

This Procedural Bulletin is intended to provide a ready outline reference for performance of the assay. These abbreviated directions for use are not intended to replace the complete Package Insert. It is the obligation of every manufacturer of medical devices labeled FOR *IN VITRO* DIAGNOSTIC USE to provide a complete Package Insert in accordance with FDA labeling regulation (21CFR 809.10).

Quidel Corporation provides CLSI procedures for your use. The procedures are required to include the same information as listed in the Package Insert. Any modifications to this document are the sole responsibility of the Laboratory.

Lyra® Adenovirus Assay

CLIA Complexity: High

INTENDED USE

The Lyra Adenovirus Assay is a real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the qualitative detection of human adenovirus (HAdV) viral DNA isolated from nasal and nasopharyngeal swab specimens obtained from individuals exhibiting signs and symptoms of acute respiratory infections. The intended use of this test is to aid in the diagnosis of HAdV in conjunction with other clinical and laboratory findings.

The test detects, but does not differentiate, HAdV species (A, B, C, D, E, and F) or serotypes (HAdV 1-52).

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

SUMMARY AND EXPLANATION

Adenoviruses (HAdV; family Adenoviridae) are non-enveloped, double stranded DNA viruses. At the present time there are 52 serotypes, further divided into 6 groups, A to F. Most HAdVs are associated with respiratory and ocular infections. Generally, HAdV infections in adults have a low morbidity with the exceptions of immunocompromised individuals and those living in overcrowded conditions, in which infections can cause atypical pneumonia. Virus spread is commonly through aerosolized droplets and fomites with infection of mucous membranes of the eye, respiratory tract and gut.

PRINCIPLE OF THE PROCEDURE

The assay detects viral nucleic acids that have been extracted from a patient sample. A real-time polymerase chain reaction (PCR) is carried out under optimized conditions in a single tube generating amplicons for HAdV and the Process Control (PRC). Identification of HAdV and the PRC occurs by the use of target-specific primers and fluorescent-labeled probes that hybridize to conserved regions in the genomes of HAdV and the PRC.

Lyra Probe Labels	
Target	Dye
HAdV	FAM
PRC	Cy5

The following is a summary of the procedure:

1. **Sample Collection:** Obtain nasal or nasopharyngeal swabs specimens using standard techniques from symptomatic patients. Transport, store, and process these specimens according to established laboratory procedures.¹

2. **Nucleic Acid Extraction:** Extract nucleic acids from the specimens with the bioMérieux® NucliSENS® easyMAG® System following the manufacturer’s instructions and using the appropriate reagents (See **Materials Required but Not Provided**). Use of other extraction systems with the Lyra Adenovirus Assay has not been validated. Validation of these other systems is the responsibility of the end user. Prior to the extraction procedure, add 20 µL of the 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 the Rehydration Solution. The Master Mix contains oligonucleotide primers, fluorophore and quencher-labeled probes targeting conserved regions of HAdV, as well as the PRC sequence.
4. **Nucleic Acid Amplification and Detection:** Add 15 µL of the rehydrated Master Mix to each plate well. Then add 5 µL of extracted nucleic acids (specimen with PRC) to the plate well. Place the plate into the Applied Biosystems® 7500 Fast or Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument (“7500 Fast Dx Instrument”).

Once the plate is added to the instrument, initiate the assay protocol. This protocol initiates amplification of the DNA target amplicons. The Lyra Adenovirus 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 by 45 cycles on the 7500 Fast or 7500 Fast Dx Instrument, the sample is reported as positive for the detected nucleic acid.

MATERIALS PROVIDED

Cat. #M113

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

Component	Quantity
Rehydration Solution Part M5003	1 vial/kit 1.9 mL
Lyra Adenovirus Master Mix Part M5072 Lyophilized Contents: DNA polymerase enzyme Primers and probes dNTPs Stabilizers	12 vials/kit, 8 reactions/vial
Process Control (PRC) Part M5005 Identity: MS2 Bacteriophage	1 vial/kit 2.0 mL

OPTIONAL MATERIALS

- External controls for HAdV (i.e. Lyra Adenovirus Control Set, #M110 which serves as an external processing and extraction control).

MATERIALS REQUIRED BUT NOT PROVIDED

- Micropipettors (range between 1 to 10 µL and 100 to 1000 µL)
- Non-aerosol pipette tips
- 7500 Fast Dx instrument or 7500 Fast (software version 1.4.1 or higher)
- 96 well PCR plate
- Optical plate films
- Plate centrifuge for ABI 96 well plate
- NucliSENS easyMAG software (version 2.0)
- NucliSENS easyMAG Buffers 1, 2, 3

- NucliSENS easyMAG Lysis Buffer
- NucliSENS easyMAG Silica Magnetic Beads
- NucliSENS easyMAG disposables
- Biohit pipettor

WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use.
- The assay has been validated using NucliSENS easyMAG software version 2.0 and 7500 Fast Dx Software version 1.4.1 or higher. Please contact Quidel Technical Support prior to modifying or upgrading beyond these versions 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 nucleic acid extraction systems other than the NucliSENS easyMAG System has not been validated. Validation of these systems is the responsibility of the end-user.
- Using cycling conditions other than those indicated in the **Set Up of Thermocycler Program (7500 Fast Dx Instrument)** section may give erroneous results.
- 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.
- 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.
- Testing should be performed in an area with adequate ventilation.
- Dispose of containers and unused contents in accordance with Federal, State and Local regulatory requirements.
- Wear suitable protective clothing, gloves, and eye/face protection when handling the contents of this kit.
- Wash hands thoroughly after handling.
- For additional information on hazard symbols, safety, handling and disposal of the components within this kit, please refer to the Safety Data Sheet (SDS) located at quidel.com.

STORAGE AND HANDLING OF KIT REAGENTS

- Store the unopened kit at 2°C to 8°C until the expiration date listed on the outer kit box.
- The rehydrated Master Mix may be kept at room temperature or at 2°C to 8°C for up to 4 hours or at –20°C for up to 3 days.

