July 2025

QIAstat-Dx®
Meningitis/Encephalitis (ME) Panel
Summary of Safety and Performance

Σ 6

Version 1

IVD

For In vitro Diagnostic Use

For use with QIAstat-Dx Analyzer 1.0 and QIAstat-Dx Analyzer 2.0

CE 0197

REF 691612

QIAGEN, GmbH, QIAGEN Strasse 1, 40724 Hilden, GERMANY

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Sample to Insight

Summary of Safety and Performance

This Summary of Safety and Performance (SSP) is intended to provide public access to an up-to-date summary of the main aspects of the safety and performance of the device.

The SSP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users.

The following information is intended for professional users.

Document revision: 01
Date issued: July 2025
Manufacturer's reference number for the SSP: HB-3697-SPR

1. Device identification and general information	
1.1 Device trade name(s)	QIAstat-Dx Meningitis/Encephalitis (ME) Panel
1.2 Manufacturer's name and address	QIAGEN GmbH, QIAGEN Strasse 1, 40724 Hilden, Germany
1.3 Manufacturer's single registration number (SRN)	DE-MF-000004949
1. 4 Basic UDI-DI	4053228RMEQSTA000000001ML
1.5 European Medical Device Nomenclature (EMDN) description / text	W0105070505 Meningitis / Encephalitis Infections - Multiplex NA Reagents
1.6 Risk Class of the device	Class C
1.7 Year when the first certificate was issued under Regulation (EU) 2017/746 covering the device	2025
1.8 Authorised representative if applicable; name and the SRN	Not Applicable
1.9 Notified body and the single identification number (SIN)	TÜV Rheinland LGA Products GmbH, Tillystrase 2 90431 Nürnberg, GERMANY 0197
2. Intended purpose and other indications	
2.1 Intended purpose	The QIAstat-Dx Meningitis/Encephalitis (ME) Panel is a qualitative multiplexed nucleic acid real-time PCR-based in vitro diagnostic test intended for use with the QIAstat-Dx Analyzer 1.0 and QIAstat-Dx Analyzer 2.0. The QIAstat-Dx ME Panel is capable of simultaneous detection and identification of multiple bacterial, viral, and yeast nucleic acids from cerebrospinal fluid (CSF) specimens obtained via

	lumbar puncture from individuals with signs and/or symptoms of meningitis and/or encephalitis. The following organisms are identified and differentiated* using the QIAstat-Dx ME Panel: *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis* (encapsulated), *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pyogenes*, Cytomegalovirus, Herpes simplex virus 1, Herpes simplex virus 2, Human herpesvirus 6, Enterovirus, Human parechovirus, Varicella zoster virus and *Cryptococcus neoformans/gattii**. The QIAstat-Dx ME Panel is indicated as an aid in the diagnosis of specific agents of meningitis and/or encephalitis and results must be used in conjunction with other clinical, epidemiological, and laboratory data. Results from the QIAstat-Dx ME Panel are not intended to be used as the sole basis for diagnosis, treatment, or other patient management decisions. Positive results do not rule out co-infection with organisms not included in the QIAstat-Dx ME Panel. Not all agents of CNS infection are detected by this test. The agent or agents detected may not be the definite cause of the disease. Negative results do not preclude central nervous system (CNS) infection. The QIAstat-Dx ME Panel is not intended for testing of specimens collected from indwelling CNS medical devices. The QIAstat-Dx ME Panel is intended to be used in conjunction with standard of care (e.g. culture for organism recovery, serotyping, and antimicrobial susceptibility testing). The QIAstat-Dx ME Panel is intended for in vitro diagnostic use by laboratory professionals only. **Cryptococcus neoformans* and *Cryptococcus gattii* are not differentiated.
2.2 Indication(s) and target population(s)	The QIAstat-Dx Meningitis/Encephalitis (ME) Panel is a real-time PCR test to detect multiple bacterial, viral, and yeast nucleic acids

	from cerebrospinal fluid (CSF) specimens obtained via lumbar puncture from individuals with signs and/or symptoms of meningitis and/or encephalitis. The QIAstat-Dx Meningitis/Encephalitis (ME) Panel is for in vitro diagnostic use.
2.3 Indication whether it is a device for near-patient testing and/or a companion diagnostic	The device is not for near patient testing. The device is not a companion diagnostic.
2.4 Limitations and/or contra-indications	• Results from the QIAstat-Dx ME Panel are not intended to be used as the sole basis for diagnosis, treatment, or other patient management decisions. • Positive results do not rule out co-infection with organisms not included in the QIAstat-Dx ME Panel. The agent or agents detected may not be the definite cause of the disease. • Not all agents of CNS infection are detected by this test, and sensitivity in clinical use may differ from that described in the package insert. • The QIAstat-Dx ME Panel is not intended for testing of specimens collected from indwelling CNS medical devices. • A negative result with the QIAstat-Dx ME Panel does not exclude the infectious nature of the syndrome. Negative assay results may originate from several factors and their combinations, including sample handling mistakes, variation in the nucleic acid sequences targeted by the assay, infection by organisms not included in the assay, organism levels of included organisms that are below the limit of detection for the assay and use of certain medications, therapies, or agents. • The QIAstat-Dx ME Panel is not intended for testing of samples other than those described in this Instructions for Use. Test performance characteristics have been established only with CSF. • The QIAstat-Dx ME Panel is intended to be used in conjunction with standard of care (e.g., culture for organism recovery,

	serotyping, and antimicrobial susceptibility testing). The results from the QIAstat- Dx ME Panel must be interpreted by a trained healthcare professional within the context of all relevant clinical, laboratory, and epidemiological findings. • The QIAstat-Dx ME Panel can be used only with the QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0.* * DiagCORE Analyzer instruments running QIAstat-Dx software version 1.4 or 1.5 can be used as an alternative to the QIAstat-Dx Analyzer 1.0. • The QIAstat-Dx ME Panel is a qualitative assay and does not provide a quantitative value for detected organisms. • Bacterial, viral, and fungal nucleic acids may persist *in vivo*, even if the organism is not viable or infectious. Detection of a target marker does not imply that the corresponding organism is the causative agent of the infection or the clinical symptoms. • Detection of bacterial, viral, and fungal nucleic acids depends on proper sample collection, handling, transportation, storage, and loading into the QIAstat-Dx ME Panel Cartridge. Improper operations for any of the aforementioned processes can cause incorrect results, including false-positive or false-negative results. • The assay sensitivity and specificity for the specific organisms and for all organisms combined are intrinsic performance parameters of a given assay and do not vary depending on prevalence. In contrast, both the negative and positive predictive values of a test result are dependent on the disease/organism prevalence. Please note that a higher prevalence favors the positive predictive value of a test result, while a lower prevalence favors the negative predictive value of a test result. • Accidental contamination of the CSF sample with *Propionibacterium acnes* – a common commensal skin flora organism- can generate an unexpected signal (low positive) for *Mycoplasma pneumoniae* target in the QIAstat-Dx ME Panel. Standard CSF sample handling should prevent this potential contamination.

	• Results obtained during co-infection study in the analytical verification show a potential inhibition of HSV1 detection when *S. pneumoniae* is present in the same sample. As this effect was observed even with low concentrations of *S. pneumoniae*, negative results for HSV1 in *S. pneumoniae*-positive samples should be interpreted with caution. The opposite effect (inhibition of *S. pneumoniae* when HSV1 is present in the same sample) was not observed at the highest tested concentration of HSV1 (1.00E+05 $TCID_{50}$/mL). • Due to the sensitive nature of the pathogen detection by the QIAstat-Dx ME Panel and to prevent contamination of the specimen it is key to follow standard microbiological laboratory practices. Clinical laboratory personnel could be the source of pathogens (e.g. S. *pneumoniae*, *H. influenzae*, etc.) that are detectable by the QIAstat-Dx ME Panel. • Contamination of the specimen could happen while the specimen is being collected, transported, or tested. Adherence to best practice sample handling and testing procedures is recommended to minimize the risk of contamination that could lead to false positive results. Additional precautions may include extra PPE, such as a face mask, especially when experiencing signs or symptoms of a respiratory infection. • Only *E. coli* strains possessing the K1 capsular antigen will be detected. All other *E. coli* strains/serotypes will not be detected. • Only encapsulated strains of *N. meningitidis* will be detected. Unencapsulated *N. meningitidis* will not be detected.
3. Device description	
3.1 Description of the device, including the conditions to use the device	**a) General description of the device, including its intended purpose and intended users** The QIAstat-Dx ME Panel Cartridge is a disposable plastic device that allows performance of fully automated molecular assays for the detection and identification of nucleic acids from multiple agents, directly from CSF samples. The main features of the QIAstat-Dx ME Panel Cartridge include compatibility with a liquid sample type,

	hermetical containment of the pre-loaded reagents necessary for testing, and true walk-away operation. All sample preparation and assay testing steps are performed within the cartridge. All reagents required for the complete execution of a test run are pre-loaded and self-contained in the QIAstat-Dx ME Panel Cartridge. The user does not need to come in contact with and/or manipulate any reagents. During the test, reagents are handled within the cartridge in the Analytical Module of the QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0 by pneumatically operated microfluidics and make no direct contact with the actuators. The QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0 houses air filters for both incoming and outgoing air, further safeguarding the environment. After testing, the cartridge stays hermetically closed at all times, greatly enhancing its safe disposal. Within the cartridge, multiple steps are automatically performed in sequence using pneumatic pressure to transfer samples and fluids via the transfer chamber to their intended destinations. The QIAstat-Dx ME Panel is for use with CSF. All samples should be treated as potentially hazardous. The CSF specimen should be collected via lumbar puncture and should not be centrifuged or diluted CSF specimens should be collected and handled according to the recommended procedures. The QIAstat-Dx ME Panel is intended for in vitro diagnostic use by laboratory professionals only. **b) Description of the principle of the assay method or principles of operation of the instrument** After the QIAstat-Dx ME Panel Cartridge containing the sample is introduced into the QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0, the following assay steps occur automatically: • Resuspension of Internal Control; • Cell lysis using mechanical and chemical means; • Membrane-based nucleic acid purification;

	• Mixing of the purified nucleic acid with lyophilized master mix reagents; • Transfer of defined aliquots of eluate/master mix to different reaction chambers; • Performance of multiplex real-time RT-PCR testing within each reaction chamber. **Note:** An increase in fluorescence, indicating detection of the target analyte, is detected directly within each reaction chamber.
3.2 In case the device is a kit, description of the components (including regulatory status of components, for example, IVDs, medical devices and any Basic UDI-DIs)	The kit contents are: • 6 individually packaged cartridges containing all reagents needed for sample preparation and multiplex real-time RT-PCR, plus Internal Control • 6 individually packaged transfer pipettes for dispensing liquid sample into the QIAstat-Dx ME Panel Cartridge The kit contents are not sold separately. The QIAstat-Dx ME Panel meets the definition of an in vitro diagnostic device (IVDR Article 2(2)) since it is intended for the detection and identification of pathogens associated with Meningitis/Encephalitis illness and therefore provides information on the physiological state. Risk Class C (Annex VIII Rule 3 (c))
3.3 A reference to previous generation(s) or variants if such exists, and a description of the differences	The difference between the subject device, QIAstat-Dx ME Panel (IVDR) and the previous version: QIAstat-Dx ME Panel (IVDD), are listed in the table below.

	QIAstat-Dx ME Panel (IVDR) (Cat. No. 691612)	QIAstat-Dx ME Panel (IVDD) (Cat. No. 691611)
Specimen Storage and handling	If immediate testing is not possible, recommended storage condition for CSF are: •Room temperature (15–25°C) up to 24 hours •Refrigerated (2–8°C) up to 7 days	Recommended storage condition for CSF is room temperature (15–25°C) up to 12 hours.
Target differentiation	The panel detects and reports Cytomegalovirus (CMV).	The panel does not report Cytomegalovirus (CMV).
Inclusivity	The inclusivity of some targets were upgraded to cover a wider range of genetic variability. All strains tested were detected.	The inclusivity of some targets was limited due to the smaller number of strains covered. Five strains are reported as not detected.

3.4 Description of accessories intended to be used in combination with the device	Not applicable.
3.5 Description of any other devices and products which are intended to be used in combination with the device	The QIAstat-Dx ME Panel is designed for use with the QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0. Please note that the QIAGEN kit Instructions for Use and the Assay Definition File (ADF) for the QIAstat-Dx ME Panel are available at **www.qiagen.com**.
4. Reference to any harmonised standards and CS applied	
4 Harmonised standards and Common Specifications (CS) applied	Harmonized Standards: • EN ISO 13485:2016+AC:2018+A11:2021 – Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2016) • EN ISO 14971:2019+A11:2021 – Medical devices – Application of risk management to medical devices • EN ISO 15223-1:2021 – Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements • EN ISO 20916:2024 – *In vitro* diagnostic medical devices - Clinical performance studies using specimens from human subjects - Good study practice (ISO 20916:2019) There are no common specifications established by the European Commission applicable to QIAstat-Dx Meningitis/Encephalitis (ME) Panel.
5. Risks and warnings	
5.1 Residual risks and undesirable effects	Risks have been mitigated as far as possible and deemed as acceptable, the use of the device is judged safe. There are no undesirable effects.
5.2 Warnings and precautions	Please be aware that you may be required to consult your local regulations for reporting serious incidents that have occurred in

	relation to the device to the manufacturer and the regulatory authority in which the user and/or the patient is established. • The QIAstat-Dx ME Panel is for in vitro diagnostic use. • The QIAstat-Dx ME Panel is to be used by laboratory professionals trained in the use of QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0. **Safety information** • When working with chemicals, always wear a suitable lab coat, disposable gloves, and protective goggles. For more information, please consult the appropriate safety data sheets (SDSs). These are available online in convenient and compact PDF format at **www.qiagen.com/safety** where you can find, view, and print the SDS for each QIAGEN kit and kit component. • Observe standard laboratory procedures for keeping the working area clean and contamination-free. Guidelines are outlined in publications such as the *Biosafety in Microbiological and Biomedical Laboratories* from the European Center for Disease Control and Prevention.(**www.ecdc.europa.eu/en/about-us/networks/disease-andlaboratory-networks/erlinet-biosafety**). • Specimens and samples are potentially infectious. Follow your institution's safety procedures for handling biological samples. Discard sample and assay waste according to your local safety procedures. • Always wear appropriate personal protective equipment and follow your institution's safety procedures for handling biological samples. Handle all samples, cartridges, and transfer pipettes as if they are capable of transmitting infectious agents.

