GeneXpert
Powered By CEPHEID INNOVATION

Xpert Check™ Package Insert

REF **XPERTCHECK-CE-5**

Cepheid

In Vitro Diagnostic Medical Device IVD CE

301-3985, Rev. G December 2019

Trademark Information

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Preface

About This Document

The *Xpert Check™ Package Insert* provides instructions on running Xpert Check software for checking module performance.

Safety Information

Read and understand any safety information presented in this document before you begin operating the instrument. Make sure you follow the precautionary statements presented in this guide:

Caution

Indicates that damage to the system, loss of data, or invalid results could occur if the user fails to comply with the advice given.

Important

Highlights information that is critical for the completion of a task or the optimal performance of the system.

Note

Identifies information that applies only in special cases.

Related Documents

For other information outside the scope of this document, see the following publications:

- GeneXpert Dx Operation Manual
- Infinity Operation Manual

Cepheid Headquarters Locations

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Technical Assistance

Before contacting Cepheid Technical Support, collect the following information:

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

Region	Telephone	Email
US	+ 1 888 838 3222	techsupport@cepheid.com
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Belgium, Netherlands and Luxembourg	+ 33 563 825 319	support@cepheideurope.com
Brazil and Latin America	+ 55 11 3524 8373	latamsupport@cepheid.com
China	+ 86 021 5406 5387	techsupportchina@cepheid.com
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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.

Table of Symbols

Symbol	Meaning
REF	Catalog number
IVD	*In vitro* diagnostic medical device
LOT	Batch code
	Do not reuse
	Caution
	Consult instructions for use
	Manufacturer
CC	Country of manufacture
Σ	Contains sufficient for <n> tests
	Expiration date
CONTROL	Control
CE	CE marking - European Conformity
EC REP	Authorized representative in the European Community
	Temperature limitation
	Biological risks

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CE IVD

Table of Contents

1 Introduction 1-1

1.1 Proprietary Name 1-1

1.2 Common or Usual Name 1-1

1.3 Intended Use 1-1

1.4 Summary and Explanation 1-1

1.5 Reagents and Instruments 1-2

1.5.1 Materials Provided 1-2

1.5.2 Storage and Handling 1-2

1.5.3 Materials Required but Not Provided 1-3

1.6 Limitations 1-3

1.7 Warnings and Precautions 1-3

1.8 Chemical Hazards 1-4

1.9 Assistance and Contact Information 1-4

1.10 Software Buttons, Icons and Symbols 1-5

2 Procedure 2-1

2.1 System Preparation 2-1

2.1.1 GeneXpert Dx Preparation 2-1

2.1.2 Infinity-48 Preparation 2-1

2.1.3 Infinity-48s or Infinity-80 Preparation 2-2

2.2 GeneXpert and Infinity Optics Cleaning 2-2

2.2.1 Lens Cleaning Procedure 2-2

2.3 Data Collection Procedure: GeneXpert Dx and Infinity 2-5

2.3.1 Xpert Check Completion For Non-internet Connected Users . . . 2-24

2.3.2 Obtaining the Xpert Check Code for Non-Internet Connected Users 2-33

2.4 Return System to Normal Operation 2-40

2.4.1 GeneXpert Dx 2-40

2.4.2 Infinity-48 2-40

2.4.3 Infinity-48s or Infinity-80 2-40

2.5 Information Key Screen 2-41

2.5.1 Reasons to Repeat Xpert Check with a New Cartridge 2-41

2.5.2 Reasons to Repeat Xpert Check with the Same Cartridge 2-41

2.5.3 Application of Xpert Check Code 2-41

List of Figures

Figure 2-1 Lens Cleaning Brush (300-8330) . . . 2-2
Figure 2-2 Inserting the Cleaning Brush into the I-CORE Slit . . . 2-3
Figure 2-3 Terms of Service Screen . . . 2-6
Figure 2-4 Xpert Check Login Screen . . . 2-7
Figure 2-5 Login Error Screen . . . 2-7
Figure 2-6 Home Screen . . . 2-8
Figure 2-7 Contact Information Screen - Page 1 . . . 2-9
Figure 2-8 Contact Information Screen - Page 2 . . . 2-9
Figure 2-9 Open Module Doors Screen . . . 2-10
Figure 2-10 Module preparation Screen . . . 2-10
Figure 2-11 Select modules for data collection Screen . . . 2-11
Figure 2-12 Confirm module selection Screen . . . 2-12
Figure 2-13 Error Screen Examples . . . 2-12
Figure 2-14 Scanning the Cartridge Barcode Screen . . . 2-13
Figure 2-15 Confirm skip Screen . . . 2-14
Figure 2-16 Venting the Cartridge by Opening and Closing the Cartridge Lid - Animated Screen . . . 2-15
Figure 2-17 Loading the Cartridge into the Module . . . 2-16
Figure 2-18 Data Collection Screen . . . 2-17
Figure 2-19 Test Completion Screen - Successful . . . 2-18
Figure 2-20 Test Completion Screen - Unsuccessful Module Checking Example . . . 2-18
Figure 2-21 Confirm Continue Screen Overlay . . . 2-19
Figure 2-22 Uploading Xpert Check Data Screen . . . 2-20
Figure 2-23 Upload incomplete Error Screen . . . 2-21
Figure 2-24 Downloading Xpert Check code Screen . . . 2-21
Figure 2-25 Applying Xpert Check code Screen . . . 2-22
Figure 2-26 Xpert Check complete Screen . . . 2-22
Figure 2-27 Exit the Program . . . 2-23
Figure 2-28 Confirm exit Screen . . . 2-23
Figure 2-29 Data collection in progress Screen . . . 2-24
Figure 2-30 Test Completion screen - Successful . . . 2-24
Figure 2-31 Write Xpert Check data to CD Screen - Step 1 . . . 2-25
Figure 2-32 Write Xpert Check data to CD Screen - Step 2 . . . 2-26
Figure 2-33 CD Writing Program - Opening Screen . . . 2-27

Figure 2-34 CD Writing program - Insert a writable disk to continue Screen - Example 2-28
Figure 2-35 CD Writing/Burning Progress Screen. 2-29
Figure 2-36 CD Writing Completion Screen 2-30
Figure 2-37 Final Screen from Windows 7 After CD Writing has Completed 2-30
Figure 2-38 Send the CD to your Authorized Service Provider Screen - Step 3 2-31
Figure 2-39 Error writing Xpert Check data CD Screens - Two Examples 2-31
Figure 2-40 Exiting Screen 2-32
Figure 2-41 Data CD Labeling Example 2-32
Figure 2-42 Home Screen, showing Enter Xpert Check Code Button. 2-34
Figure 2-43 Enter Xpert Check code Screen. 2-34
Figure 2-44 Xpert Check Code File - Example 2-36
Figure 2-45 Applying Xpert Check code Screen Example 2-37
Figure 2-46 Xpert Check complete Screen 2-37
Figure 2-47 Xpert Check status Screen 2-38
Figure 2-48 Xpert Check Summary Report Example - Page 1 2-39
Figure 2-49 Information key Screen 2-41

1 Introduction

Important **Read and understand this entire document before performing the data collection procedure.**

1.1 Proprietary Name

Xpert Check™

1.2 Common or Usual Name

Xpert Check

1.3 Intended Use

The Xpert Check kit is part of a check, verification, and hardware test system for 6-Color GeneXpert modules. The Xpert Check kit is used to check the optical system, verify the thermal system and perform a series of system-level tests to ensure full system functionality within Cepheid's instrument servicing specifications. One Xpert Check cartridge is usually used to check a single module in conjunction with the Xpert Check software. In certain cases where a retest is required, multiple cartridges may be necessary to test a module.

1.4 Summary and Explanation

The GeneXpert (GX) module is the basis for all GeneXpert instrument systems worldwide. Cepheid recommends that the system be checked for proper operation on an annual basis. Based upon the usage and care of each system, checks may be recommended more frequently. The system is designed to detect module issues with the internal assay controls.

The Xpert Check kit includes reagents for the optical checking and performance verification of the module. Probe Check Controls (PCCs) verify reagent rehydration, PCR tube filling in the cartridge, probe integrity, and reagent stability. Thermal performance is verified via proprietary thermal probe chemistries, and module hardware performance is tested and verified by a suite of subsystem-specific tests which exercise all critical elements of the GX module.

The Xpert Check process consists of two phases. The first phase is the execution of module testing using the cartridges contained within this kit. The second phase consists of a Cepheid Quality Assurance Review, followed by the issuance of an Xpert Check code to complete the Xpert Check process. **The Xpert Check process is not complete until this code is applied to the system**.

1.5 Reagents and Instruments

1.5.1 Materials Provided

The Xpert Check kit contains the following:

Table 1-1. Kit Contents

Description	Quantity
Xpert Check cartridges with integrated reaction tubes	**5 per kit**
Each cartridge contains the following materials:	
• Bead 1	**1 per cartridge**
• Reagent 1	**1.0 mL per cartridge**
I-CORE Lens Cleaning Brush	**4 per kit**
PI/Software (P/N 950-0413)	**1 per kit**
Data CD	**1 per kit**

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

1.5.2 Storage and Handling

- Store the Xpert Check cartridges at 2-28 °C. Wait at least 10 minutes after removal from cold storage before using, at allow a cartridge to reach ambient temperature.
- Use the cartridge within 48 hours of opening the foil pouch.
- Discard cartridges that have been removed from their foil-wrapped pouches outside of the approved usage interval.
- Do not use cartridges that have passed the expiration date.
- Do not open a cartridge lid until you are ready to perform testing.
- Cartridge lid must be opened (vented) prior to use of a cartridge; however, no sample is required for testing.
- Discard all used and unused materials, including cleaning brushes and cartridges once the Xpert Check session is completed.

Note Contents of cartridges are non-hazardous.

1.5.3 Materials Required but Not Provided

- GeneXpert Dx or Infinity System with Cepheid-supplied computer and barcode scanner.
- 6-color GeneXpert instrument.

1.6 Limitations

- For use only with 6-Color GeneXpert modules (running GeneXpert Dx software version 4.0 and above). 4-Color GeneXpert modules (including Bio-threat modules) and Dual-Cal modules cannot run Xpert Check and must be tested by Cepheid Service.
- Use of the Xpert Check kit does not guarantee that the GeneXpert instrument will be free of hardware failures, nor does it take the place of a Cepheid Service Agreement.

1.7 Warnings and Precautions

Support for Windows XP ended April 8, 2014. Microsoft no longer provides security updates or technical support for the Windows XP operating system. It is critical that you upgrade now to a newer operating system, such as Windows 10.

Important

Please contact https://www.microsoft.com/en-us/microsoft-365/windows/end-of-windows-xp-support for Windows XP support information.

In addition, please contact your local Cepheid Technical Support if you have questions about using Windows XP.

After January 14, 2020, Microsoft will no longer provide security updates or support for PCs running Windows 7. It is recommended that you upgrade to Windows 10.

Important

Please contact https://www.microsoft.com/en-us/microsoft-365/windows/end-of-windows-7-support for Windows 7 support information.

In addition, please contact your local Cepheid Technical Support if you have questions about using Windows 7.

- Follow your institution’s safety procedures for working with chemicals.
- Do not add sample or other reagents to the Xpert Check cartridges.
- Do not use a cartridge that has a damaged reaction tube.
- Do not use cartridges from visibly damaged or compromised foil pouches.
- Contact your local Cepheid Technical Support office for replacement of damaged kit contents.
- Do not use a cartridge if it is dropped.

- Each single-use Xpert Check cartridge is used to process one test. Do not reuse spent cartridges.
- Each cleaning brush is intended for use in a single module. Do not re-use brushes in multiple modules.
- Do not open a cartridge package or break the lid seal until you are ready to perform testing.
- Allow the Xpert Check cartridge to come to ambient temperature prior to use if it has been placed in cold storage. Wait at least 10 minutes after removal from cold storage before using.
- Do not store single cartridges. Cartridges left over from an Xpert Check session, including pouched/unopened cartridges should be discarded along with spent cartridges.
- Do not use cartridges whose shelf life has expired. The system will detect expired cartridges and abort the test.
- Once a cartridge barcode has been scanned, do not substitute another cartridge in place of the scanned cartridge.
- If using an internet-enabled Xpert Check, up-to-date anti-virus software must be installed on the desktop or laptop computer with updated virus definition files, prior to executing Xpert Check.
- Prior to running Xpert Check, ensure that the environmental operating temperature is within the correct limits (15 °C–30 °C). Xpert Check will render a system's modules unavailable if the internal temperature is above 40 °C. The internal temperature can be verified in the Maintenance section of the GeneXpert DX software. Do not proceed under these conditions.
- Xpert Check expects the same computer to be used throughout the entire process. The computer installed with the GeneXpert system should be used, and not another computer from a different GeneXpert system.
- The Xpert Check code will expire if not applied within 45 days of completion of running Xpert Check.

1.8 Chemical Hazards

According to Regulation (EC) No. 1272/2008 (CLP), this material is not considered hazardous.

1.9 Assistance and Contact Information

For a complete listing of Cepheid technical support, service support, sales support, and headquarters contacts, please see Technical Assistance, in the Preface of this document.

1.10 Software Buttons, Icons and Symbols

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	**Information.** Click on this icon to obtain additional information. Displays the Information Key workspace screen which has an explanation of the various module icon displays.
	**Continue**. This icon is located at the bottom of most screens. Click on this icon to advance the display to the next screen.
	**Continue to End.** Clicking on this icon moves the user to the last screen.
	**Exit**. Exits the Xpert Check application.
	**About**. Brings up the About screen which brings up the name of the software, the software version number, copyright notice, etc.
	**Home**. Go to the Home screen.
	**Repeat/Retry**. Retry loading an Xpert check cartridge to attempt to check a module that has had an unsuccessful test of a minor nature or if the cartridge has not been vented by the user. Used on the ‘Check Test’ screen.
	**Back.** Clicking on this icon takes the user to the previous screen.
	**Cancel.** Cancel the current operation. In most cases this will mean going back to the previous screen. In some cases, it may mean going back to the screen before the one that started the current operation.

Table 1-2. Software Buttons, Icons and Symbols

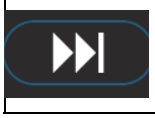
Symbol	Definition
	**Select none of the modules for check.** Deselects all modules for checking. If you only want to check a few modules, you may deselect ALL of them, and then reselect only the ones you wish to check.
	**Select all of the modules for checking**. The default setting for the system.
	**Connectivity Status.** Indicates the system is able to reach the Xpert Connectivity Center.
	**Connectivity Status.** Indicates the system is not able to reach the Xpert Connectivity Center.
	**Module unsupported for Xpert Check.** Skip the current module and do NOT attempt to check the current module.
	Module selected for Xpert Check. Module will be included when Xpert Check is run.
	**Skip Current Module.** Skip the current module and do not attempt to Xpert Check the current module. Used on the 'Load Xpert Check Cartridges' screen.
	**Skip Remaining Modules.** Skip all the remaining modules and do NOT attempt to Xpert Check them. Used on the 'Load Xpert Check Cartridges' screen.

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	Module not selected for Xpert Check. Module will not be included when Xpert Check is run.
	**Module unavailable for Xpert Check.** Module will not be included when Xpert Check is run.
	Indicates a module with data collection in progress.
	Indicates data collection complete.
	**Retest required. I**ndicates an incomplete Xpert Check data collection. A message will notify the user that the test must be rerun. A further message will indicate if the existing cartridge can be reused for the test or if a new cartridge must be used.
	**Service required.** Contact the Cepheid Authorized Service Provider (ASP) or your local Cepheid Technical Support office.

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	**Lost communication.** Contact the Cepheid Authorized Service Provider (ASP) or your local Cepheid Technical Support office.
	**Burn.** Burn a CD containing the collected Xpert check information (for users without an active internet connection).
	**Collect Xpert Check Data.** Leads the user through the Xpert Check data collection process.
	**Enter Xpert Check code.** Go to the 'Enter Xpert Check Code' screen.
	**Xpert Check Status.** Go to the Xpert Check Status screen to review Xpert Check status.
	**Upload Xpert Check Data File.** Go to the 'Upload Xpert Check Code Data File' screen.
	**Upload Xpert Check Data CD.** Go to the 'Upload Xpert Check Code Data CD' screen.
	**Write Xpert Check Code.** Write an Xpert Check Code to a file.
	**Read Xpert Check Code.** Open a file to read the Xpert Check code.
	**Scan.** Turn the barcode scanner on, and accept the next scanned input.
	**View and Print.** Launch the Adobe Reader so you can view and then print a PDF file.

2 Procedure

2.1 System Preparation

Note Prepare the system for Xpert Check by following one of the three procedures listed in this section for the GeneXpert Dx, the Infinity-48, Infinity 48s or the Infinity-80.

Important **Authorized Service Providers (ASPs) who perform Xpert Check but won't be on-site when the Xpert Check code numbers come back (non-internet connection sites), should leave the user name and password for the users to log in later to enter the codes (see section 2.3.2).**

2.1.1 GeneXpert Dx Preparation

1. Create an Administrator or Basic level User Name and Password in the GeneXpert software if one does not exist. Xpert Check requires this logon credential to be established prior to starting.
2. Have your Authorized Service Provider (ASP) code available before continuing to the next steps.
3. Exit the GeneXpert Dx software.
4. Go to Section 2.2, GeneXpert and Infinity Optics Cleaning.

2.1.2 Infinity-48 Preparation

1. Create an Administrator or Basic level User Name and Password in the GeneXpert software if one does not exist. Xpert Check requires this logon credential to be established prior to starting.
2. Have your Authorized Service Provider (ASP) code available before continuing to the next steps.
3. Restart the Xpertise software and switch the system from Automatic mode to Manual mode. Follow the instructions in the GeneXpert Infinity System Operator Manual for the Infinity-48.
4. Go to Section 2.2, GeneXpert and Infinity Optics Cleaning.

2.1.3 Infinity-48s or Infinity-80 Preparation

1. Create an Administrator or Basic level User Name and Password in the GeneXpert software if one does not exist. Xpert Check requires this logon credential to be established prior to starting.
2. Have your Authorized Service Provider (ASP) code available before continuing to the next steps.
3. Exit the Infinity System software.
4. Open the glass doors following the instructions in the *Infinity Operator Manual*.
5. Go to Section 2.2, GeneXpert and Infinity Optics Cleaning.

2.2 GeneXpert and Infinity Optics Cleaning

This procedure describes the method for removing dust and tube debris from the surface of rod lenses of the excite and detect blocks for GeneXpert Dx and Infinity modules prior to performing the Xpert Check procedure.

Note This procedure applies only to GeneXpert 6-color modules.

Materials Required or Recommended for Cleaning

- 300-8330 –Applicator brush (Quantity of four Included in the Xpert Check kit)
- Disposable gloves

Estimated Cleaning Time: 30 Seconds per module.

2.2.1 Lens Cleaning Procedure

1. Select the module to be checked and manually open the door of the module.
2. If necessary, remove the cartridge from the module.

Biological Risks

Remove the cartridge from the GeneXpert modules prior to cleaning. Failure to remove a cartridge could result in personnel being exposed to biological hazards and/or liquid biological materials spilling into the instrument and causing damage to the instrument.

3. Locate the brush provided in the Xpert Check kit (see Figure 2-1).

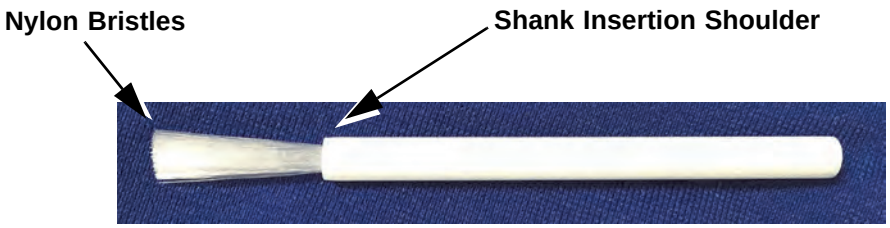


Figure 2-1. Lens Cleaning Brush (300-8330)

Note

The brush is designed so that it will easily insert into the I-CORE slit and make contact with the rod lenses of the excite and detect blocks.

Biological Risks

Make sure you wear disposable gloves for the cleaning process. Wearing gloves prevents you from being exposed to biologically hazardous materials.

4. Wearing disposable gloves, insert the brush into the I-CORE slit in a tilted manner up to the shank insertion shoulder, as shown in Figure 2-2.

Note

Make sure that all the bristles are fully inserted (up to the shoulder of the plastic shank of the brush) so that it does not cause unnecessary damage to the brush.

Caution

Do not insert any objects into the I-CORE slit except the provided brush. Inserting any other object may damage the I-CORE.

Caution

Do not apply any solution (such as ethanol or bleach) onto the brush bristles. The brush must be completely dry when inserting it into the I-CORE slit.

Important

The brush is intended for single-use and should not be used on more than one module. Use a new brush for each module to be cleaned.

Figure 2-2. Inserting the Cleaning Brush into the I-CORE Slit

5. Insert the brush into the I-CORE slit completely up to the plastic shank (shoulder) of the brush. Hold the brush firmly in the I-CORE slit, and perform cleaning of the rod lenses as described below. The entire cleaning process should take approximately 30 seconds per module.

Note

Cleaning is done by moving the brush in an up and down direction within the I-CORE slit. Brush rotation, even if it has to be done, is not the main action that results in optics cleaning.

   A. Begin by brushing from the top of the I-CORE slit to the bottom, making sure to apply a uniform pressure when brushing from the top to the bottom of the I-CORE slit. This will ensure that most of the tube debris and dust is brushed off from the surface of the lenses.
   B. Rotate the brush from left to right and back again, approximately 180°.
   C. Brush once more from the top of the I-CORE slit to the bottom.
   D. Rotate the brush again from left to right and back again, approximately 180°.
   E. Finally, brush again from the top of the I-CORE slit to the bottom.

6. When lens cleaning is complete, remove and discard the used brush and gloves as hazardous waste.

Important

Dispose of gloves and brushes according to your institution's safety policies and procedures for hazardous waste.

7. Proceed to Section 2.3, Data Collection Procedure: GeneXpert Dx and Infinity.

2.3 Data Collection Procedure: GeneXpert Dx and Infinity

Important

Before collecting data, be sure to prepare the system for checking as described in Section 2.1, System Preparation.
Internet-connected users should verify their system's connectivity status prior to beginning the Xpert Check process.

Note

Use care in inserting CD1 into the DVD drive. Be sure the CD is fully seated in the tray before closing the drive door.

1. Place Software CD1 in the computer connected to the GeneXpert Dx. For the Infinity, connect the DVD drive following the instructions in the Infinity Operator Manual and insert the CD into the DVD drive.
2. This step varies with the operating system installed on your computer:
   - **Windows XP**: On the computer desktop, right-click the My Computer icon and a drop-down menu will appear. Click Explore, then right-click on the applicable drive letter for your DVD drive.
     Select Explore from the drop-down menu, and the files located on the CD will then be displayed.
     Find and right-click the XpertCheck.exe application, and when the drop-down menu appears, click Run to install as Administrator. When the software has been installed, a "wrench" icon will appear on the desktop.
   - **Windows 7, Windows 10**: On the computer desktop, right-click the Computer icon and a drop-down menu will appear. Click Open, then right-click on the applicable drive letter for your DVD drive.
     Select Open from the drop-down menu, and the files located on the CD will then be displayed.
     Find and right-click the XpertCheck.exe application, and when the drop-down menu appears, click Run to install as Administrator. When the software has been installed, a "wrench" icon will appear on the desktop.

Note

The software may take some time to load from the CD.

3. Double-click the "wrench" icon to launch the Xpert Check program.
4. The Terms of Service screen appears first. Use the scroll bar to read through the entire document. You will be asked to click the check box (bottom of the screen) to verify that you have read and agree to the Terms of Service before continuing. See Figure 2-3.

Note

The Xpert Check software runs on Windows XP, Windows 7 or Windows 10. The screens shown in this manual are from Xpert Check software running on Windows 7. Screens for Xpert Check software running on Windows XP or Windows 10 will be similar.

Support for Windows XP ended April 8, 2014. Microsoft no longer provides security updates or technical support for the Windows XP operating system. It is critical that you upgrade now to a newer operating system, such as Windows 10.

Important

Please contact https://www.microsoft.com/en-us/microsoft-365/windows/end-of-windows-xp-support for Windows XP support information.

In addition, please contact your local Cepheid Technical Support if you have questions about using Windows XP.

After January 14, 2020, Microsoft will no longer provide security updates or support for PCs running Windows 7. It is recommended that you upgrade to Windows 10.

Important

Please contact https://www.microsoft.com/en-us/microsoft-365/windows/end-of-windows-7-support for Windows 7 support information.

In addition, please contact your local Cepheid Technical Support if you have questions about using Windows 7.

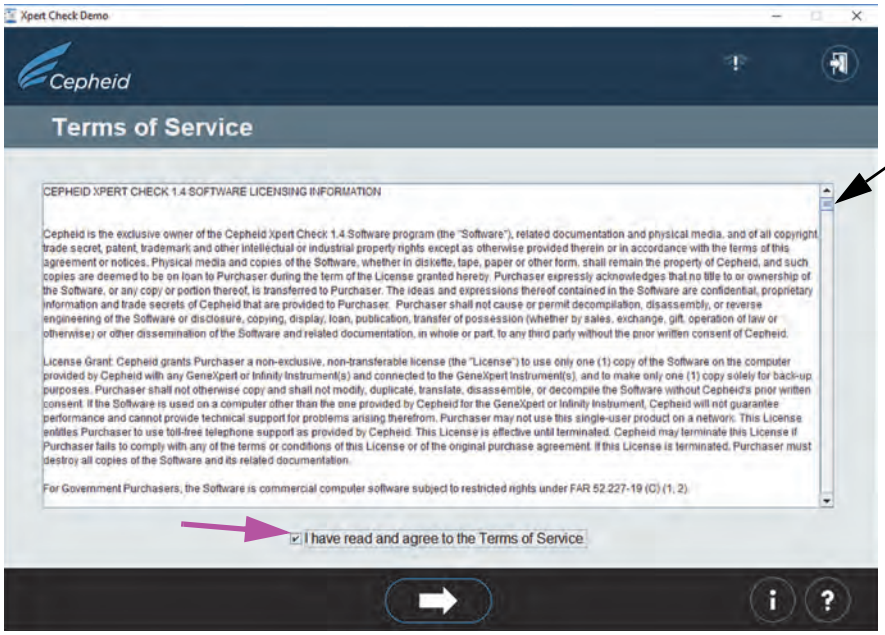


Figure 2-3. Terms of Service Screen

5. After agreeing to the Terms of Service, the Login screen will appear. Log in with your GeneXpert Dx or Infinity designated Administrator level USER NAME and PASSWORD (previously assigned to you by your system administrator). After entering your login information, click the forward arrow button at the bottom of the screen to advance to the Xpert Check Home screen. See Figure 2-4.

Note

The user name and password are the same ones you used for the GeneXpert Dx or Xpertise software.

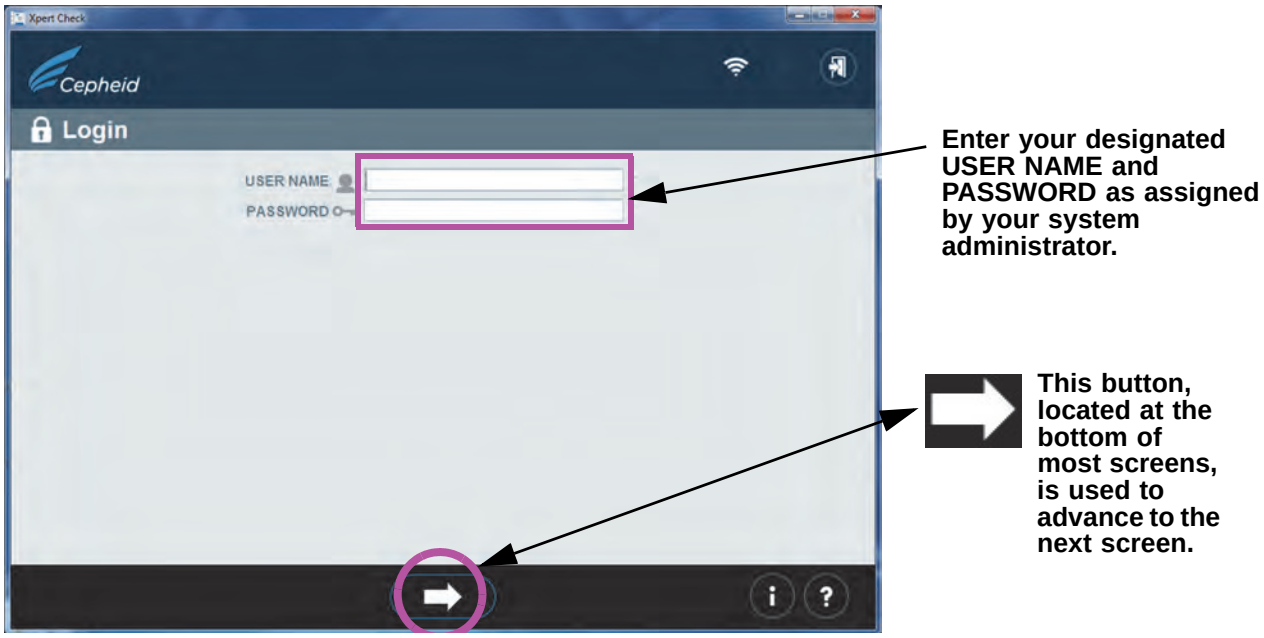


Figure 2-4. Xpert Check Login Screen

In case of a login error, the following screen will appear. See Figure 2-5.

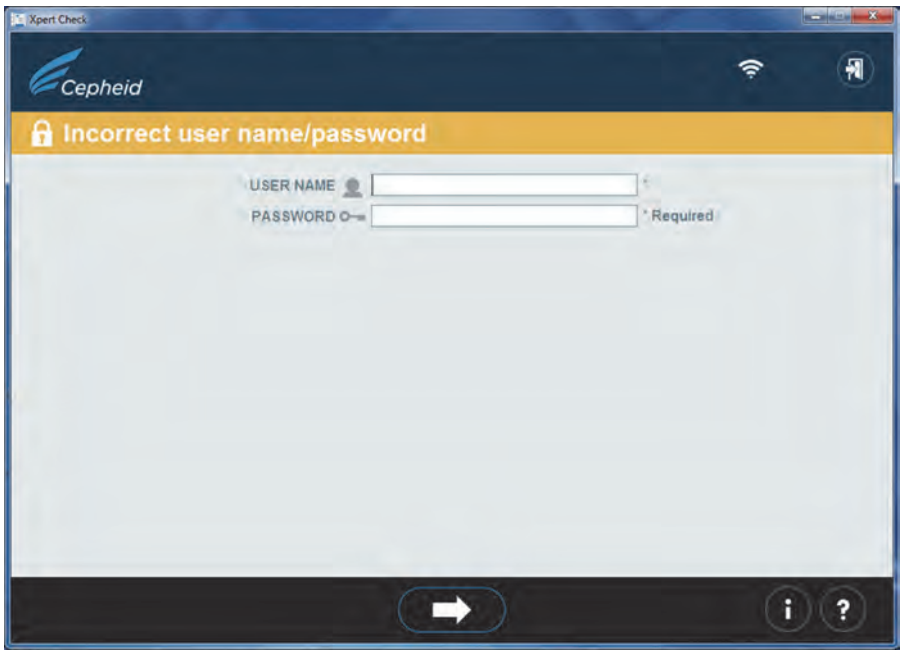


Figure 2-5. Login Error Screen

6. If a login error occurs, recheck the USER NAME and PASSWORD entries for errors. If necessary, reenter the information and retry. After entering your login information, click the forward arrow button at the bottom of the screen to advance to the Xpert Check Home screen.

7. Obtain a sufficient number of cartridges for the number of modules to be tested.

Important **Do not open cartridge packages until you are ready to scan the cartridge barcodes (in Step 17).**

Note When determining the number of cartridges that will be needed for this test, the user should be aware of the number of modules that they will be checking.

8. Click the Collect Xpert Check Data icon on the Home screen (See Figure 2-6). After a few seconds, the first Contact Information screen (Figure 2-7) will appear.

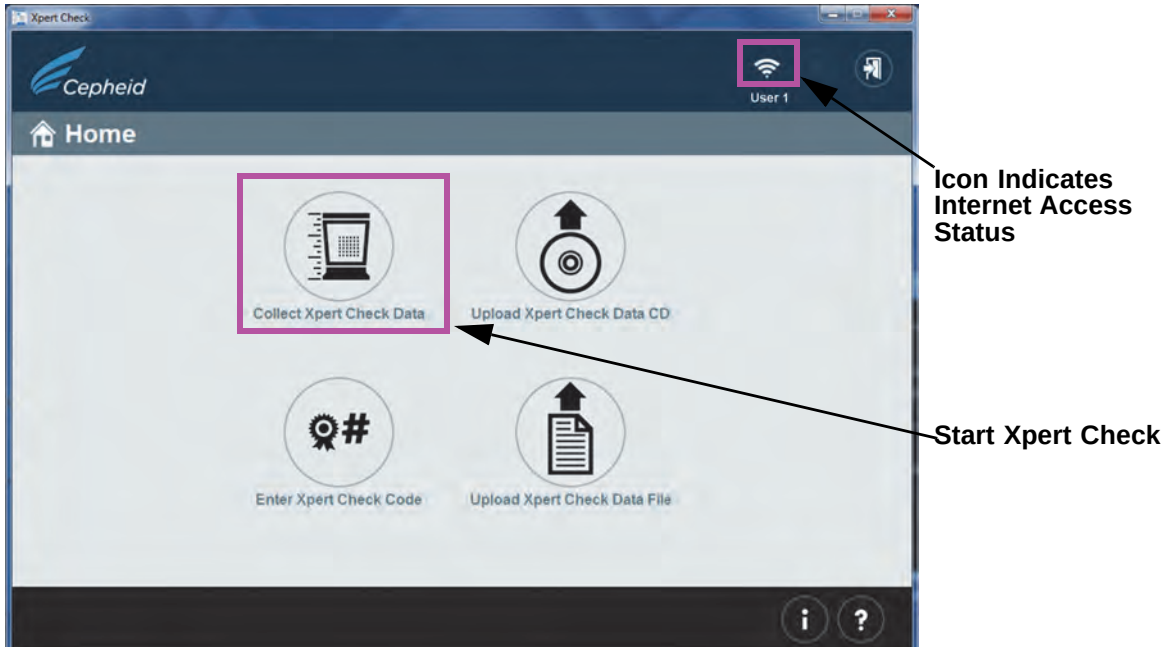
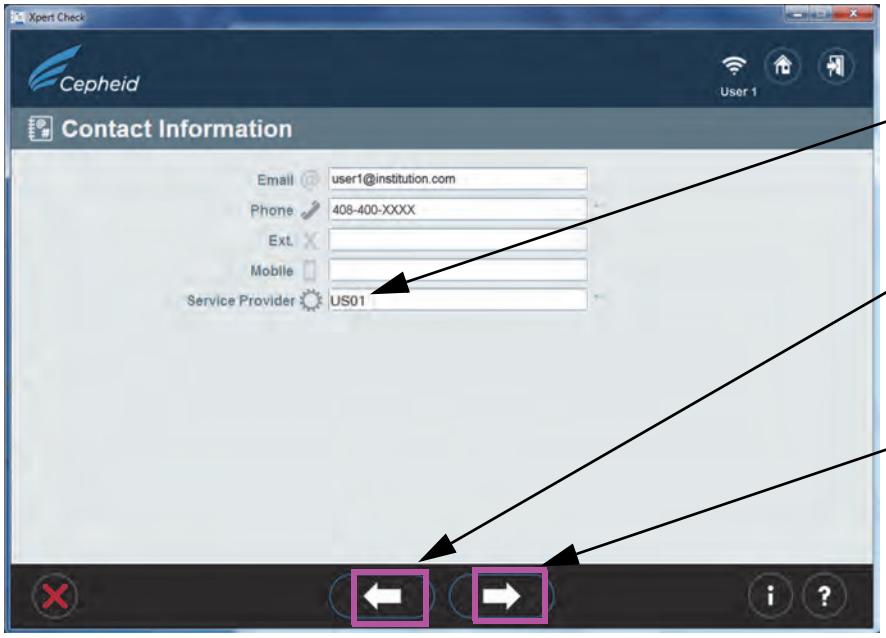


Figure 2-6. Home Screen

9. When the first of two Contact Information screens appear (see Figure 2-7 and Figure 2-8), fill out the fields in the two screens. Use the large navigation arrows at the bottom of the screens to move between the two screens.
   Note that fields marked with "*" (at the right of the entry area) are mandatory fields.

Figure 2-7. Contact Information Screen - Page 1



In this mandatory field, enter your Authorized Service Provider's ID code. The ID code is four characters, as described in

Clicking on this icon will take the user back to the first Contact Information

Clicking on this icon will take the user to the Open Module Doors screen

Figure 2-8. Contact Information Screen - Page 2

Note

The ASP-provided ID code for the Service Provider on the Contact Information screen consists of four characters. (As examples: US01, 1203, etc.)

10. When all information has been entered, click the forward arrow button at the bottom of page 2 of the Contact Information screen. The Open Module Doors screen will appear. See Figure 2-9. Manually open all module doors to enable cartridge loading.

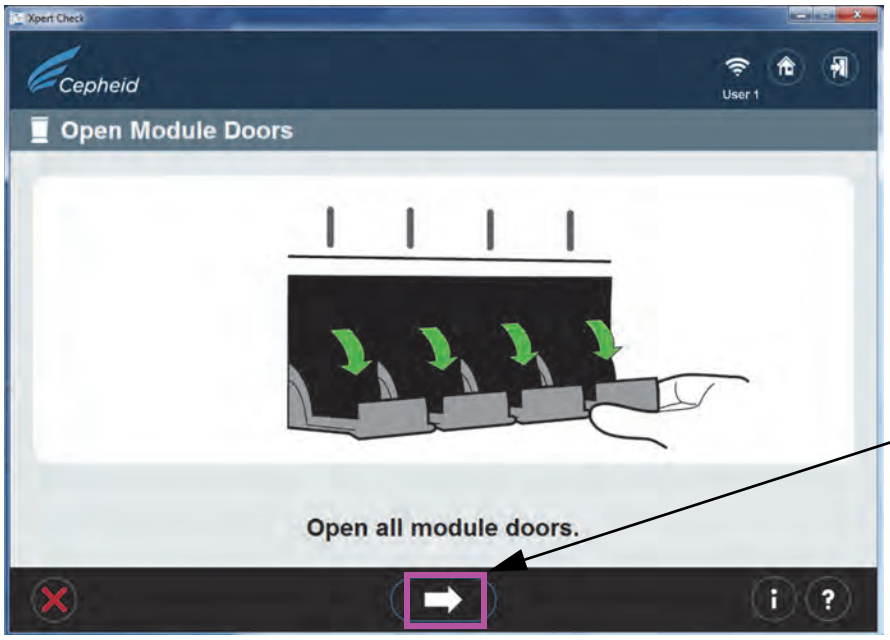


Figure 2-9. Open Module Doors Screen

11. After opening all the module doors, click the forward arrow button at the bottom of the screen. The Module preparation screen may appear, showing the message Wait while modules are being prepared. (See Figure 2-10.)

Important

Note that the Module preparation screen will appear only if the firmware in the modules is not 3.0.3. The screen indicates that the software is upgrading/downgrading the firmware to the modules. The next screen you see will be the screen shown in Figure 2-11, the Select Modules screen.

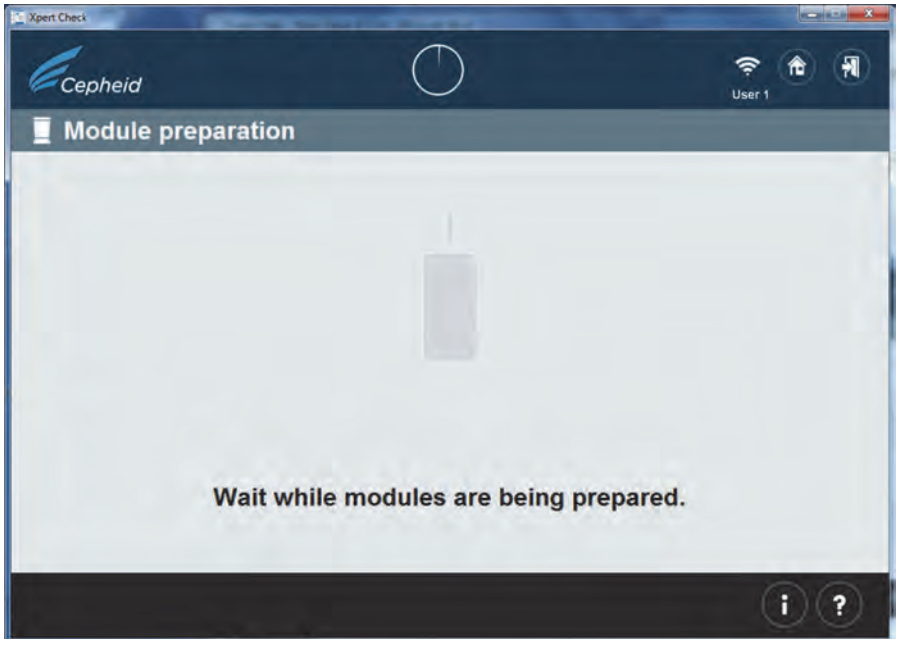


Figure 2-10. Module preparation Screen

12. Follow the on-screen software instructions in Figure 2-11. By default, all detected modules will be marked as selected for checking.

    On this screen, the user can click on individual modules to exclude them from being checked, if required. The modules will disappear as they are excluded.

Note

For excluded modules (not selected for checking), the door position (open or closed) does not matter.

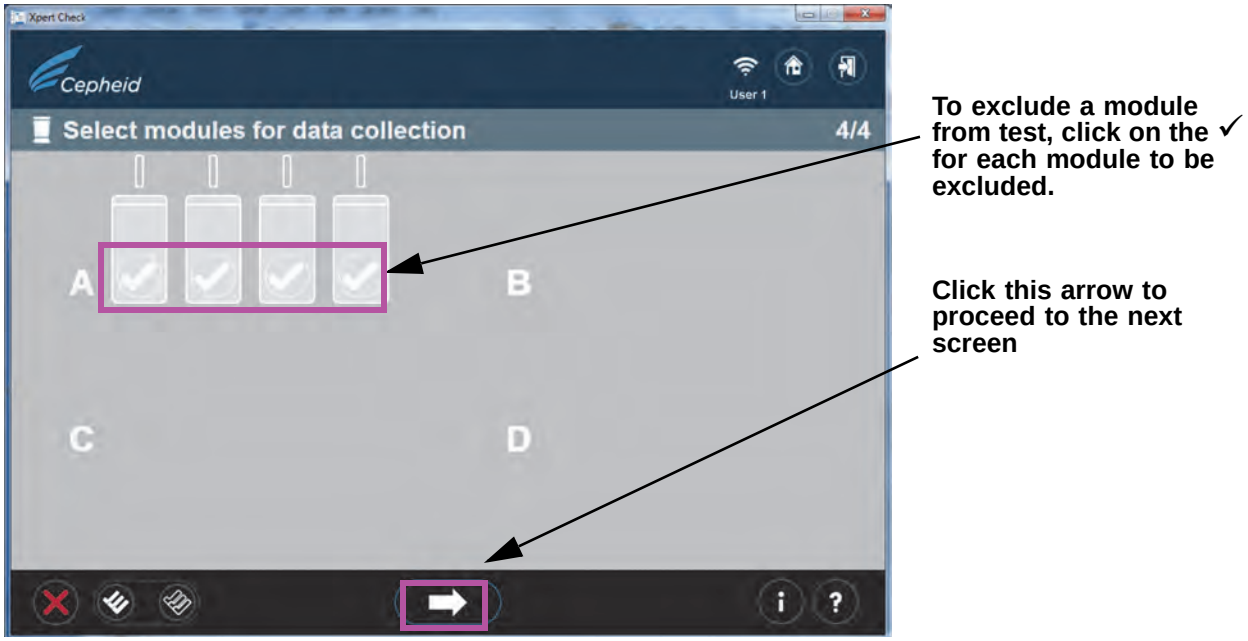
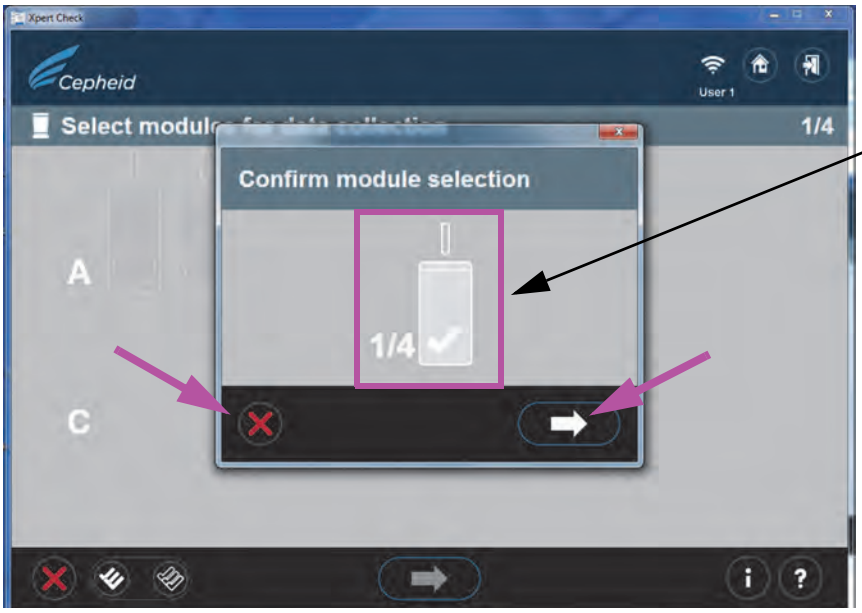


Figure 2-11. Select modules for data collection Screen

Important

GX-XVI and Infinity systems only: When selecting modules on screen, make a note of which module lights are blinking on the system as you select each bank, to ensure cartridges are placed in the correct modules for testing.

13. After confirming the module selection shown in Figure 2-11, click the white arrow at the bottom of the screen overlay, to begin scanning cartridges. If the module selection shown is incorrect, click the red X at the bottom left corner of the screen to return to the Select Modules screen and change your selection. See Figure 2-12.



Module selection is shown here. In this example, one module is selected for checking.

Figure 2-12. Confirm module selection Screen

14. In case of an error in the preceding step, in which either no modules have been selected, or all modules have been excluded, one of the following screens will appear (Figure 2-13). Follow the on-screen instructions to select a module, or start over by returning to the Home screen or exiting the program.

