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Comparison of LUMIPULSE® G1200 With Kryptor and Modular E170 for the Measurement of Seven Tumor Markers

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Background: Tumor marker measurements are becoming essential for prognosis and follow-up of patients in oncology. In this context, we aimed to compare a new analyzer, Lumipulse® G1200 (Fujirebio group, distributed in Europe by the Innogenetics group) with Kryptor® (Thermo Fisher Scientific B.R.A.H.M.S, Asnières, France) and Modular® Elecsys E170 (Roche Diagnostics, Meylan, France) for the measurement of seven tumor markers: PSA, AFP, CEA, CA 15-3, CA 125, CA 19-9, and Cyfra 21-1. *Methods:* A total of 471 serum samples from patients with elevated tumor markers and 100 serum from healthy patients were analyzed with Lumipulse® G1200 and either Kryptor® (for AFP) or Modular® (for the six other markers). *Results:* The good precision of Lumipulse® G1200 assays was confirmed with CVs $< 2.5\%$ and $< 5.0\%$, obtained, respectively, for within-run imprecision and intermediate imprecision (except for Cyfra 21-1: CV $< 13\%$). For all markers, Lumipulse results were well correlated with Modular or Kryptor results ($r \geq 0.94$). Concordance of results interpretation was $> 95\%$ and tumor marker kinetics were all similar. *Conclusion:* We confirmed the analytical performances of Lumipulse® tumor marker assays except for the CYFRA 21-1 assay for which performances were poor in this study. We noticed a few discrepancies for the CEA assay. Besides, values obtained for CA 19-9 were higher with Lumipulse leading to a bias (slope $= 1.5$). But for the four other tumor markers assays (PSA, AFP, CA 125, CA 15-3), the results were directly transferable between Lumipulse and Kryptor or Modular, thus facilitating an eventual substitution of one system by another. J. Clin. Lab. Anal. 30:5–12, 2016.

Key words: imprecision; evaluation; comparability; kinetic; luminescent measurements; prostate-specific antigen; alpha-fetoproteins; mucin-1; CA-125 antigen; CA-19-9 antigen

INTRODUCTION

As the incidence of cancers increased in the last century, tumor marker measurements became increasingly important for the evaluation of prognosis, patient follow-up under treatment and early detection of relapses.

This study focused on seven tumor markers assessed in daily routine. First, alpha-fetoprotein (AFP) is a glycoprotein of 70 kDa, produced physiologically by the yolk sac and the liver during fetal development and abnormally produced by malignant hepatocytes or germ-cell tumor (1–3). The second one, the prostate specific antigen (PSA) produced by prostate epithelial cells, is elevated in various prostatic disorders such as benign prostate hyperplasia or prostate cancer (4, 5). Carcinoembryonic antigen (CEA) is a glycophosphatidyl-inositol (GPI)-anchored, intercellular adhesion molecule normally produced only during fetal development. CEA is upregulated in various types of cancer like lung or colorectal cancer (6, 7), in which it inhibits cell differentiation and anoikis (8,9), thus increasing tumorogenecity and metastasis potential. Mucin-1 is a transmembrane dimeric protein expressed on normal secretory cells, implicated in the formation of gels and

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chemical barriers. In malignant conditions, such as breast cancer (10, 11), mucin-1 is increased, abnormally glycosylated and detected by CA 15-3 assays. CA 125 is a glycoprotein secreted by normal endometrium and present in the epithelia of many organs such as ovaries, colon, lung, kidney, pancreas, and gall bladder. It increases in ovarian cancer (12, 13), as well as in benign ovarian conditions and serous inflammation. CA 19-9 is a modified sialylated Lewis blood group antigen, increased in pancreatic cancer and other gastrointestinal conditions like jaundice or cirrhosis (14–16). Last, Cyfra 21-1 is a soluble fragment of cytokeratin 19, an intermediate filament protein important for epithelial cell stability. Cyfra 21-1 concentration is increased in many types of cancer, especially nonsmall-cell lung carcinoma (17–19). So, these circulating tumor markers became important in clinical and biological practice.

