anti-MAG Antibodies ELISA

MAG = Myelin Associated Glycoprotein

For *In Vitro* Diagnostic Use

EK-MAG 96 tests

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Version A5

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ENGLISH

INTENDED USE

The anti-MAG Antibodies ELISA is an *in vitro* diagnostic assay for the semi-quantitative determination of anti-MAG IgM antibodies in human serum samples of patients with symptoms of demyelinating peripheral neuropathy and/or patients with IgM monoclonal gammopathy and neurological symptoms. The assay is intended as an aid to diagnosis of anti-MAG neuropathy in conjunction with other clinical and laboratory findings.

For laboratory use by healthcare professionals only. Not automated.

PRINCIPLE OF THE ASSAY

The anti-MAG Antibodies ELISA allows the measurement of IgM antibodies against the Myelin Associated Glycoprotein (MAG) in serum by sandwich ELISA. The microtiter plate is coated with purified MAG from human brain. Patient sera, controls, and calibrators are added to the wells of the microtiter plate. After 2 hours of incubation at 2-8 °C and washing steps, a detection antibody conjugated to horseradish peroxidase (HRP) detects the anti-MAG antibodies bound to the human MAG on the plate. After another 2 hours of incubation and further washing steps, the chromogenic HRP substrate, tetramethylbenzidine (TMB), is added (blue color formation) followed by a stopping reaction (change to yellow color). The absorption is measured at 450 nm.

The level of anti-MAG antibodies is determined using the calibration curve generated from the measured calibrator values and is expressed as BÜHLMANN Titer Unit (BTU).

REAGENTS SUPPLIED AND PREPARATION

Reagents	Quantity	Code	Reconstitution
Microtiter Plate 96 wells precoated with human MAG	12 x 8-well strips with frame	B-MAG-MP	Ready to use
Plate Sealer	3 pieces	-	Ready to use
Wash Buffer Concentrate (10x)	1 bottle x 100 mL	B-MAG-WB	Dilute with 900 mL of deionized water
Incubation Buffer with preservatives	1 bottle x 100 mL	B-MAG-IB	Ready to use
Calibrators A to D[1] lyophilized with preservatives	4 vials	B-MAG-CASET	Add 1 mL of Incubation Buffer
Control Low and High[2] lyophilized with preservatives	2 vials	B-MAG-CONSET	Add 1 mL of Incubation Buffer
Enzyme Label IgM anti-human IgM antibody conjugated to HRP in a buffer matrix with preservatives	1 vial x 11 mL	B-MAG-ELM	Ready to use Blue solution
TMB Substrate TMB in citrate buffer	1 vial x 11 mL	B-TMB	Ready to use
Stop Solution 0.25 M sulfuric acid	1 vial x 11 mL	B-STS	Ready to use **Corrosive agent**

Table 1

[1] After reconstitution, calibrators A, B, C and D contain 70000, 15000, 3000 and 1000 BÜHLMANN Titer Units (BTU) of anti-MAG antibodies, respectively.

[2] The controls contain lot specific amounts of anti-MAG antibodies. Refer to the additional QC datasheet for actual levels.

STORAGE AND SHELF LIFE OF REAGENTS

Sealed / unopened reagents	
Store at 2-8 °C. Do not use the reagents beyond the expiration date printed on the labels.	
Opened / reconstituted reagents	
Microtiter Plate	Return unused strips immediately to the foil pouch containing the desiccant packs and reseal along the entire edge of zip-seal. Store for up to 3 months at 2-8 °C.
Diluted Wash Buffer	Store for up to 3 months at 2-8 °C.
Incubation Buffer	
Enzyme Label IgM	
TMB Substrate	
Controls	Aliquot after reconstitution and store at ≤ -20 °C. Store for up to 3 months at ≤ -20 °C.[1]
Calibrators	
Stop Solution	Store for up to 3 months at 18-28 °C.

Table 2

[1] Reconstituted calibrators and controls can be subject to three freeze-thaw cycles during the 3 months.

