GeneXpert®
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# Xpert® Omni MTB/RIF Ultra

REF **OMNIMTB/RIF-ULT-10**

## Instructions For Use

IVD CE

Cepheid®

*In Vitro* Diagnostic Medical Device

302-3906, Rev. B. February 2021

## Trademark, Patents and Copyright Statements

# Xpert® Omni MTB/RIF Ultra

For *in vitro* diagnostic use.

## 1 Proprietary Name

Xpert® Omni MTB/RIF Ultra

## 2 Common or Usual Name

Xpert Omni MTB/RIF Ultra Assay

## 3 Intended Use

The Xpert Omni MTB/RIF Ultra Assay, performed on the GeneXpert® Omni System is a semi-quantitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of *Mycobacterium tuberculosis* (MTB) complex DNA in unprocessed sputum samples or concentrated sediments prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex is detected, the Xpert Omni MTB/RIF Ultra Assay can also detect rifampin-resistance associated mutations of the *rpoB* gene.

The Xpert Omni MTB/RIF Ultra Assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than 3 days of therapy in the last 6 months. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings.

## 4 Summary and Explanation

Globally, about 1.7 billion people are infected with MTB.[1] In 2018, 10.0 million people developed active disease, and 1.45 million people lost their lives to the illness.[2] The route of transmission of pulmonary TB is through the air, which makes this a highly transmissible disease. Given the infectious nature of pulmonary TB, fast and accurate diagnosis is an important element of TB treatment and control.

Treatment involves prolonged administration of multiple drugs and is usually highly effective. However, *M. tuberculosis* strains may become resistant to one or more of the drugs, making cure much more difficult to achieve. Four common first-line drugs used in anti-tuberculosis therapy are isoniazid (INH), rifampin (also known as rifampicin, RIF), ethambutol (EMB), and pyrazinamide (PZA). As documented by World Health Organization, RIF resistance may also indicate resistance to a number of other anti-TB drugs.[3] It is most commonly seen in multi-drug resistant (MDR-TB) strains (defined as resistant to both RIF and INH) and has a reported frequency of greater than 95% in such isolates.[4,5,6] Resistance to RIF or other first-line drugs usually indicates the need for full susceptibility testing, including testing against second-line agents.

Molecular detection of TB and *rpoB* gene mutations associated with RIF resistance greatly reduces the time to diagnosis of both drug-susceptible and MDR tuberculosis. With the Xpert Omni MTB/RIF Ultra Assay, this can be accomplished in unprocessed sputum samples and in prepared sediments in less than 80 minutes. The rapid detection of MTB and RIF resistance allows the physician to make critical patient management decisions regarding therapy during a single medical encounter.

# 5 Principle of the Procedure

The GeneXpert Omni System integrates and automates sample processing, nucleic acid amplification, and detection of the target sequences in simple or complex samples using real-time PCR and melt peak detection. The system consists of an instrument, a mobile device, and preloaded software for running tests on patient samples and viewing the results. The system requires the use of single-use disposable GeneXpert 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 Omni System Operator Manual*.

Xpert Omni MTB/RIF Ultra Assay includes reagents for the detection of MTB and RIF resistance and a sample processing control (SPC) to control for adequate processing of the target bacteria and to monitor for the presence of inhibitor(s) in the PCR reaction and subsequent melt peak detection. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The primers in the Xpert Omni MTB/RIF Ultra Assay amplify a portion of the *rpoB* gene containing the 81 base pair "core" region and portions of the multi-copy *IS1081* and *IS6110* insertion elements target sequences. The melt analysis with four *rpoB* probes is able to differentiate between the conserved wild-type sequence and mutations in the core region that are associated with RIF resistance. The two insertion element probes enhance the detection of *Mycobacterium tuberculosis* complex due to the multi-copy insertion element target sequences in most TB strains.

# 6 Materials Provided

The Xpert Omni MTB/RIF Ultra Assay kits contain sufficient reagents to process 10 samples. The kits contain the following:

| | |
|---|---|
| **Xpert Omni MTB/RIF Ultra Assay Cartridges with Integrated Reaction Tubes** | **10 per kit** |
| Bead 1 and Bead 2 (freeze-dried) | 2 of each per cartridge |
| Bead 3 | 1 of each per cartridge |
| Reagent 1 | 4 mL per cartridge |
| Reagent 2 | 4 mL per cartridge |
| **Sample Reagent Bottles** | **10** |
| Sample Reagent | 8 mL per bottle |
| **Disposable Transfer Pipettes** | **12 per kit** |
| **Quick Reference Guide** | 1 |

**Note** Sample Reagent (SR) can be colorless to yellow to amber. Color may intensify with time, but color has no effect on performance.

**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.

**Note** The transfer pipettes have a single mark representing the minimum volume of treated sample necessary to transfer to the cartridge. Use only for this purpose. All other pipettes must be provided by the laboratory.

# 7 Storage and Handling

- Store the Xpert Omni MTB/RIF Ultra Assay cartridges at 2-35 °C.
- Do not open a cartridge lid until you are ready to perform testing.

# 8 Materials Required but Not Provided

- GeneXpert Omni System (catalog number varies by configuration):
  - Mobile device with software version 1.3 or higher
  - Instrument with software version 1.3 or higher
- Printer: If a printer is required, contact Cepheid Sales Representative to arrange for the purchase of a recommended printer.
- Leak-proof, sterile screw-capped collection containers
- Disposable gloves
- Labels and/or indelible labeling marker
- Sterile pipettes for sample processing

# 9 Warnings, Precautions, and Chemical Hazards

## 9.1 Warnings and Precautions

- 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[7] and the Clinical and Laboratory Standards Institute.[8]
- Wear protective disposable gloves, laboratory coats and eye protection when handling samples and reagents. Wash hands thoroughly after handling samples and test reagents.
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- Do not substitute Xpert Omni MTB/RIF Ultra Assay reagents with other reagents.
- Do not open the Xpert Omni MTB/RIF Ultra Assay cartridge lid except when adding treated sample.
- Do not use a cartridge that has been dropped after removing it from the kit.
- Do not use a cartridge that has been dropped or shaken or has spilled contents of cartridge after you have added the treated sample. Shaking or dropping the cartridge after opening the lid may yield false or non-determinate results.
- Do not place the Sample ID label on the cartridge lid or on the bar code label.
- Do not use a cartridge if it appears wet or if the lid seal appears to have been broken.
- Do not use a cartridge that has a damaged reaction tube.
- When processing more than one sample at a time, open only one cartridge; add the Sample Reagent-treated sample and close the cartridge lid before processing the next sample. Change gloves between samples.
- Each Xpert Omni MTB/RIF Ultra Assay cartridge is used to process one test. Do not reuse processed cartridges.
- Good laboratory practices should be followed, and gloves should be changed between handling each patient specimen in order to avoid contamination of specimens or reagents. Regularly clean the work surface/areas with 10% bleach then wipe the surface again with 70% ethanol or isopropyl alcohol before and after processing specimens.
- 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.

## 9.2 Chemical Hazards[9,10]

**DANGER** 

### Hazard Statements

- Flammable liquid and vapor
- Causes severe skin burns and eye damage.
- Causes serious eye damage
- Suspected of causing genetic defects.
- Suspected of damaging fertility or the unborn child.
- May cause damage to organs through prolonged or repeated exposure.

### Precautionary Statements

**Prevention**

- Obtain special instructions before use.
- Do not handle until all safety precautions have been read and understood.
- Keep away from heat, sparks, open flames and/or hot surfaces. - No smoking.
- Keep container tightly closed.
- Do not breathe mists, vapors, and/or spray.
- Wash thoroughly after handling.
- Wear protective gloves/protective clothing/eye protection/face protection.
- Use personal protective equipment as required.

**Response**

- In case of fire: Use appropriate media for extinction.
- IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.
- Immediately call a POISON CENTER or doctor/physician.
- IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower.
- Wash contaminated clothing before reuse.
- Specific treatment, see supplemental first aid information.
- IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
- IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
- IF exposed or concerned: Get medical advice/attention.
- Get medical advice/attention if you feel unwell.

