Atellica IM Analyzer

Performance of First Trimester Maternal Screening Biomarkers: Pregnancy-associated Plasma Protein A (PAPP-A) and Free Beta Human Chorionic Gonadotropin (FBHCG) on the Atellica IM Analyzer

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Clinical Brief

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Abstract

Background: Serum PAPP-A and FBHCG are biochemical markers of Down syndrome and other chromosomal anomalies during the first trimester of pregnancy. A combination of maternal age-related risk factors and PAPP-A, FBHCG, and fetal nuchal translucency measurements can substantially increase the efficiency of prenatal screening. The Atellica® IM PAPP-A and FBHCG Assays are CE-marked assays intended for in vitro diagnostic use in the quantitative measurement of PAPP-A and FBHCG in human serum using the Atellica® IM Analyzer. The assays are not available in all countries.

Method: The ADVIA Centaur® XP PAPP-A and FBHCG Assay reagents were transferred to the Atellica IM Analyzer without modification. The PAPP-A and FBHCG assays have similarly designed components. One capture antibody is bound to paramagnetic microparticles, while another antibody is labeled with acridinium ester (NSP-DMAE) to form a sandwich with the analyte. Following incubation, wash, and magnetic separation steps, acid and base reagents are added. The resulting chemiluminescence is measured.

Results: The reportable range of the Atellica IM PAPP-A Assay is 0.01–10 IU/L; the range of the Atellica FBHCG Assay is 0.14–200 IU/L. Linearity studies following CLSI EP06-A were performed for both assays in their measurement ranges. Assay method comparison per CLSI EP09-A3 between the Atellica IM assays and the corresponding ADVIA Centaur assays resulted in a Passing-Bablok regression slope of 0.96, intercept of 0.00, and Pearson r value of 1.00 for PAPP-A (130 samples ranging from 0.01–8.72 IU/L) and a slope of 0.95, intercept of -0.98, and Pearson r value of 1.00 for FBHCG (131 samples ranging from 0.29–184.47 IU/L). In a precision study of three reagent lots and four samples carried out over 20 days, repeatability CV was 2.7–3.6% for PAPP-A and 1.3–1.5% for FBHCG; within-lab CV was 3.4–4.4% for PAPP-A and 2.3–2.6% for FBHCG. Functional sensitivity (limit of quantitation [LoQ]) was 0.01 IU/L for PAPP-A and 0.14 IU/L for FBHCG.

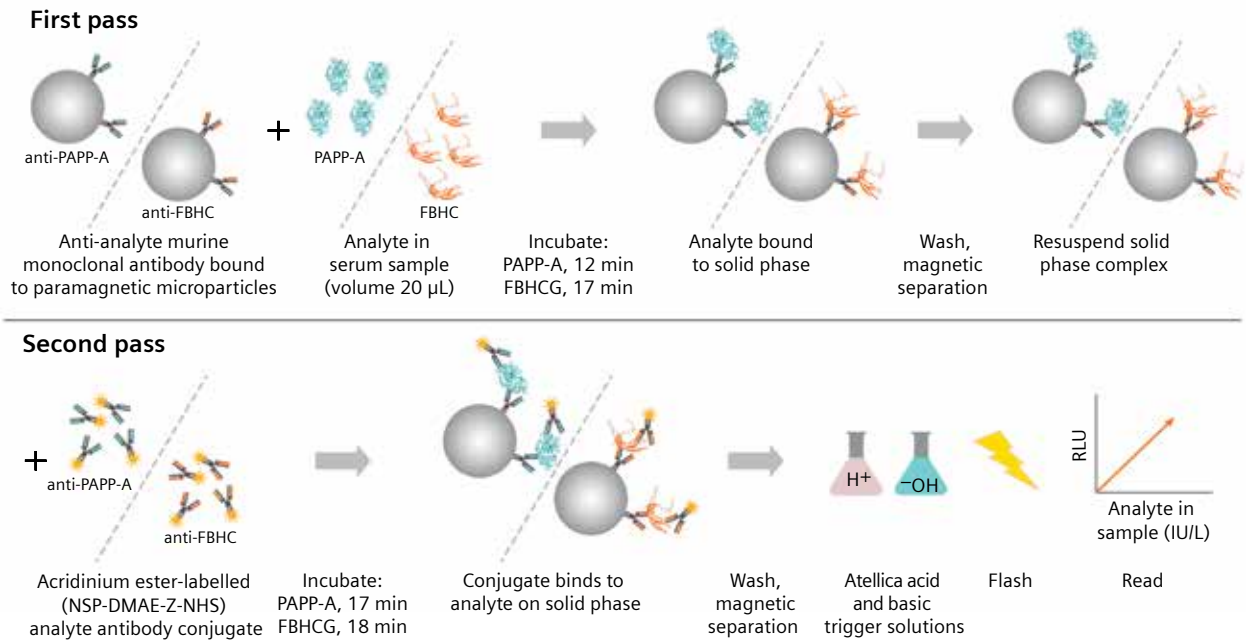
Discussion and Conclusions: The PAPP-A and FBHCG assay results show that the performance of the assays on the Atellica IM Analyzer is equivalent to that on the ADVIA Centaur XP system. The results also align with the maternal screening criteria of the Fetal Medicine Foundation for accuracy and precision.

