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: September 11, 2012

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

DUE DATE: September 26, 2012

Samples:
There are five (5) vials labeled **MS286** to **MS290**, 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 286 to AF 290) containing AFP in amniotic fluid have also been included. In addition, five extra vials **FT 286 to FT 290** 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 286 to FT 290** 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 September 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 September 26, 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-outs for 2013 have been tentatively scheduled for:

Ship-out date	**Due date**
January 29, 2013	February 13, 2013
May 7, 2013	May 22, 2013
September 10, 2013	September 25, 2013

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 286	**9/14/1986**	**W**	**150**	**None**	**3**	**1**	**5/4/2012**	**9/7/2012**
MS 287	9/15/1982	W	130	None	2	1	5/25/2012	9/7/2012
MS 288	**9/14/1984**	**A**	**140**	**None**	**5**	**1**	**5/11/2012**	**9/7/2012**
MS 289	9/15/1983	B	180	Diabetic	3	2	5/18/2012	9/7/2012
MS 290	**9/14/1987**	**H**	**160**	**None**	**2**	**0**	**4/20/2012**	**9/7/2012**

Specimen	GA[4]
AF 286	**18.0**
AF 287	20.0
AF 288	**17.0**
AF 289	19.0
AF 290	**20.0**

***Note: MS286, MS288 and MS290** are the serum sample matched to the amniotic fluid sample **AF286, AF288 and AF290, 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]
September 2012

Dear Laboratory Director,

Below you will find a summary and critique of the Proficiency Testing mail-out from September 11, 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 286	MS 287	MS 288	MS 289‡	MS 290
	Gestational Age (weeks)	18.0	15.0	17.0	16.0	20.0
Maternal Race	Ethnic Group	White	White	Asian	Black	Hispanic
Maternal Weight	Pounds (lbs)	150	130	140	180	160
Maternal Age	Years	26	30	28	29	25
Alpha-Fetoprotein (AFP)	Mean ng/ml ± Std. Dev.	32.2 ± 2.2	42.2 ± 2.9	323.9 ± 21.9	48.2 ± 2.9	208.6 ± 16.1
	MOM ± Std. Dev.	0.72 ± 0.04	1.32 ± 0.09	8.07 ± 0.50	1.69 ± 0.19	3.67 ± 0.24
Unconjugated Estriol (uE3)	Mean ng/ml ± Std. Dev.	0.65 ± 0.06	0.69 ± 0.08	0.98 ± 0.09	0.81 ± 0.10	1.65 ± 0.11
	MOM ± Std. Dev.	0.57 ± 0.13	1.21 ± 0.42	1.06 ± 0.25	1.19 ± 0.30	0.95 ± 0.17
human Chorionic Gonadotrophin (hCG)	Mean IU/ml ± Std. Dev.	44.9 ± 6.5	40.1 ± 5.1	30.2 ± 2.3	21.9 ± 2.3	16.2 ± 1.6
	MOM ± Std. Dev.	2.21 ± 0.26	0.98 ± 0.10	1. 22 ± 0.13	0.80 ± 0.08	1.00 ± 0.09
Dimeric Inhibin-A (DIA)	Mean pg/ml ± Std. Dev.	282.5 ± 27.2	142.7 ± 12.0	124.5 ± 11.1	119.7 ± 10.3	186.5 ± 17.2
	MOM ± Std. Dev.	1.65 ± 0.18	0.72 ± 0.09	0.71 ± 0.09	0.75 ± 0.10	1.01 ± 0.14
Neural Tube Screen (Positive, Negative) Percent	Pos. (+) or Neg. (-)	(-) (100%)	(-) (100%)	(+) (100%)	(-) (84%)	(+) (100%)
	Recommended Action**	NFA	NFA	G = 85% U = 96% A = 88% R = 0%	NFA	G = 85% U = 96% A = 88% R = 0%
	NTD Risk 1 in	10,000	4,112	8	430	20
Trisomy-21 Screen (Positive, Negative) Percent 1. Triple test	Pos. (+) or Neg. (-)	(+) (87%)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)
	Recommended Action**	G = 71% U = 57% A = 71%	NFA	NFA	NFA	NFA
	Risk Est. 1 in	95	5,150	8,050	8,811	8,550
2. Quad Test	Pos. (+) or Neg. (-)	(+) (88%)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)
	Recommended Action **	G = 77% U = 58% A = 77%	NFA	NFA	NFA	NFA
	Risk Est. 1 in	80	17,000	20,000	20,000	20,000
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	6,870	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 286 Wk 18.0	This specimen was obtained from a 26 year old white woman (Gravida = 3, Parity = 1) in her 18th week of gestation with a body weight of 150 lbs. She had a family (sibling) history of pregnancy complications. Her sample screened negative for NTD; however, her aneuploidy screen was positive for Trisomy-21 (88% by quad, 87% 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, 77 %, ultrasound, 58 % and amniocentesis, 77 %; while by those using the triple tests were: genetic counseling, 71%; ultrasound, 57% and amniocentesis, 71%. Specimen MS286 resulted in a negative T18 screen in 100% of the participating labs. The sample was paired to an amniotic fluid specimen (AF286) which had a low AFP level (MOM = 0.53).
MS 287 Wk 15.0	This specimen was obtained from a 30 year old white woman (Gravida = 2, Parity = 1) in her 15th week of gestation with a body weight of 130 lbs. A race correction was not 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 288 Wk 17.0	This specimen was obtained from a 28 year old asian woman (Gravida = 5, Parity = 1) in her 17th week of gestation with a body weight of 140 lbs. She had a personal history of pregnancy complications and her specimen resulted in a positive screen for NTD (highly elevated MSAFP) with no body weight but an ethnic correction indicated. The labs agreed that both Trisomy screens were negative. Specimen MS288 was paired with a non-elevated AFP amniotic fluid specimen. See critique for further discussion of this highly-elevated MSAFP sample.
MS 289 Wk 16.0	This specimen was obtained from a 29 year old Black woman (Gravida = 3, Parity = 2) in her 16th week of gestation with a body weight of 180 lbs. She had a family reproductive history that was unremarkable. Her sample screened negative for NTD, as was her aneuploidy screen for Trisomies-21 and 18. However, a diabetic status correction was indicated. This sample was not paired to an amniotic fluid specimen.
MS 290 Wk 20.0	This specimen was obtained from a 25 year old Hispanic woman (Gravida = 2, Parity = 0) in her 20th week of gestation with a body weight of 160 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 MS290 sample was paired to an amniotic fluid specimen (AF260), which was elevated (AFP MOM = 2.92). Please see Critique for further discussion of this sample.

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=20; all-lab Consensus Values

Sample#	Values	Summary Comments:
AF 286 Wk 18.0	AFP = 5.0 ± 0.5 µg/ml MOM = 0.53 ± 0.05	The AF286 sample was targeted for a low AFAFP value in the routine gestational age screening range. All labs called AF286 a non-elevated specimen for NTD. This AF sample was matched to maternal serum specimen MS286, whose AFP was also low (MOM = 0.72).
AF 287 Wk 20.0	AFP = 6.8 ± 0.8 µg/ml MOM = 1.09 ± 0.17	The AF287 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 288 Wk 17.0	AFP = 8.8 ± 1.2 µg/ml MOM = 0.76 ± 0.11	The AF288 sample was targeted for a screen negative AFAFP value in the routine gestational age screening range. All labs reported this specimen as a screen negative AFAFP value. The AF283 specimen was paired with maternal serum sample MS288, whose AFP was highly elevated (MOM = 8.07). Please see critique for further discussion of samples MS288 and AF288.
AF 289 Wk 19.0	AFP = 8.5 ± 1.1 µg/ml MOM = 1.11 ± 0.14	The AF289 sample was targeted as an NTD negative screen in the upper gestational screening range. All labs categorized AF289 as a negative NTD screen specimen. This specimen had no maternal serum counterpart.
AF 290 Wk 20.0	AFP = 18.5 ± 2.1 µg/ml MOM = 2.92 ± 0.38	The AF290 sample was targeted for an elevated AFAFP value in the routine gestational age range. Most labs called AF290 a positive NTD screen for AFAFP specimen. The AF290 sample was matched to maternal serum specimen MS290 whose AFP was also elevated (MOM = 3.67).

II. Non-Graded Results Section:

Table 2: First Trimester Maternal Serum all-lab Results

Samples *N = 17	**Sample #**	**FT 286**	**FT 287**	**FT 288**	**FT 289**	**FT 290**
	Gestational Age (weeks)	11.9	11.2	13.1	11.5	11.2
Maternal Race	Ethnic Group	White	Asian	White	Hispanic	Black
Maternal Weight	Pounds (lbs)	140	120	125	160	150
Maternal Age	Years	25	27	21	30	29
Fetal Physical Measurements	Crown Rump Length (mm)	53	45	69	48	45
	NT Thickness (mm)	2.90	1.10	1.55	1.08	1.20
	NT – MOM ± Std. Dev.	2.24 ± 0.14	0.97 ± 0.05	0.94 ± 0.05	0.91 ± 0.05	1.06 ± 0.05
Human Chorionic Gonadotrophin (hCG) Total	Mean IU/mL ± Std. Dev.	172.0 ± 31.4	89.3 ± 12.6	65.3 ± 8.1	90.3 ± 11.8	78.8 ± 10.9
	MOM ± Std. Dev.	2.23 ± 0.29	1.00 ± 0.15	0.93 ± 0.12	1.23 ± 0.12	0.96 ± 0.12
Pregnancy-Associated Plasma Protein–A (PAPP-A)	Mean ng/mL*** ± Std. Dev.	1006.0 ± 717.2	1684.8 ± 1120.6	2611.5 ± 1653.0	1955.5 ± 1295.2	1560.8 ± 1121.5
	MOM ± Std. Dev.	0.97 ± 0.59	1.81 ± 1.00	1.34 ± 0.77	2.49 ± 1.27	1.84 ± 1.22
Trisomy-21 Screen (Positive, Negative) Percent	Pos (+) or Neg. (-)	(+) (93%)	(-) (100%)	(-) (100%)	(-) (100%)	(-) (100%)
	Recommended Action **	G = 100% U = 43% A = 50% C = 57%	NFA	NFA	NFA	NFA
	Risk Estimate 1 in	10	11,000	15,100	10,000	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	862	10,000	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 286 Wk 11.9	This specimen was procured from a 25 year old white woman of average body weight (140 lbs.). Her gestational age at the time of screening was 11.9 weeks. She had a prior family history of pregnancy complications and adverse outcomes. This FT specimen was screen positive for Trisomy-21 and 93% of testing labs were in agreement (see Critique). The FT286 risk estimate for Trisomy-21 was 1 in 10, while the Trisomy-18 risk was 1 in 862 with 100% of testing labs in agreement that the T18 screen was negative.
FT 287 Wk 11.2	This specimen was procured from a 27 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 FT287 risk estimate for Trisomy-21 was 1 in 11,000, and the Trisomy-18 risk was 1 in 10,000.
FT 288 Wk 13.1	This specimen was obtained from a 21 year old white woman of average body weight (125 lbs.). Her gestational age at the time of screening was 13.1 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 FT288 risk estimate for Trisomy-21 was 1 in 15,100, and the Trisomy-18 risk was also 1 in 10,000.
FT 289 Wk 11.5	This specimen was obtained from a 30 year old Hispanic woman with a body weight of 160 lbs. Her gestational age at the time of screening was 11.5 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 FT289 risk estimate for Trisomy-21 was 1 in 10,000 and the Trisomy-18 risk was 1 in 10,000.
FT 290 Wk 11.2	This specimen came from a 29 year old black woman of body weight (150 lbs.). Her gestational age at the time of screening was 11.2 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 FT290 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 **MS290** was targeted as a positive specimen for NTD (Figs. 1 and 3) and was matched to the elevated **AF290** sample (Fig. 2). All labs (100%) agreed that specimen **MS290** was screen positive for NTD and negative for both Trisomy screens. The **MS290** sample generated further action and follow-up recommendations that consisted of the following: genetic counseling, 85%; ultrasound, 96%; amniocentesis, 88%; and repeat sample, 0%. 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 but 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 **MS286** was obtained from a white woman with a prior sibling history of pregnancy complications. The MOM values for specimen **MS286** (MSAFP-MOM = 0.72, MSuE3-MOM = 0.57, MShCG-MOM = 2.21, DIA-MOM = 1.65) resulted in a T21 positive screen with the majority of labs in agreement (87% by triple and 88% by quad test). The T21 risk was 1 in 95 by triple test and 1 in 80 by quad test (Figs. 5, 6). The recommended further actions for the sample **MS286** were genetic counseling, 71%; ultrasound, 57%; and amniocentesis, 71% from labs performing the triple screen, and genetic counseling, 77%; ultrasound, 58% and amniocentesis was 77% from labs

performing the quad screen. Thus, the specimen **MS286** was designed to represent a positive screen for Down Syndrome with a canonical profile of low MSAFP and low MSuE3, together with elevated MShCG and MSDIA.

Two other specimens, **MS287** and **MS289**, produced negative screens for NTD, T21, and T18, with no corrections for body weight or race being indicated. Some labs assigned **MS289** a NTD risk due to laboratory cutoff values, race, and diabetic status; however an all lab consensus was not attained.

The **MS288** specimen at 17 weeks was a high profile case involving discordant levels of MSAFP and AFAFP values. Sample **MS288** resulted in a positive screen for NTD based on a highly elevated MSAFP MOM value (8.07), but normal MShCG (MOM = 1.22), uE3 (MOM = 1.06), and DIA (MOM = 0.71) values, and was negative for T21 and T18. The follow-up actions recommended for **MS288** were genetic counseling, 85%; ultrasound, 96%; amniocentesis, 77%; and repeat testing, 0%. In contrast to the MSAFP, the AFAFP measurement resulted in a non-elevated AFP value. The sample **MS288** was modeled after an actual literature case study of a 28 year old woman of Chinese descent in her 17th week of gestation who exhibited an excessive increase of MSAFP with a MOM of 6.9 (Entezami, 1996). The patient had experienced three previous miscarriages, all occurring in the first three months of pregnancy. Several years later, she completed an uncomplicated pregnancy with a spontaneous delivery of a normal female infant of average birth weight. Following a family trip to China, the woman had been infected with an acute case of Hepatitis B virus, and after several weeks, a chronic course of the Hepatitis B ensued. The woman then became pregnant again.

In the above case report, hepatitis serology test results confirmed the presence of HB_sAg in the 18th week of pregnancy; however, liver function enzymes (gamma-glutamyl transpeptidase; glutamic oxalo-transaminase; glutamic pyruvic transaminase) proved to be normal. Because of the patient's medical history, an upper abdominal sonography was performed in the 21st week of pregnancy; it revealed a moderately-sized liver tumor mass. A later magnetic resonance imaging (MRI) and a fine needle biopsy performed at 32 weeks confirmed the malignant state of the tumor mass as a primary hepatocellular carcinoma (**HCC**) or hepatoma. This served to explain the excessively elevated MSAFP levels. Chest X-rays showed no presence of liver tumor cell clusters (spots) and liver function enzymes and bilirubin levels remained normal. At 33 weeks gestation, a normal baby girl was delivered by cesarean section. Eleven days after delivery, the patient underwent surgical excision to remove the enlarged hepatoma. Postoperatively, the MSAFP levels diminished to normal values (5-10 ng/ml) and the patient received adjuvant treatment using chemoembolization of the right hepatic artery and went into remission. Thus, the non-pregnancy related clinical complications produced an apparently positive screen for a prenatal NTD, which turned out to be a false positive result, caused by the presence of an AFP-producing liver tumor. In conclusion high MSAFP without concomitant elevated AFAFP levels should alert the lab and the physician to the possibility of non-pregnancy related liver disease.

In a second reported case, HCC was detected by routine second trimester screening of MSAFP in a Taiwanese woman (Jeng, 1995). A 28 year old pregnant woman in her 16th week of gestation was found to have extremely high levels of MSAFP (34,000 ng/ml). The woman, a known Hepatitis B carrier, had been diagnosed with chronic HB_sAg positive hepatitis several years prior to her pregnancies. A pregnancy four years earlier had been terminated at 8 weeks after multiple hepatitis drug therapy treatment had already been administered. Abdominal ultrasonography at 16 weeks gestation showed a well-defined mass in the right lobe of the liver and further tests confirmed the presence of a hepatoma. Following medical termination of the pregnancy at 21 weeks, a well-encapsulated tumor mass (Stage-II cancer) was removed from the surface of the right lobe of the liver. Follow-up AFP levels showed a gradual decrease and return to normal non-pregnant adult levels within several weeks.

In a third case report, the presence of HCC in a 31 year old pregnant Israeli woman was described following routine prenatal screening for MSAFP (Goldberg, 1991). The woman had undergone physical examination on two previous hospital visits at 8 and 12 weeks of pregnancy. No notable pathologies were observed. Following routine prenatal MS screening at 16 weeks, a MSAFP mass value of 62,000 ng/ml was obtained. A repeat MSAFP determination yielded a value of 116,000 ng/ml. Examination by abdominal palpation detected an enlarged liver mass below the rib cage. Subsequent ultrasound scanning of the abdomen revealed an extended liver node corresponding to a HCC. A pregnancy ultrasound demonstrated a normal fetus with physical measurements (bi-parietal diameter, femur length, abdominal circumference) consistent with the estimated gestational age based on LMP. The amniocentesis results indicated a normal karotype and an AFAFP level within gestational age limits. Lab findings showed that hemoglobin, white cell counts, creatinine, and liver function enzyme assays were normal,

while a HB_sAg test was positive. Due to these laboratory findings, a therapeutic abortion was performed at 20 weeks gestation; thereafter chemotherapy was administered.

A fourth case of HCC was present in a 3rd trimester pregnancy which involved a 17 year old South African woman in her 32nd week of pregnancy (Seaward, 1986). In South Africa, HCC is relatively common in blacks with a gender ratio of 8 males to one female. Her MSAFP level was 90 ng/ml (0.7 MOM), and within 3 weeks rose to 180 ng/ml (MOM=1.8). Ultra-sonography revealed a singleton fetus with a mature placenta and reduced amniotic fluid volume consistent with a mild intra-uterine retardation (IUGR). MSAFP levels are known to be low in some cases of IUGR (Mizejewski, 2003). Sonography also demonstrated a tumor mass in the right liver lobe. At 36 weeks, the tumor had doubled in size; hence, labor was induced resulting in a normal vaginal delivery of a small-for-gestational age female infant. Following delivery, both the tumor and spleen were enlarged and a percutaneous needle biopsy confirmed the presence of a primary HCC with no underlying cirrhosis. Subsequently, the MSAFP levels were reduced to normal and the patient was started on palliative adriamycin chemotherapy. At the time of that report, there were no published cases of cancer surgery having been performed during pregnancy. However, prognosis is so poor that early diagnosis and tumor removal offer the only hope of successful treatment. In seven other published African cases of HCC during pregnancy, maternal death was recorded in all cases, live infants were born in 3, intra-uterine death occurred in 2, and spontaneous abortion happened in 2 cases (Seaward, 1986).

