REF **201800 NeuMoDx™ BKV 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™ BKV Quant Assay is an automated, *in vitro* nucleic acid amplification test for the identification and quantification of BK virus (BKV) DNA in samples extracted from human Plasma/Serum and Urine. The NeuMoDx BKV Assay implemented on the NeuMoDx™ 288 Molecular System and NeuMoDx™ 96 Molecular System (NeuMoDx™ System(s)) incorporates automated DNA extraction to isolate the target nucleic acid from the specimen and real-time polymerase chain reaction (PCR) to target the sequences in the BKV genome.

The NeuMoDx BKV Quant Assay is intended as an aid in the diagnosis and monitoring of BK virus infection, together with other clinical and laboratory findings.

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, while serum should be collected in serum collection tubes or separation tubes (SST). To test a urine specimen, a urine sample is collected in a standard urine collection cup with no preservatives or additives. To prepare for testing, plasma/serum or urine, 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. For plasma/serum specimens, a 550 µL aliquot of the sample is mixed with NeuMoDx™ Lysis Buffer 1 from the instrument, or alternatively a 100 µL aliquot of the plasma/serum sample is mixed with NeuMoDx™ Lysis Buffer 5. For urine samples, a 550 µL aliquot of the sample is mixed with NeuMoDx™ Lysis Buffer 2 from the instrument. The NeuMoDx™ System automatically performs all the steps required to extract the target nucleic acid, prepare the isolated DNA for real-time PCR amplification, and if present, amplify and detect the products of amplification. The NeuMoDX™ BKV 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.

BK polyomavirus (BKV) is a member of the Polyomaviridae family of double-stranded DNA (dsDNA) viruses. BKV causes a common childhood infection without major clinical sequelae, and >80% of adults are seropositive for BKV.[1] Primary infection with this dsDNA virus is generally asymptomatic and occurs in childhood. The most common symptoms, when symptoms are noted, are fever and nonspecific upper respiratory infection.[2] After primary infection has occurred, the virus can remain latent in many sites, most notably the kidney. Transmission may occur by means of exposure to bodily fluids. In states of relative or absolute cellular immunodeficiency, the virus can become reactivated and cause disease.[2]

PCR-based viral load quantitation in the plasma/serum and urine is the standard clinical tool for monitoring BKV reactivation. Studies reporting quantitative BKV PCR results demonstrate a positive correlation between higher viral loads and an increased probability of developing BKV-associated nephropathy (BKVAN)[1]. Other clinical tools used to describe BKV aggregates in the urine is electron microscopy that cast-like three-dimensional BKV aggregates. However, the assay is not feasible for routine clinical practice due to the cost and limited availability of electron microscopy.[1]

PRINCIPLES OF THE PROCEDURE

The NeuMoDx™ BKV Quant Assay on the NeuMoDx™ System utilizes the NeuMoDx™ BKV Quant Test Strip, NeuMoDx™ BKV Calibrator Kit, NeuMoDx™ BKV External Control Kit, NeuMoDx™ Lysis Buffer 1, NeuMoDx™ Lysis Buffer 2, NeuMoDx™ Lysis Buffer 5 and NeuMoDx™ general use reagents to perform the analysis. The storage temperature of the reagents is +15/+30°C.

The NeuMoDx™ BKV Quant Assay combines automated DNA extraction, amplification, and detection by real-time PCR. Plasma/serum or urine 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 paramagnetic particles. The particles, 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. proprietary freeze-dried amplification reagents (STAT-NAT® technology) containing all the elements necessary for PCR amplification of the BKV-specific and SPC1 targets. 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, essentially eliminating the risk of post-amplification contamination.

The 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.[3]

TaqMan® probes labeled with fluorophores at the 5' end, and quenchers at the 3' end, are used to detect BKV 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 final 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.

REAGENTS/CONSUMABLES

Material Provided

REF	Contents	Units per package	Tests per unit	Tests per package
201800	**NeuMoDx™ BKV Quant Test Strip** *Freeze-Dried PCR reagents containing BKV-specific TaqMan® probes and primers in addition to SPC1-specific TaqMan® probe and primers.*	6	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*
800600	**NeuMoDx™ BKV Calibrator Kit** *Single use sets of BKV High and Low Dried-Calibrators to establish validity of standard curve*
900601	**NeuMoDx™ BKV External Control Kit** *Single use sets of BKV Positive dried-controls and Negative controls to establish daily validity of NeuMoDx BKV Quant Assay*
400400	**NeuMoDx™ Lysis Buffer 1**
400500	**NeuMoDx™ Lysis Buffer 2**
400900	**NeuMoDx™ Lysis Buffer 5**
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**

Instrumentation Required

NeuMoDx™ 288 Molecular System [REF 500100] or **NeuMoDx™ 96 Molecular System** [REF 500200]

WARNINGS & PRECAUTIONS

- The NeuMoDx™ BKV 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™ BKV Quant Test Strips protected from light and humidity in their aluminium envelopes.
- A valid test calibration (generated by processing high and low calibrators from the NeuMoDx™ BKV Calibrator Kit REF 800600) must be available before test results can be generated for clinical samples.
- NeuMoDx™ BKV External Control Kit (REF 900601) must be processed every 24 hours throughout testing with the NeuMoDx™ BKV Quant Assay.
- Minimum specimen volume is dependent on the tube size, specimen carrier, and specimen volume workflow as defined below. Volume below the specified minimum may result in a "Quantity Not Sufficient" Error.
- Performing a BKV assay on specimens stored at improper temperatures or beyond the specified storage times may produce invalid or erroneous results when using the NeuMoDx™ BKV Quant Test Strip.
- 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™ BKV 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™ BKV Quant Test Strip or NeuMoDx™ Extraction Plate, or the top surface of the NeuMoDx™ Lysis Buffer 1, 2 and 5 containers; 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 I.F.U 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 in accordance with the OSHA Standard on Bloodborne Pathogens[4], Biosafety Level 2[5] or other appropriate biosafety practices[6,7] 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.
- Results from the NeuMoDx™ BKV Quant Assay should be interpreted in conjunction with other clinical and laboratory findings.
- As with other tests, negative results do not rule out BKV infection.

