Fetal Defect Marker Proficiency Test Mailout from January 23, 2007
February, 2007

Dear Laboratory Director,

Below you will find a summary and critique of the Proficiency Testing mail-out from January 23, 2007 for Fetal Defect Markers, including AFP, uE3, hCG, and dimeric inhibin-A. Your laboratory's results and grades are printed on a separate sheet; also included are the grades from the previous two PT events. Please review and sign your evaluation. Retain the signed packet in your files. You will need it for your next laboratory survey to demonstrate participation in the NYSPT program.

Maternal Serum: Summary of Sample Results

Samples *N = 31	**Sample #**	**MS 201**	**MS 202**	**MS 203**	**MS 204**	**MS 205**
	Gestational Age (weeks)	20.0	16.0	17.0	15.0	18.0
Maternal Race	Ethnic Group	White	Asian	Black	Hispanic	White
Maternal Weight	Pounds (lbs)	120	90	150	180	140
Maternal Age	Years	20	23	24	21	37
Alpha-Fetoprotein (AFP)	Mean ng/mL	26.09 ± 2.49	45.22 ± 3.91	89.23 ± 7.73	115.91 ± 15.16	25.27 ± 2.24
	MoM	0.39 ± 0.03	1.01 ± 0.11	2.12 ± 0.17	4.67 ± 0.39	0.55 ± 0.04
Unconjugated Estriol (uE3)	Mean ng/mL	1.68 ± 0.71	1.97 ± 0.86	3.32 ± 1.51	2.17 ± 0.96	1.84 ± 0.79
	MoM	0.45 ± 0.13	1.16 ± 0.31	1.77 ± 0.41	1.91 ± 0.48	0.79 ± 0.23
human Chorionic Gonadotrophin (hCG)	Mean IU/mL	51.51 ± 6.25	28.22 ± 3.23	29.10 ± 2.60	32.29 ± 3.69	36.83 ± 3.64
	MoM	2.49 ± 0.30	0.68 ± 0.08	1.09 ± 0.11	0.92 ± 0.15	1.60 ± 0.18
Dimeric Inhibin-A (DIA)	Mean pg/mL	392.53 ± 42.05	79.31 ± 5.95	115.39 ± 11.02	85.82 ± 6.64	380.85 ± 37.96
	MoM	1.88 ± 0.36	0.38 ± 0.08	0.70 ± 0.08	0.50 ± 0.06	2.20 ± 0.33
Neural Tube Screen (Positive, Negative)	Pos (+) or Neg. (-)	Neg. (100%)	Neg. (100%)	Neg. (90%)	Pos. (100%)	Neg. (100%)
	Further Action R,U,A	NFA	NFA	NFA	R = 20% U = 96% A = 60%	NFA
	NTD Risk	10,000	10,000	1200	6	10,000
Trisomy-21 Screen (Positive, Negative)	Pos (+); Neg.(-)	Pos. (100%)	Neg. (100%)	Neg. (100%)	Neg. (100%)	Pos. (97%)
1. Triple test	Recommended Action	U = 65% A = 80%	NFA	NFA	NFA	U = 85% A = 80%
	Risk Est.	12	10,000	10,000	10,000	42
2. Quad Test	Pos (+); Neg. (-).	Pos. (100%)	Neg. (100%)	Neg. (100%)	Neg. (100%)	Pos. (100%)
	Recommended Action **	U = 60% A = 72%	NFA	NFA	NFA	U = 80% A = 72%
	Risk Est.	10	20,000	20,000	25,000	10
Trisomy-18 Screen (Positive, Negative)	Pos (+)/Neg. (-)	Neg. (-)	Neg. (-)	Neg. (-)	Neg. (-)	Neg. (-)
	Risk Est.	1,400	15,000	15,000	15,000	3,300

*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 ± SD; (B) = borderline positive or negative, risk reflects central tendency (Modal number for Down positive/borderline screen). NFA = no further action; FA = further action; R = repeat; U = ultrasound, and A = amniocentesis. **This percentage is normalized to labs requesting further action. ‡ Insulin Dependent Diabetic pregnancy.