- The rehydrated Master Mix should be recapped, sealed with parafilm, and stored in an upright position. Protect the Master Mix from light during storage.

INDICATIONS OF INSTABILITY OR DETERIORATION OF REAGENTS

Cloudiness of the Rehydration Solution may indicate deterioration of this reagent. Contact Quidel Technical Support for a replacement.

SPECIMEN COLLECTION, STORAGE, AND HANDLING

Specimens used for the validation of the Lyra Adenovirus Assay were obtained using standard techniques from patients with upper respiratory tract infection symptoms. These specimens were collected, transported, stored, and processed according to CLSI M41-A. Briefly, samples should be transported refrigerated at 2°C to 8°C. Unextracted samples can be stored refrigerated (2°C to 8°C) or frozen at –20°C for up to 7 days before processing.

A series of studies were performed evaluating a number of routinely used viral transport medium at a volume of 2mL: M4, M4-RT, M5, M6, and UTM. No significant difference in assay performance was seen between the five different types of viral transport media.

NUCLEIC ACID EXTRACTS STORAGE

Nucleic acid extracts can be stored at room temperature (20°C to 25°C), 2°C to 8°C, or at ≤–20°C for up to 30 days. The extracted DNA is stable for up to three freeze/thaw cycles when stored at ≤–20°C.

SET UP OF NUCLEIC ACID EXTRACTION PROGRAM (NUCLISENS EASYMAG SYSTEM)

Note: A HAdV positive processing/extraction control (i.e. Lyra Adenovirus Control Set, Cat. #M110 or previously characterized positive HAdV specimen) and a negative external control (i.e. viral transport media or previously characterized HAdV 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 the NucliSENS easyMAG System software.

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 may 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 may 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 PRC 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. Assign silica beads to samples as follows:

a. Click the reagents symbol (number 1 in the picture below). The lot number of the silica beads should appear below the Silica tab (number 2 in the picture below).

b. Highlight and select the samples for which beads need to be assigned (number 3 in the picture below).

c. Click the  positioning icon (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.



The screenshot shows the 'Assign Kit Reagents' screen in the easyMAG 2.0 software. The interface is divided into several sections:

- Info:** Run: RUN_01, Protocol: Generic 2.0.1, Size: 24.
- Barcode Input:** Type: [Barcode icon], Position: A, B, C.
- Assign Kit Reagents:** A table with columns for Silica, Internal Control, and Diluent. Each row represents a sample (sample_1 to sample_24) with a reagent icon and a lot number.

Numbered callouts in the image indicate the following steps:

- 1: Click the reagent icon (bead symbol) for a sample.
- 2: The lot number of the silica beads appears below the Silica tab.
- 3: Highlight and select the samples for which beads need to be assigned.
- 4: Click the positioning icon (green checkmark and up arrow) to assign the silica lot number to the selected samples.
- 5: 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.



13. Print work list by touching 'Load Run' icon followed by pressing the 'Print Work List' icon.



14. Press the 'Dispense Lysis' button. The on-board lysis will take approximately 12 minutes to complete.

15. 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 8 times into 8 wells of an ELISA strip plate. Discard tip.
- e. After Lysis is complete (Note: 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 from the strip wells, then dispense 100 μL of magnetic silica mixture into the strip wells, and aspirate 100 μL of magnetic silica mixture into the strip wells again to mix the solution.
- f. Insert tips into liquid within the sample vessels. Aspirate 800 μL , then dispense 900 μL of magnetic silica mixture back into the vessel. Aspirate 1000 μL of magnetic silica mixture from the vessel, and dispense 1000 μL of magnetic silica back into the vessel. Repeat aspiration / dispensing of 1000 μL two more times.



16. Close the instrument, and press the 'Start' button to begin the run.

17. Upon completion of the run, transfer purified nucleic acid to nuclease-free tubes. Eluates can be stored at room temperature (20°C to 25°C), 2°C to 8°C, or at $\leq -20^\circ\text{C}$ for 1 month. The extracted DNA is stable for up to three freeze/thaws cycles when stored at -20°C .

SET UP OF THERMOCYCLER PROGRAM

7500 Fast and 7500 Fast Dx Instrument

1. Launch the 7500 Fast and 7500 Fast Dx Software package (version 1.4.1 or higher).
2. The **Quick Startup document** dialog window will open. Select the **Create New Document** button to start the **New Document Wizard**. Follow the steps below to initiate the Lyra Adenovirus Assay protocol.

a. Define Document: Most of the following should be the default setting. If not, change accordingly.

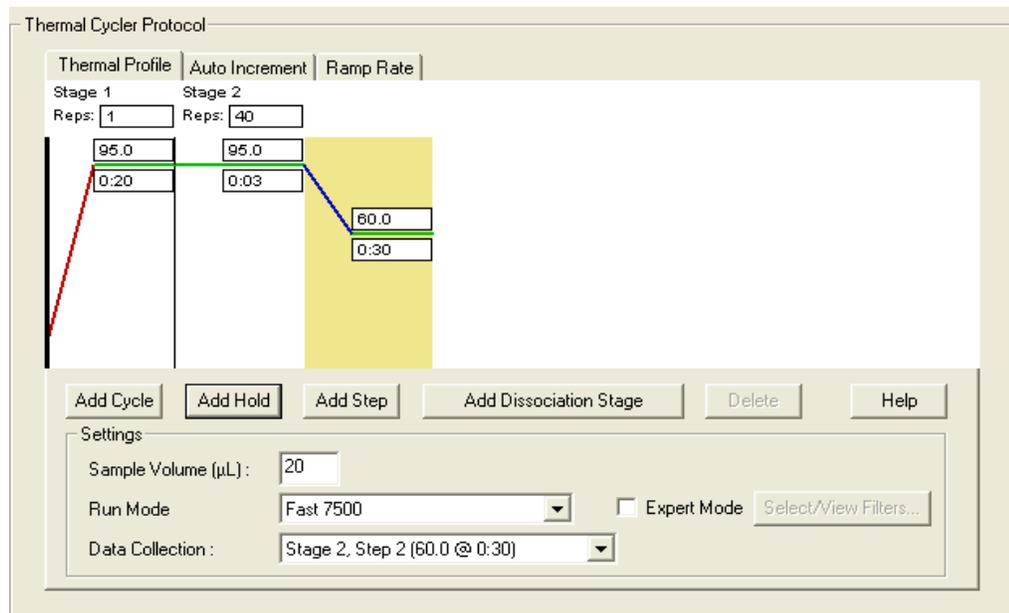
- i. Confirm or enter the following information:

Assay:	Standard Curve (Absolute Quantitation)
Container:	96-Well Clear
Template:	Blank Document
Run Mode:	Fast 7500
Operator:	<i>your operator name</i>
Comments:	SDS v1.4.1
Plate Name:	'Lyra HAdV'

- ii. Select the **Next** button.
- iii. Select Detectors: New detectors for HAdV and the 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. Enter the following information for each detector:

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

- iv. Select a unique color to represent each detector.
 - v. Highlight the new detectors and add to the **Detectors in Document** column using the **Add** button.
 - vi. Select **(none)** from the **Passive Reference** drop-down menu.
 - vii. Select the **Next** button.
 - viii. Select the **Finish** button without setting any wells.
- b. 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.
- c. Define the Thermocycler Protocol:
- i. Select the **Instrument** tab to set up the Lyra Adenovirus Assay cycling times and temperatures.
 - ii. Under **Thermal Profile** there should be a default 2-stage protocol (see figure below). 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).

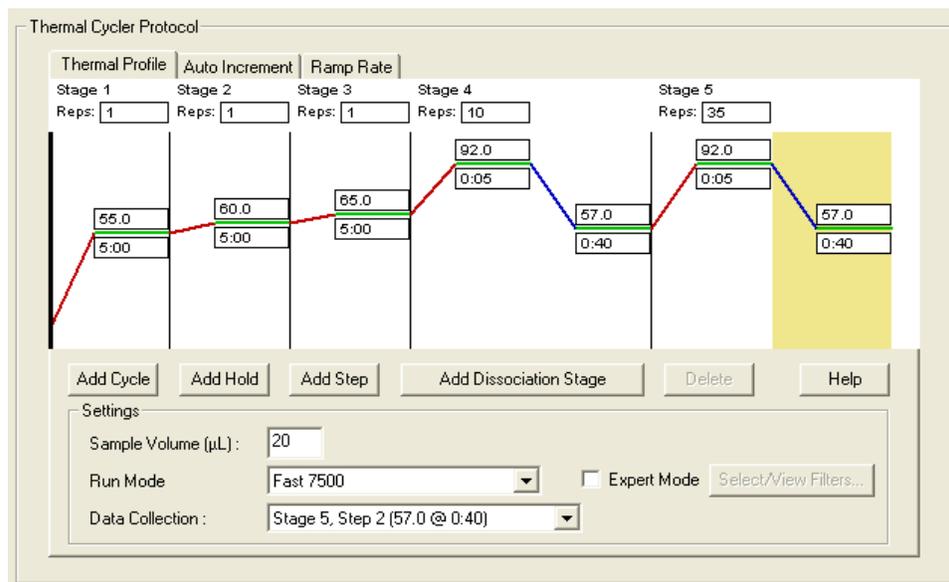


- iii. Make the following changes to the default **Thermal Cycler Protocol**:
 1. Stage 1
 - a. Reps: 1
 - b. Temp: 55
 - c. Time: 5:00
 2. Select the bar between Stage 1 and Stage 2. Select the **Add Hold** button to add another stage.
 3. Stage 2
 - a. Reps: 1
 - b. Temp: 60
 - c. Time: 5:00

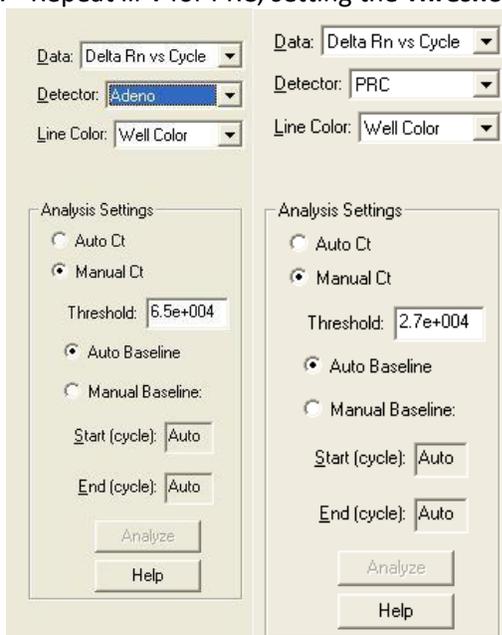
4. Select the bar between Stage 2 and Stage 3. Select the **Add Hold** button to add another stage.
 5. Stage 3
 - a. Reps: 1
 - b. Temp: 65
 - c. Time: 5:00
 6. Stage 4 (2-Step Amplification Stage)
 - a. Reps: 10
 - b. Step 1
 - i. Temp: 92
 - ii. Time: 0:05
 - c. Step 2
 - i. Temp: 57
 - ii. Time: 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 Amplification 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 may be removed by pressing the **Delete** button after highlighting the stage between the vertical lines.
- iv. 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.'	

- v. A figure of the final protocol is shown below
**Note that, according to this protocol, the 7500 Fast and 7500 Fast Dx Instrument will perform 45 cycles. It is programmed, however, to only capture data from the last 35 cycles. Therefore, the end result (and the results interpretation table shown below) will show Cts values between 1 and 35 only.*



- d. Set threshold for each analyte as follows (see figure below):
- Select the **Results** tab.
 - Select the **Amplification Plot** tab.
 - Select HAdV from the **Detector** tab in the top right corner.
 - In the **Analysis Settings** block, set the **Threshold** to **6.5e+004**.
 - Select the **Auto Baseline** radio button.
 - Repeat iii-v for PRC, setting the **Threshold** to **2.7e+004**.



