RIDA®GENE MRSA

REF PG0605

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1. Intended use

For *in vitro* diagnostic use. The RIDA®GENE MRSA test, performed on the Roche LightCycler® 480 II, is a multiplex real-time PCR for the direct qualitative detection of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) DNA in untreated human nasal/throat swabs, wound swabs, and culture in asymptomatic individuals and in individuals showing signs and symptoms of infection caused by MRSA.

The RIDA®GENE MRSA Test is intended to support the diagnosis of staphylococcus infections (methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *Staphylococcus aureus* (MSSA)) in asymptomatic individuals and in individuals showing signs and symptoms of infection caused by MRSA in connection with other clinical and laboratory findings.

Negative results do not rule out staphylococcus infection (methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *Staphylococcus aureus* (MSSA)) and should not be used as the sole basis for diagnosis.

The product is intended for professional use.

2. Summary and explanation of the test

Staphylococci are widespread as natural colonizers of the skin and mucosa of the oropharynx in humans and animals. They are divided into coagulase-positive (*S. aureus*) and coagulase-negative staphylococci (such as *S. epidermidis*). *Staphylococcus aureus* is one of the most significant pathogens of nosocomial infections in hospitals and other healthcare facilities.[1,2] The pathogen is transmitted through medical personnel or other patients. An estimated 30% of the healthy population is colonized with *S. aureus* (asymptomatic carriers). Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most frequent pathogens of nosocomial infections worldwide (hospital-acquired MRSA or just HA-MRSA). In addition to HA-MRSA infections, there are also community-acquired MRSA (CA-MRSA) infections that can be caught outside of the hospital.[3,4] In recent years, livestock-associated MRSA or LA-MRSA infections have occurred in the context of fattening animals, in particular among pig farmers.[5,6] The methicillin (oxacillin)-resistance of *S. aureus* is mediated by the penicillin-binding protein PBP2a, which is encoded by the chromosomal *mecA* gene. The *mecA* gene is localized on the variable and unstable *SCCmec* gene cassette (staphylococcal cassette chromosome mec). To date, 14 SCCmec cassette types have been described, of which types I to V occur most frequently.[3,7,8]
The SCCmec cassette type XI (SCCmec XI), which contains another mecA homolog (also termed mecC or mec_{LGA251}, was described for the first time in 2011. The *mecC* gene has only a nucleotide homology of 70% with *mecA* and is not detectable using normal *mecA*-specific PCRs and PBP2a-agglutination tests. It has been described in *S. aureus* isolates of humans and cattle.[9]

In contrast to infections with MSSA (methicillin-sensitive *Staphylococcus aureus*), MRSA infections are associated with an elevated morbidity, mortality, extended hospital stays and greater treatment costs.[10,11] Risk factors for MRSA infection in healthcare facilities are contact with patients with a MRSA infection, a known history of MRSA, the length of hospital stay and long-term antibiotic therapy.[12]
Each MRSA infection generates up to $10,000 in additional costs.[13] In the European Union, more than 150,000 hospital patients suffer from a MRSA infection. The resulting hospital costs to the European healthcare system are estimated at €380 million.[14]
Early, rapid and systematic MRSA screening allows infected patients to be specifically treated and appropriate hygiene methods to be introduced to prevent the transmission and spread of MRSA.
Using conventional culturing methods, 48 to 72 hours are needed to detect MRSA. Real-time PCR tests allow early and fast MRSA screening on the date of hospital admission as part of the infection prevention program (“search and destroy” strategy).[15]

3. Test principle

RIDA®GENE MRSA is a multiplex real-time PCR for direct qualitative detection and differentiation between methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) in culture samples of human nose and nose/throat swab specimens. After isolating the DNA, the specific gene fragments (if present) of MRSA (the mecA/*mecC*- gene, SCCmec/orfX junction and the SA442 gene) are amplified. The amplified target sequences are detected using hydrolysis probes that are labeled with a quencher at one end and a fluorescent reporter dye (fluorophore) at the other. The probes hybridize to the amplicon in the presence of a target sequence. During extension, the Taq-Polymerase separates the reporter from the quencher. The reporter emits a fluorescent signal that is detected by the optical unit of a real-time PCR device. The fluorescent signal increases with the quantity of formed amplicons. The RIDA®GENE MRSA test contains Internal Control DNA (ICD) for controlling sample preparation and/or any potential PCR inhibition.

4. Reagents provided

Table 1: Reagents provided (The reagents provided in the kit are sufficient for 100 determinations.)

Kit code	Reagent	Amount		Lid color
1	Reaction Mix	2x	1100 µl	Yellow
2	Taq-Polymerase	1x	11 µl	Red
D	Internal Control DNA	2x	1800 µl	Brown
L	Lysis Buffer 1	2x	12 ml	colorless
N	PCR Water	1x	500 µl	White
P	Positive Control	1x	200 µl	Blue

5. Storage instructions

- Protect all reagents from light and store between -16 °C and -28 °C. All reagents can be used unopened until the expiration date. After expiry the quality guarantee is no longer valid.
- All reagents should be carefully thawed prior to use (e.g., in a refrigerator at 2 °C to 8 °C).
- Repeated freezing/thawing of up to 15 times does not have an impact on the test property (if necessary, create aliquots after the first thaw and refreeze reagents immediately).
- Cool all reagents appropriately during PCR preparation (2 °C to 8 °C).

