REF **201200 NeuMoDx™ TV/MG Test Strip** ℞ only

CAUTION: For US Export Only

IVD For *in vitro* diagnostic use with the NeuMoDx 288 and NeuMoDx 96 Molecular Systems

For insert updates, go to: www.qiagen.com/neumodx-ifu
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

INTENDED USE

The NeuMoDx TV/MG Assay, as performed on the NeuMoDx 96 Molecular System and NeuMoDx 288 Molecular System (NeuMoDx Molecular System(s)), is a rapid, automated, qualitative *in vitro* nucleic acid amplification test for the direct detection and differentiation of DNA from *Trichomonas vaginalis* (TV) and/or *Mycoplasma genitalium* (MG) in clinical urogenital specimens. The assay utilizes real-time polymerase chain reaction (PCR) for the detection of *Trichomonas vaginalis* and *Mycoplasma genitalium* DNA in clinician-collected vaginal swab specimens, self-collected vaginal swab specimens (collected in a clinical setting) and endocervical swab specimens, all collected using a polyester tip swab with a plastic applicator in a universal transport medium (Universal Transport Medium, UTM-RT®, Copan Diagnostics, CA, USA, or BD™ Universal Viral Transport System, BD™ UVT, Becton, Dickinson and Company, MD, USA or equivalent), and male and female urine. The NeuMoDx TV/MG Assay is intended to be used as an aid in the diagnosis of *Trichomonas vaginalis* and/or *Mycoplasma genitalium* urogenital infections in symptomatic and asymptomatic patients, but not to guide or monitor treatment for TV or MG infections. Concomitant cultures may be necessary to recover organisms for epidemiological testing and/or further susceptibility testing.

SUMMARY AND EXPLANATION

The NeuMoDx TV/MG Assay is designed to detect and differentiate TV and MG DNA simultaneously. The assay targets the region encoding a hypothetical protein (TVAG_305840) in the TV genome and the sequences encoding the IgG-blocking protein M and thymidylate kinase in the MG genome. Multiple regions are targeted for MG to minimize the chance of false negatives, should mutation occur at one of the targeted regions. The NeuMoDx TV/MG Assay includes a DNA Sample Process Control (SPC1) to monitor for the presence of potentially inhibitory substances and system, process, or reagent failures that may be encountered during the extraction and amplification processes.

To test a urine specimen using the NeuMoDx TV/MG Assay, a urine sample is collected in a standard urine collection cup with no preservatives or additives. To prepare for testing, an aliquot of the urine is dispensed into a secondary tube compatible with the NeuMoDx Molecular System and loaded onto the system in a designated sample carrier. For each sample, a 550 µL aliquot of the urine sample is mixed with NeuMoDx Lysis Buffer 2 and the NeuMoDx Molecular System automatically performs all the steps required to extract the target nucleic acid, prepare the isolated DNA for real-time polymerase chain reaction amplification, and if present, amplify and detect the products of amplification (sections of the targeted gene sequences of the TV and MG genomes).

To test a swab specimen using the NeuMoDx TV/MG Assay, an endocervical swab, clinician- or self-collected vaginal swab sample must be collected using a polyester tip swab with plastic applicator in 3 mL of universal transport medium (UTM-RT, UVT) or equivalent. The swab sample may be tested directly from the primary transport medium tube or an aliquot dispensed into a secondary tube compatible with the NeuMoDx System and loaded onto the NeuMoDx System using the appropriate sample carrier to begin processing. For each sample, a 400 µL aliquot of the transport media is mixed with NeuMoDx Lysis Buffer 2 and 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 targets of amplification (sections of the targeted gene sequences of the TV and MG genomes).

Trichomonas vaginalis is a free-living protozoan that can colonize mucosal epithelial surfaces. It is the causative agent of the most common non-viral sexually transmitted infection (STI) worldwide and accounts for nearly half of all curable STIs globally.[1] The prevalence of TV infection is best documented in the United States, where the rates are consistently higher than those of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections, combined.[2] Although there are no recommendations for routine screening for TV infections among women in the general population, diagnostic testing for TV is recommended by the Center of Disease Control (CDC) in the United State in women seeking care for vaginal discharge and in asymptomatic patients or women receiving care in high-prevalence settings.[3] The CDC recommends screening of HIV positive pregnant women for TV, since TV infection is a high-risk factor for vertical HIV transmission.[3] The prevalence of TV infection is less understood in male populations as compared to female populations. Although usually an asymptomatic disease in men, *T. vaginalis* has been associated with 5% to 15% of nongonococcal urethritis cases. Currently there are no screening recommendations for men.

Despite the growing accessibility of molecular detection methods, broth culture remains the gold standard for *T. vaginalis* detection. Furthermore, the diagnosis of trichomoniasis has traditionally depended on the microscopic observation of motile protozoa from vaginal or cervical samples and from urethral or prostatic secretions. Although these two methods remain the most widely used diagnostic tests for trichomoniasis, detection of *T. vaginalis* using nucleic acid amplification testing (NAAT) has been shown to be the most sensitive approach for the diagnosis of this infection. The sensitivity of culture compared with NAAT ranges from 35-78%, while its specificity is usually considered to be 100%.[4-6] Similarly, the specificity of wet-mount microscopy is generally high, whereas its sensitivity is poor compared with NAAT even among symptomatic women, with reported rates ranging from 34-58%.[4-6] Because of its superior sensitivity to culture and wet-mount microscopy, NAAT is now the first choice recommended by CDC. Microscopy should never be used as a screening method for asymptomatic women.[7]

