

Performance evaluation of the KRYPTOR Compact PLUS analyzer-based B.R.A.M.S CgA II KRYPTOR assay for chromogranin A measurement

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Research

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Abstract

Background: Numerous immunoassays have been developed to measure the levels of chromogranin A (CgA), a useful biomarker for diagnosing and monitoring generally heterogeneous neuroendocrine tumors (NETs). Here, we evaluated the imprecision and linearity of three such assays: KRYPTOR (ThermoFisher Scientific), NEOLISA (EuroDiagnostica), and CgA-RIA (CisBio) using 123 samples for each assay.

Results: The correlation coefficients between the assays were 0.932 (CgA-RIA versus NEOLISA), 0.956 (KRYPTOR versus CgA-RIA), and 0.873 (NEOLISA versus KRYPTOR). KRYPTOR showed good precision, with percent coefficients of variation less than 5% for low and high concentration quality controls. Linearity was maintained over a wide concentration range. Comparison of CgA levels from three disease entities (NETs, non-NET pancreatic tumors, and prostate cancer) and healthy controls showed that patients with NETs had significantly higher CgA levels ($n = 57$, mean: 1.82 ± 0.43 log ng/mL) than healthy individuals ($n = 20$, mean: 1.51 ± 0.23 log ng/mL; $P = 0.018$). No other significant differences between groups were observed.

Conclusion: All three immunoassays showed strong correlations in measured CgA levels. Because KRYPTOR operation uses a fully automated random-access system and requires shorter incubation times and smaller sample volumes, the KRYPTOR assay may improve laboratory workflow while maintaining satisfactory analytical performance.

1. Background

Chromogranin A (CgA) is a useful biomarker for diagnosis and monitoring of the extremely heterogeneous neuroendocrine tumors (NETs) [1]. NETs can arise in the stomach, intestines, rectum, pancreas, lungs, and adrenal and thyroid glands. One common feature of all NETs is that they originate from specialized cells belonging to the neuroendocrine (NE) system [2]. NE cells produce, mature, and exocytose secretory granules containing general neuroendocrine markers, such as CgA, and site-specific markers, such as amine and peptide hormones [3]. Although some NE cells are localized to a certain anatomic site and have precise functions (e.g., adrenal, pituitary, parathyroid), those belonging to the diffuse NE system make up a poorly defined thin layer dispersed throughout the bronchopulmonary and gastrointestinal systems [4]. Because NETs can arise in diverse anatomical sites and exhibit varying degrees of hormone secretion, diagnosis via tissue biopsy or imaging is limited. A specific amine or peptide hormone may serve as a biomarker for a specific type of NET. For example, gastrin may be used as a biomarker for gastrinoma, insulin for insulinoma, serotonin for small bowel NET, and glucagon for glucagonoma [4]. However, a more universal biomarker for all of these conditions is needed to facilitate early diagnosis. To date, CgA is the best available circulating biomarker for such applications.

CgA was the first of the eight members of the granin family to be identified. Granins are the major components of the soluble core of dense-core secretory granules in NE cells and are therefore secreted by these cells. Additionally, granins are thought to play important roles in granulogenesis, secretory protein

sorting, and secretory granule maturation and condensation [5, 6]. CgA is a heat-stable, hydrophilic protein composed of 439 amino acids. After translation, CgA undergoes post-translational processing to generate small peptides with specific biological activities, such as pancreastatin (corresponding to residues 250–301) and catestatin (corresponding to residues 352–372) [7]. CgA mRNAs and proteins are found in all types of neurons [8], indicating their potential as universal biomarkers.

Numerous immunoassays have been developed for measuring CgA levels. Among these, the B.R.A.M.S. CgA \times KRYPTOR assay (ThermoFisher Scientific, Waltham, MA, USA; KRYPTOR) uses time-resolved amplified cryptate emission (TRACE) technology, which allows for spectral and temporal distinction between signals of interest and unwanted background signals [9]. Moreover, the B.R.A.H.M.S. KRYPTOR Compact PLUS analyzer, which is the platform utilized for the assay, is a fully automated random-access system that requires less hands-on time and produces results more quickly.

