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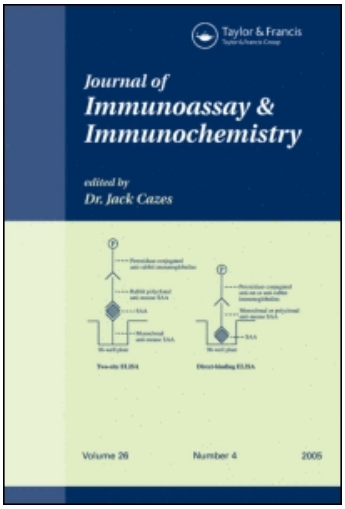

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ADVANTAGES OF THE AMDL-ELISA DR-70 (FDP) ASSAY OVER CARCINOEMBRYONIC ANTIGEN (CEA) FOR MONITORING COLORECTAL CANCER PATIENTS

Andrea L. Small-Howard[a]; Holden Harris[a]
[a] AMDL Inc., Tustin, CA, USA

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ADVANTAGES OF THE AMDL-ELISA DR-70 (FDP) ASSAY OVER CARCINOEMBRYONIC ANTIGEN (CEA) FOR MONITORING COLORECTAL CANCER PATIENTS

Andrea L. Small-Howard and Holden Harris
AMDL Inc., Tustin, CA, USA

□ *The DR-70® (FDP) test was the first cancer test cleared by USFDA for monitoring colorectal cancer (CRC) since Carcinoembryonic Antigen (CEA) in 1982. Conservatively, 50% of biopsy-positive CRC patients have negative CEA values. DR-70 and CEA values were compared for 113 CRC monitoring patients. Total concordance rates for DR-70 and CEA were 0.665 and 0.686, respectively. CRC patient pairs were grouped based on their CEA value to deduce DR-70's effectiveness at monitoring patients with low CEA values. DR-70 had 12% to 100% greater positive concordance rates than CEA in this group. DR-70 is a welcome new option for CRC patients.*

Keywords carcinoembryonic antigen, CEA, colorectal cancer, DR-70®, FDP, fibrin-fibrinogen degradation products

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INTRODUCTION

Awareness of the importance of CRC screening[1] and early treatment has risen,[2] but CRC is presently still a significant health concern in the United States.[3] In 2007, the Surveillance, Epidemiology and End Results (SEER) program estimated there were 153,760 new colorectal cancer patients[4] with a five year survival prediction of 50%. CRC accounts for approximately 10.6% of all new cancer cases and approximately 10% of all cancer deaths in the United States.[5] Colorectal cancer (CRC) remains the second leading cause of cancer death in the United States,[5] despite a reported decrease in colorectal cancer mortality over the past forty years. This decreased rate is related to increased screening, intervention, and monitoring programs.

Monitoring programs have emerged as an important tool in enhancing survival in post-operative CRC patients.[6] For CRC, approximately half of all patients treated will experience disease recurrence.[7] Curative

Address correspondence to Andrea L. Small-Howard, Ph.D., AMDL Inc., 2492 Walnut Ave., Suite 100, Tustin, CA 92780, USA. E-mail: asmallhoward@amdl.com

retreatment options exist, and retreatment options are applied with a modest decrease in CRC mortality (approximately 10–15%).[8–10] However, in order to enhance the survival benefit of CRC monitoring programs, "the availability of sensitive and specific tests to identify recurrences at a treatable stage" needs improvement.[6]

The AMDL-ELISA DR-70 (FDP) test (AMDL Diagnostics, Inc., Tustin, CA) is the first new in vitro diagnostic cancer test to be cleared by the US FDA for monitoring colorectal cancer (CRC) since January 14, 1982 when Carcinoembryonic Antigen (CEA) was approved. CEA has been in routine usage for many years as a blood test for monitoring CEA, but it also has well known limitations that are related to the nature of the tumor marker.[6] CEA has been characterized as an oncofetal marker, which implies that it is only present during cancer progression or normal embryogenesis. Evidence exists that contradicts its classification as a pure oncofetal marker; as there are reports of this antigen's presence in healthy organs and its elevation due to benign conditions that affect the liver,[11–14] lungs,[15] and the gastrointestinal system.[16] Also, CEA is not a good target for a blood test because CEA is normally firmly attached to cancer cells due to its role as an adhesion molecule.[15] In contrast, the DR-70 (FDP) antigen is freely diffusible in the blood.

