*recom*CLIA Control Set HEV IgG
*recom*CLIA Control Set HEV IgM

MIKROGEN DIAGNOSTIK

IVD

Instructions for use (English)

1 Intended purpose

*recom*CLIA Control Set HEV IgG:
The *recom*CLIA Control Set HEV IgG consists of a positive and a negative control, which can only be used in combination with the *recom*CLIA HEV IgG test kit.
In general, the *recom*CLIA Control Sets are intended for use in quality assurance of analytical laboratories. Target values, where applicable, and acceptable deviation intervals for negative and positive controls are independent of the batch of the corresponding *recom*CLIA test kits. Results in the target range confirm correct test performance of the corresponding *recom*CLIA test kit.
*recom*CLIA Control Sets and respective *recom*CLIA test kits can only be performed using the KleeYa® Instrument by professional users in a suitable laboratory, with the Control Sets not necessarily required for test evaluation.

*recom*CLIA Control Set HEV IgM:
The *recom*CLIA Control Set HEV IgM consists of a positive and a negative control, which can only be used in combination with the *recom*CLIA HEV IgM test kit.
In general, the *recom*CLIA Control Sets are intended for use in quality assurance of analytical laboratories. Target values, where applicable, and acceptable deviation intervals for negative and positive controls are independent of the batch of the corresponding *recom*CLIA test kits. Results in the target range confirm correct test performance of the corresponding *recom*CLIA test kit.
*recom*CLIA Control Sets and respective *recom*CLIA test kits can only be performed using the KleeYa® Instrument by professional users in a suitable laboratory, with the Control Sets not necessarily required for test evaluation.

2 Summary and explanation

The Hepatitis E Virus is one of the most common viral causes of acute hepatitis worldwide. Therefore, IgG and IgM HEV antibody detection using the recomCLIA HEV IgG, IgM can support correct diagnosis, reduce complications and unnecessary laboratory testing, and allow the physician to determine appropriate treatment. An HEV infection may present as clinically inapparent to fulminant.

There are four predominant human-pathogenic genotypes (1-4), which differ in their geographical distribution, modes of transmission and potential complications. HEV genotype 1 and 2 infections occur primarily in developing countries where transmission predominantly occurs through the faecal-oral route via contaminated drinking water. HEV genotypes 3 and 4, which are widespread in industrialised countries, are predominantly transmitted through the consumption of inadequately cooked pork. In Europe, most cases are caused by HEV genotype 3 and are often asymptomatic. The human-pathogenic HEV genotypes show serological cross-reactivity and are classified under a single serotype.

3 Test principle

The *recom*CLIA Control Set HEV IgG and *recom*CLIA Control Set HEV IgM contain control sera of human origin. It is used and evaluated the same way as patient samples in the *recom*CLIA HEV IgG and IgM test procedure. Test procedure and evaluation of results are carried out according to the instructions for use of the *recom*CLIA HEV IgG, IgM test system. Positive control sera show a positive overall result, negative control sera show a negative overall result.
The certificate of analysis is independent of the respective *recom*CLIA kit batch and can be accessed electronically via the website of MIKROGEN. The positive control has a target value and a valid range, the negative control has a valid range.
The *recom*CLIA Control Set HEV, IgG and IgM, can be used for internal quality controls, such as after calibration, rebooting and reagent batch changes.

4 Reagents

4.1 Package contents

The positive and negative controls, provided in a single package, are each sufficient to perform 2 x 25 tests.

***recom*CLIA Control Set HEV IgG (art. no. 75002)** contains:

CONTROL + IgG	**2 x 375 µl positive control (orange cap)** ready-to-use human origin, anti-HIV 1/2, anti-HCV and HBs Ag negative contains preservative: Methylisothiazolinone (MIT) (0.1%) contains ingredient of animal origin: Bovine serum albumin (BSA) (0.05%)
CONTROL − IgG	**2 x 375 µl negative control (colourless cap)** ready-to-use human origin, anti-HIV 1/2, anti-HCV and HBs Ag negative contains preservative: MIT (0.1%) contains ingredient of animal origin: BSA (0.2%)
INSTRU	**1 instructions for use**

The processing of the *recom*CLIA Control Set HEV IgG requires the mandatory use of *recom*CLIA HEV IgG, MIKROGEN (article no. 75004).