Introduction: During the first trimester of pregnancy, low maternal levels of pregnancy-associated plasma protein-A (PAPP-A, a large molecular weight glycoprotein produced by the trophoblast) and elevated levels of the free β subunit of human chorionic gonadotropin (FBHCG, a 39.5 KDal pituitary glycoprotein hormone) are associated with Down syndrome and other fetal trisomies.[1-4] First trimester screening for Down syndrome and other trisomies is conducted between 11 and 14 weeks of pregnancy by evaluating these analytes in conjunction with maternal age-related risk data and fetal nuchal translucency (NT).[5]

Using this method, studies have demonstrated that Down syndrome detection rates of 85–90% at a 5% false-positive rate may be achieved.[6]

The Siemens Healthineers Atellica® IM PAPP-A Assay is standardized to an internal standard manufactured using human serum of known PAPP-A concentrations. The Atellica IM FBHCG Assay is traceable to the World Health Organization (WHO) 1st International Reference Preparation of Chorionic Gonadotrophin Beta Subunit Human; NIBSC code: 75/551. Both assays use the Bio-Rad LIQUICHEK Maternal Serum 1st Trimester Controls and unmodified ADVIA Centaur XP PAPP-A and FBHCG assay reagents and calibrators. Assigned values for calibrators are traceable to each assay's respective standardization. These assays are CE-marked to be used together in combination with other parameters to evaluate the risk of Trisomy 21 (Down syndrome) during the first trimester of pregnancy. Further testing is required for diagnosis of chromosomal aberrations.

Principle of the Assay



Methods

Precision (repeatability and within-lab: CLSI protocol EP05-A3).

- Four pooled serum samples/assay spanning each assay's measuring interval.
- Tested in duplicate over 20 days: 2 runs per day, 3 reagent lots, 240 results/sample.
- Imprecision of the combined three lots of data was calculated for repeatability (within-run CV) and within-lab (total CV) imprecision.

Detection capability (Limit of blank [LoB], limit of detection [LoD], and limit of quantitation [LoQ]: CLSI protocol EP17-A).

- LoB = highest measurement likely to be observed for a blank sample.
- LoD = lowest concentration detectable with 95% probability.
- LoQ (functional sensitivity) = lowest concentration providing 20% CV.

Dilution linearity (CLSI protocol EP06-A. Acceptance criterion = <LoD or <10% deviation from linearity, whichever is greater).

- Dilution levels (1-9) for each assay: 0%, 12.5%, 25%, 37.5%, 50%, 62.5%, 75%, 87.5%, 100%.
- FBHCG Level 9 = high normal nonpregnant female + first trimester pregnancy sera spiked with purified FBHCG to the desired concentration.
- FBHCG Level 1 = Normal female (nonpregnant) serum.
- PAPP-A Level 9 = second trimester pregnancy serum.
- PAPP-A Level 1 = Normal female (nonpregnant) serum.

Method comparison (CLSI protocol EP09-A3).

- One reagent lot and one calibrator lot/assay.
- One Atellica IM Analyzer and ADVIA Centaur XP system.
- First-trimester pregnancy serum samples: PAPP-A n = 130; FBHCG n = 131.

Clinical performance (originally established using the ADVIA Centaur XP assays which uses the same reagents as the Atellica IM assays).

- Determined indicative medians at 11–14 weeks of gestation.
- Analysed 916 first-trimester samples provided by the Fetal Medicine Research Institute (Kings College Hospital NHS Foundation Trust, stored at -70°C).
- Nontrisomy samples (n = 842): 841 PAPP-A; 842 FBHCG.
- Trisomy 21 samples (n = 60, per prenatal karyotype due to high risk of aneuploidy).
- All samples from nonsmoking Caucasian women with singleton pregnancies.