MATERIALS REQUIRED BUT NOT PROVIDED

- Precision pipettes with disposable tips: 0.5-10 µL and 100-1000 µL
- Disposable polystyrene or polypropylene tubes for the preparation of sample dilutions
- 1000 mL cylinder for the dilution of the wash buffer
- Microtiter plate washer
- Blotting paper
- Microtiter plate shaker
- Microtiter plate reader for measurement of absorbance at 450 nm

WARNINGS AND PRECAUTIONS

Safety precautions

- This test is for *in vitro* diagnostic use only.
- It is recommended that the test be handled by qualified personnel, in accordance with Good Laboratory Practice (GLP):
  - The calibrators, controls and microtiter plate of this kit contain components of human origin. Although tested and found negative for HBV, HCV and HIV1/2, the reagents should be handled as if capable of transmitting infections.
  - The incubation buffer and the enzyme label contain potentially infectious substances of animal origin.
- This kit contains components classified in accordance with the Regulation (EC) No. 1272/2008:
  - The stop solution contains sulfuric acid (conc. 2.5-5 %), thus the reagents may cause skin irritation (H315), serious eye irritation (H319), and may be corrosive to metals (H290).
  - The calibrators, and controls contain gentamicin sulfate (powder), thus, the reagents may cause an allergic skin reaction (H317) and allergy or asthma symptoms or breathing difficulties if inhaled (H334). And they contain Thiomersal (powder), thus, the reagent is fatal if swallowed, in contact with skin, or if inhaled (H300+H310+H330).
  - The incubation buffer and enzyme label contain gentamicin sulfate (conc. < 1 %), thus, the reagents may cause an allergic skin reaction (H317).
- Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, immediately wash with generous amounts of water; otherwise, irritation/burns can occur.
- Reagents, patient specimen and any discarded materials have to be treated as hazardous waste according to the national biohazard safety guideline or regulation.

Technical precautions

- Read the instructions carefully prior to carrying out the test. Test performance will be adversely affected, if reagents are incorrectly diluted, modified or stored under conditions other than those as detailed in this instruction for use.
- Components must not be used after the expiry date printed on the labels.
- Do not mix different lots of reagents.
- Every effort should be made to ensure that no cross contamination occurs between reagents, samples or between wells.
- Microwells cannot be re-used.

ELISA procedure

Temperature of reagents

- Prepare reagents before starting the assay procedure. Steps 3-9: Reagents used in steps 3-9 must be cold (2-8 °C) and kept cold while pipetting and washing. Recommendation: Prepare the wash buffer the day before performing the assay and place it into the fridge overnight.
- Perform all wash steps with cold(!) (2-8 ˚C) wash buffer.
- Adjust TMB substrate and stop solution to room temperature (18-28 °C) at the start of the assay procedure.

Washing steps

- Wash steps 3, 6 and 9 are crucial to remove residues resulted from the production process and/or potentially unbound antibodies in the wells.
- An automated washer operating in “plate mode” is strongly recommended, i.e. each process step (dispense/aspiration) is carried out on all of the strips, sequentially, before the instrument continues with the next washing cycle.
- Make sure that all wells are completely empty after the last washing cycle.

Substrate incubation

- Step 11: Shake the microtiter plates during incubation with substrate. Depending on the model of the plate shaker we recommend 400-600 rpm. The solution should move in the wells but must not spill over.

Additional sample dilution

- Samples exceeding 70000 BTU can be diluted into the analytical measurement range (> 1000 BTU, < 70000 BTU). Use incubation buffer for dilution of serum samples.

SPECIMEN COLLECTION AND STORAGE

The procedure requires < 0.1 mL of blood or < 50 µL of serum, respectively.

Collect blood into plain venipuncture tubes without any additives and avoid hemolysis. Perform serum preparation according to manufacturer’s instructions. Decant the serum.

Serum samples can be stored at 2-8 °C for up to 16 days or at -20 °C up to 12 months. Frozen samples should be thawed and mixed thoroughly by gentle swirling or inversion prior to use.
We recommend preparing aliquots of serum samples before freezing in order to avoid repeated freeze/thaw cycles.