Maternal Serum Analytes: Summary of Test Results

N = 31 All-Lab Consensus Values.

Sample #	Summary Comments (Mock specimens):
MS 201 Wk 20.0	This specimen was procured from a 20 year old Caucasian woman (Gravida = 1, parity = 0) with a body weight of 120 lbs. To date, her first pregnancy appeared to follow an uncomplicated course of gestation and her sample was deemed screen negative for NTD. In contrast, all labs were in agreement that her T-21 screen was positive (100%). Recommendations of further action from labs performing the triple screen were ultrasound, 65%; amniocentesis, 80%; while the quad screen was ultrasound 60%; amniocentesis 72%. The trisomy-18 (T18) screen for this patient was negative. This specimen was paired to amniotic fluid specimen AF-201 which produced a correspondingly low AFAFP value (MOM = 0.5).
MS 202 Wk 16.0	This specimen, MS202 originated from a 23 year old Asian woman (Gravida = 2, Parity = 1) with a bodyweight of 90 lbs. Her family history indicated no pregnancy complications. Her sample was classified as screen negative for both NTDs and trisomies. All labs were in agreement with both screen assessments. Race and body weight algorithm adjustments were indicated. The MS202 sample was not matched with an amniotic fluid specimen.
MS 203 Wk 17.0	This specimen was obtained from a 24 year old Afro-American woman (Gravida = 2, Parity = 1) with a body weight of 150 lbs. She had a family history of pregnancy complications and adverse outcomes. Her sample was screen negative for both NTD and Trisomies 21 and 18. All labs agreed that both trisomy screens were negative and the lab consensus for the negative NTD screen was 90%. Note that this patient's sample required two algorithm adjustments, race and body weight, which may have influenced her NTD negative screen assessment (see critique). MS203 was paired with amniotic fluid sample, AF203.
MS 204 Wk 15.0	Specimen MS204 represented a sample obtained from a 21 year old Hispanic woman (Gravida = 2, Parity = 0) with a body weight of 180 lbs. She had reported a personal history of pregnancy loss. Her sample was deemed screen positive (100%) for NTD with further recommended action as: repeat specimen 20%; ultrasound, 96%; and amniocentesis, 60%. This specimen screened negative for both trisomies. All labs were in agreement with the screen assessments. A body weight correction was indicated in her risk assessement. This specimen was not matched to an amniotic fluid sample.
MS 205 Wk 18.0	Specimen MS205 was obtained from a 37 year old Caucasian woman (Gravida = 1, Parity = 0) with a body weight of 140 lbs. Her sample, a first pregnancy specimen, was screen negative for NTD; however, her specimen was screen positive for Trisomy-21 with all labs in agreement. Recommendations of further action from labs performing the triple screen were ultrasound, 85% and amniocentesis, 80%; correspondingly, the quad screen was ultrasound 80%; and amniocentesis 72%. The trisomy-18 (T18) screen for this patient was negative. This specimen did not have an amniotic fluid counterpart.

Notice of Gravida/Parity Clarification for Present and Future Mailouts;

This notice regards the demographic data provided for the mock patients in the FEDM program. For the sake of uniformity, it will be understood that gravida indicates a pregnant woman and parity is the state of having given birth to an 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; also, multiple birth is 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.