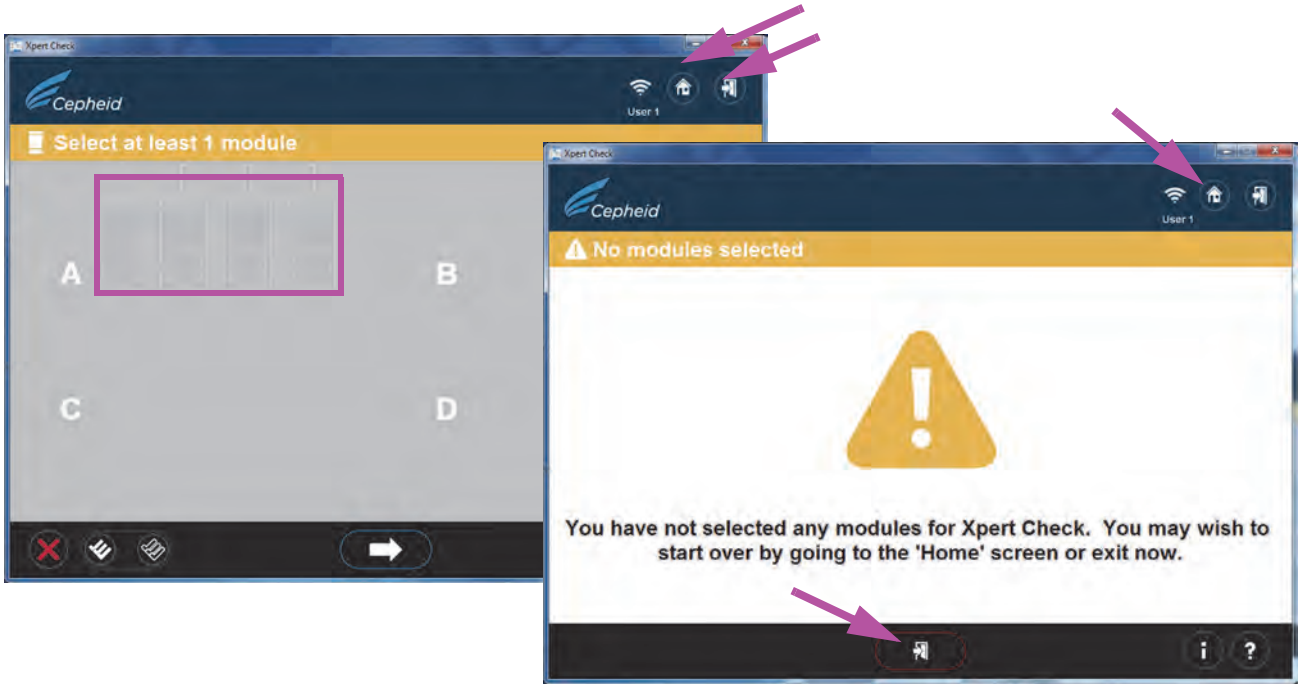


Figure 2-13. Error Screen Examples

15. After confirming your module selection, you will advance to the Scan cartridge screen, where you will be prompted to scan the barcode on the Xpert Check cartridge.

Note Verify you have enough cartridges on hand to perform the check procedure for the desired number of modules.

16. Remove the test kit cartridge from the package for the module you've previously selected, opening only one cartridge at a time.

Important **Allow the cartridge to reach ambient temperature before proceeding. Do not remove a cartridge from refrigerated storage and immediately use the cartridge to run this test.**

17. Scan the cartridge barcode. Figure 2-14 shows a cartridge barcode being scanned. Do not substitute a cartridge with another after it's been scanned.

Note If the barcode cannot be scanned, skip the cartridge and contact your ASP or local Cepheid Technical Support office for a replacement cartridge, if necessary. If the barcode scanner is damaged, missing or incorrectly configured, contact your ASP or local Cepheid Technical Support office for guidance.

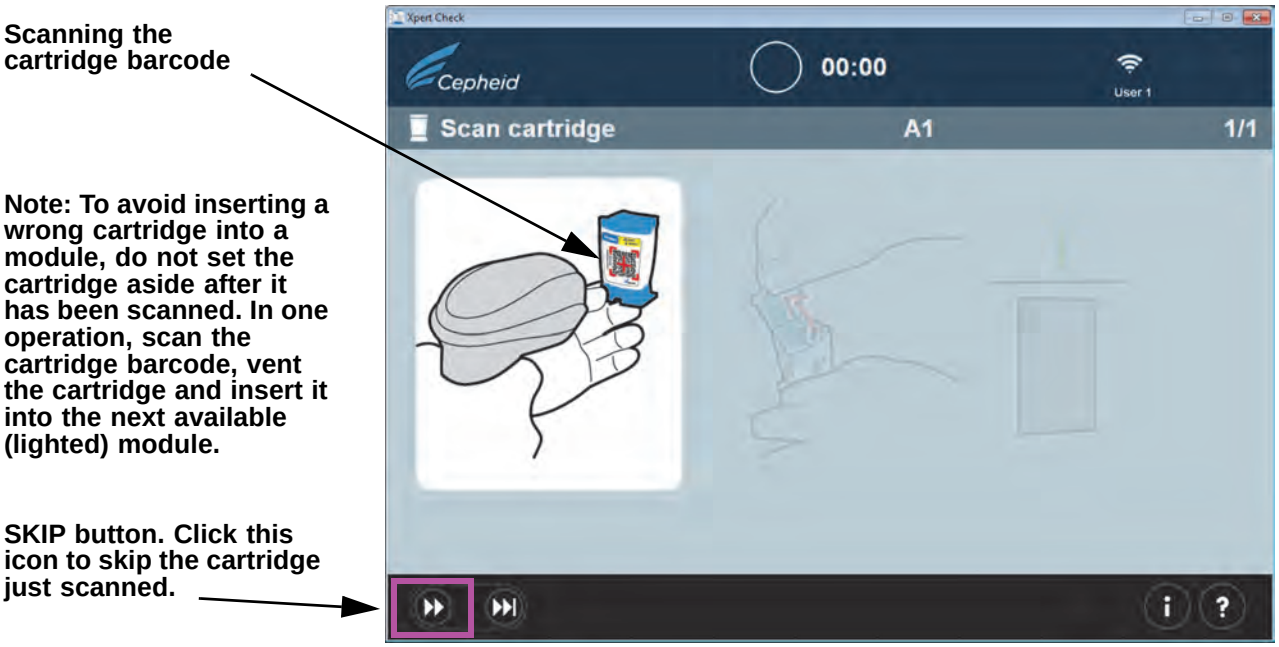


Figure 2-14. Scanning the Cartridge Barcode Screen

A. After scanning the barcode of the cartridge, ensure you open (vent) the cartridge lid and then close it for each cartridge as directed by the software in Step B through Step E below.

Important **Do Not add a sample or reagent to the cartridge. Use ONLY the cartridges in the Xpert Check kit provided.**

Note After a cartridge barcode is scanned a green light will blink on the system above the module door where the cartridge is to be loaded. (See Figure 2-17.)

Note

If, for some reason, you want to skip the cartridge just scanned, click the SKIP button at the bottom of the screen. An overlay, shown in Figure 2-15, will appear, asking for confirmation on skipping the cartridge. To SKIP the cartridge, click the forward arrow at the bottom of the confirmation screen. To proceed without skipping the cartridge, click the "X" icon at the left bottom corner of the screen. You are urged to rescan a cartridge (or substitute a new cartridge if necessary) to ensure a module is not skipped.

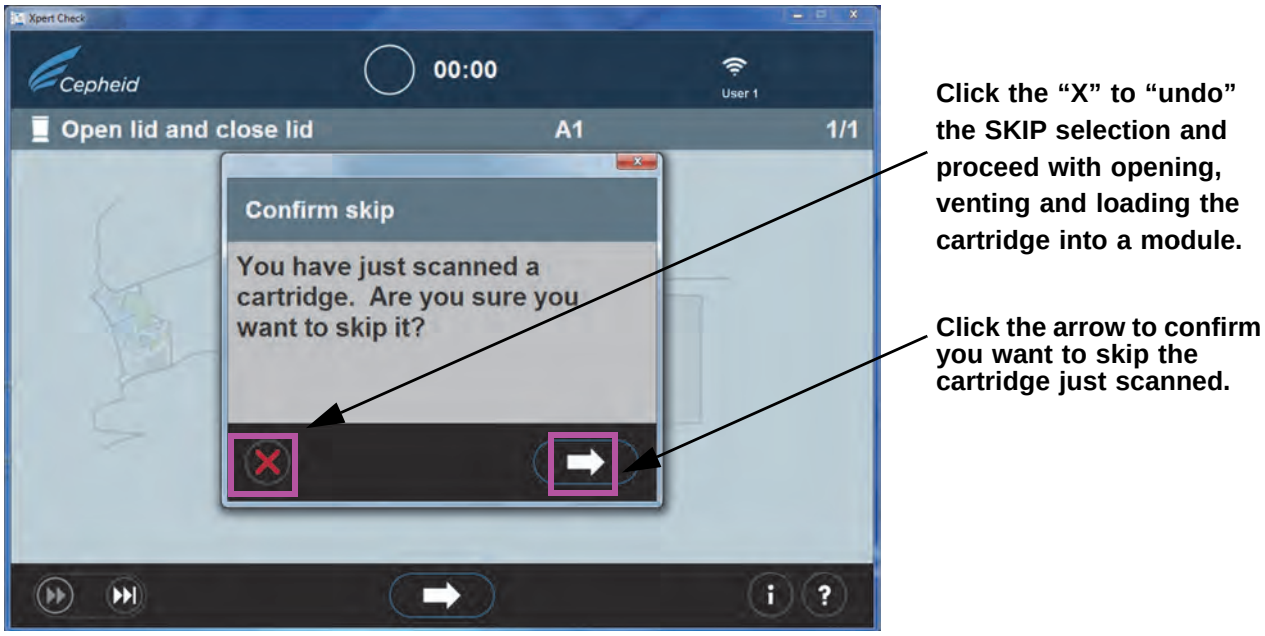


Figure 2-15. Confirm skip Screen

B. Venting the cartridge (shown in Figure 2-16), for two seconds is sufficient. This screen is animated, showing the cartridge lid being opened and closed. After venting, click the forward arrow at the bottom of the screen to continue.

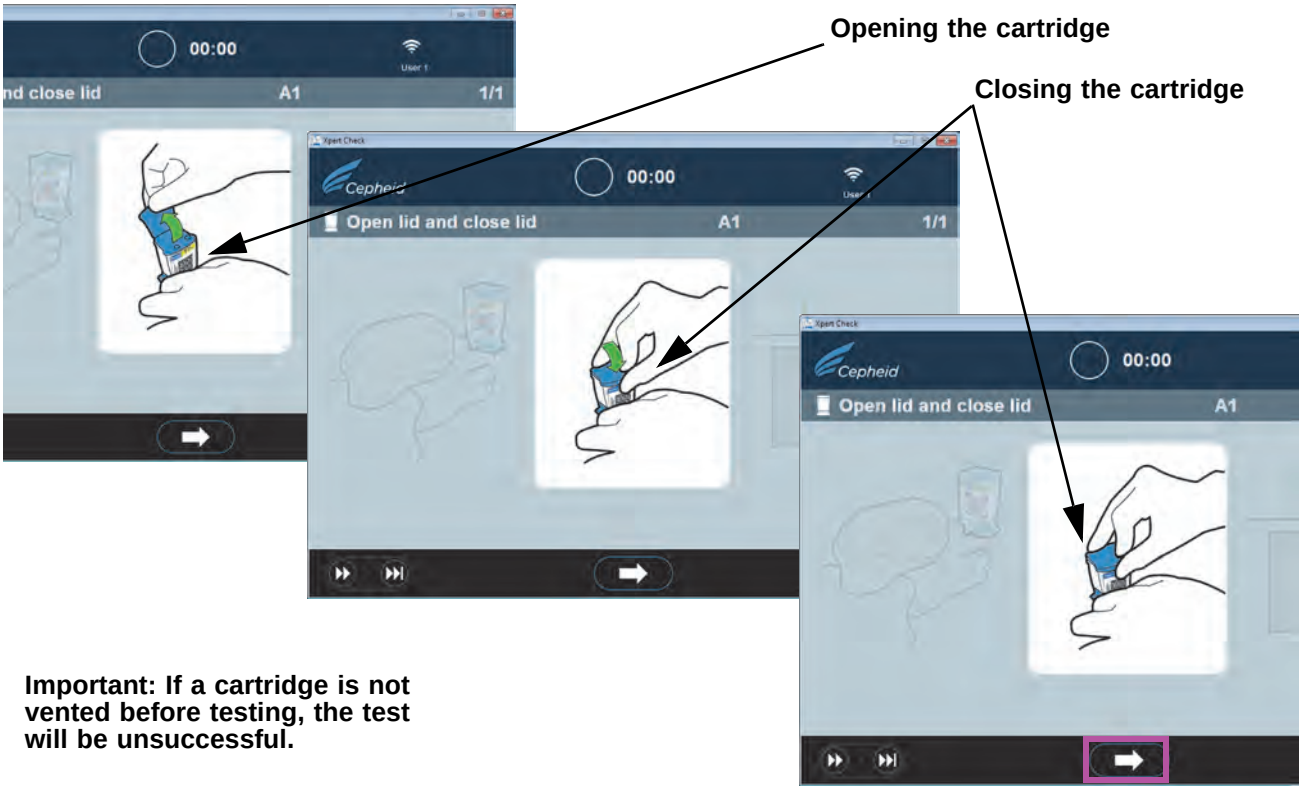


Figure 2-16. Venting the Cartridge by Opening and Closing the Cartridge Lid - Animated Screen

C. Close the cartridge lid and ensure the module door is fully opened to receive the cartridge.

D. Load the cartridge into the module (with the cartridge reaction tube (tab) facing away from you), as directed by the animated software screens. See Figure 2-17.

Note

Be sure to load scanned cartridges in sequence in the next available module. This will avoid loading cartridges in the wrong location or leaving modules empty.

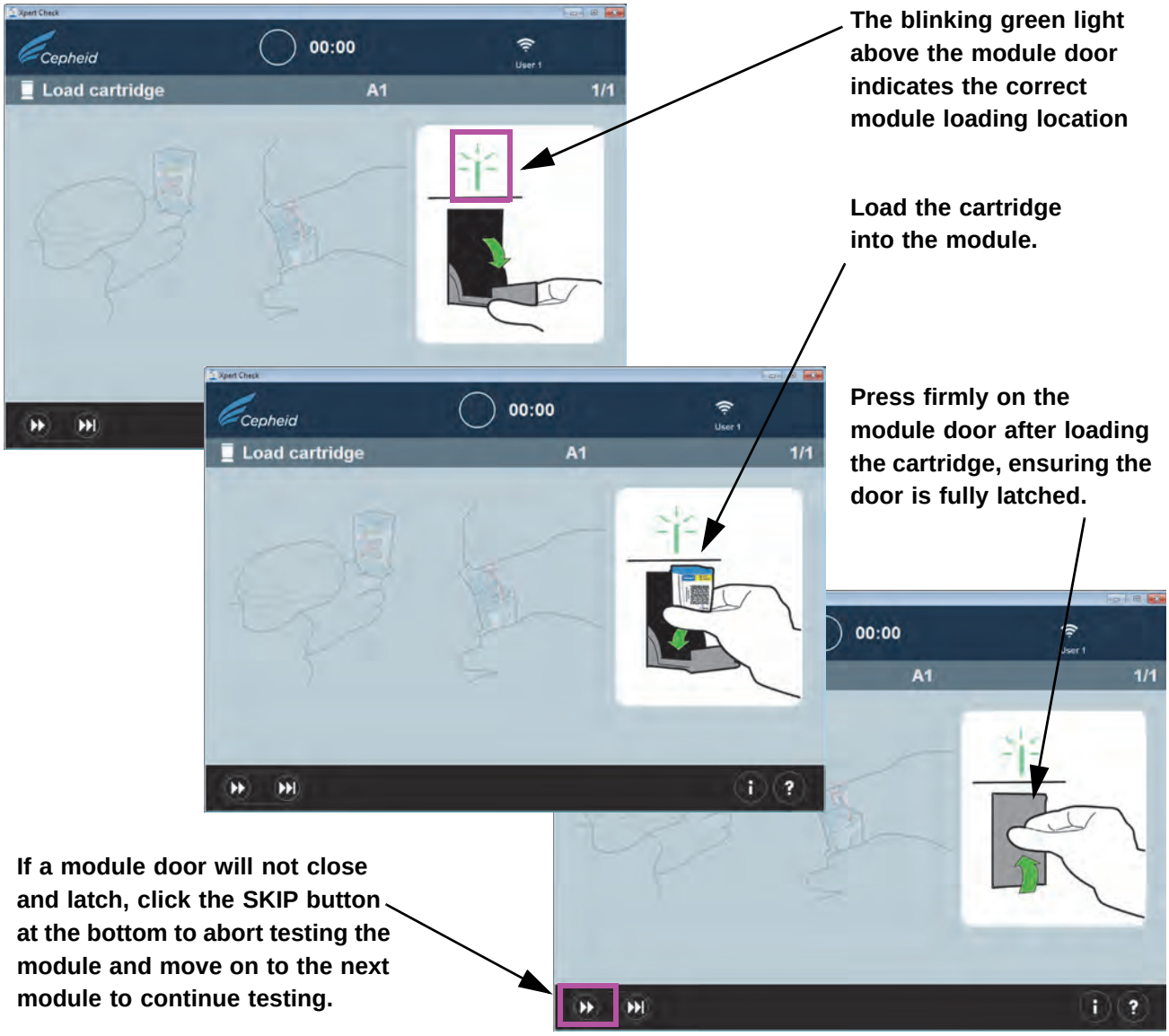


Figure 2-17. Loading the Cartridge into the Module

E. If you are checking additional modules, continue by scanning the next cartridge. Place each individually scanned cartridge into the next selected open module, pressing the module door securely closed until it latches. **As each module door is closed and latched, data collection will automatically start on that specific module.** The blinking green light above the module will then become steady green, indicating that checking has started.

Important

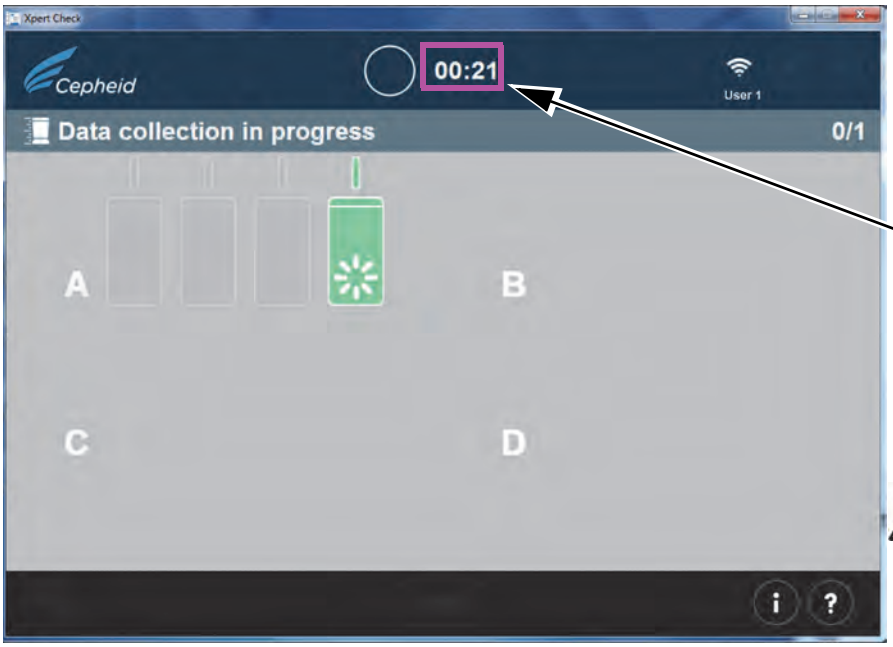
If a module door is not closed completely (until it latches) after loading a cartridge, the screen will continue to display a message to insert a cartridge, and the check will not run.

If you are unable to close and latch a module door after several tries, press the SKIP button at the bottom of the screen to skip the module with the faulty door and move ahead. Notify your ASP or local Cepheid Technical Support office so the module can be serviced.

18. Checking will take approximately 20 minutes to complete after the final module has been loaded for testing. When checking begins, the Data collection in progress screen appears, as shown in Figure 2-18.

Important

If necessary, a retest of a previously run module may be started without waiting for the present module to complete its test, as described in steps 19b through 19d.



Countdown clock, showing estimated time to test completion (21 minutes).

Note: In this example, one module is being tested.

Do not exit the software program while data collection is in progress!

Figure 2-18. Data Collection Screen

Important

If you do not have an internet connection, skip to section 2.2.1 for the remainder of this procedure. If you have an internet connection, continue with step 19.

19. After test completion, the module door will open and the light above the module door will turn off. Screens similar to those shown in Figure 2-19 or Figure 2-20 will appear. Press the right arrow to continue.

    A. Figure 2-19 shows the completion of a successful Xpert Check data collection.

    When the test is complete, click the forward button at the bottom of the screen to begin uploading Xpert Check test results to the Xpert Connectivity Center.

Important

When uploading test results, especially multiple files, verify the selected folder destination is correct.

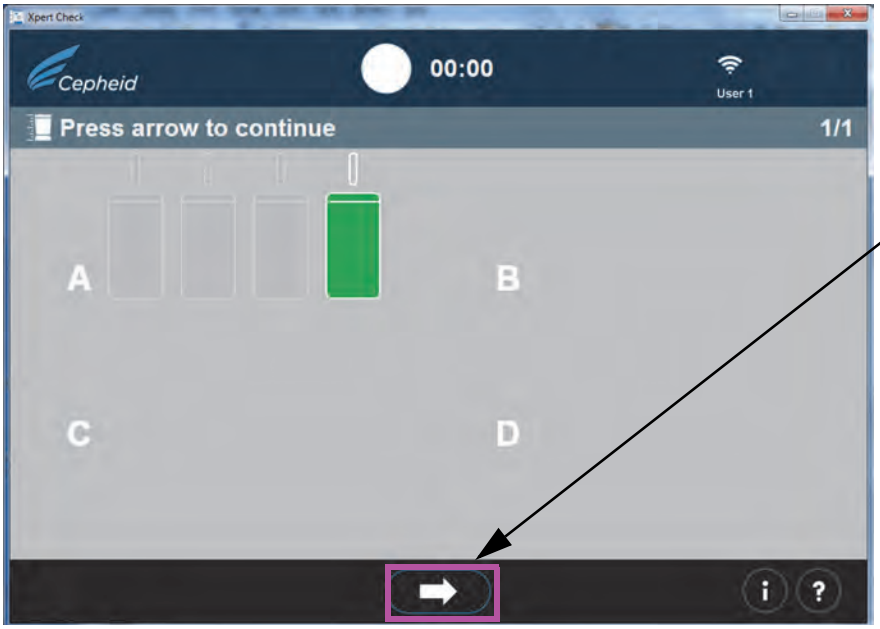


Figure 2-19. Test Completion Screen - Successful

B. If the test was unsuccessful, the screen shown in Figure 2-20 will appear, showing module status. A test retry must be performed. Click the Retry icon in the lower left-hand corner of the screen.

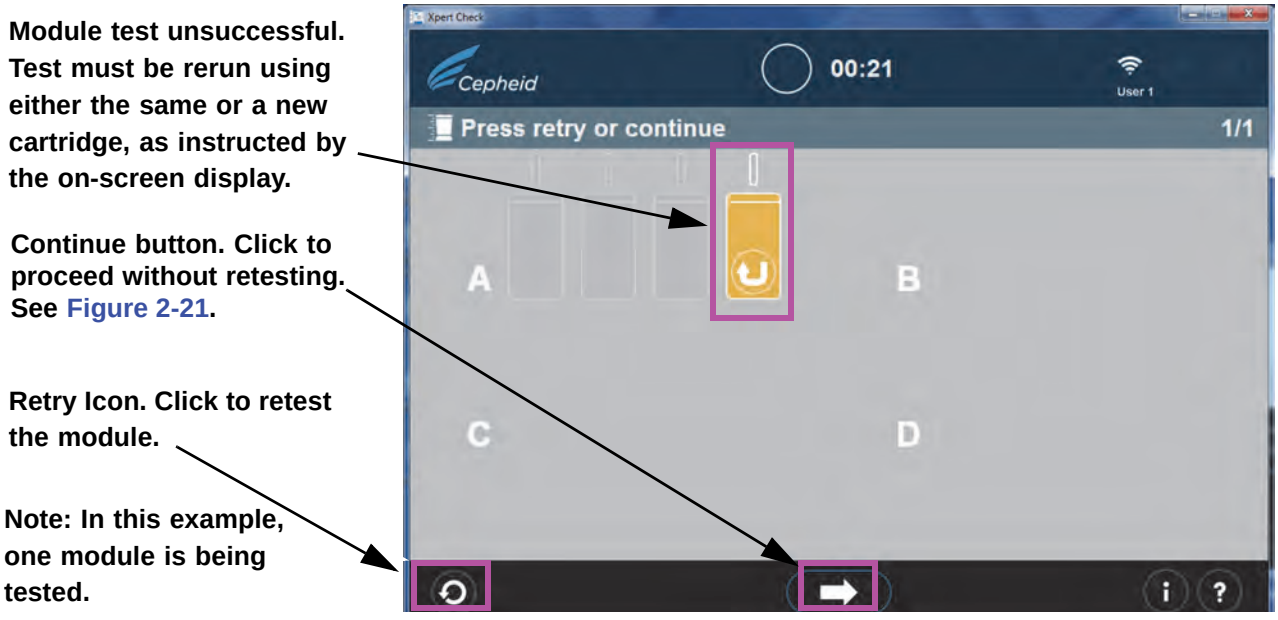


Figure 2-20. Test Completion Screen - Unsuccessful Module Checking Example

C. If the Continue arrow at the bottom of the screen is pressed when there is an unsuccessful module test displayed (as shown in Figure 2-20), the Confirm continue screen will appear. See Figure 2-21.

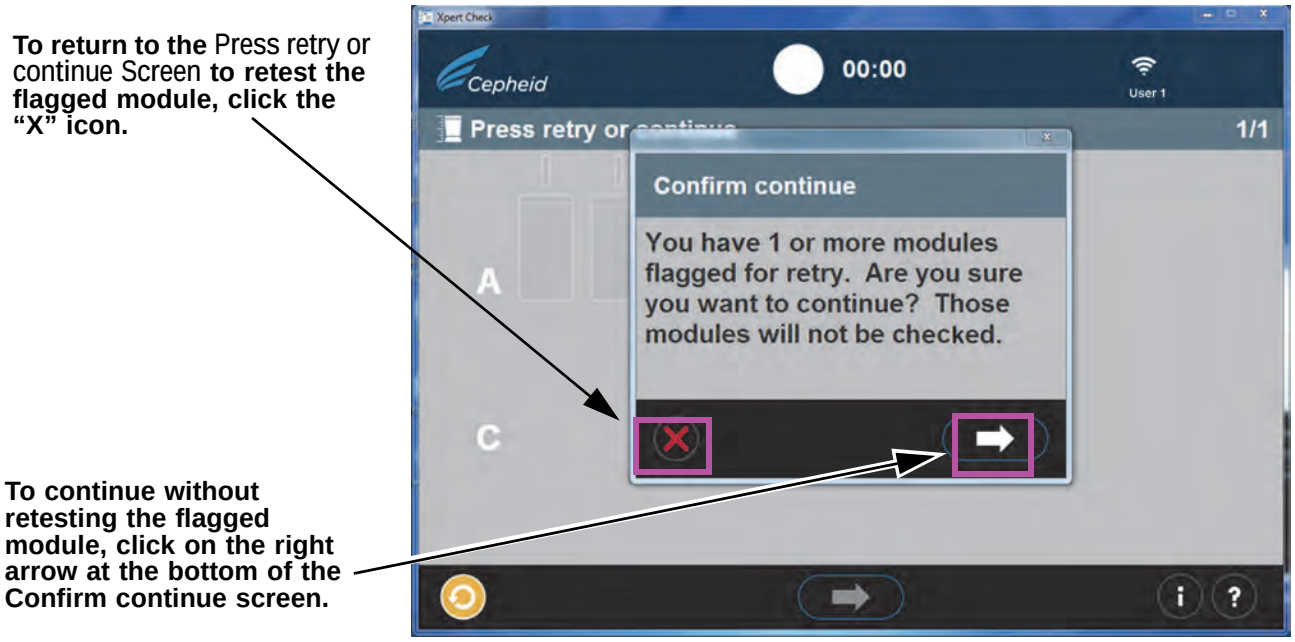


Figure 2-21. Confirm Continue Screen Overlay

You have the option of continuing by pressing the right arrow on the Confirm continue screen overlay. Choosing this option will result in the flagged module not being retested, and you will begin uploading check data as described in Step 20.

Another option is to return to the Press retry or continue Screen to Retry (retest) the flagged module by clicking the red "X" icon at the bottom left of the Confirm continue screen. The Retry procedure is described in Step D which follows.

D. If the Retry icon (shown above in Figure 2-21 at the bottom of the screen) appears, click the Retry icon and you will return to the Scan Barcode screen (Figure 2-14) to complete the retest on the affected module(s).

Note that the retest can be of two possible types:

1) Retry with the same cartridge: For example, a message may appear telling you to vent the cartridge, rescan it, and put it back in the module.

2) Retry with a new cartridge: If the cartridge was defective, or had already been used, you will be asked to replace it by scanning the barcode on a new cartridge, venting it, and loading it into the module.

Note During the course of running retests, modules may need to be skipped if the user runs out of Xpert Check cartridges. Please contact your ASP or local Cepheid Technical Support office for additional Xpert Check cartridges. Rerun Xpert Check on any modules that were skipped.

Note At the completion of the Xpert Check data collection process, modules determined to require service will be flagged with an orange module icon (See Figure 2-20). Please contact your local ASP or local Cepheid Technical Support office for further assistance in servicing or replacing modules.

20. After successful test completion and Xpert Check data collection, click the forward arrow to display the screen shown in Figure 2-22, if you have an active internet connection. However, if you have never been internet connected, or have lost your functioning internet connection sometime during the Xpert Check test, a Download Xpert Check code error screen or an Upload incomplete error screen (Figure 2-23) may appear instead, instructing you to write Xpert Check data to a data CD to send to your ASP or local Cepheid Technical Support office. In this case, continue to the instructions beginning at Step 4 (under Section 2.3.1) of this procedure to continue as a user without an internet connection.

Note

With a functioning internet connection, the system should proceed normally (with Step 21), and the Xpert Check code should begin downloading, as shown in Figure 2-24.

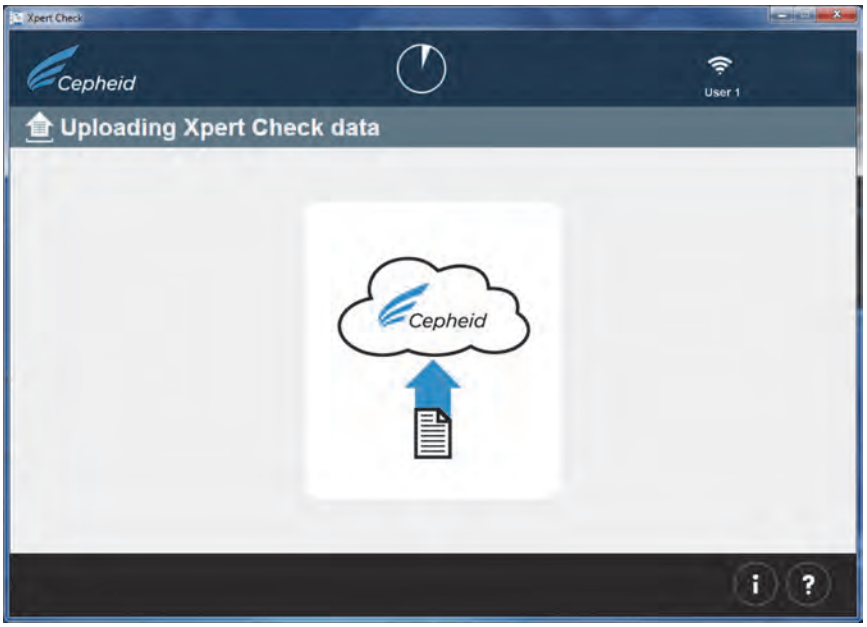


Figure 2-22. Uploading Xpert Check Data Screen

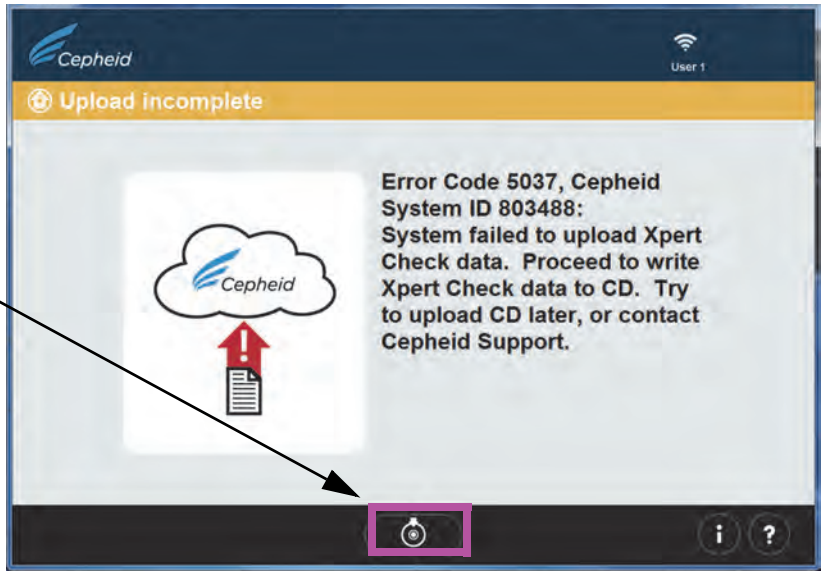


Figure 2-23. Upload incomplete Error Screen

21. When the Xpert Check data has finished uploading, a Quality Assurance check will be performed on the data. If the check is acceptable, the Xpert Check code will automatically download. See Figure 2-24.

    If the test is not acceptable, the affected module(s) will require service or replacement and will be flagged with an orange icon. Please contact Cepheid or your local ASP or the local Cepheid Technical Support office for further assistance.

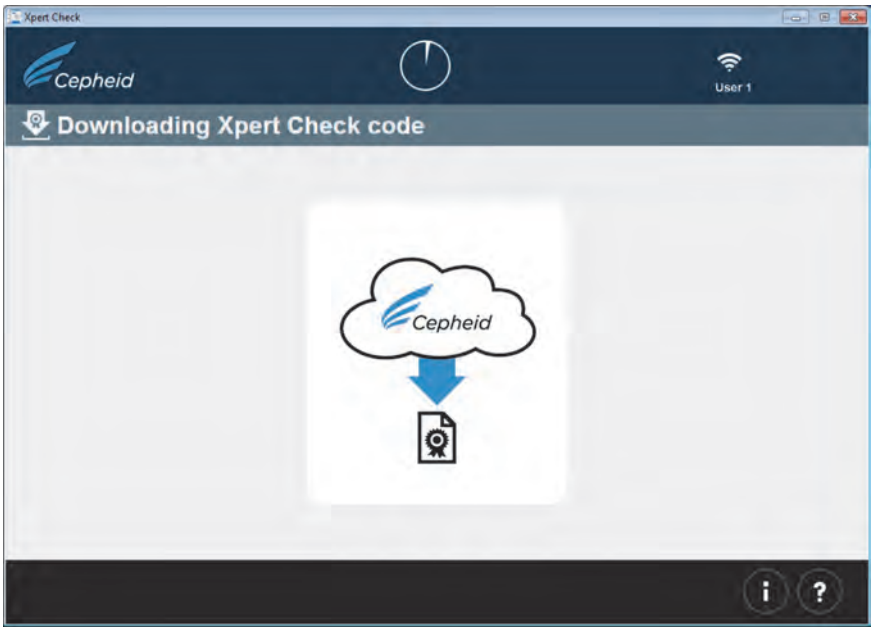


Figure 2-24. Downloading Xpert Check code Screen

22. After the Xpert Check test results have downloaded, the Xpert Check code will be applied to each successfully tested module, and those modules will then be identified with a + symbol. See Figure 2-25. As shown here, one module is being checked.

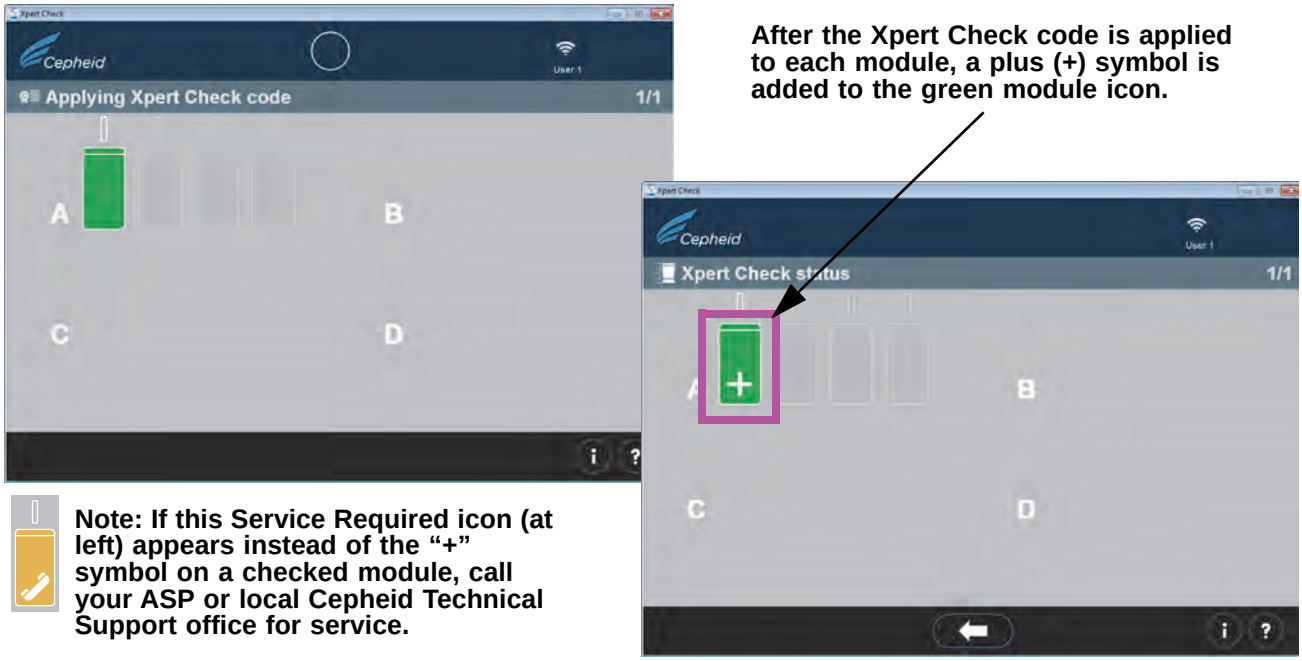


Figure 2-25. Applying Xpert Check code Screen

Note

In the screen shown in Figure 2-25, some modules may display the service required icon or may be grayed out if they were skipped.

23. After all the Xpert Check codes have been applied to the successfully-tested modules (those green modules which appear with the plus symbols applied), the Xpert Check complete screen will appear. See Figure 2-26. This screen shows the location of the Xpert Check Data report, which is available for review, if desired.

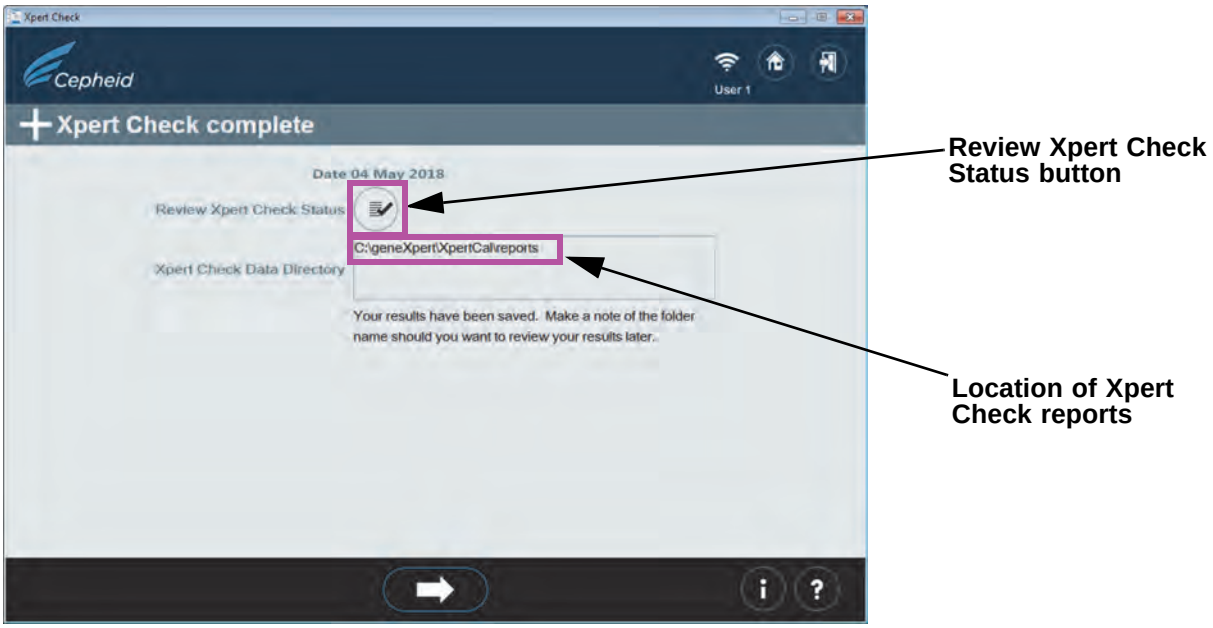


Figure 2-26. Xpert Check complete Screen

24. Remove and discard all Xpert Check cartridges. Do not save partial kits (all unused cartridges must be discarded).When complete, click the Exit icon at the top or bottom of the screen to exit the program. See Figure 2-27.

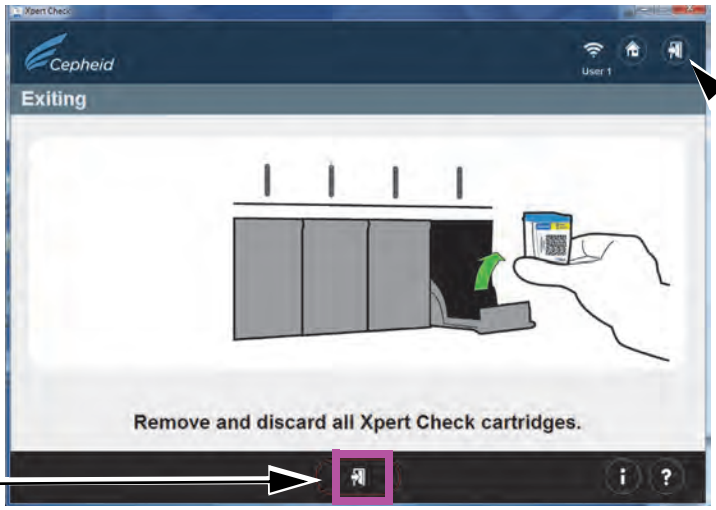


Figure 2-27. Exit the Program

25. The screen shown in Figure 2-28 appears only if you click the exit arrow in the upper right of the screen.

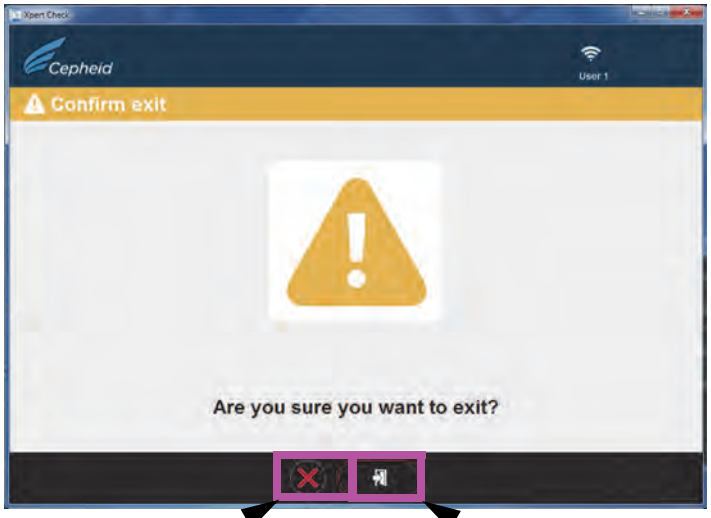


Figure 2-28. Confirm exit Screen

This completes the Xpert Check Test for an internet-connected user.

Note Contact your Authorized Service Provider or the local Cepheid Technical Support office concerning modules requiring service.

Note To view your Xpert Check results, see Step 22 and Figure 2-26, which shows the file path and location of Xpert Check results and the Xpert Check Summary report.

2.3.1 Xpert Check Completion For Non-internet Connected Users

For Non-internet connected users, you should have completed Step 1 through Step 17 of section 2.2 to collect data before starting this section.

1. This section begins with the Data collection in progress screen, which is similar to step 17 in section 2.2, and the screen shown in Figure 2-18 for internet-connected users.

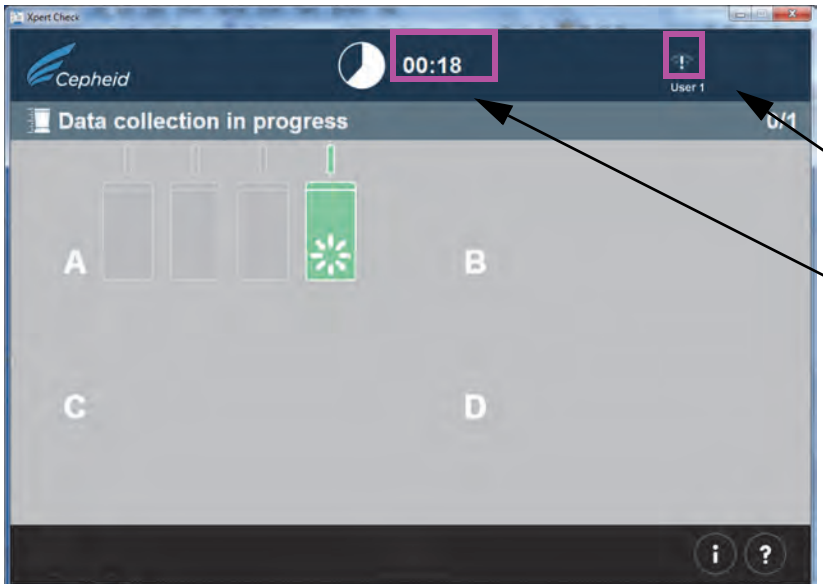


Figure 2-29. Data collection in progress Screen

2. After test completion, the module door will open and the light above the module will turn off. A screen similar to that shown in Figure 2-30 will appear. Press the right arrow at the bottom of the screen to advance to the next screen.

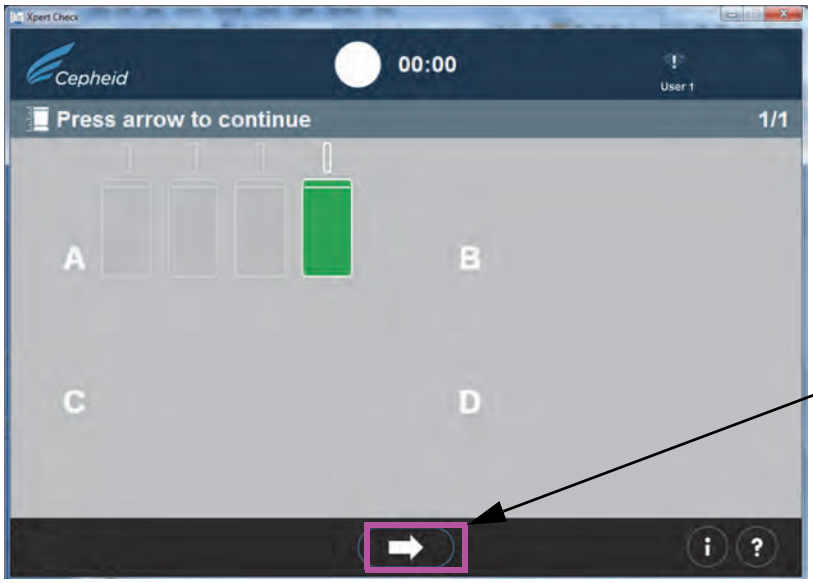


Figure 2-30. Test Completion screen - Successful

3. When the Write Xpert Check data to CD screen appears (Figure 2-31), you will be prompted to press the Eject button to remove the existing Xpert Check Software CD so you can insert the blank data CD.

