GeneXpert
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Xpert® SA Nasal Complete

REF **GXSACOMP-10**

In Vitro Diagnostic Medical Device IVD Rx only

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Xpert® SA Nasal Complete

For *In Vitro* Diagnostic Use Only

℞only

1. Proprietary Name

Xpert® SA Nasal Complete

2. Common or Usual Name

Xpert SA Nasal Complete test

3. Intended Use

The Cepheid® Xpert SA Nasal Complete test performed in the GeneXpert® Dx System is a qualitative *in vitro* diagnostic test designed for rapid detection of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) from nasal swabs in patients at risk for nasal colonization. The test utilizes automated real-time polymerase chain reaction (PCR) to detect MRSA/SA DNA. The Xpert SA Nasal Complete test is intended to aid in the prevention and control of MRSA/SA infections in healthcare settings. The Xpert SA Nasal Complete test is not intended to diagnose, guide or monitor treatment for MRSA/SA infections, or provide results of susceptibility to methicillin. A negative result does not preclude MRSA/SA nasal colonization. Concomitant cultures are necessary to recover organisms for epidemiological typing or for further susceptibility testing.

4. Summary and Explanation

Staphylococcus aureus (*S. aureus*) is a well-documented human pathogen that causes both community- and healthcare-associated infections. The infections range in severity from uncomplicated skin wounds to life-threatening illnesses including endocarditis, sepsis, and osteomyelitis. *S. aureus* continues to be a major cause of morbidity and mortality in a variety of healthcare institutions, including hospitals and long term care facilities. Nasal carriers of *S. aureus* are at increased risk for health-care associated infections with this organism; overall, more than 80% of health-care associated *S. aureus* infections can be traced to an endogenous source.[1] More specifically, 20 to 30% of surgical-site infections are caused by *S. aureus* and over half of these arise from endogenous flora.[2] *S. aureus* infections are usually acute and elicit a large inflammatory response. If untreated, the infection may spread to surrounding tissue or the bloodstream, which may lead to infections in multiple organs. Some of the more serious infections produced by *S. aureus* are bacteremia, pneumonia, osteomyelitis, acute endocarditis, toxic shock syndrome, myocarditis, pericarditis, meningitis, chorioamnionitis, scalded skin syndrome, and abscesses of the muscle, urogenital tract, central nervous system, and various intra-abdominal organs.[3]

In the early 1950s, acquisition and spread of beta-lactamase-producing plasmids prevented the effectiveness of penicillin for treating *S. aureus* (SA) infections. In 1959, methicillin, a semi-synthetic penicillin, was introduced into clinical use. However, by 1960, methicillin-resistant *S. aureus* (MRSA) strains were identified. This was determined to be the result of *S. aureus* acquiring the *mecA* methicillin resistance gene. In the United States today, MRSA is responsible for approximately 25% of healthcare-associated 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* 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.[4-8] 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. Results from a recent, well-controlled, multi-center clinical trial, showed that rapid identification of *S. aureus* nasal carriers using real-time PCR, followed by immediate implementation of procedures to decolonize nasal and extranasal sites can reduce the number of surgical-site *S. aureus* infections acquired in the hospital by nearly 60%.[1]

5. Principle of the Procedure

The GeneXpert Dx System automates and integrates sample purification, nucleic acid amplification, and detection of the target sequence in simple or complex samples using real-time PCR and RT-PCR tests. The system consists 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 *GeneXpert Dx System Operator Manual*.

The Xpert SA Nasal Complete test includes reagents for the detection of MRSA and SA. A sample processing control (SPC) and a Probe Check Control (PCC) are also included. The SPC is present to control for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR reaction. The PCC verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The Cepheid Xpert SA Nasal Complete test is a rapid, automated diagnostic test for qualitative detection of proprietary sequences for the staphylococcal protein A (*spa*) gene, the gene for methicillin resistance (*mecA*), and the staphylococcal cassette chromosome *mec* (SCC*mec*) inserted into the SA chromosomal *attB* site, from nares specimens of patients at risk for nasal colonization.

6. Reagents and Instruments

6.1 Materials Provided

The Xpert SA Nasal Complete test kit contains sufficient reagents to process 10 specimens or quality control samples. The kit contains the following:

Xpert SA Nasal Complete Cartridges with Integrated Reaction Tubes and Elution Reagent vials	**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 SA Nasal Complete Elution Reagent (Guanidinium Thiocyanate)	**1 vial x 2.0 mL per pouch**
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 postmortem testing. During processing, there was no mixing of the material with other animal materials.

6.2 Materials Required but Not Provided

- GeneXpert Dx System (catalog number varies by configuration): GeneXpert instrument, computer with proprietary software, hand-held barcode scanner and Operator Manual
- Printer (If a printer is required, contact Cepheid Technical Support to arrange for the purchase of a recommended printer.)
- Vortex mixer
- Swab for transfer of the specimen, such as the swab found in the Cepheid Sample Collection Device 900-0370 (Dual Swab in Liquid Stuart Media), the Copan Dual Swab and Transport Systems (139C LQ STUART or 138C LQ AMIES)
- Disposable, transfer pipettes, (VWR 14670-331, Samco 2S-PL-232-1S), or equivalent
- Gauze (VWR 82030-638), or equivalent