PRODUCT STORAGE, HANDLING & STABILITY

- NeuMoDx™ BKV Quant Test Strips are stable in the primary packaging at 15 to 30°C through the stated expiration date on the immediate product label.
- A NeuMoDx™ BKV 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™ BKV Quant Test Strips will need to be opened (extract the strips from the pouch) and loaded on the NeuMoDx System. Do not remove the aluminium foil from the strip during the loading on the NeuMoDx System.
- The NeuMoDx™ calibrators and controls are non-infectious but should be discarded in laboratory biohazard waste after use as they will contain target material after processing on the system 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/serum specimens stored in primary tubes.
3. To prepare plasma specimens, whole blood should be collected in sterile tubes using EDTA as the anticoagulant. Serum specimens should be prepared in serum separator tubes. Urine samples should be collected in sterile tubes or cups. 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 to 8°C prior to plasma/serum preparation. Samples preparation should be performed according to manufacturer instructions.

5. Ambient temperature storage of fresh unprocessed Urine should be minimized, since the low pH and high urea content rapidly denature DNA, especially at 25 °C and above.
6. Prepared plasma/serum and urine specimens 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.
7. Prepared plasma/serum and urine specimens should be stored between 2 to 8 °C for no longer than 8 days prior to testing and a maximum of 24 hours at room temperature.
8. Prepared specimens may be stored at < -20°C for up to 8 weeks for plasma and 2 weeks for serum before processing; both plasma and serum 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 - 30°C); vortex to generate a uniformly distributed sample.
    b. Once frozen samples are thawed, testing should occur within 24 hours.
    c. Freezing of plasma/serum in primary collection tubes is not recommended.
9. Once processed, Urine samples may be stored at 2 to 8 °C.
10. If specimens are shipped, they should be packaged and labeled in compliance with applicable country and/or international regulations.
11. Label specimens clearly and indicate specimens are for BKV testing.
12. Proceed to *Test Preparation* section.

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

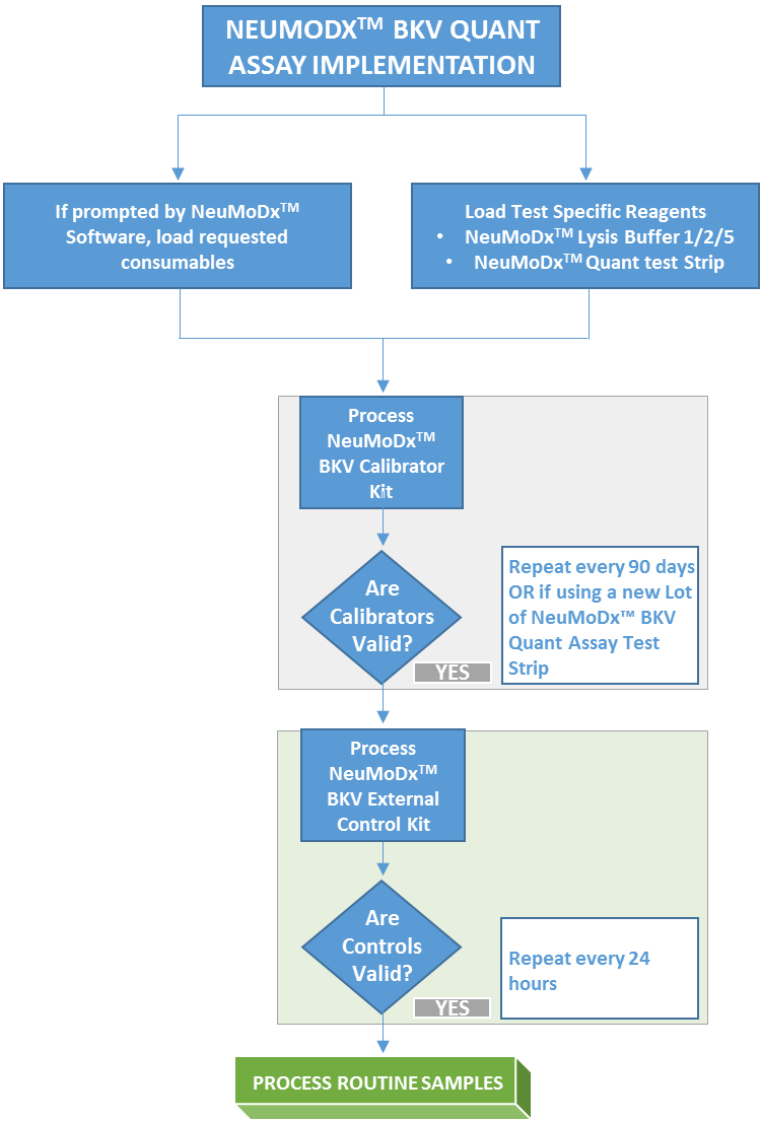

Figure 1: NeuMoDx BKV Quant Assay Implementation Workflow

INSTRUCTIONS FOR USE

Test Preparation

For Plasma/Serum samples, the NeuMoDx BKV Quant Assay can be run directly from primary blood collection tubes or from specimen aliquots in secondary tubes. Processing can be run using one of two specimen volume processing workflows — 550 µL specimen volume workflow or 100 µL specimen processing workflow. Urine samples are run using the 550 µL specimen volume workflow only.

