BECKMAN COULTER

ACCESS
Immunoassay Systems

Instructions For Use

Access CEA
Carcinoembryonic Antigen

REF 33200

FOR PROFESSIONAL USE ONLY

For *in vitro* diagnostic use

Rx Only

For use on DxI 9000 Access Immunoassay Analyzer

PRINCIPLE

WARNING

The concentration of CEA in a given specimen determined with different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the CEA assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining CEA values is changed, additional sequential testing should be carried out to confirm baseline values.

Caution: For U.S.A. only, Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to by or on the order of a physician.

INTENDED USE

The Access CEA assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of Carcinoembryonic Antigen (CEA) levels in human serum, using the Access Immunoassay Systems. CEA measured by the Access Immunoassay Systems is used as an aid in the management of cancer patients in whom changing CEA concentrations have been observed.

SUMMARY AND EXPLANATION

Carcinoembryonic antigen (CEA), first described by Gold and Freedman in 1965, was isolated from extracts of liver metastases of colon adenocarcinomas and normal fetal digestive tract.[1,2] It is considered one of the most extensively investigated human tumor associated antigens. An immunologically heterogenous group of glycoproteins, CEA is approximately 200,000 daltons with 50-85% carbohydrates by weight.[3] CEA is a member of the immunoglobulin superfamily and appears to have functions of an intercellular adhesion molecule.[4] In addition, molecules structurally related to CEA (i.e. NCA, NCA-2, NFA) have been reported in normal adult tissues.[5,6,7]

The measurement of serum CEA has shown substantial benefit in the prognosis and management of patients with malignant diseases, especially colorectal cancer.[8,9,10,11,12] Serial measurements can be used to monitor patients for progression, regression or recurrence of cancer following treatment. A persistent elevation of CEA following therapeutic or surgical intervention signals residual disease or recurrence, whereas decreasing levels to within the normal range is indicative of successful intervention.[8,11,13]

CEA is also elevated in the serum of patients with non-malignant diseases and in heavy smokers, therefore CEA should not be used in the diagnosis of cancer or for screening asymptomatic patients.

METHODOLOGY

Assay type: one-step, sandwich

The Access CEA assay is a two-site immunoenzymatic “sandwich” assay using two mouse monoclonal anti-CEA antibodies (MAb) which react with different epitopes of CEA. A sample is added to a reaction vessel, along with the first anti-CEA MAb-alkaline phosphatase conjugate and the second anti-CEA MAb bound to paramagnetic particles.

After incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of analyte in the sample. Analyte concentration is automatically determined from a stored calibration.

SPECIMEN

SPECIMEN COLLECTION AND PREPARATION

1. Serum is the recommended sample.
2. Observe the following recommendations for handling, processing, and storing blood samples:[14,15]
   - Collect all blood samples observing routine precautions for venipuncture.
   - For serum, allow samples to clot adequately before centrifugation.
   - Keep tubes stoppered at all times.
   - Physically separate serum from contact with cells as soon as possible.
   - Store samples, tightly stoppered, at room temperature (15 to 30°C) for no longer than eight hours.
   - If the assay will not be completed within eight hours, refrigerate the samples at 2 to 8°C.
   - If the assay will not be completed within 48 hours, or for shipment of samples, freeze at -20°C or colder.
3. Use the following guidelines when preparing specimens:
   - Ensure residual fibrin and cellular matter has been removed prior to analysis.
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
4. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

REAGENTS

CONTENTS

Access CEA Reagent Pack

Ref. No. 33200: 100 determinations, 2 packs, 50 tests/pack

The same reagent formulation is used on all Access Immunoassay Systems.

Well	Contents	Ingredients
R1a:	3.3 mL	Solid phase: Paramagnetic particles coated with mouse anti-CEA MAb, suspended in TRIS buffered bovine serum albumin (BSA), with < 0.1% sodium azide and 0.1% ProClin* 300.
R1b:	2.74 mL	Diluent: Phosphate buffer, protein (bovine, murine) with < 0.1% sodium azide and 0.1% ProClin 300.
R1c:	3.24 mL	Conjugate: Mouse anti-CEA MAb bound to alkaline phosphatase (bovine), diluted in phosphate buffer, protein (bovine), < 0.1% sodium azide and 0.1% ProClin 300.

*ProClin is a trademark of LANXESS Corp.

WARNING AND PRECAUTIONS

- **For *in vitro* diagnostic use.**
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- For hazards presented by the product refer to the following sections: REACTIVE INGREDIENTS and GHS HAZARD CLASSIFICATION.