AMNIOTIC FLUID AFP (NTD-analysis):
N=31; All-Lab Consensus Values

Sample	Values		Summary Comments:
AF 201 Wk 20.0	AFP= MOM=	3.5 ± 0.5 µg/ml 0.5 ± 0.1	This sample was targeted for a normal AFAFP value in the upper routine gestational age screening. All labs acknowledged this specimen as a lower AFAFP value, but screen negative for NTD. The AF201 specimen was paired with specimen MS201.
AF 202 Wk 16.0	AFP= MOM=	14.1 ± 2.1 µg/ml 1.0 ± 0.1	This sample was targeted for the normal AFAFP value in the lower routine gestational age screening range. All labs categorized this as a normal specimen. AF202 was not matched to a MS sample.
AF 203 Wk 17.0	AFP= MOM=	26.5 ± 3.8 µg/ml 2.2 ± 0.2	This sample was targeted for a borderline elevated AFAFP value in the routine gestational age group. Most labs (93%) called it an elevated specimen for NTD depending on the individual lab MoM cutoff values. This AFAFP sample was matched to MS203 (see critique) which screened negative for NTD.
AF 204 Wk 18.0	AFP= MOM=	9.8 ± 1.4 µg/ml 1.0 ± 0.1	This sample was targeted for the normal AFAFP value in the routine gestational screening range. All labs categorized this as a normal specimen; it had no maternal serum counterpart.
AF 205 Wk 20.0	AFP= MOM=	6.2 ± 0.8 µg/ml 0.9 ± 0.1	This sample was targeted for a normal AFAFP value in the upper routine gestational age screening range. All labs classified this as a non-elevated specimen. This AFAFP sample was not matched to an MS sample.

Fetal Defect Proficiency Test Mailout 1/23/07 Critique of Maternal Serum and Amniotic Fluid Values:

The all-lab results of the targeted values for the NTD and the Trisomy Screen were within expectations of our projected target values, risks, and outcomes. As displayed in the above tables, maternal sera MS204 and MS203 were targeted as positive and borderline positive for NTD, respectively (Fig. 1 and 3). Specimen MS204 was from a patient with a prior pregnancy loss and presently screened positive for NTD. The all lab recommended actions (see below) were expectedly aggressive; correspondingly, the NTD screen resulted in a 1:6 risk for open neural tube defects (ONTD) and expectedly, the MS204 positive screen achieved a 100% all-lab consensus. The recommended action for the MS204 specimen was: sample repeat, 20%; ultrasound; 96%; and amniocentesis, 60%. Sample MS203, a borderline NTD screen result, was obtained from an Afro-American woman with a prior history of family pregnancy complications; however, her AF specimen screen resulted in an elevated AFP value (see Figure-2). The negative screen consensus (90%) for sample MS203, even in the face of an MS-MoM of 2.1, was probably influenced by the algorithm adjustments including both maternal race and body weight in addition to individual lab cutoff values. In view of these MS203 screen results (MoM = 2.1), her paired amniotic fluid AFP specimen proved to be elevated by all lab consensus indicating the need for Ache and possibly fetal hemoglobin analysis. It is germane to this discussion that the all-lab median MSAFP cutoff value for the Afro-American population (in our participating labs) is 2.5 MOM. Specimens MS201, MS202, and MS205 were targeted and achieved negative screens for NTD, and all labs recommended no further action. Of these samples, MS201 and MS205 produced positive screens for Triosmy-21 which is discussed below. Finally, the MS202 specimen was obtained from a woman of Asian descent which would indicate a body weight adjustment (90 lbs) in her risk assessment; in addition, some labs may employ ethnic-derived medians.

Specimen MS203, with a matched AFAFP, provided an interesting case in that the MSAFP specimen was all lab screen negative, while her paired AFAFP specimen screened positive (MOM = 2.2) due to lab cutoff differences (Fig. 1 & 2). This patient had a family history of severe pregnancy complications and adverse outcomes; thus, a paired maternal serum sample was obtained at time of amniocentesis. Her MSAFP MoM of 2.1, although screen negative for a black population, was accompanied by an amniocentesis outcome which proved to be NTD screen positive for AFAFP. A high definition Stage-II ultrasound and an Ache analysis later confirmed the presence of a small open NTD lesion in the spinal cord from the fetus of this mock patient. An all-lab NTD risk assessment for MS203 had been calculated as 1 in 1200 for maternal serum alone.