- e. Save the new protocol as a template for future uses.
- At the top of the screen select **File** and then **Save As**.
 - Save In:** D:\Applied Biosystems\7500 Fast System\Templates\.
 - File name:** 'Lyra HAdV.'
 - Save as type:** 'SDS Templates (*.sdt).'
- f. Exit the software.

ASSAY PROCEDURE

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

Nucleic Acid Extraction Procedure

Refer to the section titled: Set Up of Nucleic Acid Extraction Program NucliSENS easyMAG System (above).

1. Add 20 µL of the PRC to the sample extraction well.
2. Add 180 µL of patient sample or external control to a sample extraction well.
3. Follow extraction procedure as per manufacturer's instructions.
4. Eluates can be stored at room temperature (20°C to 25°C), 2°C to 8°C, or at –20°C for 1 month. The extracted DNA is stable for up to three freeze/thaws cycles when stored at –20°C.

Master Mix Rehydration Procedure

1. Determine the number of specimens 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 1-2 minutes to allow rehydration of pellet.
6. Gently pipette up and down 2-3 times (avoiding the formation of bubbles) prior to dispensing into the first plate well.

Note: The volume of the rehydrated Master Mix is sufficient for eight reactions.

Note: The rehydrated Master Mix may be kept at room temperature for up to 4-hours or at 2°C to 8°C or ≤–20°C for up to 3 days (see Storage and Handling of Kit Reagents section for additional storage options).

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 PRC) into the plate wells. Mixing of reagents is not required.
3. Seal the plate.

Note: Use a micropipettor with a new non-aerosol tip with each extracted specimen.

Note: Quidel suggests each thermocycler run should include a well with a HAdV external positive control and a negative control (containing a PRC). Run controls in keeping with Local, State, and/or Federal regulations or accreditation requirements and your laboratory's standard quality control procedures.

4. Centrifuge the plate for a minimum of 15 seconds. Ensure that all liquid is at the bottom of the tube.
5. Insert plate into the thermocycler.

Amplification Protocol –7500 Fast and 7500 Fast Dx Instrument

1. Switch on 7500 Fast and 7500 Fast Dx Instrument.
2. Launch the 7500 Fast and 7500 Fast Dx Software package (version 1.4.1 or higher).
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 HAdV
Run Mode:	Fast 7500
Operator:	<i>your operator name</i>
Comments:	SDS v1.4.1 (<i>add more if needed</i>)
Plate Name:	YYMMDD-Lyra HAdV

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 HAdV and PRC.
 - c. Use the **Well Inspector** to enter the sample names. Patient IDs may be entered in the **Well Inspector** window; however, it is recommended that this is done prior to resuspending 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 HAdV.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:
 - a. **IMPORTANT:** When the run is finished, press OK. 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". Enter "**Data analysis post run**" and any other comments relevant to the run.

INTERPRETATION OF RESULTS

Interpretation of the Lyra Adenovirus Assay Results			
Assay Result	Detector: HAdV	Detector: PRC	Interpretation of Results
HAdV Negative	Ct <5.0 or Ct >35.0	5.0 ≤ Ct ≤ 35.0	No HAdV viral DNA detected; PRC Detected
HAdV Positive	5.0 ≤ Ct ≤ 35.0	N/A*	HAdV viral DNA detected
Invalid	Ct <1.0 or Ct >35.0	Ct <1.0 or Ct >35.0	No HAdV viral DNA and no PRC detected; invalid test. Retest the same purified sample. If this test is also invalid, re-extract and retest another aliquot of the same sample or obtain a new sample and retest.
Invalid	Undetermined	Undetermined	Not determined. Retest the same purified sample. If the test is also invalid, re-extract and retest another aliquot of the same sample or obtain a new sample and retest.
*No Ct value is required for the PRC to make a positive call.			

QUALITY CONTROL

The Lyra Adenovirus Assay incorporates several controls to monitor assay performance.

1. The PRC should be used during extraction and amplification in the assay. This control should be added to each sample aliquot prior to extraction (please refer to the section titled Principle of the Procedure for further information).
2. Commercially available external positive HAdV controls may be treated as a patient specimen and should be used in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's standard quality control procedures. Previously characterized positive HAdV specimens may be used in lieu of a commercial HAdV control.

3. Viral transport media (UTM, M4, M4-RT, M5, or M6) or previously characterized negative specimen (containing a PRC) may be used as an external negative control. This must be treated as a patient specimen and should be performed in accordance with Local, State, and/or Federal regulations or accreditation requirements and your laboratory's standard quality control procedures.

