Cepheid®

Instructions For Use

Xpert® MRSA/SA SSTI

For use with GeneXpert® System with Touchscreen

Catalog Numbers

REF GXMRSA/SA-SSTI-10

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℞only IVD *In Vitro* Diagnostic Medical Device

Trademark, Patents and Copyright Statements

See Revision History for a description of changes.

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Product Information

Proprietary Name

Xpert® MRSA/SA SSTI

Common or Usual Name

Xpert MRSA/SA SSTI test

Intended Use, Summary, and Principle of Procedure

Intended Use

The Xpert MRSA/SA Skin and Soft Tissue Infection test (Xpert MRSA/SA SSTI test) performed in the GeneXpert® Instrument Systems is a qualitative *in vitro* diagnostic test intended for the detection of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) from skin and soft tissue infection swabs. The test utilizes automated real-time polymerase chain reaction (PCR) to detect MRSA/SA DNA. The Xpert MRSA/SA SSTI test is indicated for use in conjunction with other laboratory tests such as microbiology culture, and clinical data available to the clinician as an aid in the detection of MRSA/SA from skin and soft tissue infections. The Xpert MRSA/SA SSTI test is not intended to monitor treatment for MRSA/SA infections. Concomitant cultures for SA and MRSA are necessary to recover organisms for susceptibility testing or epidemiological typing. In a mixed culture containing MRSA/SA and other organisms (e.g. Gram-negative bacilli, yeast), results can be false negative or variable depending on the concentration of MRSA/SA present, particularly if the concentration of MRSA/SA is close to the limit of detection (LoD) of the test.

Summary and Explanation

Staphylococcus aureus (SA) is a well-documented human opportunistic pathogen and a major nosocomial pathogen that causes a range of diseases. Some of the diseases involve the skin and soft tissue infections, including carbuncles and boils, and postoperative wound infections of various sites. As a nosocomial pathogen, *S. aureus* has been a major cause of morbidity and mortality. *S. aureus* infections are often acute

and pyogenic and, if untreated may spread to surrounding tissue or via bacteremia to metastatic sites (involving other organs). Some of the more serious infections produced by *S. aureus* are bacteremia, pneumonia, osteomyelitis, acute endocarditis, toxic shock syndrome, food poisoning, myocarditis, pericarditis, cerebritis, meningitis, chorioamnionitis, scalded skin syndrome, and abscesses of the muscle, urogenital tract, central nervous system, and various intra-abdominal organs. [1]

In the early 1950s, acquisition and spread of beta-lactamase-producing plasmids thwarted the effectiveness of penicillin for treating *S. aureus* infections. In 1959, methicillin, a synthetic penicillin, was introduced. However, by 1960, methicillin-resistant *S. aureus* strains were identified. This was determined to be the result of *S. aureus* acquiring the *mecA* gene. In the U.S. today, MRSA is responsible for approximately 25% of nosocomial infections and reports of community-acquired MRSA are increasing, resulting in significant morbidity and mortality. Attributable mortalities of 33% and 16% have been reported for MRSA and methicillin-sensitive *S. aureus* (SA) bacteremias, respectively. There are also rising cost concerns for MRSA infections. In attempts to limit the spread of these infections, control strategies and policies are being developed and implemented in healthcare settings. Controlling MRSA is a primary focus of most hospital infection control programs. Currently, the standard method for detecting MRSA and SA is culture, which is very laborious and can require several days to generate a definitive result.[2,3,4,5,6,7]

Principle of the Procedure

The GeneXpert Instrument Systems automate and integrate sample purification, nucleic acid amplification, and detection of the target sequences in simple or complex samples using real-time PCR tests. The systems consist of an instrument, personal computer, and preloaded software for running tests and viewing the results. The system requires the use of single-use disposable cartridges that hold the PCR reagents and host the PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the system, see the appropriate system operator manual.

The Xpert MRSA/SA SSTI test includes reagents for the detection of MRSA and SA as well as a sample processing control (SPC) to control for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR reaction. The SPC also ensures the PCR reaction conditions (temperature and time) are appropriate for the amplification reaction and that the PCR reagents are functional. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The primers and probes in the Xpert MRSA/SA SSTI test detect proprietary sequences for the staphylococcal protein A (*spa*), the gene for methicillin resistance (*mecA*), and the staphylococcal cassette chromosome *mec* (SCC*mec*) inserted into the SA chromosomal *attB* site.

Reagents, Instruments, and Materials

Reagents

Material Provided

The Xpert MRSA/SA SSTI kit contains sufficient reagents to process 10 specimens or quality control samples. The kit contains the following:

Xpert MRSA/SA SSTI Cartridges with Integrated Reaction Tubes	**10**
Bead 1, Bead 2, and Bead 3 (freeze-dried)	1 per cartridge
Reagent 1	3.0 mL per cartridge
Reagent 2 (Sodium Hydroxide)	3.0 mL per cartridge
Xpert MRSA/SA SSTI Elution Reagent (Guanidinium thiocyanate)	**10 x 2.0 mL**
CD	**1 per kit**

- Assay Definition File (ADF)
- Instructions to import ADF into GX software
- Instructions for Use (Package Insert)

Note Safety Data Sheets (SDS) are available at www.cepheid.com or www.cepheidinternational.com under the **SUPPORT** tab.

Note The bovine serum albumin (BSA) in the beads within this product was produced and manufactured exclusively from bovine plasma sourced in the United States. No ruminant protein or other animal protein was fed to the animals; the animals passed ante- and post-mortem testing. During processing, there was no mixing of the material with other animal materials.

Materials Required but Not Provided

- GeneXpert system with touchscreen running Cepheid OS software version 2.0 or higher
- Printer: If a printer is required, contact Cepheid Technical Support to arrange for the purchase of a recommended printer.
- Cepheid Sample Collection Device (900-0370) or Copan equivalent
- Vortex mixer
- Disposable transfer pipettes

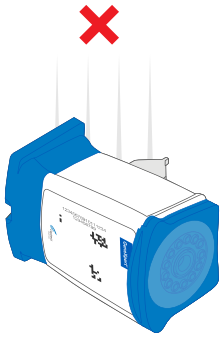
- Sterile Gauze

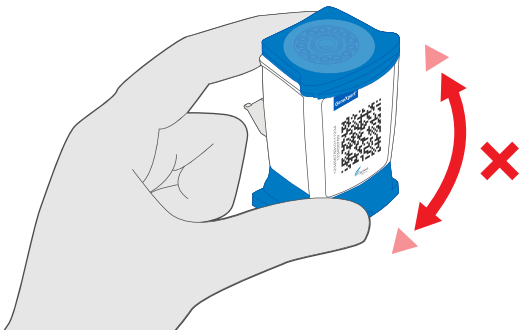
Materials Available but Not Provided

KWIK-STIKs™ from Microbiologics catalog #0158MRSA and catalog #0360MSSA as external positive controls and #0371MSSE (methicillin-susceptible *Staphylococcus epidermidis*) as external negative control.