6. Reagents required but not provided

The RIDA®GENE MRSA multiplex real-time PCR test can be used with the following real-time PCR devices:

Table 2: Necessary equipment

Real-time PCR devices	
Roche	LightCycler® 480II
Agilent Technologies	Mx3005P
Applied Biosystems	ABI 7500
Bio-Rad	CFX96™

Should you wish to use other real-time PCR devices, please contact R-Biopharm AG to check compatibility at pcr@r-biopharm.de.

- Sterile swab collection system (e.g., eSwab®, Copan Diagnostics Inc.)
- RIDA®GENE Color Compensation Kit I (PG0001) when using LightCycler® 480II
- Real-time PCR consumables (plates, reaction vials, films)
- Centrifuge with rotor for reaction vials or plates
- Vortexer
- Thermoshaker
- Pipettes (0.5 to 20 µl, 20 to 200 µl, 100 to 1,000 µl)
- Pipette tips with filters
- Powder-free disposable gloves
- PCR water (nuclease-free)

7. Warnings and precautions for the users

- This test must be carried out only by trained laboratory personnel. The guidelines for working in medical laboratories must be followed.
- Always adhere strictly to the instructions for use when carrying out this test.
- Do not pipette samples or reagents using your mouth. Avoid contact with broken skin and mucous membranes.
- Wear personal protective equipment (appropriate gloves, lab coat, safety glasses) when handling reagents and samples, and wash hands after completing the test.
- Do not smoke, eat, or drink in areas where samples are handled.
- Ensure that the extraction, PCR preparation, and PCR are carried out in different rooms in order to avoid cross-contaminations.
- Clinical samples must be viewed as potentially infectious and must be disposed of appropriately, like all reagents and materials that come into contact with potentially infectious samples.
- Dispose of test kit once the expiration date has lapsed.
- Users are responsible for proper disposal of all reagents and materials after use. For disposal, please adhere to national regulations.

For further details, see the safety data sheets (SDSs) at www.r-biopharm.com.

8. Collection and storage of samples

8.1 DNA preparation from swabs

The following isolation method is recommended for isolating DNA from swabs: Add 200 µl Lysis Buffer 1 to a preparation vial. Dip the swab tip into the pre-pipetted lysis buffer 1 and break or cut off the stick. When using swabs with medium, 100 µL of the swab medium can be added to the 200 µL lysis buffer and treated further. Seal the preparation vials tightly and vortex vigorously for 60 seconds. Heat for 10 minutes at 95 °C in a heating block while shaking. Then centrifuge for 1 min at 13,000 x g and use the supernatant as the specimen.

Note: Repeat if the preparation becomes highly opaque while centrifuging.

The RIDA®GENE MRSA test contains Internal Control DNA that indicates potential PCR inhibition, checks the integrity of the reagents, and confirms successful nucleic acid extraction. The Internal Control DNA can be used either only as an inhibition control or as an extraction control for specimen preparation and as an inhibition control.

If the Internal Control DNA is used only as an inhibition control, 1 µl of the Internal Control DNA must be added to the master mix for each reaction (see Table 4).

If the Internal Control DNA is used as an extraction control for sample preparation **and** as an inhibition control, 20 µl of the Internal Control DNA must be used for each sample during extraction. The Internal Control DNA should be added to the specimen/lysis buffer mix and should **not** be added directly to the specimen material. We recommend pipetting 1 µL per reaction of the Internal Control DNA to both the PCR mix for the negative control and the positive control.

8.2 DNA preparation from culture specimens

The following isolation method is recommended for isolating DNA from culture specimens: Add 200 µl Lysis Buffer 1 to a preparation vial. Using an inoculation loop, collect several colonies and suspend them in the pre-pipetted lysis buffer 1. Break or cut off the stick of the inoculation loop. Seal the preparation vials tightly and vortex vigorously for 60 seconds. Heat for 10 minutes at 95 °C in a heating block while shaking. Then centrifuge for 1 min at 13,000 x g and use the supernatant as the specimen.

Note: Repeat if the preparation becomes highly opaque while centrifuging.

The RIDA®GENE MRSA test contains Internal Control DNA that indicates potential PCR inhibition, checks the integrity of the reagents, and confirms successful nucleic

acid extraction. The Internal Control DNA can be used either only as an inhibition control or as an extraction control for specimen preparation and as an inhibition control.

If the Internal Control DNA is used only as an inhibition control, 1 µl of the Internal Control DNA must be added to the master mix for each reaction (see Table 4).

If the Internal Control DNA is used as an extraction control for sample preparation **and** as an inhibition control, 20 µl of the Internal Control DNA must be used for each sample during extraction. The Internal Control DNA should be added to the specimen/lysis buffer mix and should **not** be added directly to the specimen material. We recommend pipetting 1 µL per reaction of the Internal Control DNA to both the PCR mix for the negative control and the positive control.

