Product References:

UC-TIB-AdV	**53-0400-UC**	**09838872001**	**Version 7.0**
UC_TIB_AdV v01.00 USAP		**09915478001**	**Last revision date 04.11.2025**

UC-TIB-AdV

Real time PCR kit for quantification of human Adenovirus

For use with the **cobas**® **omni** utility channel on the **cobas**® 6800/8800 Systems

Instructions For Use

CE IVD

TIB MOLBIOL

REVISION NOTE COMPARED TO THE PREVIOUS VERSION

Revision date	Update Description
28/07/2021	Initial release
08/12/2022	Change of Legal Manufacturer
06/02/2023	PC and STD-Volumes corrected
04/08/2023	Adjustments to latest recommendations, e.g. material-numbers
15/05/2024	e-labdoc availability of the USAP deleted
04/03/2025	**integration of cobas®** 6800/8800 systems with software version 2.0 or higher
04/11/2025	availability of UCAP for cobas® 6800/8800 software version 2.0 integrated

This Instructions For Use can be downloaded by following the procedure below:

- Go to the website : http://e-labdoc.roche.com

- Search for Method Sheet Catalog No.:

- **09838872001 Doc Ver. 7.0 (UC-TIB-AdV)**

- Download the Instructions For Use

Please contact your local Roche Representative if you have any question.

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GLOSSARY

(-) Ctrl	Negative Control
(+)_Ctrl	Positive Control
AdV	Adenovirus
Ct	Cycle threshold
DNA	DeoxyriboNucleic Acid
EDTA	EthyleneDiamineTetraacetic Acid
dTTP	DeoxyThimidine Triphosphate
dUTP	DeoxyUridine Triphosphate
Em.	Emission
Ex.	Excitation
EAN	European Article Number
IC	Internal Control
IU	International Unit
IVD	*In vitro* diagnostics
IVDMD	*In vitro* Diagnostic Medical Device
LoD	Limit of Detection
$LoD_{95\%}$	Limit of Detection at 95 % of targets
LoQ	Limit of Quantification
LLoQ	Lower Limit of Quantification
MGP	Magnetic Glass Particle
MMX	Master Mix
PC	Positive Control
PCR	Polymerase Chain Reaction
P/N	Part Number
PP	Primers and Probes
PROBIT	Probability + Unit
RNA	RiboNucleic Acid
RUI	Remote User Interface
STD	Standard
ULoQ	Upper Limit of Quantification
UC	utility channel
USAP	utility channel Specific Analysis Package
WHO	World Health Organization

1. INTRODUCTION

Real time Polymerase Chain Reaction is a nucleic acid amplification method used to detect and quantify specific DNA sequences obtained after extraction or by reverse transcription of RNA. Real time PCR technology allows a rapid and specific measurement of the presence of genes from microorganisms associated with infectious diseases, cancer and genetic abnormalities. TIB Molbiol kits are based on this powerful technology to accurately detect the presence of pathogens for a number of infectious diseases.

One of the primary benefits of this technology is the ability to quantify the amplified DNA during the reaction in real time, resulting in a more accurate detection of genetic sequences. TIB Molbiol assays use TaqMan® DNA probes that hybridize with the target DNA strand. These probes are labeled with a fluorescent dye allowing real time measurements during the PCR process. The generated fluorescent signals are then detected and quantified using an instrument such as a thermal cycler.

2. GENERAL INFORMATION

2.1. INTENDED USE

UC-TIB-AdV is an automated *in vitro* nucleic acid amplification test for the detection and quantification of human Adenovirus (AdV) DNA in human EDTA plasma samples.

This test is intended for use as an aid in the diagnosis of human AdV infections and for monitoring AdV DNA levels such as in transplanted and immunocompromised patients. The results from **UC-TIB-AdV** must be interpreted within the context of all relevant clinical and laboratory findings.

2.2. PATHOGEN INFORMATION

Human AdV are double-stranded non-enveloped DNA viruses of the family *Adenoviridae* and belong to the genus Mastadenovirus. Human AdV were first isolated in the 1950s from explanted adenoid tissue and are now classified into seven species A-G with at least 62 different serotypes (AdV-1 to AdV-62). They have a worldwide distribution with considerable geographical variations in the prevalence of various species and serotypes, without seasonal pattern of infection ①.

While some are endemic in parts of the world and infection is usually acquired during childhood, other types cause sporadic infection and occasional outbreaks. Some AdV types can establish persistent asymptomatic infections in the tonsils, adenoids, and intestines of infected hosts, and shedding can occur for months or years. Reactivation of latent infections in immunocompromised hosts, such as transplant recipients, can result in a life-threatening disseminated disease ②.

All AdV are transmitted by direct contact, fecal-oral transmission, and occasionally waterborne transmission. They can cause mild to severe illness, though serious illness is less common. The symptoms of the disease depend on the preferred tissue tropism of the AdV. In immunocompetent individuals, AdV infections often manifest as upper respiratory tract infections, pharyngonconjunctival fever, or diarrhea. As in the case of other viral respiratory pathogens, community outbreaks of AdV infections may occur, especially with respiratory tract infections and keratoconjunctivitis ③.

In immunocompromised hosts, adenovirus infections may present as respiratory tract infection, hepatitis, enteritis, hemorrhagic cystitis, disseminated infections, and graft loss in organ transplant recipients. High risk individuals include patients with primary immunodeficiencies (especially severe combined immunodeficiency syndrome), allogenic hematopoietic stem cell transplant and solid organ transplant recipients ④⑤.

Note: See the corresponding publications ①②③④⑤ in chapter References on Page 19.

2.3. PRINCIPLE

The AdV detection is performed on the **cobas®** 6800/8800 Systems with the **UC-TIB-AdV** on human EDTA plasma samples. The viral load is quantified with an AdV standard curve calibrated using the World Health Organization (WHO) international standard. In addition, the test utilizes two external controls: a Positive Control provided in this kit and a Negative Control (Roche P/N 09051953190).

The **UC-TIB-AdV** used in combination with the **cobas® omni** utility channel is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection.

The **UC-TIB-AdV** works with the optimal conditions (defined parameters from sample preparation to result analysis) included in the USAP. The **UC-TIB-AdV** is assigned to the **cobas® omni** Utilily Channel 192 Reagent Kit (192-test cassette) and then transferred to the **cobas®** 6800/8800 Systems in order to perform the **UC-TIB-AdV**.

Nucleic acid from patient samples, external controls (Positive and Negative) and the added internal control are extracted simultaneously. The four standard curve points are processed in the same way in order to measure the quantification of each sample. Nucleic acid is released by addition of proteinase and lysis reagent to the sample and the released nucleic acid binds to the silica surface of the added magnetic glass particles. Unbound substances and impurities, such as denatured protein, cell debris and potential PCR inhibitors are removed with subsequent wash reagent steps, and purified nucleic acid is eluted from the glass particles with elution buffer at elevated temperature.

