MIKROGEN DIAGNOSTIK

IVD

Instructions for use (English)

## 1 Purpose

The *recom*Line ANA/ENA test is an in vitro test for the qualitative detection of IgG auto-antibodies against nuclear and cytoplasmatic antigens in rheumatoid autoimmune diseases (collagenosis) in human serum or plasma.

## 2 Intended use

The *recom*Line ANA/ENA is a line immunoassay based on recombinant antigens, which is performed for the detection of IgG antibodies against characteristic cytoplasmatic or nuclear antigens in systemic rheumatoid autoimmune diseases. The line immunoassay is used as a confirmation test to distinguish autoimmune-related rheumatoid diseases from rheumatic diseases that have a different cause but comparable symptoms.

## 3 Test principle

Recombinant proteins (RNP68, RNPA, RNPC, SmB, Ro/SSA60, Ro/SSA52, La/SSB, Rib-P, PCNA, CENPB, Scl70, Jo-1), native histone, human dsDNA and synthetically produced SmD have been fixed on nitrocellulose membrane test strips.

1. The test strips are incubated with the diluted serum or plasma sample, and the specific antibodies bind to the antigens on the test strip.
2. Unbound antibodies are then flushed away.
3. In a second step, the strips are incubated with anti-human immunoglobulin antibodies (IgG), which are coupled to horseradish peroxidase.
4. Unbound conjugate antibodies are then flushed away.
5. Specifically bound antibodies are detected with a staining reaction catalysed by the peroxidase. If an antigen-antibody reaction has taken place, a dark band will appear on the strip at the corresponding position.

There are control bands at the upper end of the test strips:

a) The reaction control under the strip number must show a reaction to each serum / plasma sample.
b) The conjugate control band (IgG) is used to check the detected antibody class. This test strip is used to detect IgG antibodies, the IgG conjugate control band takes the form of a distinctively coloured band.
c) "Cut-off control": The intensity of this band allows the assessment of the reactivity of each of the antigen bands (see 9.2. Evaluation).

## 4 Reagents

### 4.1 Package contents

The reagents in this package are sufficient for 20 tests.
The test kit contains:

| | |
|---|---|
| WASHBUF A 10 X | **100 ml** wash Buffer A 10x (**10 times concentration**) Contains phosphate buffer, NaCl, KCl, detergent, preservative: MIT (0.1%) and oxypyrion (0.2%) |
| SUBS TMB | **40 ml** tetramethylbenzidine chromogenic substrate (**TMB, ready to use**) |
| MILKPOW | **5** g skimmed milk powder |
| INSTRU | **1** Instructions for use |
| EVALFORM | **1** Evaluation form |
| TEMPEVAL | **1** Evaluation stencil |
| TESTSTR | **2** tubes, each with 10 numbered test strips |
| CONJ IgG | **500 µl** anti-human IgG conjugate 100x **(one hundred-fold concentration, green sealing cap**) From rabbit, contains $NaN_3$ (<0.1%), MIT (<0.1%) and chloroacetamide (<0.1%) |

### 4.2 Additional reagents, materials and devices required

- Incubation trays (can be purchased as needed from MIKROGEN)
- Deionised water (high quality)
- Plastic forceps
- Horizontal shaker
- Vortex mixer or other rotators
- Vacuum pump or similar device
- Volumetric cylinders, 50 ml and 1000 ml
- Micropipettes with disposable tips, 20 µl and 1000 µl
- 10 ml pipette or dispenser
- Timer
- Absorbent paper towels
- Disposable protective gloves
- Waste container for bio-hazardous materials

## 5 Shelf life and handling

- Store reagents at +2 to +8°C before and after use, **do not freeze**.
- Subject all ingredients to room temperature (+18 to +25 °C) for at least 30 minutes before beginning the test. The test procedure is carried out at room temperature.
- Wash buffer, milk powder, dilution buffer, conjugates and TMB can be exchanged between different *recom*Line and/or *recom*Blot test systems if these components have the same symbol. Special attention should be paid to the expiry dates of these components.
- Mix the concentrated reagents and patient serums thoroughly before use. Avoid foaming.
- Only open the tube containing the test strip immediately before use to avoid condensation. Strips that are not required remain in the tube and continue to be stored at +2°C to +8°C (reseal tubes well, test strips must not be exposed to humidity before starting the test!).
- The strips are marked with the serial number, as well as the test code.
- The packages bear an expiration date. After this has been reached, no guarantee of quality can be offered.
- Protect kit components from direct sunlight throughout the entire test procedure. The substrate solution (TMB) is especially sensitive to light.
- The test should only be carried out by trained and authorised personnel.
- In the event of substantial changes to the product or the instructions for use by the user himself, the application range may not coincide with that specified by MIKROGEN.
- Cross-contamination of patient samples or conjugates can lead to inaccurate test results. Carefully add patient samples, test strips and the conjugate solution. Make sure that incubation solutions do not flow over into other wells. Carefully remove liquids.
- The strips must be completely wetted and submerged throughout the entire procedure.
- Automation is possible; you will receive further information from MIKROGEN.