In this study, we evaluated the analytical performance of KRYPTOR to determine if it may improve workflow in laboratories. Three CgA assays were compared: KRYPTOR, NEOLISA Chromogranin A (EuroDiagnostica, Malmö, Sweden [NEOLISA]), and CgA-RIA CT (CisBio Codolet, France [CgA-RIA]). To assess the analytical performance of KRYPTOR, we evaluated its linearity, precision, and correlation with the other two CgA assays. We also compared measured CgA levels in samples from patients with three different disease entities (NETs, non-NET pancreatic tumors, prostate cancer) to healthy individuals to determine whether serum CgA can be used to discriminate among these groups.

2. Results

2.1 Patient demographics

In total, 123 samples were collected from 118 patients. Patient demographics are shown in Table 1. The mean age of the patients was 59.9 years (range: 17–90 years). The male to female ratio was 1.622:1. The most common diagnosis among the patients was prostate cancer (25.4%) followed by gastroenteropancreatic-NETs (19.5%). The NETs diagnosed in most patients were of pancreatic origin. Twenty-three (19.5%) patients were taking proton pump inhibitors (PPIs).

Table 1
Patient demographics

Variables	Patients (n = 118)
Age, years	
Mean (SD)	59.9 (17.1)
Sex, n (%)	
Male	73 (61.9)
Female	45 (38.1)
Main diagnosis, n (%)	
GEP-NET	
Pancreas	19 (16.1)
Liver	1 (0.8)
Stomach	1 (0.8)
1 (0.8)	
Rectum	1 (0.8)
Paraganglioma	1 (0.8)
Pituitary	
Tumor	19 (16.1)
Other	2 (1.7)
Thyroid disease	6 (5.1)
Adrenal gland tumor	12 (10.2)
Prostate cancer	30 (25.4)
Pancreatic tumor	14 (11.9)
Liver	
Hepatitis	1 (0.8)
HCC	1 (0.8)
Von Hippel - Lindau disease	2 (1.7)
MEN1	1 (0.8)

GEP-NET, gastroenteropancreatic neuroendocrine tumor; HCC, hepatocellular carcinoma; MEN1, multiple endocrine neoplasia type 1

Variables	Patients (n = 118)
Other	6 (5.1)
PPI administration, n (%)	23 (19.5)
GEP-NET, gastroenteropancreatic neuroendocrine tumor; HCC, hepatocellular carcinoma; MEN1, multiple endocrine neoplasia type 1	

<Insert Table 1 here>

2.2 Assay characteristics

The characteristics of three different assays compared in this study are summarized in Table 2. All assays utilized two types of monoclonal antibodies with antigenic sites at different regions on CgA. NEOLISA and CgA-RIA operated in batch mode, while KRYPTOR operated in random-access mode. The required sample volume was 50 µL for NEOLISA and CgA-RIA but only 14 µL for KRYPTOR.

Table 2
Comparison of the three assays used in this study

	Assay		
	NEOLISA Chromogranin A	B.R.A.M.S. CgA \boxtimes	CgA-RIA CT
Method	ELISA	TRACE*	RIA
Company name	EuroDiagnostica (Malmö, Sweden)	Thermo Fisher Scientific (Waltham, MA USA)	CisBio (Codolet, France)
Antibody	2 monoclonal	2 monoclonal	2 monoclonal
Epitope	Residues 236–251, 264–279 [10]	Residues 250–301, unknown [11]	Residues 145–245 [12]
Unit	ng/mL, nmol/L, U/L	ng/mL	ng/mL
Recommended specimen	Serum, EDTA/heparin plasma	Serum, EDTA plasma	Serum, plasma
Cut-off	Heparin plasma: ≤ 108 ng/mL (or 3.0 nM or 35 U/L)	Serum: < 101.9 ng/mL	Serum: < 98 ng/mL
Operating mode	Batch	Random access	Batch
Incubation time	105 min	29 min	120 min
Required sample volume	50 µL	14 µL	50 µL
*TRACE: time-resolved amplified cryptate emission			

<Insert Table 2 here>

2.3 Correlation

2.3.1 CgA-RIA versus NEOLISA

A comparison of the CgA-RIA and NEOLISA assays is shown in Fig. 1A and B. Of the 123 samples collected, 90 were quantified using both assays. The results were compared using Passing-Bablok regression and Bland-Altman analysis. The slope of the regression line was 1.224 (95% confidence interval [CI]: 1.072–1.414) and the correlation coefficient was 0.932. The average bias between the methods was 0.036 log ng/mL (CgA-RIA – NEOLISA) with no specific trend as CgA levels increased.