But, it is well known that tumor marker concentrations in a given sample measured by different analyzers vary according to assay methods, antibodies used, and reagent specificities. Hence, it is of great importance that results given by different analytical systems are exact, precise, and above all comparable. Especially when a changeover of system is taking place in a laboratory, it is important to know if the new tumor marker assays are comparable to the existing ones for accurate result interpretation.

The Lumipulse® G1200 (Fujirebio group, distributed in Europe by the Innogenetics group) is a fully automated chemiluminescent enzyme immunoassay analyzer. It is launched by Fujirebio, well known for its expertise in oncology, and is widely used in Japan since 2008. It has been recently introduced in Europe via its affiliated companies of the Innogenetics group (in France, Innogenetics SARL, a Fujirebio company, Les Ulis, France) with a large assay menu including Fujirebio markers in various fields like endrocrinology and oncology. Unlike other systems, both the analyzer and the monoclonal antibodies (mAb) are provided by the same manufacturer, Fujirebio, and should guarantee good performances.

Tumor marker measurement systems differ in many aspects but often have in common the mAb used, manufactured by Fujirebio Diagnostics (20). Thus, a relative agreement between the different methods is expected. Actually, while some systems give equivalent results (21–23), some show no transferability (24–28).

The aim of this study was to evaluate Lumipulse G1200 performances for the measurement of AFP, PSA, CEA, CA 15-3, CA 125, CA 19-9, and Cyfra 21-1. Results transferability with our routine analyzers, Kryptor and Modular Elecsys was carried out using individual results and kinetics of tumor markers established during patient follow-up. Moreover, the practicability of the system under routine laboratory conditions was also evaluated.

MATERIALS AND METHODS

Instruments

Lumipulse® G1200 is a fully automated chemiluminescence-based enzyme immunoanalyzer (CLEIA). It is a midsized analyzer, with a unique mono-test cartridge concept and continuous sample loading. All measurements are performed in 25 min, allowing a highthroughput of 120 tests per hour.

All assays relay on two mAb, one labeled with alkaline phosphatase (ALP) and the other one coated on iron beads. Chemiluminescence is produced after AMPPD (3-(2′-Spiroadamantane)-4-methoxy-4-(3′′−phosphoryloxy)phenyl−1,2−dioxetane) hydrolysis by ALP into an unstable product which stabilizes by emitting light, measured at 477 nm.

Kryptor® (Thermo Fisher Scientific B.R.A.H.M.S, Asnières, France) is an automated analyzer with a patented detection system, Time Resolved Amplified Cryptate Emission (TRACE). TRACE technology is based on a nonradiative energy transfer between a donor (cage-like structure with an europium ion (cryptate)) and an acceptor (XL665, an algual alophycocianin) (29), both coupled to a mAb specific to each assay.

Modular® Elecsys E170 (Roche Diagnostics, Meylan, France) is an electrochemiluminescence-based immunoanalyzer. The Elecsys AFP assay for Modular analyzer uses a mAb labeled with biotin and another mAb coupled with Ruthenium. In the presence of the antigen (AFP), immunocomplexes are immobilized onto the surface of the electrode with magnetic beads labeled with streptavidin. Application of an electric voltage to the electrode then induces chemiluminescence detected by a spectrophotometer.

Samples and controls

According to the Clinical and Laboratory Standard Institute (CLSI) guidelines (30), document EP9-A2, samples were selected to cover a clinically meaningful range of concentrations. A first series of samples represented high values of tumor marker concentrations. They were screened from the Pitié-Salpêtrière laboratory database. Samples collected between April 2011 and January 2012 with at least one tumor marker above reference system cut-off value were selected. They had been first analyzed as part of routine activity with the reference systems, and then stored at −20°C. Before analysis on the Lumipulse G1200, they were thawed at room temperature, homogenized, and centrifuged.

