Snibe Diagnostic

CE 0123 REF 130263001M:100 tests/kit
130663001M: 50 tests/kit
130763001M: 30 tests/kit

MAGLUMI® FA (CLIA)

INTENDED USE

The kit is an in vitro chemiluminescence immunoassay for the quantitative determination of Folate (FA) in human serum, plasma and red blood cells using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer and Biolumi series Integrated System. Folate measurements are used for an aid in the diagnosis and treatment of individuals with suspected or confirmed anemias.

SUMMARY

Folic acid, also known as pteroyglutamic acid, consists of a pteridine ring linked to p-aminobenzoic acid, in turn linked to glutamic acid, and are referred to as dihydro- or tetrahydrofolates[1]. Folate metabolism plays a vital role in nucleic acid synthesis, methionine regeneration, shuttling and redox reactions of one carbon units required for normal metabolism and regulation[2]. Folates occur in a wide variety of foods of both plant and animal origin. Liver, mushrooms, and green leafy vegetables are rich sources of folate in human diets; while oilseed meals and animal by-products are important sources of folate in animal feeds[3]. Folate stores in well-nourished adult men are 12 to 28 mg, and based on biopsies, the liver contains about half of the total. A substantial amount of folate is secreted in bile, with bile folate flux over five times higher than usual daily intake-most of which is reabsorbed in the small intestine[4].

Macrocytic anemias fall into two categories: those associated with megaloblastic hemopoiesis and those associated with normoblastic hemopoiesis. The most common causes of megaloblastic hemopoiesis are vitamin B12 or folate deficiency. Disruption of vitamin B12 or folate metabolic pathways may also cause this type of disturbed hemopoiesis as may vitamin B12 or folate-independent mechanisms that interfere with DNA synthesis[5].

Low folate intake, malabsorption as a result of gastrointestinal diseases, pregnancy, and drugs such as phenytoin are causes of folate deficiency[6-8]. Other situations in which the risk of folate deficiency increases include lactation, alcoholism[4] and hepatitis[9].

RBC folate concentrations can be regarded as better folate status measures because they are integrative measures of folate intakes over RBC's 90~120d lifespan, whereas serum folate concentrations reflect recent intakes. The higher folate concentrations in RBC compared with serum also made RBC measurements easier[10].

TEST PRINCIPLE

Competitive chemiluminescence immunoassay.

By incubating sample with pretreatment reagent 2 and reconstituted pretreatment reagent 1, folate is released from endogenous folate binding proteins.

FA present in the samples compete with FA antigen labeled with ABEI for binding sites on the FA-binding protein immobilized on the magnetic microbeads, and form immuno-complexes. After precipitation in a magnetic field, the supernatant is decanted and then a 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 inversely proportional to the concentration of FA present in the sample.

REAGENTS

Kit Contents

Component	Description	100 tests/kit	50 tests/kit	30 tests/kit
Magnetic Microbeads	Magnetic microbeads coated with FA-binding protein antibody (~8.00 μg/mL), containing FA-binding protein (~1.20 μg/mL) in PBS buffer, NaN_3 (<0.1%).	2.5 mL	2.0 mL	1.0 mL
Calibrator Low	A low concentration of FA antigen, ascorbic acid (5.00 g/L).	2.0 mL	1.0 mL	1.0 mL
Calibrator High	A high concentration of FA antigen, ascorbic acid (5.00 g/L).	2.0 mL	1.0 mL	1.0 mL
Pretreament Reagent 2	NaOH (0.4%).	7.5 mL	4.5 mL	2.7 mL
ABEI Label	ABEI labeled with FA antigen (~208 ng/mL) in PBS buffer, NaN_3 (<0.1%).	12.5 mL	7.5 mL	4.8 mL
DTT Buffer	PBS buffer, NaN_3 (<0.1%).	15.0 mL	15.0 mL	15.0 mL
Pretreament Reagent 1	DTT (30.0 mg, lyophilized)	1 bottle	1 bottle	1 bottle
Control 1	A low concentration of FA antigen (5.00 ng/mL), ascorbic acid (5.00 g/L).	2.0 mL	2.0 mL	2.0 mL
Control 2	A high concentration of FA antigen (12.0 ng/mL), ascorbic acid (5.00 g/L).	2.0 mL	2.0 mL	2.0 mL
Pretreament Reagent 1 is lyophilized and must be reconstituted with DTT Buffer.				

