Section 13, Product Insert

Lyra™ Influenza A Subtype H7N9 Assay
Instructions for Use

For the qualitative detection and identification of avian influenza A (H7N9) virus (detected in China in 2013) viral RNA extracted from nasal swab and nasopharyngeal swab specimens.

For Use under an
Emergency Use Authorization Only

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Intended Use

The Lyra™ Influenza A Subtype H7N9 Assay is intended for the *in vitro* qualitative detection and identification of viral RNA from the Avian Influenza A (H7N9) Virus (detected in China in 2013) in nasal and nasopharyngeal swabs from patients with signs and symptoms of respiratory infection. The assay is performed on the Applied Biosystems® 7500 Fast Dx instrument. It is indicated for the presumptive identification of virus in patients who may be infected with the Avian Influenza A (H7N9) Virus (detected in China in 2013) from nasal and nasopharyngeal swab specimens in conjunction with clinical and epidemiological risk factors.

The Lyra™ Influenza A Subtype H7N9 Assay targets the hemagglutinin (HA) gene of the Avian Influenza A (H7N9) Virus (detected in China in 2013), which may react to other influenza A/H7 viruses of the Eurasian Lineage.

The presence of influenza A viral RNA in a nasal or nasopharyngeal swab specimen must first be established using an FDA-cleared influenza A device and must also be determined as "un-subtypable" by FDA-cleared influenza device(s) with subtyping capabilities for all currently circulating influenza A viruses in the United States (i.e., seasonal A/H3 and A/H1 pandemic) prior to testing with the Lyra™ Influenza A Subtype H7N9 Assay.

Testing with the Lyra™ Influenza A Subtype H7N9 Assay should not be performed unless the patient meets clinical and epidemiologic criteria for testing suspect specimens.

Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other patient management decisions.

If infection with a novel influenza A virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for novel virulent influenza viruses and sent to state or local health department for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.

The Lyra™ Influenza A Subtype H7N9 Assay is for use under the Food and Drug Administration's Emergency Use Authorization only.

Summary and Explanation

Human infections with a novel avian influenza A (H7N9) virus as well as poultry infections continue to be reported in China. While some mild illnesses in human H7N9 cases have been observed, most patients have had severe respiratory illness, with about one-third resulting in death.. No cases of this novel virus outside of Asia have been reported, and it has not been detected in people or birds in the United States.

Chinese authorities continue to investigate novel avian influenza A (H7N9) cases. Although many patients infected with this virus are reported to have had contact with or exposure to poultry, some cases reportedly have not had such contact or exposure. Close contacts of confirmed H7N9 patients are being followed to determine whether any human-to-human transmission of H7N9 is occurring. No sustained person-to-person transmission of this virus has been found at this time.

It's likely that sporadic cases of H7N9 associated with poultry exposure will continue to occur in China. Cases associated with poultry exposure also may be detected in neighboring countries, and it is possible that this virus may be detected in the United States at some point, likely in a traveler returning from an affected area. Most concerning is the pandemic potential of this virus. Influenza viruses constantly

change and it is possible that this novel virus could gain the ability to easily and sustainably spread between people, triggering a pandemic.

Principle of the Procedure

The Lyra™ Influenza A Subtype H7N9 Assay detects and identifies the Avian Influenza A (H7N9) Virus (detected in China in 2013) viral RNA that has been extracted from a patient sample using the NucliSENS® easyMAG® automated extraction platform. A multiplex real-time RT-PCR reaction is carried out under optimized conditions in a single tube generating amplicons for the targeted virus (if present) and the Process Control (PRC) present in the sample. This reaction is performed utilizing the Applied Biosystems 7500 Fast Dx platform. Identification of the Avian Influenza A (H7N9) Virus (detected in China in 2013) occurs by the use of target specific primers and a fluorescent-labeled probe that hybridizes to a conserved region of the hemagglutinin gene of the Avian Influenza A (H7N9) Virus (detected in China in 2013).

Lyra™ Probe Labels	
Target	**Dye**
Influenza A/H7	FAM
Process Control (PRC)	Quasar® 670

The following is a summary of the procedure:

1. **Sample Collection:** Obtain nasal swabs or nasopharyngeal swabs using standard techniques from symptomatic patients. These specimens are transported, stored, and processed according to established laboratory procedures.[i]

2. **Nucleic Acid Extraction:** Extract nucleic acids from the specimens with the NucliSENS® easyMAG® System following the manufacturer's instructions and using the appropriate reagents (See **Materials Required but Not Provided**).

   Prior to the extraction procedure add 20 µL of the Process Control (PRC) to each 180 µL aliquot of specimen. The PRC serves to monitor inhibitors in the extracted specimen, assures that adequate amplification has taken place and confirms that the nucleic acid extraction was sufficient.

3. **Rehydration of Master Mix:** Rehydrate the lyophilized Master Mix using 135µL of Rehydration Solution. The Master Mix contains oligonucleotide primers, fluorophore and quencher-labeled probes targeting conserved region of the hemagglutinin gene of the Avian Influenza A (H7N9) Virus (detected in China in 2013), as well as the process control sequence. The probes are dual labeled with a reporter dye attached to the 5' end and a quencher attached to the 3' end. The rehydrated Master Mix is sufficient for eight reactions.

4. **Nucleic Acid Amplification and Detection:** Add 15 µL of the rehydrated Master Mix to each plate well. 5 µL of extracted nucleic acids (specimen with PRC) is then added to the plate well. Place the plate into the Applied Biosystems® 7500 Fast Dx instrument.

   Once the reaction plate is added to the instrument, the assay protocol is initiated. This protocol initiates reverse transcription of the RNA targets generating complementary DNA, and the subsequent amplification of the target sequences occurs. The Lyra™ Influenza A Subtype H7N9 Assay is based on TaqMan® chemistry, and uses an enzyme with reverse transcriptase, DNA polymerase, and 5'-3' exonuclease activities. During DNA amplification, this enzyme cleaves the probe bound to the complementary DNA sequence, separating the quencher dye from the reporter dye. This step generates an increase in fluorescent signal upon excitation by a light source of the appropriate wavelength. With

each cycle, additional dye molecules are separated from their quenchers resulting in additional signal. If sufficient fluorescence is achieved the sample is reported as positive for the detected target sequence.