9. Test procedure

9.1 Master Mix preparation

The total number of the reactions needed for PCR (samples and control reactions) must be calculated. One positive control and one negative control must be included in each test run.

Adding an additional 10 % volume to the master mix is recommended in order to balance out the pipette loss (see Table 3, Table 4). Prior to use, thaw, mix and briefly centrifuge the Reaction Mix, the Taq-Polymerase, the Positive Control, the PCR Water and the Internal Control DNA. Always cool reagents appropriately during work steps (2 °C to 8 °C).

Table 3: Example of the calculation and production of the master mix for 10 reactions (ICD extraction and inhibition control)

Kit code	Components of the master mix	Quantity per reaction	10 reactions (plus 10%)
1	Reaction Mix	19.9 µl	218.9 µl
2	Taq-Polymerase	0.1 µl	1.1 µl
	Total	**20 µl**	**220 µl**

Mix the master mix and then centrifuge for short time.

Table 4: Example of the calculation and production of the master mix for 10 reactions (ICD only as inhibition control)

Kit code	Components of the master mix	Quantity per reaction	10 reactions (plus 10 %)
1	Reaction Mix	19.9 µl	218.9 µl
2	Taq-Polymerase	0.1 µl	1.1 µl
D	Internal Control DNA	1.0 µl	11.0 µl
	Total	**21.0 µl**	**231.0 µl**

Mix the master mix and then centrifuge for short time.

9.2 Preparation of the PCR Mix

Pipette 20 µl of the master mix into each reaction vial (vial/plate).

Negative control: Add 5 µl of the PCR Water to the pre-pipetted master mix.

Note: We recommend pipetting 1 µL of the Internal Control DNA into the PCR mix for the negative control when using the Internal Control DNA as extraction control for specimen preparation and as inhibition control.

Samples: Add 5 µl eluate to the pre-pipetted master mix.

Positive control: Add 5 µl of the Positive Control to the pre-pipetted master mix.

Note: We recommend pipetting 1 µL of the Internal Control DNA into the PCR mix for the positive control when using the Internal Control DNA as extraction control for specimen preparation and as inhibition control.

Seal the reaction vials or plates, briefly centrifuge at slow speed, and transfer into the real-time PCR device. Start PCR according to PCR device set-up (see Table 5, Table 6).

9.3 PCR device set-up

9.3.1 DNA real-time PCR profile

Table 5: DNA real-time PCR profile for LightCycler® 480II

Initial denaturation	1 min, 95 °C
Cycles	45 cycles
PCR Denaturation Annealing/Extension	10 sec, 95 °C 15 sec, 60 °C
Temperature transition rate/ ramp rate	Maximum

Note: Annealing and extension take place in the same step.

Table 6: DNA real-time PCR profile for Mx3005P, ABI 7500, and CFX96™

Initial denaturation	1 min, 95 °C
Cycles	45 cycles
PCR Denaturation Annealing/Extension	15 sec, 95 °C 30 sec, 60 °C
Temperature transition rate/ ramp rate	Maximum

Note: Annealing and extension take place in the same step.

9.4 Detection channel setting

Table 7: Selection of appropriate detection channels

Real-time PCR device	Detection	Detection channel	Comment
Roche LightCycler® 480 II	SCCmec / orfX junction	465/510	**RIDA®GENE Color Compensation Kit I (PG0001) is required.**
	ICD	533/580	
	SA442 (*S.aureus*)	533/610	
	mecA / mecC	618/660	
Agilent Technologies Mx3005P	SCCmec / orfX junction	FAM	**Set the reference dye to none.**
	ICD	HEX	
	SA442 (*S.aureus*)	ROX	
	mecA / mecC	Cy5	
ABI 7500	SCCmec / orfX junction	FAM	**Set the ROX passive reference dye to none.**
	ICD	VIC	
	SA442 (*S.aureus*)	ROX	
	mecA / mecC	Cy5	
Bio-Rad CFX96™	SCCmec / orfX junction	FAM	**-**
	ICD	VIC	
	SA442 (*S.aureus*)	ROX	
	mecA / mecC	Cy5	

10. Quality control

Samples are evaluated using the analysis software of the respective real-time PCR device according to the manufacturer's instructions. Negative and positive controls must show the correct results (see Table 8, Fig. 1, Fig. 2, and Fig. 3).

The Positive Control comes in a concentration of 10^3 copies/µl. It is used in a total quantity of 5 x 10^3 copies in every PCR run.

Table 8: A valid PCR run must meet the following conditions:

Sample	Result	ICD Ct	Target gene Ct
Positive control	Positive	N/A *1	See Certificate of Analysis
Negative control	Negative	Ct > 20	Not detectable

**1 A Ct value for the ICD is not needed to obtain a positive result of the positive control.*

The positive and negative controls are valid when they meet the conditions specified in the table. The Ct range for the positive control is specified on the Quality Assurance Certificate included with the product. If one of the two controls does not meet the conditions for a valid run, all the reactions need to be re-analyzed, including the controls.