A second series of samples represented normal tumor marker values and were obtained from sera of blood donors collected at the "Etablissement Français du Sang, Paris" and immediately analyzed with both systems. The

clinical status of patients with elevated marker concentration was not documented but the healthy donors were considered to be free of any tumoral disease because they were screened with a questionnaire.

For the quality controls (QC), three levels of Seronorm™ Immunoassay QC (Alere) were used. The low level was near the cut-off value of both systems, while the medium and high levels explored the pathological concentrations. During the study, those controls were stored at −20°C; then thawed and kept at 4°C for a week. Due to the absence of Cyfra 21-1 in this control, two levels of Kryptor Cyfra 21-1 QC were also used. Those controls were stored at −20°C, then thawed and kept at 4°C for a day.

All assays were performed according to manufacturer's recommendations.

Imprecision evaluation

Measurements were performed twice a day during 10 days for the intermediate imprecision evaluation and ten times in a single run for within-run imprecision.

Method and kinetic comparisons

Method comparison was conducted according to CLSI guidelines (30) using 551 results obtained from 360 patient samples. All outliers values were controlled with both systems. Passing-Bablock regression and Bland-Altman diagrams were plotted using MedCalc 12®, with a percent *y* scale for Bland-Altman diagrams, rather than an absolute scale, because the standard deviation increased with the concentration. Cut-off values comparison was performed using manufacturer's reference values to discriminate positive results from negative results and then calculate positive and negative concordance.

Kinetic patterns were established from serial measurements of these markers during chemotherapy. Curves were obtained by plotting logarithm of tumor marker concentrations in function of the time with either Kryptor or Modular and Lumipulse results. The pairs of kinetics obtained were compared on their shapes, half-lives, doubling-times, and nadir values.

RESULTS

Only 471 out of 577 samples initially selected were retrieved and analyzed to obtain a total of 630 tumor marker results. Results ten times superior to Lumipulse assays linearity limits were excluded, leaving 551 tumor marker results from 360 patient samples for the method comparison.

Analytical performances

The analytical performances of the seven tumor marker assays are summarized in Table 1. Within-run imprecision and intermediate imprecision CVs were very good for AFP, PSA, CEA, and the three CA markers, with CVs below 2.5% and 5.0%, respectively, for all three levels of controls. Imprecision was slightly better for medium and high concentrations with intermediate imprecision CVs below 3.5%. These performances were comparable to those obtained by Cho in a previous study (31).

Cyfra 21-1 assay seemed less precise than the others, with within-run imprecision CV below 8.5% and intermediate imprecision CV below 13%. But its imprecision was assessed with only ten measurements and with a different control material (Cyfra 21-1 Kryptor QC) and should be verified with more measurements.

Method comparison

The method comparison consisted in a Passing-Bablock regression analysis (32) and a Bland-Altman difference plot (33), using concentrations within and above linearity limits of both systems (Fig. 1).

As summarized in Table 2, Passing-Bablock regression parameters exhibited a good correlation between analyzers for PSA, AFP, CEA, CA 125, CA 15-3, and Cyfra 21-1 ($r \geq 0.94$) with slopes ranging from 0.86 to 1.13 and intercepts ranging from −4.9 to 0.4. For CA 19-9, results were higher with Lumipulse than with Kryptor (slope = 1.5), indicating the presence of a proportional bias between Lumipulse and Kryptor results.

Linear regression results were similar when including only values within the linearity range of both systems (data not shown) and confirmed results obtained by Cho (31).

The Bland-Altman plots for PSA, AFP, CA 15-3, CA 125, and Cyfra 21-1 (Fig. 1A, B, C, D, and G) showed very good means of differences (−10% to 7%) and 95% limits of agreement (−60% to +50%), thus confirming the possible result transferability between Lumipulse and analyzers used in this study (Kryptor and Modular). For CA 19-9 (Fig. 1E), the mean of differences was 16% with a large 95% confidence interval (−82% to +113%). Furthermore, differences between assays increased with the analyte concentration, confirming the presence of a significant proportional bias and a poor result transferability between Lumipulse and Kryptor CA 19-9 results. This result contrasts with the fact that both assays use the same monoclonal antibody (26) (Centocor 1116-NS-19-9) but is concordant with previous studies which demonstrated that Kryptor tends to underestimate CA 19-9 values (26) compared to chemiluminescence-based analyzers.