Regarding the trisomy screen, MS201 (gravida = 1, parity = 0) was intended to produce a positive Trisomy-21 (T21) screen with both the triple and quad testing platforms, which indeed was the case. The labs reporting either triple or quad testing concluded that sample MS201 was T21 screen positive (100% all lab consensus). Further action recommended for the T21 screen was determined as 65% ultrasound (US) and 80% amniocentesis (AM) for labs using the triple screen, and 60% US and 72% AM for labs employing the quad screen. Further recommended action on MS201 reflected the severity of the risk ratio assessment of 1:12 risk from the triple test versus 1:10 risk from the quad test, regardless of the software program employed. Note from the point distribution graphs comparing the triple with the quad test (Figs. 5 and 6) that the MS201 point cluster in the quad assay was just slightly lower than the MS201 cluster in the triple test. Again, the quad test clearly signaled a higher risk for Down syndrome while the triple test yielded a nearly equivalent risk; overall both signaled a very high risk for Down Syndrome.

The trisomy screen specimen for MS205 also produced a clearly positive Trisomy-21 (T21) screen with both the triple and quad testing platforms in which all labs agreed. The labs reporting either triple or quad testing resulted in a majority T21 positive screen consensus. Further action recommended for the T21 screens were recorded as 85% ultrasound (US) and 80% amniocentesis (AM) for labs using the triple screen; and 80% US and 72% AM for labs employing the quad screen. The risk ratio assessment was 1:42 for the triple test versus 1:10 for the quad test. Again, it was evident from the point distribution graphs comparing the triple with the quad test (Figs. 5 and 6) that the MS205 point cluster in the quad results was indeed lower than of the MS205 in the triple test. The risk of T21 in the MS205 specimen was far greater than that expected from maternal age alone (1:190) with both screening platforms indicating a very high risk for Down Syndrome.

The performances of the various kits for maternal serum analytes (AFP, uE3, hCG) are presented in a bar graph format (Figures 7-9) for each of the five MS samples. As shown in the MS-AFP graph, AFP mass measurements among the individual kits largely agreed, although Bayer-Centaur was somewhat higher (20%) while DPC Immulite and Beckman Unicel were slightly lower for some samples. For uE3, the all lab median was higher than 1.0 (1.3) due to the labs employing DPC Immulite and DPC Immulite 2000 which yielded values averaging nearly two times higher than the median (see dotted line). In contrast, Diagnostic Systems Lab RIA/EIA results were at the mean level while Beckman Access measured uE3 values nearly one-third lower than the median. These results continue to demonstrate some inherent differences as to how these assays recognize the uE3 in our mock sample preparations. Regarding the hCG kits, laboratories employing Abbott Axsym displayed higher mean values reaching nearly 1.3 times higher than the medians while Bayer-Centaur, Immulite, and Beckman Access yielded approximate mean (1.0) hCG values. In order to enhance uniformity among the various kits employed to measure hCG, we incorporate an intact (total) hCG recombinant analyte into our PT specimens. Labs lacking peer group companions and in-house assays will continue to be deemed non-gradable (NG) for hCG as well as other analyte groups as the situation dictates.

The bar graph in Figure 10 is provided to display kit performance among the amniotic fluid (AF-AFP) test samples. As shown in the amniotic fluid bar graph, overall kit performance approached that observed with the maternal serum samples. While Bayer-Centaur, and to a lesser extent Abbott-Axsym Kits kits were higher, Beckman Access and DPC Immulite were slightly lower than the all-lab mean as seen in previous mailouts. It was of interest that specimen AF203 produced a positive NTD screen (MOM = 2.2) in the face of a MSAFP screen MoM value of 2.1 (see above discussion and Figures 1&2). Note that the point distribution in the AFAFP MOM values produced a range of values extending from 1.69 to nearly 2.59 MOM, while the MSAFP values extended from 1.8 to 2.5 MoM. Finally, please be advised that these samples are derived from actual AF samples, and therefore these results are directly relevant to patient screening.