If the specified values are not met, check the following items before repeating the test:

- Expiration date of the reagents used
- Functionality of the equipment being used
- Correct test procedure

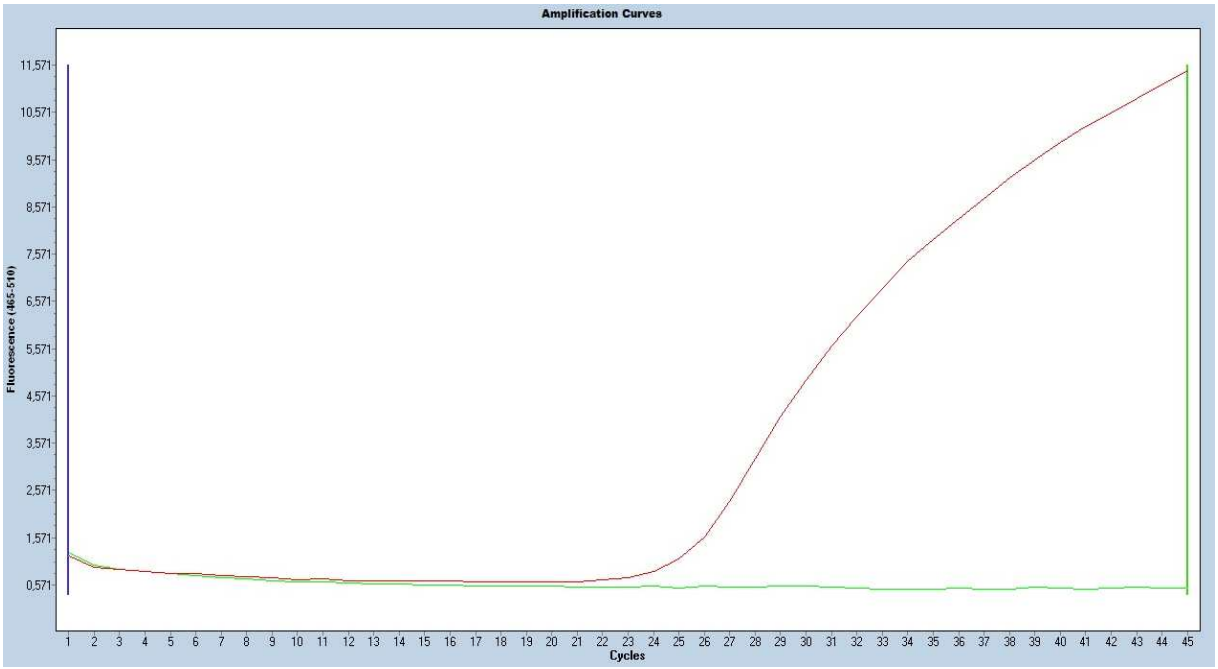

Fig. 1: Correct run of the positive control (red) and negative control (green) (SCCmec / orfX junction) on the LightCycler® 480II