Results

Precision (repeatability and within lab): The standard deviation (SD) and coefficient of variance (CV) on the Atellica IM Analyzer is compared to precision data in the ADVIA Centaur XP Instructions For Use (IFU). The data was generated with a different sample set. The precision results indicate that the Atellica IM PAPP-A and FBHCG Assays demonstrate similar precision profiles when compared to the respective ADVIA Centaur XP assays.

			Repeatability (Within Run)		Within Lab (Total)	
Assay	Sample	Mean (IU/L)	SD (IU/L)	CV (%)	SD (IU/L)	CV (%)
Atellica IM PAPP-A assay (n = 240)	1	0.32	0.01	2.7	0.01	3.4
	2	1.54	0.04	2.7	0.05	3.4
	3	4.17	0.12	2.9	0.17	4.1
	4	9.03	0.32	3.6	0.40	4.4
ADVIA Centaur XP PAPP-A assay (n = 240)	1	0.29	0.01	2.2	0.01	3.7
	2	1.52	0.03	2.3	0.05	3.2
	3	4.17	0.10	2.3	0.16	3.7
	4	7.78	0.20	2.5	0.35	4.5
Atellica IM FBHCG assay (n = 240)	1	8.31	0.12	1.5	0.19	2.3
	2	20.03	0.31	1.5	0.51	2.5
	3	81.17	1.05	1.3	2.11	2.6
	4	177.70	2.30	1.3	4.02	2.3
ADVIA Centaur XP FBHCG assay (n = 240)	1	8.96	0.21	2.3	0.32	3.6
	2	21.36	0.44	2.1	0.63	2.9
	3	89.43	1.81	2.0	2.47	2.8
	4	170.78	2.97	1.7	4.17	2.4

Detection capability: The highest LoD and LoQ values of the three lots of reagents are reported in comparison to the values reported in the ADVIA Centaur XP system IFU.[7]

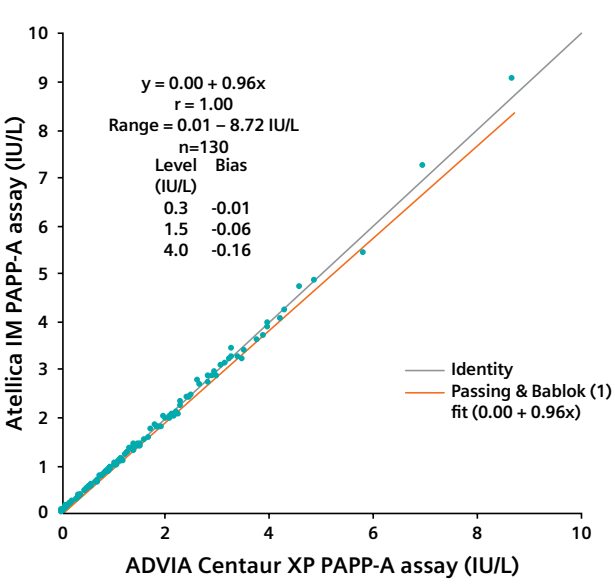
Assay	Limit of Detection (IU/L)			Limit of Quantitation (IU/L)		
	Lot 1	Lot 2	Lot 3	Lot 1	Lot 2	Lot 3
Atellica IM PAPP-A assay	0.005	0.005	0.005	0.01	0.01	0.01
ADVIA Centaur XP PAPP-A assay	0.01	0.01	0.01	0.01	0.01	0.01
Atellica IM FBHCG assay	0.10	0.10	0.11	0.13	0.14	0.11
ADVIA Centaur XP FBHCG assay	0.09	0.06	0.05	0.19	0.28	0.14

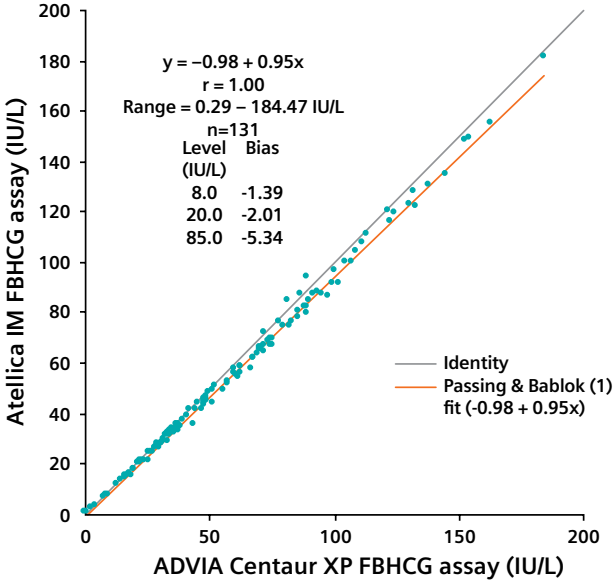
Dilution linearity: The Atellica IM PAPP-A and FBHCG Assays met the acceptance criterion of <LoD or <10% deviation from linearity, whichever is greater.[7]

