Elecsys Rubella IgG

cobas®

REF		Σ	SYSTEM
07027770190	07027770500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
RUBIGG	10024

Please note

The measured anti-Rubella IgG value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the Rubella IgG assay used.

Anti-Rubella IgG values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations.

Therefore, the results reported by the laboratory to the physician should include:
"The following results were obtained with the Elecsys Rubella IgG assay. Results from assays of other manufacturers cannot be used interchangeably."

Intended use

Immunoassay for the in vitro quantitative determination of IgG antibodies to Rubella virus in human serum and plasma.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Rubella virus is the etiological agent of German measles, a commonly mild rash disease which occurs usually during childhood.[1,2] It is spread by small droplets via the respiratory route.[1,2,3,4] Postnatal acquired infection is seldom associated with complications.[1,2]

However, Rubella can be a serious disease when a pregnant woman becomes infected especially during the first trimester of pregnancy.[1,2,3,4] Rubella virus can be transmitted through the placenta and results in fetal death or causes severe malformations to the fetus, commonly summarized as congenital Rubella syndrome (CRS).[1,3] CRS can manifest with blindness, deafness, congenital heart disease and/or mental retardation.[2,3,4]

Today, infant vaccination programs and the vaccination of women in child-bearing age who are susceptible to Rubella infection have considerably reduced the incidence of acute Rubella infection and that of CRS.[1,2,3,4]

Detection of Rubella-specific antibodies is used to determine the immune status of an individual and contribute to the diagnosis of acute Rubella infection.[4]

The presence of IgG antibodies to Rubella virus indicates a previous exposure either by vaccination or prior Rubella infection and is indicative of immunity.[5]

Detection of Rubella-specific IgM antibodies can be indicative of acute or recent Rubella infection.[4,5] Seroconversion of specific Rubella antibodies or a significant rise of the anti-Rubella IgG titer from a first to a second sample may further support the diagnosis of acute Rubella infection.

Recombinant Rubella-like particles (RLP) have proven to replace authentic Rubella virus as an antigen in diagnostic assays. A recombinant part of the E1 (envelope1) protein of Rubella virus is used to supplement the assay.

The quantitative determination of anti-Rubella IgG is used as an aid in the determination of the immune status to Rubella and the diagnosis of acute infection.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample are incubated with biotinylated monoclonal anti-human IgG antibody, RLP (Rubella-like particles) and a ruthenylated monoclonal anti-Rubella antibody fragment. In addition a biotinylated Rubella virus-specific recombinant antigen E1 (E. coli) and E1 labelled with ruthenium complex[a)] react with anti-Rubella IgG from the sample to form a sandwich complex.
- 2nd incubation: Addition of streptavidin-coated microparticles.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as RUBIGG.

M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-h IgG-Ab~biotin, 1 bottle, 19.7 mL:
Biotinylated monoclonal anti-human IgG antibody (mouse); Rubella-like particles (RLP), phosphate buffer, pH 6.8; preservative.

R2 Anti-Rubella-Ab-fragment~$Ru(bpy)_3^{2+}$, recombinant E1~biotin, recombinant E1~$Ru(bpy)_3^{2+}$, 1 bottle, 19.7 mL:
Ruthenylated monoclonal anti-Rubella antibody fragment; biotinylated recombinant E1; ruthenylated recombinant E1, phosphate buffer, pH 6.8; preservative.

RUBIGG Cal1 Negative calibrator 1, 1 bottle of 1.0 mL:
Human serum, non-reactive for anti-Rubella IgG; preservative.

RUBIGG Cal2 Positive calibrator 2, 1 bottle of 1.0 mL:
Anti-Rubella IgG approximately 400 IU/mL in human serum; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317 May cause an allergic skin reaction.

Prevention:

P261 Avoid breathing dust/fume/gas/mist/vapours/spray.

P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved by the FDA or that are in compliance with the legal rules applicable to placing in vitro diagnostic medical devices for human use on the market in the European Union.
However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[6,7]

The negative calibrator (RUBIGG Cal1) has been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

Positive calibrator (RUBIGG Cal2): Materials of human origin were tested for HIV and hepatitis C. The findings were negative.

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

Calibrators:

The calibrators are supplied ready-for-use in bottles compatible with the system.

Unless the entire volume is necessary for calibration on the analyzer, transfer aliquots of the ready-for-use calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

Perform **only one** calibration procedure per aliquot.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	16 weeks
on the analyzers at 20-25 °C	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, Na-heparin, K_2-EDTA, K_3-EDTA and Na-citrate plasma.

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 2 IU/mL + coefficient of correlation ≥ 0.95.

Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower values (IU/mL) for individual patient specimens. In order to minimize dilution effects it is essential that respective sampling devices are filled completely according to manufacturer's instructions.