LIMITATIONS

- This test does not differentiate HAdV serotypes or species. Additional testing is required if serotype or species differentiation is required.
- Negative results do not preclude infection with HAdV and should not be the sole basis of a treatment decision.
- Always include one negative control (containing a PRC) and at least one positive control in each amplification/detection run performed.
- Failure of controls (positive, negative, and/or PRC) invalidates the run and results should not be reported.
- If the positive control is not positive within the specified Ct range, but the negative control is valid, repeat testing should be done starting from the purified nucleic acid and using a new aliquot of the positive control. If repeat results are still invalid, results should not be reported and testing should be repeated from the original sample or a new sample should be collected and tested.
- If the PRC is not positive or the negative control is invalid, repeat testing should be done starting from the original sample using new aliquots of the PRC and negative control. If repeat results are still invalid, results should not be reported and a new sample should be collected and tested.
- 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.
- The performance of the assay has not been established in individuals who received nasally administered corticosteroids.
- The performance of the assay has not been established in individuals who received nasally administered Influenza vaccine.
- The effect of interfering substances has only been evaluated for the substances listed in the labeling. Interference by substances other than those described in the "Analytical Specificity – Interfering Substances" section below can lead to erroneous results.
- The effect of cross-reactivity and interference has only been evaluated with the microorganisms listed in the labeling. Cross-reactivity with respiratory tract organisms other than those listed in the "Microbial Cross-Reactivity and Interference" section below can lead to erroneous results.
- The analyte target of the assay (HAdV nucleic acid sequence) may persist *in vivo*, independent of virus viability. Detection of the analyte target does not imply that the corresponding virus is infectious, nor does it imply that the virus is the causative agent of clinical symptoms.
- The detection of a viral sequence is dependent upon proper specimen collection, handling, transportation, storage, and preparation (including extraction). Failure to observe proper procedures in any one of these steps can lead to incorrect results. There is a risk of false negative values resulting from improperly collected, transported, or handled specimens.
- There is a risk of false positive values resulting from cross-contamination by the target organism, its 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 target of the assay.
- Performance of the Lyra Adenovirus Assay was not established in immunocompromised patients.
- In the analytical reactivity (inclusivity) study, three HAdV types tested required repeat analysis and were ultimately detected at 250x LOD (ADV-21/Serotype B) and 6x LOD (ADV-15 and ADV-17/Serotype D) for their respective serotypes.
- Positive and negative predictive values are highly dependent on prevalence and may vary depending on the population tested. Performance of the Lyra Adenovirus Assay using the 7500 Fast Dx Instrument was established during the 2013 and 2014 winter seasons.

EXPECTED VALUES

A prospective clinical study was performed with the Lyra Adenovirus Assay using the 7500 Fast Dx Instrument. Testing was performed with one thousand two hundred and forty-one (1241) nasal and nasopharyngeal swab specimens collected from three sites throughout the United States during the 2013 and 2014 winter seasons (January-March 2013 and December-February 2014). The overall prevalence (all sites combined) for HAdV averaged 2.8%. The table below provides the expected values for HAdV.

Expected Values for the Winter of 2013 and 2014 (Combined)					
Age	# Tested	Lyra Adenovirus Assay Positive	Expected Value	Total Positive by Reference Method	Observed Prevalence
<1	73	8	11.0%	1	1.4%
1 to 5	452	60	13.3%	24	5.3%
6 to 10	157	10	6.4%	4	2.5%
11 to 15	67	4	6.0%	2	3.0%
16 to 21	55	3	5.5%	1	1.8%
>21	437	4	0.9%	3	0.7%
Total	1241	89	7.2%	35	2.8%

CLINICAL PERFORMANCE

The evaluation of the Lyra Adenovirus Assay occurred in a prospective multi-center study using one thousand two hundred and forty-one (1241) fresh specimens collected from the upper respiratory tract at three sites in the United States (one in-house). This data was supplemented with results obtained from testing one hundred five (105) retrospectively selected frozen specimens collected from the upper respiratory tract at a single site in the United States. All of the prospective and retrospective specimens were processed with the NucliSENS easyMag System to extract viral nucleic acids. The 7500 Fast Dx Instrument was used with the Lyra Adenovirus Assay for the amplification and detection of the DNA target.

Prospective Clinical Study

For the prospective study, performance of the Lyra Adenovirus Assay on the 7500 Fast Dx Instrument was compared to an FDA-cleared direct detection kit for respiratory specimens. The kit is a composite method of viral culture with direct fluorescent antigen staining (CDFA) followed by direct fluorescent antibody staining of the specimen (SDFA). A specimen was called positive if either the CDFA or the SDFA were positive. For a specimen to be called negative, it must be negative for both CDFA and SDFA.

The gender and age demographics for the prospectively collected specimens are listed below.

Age and Gender Distribution for Prospective Clinical Study		
Gender	Female	Male
Total	651	590
Age		
<1	31	42
1 to 5	210	242
6 to 10	86	71
11 to 15	31	36
16 to 21	33	22
>21	260	177

One thousand two hundred forty-one (1241) fresh specimens were collected and transported to each laboratory for testing with the Lyra Adenovirus Assay. Sites 2 and 3 performed the extraction and testing for all

samples collected at their site. Specimens collected at site 1 were sent to an in-house testing lab where they were extracted and tested using the Lyra Adenovirus Assay. Samples collected at these sites were extracted within 72 hours of collection using the NucliSENS easyMag System and then tested using the Lyra Adenovirus Assay run on the 7500 Fast Dx Instrument. All reference testing with the comparator method was conducted at an in-house testing lab. Specimens were shipped to this location daily with cold packs and were cultured within 72 hours of collection.

Two (2) specimens were invalid when initially tested with the Lyra Adenovirus Assay. The specimens were re-tested according to the instructions for use and were invalid upon repeat testing. The specimens have been removed from the data presented below. The table below details the HAdV results for the remaining one thousand two hundred thirty-nine (1239) specimens.

Combined Site Data – Prospective Samples			
Lyra Adenovirus Assay	Comparator: CDFA with SDFA		
	Positive	Negative	Total
Positive	35	54*	89
Negative	0	1150	1150
Total	35	1204	1239
95% CI			
Sensitivity	35/35	100%	90.1% to 100%
Specificity	1150/1204	95.5%	94.2 % to 96.5%

*Forty-five (45) of the fifty-four (54) positives were positive by an additional FDA cleared PCR assay. Four (4) of the fifty-four (54) positives were negative by an additional FDA cleared PCR assay. Two (2) of the fifty-four (54) positives were invalid by an additional FDA cleared PCR assay. Three (3) of the fifty-four (54) positives had insufficient volume for additional testing.

Retrospectively Selected Specimens

Due to the low prevalence of adenovirus at the clinical sites during the study period, a set of retrospectively selected samples were also tested. One hundred five (105) frozen nasopharyngeal swab specimens were obtained from a pediatric hospital in the Southern United States. These specimens were selected based on a qualitative result previously generated by an FDA-cleared respiratory panel. All specimens were stored frozen at -70°C until they were shipped to an in-house testing lab where they were extracted and tested with the Lyra Adenovirus Assay and the comparator, an FDA-cleared PCR assay. The operator performing the testing was blinded to the identity of these specimens. The table below shows the agreement of the Lyra Adenovirus Assay with the comparator (an FDA-cleared PCR assay).