REACTIVE INGREDIENTS

⚠ CAUTION

Sodium azide preservative may form explosive compounds in metal drain lines. See NIOSH Bulletin: Explosive Azide Hazard (8/16/76).
To avoid the possible build-up of azide compounds, flush wastepipes with water after the disposal of undiluted reagent. Sodium azide disposal must be in accordance with appropriate local regulations.

GHS HAZARD CLASSIFICATION

PMP (Compartment R1a)	WARNING	
		
	H317	May cause an allergic skin reaction.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
Diluent (Compartment R1b)	DANGER	

	H317	May cause an allergic skin reaction.
	H318	Causes serious eye damage.
	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
	P310	Immediately call a POISON CENTER or doctor/physician.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		Polyoxyethylated Octyl Phenol 1 - 5%
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
Conjugate (Compartment R1c)	WARNING	

	H317	May cause an allergic skin reaction.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%

SDS	Safety Data Sheet is available at beckmancoulter.com/techdocs

MATERIALS NEEDED BUT NOT SUPPLIED WITH REAGENT KIT

1. Access CEA Calibrators
   Provided at zero and approximately 1, 10, 100, 500 and 1,000 ng/mL.
   Ref. No. 33205

2. Quality Control (QC) materials:
    - Access CEA QC Provided at approximately 3 and 300 ng/mL
      Ref. No. 33209
    - Commercial control material
3. Lumi-Phos PRO
   Ref. No. B96000
4. UniCel DxI Wash Buffer II
   Ref. No. A16793
5. Optional materials for dilution:
    - Access CEA Diluent
      Ref. No. 33206

REAGENT PREPARATION

Provided ready to use.

REAGENT STORAGE AND STABILITY

Stability	
Unopened at 2 to 10°C	Up to stated expiration date
After opening at 2 to 10°C	28 days

- Store upright.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Signs of possible deterioration are a broken elastomeric layer on the pack or quality control values out of range.
- If the reagent pack is damaged (e.g., broken elastomer), discard the pack.

CALIBRATION

CALIBRATION INFORMATION

An active calibration is required for all tests. Calibration is required every 28 days. See calibrator Instructions For Use (IFU) for additional calibration information. Refer to the appropriate system manuals and/or Help system for information on calibration method, configuring calibrators, calibrator test request entry, and reviewing calibration data.

QUALITY CONTROL

Quality control materials are essential for monitoring the system performance. Quality controls with varying concentration ranges should be run individually at least once every 24 hours when the assay is being performed.[16] Quality control ranges should be determined by each laboratory's individual requirements. Follow applicable regulations and guidelines for quality control.

TESTING PROCEDURE(S)

PROCEDURE

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.
3. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
4. Use 35 µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
5. The system default unit of measure for sample results is ng/mL.

LIMITATIONS

1. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce human anti-animal antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other antibodies such as human anti-goat antibodies may be present in patient samples.[17,18] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
2. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[19] Carefully evaluate results if the sample is suspected of having these types of interferences.
3. The results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests, and other appropriate information. Elevated levels of CEA may occur in non-neoplastic conditions, therefore, the Access CEA assay is not intended for the diagnosis of, or for screening of cancer.
4. Access CEA assay does not demonstrate any hook effect up to 100,000 ng/mL.

RESULTS INTERPRETATION

Test results are determined automatically by the system software. Test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

REPORTING RESULTS

MEASURING INTERVAL

0.2 - 1,000 ng/mL

Samples can be accurately measured within the measuring interval defined as the lower Limit of Quantitation (LoQ) and the highest calibrator value.

1. If a sample contains less than the lower limit for the assay, report the result as less than that value.
2. If a sample contains more than the stated value of the highest calibrator, report the result as greater than that value. Alternatively, the sample may be diluted to obtain a result.
   - For manual dilutions, dilute one volume of sample with nine volumes of Access CEA Calibrator S0 or Access CEA Diluent. Refer to the appropriate system manuals and/or Help system for instructions on entering a sample dilution in a test request. The system reports the results adjusted for the dilution.

EXPECTED VALUES

1. Each laboratory should validate or establish its own reference intervals to assure proper representation of specific populations.
2. CEA concentrations were measured in human serum samples from 301 apparently healthy blood donors (including smokers and non-smokers), using the Access CEA assay:

	n	0.0-3.0 (ng/mL)	3.1-5.0 (ng/mL)	5.1-10.0 (ng/mL)	> 10.0 (ng/mL)
Non-smokers	151	95.4%	3.9%	0.7%	0.0%
Smokers	150	82.0%	8.7%	8.0%	1.3%
Total	301	88.7%	6.3%	4.3%	0.7%

PERFORMANCE CHARACTERISTICS

ASSAY CRITERIA AND REPRESENTATIVE DATA

Representative data is provided for illustration only. Performance obtained in individual laboratories may vary.