The control barcode labels are provided.

Warnings and Precautions

- For *in vitro* diagnostic use.
- For professional use only.
- Exercise the normal precautions required for handling all laboratory reagents.
- Personal protective measures should be taken to prevent any part of the human body from contacting samples, reagents, and controls, and should comply with local operating requirements for the assay.
- A skillful technique and strict adherence to the package insert are necessary to obtain reliable results.
- Do not use kit beyond the expiration date indicated on the label.
- Do not interchange reagent components from different reagents or lots.
- Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).
- All waste associated with biological samples, biological reagents and disposable materials used for the assay should be considered potentially infectious and should be disposed of in accordance with local guidelines.
- This product contains sodium azide. Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. Immediately after disposal, flush with a large volume of water to prevent azide build-up. For additional information, see Safety Data Sheets available for professional user on request.

Note: If any serious incident has occurred in relation to the device, please report to Shenzhen New Industries Biomedical Engineering Co., Ltd. (Snibe) or our authorized representative and the competent authority of the Member State in which you are established.

Reagent Handling

- To avoid contamination, wear clean gloves when operating with a reagent kit and sample. When handling reagent kit, replace the gloves that have been in contact with samples, since introduction of samples will result in unreliable results.
- Do not use kit in malfunction conditions; e.g., the kit leaking at the sealing film or elsewhere, obviously turbid or precipitation is found in reagents (except for Magnetic Microbeads) or control value is out of the specified range repeatedly. When kit in malfunction conditions, please contact Snibe or our authorized distributor.
- To avoid evaporation of the liquid in the opened reagent kits in refrigerator, it is recommended that the opened reagent kits to be sealed with reagent seals contained within the packaging. The reagent seals are single use, and if more seals are needed, please contact Snibe or our authorized distributor.
- Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.
- Use always the same analyzer for an opened reagent integral.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- For further information about the reagent handing during system operation, please refer to Analyzer Operating Instructions.

Storage and Stability

- Do not freeze the integral reagents.
- Store the reagent kit upright to ensure complete availability of the magnetic microbeads.
- Protect from direct sunlight.

Stability of the Reagents	
Unopened at 2-8°C	until the stated expiration date
Opened at 2-8°C	6 weeks
On-board	4 weeks

Stability of Controls	
Unopened at 2-8°C	until the stated expiration date
Opened at 10-30°C	6 hours
Opened at 2-8°C	6 weeks
Frozen at -20°C	3 months
Frozen and thawed cycles	no more than 2 times

SPECIMEN COLLECTION AND PREPARATION

Specimen Types

Only the specimens listed below were tested and found acceptable.

Specimen Types	Collection Tubes
Serum	Tubes without additive/accessory, or tubes containing clot activator or clot activator with gel
Plasma	Li-heparin, Na-heparin
Whole blood	K2-EDTA, Li-heparin, Na-heparin

- The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing. Not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. Follow tube manufacturers' instructions carefully when using collection tubes.

Specimen Conditions

Serum and Plasma Folate

- Do not use heat-inactivated samples or grossly hemolyzed/hyperlipidaemia specimens and specimens with obvious microbial contamination.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some serum specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the serum 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.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

RBC Folate

- If testing is not done within 24 hours for whole blood specimens, determine the hematocrit and freeze the whole blood specimen or hemolysate at -20°C.
- If the hemolysate is frozen, thaw and mix it by inverting the tube several times.
- RBC hemolysate should be prepared according to the instructions.

Preparation for Analysis

- Folates are light sensitive. Minimize exposure to light during sample handling and storage[15].

Serum and Plasma Folate

- Inspect all specimens for foam. Remove foam with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.
- Frozen specimens must be completely thawed before mixing. Mix thawed specimens thoroughly by low speed vortexing or by gently inverting. Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous. If specimens are not mixed thoroughly, inconsistent results may be obtained.
- Specimens should be free of fibrin, red blood cells, or other particulate matter. Such specimens may give reliable results and must be centrifuged prior to testing. Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.
- The sample volume required for a single determination of this assay is 80 μL.