PAPP-A Level	Observed (y) IU/L	Expected (x) IU/L	Linear Fit IU/L	Nonlinear Fit IU/L	Deviation from Linearity	
					IU/L	%
1	0.01	0.01	0.01	0.01	0.00	-0.1
2	1.91	1.78	1.83	1.89	0.06	3.0
3	3.68	3.54	3.65	3.69	0.04	1.2
4	5.50	5.31	5.47	5.45	-0.02	-0.4
5	7.18	7.08	7.29	7.18	-0.11	-1.5
6	8.85	8.84	9.11	8.90	-0.21	-2.3
7	10.69	10.61	10.93	10.64	-0.29	-2.7
8	12.49	12.38	12.75	12.42	-0.33	-2.7
9	14.15	14.15	14.57	14.25	-0.32	-2.3

FBHCG Level	Observed (y) IU/L	Expected (x) IU/L	Linear Fit IU/L	Nonlinear Fit IU/L	Deviation from Linearity	
					IU/L	%
1	0.00	0.00	0.00	0.00	0.00	0.1%
2	26.86	27.86	28.88	26.80	-2.08	-7.7%
3	57.25	55.73	57.77	56.33	-1.44	-2.5%
4	85.58	83.59	86.65	87.36	0.71	0.8%
5	120.21	111.45	115.53	118.70	3.16	2.6%
6	145.64	139.31	144.42	149.13	4.71	3.2%
7	177.89	167.17	173.30	177.44	4.14	2.3%
8	202.06	195.03	202.18	202.42	0.24	0.1%
9	222.90	222.90	231.06	222.88	-8.19	-3.7%

Method comparison: The results of the Passing-Bablok regression analysis and Pearson correlation coefficient indicate that the Atellica IM and ADVIA Centaur XP PAPP-A and FBHCG assays are equivalent.[7]



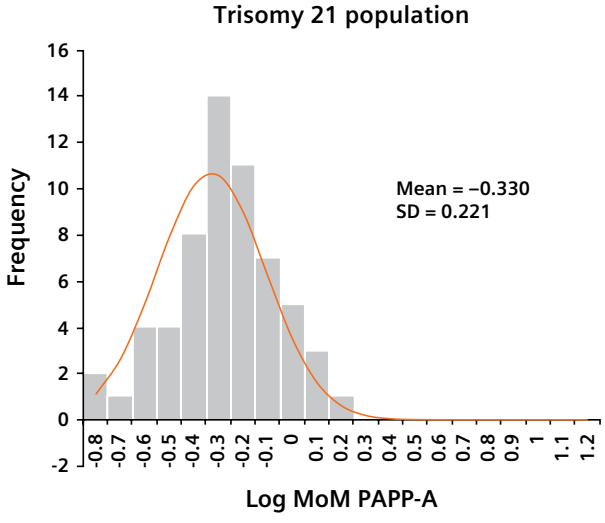


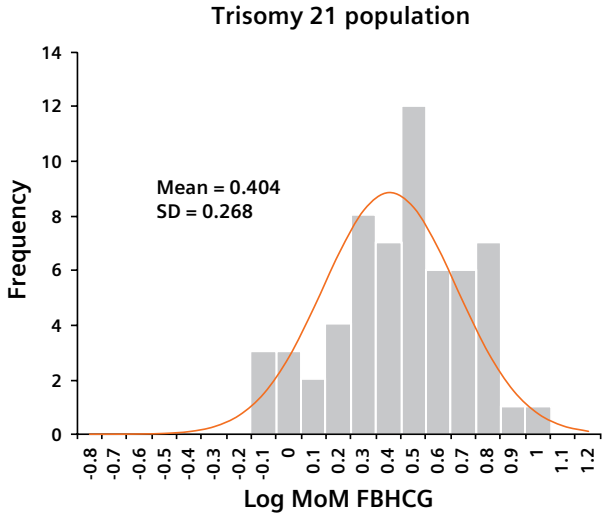
Clinical performance: Median, 5th percentile, and 95th percentile PAPP-A and FBHCG values were determined using the ADVIA Centaur XP assays for normal trimester pregnancies between 8 and 13 completed gestational weeks, and for trisomy pregnancies between 11 and 13 completed gestational weeks.[7]