The **UC-TIB-AdV** contains the AdV primers and probes which are used in combination with the **cobas® omni** utility channel Master Mix Reagent 2 (UC MMX-R2) and the 192-test cassette included in the **cobas® omni** utility channel Reagent Kit provided by Roche. Selective amplification of target nucleic acid from the sample, the positive control and the 4 Standard Curve Points is achieved by the use of target virus-specific forward and reverse primers which are selected from conserved regions of the AdV hexon gene.

The 192-test cassette contains an internal control (IC) recognized by specific primers and probes included in the **cobas® omni** utility channel Master Mix Reagent 2 (UC MMX-R2). Selective amplification of the IC is achieved by the use of sequence-specific forward and reverse primers, which have no homology with the AdV genomes. A thermostable DNA polymerase enzyme is used for amplification. The target and IC sequences are amplified simultaneously utilizing a universal PCR amplification profile with predefined temperature steps and number of cycles. The master mix includes deoxyuridine triphosphate (dUTP), instead of deoxythimidine triphosphate (dTTP), which is incorporated into the newly synthesized DNA (amplicon). Any contaminating amplicon from previous PCR runs is eliminated by the AmpErase enzyme, which is included in the PCR mix.

The probes are labeled with target-specific fluorescent reporter dyes allowing simultaneous detection of the AdV target and IC in two different target channels. The fluorescent signal of the intact probes is suppressed by the quencher dye. During the PCR amplification step, hybridization of the probe with the specific single-stranded DNA templates results in cleavage by the 5'-to-3' nuclease activity of the DNA polymerase resulting in separation of the reporter and quencher dyes and the generation of a fluorescent signal. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dye is concomitantly increased. Real time detection and discrimination of PCR products is accomplished by measuring the fluorescence of the released reporter dyes for the viral targets and IC.

The quantification of AdV DNA is ensured by the four AdV standards (STD1, STD2, STD3 and STD4) provided in the **UC-TIB-AdV**. AdV standards quantified in International Unit per milliliter are used for calibration of the assay and are processed as patient samples on the **cobas®** 6800/8800 Systems. Data management is performed by the **cobas® omni** utility channel Optimization Tool software used in combination with the **UC-TIB-AdV** Offline Quantification Tool which assigns test results for all tests as either target not detected, AdV DNA detected < LLoQ (lower limit of quantification), AdV DNA detected > ULoQ (upper limit of quantification), or a value in the linear range LLoQ < *x* < ULoQ. Results of the **UC-TIB-AdV** Offline Quantification Tool can be printed as a report.

2.4. TARGET SEQUENCE

The primers are designed to hybridize with specific sequences in the target pathogen.

Pathogen	Target gene
Adenovirus (species A to G)	Hexon

The probes are designed to hybridize with a specific sequence in the target pathogen. They include a fluorescent reporter dye at the 5' end, the fluorescence of which is quenched by a second dye at the 3' end. The probes only emit a signal if they are bound to the amplified product.

Pathogen	Reporter dye
Adenovirus	FAM

2.5. KIT CONTENTS

The **UC-TIB-AdV** contains the following reagents to perform up to 192 reactions:

Table 1. UC-TIB-AdV (09838872001)

Reagents	Cap ID	Ingredients	Quantity per kit	Safety symbol and warning
Adenovirus Primers and Probes (FAM)		Tris buffer, 0.015 % EDTA, 0.05 % sodium azide	0.600 mL (1 x 0.600 mL) 192 reactions	Not Applicable
Adenovirus Positive Control		Titered synthetic AdV C2 DNA, Tris buffer, 0.015 % EDTA, 0.1 % ProClin® 300 preservative, 0.002 % RNA carrier	12.25 mL (7 x 1.75 mL) 35 reactions	 Warning H317: May cause an allergic skin reaction. P261: Avoid breathing dust/fumes/gas /mist/vapors/spray. P272: Contaminated work clothing should not be allowed out of the workplace. P280: Wear protective gloves. P302 + P352: IF ON SKIN wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P362 + P364: Wash contaminated clothing before reuse.
Adenovirus Standard Curve Point 1 (1.0E6 c/mL)			1.05 mL (1 x 1.05 mL) 3 reactions	
Adenovirus Standard Curve Point 2 (1.0E5 c/mL)				
Adenovirus Standard Curve Point 3 (1.0E4 c/mL)				
Adenovirus Standard Curve Point 4 (1.0E3 c/mL)				

3. REQUIRED MATERIALS (NOT SUPPLIED)

3.1. MATERIAL AND CONSUMABLES

The table below lists the materials required to run the **UC-TIB-AdV** on **cobas®** 6800/8800 Systems**.**

Table 2. Materials and consumables for use on **cobas®** 6800/8800 Systems

Material	Roche P/N
cobas® omni Processing Plate	05534917001
cobas® omni Amplification Plate	05534941001
cobas® omni Pipette Tips	05534925001
cobas® omni Liquid Waste Container	07094388001
cobas® omni Lysis Reagent	06997538190
cobas® omni MGP Reagent	06997546190
cobas® omni Sample Diluent Reagent	06997511190
cobas® omni Wash Reagent	06997503190

cobas® Buffer Negative Control Kit	09051953190
cobas® omni utility channel 192 Reagent Kit	09052011190
Solid Waste Bag and Solid Waste Container or Solid Waste Bag With Insert and Kit Drawer Solid Waste Bag	07435967001 and 07094361001 or 08030073001 and 08387281001
cobas® omni Secondary Tubes 13x75 (optional)	06438776001
Repeater pipette with a 10 mL pipette tip	N/A

► Refer to the **cobas® omni** utility channel Reagent Kit and **cobas® omni** utility channel User Assistance Version 4.4 or higher.
► Refer to the **cobas®** 6800/8800 Systems User Assistance for additional information on secondary tubes.

Note: Contact your local Roche representative for a detailed order list for sample racks, racks for clotted tips and rack trays accepted on the instruments.

3.2. INSTRUMENTATION

The table below lists the instruments required to run **UC-TIB-AdV** on **cobas®**6800/8800 Systems.

Table 3. Instrumentation

Equipment	Roche P/N
cobas® 6800 System (Option Moveable)	05524245001 and 06379672001
cobas® 6800 System (Fix)	05524245001 and 06379664001
cobas® 8800 System	05412722001
Sample Supply Module	06301037001
TWN3 Legic NFC USB (RFID Reader/Writer)	07450460001
External PC with remote connection provided by the customer	N/A
Barcode Printer	N/A

► Refer to the **cobas®** 6800/8800 Systems User Assistance for proper maintenance of instruments.