**Storage/Disposal**

- Dispose of content and/or container in accordance with local, regional, national, and/or international regulations.

# 10 Sample Collection, Transport, and Storage

Collect sputum or aerosol-induced sputum following your institution's standard procedures. Refer to national biosafety regulations or WHO recommendation[11] for detailed instructions.

## 10.1 Collection

The best time to collect a specimen is in the morning, just after waking up.

1. If the patient is not assisted by a healthcare specialist, make sure the patient is alone in a well-ventilated room or outside with no one around, to avoid possible disease transmission through droplets.
2. Ask the patient to rinse the mouth with water. Sputum should not contain any food particles. See Figure 1.

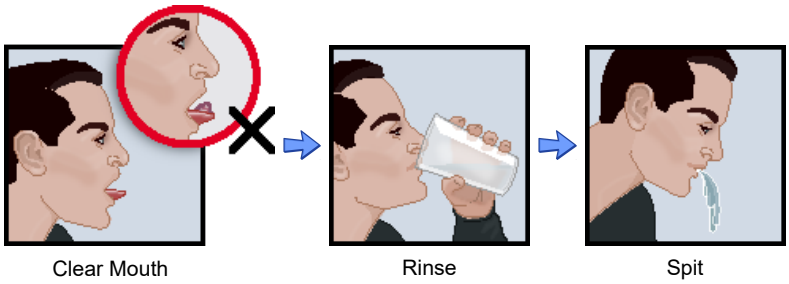



**Figure 1. Patient rinses mouth with water.**

3. Open the container only when ready to produce a sputum.
4. Inhale and exhale repeatedly 3 times to full lung capacity then exhale the air with an explosive cough. See Figure 2. This should produce mucus from the lungs that can be expectorated into the container.

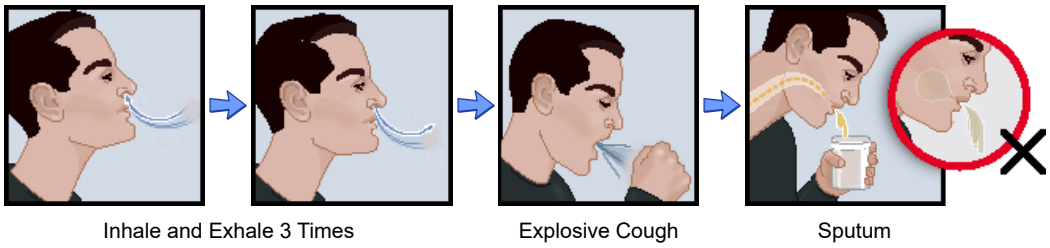



**Figure 2. Patient expectorates into container.**

"Spit" from the mouth or nasal discharge is NOT adequate specimen. Make sure to expectorate into the container without contaminating the outside. Required volume of sputum: at least 1 mL or more. See Table 1 to determine adequate specimen volume.

**Table 1. Required Specimen Volume**

| Specimen Type | Minimum Volume for One Test | Maximum Sample Volume | Sample to Sample Reagent (SR) Ratio |
|---|---|---|---|
| Sputum sediment | 0.5 mL | 2.5 mL | 1:3[a] |
| Unprocessed sputum | 1 mL | 4.0 mL | 1:2 |

[a] 1:2 sample to SR ratio should be used with sample volume of 0.7 mL or greater for one test.

5. Tightly close the container and bring it to the testing location immediately. See Figure 3.

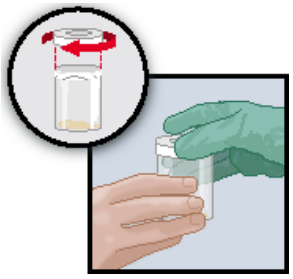


**Figure 3. Tightly close the container.**

6. Test unprocessed sputum or concentrated/decontaminated sputum sediment.

## 10.2 Storage and Transport

Sputum sediment: Store resuspended sediment at 2–8°C for up to 7 days.

Unprocessed sputum: Store unprocessed sputum at 2–40°C for up to 15 days.

# 11 Assay Procedure

## 11.1 Procedure for Decontaminated, Concentrated Sputum Sediments

**Note** Reject specimens with obvious food particles or other solid particulates.

*Volume Requirements*: Sputum sediments prepared according to the method of Kent and Kubica[12] and re-suspended in 67 mM Phosphate/$H_2O$ buffer) can be tested using the Xpert Omni MTB/RIF Ultra Assay. After resuspension, keep at least 0.5 mL of the resuspended sediment for the Xpert Omni MTB/RIF Ultra Assay. For all volumes less than 0.7 mL perform steps 1–6. These steps require 3 parts Sample Reagent (SR) to 1 part sediment in order to generate adequate volume (~2 mL) for the optimum performance of the assay.

If the sample volume is equal to or greater than 0.7 mL, adequate test volume can be produced by adding 2 parts SR to 1 part sediment. In this example 1.4 mL of SR would be added to 0.7 mL sediment. These volumes scale at a ratio of 2 parts SR to 1 part sediment.

1. Bring the cartridge to 15–40°C. Label each Xpert Omni MTB/RIF Ultra Assay cartridge with the Sample ID. See Figure 4.

**Note** Write on the side of the cartridge or affix an ID label. Do not put the label on the lid of the cartridge or over the existing 2D barcode on the cartridge.


**Figure 4. Writing on the Cartridge with a Permanent Marking Pen**

2. Mix the sediment by vortexing or use a pipette to aspirate and eject the material enough times to assure that all organisms are in suspension.
3. Transfer 0.5 mL of the total resuspended pellet to a conical, screw-capped tube for the Xpert Omni MTB/RIF Ultra Assay using a transfer pipette.

**Note** Store re-suspended sediments at 2 to 8°C if they are not immediately processed. Do not run the Xpert Omni MTB/RIF Ultra Assay test on a resuspended sediment that has been refrigerated for > 7 days.

4. Transfer 1.5 mL of Xpert Omni MTB/RIF Ultra Assay Sample Reagent (SR) to 0.5 mL of resuspended sediment using a transfer pipette. Tighten cap securely.
5. Shake vigorously 10 to 20 times or vortex for at least 10 seconds.

**Note** One back-and-forth-movement is a single shake.

6. Incubate for 10 minutes at 15–40°C, and then shake the specimen vigorously 10 to 20 times or vortex for at least 10 seconds.
7. Incubate the sample at 15–40°C for an additional 5 minutes.

## 11.2 Procedure for Unprocessed Sputum

*Volume Requirement*: ≥ 1 mL of unprocessed sputum is required.

1. Bring the cartridge to 15–40°C. Label each Xpert Omni MTB/RIF Ultra Assay cartridge with the Sample ID. See Figure 4.

**Note** Write on the side of the cartridge or affix an ID label. Do not put the label on the lid of the cartridge or over the existing 2D barcode on the cartridge.

2. After receiving the sample in a leak-proof sputum collection container, carefully open the lid of the sputum collection container and examine the contents to be sure there are no food particles or other solid particles. See Figure 5.

**Note** Reject specimens with obvious food particles or other solid particulates.

**Figure 5. Opening the Sample Container**

3. Pour approximately 2 times the volume of the SR into the sputum (2:1 dilution, SR:sputum). See Figure 6.

**Note** Discard the leftover SR and the bottle in a chemical waste container.

**Figure 6. Examples of 2:1 Dilutions**

4. Replace and secure the lid. Shake vigorously 10 to 20 times or vortex for at least 10 seconds.

**Note** One back-and-forth-movement is a single shake.

5. Incubate the sample for 10 minutes at 15–40°C.
6. Shake the specimen vigorously 10 to 20 times or vortex for at least 10 seconds. Incubate the sample at 15–40°C for an additional 5 minutes.

**Note** Ensure that the specimen is liquefied completely. If specimen is not liquefied, repeat step 6.

## 11.3 Preparing the Cartridge

**Before you prepare the cartridge, ensure that:**

**Important**

- **The Xpert Omni MTB/RIF Ultra Assay definition file (ADF) has been downloaded to the mobile device and installed on the Omni instrument.**
- **The Omni instrument is connected to the mobile device.**

**Note**

After adding the sample reagent-treated sample to the cartridge, the sample stays stable for this length of time:

- *Sputum-sediment* sample for 1.5 hours
- *Unprocessed sputum* sample for 2.5 hours

Once the sample is added to the cartridge, the cartridge should remain at 15–40°C prior to starting the test.