CEA Lumipulse and Kryptor assays were well correlated ($r \geq 0.980$), yet some discrepancies were noted on

TABLE 1. Precision Performances of Lumipulse G1200 in Measuring Seven Tumor Markers

	Number of measurements	Mean concentration	Coefficient of variation (%)	
			Within-run Imprecision	Intermediate fidelity
CA 15-3				
Low	24	32.44	1.24	3.63
Medium	22	66.73	0.87	2.56
High	19	88.28	1.11	2.79
CA 125				
Low	22	31.55	1.61	4.90
Medium	21	55.88	1.20	2.96
High	20	98.69	1.20	3.08
CA 19-9				
Low	21	31.69	2.07	3.41
Medium	21	149.00	1.01	2.68
High	18	241.42	0.90	2.75
CEA				
Low	22	3.86	2.41	3.72
Medium	18	14.10	0.89	3.09
High	21	44.66	1.14	2.94
AFP				
Low	22	7.98	1.59	2.98
Medium	22	122.15	1.40	2.87
High	22	249.72	1.46	2.43
PSA				
Low	24	3.94	1.29	2.28
Medium	21	10.65	0.90	2.05
High	22	15.73	1.22	1.85
Cyfra21-1				
Low	10	1.67	4.80	12.95
High	9	11.04	8.45	8.44

CA, Carbohydrate antigen; CEA, Carcinoembryonic antigen; AFP, Alpha-foetoprotein; PSA, Prostate Specific Antigen. Units are kU/L for CA 15-3, CA 125 and CA 19-9 and ng/ml for PSA, AFP, CEA, and Cyfra 21-1. Seronorm Immunoassay QC was used for all markers except for Cyfra 21-1 (Kryptor QC).

the Passing-Bablock and Bland-Altman plots (Fig. 1F) with a mean difference of +20% and large 95% limits of agreement (−45 to +85%), suggesting a poor result transferability between Lumipulse and Kryptor CEA results.

One patient, suffering from colic adenocarcinoma, had discordant Lumipulse and Kryptor results. At different sampling times, one CA 125 and two CA 19-9 Lumipulse results were two to three times higher than Kryptor's but no analytical explanation was found. Consequently, those results were considered as outliers and excluded from the analysis.

Cut-off values comparison

We compared all tumor marker concentrations to the respective cut-off value recommended by each manufacturer. For all tumor markers, positive and negative concordances were ≥95% (except for CA 19-9, 93%), meaning that for 95% of patients, the clinical interpretation of a tumor marker measurement did not differ whether the analysis was performed with Lumipulse or Kryptor (or Modular for AFP). For CA 15-3, CA 125, and AFP, discordances concerned samples with values above Kryptor cut-off and below Lumipulse cut-off. For CA19-9, the bias was responsible for some of the discrepancies observed (mostly values above Lumipulse cut-off and below Kryptor cut-off). For PSA, CEA, and CYFRA 21-1, discordances were observed in less than 1% of samples, thus interpretation results did not differ between Lumipulse and Kryptor. All these discrepancies affected only borderline values, limiting false clinical interpretations.

Patient kinetics comparison

Tumor marker measurement plays a critical role in the monitoring of patients with cancer. For this purpose, several studies (34–37) have suggested that a kinetic approach is more appropriate than individual tumor marker measurements because it allows the calculation of parameters such as half-life, doubling time, and the representation of the exponential nature of tumor growth.

