09
mean-3SD	16.60	12.93	13.38	22.47	27.78
N	9	9	9	9	9
median	21.60	19.40	17.10	33.10	34.30
mean/All kit median	1.00	1.00	1.00	1.00	1.00

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG DPC Immulite 2000 (DPD/DP5) mean:					
mean	19.2	16.4	15.5	26.7	30.8
SD	1.9	1.2	1.1	2.2	2.8
%CV	9.9%	7.2%	7.4%	8.2%	9.0%
mean+3SD	24.9	20.0	18.9	33.2	39.1
mean-3SD	13.5	12.9	12.0	20.1	22.5
N	8	8	8	8	8
median	18.8	16.4	15.9	27.3	30.0
mean/all kit median	0.90	0.85	0.88	0.82	0.87

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG MoMs All Lab Mean:					
mean	1.08	0.95	1.07	0.77	1.45
SD	0.10	0.11	0.11	0.10	0.16
%CV	9.5%	11.3%	10.3%	13.0%	11.0%
mean+3SD	1.39	1.28	1.41	1.08	1.93
N	26	26	26	26	26

	MS 281	MS 282	MS 283	MS 284	MS 285
MS hCG kit average:					
mean	21.5	18.6	17.4	31.4	35.4
SD	2.4	2.0	1.9	4.2	4.7
all kit median	21.4	19.3	17.5	32.5	35.4

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	MS 281	MS 282	MS 283	MS 284	MS 285
MS Inhibin A all lab mean:					
Mean	145.8	199.8	209.2	141.0	240.4
SD	13.8	18.3	19.8	13.2	24.8
%CV	9.5%	9.1%	9.5%	9.4%	10.3%
mean + 3SD	187.2	254.7	268.6	180.6	314.8
mean- 3SD	104.3	145.0	149.7	101.3	166.0
N	26	26	26	26	26
All Lab Median	150.0	202.5	213.0	142.5	247.9
mean/all kit median	0.99	0.98	0.98	0.98	0.99
MS Inhibin A Beckman Unicel (BCU/BC1) mean:					
Mean	151.0	204.3	215.3	143.5	244.1
SD	10.5	12.9	11.9	9.8	20.6
%CV	6.9%	6.3%	5.5%	6.8%	8.4%
mean + 3SD	182.5	242.9	251.0	172.9	305.9
mean- 3SD	119.5	165.8	179.6	114.1	182.3
N	11	11	11	11	11
kit median	150.3	200.4	212.5	142.0	242.2
mean/all kit median	1.02	1.00	1.01	1.00	1.00
MS Inhibin A Beckman Access/2 (BCX/BC1) mean:					
Mean	147.9	205.4	214.2	145.4	249.2
SD	8.2	11.7	11.9	8.0	14.0
%CV	5.5%	5.7%	5.6%	5.5%	5.6%
mean + 3SD	172.4	240.4	250.0	169.5	291.3
mean- 3SD	123.4	170.4	178.4	121.3	207.1
N	12	12	12	12	12
kit median	150.4	208.8	216.7	147.5	253.1
mean/All kit median	1.00	1.01	1.00	1.01	1.02
MS Inhibin A Diagnostic System Labs (DS1) mean:					
Mean	118.1	161.1	166.6	113.8	191.9
SD	11.9	7.6	18.3	9.5	20.3
%CV	10.1%	4.7%	11.0%	8.3%	10.6%
mean + 3SD	153.8	184.1	221.5	142.1	252.7
mean- 3SD	82.3	138.2	111.7	85.4	131.1
N	3	3	3	3	3
kit median	116.5	160.2	167.2	111.0	185.0
mean/all kit median	0.80	0.79	0.78	0.79	0.79
MS Inhibin A kit average:					
mean	139.0	190.3	198.7	134.2	228.4
SD	18.2	25.3	27.8	17.7	31.7
all kit median	147.9	204.3	214.2	143.5	244.1