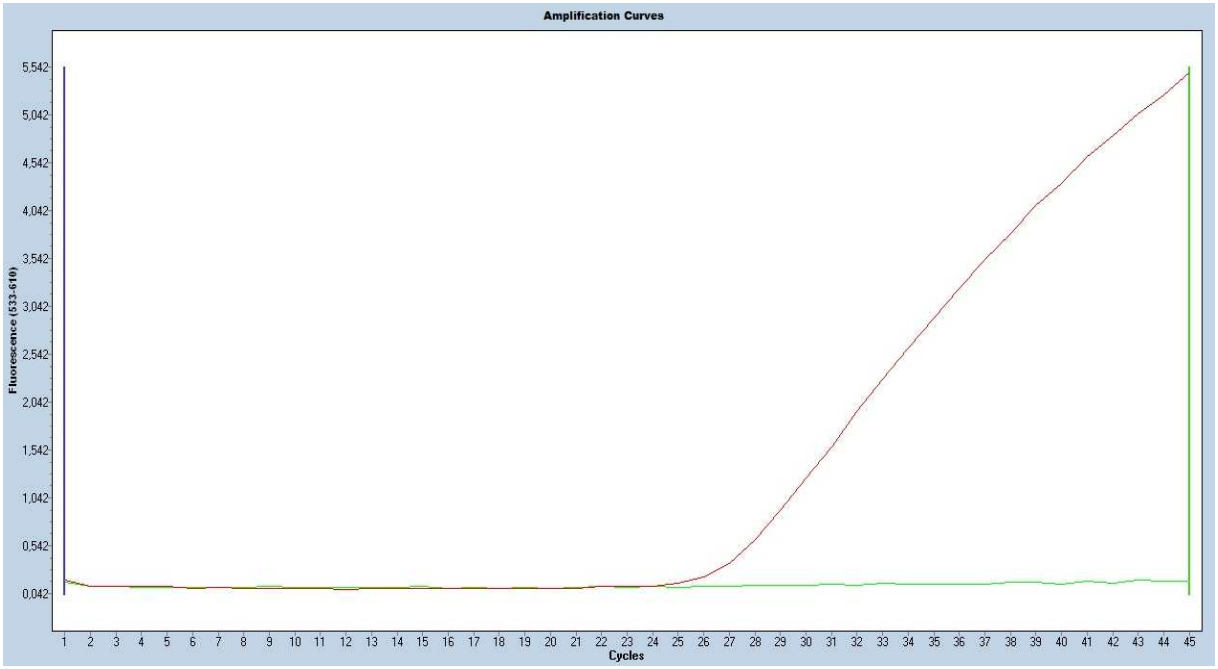

Fig. 2: Correct run of the SA442 positive control (red) and negative control (green) (SA442 (*S.aureus*)) on the LightCycler® 480II

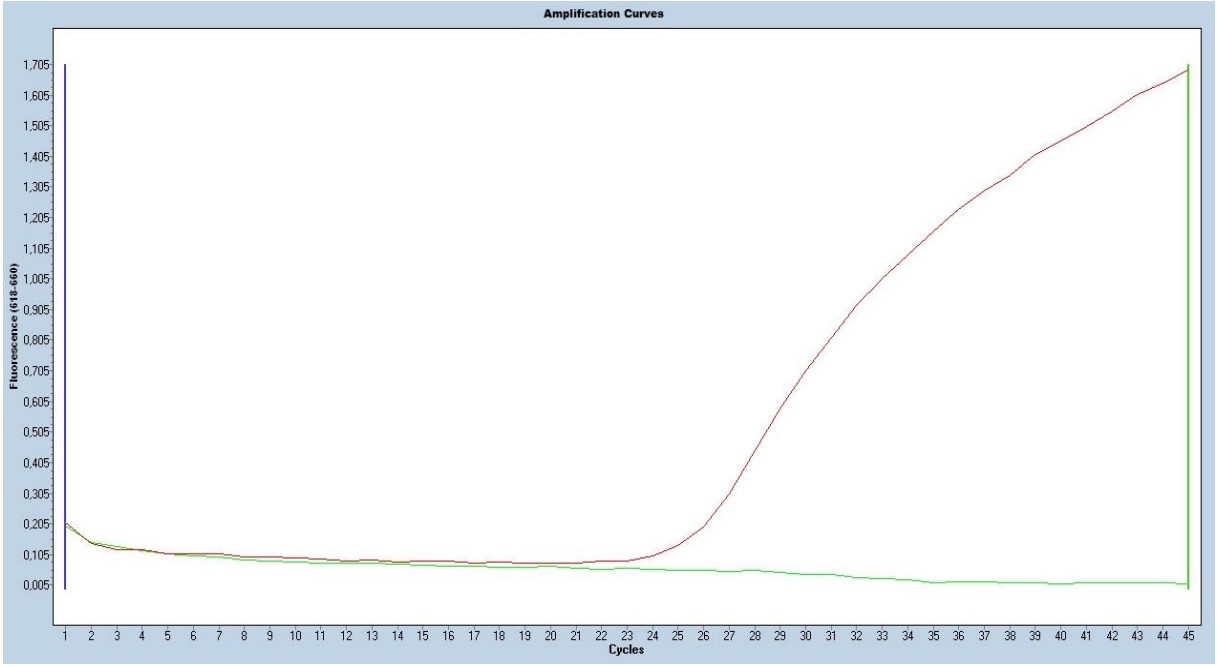

Fig. 3: Correct run of the positive control (red) and negative control (green) (mecA/mecC) on the LightCycler® 480II

11. Sample interpretation

The result interpretation is done according to Table 9.

Table 9: Sample interpretation

Detection of				
SCCmec / orfX junction	**SA442 (*S.aureus*)**	**mecA / mecC**	**ICD**	**Result**
positive	**positive**	**positive**	**positive/ negative**	***MRSA**** **detectable (see Limitations of the method under point 8)**
positive	**positive**	negative	**positive/ negative**	**MRSA not detectable; MSSA** detectable (see Limitations of the method under point 7)**
negative	**positive**	negative	**positive/ negative**	**MSSA detectable**
negative	negative	**positive**	**positive/ negative**	**MRSA not detectable (see Limitations of the method under point 9)**
negative	**positive**	**positive**	**positive/ negative**	**MRSA not detectable; MSSA detectable (see Limitations of the method under point 8)**
positive	negative	**positive**	**positive/ negative**	**MRSA not detectable (see Limitations of the method under point 7)**
negative	negative	negative	**positive**	**Target gene not detectable**
negative	negative	negative	**negative**	**Invalid**
positive	negative	negative	**positive/ negative**	**Neither MRSA nor MSSA are detectable (see Limitations of the method under point 7)**

* MRSA = methicillin-resistant *S. aureus*

** MSSA = methicillin-sensitive *S. aureus*

A specimen is rated positive if the specimen DNA and the Internal Control DNA show an amplification signal in the detection system.

