REF 202500 NeuMoDx™ HHV-6 Quant Test Strip

Rx Only

CAUTION: For US Export Only

IVD For *In Vitro* Diagnostic Use with the NeuMoDx™ 288 and NeuMoDx™ 96 Molecular Systems

This package insert must be read carefully prior to product use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.
For detailed instructions, refer to the NeuMoDx™ 288 Molecular System Operator's Manual; P/N 40600108
For detailed instructions, refer to the NeuMoDx™ 96 Molecular System Operator's Manual; P/N 40600317

CE

INTENDED USE

The NeuMoDx™ HHV-6 Quant Assay is an automated, *in vitro* nucleic acid amplification test for the quantification and differentiation of Human betaherpesvirus 6A (HHV-6A) DNA and/or Human betaherpesvirus 6B (HHV-6B) DNA in EDTA Plasma from immunocompromised transplant patients[1,2].

The NeuMoDx™ HHV-6 Quant Assay as performed on the NeuMoDx™ 288 Molecular System and NeuMoDx™ 96 Molecular System incorporates automated DNA extraction to isolate the target nucleic acids from the specimen and real-time PCR to target two highly conserved regions in the HHV-6A and HHV-6B genomes.

The assay is intended for use as an aid in the monitoring of HHV-6A and/or HHV-6B DNA levels in EDTA plasma. This assay is intended for use in conjunction with clinical presentation and other laboratory markers of disease progression for the clinical management and monitoring of HHV-6A and/or HHV-6B infections.

The NeuMoDx™ HHV-6 Quant Assay is not intended for use as a screening test for the presence of HHV-6A and/or HHV-6B DNA in blood or blood products.

The NeuMoDx™ HHV-6 Quant Assay is intended for use by trained clinical laboratory personnel specifically instructed and trained in the techniques of real-time PCR and in vitro diagnostic procedures and/or NeuMoDx™ Molecular Systems. The NeuMoDx™ HHV-6 Quant Assay is not intended for self-testing or point-of-care use.

SUMMARY AND EXPLANATION

Human whole blood collected in sterile blood collection tubes containing EDTA as an anticoagulation agent or in plasma preparation tubes (PPT) may be used for the preparation of plasma. To initiate testing, plasma in a primary or secondary specimen tube compatible with the NeuMoDx™ System, is loaded onto the NeuMoDx™ System using a designated specimen tube carrier to begin automated processing.

A 550 µL aliquot of the plasma specimen is mixed with NeuMoDx™ Lysis Buffer 1 and the NeuMoDx™ System automatically performs all the steps required to extract the target nucleic acids, prepare the isolated DNA for real-time PCR amplification, and if present, amplify and detect the products of amplification. The NeuMoDx™ HHV-6 Quant Assay includes a DNA Sample Process Control (SPC1) to help monitor for the presence of potential inhibitory substances as well as NeuMoDx™ System or reagent failures that may be encountered during the extraction and amplification process.

Human herpes virus 6 (HHV-6) is part of the Betaherpesvirus subfamily and encompasses two different species, HHV-6A and HHV-6B[2]. It is a DNA virus, which has tropism for central nervous system tissues, tonsils, salivary glands, kidneys, liver, lymph nodes, endothelial cells, and monocytes/macrophages[4]. The primary syndrome associated with HHV-6 infection is exanthema subitum (roseola or sixth disease)[1,2,3,4]. This is almost exclusively a childhood illness and accounts for 10% to 30% of emergency department visits children under 2 years of age[1]. Like all herpesviruses, HHV-6 can establish lifelong latency following initial infection, in haematopoietic stem cells and germinal cells among others, thus allowing the horizontal as well as vertical transmission[2]. This phenomenon was described in 0.2 to 1% of general population[4]. In the immunocompromised host, latent virus can reactivate to cause severe illness, including pneumonitis, CNS disease, and delayed bone marrow engraftment or graft versus host disease (GVHD). The incidence of HHV-6 reactivation ranges from approximately 0% to 80% (avg. 30% to 50%) in solid organ (SOT) or bone marrow (BMT) transplant patients, with a slight preference for BMT[1]. HHV-6A reactivation is rarely identified after transplantation, conversely to HHV-6B. HHV-6B reactivation affects approximately 40% of subjects within the first few months. It is the most frequent infectious cause of encephalitis after HCT (1% of cases). Patients who develop HHV-6B encephalitis typically have concurrent detection of HHV-6B in the plasma with viral loads ≥10,000 copies/mL[3].

PRINCIPLES OF THE PROCEDURE

The NeuMoDx™ HHV-6 Quant Assay on the NeuMoDx™ System utilizes the NeuMoDx™ HHV-6 Quant Test Strip, NeuMoDx™ HHV-6 Calibrators, NeuMoDx™ HHV-6 External Controls, NeuMoDx™ Lysis Buffer 1, and NeuMoDx™ general use reagents to perform the analysis. The NeuMoDx™ HHV-6 Quant Assay combines automated DNA extraction, amplification, and detection by real-time PCR. Plasma specimens in NeuMoDx™ System compatible primary or secondary specimen tubes are placed into a specimen tube carrier, which is then loaded onto the NeuMoDx™ System for processing. No further operator intervention is necessary.

The NeuMoDx™ Systems use a combination of heat, lytic enzyme, and extraction reagents to automatically perform cell lysis, DNA extraction and removal of inhibitors. The released nucleic acids are captured by magnetic affinity microspheres. The microspheres, with the bound nucleic acids, are loaded into the NeuMoDx™ Cartridge where the unbound, non-DNA components are further washed away with NeuMoDx™ Wash Reagent and the bound DNA is eluted using NeuMoDx™ Release Reagent. The NeuMoDx™ Systems then use the eluted DNA to rehydrate the SENTINEL CH. S.p.A. proprietary freeze-dried amplification reagents containing all the elements necessary for PCR amplification of the HHV-6-specific targets and

SPC1 target. Upon reconstitution of the lyophilized PCR reagents, the NeuMoDx™ System dispenses the prepared PCR-ready mixture into the NeuMoDx™ Cartridge. Amplification and detection of the control and target DNA sequences (if present) occur in the PCR chamber area of the NeuMoDx™ Cartridge. The NeuMoDx™ Cartridge is also designed to contain the amplicon following real-time PCR and essentially eliminate the risk of post-amplification contamination.

The genomic targets for NeuMoDx™ HHV-6 Quant Test Strip are U31 and U67 genes of HHV-6A and HHV-6B viral genomes. These amplified targets are detected in real time using hydrolysis probe chemistry (commonly referred to as TaqMan® chemistry) using fluorogenic oligonucleotide probe molecules specific to the amplicons for their respective targets. TaqMan® probes consist of a fluorophore covalently attached to the 5'-end of the oligonucleotide probe and a quencher at the 3'-end. While the probe is intact, the fluorophore and the quencher are in proximity, resulting in the quencher molecule quenching the fluorescence emitted by the fluorophore via FRET (Förster Resonance Energy Transfer). TaqMan® probes are designed such that they anneal within a DNA region amplified by a specific set of primers. As the Taq DNA polymerase extends the primer and synthesizes the new strand, the 5' to 3' exonuclease activity of the Taq DNA polymerase degrades the probe that has annealed to the template. Degradation of the probe releases the fluorophore and breaks the close proximity to the quencher, thereby overcoming the quenching effect due to FRET and allowing fluorescence detection of the fluorophore. The resulting fluorescent signal detected in the NeuMoDx™ System quantitative PCR thermal cycler is directly proportional to the fluorophore released and can be correlated to the amount of target DNA present[5].