RBC Folate

- Reconstitute Sample Release Agent (REF: 130299026M): add 0.2g Ascorbic acid into the 100 mL bottle, then add 100 mL deionized water to dissolve. Let the reconstituted mixture stand at room temperature for 15 minutes and mix by inverting the bottle occasionally.
- Collect the whole blood sample in a tube containing heparin or EDTA and invert the sample several times to mix.
- Determine and record the hematocrit.
- Dispense 0.9 mL of reconstituted Sample Release Agent into a test tube or sample cup, then add 30 μL whole blood sample.
- Cap and invert the tube several times or vortex gently to mix. Avoid foaming.
- Let the hemolysate stand protected from light, at room temperature, for a minimum of 90 minutes, but less than 180 minutes.
- Do not mix the hemolysate again before placing the sample on the system.

Specimen Storage

Storage Temperature	Specimen Types		
	Serum/ Plasma	Whole Blood	Hemolysis product
10-30°C	8 hours	8 hours	4 hours
2-8°C	7 days	48 hours	24 hours
-20°C	3 months	2 months	3 months

Frozen specimens subjected to up to 3 freeze/thaw cycles have been evaluated.

Specimen Shipping

- Package and label specimens in compliance with applicable local regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

Specimen Dilution

- Serum and plasma samples, FA concentrations above the analytical measuring interval, can be diluted with manual dilution procedure. The recommended dilution ratio is 1:5. The concentration of the diluted sample must be >4.8 ng/mL.
- For manual dilution, multiply the result by the dilution factor.
- Please choose applicable diluents or ask Snibe for advice before manual dilution.
- Do not dilute the RBC hemolysis sample.

PROCEDURE

Materials Provided

FA (CLIA) assay, control barcode labels.

Materials Required (But Not Provided)

- Sample Release Agent.
- General laboratory equipment.
- Fully-auto chemiluminescence immunoassay analyzer Maglumi 600, Maglumi 800, Maglumi 1000, Maglumi 2000, Maglumi 2000 Plus, Maglumi 4000, Maglumi 4000 Plus, MAGLUMI X8, MAGLUMI X3, MAGLUMI X6, or Integrated System Biolumi 8000 and Biolumi CX8.
- Additional accessories of test required for the above analyzers include Reaction Module, Starter 1+2, Wash Concentrate, Light Check, Tip, and Reaction Cup. Specific accessories and accessories' specification for each model refer to corresponding Analyzer Operating Instructions.
- Please use accessories specified by Snibe to ensure the reliability of the test results.

Assay Procedure

Preparation of the Reagent

- Take the reagent kit out of the box and visually inspect the integral vials for leaking at the sealing film or elsewhere. If there is no leakage, please tear off the sealing film carefully.
- The recombination of Pretreatment Reagent 1: The Pretreatment Reagent 1 provided by this kit is lyophilized. Remove 1 mL of DTT buffer from the kit to the glass bottle of Pretreatment Reagent 1 before use, close the plug and shake gently, let the reconstituted mixture stand at room temperature for 3 minutes. All the reconstituted liquid was transferred to the DTT Buffer component of the kit. Shake gently until well mixed.
- Do not cross use of pipette during preparation to avoid abnormal or incorrect results.
- Open the reagent area door; hold the reagent handle to get the RFID label close to the RFID reader (for about 2s); the buzzer will beep; one beep sound indicates successful sensing.
- Keeping the reagent straight insert to the bottom along the blank reagent track.
- Observe whether the reagent information is displayed successfully in the software interface, otherwise repeat the above two steps.
- 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.

Assay Calibration

- Select the assay to be calibrated and execute calibration operation in reagent area interface. For specific information on ordering calibrations, refer to the calibration section of Analyzer Operating Instructions.
- Execute recalibration according to the calibration interval required in this package insert.

Quality Control

- When new lot used, check or edit the quality control information.
- Scan the control barcode, choose corresponding quality control information and execute testing. For specific information on ordering quality controls, refer to the

quality control section of the Analyzer Operating Instructions.