6.3 Materials Available but Not Provided

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

7. Warnings and Precautions

- For in vitro diagnostic use.
- For prescription use 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[9] and the Clinical and Laboratory Standards Institute.[10]
- 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.
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- The Xpert SA Nasal Complete test can detect MRSA and/or SA DNA from non-viable organisms. The probability of this occurring increases for patients on antibiotics.
- The Xpert SA Nasal Complete test does not provide antimicrobial susceptibility testing results. Additional time is required to culture and perform susceptibility testing.
- Do not substitute Xpert SA Nasal Complete test reagents with other reagents.
- Do not open the Xpert SA Nasal Complete test cartridge lid except when adding sample and reagent.
- Do not use a cartridge that has been dropped or shaken after you have added the sample and reagent.
- Do not open a cartridge package until you are ready to perform testing.
- Do not use a cartridge that has a damaged reaction tube.
- Each single-use Xpert SA Nasal Complete 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 procedures. 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.

8. Chemical Hazards[11,12]

- 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 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 persists: Get medical advice/attention.
  - IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician if you feel unwell.
  - Rinse mouth

9. Storage and Handling

- Store the Xpert SA Nasal Complete 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 reagent that has become cloudy or discolored.
- Use the cartridges within 2 weeks of opening the foil package.

10. Specimen Collection, Transport and Storage

1. Follow your institution's guidelines for collecting nasal swab samples for MRSA/SA testing. For swab information, see Section 6.3, Materials Available but Not Provided. Swabs may be used dry or pre-moistened with sterile saline when using the Cepheid Sample Collection Device or Copan Liquid Stuart Collection Device. Swabs should be pre-moistened with the media-filled sponge when using the Copan Liquid Amies Collection Device.

2. Place the specimen swab back in the plastic transport tube (liquid Stuarts medium, Cepheid Collection Device or Copan recommended) and send to the GeneXpert testing area. Store the remaining untested swab at 2 – 8 °C for microbiology culture in appropriate transport system and culture within 4 days.

3. Store specimen at room temperature (15 – 28 °C) if it will be processed within 24 hours, otherwise store at 2 – 8 °C. The swab specimen is stable for up to 5 days when stored at 2 – 8 °C.

11. Procedure

Operators should receive training on basic operation of the GeneXpert instrument and Xpert test(s) in accordance with your institution's guidelines.

11.1 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 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 Reagent vial lid and vortex at high speed for 10 seconds.
5. Open the cartridge lid. Using a transfer pipette, transfer the entire contents of the Elution Reagent to the sample chamber of the Xpert SA Nasal Complete test cartridge. See Figure 1.
6. Close the cartridge lid.

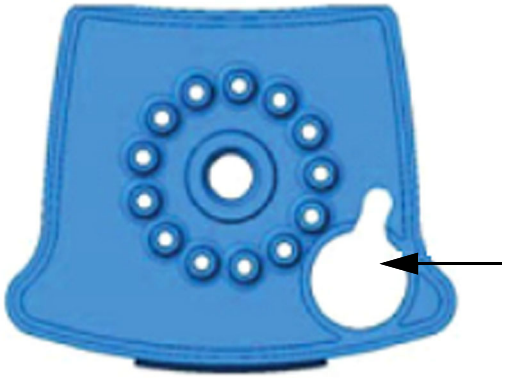

Figure 1. Xpert SA Nasal Complete Cartridge (Top View)

11.2 Starting the Test

Important **Before starting the test, make sure the Xpert SA Nasal Complete assay definition file is imported into the software. This section lists the basic steps of running the test. For detailed instructions, see the *GeneXpert Dx System Operator Manual*.**

1. Turn on the GeneXpert Dx instrument and then turn on the computer. The GeneXpert software will launch automatically.
2. Log on to the GeneXpert Dx System software using your user name and password.
3. In the GeneXpert Dx System window, click **Create Test**. The Create Test window appears.
4. Scan in or type in the Patient ID (optional). If typing the Patient ID, make sure the Patient ID is typed correctly. The Patient ID is associated with the test results and is shown in the **View Results** window.
5. In the Sample ID box, scan or type the sample ID. Make sure you type the correct sample ID (sample ID is associated with the test result and is shown in the **View Results** window and all the reports). The **Scan Cartridge** dialog box appears.
6. Scan the barcode on the Xpert SA Nasal Complete test cartridge. The **Create Test** window appears. Using the barcode information, the software automatically fills the boxes for the following fields: Select Assay, Reagent Lot ID, Cartridge SN, and Expiration Date.
7. Click **Start Test**. Enter your password, if requested.
8. Open the instrument module door with the blinking green light and load the cartridge.
9. Close the door. The test starts and the green light stops blinking. When the test is finished, the light turns off.
10. Wait until the system releases the door lock before opening the module door and removing the cartridge.
11. Dispose of the used cartridges in the appropriate specimen waste containers according to your institution's standard practices.

11.3 Viewing and Printing Results

For detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual*.

12. Quality Control

CONTROL

Each test includes a Sample Processing Control (SPC) (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 that is included in each cartridge to verify adequate processing of Xpert SA Nasal Complete 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 ensures the PCR reaction conditions (temperature and time) are appropriate for the amplification reaction and that the PCR reagents are functional, and detects specimen-associated inhibition of the real-time PCR test. 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 Dx System measures 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 — External controls may be used in accordance with local, state, and federal accrediting organizations, as applicable.

