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White Paper

Analytical Performance of Dimension Vista Oncology Panel and Comparison to Commercially Available Oncology Assays

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Introduction

Cancer is a leading cause of death worldwide: it accounted for 7.9 million deaths (around 13% of all deaths) in 2007. Lung, stomach, liver, colon, and breast cancer cause the most cancer deaths each year; approximately 1.3 million, 803,000, 639,000, 610,000, and 519,000 global deaths occur each year, respectively, for each of these cancer types. Additionally, deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030.[1]

Some of the most common cancer types, such as breast cancer, cervical cancer, and colorectal cancer, have high cure rates when detected early and treated according to best practice. Principal treatment methods are surgery, radiotherapy, and chemotherapy. Fundamental for adequate treatment is an accurate diagnosis through imaging technology (ultrasound, endoscopy, or radiography) and laboratory (pathology) investigations.

While total PSA and free PSA are frequently used in early detection of prostate cancer, the majority of serum-based cancer markers available for routine clinical laboratory testing, including total PSA, are used in monitoring a patient's response to treatment. Markers used exclusively for monitoring include AFP for non-seminomatous testicular cancer, CEA, CA 15-3 for breast cancer, CA 19-9 for pancreatic cancer, and CA 125II for epithelial ovarian cancer. Siemens now offers AFP, CEA, CA 15-3,† CA 19-9,† CA 125II,™† TPSA, and FPSA methods utilizing LOCI® technology on the Dimension Vista® System.

LOCI oncology assays have large measurement ranges and demonstrate good performance characteristics

The Vista LOCI AFP, CEA, CA 15-3, CA 19-9, CA 125II, TPSA, and FPSA assays are homogeneous sandwich immunoassays using LOCI technology. Illumination of sandwich complexes at 680 nm generates singlet oxygen, which triggers a chemiluminescent signal proportional to the amount of antigen in the reaction. Both internal and external studies were conducted to examine the analytical performance of these methods. Table 1 shows the Limit of Blank (LoB), Limit of Detection (LoD), analytical range, extended range (with system autodilute capabilities), and the expected values for these seven Dimension Vista cancer markers.

† Uses antibodies licensed to Siemens through agreement with Fujirebio® Diagnostics, Inc.

Table 1: LOCI Oncology Characteristics

Method	LoB	LoD[1A]	Measurement Range	Extended Range	Expected Values/ Cutoffs[1B]
AFP	0.2 ng/mL	0.5 ng/mL	0.5 – 1,000.0 ng/mL	1:20	< 8.0 ng/mL
CEA	0.12 ng/mL	0.2 ng/mL	0.2 – 1,000.0 µg/L	1:10	< 3.0 ng/mL[1C] < 5.0 ng/mL[1D]
CA 15-3	0.3 U/mL	1.0 U/mL	1.0 – 300.0 U/mL	1:10	< 35.0 U/mL
CA 19-9	1.0 U/mL	2.0 U/mL	2.0 – 1,000.0 U/mL	1:20 & 1:100	< 37.0 U/mL
CA 125II	0.5 U/mL	1.5 U/mL	1.5 – 1,000.0 U/mL	1:10	< 35.0 U/mL
TPSA	0.008 ng/mL	0.010 ng/mL	0.010 – 100 ng/mL	1:20	< 4.0 ng/mL
FPSA	0.005 ng/mL	0.015 ng/mL	0.015 – 20 ng/mL	1:10	FPSA/TPSA ratio ≥20%

1A. LoD testing incorporated 2 instruments, 2 reagent lots, and 1 calibrator lot. The LoD and LoB listed are greater than the highest value obtained with a single instrument, as determined by a non-parametric approach.[2]
1B. In a normal, healthy population
1C. Non-smokers
1D. Smokers

Analytical Performance of Dimension Vista Oncology Panel and Comparison to Commercially Available Oncology Assays

Table 2 shows the results of precision assessed at clinical laboratories within the United States. Testing and analysis were performed in accordance with CLSI EP5-A2.[3]