TaqMan® probes labeled with fluorophores at the 5' end, and quenchers at the 3' end, are used to detect HHV-6A DNA, HHV-6B DNA and SPC1 DNA. The NeuMoDx™ System software monitors the fluorescent signal emitted by the TaqMan® probes at the end of each amplification cycle. When amplification is complete, the NeuMoDx™ System software analyzes the data and reports a result (POSITIVE / NEGATIVE / INDETERMINATE / UNRESOLVED/ NO RESULT). If a result is positive and the calculated concentration is within the limits of quantitation, the NeuMoDx™ System software also provides a quantitative value associated with the sample or reports if the calculated concentration is outside of the linear range.

REAGENTS/CONSUMABLES

Material Provided

REF	Contents	Tests per unit	Tests per package
202500	NeuMoDx™ HHV-6 Quant Test Strip *Freeze-Dried PCR reagents containing HHV-6A specific TaqMan® probes and primers, HHV-6B specific TaqMan® probes and primers in addition to SPC1-specific TaqMan® probe and primers.*	16	96

Reagents and Consumables Required but Not Provided (Available Separately from NeuMoDx)

REF	Contents
100200	NeuMoDx™ Extraction Plate *Dried paramagnetic particles, Lytic enzyme, and sample process controls.*
801000	NeuMoDx™ HHV-6 Calibrators *Single use sets of HHV-6A and HHV-6B High and Low Dried-Calibrators to establish standard curve.*
901000	NeuMoDx™ HHV-6 External Controls *Single use sets of HHV-6A and HHV-6B Positive dried-controls and Negative controls to establish daily validity of NeuMoDx™ HHV-6 Quant Assay*
400400	NeuMoDx™ Lysis Buffer 1
400100	NeuMoDx™ Wash Reagent
400200	NeuMoDx™ Release Reagent
100100	NeuMoDx™ Cartridge
235903	Hamilton CO-RE Tips (300 µL) with Filters
235905	Hamilton CO-RE Tips (1000 µL) with Filters

For the reagents and consumables details please refers to the related insert

Instrumentation Required

NeuMoDx™ 288 Molecular System (REF 500100) or NeuMoDx™ 96 Molecular System (REF 500200).
NeuMoDx System Software version 1.9.2.6 or higher.

WARNINGS & PRECAUTIONS

- The NeuMoDx™ HHV-6 Quant Test Strip is for in vitro diagnostic use with NeuMoDx™ Systems only.
- Read all the instructions contained in the kit insert before performing the test.
- Do not use the reagents or consumables after the listed expiration date.
- Do not use any reagents if the safety seal is broken or if the packaging is damaged upon arrival.

- Do not use consumables or reagents if the protective pouch is open or broken upon arrival.
- Do not mix up reagents for amplification from other commercial kits.
- Do not reuse.
- Keep all NeuMoDx™ HHV-6 Quant Test Strips protected from light and humidity in their aluminum envelopes.
- A valid test calibration, generated by processing high and low calibrators from the NeuMoDx™ HHV-6 Calibrators (REF 801000), must be available before test results can be generated for clinical samples.
- NeuMoDx™ HHV-6 External Controls (REF 901000) must be processed every 24 hours throughout testing with the NeuMoDx™ HHV-6 Quant Test Strip.
- Minimum specimen volume is dependent on the tube size, specimen carrier, and specimen volume as defined below. Volume below the specified minimum may result in a "Quantity Not Sufficient" Error.
- The use of specimens stored at improper temperatures or beyond the specified storage times may produce invalid or erroneous results.
- Avoid microbial and deoxyribonuclease (DNase) contamination of all reagents and consumables. The use of sterile DNase-free disposable transfer pipettes is recommended if using secondary specimen tubes. Use a new pipette for each specimen.
- To avoid contamination, do not handle or break apart any NeuMoDx™ Cartridge post-amplification. Do not retrieve NeuMoDx™ Cartridges from the Biohazard Waste Container (NeuMoDx™ 288 Molecular System) or Biohazard Waste Bin (NeuMoDx™ 96 Molecular System) under any circumstances. The NeuMoDx™ Cartridge is designed to prevent contamination.
- In cases where open-tube PCR tests are also conducted by the laboratory, care must be taken to ensure that the NeuMoDx™ HHV-6 Quant Test Strip, the additional consumables and reagents required for testing, personal protective equipment such as gloves and lab coats, and the NeuMoDx™ System are not contaminated.
- Clean, powder-free, nitrile gloves should be worn when handling NeuMoDx™ reagents and consumables. Care should be taken not to touch the top surface of the NeuMoDx™ Cartridge, the foil seal surface of the NeuMoDx™ HHV-6 Quant Test Strip or NeuMoDx™ Extraction Plate, or the top surface of the NeuMoDx™ Lysis Buffer 1 container; handling of the consumables and reagents should be done by touching side surfaces only.
- Safety Data Sheets (SDS) are provided for each reagent (as applicable) at www.neumodx.com/client-resources.
- A vertical bar in the text margin indicates changes in comparison to the previous insert version.
- Wash hands thoroughly after performing the test.
- Do not pipette by mouth. Do not smoke, drink, or eat in areas where specimens or reagents are being handled.
- Always handle specimens as if they are infectious and in accordance with safe laboratory procedures such as those described in the OSHA Standard on the Bloodborne Pathogens[6]. Biosafety Level 2[7] or other appropriate biosafety practices[8,9] should be used for materials that contain or are suspected of containing infectious agents.
- Dispose of unused reagents and waste in accordance with country, federal, provincial, state and local regulations. Follow recommendations in the Safety Data Sheet (SDS).

PRODUCT STORAGE, HANDLING & STABILITY

- NeuMoDx™ HHV-6 Quant Test Strips are stable in the primary packaging at +15 °C/+30 °C through the stated expiration date on the immediate product label.
- A NeuMoDx™ HHV-6 Quant Test Strip loaded into the NeuMoDx™ System is stable for 32 days; the NeuMoDx™ System software will prompt the removal of the test strips that have been in-use on board the NeuMoDx™ System for longer than 32 days and new NeuMoDx™ HHV-6 Quant Test Strips will need to be opened (extract the strips from the pouch) and loaded on the NeuMoDx™ System. Do not remove the aluminum foil from the strip when loading onto the test strip carrier.
- The NeuMoDx™ HHV-6 calibrators and controls are non-infectious but should be discarded in laboratory biohazard waste after use as they will contain target material which may cause contamination if not handled properly.

SPECIMEN COLLECTION, TRANSPORT & STORAGE

1. Handle all specimens as if they are capable of transmitting infectious agents.
2. Do not freeze whole blood or plasma specimens stored in primary tubes.
3. To prepare plasma specimens, whole blood should be collected in sterile tubes using EDTA as the anticoagulant. Follow the specimen collection tube manufacturer instructions.
4. Whole blood collected in devices listed above may be stored and/or transported for up to 24 hours at +2 °C/+8 °C prior to plasma preparation. Samples preparation should be performed according to manufacturer instructions.
5. Prepared plasma may be stored on the NeuMoDx™ System for up to 24 hours prior to processing. If additional storage time is required, it is recommended that the specimens be either refrigerated or frozen as secondary aliquots.
6. Prepared plasma specimens should be stored at +2 °C/+8 °C for no longer than 8 days prior to testing and a maximum of 24 hours at room temperature.
7. Prepared specimens may be stored at < -20 °C for up to 8 weeks before processing; samples should not be subjected to more than 2 freeze/thaw cycles prior to use:
    a. If samples are frozen, allow the samples to completely thaw at room temperature (+15 °C/+30 °C) prior to testing; vortex to generate a uniformly distributed sample.

b. Once frozen samples are thawed, testing should occur within 24 hours.