1. Open the cartridge lid, and then open the sample container.
2. Using the provided transfer pipette, aspirate the liquefied sample to just above the line on the pipette. Do not process the sample further if there is insufficient volume. See Figure 7.


**Figure 7. Aspirating to the line on the pipette**

3. Transfer the sample into the sample chamber of the Xpert Omni MTB/RIF Ultra cartridge. Dispense the sample slowly to minimize the risk of aerosol formation. See Figure 8.

**Figure 8. Dispensing Sample into the Sample Chamber of the Cartridge**

4. Close the cartridge lid firmly. If retesting is required, remaining liquefied sample may be kept as indicated in Table 2.

**Table 2. Liquefied Hold Times and Temperature**

| Liquefied Sample Type | Hold Time | Temperature |
|---|---|---|
| Unprocessed Sputum | 2.5 hours | 15–40°C |
| Sputum Sediment | 1.5 hours | 15–40°C |

## 11.4 Number of Runs that can be Performed on Full Battery Charge

A minimum of 2 assay runs can be performed on 1 full Omni *internal* battery charge.

A minimum of 4 assay runs can be performed on 1 full Omni *external* battery charge.

## 11.5 Starting the Test

1. Turn on the Omni instrument. Press in and hold the red power button on the back of the Omni instrument for 2 seconds.

**Note** It takes about two minutes to start up the instrument. During this time, the instrument performs a self-test procedure that includes opening and closing the cartridge door. When the instrument is ready, the white flashing activity light illuminates.

2. Turn on the mobile device. Press and hold the power button on the right side of the mobile device.
3. Swipe the mobile device home screen to unlock the mobile device.
4. In the Launcher application, tap the **Omni** icon to start the Omni mobile application (see Figure 9). The Cepheid login screen appears.

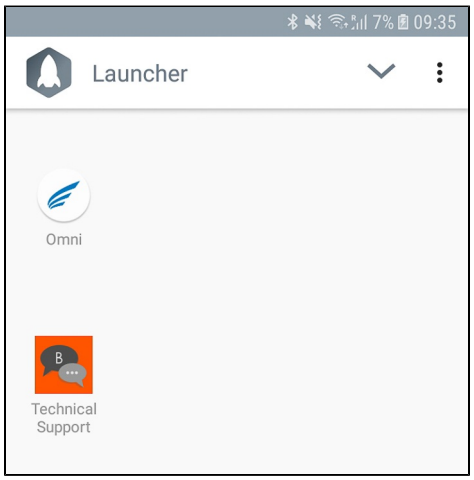



**Figure 9. Omni Application**

5. On the Cepheid login screen, tap **LOGIN**.
6. Tap in the **User Name** field and use the keyboard to type in your user name. Figure 10 shows an example of a user name typed into the field (e.g., my.institution01@gmail.com).

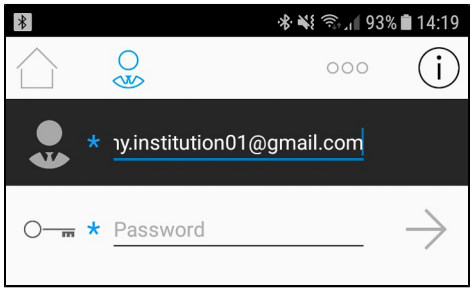



**Figure 10. User Name and Password Fields**

7. Tap in the **Password** field, type the password, and tap the **adjacent arrow** to enter login information (see Figure 10). The Home screen appears.
8. Verify that the instrument icon(s) appear at the bottom of the screen as shown in Figure 11.

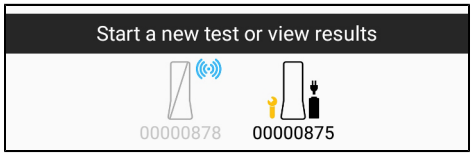



**Figure 11. Example of an Omni Instrument Connected to Mobile Device**

9. On the Home screen, tap the **Start New Test** icon (see Figure 12). The Patient ID screen appears.

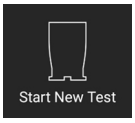



**Figure 12. Start New Test Icon on Home Screen**

10. Enter the Patient ID by manually entering or scanning it.

    - **Manual Entry:** Tap in the **Patient ID** field and enter the Patient ID.
    - **Barcode Scan:** If you have a Patient ID barcode on a paperwork test order, click the barcode icon adjacent to the **Patient ID** field. Aim the rear camera of the mobile device at the barcode on the paper to scan the barcode. When looking at the screen, overlay the barcode with the crosshairs and hold the mobile device still. When the mobile device recognizes the barcode, a beep sounds, and the Barcode dialog box opens. Verify that the ID in the dialog box matches the ID on the test order and click **CONFIRM**.

11. Scroll down to locate and tap the **forward arrow** at the bottom of the Patient ID screen. The Sample ID screen opens.

**Note** You can enter additional patient information (patient date of birth, patient name, patient gender, and patient address) in fields on the Patient ID screen, if pre-configured by your institutional administrator.

12. Enter the Sample ID by manually entering or scanning or randomly generating a Sample ID (see Figure 13):
    - **Manual Entry:** Tap the **Enter Sample ID** icon, then type the Sample ID in the **Sample ID** field. OR
    - **Barcode Scan:** Tap the **Scan Sample Barcode** icon. Aim the rear camera of the mobile device at the Sample ID barcode on the sample container. When the mobile device recognizes the barcode, a beep sounds, and the Sample ID appears in the **Sample ID** field. OR
    - **Generate ID:** Tap the **Generate Sample ID** icon. A random ID generator generates the Sample ID in the **Sample ID** field that you can record on the sample container or test order.


**Figure 13. Sample ID Icons**

**Note** You can enter additional sample information (test type, sample type description, and notes) in fields on the Sample ID screen.

13. Scroll down to locate and tap the **forward arrow** at the bottom of the Sample ID screen.
14. Using the screen animation on the mobile device as a guide, put the back of the mobile device close to the GeneXpert cartridge label to read the NFC tag embedded in the cartridge label (see Figure 14). **DO NOT** hold the reaction tube located at the back of the cartridge. When the mobile device reads the cartridge, it emits a single beep.

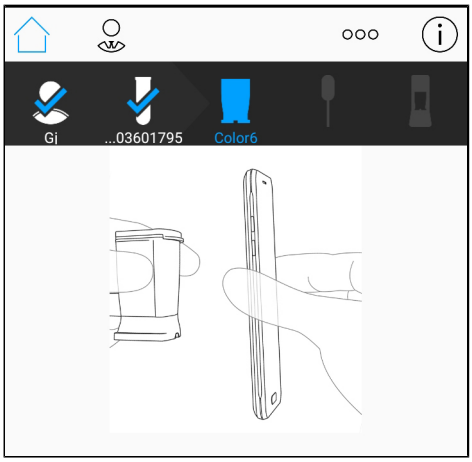



**Figure 14. Scan Cartridge with Mobile Device**

15. Verify that the correct cartridge was scanned and that the assay name shown on the screen matches closely with the assay name on the cartridge.

**Note** The assay name shown in the **Assay Name** field may not match exactly the assay name on the cartridge which may be abbreviated.

16. Scroll down to locate and tap the **forward arrow** at the bottom right of the screen. Animation on the screen appears as a guide to help you load the sample into the cartridge.