Note In the following step, use care in inserting the blank CD into the DVD drive. Be sure the CD is fully seated in the tray before closing the drive door.

Important **If you have been running this test as an internet-connected user and then lost your internet connection and received an error screen (Figure 2-23), resume your procedure beginning with the following Step 4, continuing through Step 12.**

4. Insert the blank CD into the DVD drive of the computer and close the DVD drive tray fully to ensure the CD will be recognized.

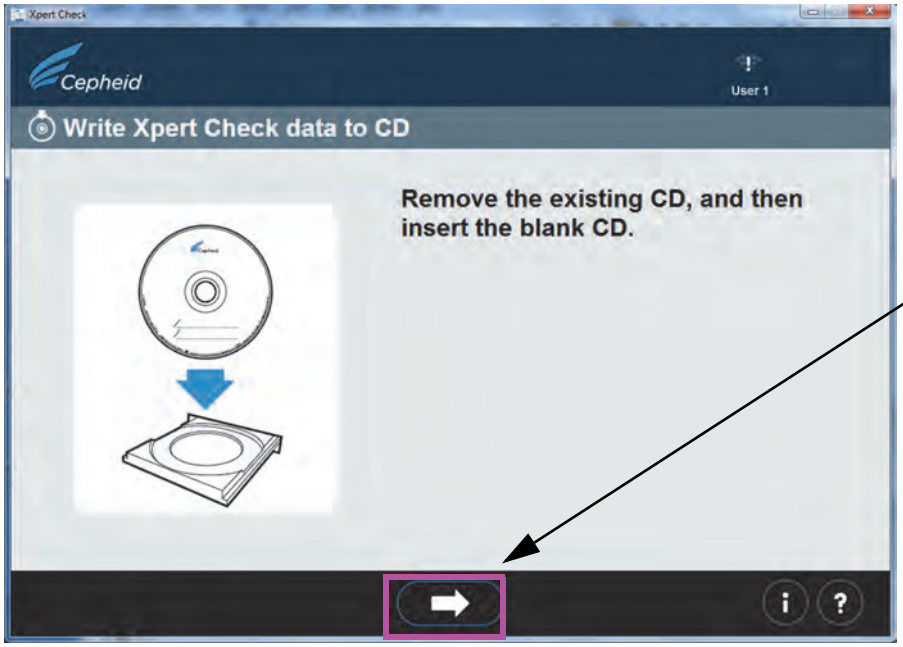


Figure 2-31. Write Xpert Check data to CD Screen - Step 1

5. After inserting the blank CD, the screen will change briefly, indicating the CD has been recognized. See Figure 2-32. This screen will remain displayed until the CD writing process is complete.

Note It is not necessary for the user to locate the file to write because that process is automatic.

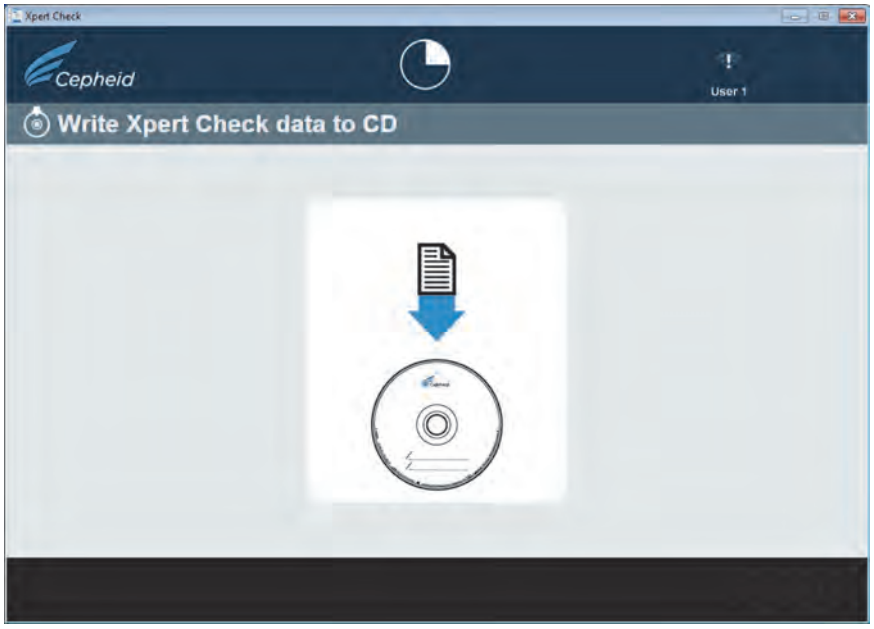


Figure 2-32. Write Xpert Check data to CD screen - Step 2

6. The CD Writing Wizard or Burn to Disc screen (Figure 2-34) will then appear as an overlay of the screen shown above, in Figure 2-32.

   The next screens (Figure 2-33 though Figure 2-37) show the CD writing program screens as you progress through the writing process.

   - Windows® XP users: Follow the screens on the left side of the figure.
   - Windows® 7 users: Follow the screens on the right side of the figure.
   - Windows®10 users: Follow the screens at the bottom of the figure.

   A. On the first screen, after successful recognition of the blank CD, you will be asked to provide a name for the CD that you will be writing. DO NOT simply click the Next button (as suggested on the screen) to continue the writing process with the default name that appears. Instead, type in your facility's name, such as "XYZ Hospital," in the space provided and click Next. See Figure 2-33.

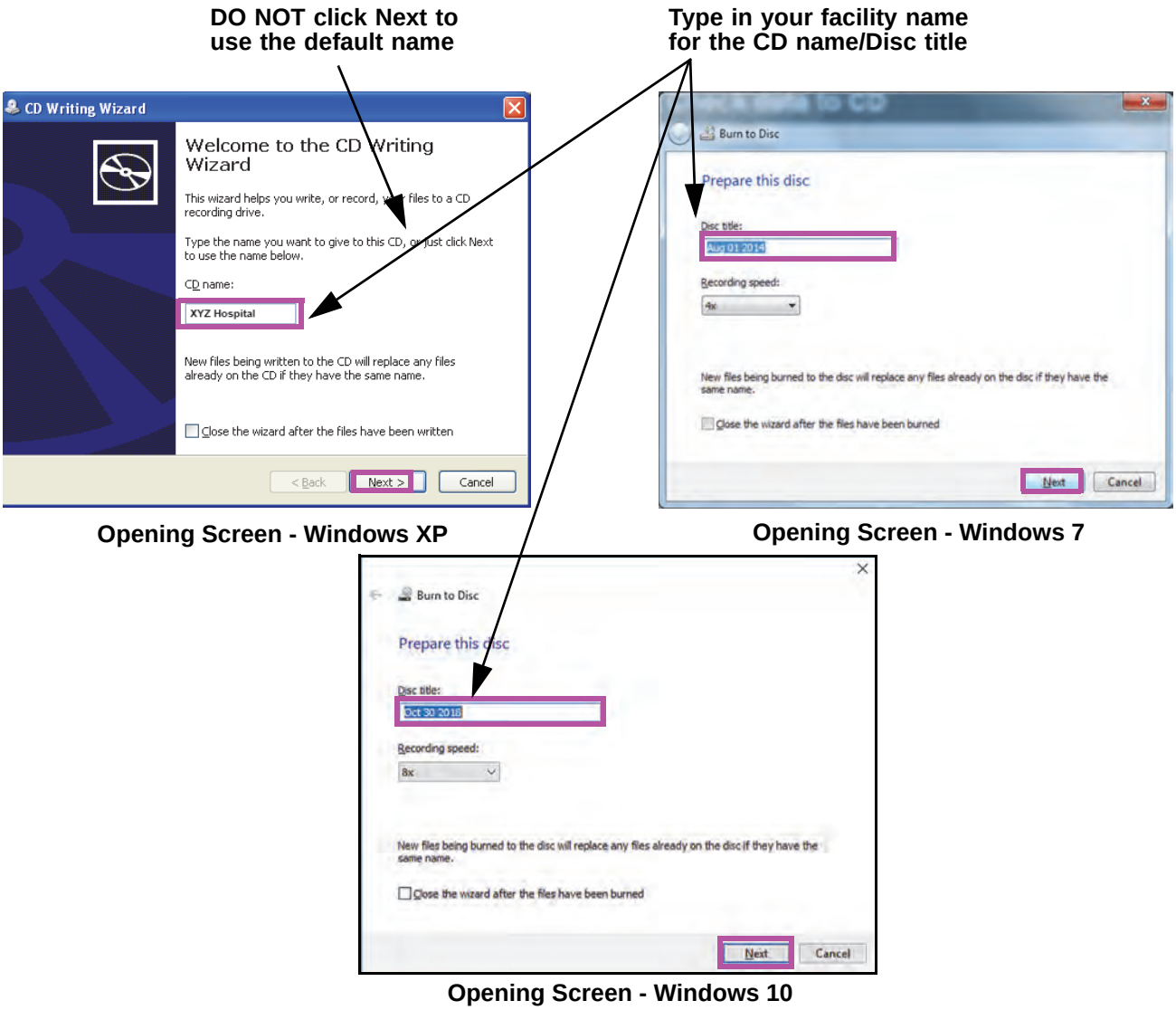


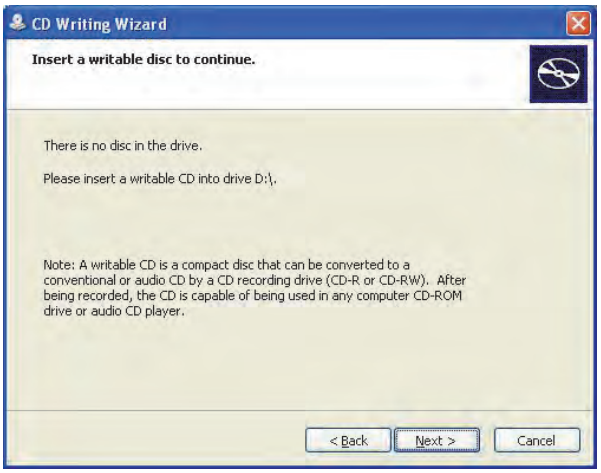
Figure 2-33. CD Writing Program - Opening Screen

B. If the CD is not recognized, the screen shown in Figure 2-34 may appear, instead of the screen in Figure 2-35, asking you to insert a writable disc to continue. Writable discs, in this case, are CDs on which you can store files. Writable discs can only be written to once, meaning that once any files are copied to the disc, they are there permanently.

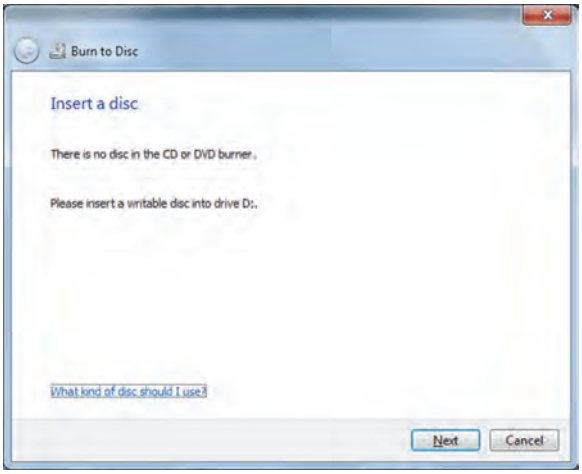
   A disc that has data on it is not considered to be a writable disc and will result in an error screen, as shown in Figure 2-39.

Note

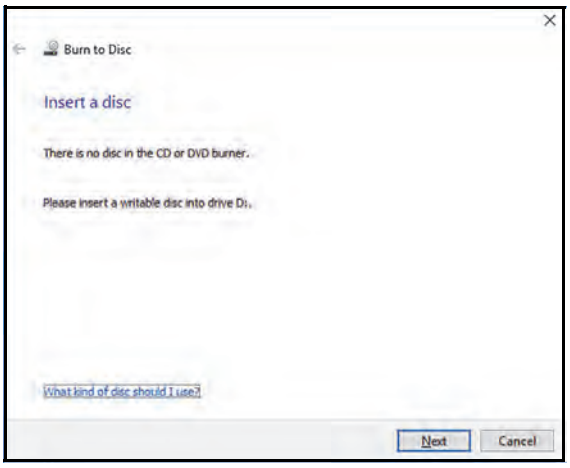
If you are unsuccessful with any part of the CD writing process, you may contact your ASP or local Cepheid Technical Support office for assistance. It is safe for you to close the Xpert Check software now because the Xpert Check files have been saved to the hard drive and you will not lose data.



Insert a Disc Screen - Windows XP



Insert a Disc Screen - Windows 7

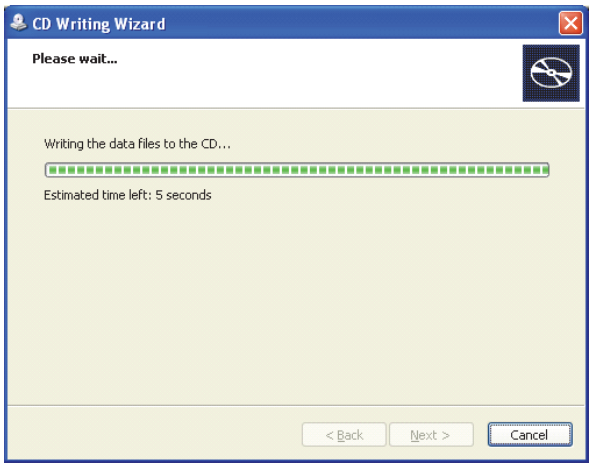


Insert a Disc Screen - Windows 10

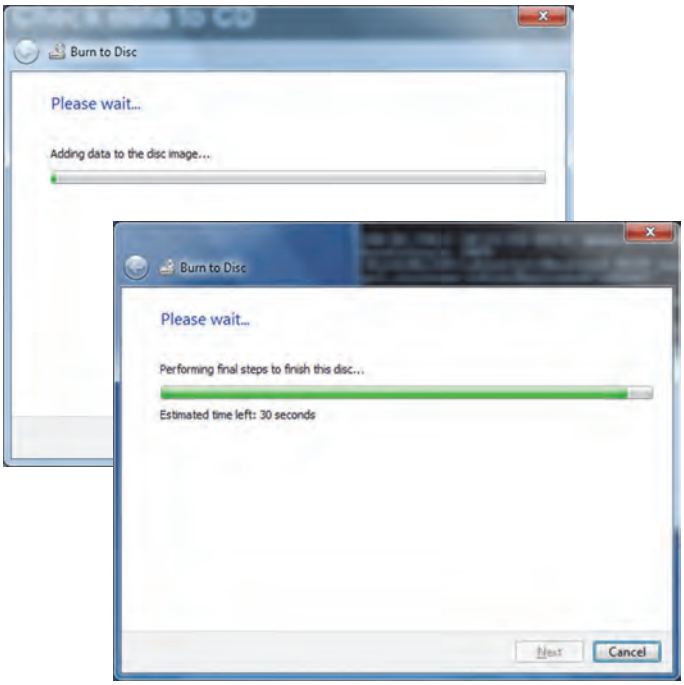
Figure 2-34. CD Writing program - Insert a writable disk to continue Screen - Example

C. After successful recognition and naming of the CD, click the Next button to continue. The writing process will begin automatically.

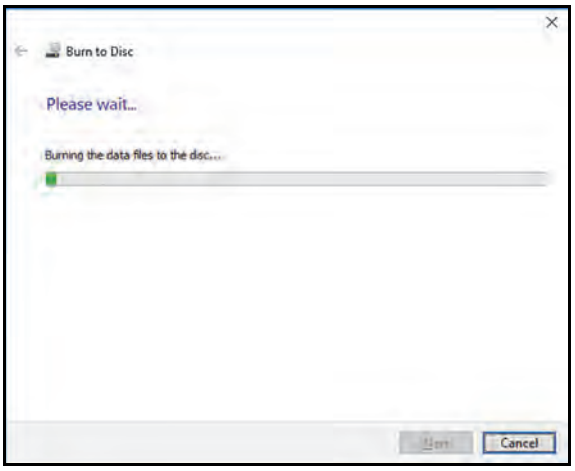
D. During the writing/burning process, a progress bar will appear on the screen. See Figure 2-35.



File Writing Progress Screen - Windows XP



File Burning Progress Screens - Windows 7

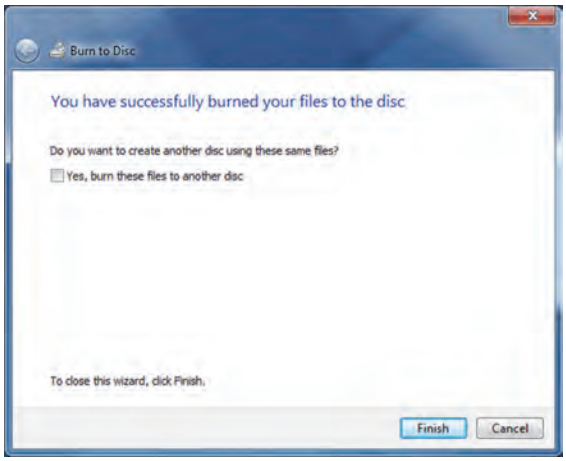


File Burning Progress Screen - Windows 10

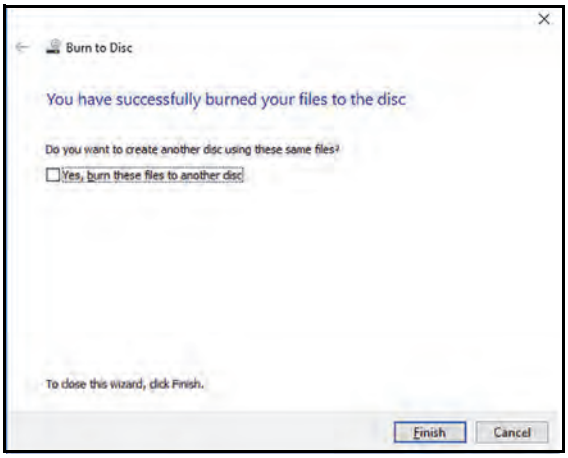
Figure 2-35. CD Writing/Burning Progress Screen

E. When the writing of the CD is complete, the screen shown in Figure 2-36 will appear. Click the Finish button to exit the CD writing program.

Completion Screen - Windows XP



Completion Screen - Windows 7



Completion Screen - Windows 10

Figure 2-36. CD Writing Completion Screen

F. On a Windows 7 computer, you may see the screen displayed in Figure 2-37 after a successful CD write. Click the OK button as many times as necessary for it to disappear, before continuing.

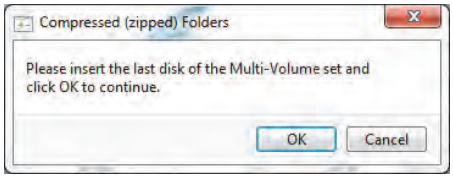


Figure 2-37. Final Screen from Windows 7 After CD Writing has Completed

7. After clicking the Finish button on the CD writing screen, the Send the CD to your Authorized Service Provider Screen will appear (see Figure 2-38). Remove the completed Xpert Check data CD from the disk drive and prepare the label, as described in Step 10.

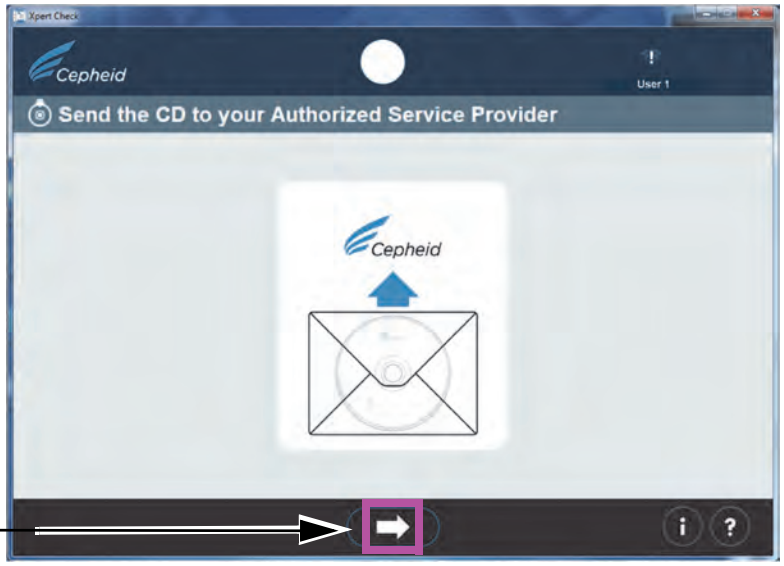
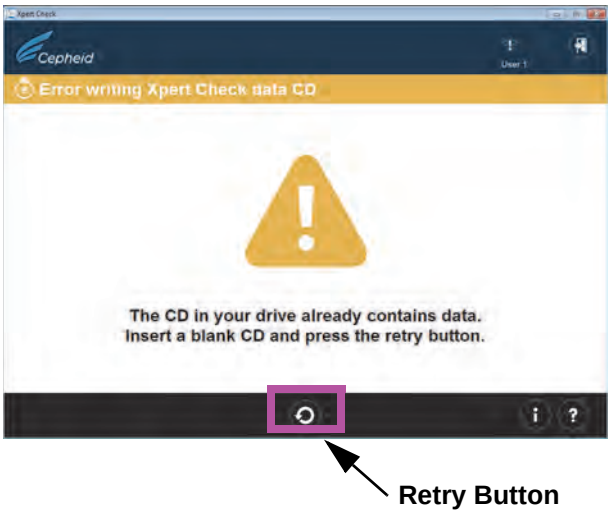


Figure 2-38. Send the CD to your Authorized Service Provider Screen - Step 3

8. If a problem has occurred anytime during the CD writing process, an error code screen may appear. (See Figure 2-39).

   - If a CD you have inserted already contains data as shown in the error screen below at the left, remove the CD and insert a blank CD, and then press the Retry button.
   - In the case of a read or write error, the screen shown at the right may appear and you must exit the program. Contact your ASP or the local Cepheid Technical Support office for assistance, if necessary.

Disc is not Writable (Already Contains Data)



General Write Failure

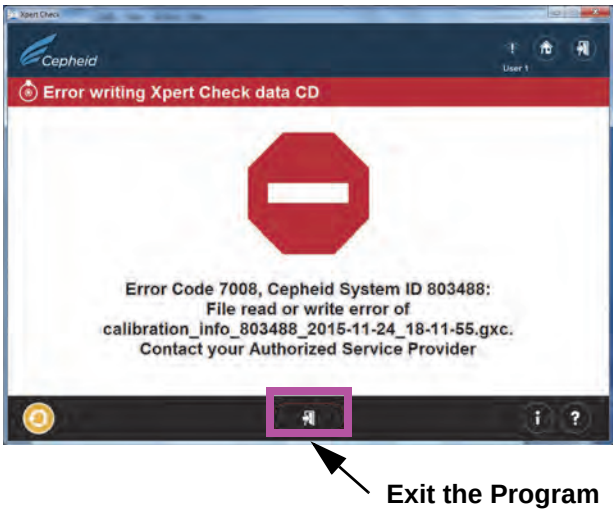


Figure 2-39. Error writing Xpert Check data CD Screens - Two Examples

9. After test completion, the Exiting screen will appear with the message Remove and discard all Xpert Check cartridges (see Figure 2-40).

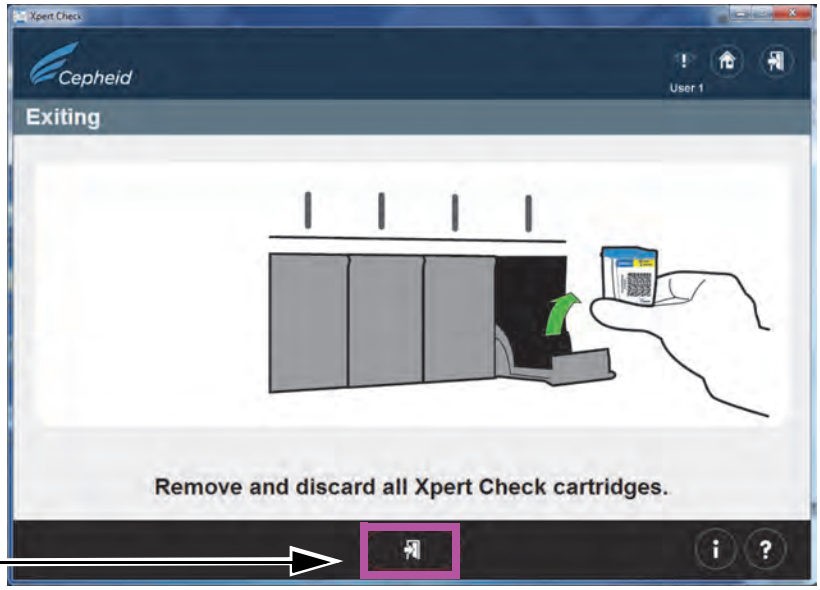


Figure 2-40. Exiting Screen

10. Use a felt-tip pen to write on the label of the Xpert Check data CD you have just created by writing the date, instrument identification and facility/location of the test performed. See a label example in Figure 2-41.

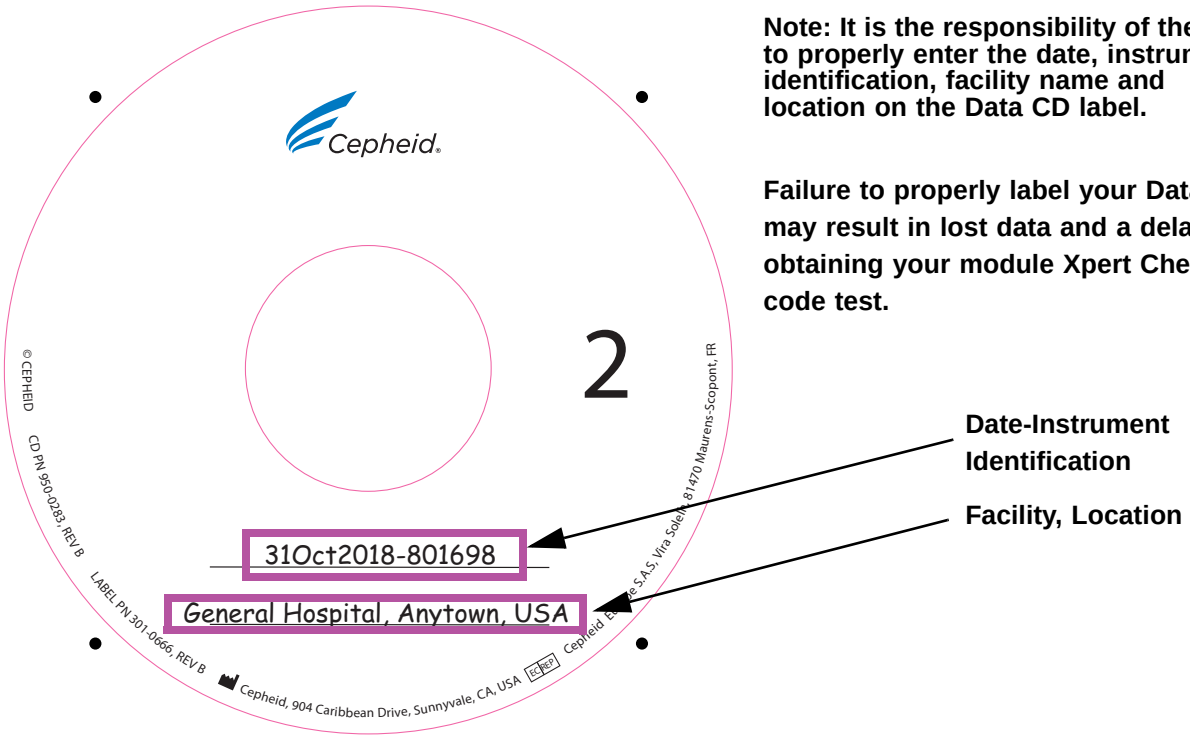


Figure 2-41. Data CD Labeling Example

11. You have the option to copy the calibration_info.gxc data file (located on the Xpert Check data CD just written) and E-mail the data file directly to your ASP or the local Cepheid Technical Support office instead of mailing the CD. If E-mail is not an option, place the Xpert Check CD2 into the provided CD shipping envelope and mail it to your local Authorized Service Provider (ASP) or the local Cepheid Technical Support office for data quality assurance checking and the issuing of your Xpert Check code.
12. Your ASP or the local Cepheid Technical Support office will perform the quality assurance review and, if successful, send back your Xpert Check code either by E-mail or regular mail, depending on what method you have previously set up with them.

Note Discard all remaining materials from the kit. DO NOT save unopened kit pouches for later use. DO NOT discard your Software CD. For users who E-mailed their file and have not shipped their data CD: DO NOT discard your Data CD.

13. Restart your GeneXpert Dx or Infinity system and computer.

Note You can continue to use your system and GeneXpert DX software while awaiting your Xpert Check code.

2.3.2 Obtaining the Xpert Check Code for Non-Internet Connected Users

Note Ensure the system is in the same configuration as when Xpert Check was run (i.e., no software updates or changes have been made and no new GX systems have been moved to or from this computer). In the case of any module servicing and/or replacement that may occur between data collection and application of the Xpert Check Code, new or modified modules will be ignored for the purposes of the Xpert Check testing process.

Note In the following step, use care in inserting the CD into the DVD drive. Be sure the CD is fully seated in the tray before closing the drive door.

1. Exit the GX Dx software.
2. To finish the Xpert Check process, place the Software CD in the DVD drive of the computer connected to the GeneXpert Dx instrument or in the kiosk computer for the Infinity.
3. Click on My Computer, then double-click on the applicable drive letter for your DVD drive. The files located on the CD will then be displayed. Find and double-click the XpertCheck.exe application/shortcut to launch the software.
4. Log in with your GeneXpert Dx or Infinity designated USER NAME and PASSWORD (see the IMPORTANT note in section 2.2). Also see Figure 2-4 for the Login screen.

   After entering your login information, click the forward arrow button at the bottom of the screen to advance to the next screen (the Xpert Check Home screen).

Note

The user name and password are the same ones you used for the GeneXpert Dx or Xpertise software. If an ASP (FSE) previously performed Xpert Check and is not now on site, the user name and password should have been provided for this step to enter the code. If the user name or password are not now available, contact your ASP or your local cepheid Technical Support office.

5. Click on the Enter Xpert Check Code button. See Figure 2-42. The Enter Xpert Check code screen will appear. See Figure 2-43.

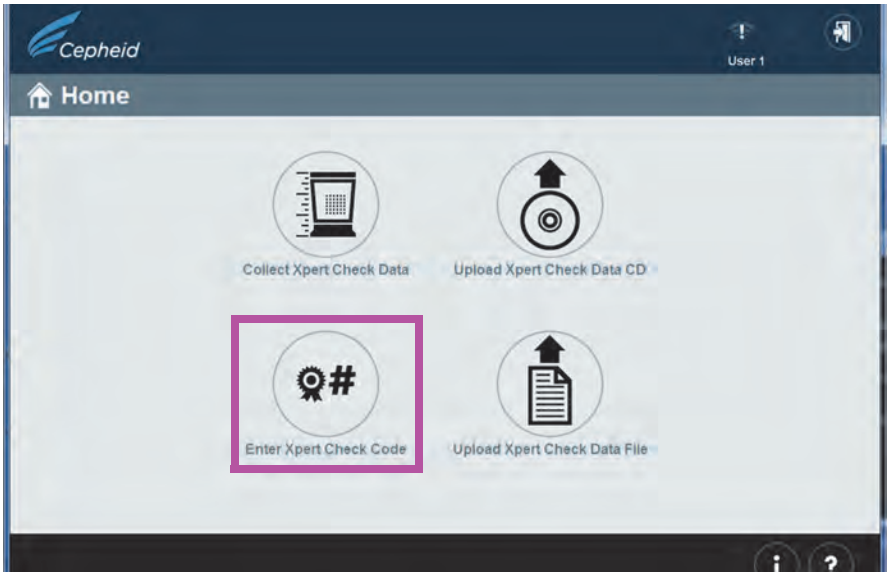


Figure 2-42. Home Screen, showing Enter Xpert Check Code Button

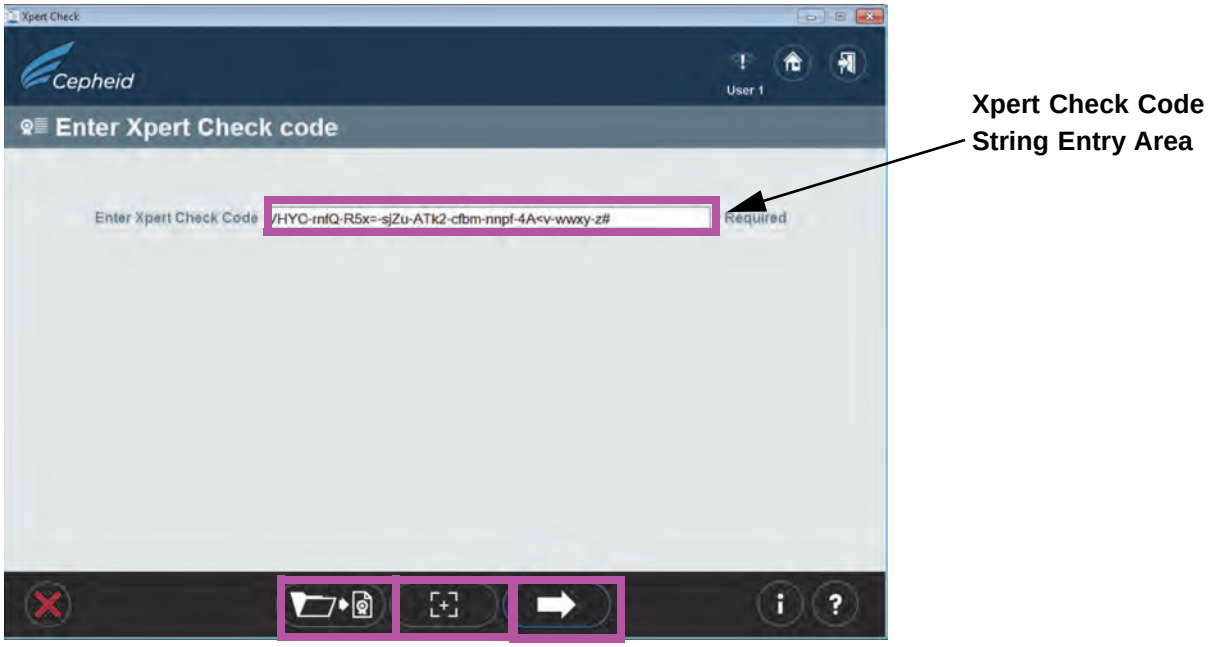


Figure 2-43. Enter Xpert Check code Screen

6. Enter your Xpert Check code as described below.

   In this step, there are various ways to enter the Xpert Check code. Your four options are listed below, beginning with the simplest (recommended) method.

   A. Option 1: Use your scanner to input the barcode as follows: First, click on the icon located in the bottom center of the screen. The Xpert Check Code File (Figure 2-44) will appear on your screen. Position your scanner to scan the barcode on the Code form, using care to avoid any reflection on the monitor that may interfere with your scanner. See Figure 2-44 for an example of an Xpert Check Code File.

   B. Option 2: Print a copy of the Xpert Check Code File and place the copy on a flat surface, facing up. Use your scanner to scan the barcode on the printed page. See Figure 2-44 for an example of a Xpert Check Code File.

   C. Option 3: Copy and paste the code string into the Enter code screen from the screen's display. The code string is visible on Figure 2-44.

   D. Option 4: Type in the code string manually using the information on your screen or printed page.

   When you have successfully entered the code, click the forward arrow at the bottom of the screen to continue. The Applying Xpert Check code screen will appear. See Figure 2-45.

Cepheid

Xpert Check Code File

Here is the Xpert Check code for the recent data collection of your modules for the system identified below.

Xpert Check data collection performed on 30 October 2018 15:02:31 PST

GX Instrument Name:	My GeneXpert
Cepheid System ID:	123456
Software Version:	Xh1.4
Data Collected By:	admin1
Institution Name:	Institution1
Laboratory Name:	Lab1
Street Address:	100 Main Street, Suite 202
City:	New York
State/Province:	NY
Postal Code:	10001
Country:	USA
Email:	user@institution.com
Facility Phone Number:	408 400-0000
Extension:	
Mobile:	
ASP Code:	US01

Scan or enter the Xpert Check code to complete the Xpert Check process.

1. Cepheid recommends that system performance should be evaluated annually using Xpert Check.

2. Cepheid declares that the I-CORE modules in the GeneXpert® Instrument were checked using an Xpert Check product. NIST traceable qualification standards are used to control the parameters for the fluorescence standards of concentration, brightness, and spectrum. Cepheid products are manufactured, quantified and controlled under a Quality System compliant with ISO 13485 and QSR requirements.

GeneXpert® Xpert Check Version: Xh1.4

Page 1 of 1

Figure 2-44. Xpert Check Code File - Example

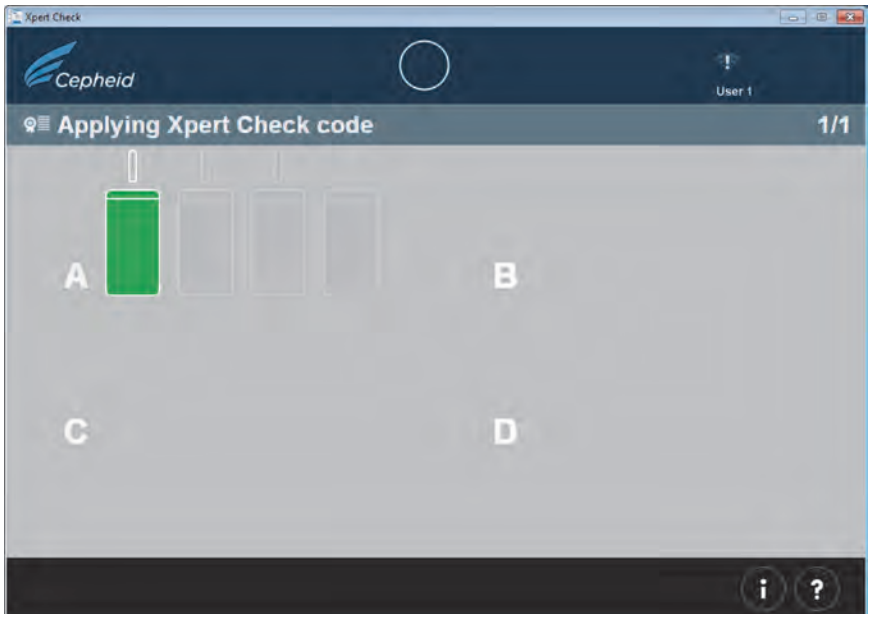


Figure 2-45. Applying Xpert Check code Screen Example

E. After the Xpert Check code has been applied, the Xpert Check Complete screen will appear with the location of the Xpert Check Report displayed in the Xpert Check Data Directory area. Write down the file path and location of the Xpert Check Report file, as shown. See Figure 2-46.

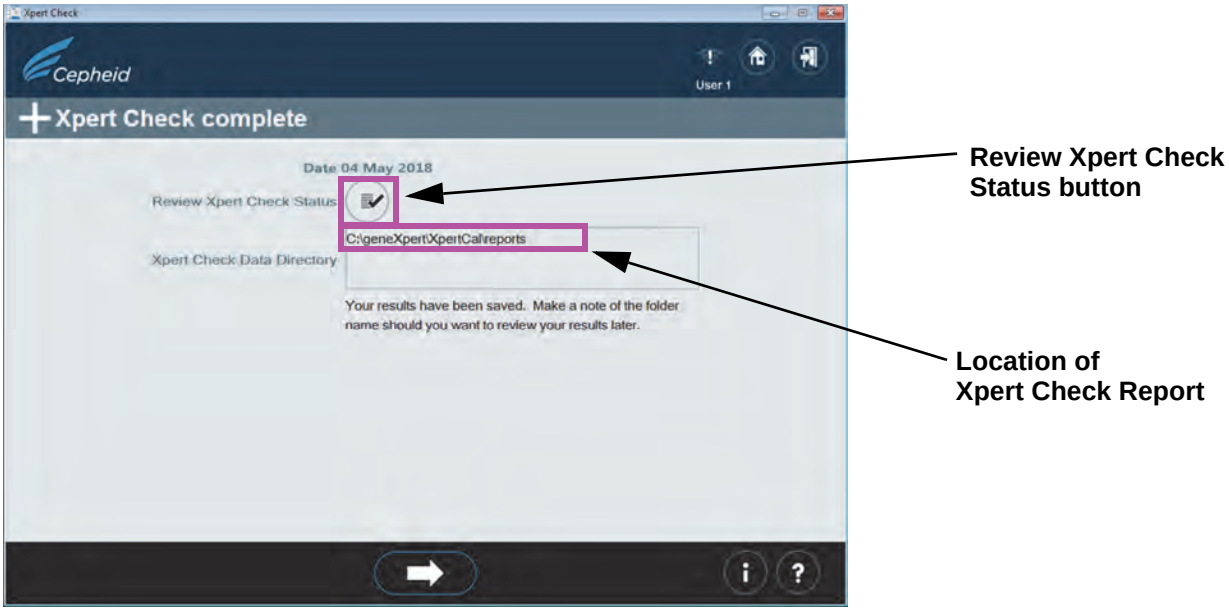


Figure 2-46. Xpert Check complete Screen

F. Click the Review Xpert Check Status button (see Figure 2-46).

G. The Xpert Check status screen will appear. See Figure 2-47. In the Xpert Check status screen, the successfully checked modules are indicated by a + symbol on a green module.

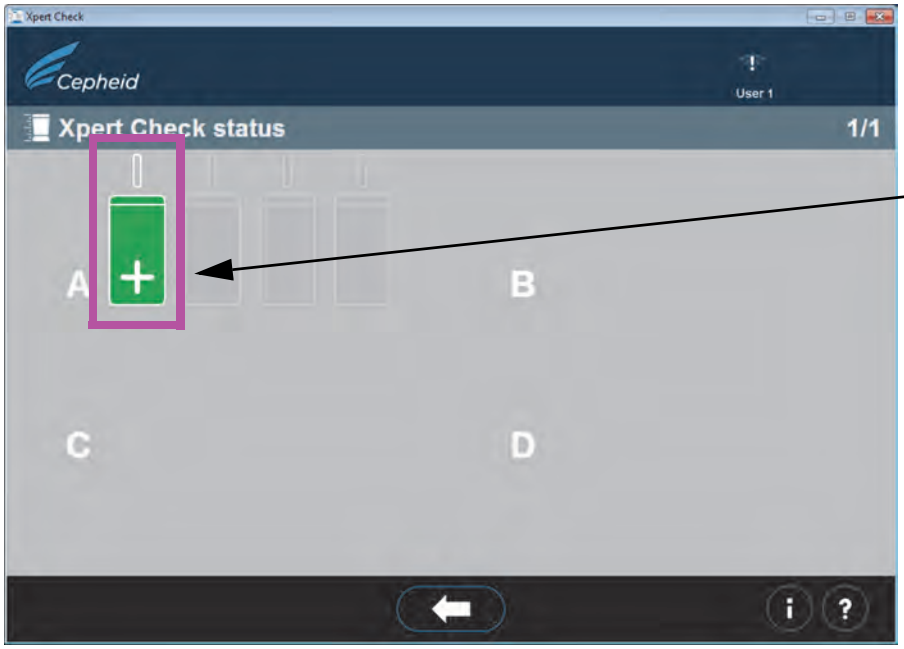


Figure 2-47. Xpert Check status Screen

Note

If the Xpert Check report on the computer has been deleted, contact your ASP or the local Cepheid Technical Support office for assistance.

7. Identify the generated Xpert Check Report file in the folder C:\GeneXpert\XpertCal\Reports.

8. Identify the generated Xpert Check Summary Report file in the folder C:\GeneXpert\XpertCal\Reports.

   A. See Figure 2-48 for an example of a Xpert Check Summary Report.

      The Xpert Check Summary Report lists the modules that had an unsuccessful test and require retesting or service.

      The modules requiring retesting or service are listed by serial number in Table 1 on the form in Figure 2-48. When requesting service, provide these listed serial numbers to your ASP or the local Cepheid Technical Support office.

      Gateway information is provided in Table 2 of the form.

Xpert Check Summary Report

Please Note:

Xpert Check data collection performed on 30 October 2018 09:37:04 PDT
All modules that DID NOT pass Xpert Check are listed in Table 1: Modules Requiring Service.
Gateway Informations are provided in Table 2.
Complete test results for each module are listed in Table 3: Detailed Test Results by Module.

GX Instrument Name:	My 6Color
Cepheid System ID:	12345
Data Collected By:	User1
Institution Name:	Institution1
Laboratory Name:	Laboratory Sunnyvale
Street Address:	123 Main Street
City:	Sunnyvale
State/Province:	CA
Postal Code:	90001
Country:	USA
Email:	User1@Institution1.com
Facility Phone Number:	408-400-XXXX
Extension:	
Mobile:	
ASP Code:	US03

Table 1: Modules Requiring Service

Module Serial Number / Location	Module Status
639563/A2	Skipped and Retest required
639565/A1	Requiring Service

Table 2: Gateway Information

Gateway Serial Number	MAC Address
804471	00:21:38:00:2E:1B
804470	00:21:38:00:2E:1A

GeneXpert® Xpert Check Version: Xh1.4 Page 1 of 2

Figure 2-48. Xpert Check Summary Report Example - Page 1

2.4 Return System to Normal Operation

Note Return the system to normal operation by following one of the three procedures listed in this section for the GeneXpert Dx, the Infinity-48, the Infinity 48s, or the Infinity-80.

2.4.1 GeneXpert Dx

Ensure all Xpert Check cartridges and CDs have been removed from the GeneXpert Dx.

1. Restart your GeneXpert system and computer. Follow the instructions in the GeneXpert Dx System Operator Manual.
2. The system will be ready for full operation.

2.4.2 Infinity-48

Ensure all Xpert Check cartridges and CDs have been removed from the Infinity-48.

1. Restart the Xpertise software and switch the system from Manual mode back to Automation mode. Follow the instructions in the GeneXpert Infinity System Operator Manual for the Infinity-48.
2. The system will be ready for full operation.

2.4.3 Infinity-48s or Infinity-80

Ensure all Xpert Check cartridges and CDs have been removed from the Infinity-48s or Infinity-80.

1. Restart the Xpertise software. Follow the instructions in the GeneXpert Infinity System Operator Manual.
2. The system will be in Automation mode, ready for full operation.