	• Handle all samples, cartridges, and transfer pipettes as if they are capable of transmitting infectious agents. Always observe safety precautions as outlined in relevant guidelines, such as the Clinical and Laboratory Standards Institute® (CLSI) *Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline* (M29), or other appropriate documents provided by local authorities. • The QIAstat-Dx ME Panel Cartridge is a closed, single-use device that contains all reagents needed for sample preparation and multiplex real-time RT-PCR within the QIAstat-Dx Analyzer 1.0 and the QIAstat-Dx Analyzer 2.0. Do not use a QIAstat-Dx ME Panel Cartridge that is past its expiration date, appears damaged, or leaks fluid. • Dispose of samples, used or damaged cartridges, and transfer pipettes in accordance with all national, state and local health and safety regulations and laws. **Emergency information** CHEMTREC Outside USA & Canada +1 703-527-3887 The following hazard and precautionary statements apply to components of the QIAstat-Dx ME Panel.  Contains: ethanol; guanidine hydrochloride; guanidine thiocyanate; isopropanol; proteinase K; t-Octylphenoxypolyethoxyethanol. Danger! Highly flammable liquid and vapor. Harmful if swallowed or if inhaled. May be harmful in contact with skin. Causes severe skin burns and eye damage. May

	cause allergy or asthma symptoms or breathing difficulties if inhaled. May cause drowsiness or dizziness. Harmful to aquatic life with long lasting effects. Contact with acids liberates very toxic gas. Corrosive to the respiratory tract. Keep away from heat/sparks/open flames/hot surfaces. No smoking. Avoid breathing dust/fume/gas/mist/vapors/spray. Wear protective gloves/protective clothing/eye protection/face protection. Wear respiratory protection. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. IF exposed or concerned: Immediately call a POISON CENTER or doctor. Rinse mouth. Do NOT induce vomiting. Remove person to fresh air and keep comfortable for breathing. Wash contaminated clothing before reuse. Store in a well-ventilated place. Keep container tightly closed. Dispose of contents/ container to an approved facility in accordance with local, regional, national and international regulations. **Laboratory precautions** To guard against possible contamination of the specimen and work area standard laboratory safety and cleaning procedures should be used, including the following precautions: • Samples should be processed in a biosafety cabinet or a similar clean surface ensuring the user's protection. If a biosafety cabinet is not used, a dead air box (e.g., AirClean PCR workstation), a splash shield (e.g., Bel-Art Scienceware Splash Shields), or a face shield should be used when preparing samples. • A biosafety cabinet that is used for performing pathogen testing (e.g. culture) should not be used for sample preparation or cartridge loading. • Prior to processing samples, thoroughly clean the work area using a suitable cleaner such as freshly prepared 10% bleach or a similar disinfectant. To avoid residue buildup and potential damage to the specimen or interference from disinfectants, wipe disinfected surfaces with water. • Samples and cartridges should be handled one at a time.

	• Use clean gloves to remove materials from bulk packaging bags and reseal bulk packaging bags when not in use. • Change gloves and clean the work area between each sample. • Discard used cartridges in an appropriate biohazard container immediately after the run has been completed. • Avoid excessive handling of cartridges after test runs. • Avoid damaging the cartridge (refer to Safety Information for handling of damaged cartridges). • Use clean gloves to remove materials from bulk packaging boxes, and close bulk packaging when not in use. Due to sensitive nature of the pathogen detection by QIAstat-Dx Meningitis/Encephalitis Panel and to prevent contamination of the specimen, it is key to follow standard microbiological laboratory practices. Clinical laboratory personnel could be the source of pathogens (e.g. *S. pneumoniae*, *H. influenzae*, HSV-1, etc.) that are detectable by the QIAstat-Dx Meningitis/Encephalitis Panel. Contamination of the specimen could happen while the specimen is being collected, transported, or tested. Adherence to best practice sample handling and testing procedures is recommended to minimize the risk of contamination that could lead to false positive results. Additional precautions may include extra PPE, such as face mask, especially when experiencing signs or symptoms of a respiratory infection or an active herpes sore/fever blister. **Precautions Related to Public Health Reporting** State and local public health authorities have published guidelines for notification of reportable diseases in their jurisdictions (e.g., following the Official Journal of the European Union 6.7.2018 L 170/1, the list includes *Listeriosis* disease, as well as invasive disease caused by *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*) to determine necessary measures for verification of results to identify and trace outbreaks and for epidemiological investigations. Laboratories are responsible for following their state or local regulations for submission of clinical material or isolates on positive specimens to their state public health laboratories.

5.3 Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN), if applicable	Not applicable.
6. Summary of the performance evaluation and post-market performance follow-up (post)	
6.1 Summary of scientific validity of the device	Infections of the central nervous system (CNS), manifesting as meningitis or encephalitis, are critical medical conditions with potentially severe outcomes. Meningitis involves inflammation of the meninges surrounding the brain and spinal cord, while encephalitis is characterized by inflammation of the brain parenchyma, often accompanied by altered mental status and other neurological symptoms. Infectious meningitis carries high rates of mortality and long-term complications including neurologic deficits and cognitive impairment. Although parasitic and non-infectious meningitis can occur, the most common causes of meningitis are bacteria, viruses and fungi. *N. meningitidis*, *H. influenzae*, *S. pneumoniae* and *S. agalactiae* are the main bacterial etiologies overall. In neonates, *L. monocytogenes, S. agalactiae,* and *E. coli* are also frequently observed. Viral meningitis has a clinical presentation similar to bacterial meningitis with common symptoms of fever, stiff neck, headache, photophobia, and altered mental status. However, viral meningitis has significantly less mortality compared with other types of meningitis, without sequelae in immunocompetent patients, and treatment is limited to supportive measures in most cases. The most common causes of viral meningitis are enteroviruses, HSV-1, HSV-2, and VZV, although other viral origins of meningitis may include mumps virus, West Nile virus, CMV and HIV. The dominant underlying cause of fungal meningitis is *Cryptococcus*, followed by *Coccidioides*, *Histoplasma,* and *Candida*. *C. neoformans*. CNS infections mostly affect immunocompromised individuals whereas *C. gattii* infection also occurs in apparently immunocompetent individuals. Meningitis can be classified as acute (< 5 days), subacute (5-30 days) or chronic (> 30 days). Bacterial meningitis

	often has an acute presentation with rapid symptom onset, in which case urgent medical care is essential. Subacute or chronic meningitis is typically due to viruses, fungi, or mycobacteria. Regarding encephalitis, viruses represent the most common cause, although the condition may also be associated with bacterial or fungal meningitis with secondary encephalitic features or with non-infectious causes (e.g., autoimmune disease, encephalitis of unknown origin). Of the more than 40 viruses associated with encephalitis, HSV (HSV-1 and HSV-2), VZV, enterovirus, and tick-borne encephalitis are the most common causes. Other herpesviruses that may be responsible for encephalitis include HHV-6, CMV, EBV and, rarely, HHV-7 or HHV-8. Uncommon pathogens resulting in encephalitis include certain fungi (e.g., *C. neoformans*, *Candida* spp.) and parasites (e.g., *Plasmodium* spp.). Because of the high mortality of certain types of meningitis and encephalitis, it is important to initiate treatment and go through the diagnostic steps simultaneously. Distinguishing between bacterial, viral or other causes is important, to ensure the necessary treatment adjustments are made and to prevent unnecessary antibiotics use. A clinician's diagnosis must be informed by historical information (e.g., duration of symptoms, travel and country of origin) as well as an understanding of the appropriate diagnostic testing based on the probable underlying cause. CSF sampling via lumbar puncture plays a central role in the diagnosis of meningitis and can be used to assess physical, cytologic, biochemical, microbiologic, and immunologic parameters. Basic CSF characteristics such as appearance, opening pressure, white blood cell count, and protein and glucose levels are informative on whether the patient's meningitis has a bacterial, viral or fungal origin. A more precise etiology can be determined with a CSF culture, by Gram staining (for bacteria), antigen testing or with molecular tools as well as more specific tests (e.g., India ink stain, burgdorferi antibody testing). Molecular tools that target genetic material from pathogens, such as the PCR, have been shown to be fast, cheap, and efficient in identifying different causes of infectious meningitis, such as bacteria, viruses, or fungi. CSF PCR is the best choice for certain viruses such as HSV-2, enteroviruses, HPeV, VZV, and CMV, whereas CSF serology is the

	preferred option for others (e.g., West Nile virus, La Crosse encephalitis virus and mumps virus). Similar to meningitis, molecular evaluation of CSF samples is a central tool in etiological diagnosis of encephalitis. PCR analysis for the detection of HSV, VZV, and enterovirus is mandatory and additional virologic studies may be necessary, based on epidemic context, geographic region, season and patient characteristics (e.g., immunosuppression). In immunocompromised patients, only minimal CSF pleocytosis may be observed, making other diagnostic methods, including PCR, especially important. Syndromic testing (i.e., testing for multiple pathogens simultaneously) is enabled with the introduction of multiplex PCR panels, which have been commercialized and can detect common sources of CNS infections. The QIAstat-Dx ME Panel, the device associated with this report, is able to detect 16 pathogens: 7 viruses (CMV, HSV [HSV-1 and HSV-2], HHV-6, enterovirus, HPeV and VZV), 8 bacteria (*E. coli* K1, *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, *S. agalactiae*, *S. pneumoniae*, *M. pneumoniae*, *S. pyogenes*) and 1 fungus (*C. neoformans/gattii*). All have very well-established roles as causative agents of CNS infections and they represent some of the most prevalent causes of meningitis and encephalitis. In conclusion, infectious meningitis and encephalitis are serious conditions that often require identification of the underlying cause to ensure proper treatment is provided to the patient. The QIAstat-Dx ME Panel targets 16 pathogens that each are able to result in the development of meningitis or encephalitis.
6.2 Summary of performance data from the equivalent device, if applicable	Not Applicable
6.3 Summary of performance data from conducted studies of the device prior to CE-marking	See Appendix 01 (Analytical), Appendix 02 (Clinical) - extracted from the Instruction for Use
6.4 Summary of performance data from other sources, if applicable	Not Applicable

6.5 An overall summary of the performance and safety	The overall performance and safety of the QIAstat-Dx Meningitis/Encephalitis (ME) is based on: **Scientific Validity** Assessment of scientific validity based on a systematic literature review, assessment of available/retrieved/new data relevant to the QIAstat-Dx ME Panel and its intended purpose demonstrated the scientific validity of the QIAstat-Dx ME Panel for its Intended Use. **Analytical Performance** The assessment of these studies showed that the analytical performance of the QIAstat-Dx ME Panel is adequate for its Intended Use. **Clinical Performance** Clinical performance was demonstrated based on a study with clinical performance indicators [Positive Percent Agreement (PPA), Negative Percent Agreement (NPA)]. A literature evaluation was conducted to identify publications assessing clinical performance of the device which confirmed the acceptable performance of the QIAstat-Dx ME Panel for its Intended Use against the state of the art in medicine. The assessment of scientific validity, analytical performance, and clinical performance allows to constitute the clinical evidence for the QIAstat-Dx ME Panel. The benefit-risk assessment based on systematic literature and database review, risk assessment activities (medical risk assessment, product and manufacturing process risk assessment), vigilance activities conducted, and the experience gained from routine diagnostic testing supported a favorable benefit-risk ratio for the QIAstat-Dx ME Panel.
6.6 Ongoing or planned post-market	Based on the collected evidence it was concluded that the QIAstat-Dx Meningitis/Encephalitis (ME) Panel is safe and effective for its intended use and no unacceptable residual risks remain. However,

performance follow-up	an additional shelf life study will be performed to test the upper limit (25±2°C) of the intended room temperature storage claim (15–25°C) and to support the current shelf life claim of 9 months.
7. Metrological traceability of assigned values	
7.1 Explanation of the unit of measurement, if applicable	Not applicable.
7.2 Identification of applied reference materials and/or reference measurement procedures of higher order used by the manufacturer for the calibration of the device	Not applicable.
8. Suggested profile and training for users	
8.1 Suggested profile and training for users	The QIAstat-Dx Meningitis/Encephalitis (ME) Panel is a qualitative multiplexed nucleic acid real-time PCR–based in vitro diagnostic test intended for use with the QIAstat-Dx Analyzer 1.0 and QIAstat-Dx Analyzer 2.0. The QIAstat-Dx ME Panel is capable of simultaneous detection and identification of multiple bacterial, viral, and yeast nucleic acids from cerebrospinal fluid (CSF) specimens obtained via lumbar puncture from individuals with signs and/or symptoms of meningitis and/or encephalitis. The QIAstat-Dx ME Panel is intended for *in vitro* diagnostic use by laboratory professionals only.