Materials Provided

SKU # EUA-M100-S

Detection Kit (96 Reactions) – Store at 2° to 8°C

#	Component	Quantity
❶	**Rehydration Solution** Part M5003	1 vial/kit 1.9 mL
❷	**Lyra™ Influenza A Subtype H7N9 Master Mix** Part M5104 Lyophilized Contents: DNA polymerase enzyme with reverse transcriptase activity Oligonucleotide primer pairs; Oligonucleotide probes dNTPs (dATP, dCTP, dGTP, dUTP, dTTP) Stabilizers	12 vials/kit, 8 reactions/vial
CONTROL	**Process Control** Part M5005	1 vial/kit 2.0 mL
Positive Control	**Avian Influenza A (H7N9) Synthetic DNA** Part M5133	1 vial/kit 1.0 mL

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Materials Required But Not Provided

- Micropipettors (range between 1 to 10 µL and 100 to 1000 µL)
- Non-aerosol pipette tips
- Applied Biosystems®7500Fast Dx software version 1.4
- Applied Biosystems®7500Fast Dx 96 well PCR plate
- Applied Biosystems®optical plate films
- Plate centrifuge for Applied Biosystems® 96 well plate
- bioMérieux NucliSENS easyMAG software version 2.0
- bioMérieux NucliSENS easyMAG Buffers 1, 2, 3
- bioMérieux NucliSENS easyMAG Lysis Buffer
- bioMérieux NucliSENS easyMAG Silica Magnetic Beads
- bioMérieux NucliSENS easyMAG disposables
- Biohit pipettor

Warnings and Precautions

- The presence of influenza A viral RNA in the nasal or nasopharyngeal swab specimen must first be established using an FDA-cleared influenza A device and must also be determined as "un-subtypable" by FDA-cleared influenza detection device(s) with subtyping capabilities for all currently circulating influenza A viruses in the United States (i.e., seasonal A/H3 and A/H1 pandemic) prior to testing with the Lyra™ Influenza A Subtype H7N9 Assay.

- For *In Vitro* Diagnostic Use
- The assay has been validated using bioMérieux NucliSENS easyMAG software version 2.0. Please contact Quidel Technical Support prior to modifying or upgrading beyond this version of software.
- The assay has been validated using Applied Biosystems 7500Fast Dx software version 1.4. Please contact Quidel Technical Support prior to modifying or upgrading beyond this version of software.
- 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.
- Use of this product should be limited to personnel with sufficient training in PCR and RT-PCR techniques.
- Treat all specimen/samples as potentially infectious. Follow universal precautions when handling samples, this kit and its contents.
- Proper sample collection, storage and transport are essential for correct results.
- Store assay reagents as indicated on their individual labels.
- Wear suitable protective clothing, gloves, eye and face protection when using this kit.
- For accurate results, pipette carefully using only calibrated equipment.
- Thoroughly clean and disinfect all surfaces with a 10% bleach solution followed by molecular grade water.
- Use micropipettes with an aerosol barrier or positive displacement tips for all procedures.
- Avoid microbial and cross contamination of the kit reagents. Follow Good Laboratory Procedures.
- Do not mix reagents from kits with different lot numbers.
- Do not use reagents from other manufacturers with this kit.
- Do not use product after its expiration date.
- Proper workflow planning is essential to minimize contamination risk. Always plan laboratory workflow in a uni-directional manner, beginning with pre-amplification and moving through amplification and detection.
- Use dedicated supplies and equipment in pre-amplification and amplification areas.
- Do not allow cross movement of personnel or equipment between areas.
- Keep amplification supplies separate from pre-amplification supplies at all times.
- Do not open sample tubes or unseal plates post amplification.
- Dispose of amplified material carefully and in accordance with local laws and regulations in order to minimize the risk of amplicon contamination.
- Do not use supplies dedicated for reagent or sample preparation for processing target nucleic acid.
- MSDS is available upon request or can be accessed on the product website.

Storage and Handling of Kit Reagents

- Store the unopened kit at 2° to 8°C until the expiration date listed on the outer kit box.
- The rehydrated Master Mix may be stored at room temperature (20° to 25°C) for up to 24 hours. For longer storage the rehydrated Master Mix should be recapped, sealed with parafilm and stored in an upright position at ≤–20°C for up to 14 days. Protect the Master Mix from light during storage.

Indications of Instability or Deterioration of Reagents: Cloudiness of the Rehydration Solution, when within expiration, may indicate deterioration of this reagent. Contact Quidel Technical Assistance for a replacement.

Specimen Collection, Storage and Handling

Nasal and nasopharyngeal specimens should be collected, transported, stored, and processed according to CLSI M41-A. Specimens should be stored at 2° to 8°C until tested. If specimens cannot be tested within 72 hours of collection, they should be frozen at -70°C or colder until tested.

The following viral transport media (M4, M4-RT, M5, M6, and UTM) (1 mL and 3 mL) are compatible with the Lyra™ Influenza A+B assay.

Nucleic Acid Extracts Storage

Eluates from the NucliSENS easyMAG can be stored at room temperature (20° to 25°C) for 2 hours, at 2° to 8°C for 8 hours and 1 month at –20° to –70°C.

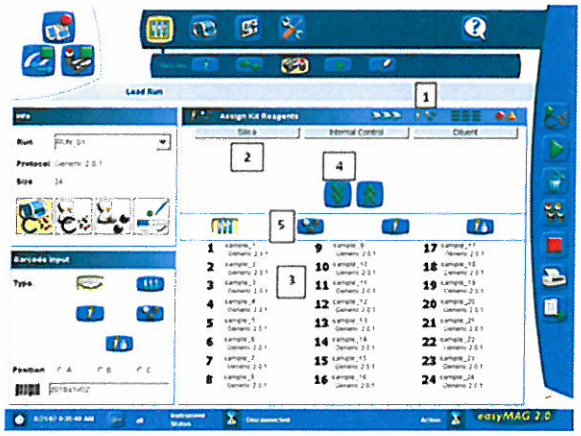
bioMérieux NucliSENS easyMAG Nucleic Acid Extraction Programming Instructions

Note: The Avian Influenza A (H7N9) Synthetic DNA Positive Control (i.e. Lyra™ Influenza A Subtype H7N9 Assay Positive Control #M5133), and a negative process control (i.e., viral transport media or previously characterized influenza A and influenza B negative specimen) should be included in each extraction run.

1. Turn on the instrument and wait for instrument light to appear orange. Then switch on the computer/launch easyMAG software. Do not log into software until the light on the instrument has turned green.
2. Barcode reagents after pressing the 'Instrument'  and 'Reagent Inventory'  buttons.
3. To enter samples, press the 'Daily Use'  button, which will default to the 'Define Request'  screen. Select the following settings:
   a. Sample ID: Enter the **sample name** using the keyboard.
   b. Matrix: Select **Other** from the drop-down menu
   c. Request: Select **Generic** from the drop-down menu
   d. Volume (mL): Select **0.200** from the drop-down menu
   e. Eluate (µL): Select **50** from the drop-down menu
   f. Type:Primary
   g. Priority: Normal
4. Upon pressing the 'Save'  button, the sample will appear in the 'Unassigned Sample' window on the left side of the screen. Press the 'Enter New Extraction Request'  button, and repeat the process for additional samples. Alternatively multiple samples can be entered by pressing the 'Auto Create New Extraction Requests'  button.
5. Once all samples are created, go to 'Organize Runs' by clicking on the  icon near the top of the page. Create a run by pressing the 'Create Run'  button. Enter a run name or use the default.
6. Add samples to the run by using the 'Auto Fill Run'  button (auto fills up to 24 samples from the 'Unassigned Sample list' on the left hand side of the screen). Alternatively, individual samples can be moved into and out of the run by using the left and right 'Positioning icons'  after

selecting the appropriate sample. The sample order within the run can be changed using the 'Move Extraction Request Up/Down' buttons  .