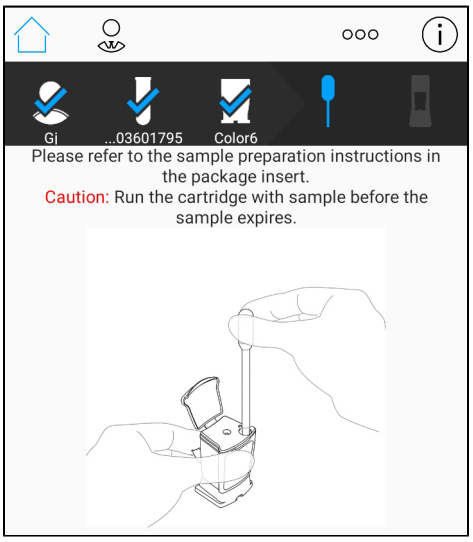



**Figure 15. Loading Sample into Cartridge**

## 11.6 Loading Cartridge on the GeneXpert Omni

1. Scroll down to locate and tap the **forward arrow** at the bottom of the screen.
2. Tap the serial number of the instrument connected to the mobile device to use for the test. The door to the instrument opens.
3. With the cartridge label facing out, place the cartridge into the instrument so the side rails of the cartridge just enter the receiving tracks of the cartridge bay.
4. Using both hands, press the cartridge gently into the instrument.
   The loading mechanism pulls the cartridge inside the instrument and the door closes.

**C_Caution** **Do not touch or otherwise interfere with the door as it is closing. Sensors will detect interference and interrupt the test.**

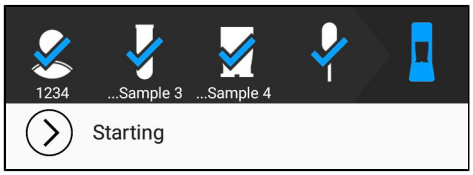
**C_Caution** **Do not try to manually open or close the instrument door at any time. Damage to the door mechanism can occur if the door is manually operated.**

**C_Caution** **Do not move the instrument once a test has started. Invalid test results can occur if the instrument is moved during processing.**

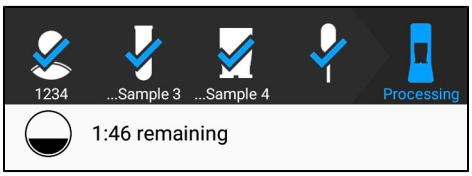
**C_Caution** **Do not tip the instrument when a test is running. In addition to causing an error and possible invalid test results, damage to the instrument can occur if the cartridge contents leak or spill into the interior of the instrument.**

After the door closes, the test request is sent to the instrument and the test begins.

The screen indicates the test is starting, as shown in the following image.




Then, the rightmost workflow icon indicates that the test is processing, and the screen displays the hours and minutes remaining until the test completes.




When the test completes, the instrument door opens and the screen provides the test result.

5. Remove the cartridge and dispose of the cartridge according to your institution's hazardous waste policies.

## 11.7 Viewing Results

1. On the Home screen, tap the **View Results** icon (see Figure 16).

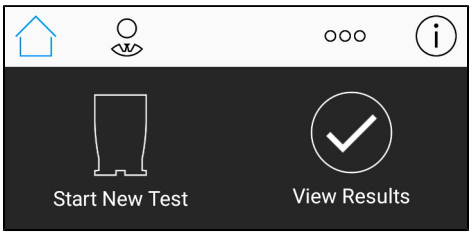



**Figure 16. View Results Icon**

The test results performed today are listed with the most recent test at the top (see Figure 17).

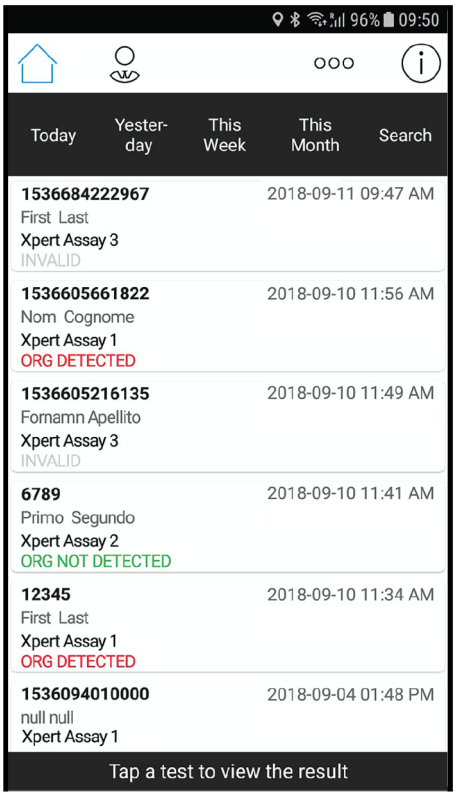



**Figure 17. View Results Screen**

2. To view the list of results for a different time period, tap one of the result period options shown at the top of the screen (see Figure 18).

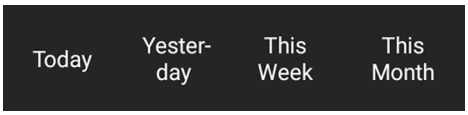



**Figure 18. Select Result Period**

3. Tap a listed test to view more information about the test and print the test result by tapping **Print Result** at the bottom of the screen. If results are not displayed, make sure that:
   - Omni instrument is turned on.
   - Mobile device is within 30 meters (100 feet) of the Omni instrument.

# 12 Quality Control

Each test includes a Sample Processing Control (SPC) and a Probe Check Control (PCC).

### Sample Processing Control (SPC)

Ensures the sample was processed correctly. The SPC contains non-infectious spores in the form of a dry spore cake that is included in each cartridge to verify adequate processing of MTB. The SPC verifies that lysis of MTB 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 assay.

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. The test result will be "Invalid" if the SPC is not detected in a negative test.

### Probe Check Control (PCC)

Before the start of the PCR reaction, the GeneXpert Omni System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity, and dye stability. The PCC passes if it meets the assigned acceptance criteria.

# 13 Interpretation of Results

The GeneXpert Omni System generates the results from measured fluorescent signals and embedded calculation algorithms. The results can be seen in the **View Results** window. See Figure 19, Figure 20, and Figure 21 for specific examples, and see Table 4 for a list of all possible results.