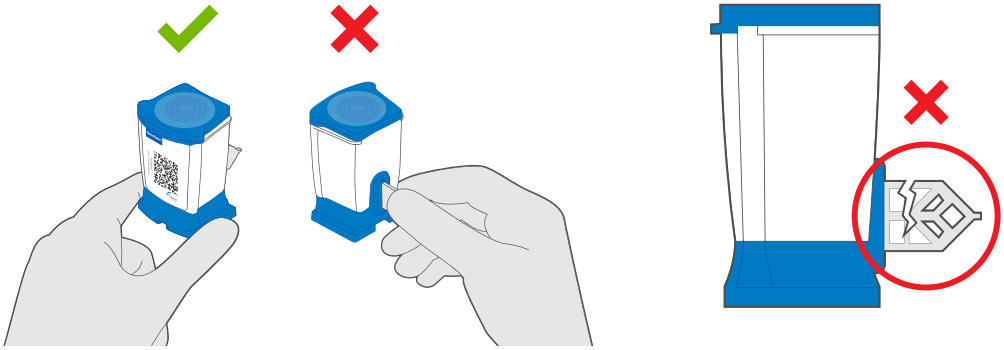
Warnings and Precautions

- For in vitro Diagnostic Use. Rx only
- Treat all biological specimens, including used cartridges, as if capable of transmitting infectious agents. Because it is often impossible to know which might be infectious, all biological specimens should be treated with standard precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention,[8] and the Clinical and Laboratory Standards Institute.[9]
- In a mixed culture containing MRSA/SA and other organisms (e.g., Gram-negative bacilli, yeast), results can be false negative or variable depending on the concentration of MRSA/SA present, particularly if the concentration of MRSA/SA is close to the LoD of the test.
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- The Xpert MRSA/SA SSTI test can detect MRSA and/or SA DNA from non-viable organisms. The probability of this occurring increases for patients on antibiotics.
- The Xpert MRSA/SA SSTI test does not provide antimicrobial susceptibility testing results. Additional time is required to culture and perform susceptibility testing.
- Do not substitute Xpert MRSA/SA SSTI test reagents with other reagents.
- Do not open the Xpert MRSA/SA SSTI test cartridge lid except when adding sample and reagents or performing a retest.
- Do not use a cartridge that has been dropped or shaken after you have added the sample and reagents.





- Hold the cartridge by the base. Do not touch the reaction tube at the rear of the cartridge, as this could cause damage that would interfere with light passing through it during the test. Do not use a cartridge that has a damaged reaction tube.



- Do not place a label on the cartridge lid or barcode label.

- Each single-use Xpert MRSA/SA SSTI test cartridge is used to process one test. Do not reuse spent cartridges.
- Biological specimens, transfer devices, and used cartridges should be considered capable of transmitting infectious agents requiring standard precautions. Follow your institution's environmental waste procedures for proper disposal of used cartridges and unused reagents. These materials may exhibit characteristics of chemical hazardous waste requiring specific national or regional disposal procedure. If national or regional regulations do not provide clear direction on proper disposal biological specimens and used cartridges should be disposed per WHO [World Health Organization] medical waste handling and disposal guidelines.
- Store the Xpert MRSA/SA SSTI test kit at 2 – 28 °C.

Chemical Hazards, Storage and Handling

Chemical Hazards[17, 18]

- UN GHS Hazard Pictogram: 
- Signal Word: WARNING
- **UN GHS Hazard Statements**
  - Harmful if swallowed
  - Causes skin irritation
  - Causes serious eye irritation
- **UN GHS Precautionary Statements**
  - **Prevention**
    - Wash thoroughly after handling.

- Do not eat, drink, or smoke when using this product.
- Avoid release to the environment.
- Wear protective gloves/protective clothing/eye protection/face protection

- **Response**
  - IF ON SKIN: Wash with plenty of soap and water.
  - Take off contaminated clothing and wash before reuse.
  - Specific treatment, see the supplemental first aid information.
  - If skin irritation occurs: Get medical advice/attention.
  - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
  - If eye irritation persist: Get medical advice/attention
  - IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician if you feel unwell.
  - Rinse mouth.
- **Storage Disposal**
  - Dispose of content and/or container in accordance with local, regional, national, and/or international regulations.

Storage and Handling

- Store the Xpert MRSA/SA SSTI cartridges and reagents at 2 – 28°C.
- Do not use reagents or cartridges that have passed the expiration date.
- Do not open a cartridge lid until you are ready to perform testing.
- Do not use any reagents that have become cloudy or discolored.

Specimen Collection, Testing, and Results

Specimen Collection

Specimen Collection, Transport and Storage

Swab specimens of skin and soft tissue infections can be taken with the Cepheid Sample Collection Device following the user institution's standard procedures. The specimen swabs are placed back in the plastic transport tube (liquid Stuarts medium, Cepheid Sample Collection Device or Copan recommended), stored at room temperature, and sent to the GeneXpert testing area for processing within the next day. The remaining untested swab for microbiology culture should be placed in appropriate transport systems and cultured within 4 days. If not sent by the next day, the specimen should be transported on ice. Alternatively, swabs may be stored at 2 – 8 °C for testing up to 5 days.

Microbiology Culture

For SSTI culturing methods, follow current laboratory standard operating procedures. For culturing, remaining untested swab specimens should be placed in appropriate transport systems and cultured within 4 days.

Procedure

Preparing the Cartridge

Important Start the test within 15 minutes of adding the sample to the cartridge.

To add the sample into the cartridge:

1. Remove the cartridge and reagent from the package.
2. Remove the swab from the transport container.
   Note Use sterile gauze to handle swab to minimize risk of contamination.
3. Insert the swab into the tube containing the elution reagent and break the swab.
4. Close the elution vial lid and vortex at high speed for 10 seconds.

5. Open the cartridge lid. Using a sterile transfer pipette, transfer the entire contents of the elution reagent to the sample chamber of the Xpert MRSA/SA SSTI cartridge.
6. Close the cartridge lid.