***recom*CLIA Control Set HEV IgM (art. no. 75003)** contains:

CONTROL + IgM	**2 x 600 µl positive control (brown cap)** ready-to-use human origin, anti-HIV 1/2, anti-HCV and HBs Ag negative contains preservative: Methylisothiazolinone (MIT) (0.1%) contains ingredient of animal origin: Bovine serum albumin (BSA) (0.05%)
CONTROL − IgM	**2 x 600 µl negative control (colourless cap)** ready-to-use human origin, anti-HIV 1/2, anti-HCV and HBs Ag negative contains preservative: MIT (0.1%) contains ingredient of animal origin: BSA (0.2%)
INSTRU	**1 instructions for use**

The processing of the *recom*CLIA Control Set HEV IgM requires the mandatory use of *recom*CLIA HEV IgM, MIKROGEN (article no. 75005) and *recom*CLIA Sample Diluent A, MIKROGEN (article no. 10120) (see instructions for use of *recom*CLIA HEV IgM).

4.2 Additionally required reagents, materials and equipment

- *recom*CLIA HEV IgG, MIKROGEN (article no. 75004)
- *recom*CLIA HEV IgM, MIKROGEN (article no. 75005)
- *recom*CLIA Sample Diluent A, MIKROGEN (article no. 10120)
- Fully automated KleeYa® Instrument, STRATEC SE (MIKROGEN article no. 31349)
- KleeYa® TRIGGER SOLUTION (Trigger Solution 1 and Trigger Solution 2), Diatron MI Plc. (MIKROGEN article no. 31334)
- 5x TBS Wash Buffer, Diatron MI Plc. (MIKROGEN article no. 31335)
- Stackable Cuvette, 1 ml, STRATEC Consumables GmbH (MIKROGEN article no. 31336)
- Disposable Anchor® Tips, 300 µl, STRATEC Consumables GmbH (MIKROGEN article no. 31337)
- Deionised water (high quality)
- Single-use protective gloves, other personal protective equipment
- Waste container for bio-hazardous material
- Solid waste bag

Optional materials:
MIKROGEN recommends processing the product line *recom*CLIA with a defoamer (for details refer to chapter 7.3 “Use of defoamer”): Defoamer “Entschäumer“, KIEHL Group (MIKROGEN article no. 31433)

For more information, please contact the Technical Support of MIKROGEN.

5 Shelf life and handling

- Store control samples at +2 °C to +8 °C before and after use, **do not freeze**.
- Shelf life:

Shelf life of controls	
Unopened at +2 °C to +8 °C	Until the stated expiry date
In-use stability +2 °C to +8 °C	3 months

After the expiry date, the quality of the r*ecom*CLIA Control Set can no longer be guaranteed.

- The storage conditions and stability of working solutions are described in chapter 7.1 “Preparation of solutions”.
- The wash buffer (5x TBS Wash Buffer) and KleeYa® TRIGGER SOLUTION (Trigger Solution 1 and Trigger Solution 2) are universal for all *recom*CLIA kits and can be used across the full range of parameters and batches. The shelf life of these components must be adhered to.
- The *recom*CLIA Sample Diluent A can be used batch-independently in combination with the corresponding *recom*CLIA test kits. The same *recom*CLIA Sample Diluent A reagent cartridge allows parallel sample processing for multiple test kits. The shelf life of *recom*CLIA Sample Diluent A must be adhered to.
- Mix control samples well but avoid foam formation.
- Tubes must be opened immediately prior to use and closed immediately following use.
- The control samples are not intended to be stored within the KleeYa® Instrument. Return the control samples to +2 °C to +8 °C immediately after successful test completion.
- Processing of the *recom*CLIA Control Set HEV IgG and *recom*CLIA Control Set HEV IgM must be performed by a trained and authorised professional user.
- In the event of significant changes to the product or modifications to its use by the user, the application may no longer align with the intended purpose outlined by MIKROGEN.

6 Warnings and safety precautions

- For *in vitro* diagnostic use only.
- All blood products must be treated as potentially infectious.
- Suitable disposable gloves must be worn throughout the entire test procedure.
- For the production of control material, donor blood free of HIV 1/2 antibodies, HCV antibodies, and free of HBs antigen is used. The product must be handled with the same precaution as a patient sample, as infectious risk cannot be excluded with certainty.
- Safety notes for reagents containing hazardous substances:

CONTROL + IgG	CONTROL − IgG	CONTROL + IgM	CONTROL − IgM
	Contains ingredient of animal origin		
	Contains human blood or plasma derivatives		
	H317: May cause allergic skin reactions		

Further information can be found in the respective safety data sheets available from MIKROGEN.
Due to space constraints, the hazard symbols of individual components cannot always be affixed to their corresponding labels. For the hazard symbols of these components, please refer to the nearest larger outer packaging or their corresponding instructions for use.