Mycoplasma genitalium is the smallest known self-replicating bacterium.[8] It lacks a cell wall and thus cannot be detected on Gram staining of a specimen.[8] MG is predominantly found in the genitourinary tract of both sexes with an estimated prevalence of 1-2% in the general population and is slightly more common in women.[9] *M. genitalium* has been increasingly recognized as an important and ubiquitous cause of several STIs, is

responsible for more STIs than *Neisseria gonorrhoeae*, and is the second-most prevalent STI next to *Chlamydia trachomatis* infection with prevalence rates up to 38% in high risk populations. [9-16] While *M. genitalium* is often the sole pathogen detected, coinfection with *C. trachomatis* is not uncommon in selected areas.[10-13]

Mycoplasma genitalium infection is strongly associated with persistent and recurrent urethritis, where up to 40% of patients may have MG detected, and with non-gonococcal urethritis (NGU).[12,14] Several studies support an association of MG infection in women with postcoital bleeding and cervicitis, endometritis and pelvic inflammatory disease (PID).[13,17-21] Most studies have found that this organism is more common among women with cervicitis than those without this condition.[11,17-18] The evidence suggests that most people infected with *M. genitalium* in the genital tract do not develop disease; *M. genitalium* infections in women are commonly asymptomatic.[11,22-23]

Despite its widespread prevalence, diagnosis of *M. genitalium* infection is performed exclusively using NAATs, owing to the poor and slow growth of the bacterium in culture.[10,24] The NeuMoDx TV/MG Assay implemented on the NeuMoDx Molecular Systems allows for automated and accurate detection of *Trichomonas vaginalis* and *Mycoplasma genitalium* simultaneously.

PRINCIPLES OF THE PROCEDURE

The NeuMoDx TV/MG Assay combines the technologies of DNA extraction and amplification/detection by real-time PCR. Specimens are collected in conventional urine specimen collection cups or swab specimen collection tubes (UTM-RT, UVT, or equivalent). The NeuMoDx System automatically aspirates an aliquot of the urine or swab specimen to mix with NeuMoDx Lysis Buffer 2 and the extraction reagents contained in the NeuMoDx Extraction Plate to begin processing. The NeuMoDx System automates and integrates DNA extraction and concentration, reagent preparation, and nucleic acid amplification and detection of the target sequence using real-time PCR. The included Sample Process Control (SPC1) helps monitor for the presence of potential inhibitory substances as well as system, process, or reagent failures. No operator intervention is necessary once the specimen is loaded onto the NeuMoDx System.

The NeuMoDx System uses a combination of heat, lytic enzyme, and extraction reagents to perform cell lysis, DNA extraction and removal of inhibitors. The released nucleic acids are captured by paramagnetic particles. 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 System then uses the eluted DNA to rehydrate proprietary NeuDry™ amplification reagents containing all the elements necessary for amplification of the TV and MG targets as well as a section of the SPC1 sequence. This enables simultaneous amplification and detection of both targets and control DNA sequences. After reconstitution of the dried PCR reagents, the NeuMoDx System dispenses the prepared PCR-ready mixture into one PCR chamber (per specimen) of the NeuMoDx Cartridge. Amplification and detection of the control and target (if present) DNA sequences occur in the PCR chamber. The NeuMoDx Cartridge, including the PCR chamber, is designed to contain the amplicon following real-time PCR, thereby essentially eliminating contamination risk post-amplification.

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 to 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 from it and breaks the close proximity to the quencher, thereby overcoming the quenching effect due to FRET and allowing an increase in fluorescence.

A TaqMan probe labeled with a fluorophore (Excitation: 470 nm & Emission: 510 nm) at the 5' end, and a dark quencher at the 3' end, is used to detect MG DNA and a TaqMan probe labeled with a fluorophore (Excitation: 585 nm & Emission: 610 nm) at the 5' end, and a dark quencher at the 3' end, is used to detect TV DNA. For detection of the Sample Process Control, the TaqMan probe is labeled with an alternate fluorescent dye (Excitation: 530 nm & Emission: 555 nm) at the 5' end, and a dark quencher at the 3' end. The NeuMoDx System monitors the fluorescent signal emitted by the TaqMan probes at the end of each amplification cycle. When amplification is complete, the NeuMoDx System analyzes the data and reports a final qualitative result (POSITIVE/NEGATIVE/INDETERMINATE/UNRESOLVED).

REAGENTS/CONSUMABLES

Material Provided

REF	Contents	Tests per unit	Tests per package
201200	**NeuMoDx TV/MG Test Strip** *Dried real-time PCR reagents containing TV/MG specific TaqMan probes and primers, Sample Process Control specific TaqMan probe and primers.*	16	96

Additional Materials Required (Available Separately)

REF	Contents
100100	**NeuMoDx Cartridge**
100200	**NeuMoDx Extraction Plate** *Dried paramagnetic particles, lytic enzyme, and Sample Process Controls*
400500	**NeuMoDx Lysis Buffer 2**
400100	**NeuMoDx Wash Reagent**
400200	**NeuMoDx Release Reagent**
235903	**Hamilton® CO-RE / CO-RE II Tips (300 µL) with Filters**
235905	**Hamilton CO-RE / CO-RE II Tips (1000 µL) with Filters**

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

WARNINGS & PRECAUTIONS

- This test is for *in vitro* diagnostic use with NeuMoDx Systems only.
- Do not use the consumables or reagents after the listed expiration date.
- Do not use any reagent 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 use urine collected in containers with preservatives. The NeuMoDx TV/MG Assay has not been validated for use with preservatives.
- Swab specimens should be collected using a polyester swab with a plastic applicator. The NeuMoDx TV/MG Assay has not been validated for use with other swab types.
- Do not collect swab specimens in transport media other than UTM-RT, UVT, or equivalent. The NeuMoDx TV/MG Assay has not been validated for use with other transport media.
- Minimum specimen volume of secondary aliquots is dependent on the tube size/specimen tube carrier 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 reagents. The use of sterile, DNase-free, disposable transfer pipettes is recommended. 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 TV/MG Test Strip, 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 surfaces of the NeuMoDx TV/MG Test Strip and NeuMoDx Extraction Plate, or the top surface of the NeuMoDx Lysis Buffer 2 container. Handling of consumables and reagents should be done by touching side surfaces only.
- Safety Data Sheets (SDS) are provided for each reagent (as applicable) at www.qiagen.com/neumodx-ifu
- Wash hands thoroughly after performing the test.
- Do not pipette by mouth. Do not smoke, drink, or eat in areas where specimens or kit reagents are being handled.
- Always handle specimens as if they are infectious and in accordance with safe laboratory procedures such as those described in *Biosafety in Microbiological and Biomedical Laboratories*[25] and in CLSI Document M29-A3.[26]
- Dispose of unused reagents and waste in accordance with country, federal, provincial, state and local regulations.