8. If specimens are shipped, they should be packaged and labeled in compliance with applicable country and/or international regulations.
9. Label specimens clearly and indicate specimens are for HHV-6A and/or HHV-6B testing.
10. Proceed to *Test Preparation* section.

The overall process for implementation of the NeuMoDx™ HHV-6 Quant Assay is summarized in *Figure 1*.

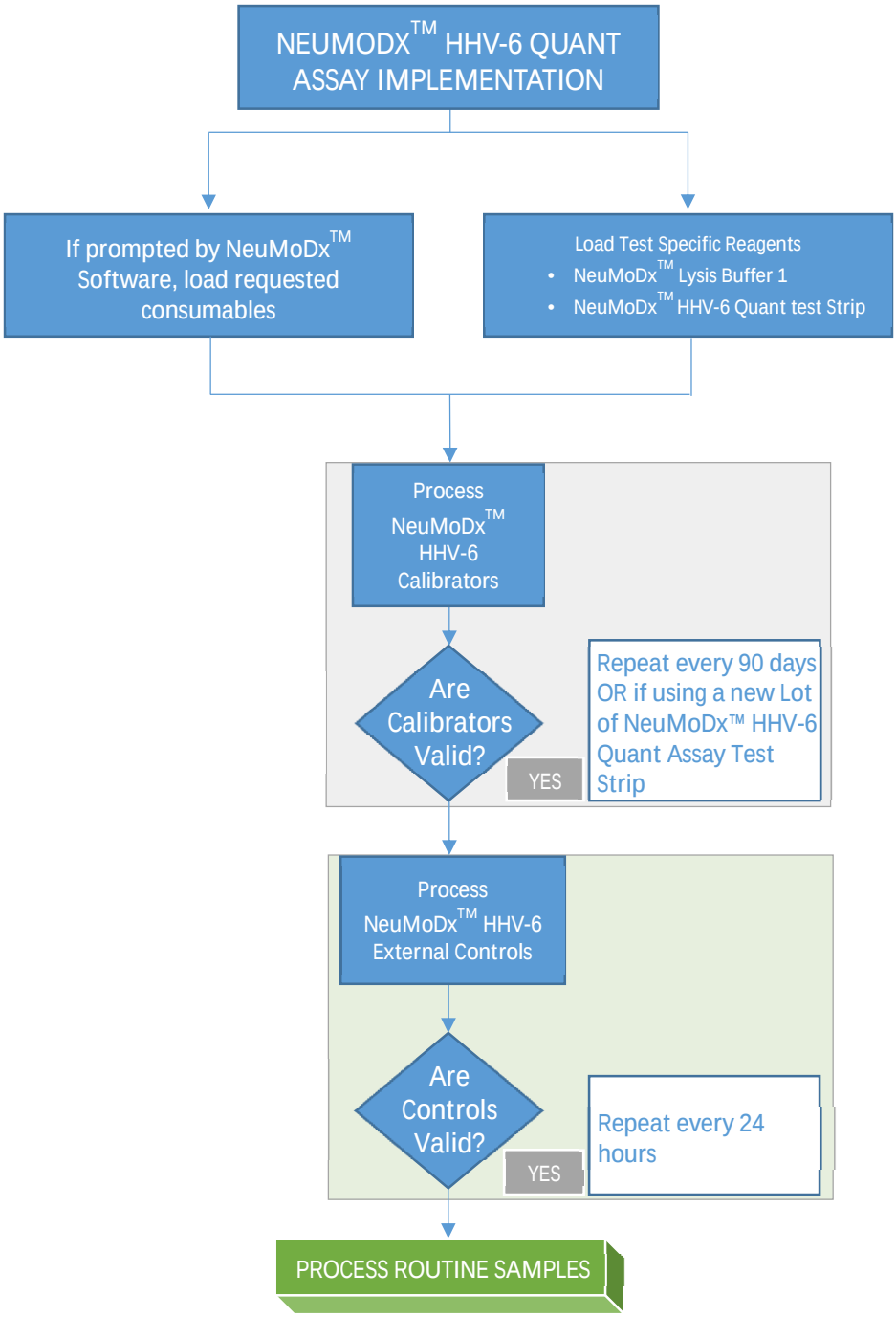

Figure 1: NeuMoDx™ HHV-6 Quant Assay Implementation Workflow.

INSTRUCTIONS FOR USE

Test Preparation

For Plasma samples, the NeuMoDx™ HHV-6 Quant Assay can be run directly from primary blood collection tubes or from specimen aliquots in secondary tubes.

1. Apply a barcode label to a specimen tube compatible with the NeuMoDx™ System. The primary blood collection tube may be labeled and placed directly into the appropriate Specimen Tube Carrier, following centrifugation as directed by the manufacturer.
2. If testing the plasma specimen in the primary collection tube, place the barcoded tube into a Specimen Tube Carrier and ensure the cap is removed prior to loading onto the NeuMoDx™ System. Minimum volumes *above* gel/buffy layer are defined below and will be met if specimens are collected and processed according to tube manufacturer instructions. Performance is not guaranteed for specimens that are collected improperly.
3. For Plasma samples in a secondary tube, transfer an aliquot of the specimen to the barcoded specimen tube compatible with the NeuMoDx™ System according to the volumes defined below:

Specimen Tube Carrier	Tube Size	Minimum Required Specimen Volume
32-Tube Specimen Tube Carrier	11–14 mm diameter by 60–120 mm height	750 µL
24-Tube Specimen Tube Carrier	14.5–18 mm diameter by 60–120 mm height	1100 µL
Low Volume Specimen Tube Carrier	1.5 mL conical bottom microcentrifuge tube	650 µL

NeuMoDx™ System Operation

For detailed instructions, refer to the NeuMoDx™ 288 and 96 Molecular Systems Operator's Manuals (p/n 40600108 & 40600317)

1. Load the test order onto the NeuMoDx™ System according to the desired tube type.
2. Cut the aluminum pouches of NeuMoDx™ HHV-6 Quant Test Strips at the point indicated by the lateral notches.
3. Remove the strips from the pouches immediately before use.
4. Before using the pouches, always ensure they are well sealed and that the desiccant sachet is still inside. Use only undamaged pouches.
5. Dispose of the aluminum pouches and their contents if the desiccant sachet turns from orange to green.
6. Populate one or more NeuMoDx™ System Test Strip carrier(s) with NeuMoDx™ HHV-6 Quant Test Strip(s) and use the touchscreen to load the Test Strip Carrier(s) into the NeuMoDx™ System.
7. If prompted by the NeuMoDx™ System software, add the necessary required consumables to the NeuMoDx™ System consumable carriers and use the touchscreen to load carrier(s) into the NeuMoDx™ System.
8. If prompted by the NeuMoDx™ System software, replace NeuMoDx™ Wash Reagent, NeuMoDx™ Release Reagent, empty the Priming Waste, Biohazard Waste Container (NeuMoDx 288 Molecular System only), Tip Waste Bin (NeuMoDx™ 96 Molecular System only), or Biohazard Waste Bin (NeuMoDx™ 96 Molecular System only), as appropriate.
9. If prompted by the NeuMoDx™ System software, process the calibrators (REF 801000) and/or external controls (REF 901000) as required. Further information regarding calibrators and controls can be found in the Results Processing section.
10. Load the calibrator/control tube(s) into a standard 32-Tube Carrier and ensure caps are removed from all tubes.
11. Place the Specimen Tube Carrier(s) on the Autoloader shelf, ensure caps are removed from all tubes, and use the touchscreen to load the carrier(s) into the NeuMoDx™ System. This will initiate processing of the loaded specimens for the test(s) identified, given a valid test order is present in the system.