	MS 281	MS 282	MS 283	MS 284	MS 285
MS Inhibin A MoM All Lab mean:					
mean	0.87	1.09	1.01	0.75	1.39
SD	0.11	0.16	0.17	0.10	0.18
%CV	12.6%	14.8%	17.2%	14.0%	12.8%
mean+3SD	1.20	1.57	1.53	1.07	1.92
mean-3SD	0.54	0.61	0.49	0.44	0.86
N	26	26	26	26	26
mean/all kit median	1.00	0.94	0.92	0.96	0.97
MS Inhibin A MoM Beckman Unicel (BCU/BC1) mean:					
Mean	0.93	1.16	1.09	0.77	1.43
SD	0.10	0.16	0.17	0.09	0.17
%CV	10.7%	14.1%	15.4%	12.0%	12.1%
mean + 3SD	1.22	1.65	1.60	1.05	1.95
mean- 3SD	0.63	0.67	0.59	0.49	0.91
N	11	11	11	11	11
Kit Median	0.87	1.09	1.03	0.76	1.37
mean/all kit median	1.07	1.00	1.00	0.99	1.00
MS Inhibin A MoM Beckman Access (BCX/BC1) mean:					
Mean	0.86	1.09	0.99	0.78	1.43
SD	0.06	0.09	0.11	0.08	0.11
%CV	6.7%	8.6%	11.2%	10.2%	8.0%
mean + 3SD	1.04	1.36	1.32	1.02	1.77
mean- 3SD	0.69	0.81	0.66	0.54	1.08
N	12	12	12	12	12
Kit Median	0.89	1.09	1.04	0.77	1.43
mean/all kit median	1.00	0.93	0.91	1.00	1.00
MS Inhibin A MoM Diagnostic System Labs (DS1) mean:					
Mean	0.81	1.70	1.32	1.01	1.67
SD	0.19	0.47	0.33	0.20	0.48
%CV	23.0%	27.4%	24.8%	19.8%	29.1%
mean + 3SD	1.36	3.10	2.30	1.61	3.12
mean- 3SD	0.25	0.30	0.34	0.41	0.21
N	3	3	3	3	3
Kit Median	0.72	1.56	1.27	1.00	1.51
mean/all kit median	0.93	1.46	1.21	1.30	1.17
MS Inhibin A MoM kit average:					
mean	0.87	1.32	1.13	0.85	1.51
SD	0.06	0.34	0.17	0.14	0.14
all kit median	0.86	1.16	1.09	0.78	1.43

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	AF 281	AF 282	AF 283	AF 284	AF 285
AF AFP All Lab mean :					
mean	27.2	9.4	7.8	9.9	6.0
SD	3.7	1.6	1.1	1.7	0.8
%CV	13.6%	16.8%	14.5%	16.8%	12.9%
mean+3SD	38.3	14.1	11.2	14.8	8.3
mean-3SD	16.2	4.6	4.4	4.9	3.7
N	22	22	22	22	22
All kit median	27.5	9.8	8.0	10.2	6.2
mean/all kit mean	0.99	0.96	0.98	0.97	0.96
AF AFP Beckman Unicel (BCU/BC1) mean:					
Mean	25.6	8.1	7.4	8.5	5.3
SD	4.2	1.1	0.7	0.7	0.5
%CV	16.4%	14.0%	9.5%	8.1%	8.5%
X+3SD	38.0	13.5	12.1	14.2	8.0
X-3SD	16.0	5.2	5.1	5.6	4.0
N	8	8	8	8	8
median	23.8	7.6	7.2	8.5	5.2
mean/all kit median	0.93	0.83	0.93	0.83	0.85
AF AFP Beckman Access/2 (BCX/BC1) mean:					
mean	27.0	9.4	8.6	9.9	6.0
SD	3.7	1.4	1.2	1.4	0.7
%CV	13.5%	14.8%	13.5%	14.5%	11.1%
mean+3SD	38.0	13.5	12.1	14.2	8.0
mean-3SD	16.0	5.2	5.1	5.6	4.0
N	6	6	6	6	6
median	25.9	9.15	8.1	9.55	5.8
mean/all kit median	0.98	0.96	1.07	0.97	0.96
AF AFP DPC Immulite 2000 (DPD/DP5) mean:					
mean	28.0	10.2	6.7	10.5	6.4
SD	1.9	0.8	0.3	0.8	0.3
%CV	6.7%	7.7%	4.5%	7.6%	5.3%
mean+3SD	33.7	12.6	7.7	12.8	7.5
mean-3SD	22.3	7.9	5.8	8.1	5.4
N	5	5	5	5	5
median	27.6	10.3	6.7	10.1	6.3
mean/all kit median	1.02	1.04	0.84	1.03	1.04
AF AFP Abbott Axsym (ABB/AB2) mean:					
mean	32.2	11.9	9.3	13.1	7.2
N	2	2	2	2	2
mean/all kit median	1.17	1.21	1.16	1.28	1.16
AF AFP kit average:					
mean	28.2	9.9	8.0	10.5	6.2
SD	2.8	1.6	1.2	1.9	0.8
all kit median	27.5	9.8	8.0	10.2	6.2