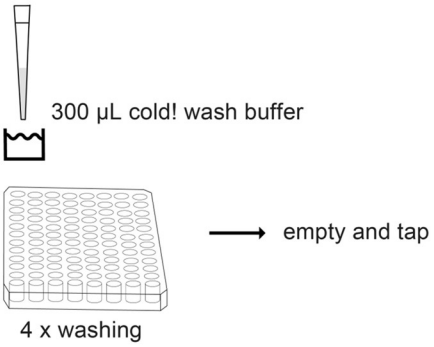
ASSAY PROCEDURE

Note: Adjust TMB substrate solution to room temperature (18-28 °C).

1. Dilute samples 1:1000 with incubation buffer. Use e.g. 1 µL of serum + 1000 µL of cold(!) (2-8 °C) incubation buffer. Mix thoroughly by vortexing and leave diluted samples as well as reconstituted calibrators and controls at 2-8 °C for 30 minutes prior to pipetting (refer to steps 4a - c).
2. Prepare a plate-frame with sufficient strips to test the required number of calibrators, controls and samples. Remove excess strips from the frame and reseal it in the foil pouch together with the desiccant packs without delay. Store refrigerated.

Note: Use cold reagents in steps 3 to 9.

3. Wash the wells four times using at least 300 µL of cold(!) (2-8 °C) wash buffer per well. Empty the wells and tap plate firmly onto blotting paper to remove remaining liquid completely.



Note: Immediately proceed to the next steps.

4a. Pipet 100 µL of incubation buffer (blank) in duplicate and

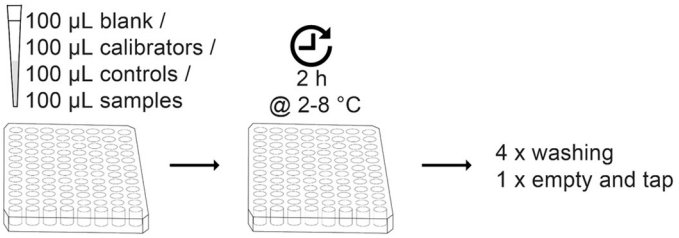
Pipet 100 µL of calibrator A-D in duplicate into the respective wells.

4b. Pipet 100 µL of the controls low and high in duplicate into the respective wells.

4c. Pipet 100 µL of each diluted sample into the subsequent wells.

5. Cover the plate with a plate sealer and incubate for 2 hours (± 5 min) at 2-8 °C (do not shake the plate).

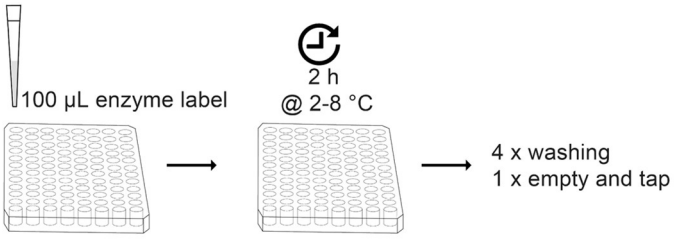
6. Remove the plate sealer. Empty the wells and wash four times using at least 300 µL of cold(!) (2-8 °C) wash buffer per well. Empty the wells and tap the plate firmly onto blotting paper in order to remove wash buffer completely.



7. Add 100 µL of enzyme label IgM to all wells.

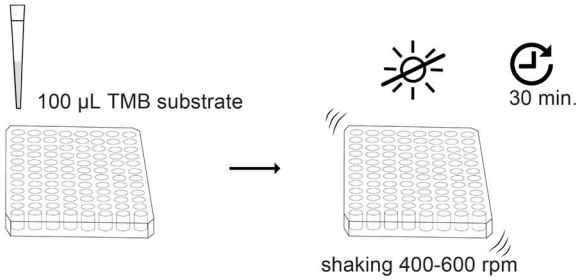
8. Cover the plate with a plate sealer and incubate for 2 hours (± 5 min) at 2-8 °C (do not shake the plate).

9. Remove the plate sealer. Empty the wells and wash four times using at least 300 µL of cold(!) (2-8 °C) wash buffer per well. Empty the wells and tap the plate firmly onto blotting paper.