Table 2: LOCI Oncology Precision Performance

Method	Material	Mean		Repeatability (% CV)		Within Lab (% CV)	
		Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
AFP (ng/mL)	MAS L1	12.3	12.1	1.0%	1.1%	1.8%	1.9%
	MAS L2	73.0	83.9	1.3%	1.2%	1.7%	2.3%
	MAS L3	134.5	155.8	1.0%	1.5%	1.8%	2.1%
	Plasma 1	239.1	237.6	1.3%	1.0%	2.5%	2.4%
	Serum 1	474.5	473.2	0.8%	1.5%	2.2%	3.0%
CEA (ng/mL)	BR L1	2.0	1.9	1.7%	2.0%	2.4%	2.8%
	BR L2	15.9	14.7	1.1%	1.1%	1.5%	1.8%
	BR L3	36.6	34.0	0.8%	1.2%	1.5%	1.9%
	Plasma 1	229.3	229.4	1.2%	1.1%	1.9%	2.7%
	Serum 1	65.3	71.8	0.9%	1.2%	1.7%	2.5%
CA 15-3 (U/mL)	BR L1	24.0	24.5	2.1%	2.8%	2.5%	3.9%
	BR L2	65.4	61.9	2.3%	1.5%	2.6%	3.2%
	BR L3	157.3	165.4	2.2%	1.8%	2.3%	3.4%
	Plasma 1	187.3	N/A	1.4%	N/A	1.8%	N/A
	Serum 1	36.1	N/A	1.9%	N/A	2.0%	N/A
CA 19-9 (U/mL)	BR L1	54.5	58.5	2.5%	2.8%	3.9%	4.0%
	BR L2	159.8	170.6	2.2%	1.3%	2.8%	2.6%
	BR L3	400.6	420.7	1.7%	1.3%	2.8%	2.3%
	Plasma 1	268.6	N/A	1.6%	N/A	3.1%	N/A
	Serum 1	26.1	N/A	3.2%	N/A	5.5%	N/A
CA 125II (U/mL)	BR L1	25.2	24.9	2.3%	2.0%	2.9%	2.7%
	BR L2	62.6	61.9	2.2%	1.5%	3.0%	3.2%
	BR L3	165.7	165.4	1.9%	1.8%	2.6%	3.4%
	Plasma 1	152.3	N/A	1.2%	N/A	1.9%	N/A
	Serum 1	39.0	N/A	2.4%	N/A	2.9%	N/A
TPSA (ng/mL)	MAS L2	14.665	14.503	1.8%	1.2%	2.8%	1.8%
	BR L2	2.319	2.307	2.4%	2.3%	4.1%	2.8%
	Serum 1	0.481	0.475	2.1%	2.4%	4.1%	2.4%
	Serum 2	76.406	74.588	1.9%	2.2%	3.2%	2.9%
FPSA (ng/mL)	BR L3	10.893	10.780	3.6%	4.0%	4.2%	4.9%
	Serum 1	0.171	0.179	4.4%	2.9%	5.0%	4.7%
	Serum 2	3.673	3.693	3.1%	2.4%	3.3%	2.7%

MAS: MAS Liquimmune® Immunoassay Control
BR: Bio-Rad Lyphochek® or Liquichek® Immunoassay Plus or Tumor Marker Control

Table 3 demonstrates results of testing when a number of endogenous interferences, including rheumatoid factor, are present in a sample around the upper limit of normal compared to a sample which does not contain the interferent. Testing was performed using the paired difference method.[4]

Table 3: LOCI Oncology Performance in Samples with Endogenous Interferences

		Method Results (% bias from sample with no interferent)						
Interferent	[Test] SI Units	AFP[3A,3B]	CEA[3A,3B]	CA 15-3[3C]	CA 19-9[3D]	CA 125II	TPSA	FPSA
Bilirubin – unconjugated	20 mg/dL	–2.3	0.1	–6.0c	–2.3	–2.1	2.7	0.9
Bilirubin – conjugated	60 mg/dL	–9.5	7.4	–4.8	–3.5	–4.3	–1.5	–1.2
Hemoglobin (monomer)	1,000 mg/dL	–4.8	–6.4	1.7	–8.0	–3.0	–5.7	–5.6
Lipemia (Intralipid®)	3,000 mg/dL	–2.0	–1.5	–1.6	–9.4	5.6	–3.9	–3.2
Triglyceride	3,000 mg/dL	–2.8	7.5	–7.1	8.8	5.6	–3.9	–3.2
Uric acid	20 mg/dL	–2.5	–1.9	1.1	–0.9	–3.1	–1.8	–2.7
Urea	500 mg/dL	0.7	–3.8	–2.0	1.0	–1.2	1.2	2.2
Creatinine	30 mg/dL	0.5	2.1	–0.4	1.7	1.1	1.2	1.7
Cholesterol	500 mg/dL	–5.6	–8.2	0.3	–2.3	–1.7	–0.9	–1.8
IgG	5 g/dL	–2.1	–2.7	–0.2	–6.0	–5.0	–7.1	–5.7
Albumin	6 g/dL	–1.4	–1.2	–2.5	–5.7	0.8	–2.9	–5.7
Protein: Total	12 g/dL	5.1	5.7	0.4	–7.7	–4.9	–9.4	–6.8
Rheumatoid Factor	1,500 IU/mL	2.0	–6.3	7.0	–9.2	–1.7	NA	NA

