



130217020M:100 tests/kit  
130617020M: 50 tests/kit

# MAGLUMI® Anti-tissue Transglutaminase IgA (CLIA)

## INTENDED USE

The kit is an *in vitro* chemiluminescence immunoassay for the quantitative determination of Anti-tissue Transglutaminase IgA (tTG IgA) in human serum and plasma 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 celiac disease in suspected or confirmed patients.

## SUMMARY

Celiac Disease is a gluten-sensitive disease that afflicts primarily the small bowel, resulting in the shortening of villi, increased numbers of intraepithelial lymphocytes, and crypt hyperplasia<sup>1</sup>. Celiac disease is induced by the ingestion of gluten, which is derived from wheat, barley, and rye<sup>2</sup>. Celiac disease is often accompanied by extraintestinal manifestations, which can be the result of aberrant immune responses but also malabsorption; These concurrent conditions can affect various systems and organs, and include manifestations in the skin, musculoskeletal and central nervous system; Anaemia, osteoporosis, dermatitis herpetiformis and gluten ataxia are among the most commonly seen characteristics; In the paediatric population, celiac disease can lead to severe growth disorders, such as short stature and delayed puberty due to hypogonadism<sup>3</sup>. The only effective treatment for celiac disease is complete removal of gluten from the diet<sup>4</sup>. The gold standard for celiac disease diagnosis is represented by the combination of mucosal changes detected by duodenal biopsy and by positivity of serological tests including tissue transglutaminase (tTG) antibodies and deamidated gliadin peptide (DGP) antibodies<sup>5</sup>. Tissue transglutaminase or transglutaminase 2 is a calcium dependent ubiquitous enzyme consisting of 686 amino acids, which exerts several distinct physiological functions<sup>6</sup>. It is a widely expressed protein and its expression and enzymatic activity is increased in several diseases, including celiac disease<sup>7</sup>. Immunoglobulin A (IgA) tTG is considered the best test with sensitivity and specificity but performs less well IgA-deficient individuals<sup>8</sup>. Selective IgA deficiency is more common in patients with celiac disease than in the general population. If the levels of tTG IgA are within the normal range (or if it is absent) and there is a high suspicion of celiac disease, a test for IgG antibodies against tissue transglutaminase should be performed<sup>9</sup>.

## TEST PRINCIPLE

Indirect chemiluminescence immunoassay. The prediluted sample, buffer, magnetic microbeads coated with Tissue transglutaminase antigen are mixed thoroughly and incubated, performing a wash cycle after a precipitation in a magnetic field. ABEI labeled with anti-human IgA monoclonal antibody are then added and incubated, reacting to 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 proportional to the concentration of Anti-tissue Transglutaminase IgA present in the sample.

## REAGENTS

| Component                                                                                                                                                     | Description                                                                                                                | 100 tests/kit | 50 tests/kit |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------|--------------|
| <b>Lyophilized Magnetic Microbeads</b>                                                                                                                        | Magnetic microbeads coated with Tissue transglutaminase antigen (~5.60 µg/bottle) in PBS buffer, NaN <sub>3</sub> (<0.1%). | 1 bottle      | 1 bottle     |
| <b>Magnetic Microbeads Buffer</b>                                                                                                                             | PBS buffer, NaN <sub>3</sub> (<0.1%).                                                                                      | 2.8 mL        | 2.8 mL       |
| <b>Calibrator Low</b>                                                                                                                                         | A low concentration of tTG IgA in PBS buffer, NaN <sub>3</sub> (<0.1%).                                                    | 1.0 mL        | 1.0 mL       |
| <b>Calibrator High</b>                                                                                                                                        | A high concentration of tTG IgA in PBS buffer, NaN <sub>3</sub> (<0.1%).                                                   | 1.0 mL        | 1.0 mL       |
| <b>Buffer</b>                                                                                                                                                 | BSA, NaN <sub>3</sub> (<0.1%).                                                                                             | 17.5 mL       | 9.5 mL       |
| <b>ABEI Label</b>                                                                                                                                             | ABEI labeled with anti-human IgA monoclonal antibody (~50.0 ng/mL) in Tris-HCl buffer, NaN <sub>3</sub> (<0.1%).           | 22.5 mL       | 12.0 mL      |
| <b>Diluent</b>                                                                                                                                                | PBS buffer, NaN <sub>3</sub> (<0.1%).                                                                                      | 25.0 mL       | 13.5 mL      |
| <b>Control 1</b>                                                                                                                                              | A low concentration of tTG IgA (10.0 AU/mL) in PBS buffer, NaN <sub>3</sub> (<0.1%).                                       | 1.0 mL        | 1.0 mL       |
| <b>Control 2</b>                                                                                                                                              | A high concentration of tTG IgA (100 AU/mL) in PBS buffer, NaN <sub>3</sub> (<0.1%).                                       | 1.0 mL        | 1.0 mL       |
| <b>Magnetic Microbeads is lyophilized and must be reconstituted with Magnetic Microbeads Buffer, refer to the Preparation of Magnetic Microbeads section.</b> |                                                                                                                            |               |              |