2.5 Information Key Screen

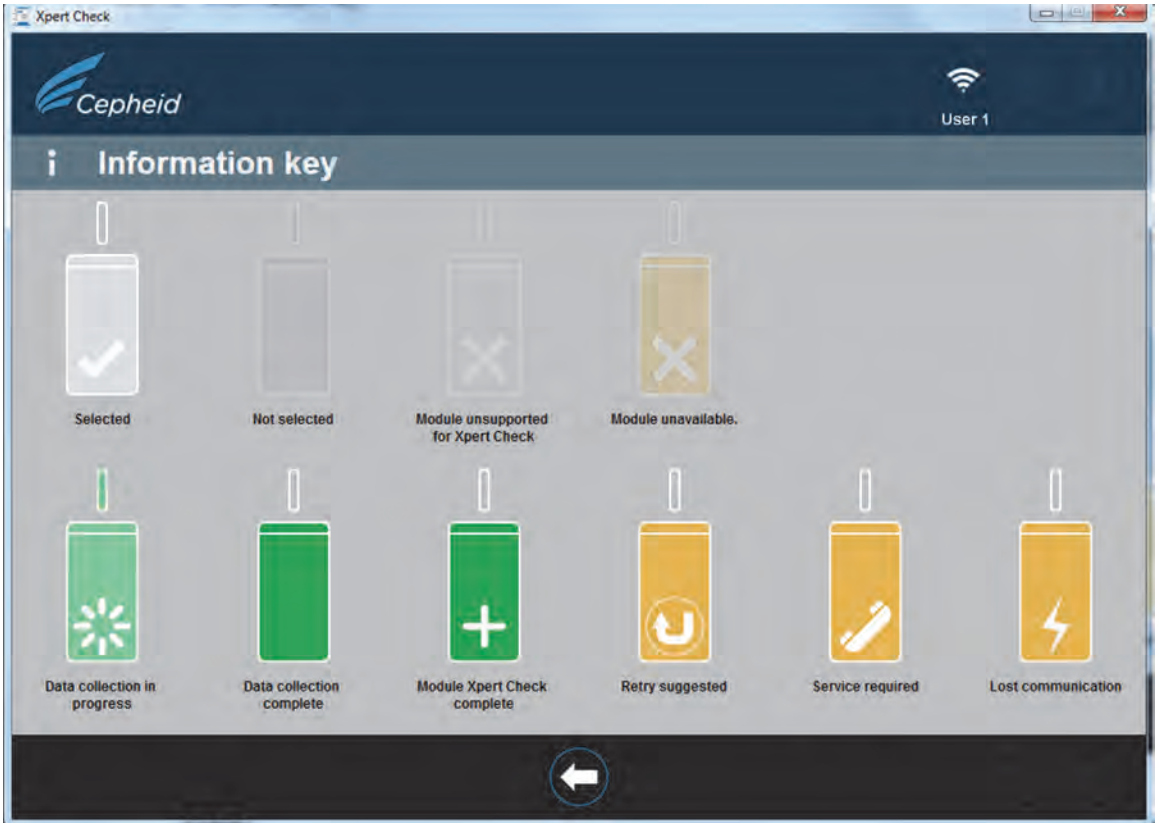


Figure 2-49. Information key Screen

2.5.1 Reasons to Repeat Xpert Check with a New Cartridge

If the onscreen instructions direct you to retest, repeat the test according to the instructions in Step B. on page 2-18.

2.5.2 Reasons to Repeat Xpert Check with the Same Cartridge

If software reports that the cartridge film seal was not broken, remove the original cartridge, rescan the cartridge barcode, open the lid, close the lid, and reinsert the cartridge. Restart the Xpert Check procedure for the affected module.

2.5.3 Application of Xpert Check Code

Xpert Check is not complete until the Cepheid-supplied Xpert Check code is applied to the system being tested. Upon receipt of the Quality Assurance Xpert Check Code from Cepheid, apply the code to your system using the Xpert Check Software to complete the Xpert Check process.

GeneXpert
Powered By CEPHEID INNOVATION

Xpert® MTB/XDR

REF **GXMTB/XDR-10**

Cepheid

In Vitro Diagnostic Medical Device

IVD CE

302-3514, Rev. B July 2020

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Cepheid AB
Röntgenvägen 5
SE-171 54 Solna,
Sweden

Xpert® MTB/XDR

For *In Vitro* Diagnostic Use

1 Proprietary Name

Xpert® MTB/XDR

2 Common or Usual Name

Xpert MTB/XDR Assay

3 Intended Use

The Xpert MTB/XDR Assay, performed on the GeneXpert Instrument Systems, is a nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of extensively drug resistant (XDR) *Mycobacterium tuberculosis* (MTB) complex DNA in unprocessed sputum samples or concentrated sediments prepared from sputum. In specimens where MTB is detected, the Xpert MTB/XDR Assay can also detect isoniazid (INH) resistance associated mutations in the *katG* and *fabG1* genes, *oxyR-ahpC* intergenic region and *inhA* promoter; ethionamide (ETH) resistance associated with *inhA* promoter mutations only; fluoroquinolone (FLQ) resistance associated mutations in the *gyrA* and *gyrB* quinolone resistance determining regions (QRDR); and second line injectable drug (SLID) associated mutations in the *rrs* gene and the *eis* promoter region.

The Xpert MTB/XDR Assay is intended for use as a reflex test for a specimen (unprocessed sputum or concentrated sputum sediments) that is determined to be MTB positive. This test is intended as an aid in the diagnosis of XDR tuberculosis (TB) when used in conjunction with clinical and other laboratory findings..

4 Summary and Explanation

Tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, remains one of the deadliest diseases in the world. In 2018, there were an estimated 10 million new cases of TB and about half a million new cases of rifampicin-resistant TB, of which 78% had multidrug-resistant TB (MDR-TB)[1]. MDR-TB, defined as resistance to isoniazid and rifampicin (two of the most effective first lines drugs), continues to be a public health threat and new treatment guidelines calling for rapid drug susceptibility testing are released by the World Health Organization (WHO)[2,3]. Nevertheless, in 2018, the global number of MDR/RR-TB cases notified was still only 39% of the estimated incident cases and the number of people enrolled in treatment was equivalent to 32%[1]. Likewise, there is also a rising concern of undiagnosed and untreated isoniazid-resistant, rifampicin-susceptible TB. Without easy access to INH-resistance testing, countries struggle to identify patients and implement the 2018 WHO treatment recommendations for Hr-TB[4]. The most worrisome cases of TB are caused by MDR MTB strains which acquired additional resistances to fluoroquinolones and any one of the second line injectable drugs, amikacin (AMK), kanamycin (KAN), or capreomycin (CAP). These highly resistant strains are termed extensively drug resistant TB (XDR-TB). XDR-TB is very difficult to treat and can lead to high rates of mortality, especially when an XDR-TB diagnosis is missed and appropriate treatment is delayed[5].

Culture and phenotypic drug susceptibility testing of MTB are time consuming, and labor-intensive and present a serious biohazard to laboratory workers, resulting in fewer accredited facilities in countries where MTB is endemic[2]. Even when available, culture-based susceptibility testing can take from weeks to months to complete. MTB may also be tested for drug resistance using fast, sensitive, and safer genotypic assays, which detect resistance by identifying mutations known to confer resistance to the first- and second-line drugs in a majority of clinical strains[2]. Genotypic testing approaches that can be reduced to a few manual steps are more amenable for near patient care, which can dramatically expand their availability to medically underserved populations in low and high endemic settings[5].

5 Principle of the Procedure

The Xpert MTB/XDR Assay is an automated *in vitro* diagnostic test for detection of XDR MTB complex DNA and resistance associated mutations. The assay is performed on Cepheid GeneXpert Instrument Systems equipped with GeneXpert 10 color modules.

The GeneXpert Instrument System integrate and automate sample processing, nucleic acid amplification, and detection of the target sequences in samples using nested real-time PCR and melt peak detection. The GeneXpert Instrument Systems consists of an instrument, personal computer, barcode scanner, and preloaded software for running tests on collected samples and viewing the results. The system requires the use of single-use disposable Xpert cartridges that contain target specific polymerase chain reaction (PCR) reagents and hosts the PCR process and melt peak detection. Because the Xpert cartridges are self-contained, risk of cross-contamination between samples is minimized. For a full description of the system, see the *GeneXpert Dx System Operator Manual*.

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

The Xpert MTB/XDR Assay cartridge has all reagents on board, except sample reagent (SR) which requires the user to add the SR to the specimen prior loading the treated specimen into the cartridge. The test is intended to be run as a reflex test for MTB positive samples.

The results are interpreted by the GeneXpert software from measured fluorescent signals and embedded calculation algorithms and are shown in the View Results window in tabular and graphic formats. It also reports if the test is invalid, has encountered an error or produces no result. The Xpert MTB/XDR detects XDR MTB with resistance to INH, ETH, FLQs, and SLIDs directly from unprocessed sputum or from concentrated sediment from sputum in less than 90 minutes.

6 Reagents and Instruments

6.1 Material Provided

The Xpert MTB/XDR kit contains sufficient reagents to process 10 patient or quality-control specimens. The kit contains the following items:

Xpert MTB/XDR Cartridges with Integrated Reaction Tubes	**10 per kit**
• Bead 1, Bead 2, Bead 3, Bead 4, and Bead 5 (freeze-dried)	1 of each per cartridge
• Sample Processing Control Bead (freeze-dried)	1 of each per cartridge
• Reagent 1	4.0 mL per cartridge
• Reagent 2	4.0 mL per cartridge
Disposable transfer pipettes	**1 bag of 12 per kit**
Sample Reagent	**10 x 8 mL per bottle**
CD	**1 per kit**
• Assay Definition Files (ADF)	
• Instructions to import ADF into the GeneXpert software	
• Instructions for Use (Package Insert)	

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 MTB/XDR kit contents at 2–28 °C until expiration data provided on the label.
- Do not open a cartridge lid until you are ready to perform testing.
- Start the test within 2.5 hours of adding SR to the specimen or within 4 hours if stored at 2–8^{0}C

- Do not use reagents or cartridges that have passed the expiration date.
- Do not use a cartridge that has leaked.

8 Materials Required but Not Provided

- GeneXpert Dx system: GeneXpert instrument equipped with GeneXpert 10 color modules., computer, barcode scanner, and operator manual
  - For GeneXpert Dx system: Software version 6.2 or higher
  - Printer: If a printer is required, contact Cepheid Sales Representative to arrange for the purchase of a recommended printer.
- Sterile screw-capped sample container
- Disposable gloves
- Labels and/or indelible labeling marker
- Sterile pipettes for sample processing

9 Warnings and Precautions

9.1 General

- For *In Vitro* Diagnostic Use

- 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[3] and the Clinical and Laboratory Standards Institute.[6,7,8]
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- Wear protective disposable gloves, laboratory coats and eye protection when handling specimens and reagents. Wash hands thoroughly after handling specimens and test reagents.

- 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].
- Sample Reagent contains sodium hydroxide (pH > 12.5) and isopropanol. Harmful if swallowed (H302), causes severe skin burns and eye damage (H314). Flammable liquid and vapor (H226).
- Performance characteristics of this test have been established with the specimen types listed in the Intended Use Section only. The performance of this assay with other specimen types or samples has not been evaluated.
- Follow your institution's safety procedures for working with chemicals and handling biological samples.

9.2 Specimen

- Specimen collection and handling procedures require specific training and guidance.
- Maintain proper storage conditions during specimen transport to ensure the integrity of the specimen (see Section 12, Procedure). Specimen stability under shipping conditions other than those recommended has not been evaluated.
- Reject specimens with obvious food particles or other solid particulates.
- Proper sample collection, storage, and transport are essential for correct results

9.3 Assay/Reagent

- Do not substitute Xpert MTB/XDR Assay reagents with other reagents.
- Do not open the Xpert MTB/XDR Assay cartridge lid except when adding sample.
- Do not use a cartridge that has been dropped after removing from the kit or shaken after the cartridge lid has been opened. 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 barcode label.
- Do not use a cartridge that has a damaged reaction tube.
- Each single-use Xpert MTB/XDR Assay cartridge is used to process one test. Do not reuse spent cartridges.
- A single-use disposable pipette is used to transfer one specimen. Do not reuse spent disposable pipettes.
- Do not use a cartridge if it appears wet or if the lid seal appears to have been broken.
- Good laboratory practices, including changing gloves between handling patient specimens, are recommended to avoid contamination of specimens or reagents.
- In the event of a spill of specimens or controls, wear gloves and absorb the spill with paper towels. Then, thoroughly clean the contaminated area with a 1:10 dilution of freshly prepared household chlorine bleach. Final active chlorine concentration should be 0.5% regardless of the household bleach concentration in your country. Allow a minimum of two minutes of contact time. Ensure the work area is dry before using 70% denatured ethanol to remove bleach residue. Allow surface to dry completely before proceeding. Or, follow your institution's standard procedures for a contamination or spill event. For equipment, follow the manufacturer's recommendations for decontamination of equipment.
- The assay has been validated using Cepheid GeneXpert Dx software version 6.2 or higher.

10 Chemical Hazards[9,10]

Sample Reagent:

- Contains Isopropyl Alcohol
- Contains Sodium Hydroxide
- Signal Word: DANGER
- UN GHS Hazard Pictograms:

- **UN GHS Hazard Statements**
  - Flammable liquid and vapor.
  - Causes severe skin burns and eye damage.
  - Causes severe 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.
- **UN GHS 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 breath mists, vapours, 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.

11 Specimen Collection, Transport and Storage

Specimens can be collected following the user institution's standard procedures.

Proper specimen collection, storage, and transport are critical to the performance of this test. Specimen stability under shipping and storage conditions other than those listed below have not been evaluated with the Xpert MTB/XDR Assay.

11.1 Transport

Specimens are recommended to be transported at 2–8 °C whenever possible.

Unprocessed sputum specimens can be kept at 2–35°C.

11.2 Untreated Specimens

Unprocessed sputum specimens can be stored at 2–35°C for 7 days (including shipping time)

Decontaminated/concentrated and resuspended sputum sediment can be stored at 2–8 °C for up to 7 days until testing is performed on the GeneXpert.

When testing unprocessed sputum or decontaminated/concentrated sputum sediment refer to Table 1 below to determine adequate specimen volume.

Table 1. Required Specimen Volume

Specimen Type	Minimum Volume for One Test	Maximum sample volume	Specimen to Sample Reagent (SR) Ratio
Sputum sediment	0.5 mL	2.5 mL	1:3[a]
Unprocessed sputum	1.0 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.

11.3 Leftover Specimens Treated with SR

Xpert MTB/XDR Assay can be used to test left over SR treated specimen from Xpert MTB/RIF or Xpert MTB/RIF Ultra Assay. However, in such cases, the volume of the leftover SR treated specimen must be ≥2mL and the mix should be stored 2–8 °C for no longer than 4 hours or up to 35 °C for no longer than 2.5 hours.

12 Procedure

12.1 Procedure for Unprocessed Sputum

Important **Start the test within 2.5 hours of adding SR to the specimen or within 4 hours if stored at 2–8 °C.**

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

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

1. Carefully open the lid of the leak-proof sputum collection container. See Figure 1.

Figure 1. Opening the sputum collection container

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

Example 1.
8 mL Sample Reagent:
4 mL: Sputum

3 ml line

Example 2.
2 mL Sample Reagent:
1 mL: Sputum

Figure 2. Examples of 2:1 dilutions

Note Discard the leftover SR and bottle in an appropriate waste container according to your institution's standard practices.

3. Secure the lid on the sample container.
4. 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 for 10 minutes at room temperature, and then shake the specimen vigorously 10 to 20 times or vortex for at least 10 seconds.
6. Incubate the sample at room temperature for an additional 5 minutes.

12.2 Procedure for Decontaminated Concentrated Sputum Sediments

Important **Start the test within 2.5 hours of adding SR to the specimen or within 4 hours if stored at 2–8 °C.**

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

Volume Requirements: Sputum sediments prepared according to the NALC-NaOH (N-Acetyl-l-Cysteine–Sodium Hydroxide) method described in Kent and Kubica[11] and re-suspended in 67 mM Phosphate/H_2O buffer can be tested using the Xpert MTB/XDR Assay. After resuspension, keep at least 0.5 mL of the resuspended sediment for the Xpert MTB/XDR Assay. For all volumes less than 0.7 mL perform steps 1 through 5 to prepare samples. These steps require 3 parts SR to 1 part sediment in order to generate adequate volume 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. Transfer 0.5 mL of the total resuspended pellet to a conical, screw-capped tube labeled with the sample and/or patient ID using a transfer pipette.

Note Store re-suspended sediments at 2–8 °C if they are not immediately processed. Do not store for more than 7 days.

2. Add 1.5 mL of Sample Reagent (SR) to 0.5 mL of resuspended sediment.
3. Shake vigorously 10 to 20 times or vortex for at least 10 seconds.

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

4. Incubate for 10 minutes at room temperature, and then shake the specimen vigorously 10 to 20 times or vortex for at least 10 seconds.
5. Incubate the sample at room temperature for an additional 5 minutes.

12.3 Preparing the Cartridge

Important **Ensure a module is ready to accept cartridge. Start the test as soon as possible and within 2.5 hours of adding the Sample Reagent-treated sample to the cartridge or within 4 hours if stored at 2–8 °C.**

Obtain the following items: Xpert cartridge, transfer pipette (provided), and an appropriately collected and labeled test sample.

1. Remove a cartridge from the package.
2. Inspect the cartridge for damage. If damaged, do not use it.
3. Bring the cartridge to room temperature. Label each Xpert MTB/XDR cartridge with the Sample ID. See Figure 3.

Figure 3. Write on Side of Cartridge.

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.

4. Open the cartridge lid, and then open the sample container.

5. Using the provided transfer pipette, aspirate the liquefied sample to the line on the pipette. Do not process the sample further if there is insufficient volume. See Figure 4.

Figure 4. Aspirating to the line on the pipette

6. Dispense the sample slowly to minimize the risk of aerosol formation. See Figure 5.

Figure 5. Xpert MTB/XDR Assay Cartridge

7. Close the cartridge lid.

12.4 Starting the Test

Important **Before starting the test, make sure that the Xpert MTB/XDR 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*.**

Note The steps you follow can be different if the system administrator changed the default workflow of the system.

1. Turn on the GeneXpert instrument:
   - If using the GeneXpert Dx instrument, first turn on the instrument and then turn on the computer. The GeneXpert Dx software will launch automatically or may require double-clicking the GeneXpert Dx shortcut icon on the Windows® desktop.
2. Log on to the GeneXpert Instrument 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 Patient or Sample ID or type in the Patient or Sample ID. If typing the Sample ID, make sure the Sample ID is typed correctly. The Sample ID is shown on the left side of the View Results window and is associated with the test results.
5. Scan the barcode on the Xpert MTB/XDR Assay cartridge. Using the barcode information, the software automatically fills the boxes for the following fields: Reagent Lot ID, Cartridge S/N, and Expiration Date. See Figure 6.

Note If the barcode on the Xpert MTB/XDR cartridge does not scan, then repeat the test with a new cartridge.

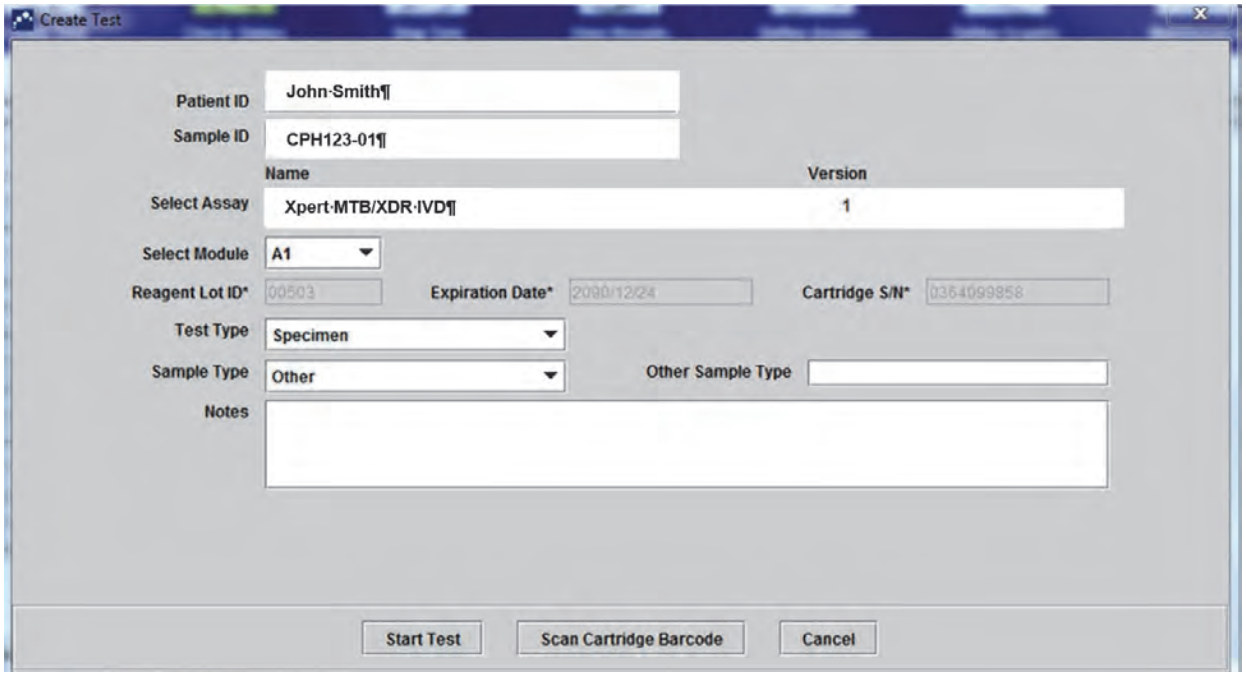


Figure 6. GX Dx Create Test Window

6. Click Start Test. Type your password in the dialog box that appears.
7. For the GeneXpert Dx Instrument:
   A. Open the instrument module door with the blinking green light and load the cartridge.
   B. Close the door. The test starts and the green light stops blinking. When the test is finished, the light turns off.
   C. Wait until the system releases the door lock before opening the module door and removing the cartridge.
8. Dispose of used cartridges in the appropriate specimen waste container according to your institution's standard practices.

13 Viewing and Printing Results

This section lists the basic steps for viewing and printing results. For more detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual*.

- Click the View Results icon to view results.
- Upon completion of the test, click the Report button of the View Results window to view and/or generate a PDF report file.

14 Quality Control

14.1 Built-in Quality Controls

CONTROL

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

- **Sample Processing Control (SPC)**— The SPC verifies that sample processing is adequate. Additionally, this control detects sample-associated inhibition of the real-time PCR assay, ensures the PCR reaction conditions (temperature and time) are appropriate for the amplification reaction, and that the PCR reagents are functional. The SPC should be positive in a negative sample and can be negative or positive in a positive sample. The SPC passes if it meets the assigned acceptance criteria.
- **Probe Check Control (PCC)—**Before the start of the PCR reaction, the GeneXpert 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.
- **Sample Volume Adequacy (SVA) control**—Before sample processing, the GeneXpert system measures if adequate volume of specimen is present in the sample chamber. If SVA check fails, it implies that adequate volume of sample required for testing has not been added to the sample chamber.

15 Interpretation of Results

The GeneXpert Instrument System generates the results from a combination of measured fluorescent signals and melting temperature (*Tm*) values. Mutations and wild type sequences are detected by the GeneXpert System using *Tm* values. Susceptibility or resistance determination depends on where the *Tm* values fall within the wild type or mutant window respectively for a particular analyte. Positive results for the Xpert MTB/XDR Assay can be MTB DETECTED and all resistance targets are NOT DETECTED or MTB DETECTED and one or more of the resistance targets is DETECTED or MTB DETECTED and/or one or more of the following resistance targets is INDETERMINATE. See Table 2 for a list of possible results for each target.

Table 2. Possible Test Results for Each Target in the Xpert MTB/XDR Assay

Drug Class	Result Call
N/A	INVALID/ERROR/NO RESULT
	MTB DETECTED
	MTB NOT DETECTED
Isoniazid	Low INH Resistance DETECTED
	INH Resistance DETECTED
	INH Resistance NOT DETECTED
	INH Resistance INDETERMINATE
Fluoroquinolone	Low FLQ Resistance DETECTED
	FLQ Resistance DETECTED
	FLQ Resistance NOT DETECTED
	FLQ Resistance INDETERMINATE
Amikacin	AMK Resistance DETECTED
	AMK Resistance NOT DETECTED
	AMK Resistance INDETERMINATE
Kanamycin	KAN Resistance DETECTED
	KAN Resistance NOT DETECTED
	KAN Resistance INDETERMINATE

Table 2. Possible Test Results for Each Target in the Xpert MTB/XDR Assay (Continued)

Drug Class	Result Call
Capreomycin	CAP Resistance DETECTED
	CAP Resistance NOT DETECTED
	CAP Resistance INDETERMINATE
Ethionamide[a]	ETH Resistance DETECTED
	ETH Resistance NOT DETECTED

a. Ethionamide will not provide an indeterminant by assay design.

Table 3 summarizes the genes targeted by the Xpert MTB/XDR Assay and codon region and nucleotides covered for each of genes interrogated to identify or infer drug resistance.

Table 3. Drug resistance determining regions targeted interrogated

Drug	Gene Target	Codon Regions	Nucleotide
Isoniazid	*inhA* promoter	NA	-1 to -32 intergenic
	katG	311-319	939-957
	fabG1	199-210	597-630
	oxyR- ahpC intergenic region	NA	-5 to -50 intergenic (or -47 to -92)[12,13]
Ethionamide	*inhA* promoter[a]	NA	-1 to -32 intergenic
Fluoroquinolones	*gyrA*	87-95	261-285
	gyrB	531-544 (or 493-505)[12,14]	1596-1632
Amikacin, Kanamycin, Capreomycin	*rrs*	NA	1396-1417
	eis promoter	NA	-6 to -42 intergenic

a. The absence of mutations in the inhA promoter region does not exclude ETH resistance. Mutations conferring ETH resistance are reported to be present in genomic regions not targeted by the Xpert MTB/XDR assay.[15]

See Table 4 for examples of possible results and corresponding interpretation. Figure 7 through Figure 15 are examples of possible Xpert MTB/XDR Assay results.

Table 4. Examples of Xpert MTB/XDR Assay Results and Interpretation

Result	Interpretation
MTB DETECTED; INH Resistance NOT DETECTED FLQ Resistance NOT DETECTED AMK Resistance NOT DETECTED KAN Resistance NOT DETECTED CAP Resistance NOT DETECTED ETH Resistance NOT DETECTED	The MTB target is present within the sample: • Mutations leading to INH, FLQs, AMK, KAN, CAP, or ETH resistance are not detected. • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.

Table 4. Examples of Xpert MTB/XDR Assay Results and Interpretation (Continued)

Result	Interpretation
MTB DETECTED; INH Resistance DETECTED FLQ Resistance DETECTED AMK Resistance DETECTED KAN Resistance DETECTED CAP Resistance DETECTED ETH Resistance DETECTED	The MTB target is present within the sample: • Mutations contributing to INH resistance have been detected in one or more of the following genes: *katG*, *fabG1*, *oxyR-ahpC* intergenic region and *inhA* promoter • Mutations contributing to FLQ resistance have been detected in one or more of the following genes: *gyrA* and *gyrB* quinolone resistance determining regions (QRDR) • Mutations contributing to AMK resistance have been detected in one or more of the following genes: *rrs* gene and *eis* promoter • Mutations contributing to KAN resistance have been detected in one or more of the following genes: *rrs* gene and *eis* promoter • Mutations contributing to CAP resistance have been detected in the following gene: *rrs* gene • Mutations contributing to ETH resistance have been detected in the following gene: *inhA* promoter • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.
MTB DETECTED; INH Resistance DETECTED FLQ Resistance NOT DETECTED AMK Resistance NOT DETECTED KAN Resistance NOT DETECTED CAP Resistance NOT DETECTED ETH Resistance NOT DETECTED	The MTB target is present within the sample: • Mutations leading to FLQs, AMK, KAN, CAP, and ETH resistance are not detected. • Mutations contributing to INH resistance have been detected in one or more of the following genes: *inhA* promotor, *katG*, *fabG1* and *oxyR-ahpC* intergenic region • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.
MTB DETECTED; INH Resistance DETECTED FLQ Resistance INDETERMINATE AMK Resistance NOT DETECTED KAN Resistance NOT DETECTED CAP Resistance NOT DETECTED ETH Resistance NOT DETECTED	The MTB target is present within the sample: • Mutations leading to AMK, KAN, CAP, and ETH resistance are not detected. • Mutations contributing to INH resistance have been detected in one or more of the following genes: *inhA* promotor, *katG*, *fabG1* and *oxyR-ahpC* intergenic region • Mutations contributing to FLQ resistance could not be determined due to the detection of only WT Tm from one or more probes and missing Tms from one or more probes targeting one or more of the following genes: *gyrA* or *gyrB*. "OR" no Tm from any of the probes targeting *gyrA* and *gyrB* genes. • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.
MTB DETECTED; Low INH Resistance DETECTED FLQ Resistance NOT DETECTED AMK Resistance NOT DETECTED KAN Resistance NOT DETECTED CAP Resistance NOT DETECTED ETH Resistance DETECTED	The MTB target is present within the sample: • Mutations leading to FLQ, AMK, KAN, and CAP resistance are not detected. • Mutations contributing to low INH resistance have been detected in *inhA* promoter region • Mutations contributing to ETH resistance have been detected in the *inhA* promoter region • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.

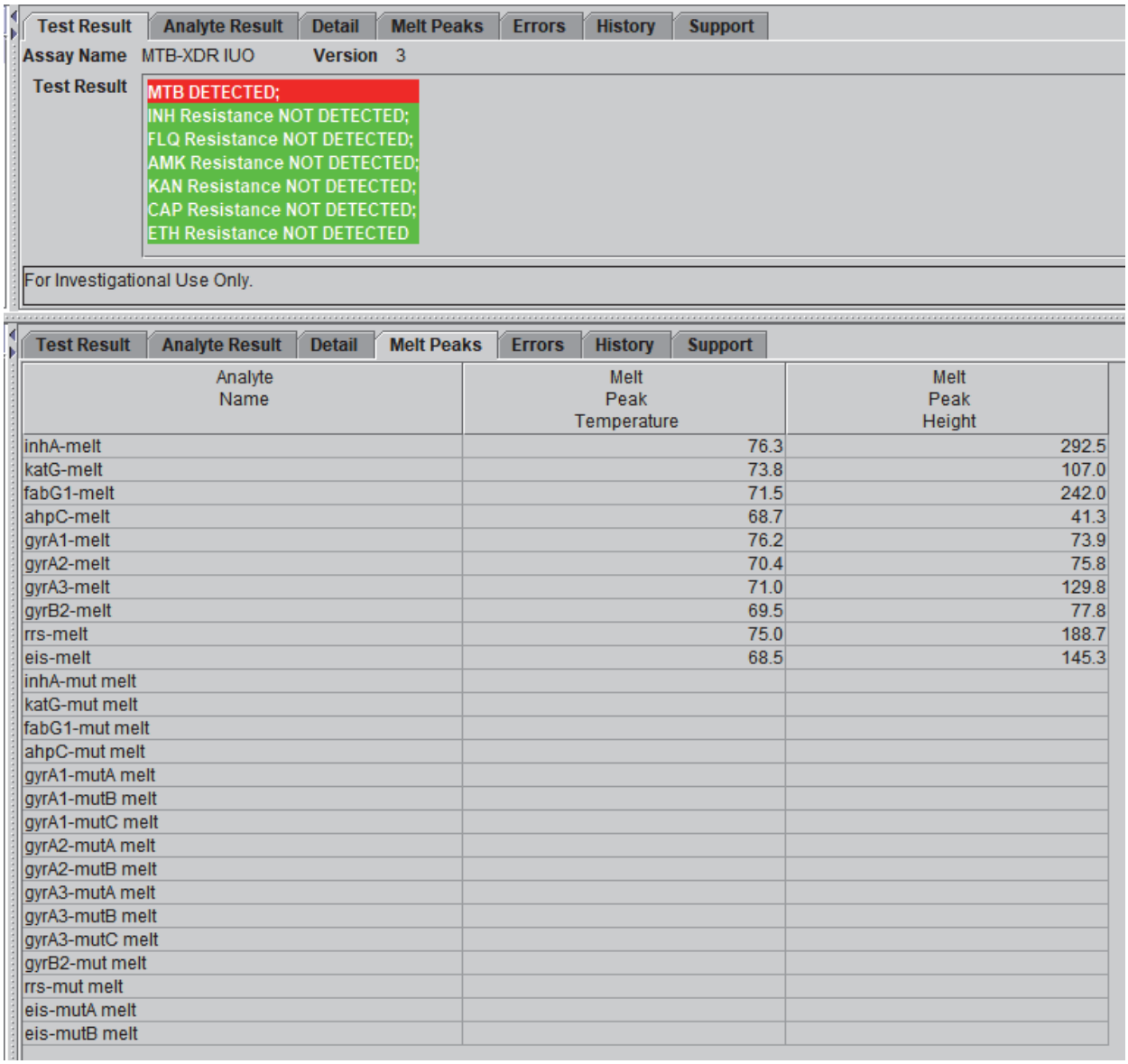
Table 4. Examples of Xpert MTB/XDR Assay Results and Interpretation (Continued)

Result	Interpretation
MTB DETECTED; INH Resistance NOT DETECTED Low FLQ Resistance DETECTED AMK Resistance NOT DETECTED KAN Resistance NOT DETECTED CAP Resistance NOT DETECTED ETH Resistance NOT DETECTED	The MTB target is present within the sample; low level FLQ, resistance is detected: • Mutations leading to INH, AMK, KAN, CAP and ETH resistance are not detected. • Mutations contributing to low FLQ resistance have been detected in the following genes: *gyrA* • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.
MTB DETECTED; INH Resistance DETECTED FLQ Resistance NOT DETECTED AMK Resistance DETECTED KAN Resistance DETECTED CAP Resistance DETECTED ETH Resistance NOT DETECTED	The MTB target is present within the sample: • Mutations leading to FLQ and ETH resistance are not detected. • Mutations contributing to INH resistance have been detected in one or more of the following genes: *katG*, *fabG1*, *oxyR-aphC* • Mutations contributing to AMK resistance have been detected in one or more of the following genes: *rrs* gene; *eis* promoter • Mutations contributing to KAN resistance have been detected in one or more of the following genes: *rrs* gene; *eis* promoter • Mutations contributing to CAP resistance have been detected in the following gene: *rrs* gene • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.
MTB DETECTED; INH Resistance DETECTED Low FLQ Resistance DETECTED AMK Resistance NOT DETECTED KAN Resistance DETECTED CAP Resistance NOT DETECTED ETH Resistance NOT DETECTED	The MTB target is present within the sample: • Mutations leading to AMK, CAP, and ETH resistance are not detected. • Mutations contributing to INH resistance have been detected in one or more of the following genes: *katG*, *fabG1*, *oxyR-ahpC* intergenic region and *inhA* promoter • Mutations contributing to Low FLQ resistance have been detected in the following gene: *gyrA* • Mutations contributing to KAN resistance have been detected in the *eis* promoter region • SPC: NA (not applicable). An SPC signal is not required because MTB amplification can compete with this control. • Probe Check: PASS. All probe check results pass.
MTB NOT DETECTED	The MTB target is not detected within the sample: • SPC: PASS. The SPC met the acceptance criteria. • 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 Retest Procedure section of this document. • MTB: INVALID. The presence or absence of MTB DNA cannot be determined. • SPC: FAIL. The MTB target result is negative, and the SPC Cycle Threshold (Ct) is not within valid range. • Probe Check: PASS. All probe check results pass.

Table 4. Examples of Xpert MTB/XDR Assay Results and Interpretation (Continued)

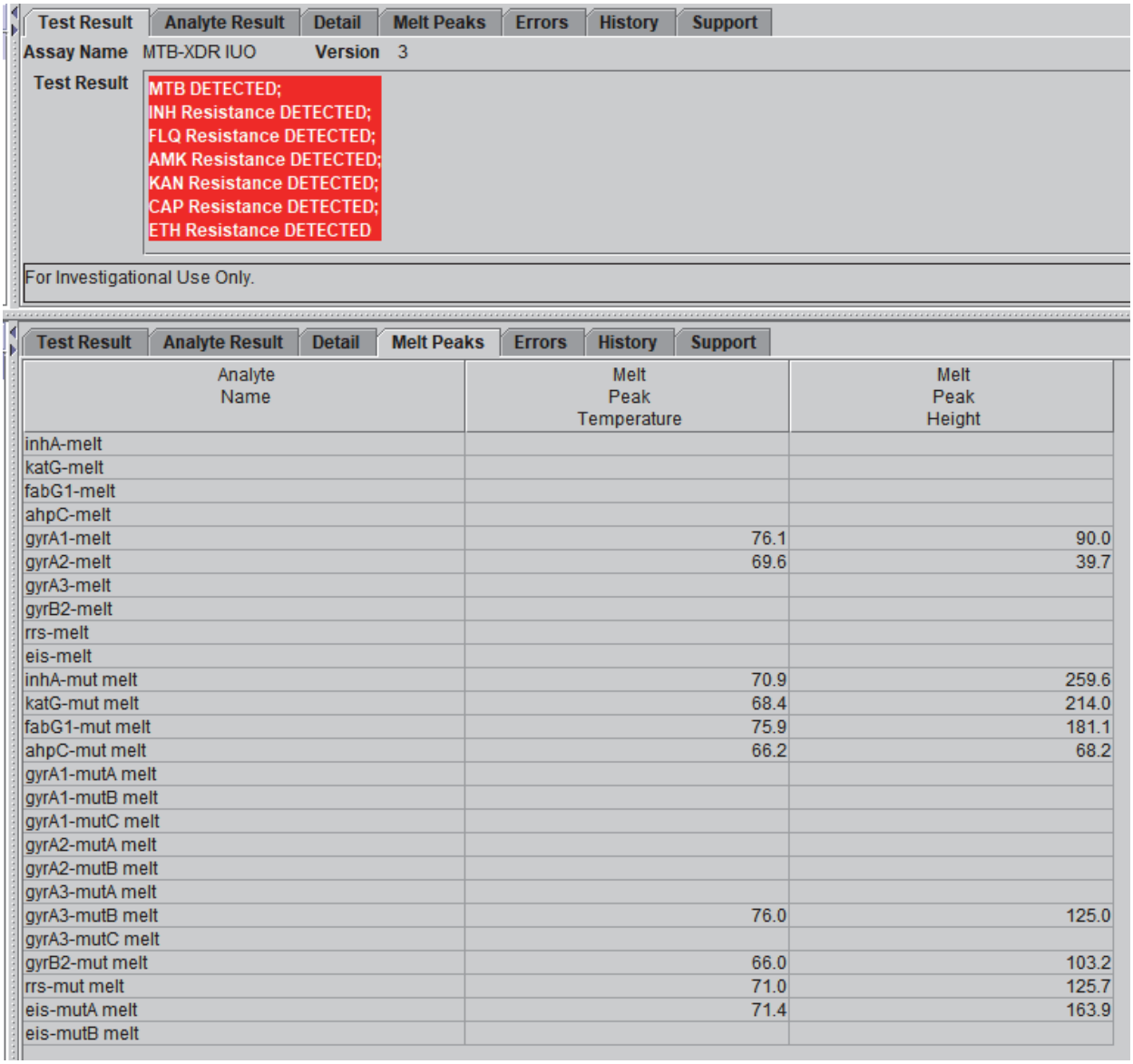
Result	Interpretation
ERROR	The presence or absence of MTB cannot be determined. Repeat the test. See the Retest Procedure section of this document. • MTB: NO RESULT • SPC: NO RESULT • Probe Check: FAIL. All or one of the probe check results failed. **Note**: If the probe check passed, the error may be caused by a system component failure, operator error or cartridge integrity issue.
NO RESULT	The presence or absence of MTB cannot be determined. Repeat the test. See the Retest Procedure section of this document. A NO RESULT indicates that insufficient data was collected. For example, the operator stopped a test that was in progress. • MTB: NO RESULT • SPC: NO RESULT • Probe Check: NA (not applicable)

Note The following figures provide representative results including melt peak tab that can be expected with the Xpert MTB/XDR Assay in the GeneXpert Dx Detailed User View. Not all possible combinations of results are shown.



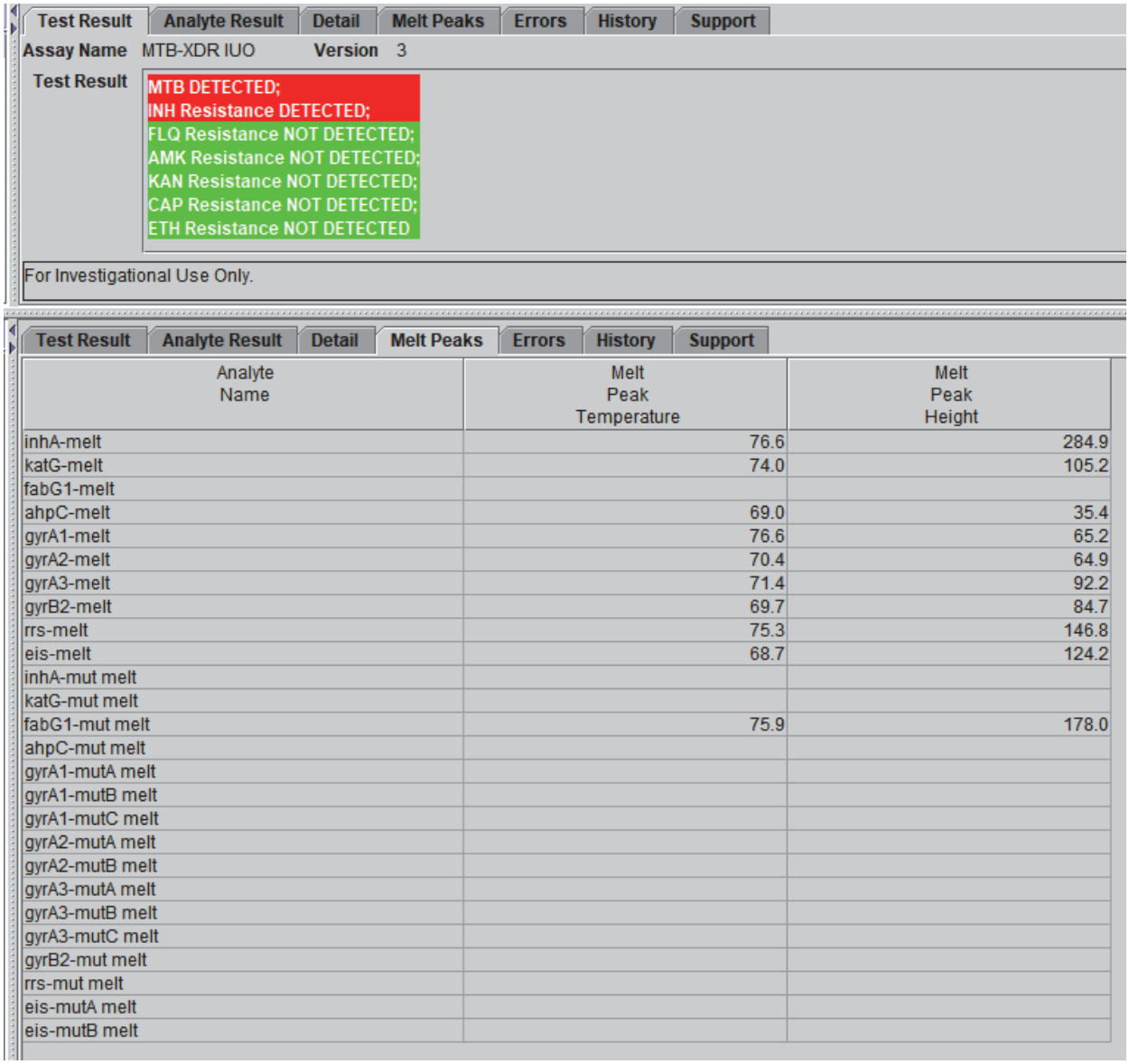
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.3	292.5
katG-melt	73.8	107.0
fabG1-melt	71.5	242.0
ahpC-melt	68.7	41.3
gyrA1-melt	76.2	73.9
gyrA2-melt	70.4	75.8
gyrA3-melt	71.0	129.8
gyrB2-melt	69.5	77.8
rrs-melt	75.0	188.7
eis-melt	68.5	145.3
inhA-mut melt		
katG-mut melt		
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt		

Figure 7. MTB DETECTED; INH, FLQ, AMK, KAN, CAP, and ETH Resistance NOT DETECTED



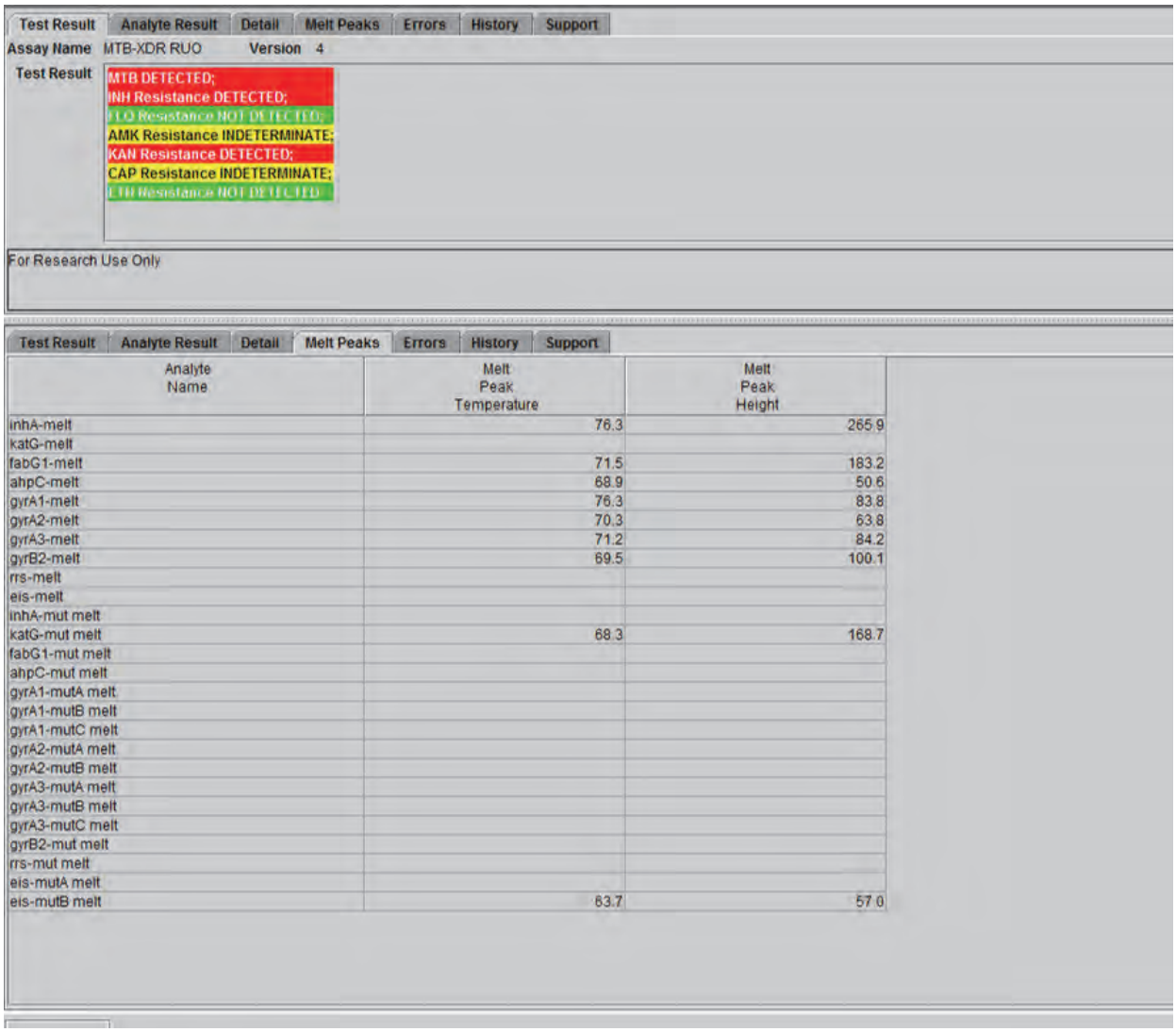
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt		
katG-melt		
fabG1-melt		
ahpC-melt		
gyrA1-melt	76.1	90.0
gyrA2-melt	69.6	39.7
gyrA3-melt		
gyrB2-melt		
rrs-melt		
eis-melt		
inhA-mut melt	70.9	259.6
katG-mut melt	68.4	214.0
fabG1-mut melt	75.9	181.1
ahpC-mut melt	66.2	68.2
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt	76.0	125.0
gyrA3-mutC melt		
gyrB2-mut melt	66.0	103.2
rrs-mut melt	71.0	125.7
eis-mutA melt	71.4	163.9
eis-mutB melt		