Concerning the use of oral contraceptives prior to pregnancy, the author of a case report describes HCC tumor occurrence in a first trimester pregnancy study (Dudley, 1982). A 33 year old Afro-American woman (gravida 5, para 4) was 9 weeks pregnant when seen by her obstetrician. Her past gynecologic history included a ruptured tubal pregnancy. Six months previous to her doctor visit, she had been treated for abdominal pain, nausea, vomiting, and fatty food intolerance. Exploratory laboratory revealed an unresectable primary HCC confirmed by biopsy. During the previous two years, the patient had been on a norethindrone and mestranol oral contraceptive regimen; however, these were discontinued at time of examination. Prior to pregnancy, the patient had received no chemotherapy. A medical abortion was performed at 10 weeks gestation after enlarged liver masses were detected in two liver lobes and liver function enzymes were elevated. Three weeks later, the woman passed away. At the time of the report, studies had shown that chronic administration of oral contraceptives correlated with the serologic presence of an anabolic non-steroid (C-17 substitution at C-19) in many patients taking birth control pills (Davis, 1975). Such anabolic steroids had been used in treating bone marrow aplasia and were suspected to be associated with the induction of HCC tumors (Pryer, 1977).

The presence of a primary hepatoma during pregnancy is a rare occurrence in the USA; however, HCC is one of the most common malignancies worldwide (Blum, 1993). Many of the published cases of pregnancy coincident with HCC have involved patients of Asian descent. Fifty percent of the HCC cases develop from cirrhosis and/or the presence of hepatitis HB_sAg. Although cases of HCC can occur many years after an HBV infection, some hepatic tumors that occur in pregnancy can arise as early as 5 years after virus exposure. Since AFP is a major tumor marker for HCC, routine prenatal screening in second trimester pregnancies can lead to discovery of hepatomas when extremely increased MSAFP levels in the range of 300 to 500 ug/ml concentrations are detected. However, this AFP range can also be observed in anacephalic fetuses which must therefore be ruled out. Abdominal sonography is frequently initiated following physical examination by liver palpation, and further clarification with MRI and fine-needle biopsy are indicational values for the correct diagnosis of HCC. The prognosis for pregnant women displaying palpable liver tumor masses is considered highly unfavorable. Early delivery and subsequent surgery of the HCC, especially in non-invasive and non-metastizing tumors, are standards of care. When chronic hepatitis is involved, AFP determinations and liver sonograms are indicated for the post-pregnancy follow-up care. It is noteworthy that women can get pregnant after successful surgery and treatment of HCC (Pritze, 1992).

Primary hepatoma is most unusual in young pregnant females without prior liver cirrhosis or hepatitis virus exposure. The presence of a malignant liver tumor during pregnancy has been associated with mild breast discomfort, thrombo-emolism, and prior use of oral contraceptives (see above Dudley, 1982). As previously shown the role of an earlier liver infection such as with hepatitis B virus has been reported to be associated with HCC in pregnancy (Goldberg, 1991). Pregnancy notably increases the risk of an unfavorable outcome for patients with HCC, proposed to be due to: 1) elevations in multiple steroid levels; and 2) increase in the vascular bed of the liver. Furthermore, AFP is known to be a growth enhancing factor for tumors and has been reported to increase cell proliferation in hepatoma cell cultures of human hepatomas, in animal tumor models, and from clinically-derived human cell isolates (Li et al, 2006; Mizejewski, 2010). In summary, maternal malignancy or other AFP-related diseases should first be ruled out when cases of highly elevated MSAFP levels are measured during pregnancy.

B) Assay Kit Performance:

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- 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 DPC Immulite 2000/2500 ranged from 40 to 60% higher than those from Beckman (Fig. 8B); however preliminary studies in our lab suggest this may derive from a matrix effect in our samples. Regarding the hCG kits (Fig. 10), the Beckman Access 2 instrument results were about 10% higher than those from Beckman UNICEL, while the Siemens Immulite 2000 results were 10% lower than those from the other assay platforms. The hCG MoM values were nearly equivalent except that Siemens Immulite 2000 was 10% lower which is similar to hCG mass values. Finally, the method comparison for Inhibin-A displayed in Fig. 9A shows that the results from the Beckman Access/2 or UNICEL were similar whereas the Diagnostic Systems Lab (DSL) assay platform results were 20-25% lower, which is also reflected in the Inhibin MOM values (Fig. 9B).

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

C) Second Trimester Screening Software Utilized:

The alpha and Benetech software packages were each used by 29.6% and 25.9%, of the labs, respectively; Robert Maciel (RMA) software was employed by 29.6%; and in-house and "other" softwares comprised 14.8%. 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.

The all lab measurement of the 11.9 week 25 year old Caucasian **FT286** specimen for total hCG resulted in a mass mean of 172.0 $\pm$ 31.4 IU/ml, with a MOM of 2.23 $\pm$ 0.29; the all-lab mass mean for PAPP-A was 1006.0 $\pm$ 717.2 ng/ml with a MOM of 0.97 $\pm$ 0.59. As a result, the all-lab T21 risk assessment for **FT286** was 1 in 10 (Fig. 13). The **FT286** sample displayed a 93% consensus T21 positive screen assessment. Further action was indicated which included genetic counseling, 100%, ultrasound, 43%, amniocentesis, 50%, and chorionic villus sampling, 57%. Finally, 100 % of labs considered the **FT286** specimen screen negative for T18 (1 in 862) using a cutoff of 1 in 100 (Fig.14).

The **FT287** Asian specimen was obtained from a 27 year old woman with a gestational age of 11.2 weeks. Assay measurements resulted in an all-lab total hCG mass measurement of 89.3 $\pm$ 12.6 IU/ml (MOM = 1.00 $\pm$ 0.15); the all-lab PAPP-A mass measurement was 1684.8 ± 1120.6 ng/ml (MOM = 1.81 $\pm$ 1.00). The all-lab T21 screen consensus for **FT287** was negative with a risk assessment of 1 in 11,000 (Fig. 13). No further actions were recommended by the labs. Finally, the **FT287** specimen also screened negative for T18 (1 in 10,000 Fig. 14).

The all lab measurement of the 13.1 week specimen **FT288** was obtained from a 21 year old caucasian woman. Total hCG measurement resulted in a mass mean of 65.3 IU/ml $\pm$ 8.1, with a MOM of 0.93 $\pm$ 0.12. In addition, the all-lab mass mean for PAPP-A was 2611.5 $\pm$ 1653.0 ng/ml with a MOM of 1.34 $\pm$ 0.77. This resulted in an all-lab T21 risk assessment of 1 in 15,100 for the **FT288** specimen and a negative screen (Fig. 13) assessment together with a negative T18 risk assessment of 1 in 10,000 (Fig. 14).

In the **FT289** 30 year old Hispanic specimen, the gestational age all-lab mean was reported as 11.5 weeks. Assay measurements for **FT289** resulted in an all-lab total hCG mass measurement of 90.3 ± 11.8 IU/ml (MOM = 1.23 ± 0.12), while the all-lab PAPP-A mass assessment was 1955.1 ± 1295.2 ng/ml (MOM = 2.49 ± 1.27). All labs agreed that the **FT289** sample was screen negative for T21 with a risk of 1 in 10,000 (Fig. 13) and negative screen for T18 with a risk assessment of 1 in 10,000 (Fig. 14).

For the 29 year old Afro-American **FT290** specimen, the gestational age all-lab mean was reported as 11.2 weeks. Assay measurements resulted in an all-lab total hCG concentration of 78.8 ± 10.9 IU/ml (MOM = 0.96 ± 0.12), while the all-lab PAPP-A concentration was 1560.8 ± 1121.5 ng/ml (MOM = 1.84 ± 1.22). The all-lab FT T21 risk assessment was 1 in 10,000 and all labs agreed that the **FT290** sample was negative for T21 (Fig. 13). Similarly, the **FT290** 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 six 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 ng/ml were plotted versus Siemens Immulite 2000 (x-axis) data in mIU/ml yielding a linear correlation with an R^2 value of 0.9466, a slope of 0.4515 and a Y intercept of 0.1266 (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 0.9704. 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 12 for the five FT samples. As shown in Fig 11A, FT hCG measurements by Beckman Access/2 were ~10-15% higher than those by Beckman UNICEL, while the Siemens Immulite DPC instruments measured approximately 10-15% below the Beckman Access 2/UNICEL instruments. Overall, the hCG MoM values reflected the mass values but the differences were somewhat diminished (Fig. 11B). The results from the three PAPP-A kits, when converted to the same mass units, were not consistent among each other (Fig. 12A). The Beckman UNICEL PAPP-A was less than 50% that of DSL, while Siemen Immulite 2000 was near 1.8 times that of DSL and the all-Lab mean. In comparison, 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 33% and 20% of the labs, respectively; Robert Maciel (RMA) software was employed by 27%; and in-house software comprised 20%. None of the labs used programs classified as "other" which are proprietary software packages.

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Section-III.

Other investigators have attempted to correlate abnormal second-trimester MS-AFP levels with adverse pregnancy outcomes (Table 3). One group determined that abnormally high MS-AFP levels were associated with low birth weight, prematurity, and antepartum hemorrhage, whereas abnormally low unexplained MS-AFP correlated with macrosomia (overgrowth disorder) and advanced gestational age at delivery (111). While the negative predictive value of this test was high (96%), the positive predictive value was disappointingly low (9%–12%). Thus, the use of this assay to formulate a treatment plan was not promising; however, the test might find value in reassuring women about their pregnancy outcome. Another group of investigators tested whether several amniotic fluid protein components (insulin-like growth factor 1 [IGF-1], IGFβP-1, leptin, AFP) correlated with the severity of IUGR (122). Among the candidate proteins, only an association with AFP levels was found to be significant. Thus, only elevated AFP levels in amniotic fluid were useful in the early (14–18 weeks) detection of populations at risk for developing IUGR. The Quad test (AFP, hCG, UE3, and Inhibin-A) was also analyzed as a predictor of adverse pregnancy outcome in association with preterm birth, IUGR, preeclampsia, and fetal loss (123). Although it was determined that the use of multiple markers had a relatively low sensitivity and positive predictive value, it was superior to using an individual screening marker alone. Finally, the use of high MS-AFP and low amniotic fluid–AFP in the second trimester (15 weeks) indicated that diagnostic ultrasound imaging should be applied in the third trimester. Subsequent sonography at 33 weeks in this latter study revealed the presence of polyhydramios, echogenic amniotic fluid images, and gastric dilatation without gross anatomic malformations. The female karotype in this study was normal, as were the amniotic fluid Ache and AFP levels. However, at a term of 35 weeks, the newborn had pyloric atresia and displayed cutaneous blisters and erosions confirmed as epidermolysis bulbosa (124), which has previously been associated with elevated MS-AFP levels (125).

The combination of prolactin (PRL) and human placental lactagen (HPL) measurements together with an AFP determination has also been employed in the clinical diagnosis of premature rupture of membranes (PROM; Refs. 126, 127) (Table 4). Although such protein determinations have been measured in MS and amniotic fluid, greater sensitivity has been achieved using vaginal secretion specimens up to 41 weeks' gestation with the MS-AFP measurements determined by ELISA assay. Using 30 ng/ml as the cutoff level, researchers reported sensitivity and specificity at 98% and 99% confidence levels, respectively (128). The investigators of this latter report stated that the results obtained with AFP alone compared with other clinical tests and echographic (ultrasound) observations were significantly better than measurement of pH together with diamino-oxidase assays and determination of PRL levels. However, in an earlier study using vaginal fluids (VFs) compared to MS and urine, VF levels of PRL and AFP were found to be 2- to 10-fold and 5- to 50-fold higher, respectively, than in paired MS and/or AF specimens. Especially in the PROM state after the 33rd week of pregnancy, VF levels of MS-AFP were predominantly higher than those found in MS, extending up to 5500 µg/ml (129). There have also been attempts to employ AFP, HPL, and PRL biomarkers in early pregnancy, although they met with less success (130, 131). In summary, only PROM studies involving HPL and AFP have continued to display their usefulness when employed in late pregnancy or at term (132).

Concluding Statements

This review has focused on the physiologic roles of AFP and its utility as a biomarker to predict perinatal distress and adverse pregnancy outcomes. Since the discovery that AFP was tumor associated in the mid-1960s, the functional roles of AFP have slowly emerged concomitantly with its ever-growing use as a biomarker in the clinical laboratory. Even though the quantitative serum levels of AFP do not always correlate with increasing size of endodermally derived tumors, the use of AFP as a tumor marker has not abated, even to the present day. Its popularity as a fetal birth defect marker increased dramatically in the 1970s and 1980s and achieved prominence in the screening of neural tube defect and chromosomal anomalies. Although AFP is not employed as a biomarker for

Down syndrome in the first trimester, its association with Trisomy-21 in the second trimester provided the underpinnings for the advances in other MS marker development in first-trimester Down syndrome pregnancies.

The discoveries of discordant AFP levels correlated with perinatal distress and adverse pregnancy outcomes slowly emerged in reports emanating from the late 1980s–1990s. With each passing decade, the physiologic roles of AFP had gradually increased, and only scant attempts were made to merge those functions with the multitude of congenital malformations that had been reported. Still prominent is the long association of AFP with immune function, which is now beginning to come into greater prominence, suggesting a role of AFP in maintaining the fetal/placental unit in a controlled state of inflammation. In the future, we can expect the role of AFP in maintaining the fetus as an allograft in the mother's body to become more clear as its relationships to the cytokines and the natural killer receptors are unraveled.

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Table 4. Summary of Univariate Data Analysis Showing the Prediction of Severe Placental Complications in Women with Unexplained Combined AFP and/or hCG for Term Pregnancies[a]

Condition	Elevated MS-AFP + hCG		Elevated MS-AFP or hCG	
	RR	RR range	RR	RR range
1. Pregnancy-induced hypertension	2.17	1.34–3.52	1.41	1.20–1.66
2. Abruption placentae	2.90	0.91–9.23	1.60	1.01–2.53
3. Intrauterine growth retardation	4.70	2.43–9.07	1.59	1.16–2.17
4. Fetal death	16.16	6.77–38.55	5.01	2.88–8.71
5. Preterm birth	8.67	3.94–19.10	2.42	1.59–3.68
6. Premature rupture of membranes	3.60	2.14–6.08	1.68	1.38–2.06

[a] Data extracted from Chandra *et al.* (120). Note the advantage of combining MSAFP with hCG. Screening was performed in the second trimester for prediction in the third trimester and term. Relative risk (RR) of 1.0 indicates no risk.

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

II. Fetal Defect Associated:

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

III. Pregnancy Condition Associated

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

* Data was extracted and compiled from the following References:

1) Mizejewski, G.J, Exp. Biol. Med, 229:439, 2004
2) Mizejewski, G.J., Obstet & Gynecol Survey 58: 804, 2003
3) Walters, BNJ, Brit. J. Obstet. Gynecology 92: 341, 1985
4) Thomas, RL, Obstet Gynecol Surveys 45: 269, 1990

ABSTRACTS

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

(1) Title: Screening for fetal aneuploidy: is maternal age relevant?

Source: Clin Obstet Gynecol 55:217-225, 2012.

Authors: Hawk AF, Saller DN.

Abstract: The process of genetic screening has evolved from a simple notation of maternal age to a complex algorithm incorporating age, maternal serum screening, and sonographic findings. The extent to which each of these variables should contribute to the overall screening result is much debated and deserves continued research. It is clear that maternal age provides useful information when used as part of this equation but should not represent the sole screening modality. The use of genetic screening in a general population should be examined in terms of cost effectiveness without sacrificing patient preference and autonomy.

(2) Title: Safety and risks associated with screening for chromosomal abnormalities during pregnancy.

Source: Ceska Gynekol 77:236-241, 2012.

Authors: Dhaifalah I, Zapletalova J.

Abstract: OBJECTIVES: To assess the risk and safety of screening for chromosomal abnormalities during pregnancy through the assessment of exposure to ultrasound and the fetal loss rate after trans-abdominal amniocentesis (AMNIO) or chorionic villus sampling (CVS). METHODS: It is a retrospective analysis of the fetal loss rate following AMNIO and CVS as a diagnostic tests for chromosomal abnormalities during pregnancy in 1391 singleton pregnancies who attended our clinic from January 2005 to December 2009 (1038 AMNIO and 353 CVS). Pregnancies were followed up to ascertain the fetal loss rate after the procedure which was defined as intrauterine demise or miscarriage before the 24th week of gestation. Review of literature was the method used for assessing the safety of ultrasound during pregnancy. RESULTS: In the group of CVS about 86% of the cases were referred because of a positive screening (screening of chromosomal abnormalities on the bases nuchal translucency and biochemical serum markers (pregnancy-associated plasma protein-A and beta-human chorionic gonadotropin)), test with mean maternal age of 31.7 years and a miscarriage rate of 0.6%. In the group of AMNIO, 40% of the cases were referred because of a positive triple test in the second trimester (screening of chromosomal abnormalities on the bases of biochemical serum markers, alpha-fetoprotein, estriol and total human chorionic gonadotropin in the second trimester of pregnancy). Mean maternal age of 33.2 years and a miscarriage rate of 0.8%. The review of the literature indicates that due to limited amount of information available on some factors (gestational age, duration and number of exposure) during the pregnancy the patient should be exposed to the least ultrasound energy necessary to obtain desired information. CONCLUSION: The fetal loss rate in our study had confirmed that the risk of both procedures is comparable and is 0.8% for AMNIO and 0.6% for CVS. The lower miscarriage rate after CVS could be explained by the theory that placenta is a spongy organ that will expand easily after the procedure allowing better healing than if the needle had been passed through the amnion which is even more stretched by the amniotic fluid, but we are a wear of that the sample size is too small for such a conclusion. According to the available evidence, exposure to diagnostic ultrasonography during pregnancy appears to be safe.

(3) Title: Second trimester serum tests for Down's Syndrome screening.

Source: Cochrane Database Syst Rev 6:CD009925, 2012.