3.3. SOFTWARE

The table below lists the software required to run **UC-TIB-AdV** on **cobas®**6800/8800 Systems.

Table 4.1 Software 1.4

Instrument	Software	Version
cobas®6800/8800 Systems	**cobas®** 6800/8800 software	1.4
External computer with remote connection (also called Remote User Interface, RUI)	**cobas® omni** utility channel Tool	3.4 or higher
	cobas® omni utility channel Optimization Tool	4.1 or higher
	UC-TIB-AdV Offline Quantification Tool	1.2 or higher
	UC_TIB_AdV_v01.00 USAP	1.0 or higher

The table below lists the software required to run UC-TIB-AdV on cobas®6800/8800 systems with software version 2.0 or higher .

Table 4.2 Software 2.0 or higher

Instrument	Software	Version
cobas®6800/8800 Systems	**cobas®** 6800/8800 software	2.0 or higher
External computer with Data Manager	**cobas® omni** RFID tool	1.1 or higher
	UC_TIB_AdV v02.00 UCAP	2.0 or higher

Note: The UC_TIB_AdV analysis package (UCAP) for cobas® 6800/8800 systems shall be installed on the instrument(s), for support please contact your Roche Service Representative.

► Refer to the **cobas® omni** utility channel User Assistance for additional information on the **cobas® omni** utility channel software.

4. REAGENT STORAGE, HANDLING, AND STABILITY

The **UC-TIB-AdV** and the **cobas® omni** utility channel Reagents should be stored and managed as specified in Tables 5 and 6. Reagents must be used before the expiry date mentioned on the corresponding packaging label.

Table 5. Reagent storage (when reagent is not on the system)

Reagent	Storage conditions
UC-TIB-AdV	2–8 °C, protected from light
cobas® omni utility channel 192 Reagent Kit	2–8 °C
cobas® Buffer Negative Control Kit	2–8 °C
cobas® omni Lysis Reagent	2–8 °C
cobas® omni MGP Reagent	2–8 °C
cobas® omni Sample Diluent	2–8 °C
cobas® omni Wash Reagent	15–30 °C

The **cobas®** 6800/8800 Systems allow Roche reagents to be used only if all of the conditions shown in Table 6 are met. Otherwise, the system automatically prevents their use. Table 6 enables the user to understand the reagent handling conditions enforced by the **cobas®** 6800/8800 Systems.

Please note that the **cobas® omni** utility channel 192 Reagent Kit cassette loaded with PCR Mix (containing Master Mix Reagent 2 (UC-MMX-R2) and **UC-TIB-AdV** (Primers and Probes) can be stored for up to seven days at 2-8 °C before first usage. After first usage, please refer to expiry conditions of the **cobas® omni** utility channel Reagent Kit in Table 6. Positive Controls ((+)_Ctrl) and Standard Curve Points need to be used within 30 days from first use and before the expiry date mentioned on the kit packaging label.

Table 6. Reagent expiry conditions enforced by the **cobas®** 6800/8800 Systems

Reagent	Expiration date	Opened-kit stability	Number of runs	On-board Stability***
cobas® omni utility channel Reagent Kit	Not passed	90 days from first use	Max 35 runs**	Max 40 hours
cobas® Buffer Negative Control Kit	Not passed	Not applicable	Not applicable	Max 10 hours
cobas® omni Lysis Reagent	Not passed	30 days from loading*	Not applicable	Not applicable
cobas® omni MGP Reagent	Not passed	30 days from loading*	Not applicable	Not applicable
cobas® omni Sample Diluent	Not passed	30 days from loading*	Not applicable	Not applicable
cobas® omni Wash Reagent	Not passed	30 days from loading*	Not applicable	Not applicable

* Time measured from the first time the reagent is loaded onto the **cobas®** 6800/8800 Systems. **While the cobas® omni utility channel cassette allows 40 runs, the positive controls provided in the **UC-TIB-AdV** is sufficient for 35 runs only. ***Cumulative time outside refrigerator.

5. PRECAUTIONS AND HANDLING REQUIREMENTS

►If the package is damaged, please contact your local Roche representative.

5.1. WARNING AND PRECAUTIONS

As with any test procedure, good laboratory practice is essential to the proper performance of this assay. Due to the high sensitivity of this test, care should be taken to keep reagents and amplification mixtures free of contamination.

- For *in vitro* diagnostic use only.
- **UC-TIB-AdV** is not evaluated for use as a screening test for the presence of AdV in blood or blood products.
- All patient samples should be handled as if infectious, using good laboratory procedures as outlined in Biosafety in Microbiological and Biomedical Laboratories and in the CLSI Document M29-A4. Only personnel proficient in handling infectious materials and the use of **UC-TIB-AdV** and **cobas®** 6800/8800 Systems should perform this procedure.
- All human-sourced materials should be considered potentially infectious and should be handled with universal precautions. If spillage occurs, disinfect immediately with a freshly prepared solution of 0.6 % sodium or potassium hypochlorite in distilled or deionized water or follow appropriate site procedures.
- **Do not freeze whole blood or any samples stored in primary tubes.**

- Use only supplied or specified required consumables to ensure optimal test performance.
- Safety Data Sheets (SDS) are available on request from your local Roche representative.
- Closely follow procedures and guidelines provided to ensure that the test is performed correctly. Any deviation from the procedures and guidelines may affect optimal test performance.
- False positive results may occur if carryover of samples is not adequately controlled during sample handling and processing.

5.2. REAGENT HANDLING

- Handle all reagents, controls, and samples according to good laboratory practice in order to prevent carryover of samples or controls.
- Before use, visually inspect each **cobas® omni** reagent cassette, sample diluent, lysis reagent, and wash reagent to ensure that there are no signs of leakage. If there is any evidence of leakage, do not use that material for testing.
- **cobas® omni** Lysis Reagent contains guanidine thiocyanate, a potentially hazardous chemical. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, wash immediately with generous amounts of water; otherwise, burns can occur.
- **UC-TIB-AdV**, **cobas® omni** MGP Reagent, and **cobas® omni** Sample Diluent contain sodium azide as a preservative. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, wash immediately with generous amounts of water; otherwise, burns can occur. If these reagents are spilled, dilute with water before wiping dry.
- Do not allow **cobas® omni** Lysis Reagent, which contains guanidine thiocyanate, to contact sodium hypochlorite (bleach) solution. This mixture can produce a highly toxic gas.
- Dispose of all materials that have come in contact with samples and reagents in accordance with country, state, and local regulations.