## 6 Warnings and precautions

- For *In vitro* diagnostic use only.
- All blood products must be treated as potentially infectious.
- After adding the patient or control material, the strips must be regarded as potentially infectious and be treated correspondingly.
- Suitable disposable gloves must be worn throughout the entire test procedure.
- The reagents contain the antimicrobial agents and preservatives sodium azide, MIT (methylisothiazolinone), oxypyrion and chloroacetamide and hydrogen peroxide. Avoid contact with the skin or mucous membrane. Sodium azide can form an explosive azide upon contact with heavy metals such as copper and lead.
- All aspirated liquids 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 appropriate disinfectants or disposed of according to your hygiene regulations. The concentrations and incubation periods of the manufacturer must be observed.
- Use incubation trays only once.
- Handle strips carefully using plastic forceps.
- Do not substitute or mix the reagents with reagents from other manufacturers.
- Read through the entire instructions for use before carrying out the test and follow them carefully. Deviation from the test protocol provided in the instructions for use can lead to erroneous results.

# 7 Sampling and preparation of reagents

## 7.1 Samples

The sample can be serum or plasma (EDTA, citrate, heparin, CPD), which needs to be separated from the blood clot as soon as possible after sampling so as to avoid haemolysis. Avoid microbial contamination of the samples. Insoluble substances must be removed from the sample before incubation.
The use of heat-inactivated, icteric, haemolytic, lipaemic or turbid samples is not recommended.

**Caution!**
**If the tests are not conducted immediately, the sample can be stored for up to 2 weeks at +2 to +8 C. Prolonged storage of the samples is possible at -20°C or below. Repeated freezing and thawing of samples is not recommended due to the risk of inaccurate results. More than 3 freezing and thawing cycles should be avoided.**

## 7.2 Preparation of solutions

7.2.1 *Preparation of ready-to-use wash buffer A*

This buffer is required for serum and conjugate dilution as well as washing steps.
The volume of wash buffer A for the corresponding number of tests must be determined before dilution.
The skimmed milk powder is at first dissolved in wash buffer A concentrate and then filled with deionised water to the final volume (dilution 1+9). The quantities required for a defined number of test strips are to be calculated according to the following formula (device-specific dead volume is not considered):

| Reagent | Formula | Example: 5 strips |
|---|---|---|
| Skimmed milk powder [g] | = number of strips x 0.1 | 0.5 g |
| Wash buffer A concentrate [ml] | = number of strips x 2 | 10 ml |
| Deionised water [ml] | = number of strips x 18 | 90 ml |
| Ready-to-use wash buffer A [ml] | = number of strips x 20 | 100 ml |

Ready-to-use wash buffer A can be stored for four weeks at 2-8 °C.
The ready-to-use wash buffer A is odourless and slightly turbid.

7.2.2 *Preparation of conjugate solutions*

The conjugate solution must be prepared just before use. It is not possible to store the ready-to-use conjugate solution.
One part of the conjugate concentrate is diluted with 100 parts of the ready-to-use wash buffer A (1+100).
The quantities required for a defined number of test strips are to be calculated according to the following formula:

| Reagent | Formula | Example: 5 strips |
|---|---|---|
| Conjugate concentrate [µl] | = number of strips x 20 | 100 µl |
| Ready-to-use wash buffer A [ml] | = number of strips x 2 | 10 ml |

The conjugate quantities are calculated without dead volume. Depending on handling (manual or on a device), please mix additional conjugate solution for 1 to 3 strips.