When using KWIK-STIK controls (see Section 6.3, Materials Available but Not Provided), follow the Microbiologics external control procedure described below:

1. Tear open the pouch at the 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). The KWIK-STIK swab is now ready for Xpert SA Nasal Complete testing.
6. If the External QC fails to perform as expected, repeat external control test and/or contact Cepheid for assistance.

13. Interpretation of Results

The results are interpreted automatically by the GeneXpert Dx System from measured fluorescent signals and embedded calculation algorithms and are shown in the **View Results** window. The possible results are:

Table 1. Xpert SA Nasal Complete Results and Interpretation

Result	Interpretation
MRSA POSITIVE; SA POSITIVE (Figure 2)	MRSA target DNA detected; SA target DNA detected. • All MRSA targets (*spa*, *mecA* and SCC*mec*) have a Ct within the valid range and endpoint above the threshold setting. • SPC – NA (not applicable); SPC is ignored since MRSA 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 MRSA or SA.
MRSA NEGATIVE; SA POSITIVE (Figure 3)	MRSA target DNA not detected; SA target DNA detected. • SA target (*spa*) has a Ct within the valid range and endpoint above the threshold setting. Target DNA for SCC*mec* is not detected and target DNA for *mecA* is or is not detected. • SA target (*spa*) has a Ct within the valid range and endpoint above the threshold setting. Target DNA for *mecA* is not detected and target DNA for SCC*mec* is detected (empty cassette variant). • SPC – NA (not applicable); SPC is ignored since SA amplification may compete with this control. • Probe Check – PASS; all probe check results pass. A **MRSA NEGATIVE; SA POSITIVE** test result does not preclude MRSA nasal colonization.
MRSA NEGATIVE; SA NEGATIVE (Figure 4)	SA target DNA not detected. • SA target (*spa*) DNA is not detected. Target DNA for *mecA* may or may not be detected; 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 threshold setting. • Probe Check – PASS; all probe check results pass. A **MRSA NEGATIVE; SA NEGATIVE** test result does not preclude MRSA or SA nasal colonization. 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 $1{:}1\times10^3$ or greater.

Table 1. Xpert SA Nasal Complete Results and Interpretation (Continued)

Result	Interpretation
INVALID (Figure 5)	Presence or absence of MRSA and SA target DNA cannot be determined. Repeat test according to instructions in the section below. • SPC – FAIL; SPC target result is negative, and the SPC Ct is not within the valid range and endpoint is below the threshold setting. • Probe Check – PASS; all probe check results pass.
ERROR	Presence or absence of MRSA and SA target DNA cannot be determined. Repeat test according to instructions in the section below. • MRSA and SA targets – NO RESULT • SPC – NO RESULT. • Probe Check – FAIL*; one or more of the probe check results failed. *If the probe check passed, the error was likely caused by the maximum pressure exceeding the acceptable range.
NO RESULT	Presence or absence of MRSA and SA target DNA cannot be determined. Repeat test according to instructions in the section below. • MRSA and SA targets – NO RESULT • SPC – NO RESULT • Probe Check – not applicable