PRODUCT STORAGE, HANDLING, & STABILITY

- NeuMoDx TV/MG Test Strips are stable in the primary packaging through the stated expiration date on the immediate product label when stored at 15-23 °C.
- Do not use consumables and reagents past the stated expiration date.
- Do not use any test product if the primary or secondary packaging has been visually compromised.
- Do not reload any test product that has previously been loaded onto another NeuMoDx Molecular System.
- Once loaded, the NeuMoDx TV/MG Test Strip may remain onboard the NeuMoDx System for 14 days. Remaining shelf life of loaded test strips is tracked by the software and reported to the user in real time. Removal of a test strip that has been in use beyond its allowable period will be prompted by the System.

SPECIMEN COLLECTION, TRANSPORT, & STORAGE

- The NeuMoDx TV/MG Test Strip has been tested using female and male neat urine specimens, clinician and self-collected vaginal swab specimens, and endocervical swab specimens. Swab specimens should be taken using a polyester tip swab with plastic applicator (UTM-RT, UVT, or equivalent). Performance with other specimen types has not been evaluated.
- Collected urine should be kept at 2-8 °C during transport.
- Collected swab specimens should be kept at the temperature recommended in the swab collection kit during transport.
- Urine and swab specimens should be stored between 2-8 °C for no longer than 7 days prior to testing and a maximum of 8 hours at room temperature.

INSTRUCTIONS FOR USE

Specimen Collection/Transport

1. First catch urine (20-30 mL) should be collected in a sterile urine collection cup.
2. Clinician and self-collected vaginal swabs and endocervical swabs should be collected following instructions provided by the manufacturer with the swab collection device.
3. If specimens are not tested within 8 hours, they should be stored at 2-8 °C for up to 7 days.

Test Preparation – Urine Specimens

1. Apply a specimen barcode label to a specimen tube compatible with the NeuMoDx System. For barcode specifications, refer to the NeuMoDx 288 and 96 Molecular System Operator's Manuals (p/n 40600108 & 40600317).
2. Gently swirl the urine specimen in the primary collection container to achieve uniform distribution.
3. Using a different transfer pipette or pipette tip for each specimen, transfer an aliquot of urine to the barcoded specimen tube compatible with the NeuMoDx System according to the volumes defined below:
    - Specimen Tuber Carrier (32-tube): 11 – 14 mm in diameter and 60 – 120 mm in height; minimum fill volume ≥ 700 µL
    - Specimen Tube Carrier (24-tube): 14.5 – 18 mm in diameter and 60 – 120 mm in height; minimum fill volume ≥ 1150 µL
    - Low Volume Specimen Tube Carrier (32-tube): 1.5 mL conical bottom microcentrifuge tube; minimum fill volume ≥ 650 µL

Test Preparation – Swab Specimens

1. Apply specimen barcode label to a specimen tube compatible with the NeuMoDx System. The primary swab collection tube may be labeled and placed directly into a 24- or 32-tube Specimen Tube Carrier. Alternatively, an aliquot of the swab medium may be transferred to a secondary tube for processing on the NeuMoDx System.
2. If testing the 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.
3. If using a secondary tube, transfer an aliquot of the transport media to the barcoded specimen tube compatible with the NeuMoDx System according to the volumes defined below:
    - Specimen Tuber Carrier (32-tube): 11 – 14 mm in diameter and 60 – 120 mm in height; minimum fill volume ≥ 550 µL
    - Specimen Tube Carrier (24-tube): 14.5 – 18 mm in diameter and 60 – 120 mm in height; minimum fill volume ≥ 1000 µL
    - Low Volume Specimen Tube Carrier (32-tube): 1.5 mL conical bottom microcentrifuge tube; minimum fill volume ≥ 500 µL

NeuMoDx System Operation

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

1. Populate one or more NeuMoDx Test Strip Carrier(s) with NeuMoDx TV/MG Test Strip(s) and use the touchscreen to load the Test Strip Carrier(s) into the NeuMoDx System.

2. 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.
3. 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.
4. Load the specimen tube(s) into the appropriate Specimen Tube Carrier(s) and ensure caps are removed from all specimen tubes.
5. Place the Specimen Tube Carrier(s) on the autoloader shelf and use the touchscreen to load the carrier(s) into the NeuMoDx System. This will initiate processing of the specimen(s) loaded for the tests identified, given a valid test order is present in the system.