LIMITATIONS

- The NeuMoDx™ HHV-6 Quant Test Strip can only be used on NeuMoDx™ Systems.
- The performance of the NeuMoDx™ HHV-6 Quant Test Strip has been established for plasma specimens prepared from whole blood, collected with EDTA as an anticoagulant. The use of the NeuMoDx™ HHV-6 Quant Test Strip with other specimen types has not been assessed and performance characteristics of the test are unknown for other specimen types.
- The NeuMoDx™ HHV-6 Quant Assay must not be used with samples from heparinized humans.
- Since detection of HHV-6A and/or HHV-6B DNA is dependent on the number of organisms present in the sample, reliable results are dependent on proper specimen collection, handling, and storage.
- Erroneous results could occur from improper specimen collection, handling, storage, technical error, or specimen tube mix-up. In addition, false negative results could occur because the number of viral particles in the sample is below the limit of detection of the NeuMoDx™ HHV-6 Quant Assay.
- Operation of the NeuMoDx™ System is limited to use by personnel trained on the use of the NeuMoDx™ System.
- If the HHV-6A, HHV-6B and SPC1 targets do not amplify, an invalid result (Indeterminate or Unresolved) will be reported and the test should be repeated.
- If a system error occurs prior to completion of sample processing, "No Result" will be reported and the test should be repeated.
- If the NeuMoDx™ HHV-6 Quant Assay result is Positive, but the quantitation value is beyond the limits of quantitation, the NeuMoDx™ System will report whether the detected HHV-6A and/or HHV-6B DNA was below Lower Limit of Quantitation (LLoQ) or above Upper Limit of Quantitation (ULoQ).
- In the event the detected HHV-6A and/or HHV-6B DNA is above ULoQ, the NeuMoDx™ HHV-6 Quant Assay may be repeated with a diluted aliquot of the original specimen. A 1:100 or 1:1000 dilution in HHV-6A and HHV-6B DNA negative plasma or Basematrix 53 Diluent (Basematrix) (SeraCare, Milford, MA) is recommended. The System will automatically calculate the concentration of the original specimen as follows: Original specimen concentration = log10 (dilution factor) + reported concentration of the diluted sample, as long as the dilution factor has been properly selected in the software before repeating.
- The occasional presence of PCR inhibitors in plasma may result in a system Quantitation Error; if this occurs, it is recommended to repeat the test with the same specimen diluted in Basematrix at 1:10 or 1:100.
- A positive result does not necessarily indicate the presence of viable organisms. However, a positive result indicates the presence of HHV-6A and/or HHV-6B DNA.
- Deletion or mutations in the conserved regions targeted by the NeuMoDx™ HHV-6 Quant Assay may affect detection or could lead to an erroneous result using the NeuMoDx™ HHV-6 Quant Test Strip.
- Results from NeuMoDx™ HHV-6 Quant Assay should be used as an adjunct to clinical observations and other information available to the physician; the test is not intended to diagnose infection.
- Good laboratory practices, including changing gloves between handling patient specimens, are recommended to avoid contamination.

RESULTS PROCESSING

Available results may be viewed or printed from the 'Results' tab in the Results window on the NeuMoDx™ System touchscreen. NeuMoDx™ HHV-6 Quant Assay results are automatically generated by the NeuMoDx™ System software using the decision algorithm and results processing parameters specified in the NeuMoDx™ HHV-6 Assay Definition File. A NeuMoDx™ HHV-6 Quant Assay result may be reported as Negative, Positive with a reported HHV-6A and/or HHV-6B concentration, Positive above ULoQ, Positive below LLoQ, Indeterminate (IND), Unresolved (UNR), or No Result (NR) based on the amplification status of the target and sample process control. Results are reported based on the ADF results processing algorithm, summarized below in *Table 1*.

Results from the NeuMoDx™ HHV-6 Quant Test Strip should be interpreted in conjunction with other clinical and laboratory findings.

Table 1: Summary of the NeuMoDx™ HHV-6 Quant Assay Results Interpretation

Result	HHV-6A/HHV-6B	Sample Process Control (SPC1)	Result Interpretation
Positive with Reported Concentration	Amplified 2.30 ≤ [HHV-6A] ≤ 6.0 $\log_{10}$ copies/mL	Amplified or Not Amplified	HHV-6A DNA detected within quantitative range
	Amplified 2.30 ≤ [HHV-6B] ≤ 6.0 $\log_{10}$ IU/mL	Amplified or Not Amplified	HHV-6B DNA detected within quantitative range
Positive, above Upper Limit of Quantitation [ULoQ]	Amplified [HHV-6A] > 6.0 $\log_{10}$ copies/mL	Amplified or Not Amplified	HHV-6A DNA detected above quantitative range
	Amplified [HHV-6B] > 6.0 $\log_{10}$ IU/mL	Amplified or Not Amplified	HHV-6B DNA detected above quantitative range

Result	HHV-6A/HHV-6B	Sample Process Control (SPC1)	Result Interpretation
Positive, below Lower Limit of Quantitation [LLoQ]	Amplified [HHV-6A] < 2.30 log_{10} copies/mL	Amplified or Not Amplified	HHV-6A DNA detected below quantitative range
	Amplified [HHV-6B] < 2.30 log_{10} IU/mL	Amplified or Not Amplified	HHV-6B DNA detected below quantitative range
Negative*	Not Amplified	Amplified	HHV-6A/HHV-6B DNA not detected
Indeterminate	Not Amplified, System Error Detected, Sample Processing Completed		All target results were invalid; retest sample†
No Result	Not Amplified, System Error Detected, Sample Processing Aborted		Sample processing was aborted; retest sample†
Unresolved	Not Amplified, No System Error Detected		All target results were invalid; retest sample†

*As with other tests, negative results do not rule out HHV-6A and/or HHV-6B infection.

†The NeuMoDx™ System is equipped with automatic Rerun/Repeat capability that the end user can choose to use to ensure that an IND/NR/UNR result is automatically reprocessed to minimize delays in result reporting.

Test Calculation

1. For samples within the Quantitation range of the NeuMoDx™ HHV-6 Quant Assay, the concentration of HHV-6A DNA and HHV-6B DNA in the samples is calculated using the relative stored standard curves in conjunction with the calibration coefficients.
   a. A calibration coefficient is calculated based on the results of the NeuMoDx™ HHV-6 Calibrators processed to establish validity of the Standard Curve, for a particular lot of the NeuMoDx™ HHV-6 Quant Test Strip, on a specific NeuMoDx™ System, for each target.
   b. The calibration coefficient is incorporated into the final determination of the concentration of HHV-6A DNA and HHV-6B DNA.
2. NeuMoDx™ HHV-6 Quant Assay results are reported in Log_{10} copies/mL and copies/mL for HHV-6A target, and in Log_{10} IU/mL and IU/mL for HHV-6B target.
3. The resulting quantitation of the unknown samples is traceable to the EDX HHV-6A verification panel (Exact Diagnostics) quantified by digital droplet PCR (ddPCR) and to the 1st WHO International Standard for HHV-6B virus DNA (National Institute for Biological Standards and Control, NIBSC code: 15/266).

Test Calibration

A valid calibration based on the Standard Curve is required to quantitate HHV-6A DNA and/or HHV-6B DNA in the specimens. To generate valid results, a test calibration must be completed for both HHV-6A and HHV-6B using the calibrators provided by NeuMoDx™ Molecular, Inc.

