Snibe Diagnostic

CE REF 130201003M: 100 tests
130601003M: 50 tests

MAGLUMI® CEA (CLIA)

INTENDED USE

The kit is an *in vitro* chemiluminescence immunoassay for the quantitative determination of Carcinoembryonic Antigen (CEA) in human serum using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer (including Maglumi 600, Maglumi 800, Maglumi 1000, Maglumi 1000 Plus, Maglumi 2000, Maglumi 2000 Plus, Maglumi 4000, Maglumi 4000 Plus, MAGLUMI X8, MAGLUMI X3 and MAGLUMI X6) and Biolumi series Integrated System (including Biolumi CX8).

SUMMARY AND EXPLANATION OF THE TEST

CEA is a heavily glycosylated cell-surface glycoprotein and one of a large family of related molecules belonging to what is now fashionably called a superfamily, which also includes immunoglobulins. This general classification is based on the degree of similarity between the domains of different proteins. Nearly 36 different glycoproteins have been identified in the CEA family, and they appear to be derived from 10 genes localized on chromosome 19 in two clusters. CEA is a non-mucinous, 180kDa glycoprotein secreted by the epithelial cells of the digestive tract in the normal fetus and in adult cancers. It exhibits β-electrophoretic mobility and contains 60% carbohydrate by weight, constituting *N*-acetylglucosamine, mannose, fucose, galactose, and sialic acid[1-4].

CEA is often a very useful test as part of the multiparametric diagnosis of cancer. The most significant use of CEA assays is in the management of cancer patients by serial monitoring to determine the following: the recurrence or metastatic spread of cancer after firstline therapy; the presence of residual or occult metastatic cancer; the effectiveness of therapy; and the prognosis and staging of patients, when used with other additional information in colorectal and lung cancer. Most colorectal patients with preoperative CEA in excess of 20 ng/mL would manifest recurrence within 14 months after surgery[5,6].

Although CEA is primarily associated with colorectal cancers, other malignancies that can cause elevated CEA concentrations are those arising from the lung, breast, stomach, ovary, pancreas, and other organs[7-10]. A number of benign conditions may also be responsible for CEA levels significantly higher than normal. These include inflammatory diseases of the lung and gastrointestinal (GI) tract and benign liver disease[11,12]. Heavy smokers, as a group, also have an elevated range of CEA values. However, the most useful clinical application of CEA analysis is as a noninvasive test for the recurrence of colorectal cancer. This is particularly diagnostic in patients whose postoperative levels initially decrease to a normal level within 6 weeks. CEA concentrations are significantly elevated when the liver is the metastatic site for a primary colorectal cancer. Patients with elevated preoperative levels of CEA that fail to reduce to normal after the first-line therapy are suspected of having residual disease or occult cancer. In all these patients, the rise or fall of CEA values generally reflects progression or regression of disease as a function of the therapeutic treatment. CEA can be used to stage disease and estimate the prognosis. A good correlation exists between preoperative CEA values and increased risk of recurrence of disease, particularly in Dukes' C stage of colorectal cancer. Fully differentiated colorectal cancer tends to secrete CEA copiously compared to undifferentiated tumors, which are associated with low levels or do not express the antigen[13].

Despite its widespread use, it is not suitable as a screening test for asymptomatic people, nor is it a reliable diagnostic test in patients with symptoms that may be due to cancer. This is because of the considerable incidence of false positives and false negatives. However, use of the CEA test as an adjunctive test in predicting prognosis and as an aid in the management of cancer patients has been widely accepted.

PRINCIPLE OF THE TEST

The CEA assay is a two-step sandwich chemiluminescence immunoassay.

The sample (or calibrator/control, if applicable) and magnetic microbeads coated with anti-CEA monoclonal antibody are mixed thoroughly, incubating and performing a wash cycle after a precipitation in a magnetic field. Then ABEI Label with anti-CEA monoclonal antibody and buffer are added, reacting to form a sandwich complexes and incubating. After precipitation in a magnetic field, the supernatant is decanted and then another wash cycle is performed. Subsequently, the Starter 1+2 are added to initiate a chemiluminescent reaction. The light signal is measured by a photomultiplier as relative light units (RLUs), which is proportional to the concentration of CEA present in the sample (or calibrator/control, if applicable).