	AF 281	AF 282	AF 283	AF 284	AF 285
AF AFP MoM All Lab Mean:					
mean	2.88	1.21	1.40	1.56	0.52
SD	0.31	0.13	0.27	0.18	0.06
%CV	10.8%	10.8%	19.1%	11.3%	10.7%
mean+3SD	3.81	1.61	2.20	2.08	0.69
mean-3SD	1.95	0.82	0.60	1.03	0.35
N	22	22	22	22	22
All median	2.80	1.20	1.36	1.50	0.52
mean/all kit median	1.03	1.01	1.03	1.04	1.00
AF AFP MoM Beckman Unicel(BCU/BC1) mean:					
Mean	2.94	1.15	1.41	1.45	0.50
SD	0.38	0.13	0.17	0.07	0.04
%CV	13.0%	11.1%	12.0%	4.9%	8.8%
X+3SD	4.09	1.53	1.92	1.66	0.63
X-3SD	1.80	0.77	0.90	1.23	0.37
N	8	8	8	8	8
median	2.83	1.14	1.36	1.47	0.51
mean/all kit median	1.03	0.92	0.96	0.91	0.98
AF AFP MoM Beckman Access (BCX/BC1) mean:					
Mean	2.82	1.20	1.58	1.56	0.51
SD	0.36	0.16	0.29	0.25	0.08
%CV	12.6%	13.1%	18.5%	15.7%	15.3%
X+3SD	3.89	1.68	2.46	2.30	0.74
X-3SD	1.75	0.73	0.70	0.82	0.28
N	6	6	6	6	6
median	2.77	1.17	1.46	1.47	0.50
mean/all kit median	0.99	0.97	1.08	0.99	1.00
AF AFP MoM DPC Immulite 2000 (DPD/DP5) mean:					
Mean	2.86	1.28	1.07	1.60	0.55
SD	0.25	0.09	0.08	0.13	0.05
%CV	8.8%	7.2%	7.1%	7.9%	9.4%
X+3SD	3.61	1.56	1.30	1.98	0.71
X-3SD	2.11	1.01	0.84	1.22	0.40
N	5	5	5	5	5
median	2.80	1.28	1.09	1.58	0.54
mean/all kit median	1.00	1.03	0.73	1.01	1.08
AF AFP MoM Abbott Axsym (ABB/AB2) mean:					
Mean	2.84	1.30	1.53	1.78	0.51
N	2	2	2	2	2
mean/all kit median	1.00	1.04	1.04	1.12	1.00
AF AFP MoM kit average:					
mean	2.87	1.23	1.40	1.60	0.52
SD	0.05	0.07	0.23	0.14	0.02
all kit median	2.85	1.24	1.47	1.58	0.51

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	FT281	FT282	FT283	FT284	FT285
FT Gestational Age All Lab Mean:					
Mean	11.2	12.0	11.5	12.5	13.0
SD	0.13	0.04	0.12	0.10	0.05
%CV	1.2%	0.4%	1.1%	0.8%	0.4%
mean+3*SD	11.6	12.1	11.9	12.8	13.1
mean-3*SD	10.8	11.8	11.1	12.2	12.8
N	17	17	17	17	17

	FT281	FT282	FT283	FT284	FT285
FT NT MoM All Lab Mean:					
Mean	1.04	1.86	1.07	0.94	0.98
SD	0.07	0.11	0.07	0.06	0.06
%CV	7.0%	6.2%	6.7%	6.8%	5.7%
mean+3SD	1.26	2.20	1.29	1.13	1.15
mean- 3SD	0.83	1.51	0.85	0.75	0.81
N	16	16	16	16	16
All Median	1.04	1.86	1.07	0.94	0.99