Figure 8. MTB DETECTED; INH, FLQ, AMK, KAN, CAP, and ETH Resistance DETECTED



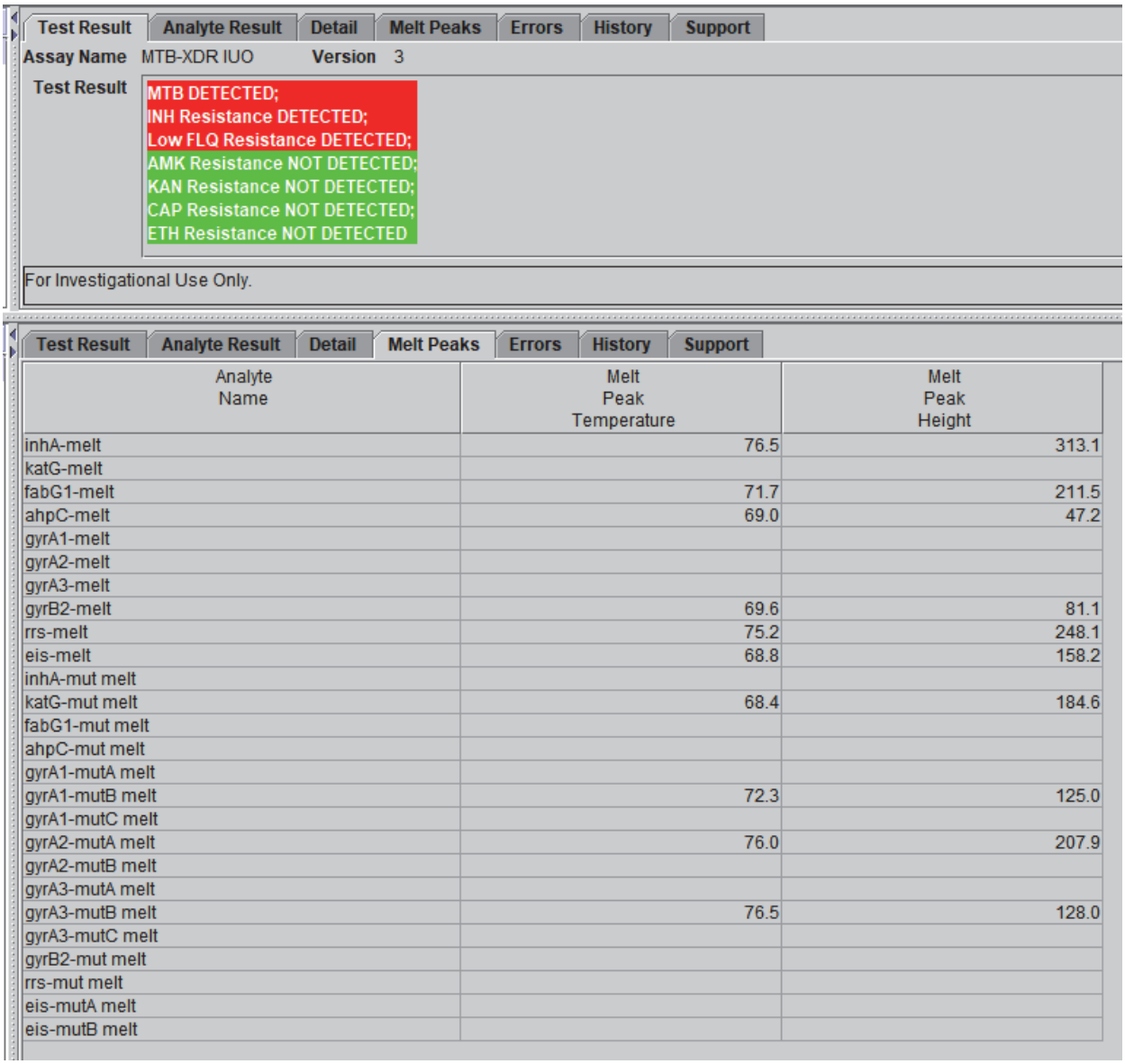
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.6	284.9
katG-melt	74.0	105.2
fabG1-melt		
ahpC-melt	69.0	35.4
gyrA1-melt	76.6	65.2
gyrA2-melt	70.4	64.9
gyrA3-melt	71.4	92.2
gyrB2-melt	69.7	84.7
rrs-melt	75.3	146.8
eis-melt	68.7	124.2
inhA-mut melt		
katG-mut melt		
fabG1-mut melt	75.9	178.0
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt		

Figure 9. MTB DETECTED; INH Resistance DETECTED



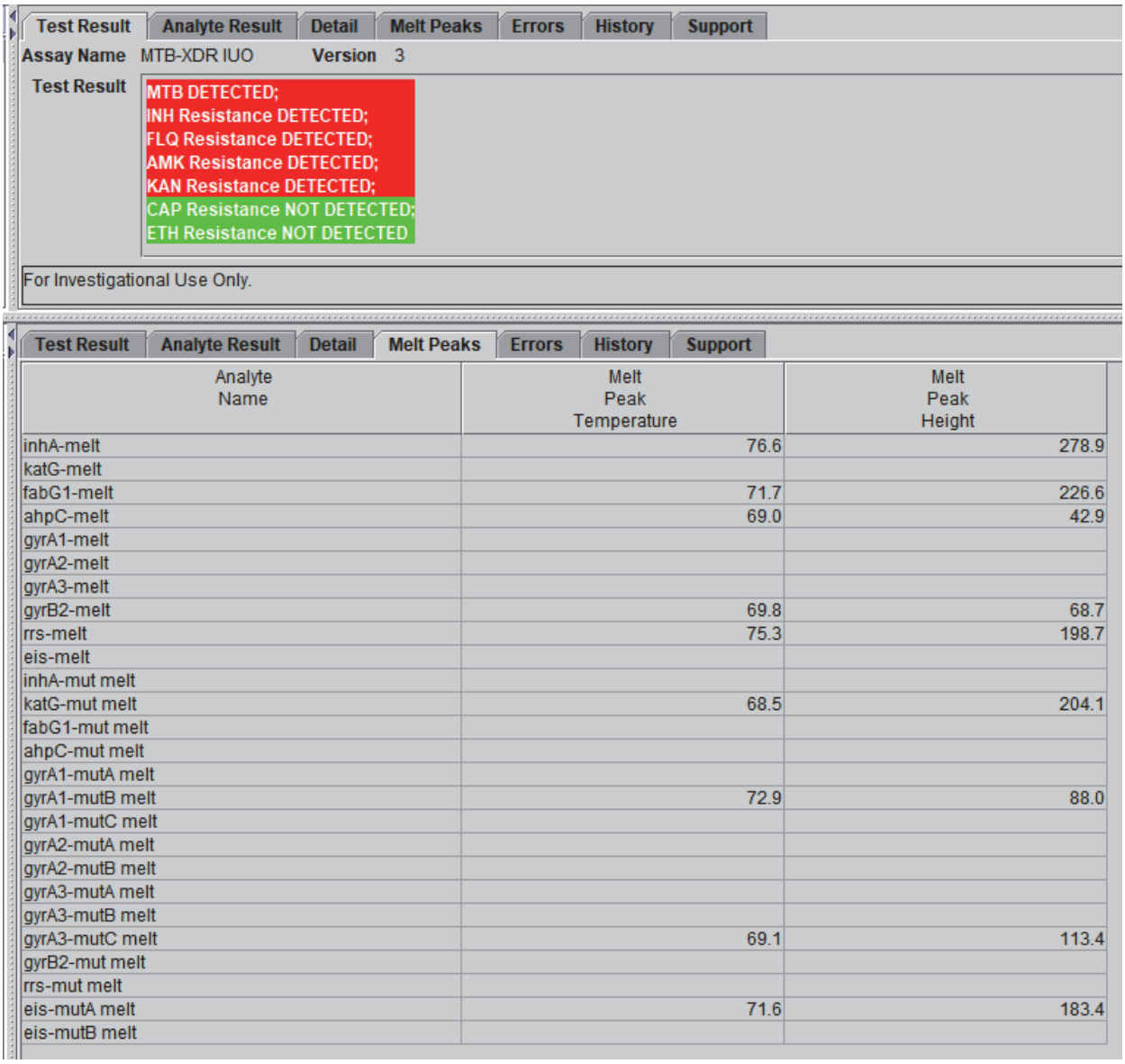
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.3	265.9
katG-melt		
fabG1-melt	71.5	183.2
ahpC-melt	68.9	50.6
gyrA1-melt	76.3	83.8
gyrA2-melt	70.3	63.8
gyrA3-melt	71.2	84.2
gyrB2-melt	69.5	100.1
rrs-melt		
eis-melt		
inhA-mut melt		
katG-mut melt	68.3	168.7
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt	63.7	57.0

Figure 10. MTB DETECTED; INH and KAN Resistance DETECTED; AMK and CAP INDETERMINATE



Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.5	313.1
katG-melt		
fabG1-melt	71.7	211.5
ahpC-melt	69.0	47.2
gyrA1-melt		
gyrA2-melt		
gyrA3-melt		
gyrB2-melt	69.6	81.1
rrs-melt	75.2	248.1
eis-melt	68.8	158.2
inhA-mut melt		
katG-mut melt	68.4	184.6
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt	72.3	125.0
gyrA1-mutC melt		
gyrA2-mutA melt	76.0	207.9
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt	76.5	128.0
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt		

Figure 11. MTB DETECTED; INH and Low FLQ Resistance DETECTED



Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.6	278.9
katG-melt		
fabG1-melt	71.7	226.6
ahpC-melt	69.0	42.9
gyrA1-melt		
gyrA2-melt		
gyrA3-melt		
gyrB2-melt	69.8	68.7
rrs-melt	75.3	198.7
eis-melt		
inhA-mut melt		
katG-mut melt	68.5	204.1
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt	72.9	88.0
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt	69.1	113.4
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt	71.6	183.4
eis-mutB melt		

Figure 12. MTB DETECTED; INH, FLQ, AMK, and KAN Resistance DETECTED

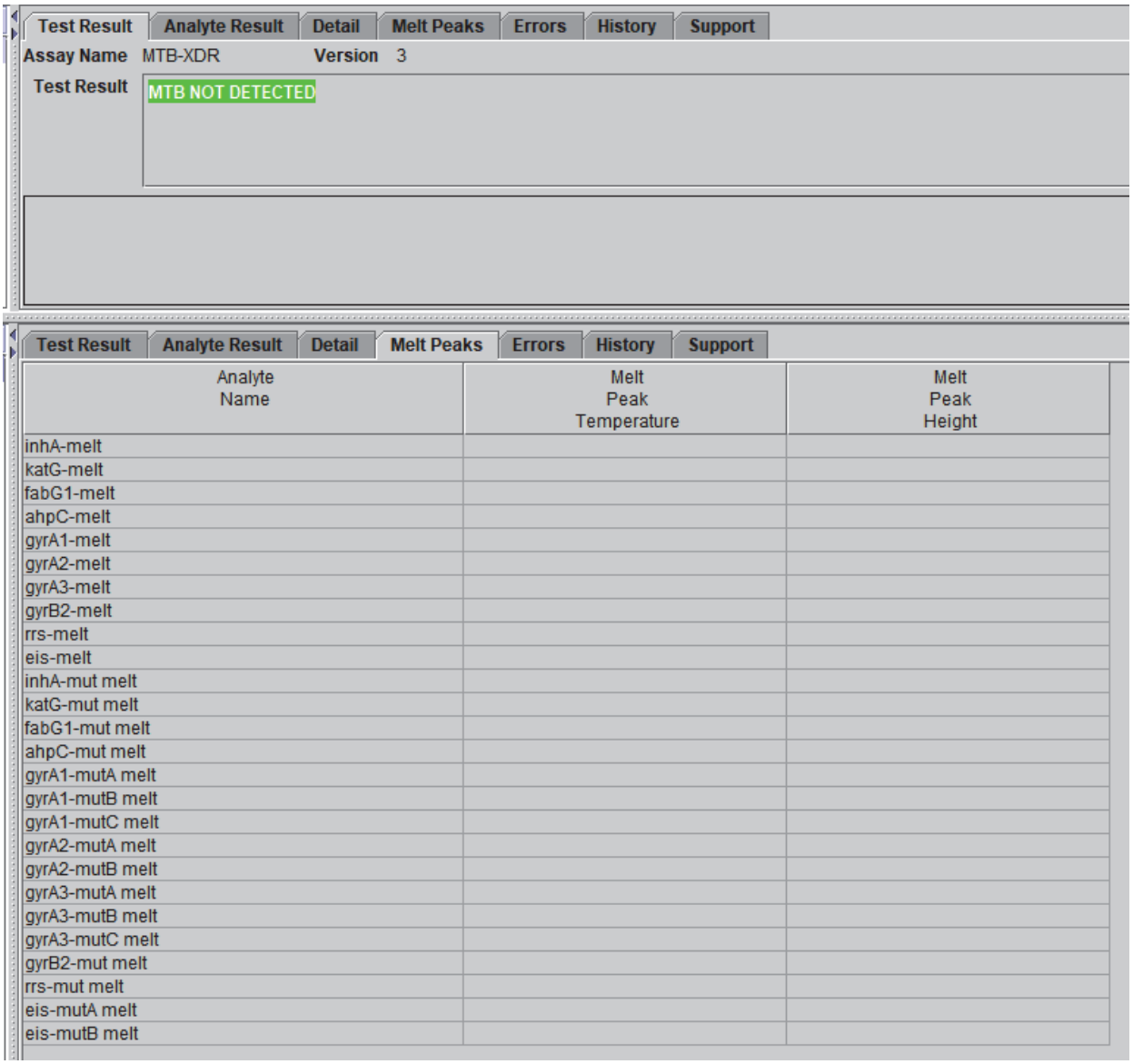
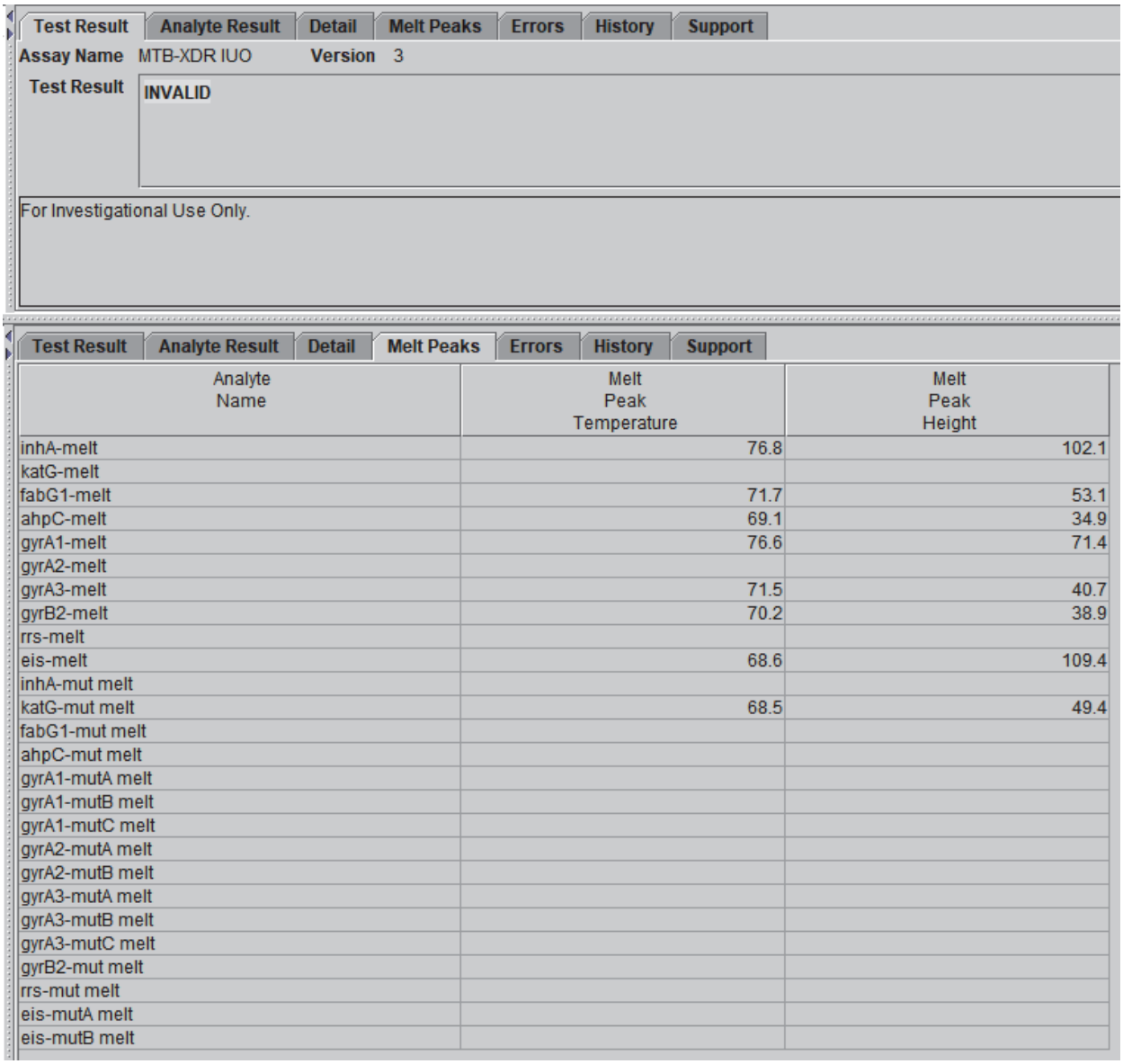


Figure 13. MTB NOT DETECTED



Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.8	102.1
katG-melt		
fabG1-melt	71.7	53.1
ahpC-melt	69.1	34.9
gyrA1-melt	76.6	71.4
gyrA2-melt		
gyrA3-melt	71.5	40.7
gyrB2-melt	70.2	38.9
rrs-melt		
eis-melt	68.6	109.4
inhA-mut melt		
katG-mut melt	68.5	49.4
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt		

Figure 14. INVALID

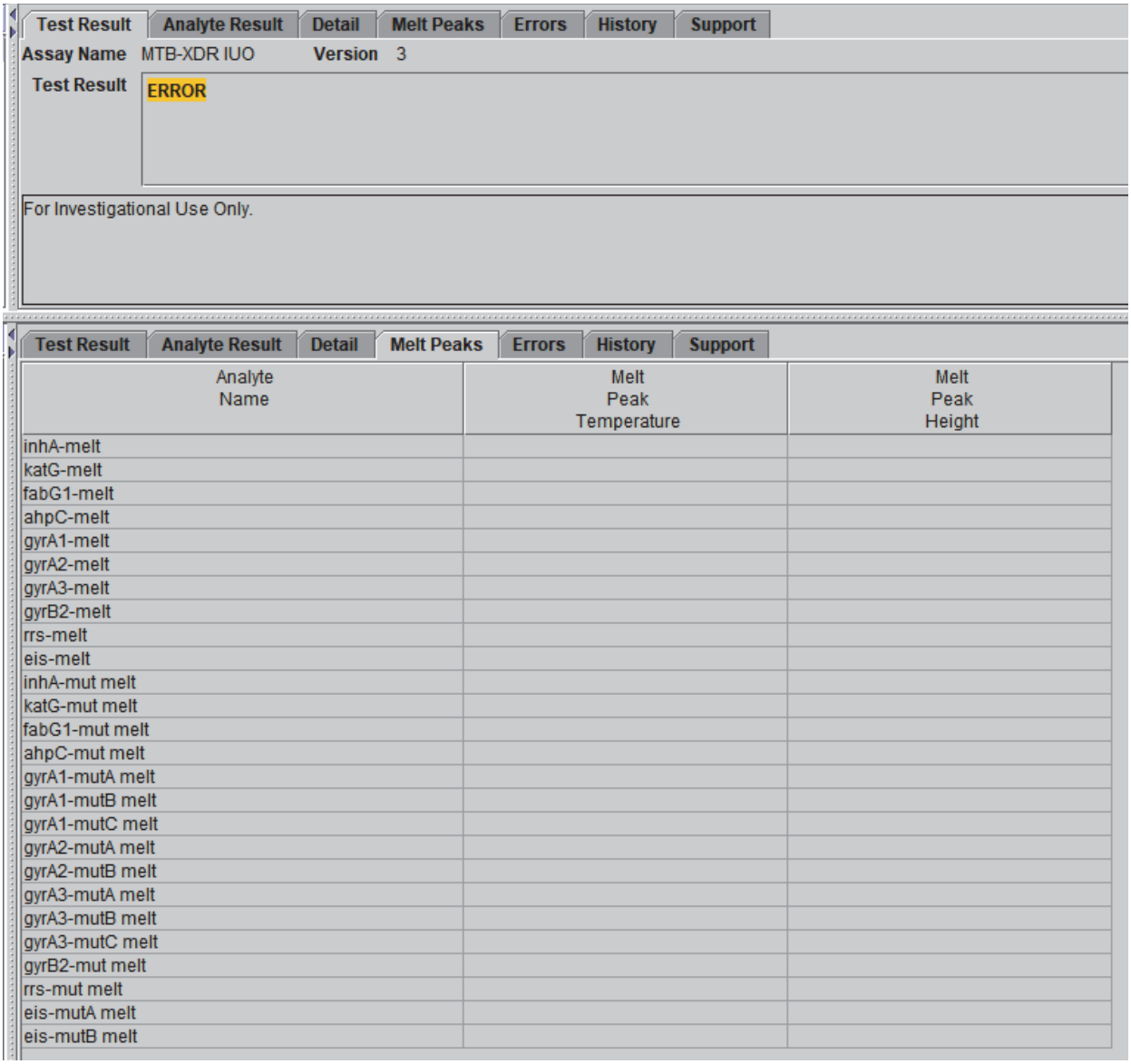


Figure 15. ERROR

16 Retests

16.1 Reasons to Repeat the Test

If any test results mentioned below occur, repeat the test according to the instructions in Section 16.2, Retest Procedure.

- An INVALID result indicates that the SPC failed. The sample was not properly processed, or PCR is inhibited or the sample was not properly collected.
- An ERROR result could be due to, but not limited to, Probe Check Control failed 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.
- An INDETERMINATE result indicates that resistance to a given drug could not definitively be concluded based on the assay algorithm (see Limitations for further explanations). Retesting with a different sample may or may not lead to a different result.

16.2 Retest Procedure

For retest, use a new cartridge (do not re-use a cartridge). If you have leftover sputum (should be ≥1.0 ml) or reconstituted sediment (should be ≥0.5 ml), always use new SR to decontaminate and liquefy the sputum before running the assay. Follow sample processing instructions according to Section 12.1, Procedure for Unprocessed Sputum or Section 12.2, Procedure for Decontaminated Concentrated Sputum Sediments.

If sufficient leftover SR-treated sample is available that has been stored for no longer than 2.5 hours up to 35 °C or has been stored no longer than 4 hours at 2–8 °C of the initial addition of SR to the sample, the leftover SR treated sample can be processed using a new cartridge. When retesting, always use a new cartridge and start the test within 30 minutes of adding processed sample to cartridge. See Section 12.3, Preparing the Cartridge.

17 Limitations

- The performance of the Xpert MTB/XDR Assay was validated using the procedures provided in this package insert. Modifications to XDR test procedure should be interpreted in conjunction with other laboratory and clinical data available to the clinician.
- The performance of the Xpert MTB/XDR Assay 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 and assay training.
- 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.
- Test results might be affected by antecedent or concurrent antibiotic therapy. Therefore, therapeutic success or failure cannot be assessed using this test because DNA might persist following tuberculosis therapy.
- A positive test result does not necessarily indicate the presence of viable organisms. It is however, presumptive for the presence of MTB complex DNA including mutations associated with INH, FLQ, AMK, KAN, CAP and ETH resistance.
- Mutations or polymorphisms in primer or probe binding regions may affect detection of new or unknown XDR-MTB strains resulting in a drug-sensitive result.
- The Xpert MTB/XDR Assay does not provide confirmation of susceptibility to INH, FLQ, AMK, KAN, CAP and ETH since mechanisms of resistance other than those detected by the assay may exist that may be associated with a lack of clinical response to treatment.
- Testing of blood, cerebral spinal fluid (CSF), gastric aspirate, stool, tissue, urine has not been evaluated for use in Xpert MTB/XDR Assay.
- Although induced sputum specimens were not included in the clinical performance evaluation of the Xpert MTB/XDR Assay, isotonic or hypertonic solutions, bronchodilators, and inhaled bronchodilators commonly used in the collection of induced sputum were tested and do not interfere with the assay. Saline induction may result in insufficient number the organisms recovered and could affect detection of *M. tuberculosis.*
- Concentrated sputum sediments used in the performance evaluation of the Xpert MTB/XDR 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.
- A negative test does not exclude the possibility of isolating MTB complex DNA from the sputum sample. The Xpert MTB/XDR Assay may be used in conjunction with mycobacterial culture to address the risk of false negative results and to recover the organism for further characterization and susceptibility testing.
- Specimens with “MTB Trace DETECTED” results when tested with the Xpert MTB/RIF Ultra Assay are expected to be below the Limit of Detection of the MTB/XDR Assay and are not recommended for testing with the Xpert MTB/XDR Assay.
- The Xpert MTB/XDR Assay by design does not differentiate between the species of the MTB-complex (i.e., *MTB, M. bovis, M. africanum, M. canettii, M. microti, M. caprae, M. pinnipedi, M. mungi, and M. orygis*). In addition, culture must also be performed to determine if an NTM strain is present in addition to MTB-complex.
- 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[16,17].

- 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.
- Mixed infections with MTB and *M. marinum* may result in "INDETERMINATE" results for FLQ at $>10^4$ CFU/mL of *M. marinum* in presence of ≤408 CFU/mL of MTB.
- In rare instances, the *rrs* primers and probes may cross-react with environmental microbes or sputum microflora which may result in "INDETERMINATE" results for AMK, KAN and CAP.
- The Xpert MTB/XDR Assay determines ETH resistance associated only with mutations in the *inhA* promoter region. The absence of mutations in the inhA promoter region does not exclude ETH resistance. Mutations conferring ETH resistance are reported to be present in genomic regions not targeted by the Xpert MTB/XDR assay.[15]
- The association of mutations in the *oxyR-ahpC* and *gyrB* genes with INH and FLQ resistance respectively, has not yet been conclusively established; however published studies have reported these mutations are found in INH and FLQ resistance strains.[18,19].
- Presence of deletions or rare mutations in any of the target genes could lead to "INDETERMINATE" results for a particular drug.
- In case of samples with a mixed population of both susceptible and resistant strains, there is a likelihood that the Xpert MTB/XDR Assay may not detect the mutation, if the resistant population is present at undetectable levels for the assay.
- In samples with very low bacterial load or a mixture of both susceptible and resistant strains, the Xpert MTB/XDR Assay may not reliably distinguish between low and high FLQ resistance.

18 Clinical Performance

A blinded clinical study was conducted to evaluate the performance of the Xpert MTB/XDR test relative to microbiological and molecular reference methods. i.e. phenotypic drug susceptibility (pDST) testing and sequencing for the detection of drug resistance to INH, ETH, FLQs and SLID (AMK, KAN and CAP). In addition, the clinical performance of the Xpert MTB/XDR test was compared to the Xpert MTB/RIF or the Xpert MTB/RIF Ultra test for the detection of MTB. Two sites with known high prevalence for MDR and XDR TB provided frozen archived unprocessed sputum or concentrated sputum sediment specimens known to be positive or negative by MTB culture

Table 5 shows the sensitivity and specificity of the Xpert MTB/XDR test relative to pDST for drug resistance. The sensitivity was >90% for INH, FLQ and AMK, >85% for KAN and CAP, and >64% for ETH; the specificity was >98% for all drugs.

Table 5. Xpert MTB/XDR Test vs. pDST for Drug Resistance

Drugs	N	TP	FN	TN	FP	Sensitivity (%)	95%CI	Specificity (%)	95% CI
INH	478	244	23	209	2	91.4	87.4 – 94.2	99.1	96.6 – 99.7
FLQ	417	148	11	254	4	93.1	88.0 - 96.1	98.5	96.1 – 99.4
AMK	405	79	7	317	2	91.9	84.1 – 96.0	99.4	97.7 – 99.8
KAN	343	58	8	276	1	87.9	77.9 – 93.7	99.6	98.0 – 99.9
CAP	167	21	4	142	0	84.0	65.3 – 93.6	100.0	97.4 – 100.0
ETH	230	75	41	112	2	64.7	55.6 – 72.8	98.3	93.8 – 99.5

Table 6 shows the sensitivity and specificity of the Xpert MTB/XDR test relative to sequencing for drug resistance. The sensitivity was >93% for FLQ and greater than 96% for INH, AMK, KAN, CAP and ETH; the specificity was 100.0% for all drugs listed in the table except INH which was 98.7%.

Table 6. Xpert MTB/XDR Test vs. Sequencing for Drug Resistance

Drug	N	TP	FN	TN	FP	Sensitivity (%)	95%CI	Specificity (%)	95%CI
INH	471	241	3	224	3	98.8	96.5 - 99.6	98.7	96.2 - 99.5
FLQ	469	152	11	306	0	93.3	88.3 - 96.2	100.0	98.8 – 100.0
AMK	463	81	3	379	0	96.4	90.0 - 98.8	100.0	99.0 – 100.0
KAN	463	88	3	372	0	96.7	90.8 - 98.9	100.0	99.0 – 100.0
CAP	463	78	3	382	0	96.3	89.7 - 98.7	100.0	99.0 – 100.0
ETH	473	104	3	366	0	97.2	92.1 – 99.0	100.0	99.0 – 100.0

Table 7 shows the positive percent agreement (PPA) and the negative percent agreement (NPA) of the Xpert MTB/XDR test relative to the Xpert MTB/RIF test for MTB detection to be 98.9% and 93.8%, respectively.

Table 7. Xpert MTB/XDR Test vs. Xpert MTB/RIF Test for MTB Detection

		Xpert MTB/RIF Test		
		MTB Detected	**MTB Not Detected**	**Total**
Xpert MTB/XDR Test	MTB Detected	273	2a	275
	MTB Not Detected	3b	30	33
	Total	276	32	308
PPA			98.9% (95%CI: 96.9-99.6)	
NPA			93.8% (95%CI: 79.9-98.3)	

Table 8 shows the PPA and NPA of the Xpert MTB/XDR test relative to the Xpert MTB/RIF Ultra test for MTB detection to be 99.5% and 100.0%, respectively.

Table 8. Xpert MTB/XDR Test vs. Xpert MTB/RIF Ultra Test for MTB Detection

		Xpert MTB/RIF Ultra Test		
		MTB Detected	**MTB Not Detected**	**Total**
Xpert MTB/XDR Test	MTB Detected	207	0	207
	MTB Not Detected	1[a]	14	15
	Total	208	14	222
PPA			99.5% (95%CI: 97.3-99.9)	
NPA			100.0% (95%CI: 78.5-100.0)	

a. The Xpert MTB/RIF Ultra result was MTB Detected Trace.

Of the 531 Xpert MTB/XDR runs performed in conjunction with this study, 15 gave non-determinate (“Error”, “Invalid”, or “No Result”) results on the first attempt. Upon retest of these 14 specimens one result remained non-determinate. The initial non-determinate rate was 2.8% (15/531) and the overall non-determinate rate was 0.2% (1/531).

19 Analytical Performance

19.1 Analytical Sensitivity (Limit of Detection)

Studies were performed to determine the analytical limit of detection (LoD) of the Xpert MTB/XDR Assay with two lots of reagents across three testing days. An MTB positive result is based on the detection of the single copy *inhA* target. The higher LoD observed per strain and per lot as determined by probit analysis was selected for verification. Verification of the estimated LoD claim was performed on one reagent lot across a minimum of three testing days. The LoD was established *using a representative MTBC member, Mycobacterium bovis BCG (Bacille Calmette-Guerin)* spiked into a MTB negative, unprocessed sputum and into a MTB negative, decontaminated/concentrated sputum sediment.

The LoD is the lowest concentration reported in CFU/mL that can be reproducibly distinguished from negative samples with ≥ 95% confidence. Replicates of 20 were evaluated at five to eight concentrations with two different reagent lots over the 3 days and the LoD was determined using Probit analysis.

The higher LoD observed for each specimen type and lot as determined by probit analysis was selected for verification. Verification of the estimated LoD claim was performed on one reagent lot across a minimum of three testing days with a claim based on a minimum of 19 of 20 positive replicates. The LoD point estimates in CFU/mL are provided in Table 9.

Table 9. Analytical Sensitivity (Limit of Detection)

Specimen Type	LoD Point Estimate, CFU/mL
Unprocessed Sputum	136
Sediment	86

19.2 Analytical Specificity (Exclusivity)

The analytical specificity of the Xpert MTB/XDR Assay was evaluated by testing a panel of panel of 57 organisms consisting of 21 bacteria, 1 fungus, 7 viruses and 28 Non- tuberculous mycobacteria (NTM) representing common respiratory pathogens or those potentially encountered in the respiratory tract and/or oropharyngeal flora. Three replicates of each bacterial and yeast strain were tested at concentrations of $\geq 1 \times 10^6$ CFU/mL. All viruses were tested at $\geq 1 \times 10^5$ (Tissue Culture Infectious Dose) $TCID_{50}$/ml. DNA or RNA were tested for 2 bacterial and 1 fungal strain at concentrations of $\geq 10^6$ copies/ml, as whole organisms were not available or could not be accessed due to biosafety restrictions. Three replicates of each virus were tested at concentrations of $\geq 1 \times 10^5$ $TCID_{50}$/mL. The analytical specificity was 100%. The organisms tested are listed in Table 10, Table 11, and Table 12. None of the organisms tested resulted in cross-reactivity with the MTB detection probe generating "MTB NOT DETECTED" result for all the organisms and for all the replicates tested. The table below lists the organisms tested for the analytical specificity assay. *Aspergillus fumigatus* was analytically tested and showed no interference or cross reactivity. Cross reactivity with any other fungal species is not evident by *in silico* analysis.

Table 10. Analytical Specificity of the Xpert MTB/XDR Assay (Bacteria/Fungi)

Organism
Acinetobacter baumannii
Chlamydophila pneumoniae[a]
Citrobacter freundii
Corynebacterium xerosis
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria meningitidis[a]
Neisseria mucosa
Nocardia asteroids
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus epidermidis
Stenotrophomonas maltophilia
Streptococcus agalactiae
Streptococcus mitis
Streptococcus mutans
Streptococcus pneumoniae
Streptococcus pyogenes
Aspergillus fumigatus[a]

a. Genomic DNA

Table 11. Analytical Specificity of the Xpert MTB/XDR Assay (Viruses)

Organism
Coronavirus 229E
Human metapneumovirus (hMPV) 16 Type A1
Parainfluenza Virus Type 1
Parainfluenza Virus Type 2
Parainfluenza Virus Type 3
Respiratory Syncytial Virus
Rhinovirus 1A

Table 12. Analytical Specificity of the Xpert MTB/XDR Assay (NTM)

Organism
Mycobacterium asiaticum
Mycobacterium avium NJH
Mycobacterium celatum
Mycobacterium chelonae
Mycobacterium flavescens
Mycobacterium fortuitum subsp. Fortuitum
Mycobacterium gastri
Mycobacterium gordonae
Mycobacterium gordonae
Mycobacterium gordonae
Mycobacterium genavense
Mycobacterium haemophilum
Mycobacterium malmoense
Mycobacterium marinum
Mycobacterium phlei
Mycobacterium scrofulaceum
Mycobacterium simiae
Mycobacterium szulgai
Mycobacterium terrae
Mycobacterium thermoresistibile
Mycobacterium triviale
Mycobacterium vaccae
Mycobacterium xenopi
Mycobacterium avium
Mycobacterium intracellulare
Mycobacterium abscessus
Mycobacterium marinum
Mycobacterium kansasii

19.3 Analytical Reactivity (Inclusivity)

The analytical reactivity (inclusivity) of the Xpert MTB/XDR Assay was evaluated using a phylogenetically diverse panel consisting of susceptible and drug resistant MTB strains to evaluate the accuracy of the drug susceptibility results of the assay. The panel of twenty-two (22) MTB-complex (MTBC)-strains included eight (8) drug susceptible strains with wild-type target genes (Table 13) and fourteen (14) well characterized drug resistant strains (Table 14). All strains were tested in triplicate at concentrations at or near 3 X LoD of the *inhA* promotor target. The copy number tested for genomic DNA lysates was based on a fluorescent dye binding assay specific for double-stranded DNA (dsDNA).

The drug susceptible strains were tested and include five strains of MTB (AR2, GD139, AH1, HR36, H37Rv) and three MTB-complex mycobacterial species (*M. bovis, M. canetti* and *M. microti)*. The MTB strains were selected to broadly represent the range of genetic diversity and include one representative from each of the major phylogenetic lineages based on SNP-cluster groups (SCGs)[20].

The 14 drug resistant MTB strains were tested using genomic DNA lysates from well characterized specimens which contain 16 clinically significant canonical mutations with at least one of each of the eight regions targeted by the assay. These mutations are commonly present in multi-drug resistant or extensively drug resistant strains of MTB worldwide with the exception of a mutation in the *gyrB* gene.

Table 13 summarizes the results with drug susceptible strains showing number of correct results for each of the individual analytes in the assay. All panel members generated “MTB DETECTED; RESISTANCE NOT DETECTED” The Xpert MTB/XDR Assay correctly identified all replicates of the strains tested near the limit of detection with wild type results for all probes except *oxyR-ahpC*. Since the *oxyR-ahpC* target has a higher LoD than the other targets in the assay, some replicates tested did not yield Tm results.

The results in Table 14 shows the assay also correctly identified expected resistance mutations in all 14 strains resistant to Isoniazid with mutations in *inhA* promoter, *katG* and *oxyR-ahpC* intergenic region; SLIDs resistance with mutations *rrs* and *eis* promoter region; and FLQ resistance with mutations in *gyrA*.

Table 13. Analytical Reactivity (Inclusivity) for Drug Susceptible Strains

Sample	Strain Lineage	inhA	katG	fabG1	ahpC[a]	gyrA1	gyrA2	gyrA3	gyrB2	rrs	eis
(*M.bovis BCG)*	1	PASS	PASS	PASS	FAIL	PASS	PASS	PASS	PASS	PASS	PASS
M.bovis	1	PASS	PASS	PASS	FAIL	PASS	PASS	PASS	PASS	PASS	PASS
MTB (AR2)	2	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB (GD139)	3	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB (AH1)	4	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB (HR36)	5	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
*MTB (*HR37Rv)	4	PASS	PASS	PASS	FAIL	PASS	PASS	PASS	PASS	PASS	PASS
M.canetti	Not assigned	PASS	PASS	PASS	FAIL	PASS	PASS	PASS	PASS	PASS	PASS
M.microti	Not assigned	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS

a. The LoD for oxyR-*ahpC* is higher than that of *inhA* used for determination of MTB positivity. “PASS” indicates all the replicates tested generated the expected wild type Tm; “FAIL” indicates at least one or more replicates generated no Tm values.

Table 14. Analytical Reactivity (Inclusivity) for Drug Resistant Strains (# positive results / total tested)

Strain ID	Gene	Expected Mutation	MTB Detected	Mutant Probe Tm Detected (# positive/tested)	Correct RESISTANCE DETECTED Calls (# positive/tested)
Clinical	gyrA	GAC 94 TAC	3 / 3	gyrA1-MutB (3/3); gyrA3-MutC (3/3)	FLQ [3/3]
	katG	AGC 315 ACC		katG Mut (3/3)	INH [3/3]
	fabG1	G609A		fabG1 Mut (3/3)	INH [3/3]
Clinical	gyrA	GGC 88 GCC, GCG 90 GTG, TCG 91 CCG	3 / 3	gyrA1-MutB (2/3),[a] gyrA1-MutC (2/3), gyrA2-MutA (3/3), gyrA3-MutB (1/3)	FLQ [3/3]
	katG	AGC 315 ACC		katG Mut (3/3)	INH [3/3]
	rrs	A1410G		rrs-Mut (3/3)	AMK, CAP, KAN [3/3]
Clinical	gyrA	GAC 94 GGC	3 / 3	gyrA3-MutB (3/3)	FLQ [3/3]
	katG	AGC 315 ACC		katG Mut (3/3)	INH [3/3]
	rrs	A1410G		rrs-Mut (3/3)	AMK, CAP, KAN [3/3]
14-14194	gyrA	GAC 94 GCC	3 / 3	gyrA1-MutA, gyrA2-MutA	FLQ [3/3]
	katG	AGC 315 ACC		katG-Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH, ETH [3/3]
15-14175	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	eis	-10G/A		eis-Mut (3/3)	AMK, KAN [3/3]
15-14191	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	eis	-10G/A		eis-Mut (3/3)	AMK, KAN [3/3]
16-05612	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH, ETH [3/3]
	eis	-12C/T		eis-Mut (3/3)	AMK, KAN [3/3]

Table 14. Analytical Reactivity (Inclusivity) for Drug Resistant Strains (# positive results / total tested) (Continued)

Strain ID	Gene	Expected Mutation	MTB Detected	Mutant Probe Tm Detected (# positive/tested)	Correct RESISTANCE DETECTED Calls (# positive/tested)
16-05613	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH, ETH [3/3]
	eis	-12C/T		eis-Mut (3/3)	AMK, KAN [3/3]
14-13764	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	ahpC	-48G/A		ahpc-Mut (3/3)	INH [3/3]
14-13806	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	ahpC	-48G/A		ahpc-Mut (3/3)	INH [3/3]
Clinical	gyrA	GCG 90 GTG, GAC 94 GGC	3 / 3	gyrA3-MutB (3/3)	FLQ [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH [3/3]
	ahpC	G-6A		ahpC (2/3)[b]	INH [3/3]
Clinical	katG	AGC 315 ACC	3 / 3	katG Mut (3/3)	INH [3/3]
Clinical	gyrB2	ACC 539 AAC	3 / 3	gyrB2 WT[c]	*No resistance detected [0/3]
	rrs	A1410G		rrs-Mut (3/3)	AMK, CAP, KAN [3/3]
	gyrA	GCG 90 GTG		gyrA1 MuB (3/3), gyrA2 MutA (3/3), gyrA3 MutB (3/3)	FLQ [3/3]
	ahpC	g -6 a		ahpC Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA Mut (3/3)	INH, ETH [3/3]
Clinical	gyrA	TCG 91 CCG	3 / 3	gyrA1-MutB (3/3), gyrA2-MutA (3/3), gyrA3-MutC (3/3)	FLQ [3/3]
	inhA	C -15 T		inhA Mut (3/3)	INH, ETH [3/3]

a. This sample containing three different mutations in the *gyrA* gene did not generate mutant Tms for all the three *gyrA* probes all the time. However, for the correct resistance call to be made, at least one probe needs to generate a mutant Tm, call was correctly made for all the replicates, since at least one *gyrA* probe always generated at least one mutant Tm when tested.

b. This sample is a katG / ahpC double mutant. The replicate with a missed ahpC mutant Tm was called INH-R due to the presence of the katG mutation, which was detected by the assay.

c. This specific mutation is not detected by the assay. However, there is limited clinical evidence that this mutation may actually contribute to FLQ resistance (Low confidence mutation for FLQ-Resistance).

19.4 Interfering Substances Study

Performance of the Xpert MTB/XDR Assay was evaluated in the presence of 36 potentially interfering substances that may be present in the sputum. Potentially interfering substance classes include endogenous substances that are may be present in the specimen and exogenous substances that might be introduced into the specimen. Isotonic or hypertonic solutions, bronchodilators, and inhaled bronchodilators commonly used in the collection of induced sputum were tested and do not interfere with the assay. Saline induction may result in insufficient number the organisms recovered and could affect detection of M. tuberculosis.

The substances tested are listed in Table 15 with active ingredients and concentrations tested shown. Negative samples (n = 8) were tested per each substance to determine the effect on the performance of the sample processing control (SPC). Positive samples (n = 8) *Mycobacterium bovis, Bacille Calmette-Guerin (BCG)* spiked at 3x the analytical Limit of Detection for TB positivity were tested per substance. All substances were tested in MTB-negative pooled human sputum background included in this study. All positive and negative replicates were identified correctly using the Xpert MTB/XDR Assay, except for Zicam gel (50% w/v; resulted in “MTB NOT DETECTED” in 11.1% of the replicates tested).

Table 15. Potentially Interfering Substances in the Xpert MTB/XDR Assay

Substance/Class	Description / Active Ingredient	Concentration Tested
Blood (human)	Blood 5% (v/v)	5% (v/v)
Human DNA/Cells	HELA 229 cell line	10^6 cells/mL
White Blood Cells (human)	WBC/Pus matrix (30% buffy coat; 30% plasma; 40% PBS)^	100% (v/v)
Antimycotic; Antibiotic	Nystatin 500KU (100%)	20% (v/v)
Germicidal Mouthwash	Chlorhexidine gluconate (0.12%) oral rinse, USP	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 12.5mM Citrate
Gastric Acid	pH 3 to 4 solution in water, neutralized with sodium bicarbonate	100% (v/v)
Anesthetics (endotracheal intubation)	Lidocaine HCl 4%	4% (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 mg/5mL)	100 µg/mL
Oral anesthetics	Orajel (20% Benzocaine)	5% (w/v)
Anti-viral drugs	Acyclovir	50 µg/mL
Antibiotic, nasal ointment	Neosporin (400U Bactracin, 3.5mg Neomycin, 5000U Polymyxin B)	5% (w/v)
Tobacco	Nicogel 40% tobacco extract	0.5%
Anti-tuberculosis drugs	Streptomycin 1mg/mL	25µg/mL
Anti-tuberculosis drugs	Ethambutol 1mg/mL	50 µg/mL
Anti-tuberculosis drugs	Isoniazid 50mg/5ml	50 µg/mL
Oral expectorants	Guaifenesin (400mg/tablet)	5 mg/mL
Anti-tuberculosis drugs	Pyrazinamide (500mg/tablet)	100 µg/mL
Nasal gel (Homeopathic)	Zicam gel	50% (w/v)
		20% (w/v)
Nasal spray	Phenylephrine 1%	0.5% (v/v)
Anti-tuberculosis drugs	Rifampicin (300mg/tablet)	25 µg/mL
Allergy relief medicine (Homeopathic)	100% Pure Tea tree oil (<5% Cineole, >35% Terpinen-4-01)	0.5% (v/v)
Nebulizing solutions	Pentamidine isethionate	300ng/ml
Anti-tuberculosis drugs	Amoxicillin	25 µg/mL
Bronchodilator	Epinephrine	1mg/mL
Anti-tuberculosis drugs	Amikacin	70ug/ml
Anti-tuberculosis drugs	Capreomycin	50ug/ml
Anti-tuberculosis drugs	Kanamycin	50ug/ml
Anti-tuberculosis drugs	Ethionamide	50ug/ml
Flu Mist Qual Nasal	Influenza Virus Vaccine Live-nasal	5%

19.5 Carry-over Contamination Study

A study was conducted to demonstrate that carry-over, cross contamination does not occur when using the single-use, self-contained Xpert MTB/XDR cartridges. The study consisted of processing a negative sample immediately following processing a high concentration of *Mycobacterium bovis-Bacille Calmette-Guerin* (BCG) at 1 x 10^{+6} CFU/mL in human sputum the same Gene Xpert module. This testing scheme was repeated at least 20 times in two GeneXpert modules producing a total of 41 runs resulting in 20 positives and 21 negatives per module.