2.3.2 CgA-RIA vs. KRYPTOR

A comparison of the CgA-RIA and KRYPTOR assays is shown in Fig. 1C and D. Of the 123 samples collected, 118 were quantified by both assays. The results were compared using Passing-Bablok regression and Bland-Altman analysis. The slope of the regression line was 0.9667 (95% CI: 0.9054–1.024), and the correlation coefficient was 0.956. The average bias between the methods was – 0.078 log ng/mL (KRYPTOR – CgA-RIA) with no specific trend as CgA levels increased.

2.3.3 NEOLISA versus KRYPTOR

A comparison of the NEOLISA and KRYPTOR assays is shown in Fig. 1E and F. Of the 123 samples collected, 118 were quantified by both assays. The results were compared using Passing-Bablok regression and Bland-Altman analysis. The slope of the regression line was 1.223 (95% CI: 1.055–1.408), and the correlation coefficient was 0.873. The average bias between the methods was – 0.052 log ng/mL (NEOLISA – KRYPTOR) with no specific trend as CgA levels increased.

The categorical distribution of all samples according to the cut-off value of each assay is summarized in Table 3. Agreement between the qualitative results for CgA-RIA and KRYPTOR assays was 90.24% (111/123; κ : 0.763; 95% CI: 0.700–0.826). For KRYPTOR versus NEOLISA, the agreement was 91.06% (112/123; κ : 0.760; 95% CI: 0.692–0.828). For CgA-RIA versus NEOLISA, the agreement was 92.68% (114/123; κ : 0.826; 95% CI: 0.771–0.881). There were 16 discrepant samples in total. These samples measured a mean CgA value of 150.58 ng/mL (standard deviation [SD] = 53.23 ng/mL) using CgA-RIA with a cut-off of 98 ng/mL. The average values obtained by NEOLISA and KRYPTOR were 112.62 ng/mL (SD = 26.75 ng/mL) and 100.32 ng/mL (SD = 49.04 ng/mL), respectively.

Table 3
Classification of CgA values measured with KRYPTOR, CgA-RIA, and NEOLISA

CgA		Below cut-off	Above cut-off	Total	Cohen's κ
NEOLISA					
CgA-RIA	Below cut-off*	82	0	82	0.826 (95% CI: 0.771–0.881)
	Above cut-off*	9	32	41	
	Total	91	32	123	
CgA-RIA					
KRYPTOR	Below cut-off†	82	12	94	0.763 (95% CI: 0.700–0.826)
	Above cut-off†	0	29	29	
	Total	82	41	123	
KRYPTOR					
NEOLISA	Below cut-off‡	87	4	91	0.760 (95% CI: 0.692–0.828)
	Above cut-off‡	7	25	32	
	Total	94	29	123	
*Cut-off value of CgA-RIA CT: < 98 ng/mL					
†Cut-off value of KRYPTOR: < 101.9 ng/mL					
‡Cut-off value of NEOLISA: ≤ 108 ng/mL					

<Insert Table 3 here>

2.4 Linearity

To validate the linearity of the KRYPTOR assay, five concentrations were prepared using quality control materials of low and high concentrations provided with the kit. Each sample was measured twice, and the average values are plotted in Supplementary Fig. 1. The equation for the linear regression line was $y = 0.9993x - 6.5174$, and its determination coefficient was 0.9998.

2.5 Precision

The within-run %CVs for low (75.55 ng/mL; SD = 1.44 ng/mL) and high (486.6 ng/mL; SD = 10.46 ng/mL) concentration samples were 1.72% and 1.44%, respectively. For between-run %CVs, the values were 1.94% and 2.26% for the low and high concentration samples, respectively. All %CVs were within 5%, indicating good assay precision. The precision data are summarized in Table 4.

Table 4

Within-run, between-day, and total imprecision as recommended by Clinical and Laboratory Standard Institute (CLSI EP15-A3 [13])*

Chromogranin A	Mean	SD	Imprecision (%CV)		
			Within run	Between day	Total
Low	75.55	1.44	1.72	1.94	1.19
High	486.6	10.46	1.44	2.26	1.86

*In total, 25 replicates were tested at each concentration, including five replicates tested per day for five separate days. Concentrations are in ng/mL.