Figure 1 Xpert MRSA/SA SSTI Cartridge (Top View)

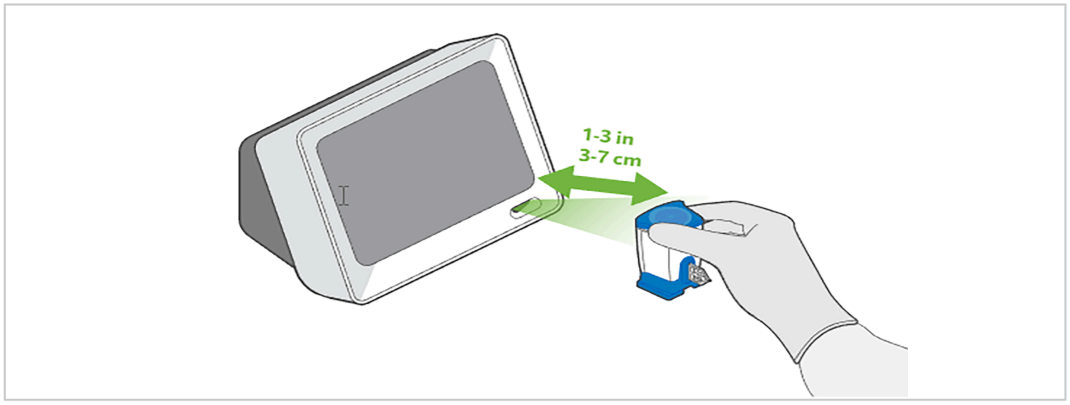
Starting the Test: GeneXpert System with Touchscreen

Important **Before you start the test, make sure that:**

- **The system is running the correct Cepheid OS software version shown in section - Materials Required but Not Provided.**
- **The correct assay definition file is imported into the software.**

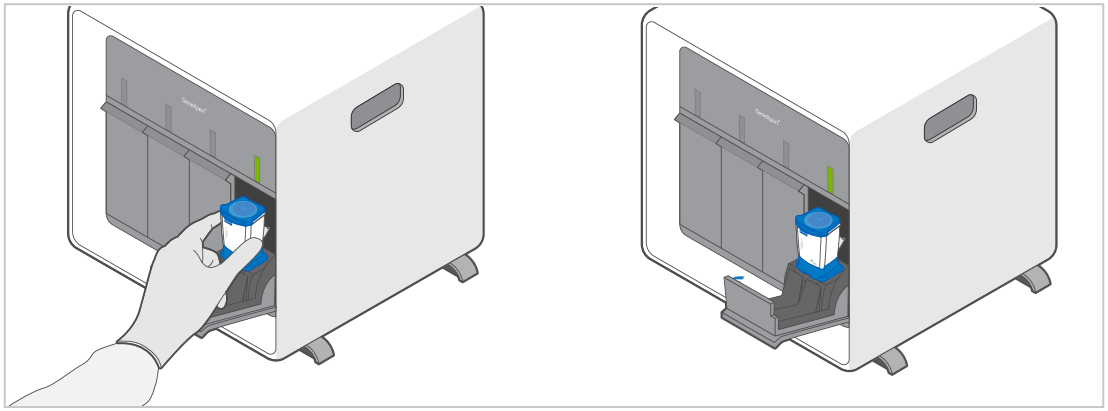
Note The default workflow is shown. Your system administrator may alter the workflow.

1. Turn on GeneXpert system with touchscreen.
2. Log on to system software using your username and password.
3. On the Modules tab, touch **Start Test**.
4. Follow onscreen prompts to create new test and enter patient and sample information.
5. Scan or manually input the cartridge serial number. If scanning, hold the cartridge about 1-3 inches (3-7 cm) away from the scanner. The scanner projects a green crosshair, which you center on the barcode. Scanning is complete when you hear an audible beep. Touch **Continue**.

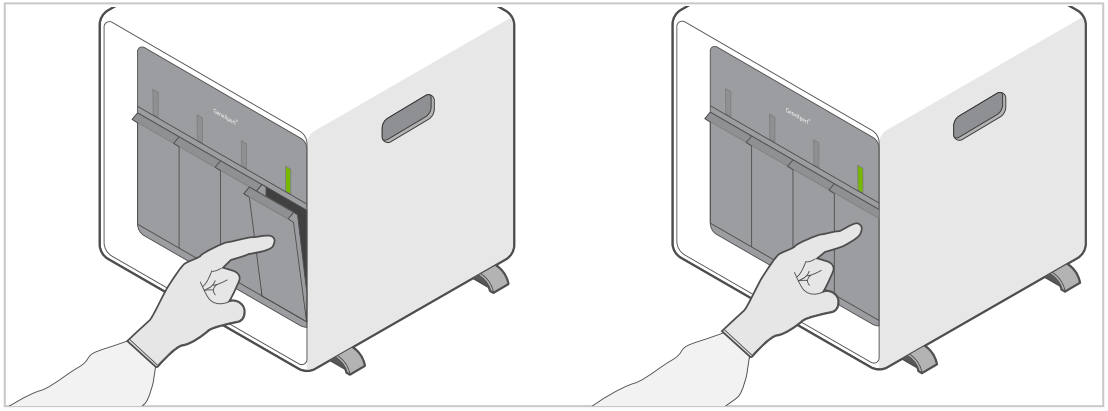


6. Select the desired test and touch **Continue**.
7. Watch the cartridge preparation video, if needed.

8. On the Confirm screen, review all data and touch **Confirm**.
9. Open the module door under flashing green light and insert the cartridge.



10. Close cartridge module door completely by pressing until it latches. The test starts.



11. When the test completes, the **Results Summary** screen appears. Open the module door and remove cartridge.
12. Dispose of used cartridge in appropriate waste container according to your institution's standard practices.

Viewing Results: GeneXpert System with Touchscreen

The GeneXpert system with touchscreen results screen will automatically interpret test results for you and clearly show them in the **View Results** window.

1. Tap **Results**.
2. Tap the test to be viewed in the Results screen.
3. Click **OK**.
4. To generate a PDF report file, touch **View Report**. More detailed instructions for viewing and uploading results are available in your system operator manual.

Quality Control

Built-in Quality Controls

Each test includes a Sample Processing Control (SPC or BG3 in the view result screen for the administrative level user) and Probe Check Control (PCC).

- **Sample Processing Control (SPC)** — Ensures the sample was processed correctly. The SPC is included in each cartridge to verify adequate processing of Xpert MRSA/SA SSTI test sample. The SPC verifies that lysis of *S. aureus* has occurred if the organisms are present and verifies that specimen processing is adequate. Additionally, this control detects specimen-associated inhibition of the real-time PCR test, ensures the PCR reaction conditions (temperature and time) are appropriate for the amplification reaction, and that the PCR reagents are functional. The SPC should be positive in a negative sample and can be negative or positive in a positive sample. The SPC passes if it meets the validated acceptance criteria.
- **Probe Check Control (PCC)** — Before the start of the PCR reaction, the GeneXpert Instrument Systems measure the fluorescence signal from the probes to monitor bead rehydration, reaction-tube filling, probe integrity, and dye stability. Probe Check passes if it meets the assigned acceptance criteria.