Revision History

SSP Revision Number	Date issued	Change description	Revision validated by the Notified Body
01	July 2025	1st revision	□ Yes Validation Language: English ☑ No (only applicable for class C (IVDR, Article 48 (7)) for which the SSP is not yet validated by the NB)

Appendix

Appendix 1: Analytical performance

The analytical performance shown below was demonstrate using QIAstat-Dx Analyzer 1.0. The QIAstat-Dx Analyzer 2.0 uses the same Analytical Module as QIAstat-Dx Analyzer 1.0 therefore the performance is not impacted by QIAstat-Dx Analyzer 2.0.

Limit of detection

The Limit of Detection (LoD) is defined as the lowest concentration at which ≥95% of samples tested generate a positive call.

The LoD for each QIAstat-Dx ME Panel pathogen was assessed by analyzing dilutions of analytical samples prepared from stocks obtained from commercial suppliers (ZeptoMetrix® and ATCC®).

The LoD concentration was determined for a total of 40 pathogen strains. The LoD of the QIAstat-Dx ME Panel was determined per analyte using selected strains representing individual pathogens that are possible to detect with the QIAstat-Dx ME Panel. All sample dilutions were prepared using artificial CSF. To confirm the established LoD concentration, the required detection rate of all replicates was ≥95%. Additional testing of samples prepared using negative clinical CSF was conducted to assess equivalency.

At least 4 different cartridge lots and at least 3 different QIAstat-Dx Analyzers were used for LoD determination for every pathogen.

Individual LoD values for each QIAstat-Dx ME Panel target is shown in Table 1.

Table 1. Limit of Detection results

Pathogen	Strain	Supplier	LoD concentration*	Units	Detection rate
HSV1	HF	ATCC	2.81E+02	$TCID_{50}$/mL	30/30
HSV1	Macintyre	ZeptoMetrix	3.38E+02	$TCID_{50}$/mL	30/30
HSV2	G	ATCC	2.81E+01	$TCID_{50}$/mL	30/30
HSV2	HSV-2. (Strain: MS)	ZeptoMetrix	1.26E+01	$TCID_{50}$/mL	29/30
Escherichia coli K1	Strain C5 [Bort]; O18ac:K1:H7	ATCC	3.48E+02	CFU/mL	30/30
Escherichia coli K1	NCTC 9001. Serovar O1:K1:H7	ATCC	7.86E+02	CFU/mL	30/30
Haemophilus influenzae	type b (cap)	ATCC	3.16E+02	CFU/mL	32/32
Haemophilus influenzae	Type e [strain AMC 36-A-7]	ATCC	2.54E+03	CFU/mL	30/30
Listeria monocytogenes	Type 1/2b	ZeptoMetrix	1.86E+03	CFU/mL	30/30
Listeria monocytogenes	Type 4b. Strain Li 2	ATCC	2.10E+04**	CFU/mL	20/20
Neisseria meningitidis (encapsulated)	Serotype B. M2092	ATCC	8.28E-02	CFU/mL	31/32
Neisseria meningitidis (encapsulated)	Serotype Y. M-112 [BO-6]	ATCC	1.33E+01	CFU/mL	30/30
Streptococcus agalactiae	Z019	ZeptoMetrix	1.75E+03	CFU/mL	31/31
Streptococcus agalactiae	G19 group B	ATCC	3.38E+03	CFU/mL	29/30
Streptococcus pneumoniae	19F	ZeptoMetrix	7.14E+02	CFU/mL	29/30
Streptococcus pneumoniae	Serotype 1. NCTC 7465	ATCC	6.22E-01	CFU/mL	29/29
Streptococcus pyogenes	Z472; Serotype M1	ZeptoMetrix	1.80E+03	CFU/mL	30/30
Streptococcus pyogenes	Bruno [CIP 104226]	ATCC	9.10E+01	CFU/mL	31/31

Pathogen	Strain	Supplier	LoD concentration*	Units	Detection rate
Mycoplasma pneumoniae	PI 1428	ATCC	9.48E+01	CFU/mL	31/31
Mycoplasma pneumoniae	M129	ZeptoMetrix	9.99E+01	CCU/mL	30/30
Cytomegalovirus	AD-169	ZeptoMetrix	2.45E+00	$TCID_{50}$/mL	30/30
Cytomegalovirus	Davis	ATCC	1.00E+01	$TCID_{50}$/mL	30/30
Enterovirus A	Coxsackievirus A16	ZeptoMetrix	3.79E+00	$TCID_{50}$/mL	31/31
Enterovirus A	A6, species A. Strain Gdula	ATCC	1.60E+02	$TCID_{50}$/mL	31/31
Enterovirus B	Coxsackievirus B5	ZeptoMetrix	8.91E+01	$TCID_{50}$/mL	30/30
Enterovirus B	Coxsackievirus A9, species B	ZeptoMetrix	4.36E+01	$TCID_{50}$/mL	28/29
Enterovirus C	Coxsackievirus A17, species C. Strain G-12	ATCC	1.58E+01	$TCID_{50}$/mL	30/30
Enterovirus C	Coxsackievirus A24. Strain DN-19	ATCC	4.99E+00	$TCID_{50}$/mL	30/30
Enterovirus D	EV 70, species D, strain J670/71	ATCC	4.99E+01	$TCID_{50}$/mL	30/31
Enterovirus D	Enterovirus D68. Strain US/MO/14-18947	ATCC	5.06E+02	$TCID_{50}$/mL	30/30
HHV-6	HHV-6A. (Strain: GS) Lysate	ZeptoMetrix	3.13E+04	cp/mL	32/32
HHV-6	HHV-6B. (Strain: Z29)	ZeptoMetrix	7.29E+04	cp/mL	30/30
HPeV	Serotype 1. Strain Harris	ZeptoMetrix	1.07E+03	$TCID_{50}$/mL	31/31
HPeV	Serotype 3	ZeptoMetrix	3.38E+01	$TCID_{50}$/mL	30/30
VZV	Ellen	ZeptoMetrix	1.71E+03	cp/mL	30/30
VZV	Oka	ATCC	5.00E-02	$TCID_{50}$/mL	31/31
Cryptococcus neoformans	Serotype D strain WM629, type VNIV	ATCC	2.21E+03	CFU/mL	31/31

Pathogen	Strain	Supplier	LoD concentration*	Units	Detection rate
Cryptococcus neoformans	*C. neoformans* H99	ATCC	1.64E+02	CFU/mL	31/31
Cryptococcus gattii	Serotype B strain R272, type VGIIb	ATCC	1.32E+04	CFU/mL	30/30
Cryptococcus gattii	A6MR38 [CBS 11545]	ATCC	2.60E+03	CFU/mL	29/29

*The highest LoD is reported.
** Highest LoD was obtained in artificial CSF.

Inclusivity (analytical reactivity)

The Inclusivity (analytical reactivity) study extended the list of pathogen strains tested during the QIAstat-Dx ME Panel Limit of Detection (LoD) Study to confirm the reactivity of the detection system in the presence of different strains of the same organisms at a concentration near or above the respective Limit of Detection.

A variety of clinically relevant strains of each target organism of the QIAstat-Dx ME Panel (Inclusivity Strains) representing organism subtypes, strains, and serotypes of different temporal and geographic diversity of each analyte were included in the study. Analytical Reactivity (Inclusivity) was performed in two steps:

- In vitro testing: Analytical samples of every target included in the QIAstat-Dx ME Panel were tested to assess the reactivity of the assay. A collection of 187 samples representative of relevant strains, subtypes, serotypes, and genotypes for the different organisms (e.g. a range of different meningitis/encephalitis strains isolated from around the world and in different calendar years) were included in the study (Table 2). All inclusivity strains tested as part of the study were detected by the panel.

- In silico analysis: to make assay reactivity predictions of all primers-probe oligonucleotide sequences included in the panel against publicly available sequence

databases to detect any possible cross-reaction or unexpected detection of any primer set, in silico analysis was performed. In addition, strains not available for in vitro testing were included in in silico analysis to confirm the predicted inclusivity of the different strains of the same organisms (Table 3). In silico analysis confirmed inclusivity (no critical patterns causing a negative impact) for all the existing strains of the QIAstat-Dx ME Panel targets, including all relevant subtypes defined by on-panel organism.

Based on in vitro and in silico analysis, the QIAstat-Dx ME panel primers and probes are inclusive for clinically prevalent and relevant strains of each pathogen. All inclusivity strains tested as part of the study were detected by the panel. Inclusivity was confirmed by in silico analysis (no critical patterns causing a negative impact) for all the existing strains of the QIAstat-Dx ME Panel targets.

Table 2. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
***Escherichia coli* K1**	**Strain C5 [Bort]; O18ac:K1:H7**	**ATCC**	**700973**	**1x**
***Escherichia coli* K1**	**NCTC 9001. Serovar O1:K1:H7**	**ATCC**	**11775**	**1x**
Escherichia coli K1	Sc15 02:K1:H6	ATCC	11101	1x
Escherichia coli K1	O-16, F1119-41. Serotype O15:K1:H-	BEI Resources	NR-17674	0.3x
Escherichia coli K1	O-2, U9-41	BEI Resources	NR-17666	1x
Escherichia coli K1	Strain Bi 7509/41; O7:K1:H-	NCTC	9007	1x
Escherichia coli K1	Strain H61; O45:K1:H10	NCTC	9045	0.3x
Escherichia coli K1	0.1285; O18:H7:K1	ZeptoMetrix	0804140	1x
Escherichia coli K1	NCDC F 11119-41	ATCC	23511	3x
Escherichia coli K1	O7:K1:H-	CCUG	28	3x
Haemophilus influenzae	**Type e [strain AMC 36-A-7]**	**ATCC**	**8142**	**1x**

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Haemophilus influenzae	**type b (cap)**	**ATCC**	**10211**	**1x**
Haemophilus influenzae	L-378	ATCC	49766	0.1x
Haemophilus influenzae	Non-typeable [strain Rd [KW20]	ATCC	51907	0.3x
Haemophilus influenzae	Non-typeable [strain 180-a]	ATCC	11116	1x
Haemophilus influenzae	Type a [strain AMC 36-A-3]	ATCC	9006	0.1x
Haemophilus influenzae	Type d [strain AMC 36-A-6]	ATCC	9008	0.3x
Haemophilus influenzae	Type f [strain GA-1264]	ATCC	700223	1x
Haemophilus influenzae	Type c [strain C 9007]	ATCC	49699	0.1x
Haemophilus influenzae	Rab Strain	ATCC	31512	0.3x
Listeria monocytogenes	**Type 4b. Strain Li 2**	**ATCC**	**19115**	**1x**
Listeria monocytogenes	**Type ½b**	**ZeptoMetrix**	**0801534**	**1x**
Listeria monocytogenes	Type 4b	ZeptoMetrix	0804339	1x
Listeria monocytogenes	FSL J2-064	BEI Resources	NR-13237	1x
Listeria monocytogenes	Gibson	ATCC	7644	1x
Listeria monocytogenes	1071/53. Serotype 4b	ATCC	13932	3x
Listeria monocytogenes	Type 1/2a. Strain 2011L-2676	ATCC	BAA-2659	0.3x
Listeria monocytogenes	Serotype 4a	ZeptoMetrix	0801508	1x
Listeria monocytogenes	Serotype 1/2a	ATCC	19111	0.3x
Listeria monocytogenes	Li 23. Serotype 4a	ATCC	19114	1x
***Neisseria meningitidis* (encapsulated)**	**Serotype Y. M-112 [BO-6]**	**ATCC**	**35561**	**1x**

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Neisseria meningitidis (encapsulated)	**Serotype B. M2092**	**ATCC**	**13090**	**1x**
Neisseria meningitidis (encapsulated)	79 Eur. Serogroup B	ATCC	23255	0.3x
Neisseria meningitidis (encapsulated)	Serogroup C, M1628	ATCC	13102	0.3x
Neisseria meningitidis (encapsulated)	sequence with variant _ctrA_ gene	IDT	gBlock	0.1x
Neisseria meningitidis (encapsulated)	Serotype B. M997 [S-3250-L]	ATCC	13092	0.1x
Neisseria meningitidis (encapsulated)	Serotype D. M158 [37A]	ATCC	13113	1x
Neisseria meningitidis (encapsulated)	W135	ATCC	43744	0.1x
Neisseria meningitidis (encapsulated)	Serogroup A, M1027 [NCTC10025]	ATCC	13077	3x
Neisseria meningitidis (encapsulated)	MC58	ATCC	BAA-335	0.3x
Streptococcus agalactiae	**G19 group B**	**ATCC**	**13813**	**1x**
Streptococcus agalactiae	**Z019**	**ZeptoMetrix**	**0801545**	**1x**
Streptococcus agalactiae	MNZ929	BEI Resources	NR-43898	0.3x
Streptococcus agalactiae	Z023	ZeptoMetrix	0801556	0.3x
Streptococcus agalactiae	M-732. Serotype III	ATCC	31475	0.1x
Streptococcus agalactiae	2603 V/R. Serotype V	ATCC	BAA-611	0.1x
Streptococcus agalactiae	Serotype III. Typing strain D136C(3) [3 Cole 106, CIP 82.45]	ATCC	12403	0.3x