KIT COMPONENTS

Material Provided

Components	Contents	100 tests (REF: 130201003M)	50 tests (REF: 130601003M)
Magnetic Microbeads	Magnetic microbeads coated with anti- CEA monoclonal antibody, containing BSA, NaN_3 (<0.1%).	2.5 mL	2.0 mL
Calibrator Low	CEA antigen, bovine serum, NaN_3 (<0.1%).	2.5 mL	2.0 mL
Calibrator High	CEA antigen, bovine serum, NaN_3 (<0.1%).	2.5 mL	2.0 mL
Buffer	Containing BSA, NaN_3 (<0.1%).	22.5 mL	12.5 mL
ABEI Label	Anti-CEA monoclonal antibody labeled with ABEI, containing BSA, NaN_3 (<0.1%).	12.5 mL	7.5 mL
Diluent	0.9%NaCl.	25.0 mL	15.0 mL
Internal Quality Control	CEA antigen, bovine serum, NaN_3 (<0.1%).	2.0 mL	2.0 mL
All reagents are provided ready-to-use.			

Accessories Required But Not Provided

MAGLUMI and Biolumi Series:

Reaction Module	REF: 630003
Starter 1+2	REF: 130299004M, 130299027M
Wash Concentrate	REF: 130299005M
Light Check	REF: 130299006M
Reaction Cup	REF: 130105000101

Please order accessories from Shenzhen New Industries Biomedical Engineering Co., Ltd. (SNIBE) or our authorized representatives.

CALIBRATION

Traceability: This method has been traceable to the WHO 1st International Reference Preparation 73/601.
Test of assay specific calibrators allows the RLU values to adjust the assigned master curve. Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve(10 calibrations) provided via the reagent Radio Frequency Identification (RFID) CHIP.
Recalibration is recommended if any of the following conditions occurs:

- After each change of lots (Reagent or Starter 1+2).
- Every 4 weeks and/or each time a new reagent kit is used (recommended).
- After instrument service is required.
- If controls lie outside the expected range.

QUALITY CONTROL

Follow government regulations or accreditation requirements for quality control frequency.
Internal quality control is only applicable with MAGLUMI and Biolumi systems. For instructions for use and target value refer to ***CEA(CLIA) Quality Control Information***. User needs to judge results with their own standards and knowledge.
For detailed information about entering quality control values, refer to the corresponding Analyzer Operating Instructions.
To monitor system performance and chart trends, commercially available quality control materials are required. Treat all quality control samples the same as patient samples. A satisfactory level of performance is achieved when analyte values obtained are within the acceptable Control Range for the system or within your range, as determined by an appropriate internal laboratory quality control scheme. If the quality control results do not fall within the Expected Values or within the laboratory's established values, do not report results. Take the following actions:

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the instructions for use.
- Rerun the assay with fresh quality control samples.
- If necessary, contact your local technical supporters or distributors for assistance.

SPECIMEN COLLECTION AND PREPARATION

- Use standard sampling tubes or tubes containing separating gel. Collect blood aseptically following the universal precautions for venipuncture.
- Ensure that complete clot formation in specimens has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time.
- If the specimen is centrifuged before a complete clotting, the presence of fibrin may cause erroneous results. Samples must be free of fibrin and other particulate matter.
- Do not use hemolyzed or grossly lipemic specimens as well as specimens containing particulate substance or exhibiting obvious microbial contamination. Inspect all specimens for bubbles, and remove bubbles before analysis for optimal results.
- Avoid repeated freezing and thawing. The serum sample can be frozen and thawed for only once. Stored samples should be thoroughly mixed prior to use (Vortex mixer). Frozen specimens must be mixed THOROUGHLY after thawing by LOW speed vortexing. Please ask local representative of SNIBE for more details if you have any doubt.
- Centrifuged specimens with a lipid layer on the top must be transferred to a sample cup or a secondary tube. Care should be taken to transfer only the clarified specimen without the lipemic material.
- All samples (patient specimens and controls) should be tested within 3 hours when placed on board the MAGLUMI and Biolumi Systems. Refer to the SNIBE service for more details of onboard sample storage constraints.
- Specimens removed from the separator, cells or clot may be stored up to 7 day at 2-8°C, and stored up to 6 months frozen at -20°C or colder.
- Before shipping specimens, it is recommended that specimens be removed from the serum separator, red blood cells or clot. When shipped, specimens should be packaged and labeled in compliance with applicable state, federal and international regulations covering the transport of clinical specimens and infectious substances. Specimens should be shipped frozen.
- The sample volume required for a single determination of CEA is 40 µL.