External Controls

KWIK-STIKs (Microbiologics, catalog # 0158MRSA [SCC*mec* type II] and catalog #0360MSSA as positive controls and#0371MSSE as negative control) may be used for training, proficiency testing, and external QC of the GeneXpert Instrument Systems. MRSA strains representing other SCC*mec* types, if available, may be used as additional external positive controls to monitor test primers and probes not directly controlled in the test. External controls may be used in accordance with accrediting institutions and government regulations, as applicable. Follow the Microbiologics external control procedure described below:

1. Tear open the pouch at notch and remove the KWIK-STIK.
2. Pinch the bottom of the ampoule in the cap to release the hydrating fluid.
3. Hold vertically and tap to facilitate flow of fluid through shaft into bottom of unit containing pellet.
4. To facilitate dissolution of the lyophilized cell pellet, crush the pellet and gently pinch the bottom chamber.
5. Pull apart the KWIK-STIK to release the swab, and insert the swab into the tube containing the elution reagent (screw cap).
6. The KWIK-STIK swab is now ready for Xpert MRSA/SA SSTI testing.
7. If the External QC fails to perform as expected, repeat external control test and/or contact Cepheid for assistance.

Results

The results are interpolated by the GeneXpert Instrument Systems from measured fluorescent signals and embedded calculation algorithms and will be shown in the View Results window. Possible results are:

Table 1. Xpert MRSA/SA Results and Interpretation

Result	Interpretation
MRSA POSITIVE/ SA POSITIVE	The Xpert MRSA/SA SSTI test can detect MRSA and/or SA DNA from non-viable organisms. MRSA target DNA sequences are detected/SA target DNA sequence is detected. • MRSA POSITIVE - all MRSA targets (*spa*, *mecA*, and SCC*mec*) have a cycle threshold (Ct) within the valid range and an endpoint above the minimum setting. • SPC — NA (not applicable); SPC is ignored because MRSA amplification may compete with this control. • Probe Check — PASS; all probe check results pass.
MRSA NEGATIVE/ SA POSITIVE	The Xpert MRSA/SA test can detect MRSA and/or SA DNA from non-viable organisms. MRSA target DNA sequences are not detected/SA target DNA sequence is detected. • SA POSITIVE — the SA target (*spa*) has a Ct within the valid range and an endpoint above the minimum setting. Target DNA for SCC*mec* is not detected, target DNA for *mecA* may or may not be detected, or target DNA for SCC*mec* is detected and target DNA for *mecA* is not detected ("empty cassette"). • SPC — NA (not applicable); SPC is ignored because SA amplification may compete with this control. • Probe Check — PASS; all probe check results pass. A Positive test result does not necessarily indicate the presence of viable organisms. It is, however, presumptive for the presence of SA.
MRSA NEGATIVE/ SA NEGATIVE	*Staphylococcus aureus* target DNA sequence is not detected. SPC meets acceptance criteria. • NEGATIVE — the *Staphylococcus aureus* target (*spa*) DNA is not detected. Target DNA for *mecA* may or may not be detected, or target DNA for SCC*mec* may or may not be detected. • SPC — PASS; SPC has a Ct within the valid range and endpoint above the endpoint minimum setting. • Probe Check — PASS; all probe check results pass. A False Negative for MRSA (a result of **MRSA NEGATIVE; SA POSITIVE** instead of **MRSA POSITIVE; SA POSITIVE)** could be obtained if both MRSA and SA are present in the sample at an MRSA:SA ratio of 1:1x10^{6} or greater. In the clinical studies, 5 of the 246 MRSA positive cultures had mixed infections of MRSA and SA. Xpert MRSA/SA SSTI identified 3 of the 5 mixed infections as MRSA-positive and 2 of the 5 as SA-positive/MRSA-negative.
INVALID	Presence or absence of MRSA/SA target DNA sequences cannot be determined, repeat test according to instructions in the section below. SPC does not meet acceptance criteria, the sample was not properly processed, or PCR was inhibited. • INVALID — Presence or absence of *Staphylococcus aureus* DNA cannot be determined. • SPC-FAIL — SPC target result is negative and the SPC Ct is not within valid range and endpoint below minimum setting. • Probe Check — PASS; all probe check results pass.

Result	Interpretation
ERROR	Presence or absence of MRSA/SA target DNA sequences cannot be determined, repeat test according to instructions in the section below. The Probe Check Control failed, which is probably due to an improperly filled reaction tube, a probe integrity problem, or because the maximum pressure limits were exceeded. • MRSA — NO RESULT • SA — NO RESULT • SPC — NO RESULT • Probe Check — FAIL*; one or more of the probe check results fail. * If the probe check passed, the error is caused by a system component failure.
NO RESULT	Presence or absence of MRSA/SA target DNA sequences cannot be determined, repeat test according to instructions in the section below. Insufficient data were collected to produce a test result. For example, this can occur if the operator stopped a test that was in progress. • MRSA — NO RESULT • SA — NO RESULT • SPC — NO RESULT • Probe Check — NA (not applicable)

Reasons to Repeat the Test

Repeat the test using a new cartridge (do not re-use the cartridge) and new reagents. Perform the retest procedure within 3 hours of an indeterminate result.

- An **INVALID** result indicates that the control SPC failed. The sample was not properly processed or PCR was inhibited.
- An **ERROR** result indicates that the Probe Check Control failed and the test was aborted possibly due to the reaction tube being filled improperly, a reagent probe integrity problem was detected, or because the maximum pressure limits were exceeded.
- A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress.
- If an External QC fails to perform as expected, repeat external control test and/or contact Cepheid for assistance.

Retest Procedure

To perform a retest:

If retesting within 3 hours of an indeterminate result*:

1. Transfer remaining contents from the sample chamber to a new elution reagent using a disposable transfer pipette.
2. Vortex and add the entire contents of the elution reagent to the sample chamber of the new MRSA/SA SSTI cartridge.
3. Close the lid and start new test.
   *If the retest cannot be performed within 3 hours, use a new sample.