## Warnings and Precautions

- For *in vitro* diagnostic use.
- For laboratory 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 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                          |
| <b>Stability of Controls</b> |                                  |
| Unopened at 2-8°C            | until the stated expiration date |
| Opened at 10-30°C            | 24 hours                         |
| Opened at 2-8°C              | 6 weeks                          |
| Frozen at -20°C              | 3 months                         |
| Frozen and thawed cycles     | no more than 3 times             |

## SPECIMEN COLLECTION AND PREPARATION

### Specimen Types

Only the specimens listed below were tested and found acceptable.

| Specimen Types | Collection Tubes                                                                                 |
|----------------|--------------------------------------------------------------------------------------------------|
| <b>Serum</b>   | Tubes without additive/accessory, or tubes containing clot activator or clot activator with gel. |
| <b>Plasma</b>  | K2-EDTA or Na-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

- 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.

### Preparation for Analysis

- 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. Specimens 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.

### Specimen Storage

Specimens removed from the separator, red blood cells or clot may be stored up to 6 hours at 10-30°C or 7 days at 2-8°C, or 6 months frozen at -20°C. Frozen specimens subjected to 1 freeze/thaw cycle 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

- Samples, with tTG IgA concentrations above the analytical measuring interval, can be diluted with Diluent either by following automated dilution protocol or manual dilution procedure. The recommended dilution ratio is 1:20(sample volume:total volume). The concentration of the diluted sample must be >20 AU/mL.
- For manual dilution, multiply the result by the dilution factor. For dilution by the analyzers, the analyzer software automatically takes the dilution into account when calculating the sample concentration.

## PROCEDURE

### Materials Provided

Anti-tissue Transglutaminase IgA (CLIA) assay, control barcode labels.

### Materials Required (But Not Provided)

- 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 X3, MAGLUMI X6,MAGLUMI X8, 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.

#### Preparation of Magnetic Microbeads

- The Magnetic Microbeads is provided in a lyophilized form. The vial containing the lyophilized magnetic microbeads must be opened carefully and reconstituted with the Magnetic Microbeads Buffer.**
- Remove 2 mL Magnetic Microbeads Buffer from the magnetic microbeads tube (blue collar and serrated reagent tube on the bottom) into the vial containing lyophilized magnetic microbeads before use, cover with a rubber stopper, and gently shake. Allow the dissolved magnetic microbeads to stand for 10-15 minutes.**
- Swirl gently to ensure homogeneity. Avoid heavy shaking when dissolving (avoid formation of foam).**
- Transfer all reconstituted magnetic microbeads in vial to the magnetic microbeads tube and mix it with the remaining Magnetic Microbeads Buffer evenly, then place prepared kit onto the analyzer.**
- After use, the kit including the reconstituted magnetic microbeads should be stored at 2-8°C in an upright position.**

- 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 Snibe internal reference standard.

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<sup>9</sup>.

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 Anti-tissue Transglutaminase IgA 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 systems 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 Anti-tissue Transglutaminase IgA (CLIA) Controls (REF: 160201443MT) from Snibe or our authorized distributors for more.

**■ RESULTS**

**Calculation**

The analyzer automatically calculates the tTG IgA 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 AU/mL. For further information please refer to the Analyzer Operating Instructions.

**Interpretation of Results**

The expected range for the tTG IgA assay was obtained by testing 126 tTG IgA positive patients and 130 tTG IgA negative people, gave the following expected value by ROC curve:

- Non-reactive: A result less than 20.0 AU/mL (<20.0 AU/mL) is considered to be negative.
- Reactive: A result greater than or equal to 20.0 AU/mL (≥20.0 AU/mL) is considered to be positive.