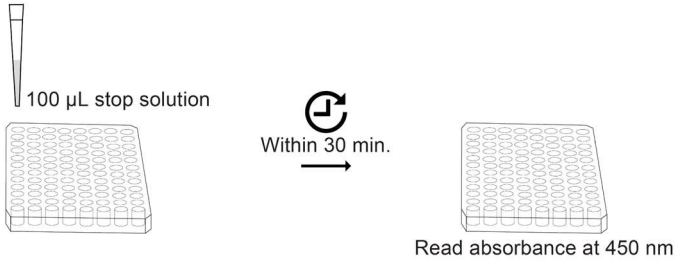
10. Add 100 µL of TMB substrate solution (equilibrated to room temperature) to each well.

11. Cover the plate with a plate sealer, protect the plate from light and incubate on a plate shaker set at 400-600 rpm, at 18-28 °C for 30 ± 2 minutes.



12. Add 100 µL of stop solution to all wells. Remove air bubbles with a pipette tip. Proceed to step 13 within 30 minutes.

13. Read the absorbance at 450 nm in a microtiter plate reader.



QUALITY CONTROL

Thorough understanding of this instruction for use is necessary for the successful use of the product. Reliable results will be obtained only by using precise laboratory techniques and accurately following this instruction for use.

The anti-MAG Antibodies ELISA kit comes with two controls: controls low and high. The controls have assigned value ranges indicated on the QC datasheet supplied with each kit. The control measurements must be within the indicated value ranges to obtain valid results.

In addition to kit controls, we recommend the use of serum pools for internal quality control.

The reproducibility of standard curve parameters and control values should be within established limits of laboratory acceptability. If the performance of the assay does not meet the established limits and repetition has excluded errors in technique, check the following issues: *i)* temperature controlling (reagents used in step 3-9 kept at 2-8 °C); *ii)* accuracy of thermometers, pipetting and timing devices; *iii)* ELISA reader settings; *iv)* expiration dates of reagents; v) storage and incubation conditions; *vi)* color of TMB substrate solution (should be colorless); *vii)* purity of water; *viii)* aspiration and washing methods.

STANDARDIZATION AND METROLOGICAL TRACEABILITY

There are no internationally or nationally recognized reference materials or reference measurement procedures for anti-MAG antibodies in serum samples. The anti-MAG Antibodies ELISA is standardized against an internally established reference material. Calibrator and control values are assigned according to a value transfer protocol (ref. 1, 2), to guarantee metrological traceability and are indicated in arbitrary BÜHLMANN Titer Units. The 95 % confidence interval of the combined uncertainty of product calibrators and controls is lower than 35 %.

CALCULATION OF TEST RESULTS

Standard curve

Use a software program capable of the following calculations:

- subtract the blank OD value from each calibrator well to calculate the calibrator value.
- Establish a standard curve using a 4-parameter logistic (4 PL) fit.

Controls and Samples

Use a software program capable of the following calculations;

- subtract the blank OD value from each control/ sample well. Calculate anti-MAG antibody level of the controls/sample in each well, in BTU, using the established standard curve.

Note: Results presented in table 6 and figure 1 are examples and are provided for demonstration purposes only. A calibration curve must be generated for each set of samples to be tested.

LIMITATIONS

- This test has not been validated for CSF, and plasmapheresis.
- Intravenous immunoglobulins (IVIg) and cryoglobulins may affect test results.

RESULT INTERPRETATION

Result	Interpretation
< cut-off	Negative result
≥ cut-off	Positive result (indication of anti-MAG antibody presence)

Table 3

Test results should be interpreted in conjunction with information available from the clinical assessment of the patient and other diagnostic procedures.

REFERENCE INTERVALS AND CUT-OFF

The reference interval of the anti-MAG Antibodies ELISA test was established according to CLSI EP28-A3 with 141 serum samples from apparently healthy individuals aged 18 to 70 years. The results are provided in table 4.

Reference Interval [BTU]	
2.5th percentile (90 % CI)	**97.5th percentile (90 % CI)**
0 (0 - 0)	0 (0 - 988)

Table 4

Thousand (1000) BTU is an established cut-off and used in published studies (ref. 5, 6, 9).
Deviating cut-off values have also been used in scientific literature (ref. 3, 4, 7, 8, table 13) and titer categories for positive test results have been proposed (ref. 10).