Calibrators

1. NeuMoDx™ HHV-6 Calibrators are provided in a kit (REF 801000) and are composed of a dried pellet of synthetic HHV-6A DNA and HHV-6B DNA and specific buffer.
2. A set of HHV-6 calibrators needs to be processed with each new lot of NeuMoDx™ HHV-6 Quant Test Strips, if a new HHV-6 Assay Definition File is uploaded to the NeuMoDx™ System, if the current set of calibrators has past the validity period (currently set at 90 days), or if the NeuMoDx™ System software is modified.
3. The NeuMoDx™ System software will notify the user when the calibrators need to be processed; a new lot of test strips cannot be used for testing until the calibrators have been processed successfully.
4. If a new set of HHV-6 calibrators needs to be processed, read all the instructions contained in the NeuMoDx™ HHV-6 Calibrators insert before performing the test.
5. Calibration validity is established as follows:
   a. Two calibration coefficients need to be generated, one for HHV-6A and one for HHV-6B by processing a set of two calibrators for each target – high and low – to establish validity for each curve.
   b. To generate valid results, at least 2 out of the 3 replicates must give results within predefined parameters. The low calibrator nominal target is 3.0 log10 copies/mL and the high calibrator nominal target is 5.0 log10 copies/mL for HHV-6A calibrator set, while the low calibrator nominal target is 3.0 log10 IU/mL and the high calibrator nominal target is 5.0 log10 IU/mL for HHV-6B calibrator set.
   c. A calibration coefficient is calculated to account for expected variation between test strip lots; this calibration coefficient is utilized in determination of final HHV-6A and/or HHV-6B concentration.
6. If one or both the calibrators fail the validity check, repeat processing of the failed calibrator(s) using a new vial. In the event one calibrator fails validity, it is possible to only repeat the failed calibrator as system does not require the user to run both calibrators again.
7. If the calibrator(s) fail the validity check a second consecutive time, contact QIAGEN Technical Support.

Quality Control

Local regulations typically specify that the laboratory is responsible for control procedures that monitor accuracy and precision of the complete analytical process, and must establish the number, type, and frequency of testing control materials using verified performance specifications for an unmodified, approved test system.

External Controls

1. HHV-6A and HHV-6B External Controls (REF 901000) are provided by NeuMoDx™. The positive controls contain a dried pellet of synthetic HHV-6A and HHV-6B DNA. The negative control is buffer.
2. Positive and negative external controls need to be processed once every 24 hours. If a set of valid external controls does not exist, the NeuMoDx™ System software will prompt the user for these controls to be processed before sample results can be reported.
3. If external controls are required, prepare the positive and negative controls as indicated in the HHV-6 External Controls insert before performing the test.
4. Using the touchscreen and a Specimen Tube Carrier placed on the autoloader shelf, load the positive and negative controls into the NeuMoDx™ System. The NeuMoDx™ System will recognize the barcode and begin processing the external control tubes unless reagents or consumables required for testing are not available.
5. Validity of external controls will be assessed by the NeuMoDx™ System based on the expected result. The positive control should provide a HHV-6A and HHV-6B Positive result and the negative control should provide a HHV-6A and HHV-6B Negative result.
6. Discrepant result handling for external controls should be performed as follows:
    a. A Positive test result reported for a negative control sample indicates a specimen contamination problem, and the laboratory's quality control procedures need to be examined to find a root cause. Ensure to use separate areas for sample preparation, control handling, and Realt-Time PCR set up. Please refer to *NeuMoDx 288 or 96 Molecular System Operator's Manual* for additional troubleshooting tips.
    b. A Negative test result reported for a positive control sample may indicate a reagent or instrument related problem.
    c. In either of the above instances, or in the event of a No Result (NR), Unresolved (UNR), or Indeterminate (IND) result, repeat the failed control(s) with a new Freshly prepared vial of the control(s) failing the validity test.
    d. If positive NeuMoDx™ HHV-6 External Controls continue to report a Negative result, contact QIAGEN Technical Support.
    e. If negative NeuMoDx™ HHV-6 External Controls continue to report a Positive result, attempt to eliminate all sources of potential contamination, including replacing ALL reagents before contacting QIAGEN Technical Support.
7. If the External Controls do not provide the expected results, it is required to repeat a set of positive and negative controls. Samples will not be processed until a valid set of External Control set is processed by the system. In the eventuality that samples are in processing while external controls expire, the system will require a valid set of External Control set to be run. If the External control set fails to give valid results, sample results will not be reported.

Sample Process (Internal) Controls

An exogenous Sample Process Control (SPC1) is incorporated in the NeuMoDx™ Extraction Plate and undergoes the entire process of nucleic acid extraction and real-time PCR amplification with each sample/control/calibrator. The primers and probe specific for SPC1 are included in each NeuMoDx™ HHV-6 Quant Test Strip enabling detection of the presence of SPC1 along with the target HHV-6A and/or HHV-6B DNA (if present) via multiplex real-time PCR. Detection of SPC1 amplification allows the NeuMoDx™ System software to monitor the efficacy of the DNA extraction and PCR amplification processes.

Invalid Results

If a NeuMoDx™ HHV-6 Quant Assay performed on the NeuMoDx™ System fails to produce a valid result, it will be reported as Indeterminate (IND), No Result (NR), or Unresolved (UNR) based on the type of error that occurred. The test should be repeated to obtain a valid result.

An Indeterminate result will be reported if a NeuMoDx™ System error is detected during sample processing. In the event an IND result is reported, a retest is recommended.

A No Result will be reported if a NeuMoDx system error is detected, and sample processing is aborted. In the event of a No Result, a retest is recommended.

An UNR result will be reported if no target is detected and there is no amplification of HHV-6A DNA, HHV-6B DNA, or the SPC1, which indicates possible reagent failure or the presence of inhibitors. In the event an UNR result is reported, a retest may be performed as a first step. If a retest fails, a diluted specimen may be used to mitigate the effects of any sample inhibition (see limitations section for further instructions).

See the NeuMoDx 288 Molecular System Operator's Manual (PN: 40600108) or the NeuMoDx 96 Molecular System Operator's User Manual (PN: 40600317) for a list of error codes that may be associated with Invalid Results.

PERFORMANCE CHARACTERISTICS[10,11,15]

Analytical Sensitivity – Limit of Detection[12]

The Analytical Sensitivity of the NeuMoDx™ HHV-6 Quant Assay was characterized by testing a dilution series of the EDX HHV-6A Verification Panel (Exact Diagnostics) and HHV-6B Verification Panel (Exact Diagnostics, calibrated against the 1st WHO International Standard for HHV-6B, 15/266), in HHV-6A/HHV-6B negative plasma samples, to determine the Limit of Detection (LoD) on the NeuMoDx™ Systems. Limit of Detection is defined as the minimum detectable concentration, with 95% hit rate. This is calculated by Probit analysis applied to experimental data, with 95% Confidence Interval (CI). The study was performed over 3 days across multiple systems with multiple lots of NeuMoDx™ reagents. Each system processed 42 replicates at each dilution level (positive samples) and 8 replicates for negative samples per day. Detection rates are depicted in *Table 2.*

Table 2: Positive Detection Rates for LoD Determination of the NeuMoDx™ HHV-6 Quant Assay

HHV-6A					HHV-6B				
Target Concentration [copies/mL]	Target Concentration [log_{10} copies/mL]	Number of Valid Tests	Number of Positives	Detection Rate	Target Concentration [IU/mL]	Target Concentration [log_{10} IU/mL]	Number of Valid Tests	Number of Positives	Detection Rate
200	2.30	45	44	97.8%	200	2.30	46	44	95.7%
80	1.90	45	32	71.1%	100	2.00	42	24	57.1%
60	1.78	43	26	60.5%	80	1.90	44	19	43.2%
40	1.60	42	10	23.8%	60	1.78	43	14	32.6%
20	1.30	44	1	2.3%	40	1.60	43	5	11.6%
0	0	47	0	0%	0	0	48	0	0%

The LoD of the NeuMoDx™ HHV-6 Quant Assay was determined by probit-style analysis to be 123.5 copies/mL (2.09 log_{10} copies/mL) (95% Confidence Interval: 102.1 to 145.0 copies/mL) for HHV-6A and 178.2 IU/mL (2.25 log_{10} IU/mL) (95% Confidence Interval: 151.3 to 205.0 IU/mL) for HHV-6B.