7. Obtain 1 to 3 (for 8 to 24 samples, respectively) sample vessel(s), and add 20 µL of Process Control to each sample well used.
8. Add 180 µL of each sample to the appropriate well as designated.
9. Go to 'Load Run' by pressing the  button near the top of the screen. Insert tips and sample vessel(s) into the instrument
10. Enter the barcode(s) of the sample vessel(s)
11. Enter the barcode(s) of silica beads to be used
12. Close the instrument lid.
13. Assign silica beads to samples as follows:
    a. Click the reagents symbol below number 1 in the picture below. The lot number of the silica beads should appear below the Silica tab at number 2 in the picture below.
    b. Highlight and select the samples in the run for which beads need to be assigned (in the box containing number 3 in the picture below)
    c. Click the  positioning icon (below number 4 in the picture below) to assign the silica lot number to the selected samples
    d. If the bead symbol to the right of number 5 in the picture below is selected, the silica bead lot number should be displayed for each sample



14. Print work list by touching 'Load Run' icon followed by pressing the 'Print Work List' icon  .
15. Press the 'Dispense Lysis'  button. The on-board lysis will take approximately 12 minutes to complete.
16. For each sample vessel, prepare magnetic particles using the Biohit pipettor and tips for up to eight reactions as follows:
    a. Using 1 tip and Program 1, aspirate 550 µL nuclease-free water and dispense into a 1.5 mL DNAse / RNAse free microfuge tube.

b. Vortex the magnetic silica. Using 1 tip and Program 1, aspirate 550 µL of magnetic silica, dispense into the water and mix by vortexing.
c. Using 1 tip and Program 2, aspirate 1050 µL of the magnetic silica mixture and dispense 25 µL back into the same tube.
d. Dispense 125 µL magnetic silica mixture each into 8 wells of an ELISA strip plate. Discard tip.
e. After Lysis is complete (NB: the 'Instrument Status' at the bottom of the screen must be '**IDLE**'!), using 8 tips and Program 3, aspirate 100 µL of magnetic silica mixture in strip wells, dispense 100 µL of magnetic silica mixture in strip wells, and aspirate 100 µL of magnetic silica mixture in strip wells.
f. Insert tips into liquid within the sample vessels. Aspirate 800 µL then dispense 900 µL of magnetic silica mixture back into vessel. Aspirate 1000 µL of magnetic silica mixture from vessel and dispense 1000 µL of magnetic silica back into vessel. Repeat aspiration / dispensing of 1000 µL two more times.

17. Close the instrument and press the 'Start'  button to begin the run.
18. Upon completion of run, transfer purified nucleic acid to nuclease-free tubes. Eluates from the easyMAG can be stored at room temperature (20° to 25°C) for 2 hours, at 2° to 8°C for 8 hours and 1 month at -20° to –70°C.

Applied Biosystems 7500 Fast Dx Programming Instructions

1. Launch the 7500 Fast Dx software package.
2. The **Quick Startup document** dialog window will open. Select the **Create New Document** button to start the **New Document Wizard**. Follow each step to initiate the Lyra™ Influenza A Subtype H7N9 Assay protocol.
   a. Define Document: Most of the following should be the default setting. If not, change accordingly.
      i. Confirm or enter the following information.

Assay:	Standard Curve (Absolute Quantitation)
Container:	96-Well Clear
Template:	Blank Document
Run Mode:	Fast 7500
Operator:	*your operator name*
Comments:	SDS v1.4
Plate Name:	'Lyra Influenza A H7N9'

      ii. Select the **Next** button.

   b. Select Detectors: New detectors for Influenza A, and the process control (PRC) must be added. For each target, select the **New Detector** button to open the **New Detector** pop-up window. Alternatively, use the **Create Another** button from within the **New Detector** pop-up window for the last two detectors.

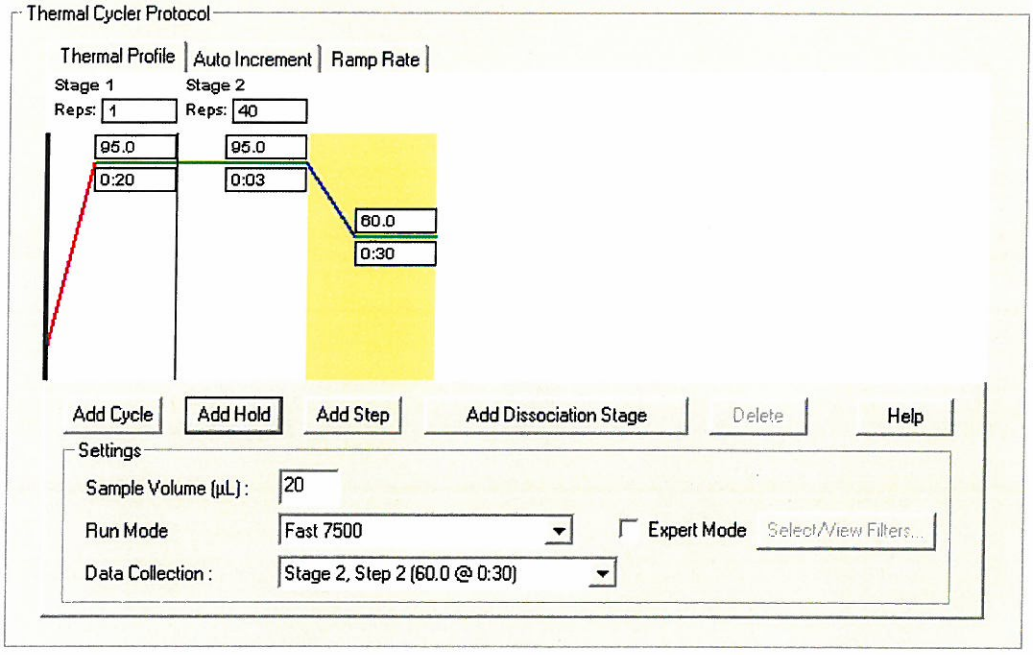
i. Enter the following information for each detector.