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For many CRC patients with biopsy confirmed cancer, CEA levels are not measurable above the physiological background. Data was taken directly from three independent studies[17–19] and presented directly in Table 1 below to assess the need for an additional CRC monitoring tool. Approximately 50% of all CRC patients with low CEA values can not use the CEA test to monitor their cancer because their CEA levels fall below the manufacturer's defined physiological background level. In the table below, CEA Low Responders is the term given for biopsy positive cancer patients with low CEA values. All of the numbers in the table have been published in the referenced papers.

The DR-70 test measures both Fibrin and Fibrinogen Degradation Products (referred to collectively as FDP in this paper) in human serum samples. Measuring multiple FDP species prevents the DR-70 (FDP) immunoassay from underestimating the cancer-related levels of FDP.[20] Refer to

TABLE 1 Literature Based Definition of the % of CRC Patients Not Able to Use CEA

Study	Year	Number of Patients	% Below CEA Cut-Off by Duke's Stage				Overall % CEA Low Responders
			A	B	C	D	
[17]Landenson et al.	1980	203	97	75	55	35	58
[18]Wang, J.Y. et al.	1994	318	100	68	52	21	NA
[19]Wang, W.S. et al.	2000	218	75	61	29	NA	53

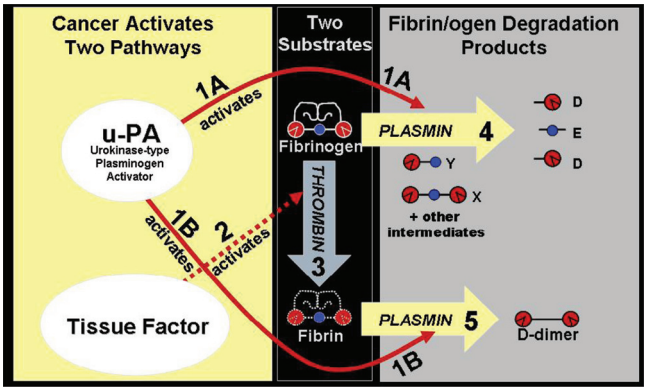

FIGURE 1 Cancer Elevates FDP Levels Through Two Pathways: Coagulation and Fibrinolysis. The AMDL-ELISA DR-70® (FDP) test measures the FDP produced by multiple pathways, unlike other FDP assays which only measure one pathway or one pathway product. Researchers have established that cancer causes elevated levels of both urokinase-type plasminogen activator (u-PA)[23–25] and tissue factor (TF).[26–28] Both the u-PA and TF pathways effect the production of FDP in cancer cells. The u-PA pathway (1A and 1B) activates plasmin by transforming plasminogen, the inactive precursor of plasmin, into functional plasmin.[23–25] The TF pathway (2) alters the extrinsic coagulation system causing an activation of thrombin.[26–29] Thrombin (3) converts Fibrinogen to Fibrin.[30] The type of FDP produced will be different depending upon which of the two substrates is digested by plasmin. When fibrinogen is the substrate for plasmin (4), fragments D and E are the end products with fragments X and Y as intermediate products in this digestion. When fibrin is the substrate of plasmin (5), D-dimer is the end product. As a result of either pathway (4) or (5), cancer will cause an elevation in FDP levels as measured by the DR-70 (FDP). Tests that measure only one of the individual FDP species, i.e., D-dimer tests, will miss up to half of the FDP generated as a result of cancer physiology.

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Figure 1 for a schematic describing how the DR-70 (FDP) assay measures FDP generated from all of the major cancer induced FDP production pathways. Researchers have established a strong link between increased FDP levels and cancer.[20–22] This strong link is based on multiple factors including: a cancer-caused redirection of the coagulation cascade and a cancer-related increase in proteolysis within tumors as they grow and metastasize.