Thus, the follow-up of patients with cancer often includes tumor markers kinetics, performed by plotting log tumor marker concentration in function of time and

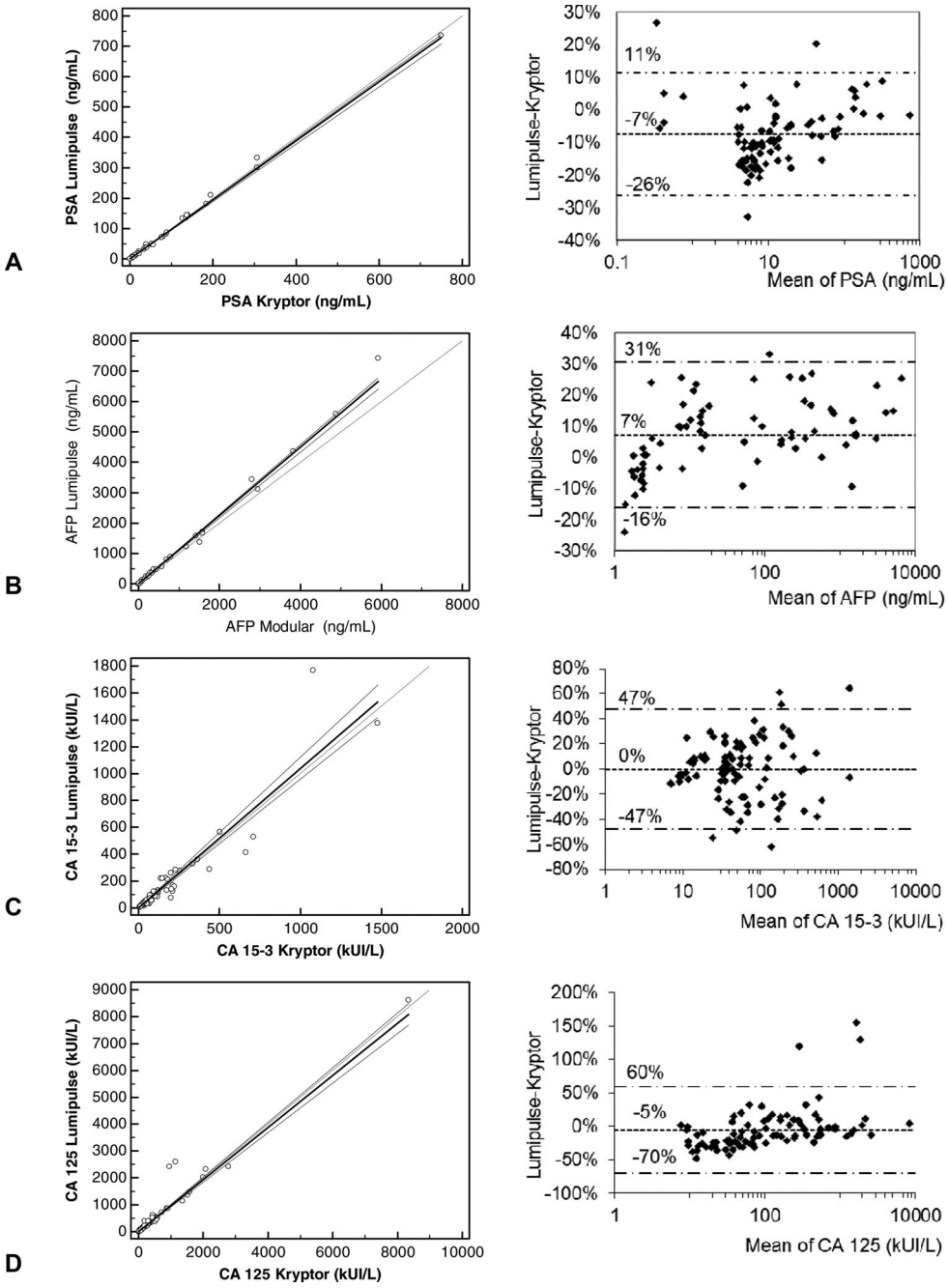

Fig. 1. Method comparison for PSA (A), AFP (B), CA 15-3 (C), CA 125 (D), CA 19-9 (E), CEA (F) and Cyfra 21-1 (G). Left column: Passing-Bablock regression plots with the regression line (solid line), the confidence interval for the regression line (dashed lines) and the identity line (x = y, dotted line). Right column : Bland-Altman plots with mean of differences and 95% confidence intervals.

calculating various kinetic parameters (half-life, doubling-time, and nadir), which are powerful indicators of therapeutic efficiency.