3A. Bilirubin (both conjugated and unconjugated) was tested at 80 mg/dL
3B. Rheumatoid Factor was tested at ~ 500 IU/mL
3C. Unconjugated bilirubin was tested at 60 mg/dL
3D. Hemoglobin was tested at 500 mg/dL and triglycerides were tested at 1,000 mg/dL
NA. Data not available

One-step sandwich immunoassays are susceptible to a high-dose "hook effect," where an excess of antigen prevents simultaneous binding of the capture and detection antibodies to a single analyte molecule.[5] To test for hook effect, samples with the analyte concentrations indicated in Table 4, were run neat and diluted. Instrument response was compared versus that of the highest level calibrator. Any instrument response below that of the highest calibrator was taken as evidence of a hook effect at the indicated concentration. For CA 19-9, testing was performed using native samples, while for all other markers, hook effect testing was performed with spiked samples. Up to the concentrations listed in Table 4, the various LOCI oncology assays demonstrated no hook effect. For all methods, these concentrations of analyte are well above typical clinical values.

Table 4: LOCI Oncology Hook Effect Performance

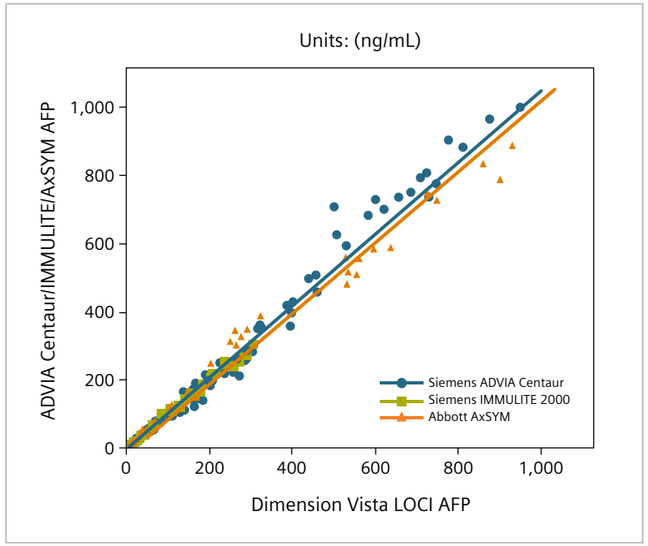
Method	No Hook Less than or Equal to...
AFP	1,000,000 ng/mL
CEA	225,000 ng/mL
CA 15-3	20,000 U/mL
CA 19-9	1,000,000 U/mL
CA 125II	110,000 U/mL
TPSA	50,000 ng/mL
FPSA	50,000 ng/mL

LOCI Oncology Performance Compared to Other Siemens and Manufacturers' Assays

LOCI oncology assays were compared with the assays on the Siemens Dimension,® ADVIA Centaur,® IMMULITE,® and various manufacturers' platforms. Results are shown in Figures 1-7.

Figure 1: ADVIA Centaur/IMMULITE/Abbott AxSYM® AFP vs. Dimension Vista LOCI AFP

Data was collected at an external site within the United States and internally at Siemens; the same samples were not used for all comparisons. Passing-Bablok regression analysis generated the results shown in the table below.