LIMITATIONS

- The NeuMoDx TV/MG Test Strip can only be used on NeuMoDx Molecular Systems.
- The performance of the NeuMoDx TV/MG Test Strip has been established with male and female urine specimens, self-collected and clinician-collected vaginal swabs, and endocervical swab specimen. Use of the NeuMoDx TV/MG Test Strip with other clinical sources has not been assessed and performance characteristics are unknown for other specimen types.
- Because detection of TV and MG 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 organisms in the specimen is below the analytical sensitivity of the test.
- Operation of the NeuMoDx System is limited to use by personnel trained on the use of the NeuMoDx System.
- If the Sample Process Control does not amplify and the NeuMoDx TV/MG Assay result is Negative, an invalid result (Indeterminate or Unresolved) will be reported and the test should be repeated.
- A positive test result does not necessarily indicate the presence of viable organisms. It is, however, presumptive for the presence of TV and/or MG DNA.
- While there are no known strains/isolates of TV lacking the region for TVAG_305840 or of MG lacking the genes encoding the IgG-blocking protein M and thymidylate kinase, the occurrence of such a strain could lead to an erroneous result using the NeuMoDx TV/MG Assay.
- Mutations in primer/probe binding regions may affect detection using the NeuMoDx TV/MG Assay.
- Results from NeuMoDx TV/MG Assay should be used as an adjunct to clinical observations and other information available to the physician.
- Test results may be affected by concurrent antibiotic therapy as TV and MG DNA may continue to be detected following antimicrobial therapy.
- Good laboratory practices, including changing gloves between handling patient specimens, are recommended to avoid contamination of specimens.

RESULTS

NeuMoDx Molecular Systems

Available test results may be viewed or printed from the 'Results' tab in the Results window on the NeuMoDx System touchscreen. A test result is called Positive (POS), Negative (NEG), Indeterminate (IND), or Unresolved (UNR) based on the amplification status of the target and the Sample Process Control (SPC1).

Criteria for a positive or negative call are specified in the NeuMoDx System TV/MG Assay Definition File (ADF) as installed on the System(s). Results are reported based on the ADF decision algorithm, summarized in *Table 1*, below.

Table 1. Summary of TV/MG Assay Decision Algorithm

RESULT	TV and/or MG TARGETS	PROCESS CONTROL (SPC1)
POS	Amplified	Amplified or Not Amplified
NEG	Not Amplified	Amplified
IND	Not Amplified, System Error Detected	
UNR	Not Amplified, No System Error Detected	

Invalid Results

If a NeuMoDx TV/MG Assay performed on the NeuMoDx System fails to produce a valid result, it will be reported as either Indeterminate or Unresolved based on the type of error that occurred, and 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.

An Unresolved result will be reported if no target is detected and there is no amplification of the Sample Process Control, which indicates possible reagent failure or the presence of inhibitors.

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.

1. External (User-Defined) control materials will not be provided by NeuMoDx Molecular, Inc. Appropriate controls must be chosen and validated by the laboratory. Note that a separate set of User-Defined controls for the TV/MG test should be defined for both urine and swab matrices and the controls must meet the same minimum volume specifications as clinical samples specified above based on the Specimen Tube Carrier size. The user may define the specific barcodes per Positive and Negative Control and per matrix.
2. Recommended: A 1:2000 dilution of NATtrol™ *T. vaginalis* External Run Controls (ZeptoMetrix NATTVPOS-6MC) and 1:200 dilution of NATtrol *Mycoplasma genitalium* External Run Control (ZeptoMetrix NATMGN-ERC) in KOVA Liqua-TROL® (KOVA International 87123) for the urine matrix control and with UTM-RT media for the swab matrix control. Negative control should consist only of KOVA Liqua-TROL or UTM-RT media. When processing controls, place the labeled controls in a specimen tube carrier and use the touchscreen to load the carrier into NeuMoDx System from the autoloader shelf. Once defined by the user, the NeuMoDx System will recognize the barcodes and start processing controls unless adequate reagents or consumables required for testing are not available.
3. The primers and probe specific for Sample Process Control 1 (SPC1) are included in each NeuMoDx TV/MG Test Strip. This Sample Process Control allows the NeuMoDx System to monitor the efficacy of the DNA extraction and PCR amplification processes.
4. A positive test result reported for a negative control sample may indicate a specimen contamination problem. Please refer to NeuMoDx *288 or 96 Molecular System Operator's Manual* for troubleshooting tips.
5. A negative result reported for a positive control sample may indicate there is a reagent or NeuMoDx System related problem. Please refer to *NeuMoDx 288 or 96 Molecular System Operator's Manual* for troubleshooting tips.

PERFORMANCE CHARACTERISTICS

Clinical Performance – Urine Specimens

Clinical performance characteristics of the NeuMoDx TV/MG Assay were determined through a method comparison study using residual and prospectively collected clinical urine specimens sourced from three geographically diverse clinical laboratory locations.

Clinical residual TV positive specimens and prospective urine specimens from symptomatic and asymptomatic patients were de-identified and given a unique ID number by clinical laboratories, establishing a confidential list linking the patient ID to the de-identified specimens tested for study purposes. Additional MG and TV/MG positive samples were contrived in negative urine to compensate for a low incidence of MG and TV/MG co-infection. A total of 166 specimens provided from two clinical laboratories and 46 contrived samples were tested. Among the 212 total samples, 43 samples were identified as TV positive and 46 samples were identified as MG positive by reference lab testing. Sixteen samples tested positive for both TV and MG, indicating a dual or co-infection. The test status of these samples was withheld from the operator to implement a "single blind study." Results reported from the specific CE-IVD and FDA cleared, legally marketed molecular devices utilized by the laboratories for standard of care testing were used to perform the method comparison analysis.

Results of the NeuMoDx TV/MG Assay provided a Clinical Sensitivity of 98.3% for the TV target and 100% for the MG target, both reported at 95% confidence interval (CI). The Clinical Specificity from the study was determined to be 100% for both TV and MG targets, again using 95% CI. The lower and upper limits of the 95% CI presented in *Tables 2A* and *2B* below were calculated using the Wilson procedure.