Name	Reporter Dye	Quencher Dye	Color
Influenza A	FAM	(none)	(Select)
PRC	Cy5	(none)	(Select)

ii. Select a unique color to represent each detector.
iii. Highlight the new detectors and add to the **Detectors in Document** column using the **Add** button.
iv. Select **(none)** from the **Passive Reference** drop-down menu.
v. Select the **Next** button.
vi. Select the **Finish** button without setting any wells.

c. The wizard will close and the software will open, starting with the **Setup** tab. This will show the sample plate that was set up during the quick start. For the initial set up, nothing needs to be changed here.

d. Defining the Thermocycler Protocol: Select the **Instrument** tab to set up the Lyra™ Influenza A Subtype H7N9 Assay RT-PCR cycling times and temperatures. Under **Thermal Profile** there should be a default 2-stage protocol. Each stage will have 3 user-editable text boxes. The top box value represents the number of reps or cycles for that stage. The middle box value represents the temperature (˚C) and the lowest box value represents the time (minutes: seconds).



i. Make the following changes to the default **Thermal Cycler Protocol**:
   1. Stage 1
      a. Reps: 1
      b. Temp: 55
      c. Time: 5:00
   2. Select the bar between Stage 1 and Stage 2. Select the **Add Hold** button to add another stage.
   3. Stage 2

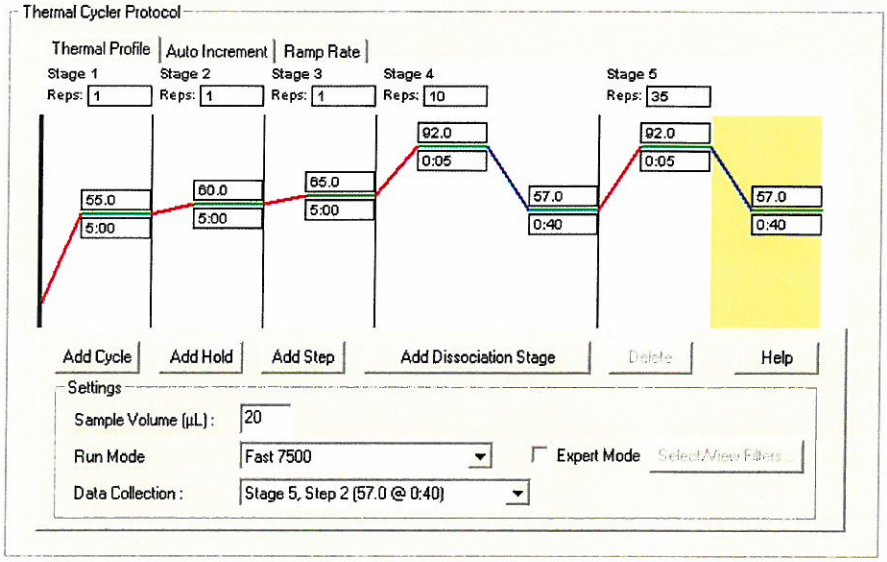
a. Reps: 1
b. Temp: 60
c. Time: 5:00

4. Select the bar between Stage 2 and Stage 3. Select the **Add Hold** button to add another stage.
5. Stage 3
   a. Reps: 1
   b. Temp: 65
   c. Time: 5:00
6. Stage 4 (2-Step Dissociation Stage)
   a. Reps: 10
   b. Step 1
      i. Temp: 92
      ii. Time: 0:05
   c. Step 2
      i. Temp: 57
      ii. Time: 0:40
7. Select the bar to the right of Stage 4. Select the **Add Cycle** button to add another stage.
8. Stage 5 (2-Step Dissociation Stage)
   a. Reps: 35
   b. Step 1
      i. Temp: 92
      ii. Time: 0:05
   c. Step 2
      i. Temp: 57
      ii. Time: 0:40
9. If a wrong stage is added the stage can be removed by pressing the **Delete** button after highlighting the stage between the vertical lines

ii. Under **Settings** enter the following:

Sample Volume (µL):	20 (default)
Run Mode:	7500 Fast (default)
Data Collection:	Stage 5, Step 2(57.0 @ 0:40)
NOTE: Do not check the check box next to 'Expert Mode'.	

iii. Final protocol



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373 e. Set threshold for each analyte.

374 i. Select the **Results** tab.

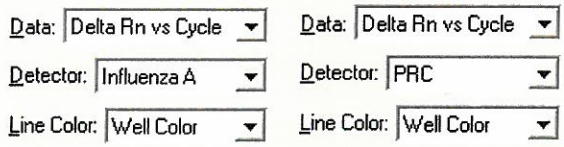
375 ii. Select the **Amplification Plot** tab.

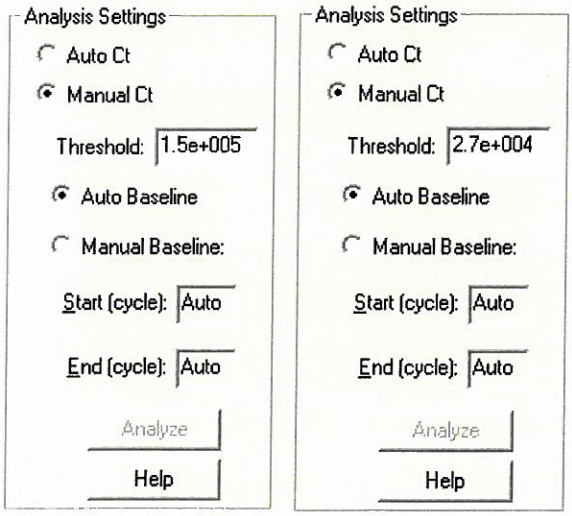
376 iii. Select Influenza A from the Detector tab in the top right corner.

377 iv. In the **Analysis Settings** block, set the **Threshold** to **1.5e5.**

378 v. Select the **Auto Baseline** radio button.

379 vi. Repeat iii-v for PRC setting the **Threshold** to **2.7e4.**





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382 f. Save the new protocol as a template for future use.

i. At the top of the screen select **File** and then **Save As.**
ii. **Save In:** D:\Applied Biosystems\7500 Fast System\Templates\
iii. **File name:** 'Lyra Influenza A H7N9'
iv. **Save as type:** 'SDS Templates (*.sdt)'

g. Exit the software.

Assay Procedure

Run the following procedures at controlled room temperature of 20° to 25°C.

Master Mix Rehydration Procedure

1. Determine the number of specimens extracted to be tested and obtain the correct number of eight-test lyophilized Master Mix vials for testing.
2. Return unused reagents to the appropriate storage conditions.
3. Open Master Mix carefully to avoid disruption of the pellet.
4. Add 135 µL of Rehydration Solution to the Master Mix.
5. Place vial at room temperature for 1 to 2 minutes to allow rehydration of pellet.
6. Gently pipette up and down 2 to 3 times avoiding the formation of bubbles prior to dispensing into the first PCR tube.

Note: The rehydrated Master Mix is sufficient for 8 reactions.