1. Apply specimen barcode label to a specimen tube compatible with the NeuMoDx™ System. The primary blood collection tube may be labeled and placed directly into a 32-tube Specimen Tube Carrier, following centrifugation as directed by the manufacturer.
2. If testing the plasma/serum 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.

Blood Collection Tube Type	Minimum Required Specimen Volume	
	550 µL Workflow	100 µL Workflow
SST – 3.5 mL	1550 µL	1150 µL
PPT/SST – 5.0 mL	1800 µL	1400 µL
PPT/SST – 8.5 mL	2500 µL	2150 µL
K_2EDTA/Serum – 4.0 mL	1050 µL	650 µL
K_2EDTA/Serum – 6.0 mL	1250 µL	850 µL
K_2EDTA/Serum – 10.0 mL	1600 µL	1200 µL

3. For Urine samples, or Plasma/Serum 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	
		550 µL Workflow	100 µL Workflow (Plasma/Serum Only)
32-Tube Specimen Tube Carrier	11–14 mm diameter by 60–120 mm height	700 µL	350 µL
24-Tube Specimen Tube Carrier	14.5–18 mm diameter by 60–120 mm height	1100 µL	750 µL
Low Volume Specimen Tube Carrier	1.5 mL conical bottom microcentrifuge tube	650 µL	250 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 specimen and tube type:
   - 550 µL specimen volume is tested by defining the specimen type as "**Plasma**", "**Serum**", or "**Urine**"
   - 100 µL specimen volume is tested by defining the specimen type as "**Plasma2**" or "**Serum2**"
   - If not defined in the test order, the **Plasma** specimen type in a **Secondary Tube** will be used as default.
2. Cut the aluminum pouches of NeuMoDx™ BKV Quant Test Strip 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 packages.
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™ BKV 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 800600) and/or external controls (REF 900601) as required. Further information regarding calibrators and controls can be found in the *Results Processing* section.
10. Load the specimen/calibrator/control tube(s) into a standard 32-Tube Carrier and ensure caps are removed from all tubes.
11. Place the Specimen Tube Carrier in any open position on the Autoloader shelf and use the touchscreen to load carrier 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™ BKV Quant Test Strip can only be used on NeuMoDx™ Systems.
- The performance of the NeuMoDx™ BKV Quant Test Strip has been established for plasma and serum specimens prepared from whole blood, collected with EDTA as anti-coagulant, and for urine specimens; the use of the NeuMoDx™ BKV Quant Test Strip with other clinical specimen types has not been assessed and performance characteristics of the test are unknown for other specimen types.
- A small increase in the limit of detection and lower limit of quantitation of the NeuMoDx BKV Quant Assay has been observed when using 100 µL specimen volume workflow.
- The NeuMoDx BKV Quant Assay must not be used with samples from heparinized humans.
- Since detection of BKV is dependent on the number of organisms present in the sample, reliable results are dependent on proper specimen collection, handling, and storage.
- Calibrators and external controls must be processed as recommended in the package inserts and if prompted by NeuMoDx™ System software before processing routine clinical samples.
- 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™ BKV Quant Assay.
- Operation of the NeuMoDx™ System is limited to use by personnel trained on the use of the NeuMoDx™ System.
- If both the BKV target and the SPC1 target do not amplify, an invalid result (Indeterminate, No Result, or Unresolved) will be reported and the test should be repeated.
- If the NeuMoDx™ BKV Quant Assay result is Positive, but the quantitation value is beyond the limits of quantitation, the NeuMoDx™ System will report whether the detected BKV was below Lower Limit of Quantitation (LLoQ) or above Upper Limit of Quantitation (ULoQ).
- In the event the detected BKV was below LLoQ, the NeuMoDx™ BKV Quant Assay may be repeated (if desired) with another aliquot of the specimen.
- In the event the detected BKV is above ULoQ, the NeuMoDx™ BKV Quant Assay may be repeated with a diluted aliquot of the original specimen. A 1:1000 dilution in BKV negative plasma or Basematrix 53 Diluent (Basematrix) (SeraCare, Milford, MA) is recommended. The concentration of the original specimen can be calculated as follows:

  $$\textit{Original specimen concentration} = \log_{10}(\textit{dilution factor}) + \textit{reported concentration of the diluted sample.}$$

- The occasional presence of PCR inhibitors in plasma/serum or urine 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 is presumptive for the presence of BKV DNA.
- Deletion or mutations in the conserved regions targeted by the NeuMoDx™ BKV Quant Assay may affect detection or could lead to an erroneous result using the NeuMoDx™ BKV Quant Test Strip.
- Results from NeuMoDx™ BKV 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™ BKV Quant Assay results are automatically generated by the NeuMoDx™ System software using the decision algorithm and results processing parameters specified in the NeuMoDx™ BKV Assay Definition File (BKV ADF). A NeuMoDx™ BKV Quant Assay result may be reported as Negative, Positive with a reported BKV 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 decision algorithm, summarized below in *Table 1*.