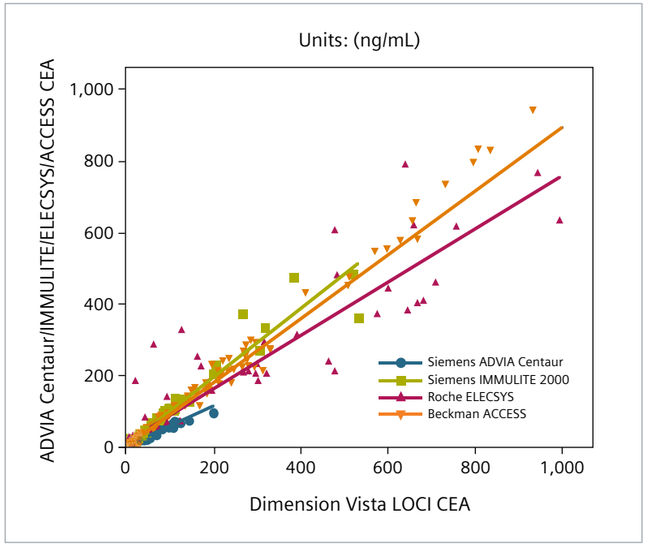


Comparison Assay[A]	Slope	Intercept	N	Dimension Vista Range
Siemens ADVIA Centaur	1.06	0.6	164	1.6 – 942.2
Siemens IMMULITE 2000	1.02	–0.9	49	2.2 – 299.3
Abbott AxSYM	1.06	0.0	80	1.0 – 924.0

A. Upper limit of AFP assay range (without dilution) is 363 ng/mL for IMMULITE, all others are 1,000 IU/mL

Figure 2: ADVIA Centaur/IMMULITE/Roche ELECSYS®/Beckman ACCESS® vs. Dimension Vista LOCI CEA

Data was collected at an external site within the United States and internally at Siemens; the same samples were not used for all comparisons. Passing-Bablok regression analysis generated the results shown in the table below.

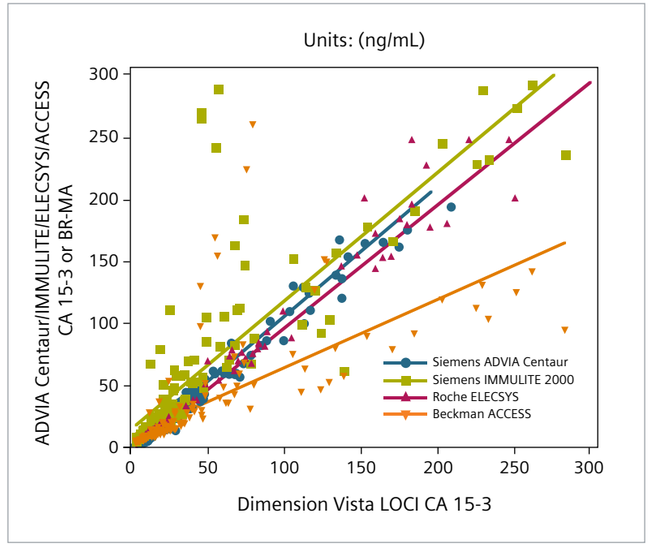


Comparison Assay[B]	Slope	Intercept	N	Dimension Vista Range
Siemens ADVIA Centaur	0.62	0.4	93	0.4 – 199.8
Siemens IMMULITE 2000[B]	1.09	0.3	100	0.4 – 531.8
Roche ELECSYS	0.85	0.7	112	0.5 – 990.0
Beckman ACCESS	0.96	–0.1	120	0.6 – 930.3

B. Upper limit of CEA assay range (without dilution) is 100 ng/mL for ADVIA Centaur and 550 ng/mL for IMMULITE, all others are 1,000 ng/mL

Figure 3: ADVIA Centaur/IMMULITE/ELECSYS/ACCESS vs. Dimension Vista LOCI CA 15-3

Data was collected at external sites within the United States and internally at Siemens; the same samples were not used for all comparisons. Passing-Bablok regression analysis generated the results shown in the table below.



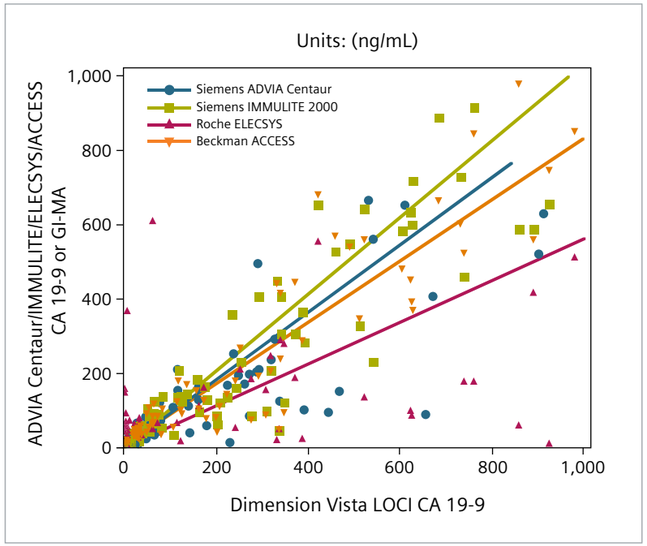
Comparison Assay[C]	Slope	Intercept	N	Dimension Vista Range
Siemens ADVIA Centaur	1.10	–3.2	234	4.7 – 208.0
Siemens IMMULITE 2000[D]	1.17	2.5	158	3.2 – 282.5
Roche ELECSYS	0.99	–0.2	74	6.7 – 249.8
Beckman ACCESS[D]	0.61	1.4	162	3.2 – 282.5