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Streptococcus agalactiae	3139 [CNCTC 1/82] Serotype IV	ATCC	49446	0.3x
Streptococcus agalactiae	Typing strain H36B – type Ib	ATCC	12401	0.1x
Streptococcus agalactiae	D136C(3). Lancefield's group B | Type III	CCUG	29782	0.3x
Streptococcus agalactiae	CDC SS700 [A909; 5541], type 1c	ATCC	27591	0.1x
Streptococcus pneumoniae	**19F**	**ZeptoMetrix**	**0801439**	**1x**
Streptococcus pneumoniae	**Serotype 1. NCTC 7465**	**ATCC**	**33400**	**1x**
Streptococcus pneumoniae	DCC1476 [Sweden 15A-25]	ATCC	BAA-661	0.3x
Streptococcus pneumoniae	*Diplococcus pneumoniae*; Type 3. Strain [CIP 104225]	ATCC	6303	1x
Streptococcus pneumoniae	Serotype 19A. Hungary 19A-6 [HUN663]	ATCC	700673	1x
Streptococcus pneumoniae	Serotype 11A. Type 43	ATCC	10343	0.3x
Streptococcus pneumoniae	Z319; Serotype 12F	ZeptoMetrix	0804016	0.3x
Streptococcus pneumoniae	Serotype 14. VH14	ATCC	700672	1x
Streptococcus pneumoniae	Serotype 5. SPN1439-106 [Colombia 5-19]	ATCC	BAA-341	1x
Streptococcus pneumoniae	Serotype 5. SPN1439-106 [Colombia 5-19]	ATCC	BAA-341	1x
Streptococcus pyogenes	**Z472; Serotype M1**	**ZeptoMetrix**	**0804351**	**1x**
Streptococcus pyogenes	**Bruno [CIP 104226]**	**ATCC**	**19615**	**1x**
Streptococcus pyogenes	C203 -Type 3	ATCC	12384	0.3x
Streptococcus pyogenes	Group a, type 14	ATCC	12972	1x
Streptococcus pyogenes	Group a, type 23	ATCC	8133	0.3x
Streptococcus pyogenes	Z018; Serotype M58	ZeptoMetrix	0801512	10x
Streptococcus pyogenes	Lancefield's group A / C203 S	ATCC	14289	0.1x

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Streptococcus pyogenes	Group a, type 12. Typing strain T12 [F. Griffith SF 42]	ATCC	12353	1x
Streptococcus pyogenes	NCTC 8709 (Type 6 glossy)	ATCC	12203	0.1x
Streptococcus pyogenes	Serotype M1. MGAS 5005	ATCC	BAA-947	100x
Mycoplasma pneumoniae	**M129**	**ZeptoMetrix**	**0801579**	**1x**
Mycoplasma pneumoniae	**PI 1428**	**ATCC**	**29085**	**1x**
Mycoplasma pneumoniae	FH strain of Eaton Agent [NCTC 10119]	ATCC	15531	0.1x
Mycoplasma pneumoniae	UTMB-10P	ATCC	49894	0.3x
Mycoplasma pneumoniae	MAC	ATCC	15492	0.1x
Enterovirus	**A6, species A. Strain Gdula**	**ATCC**	**VR-1801**	**1x**
Enterovirus	**Coxsackievirus A16**	**ZeptoMetrix**	**0810107CF**	**1x**
Enterovirus	A10. M.K. (Kowalik)	ATCC	VR-168	0.1x
Enterovirus	A2 Fl [Fleetwood]	ATCC	VR-1550	0.3x
Enterovirus	A12 – Texas 12	ATCC	VR-170	1x
Enterovirus	Species A, BrCr	ATCC	VR-1775	0.1x
Enterovirus	Species A, Serotype EV-A71 (2003 Isolate)	ZeptoMetrix	0810236CF	1x
Enterovirus	Tainan/4643/1998	BEI Resources	NR-471	0.1x
Enterovirus	Enterovirus 71. Strain H	ATCC	VR-1432	0.3x
Enterovirus	A7 – 275/58	ATCC	VR-673	0.3x
Enterovirus	**Coxsackievirus A9, species B**	**ZeptoMetrix**	**0810017CF**	**1x**
Enterovirus	**Coxsackievirus B5**	**ZeptoMetrix**	**0810019CF**	**1x**
Enterovirus	Species B, Echovirus 6	ZeptoMetrix	0810076CF	0.3x
Enterovirus	Species B, Serotype CV-B1, Strain Conn-5	ATCC	VR-28	1x
Enterovirus	Species B, Echovirus 9	ZeptoMetrix	0810077CF	0.3x
Enterovirus	Species B, Coxsackievirus B3	ZeptoMetrix	0810074CF	3x

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Enterovirus	Echovirus 18. Strain H07218 472	NCTC	0901047v	3x
Enterovirus	Coxsackievirus B4	ZeptoMetrix	0810075CF	1x
Enterovirus	Species B, Serotype E-11	ATCC	VR-41	3x
Enterovirus	Species B, Serotype CV-B2. Strain Ohio-1	ATCC	VR-29	1x
Enterovirus	**Coxsackievirus A17, species C. Strain G-12**	**ATCC**	**VR-1023**	**1x**
Enterovirus	**Species C, Coxsackievirus A24. Strain DN-19**	**ATCC**	**VR-583**	**1x**
Enterovirus	Species C, Coxsackievirus A21. Strain Kuykendall [V-024-001-012]	ATCC	VR-850	0.3x
Enterovirus	Species C, A11-Belgium-1	ATCC	VR-169	0.1x
Enterovirus	Species C, A13 – Flores	ATCC	VR-1488	10x
Enterovirus	Species C, A22 – Chulman	ATCC	VR-182	0.1x
Enterovirus	Species C, A18 – G-13	ATCC	VR-176	0.3x
Enterovirus	Species C, CV-A21. Strain H06452 472	NCTC	0812075v	0.3x
Enterovirus	Species C, CV-A21. Strain H06418 508	NCTC	0812074v	0.3x
Enterovirus	Species C, A20 IH35	IDT	gBlock	1x
Enterovirus	**Species D, Enterovirus D68. Strain US/MO/14-18947**	**ATCC**	**VR-1823**	**1x**
Enterovirus	**EV 70, species D, strain J670/71**	**ATCC**	**VR-836**	**1x**
Enterovirus	Species D, Enterovirus D68. USA/2018-23089	BEI Resources	NR-51998	1x
Enterovirus	Species D, D68. Strain F02-3607 Corn	ATCC	VR-1197	0.3x
Enterovirus	Species D, Type 68. 2007 Isolate	ZeptoMetrix	0810237CF	1x
Enterovirus	Species D, Enterovirus D68. Strain US/KY/14-18953	ATCC	VR-1825	0.3x
Enterovirus	Species D, Enterovirus D68. Strain Fermon	ATCC	VR-1826	1x
Enterovirus	Species D, Type 68 Major Group (09/2014 Isolate 2)	ZeptoMetrix	0810302CF	1x

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Enterovirus	Species D, Enterovirus D68. US/MO/14-18949	BEI Resources	NR-49130	0.3x
Enterovirus	Species D, Enterovirus D68. Strain US/IL/14-18952	ATCC	VR-1824	1x
Cryptococcus gattii	**Serotype B strain R272, type VGIIb**	**ATCC**	**MYA-4094**	**1x**
Cryptococcus gattii	**A6MR38 [CBS 11545]**	**ATCC**	**MYA-4877**	**1x**
Cryptococcus gattii	A1M R265	ATCC	MYA-4138	0.1x
Cryptococcus gattii	R265	BEI Resources	NR-50184	0.1x
Cryptococcus gattii	Alg166	BEI Resources	NR-50195	0.01x
Cryptococcus gattii	Alg254	BEI Resources	NR-50198	0.01x
Cryptococcus gattii	Serotype C strain WM779, type VGIV	ATCC	MYA-4563	0.3x
Cryptococcus gattii	110 [CBS 883]	ATCC	14248	0.01x
Cryptococcus gattii	Serotype B strain WM161, type VGIII	ATCC	MYA-4562	0.1x
Cryptococcus gattii	Serotype B strain WM179, type VGI	ATCC	MYA-4560	0.01x
Cryptococcus neoformans	**Serotype D strain WM629, type VNIV**	**ATCC**	**MYA-4567**	**1x**
Cryptococcus neoformans	**C. neoformans H99**	**ATCC**	**208821**	**1x**
Cryptococcus neoformans	var. Grubii.Strain D	ATCC	13690	3x
Cryptococcus neoformans	NIH9hi90	BEI Resources	NR-50335	0.3x
Cryptococcus neoformans	Var grubiiYL99α	BEI Resources	NR-48776	0.1x
Cryptococcus neoformans	Serotype AD strain WM628, type VNIII	ATCC	MYA-4566	0.1x
Cryptococcus neoformans	Serotype A	ZeptoMetrix	0801803	0.1x
Cryptococcus neoformans	NIH306	BEI Resources	NR-50332	0.1x
Cryptococcus neoformans	type strain, CBS 132	ATCC	32045	0.3x
Cryptococcus neoformans	Serotype A strain WM148, type VNI	ATCC	MYA-4564	0.1x

Pathogen		Strain/ subtype	Supplier	Catalog ID	Times LoD
Herpes virus 1	**simplex**	**Macintyre**	**ZeptoMetrix**	**0810005CF**	**1x**
Herpes virus 1	**simplex**	**HF**	**ATCC**	**VR-260**	**1x**
Herpes virus 1	simplex	ATCC-2011-1	ATCC	VR-1778	0.3x
Herpes virus 1	simplex	KOS	ATCC	VR-1493	1x
Herpes virus 1	simplex	Isolate 20	ZeptoMetrix	0810201CF	0.3x
Herpes virus 1	simplex	F	ATCC	VR-733	1x
Herpes virus 1	simplex	ATCC-2011-9	ATCC	VR-1789	0.1x
Herpes virus 1	simplex	P6	NCTC	1806147v	3x
Herpes virus 1	simplex	17+	NCTC	0104151v	1x
Herpes virus 1	simplex	P5A	NCTC	1806145v	1x
Herpes virus 2	**simplex**	**HSV-2. (Strain: MS)**	**ZeptoMetrix**	**0810006CF**	**1x**
Herpes virus 2	**simplex**	**G**	**ATCC**	**VR-734**	**1x**
Herpes virus 2	simplex	Isolate 11	ZeptoMetrix	0810212CF	0.1x
Herpes virus 2	simplex	ATCC-2011-2	ATCC	VR-1779	0.1x
Herpes virus 2	simplex	Isolate 15	ZeptoMetrix	0810216CF	3x
Herpes virus 2	simplex	HG52	NCTC	0104152v	0.1x
Herpes virus 2	simplex	132349 ACV-res	NCTC	0406273v	1x
Herpes virus 2	simplex	Isolate 20	ZeptoMetrix	0810221CF	0.3x
Herpes virus 2	simplex	131596	NCTC	0406272v	0.3x
Herpes virus 2	simplex	Isolate 1	ZeptoMetrix	0810006CFN	0.3x
Cytomegalovirus		**Davis**	**ATCC**	**VR-807**	**1x**

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Cytomegalovirus	**AD-169**	**ZeptoMetrix**	**0810003CF**	**1x**
Cytomegalovirus	Towne	ATCC	VR-977	0.1x
Cytomegalovirus	ATCC-2011-8	ATCC	VR-1788	0.3x
Cytomegalovirus	ATCC-2011-3	ATCC	VR-1780	0.1x
Cytomegalovirus	Toledo	NCTC	0302162v	0.3x
Cytomegalovirus	Merlin	ATCC	VR-1590	0.1x
Human herpesvirus 6	**HHV-6B. (Strain: Z29)**	**ZeptoMetrix**	**0810072CF**	**1x**
Human herpesvirus 6	**HHV-6A. (Strain: GS) Lysate**	**ZeptoMetrix**	**0810529CF**	**1x**
Human herpesvirus 6	6a. Strain U1102	NCTC	0003121v	0.3x
Human herpesvirus 6	6B – strain SF	ATCC	VR-1480	0.3x
Human herpesvirus 6	6B – strain HST	NCTC	0006111v	1x
Human herpesvirus 6	Human β-lymphotropic virus strain GS	ATCC	VR-2225	0.3x
Human parechovirus	**Serotype 1. Strain Harris**	**ZeptoMetrix**	**0810145CF**	**1x**
Human parechovirus	**Serotype 3**	**ZeptoMetrix**	**0810147CF**	**1x**
Human parechovirus	Serotype 5	ZeptoMetrix	0810149CF	0.1x
Human parechovirus	Serotype 6	ZeptoMetrix	0810150CF	1x
Human parechovirus	type 3. Strain US/MO-KC/2014/001	ATCC	VR-1887	0.3x
Human parechovirus	Parechovirus A3. Strain US/MO-KC/2012/006	ATCC	VR-1886	1x
Human parechovirus	Serotype 2. Strain Williamson	ZeptoMetrix	0810146CF	1x
Human parechovirus	Serotype 4	ZeptoMetrix	0810148CF	0.1x
Varicella zoster virus	**Ellen**	**ZeptoMetrix**	**0810171CF**	**1x**
Varicella zoster virus	**Oka**	**ATCC**	**VR-1832**	**1x**

Pathogen		Strain/ subtype	Supplier	Catalog ID	Times LoD
Varicella virus	zoster	Webster	ATCC	VR-916	10x
Varicella virus	zoster	Isolate A	ZeptoMetrix	0810172CF	10x
Varicella virus	zoster	Isolate B	ZeptoMetrix	0810173CF	1x
Varicella virus	zoster	Strain 1700	ZeptoMetrix	0810169CF	10x
Varicella virus	zoster	Strain 275	ZeptoMetrix	0810168CF	1x
Varicella virus	zoster	Strain 82	ZeptoMetrix	0810167CF	1x
Varicella virus	zoster	Strain 9939	ZeptoMetrix	0810170CF	1x
Varicella virus	zoster	Isolate D	ZeptoMetrix	0810175CF	1x

Table 3. Inclusivity in silico test results.