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 tTG IgA 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<sup>10,11</sup>. 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<sup>12</sup>.
- 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 on the Maglumi 4000 Plus:

| Sample        | Mean (AU/mL)<br>(n=180) | Within-Run |      | Between-Run |      | Reproducibility |      |
|---------------|-------------------------|------------|------|-------------|------|-----------------|------|
|               |                         | SD (AU/mL) | %CV  | SD (AU/mL)  | %CV  | SD (AU/mL)      | %CV  |
| Serum Pool 1  | 5.328                   | 0.168      | 3.15 | 0.109       | 2.05 | 0.272           | 5.11 |
| Serum Pool 2  | 21.217                  | 0.824      | 3.88 | 0.308       | 1.45 | 1.138           | 5.36 |
| Serum Pool 3  | 202.515                 | 5.879      | 2.90 | 4.488       | 2.22 | 10.634          | 5.25 |
| Plasma Pool 1 | 5.419                   | 0.183      | 3.38 | 0.110       | 2.03 | 0.281           | 5.19 |
| Plasma Pool 2 | 20.917                  | 0.676      | 3.23 | 0.351       | 1.68 | 0.944           | 4.51 |
| Plasma Pool 3 | 201.160                 | 5.206      | 2.59 | 3.646       | 1.81 | 8.549           | 4.25 |
| Control 1     | 10.045                  | 0.326      | 3.25 | 0.148       | 1.47 | 0.481           | 4.79 |
| Control 2     | 98.304                  | 3.325      | 3.38 | 0.765       | 0.78 | 5.852           | 5.95 |

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.

**Trueness**

Trueness (bias) was determined using the assay and samples in a protocol (EP15-A3) of the CLSI (Clinical and Laboratory Standards Institute). The observed mean is within the verification interval.

**Linear Range**

2.00-400 AU/mL (defined by the Limit of Quantitation and the maximum of the master curve).

**Reportable Interval**

1.00-8000 AU/mL (defined by the Limit of Detection and the maximum of the master curve\*Recommended Dilution Ratio).

**Analytical Sensitivity**

Limit of Blank (LoB) =0.500 AU/mL.

Limit of Detection (LoD) =1.00 AU/mL.

Limit of Quantitation (LoQ) =2.00 AU/mL.

| 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                                                                                                                                                                                                                                                                                                                    | 90 mg/dL              | Rheumatoid factor   | 2500 IU/mL            |
| Hemoglobin                                                                                                                                                                                                                                                                                                                   | 1000 mg/dL            | ANA                 | 398 AU/mL             |
| Intralipid                                                                                                                                                                                                                                                                                                                   | 3000 mg/dL            | HAMA                | 40 ng/mL              |
| K2-EDTA                                                                                                                                                                                                                                                                                                                      | 22.75 µmol/mL         | Heparin sodium salt | 80 IU/mL              |

**High-Dose Hook**

No high-dose hook effect was seen for tTG IgA concentrations up to 8000 AU/mL.

**Method Comparison**

A comparison of the tTG IgA assay with a commercially available immunoassay, gave the following correlations (AU/mL):

Number of samples measured: 120

Passing-Bablok: y=1.0101x-0.0582, r=0.966.

The clinical specimen concentrations were between 2.030 and 364.156 AU/mL.

**Agreement Rate Analysis**

The positive percent agreement (PPA) and negative percent agreement (NPA) of the tTG IgA assay were determined by testing 120 samples (31 positive samples and 89 negative samples) collected from expected population with celiac disease-related manifestations (diarrhea, chronic diarrhea, diarrheal irritable bowel syndrome [IBS-D], etc.) with commercial Anti-Tissue Transglutaminase IgA (ELISA) confirmation of tTG IgA positive and negative result. The PPA was 100.00% (95% CI: 88.97%–100.00%). The NPA was 100.00% (95% CI: 95.86%–100.00%). The total agreement was 100.00% (95% CI: 96.90%–100.00%).

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| ■ SYMBOLS EXPLANATIONS |                                           |  |                                                     |
|------------------------|-------------------------------------------|--|-----------------------------------------------------|
|                        | Consult instructions for use              |  | Manufacturer                                        |
|                        | Temperature limit<br>(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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