5.3. GOOD LABORATORY PRACTICES

- Do not pipette by mouth.
- Do not eat, drink, or smoke in designated work areas.
- Wear laboratory gloves, laboratory coats, and eye protection when handling samples and reagents. Gloves must be changed between handling samples and **UC-TIB-AdV** and **cobas® omni** reagents to prevent contamination. Avoid contaminating gloves when handling samples and controls.
- Wash hands thoroughly after handling samples and kit reagents, and after removing the gloves.
- Thoroughly clean and disinfect all laboratory work surfaces with a freshly prepared solution of 0.6 % sodium or potassium hypochlorite in distilled or deionized water. Follow by wiping the surface with 70 % ethanol.
- If spills occur on the **cobas®** 6800/8800 instrument, follow the instructions in the **cobas®** 6800/8800 Systems User Assistance to clean and decontaminate the surface of instrument(s) properly.

6. SAMPLE COLLECTION, STORAGE, AND TRANSPORT

Detection of AdV by Real Time PCR is dependent upon the quality of the sample collection, timely delivery of the samples to the laboratory in correct containers, and storage under the appropriate conditions before analysis.

- Store all samples at specified temperatures: sample stability is affected by elevated temperatures.
- Repeated freezing and thawing of human samples can compromise PCR sensitivity.
- Blood should be collected in Plasma Preparation Tubes for Molecular Diagnostic Test Methods or in sterile tubes using EDTA as the anticoagulant. Follow the instructions of sample collection tube manufacturer.
- Whole blood collected in Plasma Preparation Tubes for Molecular Diagnostic Test Methods or in sterile tubes using EDTA as the anticoagulant may be stored and/or transported for up to 24 hours at 2-25 °C prior to plasma preparation. Centrifugation should be performed according to the manufacturer's instructions.
- After separation, plasma specimen may be stored in secondary tubes for up to 6 days at 2-8 °C or up to 12 weeks at -15 °C to -80 °C.
- Human samples must be transported according to the regulatory requirements for the transport of potentially infectious substances. To ensure ideal storage and transport conditions, follow the manufacturer's instructions.

Note: Handle all samples and controls as if they are capable of transmitting infectious agents.

7. PROTOCOL

7.1. WORKFLOW OVERVIEW

- Do not use **cobas® omni** utility channel Reagent Kit, **cobas®** Buffer Negative Control kit, **UC-TIB-AdV**, or **cobas® omni** reagents after their expiry dates.
- Do not reuse consumables which are designed for single use only.

Table 7. Workflow overview

Step	Action	Required material	Reference Document
1	Define Tests Ordering	**cobas®** 6800/8800 Systems	**cobas®** 6800/8800 User Assistance
2	Prepare and Load Reagent Cassette		
3	Load Reagents and Consumables		
4	Prepare Samples, Control and Standard Curve Points		
5	Start Run		
6	View Results		
7	Unload Consumables		
8*	Import Results	**cobas® omni** utility channel Optimization Tool	**cobas® omni** utility channel User Assistance
9*	Interpret Results	**UC-TIB-AdV** Offline Quantification Tool	ReadMe tab

* only for **cobas®** 6800/8800 software v1.4

7.1.1. DEFINE TESTS ORDERING

- A **UC-TIB-AdV** can be ordered in any of the ways available for ordering tests on the system (i.e., from the LIS, as a manually entered test order, or as a rack-based order). Create a test order as described in **cobas®** 6800/8800 Systems user documentation. In the Sample type field, choose the sample material.
    - The Sample type field is displayed with LIS orders, manually entered test and rack-based orders.
- In the **Tests** group box, perform the following:
    - From the options in the **Test** field, choose the UC analysis package. Multiple UC analysis packages with identical PCR parameters can be assigned to the same run.
    - In the **Volume** field, choose the sample volumes. The available volumes are defined in the UC analysis package.
- Save and perform the test as described in the **cobas®** 6800/8800 Systems user documentation.

► Refer to the **cobas®** 6800/8800 Systems user documentation for more details.

7.1.2. PREPARING THE REAGENT CASSETTE

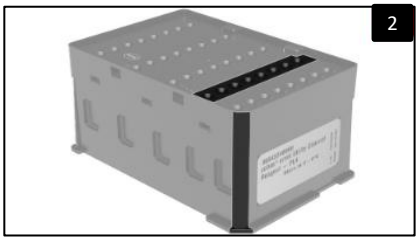
7.1.2.1. Prepare Master Mix

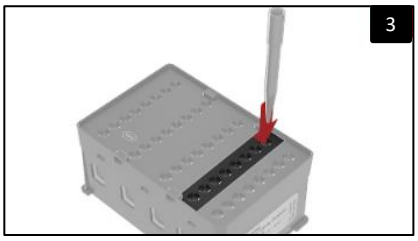
The Master Mix is prepared from the mix of Master Mix Reagent 2 (UC-MMX-R2) and **UC-TIB-AdV** primers and probes loaded in the 192-test cassette.

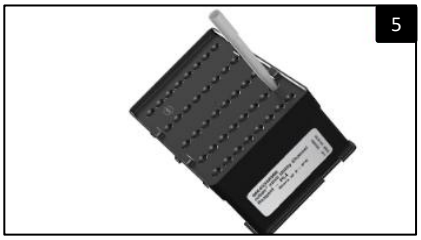

1

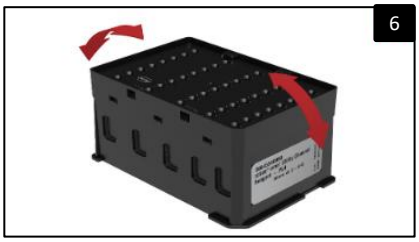
- Remove the Master Mix Reagent 2 bottles (UC-MMX-R2, see Picture 1), 192-test cassette from **cobas® omni** utility channel 192 Reagent Kit and **UC-TIB-AdV** primers and probes from their 2 °C to 8 °C storage location
- Mix the Master Mix Reagent 2 by slowly inverting the bottles 20 times
- Transfer 10.0 mL Master Mix Reagent 2 to a light-protected polypropylene tube *Note*: Refer to the **cobas® omni** utility channel User Assistance for details on transfer options steps
- Mix and spin **UC-TIB-AdV** primers and probes
- Add 0.600 mL of **UC-TIB-AdV** primers and probes
- Mix this polypropylene tube by inverting 20 times

7.1.2.2. Filling the reagent cassette









The reagent cassette is prepared by loading the PCR Mix into the reagent cassette from the **cobas® omni** utility channel 192 Reagent Kit.