WARNING AND PRECAUTIONS FOR USERS

- IVD
- For *In Vitro* Diagnostic Use.
- Follow the package insert carefully. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Safety Precautions

- **CAUTION:** This product requires the handling of human specimens. It is recommended that all human sourced materials be considered potentially infectious and handled in accordance with the 29 CFR 1910.1030 Occupational exposure to bloodborne pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.
- All samples, biological reagents and materials used in the assay should be considered potentially able to transmit infectious agents. They should therefore be disposed in accordance with the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.
- This product contains Sodium Azide. Dispose of contents and containers must be in accordance with all local, regional and national regulations.
- Refer to safety data sheets which are available on request.

Handling Precautions

- Do not use reagent kits beyond the expiration date.
- Do not interchange reagent components from different reagents or lots.
- Prior to loading the reagent kit on the system for the first time, the reagent kit requires mixing to re-suspend magnetic microbeads that have settled during shipment.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- To avoid contamination, wear clean gloves when operating with a reagent kit and samples.
- Over time, residual liquids may dry on the septum surface. These aretypically dried salts which have no effect on assay efficacy.
- For detailed discussion of handling precautions during system operation, refer to the SNIBE service information.

STORAGE AND STABILITY

- Sealed: Stored at 2-8°C until the expiration date.
- Opened at 2-8°C: Minimum stability is 4 weeks.
- On-board: Minimum stability is 4 weeks.
- To ensure the best kit performance, it is recommended to place opened kits in the refrigerator after the end of the intraday test work. It is still possible to keep on using the kit beyond the opened or on-board period if the controls are found within the expected ranges.
- Keep upright for storage to facilitate later proper resuspension of magnetic microbeads.
- Keep away from sunlight.

TEST PROCEDURE

Preparation of the Reagent

- Resuspension of the magnetic microbeads takes place automatically when the kit is loaded successfully, ensuring the magnetic microbeads are totally resuspended homogenous prior to use.
- To ensure proper test performance, strictly adhere to the corresponding Analyzer Operating Instructions. Each test parameter is identified via a RFID CHIP on the Reagent kit. For further information please refer to the corresponding Analyzer Operating Instructions.

DILUTION

Samples with concentrations above the measuring range can be diluted. After manual dilution, multiply the result by the dilution factor. After dilution by the analyzers, the analyzer software automatically takes the dilution into account when calculating the sample concentration.
The automatic sample dilution is available after dilution settings are done in the MAGLUMI and Biolumi series Fully-auto chemiluminescence immunoassay analyzer user software. Please refer to the corresponding Analyzer Operating Instructions.

High-Dose Hook

For the CEA assay, no high dose hook effect was observed when samples containing up to 200,000 ng/mL