A total of 43 kinetics (≥ 4 kinetics for each tumor marker, except only one kinetic for CYFRA 21-1) were analyzed, all of them had similar profiles, doubling times, half-lives, and nadir, whether the analyzer was Lumipulse or Kryptor (Modular for AFP). Four of them are illustrated in Figure 2. The first case (Fig. 2A), is a CA 15-3 kinetic plotted with Kryptor vs. Lumipulse results. With both systems, similar doubling-times (67 vs. 64 days), half-lives (18 vs. 15 days) and nadir (23 vs. 25 kUI/l at the same time) were calculated, thus leading to similar clinico-biological interpretations. All the three

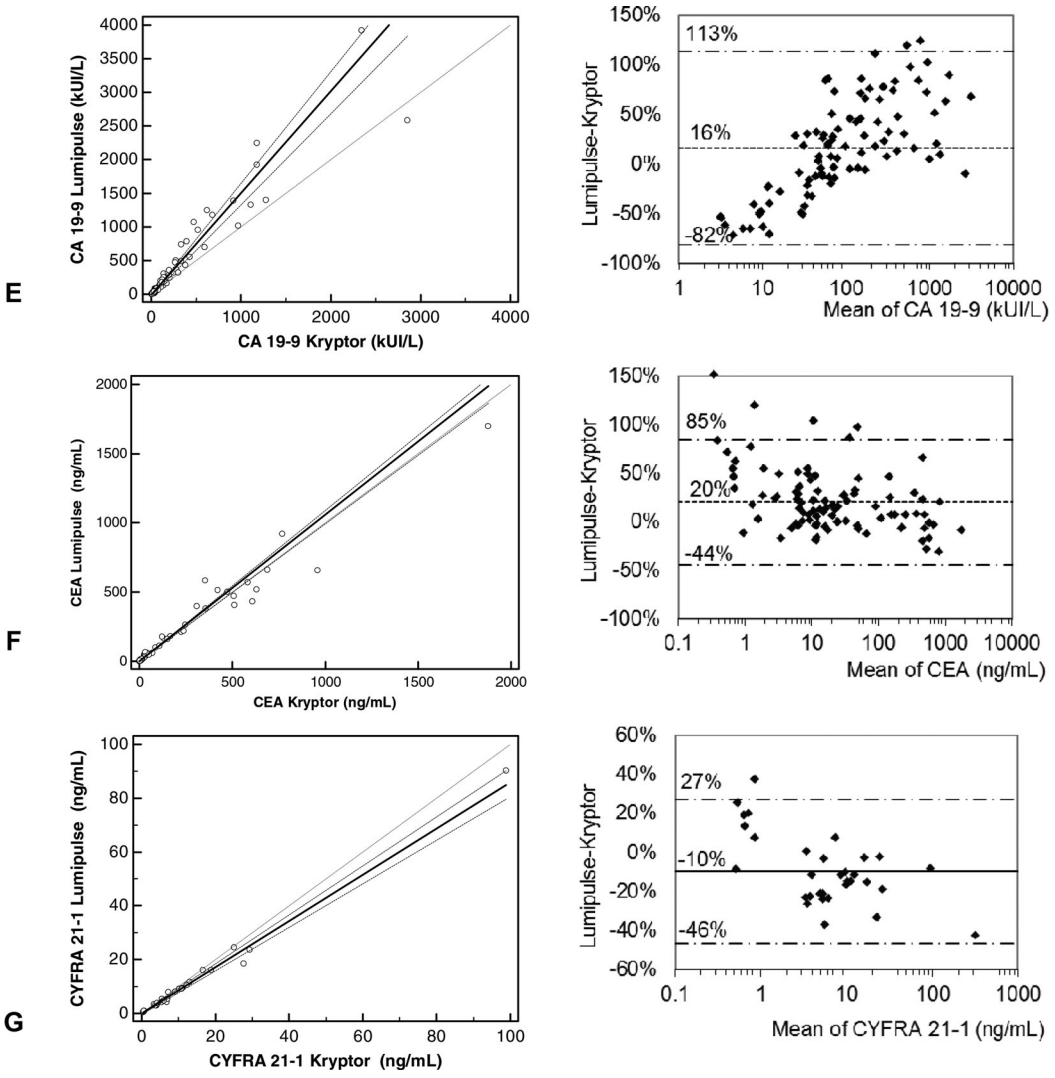

Fig. 1. Continued.

other kinetics (Fig. 2B, C, and D) had similar profiles and parameters, suggesting that CA 125 and AFP Lumipulse kinetics lead to the same clinico-biological interpretations as the reference systems kinetics. Finally, all 39 other Lumipulse kinetics (≥1 for each tumor marker) had profiles similar to Kryptor or Modular kinetics. To conclude, for all seven tumor markers, Lumipulse kinetics lead to the same clinico-biological interpretations as the reference systems, whether the objective was the evaluation of response to treatment or the early detection of relapse.

One patient out of 43 had discordant Lumipulse and Kryptor kinetics. He was suffering from gastric adenocarcinoma, treated by cetuximab and monitored by CA 19-9 kinetic (Data not shown). A quenching effect was suspected of interfering with CA 19-9 Kryptor measurement, lowering dramatically the Kryptor's results. This interference was drastically reduced after sufficient sample dilution. Cetuximab or tumoral metabolites were suspected as quenching agent. It seemed that Lumipulse was not affected by this interference.

DISCUSSION