- Position the reagent cassette by placing the slanted edge in the lower right corner (see Picture 2).
  Note: The second row from the right now contains the empty container.
- Place a 1 mL plastic pipette tip into the top septum hole of row 2 (see Picture 3).
  Note: This pipette tip allows air pressure in the container to adjust while the prepared PCR Mix is added.
- Take a repeater pipette with a 10 mL pipette tip. Load the pipette tip with 9.7 mL of the prepared PCR Mix.
- Insert the loaded pipette into the bottom septum hole of the reagent cassette. Puncture the septum deeply enough to avoid spillage in row 2 (see Picture 4).
- Tilt the reagent cassette to a 45° angle lengthwise from the bottom. Make sure the cassette is tipped along the edge where the pipette with the 10.0 mL tip is inserted (see Picture 5).
- **Slowly and carefully** pipette 9.7 mL of the prepared PCR Mix through the bottom septum into the empty container in row 2 (see Picture 5). If possible, dispense the prepared PCR Mix in a single movement.
- Ensure that the correct volume of the prepared PCR Mix is pipetted. **There is a risk of false negative results due to insufficient reagent volume.**
- Ensure that there is no fluid in the 1 mL pipette tip and then remove it from the septum.
  Note: If there is fluid in the tip, carefully rotate the tip to release the fluid from the tip back into the cassette. If fluid still remains in the 1 mL tip, perform the following: Using the repeater pipette with a 10 mL tip, remove some of the pipetted PCR Mix from the cassette vessel until no fluid remains in the 1 mL tip. Slowly and carefully pipette any fluid in the 10 mL pipette tip back into the vessel. Once both tips are empty, the tips can be removed from the cassette.
- Slowly tilt the reagent cassette 20 times to remove any air bubbles from the newly filled container (see Picture 6).
- On the label of the 192-test cassette from **cobas® omni** utility channel Reagent Kit, document the assay name (**UC-TIB-AdV**), the date the cassette was prepared, the lot number of the assay kit primers and probes used (PP Mix Lot) and check the box “P&P Added” to confirm primers and probes mix has been added

- Write the UCAP on the 192-test cassette, as described in table 8.

Table 8. To write the UCAP on the 192-test cassette

cobas® 6800/8800 Systems v1.4	cobas® 6800/8800 Systems v2.0 or higher
Using the **cobas® omni** utility channel tool: Start the **cobas® omni** utility channel tool. Choose Open a published UCAP to write a reagent cassette RFID tag button. Select the USAP zip.file in the new window and then Open. Recommended: Add **UC-TIB-AdV** Lot number to the RFID.	Using the RFID tool: Connect the RFID reader/writer to a USB port on the PC in which you have installed the RFID tool. In the Writing data on RFID tag group box, in the Reagent cassette ID field, enter the UCAP name: **U_UC_TIB_AdV**. If you have multiple cassettes for the same UCAP, in the Writing data on RFID tag group box, fill in the Custom information field. What you enter is used together with the reagent cassette lot number to track the reagent cassette lot. Recommended: Add **UC-TIB-AdV** Lot number to the RFID.

To forward the UCAP to the 192-test cassette RFID, use the RFID writer/reader:	
Place the RFID reader/writer immediately next to the RFID tag on the reagent cassette to be written.	
Choose the Write data on RFID tag button.	
To ensure that the RFID tag has been written on, choose the Read data from RFID tag button.	

- Load the prepared reagent cassette onto the **cobas®** 6800/8800 Systems. The prepared reagent cassette can be stored for up to seven days at 2-8 °C before first usage. After first usage, please refer to expiry conditions of the **cobas® omni** utility channel reagent kit in Table 6.

► Refer to the **cobas® omni** utility channel User Assistance for more details.

7.1.3. LOAD REAGENTS AND CONSUMABLES

On the Monitoring tab, choose the drawer corresponding to reagents and consumables to be loaded into the **cobas®** 6800/8800 Systems. Check their status and if necessary:

- Load the empty solid waste bag and liquid waste container
- Load the wash reagent, lysis reagent and diluent
- Load the processing plates and amplification plate cassette
- Load the Magnetic Glass Particles
- Load the Negative Control cassette
- Load tips racks

Place the rack for clotted tips onto the sample supply module.

► Refer to the **cobas®** 6800/8800 Systems User Assistance for more details.

7.1.4. PREPARE SAMPLES, CONTROL AND STANDARD CURVE

Note: If using frozen plasma samples, place the samples at room temperature until completely thawed and vortex for 3 to 5 seconds before use. Controls should be removed from storage at 2 °C to 8 °C and brought to room temperature before use.

One (+)_Ctrl has to be performed as sample in each run and for each new reagent cassette.
To guarantee that each control batch contains an appropriate (+)_Ctrl , we recommend using the entire cobas® omni utility channel 192 Reagent Kit cassette before loading a new utility channel 192 Reagent Kit cassette.

The (+)_Ctrl must be identified by a name starting with "(+)_Ctrl" in the barcode label of the tube (e.g. (+)_Ctrl_YYYYMMDD).
The name of the (+)_Ctrl must respect this structure to avoid any risk of invalid run of results.

The 4 Standard Curve Points are performed as samples for:

- Each new **UC-TIB-AdV** kit opened
- Each new reagent cassette batch

Each Standard Curve Point must be identified by a name starting with STD1, STD2, STD3 and STD4 in the barcode label of the tubes (e.g. STD1_YYYYMMDD).
The name of Standard Curve Points must respect this structure to avoid any risk of invalid run of results.

► Refer to the **cobas®** 6800/8800 Systems User Assistance to identify sample tubes with barcode.

Prepare secondary tubes for the **UC-TIB-AdV** Positive Control and 4 Standard Curve Points with the corresponding barcode: as described below:

- Vortex the 5 corresponding vials
- Transfer 0.35 mL (this volume includes 0.15 mL of dead volume) of each sample to the secondary tube with the appropriate barcode labeled.

Place the tubes with samples, Positive Control and 4 Standard Curve Points in the sample racks assigned to the assay **UC-TIB-AdV** on the **cobas®** 6800/8800 Systems.
Please note a Negative Control (**cobas®** Buffer Negative Control Kit, Roche P/N 09051953190) is automatically performed with each run by the the **cobas®** 6800/8800 Systems

7.1.5. START RUN

A run starts automatically if at least one of the samples for the run is onboard. If the run is not full and you do not want to wait for the timeout to end, start the run manually:

- Make sure that the system is in ”Ready” status
- On the Monitoring tab, next to the system overview, choose the ”Batches” button
  Note: Ensure all samples are scanned before starting the run
- Choose the ”Start manually” button

When the samples are processed, remove the rack tray with the sample racks from the output buffer of sample supply module.