# 8 Test procedure

| No. | Execution | Note |
|---|---|---|
| 1 | Subject all reagents to 18 to 25 °C (room temperature) for at least 30 minutes before beginning the test. | The test procedure is carried out at room temperature. |
| 2 | Preparing test strips<br>Immerse strips in **2 ml** ready-to-use **washing buffer A**. | Do not touch the strips with bare hands - use the forceps. The strip number points upward.<br>A well is required in the incubation tray (see 4.2) for each strip. The strips must be completely immersed. |
| 3<br>a)<br><br><br><br>b) | Incubation of samples<br>**20 µl** of an undiluted sample (human serum or plasma) are pipetted onto the test strip for each incubation mixture. (Dilution 1 + 100)<br><br>Incubate for **1 hour** with gentle shaking | Pipette the sample at one end of the immersed strip in the wash buffer A and mix as quickly as possible by carefully shaking the tray.<br>Cover incubation tray with plastic cover and place in the shaker. |
| 4<br>a)<br><br>b)<br><br>c) | Washing<br>Carefully remove the plastic cover from the incubation trays.<br><br>Gently siphon serum dilution from the individual wells.<br><br>Pipette **2 ml** of ready-to-use **wash buffer A** into each well, wash for 5 minutes with gentle shaking and then siphon off the wash buffer A. | Washing steps 8.4a-8.4c are to be carried out a total of three times. Avoid cross-contamination<br><br>The manufacturer's instructions must be observed during automatic processing. |
| 5 | Incubation with conjugate<br>Add **2 ml** ready-to-use **conjugate solution** and incubate for **45 minutes,** while shaking gently. | Cover the incubation tray with plastic cover and place in the shaker. |
| 6 | Washing<br>see 8.4 | Carry out the washing steps three times in total (see 8.4a-8.4c) |
| 7 | Substrate reaction<br>Add **1.5 ml** of the **substrate solution** and incubate for **8 minutes,** while shaking gently. | |
| 8 | Stopping the reaction<br>Remove the substrate solution.<br>**Briefly** wash with **deionised water** at least three times. | |
| 9 | Drying the strips<br>Dry strip between 2 layers of absorbent paper for **2 hours** before analysis. | Carefully remove strips from the water using plastic forceps. Store strips away from light. |
| **Caution!**<br>**Incubation solutions must not flow into other wells. Splashing must be avoided especially when opening and closing the lid.** | | |

# 9 Results

Caution:
Please do not use automated interpretation without considering the information on interpretation given below.

## 9.1 Validation – Quality Control

An analysis of the test can be carried out if the following criteria have been fulfilled:

1. Reaction control band (first band) visible as a distinctively coloured, dark band.
2. Antibody class (second band): the IgG conjugate control band must show a clear staining.
3. Cut-off control (third band): weak yet visible staining.

## 9.2 Evaluation

The evaluation of test strips may be made visually and with the aid of a computer using the *recom*Scan test strip evaluation software. The *recom*Scan software is designed to support the evaluation of test strips. Further information and related instructions for the computer-assisted evaluation is available on request from MIKROGEN. The following instructions relate to visual analysis.

9.2.1 *Assessment of band intensity*

1. Note the date and batch number, as well as the detected antibody class, on the attached evaluation form.
2. Enter the sample identification numbers in the evaluation form.
3. Now stick the corresponding test strips on to the appropriate fields on the evaluation form using a glue stick. Align the test strips with the reaction control band along the marked lines. Then use a transparent adhesive tape to attach the test strips to the left of the marked lines (do not tape over the reaction control band!). Sticking the entire test strip down flat using glue or tape can lead to changes in colour.
4. Now identify the bands of the developed test strips by referring to the printed control strip of the evaluation sheet and enter them in the evaluation form. For this purpose, carry out the assessment of the intensity of the occurring bands on the basis of Table 1.

**Table 1:** Assessment of band intensity in relation to the cut-off band

| Stain intensity of the bands | Assessment |
|---|---|
| No visible colouring | - |
| Very low intensity (lower than cut-off band) | +/- |
| Low intensity (equivalent to cut-off band) | + |
| Strong intensity (stronger than cut-off band) | ++ |
| Very strong intensity | +++ |

+, ++ and +++ are to be rated positive (p); - and +/- are to be rated negative (n)

### 9.3 Interpretation of test results

The antigen bands must be clearly visible for the evaluation of the test results. The background reaction must not be too strong. If these requirements are not met, the test must be repeated.
If at least one band shows an intensity that is equal in strength to the cut-off band ("+" or stronger), the test result is to be be rated positive.
Some of the anti-nuclear antibodies (ANA) to be detected are specific to one of the collagenosis types and thus constitute serological markers with a great diagnostic value. Significant serological markers are auto-antibodies against the following antigens:

- dsDNA for SLE
- Rib-P for SLE
- PCNA for SLE
- Scl 70 for diffuse progressive systemic scleroderma
- CENP-B for limited progressive systemic scleroderma (CREST)
- RNP 68 for MCTD
- Jo-1 for myositis

The other anti-nuclear antibodies that can be detected with the *recom*Line ANA/ENA IgG are less specific for a certain type of collagenosis and can occur in various types of collagenosis. To support test interpretation, the frequencies with which the individual auto-antibodies are involved are listed in Table 2 according to the respective collagenosis type.