For informational purposes, it was deemed of interest to comment on the software usage by our participating laboratories. The alpha and Benetech software packages are each used by 23% of the labs; RMA software is employed by 29%; while in-house software comprised 19%, and 6% of labs use programs classified as "other" which are proprietary software packages.

G.J. Mizejewski, Ph.D.

New References (Suggested reading):

1. Dashe JS, Twickler DM, Santos-Ramos R, McIntire DD, Ramus RM. Alpha-fetoprotein dection of neural tube defects and the impact of standard ultrasound. American Journal of Obstetrics & Gynecology. 195:1623-1628, 2006.
2. Oguri H, Sumitomo R, Maeda N, Fukaya T, Moriki T. Primary yolk sac tumor concomitant with carcinosarcoma originating from the endometrium: Case report. Gynecologic Onocology. 103: 368-371, 2006.
3. Rozenberg P. Bussieres L. Chevret S. Bernard JP, Malagrida L Cuckle H, Chabry C, Durand-Zaleski I, Bidat L, Lacroix I, Moulis M, Roger M, Jacquemot MC, Bault JP, Boukobza P, Boccara P, Vialard F, Giudicelli Y, Ville Y. Screening for down syndrome using first-trimester combined screening followed by second-trimester ultrasound examination in an unselected population. American Journal of Obstetrics & Gyncology. 195: 1379-1387, 2006.
4. Chen CP, Lin SP, Wang TH, Chen YJ, Chen M, Wang W. Perinatal findings and molecular cytogenetic analyses of de novo interstitial deletion of 9q (9q22.3-->q31.3) associated with Gorlin syndrome. Prenatal Diagnosis. 26: 725-729, 2006.
5. Sari N. Yalcin B, Akyuz C, Haliloglu M, Buyukparmukcu M. Infantile hepatic hemangioendothelioma with elevated serum alpha-fetoprotein [Review] [24 ref] Pediatric Hematology & Oncology 23: 639-647, 2006.
6. Mulch AD, Stallings SP, Salafia CM. Elevated maternal serum alpha-fetoprotein, umbilical vein varix, and mesenchymal dysplasia: are they related? Prenatal Diagnosis. 26:659-661, 2006.
7. Lambert-Messerlian G, Dugoff L, Vidaver J, Canick JA, Malone FD, Ball RH, Comstock CH, Nyberg DA, Saade G, Eddleman K, Klugman S, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, D'Alton ME. First- and second-trimester Down syndrome screening markers in pregnancies achieved through assisted reproductive technologies (ART): a FASTER trial study. Prenat Diagn 26:672-678, 2006.
8. Tan TY and Amor DJ. Tumour surveillance in Beckwith-Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice [Review] [39 refs]. Journal of Paediatrics & Child Health. 42: 486-490, 2006.
9. Nagata C, Iwasa S, Shiraki M, Shimizu H. Estrogen and alpha-fetoprotein levels in maternal and umbilical cord blood samples in relation to birth weight. Cancer Epidemiology, Biomarkers & Prevention. 15: 1469-1472, 2006.
10. Benn PA, Makowski GS, Egan JF, Wright D. Reproducibility of risk figures in 2nd-trimester maternal serum screening for down syndrome: comparison of 2 laboratories. Clinical Chemistry. 52: 2087-2094, 2006.
11. Kajiyama Y, Tian J, Locker J. Characterization of distant enhancers and promoters in the albumin-alpha-fetoprotein locus during active and silenced expression. Journal of Biological Chemistry. 281: 30122-20131, 2006.
12. Leong SSJ, Middelberg APJ. The refodling of different alpha-fetoprotein variants. Protein Science. 15: 2040-2050, 2006.
13. Odibo AO, Sehdev HM. Stamillio DM. Macones GA. Evaluating the thresholds of abnormal second trimester multiple marker screening tests associated with intra-uterine growth restriction. American Journal of Perinatology. 23: 363-367, 2006.
14. Wang YY, Luo J, Zhu MW, Liu LN, Ma X. Second-trimester double or triple screening for Down syndrome: a comparison of Chinese and Caucasian populations. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 94:67-72, 2006.
15. Wald NJ, Morris JK, Ibison J, Wu T, George LM. Screening in early pregnancy for pre-eclampsia using Down syndrome quadruple test markers. Prenat Diagn 26:559-564, 2006.
16. Wright D, Bradbury I, Cuckle H, Gardosi J, Tonks A, Standing S, Benn P. Three-stage contingent screening for Down syndrome. Prenat Diagn 26:528-534, 2006.
17. Tang D, Yuan R, Chai Y. Direct electrochemical immunoassay based on immobilization of protein-magnetic nanoparticle composites on to magnetic electrode surfaces by sterically enhanced magnetic field force. Biotechnology Letters 28: 559-565, 2006.