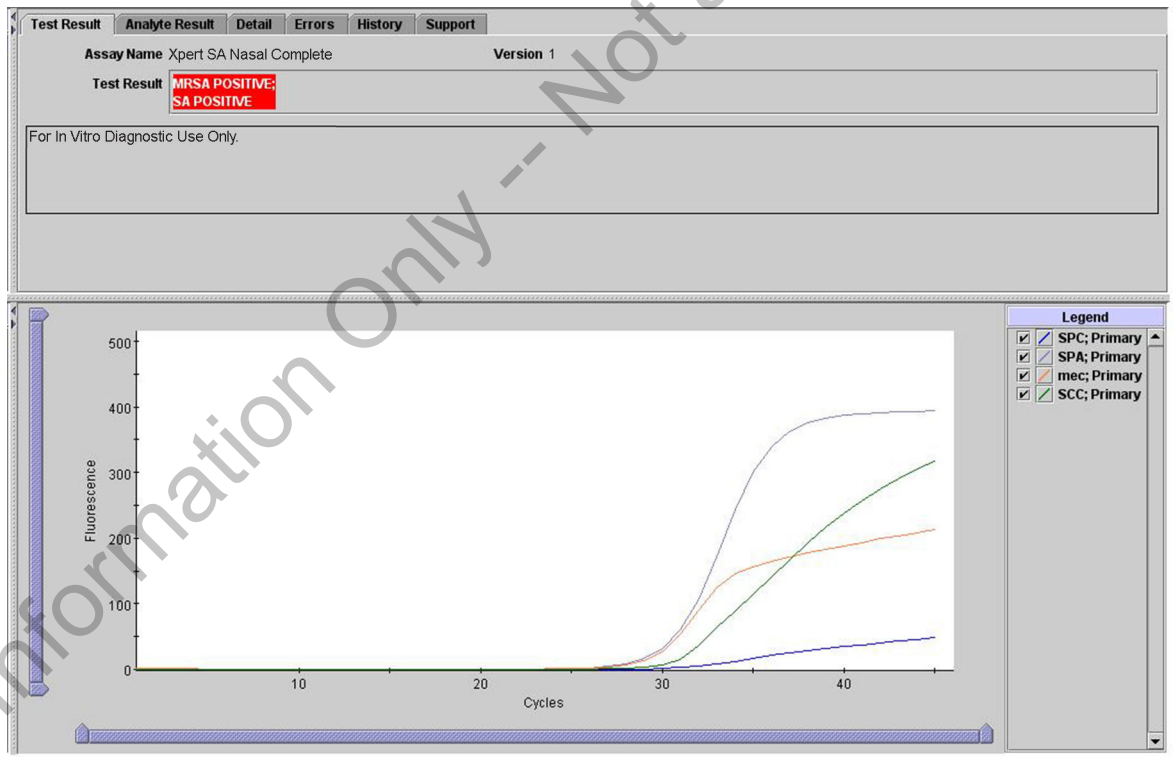

Figure 2. Example of a MRSA POSITIVE; SA POSITIVE Result

Figure 3. Example of a MRSA NEGATIVE; SA POSITIVE Result

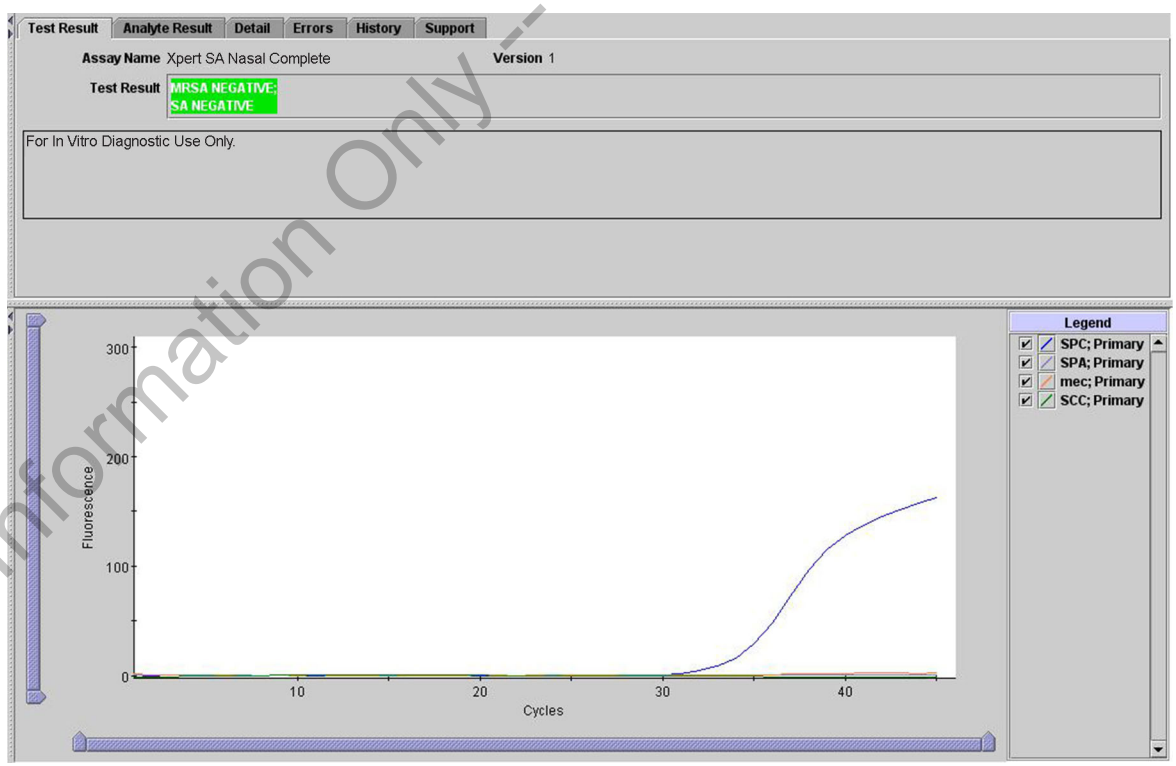

Figure 4. Example of a MRSA NEGATIVE; SA NEGATIVE Result

Figure 5. Example of an INVALID Result

14. Reasons to Repeat the Test

If any of the test results mentioned below occur, repeat the test according to the procedure above using a new sample, new cartridge (do not re-use the cartridge), and new reagent.

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 test was aborted. Possible causes include: the reaction tube was filled improperly; a reagent probe integrity problem was detected; or 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, or a power failure occurred.