Analytical Sensitivity – Lower Limit of Quantitation (LLoQ) and Upper Limit of Quantitation (ULoQ)[12]

The Lower Limit of Quantitation (LLoQ) and the Upper Limit of Quantitation (ULoQ) are defined as the lowest target level and the upper target level at which >95% detection is achieved AND the TAE ≤ 1.0. To determine the LLoQ and ULoQ, the total analytical error (TAE) was calculated for each of the HHV-6A and HHV-6B target levels that were shown to report > 95% detection in the Limit of Detection testing. TAE is defined as follows:

$$TAE = |Bias| + 2 * SD \text{ [Westgard Statistics]}$$

The bias is the absolute value of the difference between the average of calculated concentration and the expected concentration. SD refers to the standard deviation of the quantitated value of the sample.

Compiled results for the 5 levels of HHV-6A/HHV-6B plasma specimens used in the LLoQ/ULoQ study are shown in Tables 3 and 4. Based on this data set and the previously determined LoD, the LLoQ and ULoQ were determined to be 200 copies/mL (2.30 log_{10} copies/mL) and $1x10^6$ copies/mL for HHV-6A, and 200 IU/mL (2.30 log_{10} IU/mL) and $1x10^6$ IU/mL for HHV-6B.

Table 3: NeuMoDx™ HHV-6 Quant Test Strip; HHV-6A ULoQ and LLoQ, with Bias and TAE

Target Conc. [copies/mL]	Target Conc. [log_{10} copies/mL]	Average Conc. [log_{10} copies/mL]	Detection (%)	SD	Bias	TAE
10^6	6.00	5.76	100%	0.34	0.24	0.91
200	2.30	2.34	97.8%	0.30	0.03	0.63
80	1.90	2.19	71.1%	0.27	0.28	0.83
60	1.78	2.21	60.5%	0.21	0.43	0.86
40	1.60	2.18	23.8%	0.15	0.57	0.87
20	1.30	2.17	2.3%	N.A.	0.87	N.A.

Table 4: NeuMoDx™ HHV-6 Quant Test Strip; HHV-6B ULoQ and LLoQ, with Bias and TAE

Target Conc. [IU/mL]	Target Conc. [log_{10} IU/mL]	Average Conc. [log_{10} IU/mL]	Detection (%)	SD	Bias	TAE
10^6	6.00	6.06	100%	0.32	0.06	0.71
200	2.30	2.12	95.7%	0.22	0.18	0.62
100	2.00	2.04	57.1%	0.24	0.04	0.52
80	1.90	1.99	43.2%	0.26	0.08	0.61
60	1.78	1.92	32.6%	0.26	0.15	0.67
40	1.60	1.79	11.6%	0.22	0.19	0.62

Based on the outcome of these studies, the LoD of the NeuMoDx™ HHV-6 Quant Assay were determined to be 123.5 copies/mL (2.09 log_{10} copies/mL) for HHV-6A and 178.2 IU/mL (2.25 log_{10} IU/mL) for HHV-6B. The LoQ were 200 copies/mL (2.30 log_{10} copies/mL) for HHV-6A and 200 IU/mL (2.30 log_{10} IU/mL) for HHV-6B. The ULoQ is $1x10^6$ copies/mL for HHV-6A and $1x10^6$ IU/mL for HHV-6B.

Linearity[13]

Linearity of the NeuMoDx™ HHV-6 Quant Test Strip was established in plasma by preparing a dilution series using HHV-6A Verification Panel (Exact Diagnostics) and EDX HHV-6B Verification Panel (Exact Diagnostics). Eight (8) serial dilutions of HHV-6A/HHV-6B panels, prepared in HHV-6A/HHV-6B negative human plasma, were created to span a concentration range of 6 – 2 log_{10} copies/mL.
The HHV-6A/HHV-6B assay concentrations reported by the NeuMoDx™ System compared to the expected values are presented in Figures 2 and 3.