PERFORMANCE CHARACTERISTICS

Performance characteristics are based on mean results from 2 wells.

Repeatability: 3.2 – 11.8 % CV

Within-laboratory precision: 5.5 – 15.9 % CV

Repeatability and within-laboratory precision were established according to the CLSI guideline EP05-A3 using the standardized 20 days x 2 runs x 2 replicates study design. Four (4) pooled human serum samples, covering the measuring range of the assay, were tested.
A fifth negative sample at 213 BTU yielded 79/80 results (98.8 %) within category (< 1000 BTU). The results are summarized in table 7 and 8.

Reproducibility: 10.0 – 21.6 % CV

Reproducibility was established according to the CLSI guideline EP05-A3 by performing measurements using a 3 operators x 3 instruments/lots x 5 days x 5 replicates study design. Four (4) pooled human serum samples, covering the measuring range of the assay, were tested.
A fifth negative sample at 55 BTU yielded 75/75 results (100.0 %) within category (< 1000 BTU). The results are summarized in table 9 and 10.

Limit of Detection (LoD): 305 BTU

The LoD was established according to the CLSI guideline EP17-A2 using a non-parametric analysis with a proportion of false positive (α) less than 5 % and false negative (β) less than 5 % based on 120 determinations, with 60 blank and 60 low level replicates, and a **LoB of 138 BTU**.

High dose hook effect

Samples with anti-MAG antibody levels of up to 2.8×10^5 BTU can be measured without limiting the measuring range of the assay.

Cross-reactivity

The cross-reactivity of the anti-MAG Antibodies ELISA assay was tested for samples assigned with an autoimmune disease or associated presence of antibodies. The antibodies and number of samples tested are shown in table 11.

Other samples with different peripheral neuropathy disease mimics were also tested with the anti-MAG Antibodies ELISA and are presented in table 12.

One (1) out of four (4) tested samples from patients with Waldenstrom disease was slightly seropositive for anti-MAG antibodies in the range of 1000-1500 BTU.

CLINICAL PERFORMANCE

The clinical performance was assessed by meta-analysis of peer-reviewed scientific literature. Seven studies adressed the clinical performance of the anti-MAG Antibodies ELISA in the diagnosis of demyelinating peripheral neuropathy with IgM monoclonal gammopathy (ref. 3-9). Results of analysis and study details are provided in table 5 and table 13, respectively.

N neuropathy	344
N controls	447
Sensitivity (95% CI)	58.9 % (47.2 – 69.6 %)
Specificity (95% CI)	98.2 % (89.7 – 99.7 %)
ROC AUC	0.75

Table 5

CI - confidence interval
ROC AUC - area under receiver operating characteristic curve

INTERFERING SUBSTANCES

The susceptibility of the Anti-MAG Antibodies ELISA assay to oral and injectable pharmaceuticals, as well as to endogenous substances was assessed according to the CLSI guideline EP07-A3. Bias in results exceeding 20 % was considered interference.

No interference was detected with the following substances up to the listed concentrations: intravenous immunoglobulin (20 mg/mL), cladribine (273 ng/mL), Interferon alpha-2a (49.5 ng/mL), ibuprofen (0.22 mg/mL), rheumatoid factor (680 IU/mL), hemoglobin (10 mg/mL), hemolysate (10 mg/mL), triglyceride (20 mg/mL), conjugated bilirubin (0.4 mg/mL), unconjugated bilirubin (0.4 mg/mL).

TABLES AND FIGURES

Example of results

	Level [BTU]	Absorbance [OD]	Calc. Level [BTU]	CV [%]
Blank 1		0.046		
Blank 2		0.049		
Average		**0.048**		
Calibrator A	70000	2.195	70497	
Calibrator A	70000	2.188	69508	
Average	**70000**	**2.191**	**70000**	**0.2**
Calibrator B	15000	1.272	15313	
Calibrator B	15000	1.245	14693	
Average	**15000**	**1.258**	**15000**	**1.5**
Calibrator C	3000	0.417	3070	
Calibrator C	3000	0.400	2931	
Average	**3000**	**0.408**	**3000**	**2.9**
Calibrator D	1000	0.135	1009	
Calibrator D	1000	0.132	991	
Average	**1000**	**0.134**	**1000**	**1.5**
Control LOW		0.360	2602	
Control LOW		0.376	2731	
Average		**0.368**	**2666**	**3.1**
Control HIGH		1.395	18433	
Control HIGH		1.383	18090	
Average		**1.389**	**18261**	**0.6**
Sample 1		0.001	255	
Sample 1		0.009	297	
Average		**0.005**	**276**	**116.5**
Sample 2		1.092	11599	
Sample 2		0.969	9511	
Average		**1.030**	**10555**	**8.5**