Limitations

Limitations of the Procedure

- The performance of the Xpert MRSA/SA SSTI test was validated using the procedures provided in this IFU only. Modifications to these procedures may alter the performance of the test. Results from the Xpert MRSA/SA SSTI test should be interpreted in conjunction with other laboratory and clinical data available to the clinician.
- The Xpert MRSA/SA SSTI test can detect MRSA and/or SA DNA from non-viable organisms. The probability of this occurring increases for patients on antibiotics. In the pivotal clinical study the false positive rate (relative to culture) of detecting SA in patents using antibiotics, within 3 weeks prior to Xpert MRSA/SA testing, was 13.8%. The false positive rate (relative to culture) of detecting MRSA in patients using antibiotics, within 3 weeks prior to Xpert MRSA/SA testing, was 9.5%.
- A positive test result does not necessarily indicate the presence of viable organisms. It is, however, presumptive for the presence of MRSA or SA.
- Testing with the Xpert MRSA/SA SSTI test should be used as an adjunct to other methods available.
- Erroneous test results might occur from improper specimen collection, failure to follow the recommended sample collection, handling and storage procedures, technical error, sample mix-up, or because the number of organisms in the specimen is too low to be detected by the test. Careful compliance with the instructions in this insert is necessary to avoid erroneous results.
- Because the detection of MRSA and SA is dependent on the number of organisms present in the sample, reliable results are dependent on proper specimen collection, handling, and storage.
- Mutations or polymorphisms in primer or probe binding regions may affect detection of new or unknown MRSA variants resulting in a false negative result.
- In samples containing both MRSA and SA, the Xpert MRSA/SA SSTI test may not detect the methicillin-resistant SA organisms. (In the pivotal clinical trial, the Xpert MRSA/SA SSTI test failed to detect 2 of 5 MRSA culture positive samples in situations with documented MRSA/SA mixed infections.)
- In a mixed culture, the analytical LoD of MRSA is variable when extremely high concentrations of SA are present. Competition from SA was observed at an MRSA:SA ratio of $1:1x10^{6}$. In the Clinical studies, 5 of the 246 MRSA positive cultures had mixed infections of MRSA and SA. Xpert MRSA/SA SSTI identified 3 of the 5 mixed infections as MRSA positive and 2 of the 5 as SA positive/MRSA negative.
- Inhibition of the MRSA/SA SSTI test has been observed with the following substances: StaphA ⁺Septic (5% w/v), Hydrocortisone (5% w/v), and antibacterial hand sanitizer (5% w/v).
- Samples containing Mercurochrome may not be used due to its fluorescent nature.
- The Xpert MRSA/SA SSTI test will generate a false positive MRSA result when testing a mixed infection SSTI specimen containing both methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) and empty cassette methicillin-sensitive *Staphylococcus aureus* (SA).

Expected Values

In the Xpert MRSA/SA SSTI clinical study, a total of 848 SSTI specimens were included from four large hospitals across the United States. The number and percentage of positive cases by the reference culture method, calculated by age group, are presented in Table 2.

Table 2. Observed Prevalence of MRSA and SA by Culture

Age Group	Total N	MRSA By Culture		SA By Culture	
		Number Positive	Observed Prevalence	Number Positive	Observed Prevalence
Ages Less Than 3	34	11	32.4%	21	61.8%
Ages 3 to 18	100	25	25.0%	55	55.0%
Ages 19 to 65	614	188	30.6%	300	48.9%
Ages 66 and over	100	22	22.0%	35	35.0%

Specific Performance Characteristics

Clinical Performance

Performance characteristics of the Xpert MRSA/SA SSTI test were determined in a multi-site prospective investigation study at four US institutions by comparing the Xpert MRSA/SA SSTI test with reference culture. Subjects included individuals whose routine care called for collection of a swab from the patient's skin and soft tissue infection for culture.

Double swabs were collected from each subject. One swab was tested by the Xpert MRSA/SA SSTI test at the enrolling center and the other swab was tested by the site's standard method, and the remaining specimen was sent to the central laboratory for reference culture testing.

At the centralized laboratory, the specimen was enriched overnight in trypticase soy broth with 6.5% NaCl. The trypticase soy broth was then streaked onto plates with cefoxitin (for MRSA) and without cefoxitin (for SA). If either or both the SA or MRSA plates showed *S. aureus* presumptive colonies, the colonies were subcultured onto a blood agar plate. Confirmation of presumptive positive colonies was performed with catalase, tube coagulase, and Gram stain. *MecA*-mediated oxacillin resistance was tested by disk diffusion test using a 30 µg cefoxitin disk and cutoff of 21/22 mm. If the cultures for both the SA and MRSA plates were determined to be negative, the archived trypticase soy broth with 6.5% NaCl was subcultured onto blood agar followed by workup for SA/MRSA as previously described.

Performance of the Xpert MRSA/SA SSTI test was calculated relative to the reference culture results.

A total of 848 specimens were tested for MRSA and SA by Xpert MRSA/SA SSTI test and culture.

Among the 848 cases in the eligible data set, antibiotic use within the 3 weeks prior to sample collection was reported for 207 subjects, and no antibiotic use was confirmed for 441 subjects; for 200 cases, antibiotic use status was unknown. A statistically significant decrease in the positivity rate of SA with respect to culture results was observed when antibiotics were used (p=0.007); this phenomenon has also been reported in the literature.[10,11,12,13,14] The MRSA positivity rate for culture was also decreased, although to a lesser extent (p=0.022). The decrease in positivity was not observed with the Xpert MRSA/SA SSTI test when antibiotics were used nor was any inhibition observed in the test in the presence of topical antibiotics (see Interfering Substances). The decreased culture positivity rates for MRSA and SA in the presence of antibiotics caused the higher than expected false positive rates observed with the Xpert MRSA/SA SSTI test.

Five (5) of the 246 MRSA positive cultures had mixed infections of MRSA and SA. Xpert MRSA/SA SSTI identified 3 of the 5 mixed infections as MRSA-positive and 2 of the 5 as SA positive/MRSA negative.

The performance of the Xpert MRSA/SA SSTI test is summarized in Table 3 through Table 5.

Table 3. MRSA/SA Performance in Subjects with No Antibiotic Use (within 3 Weeks of Sample Collection) vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	137[a]	2	6	145
	SA+/MRSA-	3[b]	79	16	98
	SA-	6	4	188	198
	Total	146	85	210	441

a. 1 of the 137 was mixed infection of MRSA and SA.

b. 2 of the 3 were mixed infections of MRSA and SA.

Positive Percent Agreement (MRSA+) = 93.8; 95% Confidence Interval = 88.6-97.1

Negative Percent Agreement (MRSA+) = 97.3; 95% Confidence Interval = 94.7-98.8

Positive Percent Agreement (SA+/MRSA+) = 95.7; 95% Confidence Interval = 92.2-97.9

Negative Percent Agreement (SA+/MRSA+) = 89.5; 95% Confidence Interval = 84.6-93.3

Among subjects with no antibiotic use within the 3 weeks prior to sample collection, the Xpert MRSA/SA SSTI test identified 93.8% of the specimens positive for MRSA and 97.3% of the specimens negative for MRSA relative to the reference culture method, and 95.7% of the specimens positive for SA and 89.5% of the specimens negative for SA relative to the reference culture method.