Because the DR-70 test uses a different tumor marker than the CEA test, physicians have an additional blood test for monitoring CRC patients that may be superior to CEA for many of their patients with low CEA values. The purpose of this study is to determine if DR-70 is effective at monitoring CRC patients with low CEA levels.

EXPERIMENTAL

Description of the Clinical Samples

The samples for the serial monitoring study were retrospective banked samples that were collected blindly and without bias to include all patients

TABLE 2 Patient Observation Series

Number of Samples in Series	Number of Observation Pairs in Series	Total Number of Series with that Number of Pairs	Percent of the Total Samples	Cumulative Percent of Samples
2	1	1	0.9	0.9
3	2	38	33.9	34.8
4	3	48	42.9	77.7
5	4	18	16.1	93.8
6	5	3	2.7	96.5
7	6	3	2.7	99.2
8	7	1	0.9	100.0

with diagnosed colorectal cancer in the bank at the time of the collection. The serial monitoring samples for this study were obtained from two retrospective sample banks. Forty-eight serial sets were obtained from Geffen Cancer Center in Vero Beach, FL and sixty-four serial sets were from the serum banks at MD Anderson Cancer Center in Houston, TX. Institutional Review Board Approval for use of the samples and informed consent were available for each patient sample set.

Clinical information detailing the status of each patient's disease was collected at the time of each sample draw. The clinical diagnoses included Duke's Stage, grade and type (colon or rectal cancer). None of the patients had a history of malignancy within the past five years of the initial sample draw other than colorectal cancer. A breakdown of the patient series is presented in Table 2. The average number of observations per patient is 4.0.

Of the original 113 patients, one had to be dropped from further analysis due to incomplete clinical records. The 112 evaluable subjects in this CRC monitoring cohort consisted of 44 males and 68 females. The average age of the male patients was 65 while female patients averaged 62 years. The overall average age was 63 years. There was no significant difference between the average age of the males and the females in this cohort based on a student's t-test analysis for the determination of variances [$t = 1.41$, $p = 0.163$ (unequal variances)].

TABLE 3 Ethnic Distribution

Ethnic Background	Frequency	Percent
African American	7	6.3
Asian	2	1.8
Caucasian	99	88.4
Hispanic	4	3.6
Total	112	100.0

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TABLE 4 Stage of Cancer at Time of Diagnosis

Dukes Stage at Diagnosis	Frequency	Percent	Cumulative Percent
A	5	4.5	4.5
B	18	16.2	20.7
C	39	35.1	55.9
D	49	44.1	100.0
Total	111	100.0	

The ethnic composition of the cohort is shown in Table 3. Approximately 88% percent of the cohort was Caucasian; approximately 6% of African-American background; approximately 4% of Hispanic descent; and approximately 2% of Asian decent.

Table 4 presents the Dukes stage of the disease at time of diagnosis for 111 of the 112 evaluable serial patients. One patient's chart did not contain information related to the stage at time of diagnosis.

Table 5 demonstrates the relationship between Dukes Stage at diagnosis and the presence of metastases. As the Stage of the disease progressed, the percentage of patients with metastases increased.

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Statistical Analysis Plan for Association Between DR-70® (FDP)/AIA-Pack™ CEA and Disease Status

The initial objective of this analysis is to determine the overall positive, negative and total concordance values of the DR-70 (FDP) and CEA assays.[31] Then, the CRC patients will be grouped based on their CEA values to evaluate the effectiveness of the DR-70® (FDP) assay at monitoring CRC patients with low CEA values; defined as a CEA value of 30 or below.