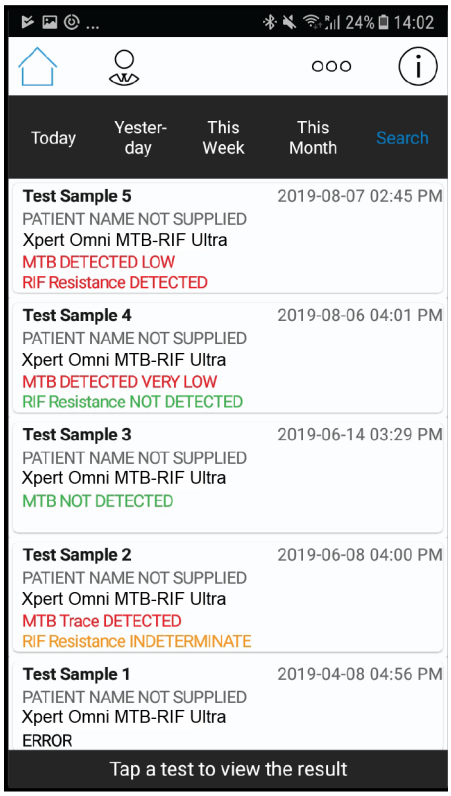



**Figure 19. Summary View showing 5 Different Test Results**

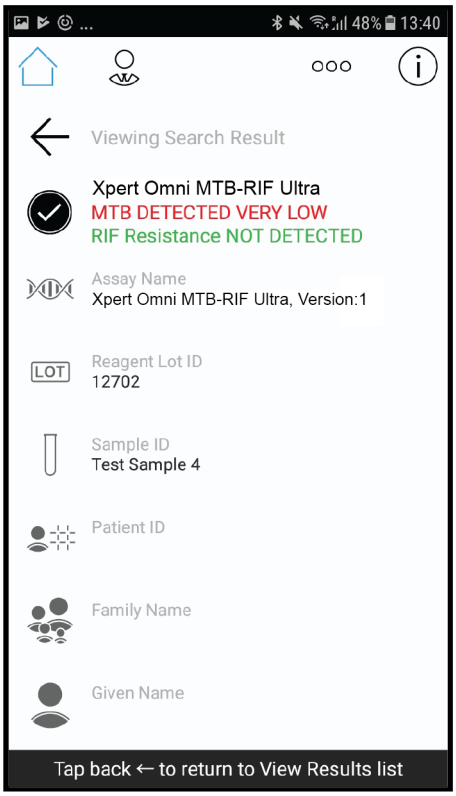



**Figure 20. MTB DETECTED VERY LOW, RIF Resistance NOT DETECTED (top half of screen)**

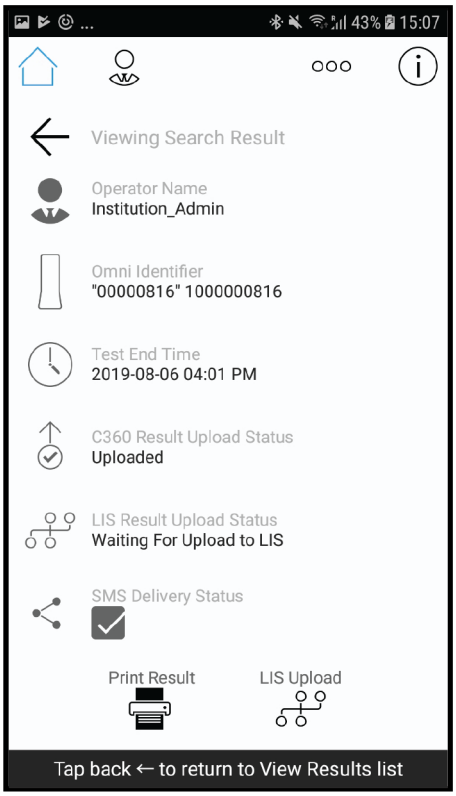



**Figure 21. MTB DETECTED VERY LOW, RIF Resistance NOT DETECTED (bottom half of screen)**

**Table 3. Xpert Omni MTB/RIF Ultra Assay Results and Interpretation**

| Result | Interpretation |
|---|---|
| **MTB DETECTED HIGH; RIF Resistance DETECTED** | The MTB target is present within the sample:<br>• A mutation in the *rpoB* gene target sequence has been detected.<br>• SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control.<br>• Probe Check: PASS. All probe check results pass. |
| **MTB DETECTED MEDIUM; RIF Resistance DETECTED** | |
| **MTB DETECTED LOW; RIF Resistance DETECTED** | |
| **MTB DETECTED VERY LOW; RIF Resistance DETECTED** | |
| **MTB DETECTED HIGH; RIF Resistance NOT DETECTED** | The MTB target is present within the sample:<br>• No mutation in the *rpoB* gene target sequence has been detected.<br>• SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control.<br>• Probe Check: PASS. All probe check results pass. |
| **MTB DETECTED MEDIUM; RIF Resistance NOT DETECTED** | |
| **MTB DETECTED LOW; RIF Resistance NOT DETECTED** | |

| Result | Interpretation |
|---|---|
| **MTB DETECTED VERY LOW; RIF Resistance NOT DETECTED** | |
| **MTB DETECTED HIGH; RIF Resistance INDETERMINATE** | The MTB target is present within the sample:<br>● RIF resistance could not be determined due to invalid melt peaks.<br>● SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control.<br>● Probe Check: PASS. All probe check results pass. |
| **MTB DETECTED MEDIUM; RIF Resistance INDETERMINATE** | |
| **MTB DETECTED LOW; RIF Resistance INDETERMINATE** | |
| **MTB DETECTED VERY LOW; RIF Resistance INDETERMINATE** | |
| **MTB Trace DETECTED; RIF Resistance INDETERMINATE** | The MTB target is present within the sample:<br>● RIF resistance cannot be determined due to insufficient signal detection.<br>● SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control.<br>● Probe Check: PASS. All probe check results pass. |
| **MTB NOT DETECTED** | The MTB target is not detected within the sample:<br>● SPC: PASS. The SPC met the acceptance criteria.<br>● Probe Check: PASS. All probe check results pass. |
| **INVALID** | The presence or absence of MTB cannot be determined. The SPC does not meet the acceptance criteria, the sample was not properly processed, or PCR was inhibited. Repeat the test. See the Section 13.1 section of this document.<br>● MTB: INVALID. The presence or absence of MTB DNA cannot be determined.<br>● SPC: FAIL. The MTB target result is negative, and the SPC Ct is not within valid range.<br>● Probe Check: PASS. All probe check results pass. |
| **ERROR** | The presence or absence of MTB cannot be determined. Repeat the test. See the Section 13.1 section of this document.<br>● MTB: NO RESULT<br>● SPC: NO RESULT<br>● Probe Check: FAIL. All or one of the probe check results failed.<br>**Note**: If the probe check passed, the error is caused by a system component failure. |
| **NO RESULT** | The presence or absence of MTB cannot be determined. Repeat the test. See the Section 13.1 section of this document. A NO RESULT indicates that insufficient data were collected. For example, the operator stopped a test that was in progress.<br>● MTB: NO RESULT<br>● SPC: NO RESULT<br>● Probe Check: NA (not applicable) |

**Table 4. Xpert Omni MTB/RIF Ultra Assay: All Possible Results**

| TB Results | RIF Results |
|---|---|
| **MTB DETECTED HIGH** | **RIF Resistance DETECTED** |
| **MTB DETECTED HIGH** | **RIF Resistance NOT DETECTED** |
| **MTB DETECTED HIGH** | **RIF Resistance INDETERMINATE** |
| **MTB DETECTED MEDIUM** | **RIF Resistance DETECTED** |
| **MTB DETECTED MEDIUM** | **RIF Resistance NOT DETECTED** |
| **MTB DETECTED MEDIUM** | **RIF Resistance INDETERMINATE** |
| **MTB DETECTED LOW** | **RIF Resistance DETECTED** |
| **MTB DETECTED LOW** | **RIF Resistance NOT DETECTED** |
| **MTB DETECTED LOW** | **RIF Resistance INDETERMINATE** |
| **MTB DETECTED VERY LOW** | **RIF Resistance DETECTED** |
| **MTB DETECTED VERY LOW** | **RIF Resistance NOT DETECTED** |
| **MTB DETECTED VERY LOW** | **RIF Resistance INDETERMINATE** |
| **MTB Trace DETECTED** [a] | **RIF Resistance INDETERMINATE** |
| **MTB NOT DETECTED** | |
| **INVALID** | |
| **ERROR** | |
| **NO RESULT** | |

[a] A **MTB Trace DETECTED** result call means that low levels of MTB Complex DNA is detected but no RIF resistant result is detected. This occurs due to the increased sensitivity of MTB Complex DNA detection using multi-copy targets *IS6110* and *IS1081* as opposed to RIF resistance detection using the single copy *rpoB* gene. Therefore, a RIF resistant or susceptible result cannot be determined in a **MTB Trace DETECTED** sample. The **MTB Trace DETECTED** sample is always **RIF Resistance INDETERMINATE**.

## 13.1 Retest Procedure

If you have *leftover unprocessed sputum* or *sputum sediment*, always use new SR to decontaminate and liquefy the sputum or the sediment before running the assay. See Section 11.1 or Section 11.2.

If you have *sufficient leftover SR-treated sample*, refer to Table 2 to determine if the sample can be used for retest.

When retesting, always use a new cartridge and start the test immediately. See Section 11.3.

## 13.2 Reasons to Repeat the Assay

Repeat the test using a new cartridge if one of the following test results occurs.

- An **INVALID** result indicates that the SPC failed. The sample was not properly processed or PCR is inhibited.
- An **ERROR** result indicates that the PCC failed and the assay was aborted possibly due to the reaction tube being filled improperly, a reagent probe integrity problem was detected, because the maximum pressure limits were exceeded, or a GeneXpert Omni System failed.
- A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress.

# 14 Limitations

Because the detection of MTB complex DNA is dependent on the number of organisms present in the sample, reliable assay results are dependent on proper specimen collection, handling, and storage. Erroneous test results might occur from improper specimen collection, failure to follow the recommended sample collection procedure, handling or storage, technical error, sample mix-up, or an insufficient concentration of starting material. Careful compliance to 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 MTB and Rifampin resistance.

Mutations or polymorphisms in primer or probe binding regions may affect detection of new or unknown MDR-MTB or rifampin resistant strains resulting in a false rifampin-sensitive result.