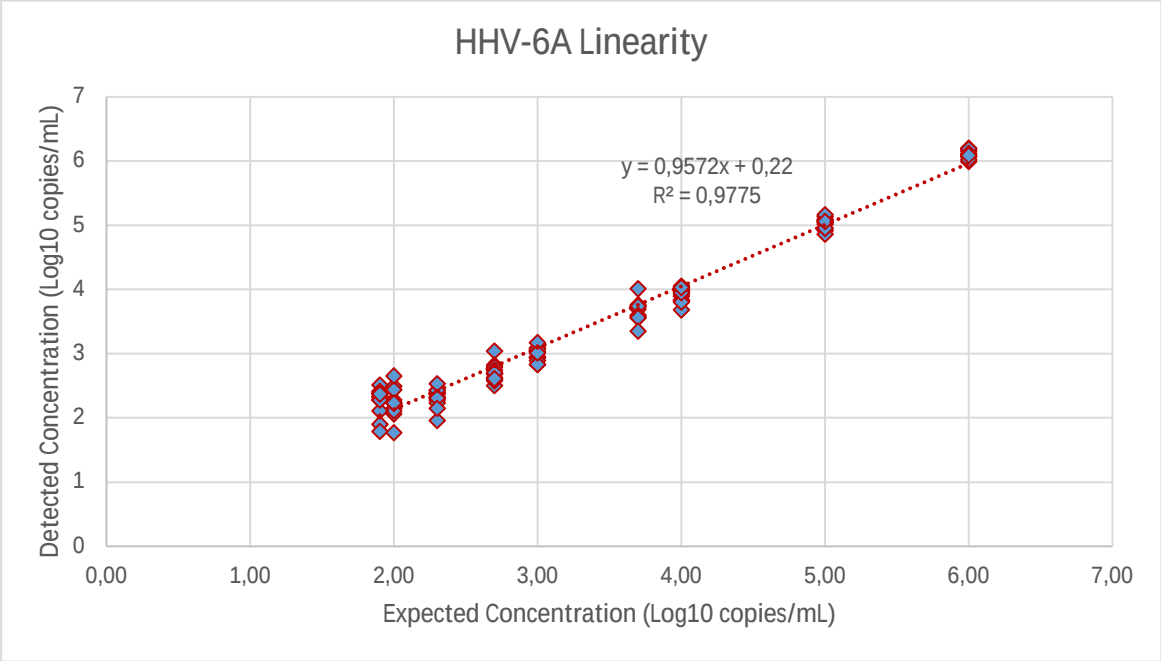

Figure 2: Linearity of the NeuMoDx™ HHV-6 Quant Assay for HHV-6A

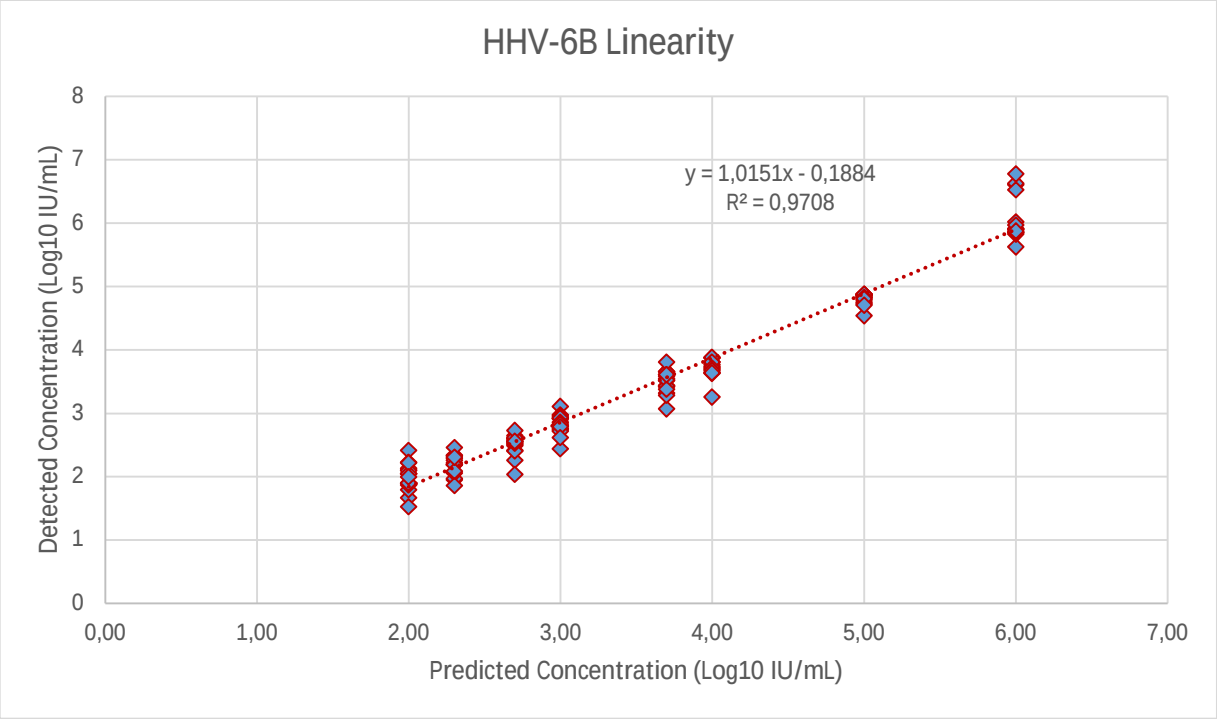

Figure 3: Linearity of the NeuMoDx™ HHV-6 Quant Assay for HHV-6B

Analytical Specificity – Cross-Reactivity[10, 11]

Analytical specificity was demonstrated by screening 22 organisms commonly found in plasma specimens as well as species phylogenetically similar to HHV-6A and HHV-6B for cross-reactivity. Organisms were prepared in pools of between 5/6 organisms and tested at a high concentration (3.48 log10 copies/mL). The organisms tested are shown in *Table 5*. No cross-reactivity was observed with any of the organisms tested, confirming 100% analytical specificity of the NeuMoDx™ HHV-6 Quant Assay.

Table 5: Pathogens Used to Demonstrate Analytical Specificity

Non-Target Organisms					
Klebsiella pneumonia	*Enterococcus faecalis*	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Staphylococcus epidermidis*	*Streptococcus pyogenes*
Human Immunodeficiency Virus-1	Hepatitis B Virus	Adenovirus type 5	Epstein-Barr Virus	Varicella-Zoster Virus	Enterovirus 68
BK virus	Herpes Simplex Virus 1	Herpes Simplex Virus 2	Human gammaherpesvirus 8	Cytomegalovirus	Human betaherpesvirus 7
HTVL-1	HTVL-2	JC Virus	SV40	Human Immunodeficiency Virus-2	

Analytical Specificity – Interfering Substances, Commensal Organisms[10, 11]

The NeuMoDx™ HHV-6 Quant Assay was evaluated for interference in the presence of non-target organisms using the same organism pools prepared for the cross-reactivity testing listed above in Table 6. Negative HHV-6A/HHV-6B plasma was spiked with the organisms pooled in groups of 4-7 and spiked with HHV-6A/HHV-6B target at a concentration of 2.78 $\log_{10}$ IU/mL (600 IU/mL; 3x LoD). No significant interference was observed in the presence of these commensal organisms as indicated by the minimal deviation of quantitation from control specimens which contained no interfering agent.

Analytical Specificity – Interfering Substances, Endogenous and Exogenous Substances[10, 11]

The NeuMoDx™ HHV-6 Quant Assay was evaluated in the presence of typical exogenous and endogenous interfering substances encountered in HHV-6A/HHV-6B clinical plasma. These included abnormally high levels of blood components as well as common antiviral medications, which are

classified in Table 6. Each substance was added to screened HHV-6A/HHV-6B -negative Human plasma spiked with 2.78 log_{10} IU/mL (600 IU/mL; 3x LoD) HHV-6A/HHV-6B and samples were analyzed for interference.
The average concentration and bias of all substances tested as compared to control samples spiked with same level of HHV-6A/HHV-6B are reported in Table 7. None of the exogenous and endogenous substances affected the specificity of the NeuMoDx™ HHV-6 Quant Assay.

Table 6: Interference Testing - Exogenous Agents (Drug Classifications)

Pool	Drug name	Classification
Pool 1	Valganciclovir	ANTIVIRAL
	Prednisone	IMMUNOSUPPRESSIVE
	Cidofovir	ANTIVIRAL
	Cefotaxime	ANTIBIOTIC
	Mycophenolate mofetil	IMMUNOSUPPRESSIVE
Pool 2	Vancomycin	ANTIBIOTIC
	Tacrolimus	IMMUNOSUPPRESSIVE
	Famotidine	HISTAMINE ANTAGONIST
	Valacyclovir	ANTIVIRAL
	Leflunomide	IMMUNOSUPPRESSIVE

Table 7: Interference Testing - Exogenous and Endogenous Agents

Endogenous (Plasma)	HHV-6A		HHV-6B	
	Average Conc.	Bias	Average Conc.	Bias
	log_{10} copies/mL	log_{10} copies/mL	log_{10} IU/mL	log_{10} IU/mL
Triglycerides (500 mg/dL)	1.91	0.24	2.10	-0.13
Conjugated bilirubin (0.25 g/L)	2.14	0.01	2.07	-0.10
Unconjugated bilirubin (0.25 g/L)	1.71	0.44	1.61	0.37
Albumin (58.7 g/L)	2.27	-0.13	2.04	-0.06
Hemoglobin (2.9 g/L)	2.23	-0.08	1.98	-0.01
Human DNA (2 mg/mL)	1.74	0.41	1.86	0.12
Exogenous (Drugs)	Average Conc.	Bias	Average Conc.	Bias
	log_{10} copies/mL	log_{10} copies/mL	log_{10} IU/mL	log_{10} IU/mL
Pool 1: Valganciclovir, Prednisone, Cidofovir, Cefotaxime, Mycophenolate mofetil	1.65	0.28	2.07	0.06
Pool 2: Vancomycin, Tacrolimus, Famotidine, Valacyclovir, Leflunomide	2.18	-0.25	1.97	0.16

Repeatability and Within Lab Precision[14]

Precision of the NeuMoDx™ HHV-6 Quant Test Strip was determined by testing 2 replicates of a 3-member panel of HHV-6A/HHV-6B specimens prepared with HHV-6A or HHV-6B plasmid twice a day, using one NeuMoDx™ 96 System across 20 days. The within-run, within-day precisions were characterized, and the overall standard deviation was determined to be ≤ 0.25 log_{10} copies/mL for HHV-6A and ≤ 0.25 log_{10} IU/mL for HHV-6B. Excellent precision was demonstrated across days and runs as shown in *Table 8*. Precision between operators was not characterized as the operator plays no significant role in the processing of samples using the NeuMoDx™ System.