In this study, we confirmed the analytical performances of Lumipulse G1200, especially its good precision with a within-run imprecision CV < 2.5% and an intermediate imprecision CV < 5.0% for PSA, CEA, AFP, CA 15-3, CA 125, and CA 19-9 assays. Cyfra 21-1 assay imprecision was not that good, with CV < 9% for within-run imprecision and CV < 13% for intermediate fidelity, possibly due to the use of a different control and the small number of measurements.

Method comparison between Lumipulse and Kryptor (or Modular for AFP) exhibited good correlations for all

TABLE 2. Passing-Bablock Regression Parameters for LUMIPULSE Assays

Marker	Reference system	*N*	Slope (95% CI)	Intercept	*r*
CA 15-3	Kryptor	96	1.04 (0.96–1.12)	−0.83	0.938
CA 125	Kryptor	85	0.96 (0.91–1.00)	−4.68	0.998
CA 19-9	Kryptor	92	1.52 (1.36–1.66)	−13.84	0.948
CEA	Kryptor	96	1.06 (0.99–1.09)	0.43	0.980
PSA	Kryptor	83	0.97 (0.94–0.98)	−0.59	0.997
Cyfra 21-1	Kryptor	31	0.86 (0.81–0.91)	0.09	0.996
AFP	Modular	68	1.13 (1.08–1.15)	−0.33	0.998

N, number of samples; *r*, correlation coefficient; CI, confidence interval.

assays ($r \geq 0.94$) and even result transferability between systems (mean of differences ± 10% and limits of agreement ± 60%) for PSA, CA 15-3, CA 125, and Cyfra 21-1 assays. On the contrary, comparison of CA 19-9 and CEA Lumipulse vs. Kryptor assays revealed a significant bias (mean of differences = 15–20%) and large limits of agreement (−80% to +110%), suggesting a poor equivalence between systems. Cut-off values comparison confirmed that Lumipulse and Kryptor (or Modular) discriminate the same samples as normal or pathological for all tumor markers except for CA 19-9. Finally, analysis of 43 patient tumor markers kinetics and comparison of their parameters demonstrated that patient follow-up by tumor markers kinetics with either Lumipulse or Kryptor (or Modular for AFP) leads to similar interpretations. Those results suggest that both analyzers are interchangeable for patient follow-up, except for CA 19-9 and CEA due to a positive bias between Lumipulse and Kryptor assays.