TABLE 5 Distribution of Metastases by Stage at Diagnosis

	Known Metastases at Time of Diagnosis		
Dukes Stage	Yes	No	Total
A	0	5	5
	0.0%	100.0%	100.0%
B	3	15	18
	16.7%	83.3%	100.0%
C	29	10	39
	74.4%	25.6%	100.0%
D	49	0	49
	100.0%	0.0%	100.0%
Total	81	30	111
	73.0%	27.0%	100.0%

Defining the Clinical Sample Set

Serial samples were taken from 112 colon cancer patients resulting in a total of 445 paired observations in which a DR-70 (FDP) reading and a determination of disease progression were obtained. In total, there were also 445 paired observations in which an AIA-Pack^{TM} CEA Assay reading and a determination of disease progression were obtained. The sequential draws covered an average longitudinal period of at least nine months. Progression of the DR-70 (FDP) value or AIA-Pack CEA Assay value in the serial monitoring set was evaluated as a percentage change between the current and previous readings (Y). The minimum percentage to specify disease progression in either assay was determined to be 15%, as will be described in detail later. Clinical disease progression (D) was determined by the Subject's physician based on their office procedures and clinical laboratory based analyses that were the standard of care during the time of the monitoring period.

Monitoring Cases for Response to Therapy

Subjects in the serial monitoring cohort were followed after surgery and or after various types of therapy including chemotherapy and radiation therapy. The response to therapy was evaluated using information provided in the records by the clinicians based on the results of clinical examinations and imaging results (i.e., bone scans, CT scans, magnetic resonance imaging studies, radiography, or ultrasound).

Response to therapy is defined as follows:

- Complete response (CR) or no evidence of disease (NED): The complete disappearance of all clinical and image-measurable disease as evidenced by the clinical exam and imaging or other diagnostic modalities as ordered by the physician.
- Partial Response (PR): In patients with metastases at the time of the original draw, a noticeable reduction in the size of primary metastatic lesions or bone metastases demonstrating at least stabilization as observed on the bone scan.
- Stable Disease (SD): No significant change in the size of primary metastatic lesions or no noticeable increase in the size of primary lesions or no new lesions as evidenced by the clinical exam and imaging or other diagnostic modalities as ordered by the physician.
- Progressive Disease (PD): Clinical or imaging results that clearly indicate the presence of lesions not seen on previous examinations or a significant increase in the size of primary or metastatic lesions.

Definition of Outcome Measure

The outcome measure for this analysis is the determination of progression of disease from time point i (clinical visit i, $i=1$ to $n-1$) to

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a succeeding time point ***j*** (clinical visit *j*, $j = i + 1$ to n). In this analysis ***n*** is the number of clinical visits for which samples are collected from a Subject after diagnosis of colorectal cancer and prior to death, loss to follow up or remission of disease.

Let $\boldsymbol{D}_{ij}$ represent the variable disease progression as measured above and allow $\boldsymbol{D}_{ij}$ to have the values

$$\boldsymbol{D}_{ij} = \begin{cases} 1 & \text{if there is progression of disease from visit } i \text{ to visit } j. \\ 0 & \text{if there is no progression of disease, the disease is either stable or responding to therapy, from visit } i \text{ to visit } j. \end{cases}$$

Determining Values of D

Disease progression from visit i to visit j will be determined by the Subject's physician based on any or all of the following:

- Examination of the subject for clinical signs and symptoms, including the results of laboratory tests that are current standard of care for the assessment of colorectal cancer disease status.
- Examination of radiographic findings (imaging) that can be used for the assessment of colorectal cancer disease status. Radiographic findings include results from CAT scans, PET scans, MRI and X-Ray images.

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Determination of Clinical Significance in Marker Value Change

To ensure that the change between the values of the test device over a time interval could not be attributed to assay variation, a 15% increase from the previous visit was determined to be the most appropriate threshold for significant % change for the determination of disease progression in the DR-70 (FDP) assay. The coefficient of variation (CV) used in the calculation for significant % change was based on an imprecision study following regulatory guidelines. In that precision study, the total CV over all runs, days, and intra-assay was computed for each control specimen analyzed. The highest CV values were observed for specimens with a low concentration of (0.21–0.42 μg/mL); however, in a study of cancer progression, such as the one being reported here, such samples constituted less than 5% of the measurements. Over 80% of the measurements had concentrations of 0.6 μg/mL or higher where the CV is lower. Therefore the CV values for the lower concentrations will not be used to determine the significant % change. If the CV values for the highest laboratory specimens with concentration of 1.31 (CV = 7.85) or 4.11 (CV = 7.14) μg/mL are averaged, the mean is 7.495%. The CV is given by the following formula.