Authors: Alldred SK, Deeks JJ, Guo B, Neilson JP, Alfirevic Z.

Abstract: BACKGROUND: Down's syndrome occurs when a person has three copies of chromosome 21 - or the specific area of chromosome 21 implicated in causing Down's syndrome - rather than two. It is the commonest congenital cause of mental retardation. Noninvasive screening based on biochemical analysis of maternal serum or urine, or fetal ultrasound measurements, allows estimates of the risk of a pregnancy being affected and provides information to guide decisions about definitive testing. OBJECTIVES: To estimate and compare the accuracy of second trimester serum markers for the detection of Down's syndrome. SEARCH METHODS: We carried out a sensitive and comprehensive literature search of MEDLINE (1980 to May 2007), EMBASE (1980 to 18 May 2007), BIOSIS via EDINA (1985 to 18 May 2007), CINAHL via OVID (1982 to 18 May 2007), The Database of Abstracts of Reviews of Effectiveness (The Cochrane Library 2007, Issue 1), MEDION (May 2007), The Database of Systematic Reviews and Meta-Analyses in Laboratory Medicine (May 2007), The National Research Register (May 2007), Health Services Research Projects in Progress database (May 2007). We studied reference lists and published review articles. SELECTION CRITERIA: Studies evaluating tests of maternal serum in women at 14-24 weeks of gestation for Down's syndrome, compared with a reference standard, either chromosomal verification or macroscopic postnatal inspection. DATA COLLECTION AND ANALYSIS: Data were extracted as test positive/test negative results for Down's and non-Down's pregnancies allowing estimation of detection rates (sensitivity) and false positive rates (1-specificity). We performed quality assessment according to QUADAS criteria. We used hierarchical summary ROC meta-analytical methods to analyse test performance and compare test accuracy. Analysis of studies allowing direct comparison between tests was undertaken. We investigated the impact of maternal age on test performance in subgroup analyses. MAIN RESULTS: Fifty-nine studies involving 341,261 pregnancies (including 1,994 with Down's syndrome) were included. Studies were generally high quality, although differential verification was common with invasive testing of only high-risk pregnancies. Seventeen studies made direct comparisons between tests. Fifty-four test combinations were evaluated formed from combinations of 12 different tests and maternal age; alpha-fetoprotein (AFP), unconjugated oestriol (uE3), total human chorionic gonadotrophin (hCG), free beta human chorionic gonadotrophin (betahCG), free alpha human chorionic gonadotrophin (alphahCG), Inhibin A, SP2, CA125, troponin, pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PGF) and proform of eosinophil major basic protein (ProMBP).Meta-analysis of 12 best performing or frequently evaluated test combinations showed double and triple tests (involving AFP, uE3, total hCG, free betahCG) significantly outperform individual markers, detecting six to seven out of every 10 Down's syndrome pregnancies at a 5% false positive rate. Tests additionally involving inhibin performed best (eight out of every 10 Down's syndrome pregnancies) but were not shown to be significantly better than standard triple tests in direct comparisons. Significantly lower sensitivity occurred in women over the age of 35 years. Women who miscarried in the over 35 group were more likely to have been offered an invasive test to verify a negative screening results, whereas those under 35 were usually not offered invasive testing for a negative screening result. Pregnancy loss in women under 35 therefore leads to under ascertainment of screening results, potentially missing a proportion of affected pregnancies and affecting the accuracy of the sensitivity. AUTHORS' CONCLUSIONS: Tests involving two or more markers in combination with maternal age are significantly more sensitive than those involving one marker. The value of combining four or more tests or including inhibin have not been proven to show statistically significant improvement. Further study is required to investigate reduced test performance in women aged over 35 and the impact of differential pregnancy loss on study findings.

(4) Title: Elevated maternal serum alpha-fetoprotein level in a fetus with Beckwith-Wiedemann syndrome in the second trimester of pregnancy.

Source: J Prenat Med 6:7-9, 2012.

Authors: Guanciali-Franchi P, Di Luzio L, Iezzi I, Celentano C, Matarrelli B, Liberati M, Palka G.

Abstract: BACKGROUND: Beckwith-Wiedemann syndrome (BWS) is a rare disorder characterized by macrosomia, macroglossia, visceromegaly, and omphalocele and an increased risk of growing tumors. Prenatal and postnatal high levels of serum alpha-fetoprotein are associated with several diseases and neoplasms including hepatoblastomas and other hepatic tumors. The diagnosis of BWS is usually made in the postnatal period on the basis of physical exam features and hypermethylation of the H19 gene. CASE: A 30-year-old woman gravida 3, para 2, underwent maternal serum screening at 15 weeks' gestation. The screening was negative for Down's syn drome (risk 1/6085), but positive for NTDs. Further ultrasound examination at 20 and 30 weeks' evidenced a fetal overgrowth and a 3-D scan at 33 weeks' gestation presented a protruding tongue, and a fixed opened mouth caused by macroglossia. CONCLUSIONS: BWS was suspected on the basis of clinical features, and molecular analysis of critical region 11p15.5 revealing the hypermethylation of H19 gene supported the diagnosis.

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

(1) Title: A Case of Hereditary Persistence of alpha-Fetoprotein: Diagnostic Usefulness of the Subfraction Profile.

Source: Jpn J Clin Oncol 42:767-769, 2012.

Authors: Waseda Y, Tanaka H, Nakagomi K, Goto S, Ido A.

Abstract: alpha-Fetoprotein is a well-established tumor marker for non-seminomatous germ cell tumors. Elevated alpha-fetoprotein levels, however, result from a variety of clinical conditions. Hereditary persistence of alpha-fetoprotein is a rare benign disorder in which serum alpha-fetoprotein levels are persistently elevated, but there are no disabilities and symptoms. A 35-year-old man was diagnosed with pT1 testicular embryonal carcinoma. Post-orchiectomy alpha-fetoprotein levels remained persistently elevated without clinical or radiographic abnormalities. His mother's elevated alpha-fetoprotein levels confirmed the diagnosis of hereditary persistence of alpha-fetoprotein. Lens culinaris agglutinin-reactive alpha-fetoprotein fractions have been reported as a useful diagnostic marker for non-seminomatous germ cell tumors; in this patient, its measurement showed high non-reactive alpha-fetoprotein levels, which indicated the low probability of residual tumors. The present case represents the third case of hereditary persistence of alpha-fetoprotein in Japan, and the first in which the alpha-fetoprotein subfraction was evaluated.

(2) Title: Clinical analysis of childhood pancreatoblastoma arising from the tail of the pancreas.

Source: J Pediatr Hematol Oncol 34:e177-181, 2012.

Authors: Xu C, Zhong L, Wang Y, Wang W, Yang Z, Kang X, Wang C.

Abstract: Pancreatoblastoma is a rare pancreatic tumor. In this study, 3 cases of childhood pancreatoblastoma that arise from the tail of the pancreas were reported. Abdominal pain and vomiting were observed in 1 case considering the huge size of the tumor. The other 2 patients, who were previously well, complained of a mass in the abdomen after a casual physical examination. Elevated serum alpha-fetoprotein levels were noted in all cases. Imaging findings indicated a well-defined heterogeneous large mass in the left retroperitoneal space. Exploratory

laparotomy revealed a large mass, arising from the tail of the pancreas. Surgery alone with complete excision of the masses was performed. Immunohistochemical staining showed that only alpha-fetoprotein was positive in all cases. All of these 3 cases have a good outcome in the follow-up without adjuvant chemotherapy. These data suggest that the diagnosis of pancreatoblastoma is difficult and should be suspected at palpation of an abdominal mass. alpha-Fetoprotein may serve as a tumor marker for preoperative diagnosis and postoperative recurrence. Pancreatoblastoma arising from the tail of the pancreas is a curable tumor, and adjuvant chemotherapy may not be necessary if the tumor can be excised completely.

(3) Title: A case of yolk sac tumor of the vagina in an infant

Source: Arch Gynecol Obstet 285:1403-1405, 2012.

Authors: Arafah M, Zaidi SN.

Abstract: We report a case of a vaginal yolk sac tumor in a 5-month-old female infant who presented with short history of bleeding per vagina. Magnetic resonance imaging showed a mass occupying most of the vagina that had lobulated outlines and heterogeneous echo texture. The serum alpha-fetoprotein was elevated, and a biopsy revealed a vaginal yolk sac tumor. The patient was given six cycles of chemotherapy and continues to be disease-free on follow up. To preserve sexual and reproductive function, we encourage consideration of chemotherapy as a sole modality to treat this rare tumor.

(4) Title: Diagnostic utility and correlation of tumor markers in the serum and cerebrospinal fluid of children with intracranial germ cell tumors.

Source: Childs Nerv Syst 28:1017-1024, 2012.

Authors: Qaddoumi I, Sane M, Li S, Kocak M, Pai-Panandiker A, Harreld J, Klimo P, Wright K, Broniscer A, Gajjar A.

Abstract: PURPOSE: In order to predict whether tumor markers assist in the histopathologic diagnosis of germ cell tumors (GCTs), we analyzed the correlation of beta human chorionic gonadotropin (betahCG) and alpha-fetoprotein (AFP) in serum and cerebrospinal fluid (CSF) samples at baseline and subsequent follow-up examinations. METHOD: A retrospective study of patients diagnosed with intracranial GCTs between July 1985 and February 2011 at our institution was conducted to review clinical, surgical, radiological, laboratory, and histopathologic data. RESULTS: Of the 67 patients eligible for the study, 42 had germinomas and 25 non-germinomatous GCTs. At baseline, serum and CSF AFP agreed in 97.9 % of patients (Cohen's Kappa 0.93). Baseline betahCG samples agreed in only 72.5 % of patients (Cohen's Kappa 0.46). In most cases, values were higher in serum for AFP and in CSF for betahCG. ROC curves estimated from logistic regression model indicated that CSF and serum samples had almost equal diagnostic utility, and the DeLong test showed that the difference in area under curves was not statistically significant. During follow-up (185 paired CSF and serum values from 43 patients), 90.3 % of AFP values correlated between CSF and serum (Cohen's Kappa 0.22, showing fair agreement). For betahCG, 96.2 % of values agreed in serum and CSF (Cohen's Kappa 0.61). CONCLUSIONS: In some patients, intracranial GCTs can be diagnosed based solely upon positive serum AFP values. In addition, marker values from serum only may be sufficient to predict tumor relapse at interval follow-up examinations.

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 34:142-153, 2012.

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.

(2) Title: Abnormal second-trimester serum analytes are more predictive of preterm preeclampsia.

Source: Am J Obstet Gynecol, 2012.

Authors: Olsen RN, Woelkers D, Dunsmoor-Su R, Lacoursiere DY.

Abstract: OBJECTIVE: We sought to determine the association of abnormal second-trimester serum analytes with early preterm preeclampsia. STUDY DESIGN: We conducted a retrospective study of 7767 subjects undergoing second-trimester serum aneuploidy screening. Values of maternal serum alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (hCG), and inhibin (INH) were calculated as multiples of the median (MoM) and evaluated by gestational age at delivery and occurrence of preeclampsia. RESULTS: Of 459 (6.5%) cases of preeclampsia, 65 (14%) delivered <34 weeks and 394 (86%) delivered >34 weeks. Elevated AFP, hCG, and INH >2 MoM were associated with preeclampsia, and the odds ratio was higher for the development of preeclampsia <34 weeks than >34 weeks (odds ratio, 8.04 vs 2.91 for AFP, 3.6 vs 2 for hCG, and 4.17 vs 3.08 for INH, P < .001 for all). The higher the MoM for each analyte the greater the likelihood of preeclampsia. CONCLUSION: Elevated AFP, hCG, and INH levels >2 MoM are associated with developing early preeclampsia, and the more elevated they are, the higher the likelihood.

(3) Title: [Second trimester screening for trisomy 21 using ADAM12-S as a maternal serum marker].

Source: Zhonghua Yi Xue Yi Chuan Xue Za Zhi 29:314-318, 2012.

Authors: Jiang T, Lv L, Yang B, Sun YJ, Zhang XJ, Sun Y, Xu QJ, Xu ZF.

Abstract: OBJECTIVE: To investigate the value of a disintegrin and metalloproteinase 12 secreting form (ADAM12-S) as a maternal serum marker in second trimester screening for trisomy 21 (Down syndrome, DS), and to develop an appropriate prenatal DS screening protocol. METHODS: Serum samples were collected from 53 pregnant women carrying a trisomy 21 fetus and 621 pregnant women with matched gestational age and weight carrying a healthy fetus. ADAM12-S concentrations were determined with a time-resolved fluorescence immunoassay (TRFIA). Curve fitting by weighted regression and other statistical methods were conducted, and the model was optimized for prenatal trisomy 21 screening program in second trimester. ADAM12-S alone or in combination with other two- or three-combination test was selected as a serum marker for prenatal second-trimester screening of trisomy 21 by calculation of detection rate (DR) and false positive rate (FPR). RESULTS: By comparison, the median multiple of the median (MoM) value of ADAM12-S in DS pregnancy group was higher than that of the control group ($P< 0.01$). When FPR = 5%, the DR of ADAM12-S was 28.3%, and the positive and negative likelihood ratios were 5.66 and 0.75, respectively. The DR of three-combination test of ADAM12-S, alpha-fetoprotein (AFP) and free beta subunit of human chorionic gonadotropin (beta-HCG) has increased to 52.80% from 39.62% of the conventional two-combination test (AFP and free beta-HCG). For women with a risk between 1/300 and 1/1000 by two-combination test for DS, the DR has increased from 39.62% to 47.12%, but FPR only increased by 0.8% after adding ADAM12-S as a maternal serum marker. CONCLUSION: Considering the increased DR of pregnancies with a risk between 1/300 and 1/1000 in second trimester, ADAM12-S may provide a feasible maternal serum maker when combined with AFP and free beta-HCG. The cost-effectiveness ratio is reasonable.

(4) Title: Impact of inherited thrombophilias on first and second trimester maternal serum markers for aneuploidy.

Source: J Matern Fetal Neonatal Med, 2012.

Authors: Derbent AU, Yanik FF, Gumus, II, Simavli S, Turhan NO.

Abstract: Objective: To evaluate first and second-trimester maternal serum markers in pregnancies complicated with inherited thrombophilias. Methods: A case-control study was conducted in 50 pregnancies complicated with hereditary thrombophilia and 100 control pregnancies. Results: Each woman with inherited thrombophilia received low molecular weight heparin (LMWH) throughout her pregnancy. Gravidity, parity, number of first-trimester and second-trimester abortions, and rate of adverse pregnancy outcomes (APO) were significantly higher in the thrombophilia group compared to the control group ($P < 0.001$ for all). Among the thrombophilia group median values of pregnancy associated placental protein-A (PAPP-A) (0.6 vs. 0.9; $P < 0.001$) and free beta-human chorionic gonadotropin (beta-hCG) (0.9 vs. 1.1; $P = 0.001$) in the first trimester; median values of alpha-fetoprotein (AFP) (0.7 vs. 1.1; $P = 0.027$), unconjugated estriol 3 (uE3) (0.9 vs. 1.1; $P < 0.001$), and hCG (0.7 vs. 1.2; $P < 0.001$) in the second trimester were significantly lower with respect to control pregnancies. Multivariate analysis revealed that low uE3 and hCG levels were independently associated with APO. Conclusion: Pregnant women with hereditary thrombophilias, all of whom were treated with LMWH, had decreased levels of all first and second trimester serum markers. In addition, levels of hCG and uE3 in the second trimester could independently predict placenta-related disorders and adverse outcomes in these patients.

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

(1) Title: Elevated midtrimester alpha-fetoprotein and delivery markers of inflammation in a preterm population.

Source: J Matern Fetal Neonatal Med, 2012.

Authors: Ho M, Faye-Petersen OM, Goldenberg RL, Carlo WA, Cliver SP, Andrews WW.

Abstract: Objective: Determine whether elevated second trimester maternal serum alpha-fetoprotein (AFP) is associated with clinical and histopathologic markers of inflammation at preterm delivery. Methods: 105 women <32 weeks' gestation were included. AFP levels were dichotomized at 2.0 multiples of the median (MoM). Rates of neonatal morbidities, clinical chorioamnionitis, cord blood IL-6 level, and placental inflammatory findings were compared. Results: Thirteen (12.4%) had elevated AFP. Fewer women with AFP >/=2 MoM had histologic placental or membrane rupture site inflammation, funisitis, or placental culture positive for Mycoplasma and Ureaplasma species, compared to those with normal AFP. Neonatal death was increased in the elevated AFP group (23.1% vs. 2.27%, RR 10.6). Elevated AFP was associated with a nonsignificant increase in indicated birth (54% vs. 35%; p = 0.225). Virtually all inflammatory findings were confined to the spontaneous delivery group. Conclusion: Elevated midtrimester AFP conveyed significant risk of neonatal death, but was negatively associated with clinical or histopathologic inflammation in preterm infants.

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

Source: Pediatr Res 71:399-406, 2012.

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.

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

Source: J Obstet Gynaecol Can 33:1218-1222, 2011.

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.

(4) Title: Does low molecular weight heparin influence the triple test result in pregnant women with thrombophilia?

Source: Isr Med Assoc J 14:247-250, 2012.

Authors: Wiener Y, Frank M, Neeman O, Kurzweil Y, Bar J, Maymon R.

Abstract: BACKGROUND: The triple test serum markers for Down's syndrome screening may be altered because of various conditions other than chromosomal trisomies. OBJECTIVES: To assess the profile of mid-trimester triple test serum markers in a cohort of women treated with low molecular weight heparin (LMWH) for thrombophilia since the first trimester. METHODS: Women with inherited or acquired thrombophilia treated with LMWH prior to 12 weeks gestation were followed between October 2006 and September 2009 at our obstetric outpatient clinic. The second-trimester screening test for Down syndrome was calculated from the combination of triple serum markers and maternal age, and expressed as a multiple of the gestation-specific normal median (MoM). Reference MoM values were calculated from the local population. Data on pregnancy outcome were obtained from patient records. RESULTS: The median human chorionic gonadotropin (hCG) level of women with inherited thrombophilia was 0.87 MoM, compared to 0.99 MoM in controls (P = 0.038) and compared to 1.355 MoM in women with acquired thrombophilia (P = 0.034). In contrast, alpha-fetoprotein MoMs did not differ significantly between women with inherited and women with acquired thrombophilia (0.88 vs. 0.99 MoM, P = 0.403). CONCLUSIONS: The triple test serum markers may be altered in thrombophilia patients treated with LMWH. Clinicians should consider offering these patients the first-trimester nuchal translucency test and other sonographic markers that are probably unaffected by the underlying maternal disease and/or treatment modality.