Data from a Single Site – Retrospectively Selected Samples			
Lyra Adenovirus Assay	Comparator: FDA-Cleared PCR Assay		
	Positive	Negative	Total
Positive	27	1*	28
Negative	0	77	77
Total	27	78	105
95% CI			
Positive Percent Agreement	27/27	100%	87.5% to 100%
Negative Percent Agreement	77/78	98.7%	93.1% to 99.8%

*One (1) of one (1) positive was positive by a third FDA-cleared PCR assay.

ANALYTICAL PERFORMANCE

Limit of Detection

The analytical sensitivity (limit of detection or LOD) of the Lyra Adenovirus Assay was determined using quantified (TCID₅₀/mL) stocks of representative serotypes from the six (6) species of HAdV serially diluted in negative nasal matrix. Each dilution tested was extracted in replicates of 20 per concentration using the NucliSENS easyMag System and tested on the 7500 Fast Dx Instrument. Testing was performed with three manufactured device lots. LOD is defined as the lowest concentration at which 95% of all replicates tested positive.

Summary of LOD Study		
Species/ Serotype	LOD (TCID ₅₀ /mL)	Avg. Ct Value
A/31	8.00 x10 ⁻²	28.5
B/3	8.00 x10 ⁻²	28.3
C/1	8.00 x10 ⁻²	28.1
D/19	1.61 x10 ¹	28.6
E/4	1.00 x10 ⁰	27.7
F/41	3.20 x10 ⁻²	28.9

Analytical Reactivity (Inclusivity)

To verify the Lyra Adenovirus Assay detects the fifty-two (52) known serotypes of HAdV, 49 serotypes were initially tested at or near the species LOD (see above). Higher concentrations were tested if the organism was not detected at the LOD. Each of the 49 serotypes tested was detected by the Lyra Adenovirus Assay. Three types were not detected at 2x LOD. These types were subjected to repeat analysis and were ultimately detected at 250x LOD (ADV-21/Serotype B) and 6x LOD (ADV-ADV-15 and ADV-17/Serotype D) for their respective serotypes.

HAdV Serotypes Reactivity Summary			
Species	Serotype	Concentration Tested (TCID ₅₀ /mL)	Multiple of LOD Detected
A	HAdV-12	1.60 x10 ⁻¹	2x LOD
	HAdV-18	1.60 x10 ⁻¹	2x LOD
B	HAdV-7	1.60 x10 ⁻¹	2x LOD
	HAdV-11	1.60 x10 ⁻¹	2x LOD
	HAdV-14	1.60 x10 ⁻¹	2x LOD
	HAdV-16	1.60 x10 ⁻¹	2x LOD
	HAdV-21	2.00 x10 ¹	250x LOD*
	HAdV-34	1.60 x10 ⁻¹	2x LOD
	HAdV-35	1.60 x10 ⁻¹	2x LOD
	HAdV-50	1.60 x10 ⁻¹	2x LOD
C	HAdV-2	1.60 x10 ⁻¹	2x LOD
	HAdV-5	1.60 x10 ⁻¹	2x LOD
	HAdV-6	1.60 x10 ⁻¹	2x LOD
F	HAdV-40	6.40 x10 ⁻²	2x LOD
D	HAdV-8	3.22 x10 ⁻¹	2x LOD
	HAdV-9	3.22 x10 ⁻¹	2x LOD

HAdV Serotypes Reactivity Summary			
Species	Serotype	Concentration Tested (TCID ₅₀ /mL)	Multiple of LOD Detected
	HAdV-10	3.22 x10 ⁻¹	2x LOD
	HAdV-13	3.22 x10 ⁻¹	2x LOD
	HAdV-15	9.66 x10 ¹	6x LOD*
	HAdV-17	9.66 x10 ¹	6x LOD*
	HAdV-20	3.22 x10 ⁻¹	2x LOD
	HAdV-22	3.22 x10 ⁻¹	2x LOD
	HAdV-23	3.22 x10 ⁻¹	2x LOD
	HAdV-24	3.22 x10 ⁻¹	2x LOD
	HAdV-25	3.22 x10 ⁻¹	2x LOD
	HAdV-26	3.22 x10 ⁻¹	2x LOD
	HAdV-27	3.22 x10 ⁻¹	2x LOD
	HAdV-28	3.22 x10 ⁻¹	2x LOD
	HAdV-29	3.22 x10 ⁻¹	2x LOD
	HAdV-30	3.22 x10 ⁻¹	2x LOD
	HAdV-32	3.22 x10 ⁻¹	2x LOD
	HAdV-33	3.22 x10 ⁻¹	2x LOD
	HAdV-36	3.22 x10 ⁻¹	2x LOD
	HAdV-37	3.22 x10 ⁻¹	2x LOD
	HAdV-39	3.22 x10 ⁻¹	2x LOD
	HAdV-43	3.22 x10 ⁻¹	2x LOD
	HAdV-44	3.22 x10 ⁻¹	2x LOD
	HAdV-45	3.22 x10 ⁻¹	2x LOD
	HAdV-46	3.22 x10 ⁻¹	2x LOD
	HAdV-47	3.22 x10 ⁻¹	2x LOD
	HAdV-48	3.22 x10 ⁻¹	2x LOD
	HAdV-49	3.22 x10 ⁻¹	2x LOD
	HAdV-51	3.22 x10 ⁻¹	2x LOD

*HAdV-15, HAdV-17, and HAdV-21 required repeat testing and were ultimately found to be detected at 6x LOD (HAdV-15 and HAdV-17) and 250x LOD (HAdV-21).

NOTE: Most viruses were re-grown and quantified in TCID₅₀ (50% Tissue Culture Infectious Dose) for LOD determination. The unit TCID₅₀ is a measure of infectivity or cytotoxicity rather than number of organisms or copies of nucleic acid. Variability in TCID₅₀/mL may not accurately reflect differences in the relative sensitivity of detection between different strains of the same organism.