All 20 positive samples were correctly reported as MTB DETECTED; INH Resistance NOT DETECTED; FLQ Resistance NOT DETECTED; AMK Resistance NOT DETECTED; KAN Resistance NOT DETECTED; CAP Resistance NOT DETECTED; ETH Resistance NOT DETECTED. All 21 negative samples were correctly reported as MTB NOT DETECTED. Under the conditions of this study, there was no evidence of any carry–over contamination when testing with very high positive *BCG* sample at the concentration of 1.0 x 10^{+6} CFU/mL.

19.6 Competitive Interference Study

Competitive interference of the assay caused by the presence of high concentrations of high concentrations of non-tuberculous Mycobacteria (NTM) on the detection of low levels of MTB in the Xpert MTB/XDR Assay was evaluated by testing the representative member of the MTBC. BCG at ~ 3 x LoD (411 CFU/mL) in the presence of different NTM strains at 1 x 10E+06 CFU/mL concentration in a background of negative control buffer. MTB positivity is based on detection of *inhA* promoter valid melt peak height and melt peak temperature. Resistance detection is based on valid mut melt peak height and mut melt peak temperature for individual analytes (*inhA, katG, gyrA1, gyrA2, gyrA3, gyrB2* and *eis*). *oxyR-ahpC and fabG1* analytes were excluded due to lower sensitivity and *rrs* was excluded due to known interference with microflora. All samples containing BCG should have results as MTB DETECTED; INH Resistance NOT DETECTED; FLQ Resistance NOT DETECTED; AMK Resistance NOT DETECTED; KAN Resistance NOT DETECTED; CAP Resistance NOT DETECTED; ETH Resistance NOT DETECTED.

Four replicates of each NTM/ BCG competitive mixture test condition along with a positive control condition with only BCG at ~3 x LoD were tested. None of the NTM strains tested interfered with the detection of 411 CFU/mL of BCG and generated the correct result as mentioned above. However, under the conditions of this study, competitive inhibitory effects were observed in the presence of only one of the two strains of *M.marinum* (ATCC 0927) tested. Interference with gyrA2 probes was observed only at challenge concentrations >10^4 CFU/mL resulting in FLQ resistance INDETERMINATE calls at these high challenge concentrations. Refer to Section 17, Limitations for further information..

Table 16. Competitive Interference by NTM on MTB detection and drug susceptibility detection

Test Condition / NTM Strain ID	NTM CFU/ mL	MTB Detected	INH	FLQ	AMK	KAN	CAP	ETH
MTB + M. avium / (NJH)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.gastir / (ATCC 15754)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.gordonae / (NJH)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.gordonae / (ATCC 14470)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.gordonae / (ATCC 35760)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.marinum / (NJH)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.marinum / (ATCC 0927)	10E+06	PASS	PASS	FAIL	PASS	PASS	PASS	PASS
	10E+05	PASS	PASS	FAIL	PASS	PASS	PASS	PASS
	10E+04	PASS	PASS	PASS	PASS	PASS	PASS	PASS
	10E+03	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.xenopi / (ATCC 700084)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.avian / (ATCC 15769)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.intracellulare / (ATCC 35771)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
MTB + M.abscessus / (ATCC 19977)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS

Table 16. Competitive Interference by NTM on MTB detection and drug susceptibility detection (Continued)

Test Condition / NTM Strain ID	NTM CFU/ mL	MTB Detected	INH	FLQ	AMK	KAN	CAP	ETH
MTB + M.kansasii / (ATCC 12478)	10E+06	PASS	PASS	PASS	PASS	PASS	PASS	PASS
"PASS" indicates all the replicates tested generated the expected "RESISTANCE NOT DETECTED" result for the relevant drugs; "FAIL" indicates at least one or more replicates generated "RESISTANCE INDETERMINATE" result for the particular drug.								

19.7 Inactivation of Mycobacteria in Sputum Samples

The disinfection capability of the Xpert MTB/XDR Sample Reagent was determined using a standardized quantitative tuberculocidal culture method.[21] 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.

20 Precision and Reproducibility

The precision and reproducibility of the Xpert MTB/XDR test was established in a multicenter (three sites), blinded study utilizing a multi-factor nested design. The study consisted of a five-member sample panel and each panel member was prepared by spiking an MTB wild type (WT) strain and an MTB mutant (MUT) strain into artificial sputum matrix. The WT and MUT strains were made from plasmids carrying either MTB XDR wild type or mutant sequences for the genes targeted by the assay, encapsulated in killed, chemically fixed E. coli.

The panel members were prepared at ~1xLoD and ~3xLoD using the melt temperatures (Tm) of the *inhA* promotor target in the Xpert MTB/XDR test, which generates the MTB DETECTED/NOT DETECTED result depending on the presence or absence of the wildtype or mutant *inhA* promoter specific Tm. Testing was conducted for six days with three lots of Xpert MTB/XDR cartridges. Each site had two operators (Op1 and Op2) who performed two runs each with two replicates/run each day. A replicate was a single cartridge test. The percent agreement for each panel member is presented in Table 17.

Table 17. Percent Agreement of Xpert MTB/XDR Test for MTB and *inhA* Detection

Sample	Site 1			Site 2			Site 3			Total Agreement by Sample
	OP 1	OP 2	Subtotal	OP 1	OP 2	Subtotal	OP 1	OP 2	Subtotal	
MTB MUT 1xLoD	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	95.8% (23/24)	97.9% (47/48)	91.7% (22/24)	91.7% (22/24)	91.7% (44/48)	96.5% (139/144)
MTB MUT 3xLoD	95.8% (23/24)	100% (24/24)	97.92% (47/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	99.3% (143/144)
MTB WT 1xLoD	100% (24/24)	91.67% (22/24)	95.8% (46/48)	91.7% (22/24)	91.7% (22/24)	91.7% (44/48)	91.7% (22/24)	100% (24/24)	95.8% (46/48)	94.4% (136/144)
MTB WT 3xLoD	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (144/144)
NEG	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	95.8% (23/24)	97.9% (47/48)	99.3% (143/144)

The performance of the Xpert MTB/XDR test in MTB WT and MUT strains at low (~1x) and moderate (~3x) LoD panel samples for each gene target where MTB was detected is presented in Table 18.

Table 18. Percent Agreement of Xpert MTB/XDR Test in MTB MUT and WT Types Specimens

Drug	Percent Concordance			
	MTB MUT 1x LoD (95% CI) [n agree/total n]	**MTB MUT 3xLoD (95% CI) [n agree/total n]**	**MTB WT 1x LoD (95% CI) [n agree/total n]**	**MTB WT 3x LoD (95% CI) [n agree/total n]**
INH	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	89.1% (82.6-93.4) [115/129]	99.3% (96.2-99.9) [143/144]
FLQ	87.80% (81.3-92.2) [122/139]	100.00% (97.4-100.0) [143/143]	81.4% (73.8-87.2) [105/129]	95.8% (91.2-98.1) [138/144]
ETH	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	99.2% (95.7-99.9) [128/129]	100.0% (97.4-100.0) [144/144]
AMK	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	91.5% (85.4-95.2) [118/129]	98.6% (95.1-99.6) [142/144]
CAP	99.30% (96.3-99.0) [138/139]	100.00% (97.4-100.0) [143/143]	98.4% (94.5-99.6) [127/129]	99.3% (96.2-99.9) [143/144]
KAN	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	91.5% (85.4-95.2) [118/129]	98.6% (95.1-99.6) [142/144]

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23 Technical Assistance

Before contacting Cepheid Technical Support, collect the following information:

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24 Table of Symbols

Symbol	Meaning
	Catalog number
	*In vitro* diagnostic medical device
	CE marking – European Conformity
	Do not reuse
	Batch code
	Consult instructions for use
	Manufacturer
	Contains sufficient for <n> tests
	Control
	Expiration date
	Temperature limitation
	Biological risks
	Caution
	Flammable Liquids
	Skin Corrosion
	Severe Health Hazards
	Country of manufacture

Cepheid AB
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Xpert® MTB/XDR

REF **GXMTB/XDR-10**

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Švedija

Xpert® MTB/XDR

In vitro diagnostiniam naudojimui.

1 Patentuotas pavadinimas

Xpert® MTB/XDR

2 Bendrinis ar įprastai naudojamas pavadinimas

Xpert MTB/XDR tyrimas

3 Paskirtis

Xpert MTB/XDR tyrimas, naudojamas su GeneXpert instrumentų sistemomis, yra pusiau pakopinis (angl. nested) tikro laiko PGR *in vitro* diagnostinis tyrimas, skirtas plačiai naudojamiems vaistams atsparaus (angl. sutr. XDR) *Mycobacterium tuberculosis* (MTB) komplekso DNR nustatymui neapdorotų skreplių mėginiuose arba koncentruotose skreplių sedimentuose. Mėginiuose su MTB Xpert MTB/XDR tyrimas taip pat gali aptikti atsparumą izoniazidui (INH) lemiančias mutacijas *katG* ir *fabG1* genuose, *oxyR- ahpC* tarpgeniniame regione ir *inhA* promotoriuje; atsparumą etionamidui (ETH) lemiančias mutacijas *inhA* promotoriuje; atsparumą fluorochinolonui (FLQ) lemiančias mutacijas *gyrA* ir *gyrB,* atsparumą chinolonui nusakančiuose regionuose (QRDR); atsparumą antros eilės injekciniams vaistams (angl. sutr. SLID) lemiančias mutacijas *rrs* gene ir *eis* promotoriaus regione.

Xpert MTB/XDR tyrimas yra naudojamas kaip refleksinis testas mėginiams (neapdorotiems skrepliams ar koncentruotiems skreplių sedimentams), kurie yra nustatyti kaip MTB teigiami. Šis tyrimas yra pagalbinė priemonė atliekant XDR tuberkuliozės (TB) diagnozę, naudojama kartu su klinikinėmis ir kitomis laboratorinėmis išvadomis ir rezultatais.

4 Santrauka ir paaiškinimas

Tuberkuliozė (TB), kurią sukelia *Mycobacterium tuberculosis*, išlieka viena mirtingiausių ligų pasaulyje. 2018 m. buvo nustatyta 10 milijonų naujų TB atvejų, kurių apie pusė milijono buvo rifampicinui atsparios TB atvejai, iš jų - 78% daugeliui vaistų atsparios TB (MDR-TB) atvejai[1]. MDR-TB, atspari izoniazidui ir rifampicinui (dvi veiksmingiausios pirmosios vaistų eilės), išlieka grėsme visuomenės sveikatai. Pasaulio sveikatos organizacijos (PSO) naujausiose gydymo gairėse rekomenduojama atlikti greitą jautrumo vaistams tyrimą[2,3]. 2018 m. bendras MDR/RR-TB atvejų skaičius buvo tik 39% visų atvejų, o gydomų asmenų - 32%[1]. Taipogi, auga susirūpinimas dėl nediagnozuotų ir negydomų izoniazidui atsparių, rifampicinui jautrių TB atvejų. Neturint galimybės atlikti atsparumo INH tyrimo, tam tikrose šalyse yra labai sudėtinga identifikuoti pacientus ir taikyti 2018 PSO rekomendacijas dėl Hr-TB gydymo[4]. Labiausiai susirūpinimą keliančius TB atvejus sukelia MDR MTB padermės, kurios yra įgijusios papildomą atsparumą fluorochinolonams (antros eilės injekciniams vaistams), amikacinui (AMK), kanamicinui (KAN) ar kapreomicinui (CAP). Šios aukštą atsparumą turinčios padermės yra vadinamos itin vaistams atspariomis TB (XDR-TB).
XDR-TB yra labai sunkiai gydoma ir pasižymi didesniu mirtingumu, ypač kai XDR-TB nėra diagnozuojama ir gydoma laiku[5].

MTB kultūros ir fenotipinio jautrumo vaistams tyrimų atlikimas ilgai trunka, jų atlikimui reikia daug darbo, šių tyrimų metu egzistuoja rimtas biologinis pavojus laboratorijos darbuotojams, todėl juos atlieka vis mažiau akredituotų įstaigų šalyse, kur MTB yra endeminė[2]. Kultūros auginimo principu paremti jautrumo nustatymo tyrimai gali trukti nuo kelių savaičių iki mėnesių. MTB jautrumą vaistams galima
nustatyti naudojant greitus, jautrius ir saugesnius genotipinius tyrimus, kurie atsparumą nustato identifikuojant mutacijas, atsakingas už atsparumą pirmos ir antros eilės vaistams daugumoje klinikinių padermių[2]. Genotipinio tyrimo metu tyrimo apimtis sumažėja iki kelių rankiniu būdu atliekamų etapų, todėl jį galima atlikti šalia paciento, taip padidinant ištyrimo galimybes šalyse su nepakankamomis medicininės priežiūros galimybės, esant žemam ar aukštam endeminiam lygiui[5].

5 Procedūros principas

Xpert MTB/XDR tyrimas yra automatizuotas *in vitro* diagnostinis tyrimas, skirtas XDR MTB komplekso DNR ir su atsparumu susijusių mutacijų aptikimui. Tyrimas yra atliekamas su Cepheid GeneXpert instrumentų sistemomis, kuriose yra GeneXpert 10 spalvų moduliai.

GeneXpert instrumento sistema integruoja ir automatizuoja mėginio apdorojimą, nukleino rūgšties amplifikaciją bei taikinio eilių aptikimą mėginiuose, naudojant pakopinį tikro laiko PGR ir lydymosi piko aptikimą. GeneXpert instrumento sistemą sudaro instrumentas, asmeninis kompiuteris, brūkšninių kodų skaitytuvas ir įdiegta programinė įranga, skirta mėginių tyrimų vykdymui ir rezultatų peržiūrai. Sistemai yra reikalingos vienkartinio naudojimo Xpert kasetės, kuriose yra taikiniui specifiniai polimerazės grandinės reakcijos (PGR) reagentai ir kuriose vyksta PGR procesas bei lydymosi piko aptikimas. Kadangi kasetės yra individualios, yra sumažinama kryžminio užterštumo tarp mėginių rizika. Išsamų sistemos aprašymą rasite *GeneXpert Dx sistemos naudotojo vadove.*

Xpert MTB/XDR tyrimo kasetėje yra reagentų, skirtų XDR MTB profilio aptikimui ir mėginio apdorojimo kontrolė (SPC), skirta adekvataus taikinio bakterijos apdorojimo atlikimui ir inhibitoriaus (-ių) stebėjimui PGR reakcijoje. Tyrimo tikrinimo kontrolė (PCC) patikrina reagento rehidraciją, PGR mėgintuvėlio užpildymą kasetėje, mėgintuvėlio integralumą ir dažų stabilumą.

Xpert MTB/XDR tyrimo kasetėje yra visi reagentai, išskyrus mėginio reagentą (SR), kurį naudotojas turi pridėti į mėginį, prieš mėginį įkeliant į kasetę. Tyrimas yra atliekamas kaip refleksinis tyrimas MTB teigiamiems mėginiams.

GeneXpert programinė rezultatus interpretuoja pagal išmatuotus fluorescencijos signalus ir apskaičiavimo algoritmus. Rezultatai „View Results“ lange yra pateikiami ir lentelės, ir grafiko formatu. Jei tyrimas yra negaliojantis, sistema aptiko klaidą ar rezultatas nėra gautas, ekrane bus rodomas atitinkamas pranešimas. Xpert MTB/XDR aptinka XDR MTB su atsparumu INH, ETH, FLQ ir SLID tiesiogiai iš neapdorotų skreplių ar koncentruotų skreplių sedimentų per mažiau nei 90 minučių.

6 Reagentai ir instrumentai

6.1 Tiekiamos medžiagos

Xpert MTB/XDR rinkinio reagentų pakanka apdoroti 10 pacientų ar kokybės kontrolės mėginių. Rinkinį sudaro:

Xpert MTB/XDR kasetės su integruotais reakcijos mėgintuvėliais	**10 vnt. rinkinyje**
• Rutuliukas 1, rutuliukas 2, rutuliukas 3, rutuliukas 4 ir rutuliukas 5 (užšaldyti, sausi)	po 1 kasetėje
• Mėginio apdorojimo kontrolės rutuliukas (užšaldytas, sausas)	po 1 kasetėje
• Reagentas 1	4.0 ml kasetėje
• Reagentas 2	4.0 ml kasetėje
Vienkartinės perkėlimo pipetės	**rinkinyje 1 maišelis su 12 vnt.**
Mėginio reagentas	**10 x 8 ml buteliuke**
CD	**1 rinkinyje**
• Tyrimo aprašymo failai (ADF)	
• ADF importavimo į GeneXpert programinę įrangą instrukcijos	
• Naudojimo instrukcijos (pakuotės aprašymas)	

Pastaba Mėginio reagentas (SR) gali būti bespalvis arba geltonos - gintaro spalvos. Ilgainiui spalva gali intensyvėti, tačiau tai neturi jokio poveikio veiksmingumui.

Pastaba Medžiagos saugos duomenų lapai (MSDL) yra pateikiami www.cepheid.com ar www.cepheidinternational.com skirtuke **SUPPORT**.

Pastaba Šiame produkte esantis jaučio serumo albuminas (BSA) buvo pagamintas išskirtinai iš jaučio plazmos Jungtinėse Amerikos Valstijose. Gyvūnai nebuvo šeriami ruminantiniais ar kitais gyvulinės kilmės baltymais; gyvūnams buvo atlikti priešmirtiniai ir pomirtiniai tyrimai. Proceso metu medžiaga nebuvo sumaišoma su kitomis gyvūninės kilmės medžiagomis.

Pastaba Ant perkėlimo pipečių yra žyma, žyminti minimalų apdoroto mėginio tūrį, kurį reikia perkelti į kasetę. Naudokite tik šiam tikslui. Visomis kitomis pipetėmis turi pasirūpinti laboratorija.

7 Laikymas ir naudojimas

- Xpert MTB/XDR rinkinio komponentus laikykite 2–28 °C temperatūroje iki etiketėje nurodytos galiojimo datos.
- Neatidarykite kasetės tol, kol nebūsite pasiruošę atlikti tyrimo.
- Tyrimas turi būti pradėtas per 2,5 valandos po SR pridėjimo į mėginį arba per 4 valandas, jei yra laikomas 2–8^{0}C temperatūroje.
- Nenaudokite reagentų ar kasečių pasibaigus jų galiojimo laikui.
- Nenaudokite kasetės, jei ji prateka.

8 Reikalingos neteikiamos medžiagos

- GeneXpert Dx sistema: GeneXpert instrumentas su GeneXpert 10 spalvų moduliais, kompiuteriu, brūkšninių kodų skaitytuvu ir naudotojo vadovu.
  - GeneXpert Dx sistema: 6.2 ar vėlesnės versijos programinė įranga.
  - Spausdintuvas: jei reikia spausdintuvo, susisiekite su Cepheid pardavimo atstovu ir pasikonsultuokite dėl rekomenduojamo spausdintuvo įsigijimo.
- Sterilus mėginių konteineris užsukamu dangteliu
- Vienkartinės pirštinės
- Etiketės ir (ar) nenutrinamas žymeklis
- Sterilios pipetės mėginių tvarkymui

9 Įspėjimai ir atsargumo priemonės

9.1 Bendra informacija

- *In vitro* diagnostiniam naudojimui.
- Su visais biologiniais mėginiais, įskaitant panaudotas kasetes, elkitės kaip su galinčiais pernešti infekcinius agentus. Kadangi nėra žinoma, kuris mėginys yra infekciškas, su visais biologiniais mėginiais reikia dirbti laikantis universaliųjų atsargumo priemonių.
- Mėginių naudojimo rekomendacijas teikia JAV Ligų kontrolės ir prevencijos centrai[3] ir Klinikinių ir laboratorinių standartų institutas.[6,7,8]
- Dirbant su chemikalais ir biologiniais mėginiais, laikykitės savo įstaigos saugos procedūrų.
- Tvarkant mėginius ir reagentus, dėvėkite vienkartines pirštines, laboratorinį chalatą ir akių apsaugą. Po mėginių ir tyrimo reagentų naudojimo, kruopščiai nusiplaukite rankas.
- Biologiniai mėginiai, perkėlimo priemonės bei panaudotos kasetės turi būti laikomos potencialiai pernešančiomis infekcinius agentus ir juos naudojant yra būtina laikytis standartinių atsargumo priemonių. Laikykitės savo įstaigos atliekų šalinimo procedūrų dėl tinkamo naudotų kasečių ir nepanaudotų reagentų išmetimo. Šios medžiagos gali demonstruoti pavojingų cheminių atliekų požymius, kuriems reikia specifinių valstybinių ar regioninių atliekų išmetimo procedūrų pritaikymo. Jei valstybinėse ar regioninėse nuostatose tinkamo išmetimo procedūros nėra aiškiai pateikiamos, biologiniai mėginiai ir panaudotos kasetės turi būti išmetamos laikantis PSO (Pasaulio sveikatos organizacijos) rekomendacijų dėl medicininių atliekų naudojimo ir išmetimo[9].
- Mėginio reagento sudėtyje yra natrio hidroksido (pH > 12.5) ir izopropanolio. Pavojingas prarijus (H302), sukelia sunkų odos nudegimą ir kenkia akims (H314). Labai degus skystis ir garai (H226).
- Šio tyrimo veiksmingumo charakteristika yra nustatyta tik su skyriuje „Paskirtis“ išvardintais mėginių tipais. Šio tyrimo veiksmingumas su kito tipo mėginiais nebuvo vertinamas.
- Dirbant su chemikalais ir biologiniais mėginiais, laikykitės savo įstaigos saugos procedūrų.

9.2 Mėginiai

- Mėginių paėmimui ir tvarkymui būtinas specifinis apmokymas ir instrukcijos.
- Mėginių transportavimo metu užtikrinkite tinkamas sąlygas, jog būtų išlaikytas mėginio integralumas (žr. skyrių 12, „Procedūra“). Esant kitoms nei nurodyta transportavimo sąlygoms, mėginių stabilumas nebuvo vertinamas.
- Nenaudokite mėginių, kuriuose yra maisto ar kitų kietų dalelių.
- Teisingų rezultatų gavimui yra būtinas tinkamas mėginių paėmimas, laikymas ir transportavimas.

9.3 Tyrimas / reagentai

- Nesukeiskite Xpert MTB/XDR tyrimo reagentų su kitais reagentais.
- Xpert MTB/XDR tyrimo kasetę atidarykite tik mėginio įdėjimo metu.
- Nenaudokite kasetės, jei ji buvo nukritusi ar supurtyta po išėmimo iš pakuotės, jei prieš tai buvo atidarytas jos dangtelis. Nepurtykite kasetės. Kasetės purtymas ar išmetimas po dangtelio atidarymo gali sukelti klaidingus rezultatus.
- Neklijuokite mėginio ID etiketės ant kasetės dangtelio ar brūkšninio kodo etiketės.
- Nenaudokite kasetės, jei reakcijos mėgintuvėlis yra pažeistas.
- Kiekviena vienkartinio naudojimo Xpert MTB/XDR tyrimo kasetė yra skirta vieno tyrimo atlikimui. Panaudotų kasečių nenaudokite pakartotinai.
- Vienkartinio naudojimo pipetė yra skirta vieno mėginio perkėlimui. Panaudotų pipečių nenaudokite pakartotinai.
- Nenaudokite kasetės, jei ji yra drėgna ar jos sandarinimo plėvelė yra pažeista.
- Siekiant išvengti mėginių ar reagentų užteršimo, rekomenduojama laikytis geros laboratorijos praktikos, įskaitant pirštinių keitimą tarp skirtingų mėginių apdorojimo.
- Išsiliejus mėginiams ar kontrolėms, dėvėdami pirštines, absorbuokite popieriniu rankšluosčiu. Tuomet, paveiktą vietą kruopščiai išvalykite 1:10 santykiu skiestu buitiniu chloro balikliu. Galutinė aktyvaus chloro koncentracija turi būti 0.5%, nepaisant buitinio baliklio koncentracijos jūsų šalyje. Sąlyčio laikas turi būti bent dvi minutės. Įsitikinkite, kad darbo paviršius yra sausas, tuomet baliklio likučius nuvalykite 70% denatūruotu etanoliu. Prieš tęsiant darbą, palaukite, kol paviršius visiškai išdžius. Arba laikykitės savo įstaigos standartinių procedūrų, taikomų užteršimo ar išsiliejimo atvejais. Norint nukenksminti įrangą, laikykitės įrangos gamintojo teikiamų instrukcijų.
- Tyrimas yra patvirtintas naudojimui su Cepheid GeneXpert Dx 6.2 ar vėlesnės versijos programine įranga.

10 Cheminis pavojus[9,10]

Mėginio reagentas:

- Sudėtyje yra izopropilo alkoholio.
- Sudėtyje yra natrio hidroksido.
- Signalinis žodis: PAVOJINGA.
- UN GHS pavojaus piktogramos:

- **UN GHS pavojaus frazės**
  - Degus skystis ir garai.
  - Sukelia sunkų odos nudegimą ir kenkia akims.
  - Sukelia sunkius akių pažeidimus.
  - Įtariama, jog gali sukelti genetinius defektus.
  - Įtariama, jog gali sukelti nevaisingumą ar persileidimą.
  - Esant ilgalaikiam ar pakartotiniam poveikiui, gali pakenkti organams.
- **UN GHS atsargumo frazės**
- **Prevencija**
  - Prieš naudojimą, turėkite specialiąsias instrukcijas.
  - Nedirbkite, jei visos saugos ir atsargumo priemonių procedūros nebuvo perskaitytos ir suprastos.
  - Laikykite atokiai nuo karščio, žiežirbų, atviros liepsnos ir (ar) karštų paviršių. Nerūkykite.
  - Konteineryje laikykite sandariai uždarytą.
  - Neįkvėpkite dulksnos, garų ir (ar) aerozolio.
  - Po naudojimo kruopščiai nusiplaukite rankas.
  - Dėvėkite apsaugines pirštines, apsauginius rūbus, akių apsaugą, veido apsaugą.
  - Dėvėkite reikiamą asmens apsaugos įrangą.
- **Atsakas**
  - Gaisro atveju: gaisro gesinimui naudokite tinkamas gesinimo priemones.

- ĮKVĖPUS: nukentėjusįjį išveskite į gryną orą ir leiskite ramiai pakvėpuoti grynu oru jam patogioje padėtyje.
- Nedelsiant skambinkite APSINUODIJIMŲ CENTRUI ar gydytojui.
- PATEKUS ANT ODOS (ar plaukų): nedelsiant nusivilkite užterštus rūbus. Odą plaukite vandeniu.
- Prieš pakartotinį dėvėjimą, užterštus rūbus išskalbkite.
- Specifinis gydymas aprašytas pirmosios pagalbos skyriuje.
- PATEKUS Į AKIS: kelias minutes kruopščiai skalaukite vandeniu. Jei yra kontaktiniai lęšiai, juos išimkite, jei galite tai padaryti. Toliau skalaukite.
- PRARIJUS: skalaukite burną. NESUKELKITE vėmimo.
- Įvykus sąlyčiui ar sunerimus: kreipkitės medicininės pagalbos.
- Jei pasijutote blogai, kreipkitės medicininės pagalbos.

- **Laikymas / išmetimas**
  - Turinį ir (ar) konteinerį išmeskite laikydamiesi vietos, regioninių, valstybinių ir (ar) tarptautinių taisyklių.

11 Mėginių paėmimas, transportavimas ir laikymas

Mėginiai gali būti paimami laikantis naudotojo įstaigos standartinių procedūrų.

Tinkamas mėginių paėmimas, laikymas ir transportavimas yra kritinis šio tyrimo veiksmingumo faktorius. Esant kitoms nei nurodyta transportavimo ir laikymo sąlygoms, mėginių stabilumas su Xpert MTB/XDR tyrimu nebuvo vertinamas.

11.1 Transportavimas

Mėginius rekomenduojama transportuoti 2–8 °C temperatūroje, kai tik tai yra įmanoma.

Neapdoroti skreplių mėginiai gali būti laikomi 2–35°C temperatūroje.

11.2 Neapdoroti mėginiai

Neapdoroti skreplių mėginiai 2–35°C temperatūroje gali būti laikomi iki 7 dienų (įskaitant transportavimo laiką).

Dekontaminuoti / koncentruoti ir resuspenduoti skreplių sedimentai 2–8 °C temperatūroje gali būti laikomi iki 7 dienų iki ištyrimo su GeneXpert.

Neapdorotų skreplių ar dekontaminuotų / koncentruotų skreplių adekvataus mėginio tūrio aprašymą rasite 1 lentelėje.

1 lentelė. Reikalingas mėginio tūris.

Mėginio tipas	Minimalus tūris vienam tyrimui	Maksimalus mėginio tūris	Mėginio ir mėginio reagento (SR) santykis
Skreplių sedimentai	0,5 ml	2,5 ml	1:3a
Neapdoroti skrepliai	1,0 ml	4,0 ml	1:2

a. 1:2 mėginio ir SR santykis turi būti naudojamas, kuomet mėginio tūris vienam ištyrimui yra 0,7 ml ar daugiau.

11.3 Mėginių, apdorotų SR, likutis

Xpert MTB/XDR tyrimas gali būti naudojamas mėginių su SR likučio, likusio po Xpert MTB/RIF ar Xpert MTB/RIF Ultra tyrimo, ištyrimui. Tačiau, tokiu atveju, mėginio, apdoroto SR likutis turi būti ≥2ml, o mišinys laikomas 2–8 °C temperatūroje ne ilgiau nei 4 valandas arba iki 35 °C temperatūroje ne ilgiau nei 2,5 valandos.

12 Procedūra

12.1 Procedūra neapdorotų skreplių mėginiams

Svarbu. Tyrimas turi būti pradėtas per 2,5 valandos po SR pridėjimo į mėginį arba per 4 valandas, jei yra laikomas 2–8ºC temperatūroje.

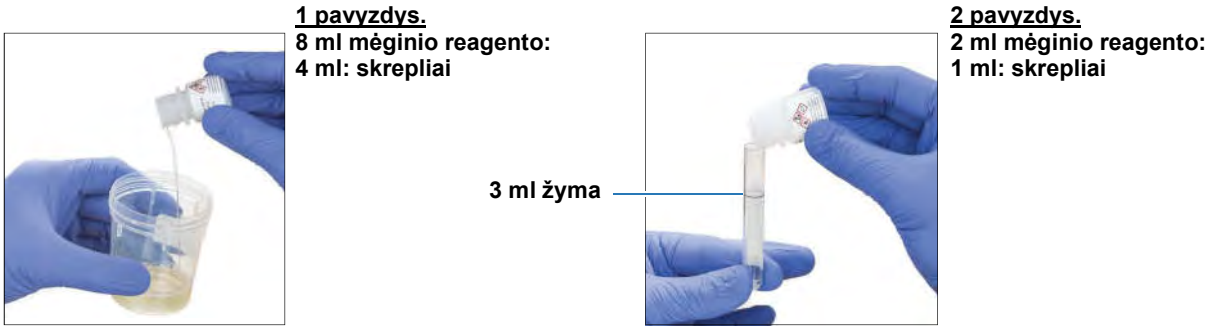
Pastaba. Nenaudokite mėginių su aiškiai matomomis maisto ar kitomis kietomis dalelėmis.

Reikalavimai tūriui: ≥1ml neapdorotų skreplių.

1. Atsargiai nuimkite sandaraus skreplių surinkimo konteinerio dangtelį. Žr. 1 iliustraciją.

1 iliustracija. Skreplių surinkimo konteinerio atidarymas.

2. Į skreplių mėginį įpilkite apie 2 kartus daugiau SR (2:1 skiedimas, SR:skrepliai). Žr. 2 iliustraciją.



2 iliustracija. 2:1 skiedimo pavyzdžiai

Pastaba. Likusį SR ir buteliuką išmeskite į tinkamą atliekų konteinerį, laikydamiesi standartinės savo įstaigos praktikos.

3. Užkimškite mėginio konteinerį.
4. Energingai papurtykite 10-20 kartų arba mažiausiai 10 sekundžių maišykite sūkurinėje purtyklėje.

Pastaba. Vienas judesys į priekį ir atgal yra vienas papurtymas.

5. 10 minučių inkubuokite kambario temperatūroje, tuomet mėginį energingai papurtykite 10-20 kartų arba mažiausiai 10 sekundžių maišykite sūkurinėje purtyklėje.
6. Dar 5 minutes inkubuokite mėginį kambario temperatūroje.

12.2 Procedūra dekontaminuotiems koncentruotiems skreplių sedimentams

Svarbu. Tyrimas turi būti pradėtas per 2,5 valandos po SR pridėjimo į mėginį arba per 4 valandas, jei yra laikomas 2–8ºC temperatūroje.

Pastaba. Nenaudokite mėginių su aiškiai matomomis maisto ar kitomis kietomis dalelėmis.

Reikalavimai tūriui: skreplių sedimentai paruošti pagal NALC-NaOH (N-acetil-l-cisteino–natrio hidroksidas) metodą, aprašytą Kent ir Kubica[11] ,ir resuspenduoti 67 mM fosfato/H2O buferyje. Po resuspendavimo, Xpert MTB/XDR tyrimui atlikti reikia bent 0,5 ml resuspenduotų sedimentų. Jei tūris mažesnis nei 0,7 ml, atlikite 1-5 mėginių paruošimo etapus. Šiems etapams reikia 3 dalių SR ir 1 dalies sedimentų,
kad būtų gautas adekvatus tūris, reikalingas optimaliam tyrimo veiksmingumui. Jei mėginio tūris yra lygus ar didesnis nei 0,7 ml, į 1 dalį mėginio galite dozuoti 2 dalis SR. Šiame pavyzdyje 1,4 ml SR yra dozuojama į 0,7 ml sedimentų. Bendrą tūrį sudaro 2 dalys SR ir 1 dalis sedimentų.

1. Perkėlimo pipete perkelkite 0,5 ml bendro resuspenduoto mišinio į kūginį mėgintuvėlį užsukamu kamšteliu, pažymėtą mėginio ir (ar) paciento ID.

Pastaba. Jei tyrimas nebus atliekamas iškart, resuspenduotus sedimentus laikykite 2–8 °C temperatūroje. Nelaikykite ilgiau nei 7 dienas.

2. 1,5 ml mėginio reagento (SR) dozuokite į 0,5 ml resuspenduotų sedimentų.
3. Energingai papurtykite 10-20 kartų arba mažiausiai 10 sekundžių maišykite sūkurinėje purtyklėje.

Pastaba. Vienas judesys į priekį ir atgal yra vienas papurtymas.

4. 10 minučių inkubuokite kambario temperatūroje, tuomet mėginį energingai papurtykite 10-20 kartų arba mažiausiai 10 sekundžių maišykite sūkurinėje purtyklėje.
5. Dar 5 minutes inkubuokite mėginį kambario temperatūroje.

12.3 Kasetės paruošimas

Svarbu. Įsitikinkite, kad modulis yra paruoštas kasetės įdėjimui. Tyrimas turi būti pradėtas kaip įmanoma greičiau arba per 2,5 valandos po mėginio su mėginio reagentu įdėjimo į kasetę arba per 4 valandas, laikant 2–8ºC temperatūroje.

Turėkite šias priemones: Xpert kasetė, perkėlimo pipetė (tiekiama) ir tinkamai paimtas ir pažymėtas tiriamasis mėginys.

1. Iš pakuotės išimkite kasetę.
2. Apžiūrėkite, ar kasetė nėra pažeista. Jei kasetė pažeista, jos nenaudokite.
3. Palaukite, kol kasetė pasieks kambario temperatūrą. Kiekvieną Xpert MTB/XDR kasetę pažymėkite mėginio ID. Žr. 3 iliustraciją.

3 iliustracija. Užrašykite ant kasetės šono.

Pastaba. Ant kasetės šono užrašykite ID ar užklijuokite ID lipduką. Neklijuokite lipduko ant kasetės dangtelio ar ant jau esančios 2D brūkšninio kodo etiketės.

4. Atidarykite kasetės dangtelį, tuomet - mėginio konteinerio dangtelį.

5. Naudodami tiekiamą perkėlimo pipetę, iki pipetės žymos įtraukite skysto mėginio. Jei tūrio nepakanka, mėginio netirkite. Žr. 4 iliustraciją.

4 iliustracija. Įtraukite iki pipetės žymos.

6. Iš pipetės mėginį išleiskite lėtai, kad nesusidarytų aerozolis. Žr. 5 iliustraciją.

5 iliustracija. Xpert MTB/XDR tyrimo kasetė

7. Uždarykite kasetės dangtelį.

12.4 Tyrimo vykdymas

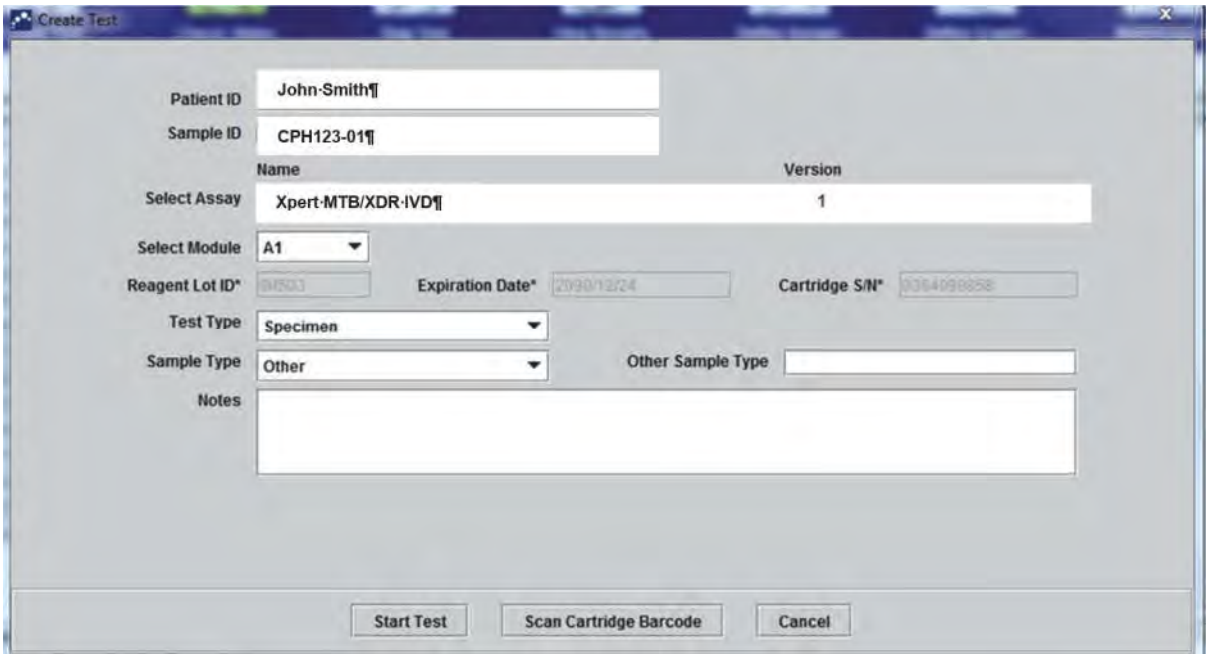
Svarbu **Prieš pradedant vykdyti tyrimą, įsitikinkite, kad Xpert MTB/XDR tyrimo aprašymo failas yra importuotas į programinę įrangą. Šiame skyriuje aprašyti pagrindiniai tyrimo vykdymo etapai. Išsamų aprašymą rasite *GeneXpert Dx sistemos naudotojo vadove.***

Pastaba. Etapai gali skirtis, jei sistemos administratorius pakeitė numatytąją sistemos darbo eigą.

1. Įjunkite GeneXpert instrumentą:
   - Jei naudojate GeneXpert Dx instrumentą, pirmiausia įjunkite instrumentą, tada - kompiuterį. GeneXpert Dx programinė įranga įsijungs automatiškai arba gali prireikti dukart pele spustelėti GeneXpert Dx sparčiosios prieigos piktogramą Windows® darbalaukyje.
2. Naudodami savo naudotojo pavadinimą ir slaptažodį, prisijunkite GeneXpert instrumento sistemos programinėje įrangoje.
3. GeneXpert Dx sistemos lange paspauskite **Create Test**. Atsidarys **Create Test** langas.

4. Nuskenuokite arba įrašykite paciento ar mėginio ID. Įsitikinkite, kad paciento ID įrašėte teisingai. Mėginio ID bus rodomas kairėje **View Results** lango pusėje ir bus susietas su tyrimo rezultatais.
5. Nuskenuokite Xpert MTB/XDR tyrimo kasetės brūkšninį kodą. Pagal brūkšninio kodo informaciją, programinė įranga automatiškai užpildys šių laukelių informaciją: **Reagent Lot ID**, **Cartridge S/N** ir **Expiration Date**. Žr. 6 iliustraciją.

Pastaba. Jei Xpert MTB/XDR kasetės brūkšninio kodo nepavyksta nuskenuoti, tyrimą kartokite naudodami naują kasetę.



6 iliustracija. GX Dx Create Test langas.

6. Paspauskite **Start Test**. Atsidariusioje lentelėje įrašykite savo slaptažodį.
7. GeneXpert Dx instrumentas:
   A. Atidarykite instrumento modulio dureles su žybsinčia žalia lempute ir įdėkite kasetę.
   B. Uždarykite dureles. Prasidėjus tyrimui, žalia leputė nustos žybsėti. Pasibaigus tyrimui, lemputė nebešvies.
   C. Palaukite kol sistema atrakins dureles, atidarykite jas ir išimkite kasetę.
8. Panaudotas kasetes išmeskite į atitinkamą mėginių konteinerį laikydamiesi savo įstaigos standartinės praktikos.

13 Rezultatų peržiūra ir spausdinimas

Šiame skyriuje aprašyti pagrindiniai rezultatų peržiūros ir spausdinimo etapai. Išsamų aprašymą rasite *GeneXpert Dx sistemos naudotojo vadove.*

- Norėdami peržiūrėti rezultatus, paspauskite **View Results**.
- Pasibaigus tyrimo vykdymui, **View Results** lange paspauskite lementą **Report**. galėsite peržiūrėti rezultatus ir (ar) sugeneruoti ataskaitos PDF failą.

14 Kokybės kontrolė

14.1 Integruotos kokybės kontrolės

CONTROL

Kiekviename tyrime yra integruota mėginio apdorojimo kontrolė (SPC) ir mėgintuvėlio patikros kontrolė (PCC).

- **Mėginio apdorojimo kontrolė (SPC)**—patikrina, ar mėginio apdorojimas yra tinkamas. Be to, ši kontrolė aptinka su mėginiu susijusį tikro laiko PGR tyrimo inhibavimą, užtikrina tinkamas PGR sąlygas (temperatūrą ir laiką), reikalingas amplifikacijai, patikrina, ar PGR reagentai yra funkcionalūs. SPC turi būti teigiama neigiamame mėginyje ir gali būti neigiama arba teigiama teigiamame mėginyje. SPC yra sėkminga, jei atitinka patvirtintus priimtinumo kriterijus.
- **Mėgintuvėlio patikros kontrolė (PCC)**—prieš pradedant PGR reakciją, GeneXpert sistema matuoja fluorescencijos signalą iš mėgintuvėlių ir patikrina rutuliukų rehidraciją, reakcijos mėgintuvėlio užpildymą, mėgintuvėlio integralumą ir dažų stabilumą. PCC yra sėkminga, jei atitinka patvirtintus priimtinumo kriterijus.
- **Mėginio tūrio adekvatumo (SVA) kontrolė**—prieš mėginio apdorojimą, GeneXpert sistema išmatuoja, ar mėginio tūris mėginio kameroje yra adekvatus. Jei SVA kontrolė yra nesėkminga, tai reiškia, jog mėginio tūris mėginio kameroje nėra adekvatus.

15 Rezultatų interpretavimas

GeneXpert instrumento sistema rezultatus interpretuoja pagal išmatuotus fluorescencijos signalus ir lydymosi temperatūros (*Tm*) vertes. Mutacijas ir laukinio tipo sekos GeneXpert sistemoje yra aptinkamos naudojant *Tm* vertes.
Jautrumo ar atsparumo nustatymas atitinkamai kiekvienai analitei priklauso nuo to, ar *Tm* vertės patenka į laukinio tipo ar mutacijų ribas. Teigiamas Xpert MTB/XDR tyrimo rezultatas gali būti **MTB DETECTED** (MTB aptikta), o visi atsparumo taikiniai **NOT DETECTED** (neaptikta) ar **MTB DETECTED** (MTB aptikta) ir vienas ar daugiau atsparumo taikinių **DETECTED** (aptikta),ar **MTB DETECTED** (MTB aptikta) ir (ar) vienas ar daugiau atsparumo taikinių **INDETERMINATE** (nenustatyta). Galimi kiekvieno taikinio rezultatai pateikti 2 lentelėje.

2 lentelė. Galimi Xpert MTB/XDR tyrimo rezultatai kiekvienam taikiniui

Vaistų klasė	Rezultatas
NETAIKOMA	NEGALIOJANTIS/KLAIDA/NĖRA REZULTATO
	MTB APTIKTA
	MTB NEAPTIKTA
Izoniazidas	Žemas atsparumas INH APTIKTAS
	Atsparumas INH APTIKTAS
	Atsparumas INH NEAPTIKTAS
	Atsparumas INH NENUSTATYTAS
Fluorchinolonas	Žemas atsparumas FLQ APTIKTAS
	Atsparumas FLQ APTIKTAS
	Atsparumas FLQ NEAPTIKTAS
	Atsparumas FLQ NENUSTATYTAS
Amikacinas	Atsparumas AMK APTIKTAS
	Atsparumas AMK NEAPTIKTAS
	Atsparumas AMK NENUSTATYTAS
Kanamicinas	Atsparumas KAN APTIKTAS
	Atsparumas AMK NEAPTIKTAS
	Atsparumas KAN NENUSTATYTAS

2 lentelė. Galimi Xpert MTB/XDR tyrimo rezultatai kiekvienam taikiniui (tęsinys)

Vaistų klasė	Rezultatas
Kapreomicinas	Atsparumas CAP APTIKTAS
	Atsparumas CAP NEAPTIKTAS
	Atsparumas CAP NENUSTATYTAS
Etionamidas[a]	Atsparumas ETH APTIKTAS
	Atsparumas ETH NEAPTIKTAS

a. Atsparumas etionamidui nebus pateikiamas kaip nenustatytas.

3 lentelėje pateikti Xpert MTB/XDR tyrimo genų taikiniai ir kodono regionai nei nukleotidai kiekvienam tiriamam genui, siekiant identifikuoti atsparumą vaistams.