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	FT281	FT282	FT283	FT284	FT285
FT hCG All Lab Mean:					
mean	80.8	169.1	78.0	75.2	70.2
SD	11.6	38.6	10.7	8.4	8.6
%CV	14.4%	22.8%	13.7%	11.2%	12.3%
mean+3SD	115.6	284.9	110.0	100.4	96.0
mean- 3SD	46.0	53.3	45.9	49.9	44.4
N	16	16	16	16	16
mean/All kit median	1.00	0.97	1.03	1.01	1.03

	FT281	FT282	FT283	FT284	FT285
FT hCG DPC Immulite 2000(DPD/DP5) mean:					
mean	68.9	125.5	66.5	66.3	61.2
SD	5.6	15.7	2.4	5.1	5.1
%CV	8.1%	12.5%	3.6%	7.7%	8.3%
mean+3SD	85.7	172.6	73.7	81.6	76.4
mean- 3SD	52.1	78.4	59.3	51.1	46.0
N	5	5	5	5	5
median	67.5	118.6	67.5	68.5	61.8
mean/All kit median	0.85	0.72	0.88	0.90	0.89

	FT281	FT282	FT283	FT284	FT285
FT hCG MoM All Lab Mean:					
Mean	0.90	2.16	0.93	0.97	0.95
SD	0.10	0.34	0.09	0.09	0.09
%CV	10.9%	15.8%	10.1%	9.6%	9.4%
mean+3*SD	1.20	3.18	1.21	1.25	1.22
mean - 3*SD	0.60	1.13	0.65	0.69	0.68
N	15	15	15	15	15
All Median	0.92	2.09	0.93	0.98	0.96

	FT281	FT282	FT283	FT284	FT285
FT hCG Beckman Unicel (BCU/BC1) mean:					
mean	80.7	174.7	75.4	74.1	68.5
SD	11.5	24.8	4.7	5.0	3.0
%CV	14.3%	14.2%	6.2%	6.8%	4.4%
mean+3SD	100.4	277.2	102.3	93.2	90.4
mean- 3SD	81.1	124.3	77.0	73.6	67.9
N	5	5	5	5	5
median	75.4	176.8	76.0	72.7	67.8
mean/All kit median	1.00	1.00	1.00	1.00	1.00

	FT281	FT282	FT283	FT284	FT285
FT hCG Beckman Access (BCX/BC1) mean:					
mean	90.8	200.8	89.7	83.4	79.2
SD	3.2	25.5	4.2	3.3	3.7
%CV	3.5%	12.7%	4.7%	3.9%	4.7%
mean+3SD	100.4	277.2	102.3	93.2	90.4
mean- 3SD	81.1	124.3	77.0	73.6	67.9
N	6	6	6	6	6
median	91.0	191.4	91.1	82.9	79.6
mean/All kit median	1.13	1.15	1.19	1.13	1.16

	FT281	FT282	FT283	FT284	FT285
FT hCG kit average:					
mean	80.1	167.0	77.2	74.6	69.6
SD	11.0	38.2	11.7	8.6	9.0
all kit median	80.7	174.7	75.4	74.1	68.5

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	FT281	FT282	FT283	FT284	FT285
FT PAPP-A All Lab Mean:					
Mean	678.1	441.2	742.5	1117.8	1180.6
SD	78.6	52.0	90.4	125.5	106.3
%CV	11.6%	11.8%	12.2%	11.2%	9.0%
mean + 3SD	914.0	597.3	1013.7	1494.2	1499.4
mean- 3SD	442.2	285.0	471.2	741.4	861.8
N	15	15	15	15	15
All Lab Median	654.6	444.4	706.8	1137.0	1159.0
mean/All kit median	0.99	0.97	1.03	1.02	1.01

	FT281	FT282	FT283	FT284	FT285
* **FT PAPP-A DPC Immullite 2000 (DPD/DP5) Mean:**					
Mean	787.2	455.1	855.5	1278.0	1308.6
SD	86.1	37.4	105.6	12.6	56.3
%CV	10.9%	8.2%	12.3%	1.0%	4.3%
mean + 3SD	1045.5	567.5	1172.2	1315.7	1477.6
mean - 3SD	528.9	342.8	538.8	1240.3	1139.5
N	3	3	3	3	3
Kit Median	739.6	466.9	820.2	1273.7	1317.5
mean/All kit median	1.15	1.00	1.19	1.16	1.12