18. Tsuboi S, Taketa K, Nouso K, Fujikawa T, Manabe K, Ohmori H, Higashi T, Shiratori Y. High level of expression of alpha-fetoprotein recetpor in gastric cancers. Tumour Biology 27:282-288, 2006.
19. Chen CK, Chang YL, Jou ST, Tseng YT, Lee YC. Treatment of mediastinal immature teratoma in a child with precocious puberty and Klinefelter's syndrome. Annals of Thoracic Surgery 82: 1906-1908, 2006.
20. Schiott KM, Christiansen M. Petersen OB, Sorensen TL, Uldbjerg N. The "Consecutive combined test" - using Double Test from week 8+0 and Nuchal Translucency Scan, for first trimester screening for down syndrome. Prenatal Diagnosis 26: 1105-1109, 2006.
21. Koelink CJL, van Hasselt P, Ploeg AD, van den Heuvel-Elbrink MM, Wijburg FA, Bijleveld CMA, van Spronsen FJ. Tyrosinernia type I treated by NTBC: How does AFP predict liver cancer? Molecular Genetics & Metabolism. 89: 310-315, 2006.
22. Nikkila A, Rydhstrom H, Kallen B. The incidence of spina bifida in Sweden 1973-2003: th eeffect of prenatal diagnosis. European Journal of Public Health. 16: 660-662, 2006.
23. Smith GCS, Shah I, White IR, Pell JP, Crossley JA, Dobbie R. Maternal and biochemical predictors of spontaneous preterm birth among nulliparous women: a systematic analysis in relation to the degree of prematurity. International Journal of Epidemiology. 35: 1169-1177, 2006.
24. Oyelese Y, Smullian JC. Placenta prevla, placenta accreta, and vasa previa. Obstetrics & Gynecology. 107: 927-941, 2006.
25. Wiwanikit V. Interaciton between alpha-fetoprotein gene and gonadotropin-releasing hormone and effects on brain sexual differentiation: Molecular funciton and biological process. Sexuality & Disability. 24: 169-173, 2006.
26. McLachlan RI, de Kretser DM. Hypogonadotropism with elevated serum testosterone: reversible causes of secondary infertifility. Nature Clinical Practice Urology. 3: 560-565, 2006.
27. Doherty D, Shurtleff DB. Pediatric perspective on prenatal counseling for myelomeningocele [Review]. Birth Defects Research 76: 645-653, 2006.

Abstracts

A). **Screening Abstract "Pick-of-the-Month":**

Title: Repeated measurement of pregnancy-associated plasma protein-A (PAPP-A) in Down syndrome screening: a validation study.

Source: Prenatal Diagnosis. 26 (8): 730-739, 2006.

Authors: Palomaki, Glenn E. Wright, David E. Summers, Anne M. Neveux, Louis M. Meier, Christian. O'donnel, Andrea. Huang, Tianhua. Knight, George J. Haddow, James E.