Table 6

Example of standard curve (OD_{450})

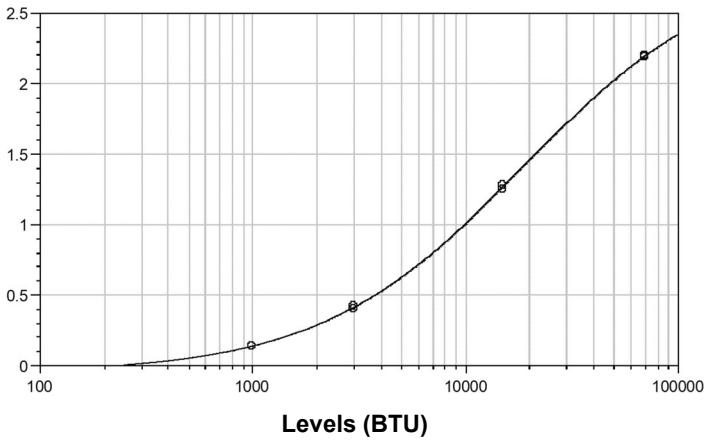


Figure 1

Within-laboratory precision

ID	Mean Level, BTU	n	Within-run		Between-run		Between-day		Within-laboratory	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
S2	2251	80	267	11.8	199	8.8	130	5.8	357	15.9
S3	8849	80	349	3.9	314	3.6	122	1.4	485	5.5
S4	19683	80	622	3.2	1492	7.6	908	4.6	1855	9.4
S5	37185	80	1684	4.5	3083	8.3	1466	3.9	3806	10.2

Table 7

ID	Description	n	Mean Level, BTU	% Within category
S1	< 1000 BTU (negative)	80	213	98.8

Table 8

Reproducibility

ID	Mean Level, BTU	n	Within-run		Between-run		Between-day		Within-laboratory	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
S2	2802	75	181	6.5	517	18.4	261	9.3	606	21.6
S3	9052	75	258	2.9	821	9.1	279	3.1	904	10.0
S4	18241	75	531	2.9	1146	6.3	1475	8.1	1942	10.6
S5	34713	75	893	2.6	2740	7.9	2023	5.8	3521	10.1

Table 9

ID	Description	n	Mean Level, BTU	% Within category
S1	< 1000 BTU (negative)	75	55	100.0

Table 10

Cross-reactivity

Antibodies		#
Anti-Neutrophil Cytoplasmatic Antibodies (ANCA)		13
Anti-Nuclear Antibodies (ANA)		23
Anti-Thyroglobulin Antibodies (anti-Tg)		5
Anti-Ribonucleoprotein Antibodies		1
Anti-Ganglioside Antibodies	anti-GD1b	4
	anti-GM1	3
	anti-GQ1b	5
Anti-Acetyl-Choline Receptor Antibodies and Anti-Muscle-Specific Tyrosine Kinase Antibodies		7

Table 11

Peripheral neuropathies	#
Alcoholic/Alcoholism	1
Diabetes	5
Peripheral neuropathy mimicking disorders	**#**
Amyotrophic lateral sclerosis	14
Chagas disease	5
Idiopathic peripheral neuropathy	1
Sarcoidosis	4
Waldenstrom disease	4
Wegener granulomatosis	1