7.1.6. VIEW RESULTS

Once the run finished, all the results obtained are reviewed on the **cobas®** 6800/8800 Systems v1.4 according to this procedure:

- On the monitor of the **cobas®** 6800/8800, go to the “Routine” tab and choose “Control batch”.
- In the list, choose the control batch to be used to create the report and/or data files.
- Click on the printer logo and select "Save as PDF”: a report file is created and stored on the IG server.
- Then, go to the sample results by clicking on “>” and select all the tests results needed.
- Click on "Export" and allocate a file name: a data file is created and stored on the IG server.

On the **cobas®** 6800/8800 Systems v2.0 or higher no manual result review is needed.

7.1.7. UNLOAD CONSUMABLES

On Monitoring tab, choose the drawer for consumables to be discharged from **cobas®** 6800/8800 Systems.

- Unload the amplification plates from the analytic module
- Unload empty control cassettes
- Empty solid waste bag
- Empty liquid waste container

7.1.8. IMPORT RESULTS

Only for **cobas®** 6800/8800 Systems v1.4

- Connect to the **cobas®** 6800/8800 Systems from the external computer (RUI).
- After connection, a new window appears, go to the "Administration" tab and choose “File management”.
- To save the report or data files (“PDF” or “.xml”) on the PC / USB device, click on “Reports” or “Exports” respectively and save files by clicking on “Download”.
- Open the “**cobas® omni** utility channel Optimization Tool” program.
- In the “Test selection” box, click on “Import data”.
- Select the ".xml” file which contains both the STD Curve and Samples/Controls then click on “Open”.
  *Note: When a new **UC-TIB-AdV** box is opened, the first RUN always contains the STD Curve.*
- In the “Growth Curve” section, go to the “Channel No.” column and select Channel 2 by using the filter option and keep it activated.
  Do not change the default order of the columns before exporting the table to “.xls” file.
- Go to the “Sample ID” column and select all STD Curve points from 1 to 4 and export them in “.xls” file (to be performed each time a new kit is opened) by right clicking in the results table and by selecting the “Exporting table to .xls file” option: Allocate a file name then click on “Save”.
  Note: In the filter window, use the search bar in order to facilitate the search of STD Curve points.
- The samples results are exported as described above for STD Curve Points, one run per “.xls” file.
  Note: To facilitate the selection of samples and controls results without STD Curve points, click to “Select all” within the window filter and deselect STD Curve points (1 – 4) only.

- After these last steps, you obtain at least 2 ".xls" files: "STD Curve".xls and "Samples".xls files.

7.1.9. INTERPRET RESULTS

Only for **cobas**® 6800/8800 Systems v1.4

The **cobas®** 6800/8800 Systems report the Ct values associated with samples. These Ct values are computed by the **UC-TIB-AdV** Offline Quantification Tool to determine the AdV DNA concentration for the samples and the Positive Control. The ADV DNA titer is expressed in International Units per milliliter (IU/mL).

The **UC-TIB-AdV** Offline Quantification Tool requires the following steps to proceed:

- To ensure the functionality of the Offline Quantification Tool, make sure the decimal and thousands separators are configured as follows:
  - In the Quantification Tool file, go to File
  - Select "Option"
  - Go to "Advanced Options"
  - In the "Editing Option"; check "Use the system separators" ; then place a coma or dot as decimal and thousands separators
- Paste the data of the STD Curve from the ".xls" file in the cell A1 of the Raw Data – STD tab
- Paste the data of the Samples from the ".xls" file in the cell A1 of the Raw Data – Samples tab
  To delete a line or clear the tab content, please use "Clear Contents" instead of the "Delete" option.
- Check the validity of the STD Curve in the STD Curve tab, which is determined by Acceptance Criteria on each parameter of the linear regression (slope, Y-Intercept and R^2). Its status is indicated as "PASSED" or "FAILED". All parameters of the linear regression must be marked as "PASSED" to obtain a "Valid STD Curve - Ready for quantification" to perform a quantification.

► Refer to the instructions in the ReadMe tab of **UC-TIB-AdV** Offline Quantification Tool to quantify each sample with the Standard Curve.

7.1.9.1. Quality control and run validity of results

Only for **cobas**® 6800/8800 Systems v1.4

In the Titers tab of the **UC-TIB-AdV** Offline Quantification Tool, the run is considered as valid when the STD Curve is PASSED, the Positive Control is PASSED and the Negative Control is PASSED.
If one of these 3 conditions is not met, the run status is noted as INVALID. Please visit the Readme tab to find more information linked to this issue.

7.1.9.2. Sample Results

Only for **cobas**® 6800/8800 Systems v1.4

All the sample values, standards and controls included are analyzed with the **UC-TIB-AdV** Offline Quantification Tool. In the Titers tab, if the run is considered as VALID, the titer of each positive sample is displayed in the column entitled Titer IU/mL, according to the rules listed in the table below.

Table 9. Results interpretation using the **UC-TIB-AdV** Offline Quantification Tool

Results	Interpretation
No quantification	ADV not detected in the sample
< Titer Min (in red)	Calculated titer is below the Lower Limit of Quantification (LLoQ) of the assay. Report results as "AdV detected, less than (Titer Min)." Titer Min = 1.0E2 IU/mL
Titer	Calculated titer is within the Linear Range of the assay – greater than or equal to Titer Min and less than or equal to Titer Max. Report results as "(Titer) of AdV detected".
> Titer Max* (in orange)	Calculated titer is above the Upper Limit of Quantification (ULoQ) of the assay. Report results as "AdV detected, greater than (Titer Max)." Titer Max = 1.0E8 IU/mL

* Sample result > Titer Max refers to AdV positive samples detected with titers above the upper limit of quantification (ULoQ). If a quantitative result is desired, the original sample should be diluted with AdV-negative human EDTA plasma and the test should be repeated. Multiply the reported result by the dilution factor.

► Refer to the Troubleshooting tab of **UC-TIB-AdV** Offline Quantification Tool for additional information on the comments and the error messages displayed.

8. PERFORMANCE EVALUATION

8.1. LIMIT OF DETECTION (LOD)

The limit of detection (LoD) of **UC-TIB-AdV** was determined by analysis of serial dilutions of the WHO International Standard for AdV (1st WHO International Standard) obtained from NIBSC (Code 16/324), in AdV-negative human EDTA plasma. Panels of 6 concentration levels plus a negative were tested on 3 lots of **UC-TIB-AdV** reagents. The study demonstrates that the **UC-TIB-AdV** detects AdV DNA at a concentration of 39.5 IU/mL determined by PROBIT with a hit rate of 95 % (Table 10).