$$CV = 100 * \frac{\sigma}{\bar{x}}$$

which is the standard deviation divided by the mean. The proportion difference between two successive measurements is given by the following formula.

$$p = \frac{x_2 - x_1}{x_1}$$

where p is the proportion difference from the previous measurement. Normal theory would suggest that 97.5% of the measurements are within the range of the following expression.

$$\bar{x} + 1.96\sigma$$

Using the expression for CV, we can solve for σ and obtain an expression that can be used to define the difference between successive measurements.

$$\bar{x} + 1.96 * \frac{CV * \bar{x}}{100}$$

Assuming that the previous measurement was a mean at that time, less than 2.5% of the time, by chance, will the following expression hold.

$$x_2 > x_1 + \frac{1.96 * CV * x_1}{100}$$

Algebraically rearranging this expression we get the following.

$$\frac{x_2 - x_1}{x_1} > \frac{1.96 * CV}{100}$$

Alternatively the following can be used.

$$\frac{x_2}{x_1} > 1 + \frac{1.96 * CV}{100}$$

Using the value of 7.495 on the previous page, this expression indicates that the proportion of difference must be greater than $7.495 * 1.96/100 = 0.1469$. For simplicity, this cut off value has been rounded up to 0.15 or 15% or the ratio should exceed 1.15. Thus if a later visit has a value that is greater than 15% higher than the previous value, it will be considered evidence of disease progression.

A 15% increase from the previous visit was also determined as the most appropriate threshold for significant % change for the determination of disease progression using the AIA-Pack™ CEA Assay from TOSOS

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Bioscience. The same evaluation, as above, was used with the CV listed in the AIA-Pack™ CEA Assay product insert.

Definition of Significance in Marker Value Change

Let δ equal the significant change in marker value for either assay, which has been determined at 15% for either assay, as described above. Let x_i be the value of the test device obtained from the assay of a blood sample drawn from the Subject at visit i and x_j be the value of the test device obtained from the assay of a blood sample drawn from the Subject at visit j.

Define $\boldsymbol{Y}_{ij}$ as

$$\boldsymbol{Y}_{ij} = \begin{matrix} 1 & \text{if } (\mathbf{x}_\mathrm{j} - \mathbf{x}_\mathrm{i}) \geq \delta \cdot \mathbf{x}_\mathrm{i} \\ 0 & \text{otherwise} \end{matrix}$$

Determining the Association Between D and Y

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With $\boldsymbol{D}_{ij}$ and $\boldsymbol{Y}_{ij}$ defined above for either assay, a 2×2 contingency table can be constructed for the analysis of this data. The contingency table has the format of Table 6. In this table the variable ***a*** represents the number of (Y_{ij}, D_{ij}) pairs that have the value of 1 for both Y_{ij} and D_{ij}. The variable ***b*** represents the number of (Y_{ij}, D_{ij}) pairs that have the value 1 for Y_{ij} and 0 for D_{ij}. The variable ***c*** represents the number of (Y_{ij}, D_{ij}) pairs that have the value 0 for Y_{ij} and 1 for D_{ij}. Lastly variable ***d*** represents the number of (Y_{ij}, D_{ij}) pairs that have the value of 0 for both Y_{ij} and D_{ij}. The accrued values of ***a, b, c***, and ***d*** are determined over all serial interval values of Y_{ij} and D_{ij}. The sum of ***a, b***, ***c*** and ***d*** is the total number of all (Y_{ij}, D_{ij}) pairs for all Subjects. This sum is designated N in Table 6.