Note: The rehydrated Master Mix may be stored at room temperature (20° to 25°C) for up to 24 hours. For longer storage the rehydrated Master Mix should be recapped, sealed with parafilm and stored in an upright position at ≤–20°C for up to 14 days. Protect the Master Mix from light during storage.

RT-PCR Set-up Procedure:

1. Add 15 µL of the rehydrated Master Mix to each plate well.
2. Add 5 µL of extracted nucleic acid (specimen with the process control) into the plate well. Mixing of reagents is not required.

Note: Use a new barrier micropipettor tip with each extracted specimen.

3. Seal the plate.
4. Centrifuge the reaction tube or plate for a minimum of 15 seconds. Ensure that all liquid is at the bottom of the tube or plate wells.
5. Insert tube or plate into the appropriate thermocycler.

Note: Previously characterized positive influenza A subtype H7N9 specimens serve as an external processing and extraction control and should be treated as a patient specimen and be included in every extraction and PCR run.

Applied Biosystems® 7500 Fast Dx Thermocycler Test Procedure

1. Switch on Applied Biosystems® 7500 Fast Dx.
2. Launch the Applied Biosystems® 7500 Fast Dx software v1.4 package.
3. The **Quick Startup document** dialog window will open.
4. Click on **Create a new document.**
5. Most of the following should be the default setting. If not, change accordingly.

Assay:	Standard Curve (Absolute Quantitation)
Container:	96-Well Clear
Template:	Lyra Influenza A H7N9
Run Mode:	Fast 7500
Operator:	*your operator name*
Comments:	SDS v1.4
Plate Name:	**YYMMDD-** Lyra Influenza A H7N9

6. Set Up Sample Plate
   a. Under the **Setup** and **Plate** tabs the plate setup will appear.
   b. Select all wells that will contain sample, right-click and select the **Well Inspector** from the drop-down menu. When the **Well Inspector** pop-up window opens, select the detectors for influenza A and PRC.
   c. Use the **Well Inspector** to enter the sample names. Patient IDs can be entered in the Well Inspector window. However it is recommended that this is done prior to re-suspending the lyophilized master mix, post run or using the import function to minimize the time the PCR reactions will sit at room temperature prior to starting the run.
   d. Save the run as **YYMMDD- Lyra Influenza A H7N9.sds**.
   e. A window will open asking for the "Reason for change of entry". Enter "**Setup**" and any other comments relevant to the run.
7. Starting the PCR
   a. Select the **Instrument** tab.
   b. Insert the 96 well PCR plate into the machine.
   c. Under **Instrument Control**, select the **Start** button to initiate the run.
8. Post PCR

IMPORTANT: When the run is finished press OK.

   a. Analyze the data by pressing the **"Analyze"** button in the top menu and save the file.
   b. Save the file by pressing **Save Document** in the task bar. A window will open asking for the "Reason for change of entry".
   c. Enter "**Data analysis post run**" and any other comments relevant to the run

Quality Control

The Lyra™ Influenza A Subtype H7N9 Assay incorporates several controls to monitor assay performance.

1. The **Process Control (PRC)** consists of an inactivated and stabilized MS2 Bacteriophage that contains an RNA genome. It must be used during extraction and amplification in the assay. This control should be added to each sample aliquot prior to extraction. The PRC serves to monitor inhibitors in the

extracted specimen, assures that adequate amplification has taken place and confirms that the nucleic acid extraction was sufficient.

2. The **Positive Control** consists of synthetic Avian Influenza A (H7N9) Virus (detected in China in 2013) target amplicon specific double-stranded DNA, and must be treated as a patient specimen and be included in every extraction and RT-PCR run.

3. Viral transport media or previously characterized negative specimen may be used as an external **Negative Control**. This must be treated as a patient specimen and be included in every extraction and PCR run.

4. Failure of either the **Positive Control** or the Negative Control invalidates the RT-PCR run and results should not be reported. The RT-PCR run should be repeated with the extracted controls and specimens first. Re-extract and retest another aliquot of the controls and the specimens or obtain new samples and retest is necessary if the controls fail again.

Expected Results from Controls:

Control Type/ Name	Used to Monitor	Influenza A/H7	Expected Ct Values	PRC	Expected Ct Values
Positive Control	Substantial reagent failure including primer and probe integrity	+	5.0≤ Ct ≤35.0	+/-	NA
Negative Control	Reagent and/or environmental contamination	-	None detected	+	5.0≤ Ct ≤35.0

Interpretation of Results from Patient Specimens

Interpretation of the Lyra™ Influenza A Subtype H7N9 Assay Results on the Applied Biosystems® 7500 Fast Dx Thermocycler

Assay Result	Detector: Influenza A/H7	Detector: Process Control	Interpretation of Results	Notes and Special Guidance
Negative	Ct<5.0 or Ct>35.0	5.0≤ Ct ≤35.0	No Avian Influenza A (H7N9) Virus (detected in China in 2013) viral RNA detected; PRC Detected.	
Influenza A/H7 Positive	5.0≤ Ct ≤35.0	NA*	Avian Influenza A (H7N9) Virus (detected in China in 2013)	Contact CDC or qualified Public Health laboratories immediately for

			viral RNA detected.	coordination of additional testing and for further guidance.
Invalid	Ct<5.0 or Ct>35.0	Ct<5.0 or Ct>35.0	No Avian Influenza A (H7N9) Virus (detected in China in 2013) viral RNA and no PRC RNA detected.	Invalid test. Retest the same purified sample. If the test is also invalid, re-extract and retest another aliquot of the same specimen or obtain a new specimen and retest.

*No Ct value is required for the Process Control to make a positive call.

Limitations

- Negative results do not preclude infection with influenza virus and should not be the sole basis of a patient treatment decision.
- Improper collection, storage or transport of specimens may lead to false negative results.
- Inhibitors present in the sample and/or errors in following the assay procedure may lead to false negative results.
- 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.
- Analyte targets (viral sequences) may persist *in vivo*, independent of virus viability. Detection of analyte target(s) does not imply that the corresponding virus(es) are infectious, nor are the causative agents for clinical symptoms.
- There is a risk of false positive values resulting from cross-contamination by target organisms, their nucleic acids or amplified product, or from non-specific signals in the assay.
- There is a risk of false negative values due to the presence of sequence variants in the viral targets of the assay.
- The assay performance was not established in immunocompromised patients.