Stable for 7 days at 20-25 °C, 21 days at 2-8 °C, 3 months at -20 °C (± 5 °C). The samples may be frozen 5 times.

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. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Specimens should not be altered subsequently with additives (biocides, anti-oxidants or substances possibly changing the pH of the sample) in order to avoid erroneous findings.

Pooled samples and other artificial material may have different effects on different assays and thus may lead to discrepant findings.

Centrifuge samples containing precipitates and thawed samples before performing the assay.

Do not use heat-inactivated samples.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels

Materials required (but not provided)

- REF 04618807190, PreciControl Rubella IgG, 16 x 1.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- REF 07299001190, Diluent Universal, 45.2 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibrators:

Place the calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

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Calibration

Traceability: This method has been standardized against the 1st International Standard for Anti-Rubella Immunoglobulin, human, code RUBI-1-94, from the National Institute for Biological Standards and Control (NIBSC), Hertfordshire, UK, formerly referred to as proposed 3rd WHO Reference Standard Preparation.

The predefined master curve is adapted to the analyzer using RUBIGG Cal1 and RUBIGG Cal2.

Calibration frequency: Calibration must be performed once per reagent lot using RUBIGG Cal1, RUBIGG Cal2 and fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl Rubella IgG.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in IU/mL.

Interpretation of the results

Numeric result	Result message	Interpretation/ further steps
< 10 IU/mL	Non-reactive	Negative for anti-Rubella IgG
≥ 10 IU/mL	Reactive	Positive for anti-Rubella IgG.* The presence of IgG antibodies to Rubella virus is an indication of previous exposure either by prior infection or by vaccination.

*The NCCLS subcommittee on Rubella Serology recommended 10 IU/mL as the cutoff level.[8]

The anti-Rubella IgG result in a given specimen, as determined by assays from different manufacturers, can vary due to differences in assay and reagent methods. Therefore, the results reported by the laboratory to the physician should include: "The following results were obtained with the Elecsys Rubella IgG assay. Results from assays of other manufacturers cannot be used interchangeably."

Patients suspected of acute Rubella infection should be tested for the presence of Rubella-specific IgM. The diagnosis of acute Rubella infection may be supported by a significant increase of the anti-Rubella IgG titer from a first to a second sample.

Limitations - interference

A test result < 10 IU/mL does not completely rule out the possibility of an acute Rubella infection. Specimens taken very early in the acute phase of infection may not contain any detectable amounts of anti-Rubella IgG or may have an antibody concentration < 10 IU/mL. The presence of anti-Rubella IgG in a single sample is not sufficient to distinguish between an acute or past infection. The lack of a significant increase of the anti-Rubella IgG titer (e.g. within 3-4 weeks) may not completely exclude acute Rubella infection. When monitoring the anti-Rubella IgG titer it is recommended that serial samples be tested by parallel measurements.

The results in HIV patients, in patients undergoing immunosuppressive therapy or in patients with other disorders leading to immune suppression should be interpreted with caution.

Specimens from neonates, cord blood, pretransplant patients or body fluids other than serum and plasma, such as urine, saliva or amniotic fluid have not been tested.

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 513 µmol/L or ≤ 30 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 205 nmol/L or ≤ 50 ng/mL
Albumin	≤ 7 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 0.4 g/dL

Criterion: For concentrations < 10 IU/mL the deviation is ≤ ± 2 IU/mL. For concentrations ≥ 10 IU/mL the deviation is ≤ ± 20 %.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

Increasing amounts of unspecific human IgG may lead to a decrease in the recovery of positive samples with the Elecsys Rubella IgG assay.

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special drug was tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested
Folic acid	≤ 3 mg/L

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

0.21-500 IU/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.21 IU/mL. Values above the measuring range are reported as > 500 IU/mL (or up to 10000 IU/mL for 20-fold diluted samples).

Lower limits of measurement

Limit of Blank and Limit of Detection

Limit of Blank = 0.17 IU/mL

Limit of Detection = 0.21 IU/mL

The Limit of Blank and Limit of Detection were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection

corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

Dilution

Samples with anti-Rubella concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:20 (either automatically by the analyzers or manually). The concentration of the diluted sample must be ≥ 10 IU/mL.

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Manual dilution can also be performed using human serum negative for IgG antibodies to Rubella.

Note: Antibodies to Rubella are heterogeneous. A non-linear dilution behavior is frequently observed.

A similar dilution behavior within the measuring range was shown when serial samples from the same individual were diluted. Serial samples of n = 12 individuals were examined. In a panel consisting of 33 samples with a concentration within the measuring range, no higher Elecsys Rubella IgG values were found upon dilution (when the dilution factor has not been taken into account).

Expected values

The Elecsys Rubella IgG assay was used to test 560 samples from clinical routine in France (site 1) and 1000 samples from clinical routine in Germany (site 2). A distribution of these values is given in the following table.