E) Abstracts of New Assay Methodologies:

(1) Title: Quantum-dot-based homogeneous time-resolved fluoroimmunoassay of alpha-fetoprotein.

Source: Anal Chim Acta 741:100-105, 2012.

Authors: Chen MJ, Wu YS, Lin GF, Hou JY, Li M, Liu TC.

Abstract: Quantum dots (QDs) with novel photoproperties are not widely used in clinic diagnosis, and homogeneous time-resolved fluorescence assays possess many advantages over current methods for alpha-fetoprotein (AFP) detection. A novel QD-based homogeneous time-resolved fluorescence assay was developed and used for detection of AFP, a primary marker for many cancers and diseases. QD-doped carboxyl-modified polystyrene microparticles (QPs) were prepared by doping oil-soluble QDs possessing a 605nm emission peak. The antibody conjugates (QPs-E014) were prepared from QPs and an anti-AFP monoclonal antibody, and luminescent terbium chelates (LTCs) were prepared and conjugated to a second anti-AFP monoclonal antibody (LTCs-E010). In a double-antibodies sandwich structure, QPs-E014 and LTCs-E010 were used for detection of AFP, serving as energy acceptor and donor, respectively, with an AFP bridge. The results demonstrated that the luminescence lifetime of these QPs was sufficiently long for use in a time-resolved fluoroassay, with the efficiency of time-resolved Forster resonance transfer (TR-FRET) at 67.3% and the spatial distance of the donor to acceptor calculated to be 66.1A. Signals from TR-FRET were found to be proportional to AFP concentrations. The resulting standard curve was logY=3.65786+0.43863.logX (R=0.996) with Y the QPs fluorescence intensity and X the AFP concentration; the calculated sensitivity was 0.4ngmL(-1). By assaying test samples against the standard curve, the coefficient of variations was <5%, indicating that QDs were suitable for this homogenous time-resolved fluoroimmunoassay. This work extended the potential applications of QDs in future homogeneous analytical bioassays. In the coming research, hepatitis B surface antigen, another primary marker for hepatocellular carcinoma, will be studied for practical detection using a QD-based homogenous multiplex fluoroimmunoassay.

(2) Title: Electrochemiluminescence immunosensor based on graphene-CdS quantum dots-agarose composite for the ultrasensitive detection of alpha fetoprotein.

Source: Talanta 89:27-32, 2012.

Authors: Guo Z, Hao T, Duan J, Wang S, Wei D.

Abstract: A novel strategy for the enhancement of electrochemiluminescence (ECL) was developed by combining CdS quantum dots (QDs), graphene (G) and agarose. This enhanced ECL was exploited to develop a label-free ECL immunosensor for the ultrasensitive detection of alpha fetoprotein (AFP). The novel G-CdS QDs-agarose composite was first coated on the glass carbon electrode surface to form a robust film, which exhibited high ECL intensity, good biocompatibility and high stability. After that 3-aminopropyl-triethoxysilane (APS), as a binding linker, was conjugated to the G-CdS QDs-agarose composite film on the electrode, the ECL signal was significantly enhanced. The fabrication of ECL immunosensor was successfully completed by immobilizing the AFP-antibody (Ab) onto the electrode through glutaric dialdehyde (GLD). The specific immunoreaction between AFP and antibody resulted in the decrease in ECL intensity and the intensity decreased linearly with the logarithm of AFP concentration in the range of 0.0005-50 pg mL(-1) with a detection limit of 0.2 fg mL(-1). The immunosensor exhibits high sensitivity, specificity, stability, reproducibility and good regeneration, thus has the potential to be used in clinical application. Besides, the highly enhanced ECL from the G-CdS QDs-agarose composite film opened new avenues to apply graphene and QDs ECL in analytical systems and ECL biosensors.

(3) Title: Simultaneous electrochemical immunoassay using CdS/DNA and PbS/DNA nanochains as labels.

Source: Biosens Bioelectron, 2012.

Authors: Kong FY, Xu BY, Xu JJ, Chen HY.

Abstract: An electrochemical method for the simultaneous detection of two different tumor markers, carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP), in one-pot, using CdS/DNA and PbS/DNA nanochains as labels was developed. Herein, magnetic beads (MBs) as bimolecule

immobilizing carriers, were used for co-immobilization of primary anti-CEA and anti-AFP antibodies. The distinguishable signal labels were synthesized by in situ growth of CdS and PbS nanoparticles on DNA chains, respectively, which were further employed to label the corresponding secondary antibodies. A sandwich-type immunoassay format was formed by the biorecognition of the antigens and corresponding antibodies. The assay was based on the peak currents of Cd(2+) and Pb(2+) dissolved from CdS and PbS nanoparticles by HNO(3) using square wave stripping voltammetry. Experimental results show that the multiplexed electrochemical immunoassay has enabled the simultaneous monitoring of CEA and AFP in a single run with wide working ranges of 0.1-100ngmL(-1) for CEA and 0.5-200ngmL(-1) for AFP. The detection limits reach to 3.3pgmL(-1) for CEA and 7.8pgmL(-1) for AFP.

F) Special Abstract Selection:

(1) Title: Predictors of Poor Perinatal Outcome following Maternal Perception of Reduced Fetal Movements - A Prospective Cohort Study.

Source: PLoS One 7:e39784, 2012.

Authors: Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, Kroll J, Jones RL, Sibley CP, Froen JF, Heazell AE.

Abstract: BACKGROUND: Maternal perception of reduced fetal movement (RFM) is associated with increased risk of stillbirth and fetal growth restriction (FGR). RFM is thought to represent fetal compensation to conserve energy due to insufficient oxygen and nutrient transfer resulting from placental insufficiency. OBJECTIVE: To identify predictors of poor perinatal outcome after maternal perception of reduced fetal movements (RFM). DESIGN: Prospective cohort study. METHODS: 305 women presenting with RFM after 28 weeks of gestation were recruited. Demographic factors and clinical history were recorded and ultrasound performed to assess fetal biometry, liquor volume and umbilical artery Doppler. A maternal serum sample was obtained for measurement of placentally-derived or modified proteins including: alpha fetoprotein (AFP), human chorionic gonadotrophin (hCG), human placental lactogen (hPL), ischaemia-modified albumin (IMA), pregnancy associated plasma protein A (PAPP-A) and progesterone. Factors related to poor perinatal outcome were determined by logistic regression. RESULTS: 22.1% of pregnancies ended in a poor perinatal outcome after RFM. The most common complication was small-for-gestational age infants. Pregnancy outcome after maternal perception of RFM was related to amount of fetal activity while being monitored, abnormal fetal heart rate trace, diastolic blood pressure, estimated fetal weight, liquor volume, serum hCG and hPL. Following multiple logistic regression abnormal fetal heart rate trace (Odds ratio 7.08, 95% Confidence Interval 1.31-38.18), (OR) diastolic blood pressure (OR 1.04 (95% CI 1.01-1.09), estimated fetal weight centile (OR 0.95, 95% CI 0.94-0.97) and log maternal serum hPL (OR 0.13, 95% CI 0.02-0.99) were independently related to pregnancy outcome. hPL was related to placental mass. CONCLUSION: Poor perinatal outcome after maternal perception of RFM is closely related to factors which are connected to placental dysfunction. Novel tests of placental function and associated fetal response may provide improved means to detect fetuses at greatest risk of poor perinatal outcome after RFM.

(2) Title: Different median levels of serum triple markers in the second trimester of pregnancy in a Thai Ethnic Group.

Source: J Obstet Gynaecol Res 38:686-691, 2012.

Authors: Wanapirak C, Sirichotiyakul S, Luewan S, Yanase Y, Traisrisilp K, Tongsong T.

Abstract: AIM: The aim of the present study was to establish Thai-specific reference ranges of triple markers for fetal Down syndrome as a function of gestational age as well as weight correction

models and to compare the false positive rates when using Thai-specific model relative to Caucasian-specific model. MATERIAL AND METHODS: A total of 993 normal Thai pregnant women were determined for mid-trimester serum levels of alpha-fetoprotein (AFP), free-beta human chorionic gonadotropin (hCG), and unconjugated estriol (uE3), using DefiaXpress system (Perkin Elmer, Waltham, MA, USA). RESULTS: The models of Thai-specific medians for AFP, b-hCG, and uE3, as well as the models for weight correction were derived and the normal reference ranges were constructed. The best fitted equation for AFP, b-hCG and uE3 are as follows: predicted median = 2.675 x 10((0.153 x GA in week)), r = 0.979; 10((-0.717 + 57.487/GA in week)) , r = 0.991; and 10((5.678-69.346/GA) (in) (week)), r = 0.99, respectively. The models were properly applied to another group of 302 Thai women, signifying that they were reliable models. The weight-adjusted gestation-specific medians derived from Caucasian models were significantly higher than those based on Thai models and the false positive rate could be reduced from 10 to 7.1% when Thai models were applied. CONCLUSION: Thai reference ranges of triple screen markers as a function of gestational age as well as weight correction models have been established. The Caucasian reference range, even after weight correction, gives a positive rate that is much higher than that it should be, strongly suggesting the need for ethnicity-specific medians.

(3) Title: Hepatitis B virus surface antigen-negative and hepatitis C virus antibody-negative hepatocellular carcinoma: Clinical characteristics, outcome, and risk factors for early and late intrahepatic recurrence after resection.

Source: Cancer, 2012 Jun 26.

Authors: Li T, Qin LX, Gong X, Zhou J, Sun HC, Qiu SJ, Ye QH, Wang L, Fan J.

Abstract: BACKGROUND: Although the incidence of hepatitis B virus surface antigen (HBsAg)-negative/hepatitis C virus antibody (HCVAb)-negative hepatocellular carcinoma (NBNC-HCC) is gradually increasing, it has been mostly ignored in previous studies. The objective of this exploratory study was to investigate the clinicopathologic characteristics and prognostic factors that influence recurrence and survival in patients with NBNC-HCC. METHODS: A retrospective analysis was performed of 675 patients with NBNC-HCC and 3529 patients with HBsAg-positive/HCVAb-negative HCC (BNC-HCC) who underwent curative resection between 1997 and 2009. Intrahepatic recurrences were classified into early (</=1 year) and late (>1 year) recurrences. Multivariate competing risks analyses with Bonferroni correction were used to evaluate independent prognostic factors. RESULTS: There were no significant differences between the NBNC-HCC and BNC-HCC groups regarding overall survival, cumulative incidence of HCC-specific death, and recurrence. However, the patients with NBNC-HCC were much older ($P < .001$), were associated less often with cirrhosis or elevated alpha-fetoprotein levels ($P < .001$), and had a much lower ratio of men to women ($P < .001$). NBNC-HCC tumors were larger ($P < .001$), but were involved less often with vascular invasion ($P = .004$). Women, serum gamma-glutamyl transpeptidase level, tumor size, tumor capsule, and tumor differentiation were identified as independent risk factors for HCC-specific survival in patients with NBNC-HCC. The cumulative incidence of HCC-specific death for women with NBNC-HCC was significantly greater than for men with NBNC-HCC ($P < .001$).Tumor capsule and vascular invasion were identified as independent risk factors for early recurrence of NBNC-HCC, whereas tumor differentiation was identified as the only significant risk factor for late recurrence. CONCLUSIONS: Patients who had NBNC-HCC had characteristics and prognostic factors that differed from those in patients who had BNC-HCC. Women with NBNC-HCC should be more closely monitored, and it may be worthwhile to evaluate estrogen administration for the maintenance of sex hormone balance and to improve these poor outcomes. Cancer 2012. (c) 2012 American Cancer Society.

(4) Title: Method comparison for determination of the tumor markers AFP, CEA, PSA and free PSA between Immulite 2000 XPI and Dimension Vista 1500.

Source: Clin Lab 58:97-105, 2012.

Authors: Zur B, Holdenrieder S, Walgenbach-Brunagel G, Albers E, Stoffel-Wagner B.

Abstract: BACKGROUND: For the Luminescent Oxygen Channeling Immunoassay (LOCI) technology as established for Dimension Vista 1500, assays have been developed for the serum tumor markers AFP, CEA, PSA and free PSA. We performed a method analysis for these parameters using the Immulite 2000 XPI. METHODS: Determination of within-day and total imprecision of the methods was carried out according to CLSI guidelines with three serum pools. In addition, parallel measurements were performed with both systems in 1,871 routine serum samples and correlations were calculated. RESULTS: Calculated total imprecision of the three serum pools for AFP was 3.8 - 4.3%, for CEA 3.3 - 4.3%, for tPSA 3.6 - 4.0% and for fPSA it was 3.5 - 8.2%. Correlations of these markers across the entire value range were very good with the following correlation coefficients: 0.997 for AFP, 0.996 for CEA, 0.971 for tPSA and 0.988 for fPSA. While values for AFP and tPSA from both methods were comparable (slopes 1.02 and 1.01), lower values were measured for CEA and fPSA with the Dimension Vista (slopes 0.83 and 0.91). For AFP, a sample cluster with considerably higher values than with Dimension Vista was observed in the lower measurement range (< 20 ng/mL). CONCLUSIONS: The assays for AFP, CEA, tPSA and fPSA, as developed with the LOCI technology for the Dimension Vista, show good comparability with results obtained from the Immulite 2000 XPI. However, lower measurement ranges for CEA and fPSA as well as individual divergences, especially with AFP, must be taken into consideration in the event of method changeover.