Table 12

TABLES AND FIGURES

Clinical performance

Study	Positive controls	Negative controls	Cut-off	Sens.	Spec.
Kuijf et al., 2009	DPN +IgM MG (n = 68)	OPN + HC (n = 139)	1500 BTU	0.72	0.97
Mata et al., 2011	MGUS PN (n = 46)		3200 BTU	0.37	
Campagnolo et al., 2015	DPN +IgM MG (n = 20)	HDC + HC (n = 3)	1000 BTU	0.94	1.00
Stork et al., 2014	DPN +IgM MG (n = 26)		1000 BTU	0.69	
Stork et al., 2016	DPN +IgM MG (n = 83)	HC (n=83)	1000 BTU	0.59	1.00
Taams et al., 2018	MGUS PN (n = 101)		1500 BTU	0.51	
Liberatore et al., 2020		OPN + HC (n = 222)	7000 BTU		1.00

Table 13

DPN+IgM MG, Demyelinating Polyneuropathy with IgM monoclonal gammopathy; MGUS PN, Polyneuropathy associated with monoclonal gammopathy of unknown significance; OPN, other polyneuropathy; HC, healthy control; HDC, hematological diseased controls

SHORT PROTOCOL

Important: The short protocol is not a substitute for the detailed information described in this instruction for use.

Before testing day

Wash Buffer Preparation

Dilute wash buffer concentrate 1:10 with deionized water

Recommendation: Prepare the wash buffer the day before performing the assay and place it into the fridge overnight.

Testing day

Samples / Controls / Calibrators Preparation

Dilute serum samples 1:1000 with (cold!) incubation buffer and mix thoroughly by vortexing

Reconstitute or thaw (aliquoted) reconstituted controls and calibrators

leave 30 minutes at 2-8 °C

anti-MAG Antibodies ELISA

Precoated microtiter plate

wash 4 x with ≥ 300 µL (cold!) wash buffer

100 µL incubation buffer, calibrators, controls or serum samples (1:1000)

incubate 2 hours (± 5 min) at 2-8 °C

wash 4 x with ≥ 300 µL (cold!) wash buffer

add 100 µL enzyme label

incubate 2 hours (± 5 min) at 2-8 °C

wash 4 x with ≥ 300 µL (cold!) wash buffer

add 100 µL TMB substrate

incubate 30 minutes (± 2 min) at 18-28 °C on a plate shaker ~400-600 rpm

add 100 µL stop solution

Read absorbance at 450 nm (within 30 minutes)

TIME TO RESULT: 5 HOURS

REFERENCES

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5. Stork, A. C. J. et al. Classical and lectin complement pathway activity in polyneuropathy associated with IgM monoclonal gammopathy. J. Neuroimmunol. 290, 76–79 (2016).

6. Stork, A. C. J. et al. Fcγ receptor IIIA genotype is associated with rituximab response in antimyelin-associated glycoprotein neuropathy. J Neurol Neurosurg Psychiatry. 85, 916–918 (2014).

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10. Vallat, J-M. et al. The Wide Spectrum of Pathophysiologic Mechanisms of Paraproteinemic Neuropathy. Neurology 96, 214-225 (2021).

CHANGELOG

Date	Version	Change
2026-09-09	A5	Precising the *Intended Use* by adding information regarding testing population, intended user and test automation. Update to chapters *Materials required but not provided, Assay procedure, Quality control, Clinical Performance, Tables and figures* (Table 12) and *Short protocol.* Revision of chapters *Warnings and precautions* and *Symbols.* Update of eIFU Symbol on front page (only applicable for English document version).

INCIDENT REPORTING IN EU MEMBER STATES

If any serious incident in relation to this device has occurred, please report without delay to the manufacturer and competent authority of your Member State.

SHIPPING DAMAGE

Please notify your distributor if this product was received damaged.

SYMBOLS

BÜHLMANN use symbols and signs listed and described in ISO 15223-1.
For definition of symbols see the symbol glossary at: www.buhlmannlabs.ch/support/downloads/
In addition, the following symbols and signs are used:

Symbol	Explanation
MP	Microtiter Plate
BUF INC	Incubation Buffer
BUF WASH 10X	Wash Buffer Concentrate (10x)
CONTROL L	Control Low
CONTROL H	Control High
CAL A - CAL D	Calibrator A - D
EL IgM	Enzyme Label IgM
SUBS TMB	TMB Substrate
SOLN STOP	Stop Solution

CE 0123