3 lentelė. Atsparumą vaistams nusakantys taikinio regionai

Vaistai	Geno taikinys	Kodono regionas	Nukleotidas
Izoniazidas	*inhA* promotorius	Netaikoma	nuo -1 iki -32, tarpgeninis
	katG	311-319	939-957
	fabG1	199-210	597-630
	oxyR- ahpC tarpgeninis regionas	Netaikoma	nuo -5 iki -50 tarpgeninis (arba nuo -47 iki -92)[12,13]
Etionamidas	*inhA* promotorius[a]	Netaikoma	nuo -1 iki -32, tarpgeninis
Fluorchinolonas	*gyrA*	87-95	261-285
	gyrB	531-544 (ar 493-505)[12,14]	1596-1632
Amikacinas, kanamicinas, kapreomicinas	*rrs*	Netaikoma	1396-1417
	eis promotorius	Netaikoma	nuo -6 iki -42, tarpgeninis

a. Mutacijų nebuvimas inhA promotoriaus regione neatmeta atsparumo ETH galimybės. Mutacijos su atsparumu ETH yra registruotos genominiuose regionuose, kurie nėra Xpert MTB/XDR tyrimo taikiniai.[15]

Galimi rezultatai ir atitinkama jų interpretacija pateikta 4 lentelėje. 7 - 15 iliustracijos yra galimų Xpert MTB/XDR tyrimo rezultatų pavyzdžiai.

4 lentelė. Xpert MTB/XDR tyrimo rezultatų ir jų interpretavimo pavyzdžiai.

Rezultatas	Interpretacija
MTB DETECTED; **INH Resistance NOT DETECTED** **FLQ Resistance NOT DETECTED** **AMK Resistance NOT DETECTED** **KAN Resistance NOT DETECTED** **CAP Resistance NOT DETECTED** **ETH Resistance NOT DETECTED**	MTB taikinys yra mėginyje: • Mutacijos, lemiančios atsparumą INH, FLQs, AMK, KAN, CAP ar ETH, neaptiktos. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.

4 lentelė. Xpert MTB/XDR tyrimo rezultatų ir jų interpretavimo pavyzdžiai (tęsinys).

Rezultatas	Interpretacija
MTB DETECTED; **INH Resistance DETECTED** **FLQ Resistance DETECTED** **AMK Resistance DETECTED** **KAN Resistance DETECTED** **CAP Resistance DETECTED** **ETH Resistance DETECTED**	MTB taikinys yra mėginyje: • Mutacijos, lemiančios atsparumą INH, yra aptiktos viename ar daugiau šių genų: *katG*, *fabG1*, *oxyR-ahpC* tarpgeniniame regione ir *inhA* promotoriuje. • Mutacijos, lemiančios atsparumą FLQ, yra aptiktos viename ar daugiau šių genų: *gyrA* ir *gyrB* atsparumą chinolonui nusakančiuose regionuose (QRDR). • Mutacijos, lemiančios atsparumą AMK, yra aptiktos viename ar daugiau šių genų: *rrs* gene ir *eis* promotoriuje. • Mutacijos, lemiančios atsparumą KAN, yra aptiktos viename ar daugiau šių genų: *rrs* gene ir *eis* promotoriuje. • Mutacijos, lemiančios atsparumą CAP, yra aptiktos šiame gene: *rrs* gene. • Mutacijos, lemiančios atsparumą ETH, yra aptiktos šiame gene: *inhA* promotoriuje. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.
MTB DETECTED; **INH Resistance DETECTED** **FLQ Resistance NOT DETECTED** **AMK Resistance NOT DETECTED** **KAN Resistance NOT DETECTED** **CAP Resistance NOT DETECTED** **ETH Resistance NOT DETECTED**	MTB taikinys yra mėginyje: • Mutacijos, lemiančios atsparumą INH, FLQs, AMK, KAN, CAP ar ETH, neaptiktos. • Mutacijos, lemiančios atsparumą INH, yra aptiktos viename ar daugiau šių genų: *inhA* promotoriuje, *katG*, *fabG1* ir *oxyR-ahpC* tarpgeniniame regione. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.
MTB DETECTED; **INH Resistance DETECTED** **FLQ Resistance INDETERMINATE** **AMK Resistance NOT DETECTED** **KAN Resistance NOT DETECTED** **CAP Resistance NOT DETECTED** **ETH Resistance NOT DETECTED**	MTB taikinys yra mėginyje: • Mutacijos, lemiančios atsparumą AMK, KAN, CAP ir ETH neaptiktos. • Mutacijos, lemiančios atsparumą INH, yra aptiktos viename ar daugiau šių genų: *inhA* promotoriuje, *katG*, *fabG1* ir *oxyR-ahpC* tarpgeniniame regione. • Mutacijos, lemiančios atsparumą FLQ, negalėjo būti nustatytos, nes buvo aptiktas tik vienas WT Tm iš vieno ar daugiau zondų ir trūksta Tms iš vieno ar daugiau zondų vienam ar daugiau šių genų taikinių: *gyrA ar gyrB*. Arba nėra Tm iš zondų *gyrA* ir *gyrB* genų taikiniams. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.
MTB DETECTED; **Low INH Resistance DETECTED** **FLQ Resistance NOT DETECTED** **AMK Resistance NOT DETECTED** **KAN Resistance NOT DETECTED** **CAP Resistance NOT DETECTED** **ETH Resistance DETECTED**	MTB taikinys yra mėginyje: • Mutacijos, lemiančios atsparumą FLQ, AMK, KAN ir CAP neaptiktos. • Mutacijos, lemiančios žemą atsparumą INH, yra aptiktos šiame gene: *inhA* promotoriaus regione. • Mutacijos, lemiančios atsparumą ETH, yra aptiktos šiame gene: *inhA* promotoriaus regione. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.

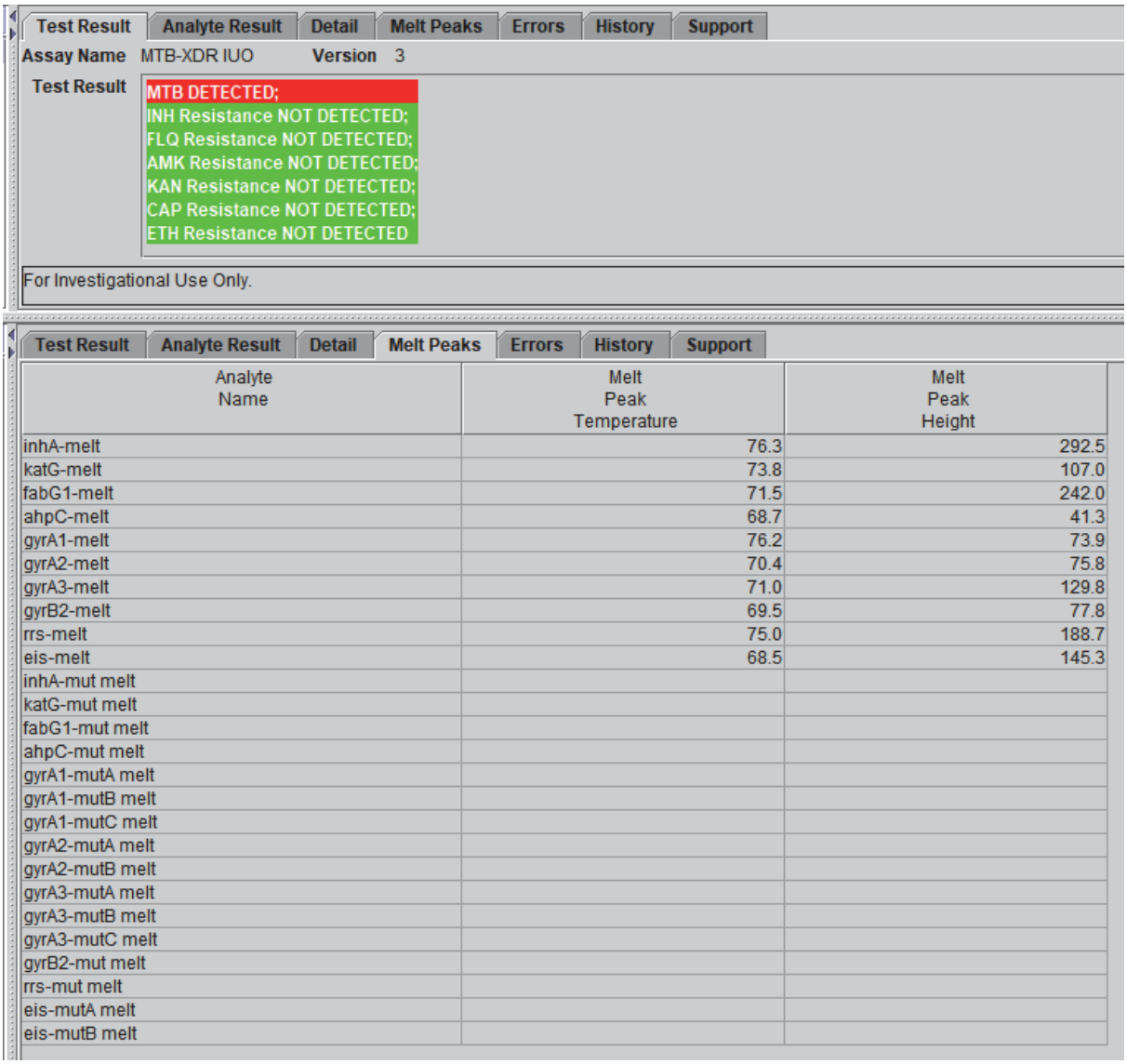
4 lentelė. Xpert MTB/XDR tyrimo rezultatų ir jų interpretavimo pavyzdžiai (tęsinys).

Rezultatas	Interpretacija
MTB DETECTED; **INH Resistance NOT DETECTED** **Low FLQ Resistance DETECTED** **AMK Resistance NOT DETECTED** **KAN Resistance NOT DETECTED** **CAP Resistance NOT DETECTED** **ETH Resistance NOT DETECTED**	MTB taikinys yra mėginyje; aptiktas žemo lygio atsparumas FLQ: • Mutacijos, lemiančios atsparumą INH, AMK, KAN, CAP ir ETH neaptiktos. • Mutacijos, lemiančios žemą atsparumą FLQ, yra aptiktos šiame gene: *gyrA*. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.
MTB DETECTED; **INH Resistance DETECTED** **FLQ Resistance NOT DETECTED** **AMK Resistance DETECTED** **KAN Resistance DETECTED** **CAP Resistance DETECTED** **ETH Resistance NOT DETECTED**	MTB taikinys yra mėginyje: • Mutacijos, lemiančios atsparmą FLQ ir ETH neaptiktos. • Mutacijos, lemiančios atsparumą INH, yra aptiktos viename ar daugiau šių genų: *katG*, *fabG1*, *oxyR-aphC.* • Mutacijos, lemiančios atsparumą AMK, yra aptiktos viename ar daugiau šių genų: *rrs* gene, *eis* promotoriuje. • Mutacijos, lemiančios atsparumą KAN, yra aptiktos viename ar daugiau šių genų: *rrs* gene, *eis* promotoriuje. • Mutacijos, lemiančios atsparumą CAP, yra aptiktos šiame gene: *rrs* gene. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.
MTB DETECTED; **INH Resistance DETECTED** **Low FLQ Resistance DETECTED** **AMK Resistance NOT DETECTED** **KAN Resistance DETECTED** **CAP Resistance NOT DETECTED** **ETH Resistance NOT DETECTED**	MTB taikinys yra mėginyje: • Mutacijos, lemiančios atsparumą AMK, CAP ir ETH neaptiktos. • Mutacijos, lemiančios atsparumą INH, yra aptiktos viename ar daugiau šių genų: *katG*, *fabG1*, *oxyR-ahpC* tarpgeniniame regione ir *inhA* promotoriuje. • Mutacijos, lemiančios žemą atsparumą FLQ, yra aptiktos šiame gene: *gyrA*. • Mutacijos, lemiančios atsparumą KAN, yra aptiktos šiame gene: *eis* promotoriaus regione. • SPC: netaikoma. SPC signalas nėra reikalingas, kadangi MTB amplifikacija gali būti atlikta su šia kontrole. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.
MTB NOT DETECTED	MTB taikinys mėginyje neaptiktas: • SPC: SĖKMINGA. SPC atitinka priimtinumo kriterijus. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.
INVALID	MTB buvimas ar nebuvimas negali būti nustatytas. SPC neatitinka priimtinumo kriterijų, mėginys nebuvo tinkamai apdorotas arba PGR buvo inhibuota. Kartokite tyrimą. Skaitykite šio dokumento skyrių „Pakartotinio tyrimo procedūra“. • MTB: NEGALIOJANTIS. MTB DNR buvimas ar nebuvimas negali būti nustatytas. • SPC: NESĖKMINGA. MTB taikinio rezultatas neigiamas, o SPC ciklo slenkstinė vertė (Ct) nepatenka į numatytas ribas. • Mėgintuvėlio patikra: SĖKMINGA. Mėgintuvėlio patikra atlikta sėkmingai.

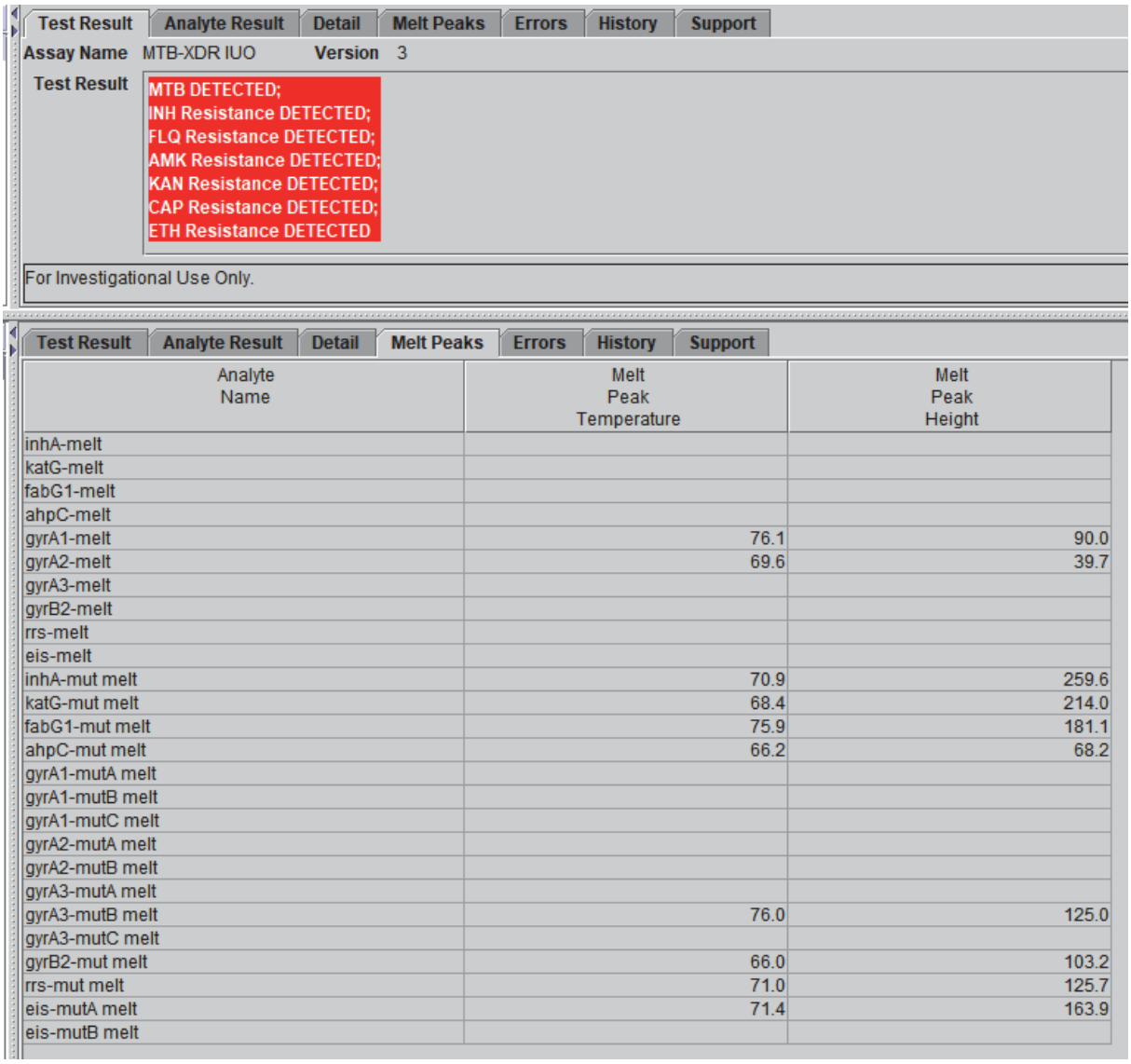
4 lentelė. Xpert MTB/XDR tyrimo rezultatų ir jų interpretavimo pavyzdžiai (tęsinys).

Rezultatas	Interpretacija
ERROR	MTB buvimas ar nebuvimas negali būti nustatytas. Kartokite tyrimą. Skaitykite šio dokumento skyrių „Pakartotinio tyrimo procedūra“. • MTB: NĖRA REZULTATO. • SPC: NĖRA REZULTATO. • Mėgintuvėlio patikra: NESĖKMINGA. Visi ar vienas mėgintuvėlio patikros rezultatas nesėkmingas. **Pastaba.** Jei mėgintuvėlio patikra yra sėkminga, klaidą galėjo sukelti sistemos komponento gedimas, operatoriaus klaida ar kasetės integralumo problemos.
NO RESULT	MTB buvimas ar nebuvimas negali būti nustatytas. Kartokite tyrimą. Skaitykite šio dokumento skyrių „Pakartotinio tyrimo procedūra“. „NO RESULT“ reiškia, kad buvo surinkta nepakankamai duomenų. Pavyzdžiui, proceso vykdymo metu operatorius sustabdė tyrimą. • MTB: NĖRA REZULTATO. • SPC: NĖRA REZULTATO. • Mėgintuvėlio patikra: netaikoma.

Pastaba. Toliau pateikiamose iliustracijose yra vaizduojami rezultatai, įskaitant lydymosi piko ąselės duomenis, kurių yra tikimasi vykdant Xpert MTB/XDR tyrimo metu GeneXpert Dx „Detailed User View“ lange. Pavaizduotos ne visos įmanomos rezultatų kombinacijos.

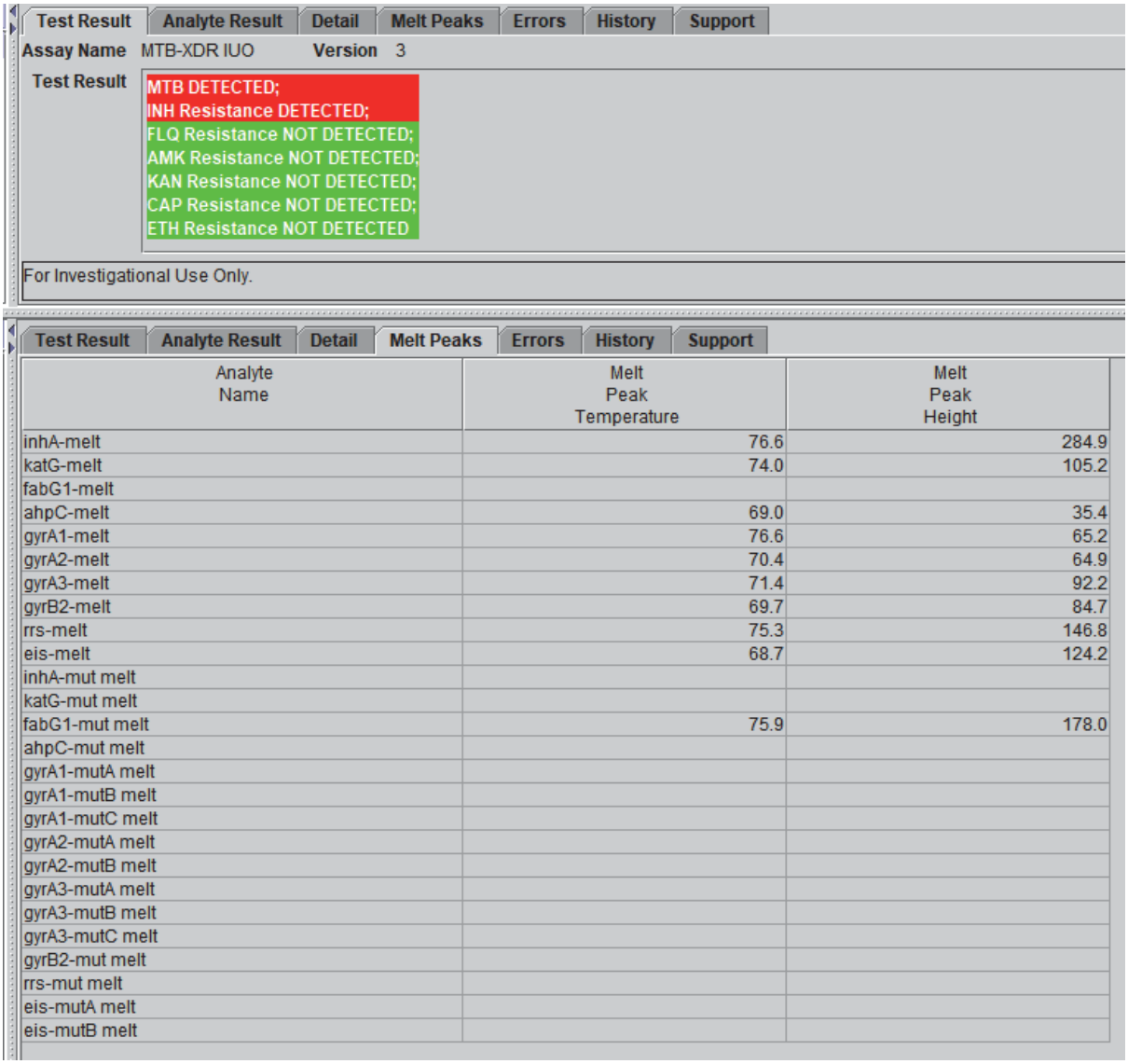


7 iliustracija. MTB APTIKTA; atsparumas INH, FLQ, AMK, KAN, CAP ir ETH NEAPTIKTAS



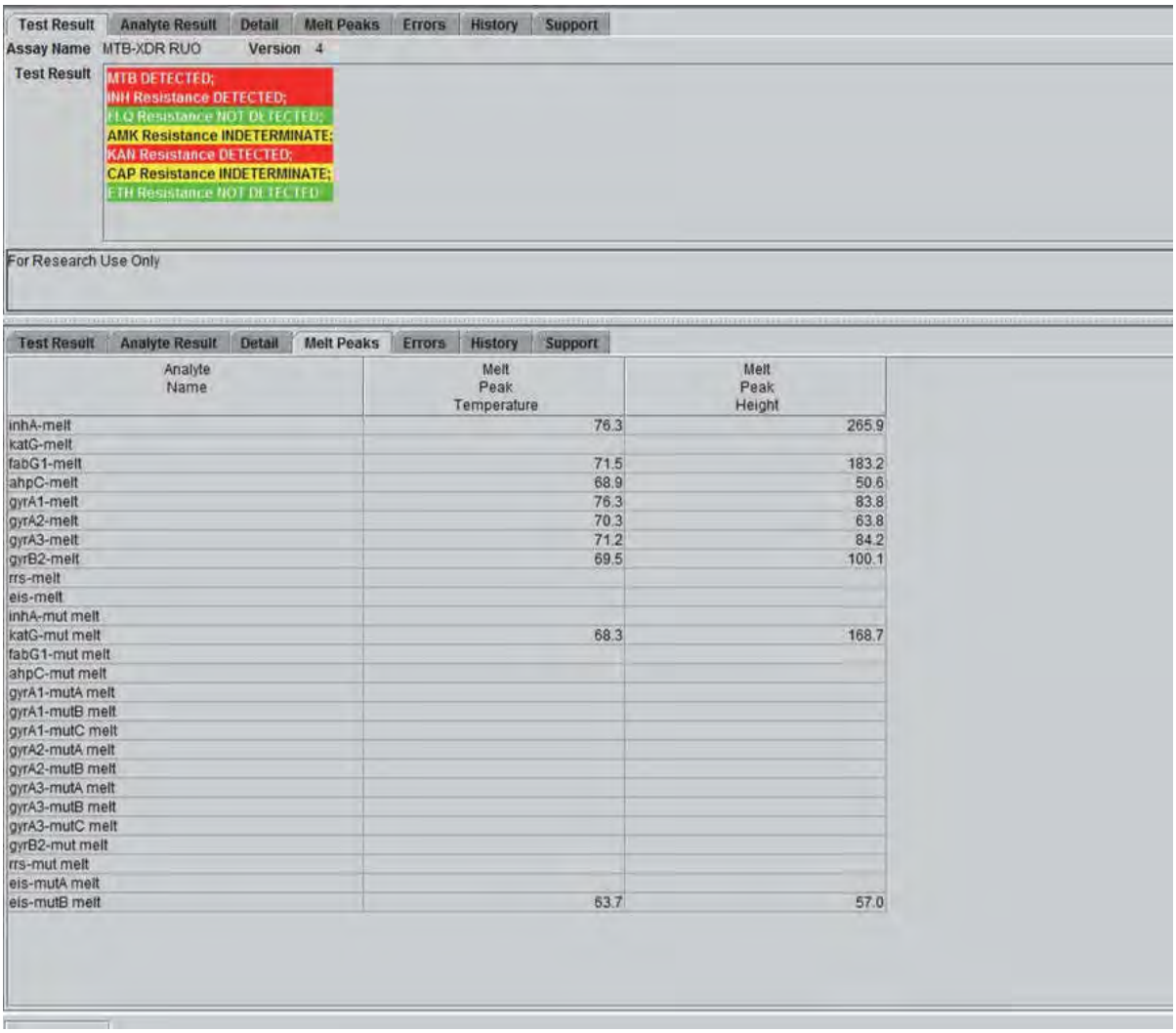
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt		
katG-melt		
fabG1-melt		
ahpC-melt		
gyrA1-melt	76.1	90.0
gyrA2-melt	69.6	39.7
gyrA3-melt		
gyrB2-melt		
rrs-melt		
eis-melt		
inhA-mut melt	70.9	259.6
katG-mut melt	68.4	214.0
fabG1-mut melt	75.9	181.1
ahpC-mut melt	66.2	68.2
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt	76.0	125.0
gyrA3-mutC melt		
gyrB2-mut melt	66.0	103.2
rrs-mut melt	71.0	125.7
eis-mutA melt	71.4	163.9
eis-mutB melt		

8 iliustracija. MTB APTIKTA; atsparumas INH, FLQ, AMK, KAN, CAP ir ETH APTIKTAS



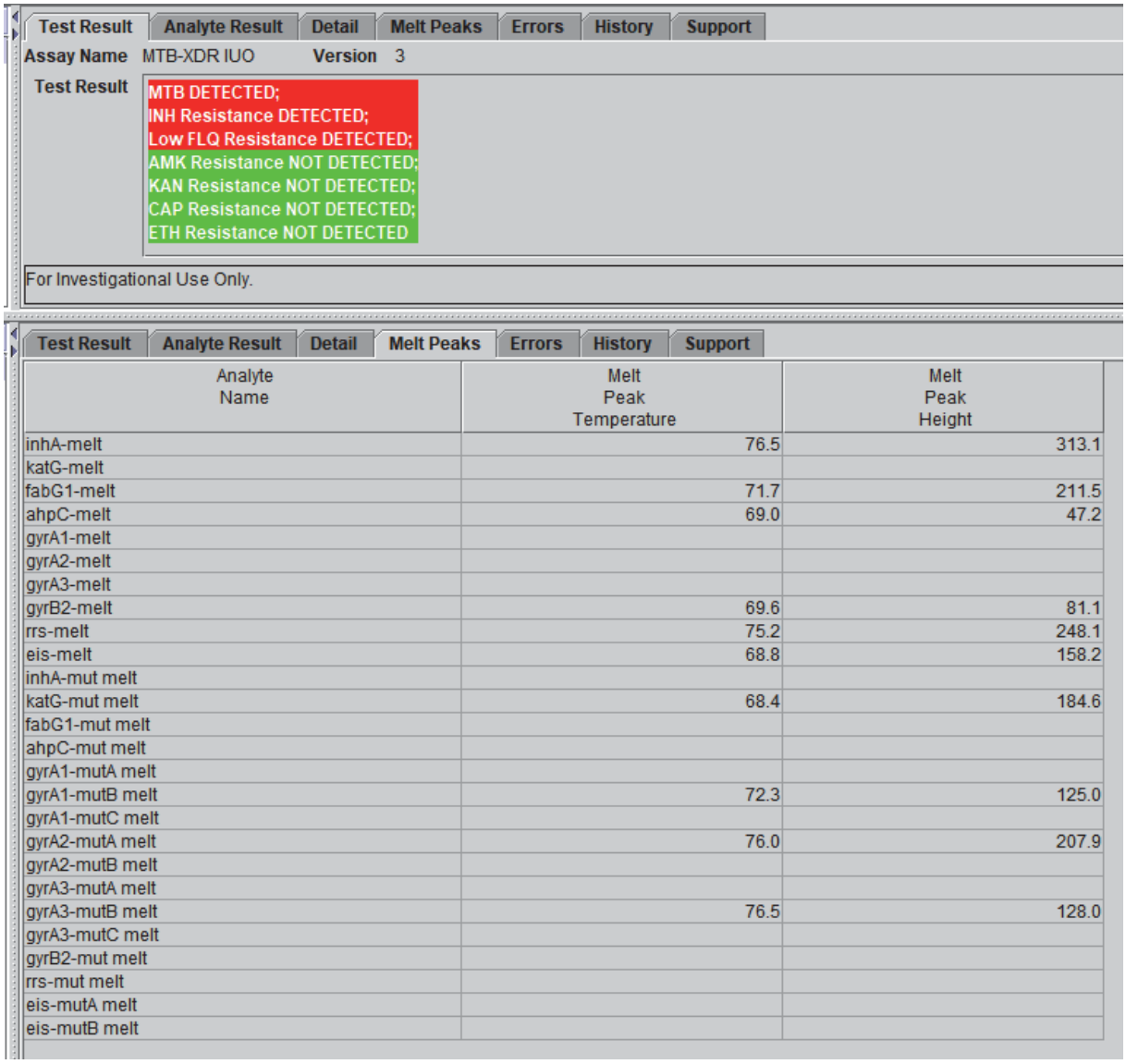
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.6	284.9
katG-melt	74.0	105.2
fabG1-melt		
ahpC-melt	69.0	35.4
gyrA1-melt	76.6	65.2
gyrA2-melt	70.4	64.9
gyrA3-melt	71.4	92.2
gyrB2-melt	69.7	84.7
rrs-melt	75.3	146.8
eis-melt	68.7	124.2
inhA-mut melt		
katG-mut melt		
fabG1-mut melt	75.9	178.0
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt		

9 iliustracija. MTB APTIKTA; atsparumas INH APTIKTAS



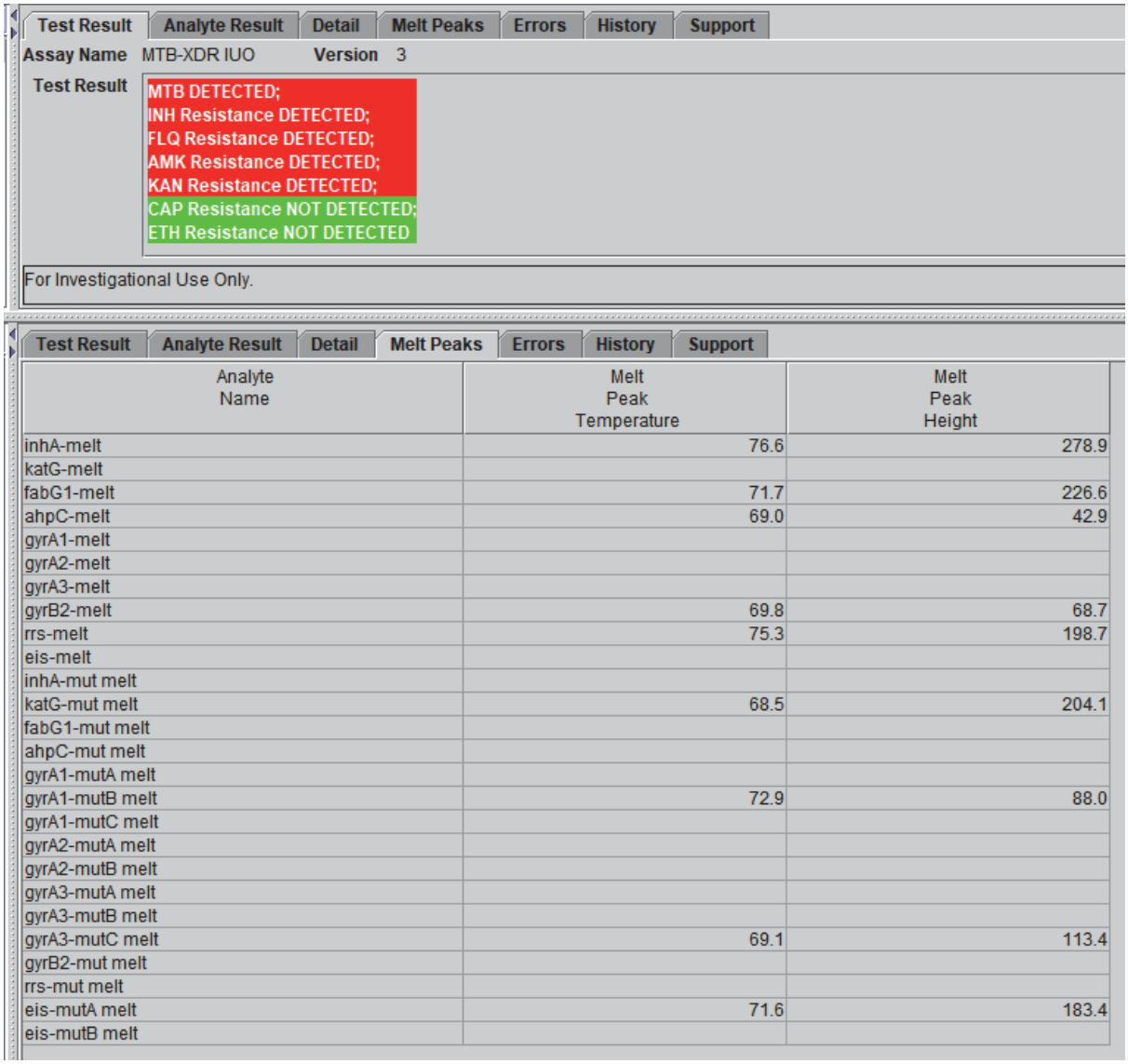
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.3	265.9
katG-melt		
fabG1-melt	71.5	183.2
ahpC-melt	68.9	50.6
gyrA1-melt	76.3	83.8
gyrA2-melt	70.3	63.8
gyrA3-melt	71.2	84.2
gyrB2-melt	69.5	100.1
rrs-melt		
eis-melt		
inhA-mut melt		
katG-mut melt	68.3	168.7
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt	63.7	57.0

10 iliustracija. MTB APTIKTA; atsparumas INH ir KAN APTIKTAS; AMK ir CAP NENUSTATYTA



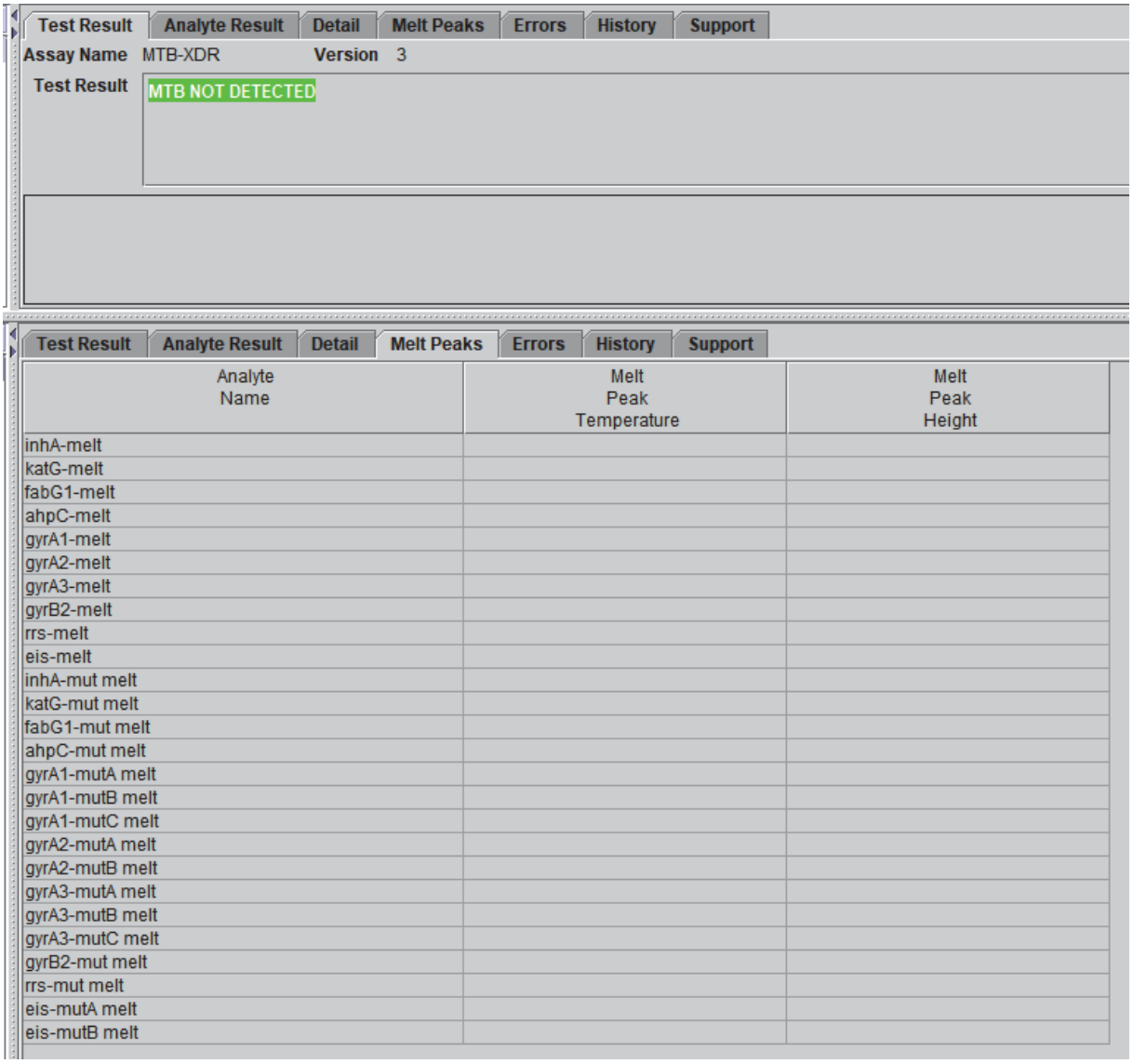
Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.5	313.1
katG-melt		
fabG1-melt	71.7	211.5
ahpC-melt	69.0	47.2
gyrA1-melt		
gyrA2-melt		
gyrA3-melt		
gyrB2-melt	69.6	81.1
rrs-melt	75.2	248.1
eis-melt	68.8	158.2
inhA-mut melt		
katG-mut melt	68.4	184.6
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt	72.3	125.0
gyrA1-mutC melt		
gyrA2-mutA melt	76.0	207.9
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt	76.5	128.0
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt		

11 iliustracija. MTB APTIKTA; atsparumas INH ir žemas atsparumas FLQ APTIKTAS

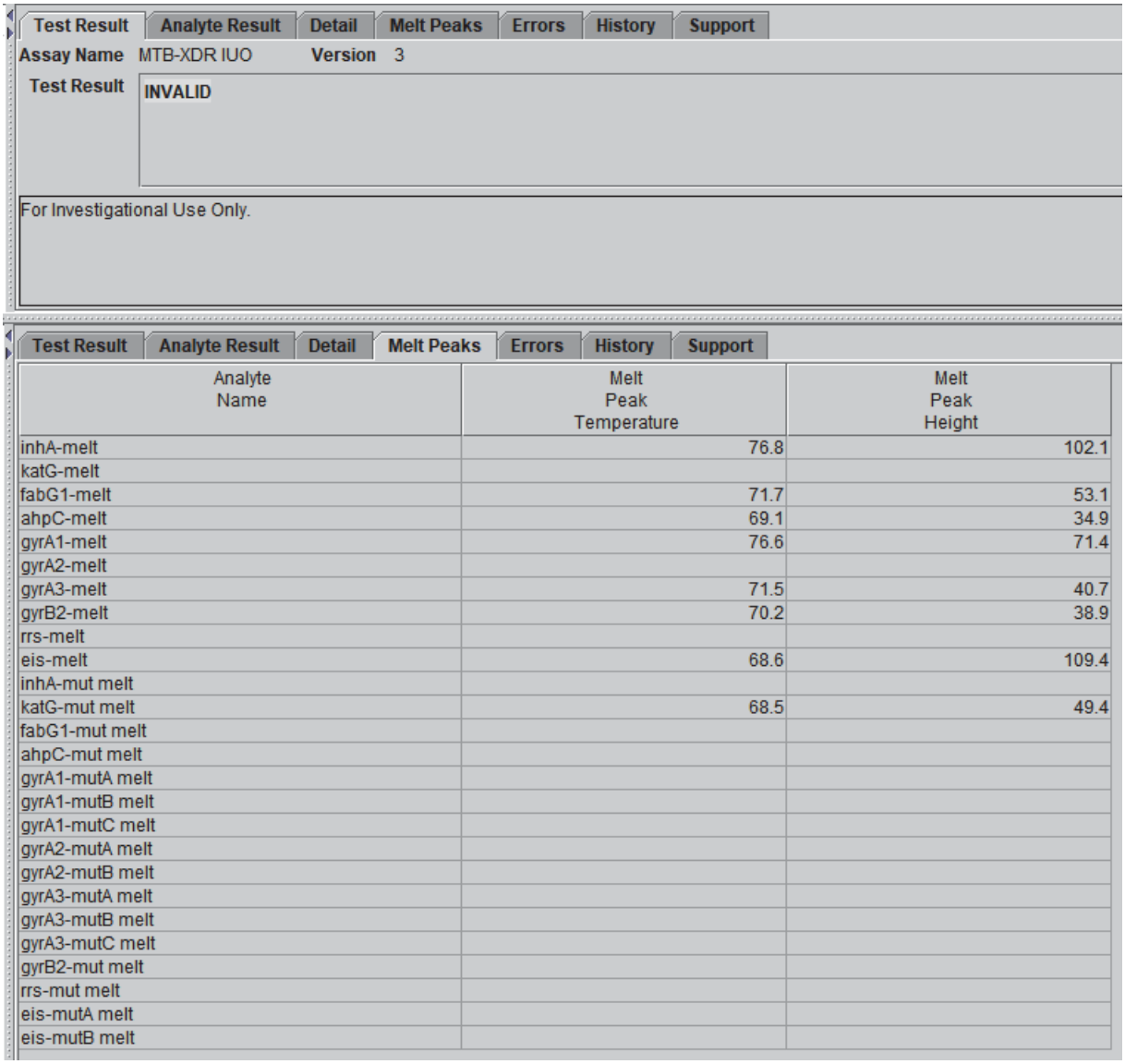


Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.6	278.9
katG-melt		
fabG1-melt	71.7	226.6
ahpC-melt	69.0	42.9
gyrA1-melt		
gyrA2-melt		
gyrA3-melt		
gyrB2-melt	69.8	68.7
rrs-melt	75.3	198.7
eis-melt		
inhA-mut melt		
katG-mut melt	68.5	204.1
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt	72.9	88.0
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt	69.1	113.4
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt	71.6	183.4
eis-mutB melt		

12 iliustracija. MTB APTIKTA; atsparumas INH, FLQ, AMK ir KAN APTIKTAS

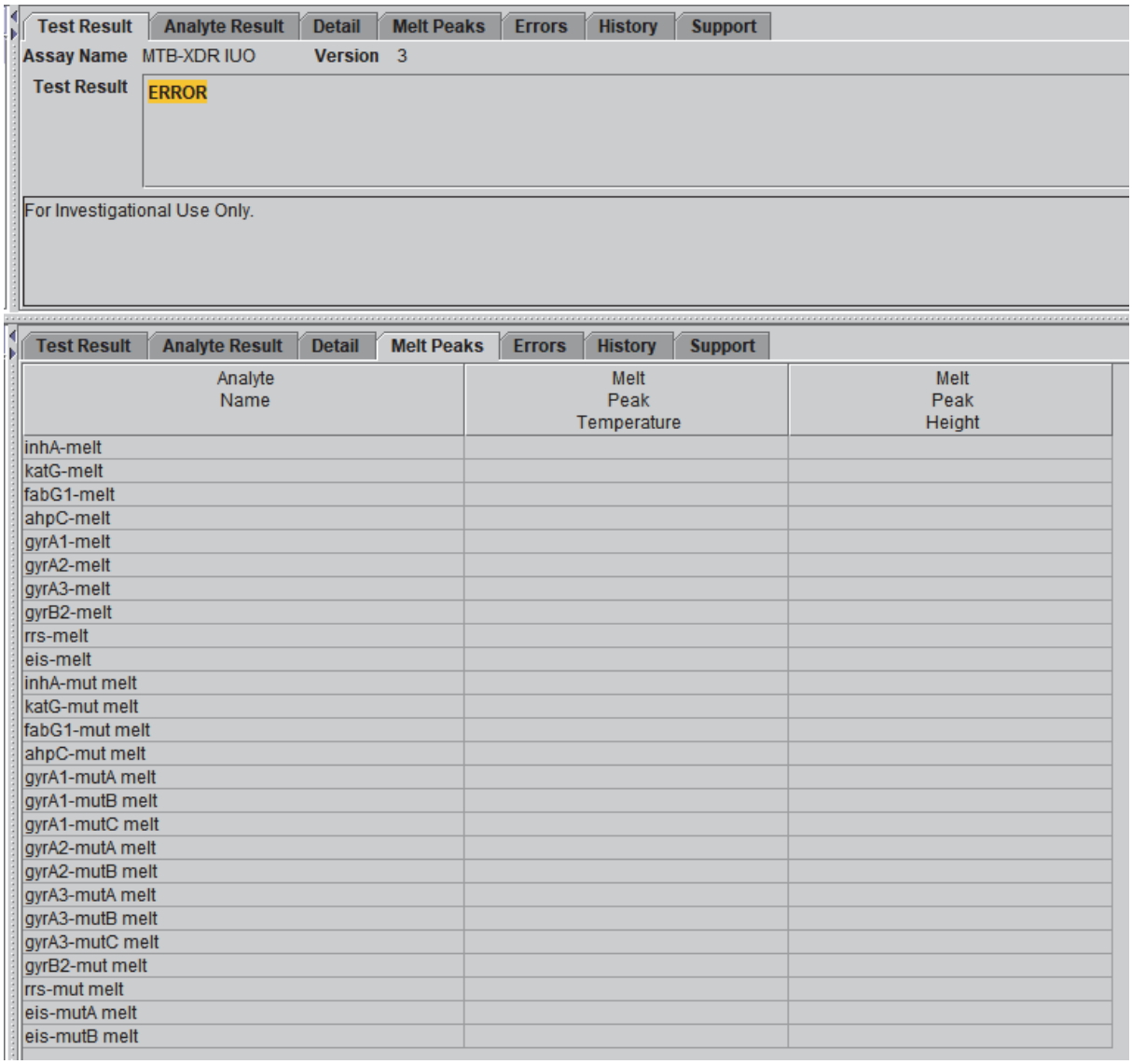


13 iliustracija. MTB NEAPTIKTA



Analyte Name	Melt Peak Temperature	Melt Peak Height
inhA-melt	76.8	102.1
katG-melt		
fabG1-melt	71.7	53.1
ahpC-melt	69.1	34.9
gyrA1-melt	76.6	71.4
gyrA2-melt		
gyrA3-melt	71.5	40.7
gyrB2-melt	70.2	38.9
rrs-melt		
eis-melt	68.6	109.4
inhA-mut melt		
katG-mut melt	68.5	49.4
fabG1-mut melt		
ahpC-mut melt		
gyrA1-mutA melt		
gyrA1-mutB melt		
gyrA1-mutC melt		
gyrA2-mutA melt		
gyrA2-mutB melt		
gyrA3-mutA melt		
gyrA3-mutB melt		
gyrA3-mutC melt		
gyrB2-mut melt		
rrs-mut melt		
eis-mutA melt		
eis-mutB melt		

14 iliustracija. NEGALIOJANTIS



15 iliustracija. KLAIDA

16 Pakartotinis tyrimas

16.1 Tyrimo kartojimo priežastys

Tyrimą kartokite laikydamiesi 16.2 skyriuje pateiktų instrukcijų, jei gavote vieną šių tyrimų rezultatų:

- **INVALID** (negaliojantis) rezultatas reiškia, kad SPC buvo nesėkminga. Netinkamai apdorotas mėginys, inhibuota PGR arba netinkamai paimtas mėginys.
- **ERROR** rezultatas gali būti gautas (bet neapsiribojant tuo) dėl nesėkmingos mėgintuvėlio patikros arba dėl viršytos maksimalaus slėgio ribos.
- **NO RESULT** reiškia, kad buvo surinkta nepakankamai duomenų. Pavyzdžiui, proceso vykdymo metu operatorius sustabdė tyrimą arba nutrūko elektros tiekimas.
- **INDETERMINATE** rezultatas reiškia, kad, remiantis tyrimo algoritmu, atsparumas nurodytam vaistui negali būti tiksliai įvertintas (žr. skyrių „Apribojimai“). Pakartotinį tyrimą atliekant su kitu mėginiu, skirtingas rezultatas gali būti gautas arba negautas.