C. Upper limit of CA 15-3 assay range (without dilution) is 200 U/mL for ADVIA Centaur and 1,000 U/mL for ACCESS; all others are 300 U/mL

D. IMMULITE and Beckman ACCESS BR-MA assays do not utilize the Fujirebio DF3 and 115D8 antibodies

Figure 4: ADVIA Centaur/IMMULITE/ELECSYS/ACCESS vs. Dimension Vista LOCI CA 19-9

Data was collected at external sites within the United States; the same samples were not used for all comparisons. Passing-Bablok regression analysis generated the results shown in the table below.



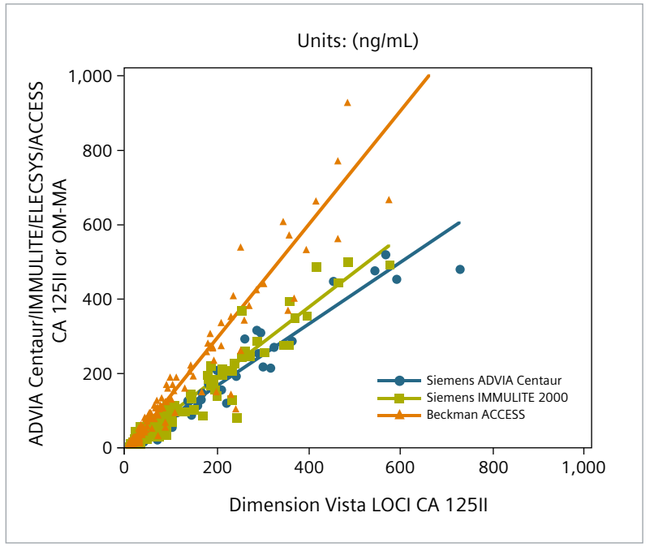
Comparison Assay[E]	Slope	Intercept	N	Dimension Vista Range
Siemens ADVIA Centaur	0.96	3.1	219	2.0 – 909.6
Siemens IMMULITE 2000[F]	1.03	8.0	134	2.1 – 923.0
Roche ELECSYS	0.74	12.5	75	3.9 – 979.2
Beckman ACCESS[F]	0.92	7.3	126	2.1 – 979.8

E. Upper limit of CA 19-9 assay range (without dilution) is 700 U/mL for ADVIA Centaur and 2,000 U/mL for ACCESS; all others are 1,000 U/mL

F. IMMULITE and Beckman ACCESS GI-MA assays do not utilize the Fujirebio 1116-NS-19-9 antibody

Figure 5: ADVIA Centaur/IMMULITE/ACCESS vs. Dimension Vista LOCI CA 125II

Data was collected at external sites within the United States; the same samples were not used for all comparisons. Passing-Bablok regression analysis generated the results shown in the table below.



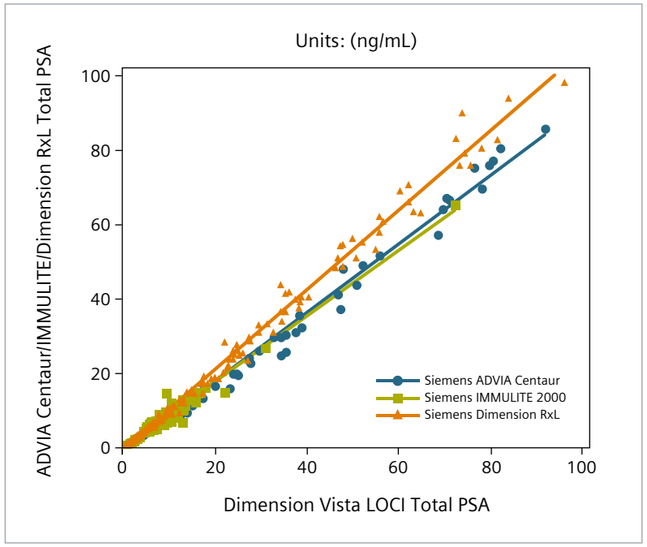
Comparison Assay[G]	Slope	Intercept	N	Dimension Vista Range
Siemens ADVIA Centaur	0.76	–0.7	247	1.1 – 726.3
Siemens IMMULITE 2000[H]	0.96	–3.2	186	3.7 – 572.5
Beckman ACCESS[H]	1.48	–5.3	188	3.7 – 816.4