During this study, we also evaluated Lumipulse practicability, as a new analyzer introduced in a biochemistry hospital laboratory. Only a short training session (2–5 h) is required to perform measurements and daily maintenances. Its user-friendly interface and its simple reagents replacement makes it easy-to-use. Additionally, its quick daily maintenance (10 min) and its constant assay duration (25 min) minimize working time spent on the analyzer.

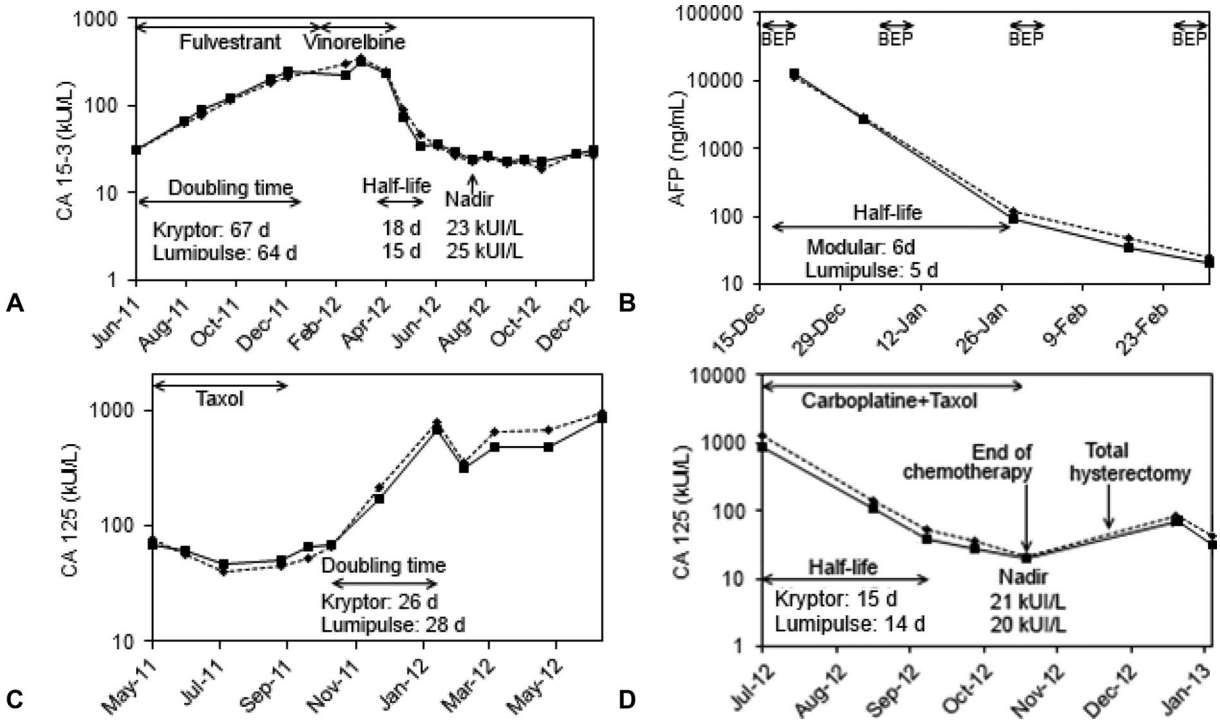

Fig. 2. Lumipulse results (plain line) and Modular results (dot line, graph C) or Kryptor (dot line, graph A, B, and D), d = days. (**A**) Ms. P, metastatic breast adenocarcinoma; (**B**) Mr. E, nonseminomatous mediastinal germinal tumor, under treatment with Bleomycin, Etoposide, and Cisplatine (BEP); (**C**) Ms. J, ovarian adenocarcinoma; (**D**) Ms B, ovarian adenocarcinoma with peritoneal carcinosis.

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