Table 1: Summary of the NeuMoDx BKV Quant Assay Decision Algorithm

Result	BKV	Sample Process Control (SPC1)	Result Interpretation
Positive with Reported Concentration	Amplified 1.3 ≤ [BKV] ≤ 8.0 $\log_{10}$ IU/mL (550 µL Workflow)* 2.3 ≤ [BKV] ≤ 8.0 $\log_{10}$ IU/mL (100 µL Workflow)*	Amplified or Not Amplified	BKV DNA detected within quantitative range
Positive, above Upper Limit of Quantitation [ULoQ]	Amplified [BKV] > 8.0 $\log_{10}$ IU/mL	Amplified or Not Amplified	BKV DNA detected above quantitative range
Positive, below Lower Limit of Quantitation [LLoQ]	Amplified [BKV] < 1.3 $\log_{10}$ IU/mL (550 µL Workflow)* [BKV] < 2.3 $\log_{10}$ IU/mL (100 µL Workflow)*	Amplified or Not Amplified	BKV DNA detected below quantitative range
Negative	Not Amplified	Amplified	BKV 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†

*550 µL Workflow is used with Plasma/Serum and Urine specimens. 100 µL workflow is used with Plasma/Serum specimens only.
†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™ BKV Quant Assay, the concentration of BKV DNA in the samples is calculated using the stored standard curve in conjunction with the calibration coefficient and specimen volume.
    a. A calibration coefficient is calculated based on the results of the NeuMoDx™ BKV Calibrator Kit processed to establish validity of the Standard Curve, for a particular lot of the NeuMoDx™ BKV Quant Test Strip, on a specific NeuMoDx™ System.
    b. The calibration coefficient is incorporated into the final determination of the concentration of BKV DNA.
    c. The NeuMoDx Software accounts for the specimen input volume when determining the concentration of BKV DNA per mL of specimen.
2. NeuMoDx™ BKV Quant Assay results are reported in $\log_{10}$ IU/mL.
3. The resulting quantitation of the unknown samples is traceable to the 1st WHO International Standard for BK virus (BKV) (14/212)[9].

Test Calibration

A valid calibration based on the Standard Curve is required to quantitate BKV DNA in the specimens. To generate valid results, a test calibration must be completed using the calibrators provided by NeuMoDx™ Molecular, Inc.

Calibrators

1. NeuMoDx™ BKV Calibrators are provided in a kit (REF 800600) and are composed of a dried pellet of synthetic BKV DNA.
2. A set of BKV calibrators needs to be processed with each new lot of NeuMoDx™ BKV Quant Test Strips, if a new BKV 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 BKV calibrators needs to be processed, read all the instructions contained in the NeuMoDx™ BKV Calibrator Kit insert before performing the test.
5. Calibration validity is established as follows:
    a) A set of two calibrators - high and low – need to be processed to establish validity.
    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 $\log_{10}$ IU/mL and the high calibrator nominal target is 5 $\log_{10}$ IU/mL.
    c) A calibration coefficient is calculated to account for expected variation between test strip lots; this calibration coefficient is utilized in determination of final BKV 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.

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. BKV External Controls are provided by NeuMoDx Molecular, Inc. in the BKV External Control Kit (REF900601). The positive controls contain a dried pellet of synthetic BKV DNA.
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 NeuMoDx BKV External Control Kit insert before performing the test.
4. Using the touchscreen and a Specimen Tube Carrier placed on the Autoloader shelf, load the positive and negative control vials into the NeuMoDx™ System. The NeuMoDx™ System will recognize the barcode and begin processing the specimen 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 BKV Positive result and the negative control should provide a BKV 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.
    b) A Negative test result reported for a positive control sample may indicate there is a reagent or instrument related problem.
    c) In either of the above instances, or in the event of an Indeterminate (IND) result or No Result (NR), repeat the failed NeuMoDx™ BKV external control(s) with a new vial of the control(s) failing the validity test.
    d) If positive NeuMoDx™ BKV external control continues to report a Negative result, contact NeuMoDx™ customer service.
    e) If negative NeuMoDx™ BKV external control continues to report a Positive result, attempt to eliminate all sources of potential contamination, including replacing ALL reagents before contacting NeuMoDx™ customer service.

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. Primers and probe specific for SPC1 are also included in each NeuMoDx™ BKV Quant Test Strip enabling detection of presence of SPC1 along with the target BKV 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™ BKV 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.

An IND 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.

An UNR result will be reported if no valid amplification of BKV DNA or SPC1 is detected, 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.

If a NeuMoDx BKV Quant Assay performed on the NeuMoDx System fails to produce valid result and sample processing is aborted prior to completion, it will be reported as a No Result (NR). In the event a NR is reported, a retest is recommended.

PERFORMANCE CHARACTERISTICS

Analytical Sensitivity – Limit of Detection[12]

The Analytical Sensitivity of the NeuMoDx™ BKV Quant Assay was characterized by testing a dilution series of the EDX BKV Verification Panel (Exact Diagnostics), calibrated against the 1st WHO International Standard for BK virus (BKV) (14/212) [9], in BKV negative plasma/serum and urine samples, to determine the Limit of Detection (LoD) on the NeuMoDx Systems. For plasma/serum (550 µL) and urine, the LoD was defined as the closest target level, experimentally determined, above the concentration determined by Probit style analysis with 95% Confidence Interval (CI). For plasma/serum (100 µL) a single sample concentration of 200 IU/mL was investigated by hit rate analysis and validated for LoD if detection rate was above 95%. 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 and 3*.