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

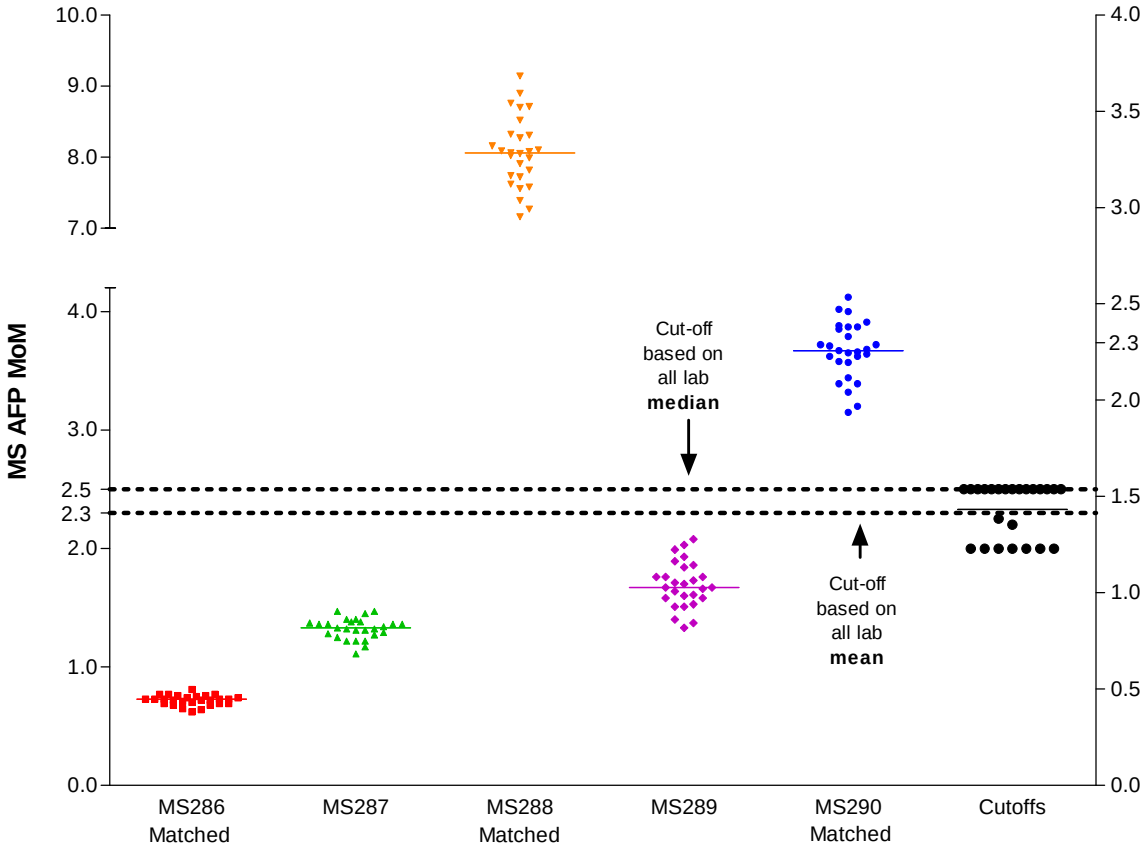


Figure 2

Amniotic Fluid AFP MoM

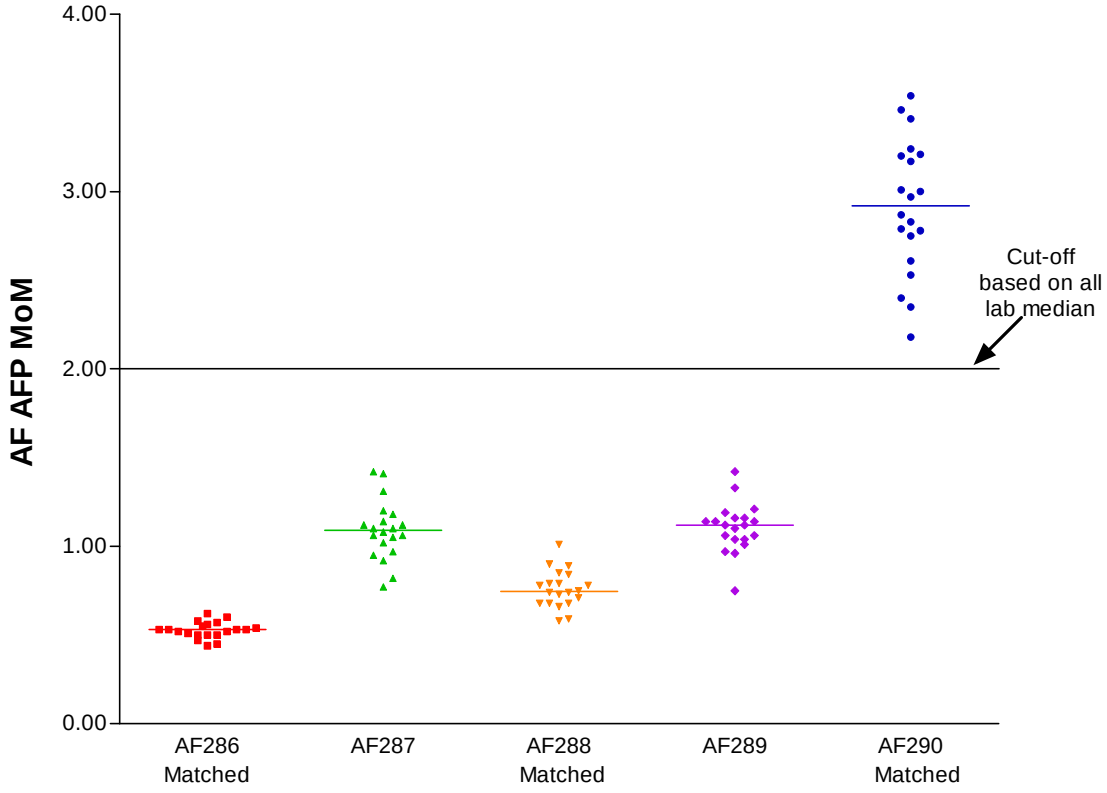


Figure 3

Graphic Distribution of Second Trimester Neural Tube Defect Risk Estimates

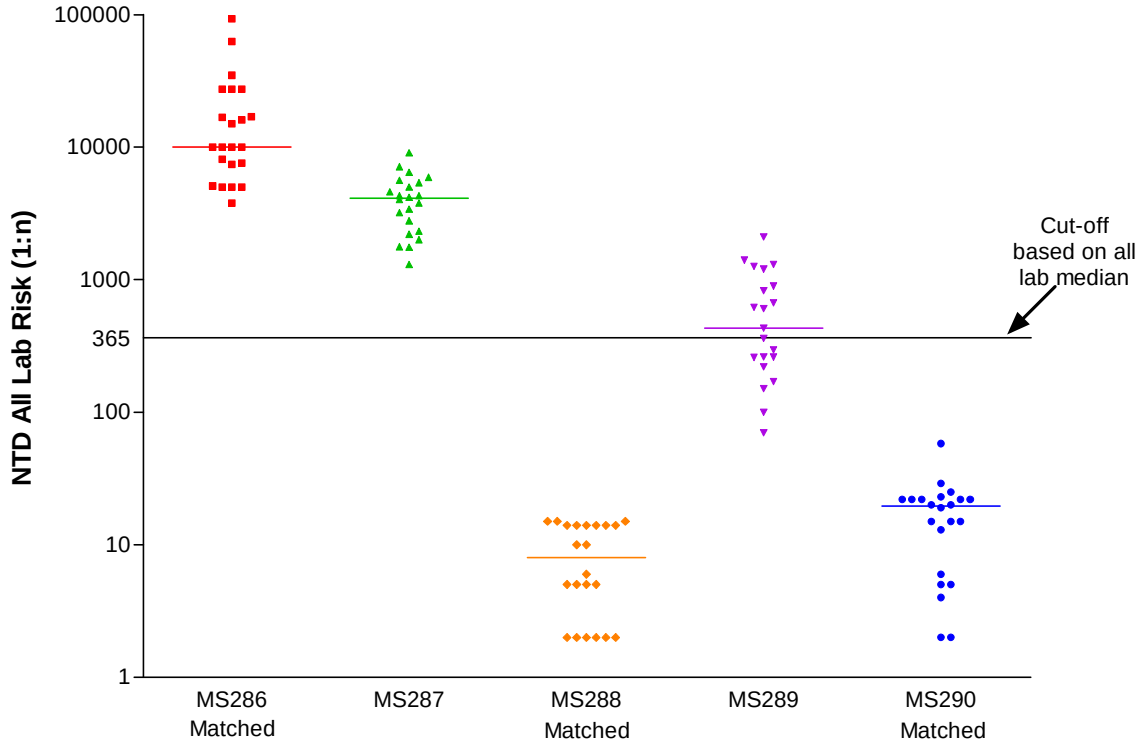


Figure 4

Graphic Distribution of Second Trimester Trisomy 18 Risk Estimates

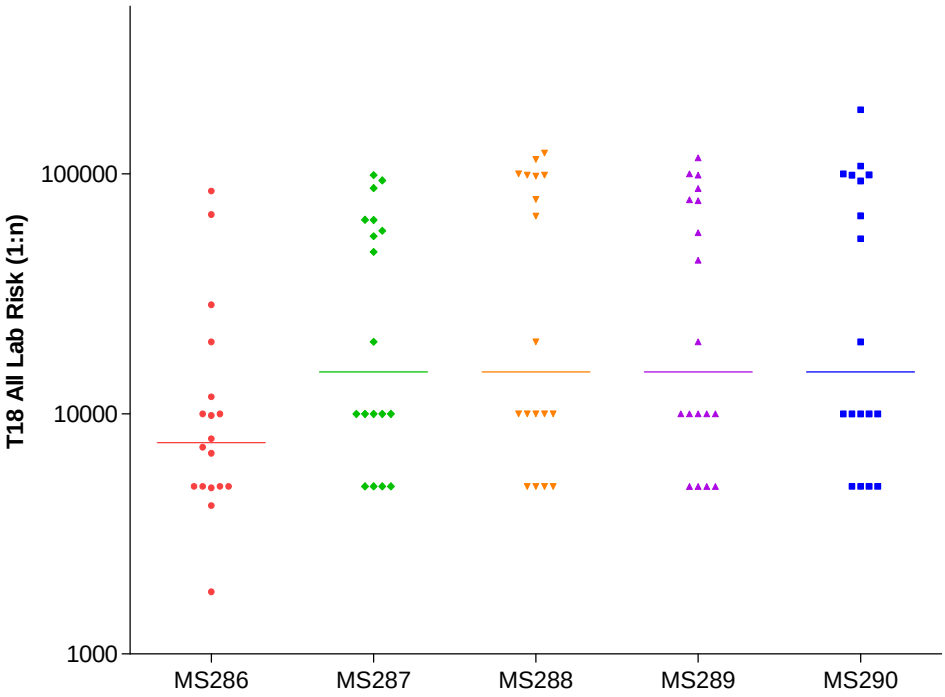


Figure 5

Graphic Distribution of Second Trimester Trisomy 21 Triple Risk Estimates

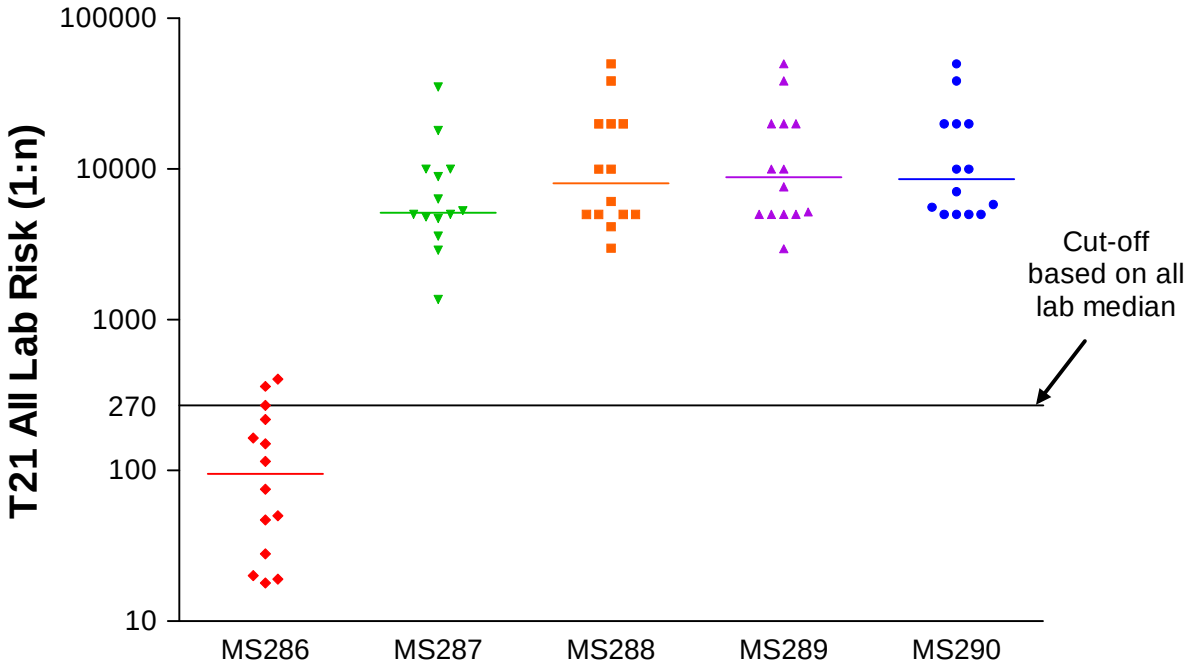
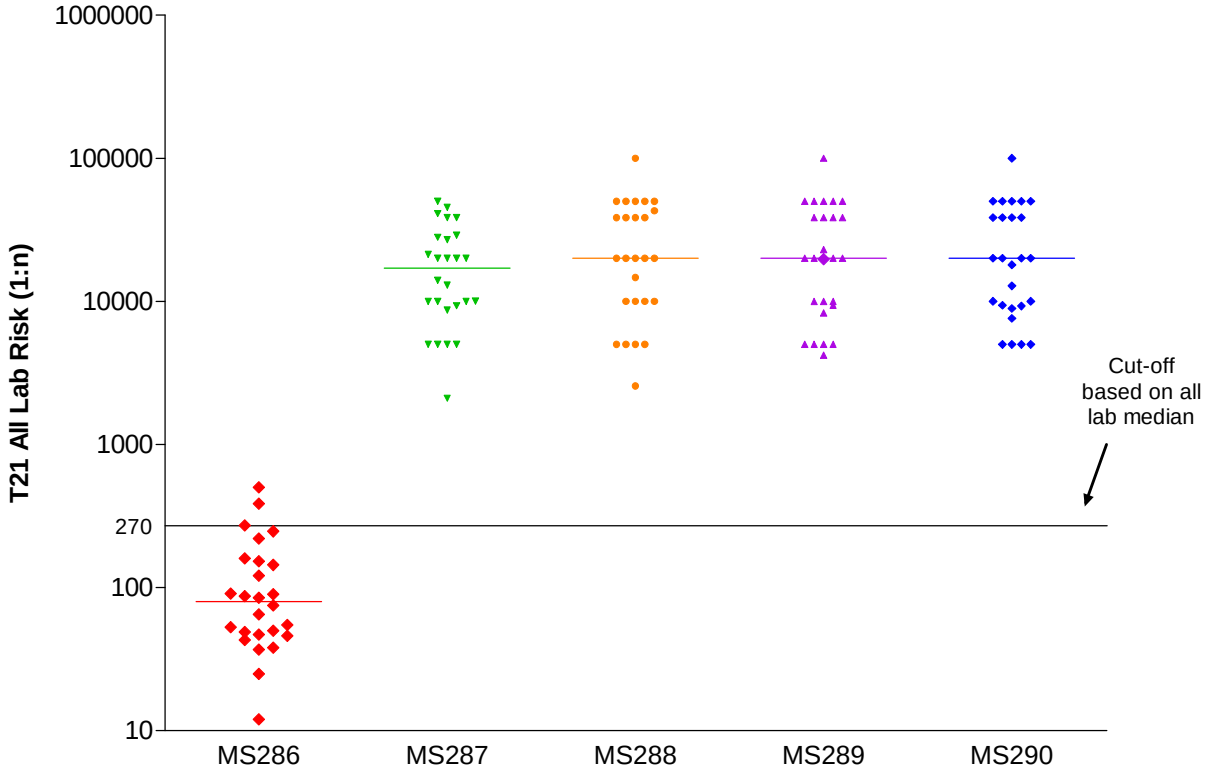


Figure 6

Graphic Distribution of Second Trimester Trisomy 21 Quadruple Risk Estimates



NYS FEDM PT 9/12
Second Trimester

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

Figure 7A

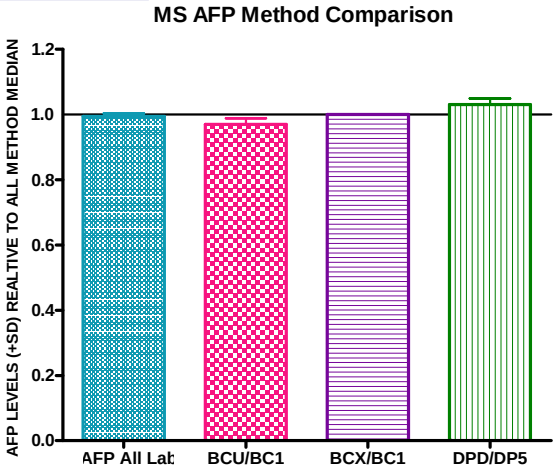


Figure 7B

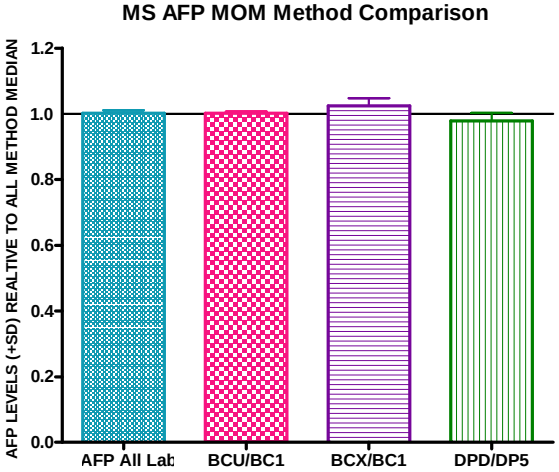


Figure 7C

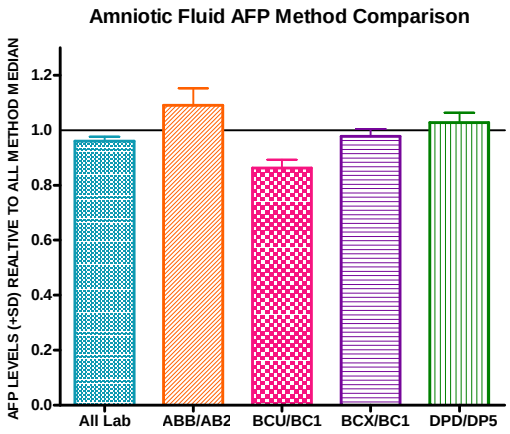


Figure 7D

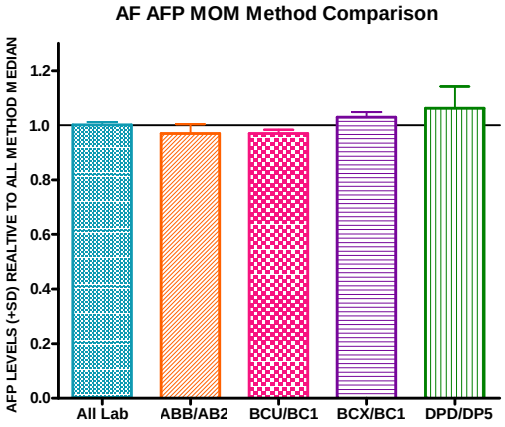


Figure 8A

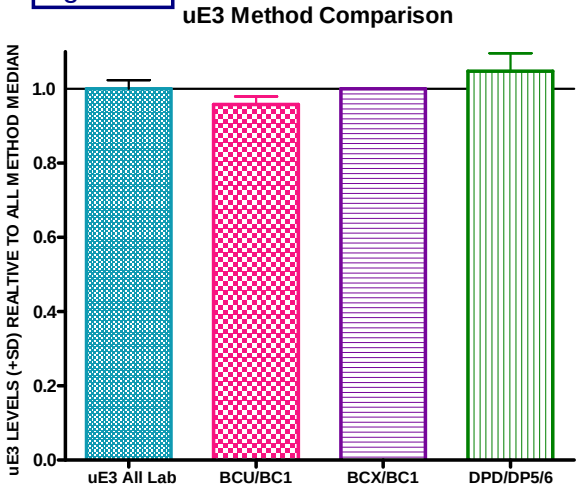
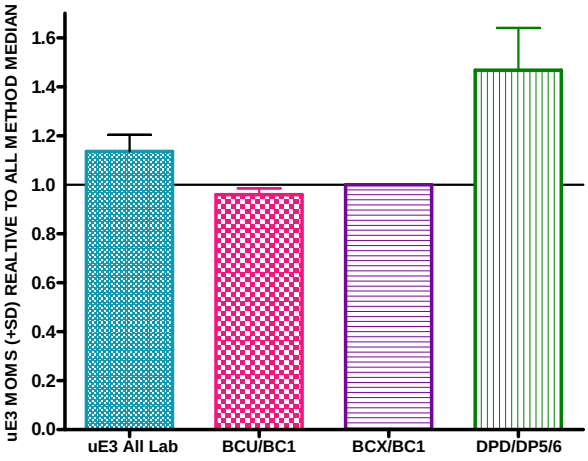