HAdV Species D serotypes 38 and 42 and Species G serotype 52 (often associated with conjunctivitis and gastroenteritis) were not evaluated for inclusivity as the sponsor could not obtain these strains. Instead, the manufacturer conducted an *in silico* analysis where they aligned their probe and primers with the target regions from a single sequence (obtained from GenBank) for each of these adenovirus types. The alignments showed that 100% agreement of the forward primer with types 38, 42, and 52. For the reverse primer, there were 3 mismatches detected on the sequences for types 38 and 42 (84% homology) and 2 mismatches with

the sequence for type 52 (89.5% homology). For the probe, there was 100% agreement with types 38 and 42 and 3 mismatches with the sequence for type 52 (85% homology).

Reproducibility Study

The reproducibility of the Lyra Adenovirus Assay was evaluated at three (3) laboratory sites (two external, one in-house). The reproducibility panel consisted of four (4) simulated samples that include moderate positive (5x LOD) and low positive (2x LOD), high negative (0.5x LOD), and negative (ADV Negative Nasal Matrix) samples. HAdV positive panel members were created by spiking HAdV type 31 into negative nasal matrix. The panels and controls (ADV Positive Control and ADV Negative Control) were extracted with the NucliSENS easy MAG System and tested with the Lyra Adenovirus Assay run on the 7500 Fast Dx Instrument. Panels and controls were tested at each site by 2 operators for 5 non-consecutive days (triplicate testing x 2 operators x 3 replicates x 5 days x 3 sites = 90 results per level for each virus). The LOD values were based on the values obtained in the LOD study.

Reproducibility Results - 7500 Fast Dx												
Panel Member ID	Site 1			Site 2			Site 3			Combined Site Data		
	Rate of Detection	AVE Ct	% CV	Rate of Detection	AVE Ct	% CV	Rate of Detection	AVE Ct	% CV	Rate of Detection	AVE Ct	%CV
HAdV High Negative (0.5x LOD)	30/30	29.0	4.9	30/30	28.9	4.2	26/30*	27.8	8.8	86/90*	28.6	6.2
HAdV Low Positive (2x LOD)	30/30	26.7	2.3	30/30	26.2	3.0	30/30	26.1	9.3	90/90	26.4	5.9
HAdV Moderate Positive (5x LOD)	30/30	25.2	1.7	30/30	24.8	3.0	30/30	24.1	6.8	90/90	24.8	4.8
HAdV Negative Nasal Matrix	0/30	N/A	N/A	0/30	N/A	N/A	0/30	N/A	N/A	0/90	N/A	N/A
HAdV Positive Control	30/30	20.5	2.5	30/30	18.2	3.9	30/30	17.1	3.7	90/90	18.6	8.5
HAdV Negative Control	0/30	N/A	N/A	0/30	N/A	N/A	0/30	N/A	N/A	0/90	N/A	N/A

*One replicate was removed from the analysis because it had an invalid PRC result. Three replicates incorrectly tested negative.

Microbial Cross-reactivity and Interference

The analytical specificity of the Lyra Adenovirus Assay was evaluated by testing a panel consisting of 30 viral, 26 bacterial, and 1 yeast strain representing respiratory pathogens or flora commonly present in the nasopharynx. The organisms were tested in the presence and absence of 2x LOD HAdV to determine if there was interference or cross-reactivity, respectively. Samples were extracted using the NucliSENS easyMAG instrument and tested in triplicate. All HAdV positive samples remained positive and all HAdV negative samples remained negative, indicating that there was no interference or cross-reactivity in the presence of the organisms tested. Each microorganism was tested three times, once in the presence of HAdV type 4, once in the presence of HAdV type 31, and once in the presence of negative nasal matrix.

Organisms used for the study were the following:

Organism	Concentration tested (TCID50/mL or CFU/mL)	Lyra Adenovirus Assay Result	
		Interference (+ HAdV)	Cross-reactivity (- HAdV)
<i>Bordetella pertussis</i>	9.08E+08	Positive	Negative
<i>Bordetella bronchiseptica</i>	5.40E+08	Positive	Negative
<i>Chlamydomphila pneumoniae</i>	0.11 ng/ µL	Positive	Negative
<i>Chlamydia trachomatis</i>	2.10E+06	Positive	Negative