A specimen is also rated positive if the specimen DNA displays an amplification signal but no amplification signal can be found in the detection system for the Internal Control DNA. Detecting the Internal Control DNA is not necessary in this

case because high amplicon concentrations can cause a weak or absent signal of the Internal Control DNA.

A specimen is rated negative if the specimen DNA does not show an amplification signal, but an amplification signal for the Internal Control DNA can be found in the detection system. An inhibition of the PCR reaction can be ruled out by the detection of the Internal Control DNA.

A specimen is invalid if the specimen DNA and the Internal Control DNA do not show an amplification signal in the detection system. There are PCR inhibitors in the sample, or an error occurred during the extraction process. The extracted sample should be diluted 1:10 with PCR water and re-amplified, or the isolation and purification of the sample should be improved.

12. Limitations of the method

1. This test is only suitable for the described swab and culture specimens.
2. Improper specimen sampling, transport, storage, and handling or a pathogen load below the test's analytical sensitivity can lead to false negative results.
3. The use of PCR-based MRSA screening methods is subject to country-specific guidelines. The user is responsible for employing and implementing these guidelines. For example, according to KRINKO in Germany, PCR-based screening methods are to be considered provisional until the ultimate results of culturing are obtained. However, they can still be used as a provisional foundation for a hospital hygiene policy.
4. In the literature, 14 SCCmec types are described. RIDA®GENE MRSA multiplex real-time PCR can detect SCCmec types I, II, III, IV, V, VI, VII, IX, X and XI. RIDA®GENE MRSA may not detect other SCCmec types and may show negative results.
5. The presence of PCR inhibitors can lead to non-evaluable results.
6. Mutations or polymorphisms in the primer or probe binding sites can interfere with the detection of new or unknown variants and can lead to false negative results using RIDA®GENE MRSA.
7. As with all PCR-based *in vitro* diagnostic tests, extremely low concentrations of the target sequences under the limit of detection (LoD) can be detected. The results obtained are not always reproducible.
8. A positive test result does not necessarily indicate the presence of viable organisms. A positive result indicates the existence of the corresponding target genes (mecA/mecC Gen, the SCCmec/orfX junction and the SA442 gene).
9. A signal may not occur in all channels for LoD specimens, even with a specimen that is MRSA-positive.
10. Given the evidence of the resistance gene, a mixed infection of MSSA (methicillin-sensitive *S. aureus*) and CoNS (coagulates-negative staphylococci) may exist.

11. If only the resistance gene mecA/mecC is detected, MRSA is not detectable. However, if the resistance gene is detected, there may also be an infection with coagulase negative Staphylococcus since it can also possess the resistance gene mecA/mecC.
12. At a tested concentration of 2.1% and above, ProntOral mouthwash (polyhexanide) shows an inhibitory effect.
13. At a tested concentration of 2.1% and above, Prontoderm nasal gel (polyhexanide) shows an inhibitory effect.
14. At a tested concentration of 1.5% and above, human blood shows an inhibitory effect.
15. As of a tested quantity of 6 mg, COS agar has an inhibitory effect.

13. Performance characteristics

13.1 Analytical sensitivity

The RIDA®GENE MRSA multiplex real-time PCR has a detection limit of ≥ 10 DNA copies/reactions for the SCCmec/orfX junction, the mecA/mecC gene and the SA442 gene (*S. aureus*).
Fig. 4, 5, 6 and 7 below show dilution series of the SCCmec/orfX junction, the mecA/mecC gene and the SA442 gene (*S. aureus*)
(In each case, 10^5 - 10^1 DNA copies/µl) on the LightCycler® 480II.