<Insert Table 4 here>

2.6 CgA values according to patient diagnosis

CgA measured using KRYPTOR on samples from patients within the three study cohorts (NETs, non-NET pancreatic tumors, prostate cancer) and from healthy individuals were compared with the Mann-Whitney U test. Samples from patients taking PPIs and one sample from the NET group that measured below the lower limit of detection (11.8 ng/mL) were excluded. Median CgA levels in patients with NETs (n = 57), non-NET pancreatic tumors (n = 12), and prostate cancer (n = 16) were 1.74 log ng/mL (interquartile range (IQR): 0.87 log ng/mL), 1.75 log ng/mL (IQR: 0.44 log ng/mL), and 1.80 log ng/mL (IQR: 0.29 log ng/mL), respectively (Fig. 2). For healthy individuals (n = 20), the median CgA level was 1.45 log ng/mL (IQR: 0.29 log ng/mL). The CgA levels in patients with NETs were significantly higher than those in healthy individuals ($P = 0.018$). However, there were no significant differences in any other comparisons.

3. Discussion

We compared three assays using three different methods: enzyme-linked immunosorbent assay (NEOLISA), TRACE (KRYPTOR), and radioimmunoassay (RIA; CgA-RIA) [11, 14, 15]. Overall, the analytical performance of KRYPTOR was acceptable. The assay was precise, with %CVs for the low and high concentration quality control materials below 5% for all conditions and showed linearity over a wide concentration range. Moreover, a comparison of the three assays showed high correlation with each other (CgA-RIA versus NEOLISA, 0.932; KRYPTOR versus CgA-RIA, 0.956; and NEOLISA versus KRYPTOR, 0.873). The cut-off value provided for each assay was applied to examine the categorical distribution of the samples used in this study. Although the cut-off values provided for KRYPTOR and CgA-RIA were based on serum samples, those for NEOLISA was based on plasma samples. To verify whether the cut-off value for NEOLISA from plasma samples was also compatible with serum samples, CgA was measured using both plasma and serum samples from five patients with different CgA concentrations. Each sample was measured twice, and the average of the two values was plotted to obtain a linear regression equation of $y = 1.264x - 0.8124$ and determinant coefficient of 0.9817 (Supplementary Fig. 2). Because the CgA levels in the serum and plasma samples measured by NEOLISA were strongly

correlated, the cut-off value of NEOLISA for plasma samples was applied to the serum sample values obtained in our study. Our findings also showed substantial agreement among the three assays. In total, 16 samples gave discrepant results in at least one of the assays. All 16 samples tested above the cut-off value when measured with CgA-RIA, which is expected because this assay had the lowest cut-off value. Moreover, the average CgA levels of these 16 discrepant samples obtained using NEOLISA and KRYPTOR were much closer to the cut-off values for each assay, i.e., 108 ng/mL (NEOLISA) and 101.9 ng/mL (KRYPTOR). The demographic characteristics of these 16 patients exhibited no specific trend.

We found that CgA levels in patients with NETs were significantly higher than from healthy individuals, whereas those from patients with non-NET pancreatic tumors and prostate cancer were not significantly different from healthy individuals. When CgA levels from the three disease groups were compared, there were no significant differences. Studies reporting an association between CgA levels and tumor location observed the highest values in ileal NETs; pancreatic NETs exhibit intermediate values; and gastric, pituitary, and parathyroid tumors had even lower values [16]. Therefore, the lack of significant differences may be explained by the fact that our NET group did not include samples from patients with ileal NETs but did include samples from 21 patients with pancreatic NETs and 20 patients with pituitary NETs. Moreover, although rare, prostate adenocarcinomas can undergo neuroendocrine differentiation during the later stages of disease progression [17]. In fact, elevated CgA levels in patients with prostate cancer has reportedly been correlated with the disease stage [18]. Patients with pancreatic adenocarcinomas have also been reported to show higher CgA levels than healthy individuals [19]. These factors may have contributed to the absence of significant differences in CgA levels for samples from patients with NETs, non-NET pancreatic tumors, and prostate cancer.

Our study had some limitations. First, the number of samples analyzed in this study was small. If samples were collected from a larger and more diverse patient cohort, their diagnoses may also have been more diverse. Thus, our analysis of CgA levels in patients with different types of NETs may have yielded significant differences between groups. Additionally, among the many factors affecting serum CgA concentrations, we only considered PPI administration. The most frequent causes of falsely (non-NET) elevated CgA levels in clinical practice are the use of PPIs, the presence of chronic atrophic gastritis, and impairment of kidney function [20, 21]. Nevertheless, we did not consider patient factors other than PPI administration that could potentially influence CgA levels.