The Xpert Omni MTB/RIF Ultra Assay performance has not been evaluated in patients less than eighteen years of age.

The Xpert Omni MTB/RIF Ultra Assay does not provide confirmation of rifampin susceptibility since mechanisms of rifampin resistance other than those detected by this device may exist that may be associated with a lack of clinical response to treatment. Specimens that have both MTB-complex DNA and rifampin-resistance associated mutations of the *rpoB* gene detected by the Xpert Omni MTB/RIF Ultra Assay should be considered for additional drug susceptibility testing.

The performance of the Xpert Omni MTB/RIF Ultra test is dependent on operator proficiency and adherence to assay procedures. Assay procedural errors may cause false positive or false negative results. All device operators should have appropriate device training.

Results of **MTB Trace DETECTED** may require further clinical information from the patients and more consideration of the clinical context for TB treatment decisions in some settings.

Concentrated sputum sediments used in the performance evaluation of the Xpert Omni MTB/RIF Ultra Assay were prepared following the NALC-NaOH method described in Kent and Kubica.[11] Use of other methods of sediment preparation may alter the performance of the test.

Lower sensitivity has been reported in the literature in pediatric patients due to the diffuse nature of MTB infection in the lungs of this patient group, and difficulties encountered in obtaining adequate specimens.[13,14]

A trained health care professional should interpret assay results in conjunction with the patient's medical history, clinical signs and symptoms, and the results of other diagnostic tests.

# 15 Clinical Performance Characteristics

## 15.1 Xpert MTB/RIF Ultra Assay

### Clinical Study Design

The performance characteristics of the Xpert MTB/RIF Ultra Assay on the GeneXpert Instrument System were evaluated for the detection of MTB-complex DNA and for the detection of RIF-resistance associated mutations in sputum specimens relative to results from culture (solid and/or liquid media) and phenotypic drug susceptibility testing (pDST), respectively. This multi-center study used prospective and archived direct (raw) sputum or concentrated sediment specimens. Subjects included those with presumptive pulmonary TB on no TB treatment or less than 3 days of treatment within 6 months of the study start (TB suspects) as well as previously TB treated subjects who were suspected of multi-drug resistant TB (MDR TB suspects).

A total of 1835 specimens were included, 1228 were prospectively collected and 607 were from frozen archived specimen banks. The specimens came from study subjects, 61% male (n=1111), 35% female (n=648); for 4% (n=76) gender was unknown. Specimens were obtained from geographically diverse regions: 12% (n=217) were from the US and 88% (n=1618) were from countries outside the US.

### Xpert MTB/RIF Ultra Assay Performance vs. Culture for MTB Detection

Up to three sputum specimens were collected from each study subject for use in the clinical study. For prospective specimens, the first sputum specimen was tested by the Xpert MTB/RIF Ultra Assay and the two additional specimens were used for TB culture. For archived specimens, Xpert MTB/RIF Ultra Assay was performed using the first specimen with sufficient volume and culture results from the standard of care testing were obtained. If the assay result was non-determinate (**ERROR**, **INVALID** or **NO RESULT**), the specimen was retested if there was sufficient volume. The acid fast bacilli

(AFB) smear status was determined by Auramine-O (AO) fluorescent or Ziehl-Neelsen (ZN) smear stain for specimens with corresponding Xpert MTB/RIF Ultra Assay result. The MTB culture status for all subjects was defined based on the MTB culture result of all specimens collected within a seven-day period for that subject.

The sensitivity of MTB detection in smear positive and smear negative specimens was 99.5% (426/428), 95% CI: 98.3, 99.9 and 73.3% (200/273), 95% CI: 67.7, 78.2, respectively. The overall specificity of MTB detection regardless of AFB smear results was 95.5% (1222/1280), 95% CI: 94.2, 96.5.

### Xpert MTB/RIF Ultra Assay Performance vs. pDST for RIF Resistance Detection

MTB positive culture isolates were tested for pDST to rifampin using the agar proportion method with Middlebrook or Lowenstein-Jensen media, the Thermo Scientific Sensititre™ Mycobacterium tuberculosis MIC Plate or the BD BACTEC™ MGIT™ 960 SIRE assay. The performance of the Xpert MTB/RIF Ultra Assay for detection of RIF-resistance associated mutations relative to the pDST was evaluated in MTB culture isolates. Results for the detection of RIF resistance associated mutations are reported by the Xpert MTB/RIF Ultra Assay only when the *rpoB* gene sequence of MTB-complex was detected. Specimens were excluded from the analysis if pDST was not done, or if **MTB NOT DETECTED** and **MTB DETECTED: RIF Resistance INDETERMINATE** were reported. Of the 67 specimens with **RIF Resistance INDETERMINATE** results, 63 were **MTB Trace DETECTED; RIF Resistance INDETERMINATE**.

The sensitivity and specificity of rifampicin detection was 96.2% (128/133), 95% CI: 91.5, 98.4 and 96.3% (314/326), 95% CI: 93.7, 97.9 respectively.

## 15.2 Xpert Omni MTB/RIF Ultra Assay

### Clinical Evaluation

Performance characteristics of the Xpert Omni MTB/RIF Ultra Assay on the GeneXpert Omni System was evaluated for the detection of MTB-complex DNA and for the detection of RIF-resistance associated mutations in sputum specimens relative to an on-market NAAT test, the Xpert MTB/RIF Ultra Assay on the GeneXpert Dx System. A multi-center study was conducted at two sites - one in South Africa and one in the United States, using archived leftover unprocessed sputum specimens or concentrated sediments prepared from induced or expectorated sputum. A total of 161 specimens were tested with the Xpert Omni MTB/RIF Ultra Assay and the comparator test. The Xpert Omni MTB/RIF Ultra Assay demonstrated a positive percent agreement (PPA) of 100.0% (95%CI: 94.9-100.0) and negative percent agreement (NPA) of 95.6% (95%CI: 89.1-98.3) for MTB detection. Results are shown in Table 5.

**Table 5. Xpert Omni MTB/RIF Ultra Assay on the GeneXpert Omni System vs. Xpert MTB/RIF Ultra Assay on the GeneXpert Dx System**

| | | Xpert MTB/RIF Ultra Assay on GeneXpert Dx System | | |
|---|---|---|---|---|
| | | MTB Detected | MTB Not Detected | Total |
| **Xpert Omni MTB/RIF Ultra on GeneXpert Omni System** | MTB Detected | 71 | 4[a] | 75 |
| | MTB Not Detected | 0 | 86 | 86 |
| | Total | 71 | 90 | 161 |
| | PPA | 100.0% (95%CI: 94.9-100.0) | | |
| | NPA | 95.6% (95%CI: 89.1-98.3) | | |

[a] Four specimens were **MTB Detected Trace DETECTED; RIF Resistance Indeterminate** by the Xpert Omni MTB/RIF Ultra Assay and **MTB Not Detected** by the Comparator Method.

The Xpert Omni MTB/RIF Ultra Assay demonstrated PPA of 95.0% (95%CI: 76.4-99.1) and NPA of 100.0% (95%CI: 92.6-100.0) for RIF resistance detection. Results are shown in Table 6.

**Table 6. Xpert Omni MTB/RIF Ultra Assay on the GeneXpert Omni System vs. Xpert MTB/RIF Ultra Assay on the GeneXpert Dx System**

| | | Xpert MTB/RIF Ultra on GeneXpert Dx System | | |
|---|---|---|---|---|
| | | RIF Detected | RIF Not Detected | Total |
| **Xpert Omni MTB/RIF Ultra on GeneXpert Omni System** | RIF Detected | 19 | 0 | 19 |
| | RIF Not Detected | 1[a] | 48 | 49 |
| | Total | 20 | 48 | 68 |
| PPA | | 95.0% (95%CI: 76.4-99.1) | | |
| NPA | | 100.0% (95%CI: 92.6-100.0) | | |

[a] One specimen was **MTB Detected Low; RIF Resistance Not Detected** by the Xpert Omni MTB/RIF Ultra Assay and **MTB Detected High; RIF Resistance Detected** by the Comparator Method.