Clinical Performance

The Lyra™ Influenza A Subtype H7N9 Assay clinical performance characteristics were estimated using clinical specimens from the 2013 respiratory season and contrived specimens. Due to the lack of available clinical specimens containing the Avian Influenza A (H7N9) Virus (detected in China in 2013), evaluation of the performance of the Lyra™ Influenza A Subtype H7N9 Assay was carried out using an alternative approach. Avian Influenza A (H7N9) Virus (detected in China in 2013) positive samples were prepared by spiking the CDC provided BPL inactivated A/Anhui/1/2013 (H7N9) virus at a concentration of approximately 2.5 x LoD in individual nasopharyngeal specimens that were characterized as influenza A negative by the FDA-cleared Lyra™ Influenza A + B Assay (k112172). The Avian Influenza A (H7N9) Virus (detected in China in 2013) negative clinical specimen were selected from characterized clinical respiratory specimens from the 2013 influenza season. A total of 87 avian influenza A (H7N9) negative specimens were selected. Twenty-six (26) of the 87 specimens were negative for influenza A as determined by the FDA-cleared Lyra™ Influenza A + B Assay (k112172), 13 of the 87 specimens were negative for respiratory viruses as determined by viral culture, 25 of the 87 specimens were positive for influenza A as determined by viral culture and/or the FDA-cleared Lyra™ Influenza A + B Assay (k112172), 12 of the 87 specimens were positive for influenza B as determined by viral culture and/or the FDA-cleared Lyra™ Influenza A + B Assay (k112172), nine of the 87 specimens were

positive for respiratory syncytial virus (RSV) as determined by the FDA-cleared Quidel Molecular RSV + hMPV Assay (k131813), one of the 87 specimens was positive for human metapneumovirus (hMPV) as determined by the FDA-cleared Quidel Molecular RSV + hMPV Assay (k131813), and one of the 87 specimens was positive for parainfluenza virus type 1 as determined by the FDA-cleared Gen-probe Prodesse ProParaflu + (k132238).

Overall, a total of 26 contrived avian influenza A (H7N9) positive specimens and 87 avian influenza A (H7N9) negative clinical specimens were tested in the study in a randomized and blinded fashion. Results of the study are summarized in the table below:

Performance Summary

Lyra™ Influenza A Subtype H7N9 Assay Result	# of Positives[1]	% Positive Agreement (95% CI)	# of Negatives[1]	% Negative Agreement (95% CI)
	26	100.0 (87.1 – 100.0)	87	100.0 (95.8 -100.0)

[1]Proportion of true positives or true negatives correctly identified

Analytical Performance

Limit of Detection (LoD)

A preliminary Limit of Detection (LoD) study was performed initially using a synthetic DNA template. The synthetic double-stranded DNA template was synthesized based on the published HA gene sequence of the A/Hangzhou/1/2013 (H7N9) virus strain, and represents a 177-base pairs sequence that matches the amplicon sequence generated using the Lyra™ Influenza A Subtype H7N9 Assay primer pair. Serial dilutions of this synthetic DNA template from $5x10^5$ to $5x10^0$ copies per reaction were tested by the Lyra™ Influenza A Subtype H7N9 Assay. The Lyra™ Influenza A Subtype H7N9 Assay detected five copies of the synthetic DNA template per reaction.

The Limit of Detection (LoD) of the Lyra™ Influenza A Subtype H7N9 Assay was further determined using a β-propiolactone (BPL) inactivated egg cultured A/Anhui/1/2013 (H7N9) virus strain. The strain was obtained upon request from the Centers for Disease Control and Prevention (CDC) after authorization by the World Health Organization (WHO) Pandemic Influenza Preparedness (PIP) Framework. The virus was titered by the CDC using EID_{50} methodology and subsequently inactivated with BPL. The virus stock was serially diluted in a negative nasopharyngeal matrix. Each dilution was extracted using the NucliSENS® easyMAG® system and tested in replicates of 20 per concentration of virus on the Applied Biosystems® 7500 Fast Dx instrument according to the Lyra™ Influenza A Subtype H7N9 Assay protocol. LoD is defined as the lowest concentration at which 95% of all replicates tested positive.

LoD Determination Study Results (Inactivated Virus)

Targets	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)			Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)		
Virus Concentration (EID_{50}/mL)	3.95×10^3	1.98×10^3	9.88×10^2	3.95×10^3	1.98×10^3	9.88×10^2
1	29.4	32.7	Negative	17.9	18.4	18.2
2	29.5	33.9	Negative	18.1	18.5	18.2
3	33.7	Negative	Negative	18.2	18.4	18.2
4	32.6	30.5	31.3	18.3	18.2	18.3
5	29.3	32.5	Negative	18.2	18.6	18.2
6	29.5	Negative	33.6	17.9	18.3	18.2
7	31.4	32.9	34.7	18.1	18.3	18.0
8	30.1	32.7	31.7	18.0	18.4	18.1
9	32.9	32.3	33.1	18.1	18.2	18.2
10	30.9	30.9	32.7	18.2	18.2	18.3
11	28.1	Negative	33.0	18.2	18.3	17.7
12	31.6	34.9	Negative	18.2	18.5	17.9
13	33.8	30.7	Negative	18.7	18.5	17.9
14	34.3	Negative	Negative	18.4	18.4	18.1
15	31.0	32.9	Negative	18.4	18.4	18.1
16	30.2	31.9	32.0	18.3	18.5	18.1
17	28.5	32.5	Negative	18.1	18.3	18.0
18	29.7	31.7	Negative	18.1	18.4	18.0
19	31.4	32.5	Negative	18.4	18.3	18.0
20	30.4	30.8	Negative	18.1	18.4	18.3
Positive Replicates/Total	**20/20**	**16/20**	**8/20**	**20/20**	**16/20**	**8/20**

Replicates						

The LoD for the Lyra™ Influenza A Subtype H7N9 Assay testing the BPL inactivated A/Anhui/1/2013 (H7N9) virus was determined to be **3.95 x 10^3 EID_{50}/mL.**

Analytical Reactivity – *In silico* Prediction

Additional isolates of the Avian Influenza A (H7N9) Virus (detected in China in 2013) are not available for testing in the U.S. *In silico* analysis was carried out to predict analytical reactivity to other isolates of the Avian Influenza A (H7N9) Virus (detected in China in 2013). A total of 13 full-length HA gene sequences of different isolates of the Avian Influenza A (H7N9) Virus (detected in China in 2013) were obtained from the National Center for Biotechnology Information (NCBI) for this analysis.

The Lyra™ Influenza A Subtype H7N9 Assay primer and probe set demonstrated 100% sequence homology to all the 10 Avian Influenza A (H7N9) Virus (detected in China in 2013) isolates recovered from human patients and the three Avian Influenza A (H7N9) Virus (Detected in China in 2013) isolates recovered from the environment and chicken included in this analysis.