**Table 2:** Frequencies of the auto-antibody detection in the *recom*Line ANA/ENA IgG (in %) in different collagenosis diseases, which were determined according to clinical symptoms and/or with antigen patterns from validation (confirmation) using 2 benchmark tests (n=226).

| | SLE* n=88 | SjS* n=42 | MCTD* n=22 | PSS* n=54 | Myositis n=20 |
|---|---|---|---|---|---|
| **RNP68** | 2 | 0 | **100** | 0 | 15 |
| **RNPA** | 15 | 0 | 95 | 0 | 0 |
| **RNPC** | 10 | 0 | 64 | 0 | 0 |
| **SmB** | 15 | 0 | 64 | 0 | 0 |
| **SmD** | **15** | 0 | 50 | 0 | 0 |
| **Ro/SSA60** | **34** | **81** | 45 | 2 | 5 |
| **Ro/SSA52** | **32** | **90** | 45 | 9 | 60 |
| **La/SSB** | 14 | **57** | 23 | 0 | 5 |
| **Rib-P** | **10** | 0 | 32 | 0 | 0 |
| **PCNA** | **5** | 0 | 5 | 0 | 0 |
| **CENPB** | 0 | 0 | 0 | **59** | 0 |
| **Scl 70** | 0 | 0 | 5 | **43** | 0 |
| **Jo-1** | 0 | 0 | 5 | 0 | **100** |
| **Histone H1** | 22 | 0 | 5 | 0 | 0 |
| **dsDNA** | **86** | 0 | 9 | 2 | 10 |

***** SLE = systemic lupus erythematosus, SjS = Sjögren's Syndrome, MCTD= Mixed Connective Tissue Disease, PSS = progressive systemic scleroderma, limited PSS (CREST) or diffuse PSS; specific auto-antibodies of collagenosis diseases in **bold**.

## 10 Limitations of the method - restrictions

- Deviations from the prescribed test procedure may result in incorrect assessments. It is essential to adhere to the prescribed incubation times.
- Serological test results must always be considered in the context of other medical assessments of the patient. The therapy indicated by serological results must always be determined within the context of the clinical data. When diagnosing a rheumatoid autoimmune disease, the clinical findings and the associated medical history must be included, in addition to the laboratory values.
- Unclear constellations of findings concerning dsDNA reactivities should be further verified using a second test system. The detection of antibodies against dsDNA can, in rare cases, show discrepant results in different test systems.
- A negative result does not exclude the possibility of an autoimmune disease.
- False-positive antigen reactivities have been observed in individual cases in pregnant women. If the medical history is unclear, the use of further test systems for clarification is recommended.
- Dark test strips: Some patient samples can produce a dark, uniform or patterned staining across the entire nitrocellulose strip. Various factors in each patient sample can be responsible for this. In case of white bands on dark background probably no antibodies have bound or there is some other reason for no detectable antibody response. The evaluation of these strips is possible only with restrictions. It is recommended to check the corresponding sample using other serological methods.

## 11 Test performance

### 11.1 Diagnostic sensitivity

The relative diagnostic sensitivity was determined using defined sera (defined using clinical symptoms (SLE: BILAG score, n=30) and/or specific antigen pattern, which was confirmed with 2 benchmark tests (n=226)).

| Defined serums | Number tested | Positive | Sensitivity (%) |
|---|---|---|---|
| SLE | 88 | 84 | 95 |
| SjS | 42 | 42 | 100 |
| PSS | 54 | 54 | 100 |
| MCTD | 22 | 22 | 100 |
| Myositis | 20 | 20 | 100 |

### 11.2 Sensitivity of auto-antibody detection

in comparison to double positive test results of a multiplex fluorescence-based microparticle test and an ELISA line (and additionally in comparison to a further line immunoassay), n=160

| ***recom*Line ANA/ENA IgG** | **Serum count [n]*** | **Sensitivity [%]** |
|---|---|---|
| **RNP68** | 31 | 93.5 |
| **RNPA** | 23 | 95.6 |
| **RNPC** | 21 | 95.2 |
| **SmB** | 31 | 90.3 |
| **SmD** | 29 | 93.1 |
| **Ro/SSA60** | 28 | 100 |
| **Ro/SSA52** | 36 | 100 |
| **La/SSB** | 19 | 100 |
| **Rib-P** | 16 | 100 |
| **PCNA** | 11 | 100 |
| **CENPB** | 23 | 100 |
| **Scl 70** | 12 | 100 |
| **Jo-1** | 11 | 100 |
| **Histone H1** | 14 | 92.9 |
| **dsDNA** | 38 | 100 |

* Number of sera tested, which with the two comparative tests are positive for the respective collagenosis markers.