From Table 6, sensitivity and specificity are computed as follows:

$$\text{Specificity: } 100 * \mathrm{d}/(\mathrm{b} + \mathrm{d})$$
$$\text{Sensitivity: } 100 * \mathrm{a}/(\mathrm{a} + \mathrm{c})$$

TABLE 6 Model Contingency Table for D and Y

	$D_{ij}=1$ Disease Progression	$D_{ij}=0$ No Progression	Total
$Y_{ij}=1$ Significant increase in tumor marker as measured by assay	a	b	$a+b$
$Y_{ij}=0$ No Significant increase in tumor marker as measured by assay	c	d	$c+d$
Total	$a+c$	$b+d$	N

From Table 6, concordance values are computed as follows:

$$\text{Positive Concordance (C+)} = a/(a+c)$$
$$\text{Negative Concordance (C−)} = d/(b+d)$$
$$\text{Total Concordance (C)} = (a+d)/N$$

Justification of Sample Size

Given the above assumptions and calculations, the minimum sample size for this study was determined to be 70 subjects with an average of 3 draws each.[31] The samples are retrospective banked samples collected blindly and unbiased. Out of a total of 445 evaluable observations, there were 112 evaluable patient serial sets with an average of 4 draws each.

RESULTS

General Effectiveness of DR-70 (FDP) or CEA for CRC Monitoring

The clinical trial results were tabulated, as described above. The results for the DR-70 (FDP) test immediately follow in Table 7 and the results for CEA are found in Table 8. In addition, the following interpretations are provided: Positive Concordance (C+), Negative Concordance (C−), Total Concordance (C), Sensitivity, and Specificity.

Based on these data the concordances for the DR-70 (FDP) vs. Clinical Disease Status are:

$$C_+(\text{Positive concordance}) = 0.652,$$
$$C_-(\text{Negative concordance}) = 0.673 \text{ and}$$
$$C \text{ (Total overall concordance)} = 0.665.$$

In estimating the specificity and sensitivity of the DR-70 (FDP) test, using a significant % change value of 15% or a ratio value of 1.15 or higher,

TABLE 7 Clinical Disease Status vs. AMDL-ELISA DR-70 (FDP)

	Clinical Disease Status		
DR-70 (FDP)	Progression	No Progression	Total
Significant increase (>15%)	88	65	153
No significant increase (<15%)	47	134	181
Total	135	199	334

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TABLE 8 Clinical Disease Status vs. the TOSOH AIA-PACK CEA

	Clinical Disease Status		
CEA	Progression	No Progression	Total
Significant Increase (>15%)	99	69	168
No Significant Increase (<15%)	35	130	166
Total	135	199	334

the estimated specificity was determined as 67% with an estimated sensitivity of 65%.

Based on these data the concordances for the TOSOH AIA-PACK CEA vs. Clinical Disease Status are:

$$C_+(\text{Positive concordance}) = 0.739,$$
$$C_-(\text{Negative concordance}) = 0.653 \text{ and}$$
$$C \text{ (Total overall concordance)} = 0.686.$$

In estimating the specificity and sensitivity of the CEA test, using a significant % change value of 15% or a ratio value of 1.15 or higher, the estimated specificity was determined as 73% with an estimated sensitivity of 65%.

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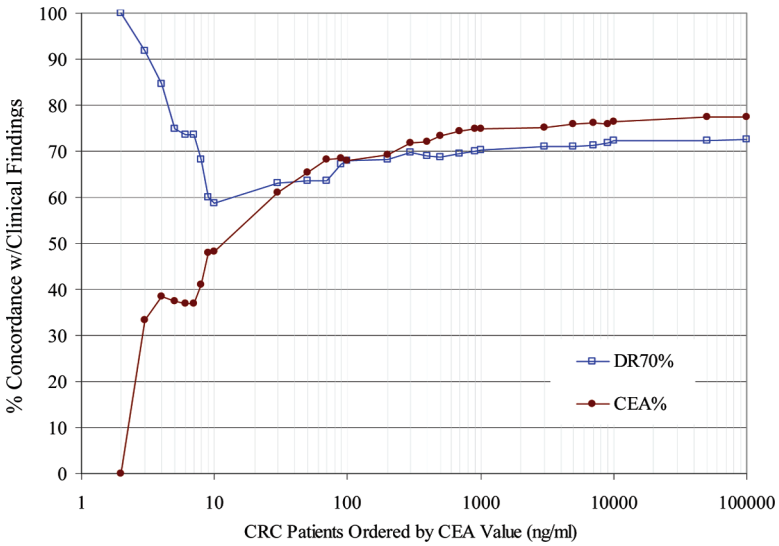