Analytical Specificity – Non-A/H7 Influenza A Viruses

Analytical specificity of the Lyra™ Influenza A Subtype H7N9 Assay was evaluated with a panel of 22 non-A/H7 influenza A viruses. The FDA-cleared Lyra™ Influenza A + B Assay (k112172) was also performed as a quality control measure for the viruses. All of the influenza A viruses tested were positive in the Lyra™ Influenza A + B Assay and negative in the Lyra™ Influenza A Subtype H7N9 Assay at the concentrations tested. The study results are shown in the table below

Analytical Specificity Study Results – Non-A/H7 Influenza A Viruses

Virus	Virus Titer in $TCID_{50}$/mL	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)	Lyra™ Influenza A + B Assay Result
A/Mexico/4108/2009 (pdm H1N1)	$2.80x10^6$	Negative	18.9	Influenza A
A/Perth/16/09 (H1N1)	$8.80x10^4$	Negative	19.2	Influenza A
A/West Virginia/06/2011 (H3N2v)	$1.00x10^4$	Negative	18.5	Influenza A
A/Pennsylvania/14/2010 (H3N2v)	$1.00x10^4$	Negative	18.0	Influenza A

Virus	Virus Titer in $TCID_{50}$/mL	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)	Lyra™ Influenza A + B Assay Result
A/Minnesota/11/2010 (H3N2v)	$1.00x10^4$	Negative	18.1	Influenza A
A/Kansas/13/2009 (H3N2v)	$1.00x10^4$	Negative	18.1	Influenza A
A/Indiana/08/2011 (H3N2v)	$1.00x10^4$	Negative	18.5	Influenza A
A/Indiana/10/2011 (H3N2v)	$1.00x10^4$	Negative	18.3	Influenza A
A/Wisconsin/07/09 (H3N2)	$2.00x10^6$	Negative	18.5	Influenza A
A/California/07/09 (H3N2)	$2.00x10^6$	Negative	22.7	Influenza A
A/Port Chalmers/1/73 (H3N2)	$4.50x10^6$	Negative	21.3	Influenza A
A/Uruguay/7/16/2007 (H3N2)	$1.00x10^6$	Negative	21.9	Influenza A
A/New Caledonia/20/1999 (H1N1)	$1.00x10^6$	Negative	20.3	Influenza A
A/Victoria/3/75 (H3N2)	$2.00x10^6$	Negative	24.0	Influenza A
A/Denver/1/57 (H1N1)	$1.00x10^6$	Negative	21.3	Influenza A
A1/Mal/302/54 (H1N1)	$1.00x10^6$	Negative	21.8	Influenza A
A/Perth/16/2009 (H3N2)	$1.00x10^8$	Negative	19.7	Influenza A
A/Aichi/2/68 (H3N2)	$1.00x10^5$	Negative	21.7	Influenza A
A/Wisconsin/67/2005 (H3N2)	$1.00x10^5$	Negative	21.8	Influenza A
A/NWS/33 (H1N1)	$1.00x10^5$	Negative	22.4	Influenza A
A/Hong Kong/8/68 (H3N2)	$1.00x10^7$	Negative	20.3	Influenza A
A/New Jersey/8/76 (H1N1)	$1.00x10^6$	Negative	22.8	Influenza A

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Analytical Specificity/Cross-Reactivity – Common Respiratory Bacteria, Yeast and Viruses

Potential cross-reactivity of the Lyra™ Influenza A Subtype H7N9 Assay was evaluated by testing an extensive list of common respiratory bacteria, yeast, and viruses (a total of 30 viruses, 26 bacteria, and one yeast). No cross-reactivity was observed with any of the 57 organisms at the concentrations tested. The study results are shown in the tables below:

Cross-Reactivity Study Results –Viruses

Organism	Concentrations Tested ($TCID_{50}$/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Adenovirus type 1	$1.51x10^5$	Negative	19.9
Coronavirus 229E	$2.46x10^7$	Negative	18.4
Coronavirus NL63	$1.41x10^5$	Negative	21.1
Coronavirus OC43	$2.42x10^7$	Negative	18.4
Coxsackievirus B4:ODH-42385	$2.00x10^7$	Negative	20.3
Cytomegalovirus	$2.14\ x10^6$	Negative	18.2
Echovirus 6	$1.52\ x10^9$	Negative	18.6
Echovirus 7	$4.58\ x10^6$	Negative	19.6
Echovirus 9	$2.17\ x10^7$	Negative	19.8
Echovirus 11	$2.17x10^6$	Negative	20.8
Enterovirus 70	$2.41x10^6$	Negative	18.0
Enterovirus 71	$2.03x10^5$	Negative	18.1
Epstein Barr Virus	$9.27x10^8$ genome equivalents/mL*	Negative	19.2
HSV Type 1 MacIntyre Strain	$5.89x10^7$	Negative	18.3
HSV Type 2 G strain	$1.96x10^6$	Negative	18.3
Human Metapneumovirus (A1)	$3.66x10^5$	Negative	18.6

Organism	Concentrations Tested ($TCID_{50}$/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Human Rhinovirus 45	$5.87x10^4$	Negative	18.2
Human Rhinovirus 52	$5.25x10^4$	Negative	18.2
Influenza A/Mexico/4108/2009	$4.08x10^5$	Negative	18.4
Influenza A/Port Chalmers	$3.55x10^8$	Negative	18.4
Influenza B/Florida/04/2006	$1.54x10^6$	Negative	18.5
Measles	$1.95x10^7$	Negative	18.1
Mumps Virus	$2.75x10^9$	Negative	18.5
Parainfluenza Type 1	$1.58x10^5$	Negative	18.8
Parainfluenza Type 2	$3.15x10^8$	Negative	18.9
Parainfluenza Type 3	$2.56x10^7$	Negative	20.8
Parainfluenza Type 4A	$1.04x10^5$	Negative	19.0
RSV A (Long)	$4.36x10^4$	Negative	18.5
RSV B Strain (Wash/18537/62)	$3.43x10^5$	Negative	18.2
Varicella Zoster Virus	$1.11x10^4$	Negative	18.3

582 *Quantified by a molecular method

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584 **Cross-Reactivity Study Results –Bacteria and Yeast**

Organism	Concentrations Tested (CFU/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Bordetella pertussis	9.08×10^8	Negative	19.7
Bordetella bronchiseptica	5.40×10^8	Negative	19.5
Chlamydophila pneumoniae	2.2 ug/mL (DNA)	Negative	18.1
Chlamydophila trachomatis	2.10×10^6	Negative	19.1
Legionella pneumophila	1.42×10^9	Negative	19.8
Mycobacterium intracellulare (ATCC 95-06)	1.53×10^9	Negative	19.1
Mycobacterium tuberculosis	9.30×10^6	Negative	19.1
Mycobacterium avium (ATCC 25291)	3.18×10^9	Negative	20.2
Mycoplasma pneumoniae	3.16×10^7	Negative	18.6
Haemophilus influenzae	4.00×10^8	Negative	19.4
Pseudomonas aeruginosa	1.32×10^9	Negative	20.9
Proteus vulgaris	6.53×10^8	Negative	19.8
Proteus mirabilis	1.19×10^9	Negative	20.7
Neisseria gonorrhoeae	1.40×10^9	Negative	21.3
Neisseria meningitidis	1.29×10^8	Negative	19.7