16.2 Pakartotinio tyrimo procedūra

Tyrimą kartokite naudodami naują kasetę (kasetės nenaudokite pakartotinai). Jei turite likusio skreplių mėginio (turėtų būti ≥1,0 ml) ar skiestų sedimentų (turėtų būti ≥0,5 ml), prieš tyrimą, skreplių dekontaminavimui ir skystinimui visuomet naudokite naują SR. Laikykitės mėginio apdorojimo instrukcijų, pateiktų 12.1 skyriuje „Procedūra neapdorotų skreplių mėginiams“ ar 12.2 skyriuje „Procedūra dekontaminuotiems koncentruotiems skreplių sedimentams“.

Jei turite pakankamai SR apdoroto mėginio, kuris buvo laikomas ne ilgiau nei 2,5 valandos iki 35 °C temperatūroje arba ne ilgiau nei 4 valandas 2–8 °C temperatūroje po pirminio SR pridėjimo į mėginį, SR apdoroto mėginio likutis gali būti tiriamas naudojant naują kasetę. Pakartotinio tyrimo metu visuomet naudokite naują kasetę, o tyrimą pradėkite per 30 minučių po apdoroto mėginio įdėjimo į kasetę. Žr. 12.3 skyrių „Kasetės paruošimas“.

17 Apribojimai

- Xpert MTB/XDR tyrimo veiksmingumas buvo patvirtintas naudojant procedūras, pateiktas šiame pakuotės aprašyme. XDR tyrimo procedūros modifikacijos turi būti interpretuojamos kartu su kitais turimais laboratoriniais ir klinikiniais duomenimis.
- Xpert MTB/XDR tyrimo veiksmingumas priklauso nuo operatoriaus įgūdžių ir tyrimo procedūros laikymosi. Bet kokios procedūros klaidos gali iššaukti klaidingai teigiamų ar neigiamų rezultatų gavimą. Visi prietaisą naudojantys operatoriai turi būti tinkamai apmokyti naudotis prietaisu bei atlikti tyrimą.
- Kadangi MTB komplekso DNR aptikimas priklauso nuo organizmų, esančių mėginyje, rezultatų patikimumas priklauso nuo tinkamo mėginio paėmimo, paruošimo ir laikymo. Klaidingi rezultatai gali atsirasti dėl netinkamo mėginio surinkimo, mėginio surinkimo procedūros nesilaikymo, netinkamo mėginio paruošimo ar laikymo, technikinių klaidų, mėginių sumaišymo arba nepakankamos pradinės medžiagos koncentracijos. Norint išvengti klaidingų rezultatų, būtina laikytis šiame pakuotės aprašyme pateiktų instrukcijų.
- Tyrimo rezultatus gali paveikti anksčiau taikytas ar taikomas gydymas antibiotikais. Todėl, ar gydymas sėkmingas ar nesėkmingas, negali būti vertinamas naudojant šį tyrimą, kadangi DNR gali išlikti ir po tuberkuliozės gydymo.
- Teigiamas tyrimo rezultatas nebūtinai indikuoja apie gyvybingų organizmų buvimą. Tačiau tai leidžia įtarti MTB komplekso DNR buvimą, įskaitant mutacijas, lemiančias atsparumą INH, FLQ, AMK, KAN, CAP ir ETH.
- Mutacijos ar polimorfizmai pradmenyse ar mėgintuvėlio surišamuosiuose regionuose gali įtakoti naujų ar nežinomų XDR-MTB padermių aptikimą ir duoti klaidingai vaistams jautrų rezultatą.
- Xpert MTB/XDR tyrimas nepatvirtina jautrumo INH, FLQ, AMK, KAN, CAP ir ETH, nes gali egzistuoti kiti, tyrimu nenustatyti atsparumo mechanizmai, susiję su klinikinio atsako į gydymą nebuvimu.
- Kraujo, smegenų skysčio, skrandžio aspirato, išmatų, audinių, šlapimo mėginiai nebuvo vertinami su Xpert MTB/XDR tyrimu.
- Nors indukuotų skreplių mėginiai nebuvo įtraukti į klinikinio Xpert MTB/XDR tyrimo veiksmingumo vertinimą, izotoniniai ar hipertoniniai tirpalai, bronchus plečiantys vaistai bei inhaliuojami bronchus plečiantys vaistai, dažnai naudojami indukuotų skreplių mėginių paėmimui, buvo ištirti ir patvirtinti kaip neinterferuojantys tyrimo. Indukcija druskos tirpalo garais gali įtakoti nepakankamą atstatytų organizmų kiekį ir neigiamai paveikti *M. tuberculosis* aptikimą.
- Xpert MTB/XDR tyrimo veiksmingumo vertinime naudoti koncentruoti skreplių sedimentai buvo paruošti naudojant Kent ir Kubica NALC-NaOH metodą[11]. Kitų sedimentų paruošimo metodų naudojimas gali neigiamai paveikti tyrimo veiksmingumą.
- Neigiamas rezultatas neatmeta MTB komplekso DNR izoliacijos skreplių mėginyje galimybės. Xpert MTB/ XDR tyrimas turi būti naudojamas kartu su mikobakterijų kultūros auginimu dėl klaidingai neigiamų rezultatų rizikos ir organizmų atkūrimo tolesniam charakterizavimo ir jautrumo ištyrimui.
- Manoma, kad mėginiuose, ištirtuose su Xpert MTB/RIF Ultra tyrimu, kurių rezultatas „MTB Trace DETECTED“ (MTB pėdsakas APTIKTAS), koncentracija yra žemiau MTB/XDR tyrimo aptikimo ribos ir jų nerekomenduojama tirti Xpert MTB/XDR tyrimu.
- Xpert MTB/XDR tyrimas nediferencijuoja MTB komplekso (t.y. *MTB, M. bovis, M. africanum, M. canettii, M. microti, M. caprae, M. pinnipedi, M. mungi, and M. orygis*) rūšių. Be to, turi būti atliekamas kultūros auginimas, jei be MTB komplekso yra ir NTM padermė.
- Literatūroje aprašytas žemas pediatrijos pacientų jautrumas dėl difuzinės MTB infekcijos prigimties plaučiuose, todėl adekvataus mėginio paėmimas šioje pacientų grupėje yra gan sudėtingas[16,17].

- Apmokytas sveikatos priežiūros specialistas tyrimo rezultatus turi interpretuoti atsižvelgiant į paciento medicininę istoriją, klinikinius požymius bei kitų diagnostinių tyrimų rezultatus.
- Kompleksinės MTB ir *M. marinum* infekcijos gali iššaukti "INDETERMINATE" (nenustatyta) rezultatą dėl FLQ prie >10^4 CFU/ml *M. marinum*, esant ≤408 CFU/ml MTB.
- Retais atvejais, *rrs* pradmenys ir zondai gali kryžmiškai reaguoti su aplinkos mikrobais ar skreplių mikroflora ir iššaukti "INDETERMINATE" (nenustatyta) rezultatus dėl AMK, KAN ir CAP.
- Xpert MTB/XDR tyrimas nustato atsparumą ETH, susijusį tik su mutacijomis *inhA* promotoriaus regione. Mutacijų nebuvimas inhA promotoriaus regione neatmeta atsparumo ETH galimybės. Mutacijos su atsparumu ETH yra registruotos genominiuose regionuose, kurie nėra Xpert MTB/XDR tyrimo taikiniai.[15]
- Mutacijų *oxyR-ahpC* ir *gyrB* genuose sąsaja su atsparumu atitinkamai INH ir FLQ, kol kas nėra galutinai nustatyta, tačiau publikuotose studijose rašoma, jog šios mutacijos yra aptinkamos INH ir FLQ atspariose padermėse.[18,19].
- Delecijos ar retos mutacijos taikinių genuose gali iššaukti „INDETERMINATE" (nenustatyta) rezultato gavimą dėl tam tikram vaistui.
- Mėginio su kompleksine ir atsparių, ir jautrių padermių populiacija, atveju, yra tikimybė, jog Xpert MTB/ XDR tyrimas neaptiks mutacijos, jei atsparios populiacijos lygis yra žemiau tyrimo aptikimo ribos.
- Mėginiuose su labai žema bakterijų koncentracija ar jautrių ir atsparių padermių kompleksu, Xpert MTB/XDR tyrimas negalės patikimai atskirti žemo ir aukšto atsparumo FLQ.

18 Klinikinis veiksmingumas

Buvo atlikta „akloji" klinikinė studija, kurios metu buvo vertinamas Xpert MTB/XDR tyrimo veiksmingumas, lyginant su mikrobiologiniais ir molekuliniais pamatiniais metodais, t.y., fenotipinio jautrumo vaistams tyrimu (pDST) bei sekoskaitos tyrimais (atsparumo INH, ETH, FLQs ir SLID (AMK, KAN and CAP) nustatymas). Be to, klinikinis Xpert MTB/XDR tyrimo veiksmingumas buvo lyginamas su Xpert MTB/RIF ar Xpert MTB/RIF Ultra tyrimu dėl MTB aptikimo. Iš dviejų vietų (žinomų dėl aukšto MDR ir XDR TB paplitimo) buvo gauti užšaldyti archyvuoti neapdoroti skreplių ar koncentruotų skreplių sedimentų mėginiai, žinomi kaip neigiami ar teigiami dėl MTB kultūros.

5 lentelėje pateiktas Xpert MTB/XDR tyrimo jautrumas ir specifiškumas, lyginant su pDST dėl atsparumo vaistams. Jautrumas yra >90% dėl INH, FLQ ir AMK, >85% dėl KAN ir CAP bei >64% dėl ETH; specifiškumas yra >98% visiems vaistams.

5 lentelė. Xpert MTB/XDR tyrimas ir pDST dėl atsparumo vaistams

Vaistai	N	TP	FN	TN	FP	Jautrumas (%)	95%CI	Specifiškumas (%)	95% CI
INH	478	244	23	209	2	91.4	87.4 – 94.2	99.1	96.6 – 99.7
FLQ	417	148	11	254	4	93.1	88.0 - 96.1	98.5	96.1 – 99.4
AMK	405	79	7	317	2	91.9	84.1 – 96.0	99.4	97.7 – 99.8
KAN	343	58	8	276	1	87.9	77.9 – 93.7	99.6	98.0 – 99.9
CAP	167	21	4	142	0	84.0	65.3 – 93.6	100.0	97.4 – 100.0
ETH	230	75	41	112	2	64.7	55.6 – 72.8	98.3	93.8 – 99.5

6 lentelėje pateiktas Xpert MTB/XDR tyrimo jautrumas ir specifiškumas, lyginant su sekoskaita dėl atsparumo vaistams. Jautrumas yra >93% dėl FLQ ir didesnis nei 96% dėl INH, AMK, KAN, CAP ir ETH; specifiškumas yra 100.0% visiems lentelėje išvardintiems vaistams, išskyrus INH, kuriam specifiškumas yra 98.7%.

6 lentelė. Xpert MTB/XDR tyrimas ir sekoskaita dėl atsparumo vaistams

Vaistai	N	TP	FN	TN	FP	Jautrumas (%)	95%CI	Specifiškumas (%)	95%CI
INH	471	241	3	224	3	98.8	96.5 - 99.6	98.7	96.2 - 99.5
FLQ	469	152	11	306	0	93.3	88.3 - 96.2	100.0	98.8 – 100.0
AMK	463	81	3	379	0	96.4	90.0 - 98.8	100.0	99.0 – 100.0
KAN	463	88	3	372	0	96.7	90.8 - 98.9	100.0	99.0 – 100.0
CAP	463	78	3	382	0	96.3	89.7 - 98.7	100.0	99.0 – 100.0
ETH	473	104	3	366	0	97.2	92.1 – 99.0	100.0	99.0 – 100.0

7 lentelėje pateiktas Xpert MTB/XDR tyrimo teigiamas atitikimas procentais (PPA) ir neigiamas atitikimas procentais (NPA) lyginant su Xpert MTB/RIF tyrimu dėl MTB aptikimo - atitinkamai 98.9% ir 93.8%.

7 lentelė. Xpert MTB/XDR tyrimas ir Xpert MTB/RIF tyrimas dėl MTB aptikimo

		Xpert MTB/RIF tyrimas		
		MTB aptikta	**MTB neaptikta**	**Iš viso**
Xpert MTB/XDR tyrimas	MTB aptikta	273	2a	275
	MTB neaptikta	3b	30	33
	Iš viso	276	32	308
PPA			98.9% (95%CI: 96.9-99.6)	
NPA			93.8% (95%CI: 79.9-98.3)	

8 lentelėje pateiktas Xpert MTB/XDR tyrimo PPA ir NPA, lyginant su Xpert MTB/RIF Ultra tyrimu dėl MTB aptikimo - atitinkamai 99.5% ir 100.0%.

8 lentelė. Xpert MTB/XDR tyrimas ir Xpert MTB/RIF Ultra tyrimas dėl MTB aptikimo

		Xpert MTB/RIF Ultra tyrimas		
		MTB aptikta	**MTB neaptikta**	**Iš viso**
Xpert MTB/XDR tyrimas	MTB aptikta	207	0	207
	MTB neaptikta	1[a]	14	15
	Iš viso	208	14	222
PPA			99.5% (95%CI: 97.3-99.9)	
NPA			100.0% (95%CI: 78.5-100.0)	

a. Xpert MTB/RIF Ultra rezultatas buvo „MTB Detected Trace“.

Iš šioje studijoje atliktų 531 Xpert MTB/XDR tyrimų vykdymų, pirmojo bandymo metu buvo gauta 15 nenustatytų rezultatų („Error“, „Invalid“ ar „No Result“). Po pakartotinio tyrimo, vienas rezultatas išliko nenustatytas. Pirminis nenustatytų rezultatų santykis buvo 2.8% (15/531), o bendras nenustatytų rezultatų santykis - 0.2% (1/531).

19 Analitinis veiksmingumas

19.1 Analitinis jautrumas (aptikimo riba)

Tris dienas buvo atliekama Xpert MTB/XDR tyrimo analitinės aptikimo ribos (LoD) nustatymo studija, kurios metu buvo naudojamos dvi reagentų partijos. MTB teigiamas rezultatas yra paremtas vienos kopijos *inhA* taikinyje aptikimu. Patvirtinimui buvo pasirinkta didesnė LoD padermėje ir partijoje, kaip nustatyta Probit analize. Apskaičiuota LoD buvo patvirtinta naudojant vieną reagentų partiją mažiausiai tris dienas. LoD buvo nustatyta *naudojant reprezentatyvų MTBC narį, Mycobacterium bovis BCG (Bacille Calmette-Guerin)*, kurio buvo pridėta į MTB neigiamą, neapdorotą skreplių mėginį ir į MTB neigiamą dekontaminuotą / koncentruotą skreplių sedimentų mėginį.

LoD yra mažiausia koncentracija, išreikšta CFU/ml vienetais, kuri gali būti pakartotinai atskiriama iš neigiamų mėginių, esant ≥ 95% pasikliovimui. 20 kartotinių 3 dienas buvo vertinami nuo penkių iki aštuonių koncentracijų, naudojant dvi skirtingas reagentų partijas, o LoD buvo nustatyta atliekant Probit analizę.

Patvirtinimui, pagal Probit analizę, kiekvienam mėginio tipui ir partijai buvo stebima didesnė LoD. Apskaičiuota LoD buvo patvirtinta naudojant vieną reagentų partiją mažiausiai tris dienas, remiantis mažiausiai 19 iš 20 teigiamų kartotinių. LoD, išreikšta CFU/ml vienetais, pateikta 9 lentelėje.

9 lentelė. Analitinis jautrumas (aptikimo riba)

Mėginio tipas	Apskaičiuota LoD, CFU/ml
Neapdoroti skrepliai	136
Sedimentai	86

19.2 Analitinis specifiškumas (išskirtinumas)

Analitinis Xpert MTB/XDR tyrimo specifiškumas buvo vertinamas tiriant 57 organizmų panelį, kurį sudarė 21 bakterija, 1 grybelis, 7 virusai ir 28 ne tuberkuliozės mikobakterijos (NTM), reprezentuojant bendrai paplitusius kvėpavimo takų patogenus ar organizmus, aptinkamus kvėpavimo takų ir (ar) burnaryklės floroje. Trys kiekvienos bakterijų ir mielų padermių kartotiniai buvo tiriami ties koncentracija ≥ 1 x 10_6 CFU/ml. Visi virusai buvo tiriami ties ≥1x10_5 (audinių kultūros infekcinė dozė) $TCID_{50}$/ml. DNR ar RNR buvo tirtos dėl 2 bakterijų ir 1 grybelio padermės ties koncentracija ≥10_6 kopijų/ml, kadangi visi organizmai nebuvo prieinami dėl biologinės saugos apribojimų. Trys kiekvieno viruso kartotiniai buvo tiriami ties koncentracija ≥ 1 x 10_5 $TCID_{50}$/ml. Analitinis specifiškumas buvo 100%. Tirti organizmai išvardinti 10 lentelėje, 11 lentelėje ir 12 lentelėje. Nė vienas tirtų organizmų kryžmiškai nereagavo su MTB aptikimo zondu, generavusiu rezultatą „MTB NOT DETECTED“ (MTB neaptikta) visuose tirtuose organizmuose ir kartotiniuose. Lentelėje žemiau pateikti organizmai, tirti dėl analitinio tyrimo specifiškumo. *Aspergillus fumigatus* buvo tirtas analitiškai ir nedemonstravo interferencijos ar kryžminio reaktyvumo. Kryžminis reaktyvumas su kitomis grybelio rūšimis nėra akivaizdus *in silico* analizėje.

10 lentelė. Analitinis Xpert MTB/XDR tyrimo specifiškumas (bakterijos / grybeliai)

Organizmas
Acinetobacter baumannii
Chlamydophila pneumoniae[a]
Citrobacter freundii
Corynebacterium xerosis
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria meningitidis[a]
Neisseria mucosa
Nocardia asteroids
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus epidermidis
Stenotrophomonas maltophilia
Streptococcus agalactiae
Streptococcus mitis
Streptococcus mutans
Streptococcus pneumoniae
Streptococcus pyogenes
Aspergillus fumigatus[a]

[a.] Genominė DNR

11 lentelė. Analitinis Xpert MTB/XDR tyrimo specifiškumas (virusai)

Organizmas
Koronavirusas 229E
Žmogaus metapneumovirusas (hMPV) 16, tipas A1
Paragripo virusas, tipas 1
Paragripo virusas, tipas 2
Paragripo virusas, tipas 3
Respiracinis sincitinis virusas
Rinovirusas 1A

12 lentelė. Analitinis Xpert MTB/XDR tyrimo specifiškumas (NTM)

Organizmas
Mycobacterium asiaticum
Mycobacterium avium NJH
Mycobacterium celatum
Mycobacterium chelonae
Mycobacterium flavescens
Mycobacterium fortuitum subsp. Fortuitum
Mycobacterium gastri
Mycobacterium gordonae
Mycobacterium gordonae
Mycobacterium gordonae
Mycobacterium genavense
Mycobacterium haemophilum
Mycobacterium malmoense
Mycobacterium marinum
Mycobacterium phlei
Mycobacterium scrofulaceum
Mycobacterium simiae
Mycobacterium szulgai
Mycobacterium terrae
Mycobacterium thermoresistibile
Mycobacterium triviale
Mycobacterium vaccae
Mycobacterium xenopi
Mycobacterium avium
Mycobacterium intracellulare
Mycobacterium abscessus
Mycobacterium marinum
Mycobacterium kansasii

19.3 Analitinis reaktingumas (įtraukiamumas)

Analitinis Xpert MTB/XDR tyrimo reaktingumas (įtraukiamumas) buvo vertinamas naudojant filogenetiškai diversinį panelį, kurį sudarė vaistams jautrios ir atsparios MTB padermės. Vertinimo metu buvo nustatomas tyrimo jautrumo rezultatų tikslumas. Į dvidešimt dviejų (22) MTB komplekso (MTBC) padermių panelį buvo įtrauktos aštuonios (8) vaistams jautrios padermės su laukinio tipo taikinio genais (13 lentelė) ir keturiolika (14) aiškiai charakterizuotų vaistams atsparių padermių (14 lentelė). Visos padermės buvo tiriamos trigubu pakartojimu ties *inhA* promotoriaus taikinio 3 X LoD koncentracija. Kopijų, tirtų dėl genominės DNR, skaičius buvo paremtas fluorescencinių dažų susirišimo tyrimu, specifišku dvigubos grandinės DNR (dsDNA).

Tirtose vaistams jautriose padermėse buvo penkios MTB padermės (AR2, GD139, AH1, HR36, H37Rv) ir trys MTB komplekso mikobakterijų rūšys (*M. bovis, M. canetti* ir *M. microti)*. Buvo parinktos plataus genetinio diversiškumo spektro MTB padermės, įskaitant vieną iš kiekvienos didžiųjų filogenetinių linijų, remiantis SNP klasterio grupėmis (SCGs)[20].

14 vaistams atsparių MTB padermių buvo tirtos naudojant genominės DNR lizatą iš aiškiai charakterizuotų mėginių, kuriuose buvo kliniškai reikšmingų kanoninių mutacijų su bent vienu iš aštuonių tyrimo taikinių regionų. Šios mutacijos yra plačiai paplitusios daugeliui vaistų atsparių MTB padermių, išskyrus mutaciją *gyrB* gene.

13 lentelėje pateikiamos vaistams jautrios padermės su teisingu rezultatu kiekvienai individualiai tyrimo analitei. Visi panelio nariai generavo „MTB DETECTED; RESISTANCE NOT DETECTED“ (MTB aptikta, atsparumas neaptiktas) rezultatą. Xpert MTB/ XDR tyrimas teisingai identifikavo visus padermių kartotinius, kurių koncentracija buvo šalia aptikimo ribos, su laukinio tipo rezultatais visiems zondams, išskyrus *oxyR-ahpC*. Kadangi *oxyR-ahpC* taikinio LoD yra didesnė nei kitų tyrimo taikinių, kai kurie kartotiniai nerodė Tm rezultatų.

14 lentelėje pateikti rezultatai rodo, kad tyrimas taip pat teisingai identifikavo tikėtinas atsparumo mutacijas visose 14 padermių, atsparių izoniazidui, su mutacijomis *inhA* promotoriuje, *katG* ir *oxyR-ahpC* tarpgeniniame regione; atsparių SLID su mutacijomis *rrs* ir *eis* promotoriaus regione ir atsparių FLQ su mutacijomis *gyrA*.

13 lentelė. Vaistams atsparių padermių analitinis reaktingumas (įtraukiamumas)

Mėginys	Padermės linija	inhA	katG	fabG1	ahpC[a]	gyrA1	gyrA2	gyrA3	gyrB2	rrs	eis
(*M.bovis BCG)*	1	TAIP	TAIP	TAIP	NE	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
M.bovis	1	TAIP	TAIP	TAIP	NE	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB (AR2)	2	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB (GD139)	3	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB (AH1)	4	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB (HR36)	5	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
*MTB (*HR37Rv)	4	TAIP	TAIP	TAIP	NE	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
M.canetti	Nepriskirta	TAIP	TAIP	TAIP	NE	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
M.microti	Nepriskirta	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP

a. oxyR-*ahpC* LoD yra didesnė nei *inhA,* naudoto MTB teigiamumo nustatymui. „TAIP“ reiškia, kad visi tirti kartotiniai generavo tikėtinio laukinio tipo Tm; „NE“ reiškia, kad bent vienas ar daugiau kartotinių negeneravo Tm verčių.

14 lentelė. Vaistams atsparių padermių analitinis reaktingumas (įtraukiamumas) (# teigiami rezultatai / iš viso tirta)

Padermės ID	Genas	Tikėtina mutacija	MTB aptikta	Zonde aptikta mutacijos Tm (# teigiami/tirta)	Teisingas ATSPARUMAS APTIKTA (# teigiami/tirta)
Klinikinis	gyrA	GAC 94 TAC	3/3	gyrA1-MutB (3/3); gyrA3-MutC (3/3)	FLQ [3/3]
	katG	AGC 315 ACC		katG Mut (3/3)	INH [3/3]
	fabG1	G609A		fabG1 Mut (3/3)	INH [3/3]
Klinikinis	gyrA	GGC 88 GCC, GCG 90 GTG, TCG 91 CCG	3/3	gyrA1-MutB (2/3),[a] gyrA1-MutC (2/3), gyrA2-MutA (3/3), gyrA3-MutB (1/3)	FLQ [3/3]
	katG	AGC 315 ACC		katG Mut (3/3)	INH [3/3]
	rrs	A1410G		rrs-Mut (3/3)	AMK, CAP, KAN [3/3]
Klinikinis	gyrA	GAC 94 GGC	3 / 3	gyrA3-MutB (3/3)	FLQ [3/3]
	katG	AGC 315 ACC		katG Mut (3/3)	INH [3/3]
	rrs	A1410G		rrs-Mut (3/3)	AMK, CAP, KAN [3/3]
14-14194	gyrA	GAC 94 GCC	3 / 3	gyrA1-MutA, gyrA2-MutA	FLQ [3/3]
	katG	AGC 315 ACC		katG-Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH, ETH [3/3]
15-14175	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	eis	-10G/A		eis-Mut (3/3)	AMK, KAN [3/3]
15-14191	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	eis	-10G/A		eis-Mut (3/3)	AMK, KAN [3/3]
16-05612	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH, ETH [3/3]
	eis	-12C/T		eis-Mut (3/3)	AMK, KAN [3/3]

14 lentelė. Vaistams atsparių padermių analitinis reaktingumas (įtraukiamumas) (# teigiami rezultatai / iš viso tirta) (tęsinys)

Padermės ID	Genas	Tikėtina mutacija	MTB aptikta	Zonde aptikta mutacijos Tm (# teigiami/tirta)	Teisingas ATSPARUMAS APTIKTA (# teigiami/tirta)
16-05613	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH, ETH [3/3]
	eis	-12C/T		eis-Mut (3/3)	AMK, KAN [3/3]
14-13764	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	ahpC	-48G/A		ahpc-Mut (3/3)	INH [3/3]
14-13806	katG	AGC 315 ACC	3 / 3	katG-Mut (3/3)	INH [3/3]
	ahpC	-48G/A		ahpc-Mut (3/3)	INH [3/3]
Klinikinis	gyrA	GCG 90 GTG, GAC 94 GGC	3 / 3	gyrA3-MutB (3/3)	FLQ [3/3]
	inhA	C -15 T		inhA-Mut (3/3)	INH [3/3]
	ahpC	G-6A		ahpC (2/3)[b]	INH [3/3]
Klinikinis	katG	AGC 315 ACC	3 / 3	katG Mut (3/3)	INH [3/3]
Klinikinis	gyrB2	ACC 539 AAC	3 / 3	gyrB2 WT[c]	*Atsparumas neaptiktas [0/3]
	rrs	A1410G		rrs-Mut (3/3)	AMK, CAP, KAN [3/3]
	gyrA	GCG 90 GTG		gyrA1 MuB (3/3), gyrA2 MutA (3/3), gyrA3 MutB (3/3)	FLQ [3/3]
	ahpC	g -6 a		ahpC Mut (3/3)	INH [3/3]
	inhA	C -15 T		inhA Mut (3/3)	INH, ETH [3/3]
Klinikinis	gyrA	TCG 91 CCG	3 / 3	gyrA1-MutB (3/3), gyrA2-MutA (3/3), gyrA3-MutC (3/3)	FLQ [3/3]
	inhA	C -15 T		inhA Mut (3/3)	INH, ETH [3/3]

a. Šis mėginys su trimis skirtingomis mutacijomis *gyrA* gene negeneravo mutacinės Tm visuose trijuose *gyrA* zonduose. Tačiau, kad būtų galima fiksuoti teisingą atsparumo rezultatą, reikia, jog bent viename zonde būtų generuojama Tm. rezultatas visiems kartotiniams nustatytas teisingai, kadangi bent vienas *gyrA* zondas visada generavo bent vieną mutacijos Tm.

b. Šis mėginys turi dvigubą katG / ahpC mutaciją. Kartotinio be ahpC mutacijos Tm pavadinta INH-R dėl KatG mutacijos buvimo.

c. Ši specifinė mutacija nebuvo aptikta. Tačiau, riboti klinikiniai duomenys rodo, kad ši mutacija gali lemti atsparumą FLQ (mažo pasikliovimo mutacija, lemianti atsparumą FLQ).

19.4 Interferuojančių substancijų studija

Xpert MTB/XDR tyrimo veiksmingumas buvo vertinamas su 36 potencialiai interferuojančioms substancijomis, kurių gali būti skreplių mėginiuose. Potencialiai interferuojančias substancijas sudarė endogeninės substancijos, kurios gali būti mėginiuose ir egzogeninės substancijos, kurios gali būti įneštos į mėginius. Izotoniniai ar hipertoniniai tirpalai, bronchus plečiantys vaistai bei inhaliuojami bronchus plečiantys vaistai, dažnai naudojami indukuotų skreplių mėginių paėmimui, buvo ištirti ir patvirtinti kaip neinterferuojantys tyrimo. Indukcija druskos tirpalo garais gali įtakoti nepakankamą atstatytų organizmų kiekį ir neigiamai paveikti *M. tuberculosis* aptikimą.

15 lentelėje yra išvardintos tirtos substancijos su aktyviais ingredientais ir tirtomis koncentracijomis. Su kiekviena substancija buvo tirti neigiami mėginiai (n = 8), siekiant nustatyti poveikį mėginio apdorojimo kontrolės veiksmingumui (SPC). Į teigiamus mėginius (n = 8) buvo pridėta *Mycobacterium bovis, Bacille Calmette-Guerin (BCG)* ties 3x analitinės TB teigiamumo aptikimo ribos. Mėginiai buvo tirti su kiekviena substancija. Visos substancijos buvo tirtos MTB neigiamame žmogaus skreplių kaupinyje. Visi teigiami ir neigiami kartotiniai buvo teisingai identifikuoti su Xpert MTB/XDR tyrimu, išskyrus Zicam gelį (50% w/v; gautas rezultatas - „MTB NOT DETECTED“ (MTB neaptikta) 11.1% iš visų tirtų kartotinių).

15 lentelė. Potencialiai Xpert MTB/XDR tyrimą interferuojančios substancijos

Substancija / klasė	Aprašymas / aktyvus ingredientas	Tirta koncentracija
Kraujas (žmogaus)	Kraujas 5% (v/v)	5% (v/v)
Žmogaus DNR / ląstelės	HELA 229 ląstelių linija	10^6 ląstelių/ml
Leukocitai (žmogaus)	WBC/Pus matrica (30% leuko-trombo sluoksnio; 30% plazmos; 40% PBS)^	100% (v/v)
Antimycotic antibiotikas	Nystatin 500KU (100%)	20% (v/v)
Germicidinis burnos skalavimo skystis	Chlorheksidino gliukonatas (0.12%), burnos skalavimo skystis, USP	20% (v/v)
Mėginių apdorojimo reagentai	Cetilpiridinio chloridas, 1% esantis 2% NaCl	0.5% (v/v) esantis 1% NaCl
Mėginių apdorojimo reagentai	Cetilpiridiniumo chloridas, 1% esantis 2% NALC	0.5% (v/v) esantis 1% NALC
Mėginių apdorojimo reagentai	Cetilpiridiniumo chloridas, 1% esantis 2% NALC plius 25 mM citrato	0.5% (v/v) esantis 1% NALC plius 12.5mM citrato
Skrandžio rūgštis	pH 3 - 4 vandens tirpalas, neutralizuotas natrio bikarbonatu	100% (v/v)
Anestetikai (endotrachėjos intubacija)	Lidokainas HCl 4%	4% (v/v)
Nebulizuojantys tirpalai	NaCl 5% (w/v)	5% (w/v)
Mucinas	Mucinas 5% (w/v)	5% (w/v)
Antibakterinis, sisteminis	Levofloxacin 25 mg/ml	5 mg/ml
Nosies kortikosteroidai	Fluticasone, 500 mcg/purškalas	5 µg/ml
Inhaliuojami bronchus plečiantys vaistai	Albuterolio sulfatas (2 mg/5ml)	100 µg/ml
Oraliniai anestetikai	Orajel (20% benzokainas)	5% (w/v)
Antivirusiniai vaistai	Acyclovir	50 µg/ml
Antibiotikas, nosies tepalas	Neosporin (400U Bactracin, 3.5mg Neomycin, 5000U Polymyxin B)	5% (w/v)
Tabakas	Nicogel, 40% tabako ekstraktas	0.5%
Antituberkulioziniai vaistai	Streptomycin 1mg/ml	25 µg/ml
Antituberkulioziniai vaistai	Ethambutol 1mg/ml	50 µg/ml
Antituberkulioziniai vaistai	Isoniazid 50mg/5ml	50 µg/ml
Geriamieji atsikosėjimą skatinantys vaistai	Guaifenesin (400mg/tabletė)	5 mg/ml
Antituberkulioziniai vaistai	Pyrazinamide (500mg/tabletė)	100 µg/ml
Nosies gelis (homeopatinis)	Zicam gelis	50% (w/v)
		20% (w/v)
Nosies purškalas	Phenylephrine 1%	0.5% (v/v)
Antituberkulioziniai vaistai	Rifampicin (300mg/tabletė)	25 µg/ml
Vaistai nuo alergijos (homeopatiniai)	100% grynas arbatmedžio aliejus (<5% Cineole, >35% Terpinen-4-01)	0.5% (v/v)
Nebulizuojantys tirpalai	Pentamidino izetionatas	300 ng/ml
Antituberkulioziniai vaistai	Amoxicillin	25 µg/ml
Bronchus plečiantys vaistai	Epinephrine	1mg/ml
Antituberkulioziniai vaistai	Amikacin	70ug/ml
Antituberkulioziniai vaistai	Capreomycin	50ug/ml
Antituberkulioziniai vaistai	Kanamycin	50ug/ml
Antituberkulioziniai vaistai	Ethionamide	50ug/ml
Nosies dulksna „Flu Mist Qual Nasal“	Gripo viruso vakcina (Live-nasal)	5%

19.5 Pernešamo užterštumo studija

Atliktos studijos metu siekta įrodyti, jog vienkartinės, uždaros Xpert MTB/XDR kasetės užkerta kelią kryžminiam užterštumui. Studijos metu neigiami žmogaus skreplių mėginiai buvo apdorojami iškart po aukštos *Mycobacterium bovis-Bacille Calmette-Guerin* (BCG) koncentracijos mėginių - 1 x 10^{+6} CFU/ml apdorojimo tame pačiame Gene Xpert modulyje. Tyrimo schema buvo kartojama mažiausiai 20 kartų su dviejuose GeneXpert moduliuose, iš viso atliekant 41 tyrimo vykdymą. Kiekviename modulyje gauta 20 teigiamų ir 21 neigiamas rezultatas.

Visi 20 teigiamų mėginių teisingai nustatyti kaip **MTB DETECTED** (MTB aptikta)**; INH Resistance NOT DETECTED** (atsparumas INH neaptiktas)**; FLQ Resistance NOT DETECTED** (atsparumas FLQ neaptiktas)**; AMK Resistance NOT DETECTED** (atsparumas AMK neaptiktas)**; KAN Resistance NOT DETECTED** (atsparumas KAN neaptiktas)**; CAP Resistance NOT DETECTED** (atsparumas CAP neaptiktas)**; ETH Resistance NOT DETECTED** (atsparumas ETH neaptiktas). Visi 21 neigiami mėginiai buvo teisingai nustatyti kaip **MTB NOT DETECTED** (MTB neaptikta). Šios studijos sąlygomis, nebuvo aptikta jokių pernešamo užterštumo įrodymų, tiriant labai stipriai teigiamus *BCG* mėginius, kurių koncentracija buvo 1.0 x 10^{+6} CFU/ml.

19.6 Konkurencinės interferencijos studija

Tiriant reprezentatyvius MTBC narius, buvo vertinama konkurencinė tyrimo interferencija, kurią sukelia aukštos koncentracijos ne tuberkuliozės *Mycobacteria* (NTM), aptinkant žemą MTB lygį. BCG ties ~ 3 x LoD (411 CFU/ml), esant skirtingoms NTM padermėms ties 1 x 10E+06 CFU/ml koncentracija neigiamos kontrolės buferio fone. MTB teigiamumas paremtas aptiktu *inhA* promotoriaus tinkamu lydymosi piko aukščiu ir lydymosi piko temperatūra. Atsparumo aptikimas paremtas *mut* lydymosi piko aukščiu ir *mut* lydymosi piko temperatūra individualioms analitėms (*inhA, katG, gyrA1, gyrA2, gyrA3, gyrB2* ir *eis*). *oxyR-ahpC and fabG1* analitės nebuvo įtrauktos dėl žemo jautrumo, o *rrs* nebuvo įtrauktas dėl žinomos interferencijos su mikroflora. Visi mėginiai su BCG demonstravo rezultatus **MTB DETECTED** (MTB aptikta); **INH Resistance NOT DETECTED** (atsparumas INH neaptiktas); **FLQ Resistance NOT DETECTED** (atsparumas FLQ neaptiktas); **AMK Resistance NOT DETECTED** (atsparumas AMK neaptiktas); **KAN Resistance NOT DETECTED** (atsparumas KAN neaptiktas); **CAP Resistance NOT DETECTED** (atsparumas CAP neaptiktas); **ETH Resistance NOT DETECTED** (atsparumas ETH neaptiktas).

Keturi kiekvieno NTM/ BCG konkurencinio mišinio kartotiniai tirti kartu su teigiamos kontrolės sąlyga tik su BCG ties ~3 x LoD. Nė viena tirta NTM padermė neinterferavo su 411 CFU/ml BCG aptikimu ir generavo teisingus rezultatus. Tačiau, šios studijos sąlygomis, konkurencinio inhibitoriaus efektas buvo stebimas esant tik vienai iš dviejų *M.marinum* (ATCC 0927) padermių. Interferencija su gyrA2 zondais buvo stebima tik ties itin aukšta >10_4 CFU/ml koncentracija, kuomet buvo gautas nenustatytas rezultatas dėl atsparumo FLQ. Išsamesnė informacija pateikta 17 skyriuje.

16 lentelė. NTM konkurencinė interferencija MTB aptikime ir jautrumo vaistams nustatyme

Tyrimo sąlyga / NTM Padermės ID	NTM CFU/ ml	MTB aptikta	INH	FLQ	AMK	KAN	CAP	ETH
MTB + M. avium / (NJH)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.gastir / (ATCC 15754)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.gordonae / (NJH)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.gordonae / (ATCC 14470)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.gordonae / (ATCC 35760)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.marinum / (NJH)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.marinum / (ATCC 0927)	10E+06	TAIP	TAIP	NE	TAIP	TAIP	TAIP	TAIP
	10E+05	TAIP	TAIP	NE	TAIP	TAIP	TAIP	TAIP
	10E+04	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
	10E+03	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.xenopi / (ATCC 700084)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.avian / (ATCC 15769)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.intracellulare / (ATCC 35771)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP
MTB + M.abscessus / (ATCC 19977)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP

16 lentelė. NTM konkurencinė interferencija MTB aptikime ir jautrumo vaistams nustatyme (tęsinys)

Tyrimo sąlyga / NTM Padermės ID	NTM CFU/ ml	MTB aptikta	INH	FLQ	AMK	KAN	CAP	ETH
MTB + M.kansasii / (ATCC 12478)	10E+06	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP	TAIP

„TAIP“ reiškia, kad visi tirti kartotiniai susijusiems vaistams generavo tikėtiną rezultatą „RESISTANCE NOT DETECTED“ (atsparumas neaptiktas); „NE“ reiškia, kad bent vienas ar daugiau kartotinių tam tikram vaistui generavo rezultatą „RESISTANCE INDETERMINATE“ (atsparumas nenustatytas).

19.7 *Mycobacteria* inaktyvavimas skreplių mėginiuose

Xpert MTB/XDR mėginio reagento dezinfekcijos galimybės buvo tiriamos naudojant standartizuotą kiekybinį tuberkuliozės kultūros metodą.[21] Į skreplių mėginius buvo pridėta aukštos koncentracijos gyvybingų *M. bovis;* mėginiai buvo sumaišyti su mėginio reagentu santykiu 2:1 ir inkubuoti 15 minučių. Po inkubacijos mėginio reagento/skreplių mišinys buvo neutralizuotas skiedimu bei filtracija ir tada kultivuojamas. *M. bovis* organizmų gyvybingumas apdorotose skrepliuose, buvo sumažėjęs mažiausiai 6 logaritminiais vienetais, lyginant su neapdorota kontrole.

Kiekviena laboratorija privalo nusistatyti mėginio reagento dezinfekcijos veiksmingumo galimybes naudojant savo standartizuotus metodus ir privalo laikytis biologinės saugos rekomendacijų.

20 Preciziškumas ir atkuriamumas

Xpert MTB/XDR tyrimo preciziškumas ir atkuriamumas buvo vertinamas keliuose centruose (trijose vietose), atliekant „akląją“ studiją, naudojant kelių faktorių pakopinį metodą. Buvo naudojamas penkių narių panelis, kurio kiekvienas narys buvo paruoštas į dirbtinę skreplių matricą pridedant MTB laukinio tipo (WT) padermės ir MTB mutavusios (MUT) padermės. WT ir MUT padermės buvo išgautos iš plazmidžių, pernešančių arba MTB XDR laukinį tipą, arba mutacijų sekas tyrimo taikinių genams, inkapsuliuotų negyvose, cheminiu būdu fiksuotose E. coli.

Panelio nariai buvo paruošti ~1xLoD ir ~3xLoD koncentracijomis, naudojant tyrimo taikinio *inhA* promotoriaus lydymosi temperatūrą (Tm), kuri generuoja rezultatą **MTB DETECTED/NOT DETECTED** (MTB aptikta / neaptikta), priklausomai nuo laukinio tipo ar muticos buvimo ar nebuvimo *inhA* promotoriui specifinėje Tm. Tyrimas buvo atliekamas šešias dienas, naudojant tris Xpert MTB/XDR kasečių partijas. Kiekvienoje vietoje dirbo po du operatorius (Op1 ir Op2), kurie kiekvieną dieną atliko po du tyrimo vykdymus dviem pakartojimais. Kartotinis - viena tirta kasetė. Kiekvieno panelio nario atitikimas procentais yra pateiktas 17 lentelėje.

17 lentelė. Xpert MTB/XDR tyrimo procentinis atitikimas dėl MTB ir *inhA* aptikimo

Mėginys	Vieta 1			Vieta 2			Vieta 3			Bendras atitikimas mėginiui
	OP 1	OP 2	Tarpinė suma	OP 1	OP 2	Tarpinė suma	OP 1	OP 2	Tarpinė suma	
MTB MUT 1xLoD	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	95.8% (23/24)	97.9% (47/48)	91.7% (22/24)	91.7% (22/24)	91.7% (44/48)	96.5% (139/144)
MTB MUT 3xLoD	95.8% (23/24)	100% (24/24)	97.92% (47/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	99.3% (143/144)
MTB WT 1xLoD	100% (24/24)	91.67% (22/24)	95.8% (46/48)	91.7% (22/24)	91.7% (22/24)	91.7% (44/48)	91.7% (22/24)	100% (24/24)	95.8% (46/48)	94.4% (136/144)
MTB WT 3xLoD	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (144/144)
NEIG	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	95.8% (23/24)	97.9% (47/48)	99.3% (143/144)

Xpert MTB/XDR tyrimo veiksmingumas su MTB WT ir MUT padermių ties žemos (~1x) ir vidutinės (~3x) LoD panelio nariais kiekvienam geno taikiniui, kuriame buvo aptikta MTB, pateikiamas 18 lentelėje.

18 lentelė. Xpert MTB/XDR tyrimo procentinis atitikimas dėl MTB MUT ir WT tipo mėginių

Vaistai	Atitikimas procentais			
	MTB MUT 1x LoD (95% CI) [n atitikimas/ bendras n]	**MTB MUT 3xLoD (95% CI) [n atitikimas/ bendras n]**	**MTB WT 1x LoD (95% CI) [n atitikimas/ bendras n]**	**MTB WT 3x LoD (95% CI) [n atitikimas/ bendras n]**
INH	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	89.1% (82.6-93.4) [115/129]	99.3% (96.2-99.9) [143/144]
FLQ	87.80% (81.3-92.2) [122/139]	100.00% (97.4-100.0) [143/143]	81.4% (73.8-87.2) [105/129]	95.8% (91.2-98.1) [138/144]
ETH	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	99.2% (95.7-99.9) [128/129]	100.0% (97.4-100.0) [144/144]
AMK	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	91.5% (85.4-95.2) [118/129]	98.6% (95.1-99.6) [142/144]
CAP	99.30% (96.3-99.0) [138/139]	100.00% (97.4-100.0) [143/143]	98.4% (94.5-99.6) [127/129]	99.3% (96.2-99.9) [143/144]
KAN	100.00% (97.3-100) [139/139]	100.00% (97.4-100.0) [143/143]	91.5% (85.4-95.2) [118/129]	98.6% (95.1-99.6) [142/144]

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