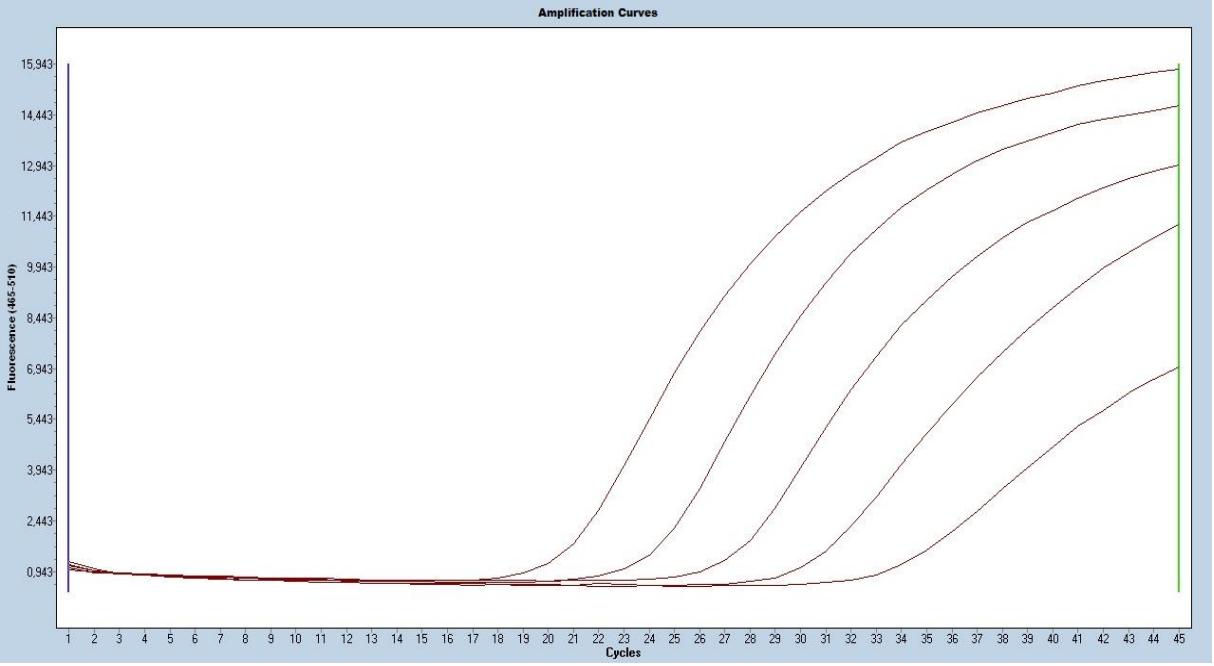

Fig. 4: Dilution series of the SCCmec/orfX junction (10^5 - 10^1 DNA copies/µl) on the LightCycler® 480II

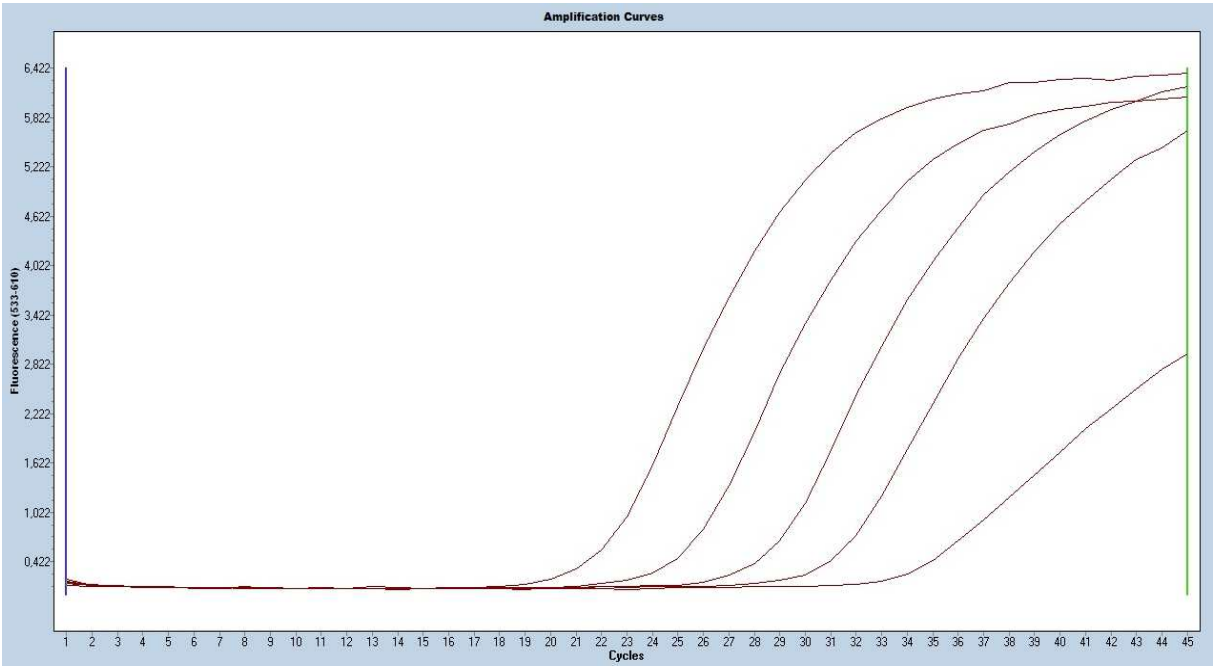

Fig. 5: Dilution series of the SA442 gene specific for *S. aureus* (10^5 - 10^1 DNA copies/µl) on the LightCycler® 480II