Table 2A. Clinical Performance Summary – NeuMoDx TV/MG Assay Detection of *T. vaginalis* (urine)

TV		CE-IVD/FDA Cleared Reference Test Result		
		POS	NEG	Total
NeuMoDx TV/MG Assay	POS	58	0	58
	NEG	1	153	154
	Total	59	153	212
Clinical Sensitivity (TV) = 98.3% (95% CI: 91.0 – 99.7%)				
Clinical Specificity (TV) = 100% (95% CI: 97.6 – 100%)				

Table 2B. Clinical Performance Summary – NeuMoDx TV/MG Assay Detection of *M. genitalium* (urine)

MG		CE-IVD/FDA Cleared Reference Test Result		
		POS	NEG	Total
NeuMoDx TV/MG Assay	POS	62	0	62
	NEG	0	114	114
	Total	62	114	176
Clinical Sensitivity (MG) = 100% (95% CI: 94.7 – 100%)				
Clinical Specificity (MG) = 100% (95% CI: 96.7 – 100%)				

Clinical Performance – Swab Specimens

Clinical performance characteristics of the NeuMoDx TV/MG Assay were determined through a method comparison study using prospectively collected clinical vaginal (self- and clinician-collected) and endocervical swab specimens.

Prospective vaginal (n = 163) and endocervical swab (n = 163) specimens were collected from consented symptomatic and asymptomatic patients, de-identified and given a unique ID number by clinical laboratories, establishing a confidential list linking the patient ID to the de-identified specimens tested for study purposes. To compensate for a low incidence of infection and co-infection, an additional three-member panel of TV, MG, and TV/MG positive samples was contrived in clinical negative vaginal and endocervical swabs for a total of 80 contrived samples per swab type. Among the 243 total vaginal swab samples, 67 were identified as TV positive and 54 as MG positive. Among the 243 total endocervical swab samples, 61 were identified as TV positive and 54 as MG positive. The test status of these samples was withheld from the operator to implement a "single blind study." Results reported from the specific CE-IVD and FDA cleared, legally marketed molecular devices utilized by the laboratories for standard of care testing were used to perform the method comparison analysis.

Results of the NeuMoDx TV/MG Assay performed on vaginal swab specimens provided a Clinical Sensitivity of 98.5% for the TV target and 96.3% for the MG target, both reported at 95% confidence interval (CI). The Clinical Specificity from the study was determined to be 95.5% for TV and 99.5% for MG, again using 95% CI. The lower and upper limits of the 95% CI presented in *Tables 3A* and *3B* below were calculated using the Wilson procedure.

Table 3A. Clinical Performance Summary – NeuMoDx TV/MG Assay Detection of *T. vaginalis* (vaginal swab)

TV		CE-IVD/FDA Cleared Reference Test Result		
		POS	NEG	Total
NeuMoDx TV/MG Assay	POS	66	8	74
	NEG	1	168	169
	Total	67	176	243
Clinical Sensitivity (TV) = 98.5% (95% CI: 90.9 – 99.2%)				
Clinical Specificity (TV) = 95.5% (95% CI: 90.9 – 97.9%)				

Table 3B. Clinical Performance Summary – NeuMoDx TV/MG Assay Detection of *M. genitalium* (vaginal swab)

MG		CE-IVD/FDA Cleared Reference Test Result		
		POS	NEG	Total
NeuMoDx TV/MG Assay	POS	52	1	53
	NEG	2	188	190
	Total	54	189	243
Clinical Sensitivity (MG) = 96.3% (95% CI: 86.2 – 99.4%)				
Clinical Specificity (MG) = 99.5% (95% CI: 96.6 – 99.9%)				

Results of the NeuMoDx TV/MG Assay performed on endocervical swab specimens provided a Clinical Sensitivity of 100% for the TV target and 96.3% for the MG target, both reported at 95% confidence interval (CI). The Clinical Specificity from the study was determined to be 96.2% for TV and 99.5% for MG, again using 95% CI. The lower and upper limits of the 95% CI presented in Tables 4A and 4B below were calculated using the Wilson procedure.

Table 4A. Clinical Performance Summary – NeuMoDx TV/MG Assay Detection of *T. vaginalis* (endocervical swab)

TV		CE-IVD/FDA Cleared Reference Test Result		
		POS	NEG	Total
NeuMoDx TV/MG Assay	POS	61	7	68
	NEG	0	175	175
	Total	61	182	243
Clinical Sensitivity (TV) = 100% (95% CI: 92.6 – 100%)				
Clinical Specificity (TV) = 96.2% (95% CI: 91.9 – 98.3%)				

Table 4B. Clinical Performance Summary – NeuMoDx TV/MG Assay Detection of *M. genitalium* (endocervical swab)

MG		CE-IVD/FDA Cleared Reference Test Result		
		POS	NEG	Total
NeuMoDx TV/MG Assay	POS	52	1	53
	NEG	2	188	190
	Total	54	189	243
Clinical Sensitivity (MG) = 96.3% (95% CI: 86.2 – 99.4%)				
Clinical Specificity (MG) = 99.5% (95% CI: 96.6 – 99.9%)				

Analytical Sensitivity – Urine

The limit of detection (LoD) of the NeuMoDx TV/MG Assay was determined in pooled healthy donor urine spiked with *Trichomonas vaginalis* strain G3 (ATCC PRA-98) or *Mycoplasma genitalium* strain G37 (ATCC 33530) indicated in *Tables 5A and 5B*. The tests were conducted with 40 replicates at each level, for which detection rates are reported below. A probit model of analysis on the hit-rate study was used to determine the limit of detection of the NeuMoDx TV/MG Assay – **0.025 cells/mL TV and 8.4 copies/mL MG** – shown below in *Figure 1*.

Table 5A. Positive Detection Rates of TV in Urine – NeuMoDx TV/MG Assay Limit of Detection Study.

TV (cells/mL)	n	# POS	% POS	LoD (Probit)
0.08	40	40	100	**0.025 cells/mL**
0.04	40	40	100	
0.02	39	38	97.4	
0.015	39	13	33.3	
0.01	39	10	25.6	
0	40	0	0	

Table 5B. Positive Detection Rates of MG in Urine – NeuMoDx TV/MG Assay Limit of Detection Study.