Table 8: Within Lab Precision – NeuMoDx™ HHV-6 Quant Assay on NeuMoDx™ System 96

Sample	Repeatability SD	Between Run SD	Within Day SD	Between Day SD	Overall (Within Laboratory) SD
HHV-6A					
5.67 log10 copies/mL	0.166	0.000	0.166	0.051	0.173
4.67 log10 copies/mL	0.071	0.000	0.071	0.048	0.086
3.67 log10 copies/mL	0.190	0.028	0.192	0.059	0.200
2.48 log10 copies/mL	0.151	0.051	0.159	0.000	0.159
HHV-6B					
5.14 log10 IU/mL	0.217	0.000	0.217	0.070	0.228
4.14 log10 IU/mL	0.155	0.000	0.155	0.056	0.165
3.14 log10 IU/mL	0.141	0.000	0.141	0.038	0.146
2.70 log10 IU/mL	0.225	0.079	0.239	0.000	0.239

Lot-to-Lot Reproducibility[14]

Lot to Lot Reproducibility of the NeuMoDx™ HHV-6 Quant Test Strip was determined using three different lots of NeuMoDx™ HHV-6 Quant Test Strips. A 4-member panel of HHV-6A and HHV-6B prepared with HHV-6A Verification Panel (Exact Diagnostics) or EDX HHV-6B Verification Panel (Exact Diagnostics) was used to assess performance on one NeuMoDx™ 96 Molecular System across 5 separate runs. The variation within and across lots was analyzed and results, expressed as standard deviation between lot, are presented in *Table 9*. The greatest Maximum standard deviation was 0.257 copies/mL. Equivalent performance was demonstrated across lots as the standard deviation of all panel members was within tolerance specification (Reproducibility SD ≤ 0.3 $\log_{10}$ copies/mL).

Table 9: Lot to Lot Reproducibility – NeuMoDx™ HHV-6 Quant Assay

Sample	Repeatability SD	Between Day SD	Within Lot SD	Between Lot SD	Reproducibility SD
HHV-6A					
4.73 x10^5 copies/mL	0.160	0.061	0.171	0.073	0.186
4.73 x10^3 copies/mL	0.166	0.087	0.188	0.069	0.200
600 copies/mL	0.099	0.088	0.132	0.091	0.160
HHV-6B					
1.38 x10^5 IU/mL	0.199	0.161	0.256	0.025	0.257
1.38 x10^3 IU/mL	0.214	0.068	0.224	0.093	0.243
600 IU/mL	0.120	0.069	0.139	0.062	0.152

Instrument-to-instrument Reproducibility[14]

Instrument to instrument Reproducibility of the NeuMoDx™ HHV-6 Quant Test Strip was determined using three different systems (one NeuMoDx™ 288 Molecular System and two NeuMoDx™ 96 Molecular System). A 4-member panel of HHV-6A/HHV-6B prepared with HHV-6A Verification Panel (Exact Diagnostics) or EDX HHV-6B Verification Panel (Exact Diagnostics) was used to assess performance. Testing was performed on the systems for 5 days. The variation within-day and between systems was characterized, and the overall standard deviation was determined to be ≤ 0.30 $\log_{10}$ copies/mL for HHV-6A and ≤ 0.30 $\log_{10}$ IU/mL for HHV-6B. Equivalent performance was demonstrated across systems as SD in quantitation of all panel members was within tolerance specification (Table 10).

Table 10: Instrument to instrument Reproducibility – NeuMoDx™ HHV-6 Quant Test Strip

Sample	Repeatability SD	Between Day SD	Within System SD	Between System SD	Reproducibility SD
HHV-6A					
5.67 log10 copies/mL	0.228	0.000	0.228	0.000	0.228
4.67 log10 copies/mL	0.149	0.000	0.149	0.021	0.151
3.67 log10 copies/mL	0.210	0.101	0.233	0.000	0.233
2.48 log10 copies/mL	0.157	0.079	0.176	0.000	0.176
HHV-6B					
5.14 log10 IU/mL	0.215	0.072	0.227	0.000	0.227
4.14 log10 IU/mL	0.259	0.014	0.260	0.023	0.261
3.14 log10 IU/mL	0.178	0.062	0.189	0.000	0.189
2.70 log10 IU/mL	0.149	0.079	0.169	0.000	0.169

REFERENCES

1. Rifai, N., Horvath, A.R., Wittwer, C.T., Tietz, N.W. (Eds.), 2018. Tietz textbook of clinical chemistry and molecular diagnostics, Sixth edition. ed. Elsevier, St. Louis, Missouri.
2. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. Clin Microbiol Rev. 2015 Apr;28(2):313-35. doi: 10.1128/CMR.00122-14. PMID: 25762531; PMCID: PMC4402955.
3. Hill JA. Human herpesvirus 6 in transplant recipients: an update on diagnostic and treatment strategies. Curr Opin Infect Dis. 2019 Dec;32(6):584-590. doi: 10.1097/QCO.0000000000000592. PMID: 31567413; PMCID: PMC7141773.
4. Agut H, Bonnafous P, Gautheret-Dejean A. Human Herpesviruses 6A, 6B, and 7. Microbiol Spectr. 2016 Jun;4(3). doi: 10.1128/microbiolspec.DMIH2-0007-2015. PMID: 27337451.
5. Navarro E, Serrano-Heras G et all. 2015. Real-time PCR Detection Chemistry. Clin Chim Acta.15;439:231-50. US Department of Labor, Occupational Safety and Health Administration. 29 CFR Part 1910.1030. Bloodborne Pathogens,
6. US Department of Health and Human Services. Biosafety in Microbiological and Biomedical Laboratories, 5th Ed. Washington,DC: US Government Printing Office, January 2009.
7. World Health Organization. Laboratory Biosafety Manual, 3rd ed.Geneva: World Health Organization, 2004.
8. CLSI. Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline — Fourth Edition (M29-A4). Clinical and Laboratory Standards Institute, 2014.
9. CLSI. Clinical and Laboratory Standards Institute. Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline—Second Edition CLSI Document MM13. Clinical and Laboratory Standards Institute; 2020
10. CLSI. Molecular Diagnostic Methods for Infectius Diseases. Approved Guideline – Third Edition. CLSI document MM03. Clinical and Laboratory Standards Institute. 2015.
11. CLSI. Quantitative Molecular Methods for Infectius Diseases; Approved Guideline – Second Edition. CLSI document MM06-A2. Clinical and Laboratory Standards Institute: 2010.
12. CLSI. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition. CLSI document EP17-A2. Clinical and Laboratory Standards Institute: 2012.
13. CLSI. Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline – First Edition. CLSI document EP06-A. Clinical and Laboratory Standards Institute: 2003.
14. CLSI. Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition. CLSI document EP05-A3. Clinical and Laboratory Standards Institute: 2014.
15. CLSI. Metrological Traceability and Its Implementation; Approved Guideline – Second Edition. CLSI Report EP32-R. Clinical and Laboratory Standards Institute: 2006.

TRADEMARKS

SYMBOLS

SYMBOL	MEANING
Rx Only	Prescription use only
	Manufacturer
	Distributor
IVD	*In vitro* diagnostic medical device
REF	Catalog number
LOT	Batch code
	Consult instruction for use
	Caution, consult accompanying documents
	Temperature limitation
	Keep dry
	Do not re-use
	Do not expose to the light
	Contains sufficient for <*n*> tests
	Use by

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