Address: Women and Infants Hospital, Providence, Rhode Island 02903, USA. gpalomaki@ipmms.org

Abstract: **Objective:** To confirm that measuring pregnancy-associated plasma protein-A (PAPP-A) in both first- and second-trimester serum samples improves Down syndrome screening. **Methods:** We selected paired first- and second-trimester stored serum samples from 34 Down syndrome pregnancies (cases) and 514 unaffected pregnancies (controls) and tested the second-trimester samples for PAPP-A and dimeric inhibin-A (DIA). First-trimester PAPP-A measurements were already available, as were second-trimester measurements of alpha-fetoprotein, unconjugated estriol (uE3), and human chorionic gonadotrophin (hCG). **Results:** PAPP-A was lower among cases than controls (0.47 MoM) in the first trimester (at an average of 12.5 weeks); in the second trimester, it was not different (0.91 MoM). Using repeated measures of PAPP-A alone, 21 of 34 cases were detected (62%, 95% CI 44% to 78%) with 5% false positive. At an observed 2% false-positive rate, the detection rates (DR) for the quadruple (69%) and serum integrated (69%) tests were lower than for the repeated measures test (75%). Modelled performance at 12 weeks was similar to these observed findings (70, 75, and 82%, respectively). If the first-trimester samples were collected at 10 weeks, however, DR would be higher (70, 81, and 91%, respectively). **Conclusion:** Adding a repeated measure of PAPP-A to existing serum markers improves Down syndrome screening to levels that are currently obtainable only by including ultrasound measurement of nuchal translucency (NT). Serum-based screening has the advantages of higher availability and reliability at a lower cost, resulting in a more effective screening strategy. A serum-based repeated measures test has a place in routine Down syndrome screening.

B). **Case History Screening "pick-of-the-month":**

Title: Beckwith-Wiedemann syndrome presenting with an elevated triple screen in the second trimester of pregnancy.

Source: Fetal Diagnosis & Therapy. 22: 18-22, 2007.

Authors: Aagaard-Tillery KM. Buchbinder A. Boente MP, Ramin KD.

Abstract: **Background:** Beckwith-Wiedemann syndrome (BWS) is a distinct clinical syndrome with unique features, is generally diagnosed postnally. Case: A 26-year-old patient, gravida 4, para 3-0-0-3, was noted to have an abnormal maternal serum screen. Amniocentesis with imaging studies was remarkable for observing a two-vessel umbilical cord and prominent maternal ovaries. The patient developed HELLP syndrome at 28 weeks and delivered a viable female infant with distinct clinical features. The diagnosis of TWS was confirmed by hypermethylation of the H19 gene on chromosome 11p15.5. **Conclusion:** This case describes a novel presentation of BWS and underscores the diagnostic potential of routine prenatal screens.

C). **Case History Therapy "Pick of the Month":**

Title: Endodermal sinus tumor of the infant vagina treated exclusively with chemotherapy.

Source: Journal of Pediatric Hematology/Oncology. 28 (11): 768-771, 2006.

Authors: Lacy Judith. Capra Michael. Allen Lisa.

Abstract: Endodermal sinus tumor (EST) of the vagina is a rare malignancy usually diagnosed before 3 years of age. Historically, the approach to therapy has included radical surgical resection, with adjuvant irradiation, and chemotherapy. An infant presented with vaginal bleeding, imaging evidence of a vaginal mass and an elevated alpha-fetoprotein level. Examination under anesthesia with vaginal biopsies confirmed the diagnosis of an EST (yolk sac) tumor of the vagina. After 5 cycles of chemotherapy, the alpha-fetoprotein had normalized and repeated vaginal biopsies for suspected residual disease was negative for malignancy. To allow preservation of sexual and reproductive function, chemotherapy as a sole modality of treatment for EST should be considered.

D). **News of Note: Abstract of New Markers and/or New Testing Agents:**

Title: Further resolution of alpha-fetoprotein glycoforms by two-dimensional isoelectric focusing and lectin affinity electrophoresis.