Among these subjects with no antibiotic use, 96.8% (427/441) were successful on the first attempt with the Xpert MRSA/SA SSTI test. The remaining 14 gave indeterminate results on the first attempt (6 **INVALID**, 7 **ERROR** and 1 **NO RESULT**). Of the 14 indeterminate on the first attempt, all gave a result on the second attempt.

Table 4. MRSA/SA Performance in Subjects with Unknown Antibiotic Use (within 3 Weeks of Sample Collection) vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	47[a]	0	4	51
	SA+/MRSA-	2	45	8	55
	SA-	1	2	91	94
	Total	50	47	103	200

a. 2 of 47 were mixed infections of MRSA and SA.

Positive Percent Agreement (MRSA+) = 94.0; 95% Confidence Interval = 83.5-98.7

Negative Percent Agreement (MRSA+) = 97.3; 95% Confidence Interval = 93.3-99.3

Positive Percent Agreement (SA+/MRSA+) = 96.9; 95% Confidence Interval = 91.2-99.4

Negative Percent Agreement (SA+/MRSA+) = 88.3; 95% Confidence Interval = 80.5-93.8

When it was unknown if subjects took antibiotics within the 3 weeks prior to sample collection, the Xpert MRSA/SA SSTI test identified 94.0% of the specimens positive for MRSA and 97.3% of the specimens negative

for MRSA relative to the reference culture method, and 96.9% of the specimens positive for SA and 88.3% of the specimens negative for SA relative to the reference culture method.

Among these subjects with unknown antibiotic use, 97.0% (194/200) were successful on the first attempt with the Xpert MRSA/SA SSTI test. The remaining 6 gave indeterminate results on the first attempt (2 **INVALID**, 3 **ERROR** and 1 **NO RESULT**). Of the 6 indeterminate on the first attempt, all gave a result on the second attempt.

Table 5. MRSA/SA Performance in Subjects with Known Antibiotic Use (within 3 Weeks of Sample Collection) vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	44	2	10	56
	SA+/MRSA-	3	31	19	53
	SA-	3	1	94	98
	Total	50	34	123	207

Positive Percent Agreement (MRSA+) = 88.0; 95% Confidence Interval = 75.7-95.5

Negative Percent Agreement (MRSA+) = 92.4; 95% Confidence Interval = 87.0-96.0

Positive Percent Agreement (SA+/MRSA+) = 95.2; 95% Confidence Interval = 88.3-98.7

Negative Percent Agreement (SA+/MRSA+) = 76.4; 95% Confidence Interval = 67.9-83.6

Among subjects with known antibiotic use within the 3 weeks prior to sample collection, the Xpert MRSA/SA SSTI test identified 88.0% of the specimens positive for MRSA and 92.4% of the specimens negative for MRSA relative to the reference culture method, and 95.2% of the specimens positive for SA and 76.4% of the specimens negative for SA relative to the reference culture method.

Among these subjects with antibiotic use, 96.1% (199/207) of these eligible specimens were successful on the first attempt with the Xpert MRSA/SA SSTI test. The remaining 8 gave indeterminate results on the first attempt (5 **INVALID** and 3 **ERROR**). Of the 8 indeterminate on the first attempt, all gave a result on the second attempt.

Empty Cassette Variants

For an isolate to be identified as MRSA-positive with the Xpert MRSA/SA SSTI test, the test for *spa* must be positive as well as the tests for *mecA* and *SCCmec*. An isolate that is positive for *spa* and SCC*mec*, but not *mecA* is reported as SA because it will be methicillin-sensitive. This situation can occur when the portion of the SCC*mec* element carrying *mecA* is excised, but the ends of this mobile element remain in place, yielding a positive SCC*mec* signal. These isolates are sometimes referred to as “empty cassette variants” and are not uncommon in the clinical environment. The significance of these isolates is to potentially confound a test for MRSA that does not detect the *mecA* gene directly. The Xpert MRSA/SA SSTI test was designed to identify these variants correctly as SA.

Among the eligible specimens included in the data analyses presented in this report, a total of 16 isolates fit the empty cassette profile resulting in positive *spa* and SCC*mec* test results, but no *mecA* detection (Ct = 0) as shown in Table 6. Fifteen (15) of the 16 were verified as MRSA true-negative isolates relative to culture, and 14 of 16 were verified as true positive SA isolates relative to culture. One isolate was identified as MRSA by culture and 2 isolates were both MRSA and SA-negative by culture.

Table 6. MRSA/SA SSTI Performance vs. Reference Culture — Empty Cassette Variants

						Xpert vs. Culture	
Subject #	Xpert Result	spa (Ct)	mecA (Ct)	SCCmec (Ct)	Culture	MRSA	SA
1	SA	23.6	0	26.0	SA	TN	TP
2	SA	14.7	0	16.5	SA	TN	TP
3	SA	20.5	0	34.0	SA	TN	TP
4	SA	18.4	0	21.0	SA	TN	TP
5	SA	15.6	0	28.4	MRSA	FN	TP
6	SA	17.2	0	31.6	SA	TN	TP
7	SA	34.1	0	35.6	Neg	TN	FP
8	SA	29.1	0	33.0	SA	TN	TP
9	SA	12.7	0	23.5	SA	TN	TP
10	SA	18.2	0	27.6	SA	TN	TP
11	SA	18.4	0	22.0	SA	TN	TP
12	SA	25.5	0	27.7	SA	TN	TP
13	SA	20.0	0	22.1	Neg	TN	FP
14	SA	26.0	0	28.3	SA	TN	TP
15	SA	23.9	0	25.7	SA	TN	TP
16	SA	19.9	0	34.0	SA	TN	TP

Analytical Performance

Analytical Sensitivity

Limit of Detection Studies

Studies were performed to determine the 95% confidence intervals for the analytical limit of detection (LoD) of *Staphylococcus aureus* (SA) cells and methicillin-resistant *Staphylococcus aureus* (MRSA) cells diluted into a surrogate wound matrix of human origin. The surrogate wound matrix consisted of a white blood cell (WBC) concentrate prepared from whole blood by centrifugation. The matrix also contained red blood cells (RBC) and plasma, and a negligible amount of anticoagulant (CPD or CPDA-1). The limit of detection is defined as the lowest number of colony forming units (CFU) per sample that can be reproducibly distinguished from negative samples with 95% confidence or the lowest concentration at which 19 of 20 replicates were positive.