G. Upper limit of CA 125II assay range (without dilution) is 1,000 U/mL for Dimension Vista, 600 U/mL for ADVIA Centaur, 500 U/mL for IMMULITE, and 5,000 U/mL for ACCESS

H. IMMULITE and Beckman ACCESS OM-MA assays do not utilize the Fujirebio OC 125 and M11 antibodies

Figure 6: ADVIA Centaur/IMMULITE/Dimension RxL vs. Dimension Vista LOCI Total PSA

Data was collected at external sites and internally at Siemens; the same samples were not used for all comparisons. Passing-Bablok regression analysis generated the results shown in the table below.

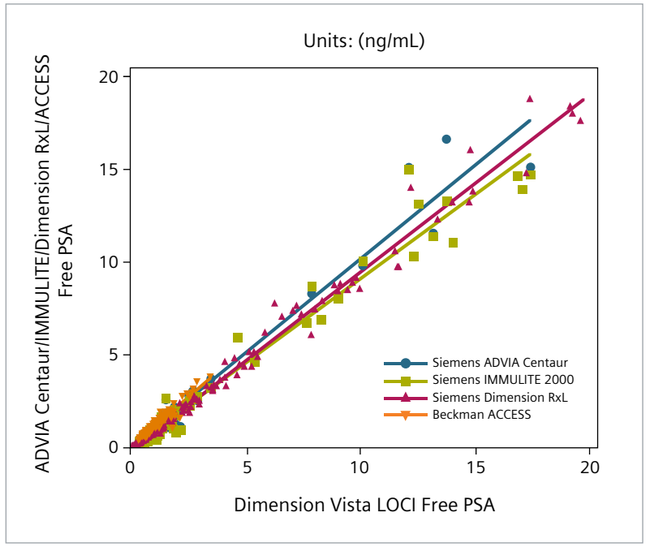


Comparison Assay[I]	Slope	Intercept	N	Dimension Vista Range
Siemens ADVIA Centaur	0.85	–0.02	138	0.29 – 91.50
Siemens IMMULITE 2000	0.89	–0.02	187	0.04 – 72.09
Siemens Dimension RxL	1.01	–0.17	287	0.07 – 95.90

I. Upper limit of PSA assay range is 100 ng/mL for ADVIA Centaur, Dimension RxL/EXL systems, and Dimension Vista. IMMULITE 2000 has an upper limit of 150 ng/mL

Figure 7: ADVIA Centaur/IMMULITE/Dimension RxL/Beckman ACCESS vs. Dimension Vista LOCI Free PSA

Data was collected at external sites and internally at Siemens; the same samples were not used for all comparisons. Passing-Bablok regression analysis generated the results shown in the table below.



Comparison Assay[J]	Slope	Intercept	N	Dimension Vista Range
Siemens ADVIA Centaur	1.03	–0.01	148	0.36 – 17.35
Siemens IMMULITE 2000	0.92	0.00	158	0.36 – 17.35
Siemens Dimension RxL	0.96	–0.08	260	0.03 – 19.70
Beckman ACCESS[K]	1.11	0.02	117	0.36 – 3.46

J. ADVIA Centaur and IMMULITE have an upper limit of 25 ng/mL, Dimension Vista and ACCESS have an upper limit of 20 ng/mL, and Dimension RxL has an upper limit of 45 ng/mL

K. Samples used for this comparison only spanned the clinically important region of the assay range

Conclusions

The Dimension Vista LOCI oncology assays have excellent precision, minimal interference from endogenous substances, are unaffected by hook up to very high analyte concentrations, and have wide analytical measurement ranges.

While comparison to other commercial methods indicates variability between assay manufacturers, it is noteworthy that for assays where an international standard exists (AFP, total PSA, and free PSA), differences between assays are minimal. Due to the variability between tumor marker assays, the NACB recommends that laboratories indicate the method used on reports and re-baseline patients when changing to a new tumor marker methodology.[6]

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