Sample Testing

- After successfully loading the sample, select the sample in interface and edit the assay for the sample to be tested and execute testing. For specific information on ordering patient specimens, refer to the sample ordering section of the Analyzer Operating Instructions.

To ensure proper test performance, strictly adhere to Analyzer Operating Instructions.

Calibration

Traceability: This method has been standardized against the WHO International Standard 03/178.

Test of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the master curve.

Recalibration is recommended as follows:

- Whenever a new lot of Reagent or Starter 1+2 is used.
- Every 7 days.
- The analyzer has been serviced.
- Control values lie outside the specified range.
- Each time a new kit is used.

Quality Control

Controls are recommended for the determination of quality control requirements for this assay and should be run in singlicate to monitor the assay performance. Refer to published guidelines for general quality control recommendations, for example Clinical and Laboratory Standards Institute (CLSI) Guideline C24 or other published guidelines[11].

Quality control is recommended once per day of use, or in accordance with local regulations or accreditation requirements and your laboratory's quality control procedures, quality control could be performed by running the FA assay:

- Whenever the kit is calibrated.
- Whenever a new lot of Starter 1+2 or Wash Concentrate is used.

Controls are only applicable with MAGLUMI and Biolumi system and only used matching with the same top seven LOT numbers of corresponding reagents. For each target value and range refer to the label.

The performance of other controls should be evaluated for compatibility with this assay before they are used. Appropriate value ranges should be established for all quality control materials used.

Control values must lie within the specified range, whenever one of the controls lies outside the specified range, calibration should be repeated and controls retested. If control values lie repeatedly outside the predefined ranges after successful calibration, patient results must not be reported and 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 package insert.
- If necessary, contact Snibe or our authorized distributors for assistance.

If the controls in kit are not enough for use, please order FA (CLIA) Controls (REF: 160201216MT) from Snibe or our authorized distributors for more.

RESULTS

Calculation

- The analyzer automatically calculates the FA 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 Analyzer Operating Instructions.

RBC Folate

- The calculation of RBC folate needs to consider the hematocrit and the 31-fold reduction in the hemolysis sample preparation process. Multiply the folate result for the hemolysate by 31 (a 1:30 dilution was made when preparing the RBC hemolysate). This value represents the folate concentration of whole blood in ng/mL. Divide this result by the hematocrit, and multiply by 100 to adjust for the hematocrit, which is a percentage.

- RBC folate (ng/mL) $=\frac{\text{(Folate result for hemolysate,ng/mL)}\times 31}{\text{hematocrit}}\times 100$

Example:

Hemolysate folate value = 6.375 ng/mL; Hematocrit = 42

RBC folate (ng/mL) $=\frac{6.375\times 31}{42}\times 100=471$

Corrected Red Blood Cell Folate

- In most cases the serum folate values are very small compared to red blood cell folate values. However, occasionally serum folate values can be elevated. If the serum folate value is high and the red blood cell folate concentration is low, calculate the corrected RBC folate value according to the following equation:

- Corrected RBC folate (ng/mL) =RBC folate (ng/mL)-serum folate (ng/mL)$\times[\frac{(100-\text{hematocrit})}{\text{hematocrit}}]$

Example:

RBC folate = 218 ng/mL; Serum folate = 21.124 ng/mL; Hematocrit of the patient = 41

Corrected RBC folate (ng/mL) =218-21.124$\times[\frac{(100-41)}{41}]$=188

Interpretation of Results

To determine the reference range for serum and RBC folate for the FA assay, data was obtained on 600 and 375 samples, respectively. The normal ranges are the inner 97.5% of the distribution of apparently healthy individuals and the deficient range represent the observed range. For sample results in the indeterminate range [3.21 to 5.21 ng/mL], clinical results and other diagnostic protocols should supplement folate results.

Category	N	Mean (ng/mL)	97.5th percentile (ng/mL)
Serum and Plasma folate			
Deficient	225	2.377	≤ 3.21
Indeterminate	/	/	3.21-5.21
Normal	375	15.062	≥ 5.21
RBC folate			
Normal	375	539	284-786

Results may differ between laboratories due to variations in population, diet and test method. It is recommended that each laboratory establish its own reference interval.

