



MAGLUMI® Folate (CLIA)

CE 0123 REF 1302633001M: 100 tests/kit
1306633001M: 50 tests/kit

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, and the assay is used for an aid in the diagnosis of individuals with suspected or confirmed anemias.

SUMMARY

Folic acid, also known as pteroylglutamic acid, consists of a pteridine ring linked to p-aminobenzoic acid, in turn linked to glutamic acid, and are referred to as dihydro- or tetrahydrofolates¹. 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 regulation². Foliates 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 feeds³. 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 intestine⁴. 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 synthesis⁵.

Adequate folic acid and vitamin B12 are required for fetal growth and development, especially during the second and third trimesters, so folic acid and vitamin B12 are important micronutrients required for DNA synthesis and epigenetic regulation⁶. Maternal folate deficiency is one of the important risk factors for fetal neural tube defects, and the most common neural tube defects are anencephaly, encephalocele and spina bifida^{7,8}. Guidelines recommend that red blood cell folate concentrations in women of childbearing age should be higher than 400 ng/mL (906 nmol/L) to minimize neural tube defects^{9,10}. Low folate intake, malabsorption as a result of gastrointestinal diseases, pregnancy, and drugs such as phenytoin are causes of folate deficiency¹¹⁻¹². Other situations in which the risk of folate deficiency increases include lactation, alcoholism and hepatitis¹³. 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 easier¹⁴.

TEST PRINCIPLE

Sandwich chemiluminescence immunoassay.

The sample, Pretreatment Reagent 1 and Pretreatment Reagent 2 are mixed thoroughly and incubated. ABEI labeled with Folic acid immune complex antibody and magnetic microbeads immobilized with FABP Ag are then added and incubated. Folic acid immune complex antibody labeled on ABEI and antigen-antibody complex bound on magnetic microbeads form sandwich 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 proportional to the concentration of Folate present in the sample.

REAGENTS

Kit Contents

Component	Description	100 tests/kit	50 tests/kit
Magnetic Microbeads	Magnetic microbeads coated with anti-FABP (~16.0 µg/mL), containing FABP Ag (~1.33 µg/mL) in PBS buffer, Na ₂ S ₂ O ₃ (<0.1%).	2.5 mL	1.5 mL
Calibrator Low	A low concentration of Folate antigen, ascorbic acid (5.00 g/L).	1.0 mL	1.0 mL
Calibrator High	A high concentration of Folate antigen, ascorbic acid (5.00 g/L).	1.0 mL	1.0 mL
Pretreatment Reagent 2	NaOH (0.4%).	5.5 mL	3.5 mL
ABEI Label	ABEI labeled with Folic acid immune complex antibody (~625 ng/mL) in PBS buffer, Na ₂ S ₂ O ₃ (<0.1%).	6.5 mL	4.0 mL
Pretreatment Reagent 1	PBS buffer, Na ₂ S ₂ O ₃ (<0.1%).	6.5 mL	4.0 mL
Control 1	A low concentration of Folate antigen (5.00 ng/mL), ascorbic acid (5.00 g/L).	1.0 mL	1.0 mL
Control 2	A high concentration of Folate antigen (12.0 ng/mL), ascorbic acid (5.00 g/L).	1.0 mL	1.0 mL

All reagents are provided ready-to-use.

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.
- The safety data sheet is available 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 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.
- Do not transfer opened integral reagents between instruments.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- For further information about the reagent handling 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, or tubes containing clot activator or clot activator with gel
Plasma	Na-heparin or LI-heparin
Whole blood	K2-EDTA, Na-heparin or LI-heparin

- The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. 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 are 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 hemolyse at -20°C.
- If the hemolyse is frozen, thaw and mix it by inverting the tube several times.
- RBC hemolyse should be prepared according to the instructions.
- Do not dilute RBC hemolyzed samples.

Preparation for Analysis

- Foliates are light sensitive. Minimize exposure to light during sample handling and storage¹⁵.

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.
- For reliable results, 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 10 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 hemolyse stand protected from light, at room temperature, for a minimum of 90 minutes, but less than 180 minutes.
- Do not mix the hemolyse 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	48 hours	24 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, with Folate concentrations above the analytical measuring interval, can be diluted with manual dilution procedure. The recommended dilution ratio is 1:5 (sample volume:total volume). The concentration of the diluted sample must be >4.80 ng/mL (10.9 nmol/L).
- For manual dilution, multiply the result by the dilution factor.
- Do not dilute the RBC hemolysis sample.

PROCEDURE

Materials Provided

Folate (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 2000, Maglumi 2000 Plus, Maglumi 4000 Plus, MAGLUMI X3, MAGLUMI X6, MAGLUMI X8, MAGLUMI X10, or Integrated System Biolumi CX8.
- For Reaction Module, Starter 1+2, Wash Concentrate, Light Check, Tip and Reaction Cup, please refer to corresponding Analyzer Operating Instructions for catalogue number.
- 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.
- 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 registering 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 registering 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 registering samples, refer to the sample 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 Q03/178. 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 28 days.
- The analyzer has been serviced.
- Control values lie outside the specified range.

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 guidelines¹⁴.