Organism	Concentrations Tested (CFU/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Neisseria mucosa	$1.61x10^9$	Negative	21.5
Klebsiella pneumoniae	$9.75x10^8$	Negative	20.8
Escherichia coli (ATCC 43895)	$1.13x10^9$	Negative	21.2
Moraxella catarrhalis (ATCC 8176)	$1.26x10^9$	Negative	20.8
Corynebacterium diptheriae (ATCC 19409)	$3.44x10^8$	Negative	18.5
Lactobacillus plantarum	$3.18x10^8$	Negative	18.4
Streptococcus pneumoniae (ATCC 6305)	$1.43x10^8$	Negative	19.3
Streptococcus pyogenes (ATCC 9898)	$6.38x10^8$	Negative	18.5
Streptococcus salivarius	$5.40x10^8$	Negative	18.3
Staphylococcus epidermidis	$9.23x10^8$	Negative	18.3
Staphylococcus aereus (ATCC 12598)	$6.08x10^8$	Negative	18.2
Candida albicans	$9.70x10^7$	Negative	18.2

Microbial Interference – Common Respiratory Bacteria, Yeast and Viruses

The performance of the Lyra™ Influenza A Subtype H7N9 Assay was also evaluated with potentially interfering common respiratory organisms. The same organisms that were tested in the Cross-Reactivity Study (described above) were used in this Microbial Interference Study. The potentially interfering organisms were evaluated with the BPL inactivated A/Anhui/1/2013

592 (H7N9) virus (as described in the LoD section) at a concentration of approximately 1x LoD using
593 the Lyra™ Influenza A Subtype H7N9 Assay. No interference was observed with any of the 57
594 organisms at the concentrations tested. The study results are shown in the tables below:

595 **Microbial Interference Study Results –Viruses**

Organism	Concentrations Tested ($TCID_{50}$/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Adenovirus type 1	$1.36x10^5$	28.7	18.4
Coronavirus 229E	$2.21x10^7$	28.2	18.1
Coronavirus NL63	$1.27x10^5$	28.9	18.6
Coronavirus OC43	$2.18x10^7$	29.8	18.3
Coxsackievirus B4:ODH-42385	$1.80x10^7$	31.4	19.2
Cytomegalovirus	$1.93x10^6$	27.6	18.2
Echovirus 6	$1.37x10^9$	31.2	18.2
Echovirus 7	$4.12x10^6$	32.0	19.2
Echovirus 9	$1.95x10^7$	32.6	18.4
Echovirus 11	$1.95x10^6$	32.8	19.3
Enterovirus 70	$2.17x10^6$	31.1	18.0
Enterovirus 71	$1.83x10^5$	29.9	18.0
Epstein Barr Virus	$8.34x10^8$ genome equivalents/mL*	29.9	18.2
HSV Type 1 MacIntyre Strain	$5.30x10^7$	28.8	18.2
HSV Type 2 G strain	$1.76x10^6$	29.7	18.2
Human Metapneumovirus (A1)	$3.29x10^5$	29.6	18.1
Human Rhinovirus 45	$5.28x10^4$	32.4	18.2

Organism	Concentrations Tested ($TCID_{50}$/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Human Rhinovirus 52	$4.73x10^4$	30.5	18.2
Influenza A/Mexico/4108/2009	$3.67x10^5$	31.1	18.3
Influenza A/Port Chalmers	$3.20x10^8$	34.8	18.2
Influenza B/Florida/04/2006	$1.39x10^6$	29.6	18.1
Measles	$1.76x10^7$	28.8	18.2
Mumps Virus	$2.48x10^9$	27.0	17.9
Parainfluenza Type 1	$1.42x10^5$	29.9	18.2
Parainfluenza Type 2	$2.84x10^8$	31.3	18.3
Parainfluenza Type 3	$2.30x10^7$	34.0	18.8
Parainfluenza Type 4A	$9.36x10^4$	29.8	18.1
RSV A (Long)	$3.92x10^4$	30.0	18.2
RSV B Strain (Wash/18537/62)	$3.09x10^5$	29.2	18.3
Varicella Zoster Virus	$9.99x10^3$	27.0	18.3

*Quantified by a molecular method

602 **Microbial Interference Study Results –Bacteria and Yeast**

Organism	Concentrations Tested (CFU/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Bordetella pertussis	$8.17x10^8$	28.0	18.9
Bordetella bronchiseptica	$4.86x10^8$	30.6	18.9
Chlamydophila pneumoniae	1.98 ug/mL (DNA)	28.8	18.3
Chlamydophila trachomatis	$1.89x10^6$	33.8	18.5
Legionella pneumophila	$1.28x10^9$	30.9	19.0
Mycobacterium intracellulare (ATCC 95-06)	$1.38x10^9$	29.5	18.3
Mycobacterium tuberculosis	$8.37x10^6$	29.4	18.5
Mycobacterium avium (ATCC 25291)	$2.86x10^9$	29.5	18.7
Mycoplasma pneumoniae	$2.84x10^7$	31.4	18.4
Haemophilus influenzae	$3.60x10^8$	31.3	19.0
Pseudomonas aeruginosa	$1.19x10^9$	29.7	19.5
Proteus vulgaris	$5.88x10^8$	30.6	18.4
Proteus mirabilis	$1.07x10^9$	29.7	19.3
Neisseria gonorrhoeae	$1.26x10^9$	30.1	19.5
Neisseria meningitidis	$1.16x10^8$	28.4	18.7

Organism	Concentrations Tested (CFU/mL)	Lyra™ Influenza A Subtype H7N9 Assay A/H7 (Ct)	Lyra™ Influenza A Subtype H7N9 Assay PRC (Ct)
Neisseria mucosa	$1.45x10^9$	32.2	19.8
Klebsiella pneumoniae	$8.78x10^8$	27.6	19.1
Escherichia coli (ATCC 43895)	$1.02x10^9$	30.3	19.1
Moraxella catarrhalis (ATCC 8176)	$1.13x10^9$	30.0	18.7
Corynebacterium diptheriae (ATCC 19409)	$3.10x10^8$	27.9	18.5
Lactobacillus plantarum	$2.86x10^8$	30.0	18.5
Streptococcus pneumoniae (ATCC 6305)	$1.29x10^8$	30.2	18.8
Streptococcus pyogenes (ATCC 9898)	$5.74x10^8$	29.1	18.6
Streptococcus salivarius	$4.86x10^8$	30.6	18.4
Staphylococcus epidermidis	$8.31x10^8$	29.2	18.3
Staphylococcus aereus (ATCC 12598)	$5.47x10^8$	27.7	18.5
Candida albicans	$8.73x10^7$	27.5	18.3

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