Figure 8B



NYS FEDM PT 9/12
Second Trimester

Figure 9A

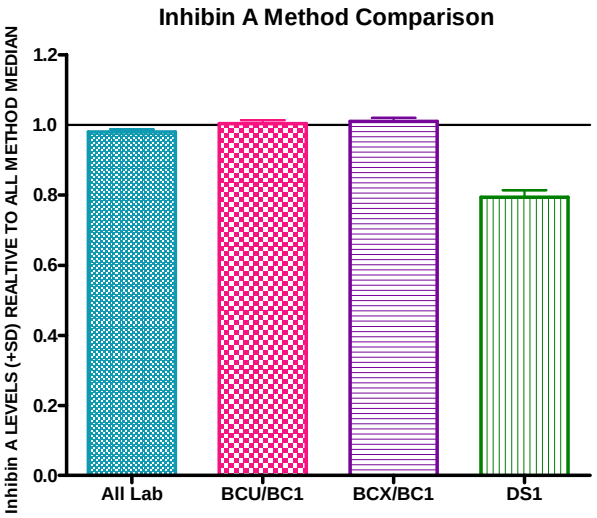


Figure 9B

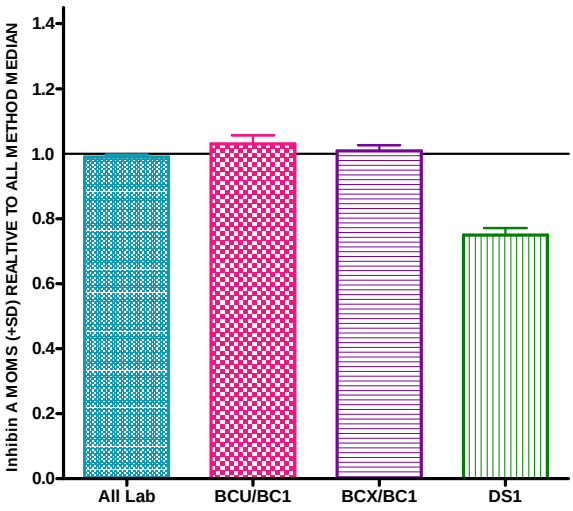


Figure 10A

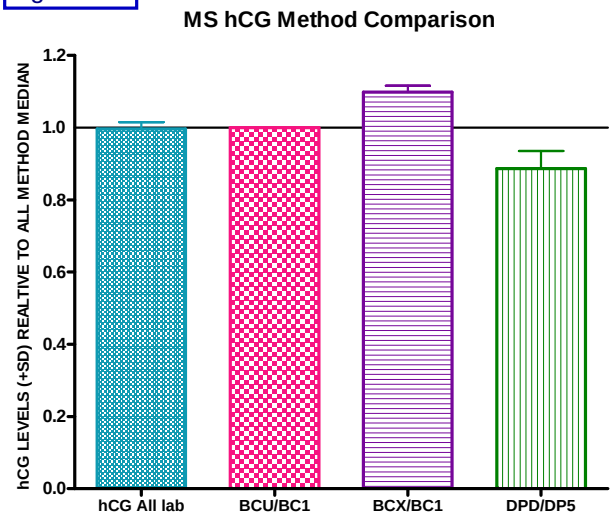
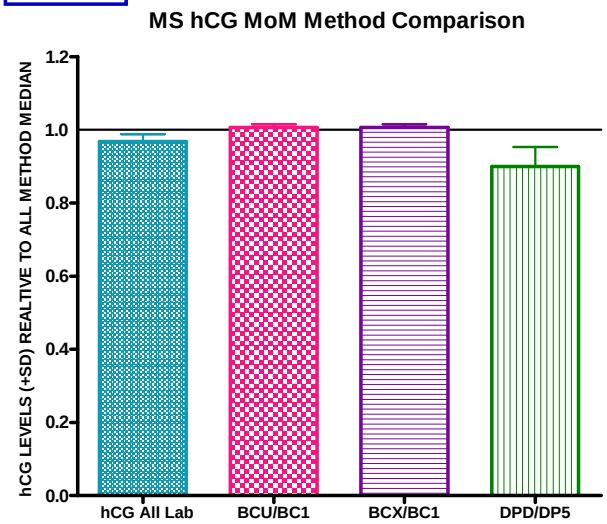


Figure 10B



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

NYS FEDM PT 9/12
First Trimester

Figure 11A

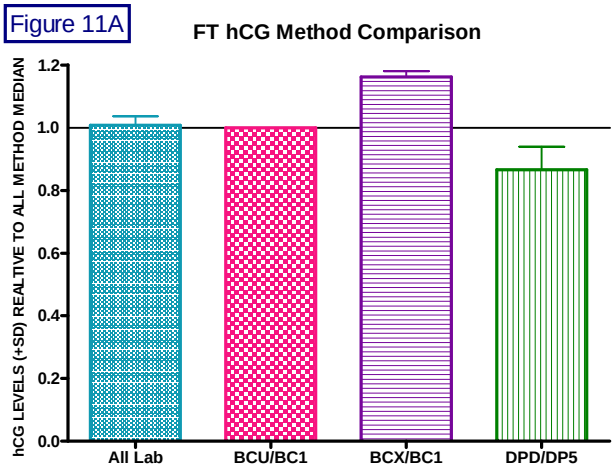


Figure 11B

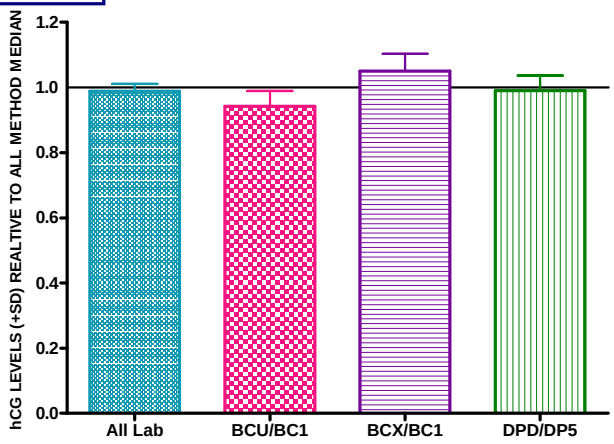


Figure 12A

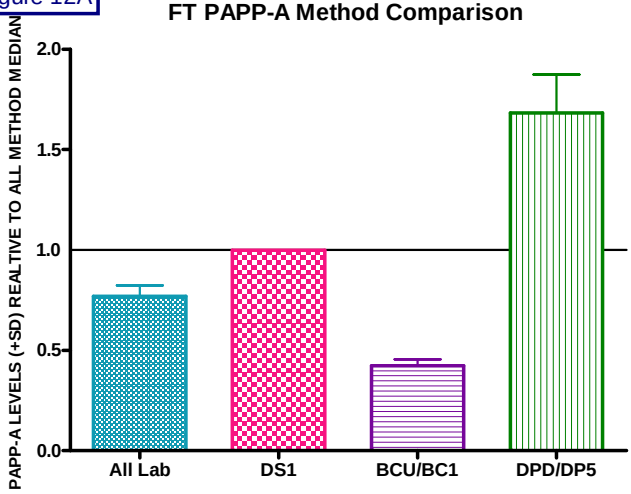
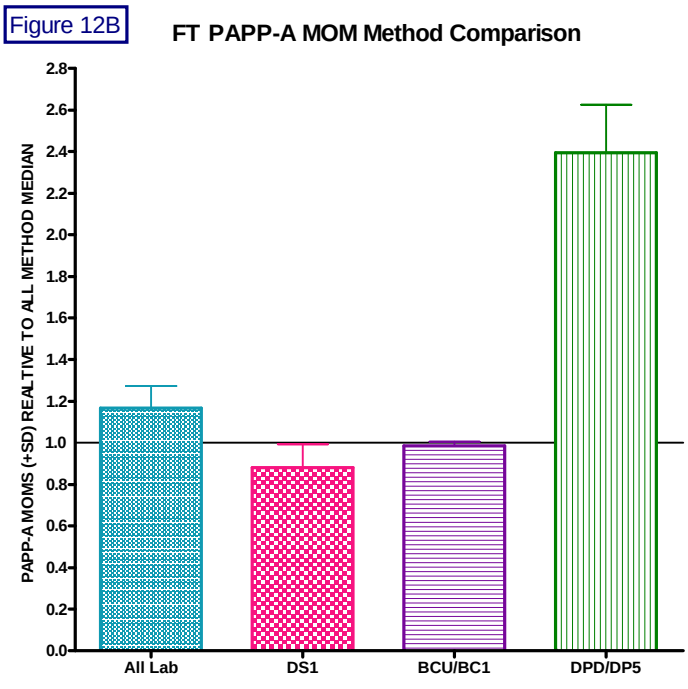


Figure 12B



ABB/AB1 = Abbott Asxym
BCX/BC1 = Beckman Access/2
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DS1 = Diagnostic Systems Labs

Figure 13

Graphic Distribution of First Trimester
Trisomy 21 Risk Estimates

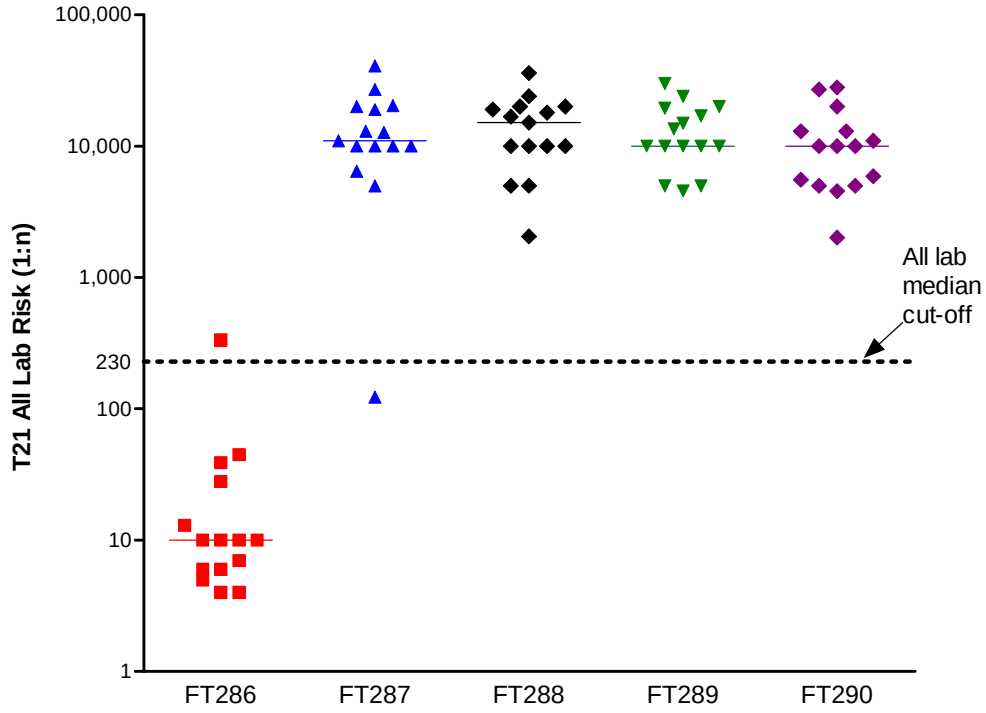


Figure 14

Graphic Distribution of First Trimester
Trisomy 18 Risk Estimates

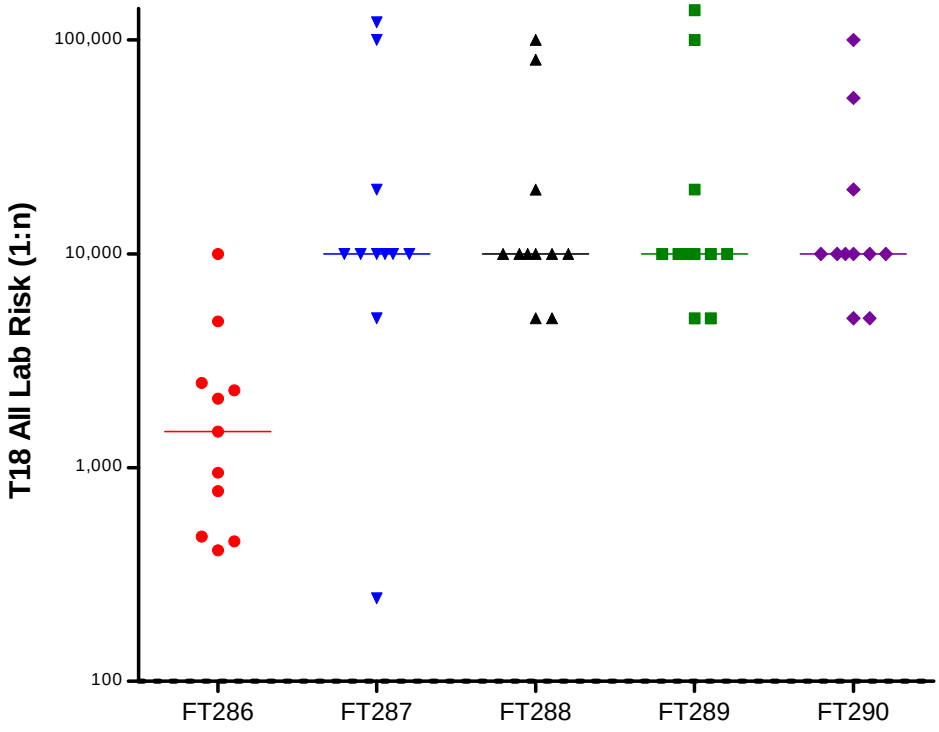


Fig. 15A

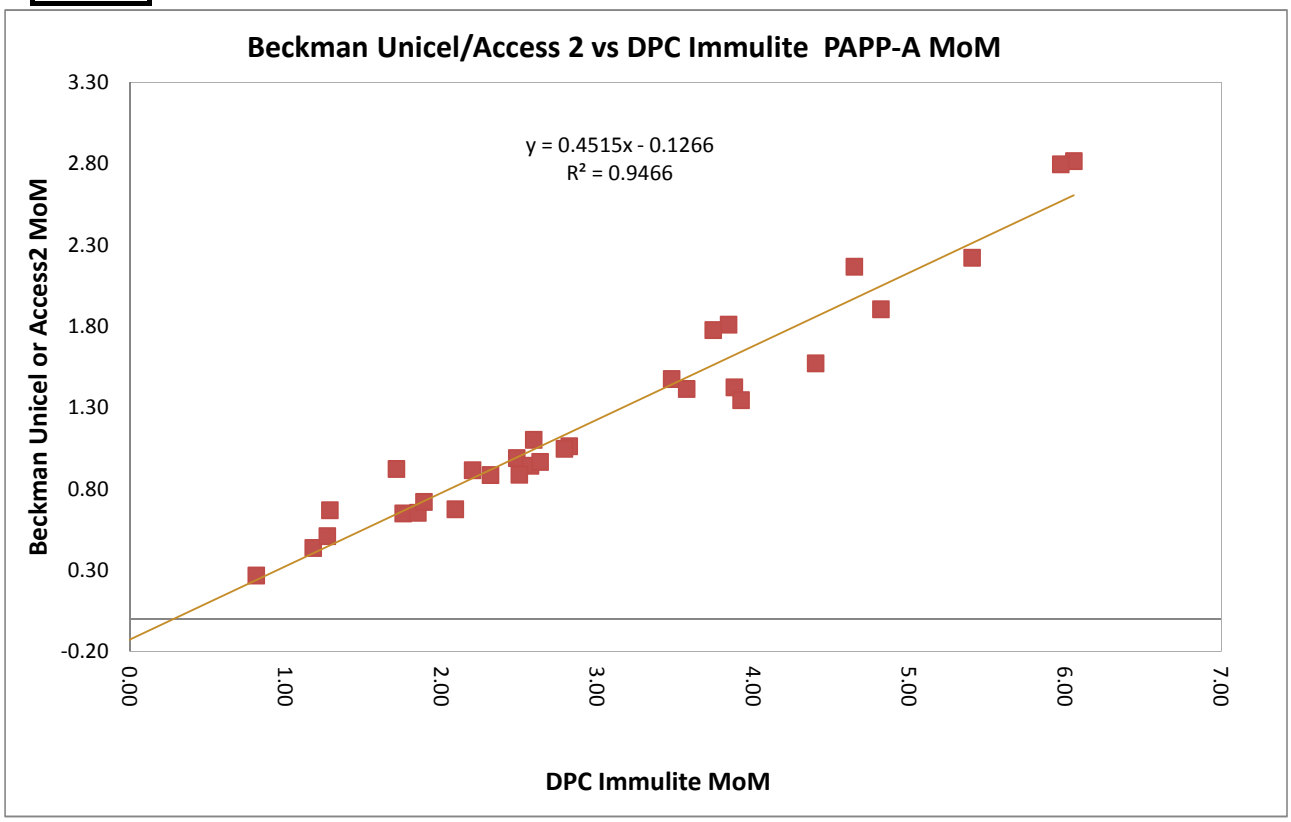
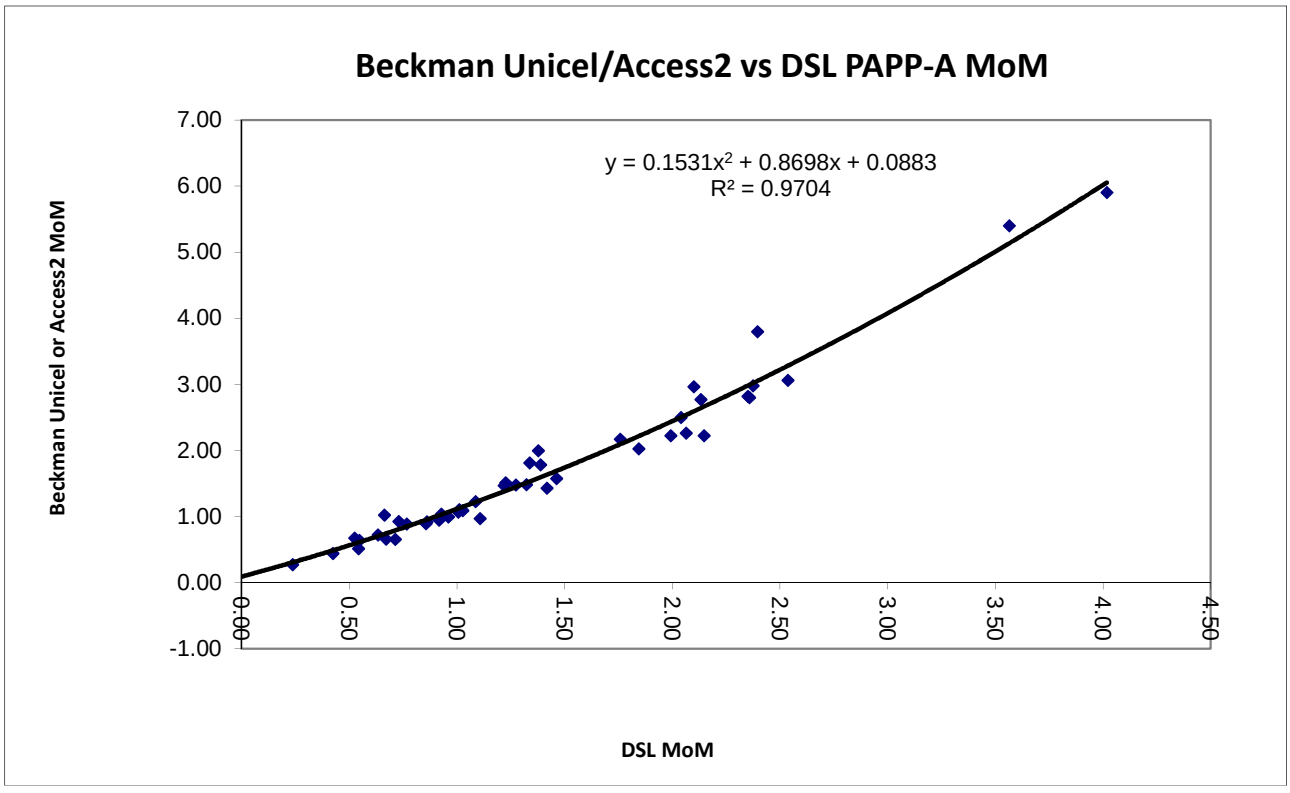