For MRSA, replicates of 20 were evaluated at each MRSA concentration tested (CFU/swab) for 6 individual isolates representing SCC*mec* types I, II, III, IVa, V, and VI. When characterized by pulsed-field gel electrophoresis (PFGE), USA100, the most common healthcare-acquired strain and USA400, one of the most common community-acquired strains were represented.

For SA, replicates of 20 were evaluated at each SA concentration (CFU/swab) for 3 individual SA isolates. USA types USA900 and USA1200 were represented.

The estimate and confidence intervals were determined using logistic regression with data (number of positive results per number of replicates at each level) over the range of CFU/swab tested. The confidence intervals were determined using maximum likelihood estimates on the logistic model parameters using the

large sample variance-covariance matrix. The LoD point estimates and 95% upper and lower confidence intervals for each SA and each MRSA SCC*mec* type tested are summarized in Table 7 and Table 8.

Table 7. 95% Confidence Intervals for Analytical LoD — SA

SA Strain ID	PFGE	LoD (CFU/swab)	Lower 95% CI	Upper 95% CI
N7129	USA900	51	42	69
102-04	USA1200	87	76	109
29213	unknown	123	97	188

Table 8. 95% Confidence Intervals for Analytical LoD — MRSA

MRSA Strain ID	SCCmec Type	PFGE	LoD (CFU/swab)	Lower 95% CI	Upper 95% CI
64/4176	I	USA500	221	195	271
N315	II	USA100	122	106	152
11373	III	unknown	124	115	155
MW2	IVa	USA400	82	68	113
ST59-MRSA-V	V	USA1000	242	208	305
HDE288	VI	USA800	183	161	223

The results of this study indicate that the Xpert MRSA/SA SSTI test will produce a positive SA result 95% of the time with 95% confidence for a wound swab containing 150 CFU and a positive MRSA result 95% of the time with 95% confidence for a wound swab containing 300 CFU.

One hundred twenty-one (121) additional *Staphylococcus aureus* strains were tested using the Xpert MRSA/SA SSTI test. Overnight cultures were grown in Brain Heart Infusion (BHI) media and adjusted to 0.5 McFarland units. All strains were tested in triplicate using 100 µL of cultures further diluted 100 thousand to one million-fold.

MRSA (78) and SA (43) strains were selected to broadly represent the range of genetic diversity found in the species *Staphylococcus aureus* based on phylogenetic structure. Selections represent primary lineages with emphasis on specific clonal complexes within which MRSA is predominantly observed. Lineages that contain MRSA and SA, as well as those that contain SA exclusively were included.

The Xpert MRSA/SA SSTI test correctly identified 116 of 121 strains. The 5 discordants were characterized by catalase, tube coagulase, and Gram stain. Detection of *mecA*-mediated oxacillin resistance was assessed by disk diffusion using a 30 µg cefoxitin disk and a diameter cut-off of 21/22 mm.

Three (3) of 78 MRSA strains were reported MRSA-negative/SA-positive using the Xpert MRSA/SA SSTI test. Further characterization indicates these strains were not resistant and were correctly reported MRSA-negative; SA-positive.

Two (2) of 43 SA strains were reported as MRSA-positive/SA-positive using the Xpert MRSA/SA SSTI test. Further characterization indicates these strains are resistant and were correctly reported MRSA-positive/SA-positive.

Each of the 12 known USA300 isolates were correctly reported MRSA-positive and SA-positive as expected.

Analytical Specificity

Cross-reactivity Study

One hundred five (105) strains were collected, quantitated, and tested using the Xpert MRSA/SA SSTI test. The 98 cultures from the American Type Culture Collection (ATCC) and 7 strains from the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) represent species phylogenetically related to *Staphylococcus aureus* or those potentially encountered in a hospital environment.

Of these, methicillin-sensitive coagulase-negative staphylococci (29) and methicillin-resistant coagulase-negative staphylococci (9) were included. The organisms tested were identified as either Gram-positive (74), Gram-negative (28), or yeast (3). The organisms were further classified as either aerobic (95) or anaerobic (10).

Two (2) or more replicates of each isolate were tested at 1.7-3.2 McFarland units. Under the conditions of the study, all isolates were reported MRSA-negative and SA-negative; none of the isolates were detected by the Xpert MRSA/SA SSTI test. Positive and negative controls were included in the study. The analytical specificity was 100%.

Evaluation of BORSA Strains

Seven (7) well-characterized borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) strains were tested, including one apparent "empty cassette" (see above). Methicillin-resistant *Staphylococcus aureus* is resistant to all ß-lactam drugs through the alternative penicillin-binding protein PBP2a encoded by *mecA* [15] . BORSA strains are *mecA*-negative, but exhibit an oxacillin minimum inhibitory concentration (MIC) ≥ 2 and ≤ 8 µg/mL. It is especially valuable to distinguish MRSA from BORSA to prevent the unnecessary and inappropriate use of vancomycin and isolation precautions not warranted for patients infected with a ß-lactam-susceptible strain[16] .

Under the conditions of this study, all 7 BORSA isolates (including the apparent "empty cassette" isolate) were reported as MRSA-negative/SA-positive at both high and low cell concentrations using the Xpert MRSA/SA SSTI test. No *mecA* signals were reported. These results demonstrate that a BORSA strain will be correctly identified as MRSA-negative/SA-positive and will not report a false positive MRSA test result using the Xpert MRSA/SA SSTI test.

Interfering Substances

In the investigational study for Xpert MRSA/SA SSTI test, 428 of the 848 specimens were observed to contain blood, and 404 were observed to contain other non-specific substances, which could potentially interfere with the test (note that some specimens contained more than one type of potential contaminant). Fisher's exact tests conducted on the data generated from swabs with and without these potential interfering substances demonstrated that their presence did not affect the test performance.

In a non-clinical study, potential interfering substances that may be present in clinical skin and soft tissue infection specimens were evaluated directly relative to the performance of the Xpert MRSA/SA SSTI test. Potential interfering substances in skin and soft tissue infections may include, but are not limited to: blood, pus, plasma, topical ointments (antibiotic/antiseptic/pain relieving), debriding agents, and tinctures. These substances are listed in Table 9 and Table 10 with the active ingredients and concentrations tested shown. Inhibition of the MRSA/SA SSTI test has been observed with the following substances: StaphA *Septic (5% w/v), Hydrocortisone (5% w/v), and antibacterial hand sanitizer (5% w/v).

Samples containing Mercurochrome may not be used due to its fluorescent nature.