- All fluids for disposal must be collected. All collecting containers must contain suitable disinfectants for the inactivation of human pathogens. All reagents and materials contaminated with potentially infectious samples must be treated with suitable disinfectants or disposed of in accordance with applicable hygiene regulations. The concentrations and exposure times specified by the manufacturer must be strictly followed.
- All waste must be disposed of in accordance with local guidelines.
- The reagents must not be substituted or mixed with those from other manufacturers.
- The entire instructions for use document must be read before performing the test. Follow the instructions exactly as described. Any deviation from the specified test protocol may lead to incorrect results.
- Any serious incident that occurs in relation to the device must be reported to the manufacturer and the competent authority of the member state in which the user and/or the patient is established.
- The reagent contains the antimicrobial agent MIT (methylisothiazolinone). Avoid contact with the skin or mucous membranes.

7 Sampling and preparation

The control samples are ready to use and are processed in the same manner as patient samples, no further preparation of the control samples is necessary.
Avoid microbial contamination of the samples.
Caution!
If the control samples are not processed immediately, the control samples must be stored at +2 °C to +8 °C.

7.1 Preparation of solutions

Dilute the wash buffer (5x TBS Wash Buffer) 1:5 (1 volume unit of the solution with 4 volume units of deionised water).
For example, 2 L of 5x TBS Wash Buffer + 8 L of deionised water.

After completion of the wash buffer preparation, the cap must be placed lightly on the container to allow proper degassing of the wash buffer solution. Wait 2 hours for the microbubbles to disappear from the buffer before use. The diluted wash buffer is stable for one month (on-board stability).

No further preparations of any other solutions are necessary.

7.2 Preparation and maintenance of the KleeYa® Instrument

- Load and prime the KleeYa® TRIGGER SOLUTION (Trigger Solution 1 and Trigger Solution 2).
- Ensure that the respective assays are loaded into the KleeYa® Software.
- Check disposables and refill if necessary.
- Perform maintenance tasks.

For further information please refer to the manual of the KleeYa® Instrument.

7.3 Use of defoamer

To avoid foam formation in the liquid waste container during high throughput runs, it is recommended to use the defoamer, provided by the KIEHL Group called “Entschäumer”.

Proceed as follows:

- Empty the liquid waste container.
- Add 20 ml of “KIEHL Entschäumer” to the empty container.
- Place container into instrument and run tests.

For more information regarding assays for analysis, please contact the Technical Support of MIKROGEN.

8 Test procedure

The processing of the *recom*CLIA Control Set HEV IgG requires the mandatory use of *recom*CLIA HEV IgG, MIKROGEN (article no. 75004).
The processing of the *recom*CLIA Control Set HEV IgM requires the mandatory use of *recom*CLIA HEV IgM, MIKROGEN (article no. 75005) and *recom*CLIA Sample Diluent A, MIKROGEN (article no. 10120).
Control samples are diluted in the same manner as patient samples in the test procedure. Test evaluation and interpretation must be conducted to the instructions for use of the respective *recom*CLIA test system and in consideration of the use of the KleeYa® Instrument and its instructions.

9 Results

The IU/ml or COI are determined according to the instructions for use of either *recom*CLIA HEV IgG or *recom*CLIA HEV IgM. The results are compared with the acceptance limits indicated on the certificate of the relevant control specimen batch. The evaluation is valid if the determined values are within those acceptance limits.

10 Limits of the method, restrictions

Control specimen are used for internal quality assurance only. They are not required for the evaluation of the corresponding test.
The measured value of the positive serum should be within the specified target value range. The negative control serum must show a negative overall result within the valid range.

11 Analytical performance characteristics

Accuracy of measurement

Precision
Intra-assay, inter-assay and inter-lot variability were determined and the coefficient of variation (CV) (%) was calculated based on the resulting IU/ml or COI for the positive control or based on the overall test result for the negative control.

Precision	*recom*CLIA Control Set HEV IgG		*recom*CLIA Control Set HEV IgM	
	Positive control	Negative control	Positive control	Negative control
Intra-assay variability[1]	≤ 5%	0%	≤ 7%	0%
Inter-assay variability[2]	≤ 10%	0%	≤ 10%	0%
Inter-lot variability[3]	≤ 1%	not determined	≤ 2%	not determined

All testings are performed according to their Ig-class with *recom*CLIA HEV IgG or *recom*CLIA HEV IgM:

[1] Ten replicates of each of three *recom*CLIA Control Set HEV, IgG or IgM, batches were tested in one approach.