### 11.3 Specificity of auto-antibody detection

The specificity was determined with the following potentially cross-reactive sera or sera of specific immunological constitution or serum matrix: autoimmune vasculitis (n=23), psoriasis (n=30), EBV IgM (n=30); blood donor serums (n=100), total number of sera=183

| ***recom*Line ANA/ENA IgG** | **Specificity [%]** |
|---|---|
| **RNP68** | 100 |
| **RNPA** | 100 |
| **RNPC** | 100 |
| **SmB** | 100 |
| **SmD** | 99.5 |
| **SSA60** | 98.9 |
| **SSA52** | 99.5 |
| **SSB** | 100 |
| **Rib-P** | 100 |
| **PCNA** | 99.5 |
| **CENPB** | 100 |
| **Scl 70** | 100 |
| **Jo-1** | 99.5 |
| **Histone** | 98.4 |
| **dsDNA** | 98.9 |

### 11.4 CDC serums

The following table shows how recomLine ANA/ENA IgC has been used to detect auto-antibodies against 10 sera made available by the Arthritis Foundation and CDC (Center for Disease Control and Prevention, Atlanta, USA). These sera are regarded as reference sera and have been confirmed in additional laboratory tests.
Further information about the sera is available from MIKROGEN, while Smolen et al. 1997 provides a detailed description.

| CDC* | **CDC#2** La/SSB | **CDC#3** RNP La/SSB SSA | **CDC#4** RNP | **CDC#5** Sm | **CDC#6** Sample: nucleolar | **CDC#7** Ro/SSA | **CDC#8** Sample: Centromer | **CDC#9** Scl70 | **CDC#10** Jo-1 | **CDC#12** Rib-P |
|---|---|---|---|---|---|---|---|---|---|---|
| **RNP68** | - | + | + | + | - | - | - | - | + | - |
| **RNPA** | - | - | + | + | - | - | - | - | - | - |
| **RNPC** | - | - | - | + | - | - | - | - | - | - |
| **SmB** | - | - | - | + | - | - | - | - | - | - |
| **SmD** | - | - | - | + | - | - | - | - | - | - |
| **Ro/SSA60** | + | + | - | - | + | + | - | - | - | - |
| **Ro/SSA52** | + | + | - | - | + | + | - | - | + | - |
| **La/SSB** | + | + | - | - | - | - | - | - | - | - |
| **Rib-P** | - | - | - | - | - | - | - | - | - | + |
| **PCNA** | - | - | - | - | - | - | - | - | - | - |
| **CENP-B** | - | - | - | - | - | - | + | - | - | - |
| **Scl 70** | - | - | - | - | - | - | - | + | - | - |
| **Jo-1** | - | - | - | - | - | - | - | - | + | - |
| **Histone H1** | - | - | - | - | + | - | - | - | - | - |
| **dsDNA** | - | - | - | + | - | + | - | - | - | - |

* The CDC sera are:
a) determined by means of a conventional Ouchterlony immunodiffusion test. In this case, the positive antigens are indicated. (According to CDC, it is quite possible to find additional positive antigens.)
b) determined by means of indirect immunofluorescence, with IFT samples to be indicated.

## 12 Literature

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We would be glad to send you further reading material on the subject of rheumatoid autoimmune diseases on request.

## 13 Explanation of symbols

| | |
|---|---|
| Σ | Content is sufficient for <n> applications<br>Number of applications |
| WASHBUF A 10 X | Wash buffer A (**ten-fold concentration**) |
| SUBS TMB | Tetramethylbenzidine chromogenic substance |
| MILKPOW | Skimmed milk powder |
| INSTRU | Instructions for use |
| EVALFORM | Evaluation form |
| TEMPEVAL | Evaluation stencil |
| TESTSTR | Tubes, each containing 10 sequentially numbered test strips |
| CONJ IgG | Anti-human IgG conjugate |
| | See instructions for use |
| CONT | Content, includes |
| IVD | In vitro diagnostic test |
| LOT | Batch/version number |
| | Do not freeze |
| REF | Order number |
| | Best before<br>Expiry date |
| y°C x°C | Store at x°C to y°C |
| | Manufacturer |

## 14 Manufacturer and version information

| | |
|---|---|
| ***recom*Line ANA/ENA IgG** | Item No. **6072** |
| **Instructions for use**<br>valid from | GARLAE013EN<br>2023-03 |

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