IU/mL	Site 1, France, n = 560		Site 2, Germany, n = 1000	
	N	% of total	N	% of total
< 5	32	5.7	19	1.9
5-< 10	5	0.9	2	0.2
10-< 20	13	2.3	12	1.2
20-< 50	34	6.1	47	4.7
50-< 100	56	10.0	82	8.2
100-< 300	244	43.6	541	54.1
300-< 500	105	18.8	151	15.1
> 500	71	12.7	146	14.6

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean IU/mL	SD IU/mL	CV %	SD IU/mL	CV %
HS[b], negative	1.19	0.064	5.4	0.084	7.0
HS, weakly positive	10.4	0.368	3.5	0.475	4.6
HS, positive	399	11.4	2.9	15.6	3.9
PC[c] Rubella IgG 1	3.01	0.096	3.2	0.155	5.2
PC Rubella IgG 2	57.9	1.27	2.2	2.42	4.2

b) HS = human serum

c) PC = PreciControl

Clinical sensitivity

Acute Rubella infection

Of 111 samples from 76 patients with primary Rubella infection (including early and late acute phase), 73 samples were found positive with the Elecsys Rubella IgG assay and 38 samples were found negative.

Rubella vaccination

234 samples from 61 individuals vaccinated against Rubella infection were examined with the Elecsys Rubella IgG assay and a comparison test. The average time interval to the first positive bleed was 11.7 days with the Elecsys Rubella IgG assay and 16.4 days with the comparison assay in a subset of 10 vaccine follow-ups.

Method comparison

a) A comparison of the Elecsys Rubella IgG assay, REF 07027770190 (**cobas e** 801 analyzer; y) with the Elecsys Rubella IgG assay, REF 04618793190 (**cobas e** 601 analyzer; x) gave the following correlations (IU/mL):

Number of serum samples measured: 179

Passing/Bablok[9]

y = 1.04x + 2.21

r = 0.996

The sample concentrations were between 0.221 and 433 IU/mL.

b) A comparison of the Elecsys Rubella IgG assay, REF 07027770190 (**cobas e** 402 analyzer; y) with the Elecsys Rubella IgG assay, REF 07027770190 (**cobas e** 801 analyzer; x) gave the following correlations (IU/mL):

Number of serum samples measured: 213

Passing/Bablok[9]

y = 1.06x + 0.198

r = 0.995

The sample concentrations were between 0.000 and 404 IU/mL.

A total of 1559 fresh samples obtained from clinical routine (antenatal screening) and 989 pre-selected frozen samples were tested at 4 different sites in comparison to commercially available Rubella IgG assays. Discordant results were re-tested by a third commercial Rubella IgG test.

10 specimens with indeterminate results in one of the assays and 3 samples which could not be retested were excluded from the final calculation of sensitivity and specificity (7 samples at site 1, 4 samples at site 2 and 2 samples at site 3).

Relative sensitivity and specificity after resolution

Study	N	Relative sensitivity (%)	Lower confidence limit (%)	Relative specificity (%)	Lower confidence limit (%)
1	552	100 (514/514)	99.4	97.4 (37/38)	-
2	996	99.9 (977/978)	99.5	100 (18/18)	-
3	198	100 (120/120)	97.5	100 (78/78)	96.2
4	789	100 (20/20)	-	100 (769/769)	99.6

Site 1: Of 17 samples which were initially discordant positive with the Elecsys Rubella IgG assay, 9 samples were also found positive by a third commercial Rubella IgG test, 6 samples were found borderline, 1 sample was found negative and 1 sample could not be retested.

Site 2: Of 2 samples which were initially discordant negative with the Elecsys Rubella IgG assay, 1 sample was found positive by a third commercial Rubella IgG test and 1 sample was found negative.

Site 4: Of 20 samples which were initially discordant positive with the Elecsys Rubella IgG assay, 20 samples were also found positive by a third commercial Rubella IgG test.

Elecsys Rubella IgG

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References

1 Edlich RF, Winters KL, Long WB 3rd, et al. Rubella and congenital rubella (German measles). J Long Term Eff Med Implants 2005;15:319-328.

2 Best JM. Rubella. Semin Fetal Neonatal Med 2007;12:182-192.

3 Duszak RS. Congenital rubella syndrome--major review. Optometry 2009;80:36-43.

4 De Santis M, Cavaliere AF, Straface G, et al. Rubella infection in pregnancy. Reprod Toxicol 2006;21:390-398.

5 Tipples GA. Rubella diagnostic issues in Canada. J Infect Dis 2011;204(Suppl2):659-663.

6 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

7 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

8 Skendzel L. Rubella Immunity. Defining the Level of Protective Antibody. Am J Clin Pathol 1996;106:170-174.

9 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

CE 0123

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