LIMITATIONS

- A skillful technique and strict adherence to the instructions are necessary to obtain reliable results.
- Bacterial contamination or heat inactivation of the specimens may affect the test results.
- A result within the expected range does not rule out the presence of disease and should be interpreted together with the patient's clinical picture and other diagnostic procedures.
- Diagnosis of a disease should not be based on the result of a single test, but should be determined in conjunction with clinical findings in association with medical judgement.
- Any therapeutical decision should also be taken on a case-by-case basis.
- Patient samples containing human anti-mouse antibodies (HAMA) may give falsely elevated or decreased values. Although HAMA-neutralizing agents are added, extremely high HAMA serum concentrations may occasionally influence results.
- CEA has a low clinical sensitivity and specificity as a tumor marker and is hence not recommended for screening. Clinically, an elevated CEA value is in itself not of diagnostic value as a test for cancer and this parameter should only be used in conjunction with other clinical observations and diagnostic parameters. Some patients with colorectal cancer do not exhibit elevated CEA values and elevated CEA levels in some patients do not change in accordance with progression or regression of disease. CEA values can be elevated in a number of benign conditions.
- Smokers constitute a distinct group with a higher range of baseline values.

RESULTS

Calculation of Results

The analyzer automatically calculates the CEA concentration in each sample by means of a calibration curve which is generated by a 2-point calibration master curve procedure. The results are expressed in ng/mL. For further information please refer to the corresponding Analyzer Operating Instructions.
Conversion factor: ng/mLx15=mIU/mL.

Interpretation of Results

The expected range for the CEA assay was obtained by testing 256 apparently healthy individuals in China, and gave the following expected value: <5.093 ng/mL(95^{th} percentile).
Results may differ between laboratories due to variations in population and test method. It is recommended that each laboratory should establish its own expected ranges.

PERFORMANCE CHARACTERISTICS

Precision

Precision for the CEA assay was determined as described in the CLSI EP5-A2. 3 human serum pools and 2 controls containing different concentration of analyte were assayed in duplicate at two independent runs per day for 20 testing days. The results are summarized in the following table:

Sample	Mean(ng/mL) (N=80)	Within-Run		Between-Run		Total	
		SD(ng/mL)	%CV	SD(ng/mL)	%CV	SD(ng/mL)	%CV
Serum Pool 1	5.291	0.258	4.88	0.294	5.56	0.391	7.39
Serum Pool 2	10.540	0.435	4.13	0.312	2.96	0.535	5.08
Serum Pool 3	512.770	10.526	2.05	2.796	0.55	10.891	2.12
Control 1	35.021	1.237	3.53	1.234	3.52	1.747	4.99
Control 2	309.086	8.693	2.81	3.221	1.04	9.270	3.00

Limit of Blank (LoB)

The LoB for the CEA assay is 0.5 ng/mL.

Limit of Detection (LoD)

The LoD for the CEA assay is 0.75ng/mL.

Measuring Range

0.5-1000 ng/mL (defined by the limit of blank and the maximum of the master curve). Values below the limit of blank are reported as <0.5 ng/mL. Values above the measuring range are reported as >1000 ng/mL.

Linearity

The assay is linear between 0.75 ng/mL and 1000 ng/mL based on a study performed with guidance from CLSI EP6-A. Nine equally distributed levels of samples were prepared by spiking a serum sample containing CEA 1100 ng/mL with a serum sample free of CEA (0.0 ng/mL). The mean sample recovery ranged between 90% to 110%.

Method Comparison

A total of 160 samples in the range of 0.587 and 902.589 ng/mL were tested by the CEA assay (y) and a commercially available immunoassay (x). The data from the resulting linear regressions are summarized as: y=0.900x+4.5942, r^2=0.9775.

Analytical Specificity

The specificity of the assay was obtained by adding AFP, NCA1 and NCA2 to serum samples at the indicated concentrations. No interference was found.

Endogenous Interference
Substances up to the following concentrations did not interfere with the assay:

- Bilirubin 66 mg/dL
- Hemoglobin 2200 mg/dL
- Triglyceride 1500 mg/dL
- RF 1500 IU/mL

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SYMBOLS EXPLANATIONS

	Consult instructions for use		Manufacturer
2°C 8°C	Temperature limit (Store at 2-8 °C)		Use-by date
Σ	Contains sufficient for		Keep away from sunlight
	This way up	EC REP	Authorized representative in the European Community
IVD	*In vitro* diagnostic medical device	CONTENTS	Kit components
REF	Catalogue number	LOT	Batch code