METHODS COMPARISON

A study based on CLSI EP09c, 3rd Edition[20] using Passing-Bablok regression and Pearson's correlation compared the Access 2 Immunoassay System and the DxI 9000 Access Immunoassay Analyzer.

N	Concentration Range* (ng/mL)	Slope	Slope 95% CI	Intercept	Intercept 95% CI	Correlation Coefficient R
153	0.46 - 1,071	0.98	0.97 - 0.99	0.058	0.0015 - 0.17	1.00

*Range is Access 2 values

LINEARITY

A study based on CLSI EP06-Ed2[21] performed on the DxI 9000 Access Immunoassay Analyzer determined the assay demonstrated linearity across the measuring interval.

IMPRECISION

A study based on CLSI EP05-A3[22] performed on the DxI 9000 Access Immunoassay Analyzer tested multiple samples in a minimum of three replicates per run in 2 runs per day for a minimum of 20 days.

ng/mL			Repeatability (Within-Run)		Between-Run		Between-Day		Within-Laboratory	
Sample	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Sample 1	126	0.45	0.02	3.5	0.01	1.5	0.01	2.0	0.02	4.3
Sample 2	120	5.1	0.10	2.1	0.04	0.8	0.06	1.2	0.13	2.5
Sample 3	126	11	0.2	1.9	0.3	2.5	0.2	1.5	0.4	3.5
Sample 4	120	89	1.9	2.2	0.8	0.9	1.1	1.3	2.4	2.7
Sample 5	120	153	2.8	1.8	1.9	1.3	2.3	1.5	4.1	2.7

ng/mL			Repeatability (Within-Run)		Between-Run		Between-Day		Within-Laboratory	
Sample	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Sample 6	120	525	18.5	3.5	6.6	1.2	16.0	3.1	25.3	4.8
Sample 7	120	865	22.4	2.6	5.3	0.6	38.6	4.5	45.0	5.2

SPECIFICITY

Antigens related to CEA were added to the zero (S0) calibrator at concentrations up to 1,000 ng/mL. Results of these samples evaluated with the Access CEA assay are expressed as CEA concentrations.

Level of added antigen (ng/mL)	NCA-50 apparent CEA level (ng/mL)	NCA-2 apparent CEA level (ng/mL)	NCA apparent CEA level (ng/mL)	NFA-1 apparent CEA level (ng/mL)
0	0.0	0.0	0.0	0.0
10	0.0	0.0	0.0	0.0
100	0.1	0.0	0.0	0.0
500	0.5	0.0	0.0	0.0
1,000	0.9	0.0	0.0	0.0

INTERFERENCE

Hemoglobin, triglycerides, bilirubin, human serum albumin and rheumatoid factor, tested up to the following concentrations, respectively, 500 mg/dL, 1,800 mg/dL, 30 mg/dL, 5 g/dL and 500 IU/mL, do not interfere with the Access CEA assay.

The following therapeutic agents were tested at the concentrations listed and the percent recovery determined. There was no significant interference from these therapeutic agents.

Substance	Concentrations Added	Mean Recovery (%)
Bleomycin	0.1 IU/mL	102.92
Cisplatin	1.5 µg/mL	100.16
Cyclophosphamide	3,000 µg/mL	102.62
Doxorubicin	100 µg/mL	99.65
Fluorouracil	360 µg/mL	102.59
Leucovorin	60 µg/mL	102.44
Methotrexate	4,500 µg/mL	101.40
Mitomycin	60 µg/mL	98.88
Tamoxifen	133 µg/mL	102.68
Vinblastine	1.2 µg/mL	98.41
Vincristine	0.7 µg/mL	99.93

DETECTION CAPABILITY

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) studies were conducted on the DxI 9000 Access Immunoassay Analyzer following CLSI guideline EP17-A2.[23] The LoB study included multiple reagent lots and 3 instruments over a minimum of 3 days. The LoD and LoQ studies included multiple reagent lots and 3 instruments over a minimum of 5 days.

	ng/mL
Limit of Blank (LoB)	0.09
Limit of Detection (LoD)	0.1
Limit of Quantitation (LoQ) ≤ 20% within-lab CV	0.2

ADDITIONAL INFORMATION

REVISION HISTORY

Revision A

New release of DxI Access Immunoassay Analyzer reagent IFU.

Revision B

Updated "Limitations" section.

Updated "Reporting Results" section.

Updated "Performance Characteristics" section.

Revision C

Updated ProClin trademark statement.

Revision D

Added French Language

Updated "For Use" section.

SYMBOLS KEY

Glossary of Symbols is available at beckmancoulter.com/techdocs (document number C02724).

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