Pathogen	Clinically relevant strains/subtypes detected
S. pneumoniae	No biological subclassification- all genomic sequences available in databases detected
HSV1	No biological subclassification- all genomic sequences available in databases detected
M. pneumoniae	No biological subclassification- all genomic sequences available in databases detected
N. meningitidis	Encapsulated serotypes (A, B, C, D, E, H, I, K, L, NG, W, W135, X, Y, Z, 29E)
C. neoformans/gattii	Serotype A (*C. neoformans var neoformans*), serotype D (*C. neoformans var grubii*), serotypes B and C (*C. gattii* including all VGI, VGII, VGIII, VGIV molecular types)
S. agalactiae	No biological subclassification- all genomic sequences available in databases detected
CMV	No biological subclassification- all genomic sequences available in databases detected
HPeV	All Human parechovirus A strains with available 5'-UTR sequence (1, 2, 3, 4, 5, 6, 7, 8, 14, 16, 17, 18, and 19), including echovirus 22 (HPeV 1) and echovirus 23 (HPeV 2). Although there were poliprotein sequences for HPeV A strains 9, 10, 11, 12, 13 and 15, no 5'-UTR sequence were available
L. monocytogenes	Serotypes 1/2a,1/2b, 1/2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e, 7

Pathogen	Clinically relevant strains/subtypes detected
HHV-6	HHV-6a and HHV-6b
H. influenzae	All encapsulated serotypes (a, b, c, d, e, f) and unencapsulated strains (nontypable, NTHi) including var. *H. aegyptius*
HSV2	No biological subclassification- all genomic sequences available in databases detected
HEV	Coxsackievirus A (CV-A1 through CV-A24), coxsackievirus B (CV-B1 through CV-B6), Echovirus (E-1 through E-33), Enterovirus A (EV-A71, EV-A76, EV-A89 through EV-A92, EV-A119, EV-A120), Enterovirus B (EV-B69, EV-B73 through EV-B75, EV-B79, EV-B80 through EV-B88, EV-B93, EV-B97, EV-B98, EV-B100, EV-B101, EV-B106, EV-B107, EV-B111), Enterovirus C (EV-C96, EV-C99, EV-C102, EV-C104, EV-C105, EV-C109, EV-C116 through EV-C118), Enterovirus D (EV-D68, EV-D70, EV-D94), Poliovirus (PV-1 through PV-3)
S. pyogenes	No biological subclassification- all genomic sequences available in databases detected
E. coli K1	K1 strains
VZV	No biological subclassification- all genomic sequences available in databases detected
	No biological subclassification- all genomic sequences available in databases detected

Exclusivity (analytical specificity)

The analytical specificity study was carried out by in vitro testing and in silico analysis to assess the potential cross-reactivity and exclusivity of the QIAstat-Dx ME Panel. On-panel organisms were tested to assess the potential for intra-panel cross-reactivity and Off-panel organisms were tested to evaluate cross-reactivity with organisms not covered by the panel content (panel exclusivity). The Off-panel organisms have been selected since they are clinically relevant (colonize the central nervous system or cause meningitis and/or encephalitis symptoms), are

common skin flora or laboratory contaminants, are genetically similar to On-panel analytes, or are microorganisms for which much of the population may have been infected.

In silico testing results

The result of the in silico analysis performed for all primer/probe designs included in the QIAstat-Dx ME Panel pointed at 6 potential cross-reactions with Off-Panel targets (listed on Table 4).

Table 4. Potential cross-reactions from *in silico* analysis.

Off-panel organism	On-panel signal
*Streptococcus pseudopneumoniae**	*Streptococcus pneumoniae*
*Listeria innocua**	*Listeria monocytogenes*
Haemophilus haemolyticus	*Haemophilus influenzae*
Cryptococcus amylolentus	*Cryptococcus neoformans/gattii*
*Cryptococcus depauperatus**	
Cryptococcus wingfieldii	

*in silico cross reactive risk was not confirmed by *in vitro* testing.

In vitro testing results

To demonstrate analytical specificity performance of the QIAstat-Dx ME Panel for pathogens which might be present in the clinical sample but not covered by the panel content, a selection of potential cross-reactive pathogens was tested (Off-Panel testing). In addition, the specificity and absence of cross-reactivity with pathogens that are part of the QIAstat-Dx ME Panel has been evaluated at high titers (On-Panel testing).

Samples (20 On-Panel and 109 Off-Panel strains) were prepared by spiking potential cross-reactive organisms into artificial CSF matrix at 10^5 $TCID_{50}$/mL for viral targets, 10^5 CFU/mL

for fungal targets, and 10^6 CFU/mL for bacterial targets, or at the highest concentration possible based on the organism stock.

All strains tested for exclusivity are detailed on Table 5a and Table 5b.

Table 5a. List of On-Panel Analytical Specificity (Exclusivity) pathogens tested

Type	Pathogen	Strain	Source
Bacteria	*Escherichia coli* K1	Strain C5 [Bort]; O18ac:K1:H7	ATCC 700973
	Haemophilus influenzae	Type e [strain AMC 36-A-7]	ATCC 8142
	Listeria monocytogenes	Type 4b. Strain Li 2	ATCC 19115
	Mycoplasma pneumoniae	M129	ZeptoMetrix 0801579
	Neisseria meningitidis	Serotype Y. M-112 [BO-6]	ATCC 35561
	Streptococcus pneumoniae	19F	ZeptoMetrix 0801439
	Streptococcus agalactiae	Z019	Zeptometrix 0801545
	Streptococcus pyogenes	Z472; Serotype M1	Zeptometrix 0804351
Virus	Cytomegalovirus	Davis	ATCC VR-807
	Enterovirus A	A6, species A. Strain Gdula	ATCC VR-1801
	Enterovirus B	Coxsackievirus B5	ZeptoMetrix 0810019CF
	Enterovirus C	Coxsackievirus A17, species C. Strain G-12	ATCC VR-1023
	Enterovirus D	Enterovirus D68. Strain US/MO/14-18947	ATCC VR-1823
	Herpes simplex virus 1	Macintyre	ZeptoMetrix 0810005CF
	Herpes simplex virus 2	HSV-2. (Strain: MS)	ZeptoMetrix 0810006CF
	Human herpesvirus 6	HHV-6B. (Strain: Z29)	ZeptoMetrix 0810072CF
	Human parechovirus	Serotype 3	ZeptoMetrix 0810147CF
	Varicella-zoster virus	Ellen	ZeptoMetrix 0810171CF
	Cryptococcus neoformans	WM629 [CBS 10079]	ATCC MYA-4567

Type	Pathogen	Strain	Source
Fungi (Yeast)	*Cryptococcus gattii*	Serotype B strain R272, type VGIIb	ATCC MYA-4094

Table 5b. List of Off-Panel Analytical Specificity (Exclusivity) pathogens tested

Type	Pathogen	Strain	Source
Bacteria	*Bacillus cereus*	Z091	ZeptoMetrix 0801823
	Citrobacter freundii	[ATCC 13316, NCTC 9750]	ATCC 8090
	Corynebacterium striatum	CDC F6683	ATCC 43751
	Corynebacterium urealyticus	3 [Garcia strain]	ATCC 43044
	Cronobacter (Enterobacter) sakazakii	CDC 4562-70	ATCC 29544
	Enterobacter aerogenes	Z052	ZeptoMetrix 0801518
	Enterobacter cloacae	CDC 442-68	ATCC 13047
	Escherichia coli (non-K1)	2003-3055	ATCC BAA-2212
	Escherichia fergusonii	Z302	ZeptoMetrix 0804113
	Escherichia hermannii	CDC 980-72	ZeptoMetrix 0804068
	Escherichia vulneris	CDC 875-72	ATCC 33821
	*Haemophilus ducreyi***	DCC1476 [Sweden 15A-25]	ATCC BAA-661
	Haemophilus haemolyticus	NCTC 10659	ATCC 33390
	Haemophilus parahaemolyticus	536 [NCTC 8479]	ATCC 10014
	Haemophilus parainfluenzae	NCTC 7857	ATCC 33392
	Klebsiella pneumoniae	NCTC 9633 [NCDC 298-53, NCDC 410-68]	ATCC 13883
	Listeria innocua	SLCC 3379	ATCC 33090
	Listeria ivanovii	Li 1979	ATCC 19119
	Morganella morganii	AM-15	ATCC 25830
	Streptococcus salivarius	C699	ATCC 13419
	Streptococcus sanguinis	DSS-10	ATCC 10556
	Streptococcus pseudopneumoniae	CDC-SS-1757	ATCC BAA-960
	Mycoplasma genitalium	M30	ATCC 49895
	Neisseria lactamica	NCDC A7515	ATCC 23970
	Neisseria mucosa	AmMS 138	ATCC 49233
	Neisseria sicca	AMC 14-D-1	ATCC 9913
	Neisseria gonorrhoeae	Z017	ZeptoMetrix 0801482

Type	Pathogen	Strain	Source
	Pantoea agglomerans = Enterobacter agglomerans	Beijerinck	ATCC 27155
	Proprionibacterium acnes	NCTC 737	ATCC 6919
	Proteus mirabilis	LRA 08 01 73 [API SA, DSM 6674]	ATCC 7002
	Pseudomonas aeruginosa	PRD-10 [CIP 103467, NCIB 10421, PCI 812]	ATCC 15442
	Salmonella bongori	CIP 82.33	ATCC 43975
	Salmonella enterica	CDC K-1891 [ATCC 25928]	ATCC 13076
	Serratia marcescens	PCI 1107	ATCC 14756
	Shigella boydii	CDC C-123	ATCC 12033
	Shigella flexneri	Z046	ZeptoMetrix 0801757
	Shigella sonnei	AMC 43-GG9	ATCC 9290
	Staphylococcus aureus	FDA 209	ATCC CRM6538
	Staphylococcus capitis	PRA 360 677	ATCC 35661
	Staphylococcus epidermidis	FDA strain PCI 1200	ATCC 12228
	Staphylococcus haemolyticus	SM 131	ATCC 29970
	Staphylococcus hominis	Z031	ZeptoMetrix 0801727
	Staphylococcus lugdunensis	LRA 260.05.79	ATCC 49576
	Staphylococcus saprophyticus	NCTC 7292	ATCC 15305
	Streptococcus anginosus	NCTC 10713	ATCC 33397
	Streptococcus bovis	Z167	ZeptoMetrix 0804015
	Streptococcus dysgalactiae	Grouping strain C74	ATCC 12388
	Streptococcus intermedius	Z126	ZeptoMetrix 0801895
	Streptococcus oralis	Z307	ZeptoMetrix 0804293
	Streptococcus mitis (tigurinus)	Clinical Isolate	ZeptoMetrix 0801695
	Streptococcus mutans	LRA 28 02 81	ATCC 35668
Virus	Adenovirus A12	Huie	ATCC VR-863
	Adenovirus C2	Adenoid 6 (NIAID 202-001-014)	ATCC VR-846
	Adenovirus D20	A.A	ATCC VR-1090
	Adenovirus E4	RI-67	ATCC VR-1572
	Adenovirus F41	Tak	ZeptoMetrix 0810085CF
	BK polyoma virus	N/A	ATCC VR-837
	Coronavirus 229E	229E	ATCC VR-740

Type	Pathogen	Strain	Source
	Coronavirus NL63	NL63 (Amsterdam I)	BEI Resources NR-470
	Coronavirus OC43	OC43	ATCC VR-1558
	Dengue virus (Type 2)*	New Guinea C	ZeptoMetrix 0810089CFHI
	Epstein-Barr Virus	B95-8	ZeptoMetrix 0810008CF
	Hepatitis B virus (HBV)*	N/A	ZeptoMetrix 0810031C
	Hepatitis C virus (HCV)*	N/A	ZeptoMetrix 0810032C
	Human herpes virus 7	SB	ZeptoMetrix 0810071CF
	Human herpes virus 8	N/A	ZeptoMetrix 0810104CF
	Human Immunodeficiency Virus*	Quantitative Synthetic Human immunodeficiency virus 1 (HIV-1) RNA	ATCC VR-3245SD
	Human Rhinovirus A1b	2060	ATCC VR-1559
	Human Rhinovirus A16	11757	ATCC VR-283
	Human Rhinovirus B3	FEB	ATCC VR-483
	Human Rhinovirus B83	Baylor 7 [V-190-001-021]	ATCC VR-1193
	Influenza A H1N1	A/Florida/3/2006	ATCC VR-1893
	Influenza A H1N1-2009	A/California/08/2009 (H1N1pdm)	ATCC VR-1895
	Influenza A H3N2	A/Port Chalmers/1/73	ATCC VR-810
	Influenza B	B/Virginia/ATCC4/2009	ATCC VR-1784
	JC polyoma virus	MAD-4	ATCC VR-1583
	Measles Virus	Edmonston	ATCC VR-24
	Mumps Virus	Jones	ATCC VR-1438
	West Nile Virus*	1986	ATCC VR-3274SD
	Parainfluenza virus 2	Greer	ATCC VR-92
	Parainfluenza virus 4	N/A	ZeptoMetrix 0810060CF
	Parvovirus B19	B19	ZeptoMetrix 0810064C
	Respiratory Syncytial Virus	A2	ATCC VR-1540
	Rotavirus	RRV (Rhesus Rotavirus)	ZeptoMetrix 0810530CF
	Rubella Virus	N/A	ZeptoMetrix 0810048CF
	St. Louis Encephalitis Virus*	Parton	ZeptoMetrix 0810080CFHI