Table 2: Positive Detection Rates for LoD Determination of the NeuMoDx BKV Quant Assay (Plasma/Serum 550 µL and Urine)

Target Concentration [IU/mL]	Target Concentration [log_{10} IU/mL]	PLASMA/SERUM 550 µL Workflow			URINE		
		Number of Valid Tests	Number of Positives	Detection Rate	Number of Valid Tests	Number of Positives	Detection Rate
50	1.70	41	41	100%	41	41	100%
20	1.30	42	42	100%	40	39	98%
10	1.00	41	35	85%	41	31	76%
5	0.30	41	16	39%	41	12	29%
NEG	0.00	20	0	0%	24	0	0%

Table 3: Positive Detection Rates for LoD Determination of the NeuMoDx BKV Quant Assay (Plasma/Serum 100 µL)

Target Concentration [IU/mL]	Target Concentration [log_{10} IU/mL]	PLASMA/SERUM 100 µL Workflow		
		Number of Valid Tests	Number of Positives	Detection Rate
200	2.30	89	88	99%

The LoD of the NeuMoDxTM BKV Quant Assay in plasma/serum (550 µL workflow) was determined to be 20 IU/mL (1.3 log_{10} IU/mL) with 95% Confidence Interval (CI) of 11.03; in urine the LoD was determined to be 20.0 IU/mL (1.3 log_{10} IU/mL) with 95% Confidence Interval (CI) of 13.09; in plasma/serum (100 µL workflow) the LoD was determined to be 200 IU/mL (2.3 log_{10} IU/mL).

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. In order to determine the LLoQ and ULoQ, the total analytical error (TAE) was calculated for each of the BKV target levels that were shown to report > 95% detection. TAE is defined as follows:

TAE = bias + 2*SD [Westgard Statistic]

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 BKV plasma/serum or urine specimens used in the LLoQ/ULoQ study are shown in *Table 4 and 5*. Based on this data set and the previously determined LoD, the LLoQ and ULoQ were determined to be 20 IU/mL (1.3 log_{10} IU/mL) and 7.58x10^7 IU/mL (here approximated to 8 log_{10} IU/mL), respectively for Plasma/Serum 550 µL and Urine and 200 IU/mL (2.3 log_{10} IU/mL) for Plasma/Serum 100 µL.

Table 4: NeuMoDx™ BKV Quant Test Strip ULoQ and LLoQ, with Bias and TAE (Plasma/Serum 550 µL and Urine)

Target Conc. [IU/mL]	Target Conc. [log_{10} IU/mL]	Plasma/Serum 550 µL					Urine				
		Average Conc. [log_{10} IU/mL]	Detection (%)	SD	Bias	TAE	Average Conc. [log_{10} IU/mL]	Detection (%)	SD	Bias	TAE
7.58x10^7	8	8	100	0.09	0.05	0.23	8	100	0.09	0.10	0.29
50	1.70	1.80	100	0.18	0.10	0.46	1.84	100	0.22	0.14	0.59
20	1.30	1.56	100	0.25	0.26	0.76	1.66	100	0.29	0.36	0.93
10	1.00	1.46	85	0.27	0.46	1.01	1.41	85%	0.41	0.41	1.22
5	0.30	1.27	39	0.48	0.97	1.92	1.31	38%	0.52	1.01	2.04

Table 5: NeuMoDx™ BKV Quant Test Strip ULoQ and LLoQ, with Bias and TAE (Plasma/Serum 100 µL)

Target Conc. [IU/mL]	Target Conc. [log_{10} IU/mL]	Plasma/Serum 100 µL				
		Average Conc. [log_{10} IU/mL]	Detection (%)	SD	Bias	TAE
7.58x10^7	8	8	100	0.09	0.07	0.25
200	2.30	2.30	99	0.39	0.003	0.78

Based on the outcome of these studies, the LoD and LLoQ of the NeuMoDx™ BKV Quant Assay were both determined to be 20 IU/mL (1.3 $\log_{10}$ IU/mL) for plasma/serum and urine with the 550 µL workflow, and 200 IU/mL (2.30 $\log_{10}$ IU/mL) for plasma/serum when using the 100 µL workflow. The ULoQ for all specimen types is 7.58×10^7 IU/mL (8 $\log_{10}$ IU/mL).

Linearity [13]

Linearity of the NeuMoDx™ BKV Quant Test Strip was established in plasma/serum and urine by preparing a dilution series using BKV Synthetic Plasmid (Integrated DNA Technologies) with established traceability to the 1st WHO International Standard for BK virus (BKV) (14/212)[9]. 11 serial dilutions of BKV Synthetic Plasmid, prepared in BKV negative BaseMatrix 53 or pooled BKV-negative human urine, were created to span a concentration range of 7.88 – 1.58 $\log_{10}$ IU/mL for plasma/serum 550 µL and urine and a concentration range of 6.88 – 2.88 $\log_{10}$ IU/mL for plasma/serum 100 µL.

The BKV assay concentrations reported by the NeuMoDx™ System compared to the expected values are presented in *Figures 2, 3* and *4*.