Fig. 15B



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
September 2012

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

Bacteriology (Comprehensive, Gram Stains, Group A Streptococcus, Gonorrhea & Chlamydia, Throat and Urine Culture)
Clinical Chemistry
Cytokines
Diagnostic Immunology (Diagnostic and Donor – including HIV)
Endocrinology
Fetal Defect Markers
Mycology (Antifungal Susceptibility, Direct Detection, Identification, and Identification - Yeast Only)
Oncology Soluble Tumor Markers
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, September 2012

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

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

Due Date: **September 26, 2012** _____

_____

Analyte Second Trimester Maternal Serum	**Analytical results**					Instrument code*	Reagent code*
	Vial **MS286**	Vial **MS287**	Vial **MS288**	Vial **MS289**	Vial **MS290**		
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, September 2012

Amniotic Fluid	Vial **AF286**	Vial **AF287**	Vial **AF288**	Vial **AF289**	Vial **AF290**	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	**MS286**	**MS287**	**MS288**	**MS289**	**MS290**	**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, September 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 286	1/1/1987	W	2.90	140	6/15/2012	**53**	9/7/2012
FT 287	1/1/1985	A	1.10	120	6/22/2012	**45**	9/7/2012
FT 288	1/1/1991	W	1.55	125	6/8/2012	**69**	9/7/2012
FT 289	1/1/1982	H	1.08	160	6/18/2012	**48**	9/7/2012
FT 290	1/1/1983	B	1.20	150	6/19/2012	**45**	9/7/2012

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

First Trimester Maternal Serum	Vial **FT 286**	Vial **FT 287**	Vial **FT 288**	Vial **FT 289**	Vial **FT 290**	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	**FT286**	**FT287**	**FT288**	**FT289**	**FT290**	**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
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,
September 2012
Summary of Results

	MS 286	MS 287	MS 288	MS 289	MS 290
Gestational Age All Lab Mean:					
Mean	18.0	15.0	17.0	16.0	20.0
SD	0.00	0.00	0.00	0.00	0.00
%CV	0.0%	0.0%	0.0%	0.0%	0.0%
mean+3*SD	18.0	15.0	17.0	16.0	20.0
mean-3*SD	18.0	15.0	17.0	16.0	20.0
N	27	27	27	27	27

	MS 286	MS 287	MS 288	MS 289	MS 290
MS AFP All Lab Mean:					
mean	32.2	42.2	323.9	48.2	208.6
SD	2.2	2.9	21.9	2.9	16.1
%CV	6.9%	6.7%	6.7%	6.1%	7.7%
mean+3SD	38.9	50.8	389.5	56.9	256.8
mean-3SD	25.5	33.7	258.4	39.4	160.4
N	27	27	27	27	27
median	32.8	42.3	325.0	48.3	209
mean/all kit median	1.00	0.98	1.00	1.00	0.99
MS AFP Beckman Unicel (BCU/BC1) mean:					
Mean	31.5	41.0	319.4	47.5	202.0
SD	2.0	2.2	15.1	1.5	13.0
%CV	6.4%	5.4%	4.7%	3.2%	6.4%
mean + 3SD	37.5	47.6	364.7	52.1	240.9
mean - 3SD	25.5	34.4	274.1	42.9	163.1
N	10	10	10	10	10
Median	31.9	42.1	322.3	47.6	200.8
mean/All kit median	0.98	0.95	0.98	0.99	0.95
MS AFP Beckman Access/2 (BCX/BC1) mean:					
mean	32.1	43.1	324.7	47.9	211.7
SD	2.4	3.1	23.7	3.6	16.5
%CV	7.6%	7.3%	7.3%	7.4%	7.8%
mean+3SD	39.5	52.5	395.9	58.6	261.2
mean-3SD	24.8	33.7	253.6	37.2	162.2
N	7	7	7	7	7
median	32.5	44.5	336.9	48.7	213.5
mean/all kit median	1.00	1.00	1.00	1.00	1.00
MS AFP Siemens Immulite 2000 (DPD/DP5) mean:					
mean	33.6	43.9	329.0	50.2	215.4
SD	1.3	2.0	15.7	2.4	14.3
%CV	4.0%	4.5%	4.8%	4.7%	6.6%
mean+3SD	37.6	49.9	376.1	57.3	258.3
mean-3SD	29.5	37.9	281.9	43.1	172.5
N	8	8	8	8	8
median	33.3	44.6	329.0	49.6	210.0
mean/all kit median	1.05	1.02	1.01	1.05	1.02
MS AFP kit average:					
mean	32.4	42.7	324.4	48.5	209.7
SD	1.1	1.5	4.8	1.5	6.9
all kit median	32.1	43.1	324.7	47.9	211.7

	MS 286	MS 287	MS 288	MS 289	MS 290
MS AFP MoM All Lab Mean:					
mean	0.72	1.32	8.07	1.69	3.67
SD	0.04	0.09	0.50	0.19	0.24
%CV	6.0%	6.6%	6.2%	11.4%	6.6%
mean+3SD	0.85	1.58	9.57	2.27	4.39
mean-3SD	0.59	1.06	6.58	1.11	2.94
N	27	27	27	27	27
All Median	0.73	1.33	8.06	1.67	3.67
mean/all kit median	1.00	1.01	0.99	1.00	1.01
MS AFP MoM Beckman Unicel (BCU/BC1) mean:					
Mean	0.72	1.31	8.24	1.69	3.64
SD	0.05	0.09	0.50	0.20	0.29
%CV	7.4%	6.8%	6.1%	11.8%	7.9%
mean + 3SD	0.88	1.58	9.74	2.29	4.51
mean - 3SD	0.56	1.04	6.74	1.09	2.77
N	10	10	10	10	10
Median	0.73	1.34	8.18	1.66	3.76
mean/all kit median	1.00	1.00	1.01	1.00	1.00
MS AFP MoM Beckman Access/2 (BCX/BC1) mean:					
Mean	0.73	1.39	8.17	1.75	3.71
SD	0.04	0.08	0.50	0.21	0.30
%CV	6.0%	5.4%	6.2%	12.0%	8.1%
mean + 3SD	0.86	1.62	9.68	2.38	4.61
mean - 3SD	0.60	1.17	6.66	1.12	2.81
N	7	7	7	7	7
Median	0.73	1.40	8.10	1.76	3.67
mean/all kit median	1.01	1.06	1.00	1.03	1.02
MS AFP MoM Siemens Immulite 2000 (DPD/DP5) mean:					
Mean	0.72	1.28	7.70	1.64	3.64
SD	0.04	0.07	0.33	0.21	0.15
%CV	5.5%	5.3%	4.3%	12.6%	4.0%
mean + 3SD	0.84	1.49	8.69	2.26	4.08
mean - 3SD	0.60	1.08	6.70	1.02	3.20
N	8	8	8	8	8
Median	0.73	1.30	7.70	1.59	3.64
mean/all kit median	1.00	0.98	0.94	0.97	1.00
MS AFP MoM kit average:					
mean	0.72	1.33	8.04	1.70	3.66
SD	0.00	0.06	0.30	0.06	0.04
all kit median	0.72	1.31	8.17	1.69	3.64

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

	MS 286	MS 287	MS 288	MS 289	MS 290
MS uE3 All Lab Mean:					
mean	0.65	0.69	0.98	0.81	1.65
SD	0.06	0.08	0.09	0.10	0.11
%CV	9.5%	12.2%	9.5%	12.5%	7.0%
mean+3SD	0.84	0.94	1.26	1.12	1.99
mean-3SD	0.46	0.43	0.70	0.51	1.30
N	26	26	26	26	26
mean/all kit median	0.98	1.03	1.02	0.99	0.98
MS uE3 Beckman Unicel (BCU/BC1) mean:					
Mean	0.63	0.66	0.94	0.77	1.59
SD	0.05	0.06	0.05	0.07	0.06
%CV	8.6%	9.5%	4.9%	9.1%	4.0%
mean+3SD	0.79	0.84	1.08	0.98	1.78
mean-3SD	0.47	0.47	0.80	0.56	1.40
N	10	10	10	10	10
mean/all kit median	0.95	0.99	0.97	0.94	0.94
MS uE3 Beckman Access/2 (BCX/BC1) mean:					
mean	0.66	0.67	0.96	0.82	1.68
SD	0.07	0.07	0.09	0.09	0.12
%CV	10.6%	11.1%	9.1%	10.8%	7.0%
mean+3SD	0.88	0.89	1.23	1.08	2.04
mean-3SD	0.45	0.44	0.70	0.55	1.33
N	7	7	7	7	7
mean/all kit median	1.00	1.00	1.00	1.00	1.00
MS uE3 Siemens Immulite/2000 (DPD/DP6) mean:					
Mean	0.66	0.74	1.04	0.85	1.68
SD	0.06	0.10	0.11	0.13	0.14
%CV	9.4%	13.0%	11.0%	15.0%	8.2%
mean+3SD	0.85	1.03	1.38	1.24	2.10
mean-3SD	0.48	0.45	0.69	0.47	1.27
N	9	9	9	9	9
mean/all Kit Median	1.00	1.11	1.08	1.05	1.00
MS uE3 kit average:					
mean	0.65	0.69	0.98	0.81	1.65
SD	0.02	0.04	0.05	0.04	0.05
all kit median	0.66	0.67	0.96	0.82	1.68

	MS 286	MS 287	MS 288	MS 289	MS 290
MS uE3 MoM All Lab Mean:					
Mean	0.57	1.21	1.06	1.19	0.95
SD	0.13	0.42	0.25	0.30	0.17
%CV	22.7%	34.9%	23.3%	25.3%	18.1%
mean+3SD	0.97	2.47	1.80	2.09	1.47
mean-3SD	0.18	-0.06	0.32	0.29	0.44
N	26	26	26	25	26
mean/all kit Median	1.09	1.25	1.14	1.12	1.08
MS uE3 MoM Beckman Unicel (BCU/BC1) Mean:					
Mean	0.49	0.96	0.90	1.00	0.84
SD	0.04	0.14	0.07	0.13	0.06
%CV	8.1%	14.6%	7.5%	13.3%	6.6%
mean+3SD	0.61	1.39	1.10	1.40	1.01
mean-3SD	0.37	0.54	0.70	0.60	0.67
N	10	10	10	10	10
mean/all kit Median	0.93	1.00	0.97	0.95	0.95
MS uE3 MoM Beckman Access/2 (BCX/BC1) Mean:					
Mean	0.53	0.96	0.93	1.06	0.88
SD	0.07	0.09	0.08	0.11	0.10
%CV	13.1%	9.4%	9.0%	10.0%	11.7%
mean+3SD	0.73	1.23	1.17	1.38	1.19
mean-3SD	0.32	0.69	0.68	0.74	0.57
N	7	7	7	7	7
mean/all kit Median	1.00	1.00	1.00	1.00	1.00
MS uE3 MoM Siemens Immulite/2000 (DPD/DP6) Mean:					
Mean	0.71	1.67	1.33	1.62	1.14
SD	0.13	0.40	0.22	0.38	0.16
%CV	17.9%	24.2%	16.8%	23.6%	13.9%
mean+3SD	1.09	2.88	2.00	2.76	1.61
mean-3SD	0.33	0.46	0.66	0.47	0.66
N	9	9	9	9	9
mean/all kit Median	1.35	1.73	1.44	1.53	1.29
MS uE3 MoM kit average:					
mean	0.57	1.20	1.05	1.23	0.95
SD	0.12	0.41	0.24	0.34	0.16
all kit median	0.53	0.96	0.93	1.06	0.88

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

	MS 286	MS 287	MS 288	MS 289	MS 290
MS hCG All Lab mean:					
mean	44.9	40.1	30.2	21.9	16.2
SD	6.5	5.1	3.5	2.3	1.6
%CV	14.4%	12.8%	11.5%	10.5%	9.6%
mean+3SD	64.3	55.6	40.6	28.7	20.8
mean-3SD	25.5	24.7	19.8	15.0	11.5
N	26	26	26	26	26
mean/all kit median	0.98	0.98	0.99	1.01	1.02
MS hCG Beckman Unicel (BCU/BC1) mean:					
mean	45.8	41.1	30.6	21.7	15.9
SD	4.8	3.0	2.4	1.4	0.9
%CV	10.5%	7.4%	7.8%	6.5%	5.5%
mean+3SD	60.32	50.29	37.79	25.87	18.51
mean-3SD	31.34	31.99	23.47	17.47	13.29
N	10	10	10	10	10
median	46.45	41.90	30.45	21.85	16.05
mean/All kit median	1.00	1.00	1.00	1.00	1.00
MS hCG Beckman Access/2 (BCX/BC1) mean:					
mean	50.7	44.5	33.0	23.9	17.8
SD	4.1	3.6	2.7	2.1	1.3
%CV	8.1%	8.2%	8.2%	8.9%	7.5%
mean+3SD	63.0	55.4	41.1	30.3	21.8
mean-3SD	38.3	33.5	24.9	17.5	13.8
N	7	7	7	7	7
median	52.5	42.6	31.7	24.0	17.4
mean/all kit median	1.11	1.08	1.08	1.10	1.12
MS hCG Siemens Immulite 2000 (DPD/DP5) mean:					
mean	38.0	34.8	27.0	20.1	14.9
SD	3.7	4.2	3.0	1.9	1.2
%CV	9.7%	12.1%	11.3%	9.7%	8.0%
mean+3SD	49.0	47.4	36.1	25.9	18.5
mean-3SD	27.0	22.1	17.9	14.2	11.4
N	8	8	8	8	8
median	38.1	34.2	26.1	20.0	15.0
mean/all kit median	0.83	0.85	0.88	0.93	0.94
MS hCG kit average:					
mean	44.8	40.1	30.2	21.9	16.2
SD	6.4	4.9	3.0	1.9	1.5
all kit median	45.8	41.1	30.6	21.7	15.9

	MS 286	MS 287	MS 288	MS 289	MS 290
MS hCG MoMs All Lab Mean:					
mean	2.21	0.98	1.22	0.80	1.00
SD	0.26	0.10	0.13	0.08	0.09
%CV	11.9%	10.0%	10.9%	9.9%	9.1%
mean+3SD	3.00	1.28	1.62	1.04	1.27
mean-3SD	1.42	0.69	0.82	0.56	0.73
N	26	26	26	26	26
mean/All Kit Median	0.94	0.98	0.96	0.97	0.99
MS hCG MoM Beckman Unicel (BCU/BC1) mean:					
mean	2.34	1.01	1.30	0.83	1.02
SD	0.22	0.09	0.10	0.05	0.07
%CV	9.5%	8.5%	7.9%	6.4%	6.6%
mean+3SD	3.00	1.27	1.60	0.99	1.22
mean-3SD	1.68	0.75	0.99	0.67	0.82
N	8	8	8	8	8
median	2.33	1.00	1.31	0.84	1.00
mean/All kit median	1.00	1.00	1.02	1.00	1.01
MS hCG MoM Beckman Access/2 (BCX/BC1) mean:					
mean	2.34	1.02	1.27	0.84	1.01
SD	0.21	0.10	0.08	0.08	0.10
%CV	8.9%	10.1%	6.3%	9.0%	10.2%
X+3SD	2.97	1.33	1.51	1.07	1.32
X-3SD	1.72	0.71	1.03	0.61	0.70
N	9	9	9	9	9
median	2.40	1.01	1.26	0.85	1.04
mean/All kit median	1.00	1.01	1.00	1.02	1.00
MS hCG MoM Siemens Immulite 2000 (DPD/DP5) mean:					
mean	1.96	0.94	1.10	0.74	0.99
SD	0.16	0.08	0.12	0.08	0.10
%CV	8.3%	9.0%	10.5%	10.2%	9.8%
X+3SD	2.45	1.19	1.45	0.97	1.27
X-3SD	1.47	0.69	0.75	0.52	0.70
N	8	8	8	8	8
median	2.00	0.92	1.11	0.75	1.00
mean/All kit median	0.84	0.93	0.86	0.90	0.97
MS hCG MoM kit average:					
mean	2.2	1.0	1.2	0.8	1.0
SD	0.2	0.0	0.1	0.1	0.0
all kit median	2.3	1.0	1.3	0.8	1.0

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

	MS 286	MS 287	MS 288	MS 289	MS 290
MS Inhibin A all lab mean:					
Mean	282.5	142.7	124.5	119.7	186.5
SD	27.2	12.0	11.1	10.3	17.2
%CV	9.6%	8.4%	8.9%	8.6%	9.2%
mean + 3SD	364.2	178.7	157.7	150.7	238.2
mean- 3SD	200.9	106.7	91.3	88.8	134.9
N	26	26	26	26	26
All Lab Median	290.2	143.7	128.3	121.3	190.7
mean/all kit median	0.99	0.98	0.97	0.98	0.98
MS Inhibin A Beckman Unicel (BCU/BC1) mean:					
Mean	286.7	145.0	127.7	123.7	189.6
SD	20.8	9.8	5.4	6.4	7.4
%CV	7.3%	6.8%	4.2%	5.2%	3.9%
mean + 3SD	349.2	174.5	143.9	143.0	211.8
mean- 3SD	224.2	115.6	111.5	104.4	167.4
N	12	12	12	12	12
kit median	286.4	144.1	127.8	121.7	190.0
mean/all kit median	1.00	1.00	1.00	1.02	1.00
MS Inhibin A Beckman Access/2 (BCX/BC1) mean:					
Mean	292.7	146.7	128.0	121.6	193.9
SD	10.0	5.6	5.3	4.2	9.6
%CV	3.4%	3.8%	4.1%	3.4%	4.9%
mean + 3SD	322.8	163.5	143.9	134.2	222.6
mean- 3SD	262.6	129.9	112.2	109.1	165.1
N	11	11	11	11	11
kit median	291.9	147.0	129.0	123.6	196.5
mean/All kit median	1.02	1.01	1.00	1.00	1.02
MS Inhibin A Diagnostic System Labs (DS1) mean:					
Mean	228.6	118.6	98.5	97.0	147.3
SD	36.5	10.9	9.6	11.2	16.7
%CV	16.0%	9.2%	9.7%	11.6%	11.3%
mean + 3SD	338.1	151.3	127.3	130.7	197.4
mean- 3SD	119.2	85.8	69.7	63.3	97.2
N	3	3	3	3	3
kit median	227.0	123.9	100.8	103.3	156.7
mean/all kit median	0.80	0.82	0.77	0.80	0.78
MS Inhibin A kit average:					
mean	269.3	136.8	118.1	114.1	176.9
SD	35.4	15.8	16.9	14.9	25.7
all kit median	286.7	145.0	127.7	121.6	189.6