Type	Pathogen	Strain	Source
Fungi (Yeast)	*Candida albicans*	CBS 562	ATCC 18804
	Candida dubliniensis	Z145	ZeptoMetrix 0801915
	Candida glabrata	CBS 138	ATCC 2001
	Candida krusei	N/A	ATCC 14243
	Candida lusitaniae	Z010	ZeptoMetrix 0801603
	Candida metapsilosis	MCO429	ATCC 96143
	Candida orthopsilosis	MCO471	ATCC 96140
	Candida viswanathii	PK 233 [NCYC 997, pK233]	ATCC 20336
	Candida parapsilosis	CBS 604	ATCC 22019
	Candida tropicalis	Vitek #8935	ATCC 750
	Cryptococcus albidus	AmMS 228	ATCC 66030
	Cryptococcus amylolentus	NRRY Y-7784	ATCC 56469
	Cryptococcus laurentii	CBS 139	ATCC 18803
	Cryptococcus uniguttulatus	AmMS 234	ATCC 66033
	Cryptococcus adeliensis = *Cryptococcus adeliae* = *Naganishia adeliensis*	TAE85 [CBS8351]	ATCC 201412
	Cryptococcus flavescens = *Papiliotrema flavescens***	*Cryptococcus laurentii* var. flavescens (Saito) Lodder et Kregervan Rij	ATCC 10668
	Cryptococcus wingfieldii = *Tsuchiyaea wingfieldii*	OTU 26	Collection Belga CBS 7118
	Filobasidium capsuligenum	ML-186	ATCC 22179
	Saccharomyces cerevisiae	NRRL Y-567	ATCC 9763
Fungi	*Aspergillus fumigatus*	Z014	ZeptoMetrix 0801716
	Cryptococcus depauperatus = *Aspergillus depauperatus* = *Filobasidiella depauperata*	K [ARSEF 2058, CBS 7842]	ATCC 64866
Parasite	*Naegleria fowleri**	Genomic DNA from *Naegleria fowleri*	ATCC 30174D
	Toxoplasma gondii	Haplogroup 2	ATCC 50611

* Quantitative Synthetic DNA or inactivated material used due to pathogen classification in hazard group III.

** Highest concentration possible due to stock restrictions.

All On-Panel pathogens resulted in specific detection, and all Off-Panel pathogens tested showed a negative result and no cross-reactivity was observed in the QIAstat-Dx ME Panel,

except for the pathogens shown in the table below (Table 6). Pathogens exhibiting cross-reactivity with the panel, and the lowest concentration where cross reactivity is detected are listed in Table 6.

Table 6. Samples showing cross-reactivity with the QIAstat-Dx ME Panel

QIAstat-Dx ME Panel Target	Potential cross-reactive organism	Claimed cross-reactive concentration in the IFU
Mycoplasma pneumoniae	*Propionibacterium acnes*	≥1.00E+04 cfu/mL
	Mycoplasma genitalium	≥1.00E+06 ccu/mL
Haemophilus influenzae	*Haemophilus haemolyticus*	≥1.00E+03 cfu/mL
Cryptococcus neoformans/gattii	*Cryptococcus wingfieldii = Tsuchiyaea wingfieldii*	≥1.00E+01 cfu/mL
	Cryptococcus flavescens = Papiliotrema flavescens	≥4.00E+03 cfu/mL
	Cryptococcus amylolentus	≥1.00E+01 cfu/mL

Co-infections

Combined samples containing a mixture of two different targets spiked at low and high concentrations into artificial CSF were tested. Selection of bacteria, viruses, and yeasts pathogens and combinations of targets tested was based on clinical relevance. Three replicates were tested per sample.

Co-infections testing demonstrated that when at least two QIAstat-Dx ME Panel pathogens of different concentrations are simultaneously present in one sample all targets can be detected by the assay. A summary of the final co-infection mixes whereby the High Positive Analyte does not inhibit the Low Positive Analyte is shown in Table 7.

Table 7. Co-infection mixes tested where concentration of the High Positive Analyte does not inhibit the Low Positive Analyte.

Low Positive Analyte		High Positive Analyte	
Pathogen	**Concentration**	**Pathogen**	**Concentration**
Escherichia coli K1	3.30E+02 cfu/mL	*Haemophilus influenzae*	1.00E+06 cfu/mL
Haemophilus influenzae	9.48E+02 cfu/mL	*Escherichia coli* K1	1.00E+06 cfu/mL
Mycoplasma pneumoniae	2.84E+02 cfu/mL	HSV1	1.00E+04 $TCID_{50}$/mL
HSV1	2.67E+02 $TCID_{50}$/mL	*Mycoplasma pneumoniae*	1.00E+03 cfu/mL
Haemophilus influenzae	9.48E+02 cfu/mL	HSV2	1.00E+02 $TCID_{50}$/mL
HSV2	3.78E+01 $TCID_{50}$/mL	*Haemophilus influenzae*	1.00E+06 cfu/mL
HHV-6	9.39E+04 $TCID_{50}$/mL	*Listeria monocytogenes*	1.00E+06 cfu/mL
Listeria monocytogenes	5.58E+03 cfu/mL	HHV-6	1.00E+05 $TCID_{50}$/mL
HSV1	2.67E+02 $TCID_{50}$/mL	*Streptococcus pneumoniae*	1.00E+02 cfu/mL
Streptococcus pneumoniae	6.78E+02 cfu/mL	HSV1	1.00E+05 $TCID_{50}$/mL
Streptococcus pneumoniae	6.78E+02 cfu/mL	Cytomegalovirus	1.00E+04 $TCID_{50}$/mL
Cytomegalovirus	3.00E+01 $TCID_{50}$/mL	*Streptococcus pneumoniae*	1.00E+06 cfu/mL
Haemophilus influenzae	9.48E+02 cfu/mL	*Streptococcus pneumoniae*	1.00E+06 cfu/mL
Streptococcus pneumoniae	6.78E+02 cfu/mL	*Haemophilus influenzae*	1.00E+06 cfu/mL
Listeria monocytogenes	5.58E+03 cfu/mL	*Streptococcus pneumoniae*	1.00E+06 cfu/mL
Streptococcus pneumoniae	6.78E+02 cfu/mL	*Listeria monocytogenes*	1.00E+06 cfu/mL
Cryptococcus neoformans	6.63E+03 cfu/mL	*Streptococcus pneumoniae*	1.00E+06 cfu/mL
Streptococcus pneumoniae	6.78E+02 cfu/mL	*Cryptococcus neoformans*	1.00E+05 cfu/mL
Neisseria meningitidis	3.99E+01 cfu/mL	*Haemophilus influenzae*	1.00E+06 cfu/mL
Haemophilus influenzae	9.48E+02 cfu/mL	*Neisseria meningitidis*	1.00E+06 cfu/mL
VZV	1.62E+02 cp/mL	*Neisseria meningitidis*	1.00E+06 cfu/mL
Neisseria meningitidis	3.99E+01 cfu/mL	VZV	1.00E+06 cp/mL

Low Positive Analyte		High Positive Analyte	
Pathogen	**Concentration**	**Pathogen**	**Concentration**
Enterovirus	4.80E+02 $TCID_{50}$/mL	*Streptococcus pyogenes*	1.00E+06 cfu/mL
Streptococcus pyogenes	1.71E+03 cfu/mL	Enterovirus	1.00E+05 $TCID_{50}$/mL
HPeV	1.01E+02 $TCID_{50}$/mL	Cytomegalovirus	1.00E+02 $TCID_{50}$/mL
Cytomegalovirus	3.00E+01 $TCID_{50}$/mL	HPeV	1.00E+05 $TCID_{50}$/mL
HPeV	1.01E+02 $TCID_{50}$/mL	Enterovirus	1.00E+05 $TCID_{50}$/mL
Enterovirus	4.80E+02 $TCID_{50}$/mL	HPeV	1.00E+05 $TCID_{50}$/mL
HHV-6	9.39E+04 $TCID_{50}$/mL	HSV1	1.00E+05 $TCID_{50}$/mL
HSV1	2.67E+02 $TCID_{50}$/mL	HHV-6	1.00E+05 $TCID_{50}$/mL
Streptococcus agalactiae	5.25E+03 cfu/mL	HSV2	1.00E+05 $TCID_{50}$/mL
HSV2	3.78E+01 $TCID_{50}$/mL	*Streptococcus agalactiae*	1.00E+06 cfu/mL

Reproducibility

For the reproducibility assessment, a multi-site scheme was followed by testing both negative and positive samples at three different study sites with varying workflow variables, such as sites, days, instruments, operators and cartridge lots that could have an impact on the precision of the system. Negative samples consisted of artificial CSF. Positive combined samples consisted of artificial CSF spiked with a representative panel of pathogens covering all types of organisms targeted by the QIAstat-Dx ME Panel (i.e. RNA virus, gram (+) bacteria, gram (-) bacteria and yeast) at the limit of detection (1x LoD) and at 3x LoD. For each site, testing was performed across 5 non-consecutive days per mix with 6 replicates per day per mix (leading to a total of 90 replicates per target, concentration, and site), a minimum of 9 different QIAstat-Dx Analyzers per site, and at least 3 operators on each testing day.

Reproducibility testing was designed to evaluate the critical variables that may impact the performance of the QIAstat-Dx ME Panel in the context of its routine and intended use.

Table 8 summarizes the results for 3x LoD and 1x LoD concentrations where it is observed that the detection rate for all targets was 100% and ≥98%, respectively. All negative samples returned a negative call 100% of the time.

Table 8. Proportion of true positive Reproducibility Results at 1x LoD and 3x LoD.

Grouping Variable(s)			Proportion		Two-Sided 95% Confidence Limit	
Target	**Concentration**	**Site**	**Fraction**	**Percentage**	**Lower**	**Upper**
Cryptococcus neoformans/gattii	**1xLoD**	**1**	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
	3xLoD	**1**	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
Enterovirus	**1xLoD**	**1**	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
	3xLoD	**1**	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
***Escherichia coli* K1**	**1xLoD**	**1**	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
	3xLoD	**1**	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
Herpes simplex virus 2	**1xLoD**	**1**	30 / 30	100.00%	88.43%	100.00%

Grouping Variable(s)			Proportion		Two-Sided 95% Confidence Limit	
Target	Concentration	Site	Fraction	Percentage	Lower	Upper
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
	3xLoD	1	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
Listeria monocytogenes	1xLoD	1	29 / 30	96.67%	82.78%	99.92%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	89 / 90	98.89%	93.96%	99.97%
	3xLoD	1	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
Mycoplasma pneumoniae	1xLoD	1	29 / 30	96.67%	82.78%	99.92%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	89 / 90	98.89%	93.96%	99.97%
	3xLoD	1	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
Streptococcus agalactiae	1xLoD	1	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%
	3xLoD	1	30 / 30	100.00%	88.43%	100.00%
		2	30 / 30	100.00%	88.43%	100.00%
		3	30 / 30	100.00%	88.43%	100.00%
		All	90 / 90	100.00%	95.98%	100.00%

Repeatability

For the repeatability study, the same sample panel was tested following a single-site scheme. Repeatability testing was designed to evaluate the precision of a QIAstat-Dx ME Panel Cartridge under similar (intra laboratory) conditions. Repeatability study was assessed with the same samples used for Reproducibility testing using Site 1.

Table 9 summarizes the results for 3x LoD and 1x LoD concentrations where it is observed that the detection rate for all targets was ≥98% and ≥93%, respectively. All negative samples returned a negative call 100% of the time.

Table 9. Proportion of true positive Repeatability Results at 1x LoD and 3x LoD.

Grouping Variable(s)		Proportion		Two-Sided 95% Confidence Limit	
Target	**Concentration**	**Fraction**	**Percentage**	**Lower**	**Upper**
Cryptococcus neoformans/gattii	**1xLoD**	60 / 60	100.00%	94.04%	100.00%
	3xLoD	60 / 60	100.00%	94.04%	100.00%
Enterovirus	**1xLoD**	57 / 60	95.00%	86.08%	98.96%
	3xLoD	60 / 60	100.00%	94.04%	100.00%
***Escherichia coli* K1**	**1xLoD**	56 / 60	93.33%	83.80%	98.15%
	3xLoD	60 / 60	100.00%	94.04%	100.00%
Herpes simplex virus 2	**1xLoD**	57 / 60	95.00%	86.08%	98.96%
	3xLoD	59 / 60	98.33%	91.06%	99.96%
Listeria monocytogenes	**1xLoD**	57 / 60	95.00%	86.08%	98.96%
	3xLoD	59 / 60	98.33%	91.06%	99.96%
Mycoplasma pneumoniae	**1xLoD**	57 / 60	95.00%	86.08%	98.96%
	3xLoD	59 / 60	98.33%	91.06%	99.96%
Streptococcus agalactiae	**1xLoD**	60 / 60	100.00%	94.04%	100.00%
	3xLoD	60 / 60	100.00%	94.04%	100.00%

Carryover

A carryover study was performed to evaluate the potential occurrence of cross-contamination between consecutive runs when using the QIAstat-Dx ME Panel on the QIAstat-Dx Analyzer 1.0. Pathogenic CSF samples with alternating high-positive (10^4–10^6 organism/mL) and negative samples, were conducted on two QIAstat-Dx Analyzer 1.0 instruments. No carryover between samples was observed in the QIAstat-Dx ME Panel, demonstrating that the system design and recommended sample handling and testing practices are effective in preventing unexpected results due to carryover or cross-contamination between samples.