Table 10. LoD of the **UC-TIB-ADV**

Matrix	$LoD_{95\%}$	95% Confidence Interval
EDTA Plasma	39.5 IU/mL	35.1 – 43.9 IU/mL

8.2. LIMIT OF QUANTIFICATION (LOQ) AND LINEAR RANGE

The linearity of the **UC-TIB-AdV** was evaluated using a dilution series consisting of 9 panel members with AdV serotype C2 (WHO reference standard) concentrations spanning the assay linear range (70 IU/mL to 3.0E8 IU/mL). Each panel member was tested in 10 replicates across 3 lots of the **UC-TIB-AdV** and the results of the study are presented in Figure 1.

The lower and upper limit of quantification (LLoQ and ULoQ) are respectively defined as the lowest and highest concentration that can be measured by the assay. The **UC-TIB-AdV** was demonstrated to be linear from 100 IU/mL (LLoQ) to 1.0E8 IU/mL (ULoQ).

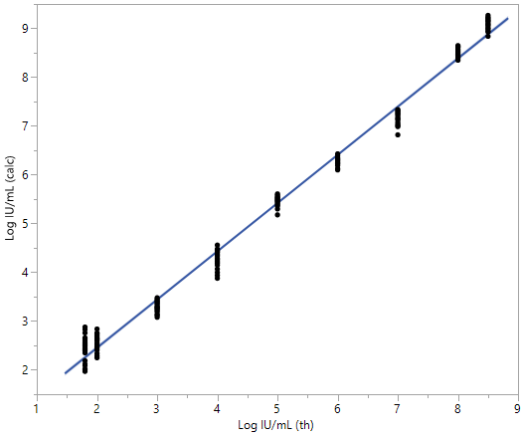


Figure 1. Linear range determination in AdV negative EDTA plasma

8.3. ANALYTICAL SPECIFICITY

The analytical specificity of the **UC-TIB-AdV** was evaluated by diluting microorganisms with AdV WHO reference standard in AdV negative EDTA plasma (Table 11). The microorganisms were added to negative human EDTA plasma and tested with and without ADV. Yeast were tested at concentrations of 1.0E6 CFU/mL. Viruses were tested at concentrations of 1.0E5 to 1.0E6 $TCID_{50}$/mL, c/mL or IU/mL, except where noted. None of the non-AdV pathogens interfered with the **UC-TIB-AdV** performance. Negative results were obtained with **UC-TIB-AdV** for all samples without an AdV target and positive results were obtained on all of the samples with an AdV target. Furthermore, the mean log_{10} titer of each of the positive AdV samples containing potentially interfering organisms was within ± 0.5 log_{10} of the mean log_{10} titer of the respective positive spike control.

Table 11. Microorganisms tested for cross-reactivity with the **UC-TIB-AdV**

Microorganism Name	Tested Concentration
Varicella Zoster Virus (HV3)	1.0E6 c/mL
Herpes Simplex Virus 1	1.0E6 $TCID_{50}$/mL
Herpes Simplex Virus 2	1.0E6 $TCID_{50}$/mL
Epstein-Barr Virus	1.0E6 c/mL
Human Herpesvirus 6	1.0E6 c/mL
Human Herpesvirus 7	1.0E5 $TCID_{50}$/mL
Human Herpesvirus 8	1.0E5 $TCID_{50}$/mL
Cytomegalovirus	1.0E5 $TCID_{50}$/mL
BK Virus	1.0E6 c/mL
JC Virus (pBRSV)	1.0E5 $TCID_{50}$/mL
Simian Virus 40	1.0E4 $TCID_{50}$/mL

Hepatitis C Virus	1.0E3 IU/mL
Human Immunodeficiency Virus 1	1.0E4 $TCID_{50}$/mL
Hepatitis B Virus	1.0E3 IU/mL
Parvovirus B19	1.0E5 $TCID_{50}$/mL
Candida albicans	1.0E6 CFU/mL
Candida glabrata	1.0E6 CFU/mL

8.4. INCLUSIVITY

At least one representative strain of each species of AdV (A to G) was tested at a concentration close to the $LoD_{95\%}$ in 3 replicates in AdV negative EDTA plasma. The inclusivity of each AdV species (from A to F) was evaluated using viral strains and the AdV 52 was assessed using target plasmid. The results demonstrated that the **UC-TIB-AdV** detects all the serotypes tested within 0.29 SD log_{10} IU/mL (Table 12).

Table 12. Detection of each AdV serotype with the **UC-TIB-AdV**

Species	Serotype
A	AdV 31
B	AdV 3
	AdV 7a
	AdV 11
C	AdV 1
	AdV 2
	AdV 6
D	AdV 17
	AdV 43
	AdV 37
E	AdV 4
F	AdV 41
G	ADV 52

8.5. INTERFERING SUBSTANCES

Potential exogenous (antimicrobial, antiviral and immunosuppressive drugs) and endogenous interfering substances were selected and tested at clinically relevant concentrations with the **UC-TIB-AdV** (see Table 13). Those were tested in the presence and absence of the AdV WHO reference standard spiked in AdV negative EDTA plasma. All potentially interfering substances were shown not to interfere with the test performance.

Table 13. Potential interfering substances tested for interference with the **UC-TIB-AdV**

Interfering Substance	Final Concentration (µg/mL)
Azathioprine	2.99
Cefotetan disodium	474.00
Cidofovir hydrate	53.60
Cyclosporine A	4.59
Everolimus	0.34
Fluconazole	74.97
Foscarnet sodium	453.15
Ganciclovir	20.80
Mycophenolate mofetil	72.40
Mycophenolic acid	114.40
Piperacillin sodium	596.00
Potassium clavulanate	6.99
Prednisone	0.30
Sirolimus	0.09
Sulfamethoxazole	399.74
Tacrolimus	0.04
Tazobactam sodium	67.60
Ticarcillin disodium	776.00
Trimethoprim	40.02
Valganciclovir hydrochloride hydrate	22.96

Interfering Substance	Final Concentration (µg/mL)
Vancomycin hydrochloride	99.98
Unconjugated bilirubin	250.00
Bovine serum albumin	58700.00
Hemoglobin human	2900.00
Human DNA	2.00
Triglyceride mix	34500.00
Conjugated bilirubin	250.00

8.6. PRECISION

The precision of the **UC-TIB-AdV** was determined by analysis of serial dilutions of the AdV WHO reference standard in AdV negative EDTA plasma. The dilution levels were tested in 10 replicates for each level over three lots of **UC-TIB-AdV** reagents over a concentration range of 1.0E02 IU/mL to 1.0E08 IU/mL using one instrument and one operator, over two days. Each sample was carried through the entire **UC-TIB-AdV** procedure on fully automated **cobas®** 6800/8800 Systems. The precision reported below represents all aspects of the test procedure (Table 14).