MG (copies/mL)	n	# POS	% POS	LoD (Probit)
20	38	38	100	**8.4 cp/mL**
15	38	38	100	
10	40	39	97.5	
5	40	31	77.5	
2.5	38	24	63.2	
0	40	0	0	

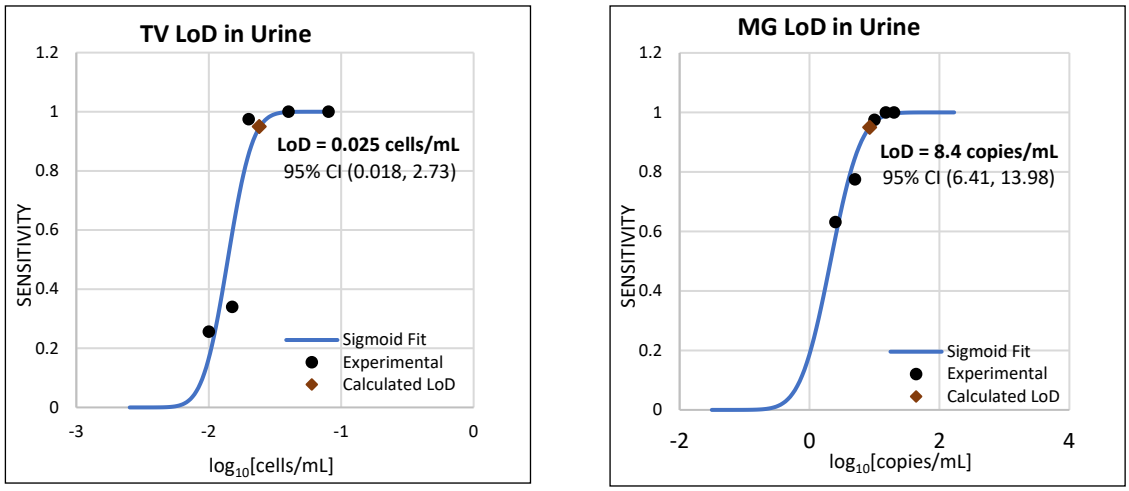

Figure 1. Probit analysis determination of NeuMoDx TV/MG Assay Limit of Detection.

Analytical Sensitivity – Vaginal Swab

The LoD of the NeuMoDx TV/MG Assay was determined in prospectively collected negative vaginal swab specimens spiked with *Trichomonas vaginalis* strain G3 (ATCC PRA-98) or *Mycoplasma genitalium* strain G37 (ATCC 33530) indicated in *Tables 6A* and *6B*. The tests were conducted with 40 replicates at each level, for which detection rates are reported below. A combination of hit-rate and probit analysis was used to determine the limit of detection of the NeuMoDx TV/MG Assay with vaginal swab specimens – **0.04 cells/mL TV and 14.8 copies/mL MG.**

Table 6A. Positive Detection Rates of TV in Vaginal Swabs – NeuMoDx TV/MG Assay Limit of Detection Study.

TV (cells/mL)	n	# POS	% POS	LoD
0.3	38	38	100	**0.04 cells/mL**
0.15	39	39	100	
0.075	40	40	100	
0.04	39	39	100	
0	39	0	0	

Table 6B. Positive Detection Rates of MG in Vaginal Swabs – NeuMoDx TV/MG Assay Limit of Detection Study.

MG (copies/mL)	n	# POS	% POS	LoD (Probit)
80	40	40	100	**14.8 cp/mL**
40	38	38	100	
20	40	39	97.5	
10	40	35	87.5	
5	39	24	61.5	
0	39	0	0	

Analytical Sensitivity – Endocervical Swab

The LoD of the NeuMoDx TV/MG Assay was determined in prospectively collected negative endocervical swab specimens spiked with *Trichomonas vaginalis* strain G3 (ATCC PRA-98) or *Mycoplasma genitalium* strain G37 (ATCC 33530) indicated in *Tables 7A* and *7B*. The tests were conducted with 40 replicates at each level, for which detection rates are reported below. A combination of hit-rate and probit analysis was used to determine the limit of detection of the NeuMoDx TV/MG Assay with endocervical swab specimens – **0.15 cells/mL TV and 17.2 copies/mL MG**.

Table 7A. Positive Detection Rates of TV in Endocervical Swabs – NeuMoDx TV/MG Assay Limit of Detection Study.

TV (cells/mL)	n	# POS	% POS	LoD
0.15	40	40	100	**0.15 cells/mL**
0.075	38	21	55.3	
0.004	39	12	30.8	
0	40	0	0	

Table 7B. Positive Detection Rates of MG in Endocervical Swabs – NeuMoDx TV/MG Assay Limit of Detection Study.

MG (copies/mL)	n	# POS	% POS	LoD (Probit)
80	38	38	100	**17.2 cp/mL**
40	40	40	100	
20	40	39	97.5	
10	40	32	80	
5	40	26	65	
0	40	0	0	

Detection of Variants

The analytical sensitivity of the NeuMoDx TV/MG Assay was further confirmed with five additional TV strains and three MG strains, listed below in *Table 8*. Targets at the specified levels were spiked into negative urine specimens prior to testing at ~1-2x the relevant LoD as listed above to confirm ≥ 95% detection. Variant strains that did not meet this requirement were retested at higher concentrations until ≥ 95% detection was achieved. The level at which this was achieved for each strain is reported in *Table 8* as the LoD for that variant.