Interfering Substances (Analytical Specificity)

The effect of potentially interfering substances on the detectability of the QIAstat-Dx ME Panel organisms was evaluated. The substances tested in the study included endogenous as well as exogenous substances that are commonly found and/or introduced into CSF specimens during specimen collection.

All QIAstat-Dx ME Panel target organisms were tested at 3x LoD in artificial CSF matrix and testing was performed in triplicates. Potential interfering substances were spiked into the samples at a level predicted to be above the concentration of the substance likely to be found in CSF sample.

All potentially interfering endogenous and exogenous substances have been evaluated and have been confirmed not to interfere with any of the panel target assays at concentrations potentially found in clinical samples. This is except for Bleach and gDNA, where interference was observed and as such the lowest concentration of the substance causing interference has been determined.

The results of interfering substances testing are provided in Table 10.

Table 10. Summary of interfering substances testing results.

Substance tested	Concentration tested	Result
Endogenous substances		
Human Blood	10 % (v/v)	No Interference
gDNA	20 µg/mL	Interference
	2.0 µg/mL	No Interference
D(+)Glucose	10 mg/mL	No Interference
L-lactate (Na)	2.2 mg/mL	No Interference
Immunoglobulin G (human)	20 mg/mL	No Interference
Albumin (human)	30 mg/mL	No Interference
Peripheral blood mononuclear cells	10,000 cells/µL	No Interference
Exogenous substances		
Chlorhexidine	0.4 % (w/v)	No Interference
Ethanol	7 % (v/v)	No Interference
Bleach	1 % (v/v)	Interference
	0.1 % (v/v)	Interference
	0.01 % (v/v)	No Interference
Acyclovir	69 µg/mL	No Interference
Amphotericin B	5.1 µg/mL	No Interference
Ampicillin	210 µg/mL	No Interference
Ceftriaxone	840 µg/mL	No Interference
Cefotaxime	645 µg/mL	No Interference
Ganciclovir	25 µg/mL	No Interference
Gentamicin	30 µg/mL	No Interference
Meropenem	339 µg/mL	No Interference
Vancomycin	180 µg/mL	No Interference
Voriconazole	11 µg/mL	No Interference
Oseltamivir	0.399 µg/mL	No Interference
Non-target microorganisms		
Epstein-Barr virus	1.00E+05 cp/mL	No Interference
Influenza A H1N1-2009	1.00E+05 $CEID_{50}$/mL	No Interference

Substance tested	Concentration tested	Result
Cutibacterium acnes	1.00E+06 CFU/mL	No Interference
Staphylococcus epidermidis	1.00E+06 CFU/mL	No Interference
Escherichia coli (non-K1)	1.00E+06 CFU/mL	No Interference
Staphylococcus aureus	1.00E+06 CFU/mL	No Interference
Measles virus	1.00E+05 $TCID_{50}$/mL	No Interference

Note: Any solvents or buffers used in the preparation of interfering substances were also tested for possible interference, none was found.

Appendix 2: Clinical performance

The clinical performance shown below was demonstrated using QIAstat-Dx Analyzer 1.0. The QIAstat-Dx Analyzer 2.0 use the same Analytical Modules as QIAstat-Dx Analyzer 1.0. Therefore, the performance is not impacted by the QIAstat-Dx Analyzer 2.0.

The performance characteristics of the QIAstat-Dx ME Panel was assessed by a multi-centre, observational, prospective and retrospective, clinical performance study, testing fresh and frozen cerebrospinal fluid (CSF) residual specimens obtained by lumbar puncture from patients with signs and symptoms of meningitis and/or encephalitis. The study was conducted at 13 geographically diverse study sites: ten (10) U.S. sites and three (3) European sites.

Between March 2022 and March 2023, a total of 1737 prospective residual CSF specimens were enrolled for the clinical study. Of those, 205 were withdrawn. The most common reason for specimen withdrawal was ineligibility. Additionally, some prospective samples could not be included in the agreement analysis due to missing data. The final dataset consisted of 1526 prospective specimens of which 553 (36.2%) were frozen before testing and 973 (63.8%) were tested fresh (Table 11).

Table 11. Demographic Summary for Prospective Samples for QIAstat-Dx ME Panel Clinical Evaluation

Sample Group	Variable	Subgroup	N	%
Prospective Fresh	**Age Group**	**<1 year**	136	14.0
		1-17 years old	87	8.9
		18-44 years old	284	29.2
		45-64 years old	267	27.4
		65-84 years old	187	19.2
		≥85 years old	11	1.1
		Unknown	1	0.1
	Gender	**Female**	498	51.2
		Male	475	48.8
Prospective Frozen	**Age Group**	**<1 year**	27	4.9
		1-17 years old	41	7.4
		18-44 years old	133	24.1
		45-64 years old	175	31.6
		65-84 years old	156	28.2
		≥85 years old	20	3.6
		Unknown	1	0.2
	Gender	**Female**	271	49.0
		Male	281	50.8
		Not available	1	0.2

Residual CSF specimens were tested with the QIAstat-Dx ME Panel and two types of comparator methods (an FDA-cleared/CE-marked molecular comparator and two validated end point PCRs followed by bidirectional sequencing (BDS) for selected targets). All targets were compared to the FDA-cleared/CE-marked molecular method except *Streptococcus pneumoniae*, *Streptococcus pyogenes,* and *Mycoplasma pneumoniae* which were compared against two validated end point PCRs followed by bi-directional sequencing for selected targets (Table 12). The standard of care testing varied across all sites but included bacterial culture,

PCR, FDA-cleared molecular/CE-marked methods and *Cryptococcus* antigen screen and culture. Standard of care culture results were collected to allow an assessment of clinical sensitivity and specificity and were investigated in cases of discordant result. Discordance testing was also carried out using lab developed single PCR assays followed by bi-directional sequencing for selected targets.

All specimens were tested against the FDA cleared/CE-marked molecular comparator however, the number of specimens tested against each set of two validated end point PCRs followed by bidirectional sequencing for selected targets were lower due to CSF volume constraints. A total of 1524 prospectively collected specimens were evaluated against an FDA-cleared molecular comparator. A total of 1372 prospectively collected specimens were evaluated against validated end point x 2 PCR for *Mycoplasma pneumoniae* followed by BDS. A total of 1373 prospectively collected specimens were evaluated against validated end point x 2 PCR for *Streptococcus pneumoniae* followed by BDS. A total of 1291 prospectively collected specimens were evaluated against validated end point x 2 PCR for *Streptococcus pyogenes* followed by BDS.

Table 12. Comparator Methods for the Clinical Evaluation of QIAstat-Dx ME Panel

Targets	Comparator method
Escherichia coli K1	FDA-cleared/CE-marked molecular test
Haemophilus influenzae	
Listeria monocytogenes	
Neisseria meningitidis (encapsulated)	
Streptococcus agalactiae	
Streptococcus pneumoniae	Validated end point x2 PCR followed by BDS
Streptococcus pyogenes	
Mycoplasma pneumoniae	
Human herpesvirus 6	FDA-cleared/CE-marked molecular test

Targets	Comparator method
Enterovirus	
Human parechovirus	
Cryptococcus gattii/Cryptococcus neoformans (Not Differentiated)	
Cytomegalovirus	
Herpes simplex virus 1	
Herpes simplex virus 2	
Varicella zoster virus	

Several analytes in the QIAstat-Dx ME Panel were of low prevalence and were not encountered in sufficiently large numbers during the prospective study to adequately demonstrate clinical performance. To supplement the results of the prospective clinical study, an evaluation of frozen archived positive retrospective specimens was performed. The specimens selected for testing had previously tested positive for one of the QIAstat-Dx ME Panel targets using the clinical laboratory standard of care method. The archived specimen testing was mixed with the prospective specimen testing at the clinical sites to ensure blinding. A total of 195 retrospective archived specimens were enrolled onto the study. Fifty-five (55) archived specimens were excluded from the analysis. A total of 140 evaluable archived specimens were used in the analysis to support the QIAstat-Dx ME Panel performance evaluation and Table 13 provides a summary of demographic information for the archived specimens.

Table 13. Demographic Summary of Evaluable Archived Specimens for QIAstat-Dx ME Panel Clinical Evaluation

Sample Group	Variable	Subgroup	N	%
Archived	**Age Group**	**<1 year**	13	9.3
		1-17 years old	14	10.0
		18-44 years old	34	24.3
		45-64 years old	32	22.9
		65-84 years old	39	27.9
		≥85 years old	8	5.7
	Gender	**Female**	78	55.7
		Male	62	44.3

In total, 1666 specimens (1526 prospectively collected and 140 preselected archived specimens) were evaluated in the clinical study.

The sensitivity or positive percentage agreement (PPA) and the specificity or negative percentage agreement (NPA) were calculated for the prospective and retrospective clinical studies combined.

Clinical sensitivity or positive percent agreement (PPA) was calculated as 100% x (TP / (TP + FN)). True positive (TP) indicates that both QIAstat-Dx ME Panel and comparator method have a positive result for the specific pathogen. False negative (FN) indicates that the QIAstat-Dx result is negative while the comparator result is positive for the specific pathogen. Specificity or Negative Percent agreement (NPA) was calculated as 100% x (TN / (TN + FP)). True negative (TN) indicates that both the QIAstat-Dx Panel and the comparator method have negative results for the specific pathogen. False positive (FP) indicates that the QIAstat-Dx Panel result is positive for the specific pathogen, but the comparator result is negative. The two-sided 95% confidence intervals were calculated.

The QIAstat-Dx ME Panel positive percent agreement and negative percent agreement against the comparator methods for clinical specimens (prospective and archived) are presented by analyte in Table 14.

Table 14. QIAstat-Dx ME Panel Clinical Specimens Performance

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
			Overall			
Overall	222 / 260	85.4%	80.6%-89.2%	25712 / 25736	99.9%	99.9%-99.9%
			Bacteria			
***Escherichia coli* K1**	4 / 6	66.7%	30.0%-90.3%	1658 / 1658	100.0%	99.8%-100.0%
Haemophilus influenzae	10 / 11	90.9%	62.3%-98.4%	1650 / 1653	99.8%	99.5%-99.9%
Listeria monocytogenes	4 / 5	80.0%	37.6%-96.4%	1659 / 1659	100.0%	99.8%-100.0%
Mycoplasma pneumoniae	0 / 0	N/A	N/A	1482 / 1482	100.0%	99.7%-100.0%
***Neisseria meningitidis* (encapsulated)**	4 / 4	100.0%	51.0%-100.0%	1659 / 1660	99.9%	99.7%-100.0%
Streptococcus agalactiae	12 / 12	100.0%	75.8%-100.0%	1652 / 1652	100.0%	99.8%-100.0%
Streptococcus pneumoniae	12 / 12	100.0%	75.8%-100.0%	1463 / 1469	99.6%	99.1%-99.8%
Streptococcus pyogenes	0 / 0	N/A	N/A	1401 / 1401	100.0%	99.7%-100.0%
Bacteria Overall	46 / 50	92.0%	81.2%-96.8%	12624 / 12634	99.9%	99.9%-100.0%
			Virus			
Cytomegalovirus (CMV)	3 / 5	60.0%	23.1%-88.2%	1656 / 1659	99.8%	99.5%-99.9%

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Enterovirus (EV)	31 / 33	93.9%	80.4%-98.3%	1630 / 1631	99.9%	99.7%-100.0%
Herpes simplex virus 1 (HSV-1)	10 / 12	83.3%	55.2%-95.3%	1652 / 1652	100.0%	99.8%-100.0%
Herpes simplex virus 2 (HSV-2)	29 / 36	80.6%	65.0%-90.2%	1627 / 1628	99.9%	99.7%-100.0%
Human Parechovirus (HPeV)	4 / 8	50.0%	21.5%-78.5%	1655 / 1656	99.9%	99.7%-100.0%
Human herpesvirus 6 (HHV-6)	25 / 30	83.3%	66.4%-92.7%	1628 / 1634	99.6%	99.2%-99.8%
Varicella zoster virus	62 / 71	87.3%	77.6%-93.2%	1593 / 1593	100.0%	99.8%-100.0%
Virus Overall	164 / 195	84.1%	78.3%-88.6%	11441 / 11453	99.9%	99.8%-99.9%
			Fungi & Yeast			
***Cryptococcus gattii* / *Cryptococcus neoformans* (not differentiated)**	12 / 15	80.0%	54.8%-93.0%	1647 / 1649	99.9%	99.6%-100.0%
Fungi & Yeast Overall	12 / 15	80.0%	54.8%-93.0%	1647 / 1649	99.9%	99.6%-100.0%

Resolution testing was performed on samples where there was discordance between QIAstat-Dx ME Panel and the comparator method results if sufficient volume remained for samples. The method for resolution was comparing to the standard of care test results or using lab developed single PCR assays followed by bi-directional sequencing for selected targets.