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 Folate assay:

- Whenever the kit is calibrated.
- Whenever a new lot of Starter 1+2 or Wash Concentrate is used.
- The first eight digits of the lot number on the controls must match those of the corresponding reagent kit. 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 Folate (CLIA) Controls (REF: 1602011043MT) from Snibe or our authorized distributors for more.

RESULTS

Calculation

The analyzer automatically calculates the Folate 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 or nmol/L. For further information please refer to the Analyzer Operating Instructions. Conversion factor: 1 ng/mL × 2.265=nmol/L

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.

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

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

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

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:

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

Example:
RBC folate = 471 ng/mL; Serum folate = 6.124 ng/mL; Hematocrit of the patient = 41

$$\text{Corrected RBC folate (ng/mL)} = 471 - 6.124 \times \left(\frac{100 - 41}{41} \right) = 462$$

Interpretation of Results

The expected range for the Folate assay was obtained by testing 596 apparently healthy individuals, gave the following expected value:
Serum Folate: 5.13-24.3 ng/mL (11.6-55.0 nmol/L) (2.5th-97.5th percentiles).
RBC Folate: 281-789 ng/mL (636-1787 nmol/L) (2.5th-97.5th percentiles).
Results may differ between laboratories due to variations in population 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 Folate results are inconsistent with clinical evidence, additional testing is needed to confirm the result.
- In people taking folic acid preparations, serum or plasma FA test results may be higher than normal.
- 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^{17,18}. 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 observed¹⁹.
- Bacterial contamination or heat inactivation of the specimens may affect the test results.
- 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.

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	SD (ng/mL)	%CV	
Serum Pool 1	2.416	0.097	4.01	0.027	1.12	0.171	7.07			
Serum Pool 2	5.006	0.124	2.47	0.099	1.98	0.321	6.41			
Serum Pool 3	15.700	0.406	2.59	0.359	2.29	0.989	6.30			
Plasma Pool 1	2.529	0.102	4.02	0.047	1.85	0.172	6.80			
Plasma Pool 2	4.946	0.129	2.61	0.124	2.50	0.316	6.39			
Plasma Pool 3	14.348	0.428	2.98	0.315	2.19	0.788	5.49			
Whole Blood Pool 1	191.542	7.567	3.95	4.366	2.28	11.732	6.13			
Whole Blood Pool 2	376.110	10.647	2.83	6.572	1.75	21.997	5.85			
Whole Blood Pool 3	1116.701	34.329	3.07	14.949	1.34	63.557	5.69			
Control 1	4.857	0.185	3.81	0.113	2.33	0.331	6.81			
Control 2	12.381	0.343	2.77	0.315	2.54	0.748	6.04			

Based on internal testing on the MAGLUMI and Biolumi systems, the overall repeatability (% CV) is estimated to be ≤ 5% for samples tested, the overall reproducibility (%CV) is estimated to be ≤ 10%. Performance of the assay at individual laboratories may vary.

Linear Range

1.50-24.0 ng/mL (3.40-54.4 nmol/L) (defined by the Limit of Quantitation and the maximum of the master curve).

Reportable Interval

1.00-120 ng/mL (2.27-272 nmol/L) (defined by the Limit of Detection and the maximum of the master curve × Recommended Dilution Ratio).

Analytical Sensitivity

Limit of Blank (LoB) = 0.500 ng/mL (1.13 nmol/L).

Limit of Detection (LoD) = 1.00 ng/mL (2.27 nmol/L).

Limit of Quantitation (LoQ) = 1.50 ng/mL (3.40 nmol/L).

Analytical Specificity

Interference

Interference was determined using the assay, three samples containing different concentrations of analyte were spiked with potential endogenous and exogenous interferences 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	Biotin	0.5 mg/dL
Intralipid	2000 mg/dL	Heparin sodium salt	80 IU/mL
Rheumatoid factor	1500 IU/mL	Heparin lithium salt	80 IU/mL
HAMA	40 ng/mL	K2-EDTA	22.75 μmol/mL
ANA	398 AU/mL		

Cross-Reactivity

Cross-reactivity was determined using the assay, three samples containing different concentrations of analyte were spiked with potential cross-reactant 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
Aminopterin	500 ng/mL
Folinic acid	100 ng/mL
Methotrexate	500 ng/mL

High-Dose Hook

No high-dose hook effect was seen for Folate concentrations up to 120 ng/mL (272 nmol/L).

Method Comparison

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

Serum: Number of samples measured: 130

Passing-Bablok: y=0.9962x+0.0044, r=0.942.

The clinical specimen concentrations were between 1.523 and 24.255 ng/mL.

Whole Blood: Number of samples measured: 130

Passing-Bablok: y=0.9939x+1.3731, r=0.948.

The clinical specimen concentrations were between 70.866 and 975.220 ng/mL.

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SYMBOLS EXPLANATIONS

	Consult instructions for use		Manufacturer
	Temperature limit (Store at 2-8°C)		Use-by date
	Contains sufficient for <n> tests		Keep away from sunlight
	This way up		Authorized representative in the European Community
	<i>In vitro</i> diagnostic medical device		Kit component
	Catalogue number		Batch code
	CE marking with notified body ID number		

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