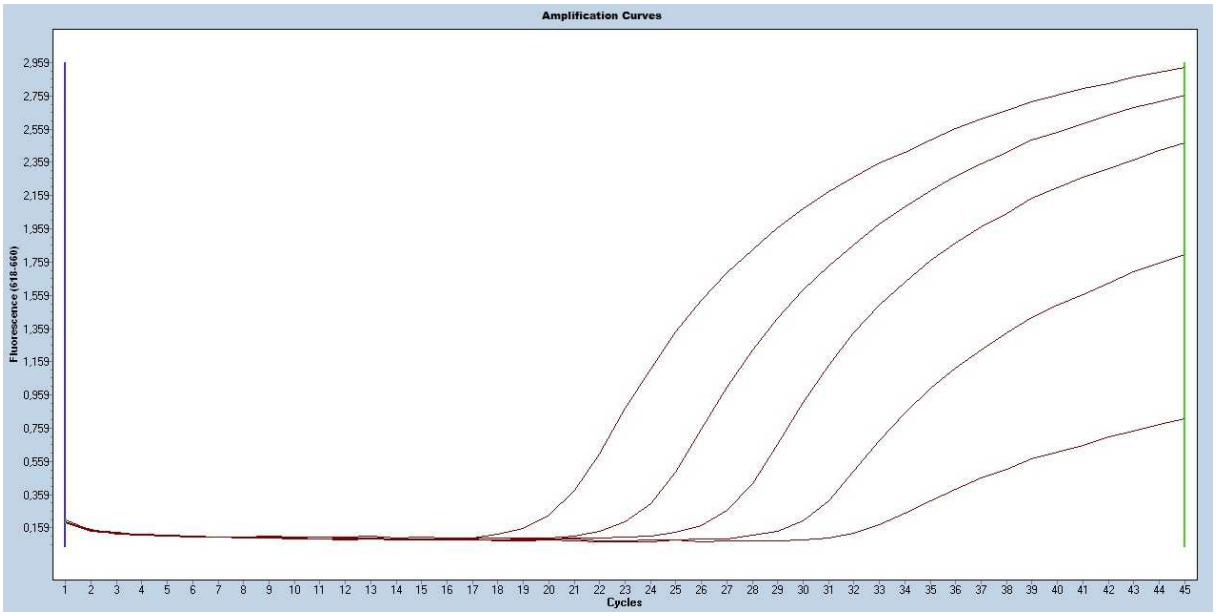

Fig. 6: Dilution series of the mecA/mecC gene (10^5 - 10^1 DNA copies/µl) on the LightCycler® 480II

The limit of detection of the overall process depends on the specimen matrix, the DNA extraction, and the DNA content.

13.2 Analytical specificity

The analytical specificity of the RIDA®GENE MRSA tests were evaluated using a panel of non-staphylococci species, methicillin-sensitive coagulase-negative staphylococci (MSCoNS), and methicillin-resistant coagulase-negative staphylococci (MRCoNS). No cross-reactivities with the following species were detected (see Table 10):

Table 10: Cross-reactivity testing

Non-staphylococci species					
Acinetobacter baumanii	-	*Acinetobacter iwofii*	-	*Aeromonas hydrophila*	-
Aspergillus fumigatus	-	*Aspergillus niger*		*Bacteroides fragilis*	-
Candida albicans	-	*Clostridium difficile*		*Candida glabrata*	-
Clostridium perfringens	-	*E. coli (O157:H7)*	-	*Enterobacter cloacae*	-
Enterococcus faecalis	-	*Enterococcus faecium*	-	*Klebsiella oxytoca*	-
Klebsiella pneumoniae	-	*Pseudomonas aeruginosa*	-	*Proteus vulgaris*	-
Streptococcus agalactiae	-	*Streptococcus mitis*	-	*Streptococcus mutans*	-
Streptococcus pneumoniae	-	*Streptococcus pyogenes*	-		
Methicillin-sensitive coagulase-negative staphylococci					
S. epidermidis	-	*S. hominis*	-	*S. warneri*	-
Methicillin-resistant coagulase-negative staphylococci					
S. haemolyticus	-	*S. epidermidis*	-	*S. saprophyticus*	-

13.3. Interfering substances

The presence of RT-PCR inhibitors and interfering substances can lead to false negative or invalid results. Correspondingly, the effects were investigated of various substances that may exist given their widespread use for respiratory infections, or widespread existence in the corresponding specimens. Inhibitory effects at the tested concentrations were observed (see Limitations of the method) for the substances ProntOral mouthwash (polyhexanide), human blood, Prontoderm nasal gel (polyhexanide) and COS agar. No interference was identified for the other substances listed (Table 11 and Table 12):

Table 11: List of the substances and concentrations used in the test (swab specimens)

Substance/additive	Concentration
RatioAllerg (beclomethasone dipropionate)	10.0% (v/v)
Octenisan nasal gel (octenidine dihydrochloride)	7.0% (w/v)
Mucin	5.0% (v/v)
Acyclovir (ointment)	0.5 % (w/v)
InfectoPyoderm (Mupirocin)	1.80 % (w/v)
Tobramycin	0.0004 % (w/v)
FeniHydrocort (hydrocortisone)	7.0 % (w/v)

Table 12: List of the substances and concentrations used in the test (culture)

Substance/additive	Concentration
MRSA agar	20 mg

14. Version history

Version number	Section and designation
2020-11-17	Previous version
2022-07-21	1. Intended use 6. Reagents required but not provided 9.4 Detection channel setting 10. Quality control
2023-03-21	5. Storage instructions

15. Explanation of symbols

General symbols

IVD	For *in vitro* diagnostic use
	Consult instructions for use
LOT	Lot number
	Use before
	Store at
REF	Item number
Σ	Number of tests
	Date of manufacture
	Manufacturer

Test-specific symbols

Reaction Mix

Taq-Polymerase

Internal Control DNA

PCR Water

Positive Control

Lysis Buffer 1

16. References

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