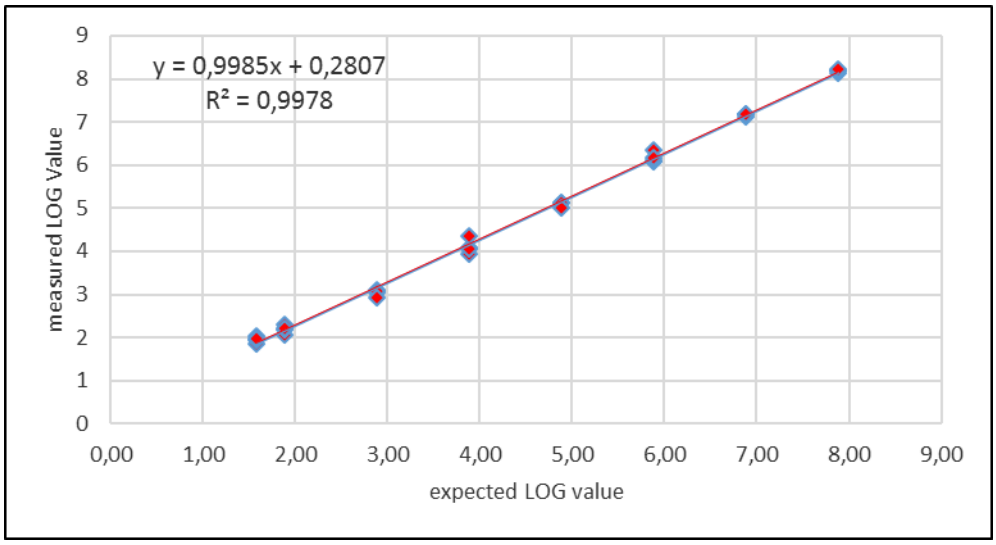

Figure 2: Linearity of the NeuMoDx™ BKV Quant Assay for plasma/serum (550 µL Workflow)

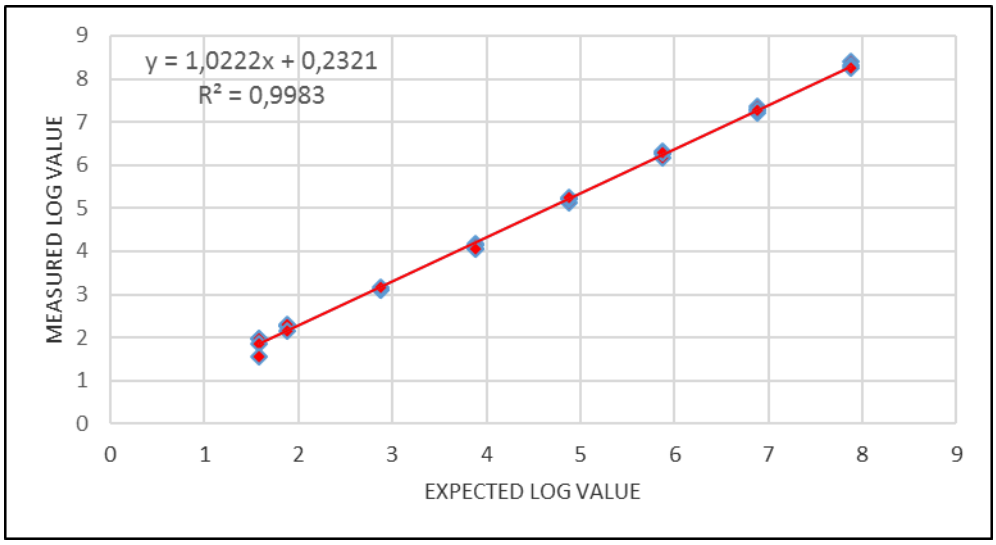

Figure 3: Linearity of the NeuMoDx™ BKV Quant Test Strip for urine specimens

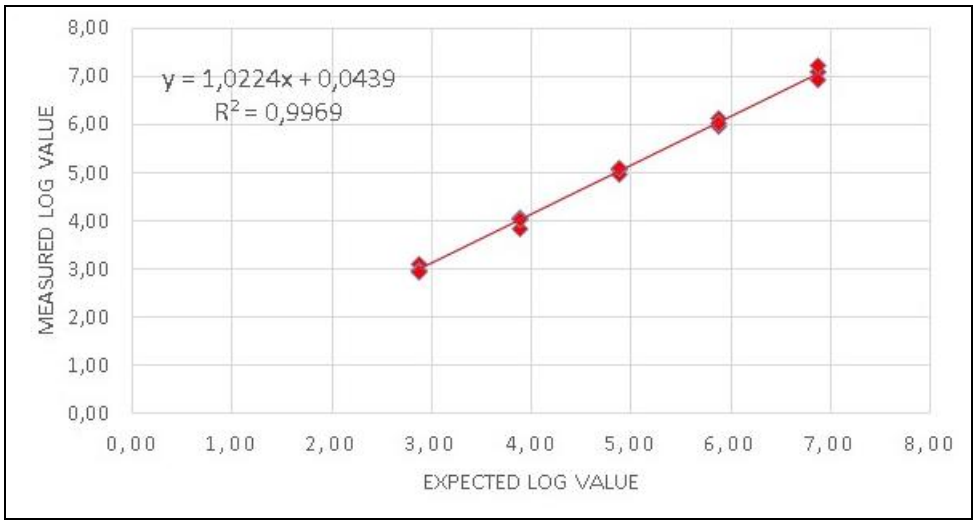

Figure 4: Linearity of the NeuMoDx™ BKV Quant Test Strip for plasma/serum (100 µL Workflow)

Linearity Across Genotypes[16]

The linearity of the NeuMoDx BKV Quant Assay across three BKV genotypes (BK Virus Dunlop, BK Virus Gardner, BK Virus AB269822_FIN-2) was characterized by testing four different concentrations of each genotype of BKV prepared in BKV negative Base Matrix 53. The BK Virus S72390 genotype does not present polymorphisms in the gene target region covered by NeuMoDxTM BKV Quant Test Strip. The study was performed by testing 4 replicates of each of 3 genotypes at 6 concentrations (10-fold dilution series). The linearity across three BKV genotypes is presented in *Table 6* and *Figure 5*.