15. Limitations

- The performance of the Xpert SA Nasal Complete test was validated using the procedures provided in this instructions for use only. Modifications to these procedures may alter the performance of the test.
- Results from the Xpert SA Nasal Complete test should be interpreted in conjunction with other laboratory and clinical data available to the clinician, and should be used as an adjunct to nosocomial infection control efforts to identify patients needing enhanced precautions. Results should not be used to guide or monitor treatment for MRSA or SA infections.
- 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.
- A positive test result does not necessarily indicate the presence of viable organisms. It is however, presumptive for the presence of MRSA or SA.
- The Xpert SA Nasal Complete test positive result does not necessarily indicate intervention eradication failure since non-viable DNA may persist. A negative result following a previously positive test result may or may not indicate eradication success.
- The performance characteristics were not established for patients ≤21 years of age.
- 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 SA Nasal Complete test may not detect the MRSA organisms. The pivotal clinical study included one sample with documented MRSA/SA mixed infection; the Xpert SA Nasal Complete test successfully identified the sample as MRSA positive/SA positive.
- 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 a MRSA:SA ratio of $1{:}1{\times}10^6$ in 7 of 8 SCC*mec* types tested. For SCC*mec* type VIII, competition from SA was observed at a MRSA:SA ratio of $1{:}1{\times}10^3$.
- Inhibition of the SA Nasal Complete test resulting in Invalid test results has been observed in the presence of inhaled nasal steroids Flonase and Nasonex in SA negative samples at concentrations greater than 5% v/v, and 10% v/v, respectively.
- Inhibition of the SA Nasal Complete test resulting in false negative test results has been observed in the presence of inhaled nasal steroids Flonase and Nasonex in MRSA positive samples at concentrations greater than 1% (v/v) and 5% (v/v), respectively.
- The Xpert SA Nasal Complete test may generate a false positive MRSA result when testing a mixed infection nasal specimen containing both methicillin-resistant coagulase-negative *Staphylococcus* and empty cassette SA.
- The Xpert SA Nasal Complete test may generate false negative MRSA results when testing borderline oxacillin resistant *S. aureus* (BORSA). The mechanism of oxacillin resistance in BORSA strains is due to an increased production of ß-lactamases, not the *mecA* gene. BORSA with oxacillin MICs of 4 – 8 µg/mL are considered borderline resistant but would be reported as MRSA negative by the Xpert SA Nasal Complete test. BORSA strains are rare in the United States.
- The Xpert SA Nasal Complete test may generate false negative MRSA results when testing modified *S. aureus* (MOD-SA). The mechanism of oxacillin resistance in MOD-SA strains is due to changes in affinity of penicillin binding proteins for oxacillin, not the *mecA* gene. MOD-SA with oxacillin MICs of 4 – 8 µg/mL are considered borderline resistant but, would be reported as MRSA negative by the Xpert SA Nasal Complete test. MOD-SA strains are rare in the United States.
- There may be an association with false positive results in specimens containing blood.
- As with all PCR based *in vitro* diagnostic tests, extremely low levels of target below the LoD of the test may be detected, but results may not be reproducible (see Section 19., Reproducibility for further details).
- Xpert SA Nasal Complete test results may sometimes be **INVALID** due to a failed SPC control, **ERROR** or **NO RESULT**, and require retesting that can lead to a delay in obtaining final results.
- As with all *in vitro* diagnostic tests, positive and negative predictive values are highly dependent on prevalence. Xpert SA Nasal Complete test performance may vary depending on the prevalence and population tested.

16. Expected Values

In the Xpert SA Nasal Complete clinical study, a total of 2487 nasal specimens were included from 8 institutions 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 22 to 30	325	10	3.1%	71	21.8%
Ages 31 to 40	359	17	4.7%	84	23.4%
Ages 41 to 50	459	28	6.1%	118	25.7%
Ages 51 to 60	487	36	7.4%	141	29.0%
Ages 61 to 70	315	25	7.9%	75	23.8%
Age > 70	542	57	10.5%	138	25.5%

17. Performance Characteristics

17.1 Clinical Performance

Performance characteristics of the Xpert SA Nasal Complete test were determined in a multi-site prospective investigation study at eight US institutions by comparing the Xpert SA Nasal Complete test with Reference Culture.

A double swab was collected from each subject. One swab was tested by the Xpert SA Nasal Complete test at the enrolling center and the other swab 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 a sheep 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 mm (R), ≥ 22 mm (S).

Performance of the Xpert SA Nasal Complete test was calculated relative to the Reference Culture results.

17.2 Overall Results

A total of 2487 specimens were tested for MRSA and SA by Xpert SA Nasal Complete test and enriched blood agar culture.

Patients receiving antibiotics within 7 days of specimen collection were ineligible for inclusion. Among the 2487 cases in the eligible dataset, antibiotic use within the 7 to 21 days prior to sample collection was reported for 141 subjects, and no antibiotic use was confirmed for 2323 subjects; for 23 cases, antibiotic status was unknown. There was no statistically significant difference in the culture positivity rate or the Xpert SA Nasal Complete test performance based on antibiotic status.

One of the MRSA positive cultures had mixed infections of MRSA and methicillin-sensitive *Staphylococcus aureus*. Xpert SA Nasal Complete correctly identified this specimen as MRSA positive/SA positive.

The performance of the Xpert SA Nasal Complete test is summarized in Table 3.

Table 3. SA Nasal Complete Performance vs. Reference Culture

		Reference Culture			
		MRSA+	**SA+/MRSA-**	**Neg/No Growth**	**Total**
Xpert	MRSA+	159	24	25	208
	SA+/MRSA-	9	393	152	554
	SA-	5	37	1683	1725
	Total	173	454	1860	2487
		MRSA:			
		Sensitivity:	91.9% (159/173) (95% CI: 86.8-95.5%)		
		Specificity:	97.9% (2265/2314) (95% CI: 97.2-98.4%)		
		PPV:	76.4% (159/208) (95% CI: 70.1-82.0%)		
		NPV:	99.4% (2265/2279) (95% CI: 99.0-99.7%)		
		SA:			
		Sensitivity:	93.3% (585/627) (95% CI: 91.1-95.1%)		
		Specificity:	90.5% (1683/1860) (95% CI: 89.1-91.8%)		
		PPV:	76.8% (585/762) (95% CI: 73.6-79.7%)		
		NPV:	97.6% (1683/1725) (95% CI: 96.7-98.2%)		

Of the Xpert SA Nasal Complete tests run on eligible specimens, 96.5% (2487/2578) of these specimens were successful on the first attempt. The remaining 91 gave indeterminate results on the first attempt (31 **INVALID**, 51 **ERROR** and 9 **NO RESULT**). The study design did not allow for repeat testing.