FIGURE 2 Positive Concordance for DR-70 or CEA Grouped by CEA values. Positive progression patient sample pairs were grouped in ascending order based on the CEA value. The % Concordance for DR-70 relative to the clinical findings was graphed in blue for each group. The % Concordance for CEA relative to the clinical findings was graphed in red for each group. Forty-six (46) of the 135 total positive progression patient pair values fell in the groups containing CEA values of 30 or less.

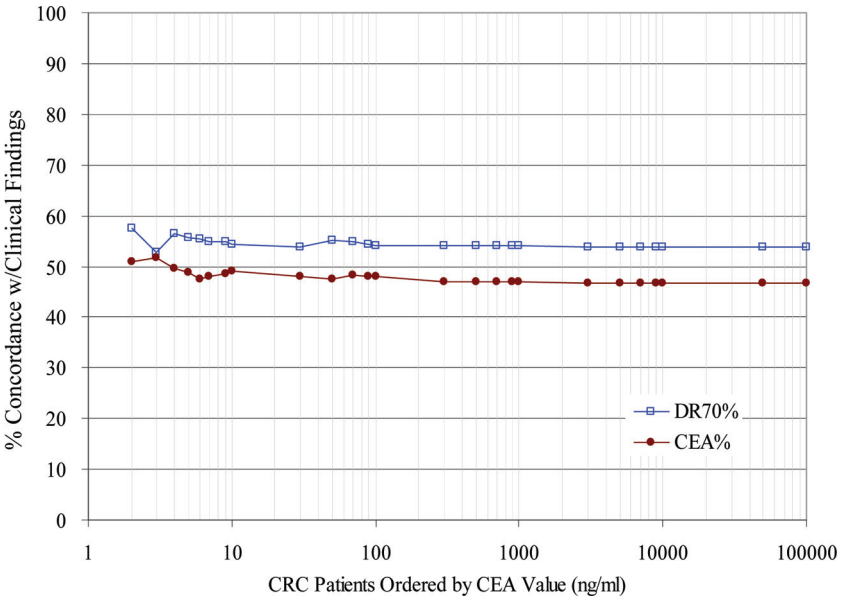

FIGURE 3 Negative Concordance for DR-70 or CEA Grouped by CEA values. Negative progression patient sample pairs were grouped in ascending order based on the CEA value. The % Concordance for DR-70 relative to the clinical findings was graphed in blue for each group. The % Concordance for CEA relative to the clinical findings was graphed in red for each group. There were a total of 199 negative progression patient pair values.

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Effectiveness of DR-70 (FDP) Test in CRC Monitoring Patients with Low CEA Values

After grouping the CRC patients' sample pairs in ascending order based on their CEA values, the following relationships were revealed. Positive concordance values of CRC patients measured with DR-70 or CEA in patient groups relative to their CEA values are provided in Figure 2. Negative concordances of CRC patients measured with DR-70 or CEA in groups relative to their CEA values are provided in Figure 3.

In Figure 2, DR-70 had between 12% and 100% greater positive concordance rates than CEA for CRC monitoring patients with low CEA values. In contrast, the negative concordance values of DR-70 and CEA showed less than 10% difference for all CRC patient groups in the trial, as depicted in Figure 3.

DISCUSSION

Overall, the results from this trial support the assertion that the AMDL-DR-70 (FDP) test is as good at monitoring CRC patients as CEA.

Based on the results presented in Table 7 and Table 8, the total concordance values for DR-70 and CEA are 0.665 and 0.686, respectively. The total concordance values for DR-70 and CEA differed by only 3.2% in this clinical trial.