Table 6: Linearity of the NeuMoDx™ BKV Quant Test Strip across Genotypes

Genotype	Linearity Equation y = NeuMoDx BKV Assay Ct x = Dilution series	R^2
BK Virus Dunlop	y = -3.4808x + 0.8595	0.9926
BK Virus Gardner	y = -3.4682x + 0.6395	0.9959
BK Virus AB269822_FIN-2	y = -3.432x + 1.2683	0.9947

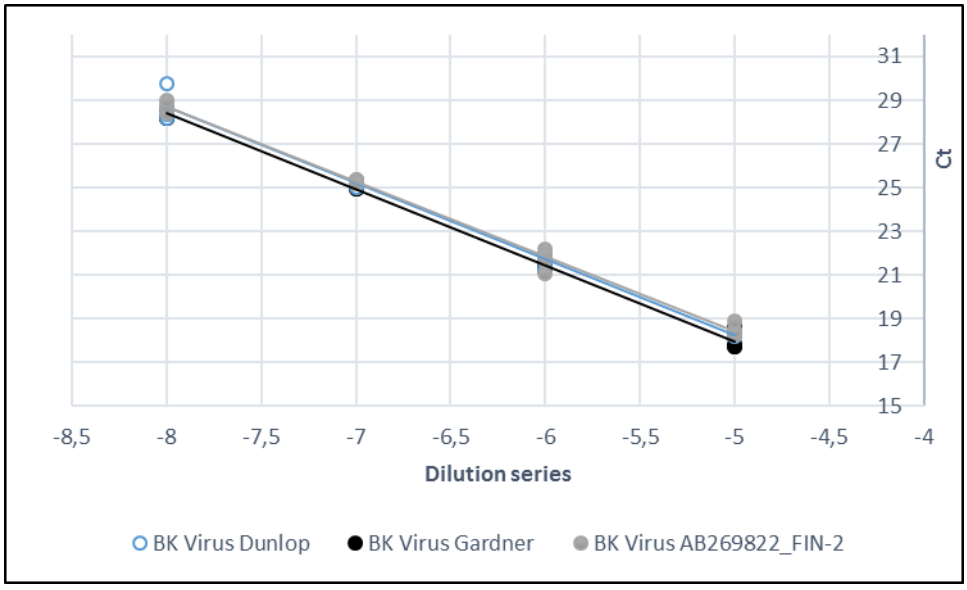

Figure 5: Linearity of the NeuMoDx™ BKV Quant Test Strip across Genotypes

Analytical Specificity – Cross-Reactivity [10,11]

Analytical specificity was demonstrated by screening 22 organisms commonly found in plasma/serum or urine specimens as well as species phylogenetically similar to BKV for cross-reactivity. Organisms were prepared in pools of between 5-6 organisms and tested at a high concentration. The organisms tested are shown in *Table* 7. No cross-reactivity was observed with any of the organisms tested, confirming 100% analytical specificity of the NeuMoDx™ BKV Quant Assay.

Table 7: Pathogens Used to Demonstrate Analytical Specificity

Non-Target Organisms					
HTLV-1/2	*Enterococcus faecalis*	*Klebsiella pneumonia*	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Streptococcus pyogenes*
Staphylococcus epidermidis	Hepatitis B Virus	Adenovirus type 5	Epstein-Barr Virus	Varicella-Zoster Virus	Hepatitis C Virus
Herpes Simplex Virus type 1	Herpes Simplex Virus type 2	Human Herpes Virus type-6	Human Herpes Virus type-7	Human Herpes Virus type-8	Human Immunodeficiency Virus-1
Human Immunodeficiency Virus-2	JC-Virus	SV40	*Cytomegalovirus*		

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

The NeuMoDx™ BKV 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 7. Negative BKV plasma was spiked with the organisms pooled in groups of 5-6, and also spiked with BKV target at a concentration of 4 $\log_{10}$ IU/mL. 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™ BKV Quant Assay was evaluated in the presence of typical exogenous and endogenous interfering substances encountered in BKV clinical plasma/serum or urine specimens. These included abnormally high levels of blood or urine components as well as common antiviral medications, which are classified in Table 8. Each substance was added to screened BKV-negative BaseMatrix 53 or human urine spiked with 3 $\log_{10}$ IU/mL BKV 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 BKV are reported in *Table 9*. None of the exogenous and endogenous substances affected the specificity of the NeuMoDx™ BKV Quant Assay.

Table *8*: 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 9: Interference Testing - Exogenous and Endogenous Agents

Endogenous (Plasma/Serum)	**Average Conc.**	**Bias**
	log_{10} IU/mL	**log_{10} IU/mL**
Triglycerides 500 mg/dL	3.09	0.16
Conjugated bilirubin (0.25 g/L)	3.09	0.16
Unconjugated bilirubin (0.25 g/L)	3.31	-0.06
Albumin (58.7 g/L)	3.12	0.13
Hemoglobin (2.9 g/L)	3.02	0.23
Endogenous (Urine)	**Average Conc.**	**Bias**
	log_{10} IU/mL	**log_{10} IU/mL**
Urobilirubin (> 2 mg/dL)	3.74	-0.09
Glucose (1000 mg/dL)	4.00	0.04
Urine pH 4	3.75	0.29
Urine pH 10	3.77	0.27
Leucocytes (1E5 cells/mL)	3.68	– 0.06
Blood 7%	3.42	– 0.32
Protein (albumin >100 mg/dL)	3.96	0.08
Talcum powder	3.92	0.12
Exogenous (Drugs)	**Average Conc.**	**Bias**
	log_{10} IU/mL	**log_{10} IU/mL**
Pool 1: Valganciclovir, Prednisone, Cidofovir, Cefotaxime, Mycophenolate mofetil	4.04	-0.06
Pool 2: Vancomycin, Tacrolimus, Famotidine, Valacyclovir, Leflunomide	4.07	-0.09