17.3 Empty Cassette Variants

For an isolate to be identified as MRSA positive with the Xpert SA Nasal Complete test, the test for *spa* must be positive as well as the test for *mecA* and SCC*mec*. 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 an test for MRSA that does not detect the *mecA* gene directly. The Xpert SA Nasal Complete 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 14 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 4. All of the 14 specimens were verified true negative MRSA isolates, and true positive SA isolates relative to Reference Culture.

Table 4. SA Nasal Complete Performance vs. Reference Culture — Empty Cassette Variants

Subject #	Xpert Result	*spa* (Ct)	*mecA* (Ct)	SCC*mec* (Ct)	Culture	Xpert vs. Culture	
						MRSA	SA
1	SA	34.2	0	36.2	SA	TN	TP
2	SA	32.4	0	34.3	SA	TN	TP
3	SA	24.6	0	26.3	SA	TN	TP
4	SA	26.9	0	29.0	SA	TN	TP
5	SA	29.1	0	31.1	SA	TN	TP
6	SA	24.4	0	26.8	SA	TN	TP
7	SA	31.8	0	33.6	SA	TN	TP
8	SA	32.3	0	34.7	SA	TN	TP
9	SA	28.5	0	31.1	SA	TN	TP
10	SA	25.8	0	27.5	SA	TN	TP
11	SA	17.4	0	19.7	SA	TN	TP
12	SA	17.4	0	18.9	SA	TN	TP
13	SA	26.9	0	29.7	SA	TN	TP
14	SA	22.6	0	24.6	SA	TN	TP

18. Analytical Performance

18.1 Analytical Specificity (Exclusivity)

Cross-reactivity Study

One hundred fourteen (114) strains phylogenetically related to *Staphylococcus aureus* or those species potentially present in nasopharyngeal flora were tested using the Xpert SA Nasal Complete test. Of these, 103 were obtained from the American Type Culture Collection (ATCC), 2 were obtained from Culture Collection, University of Göteborg, Sweden (CCUG), 1 was obtained from the German Collection of Microorganisms and Cell Cultures (DSM), 1 was obtained from Teruyo Ito, Juntendo University, Tokyo, Japan, and 7 were obtained from the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA).

The organisms tested were identified as either Gram-positive (83), Gram-negative (28), or yeast (3). Of these, methicillin-sensitive coagulase-negative staphylococci, MSCoNS (34) and methicillin-resistant coagulase-negative staphylococci, MRCoNS (12) were included. The organisms were further classified as either aerobic (106) or anaerobic (8).

Three (3) replicates of each isolate were tested at 4.5 to 9.5×10^8 CFU/mL or 1.7 - 3.2 McFarland units. Under the conditions of this study, all isolates were reported as **MRSA NEGATIVE; SA NEGATIVE** by the Xpert SA Nasal Complete test. The analytical specificity of the Xpert SA Nasal Complete test was 100%. These results demonstrate that a sample containing non *Staphylococcus aureus* species ($>1\times10^8$ CFU/mL) will not falsely trigger a positive MRSA/SA test result using the Xpert SA Nasal Complete test.

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*. BORSA strains are *mecA*-negative, but exhibit an oxacillin minimum inhibitory concentration (MIC) ≥ 1 and ≤ 8 µg/mL. It is especially valuable to distinguish MRSA from BORSA to aid in implementing appropriate management and isolation precaution options for patients infected with ß-lactam susceptible strains of *S. aureus*.

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 SA Nasal Complete 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 SA Nasal Complete test.

18.2 Analytical Sensitivity

Limit of Detection Studies

Studies were performed to determine the 95% confidence intervals for the analytical limit of detection (LoD) of methicillin-sensitive *Staphylococcus aureus* cells and methicillin-resistant *Staphylococcus aureus* (MRSA) cells diluted into a simulated nasal matrix. The nasal matrix consisted of mucin and blood in PBS with 15% glycerol. 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 SA, replicates of 20 were evaluated at various concentrations for three (3) individual isolates. USA types USA900 and USA1200 were represented.

For MRSA, replicates of 20 were evaluated at various concentrations for ten (10) individual isolates representing SCC*mec* types I, II, III, IVa, IVd, V, VI, VII, and VIII. 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 are represented. Isolates reported to contain heterogeneous subpopulations with respect to their oxacillin resistance phenotype were included.

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 5 and Table 6.