4. Conclusions

The overall analytical performance of the KRYPTOR assay was acceptable. Moreover, we observed a high correlation of KRYPTOR with other CgA assays. Because KRYPTOR operates using a fully automated random-access system and requires shorter incubation times and lower sample volumes, KRYPTOR assays may represent a superior workflow option with satisfactory analytical performance.

5. Methods

5.1 Sample collection

Residual serum samples from 123 laboratory samples for which CgA levels had been determined by NEOLISA were collected and stored at -20°C. Collected samples with known NEOLISA results were tested with KRYPTOR and CgA-RIA according to the manufacturers' recommendations.

Research involving human specimens complied with all relevant national regulations, institutional policies, and the tenets of the Helsinki Declaration (as revised in 2013). The study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (IRB no. 1-2020-0058). The requirement for informed consent was waived.

5.2 Linearity and precision

To verify the linearity of the KRYPTOR assay, two samples with low and high concentrations were mixed to produce five concentrations in the following proportions: 4:0, 3:1, 2:2, 1:3, and 0:4. Each concentration was measured twice.

The low and high concentration quality control materials provided with the kit were measured five times on each day for five days, and the percent coefficient of variation (%CV) was calculated.

5.3 CgA values relative to patient diagnosis

To detect any significant differences in CgA values according to patient diagnosis, samples were divided into three disease groups: NETs, non-NET pancreatic tumors, and prostate cancer. Diffuse NETs, paragangliomas, pituitary tumors, adrenal gland tumors, Von Hippel-Lindau disease, and multiple endocrine neoplasia type 1 were included in the NET category. Samples not corresponding to any of the three groups were excluded. Patients taking PPIs and samples with CgA values below the lower limit of detection were also excluded. Samples from the three disease groups were also compared with 20 additional samples collected from healthy control individuals.

5.4 Statistical analysis

For statistical analysis, Microsoft Excel 2013 (Seattle, WA, USA), Analyse-it for Microsoft Excel Method Evaluation Edition version 5.40.2 (Analyse-it Software, Ltd., Leeds, UK), SPSS Statistics v.23 (SPSS, Inc., Chicago, IL, USA), and Prism 8.0 (GraphPad Software, Inc, La Jolla, CA, USA) were used. Passing-Bablok regression, Bland-Altman analysis, and Cohen's kappa coefficient were used to evaluate correlation and agreement between the three assays. Linearity was evaluated by linear fit regression. The Mann-Whitney U test was used to evaluate significant differences in the distribution of CgA measurements depending on the patient's diagnosis. Results were considered statistically significant when the *P* value was less than 0.05.

Declarations

Ethics approval and consent to participate

Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013) and was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (IRB No. 1-2020-0058). The requirement for informed consent was waived because of the retrospective nature of this study, provided that all patient data were anonymized and that the study involved samples that were already available rather than some prospectively collected.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

None

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Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Figures