In addition, Figure 2 suggests that DR-70 is more effective at monitoring patients whose CEA values are 30 or less. Forty-six (46) of 135 positive progression patient pair values fell in the groups containing CEA values of 30 or less. In this group, DR-70 had between 12% and 100% greater positive concordance rates than CEA for CRC monitoring patients. The negative concordance rates were about the same for both assays across all groups when ordered by the CEA value of the patient. The difference between the negative concordance rates of these assays was less than 10% for all patient groups relative to their CEA values. Additional trials are planned to examine this same sub-group to verify the value of the test for patients with low CEA values.

The results of this trial suggest that DR-70 could have a positive impact on mortality that is associated with CRC recurrence. All of the patients in the reported trial were either post-surgery with no adjuvant therapy or post-therapy, as was described in the methods section. This holds clinical significance because disease progression in these patients would be described as disease recurrence. As reported in the introduction, approximately half of all CRC patients treated will experience disease recurrence. An additional and improved tool for the monitoring of disease recurrence could profoundly impact the mortality rate that is associated with CRC recurrence. Future studies could assess the impact of the DR-70 test on clinical outcomes in a longer term, prospective trial.

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FDP has been shown to be valuable as a tumor marker in a number of different cancers.[32–43] FDP levels correlate with cancer occurrence, stage, progression and prognosis. Among these studies, the DR-70 (FDP) assay was used to detect FDP levels in 7,839 patients and the DR-70 (FDP) assay results consistently correlated with either the positive detection or positive progression of a variety of cancers.

Researchers have established a strong link between increased FDP levels and cancer which is based on multiple factors including: a cancer-caused redirection of the coagulation cascade[44–49] and a cancer-related increase in proteolysis within tumors as they grow[50,51] and metastasize.[52–56] Clinical studies reveal that measuring FDP levels, either with the DR-70 (FDP) test or with other related tests, has significant diagnostic value for a variety of cancers. These studies demonstrate that FDP levels correlate with the cancer stage[41–43,57–60] and with the cancer progression,[41,59,61] as quantified by the number of lymph node metastases. Clinical research efforts have shown that pretreatment measurements of FDP levels have prognostic significance for post-treatment survival.[33,60,62–66] In addition to survival

prognoses, pretreatment FDP values may be used to indicate when adjuvant systemic treatments are required for surgical Subjects.[64,66]

Cancer is a disease that is characterized by disregulation at the cellular level. As cancer progresses, the cellular disregulation spreads to the systems level. The coagulation system is one of the first systems affected by cancer-related processes. As referenced in Figure 1, the coagulation pathway may be inappropriately activated in cancer patients either by the activation of the coagulation pathway alone, the fibrinolysis pathway alone, or both pathways simultaneously. Coagulation may be increased due to elevated levels of tissue factor (TF),[62,67] which acts through the extrinsic coagulation system. Alternatively, the fibrinolysis pathway may be mistakenly activated in cancer patients through elevations in the levels of urokinase-type plasminogen activator (u-PA)[44] that activates the protease plasmin. Disregulation of the coagulation system has important adverse affects on cancer patients because the coagulation system plays dual roles in homeostasis and immunity. As the cancer-related disregulation of the coagulation system increases, these clots can lead to heart attack, stroke, or pulmonary embolism. Other FDP-related tests have been helpful in predicting survival outcome based on the often fatal consequences of blood clots in cancer patients.[59,62,67] As the utility of the DR-70 (FDP) assay becomes more widely known, DR-70 should be adapted to help patients with a variety of cancers in different clinical settings.

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CONCLUSIONS

The DR-70 test appears to have additional benefits in monitoring CRC patients with low CEA values. DR-70 had between a 12% and a 100% greater positive concordance rate than CEA for CRC monitoring patients with low CEA values. Given that 50% is a conservative estimate of CRC patients with low CEA values, physicians and patients could significantly benefit from this new option for monitoring CRC cancer.

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