Source: Electrophoresis 27(17): 3480-3487, 2006.

Authors: Ichikawa E. Kuriyama S. Yuji J. Masaki T. Uchida N. Nishioka M. Taketa K.

Abstract: Human alpha-fetoprotein (AFP) from serum of patients with cirrhosis and hepatocellular carcinoma (HCC) was separated into several bands by IEF and by erythroaggulutinating bands studied directly by phytohemagglutinin (E-PHA) affinity electrophoresis. These AFP bands were directly compared in 2-D IEF and E-PHA affinity electrophoresis. IEF of serum AFP was run in 1% agarose IEF gel with 3% Pharmalyte 4.5-5.4. After IEF, a part of the gel was stained for AFP and another part of the gel corresponding to the area of separated AFP bands was cut in 1 mm x 39 mm along the focused direction and transferred to a trough in 1% agarose gel with 0.3 mg/mL E-4-PHA for second-dimensional affinity electrophoresis. Separated 2-D AFP spots were visualized by antibody-affinity blotting and identified by combining the systems of Johnson et al. (Johnson, P.J., Ho, S., Cheng, R., Chan, A et I., Cancer 1995 75, 1663-1668) for AFP-I-+IV and of Taketa et al. (Taketa , K., Ichikawa, E., Taga, H., Hirai, H., Electrophoresis 1985, 6, 492-497) for AFP-P1-5. AFP-P2, the major AFP glycoform, was composed of AFP-I, AFP-I, and AFP+II; AFP-P3, a nonspecific monosialo-AFP, was composed of AFP+II; AFP-P4, HCC-specific monosialo-AFP, was composed of AFP+II, AFP+III, and AFP+IV; and malignancy-related AFP-P5 was composed of AFP+I and AFP+II. Monosialo-AFP (AFP+II) was recovered in all the glycoforms of AFP-P2,-P3, -P4, and –P5; thus, AFP-P4 is more specific to HCC than monosialylated AFP+II.

E). **A proposed Method Application for Prenatal Screening:**

Title: Predicting the result of additional second-trimester markers from a woman's first-trimester marker profile: a new concept in Down syndrome screening.

Source: Prenatal Diagnosis 25(12): 1102-6, 2005 (December)

Authors: Maymon R. Cuckle H. Jones R. Reish O. Sharony R. Herman A.

Abstract: **Objective:** To describe a method for deciding whether an individual's first-trimester Down syndrome screening test result justifies further testing in the second trimester. **Methods:** Statistical modeling was used to estimate the distribution of second-trimester marker profiles for a given first-trimester profile and hence the probability of a final positive result, using a 1 in 250 term cut-off. A multi-variate log Gaussian model was used with published parameters. Markers were maternal serum pregnancy-associated plasma protein-A and free beta-human chorionic gonadotrophin (hCG) at 10 weeks, nuchal translucency at 11 weeks, and second-trimester maternal serum alpha-fetoprotein, total hCG, unconjugated estriol and inhibin-A. To illustrate the method, the model was applied to a published series of 24 Down syndrome and 367 unaffected pregnancies. **Results:** Modelling predicts that for 63% Down syndrome and 0.4% unaffected pregnancies having first-trimester tests, there is a 50% or more probability of a final positive result. A step-wise sequential screening policy based on immediate prenatal diagnosis for those with high probability and second-trimester testing for the remainder would have a 90% detection rate and 1.7% false-positive rate. Modelling also predicts 8.0% Down syndrome and 89% unaffected pregnancies with probabilities below 3%. A contingent screening policy restricting second-trimester testing to those with 3-49% probabilities would have an 88% detection rate and 1.4% false-positive rate. **Conclusion:** Predicting the probability of a positive final result from the first-trimester marker profile has potential utility, either as a decision aide for individual women or as a formal part of screening policy in selecting a subset of women for second-trimester testing.