### Non-determinate Rate

A total of 162 specimens were tested by the Xpert Omni MTB/RIF Ultra Assay of which 158 were valid upon initial testing (97.5%) and 4 (2.5%) were non-determinate. Of the 4 specimens with non-determinate results, all 4 yielded valid results upon repeat test. The final non-determinate rate of the Xpert Omni MTB/RIF Ultra Assay was 0.0% (0/162).

# 16 Analytical Performance Characteristics

## 16.1 Interfering Substances

A study was performed in artificial sputum matrix to assess the effects of potential interfering substances with the Xpert MTB/RIF Ultra Assay. A total of 32 potentially interfering substances were evaluated. Potentially endogenous interfering substances may include, but are not limited, to blood, pus (white blood cells), cells from the respiratory tract, mucin, human DNA, and gastric acid from the stomach. Other potentially interfering substances may include anesthetics, antibiotics, antibacterial, anti-tuberculosis drugs, anti-viral drugs, bronchodilators, inhaled bronchodilators, live intranasal influenza virus vaccine, germicidal mouthwash, specimen processing reagents, *Pneumocystis jiroveci* medication, homeopathic allergy relief medications, nasal corticosteroids, nasal gels, nasal sprays, oral anesthetics, oral expectorants, neutralizing buffers, and tobacco. These substances are listed in Table 7 with active ingredients and concentrations tested shown. Positive and negative samples were included in this study. Positive samples were tested near at 3 times the analytical limit of detection using BCG cells in replicates of 8. Negative samples, comprised of the substance absent the MTB strain, were tested per substance in replicates of 8 to determine the effect on the performance of the sample processing control (SPC).

No inhibitory effect was observed for any of the 32 potentially interfering substances tested (Table 7).

**Table 7. Interfering Substances**

| Substance | Description/Active Ingredient | Concentration Tested |
|---|---|---|
| Blood | Blood (human) | 5% (v/v) |
| Germicidal Mouthwash | Chlorhexidine gluconate (0.12%), 20% solution | 20% (v/v) |
| Specimen Processing Reagents | Cetylpyridinium chloride, 1% in 2% NaCl | 0.5% (v/v) in 1% NaCl |
| Specimen Processing Reagents | Cetylpyridinium chloride, 1% in 2% NALC | 0.5% (v/v) in 1% NALC |
| Specimen Processing Reagents | Cetylpyridinium chloride, 1% in 2% NALC plus 25 mM Citrate | 0.5% (v/v) in 1% NALC plus 12.5 mM Citrate |

| Substance | Description/Active Ingredient | Concentration Tested |
|---|---|---|
| Gastric Acid | pH 3 to 4 solution in water, neutralized with sodium bicarbonate | 100% (v/v) |
| Human DNA/Cells | HELA 229 | $10^6$ cells/mL |
| Antimycotic; Antibiotic | Nystatin oral suspension, 20% | 20% (v/v) |
| White Blood Cells (human) | WBC/Pus matrix (30% buffy coat; 30% plasma; 40% PBS) | 100% (v/v) |
| Anesthetics (endotracheal intubation) | Lidocaine HCl 4% | 30% (v/v) |
| Nebulizing solutions | NaCl 5% (w/v) | 5% (w/v) |
| Mucin | Mucin 5% (w/v) | 5% (w/v) |
| Antibacterial, systemic | Levofloxacin 25 mg/mL | 5 mg/mL |
| Nasal corticosteroids | Fluticasone 500 mcg/spray | 5 µg/mL |
| Inhaled bronchodilators | Albuterol Sulfate 2.5 mg/3mL | 75 µg/mL |
| Oral anesthetics | Orajel (20% Benzocaine) | 5% (w/v) |
| Anti-viral drugs | Acyclovir, IV 50 mg/mL | 50 µg/mL |
| Antibiotic, nasal ointment | Neosporin (400U Bacitracin, 3.5 mg Neomycin, 5000U Polymyxin B) | 5% (w/v) |
| Tobacco | Nicogel (40% tobacco extract) | 0.5% (w/v) |
| Anti-tuberculosis drugs | Streptomycin 1mg/mL | 25 µg/mL |
| Anti-tuberculosis drugs | Ethambutol 1 mg/mL | 50 µg/mL |
| Anti-tuberculosis drugs | Isoniazid 1 mg/mL | 50 µg/mL |
| Oral expectorants | Guaifenesin (400mg/tablet) | 5 mg/mL |
| Anti-tuberculosis drugs | Pyrazinamide 10 mg/mL | 10 µg/mL |
| Nasal gel (Homeopathic) | Zicam gel | 50% (w/v) |
| Nasal spray | Phenylephrine 0.5% | 1% (v/v) |
| Anti-tuberculosis drugs | Rifampicin 1mg/mL | 25 µg/mL |
| Allergy relief medicine (Homeopathic) | Tea tree oil (<5% Cineole, >35% Terpinen- 4-01) | 0.5% (v/v) |
| Live intranasal influenza virus vaccine | Live influenza virus vaccine FluMist | 5% (v/v) |
| *Pneumocystis jiroveci* medication | Pentamidine | 300 ng/mL (v/v) |
| Bronchodilator | Epinephrine (injectable formulation) | 1 mg/mL |
| Anti-tuberculosis drugs | Amoxicillin | 25 µL |

## 16.2 Analytical Sensitivity

Studies were performed to determine the analytical sensitivity or Limit of Detection (LoD) of the Xpert Omni MTB/RIF Ultra Assay using *Mycobacterium tuberculosis* strain H37Rv and *Mycobacterium bovis* BCG (Bacille Galmette-Guerin) diluted in human sputum and human sputum sediment. An MTB positive result is based on the detection of the IS1081/ IS6110 targets.

The LoD is the lowest concentration reported in CFU/mL that can be reproducibly distinguished from negative samples with 95% confidence. Replicates of at least 20 for two strains were evaluated at 8 concentrations over 3 days and the LoD was determined using probit analysis. The claimed LoD are summarized in Table 8.

**Table 8. Probit Analysis Data and Claimed LoD in CFU/mL**

| Mycobacteria Species | Specimen Type | Claimed LoD |
|---|---|---|
| *M. bovis* (BCG) | Sputum | 31.5 |
| | Sputum Sediment | 27.5 |
| *M. tuberculosis* (H37Rv) | Sputum | 12.4 |
| | Sputum Sediment | 10.5 |

## 16.3 Analytical Specificity (Exclusivity)

Cultures of 30 nontuberculous mycobacteria (NTM) strains were tested with the Xpert MTB/RIF Ultra Assay. Three replicates of each isolate were spiked into buffer and tested at a concentration of $\geq 10^7$ CFU/mL. See Table 9.

**Table 9. NTM Strains Tested for Specificity**

| | |
|---|---|
| ***Mycobacterium avium* subsp. *avium*** | ***Mycobacterium scrofulaceum*** |
| ***Mycobacterium celatum*** | ***Mycobacterium simiae*** |
| ***Mycobacterium chelonae*** | ***Mycobacterium szulgai*** |
| ***Mycobacterium gordonae*** | ***Mycobacterium thermoresistibile*** |
| ***Mycobacterium haemophilum*** | ***Mycobacterium triviale*** |
| ***Mycobacterium abscessus*** | ***Mycobacterium vaccae*** |
| ***Mycobacterium asiaticum*** | ***Mycobacterium xenopi*** |
| ***Mycobacterium flavescens*** | ***Mycobacterium smegmatis*** |
| ***Mycobacterium fortuitum* subsp. *fortuitum*** | ***Mycobacterium interjectum*** |
| ***Mycobacterium gastri*** | ***Mycobacterium peregrinum*** |
| ***Mycobacterium genavense*** | ***Mycobacterium mucogenicum*** |
| ***Mycobacterium intracellulare*** | ***Mycobacterium goodii*** |
| ***Mycobacterium kansasii*** | ***Mycobacterium shimodei*** |
| ***Mycobacterium malmoense*** | ***Mycobacterium phlei*** |
| ***Mycobacterium marinum*** | ***Mycobacterium terrae*** |

Under the conditions of the study, all of the NTM isolates were reported as **MTB NOT DETECTED**. Positive and negative controls were included in the study. The specificity was 100%.