Table 5. 95% Confidence Intervals for Analytical LoD — SA

SA Strain ID	PFGE	LoD Est. (CFU/swab)	Lower 95% CI	Upper 95% CI
N7129	USA900	154	132	197
102-04	USA1200	128	109	177
29213	unknown	94	76	138

Table 6. 95% Confidence Intervals for Analytical LoD — MRSA

MRSA Strain ID	SCC*mec* Type	PFGE	LoD Est. (CFU/swab)	Lower 95% CI	Upper 95% CI
64/4176	I	USA500	79	64	119
N315	II	USA100	94	76	131
BK2464	II	USA100	143	116	212
11373	III	unknown	52	42	77
MW2	IVa	USA400	85	69	130
BK2529[1]	IVd	USA500	256	216	334
ST59-MRSA-V	V	USA1000	127	105	170
HDE288[1]	VI	USA800	97	78	141
JCSC6082	VII	unknown	214	182	276
WA MRSA-16	VIII	unknown	292	259	384

[1] Heterogeneous oxacillin-resistant isolates

The results of this study indicate that the Xpert SA Nasal Complete test will produce a positive SA result 95% of the time with 95% confidence for a nasal swab containing 175 CFU and a positive MRSA result 95% of the time with 95% confidence for a nasal swab containing 300 CFU.

18.3 Analytical Reactivity (Inclusivity)

Two hundred forty-eight (248) *Staphylococcus aureus* strains were tested using the Xpert SA Nasal Complete test. All strains were tested in triplicate using cell stocks diluted to concentrations at or near the test cut-off. Colony forming units per test were determined by plate counts of the same volume and dilution.

MRSA (199) and methicillin-sensitive *Staphylococcus aureus* (49) 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 methicillin-sensitive *Staphylococcus aureus*, as well as those that contain methicillin-sensitive *Staphylococcus aureus* exclusively were included.

The Xpert SA Nasal Complete test correctly identified all 248 *Staphylococcus aureus* strains: 49 as **MRSA NEGATIVE, SA POSITIVE**; 199 as **MRSA POSITIVE, SA POSITIVE**. Strains represent Cooper and Feil Groups 1A, 1B, and 2, 12 SCC*mec* types and subtypes (I, II, III, IV, IVa, IVb, IVc, IVd, V, VI, VII, and VIII), 24 sequence types (STs), 75 *spa*-types, 13 PFGE types, and 18 clonal complexes (CC).

Each of the 39 known USA300 isolates were correctly reported as **MRSA POSITIVE; SA POSITIVE**. Empty cassette variants, BORSA strains and heteroresistant strains were all correctly identified using the Xpert SA Nasal Complete test.

18.4 Interfering Substances

In the investigational study for Xpert SA Nasal Complete test, 63 of the 2487 specimens were observed to contain mucus, 32 were observed to contain blood, and 7 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 MRSA sensitivity, SA sensitivity, and SA specificity. For MRSA specificity, there was a slightly higher than expected false positive rate associated with specimens containing blood.

In a non-clinical study, potential interfering substances that may be present in clinical nasal specimens were evaluated directly relative to the performance of the Xpert SA Nasal Complete test. Potentially interfering substances in nasal specimens may include, but are not limited to: nasal sprays, saline, decongestants and antihistamines (including inhaled nasal steroids), human blood, and mucous. The substances tested are listed in Table 7 with the active ingredients and concentrations tested shown.

Under the conditions of this study, no statistically significant inhibitory effects were observed in negative or positive samples in the presence of human blood, mucous, and the following nasal sprays tested at 100% (v/v) concentrations: Anefrin, NasalCrom, Neo-Synephrine, saline, Rhinolast (Astelin), and Zicam gel. Positive samples consisted of two clinical isolates each of SA (N7129 and 10204) and MRSA SCC*mec* types II (N315) and IVa (MW2) spiked near the analytical LoD determined for each isolate.

Inhibitory effects on the SA Nasal Complete test resulting in invalid test results were observed in the presence of inhaled nasal steroids Flonase and Nasonex in negative samples at concentrations greater than 5% (v/v) and 10% (v/v) respectively. Inhibitory effects on the SA Nasal Complete test resulting in false negative test results were observed in the presence of inhaled nasal steroids Flonase and Nasonex in each MRSA isolate at concentrations greater than 1% (v/v) and 5% (v/v) respectively.

Table 7. Potential Interfering Nasal Substances Tested

Substance	Active Ingredient	% Tested
TET Buffer (Control)	Control	Control
Mucous (Mucin)	Porcine mucin representing densely glycosylated proteins (mucous)	5% (w/v)
Anefrin Spray (Decongestant)	0.05% Oxymetazoline Hydrochloride	100% (v/v)
Blood	N/A	100% (v/v)
NasalCrom (Nasal Allergy Symptom Controller)	5.2 mg Cromolyn Sodium	100% (v/v)
Neo–Synephrine (Nasal Decongestant)	0.5% Phenylephrine Hydrochloride	100% (v/v)
Saline Nasal Moisturizing Spray	0.65% Sodium Chloride	100% (v/v)
Zicam Nasal Gel (Upper Respiratory Allergy Symptom Relief)	4x,12x, 30x Luffa operculata 12x, 30x Galphimia glauca 12x, 30x, 200x Histaminum hydrochloricum 12x, 30x, 200x Sulphur	100% (v/v)
Nasonex (Nasal Allergy Symptom Medication, inhaled nasal steroid)	0.05% Mometasone furoate monohydrate (anti-inflammatory corticosteroid)	100% (v/v) 50% (v/v) 25% (v/v) 10% (v/v) 5% (v/v)
Flonase (inhaled nasal steroid)	0.05% Fluticasone Propionate (corticosteroid)	100% (v/v) 50% (v/v) 25% (v/v) 10% (v/v) 5% (v/v) 1% (v/v)
Rhinolast (Astelin Antihistamine Nasal Spray)	0.1% Azelastine Hydrochloride	100% (v/v)

18.5 Evaluation of Empty Cassette Variants

Twenty-two (22) *Staphylococcus aureus* isolates identified as "empty cassette variants" were tested using the Xpert SA Nasal Complete test. Overnight cultures were adjusted to 0.5 McFarland units (~3×10^8 CFU/mL). Cultures were further diluted 100 thousand-fold or ~3000 CFU/mL. Each isolate was added to the Xpert SA Nasal Complete elution buffer reagent at ~300 CFU/test (near the test's LoD) and at ~3×10^5 CFU/test.