Unaffected population	Gestational completed weeks	Gestational week median	n	5th Percentile (IU/L)	Median (IU/L)	95th Percentile (IU/L)
PAPP-A	8	8.71	78	0.25	0.64	1.51
	9	9.43	109	0.42	1.11	2.74
	10	10.43	138	0.77	1.84	4.71
	11	11.71	177	1.25	3.17	7.21
	12	12.57	174	1.59	4.28	9.96
	13	13.29	165	2.32	5.96	14.43
FBHCG	8	8.71	78	39.79	79.51	174.28
	9	9.43	109	26.60	67.08	169.39
	10	10.43	139	23.69	58.08	169.40
	11	11.71	177	16.18	44.11	131.86
	12	12.57	174	13.41	36.02	95.06
	13	13.29	165	11.46	28.40	81.93

Trisomy 21 population	Gestational Week (Week + Days)	n	5th Percentile (IU/L)	Median (IU/L)	95th Percentile (IU/L)
PAPP-A	11+0 to 12+6	30	0.81	1.84	3.57
	13+0 to 13+6	30	1.26	3.49	7.48
FBHCG	11+0 to 12+6	30	35.13	93.17	198.99
	13+0 to 13+6	30	24.75	79.95	184.27

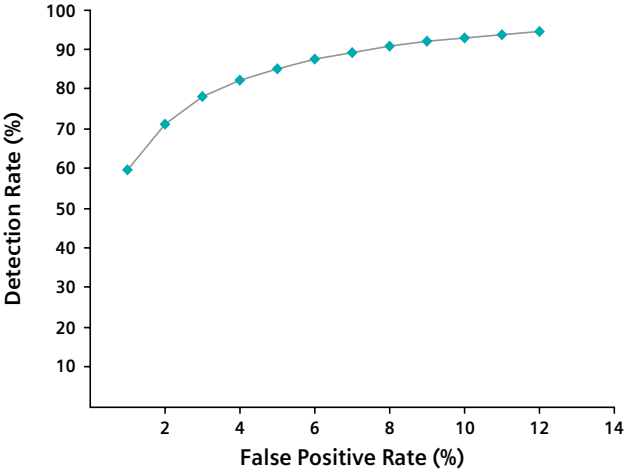
Results from unaffected and affected pregnancies were converted to multiples of the median (MoMs) to assess clinical performance. The unaffected population had mean MoMs of 0.000 with SD 0f 0.258 and 0.263 for PAPP-A and FBHCG, respectively. The Trisomy 21 population had mean MoMs of -0.330 and +0.404 for PAPP-A and FBHCG, respectively. See graph below for the MoM distribution of the affected population.





Modelling the trisomy 21 detection rate expected in clinical practice: A series of 100,000 random MoM values were selected for each marker from within the distributions of the affected and unaffected pregnancies and used to calculate likelihood ratios for the various marker combinations. Likelihood ratios used together with the age-related risk for trisomy 21 in the first trimester to calculate the expected detection rate of affected pregnancies in a population with the maternal age distribution of pregnancies in England and Wales for the year of 2001.[8,9]

The ROC plot of the modelled detection rate against the false-positive rate for the ADVIA Centaur XP FBHCG and PAPP-A assays, and the close alignment of the Atellica IM and FBHCG and PAPP-A Assays with their ADVIA Centaur XP counterparts indicate that the Atellica IM assays, when used together, can be expected to give a detection rate of 85% when assuming a 5% false-positive rate.



Conclusions

- The Atellica IM FBHCG and PAPP-A Assays were shown to have comparable detection capability and precision profiles as the ADVIA Centaur XP assays.
- The Atellica IM FBHCG and PAPP-A Assays demonstrate acceptable linearity across the assay reportable ranges.
- The Atellica IM FBHCG and PAPP-A Assays were shown to be comparable to ADVIA Centaur XP assays in method comparison.
- The ADVIA Centaur XP reagents for FBHCG and PAPP-A were successfully transferred to the Atellica IM Analyzer with comparable assay performance. Performance of these assays is aligned with the maternity screening guideline of the U.K. Fetal Medicine Foundation (FMF).

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