	MS 286	MS 287	MS 288	MS 289	MS 290
MS Inhibin A MoM All Lab mean:					
mean	1.65	0.72	0.71	0.75	1.01
SD	0.18	0.09	0.09	0.10	0.14
%CV	11.1%	12.3%	12.1%	13.4%	13.5%
mean+3SD	2.20	0.98	0.97	1.06	1.42
mean-3SD	1.10	0.45	0.45	0.45	0.60
N	26	26	26	26	26
mean/all kit median	0.98	0.99	0.99	1.00	0.99
MS Inhibin A MoM Beckman Unicel (BCU/BC1) mean:					
Mean	1.71	0.72	0.75	0.80	1.07
SD	0.13	0.06	0.06	0.08	0.11
%CV	7.7%	7.7%	8.3%	10.2%	10.0%
mean + 3SD	2.11	0.89	0.93	1.05	1.39
mean- 3SD	1.32	0.55	0.56	0.56	0.75
N	12	12	12	12	12
Kit Median	1.66	0.72	0.74	0.76	1.02
mean/all kit median	1.01	1.00	1.03	1.07	1.04
MS Inhibin A MoM Beckman Access (BCX/BC1) mean:					
Mean	1.69	0.75	0.72	0.75	1.03
SD	0.08	0.08	0.06	0.04	0.06
%CV	4.6%	10.2%	8.0%	5.8%	5.6%
mean + 3SD	1.92	0.98	0.90	0.88	1.20
mean- 3SD	1.46	0.52	0.55	0.62	0.85
N	11	11	11	11	11
Kit Median	1.71	0.73	0.74	0.77	1.04
mean/all kit median	1.00	1.04	1.00	1.00	1.00
MS Inhibin A MoM Diagnostic System Labs (DS1) mean:					
Mean	1.26	0.56	0.55	0.55	0.75
SD	0.20	0.09	0.08	0.06	0.17
%CV	15.5%	16.4%	14.9%	11.4%	22.6%
mean + 3SD	1.85	0.84	0.79	0.74	1.25
mean- 3SD	0.68	0.29	0.30	0.36	0.24
N	3	3	3	3	3
Kit Median	1.24	0.51	0.51	0.53	0.67
mean/all kit median	0.75	0.78	0.76	0.73	0.73
MS Inhibin A MoM kit average:					
mean	1.56	0.68	0.67	0.70	0.95
SD	0.25	0.10	0.11	0.13	0.17
all kit median	1.69	0.72	0.72	0.75	1.03

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	AF 286	AF 287	AF 288	AF 289	AF 290
AF AFP All Lab mean :					
mean	5.0	6.8	8.8	8.5	18.5
SD	0.5	0.8	1.2	1.1	2.1
%CV	10.0%	11.7%	14.1%	13.3%	11.6%
mean+3SD	6.5	9.2	12.5	12.0	24.9
mean-3SD	3.5	4.4	5.0	5.1	12.1
N	20	20	20	20	20
All kit median	5.2	7.2	9.3	8.7	19.2
mean/all kit mean	0.96	0.95	0.94	0.98	0.97
AF AFP Beckman Unicel (BCU/BC1) mean:					
Mean	4.6	6.2	7.6	7.8	16.8
SD	0.4	0.7	0.6	1.1	1.5
%CV	7.7%	11.7%	7.5%	14.3%	8.8%
X+3SD	5.6	8.3	9.3	11.1	21.2
X-3SD	3.5	4.0	5.8	4.5	12.3
N	8	8	8	8	8
median	4.6	6.0	7.8	8.0	16.8
mean/all kit median	0.88	0.86	0.81	0.89	0.87
AF AFP Beckman Access/2 (BCX/BC1) mean:					
mean	5.3	6.9	8.8	8.7	18.4
SD	0.2	0.5	0.7	0.6	1.0
%CV	3.3%	7.4%	7.5%	6.8%	5.6%
mean+3SD	5.8	8.4	10.8	10.5	21.5
mean-3SD	4.7	5.4	6.8	6.9	15.3
N	4	4	4	4	4
median	5.3	6.8	8.85	8.5	18.65
mean/all kit median	1.01	0.97	0.95	1.00	0.96
AF AFP DPC Immulite 2000 (DPD/DP5) mean:					
mean	5.1	7.4	10.1	8.7	19.9
SD	0.3	0.5	0.7	0.8	1.4
%CV	5.9%	6.1%	7.1%	9.4%	7.3%
mean+3SD	6.0	8.8	12.3	11.2	24.3
mean-3SD	4.2	6.0	7.9	6.3	15.6
N	5	5	5	5	5
median	5	7.2	10.3	8.6	19.7
mean/all kit median	0.99	1.03	1.08	1.00	1.04
AF AFP Abbott Axsym (ABB/AB2) mean:					
mean	5.6	7.4	9.8	10.4	21.1
N	2	2	2	2	2
mean/all kit median	1.08	1.03	1.05	1.19	1.10
AF AFP kit average:					
mean	5.1	7.0	9.1	8.9	19.0
SD	0.4	0.6	1.1	1.1	1.9
all kit median	5.2	7.2	9.3	8.7	19.2

	AF 286	AF 287	AF 288	AF 289	AF 290
AF AFP MoM All Lab Mean:					
mean	0.53	1.09	0.76	1.11	2.92
SD	0.05	0.17	0.11	0.14	0.38
%CV	8.7%	15.3%	13.9%	12.5%	13.0%
mean+3SD	0.66	1.59	1.07	1.52	4.05
mean-3SD	0.39	0.59	0.44	0.69	1.78
N	20	20	20	20	20
All median	0.53	1.09	0.75	1.12	2.92
mean/all kit median	1.00	1.00	1.02	0.99	1.00
AF AFP MoM Beckman Unicel(BCU/BC1) mean:					
Mean	0.52	1.05	0.71	1.08	2.76
SD	0.05	0.20	0.09	0.17	0.44
%CV	9.5%	19.2%	13.0%	15.6%	15.9%
X+3SD	0.66	1.65	0.98	1.59	4.08
X-3SD	0.37	0.44	0.43	0.58	1.44
N	8	8	8	8	8
median	0.53	1.07	0.71	1.09	2.77
mean/all kit median	0.99	0.97	0.97	0.97	0.95
AF AFP MoM Beckman Access (BCX/BC1) mean:					
Mean	0.55	1.11	0.76	1.14	2.94
SD	0.05	0.21	0.10	0.20	0.41
%CV	9.0%	19.0%	12.8%	17.6%	14.0%
X+3SD	0.70	1.74	1.05	1.74	4.17
X-3SD	0.40	0.48	0.46	0.54	1.71
N	4	4	4	4	4
median	0.54	1.04	0.74	1.09	2.81
mean/all kit median	1.06	1.03	1.03	1.02	1.01
AF AFP MoM DPC Immulite 2000 (DPD/DP5) mean:					
Mean	0.53	1.16	0.87	1.10	3.09
SD	0.03	0.10	0.09	0.09	0.22
%CV	6.2%	8.6%	10.9%	8.2%	7.0%
X+3SD	0.63	1.46	1.15	1.36	3.74
X-3SD	0.43	0.86	0.58	0.83	2.44
N	5	5	5	5	5
median	0.53	1.12	0.85	1.10	3.00
mean/all kit median	1.01	1.07	1.19	0.98	1.06
AF AFP MoM Abbott Axsym (ABB/AB2) mean:					
Mean	0.50	1.01	0.70	1.14	2.89
N	2	2	2	2	2
mean/all kit median	0.95	0.94	0.95	1.02	0.99
AF AFP MoM kit average:					
mean	0.52	1.08	0.76	1.11	2.92
SD	0.02	0.07	0.08	0.03	0.14
all kit median	0.52	1.08	0.73	1.12	2.91

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	FT286	FT287	FT288	FT289	FT290
FT Gestational Age All Lab Mean:					
Mean	11.9	11.2	13.1	11.5	11.2
SD	0.11	0.13	0.06	0.13	0.13
%CV	0.9%	1.2%	0.5%	1.1%	1.1%
mean+3*SD	12.2	11.6	13.2	11.9	11.6
mean-3*SD	11.6	10.8	12.9	11.1	10.9
N	17	17	17	17	17

	FT286	FT287	FT288	FT289	FT290
FT NT MoM All Lab Mean:					
Mean	2.24	0.97	0.94	0.91	1.06
SD	0.14	0.05	0.05	0.05	0.05
%CV	6.4%	4.8%	5.8%	5.3%	4.8%
mean+3SD	2.67	1.11	1.11	1.05	1.21
mean- 3SD	1.81	0.83	0.78	0.76	0.91
N	16	16	16	16	16
All Median	2.20	0.97	0.94	0.90	1.05

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	FT286	FT287	FT288	FT289	FT290
FT hCG All Lab Mean:					
mean	172.0	89.3	65.3	90.3	78.8
SD	31.4	12.6	8.1	11.8	10.9
%CV	18.3%	14.2%	12.4%	13.1%	13.8%
mean+3SD	266.3	127.3	89.6	125.7	111.4
mean- 3SD	77.7	51.4	40.9	54.8	46.3
N	16	16	16	16	16
All lab median	180.3	90.5	64.3	89.1	78.0
mean/All kit median	0.96	1.03	1.03	1.01	1.01
FT hCG Beckman Unicel (BCU/BC1) mean:					
mean	178.7	87.0	63.4	89.0	77.7
SD	12.1	6.7	6.1	2.9	7.5
%CV	6.8%	7.7%	9.6%	3.2%	9.6%
mean+3SD	248.4	117.3	86.9	126.1	113.3
mean- 3SD	158.0	88.9	60.8	81.0	67.7
N	6	6	6	6	6
median	180.3	86.0	61.5	88.8	78.3
mean/All kit median	1.00	1.00	1.00	1.00	1.00
FT hCG Beckman Access (BCX/BC1) mean:					
mean	203.2	103.1	73.9	103.5	90.5
SD	15.1	4.7	4.4	7.5	7.6
%CV	7.4%	4.6%	5.9%	7.3%	8.4%
mean+3SD	248.4	117.3	86.9	126.1	113.3
mean- 3SD	158.0	88.9	60.8	81.0	67.7
N	5	5	5	5	5
median	204.8	105.7	73.7	106.5	90.3
mean/All kit median	1.14	1.19	1.16	1.16	1.16
FT hCG DPC Immulite 2000(DPD/DP5) mean:					
mean	132.8	78.3	58.8	78.5	68.5
SD	9.5	11.1	5.7	7.9	3.1
%CV	7.1%	14.2%	9.7%	10.0%	4.5%
mean+3SD	161.2	111.7	75.9	102.0	77.7
mean- 3SD	104.4	44.9	41.7	54.9	59.4
N	5	5	5	5	5
median	131.7	71.5	60.4	76.1	68.7
mean/All kit median	0.74	0.90	0.93	0.88	0.88
FT hCG kit average:					
mean	171.6	89.5	65.4	90.3	78.9
SD	35.7	12.6	7.7	12.6	11.0
all kit median	178.7	87.0	63.4	89.0	77.7

	FT286	FT287	FT288	FT289	FT290
FT hCG MoM All Lab Mean:					
Mean	2.23	1.00	0.93	1.23	0.96
SD	0.29	0.15	0.12	0.12	0.12
%CV	13.0%	15.2%	12.6%	10.0%	12.9%
mean+3*SD	3.10	1.46	1.28	1.60	1.34
mean - 3*SD	1.36	0.54	0.57	0.86	0.59
N	15	15	15	15	15
All lab Median	2.14	0.99	0.90	1.23	0.97
mean/All kit Median	1.00	0.96	0.98	0.98	1.02
MS hCG MoM Beckman Unicel (BCU/BC1) mean:					
mean	2.24	0.92	0.88	1.15	0.92
SD	0.21	0.10	0.05	0.09	0.08
%CV	9.4%	11.3%	5.3%	7.5%	8.7%
mean+3SD	2.87	1.23	1.02	1.41	1.16
mean-3SD	1.61	0.61	0.74	0.89	0.68
N	6	6	6	6	6
median	2.22	0.98	0.88	1.17	0.91
mean/All kit median	1.00	0.89	0.93	0.91	0.98
MS hCG MoM Beckman Access (BCX/BC1) mean:					
mean	2.46	1.04	0.95	1.30	1.05
SD	0.37	0.18	0.08	0.17	0.13
%CV	15.1%	16.8%	8.5%	12.7%	12.3%
mean+3SD	3.56	1.57	1.19	1.80	1.44
mean-3SD	1.35	0.51	0.71	0.81	0.66
N	4	4	4	4	4
median	2.60	1.11	0.98	1.35	1.08
mean/All kit median	1.10	1.00	1.00	1.04	1.11
MS hCG MoM DPC Immulite2000 (DPD/DP5) mean:					
mean	2.04	1.06	0.97	1.26	0.94
SD	0.20	0.17	0.18	0.08	0.15
%CV	10.0%	16.1%	19.1%	6.6%	16.0%
mean+3SD	2.65	1.57	1.52	1.51	1.39
mean-3SD	1.43	0.55	0.41	1.01	0.49
N	5	5	5	5	5
median	2.08	1.00	0.92	1.28	0.97
mean/All kit median	0.91	1.02	1.02	1.00	1.00
FT hCG MoM kit average:					
mean	2.2	1.0	0.9	1.2	1.0
SD	0.2	0.1	0.0	0.1	0.1
all kit median	2.2	1.0	0.9	1.3	0.9

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	FT286	FT287	FT288	FT289	FT290
FT PAPP-A All Lab Mean:					
Mean	1006.0	1684.8	2611.5	1955.5	1560.8
SD	717.2	1120.6	1653.0	1295.2	1121.5
%CV	71.3%	66.5%	63.3%	66.2%	71.9%
mean + 3SD	3157.5	5046.6	7570.5	5841.1	4925.3
mean- 3SD	-1145.5	-1676.9	-2347.5	-1930.2	-1803.7
N	16	15	15	16	16
All Lab Median	557.4	1027.5	1555.0	1103.5	899.0
mean/All kit median	0.78	0.83	0.72	0.71	0.81
FT PAPP-A Beckman Unicel(BCU/BC1) Mean:					
Mean	531.3	958.5	1471.0	1084.0	857.8
SD	30.3	54.9	123.1	58.6	61.8
%CV	5.7%	5.7%	8.4%	5.4%	7.2%
mean + 3SD	622.2	1123.2	1840.5	1259.7	1043.3
mean - 3SD	440.4	793.7	1101.6	908.3	672.2
N	8	7	7	8	8
Kit Median	522.4	927.8	1536.3	1086.1	848.4
mean/All kit median	0.41	0.47	0.41	0.39	0.44
***FT PAPP-A DPC Immullite 2000 (DPD/DP5) Mean:**					
Mean	2314.9	3637.8	5243.6	4161.5	3613.7
SD	133.2	393.2	256.7	324.2	347.5
%CV	5.8%	10.8%	4.9%	7.8%	9.6%
mean + 3SD	2714.5	4817.4	6013.8	5134.2	4656.2
mean - 3SD	1915.3	2458.2	4473.4	3188.8	2571.1
N	3	3	3	3	3
Kit Median	2316.4	3585.1	5318.9	4041.1	3774.7
mean/All kit median	1.79	1.80	1.45	1.50	1.87
***FT PAPP-A Diagnostic Systems Lab (DS1) Mean:**					
Mean	1291.1	2023.3	3604.4	2770.3	1932.8
SD	12.2	292.7	707.9	195.4	335.3
%CV	0.9%	14.5%	19.6%	7.1%	17.3%
mean + 3SD	1.2	2.3	4.0	2.6	2.4
mean - 3SD	1.1	1.1	1.5	1.8	0.9
N	3	3	3	3	3
Kit Median	1291.0	2107.5	3569.8	2804.8	2051.3
mean/All kit median	1.00	1.00	1.00	1.00	1.00

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

	FT286	FT287	FT288	FT289	FT290
FT PAPP-A kit average:					
mean	1379.1	2206.5	3439.7	2671.9	2134.7
SD	895.1	1349.0	1891.7	1541.1	1389.0
all kit median	1291.1	2023.3	3604.4	2770.3	1932.8

	FT286	FT287	FT288	FT289	FT290
FT PAPP-A MoM All Lab Mean:					
Mean	0.97	1.81	1.34	2.49	1.84
SD	0.59	1.00	0.77	1.27	1.22
%CV	61.0%	55.3%	57.0%	51.0%	66.2%
mean + 3SD	2.75	4.81	3.64	6.29	5.48
mean- 3SD	-0.81	-1.19	-0.95	-1.32	-1.81
N	15	14	15	15	15
All Lab Median	0.71	1.52	1.04	1.96	1.46
mean/ All kit median	1.09	1.28	1.28	1.05	1.13
FT PAPP-A MoM Beckman Unicel(BCU/BC1) Mean:					
Mean	0.68	1.41	1.05	1.91	1.35
SD	0.08	0.22	0.09	0.22	0.36
%CV	11.6%	15.6%	8.4%	11.5%	26.4%
mean + 3SD	0.91	2.08	1.31	2.56	2.41
mean - 3SD	0.44	0.75	0.78	1.25	0.28
N	8	7	8	8	8
Kit Median	0.64	1.51	1.03	1.88	1.37
mean/All kit median	0.76	1.00	1.00	0.81	0.83
FT PAPP-A MoM DPC Immulite 2000 (DPD/DP5) Mean:					
Mean	2.09	3.57	2.79	4.82	3.92
SD	0.07	0.30	0.09	0.53	0.91
%CV	3.3%	8.5%	3.3%	11.1%	23.1%
mean + 3SD	2.29	4.48	3.06	6.41	6.64
mean - 3SD	1.88	2.66	2.51	3.22	1.20
N	3	3	3	3	3
Kit Median	2.11	3.47	2.75	4.92	3.97
mean/All kit median	2.34	2.52	2.66	2.04	2.41
FT PAPP-A MoM Diagnostic System Labs (DS1) Mean:					
Mean	0.89	1.37	1.01	2.36	1.63
N	2	2	2	2	2
Kit Median	0.89	1.37	1.01	2.36	1.63
mean/ All kit median	1.00	0.97	0.96	1.00	1.00
FT PAPP-A MoM kit average:					
mean	1.22	2.12	1.61	3.03	2.30
SD	0.76	1.26	1.02	1.57	1.41
all kit median	0.89	1.41	1.05	2.36	1.63