Repeatability and Within Lab Precision[14]

Precision of the NeuMoDx™ BKV Quant Test Strip was determined by testing 2 replicates of a 5-member panel of BKV specimens prepared with BKV plasmid twice a day, using one NeuMoDx™ 96 System across 20 days. The within-run and within-day precisions were characterized, and the overall standard deviation was determined to be ≤ 0.30 log_{10} IU/mL. Excellent precision was demonstrated across days and runs as shown in *Table 10*. Precision between operators was not characterized as the operator plays no significant role in the processing of samples using the NeuMoDx™ System.

Table 10: Within Lab Precision – NeuMoDx BKV Quant Assay on NeuMoDx Systems

Sample	Within Day SD (Log_{10} IU/mL)	Between Day SD (Log_{10} IU/mL)	Within Run SD (Log_{10} IU/mL)	Between Run SD (Log_{10} IU/mL)	Within Laboratory SD (Log_{10} IU/mL)
Plasma/serum specimen (input 550 µl)					
RISppHIGH	0.10	0.08	0.10	0.01	0.13
RISppMIDDLE	0.14	0.10	0.11	0.06	0.17
RISppMLOW	0.22	0.12	0.21	0.02	0.25
RISppLOW	0.21	0.03	0.18	0.10	0.21
RISppNEG	0.00	0.00	0.00	0.00	0.00
Urine specimen					
RISpuHIGH	0.16	0.10	0.11	0.12	0.20
RISpuMIDDLE	0.21	0.09	0.16	0.13	0.23
RISpuMLOW	0.14	0.12	0.13	0.02	0.18
RISpuLOW	0.29	0.05	0.25	0.13	0.30
RISpuNEG	0.00	0.00	0.00	0.00	0.00

Lot to Lot Reproducibility [14]

Lot to Lot Reproducibility of the NeuMoDx™ BKV Quant Test Strip was determined using three different lots of NeuMoDx™ BKV Quant Test Strips. A 5-member panel of BKV prepared with BKV plasmid was used to assess performance on one NeuMoDx™ 96 Molecular System across 3 separate runs. The variation within and across lots was analyzed and results expressed as absolute quantification bias between lot, presented in *Table 11*. Maximum overall bias was 0.27 log_{10} IU/mL. Equivalent performance was demonstrated across lots as quantitation of all panel members was within tolerance specification.

Table 11: Lot to Lot Reproducibility – NeuMoDx BKV Quant Assay

Sample	Absolute bias between Lot.1 and Lot.2 (log_{10} IU/mL)	Absolute bias between Lot.1 and Lot.3 (log_{10} IU/mL)	Absolute bias between Lot.2 and Lot.3 (log_{10} IU/mL)
Plasma/Serum specimen (550 µL)			
7 log_{10} IU/mL	0.05	0.10	0.05
4 log_{10} IU/mL	0.02	0.03	0.05
3 log_{10} IU/mL	0.20	0.05	0.15
2 log_{10} IU/mL	0.02	0.24	0.26
0 log_{10} IU/mL	0.00	0.00	0.00
Urine specimen (550 µL)			
7 log_{10} IU/mL	0.09	0.27	0.19
4 log_{10} IU/mL	0.25	0.06	0.19
3 log_{10} IU/mL	0.06	0.08	0.14
2 log_{10} IU/mL	0.03	0.11	0.14
0 log_{10} IU/mL	0.00	0.00	0.00

Instrument to instrument Reproducibility[14]

Instrument to instrument Reproducibility of the NeuMoDx™ BKV Quant Test Strip was determined using three different systems (two NeuMoDx™ 288 Molecular System and one NeuMoDx™ 96 Molecular System). A 5-member panel of BKV prepared with BKV plasmid was used to assess performance. Testing was performed in parallel 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} IU/mL. Equivalent performance was demonstrated across systems as SD in quantitation of all panel members was within tolerance specification (*Table 12*).

Table 12: Instrument to instrument Reproducibility – NeuMoDx™ BKV Quant Test Strip

Sample	Repeatability SD (Log_{10} IU/mL)	Between Day SD (Log_{10} IU/mL)	Within Instrument SD (Log_{10} IU/mL)	Between Instrument SD (Log_{10} IU/mL)	Reproducibility SD (Log_{10} IU/mL)
Plasma/serum specimen (input 550 µl)					
RISppHIGH	0.10	0.05	0.11	0.06	0.12
RISppMIDDLE	0.13	0.05	0.13	0.04	0.13
RISppMLOW	0.10	0.06	0.12	0.04	0.12
RISppLOW	0.12	0.05	0.13	0.04	0.13
RISppNEG	0.00	0.00	0.00	0.00	0.00
Urine specimen					
RISpuHIGH	0.11	0.05	0.12	0.06	0.14
RISpuMIDDLE	0.10	0.01	0.10	0.05	0.11
RISpuMLOW	0.09	0.04	0.10	0.07	0.12
RISpuLOW	0.15	0.02	0.15	0.05	0.16
RISpuNEG	0.00	0.00	0.00	0.00	0.00

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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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