All 22 isolates were correctly reported as **MRSA NEGATIVE; SA POSITIVE** at both cell concentrations. No *mecA* signals were reported. These results demonstrate that an "empty cassette variant" is correctly identified as **MRSA NEGATIVE; SA POSITIVE** and will not report a false positive MRSA test result using the Xpert SA Nasal Complete test.

18.6 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. In the 20 negative samples processed immediately following very high positive samples, all were correctly reported as **MRSA NEGATIVE; SA NEGATIVE**. All 20 positive samples were correctly reported as **MRSA POSITIVE; SA POSITIVE**.

19. 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 SA Nasal Complete kit was used at each of the 3 testing sites. Xpert SA Nasal Complete tests were performed according to the Xpert SA Nasal Complete procedure. Results are summarized in Table 8 and Table 9. Note that due to the concentrations of high negative samples being near the LoD, some positive results were expected.

Table 8. Summary of Reproducibility Results (All)[1]

Specimen ID	Site 1	Site 2	Site 3	Total Agreement
Neg (MSSE)	100.0% (20/20)	100.0% (20/20)	100.0% (20/20)	100.0% (60/60)
SA – High Neg	95.0% (19/20)	95.0% (19/20)	95.0% (19/20)	95.0% (57/60)
SA – Low Pos	85.0% (17/20)	95.0% (19/20)	100.0% (20/20)	93.3% (56/60)
SA – Mod Pos	100.0% (20/20)	100.0% (20/20)	100.0% (20/20)	100.0% (60/60)
MRSA1 – High Neg	100.0% (20/20)	95.0% (19/20)	85.0% (17/20)	93.3% (56/60)
MRSA1 – Low Pos	95.0% (19/20)	95.0% (19/20)	100.0% (20/20)	96.7% (58/60)
MRSA1 – Mod Pos	95.0% (19/20)	100.0% (20/20)	100.0% (20/20)	98.3% (59/60)
MRSA2 – High Neg	60.0% (12/20)	60.0% (12/20)	50.0% (10/20)	56.7% (34/60)
MRSA2 – Low Pos	95.0% (19/20)	95.0% (19/20)	95.0% (19/20)	95.0% (57/60)
MRSA2 – Mod Pos	100.0% (20/20)	100.0% (20/20)	100.0% (20/20)	100.0% (60/60)
% Total Agreement by Site	92.5% (185/200)	93.5% (187/200)	92.5% (185/200)	92.8% (557/600)

[1] For negative and high negative samples, %Agreement = (# negative results/total samples run); for low and moderate positive samples, %Agreement = (# positive results/total samples run).

Table 9. Summary of Ct Value Results by Sample Level and Target

SPC			
Level	**Mean**	**Std Dev**	**%CV**
Neg (MSSE)	34.3	0.72	2.1
SA High Neg	34.3	0.75	2.2
MRSA1 High Neg	34.6	0.86	2.5
MRSA2 High Neg	34.6	0.75	2.2
Spa			
Level	**Mean**	**Std Dev**	**%CV**
SA Low Pos	33.7	0.91	2.7
SA Moderate Pos	31.6	0.71	2.2
MRSA1 Low Pos	32.6	1.53	4.7
MRSA1 Moderate Pos	31.7	0.79	2.5
MRSA2 Low Pos	32.7	0.97	3.0
MRSA2 Moderate Pos	30.6	0.85	2.8
mecA			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Low Pos	33.3	0.88	2.6
MRSA1 Moderate Pos	32.2	0.82	2.5
MRSA2 Low Pos	33.4	1.02	3.1
MRSA2 Moderate Pos	31.1	0.75	2.4
***SCC**mec*			
Level	**Mean**	**Std Dev**	**%CV**
MRSA1 Low Pos	34.1	0.86	2.5
MRSA1 Moderate Pos	32.9	0.79	2.4
MRSA2 Low Pos	34.6	1.19	3.4
MRSA2 Moderate Pos	32.5	0.80	2.5

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21. Cepheid Headquarters Locations

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22. Technical Assistance

Before contacting Cepheid Technical Support, collect the following information:

- Product name
- Lot number
- Serial number of the instrument
- Error messages (if any)
- Software version and, if applicable, Computer Service Tag number

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23. Table of Symbols

Symbol	Meaning
REF	Catalog number
IVD	*In vitro* diagnostic medical device
Rx only	For prescription use only
2	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
	Warning

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IVD

24. Revision History

Description of Changes: 300-8799 Rev. H to Rev. J

Purpose: Minor correction.

Section	Description of Change
Limitations	Separated one bulleted item into two.
Empty Cassette Variants	Table 4, Row 7, column SA, cell changed from "FP" to "TP".
Analytical Specificity (Exclusivity)	"Methicillin" changed to "ß-lactam".