[2] For the positive control, one *recom*CLIA Control Set HEV, IgG or IgM, batch was measured with two *recom*CLIA HEV, IgG or IgM, kit batches in a total of 15 individual measurements within 8 days on three KleeYa® devices each.
For the negative control, four replicates of one *recom*CLIA Control Set HEV, IgG or IgM, batch were tested on three different days.

[3] The difference in precision (ΔCV) obtained when using different lots of controls was compared for the positive control. Therefore, three *recom*CLIA Control Set HEV, IgG or IgM, batches were measured with two *recom*CLIA HEV, IgG or IgM, kit batches in a total of 15 individual measurements within 8 days on three KleeYa® devices each.
For the negative control no inter-lot variability could be determined, as only a valid range but no target value is output for the negative control.

12 Literature

1. Chiu CY, Razonable RR, Yao JD, Watt KD, Chesdachai S. Clinical utility of two-step hepatitis E virus IgM antibody testing in a low-prevalence setting: A 10-year retrospective multicenter study. Hepatol Commun. 2024 Dec 11;9(1):e0611.
2. Becquart A, Guigon A, Regueme A, Coulon P, Bocket L, Hober D, Alidjinou EK, Comparison of two automated commercial assays for routine detection of anti-hepatitis E Virus IgM antibodies in clinical samples. Diagn Microbiol Infect Dis. 2024 109(1):116226.
3. Dalton H.R, Kamar N., Baylis S.A., Moradpour D., Wedemeyer H., Negro F.EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol 2018 68(6):1256-1271.
4. RKI. 2015. Hepatitis-E-Virus (HEV – akute Virushepatitis E). Falldefinitionendes RKI.
5. RKI 2014. Hepatitis E Virus. Mitteilungen des Arbeitskreises Blut des Bundesministeriums für Gesundheit.
6. Pischke S., Behrendt P., Bock C.-T., Jilg W., Manns M. P., Wedemeyer H.,Hepatitis E in Deutschland – eine unterschätzte Infektionskrankheit. Deutsches Ärzteblatt, Jg. 111, Heft 35–36, 1. September 2014.
7. Pischke S, Potthoff A, Hauröder B, Schlué J, Manns MP, Cornberg M, Wedemeyer H., Hepatitis-E: Eine Infektionskrankheit erlebt einen Bedeutungswechsel. Dtsch Med Wochenschr. 2010 135(22):1129-33.
8. Dalton HR, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. Lancet Infect Dis. 2008 8(11):698-709.
9. Mohn, U., S. Dorn, S.U. Emerson, B. Krämer, D. Wassenberg, M. Motz, R.H. Purcell. 2007. Serological test based on recombinant proteins of hepatitis E virus (HEV) is capable to detect IgG antibodies against all genotypes of HEV. Third European Congress of Virology, 1 – 5 September 2007, Nürnberg, Germany.
10. Shrestha MP, Scott RM, Joshi DM, Mammen MP Jr, Thapa GB, Thapa N, Myint KS, Fourneau M, Kuschner RA, Shrestha SK, David MP, Seriwatana, J, Vaughn DW, Safary A, Endy TP, Innis BL., Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med. 2007 356(9):895-903.
11. Myint KS, Endy TP, Gibbons RV, Laras K, Mammen MP Jr, Sedyaningsih ER, Seriwatana J, Glass JS, Narupiti S, Corwin AL., Evaluation of diagnostic assays for hepatitis E virus in outbreak settings. J Clin Microbiol. 2006 44(4):1581-3

13 Explanation of symbols

Σ	Content is sufficient for <n> applications Number of applications
CONTROL + IgG	Positive control IgG
CONTROL − IgG	Negative control IgG
CONTROL + IgM	Positive control IgM
CONTROL − IgM	Negative control IgM
INSTRU	Instructions for use
	Follow the instructions for use
IVD	*In vitro* diagnostic medical device
REF	Order number
LOT	Batch/version number
CONT	Contents, includes
	Manufacturer
	Use by Expiry date
x°C y°C	Store at x °C to y °C
	Do not freeze
	Contains human blood or plasma derivatives
BIO	Contains ingredients of animal origin
	Warning

Additions, corrections or changes to the previous version are indicated by markings in the margin.

14 Manufacturer and version data

***recom*CLIA Control Set HEV IgG** ***recom*CLIA Control Set HEV IgM**	Article no. **75002** Article no. **75003**
Instructions for use valid from	GARCCHE001EN 2025-09

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