Organism	Concentration tested (TCID50/mL or CFU/mL)	Lyra Adenovirus Assay Result	
		Interference (+ HAAdV)	Cross-reactivity (- HAAdV)
<i>Legionella pneumophila</i>	1.42E+09	Positive	Negative
<i>Mycobacterium intracellulare</i>	1.53E+09	Positive	Negative
<i>Mycobacterium tuberculosis</i>	9.30E+06	Positive	Negative
<i>Mycobacterium avium</i>	3.18E+09	Positive	Negative
<i>Mycoplasma pneumoniae</i>	3.16E+06	Positive	Negative
<i>Haemophilus influenzae</i>	4.00E+08	Positive	Negative
<i>Pseudomonas aeruginosa</i>	1.32E+09	Positive	Negative
<i>Proteus vulgaris</i>	6.53E+08	Positive	Negative
<i>Proteus mirabilis</i>	1.19E+09	Positive	Negative
<i>Neisseria gonorrhoeae</i>	1.40E+09	Positive	Negative
<i>Neisseria meningitidis</i>	1.29E+08	Positive	Negative
<i>Neisseria mucosa</i>	1.61E+08	Positive	Negative
<i>Klebsiella pneumoniae</i>	9.75E+08	Positive	Negative
<i>Escherichia coli</i>	1.13E+09	Positive	Negative
<i>Moraxella catarrhalis</i>	1.26E+09	Positive	Negative
<i>Corynebacterium diphtheriae</i>	3.44E+08	Positive	Negative
<i>Lactobacillus plantarum</i>	3.18E+08	Positive	Negative
<i>Streptococcus pneumoniae</i>	1.43E+08	Positive	Negative
<i>Streptococcus pyogenes</i>	6.38E+08	Positive	Negative
<i>Streptococcus salivarius</i>	5.40E+08	Positive	Negative
<i>Staphylococcus epidermidis</i>	9.23E+08	Positive	Negative
<i>Staphylococcus aureus</i>	6.08E+08	Positive	Negative
<i>Candida albican</i>	9.70E+07	Positive	Negative
Coronavirus 229E	2.46E+07	Positive	Negative
Coronavirus NL63	1.41E+04	Positive	Negative
Coronavirus OC43	2.42E+07	Positive	Negative
Coxsackievirus B4	2.00E+07	Positive	Negative
Coxsackievirus B5/10/2006	3.62E+05	Positive	Negative
Cytomegalovirus	2.14E+06	Positive	Negative
Echovirus 6	7.60E+08	Positive	Negative
Echovirus 7	4.45E+06	Positive	Negative
Echovirus 9	2.17E+07	Positive	Negative
Echovirus 11	2.17E+05	Positive	Negative
Enterovirus 70	2.41E+06	Positive	Negative
Enterovirus 71	2.03E+05	Positive	Negative
Epstein Barr Virus	9.27E+07	Positive	Negative
HSV Type 1 MacIntyre Strain	5.89E+06	Positive	Negative
HSV Type 2 Strain G	1.96E+06	Positive	Negative
Human Metapneumovirus (A1)	3.66E+05	Positive	Negative
Human Rhinovirus 45	2.94E+04	Positive	Negative
Human Rhinovirus 52	2.63E+04	Positive	Negative
Influenza A/Mexico/4108/2009	4.08E+05	Positive	Negative
Influenza A/Port Chalmers	3.55E+08	Positive	Negative
Influenza B/Florida/04/2006	1.54E+06	Positive	Negative
Measles	1.95E+06	Positive	Negative
Mumps Virus	2.75E+08	Positive	Negative
Parainfluenza Type 1	3.97E+06	Positive	Negative
Parainfluenza Type 2	3.15E+08	Positive	Negative
Parainfluenza Type 3	2.36E+07	Positive	Negative
Parainfluenza Type 4A	1.04E+05	Positive	Negative
RSV A (Long)	4.36E+04	Positive	Negative
RSV B (Wash/18537/62)	3.43E+05	Positive	Negative

Organism	Concentration tested (TCID ₅₀ /mL or CFU/mL)	Lyra Adenovirus Assay Result	
		Interference (+ HAdV)	Cross-reactivity (– HAdV)
Varicella Zoster Virus	1.11E+04	Positive	Negative

Analytical Specificity – Interfering Substances

The performance of Lyra Adenovirus Assay was evaluated with potentially interfering substances that may be present in nasopharyngeal specimens. The 11 potentially interfering substances were evaluated using HAdV at a concentration of 2x LOD. Each interfering substance was tested three times, once in the presence of HAdV type 4, once in the presence of HAdV type 31, and once in the presence of negative nasal matrix. All HAdV positive samples remained positive and all HAdV negative samples remained negative, indicating that there was no interference in the presence of the substances tested.

Substance Name	Concentration Tested
Mucin (Bovine Submaxillary Gland, type I-S)	60 µg/mL
Blood (human), EDTA anticoagulated	2% (vol/vol)
Neo-Synephrine	15% (vol/vol)
Afrin Nasal Spray	15% (vol/vol)
Zicam Homeopathic Non-Drowsy Allergy Relief No Drip Liquid Nasal Gel	5% (vol/vol)
Saline Nasal Spray	15% (vol/vol) of dose
Throat Lozenges	0.68 g/mL; 1/18 drop, crushed; active ingredients: 1.7 mg/mL menthol
Zanamivir	3.3-5 mg/mL
Tobramycin	4.0 µg/mL
Mupirocin	6.6-10 mg/mL
Oseltamivir phosphate	7.5-25 mg/mL

Carry-over and Cross-contamination Study

A carry-over study was conducted using a 96-sample panel consisting of 48 high positive (1.0 x 10⁵ TCID₅₀/mL HAdV type 4) and 48 negative specimens (negative nasal matrix). The high positive samples were extracted and added to the plate in a checkerboard pattern that alternated with the negative samples. This testing was repeated over a 5 day period. There was no evidence of carry-over/cross contamination with the Lyra Adenovirus Assay using the NucliSens easyMAG automated nucleic acid extraction instrument and the 7500 Fast Dx instrument.

ADDITIONAL SOURCE MATERIAL

- Guidance on Informed Consent for In Vitro Diagnostic Device Studies Leftover Human Specimens that are Not Individually Identifiable (April 2006) – <http://www.fda.gov/cdrh/oivd/guidance/1588.pdf>.
- Draft Guidance on Nucleic Acid Based In Vitro Diagnostic Devices for Detection of Microbial Pathogens (Dec 2005) – <http://www.fda.gov/cdrh/oivd/guidance/1560.html>.
- CLSI EP17-A: Guidance for Protocols for Determination of Limits of Detection and Limits of Quantitations (Vol. 2, No. 34) (Oct 2004).
- CLSI MM13-A: Guidance for the Collection, Transport, Preparation and Storage of Specimens for Molecular Methods (Vol. 25, No. 31) (Dec 2005).
- CLSI EP7-A2: Guidance for Interference Testing in Clinical Chemistry (Vol. 25, No.27 Second Ed) (Nov 2005).
- CLSI EP12-A: Guidance for User Protocol for Evaluation of Qualitative Test Performance (Vol. 22, No. 14) (Sept 2002).
- CLSI MM6-A: Guidance for the Quantitative Molecular Methods for Infectious Diseases (Vol. 23, No.28) (Oct 2003).
- CLSI EP5-A2: Guidance for Evaluation of Precision Performance of Quantitative Measurement Methods (Vol. 24, No. 25 Second Ed.) (Aug 2004).

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