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A Beckman Unicel(BCU/BC1) Mean:					
Mean	634.7	406.0	712.3	1101.1	1168.9
SD	40.2	29.4	54.4	101.5	70.3
%CV	6.3%	7.2%	7.6%	9.2%	6.0%
mean + 3SD	755.4	494.1	875.5	1405.6	1379.9
mean - 3SD	514.0	317.8	549.0	796.6	958.0
N	8	8	8	8	8
Kit Median	627.5	394.4	696.4	1090.1	1149.4
mean/All kit median	0.93	0.89	0.99	1.00	1.00

	FT281	FT282	FT283	FT284	FT285
***FT PAPP-A Diagnostic Systems Lab (DS1) Mean:**					
Mean	682.9	501.1	718.2	1031.1	1107.8
SD	56.4	37.4	88.4	113.5	123.4
%CV	8.3%	7.5%	12.3%	11.0%	11.1%
mean + 3SD	1.6	1.1	1.9	2.5	2.6
mean - 3SD	0.9	0.5	0.7	1.3	1.4
N	4	4	4	4	4
Kit Median	684.6	503.8	732.3	1022.5	1120.1
mean/All kit median	1.00	1.10	1.00	0.94	0.95

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A kit average:					
mean	701.6	454.1	762.0	1136.7	1195.1
SD	77.9	47.6	81.1	127.3	102.9
all kit median	682.9	455.1	718.2	1101.1	1168.9

***Note: The above 2 tables contain converted values (mIU/ml->ng/ml) from equations obtained based on in house correlation data.**
(see critique)

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	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM All Lab Mean:					
Mean	1.31	0.65	1.38	1.17	1.12
SD	0.72	0.33	0.78	0.72	0.65
%CV	55.3%	51.0%	56.3%	61.9%	58.0%
mean + 3SD	3.49	1.66	3.71	3.34	3.07
mean- 3SD	-0.86	-0.35	-0.95	-1.00	-0.83
N	15	15	15	15	15
All Lab Median	1.01	0.55	1.14	0.94	0.83
mean/ All kit median	1.36	1.29	1.30	1.32	1.27

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM DPC Immulite 2000 (DPD/DP5) Mean:					
Mean	2.63	1.27	2.82	2.50	2.31
SD	0.30	0.18	0.36	0.33	0.35
%CV	11.4%	13.9%	12.9%	13.1%	15.3%
mean + 3SD	3.53	1.80	3.90	3.48	3.37
mean - 3SD	1.73	0.74	1.73	1.52	1.25
N	3	3	3	3	3
mean/All kit median	2.38	2.33	2.65	2.82	2.61

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM Beckman Unicel(BCU/BC1) Mean:					
Mean	0.97	0.51	1.06	0.89	0.89
SD	0.20	0.07	0.17	0.13	0.14
%CV	20.3%	12.8%	16.2%	15.1%	15.7%
mean + 3SD	1.55	0.70	1.58	1.29	1.30
mean - 3SD	0.38	0.31	0.54	0.49	0.47
N	8	8	8	8	8
Kit Median	0.94	0.49	1.02	0.94	0.84
mean/All kit median	0.87	0.94	1.00	1.00	1.00

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM Diagnostic System Labs (DS1) Mean:					
Mean	1.11	0.54	1.01	0.86	0.77
SD	0.37	0.12	0.27	0.23	0.09
%CV	33.7%	21.3%	26.5%	27.1%	12.1%
mean + 3SD	2.23	0.89	1.81	1.55	1.05
mean - 3SD	-0.01	0.20	0.21	0.16	0.49
N	3	3	3	3	3
Kit Median	1.16	0.61	1.14	0.97	0.81
mean/ All kit median	1.00	1.00	0.95	0.97	0.87

	FT281	FT282	FT283	FT284	FT285
FT PAPP-A MoM kit average:					
mean	1.57	0.77	1.63	1.41	1.32
SD	0.92	0.43	1.03	0.94	0.86
all kit median	1.11	0.54	1.06	0.89	0.89