Table 8. Variant TV and MG Strains Tested

	Strain	n	Concentration (cells/mL)	POS	NEG	Detection Rate (%)
T. vaginalis	87464 (ATCC 30094)	20	0.04	20	0	100
	RU 393 (ATCC 393)	20	0.04	20	0	100
	JH 31A #4 (ATCC 30236)	20	0.04	20	0	100
	JH 32A #4 (ATCC 30238)*	20	0.04	19	1	95
	CDC 085 (ATCC 50143)*	20	0.12**	17	3	85
M. genitalium	M30 (ATCC 48985)	19	0.10***	19	0	100
	R32G (ATCC 48987)	19	2×10^{-4}	19	0	100
	TW 10-5G (ATCC 49123)	19	5×10^{-3}	19	0	100

* *Metronidazole resistant strain*

** *Titration of T. vaginalis strain CDC 085 was halted before ≥ 95% detection was observed; the concentration reported above is not a limit of detection claim for this strain.*

*** *Quantified in CCU/mL*

Analytical Specificity – Cross-Reactivity in the Presence of Microorganisms

A total of 84 culture isolates or DNA from microorganisms potentially cohabiting with or phylogenetically similar to TV or MG were evaluated for possible cross-reactivity when testing with the NeuMoDx TV/MG Assay. Organisms were prepared in pools of 5-6 organisms each and tested at a high concentration. Bacterial and fungal organisms were spiked into pooled TV/MG negative urine at 6.7 x 10^4 – 9 x 10^9 CFU/mL and viral agents at 10^6 copies DNA/mL, except where otherwise noted. No cross reactivity was observed with any of the microorganisms tested in this study. The list of organisms tested is shown in *Table 9*.

Table 9. List of Pathogens Used to Demonstrate Analytical Specificity

Bacteria	Bacteria	Bacteria
Achromobacter xerosis	*Kingella denitrificans*	*Pseudomonas aeruginosa*
Acinetobacter lwoffii	*Klebsiella oxytoca*	*Rahnella aquatilis*
Aerococcus viridans	*Klebsiella pneumoniae*	*Rhizobium radiobacter*
Aeromonas hydrophila	*Lactobacillus crispatus*	*Rhodospirillum rubrum*
Alcaligenes faecalis	*Lactobacillus jensenii*	*Salmonella enterica*
Atopobium vaginae	*Lactobacillus vaginalis*	*Serratia marcescens*
Bacillus subtilis	*Legionella pneumophila*	*Staphulococcus aureus*
Bacteroides ureolyticus	*Listeria monocytogenes*	*Staphylococcus epidermidis*
Bacteroides fragilis	*Micrococcus luteus*	*Steptococcus pneumoniae*
Brevibacterium linens	*Mobiluncus curtisii*	*Steptococcus pyogenes*
*Chlamydia trachomatis**	*Moraxella catarrhalis*	*Streptococcus agalactiae*
Chromobacterium violaceum	*Moraxella lacunata*	*Trichomonas tenax****
Citrobacter freundii	*Moraxella olsoensis*	*Ureaplasma urealyticum***
Corynebacterium genitalium	*Morganella morganii*	*Veillonela parvula*
Corynebacterium urealyticum	*Mycoplasma faucium*	*Vibrio parahaemolyticus*
Corynebacterium xerosis	*Mycoplasma fermentans*	*Yersinia enterocolitica*
Crytococcus neoformans	*Mycoplasma hominis*	**Fungi**
Deinococcus radiodurans	*Mycoplasma orale*	*Candida albicans*
Eikenella corrodens	*Mycoplasma penetrans***	*Candida glabrata*
Enterobacter aerogenes	*Mycoplasma pirum****	*Candida parapsilosis*
Enterobacter cloacae	*Mycoplasma pneumoniae*	*Candida tropicalis*
Enterococcus avium	*Mycoplasma primatum*	*Saccharomyces cerevisiae*
Enterococcus faecalis	*Mycoplasma salivarium****	**Viruses**
Enterococcus faecium	*Neisseria gonorrhoeae*	Cytomegalovirus
Escherichia coli	*Peptostreptococcus anaerobius*	HIV-1†
Fusobacterium nucleatum	*Prevotella bivia*	HPV-16
Gardnerella vaginalis	*Propionibacterium acnes*	HSV-1
Gemella haemolysans	*Proteus mirabilis*	HSV-2
Haemophilus ducreyi	*Providencia stuartii*	

Unless noted below, bacteria and fungi are quantified in CFU/mL and viruses are quantified in copies/mL

* *quantified in EB/mL*

** *quantified in CCU/mL*

*** *quantified in cells/mL*

† *quantified in IU/mL*

Interference – Microorganisms

The NeuMoDx TV/MG Assay was tested for interference in the presence of non-target organisms (co-habiting the urogenital tract) by evaluating the performance of the NeuMoDx TV/MG Assay at low levels of TV and MG on the NeuMoDx Molecular System. The same panel of 84 organisms [*Table 9*] used for assessing cross-reactivity was used for this study. The organisms were pooled into groups of 4-6 in pooled TV/MG negative urine and spiked with TV (0.125 cells/mL) and MG (45 copies/mL) targets. No interference was observed with any of the commensal organisms.

Interference – Endogenous and Exogenous Substances Encountered in Clinical Urine Specimens

Performance of the NeuMoDx TV/MG Assay was assessed in the presence of potentially interfering substances that may be associated with collection of urine samples from a patient *[Table 10]*. Pooled negative urine spiked with TV (0.125 cells/mL) and MG (42.5 copies/mL) were dosed with endogenous and exogenous moieties at the specified concentrations and processed. No interference was observed with any of the substances at the levels listed in *Table 10*, below.