LIMITATIONS

- Results should be used in conjunction with patient's medical history, clinical examination and other findings.
- If the FA results are inconsistent with clinical evidence, additional testing is needed to confirm the result.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies[12,13]. Additional information may be required for diagnosis.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or animal serum products can be prone to this interference and anomalous values may be observed[14].
- Serum or plasma containing red blood cells may give falsely elevated folate levels. These samples should be centrifuged prior to use. Serum or plasma samples that are hemolyzed will give falsely elevated folate levels.
- Bacterial contamination or heat inactivation of the specimens may affect the test results.

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

Precision

Precision was determined using the assay, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): duplicates at two independent runs per day for 5 days at three different sites using three lots of reagent kits (n = 180). The following results were obtained:

Sample	Mean (ng/mL) (n=180)	Within-Run		Between-Run		Reproducibility	
		SD (ng/mL)	%CV	SD (ng/mL)	%CV	SD (ng/mL)	%CV
Serum Pool 1	1.907	0.056	2.94	0.017	0.89	0.083	4.35
Serum Pool 2	3.871	0.097	2.51	0.060	1.55	0.184	4.75
Serum Pool 3	19.927	0.398	2.00	0.269	1.35	0.652	3.27
Plasma Pool 1	1.904	0.062	3.26	0.011	0.58	0.088	4.62
Plasma Pool 2	3.787	0.110	2.90	0.038	1.00	0.134	3.88
Plasma Pool 3	20.080	0.416	2.07	0.261	1.30	0.578	2.88
Whole Blood Pool 1	191.545	6.329	3.30	1.178	0.61	9.184	4.79
Whole Blood Pool 2	530.032	11.055	2.09	7.486	1.41	16.864	3.18
Whole Blood Pool 3	1044.097	33.082	3.17	8.523	0.82	43.708	4.19
Control 1	4.895	0.129	2.64	0.075	1.53	0.186	3.80
Control 2	12.151	0.258	2.12	0.138	1.14	0.336	2.77

Linear Range

0.375-24 ng/mL (defined by the Limit of Quantitation and the maximum of the master curve).

Reportable Interval

0.325-120 ng/mL (defined by the Limit of Detection and the maximum of the master curve×Recommended Dilution Ratio).

Analytical Sensitivity

Limit of Blank (LoB) =0.200 ng/mL.

Limit of Detection (LoD) =0.325 ng/mL.

Limit of Quantitation (LoQ) =0.375 ng/mL.

Analytical Specificity

Interference

Interference was determined using the assay, three samples containing different concentrations of analyte were spiked with potential endogenous and exogenous interferents in a protocol (EP7-A2) of the CLSI. The measurement deviation of the interference substance is within ±10%. The following results were obtained:

Interference	No interference up to	Interference	No interference up to
Bilirubin	60 mg/dL	Aminopterin	500 ng/mL
Intralipid	2000 mg/dL	Phenytoin	100 μg/mL
HAMA	40 ng/mL	Folic acid and calcium	100 ng/mL
Rheumatoid factor	1500 IU/mL	Methotrexate	500 ng/mL
ANA	6 (S/CO) strong positive		

Cross-Reactivity

Cross-reactivity was determined using the assay, three samples containing different concentrations of analyte were spiked with potential cross-reactants in a protocol (EP7-A2) of the CLSI. The measurement deviation of the interference substance is within ±10%. The following results were obtained:

Cross-reactant	No interference up to	Cross-reactant	No interference up to
Ferritin	100 ng/mL	Biotin	1 μg/mL
Vitamin D	100 ng/mL	Erythropoietin	1500 mIU/mL
Vitamin B12	10 ng/mL		

Method Comparison

A comparison of the FA assay with a commercially available immunoassay, gave the following correlations (ng/mL):

Number of samples measured: 120

Passing-Bablok: y=0.9914x-0.0283, r=0.953.

The clinical specimen concentrations were between 0.39 and 23.94 ng/mL.

REFERENCES

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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<n> tests		Keep away from sunlight
	This way up	EC REP	Authorized representative in the European Community
IVD	*In vitro* diagnostic medical device	CONTENTS	Kit component
REF	Catalogue number	LOT	Batch code
CE 0123	CE marking with notified body ID number		

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