Additionally, in order to determine if high concentrations of NTM would interfere with the detection of low levels of TB, six of the strains listed in Table 9 were mixed with the TB strain H37Rv in sputum to a final concentration of $10^6$ CFU/mL NTM and 36 CFU/mL H37Rv.

NTM strains tested for ability to interfere with TB (H37Rv) detected included:

- *M. abscessus*, ATCC 19977
- *M. avium* National Jewish Hospital clinical isolates
- *M. celatum*, National Jewish Hospital clinical isolates
- *M. kansasii*, ATCC 12478
- *M. gordonae*, ATCC 14470
- *M. intracellulare*, National Jewish Hospital clinical isolates

The tested NTM strains did not interfere with the detection of 36 CFU/mL of *M. tuberculosis*; thus, the signals were the same as when H37Rv was tested alone.

## 16.4 Species/Strains Tested for Specificity

The microorganisms in Table 10 including Gram-negative bacteria, Gram-positive bacteria, fungal organisms, viruses and yeast were tested for false positivity in the Xpert MTB/RIF Ultra Assay. The replicates of each isolate were spiked onto buffer and tested at a concentration of $\geq 10^7$ CFU/mL (bacteria and fungal strains) or $\geq 10^6$ copies/mL (genomic DNA for bacteria and fungi) and $\geq 10^5$ $TCID_{50}$ /mL (virus strains).

**Table 10. Species and Strains**

| | | |
|---|---|---|
| ***Acinetobacter baumannii*** | ***Klebsiella pneumoniae*** | ***Respiratory Syncytial Virus Type B*** |
| ***Aspergillus fumigatus*** | ***Moraxella catarrhalis*** | ***Rhinovirus*** |
| ***Candida albicans*** | ***Neisseria meningitidis*** | ***Staphylococcus aureus*** |
| ***Chlamydophila pneumoniae*** | ***Neisseria mucosa*** | ***Staphylococcus epidermidis*** |
| ***Citrobacter freundii*** | ***Nocardia asteroides*** | ***Stenotrophomonas maltophilia*** |
| ***Corynebacterium xerosis*** | ***Parainfluenza Virus Type 1*** | ***Streptococcus agalactiae*** |
| ***Coronavirus*** | ***Parainfluenza Virus Type 2*** | ***Streptococcus mitis*** |
| ***Enterobacter cloacae*** | ***Parainfluenza Virus Type 3*** | ***Streptococcus mutans*** |
| ***Escherichia coli*** | ***Pseudomonas aeruginosa*** | ***Streptococcus pneumoniae*** |
| ***Haemophilus influenzae*** | ***Respiratory Syncytial Virus Type A*** | ***Streptococcus pyogenes*** |
| ***Human metapneumovirus (hMPV) 16 Type A1*** | | |

Under the conditions of the study, all of the microorganisms tested were reported as **MTB NOT DETECTED**. Positive and negative controls were included in the study. The specificity was 100%.

## 16.5 Analytical Inclusivity

Forty five MTB-complex strains consisting of 20 rifampin-susceptible strains with a wild-type rpoB core region and 25 rifampin-resistant strains were tested using the Xpert Omni MTB/RIF Ultra Assay. DNA samples from a total of 45 MTB strains were tested on the GeneXpert Omni System using an Xpert Omni MTB/RIF Ultra protocol modified for DNA testing. The final reaction components and PCR cycling conditions were unchanged from the protocol designed for patient sample testing. All strains were from the laboratory collection at Hackensack University Medical Center. Collectively these strains represent isolates from 12 countries and contained 25 RIF-resistant isolates comprised of single and double rpoB core region mutations. The samples were tested by adding 100 µL of the DNA sample to the lysate chamber of the cartridge. The negative reactions used buffer as the sample. The assay correctly identified all 20 wild-type strains and correctly identified rifampin resistance in all 25 strains resistant to rifampin with mutations in the rpoB core region.

### 16.6 Analytical Inactivation of Mycobacteria in Sputum Samples

The disinfection capability of the Xpert Omni MTB/RIF Ultra sample reagent was determined using a standardized quantitative tuberculocidal culture method. Samples of sputum were spiked with a high concentration of viable *M. bovis*, mixed with sample reagent at a ratio of 2:1, and incubated for 15 minutes. Following incubation the sample reagent/sputum mixture was neutralized by dilution and filtration and then cultured. The viability of the *M. bovis* organisms from the treated sputum was reduced by at least 6 logs relative to the un-treated control.

Each laboratory must determine the effectiveness of the sample reagent disinfection properties using their own standardized methods and must adhere to recommended biosafety regulations.

## 17 Precision and Reproducibility

The precision and reproducibility of the Xpert Omni MTB/RIF Ultra test was determined by using a panel of 5 members consisting of samples prepared at ~1xLoD, 2-3xLoD, and negative samples. Testing was performed by 2 operators at 3 sites. Positive panel members were prepared by spiking inactivated MTB RIF-sensitive or MTB RIF-resistant strains into an artificial sputum matrix. The negative panel member contained only artificial sputum matrix. Each panel member was tested in replicates of 2 once per day by two operators over 6 days. Three different reagent kit lots were used.

The data were analyzed by calculating the qualitative percent agreement for each panel member. The percent agreement and lack of statistically significant differences demonstrated acceptable reproducibility and precision of the Xpert Omni MTB/RIF Ultra test on the GeneXpert Omni System. The results are shown in Table 11.

**Table 11. Percent Agreement of Qualitative Results for MTB/RIF Detection**

| Composition | Site 1 | Site 2 | Site 3 | Total Agreement (%) and 95% CI by Panel Member (n/N) |
|---|---|---|---|---|
| Negative | 100.0%<br>24/24 | 100.0%<br>24/24 | 95.8%<br>23/24 | 98.6%<br>92.5-99.8<br>(71/72) |
| ~1xLoD MTB Low Positive / RIF Susceptible | 91.7%<br>22/24 | 91.7%<br>22/24 | 100.0%<br>24/24 | 94.4%<br>86.6-97.8<br>(68/72) |
| 2-3xLoD MTB Moderate Positive / RIF Susceptible | 91.7%<br>22/24 | 100.0%<br>24/24 | 95.8%<br>23/24 | 95.8%<br>88.5-98.6<br>(69/72) |
| ~1xLoD MTB Low Positive / RIF Resistant | 100.0%<br>24/24 | 100.0%<br>24/24 | 100.0%<br>24/24 | 100.0%<br>94.9-100<br>(72/72) |
| 2-3xLoD MTB Moderate Positive / RIF Resistant | 100.0%<br>24/24 | 100.0%<br>24/24 | 100.0%<br>24/24 | 100.0%<br>94.9-100<br>(72/72) |

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# 19 Cepheid Headquarters Locations

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# 20 Technical Assistance

### Before Contacting Us

Collect the following information before contacting Cepheid Technical Support:

- The product name: GeneXpert Omni System.
- The mobile device and GeneXpert Omni Application software version.

- Any error messages you encountered and notes you have that describe the problem.
- The assay name and lot number located on the assay kit box and Xpert Cartridge label (if you think the problem is assay related).
- The serial number of the GeneXpert Omni Instrument.

### United States

Telephone: + 1 888 838 3222
Email: techsupport@cepheid.com

### France

Telephone: + 33 563 825 319
Email: support@cepheideurope.com

Contact information for other Cepheid offices is available on our website at www.cepheid.com or www.cepheidinternational.com under the **SUPPORT** tab. Select the **Contact Us** option.

# 21 Table of Symbols

| Symbol | Meaning |
|---|---|
|  | Catalog number |
|  | CE marking – European Conformity |
|  | *In vitro* diagnostic medical device |
|  | Do not reuse |
|  | Batch code |
|  | Consult instructions for use |
|  | Caution |
|  | Manufacturer |
|  | Contains sufficient for *n* tests |
|  | Control |
|  | Expiration date |
|  | Temperature limitation |
|  | Biological risks |
|  | Flammable liquids |
|  | Skin corrosion |
|  | Reproductive and organ toxicity |

| Symbol | Meaning |
|---|---|
|  | Warning |

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