Table 9. Potential Interfering SSTI Substances Tested

Substance	Active Ingredient	% Tested
TET Buffer (control)	Control	Control
Buffy Coat (wound surrogate)	WBC ($1.5e^{9}$/mL)	50% (v/v)
Whole Blood (MRSA/SA free)	N/A	50% (v/v)

Substance	Active Ingredient	% Tested
Plasma	N/A	50% (v/v)
Neosporin	400 units Bacitracin 5,000 units Polymyxin B 3.5 mg Neomycin	1% and 5% (w/v)
StaphA⁺Septic	0.2% Benzethonium Chloride, 2.5% Lidocaine HCl	1% and 5% (w/v)
Hydrocortisone	1% Hydrocortisone	1% and 5% (w/v)
Boil-Ease	20% Benzocaine	1% and 5% (w/v)
Iodine Tincture	2% Iodine	50% (v/v)

Table 10. Potential Interfering SSTI Substances Tested

Substance	Active Ingredient	% Tested
TET Buffer (control)	Control	Control
Mupirocin	0.2% Benzethonium Chloride 2.5% Lidocaine HCl	5% (w/v)
Whole Blood (MRSA/SA free)	N/A	50% (v/v)
Saline	0.65% Sodium Chloride	50% (v/v)
Antibacterial hand sanitizer	62% Ethyl alcohol	1% and 5% (w/v)
70% Isopropyl alcohol	70% Isopropyl alcohol	50% (v/v)

Evaluation of Empty Cassette Variants

Twenty-two (22) *Staphylococcus aureus* isolates identified as "empty cassette variants" were tested using the Xpert MRSA/SA SSTI test. Overnight cultures were adjusted to 0.5 McFarland units. All strains were tested from cultures further diluted 100-fold (high) and 100 thousand-fold (low).

The Xpert MRSA/SA SSTI test correctly identified all 22 isolates as MRSA-negative and SA-positive. At both cell concentrations tested, only Cts for the *spa* and SCC*mec* targets were reported. No *mecA* Cts were reported.

Carry-Over Contamination Study

A study was conducted to demonstrate that single-use, self-contained GeneXpert cartridges prevent carry-over contamination in negative samples run following very high positive samples in the same GeneXpert module. The study consisted of a negative sample processed in the same GeneXpert module immediately following a very high MRSA-positive sample (roughly 10^7 CFU/test). This was repeated 20 times between 2 GeneXpert modules for a total of 42 runs. There was no evidence of any carry-over contamination. All 21 positive samples were correctly reported MRSA-positive/SA-positive. All 21 negative samples were correctly reported MRSA-negative/SA-negative.

Reproducibility

A panel of 10 specimens with varying concentrations of SA, MRSA, and *Staphylococcus epidermidis* (negative) were tested in duplicate on 10 different days at each of the three sites (10 specimens x 2 times/day x 10 days x 3 sites). One lot of Xpert MRSA/SA kit was used at each of the 3 testing sites. Xpert MRSA/SA tests were performed according to the Xpert MRSA/SA SSTI test procedure.

Table 11. Summary of Reproducibility Results

Specimen ID	Site 1	Site 2	Site 3	Total Agreement
Neg (MSSE)	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
SA High Neg	100% (20/20)	100% (20/20)	90% (18/20)	96.7% (58/60)
SA Low Pos	100% (20/20)	100% (20/20)	95% (19/20)	98.3% (59/60)
MRSA1 High Neg	100% (20/20)	90% (18/20)	100% (20/20)	96.6% (58/60)
MRSA1 Low Pos	100% (20/20)	100% (20/20)	90% (18/20)	96.6% (58/60)
MRSA2 High Neg	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA2 Low Pos	100% (20/20)	95% (19/20)	95% (19/20)	96.6% (58/60)
% Total Agreement by Site	100% (140/140)	97.9% (137/140)	95.7% (134/140)	97.9% (411/420)

SPC			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 High Neg	34.52	0.82	2.36
MRSA2 High Neg	34.46	0.85	2.46
Neg (MSSE)	34.44	0.90	2.62
SA High Neg	34.38	0.92	2.66
Spa			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Low Pos	32.96	0.8	2.44
MRSA2 Low Pos	31.05	0.69	2.21
SA Low Pos	33.91	0.8	2.35
mecA			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Low Pos	33.25	0.80	2.40
MRSA2 Low Pos	31.50	0.68	2.16
SCCmec			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Low Pos	34.19	0.90	2.63
MRSA2 Low Pos	33.13	0.68	2.05

A second reproducibility study was performed using a panel of 4 specimens of (SA: 10X LoD, MRSA1: 10X LoD, MRSA2: 10X LoD, and Negative Control: *Staphylococcus epidermidis*). The panels were tested in duplicate on 10 different days at each of the three sites (4 specimens x 2 times/day x 10 days x 3 sites). One lot of Xpert MRSA/SA SSTI test was used at each of the 3 testing sites. Xpert MRSA/SA SSTI tests were performed according to the Xpert MRSA/SA SSTI test procedure. The correct results were obtained in 239 of 240 tests.

Table 12. Summary of Reproducibility Results

Specimen ID	Site 1	Site 2	Site 3	Total Agreement
Neg (MSSE)	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
SA Moderate Pos[a]	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)

Specimen ID	Site 1	Site 2	Site 3	Total Agreement
MRSA1 Moderate Pos[1]	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA2 Moderate Pos[1]	100% (20/20)	100% (20/20)	95% (19/20)	98.3% (59/60)
% Total Agreement by Site	100% (80/80)	100% (80/80)	98.8% (79/80)	99.6% (239/240)

a. 10X LoD

SPC			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Moderate Pos	35.72	1.87	5.24
MRSA2 Moderate Pos	36.29	2.66	7.34
SA Moderate Pos	34.55	1.19	3.44
NEG	34.45	1.06	3.09
Spa			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Moderate Pos	29.52	1.30	4.40
MRSA2 Moderate Pos	28.91	1.03	3.57
SA Moderate Pos	30.59	0.91	2.99
mecA			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Moderate Pos	29.78	1.28	4.29
MRSA2 Moderate Pos	29.32	1.24	4.22
SCCmec			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Moderate Pos	31.49	1.26	3.99
MRSA2 Moderate Pos	31.05	1.12	3.59

Appendix

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Table of Symbols

Symbol	Meaning
REF	Catalog number
IVD	*In vitro* diagnostic medical device
	Do not reuse
LOT	Batch code
	Consult instructions for use
	Caution
	Manufacturer
CC	Country of manufacture
Σ	Contains sufficient for *n* tests
CONTROL	Control
	Expiration date
	Temperature limitation
	Biological risks
Rx only	For prescription use only

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Revision History

Description of Changes: 303-0934 Rev. A

Purpose: Initial release