Table 10. Exogenous and Endogenous Interfering Agents Tested – Urine Specimens

	Substance	Concentration
Endogenous	Acidic Urine	pH 4
	Alkaline Urine	pH 9
	Bovine Serum Albumin	10 mg/mL
	Seminal Fluid	5.0% (v/v)
	Urine Metabolites	Elevated Levels*
Exogenous	Acetaminophen	3.2 mg/mL
	Azithromycin	1.8 mg/mL
	AZO Urinary Pain Relief® (phenazopyridine)	0.1 mg/mL
	Doxycycline	3.6 mg/mL
	Metronidazole Vaginal Gel	0.2 mg/mL
	Norforms® Deodorant Suppositories	0.25% (w/v)
	Progesterone	4 mg/mL**
	Talcum Powder	0.10% (w/v)
	Vagisil® Deodorant Powder	0.25% (w/v)

* The effect of elevated urine metabolite levels was evaluated by substituting urine with KOVA-Trol® I High Abnormal Urine Control with Urobilinogen (KOVA International 87533).
** Level of progesterone reported as result of dose response study from 8 mg/mL

Interference – Endogenous and Exogenous Substances Encountered in Clinical Swab Specimens
Performance of the NeuMoDx TV/MG Assay was assessed in the presence of potentially interfering substances that may be associated with collection of swab specimens from a patient *[Table 11]*. Pooled negative self-collected vaginal swabs spiked with TV (0.40 cells/mL) and MG (150 copies/mL) were dosed with endogenous and exogenous moieties at the specified concentrations and processed. No interference was observed with any of the substances at the levels listed in *Table 11*, below.

Table 11. Exogenous and Endogenous Interfering Agents Tested – Swab Specimens

	Substance	Concentration
Endogenous	Blood	7% (v/v)
	Mucin	71 mg/mL
	Peripheral Blood Mononuclear Cells	10^5 cells/mL
Exogenous	Abreva® Cream	43.8 mg/mL
	Clotrimazole Vaginal Cream	76.6 mg/mL
	K-Y® Jelly Personal Lubricant	167.7 mg/mL
	Metronidazole Vaginal Cream	122.2 mg/mL
	Miconazole-3	60 mg/mL
	Monistat® 1	80.4 mg/mL
	Preparation H® Hemorrhoidal Cream	65 mg/mL
	Progesterone	10 mg/mL
	Replens™ Moisturizer	9.45 mg/mL
	Seminal Fluid	71.2 mg/mL
	Summer's Eve® Medicated Douche	69.5 mg/mL
	Vagisil Anti-Itch Cream	5.3 mg/mL
	Vagisil Moisturizer	7.9 mg/mL
	VCF® Vaginal Contraceptive Foam	47.2 mg/mL
	Yeast Gard Advanced™ Douche	68.9 mg/mL

Lot-to-Lot Reproducibility

Lot-to-lot reproducibility of the NeuMoDx TV/MG Assay was verified by retrospective analysis of quality test data for three separate lots of the NeuMoDx TV/MG Test Strip. These data were generated through functional testing of the reagents on KOVA-Trol urine control spiked with representative strains of TV (0.1 cells/mL) and MG (40 copies/mL). A total of 32 positive and 8 negative replicates were processed per lot of NeuMoDx TV/MG Test Strip. The variation across production lots was analyzed by determining average C_t value, standard deviation and coefficient of variation percentage (%CV) shown in *Table 12*. Standard deviation values of ≤ 1 and coefficient of variation values ≤ 2.5 % for both TV and MG targets demonstrate the excellent reproducibility of NeuMoDx TV/MG Test Strip lots.

Table 12. %CV Analysis by Targets Across NeuMoDx TV/MG Test Strip Lots

	TV			MG			All Results		
	$\bar{C}_t$	C_t SD	%CV	$\bar{C}_t$	C_t SD	%CV	$\bar{C}_t$	C_t SD	%CV
TV/MG Test Strip (across 3 lots)	32.99	0.67	2.0%	35.36	0.82	2.3%	32.09	0.45	1.4%

Effectiveness of Control

The efficacy of the Sample Process Control included in the NeuMoDx TV/MG Test Strip to report any process step failures or inhibition affecting NeuMoDx TV/MG Assay performance was assessed on the NeuMoDx Molecular System using the NeuMoDx CT/NG Assay as a model. The conditions tested are representative of critical process step failures that could potentially occur during sample processing and *may not be detected* by the onboard sensors that monitor the performance of the NeuMoDx System. Effectiveness of control was evaluated by simulating failure of various sample process flow steps to mimic a potential system error and by spiking specimen with a known inhibitor to observe the effect of inefficient inhibitor mitigation on detection of the Sample Process Control (see *Table 13*). In instances where the processing errors did not adversely impact the performance of the Sample Process Control (NO WASH/NO WASH BLOWOUT), the test was repeated with specimens containing low levels of CT and NG (near LoD) to confirm the process error also had no adverse effect on the detection of CT or NG target as well. *Table 13* summarizes the results of the efficacy of control verification test.

Table 13. Effectiveness of Control Data Summary

Condition	Expected Result	Observed Result
Normal Processing	Negative	Negative
Normal Processing + Inhibitor	Unresolved	Unresolved
No Wash Reagent	Unresolved or Negative	Negative
No Wash Blowout	Unresolved or Negative	Negative
No Release Reagent	Indeterminate	Indeterminate
No PCR Master Mix Reagents	Indeterminate	Indeterminate

Cross-Contamination

The cross-contamination rate for the NeuMoDx TV/MG Assay was determined by testing four (4) runs of alternating high positive and negative TV and MG samples in UVT. Negative replicates were processed in a checkerboard configuration with high positive TV (10^5 cells/mL) and MG (10^6 CFU/mL) replicates, immediately after which four (4) additional runs of all negative replicates were processed and evaluated for evidence of cross-contamination. All replicates of the negative samples were reported negative, demonstrating the occurrence of no cross-contamination throughout sample processing on the NeuMoDx System.

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SYMBOL	MEANING
℞ only	**Prescription use only**
	**Manufacturer**
IVD	***In vitro* diagnostic medical device**
EC REP	**Authorized representative in the European Community**
REF	**Catalog number**
LOT	**Batch code**
	**Use-by date**
	**Temperature limit**
	**Humidity limitation**
	**Do not re-use**
	**Contains sufficient for <*n*> tests**
	**Consult instructions for use**
	**Caution**
	**Biological risks**
CE	**CE Mark**

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