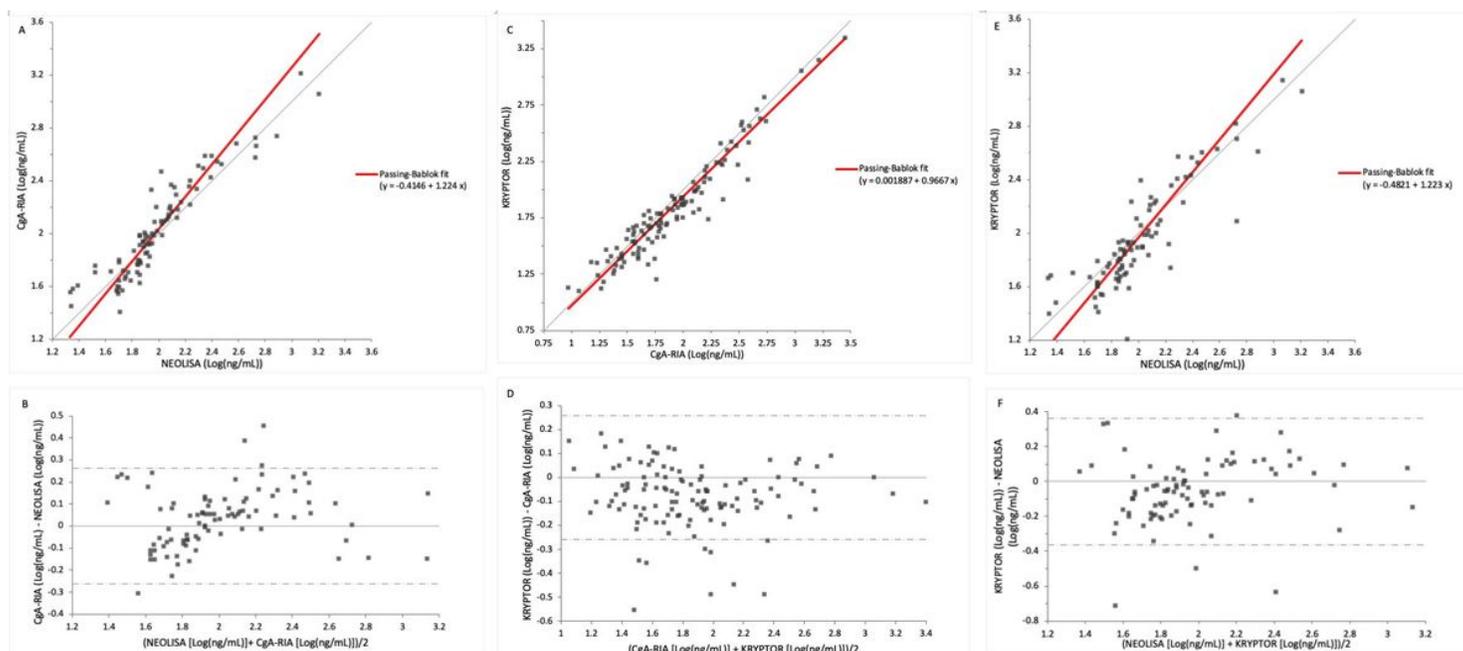


Figure 1

(A) Comparison between CgA-RIA and NEOLISA by Passing-Bablok analysis. The equation of the regression line was $y = -0.415 + 1.224x$, and correlation coefficient was 0.932. (B) Difference plot of CgA-RIA and NEOLISA measurements using Bland-Altman analysis. Average bias (0.036 log ng/mL; SD = 0.134 log ng/mL) is marked by a solid line, and the 95% confidence interval (CI) is shown by two dotted lines. (C) Comparison between KRYPTOR and CgA-RIA using Passing-Bablok analysis. The equation of the regression line was $y = 0.002 + 0.967x$, and the correlation coefficient was 0.956. (D) Difference plot of KRYPTOR and CgA-RIA measurements using Bland-Altman analysis. Average bias (-0.078 log ng/mL; SD = 0.132 log ng/mL) is marked by a solid line, and the 95% CI is shown by two dotted lines. (E) Comparison between KRYPTOR and NEOLISA using Passing-Bablok analysis. The equation of the regression line was $y = -0.482 + 1.223x$, and the correlation coefficient was 0.873. (F) Difference plot of KRYPTOR and NEOLISA measurements using Bland-Altman analysis. Average bias (-0.052 log ng/mL; SD = 0.185 log ng/mL) is marked by a solid line, and the 95% CI is shown by two dotted lines.

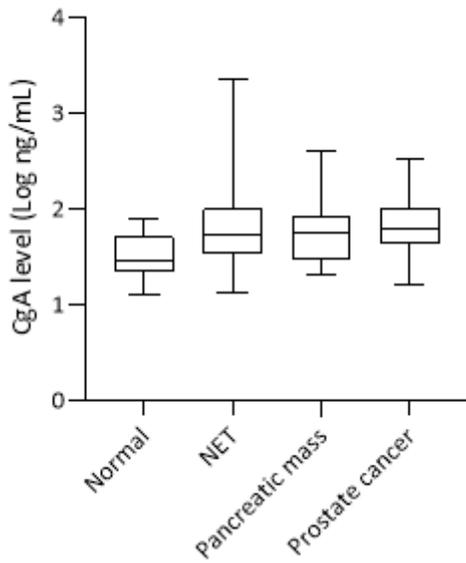


Figure 2

Box plot of CgA levels measured with KRYPTOR in relation to patient diagnosis.

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