Table 14. Precision of the **UC-TIB-AdV**

Nominal concentration (IU/mL)	Assigned concentration (IU/mL)	EDTA Plasma			
		Lot 1	Lot 2	Lot 3	All Lots
		SD	SD	SD	Pooled SD
1.0E08	2.9E+08	0.06	0.05	0.04	0.09
1.0E07	1.7E+07	0.11	0.16	0.12	0.11
1.0E06	1.9E+06	0.06	0.08	0.11	0.09
1.0E05	3.3E+05	0.04	0.03	0.05	0.06
1.0E04	2.1E+04	0.15	0.14	0.04	0.14
1.0E03	1.8E+03	0.08	0.12	0.07	0.11
1.0E02	3.6E+02	0.14	0.12	0.16	0.16

The **UC-TIB-AdV** showed high precision for three lots of reagents tested over a concentration range of 1.0E2 IU/mL to 1.0E8 IU/mL.

8.7. CLINICAL PERFORMANCE

The performance of the **UC-TIB-AdV** was demonstrated by comparison with a real time PCR CE-IVD kit for quantification of human AdV on a retrospective collection and testing of 120 plasma specimens including 21 AdV positive within the linear range of both tests and 95 negative EDTA plasma samples. All the results were valid.

The positive percent of agreement (PPA) was 100 % and negative percent of agreement (NPA) was 100 %. A Deming regression analysis was performed. The determination coefficient R^2 is 0.89, which shows a high correlation between the two methods (Figure 2).

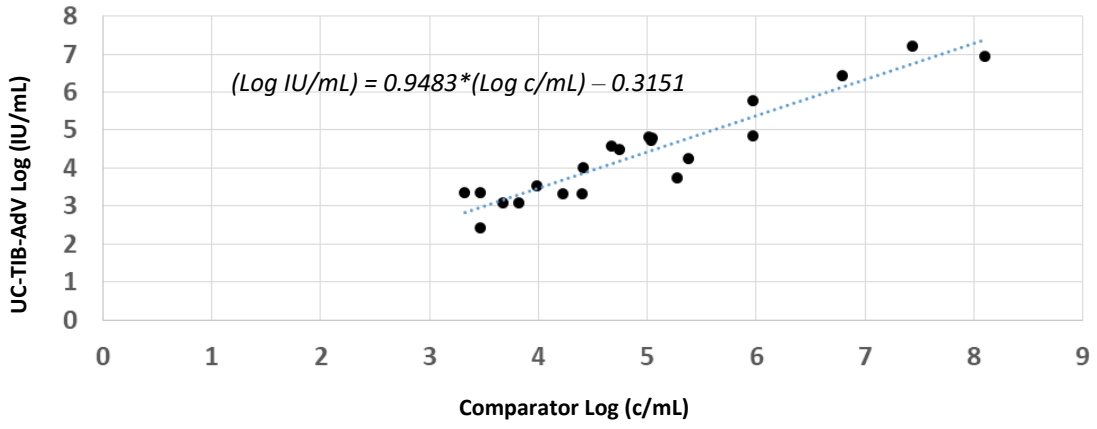


Figure 2. Correlation plot with the quantification of both assays

9. LIMITATIONS

The **UC-TIB-AdV** has been evaluated only for use in combination with the **cobas®** 6800/8800 Buffer Negative Control Kit, **cobas® omni** MGP Reagent, **cobas® omni** Lysis Reagent, **cobas® omni** Sample Diluent, and **cobas® omni** Wash Reagent for use on the **cobas®** 6800/8800 Systems.

Reliable results depend on correct sample collection, storage and handling procedures.

This test has been validated only for use with EDTA plasma. Testing of other sample types may result in inaccurate results. Plasma viral load measurements are not directly comparable to those of other sample types.

Quantification of AdV DNA may be affected by sample collection methods, patient factors (i.e. age, presence of symptoms), and/or stage of infection.

Due to inherent differences between technologies, it is recommended that, prior to switching from one technology to another, users perform method correlation studies in their laboratory to qualify technology differences. Users should follow their own specific policies/procedures.

The **UC-TIB-AdV** is not intended for use as a screening test for the presence of AdV in blood or blood products and has not been evaluated as a diagnostic test to confirm the presence of AdV infection.

10. QUALITY CERTIFICATION

TIB Molbiol is ISO 13485 certified. The **UC-TIB-AdV** has been tested against predetermined specifications to ensure product quality.

11. KEY TEST FEATURES

Sample type	EDTA Plasma
Species Groups detected	AdV A to G
Minimum amount of sample required	350 µL*
Sample processing volume	200 µL
Analytical sensitivity	39.5 IU/mL
Linear range	1.0E2 IU/mL to 1.0E8 IU/mL
Specificity	100 %

* recommended for **cobas® omni** secondary tubes, minimum volumes for other tubes may differ

12. REFERENCES

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③ Benoit Visseaux, *et al.* (2017). Prevalence of respiratory viruses among adults, by season, age, respiratory tract region and type of medical unit in Paris, France, from 2011 to 2016. *PLoS ONE 12(7): e0180888*

④ Joseph P. Lynch III and Adriana E. Kajon (2016). Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment and Prevention. *Semin Respir Crit Care Med 37:586–602*

⑤ Gustafson I, *et al.* (2008). Quantification of adenovirus DNA in unrelated donor hematopoietic stem cell transplant recipients. *J Clin Virol. 43(1):79–85*

13. SYMBOLS

REF	Catalog reference number		Refer to user manual
LOT	Batch code	CONTROL +	Positive Control
GTIN	GTIN code		Store in the dark
Σ	Contains sufficient for "n" tests		Manufacturing date (yyyy-mm-dd)
2°C 8°C	Storage range of temperatures		Legal Manufacturer
	Use by date (yyyy-mm-dd)	SW	Ancillary Software
IVD	*In vitro* diagnostic medical device		Warning

14. NOTICE TO PURCHASER

- **UC-TIB-AdV** is a product from TIB Molbiol Syntheselabor GmbH, exclusively distributed worldwide by Roche Diagnostics GmbH
- **cobas®** is a registered trademark of Roche Diagnostics GmbH

TIB Molbiol Syntheselabor GmbH, Eresburgstr. 22-23, 12103 Berlin, Germany
Telephone: (+49) 30 78 79 94-55 / Email: dna@tib-molbiol.de

Product designed and manufactured in Germany

TIB Molbiol Syntheselabor GmbH

Eresburgstr. 22-23
12103 Berlin
GERMANY

(+49) 30 78 79 94-55
dna@tib-molbiol.de
www.TIB-MOLBIIOL.com

IFU_UC-TIB-AdV-192_EN_v7.0