The QIAstat-Dx ME Panel positive percent agreement and negative percent agreement against the comparator following discrepant resolution is presented by analyte in Table 15.

Table 15. QIAstat-Dx ME Panel Clinical Specimens Performance after discrepant resolution.

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
			Bacteria			
***Escherichia coli* K1**	4 / 4	100.0%	51.0%-100.0%	1660 / 1660	100.0%	99.8%-100.0%
Haemophilus influenzae	10 / 10	100.0%	72.2%-100.0%	1651 / 1654	99.8%	99.5%-99.9%
Listeria monocytogenes	4 / 5	80.0%	37.6%-96.4%	1659 / 1659	100.0%	99.8%-100.0%
Mycoplasma pneumoniae	0 / 0	N/A	N/A	1482 / 1482	100.0%	99.7%-100.0%
***Neisseria meningitidis* (encapsulated)**	4 / 4	100.0%	51.0%-100.0%	1659 / 1660	99.9%	99.7%-100.0%
Streptococcus agalactiae	12 / 12	100.0%	75.8%-100.0%	1652 / 1652	100.0%	99.8%-100.0%
Streptococcus pneumoniae	12 / 12	100.0%	75.8%-100.0%	1463 / 1469	99.6%	99.1%-99.8%
Streptococcus pyogenes	0 / 0	N/A	N/A	1401 / 1401	100.0%	99.7%-100.0%
			Virus			
Cytomegalovirus (CMV)	3 / 3	100.0%	43.9%-100.0%	1658 / 1661	99.8%	99.5%-99.9%
Enterovirus (EV)	31 / 31	100.0%	89.0%-100.0%	1632 / 1633	99.9%	99.7%-100.0%
Herpes simplex virus 1 (HSV-1)	10 / 10	100.0%	72.2%-100.0%	1654 / 1654	100.0%	99.8%-100.0%
Herpes simplex virus 2 (HSV-2)	29 / 31	93.5%	79.3%-98.2%	1632 / 1633	99.9%	99.7%-100.0%
Human parechovirus (HPeV)	4 / 6	66.7%	30.0%-90.3%	1657 / 1658	99.9%	99.7%-100.0%
Human herpesvirus 6 (HHV-6)	26 / 28	92.9%	77.4%-98.0%	1631 / 1636	99.7%	99.3%-99.9%
Varicella zoster virus	62 / 66	93.9%	85.4%-97.6%	1598 / 1598	100.0%	99.8%-100.0%

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
			Fungi & Yeast			
***Cryptococcus gattii / Cryptococcus neoformans* (not differentiated)**	12 / 12	100.0%	75.8%-100.0%	1650 / 1652	99.9%	99.6%-100.0%
Overall	223 / 234	95.3%	91.8%-97.4%	25739 / 25762	99.9%	99.9%-99.9%

Clinical sensitivity and specificity determined against culture

The performance measure of sensitivity and specificity was calculated only for bacterial and fungi analytes for which the gold-standard CSF culture results was available in the standard of care for the clinical prospective and archived specimens. This data was used in additional performance calculations outlined in Table 16.

Table 16. Bacterial or Fungal Culture comparison for diagnostic sensitivity and specificity for all clinical samples.

	Sensitivity (compared to culture)			Specificity (compared to culture)		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
			Bacteria			
***Escherichia coli* K1**[a]	2 / 3	66.7%	20.8%-93.9%	1125 / 1126	99.9%	99.5%-100.0%
Haemophilus influenzae[b]	4 / 4	100.0%	51.0%-100.0%	1122 / 1125	99.7%	99.2%-99.9%
Listeria monocytogenes[c]	3 / 4	75.0%	30.1%-95.4%	1125 / 1125	100.0%	99.7%-100.0%
Mycoplasma pneumoniae	0 / 0	N/A	N/A	1129 / 1129	100.0%	99.7%-100.0%

	Sensitivity (compared to culture)			Specificity (compared to culture)		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
***Neisseria meningitidis* (encapsulated)[d]**	2 / 2	100.0%	34.2%-100.0%	1124 / 1127	99.7%	99.2%-99.9%
***Streptococcus agalactiae*[e]**	2 / 2	100.0%	34.2%-100.0%	1126 / 1127	99.9%	99.5%-100.0%
***Streptococcus pneumoniae*[f]**	3 / 3	100.0%	43.9%-100.0%	1118 / 1126	99.3%	98.6%-99.6%
***Streptococcus pyogenes*[g]**	0 / 0	N/A	N/A	1128 / 1129	99.9%	99.5%-100.0%
Fungi & Yeast						
***Cryptococcus gattii* / *Cryptococcus neoformans* (not differentiated) [h]**	3 / 3	100.0%	43.9%-100.0%	155 / 157	98.7%	95.5%-99.6%

[a] One false negative *Escherichia coli* K1 sample was also tested with a FDA cleared / CE marked molecular assay and also provided a negative result. There was no volume remaining to further test the sample with the validated PCR / BDS. The was one false positive *Escherichia coli* K1 sample was reported as positive with a FDA cleared / CE marked molecular assay.

[b] There were three false positive *Haemophilus influenzae* results, two samples returned negative results with a FDA cleared / CE marked molecular assay and PCR / BDS. One sample returned a positive result with the FDA cleared / CE marked molecular assay.

[c] The one false negative *Listeria monocytogenes* returned a positive result when tested with a SoC LDT assay, but returned a negative result with the validated PCR / BDS assay.

[d] There were 3 false positives Neisseria meningitidis [encapsulated] samples when compared to culture, one returned a negative result with a SoC LDT, a FDA cleared / CE marked molecular method and the validated PCR / BDS assay. One returned a positive result with a FDA cleared / CE marked molecular method and Soc LDT, however no volume was remaining to complete the validated PCR / BDS assay. The remaining sample tested positive on bacterial culture but was only identified as a gram negative diplococci, a FDA cleared / CE marked molecular method reported a positive result for this pathogen however, no volume was remaining to complete the validated PCR / BDS assay.

[e] There was one false positive sample when compared with bacterial culture, this returned a positive result with a FDA cleared / CE marked molecular method therefore PCR/BDS testing was not performed.

[f] There were eight false positive results when compared with bacterial culture. For two samples there was no comparator PCR / BDS result available. Testing of five samples using the validated PCR / BDS comparator method returned negative results, and one sample was positive using the validated PCR / BDS comparator method.

[g] There was one false positive result when compared with bacterial culture, the sample was tested with the validated PCR / BDS comparator assay but returned an inconclusive result.

[h] There were two false positive samples, one samples which was fungal culture negative, was also tested with a FDA cleared / CE marked molecular assay and returned a positive result. Cryptococcal Antigen testing was not performed for this sample at the time of collection. The second false positive sample returned a negative result when tested with a FDA cleared / CE marked molecular assay and was also negative on SoC Cryptococcal Antigen test.

Co-infection Summary

Amongst the 1667 non-withdrawn specimens with a valid QIAstat-Dx result, 245 specimens (14.7%) reported positive results for at least one analyte while the remaining 1422 (85.3%) were negative. In total 6 positive specimens shown multiple detections. Each multiple detections contained two organisms and they are summarized in Table 17.

Table 17. Co-infections combinations as Determined by the QIAstat-Dx ME Panel.

QIAstat-Dx ME Result	# Specimens
Herpes simplex virus 2 (HSV-2) + Human herpesvirus 6 (HHV-6)	2
Human herpesvirus 6 (HHV-6) + *Cryptococcus gattii / Cryptococcus neoformans* (not differentiated)	1
Streptococcus agalactiae + Human herpesvirus 6 (HHV-6)	1
Streptococcus pneumoniae + Human herpesvirus 6 (HHV-6)	1
Streptococcus pneumoniae + Varicella zoster virus	1

QIAstat-Dx ME Panel Tests Success Rate

In total, 26 out of 977 (2.7%) prospective fresh specimens, 7 out of 555 (1.3%) prospective frozen and for 3 out of 176 (1.7%) archived specimens failed on the initial tests. All specimens except 5 (3 prospective fresh and 2 prospective frozen) were retested and were successful after retest, yielding a final success rate of 99.7% for prospective fresh, 99.6% for prospective frozen and 100.0% for archived samples.

Contrived Samples Testing

Contrived specimen testing was required for all targets on the panel as there were insufficient positive specimens obtained from both prospective and archived collection efforts. Contrived specimens were prepared by spiking five different quantified strains representative of the genetic diversity of each pathogen. For each pathogen, the LoD concentration was manufactured at 2x (at least 50%) and 5x LoD spiked into screened individual unique samples of negative CSF. Contrived specimens were tested alongside negative specimens in a blinded manner. The results are summarized in Table 18.

Table 18. QIAstat-Dx ME Panel Contrived Sample Performance Summary.

Pathogen	Concentration Level	Frequency of Positive Results	Proportion (%) of Positive Results	Lower 95% Confidence Limit	Upper 95% Confidence Limit
***Escherichia coli* K1**	**2xLoD**	48 / 48	100.0%	92.6%	100.0%
	5xLoD	37 / 37	100.0%	90.6%	100.0%
	Total	85 / 85	100.0%	95.7%	100.0%
Haemophilus influenzae	**2xLoD**	57 / 57	100.0%	93.7%	100.0%
	5xLoD	36 / 36	100.0%	90.4%	100.0%
	Total	93 / 93	100.0%	96.0%	100.0%
Listeria monocytogenes	**2xLoD**	47 / 49	95.9%	86.3%	98.9%
	5xLoD	38 / 38	100.0%	90.8%	100.0%

Pathogen	Concentration Level	Frequency of Positive Results	Proportion (%) of Positive Results	Lower 95% Confidence Limit	Upper 95% Confidence Limit
	Total	85 / 87	97.7%	92.0%	99.4%
Mycoplasma pneumoniae	**2xLoD**	46 / 46	100.0%	92.3%	100.0%
	5xLoD	39 / 40	97.5%	87.1%	99.6%
	Total	85 / 86	98.8%	93.7%	99.8%
Neisseria meningitidis (encapsulated)	**2xLoD**	46 / 48	95.8%	86.0%	98.8%
	5xLoD	39 / 40	97.5%	87.1%	99.6%
	Total	85 / 88	96.6%	90.5%	98.8%
Streptococcus agalactiae	**2xLoD**	49 / 49	100.0%	92.7%	100.0%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	88 / 88	100.0%	95.8%	100.0%
Streptococcus pneumoniae	**2xLoD**	55 / 57	96.5%	88.1%	99.0%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	94 / 96	97.9%	92.7%	99.4%
Streptococcus pyogenes	**2xLoD**	47 / 49	95.9%	86.3%	98.9%
	5xLoD	40 / 40	100.0%	91.2%	100.0%
	Total	87 / 89	97.8%	92.2%	99.4%
Cytomegalovirus (CMV)	**2xLoD**	46 / 50	92.0%	81.2%	96.8%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	85 / 89	95.5%	89.0%	98.2%
Enterovirus (EV)	**2xLoD**	48 / 49	98.0%	89.3%	99.6%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	87 / 88	98.9%	93.8%	99.8%
Herpes simplex virus 1 (HSV-1)	**2xLoD**	50 / 52	96.2%	87.0%	98.9%
	5xLoD	45 / 47	95.7%	85.8%	98.8%
	Total	95 / 99	96.0%	90.1%	98.4%
Human Parechovirus (HPeV)	**2xLoD**	46 / 48	95.8%	86.0%	98.8%
	5xLoD	39 / 39	100.0%	91.0%	100.0%

Pathogen	Concentration Level	Frequency of Positive Results	Proportion (%) of Positive Results	Lower 95% Confidence Limit	Upper 95% Confidence Limit
	Total	85 / 87	97.7%	92.0%	99.4%
***Cryptococcus gattii* / *Cryptococcus neoformans* (not differentiated)**	**2xLoD**	41 / 41	100.0%	91.4%	100.0%
	5xLoD	38 / 38	100.0%	90.8%	100.0%
	Total	79 / 79	100.0%	95.4%	100.0%

The proportion of positive results was ≥95% for all prepared contrived samples 2xLoD and 5xLoD in all tested analytes.

QIAstat-Dx ME Panel performance across all specimen types

The results for all target pathogens obtained during clinical specimens testing in the prospective and retrospective studies after discordant resolution and contrived samples testing combined, is summarized in Table 19.

Table 19. QIAstat-Dx ME Panel Performance per analyte across all specimen types.

Pathogen	Positive Percent Agreement			Negative Percent Agreement		
	TP/TP+FN	%	95% CI	TN/TN+FP	%	95% CI
Overall Panel	1356 / 1388	97.7%	96.8%-98.4%	42947 / 42997	99.9%	99.8%-99.9%
			Bacteria			
***Escherichia coli* K1**	89 / 89	100.0 %	95.9%-100.0%	2720 / 2724	99.9%	99.6%-99.9%
Haemophilus influenzae	103 / 103	100.0 %	96.4%-100.0%	2703 / 2710	99.7%	99.5%-99.9%

Pathogen	Positive Percent Agreement			Negative Percent Agreement		
	TP/TP+FN	%	95% CI	TN/TN+FP	%	95% CI
Listeria monocytogenes	89 / 92	96.7%	90.8%-98.9%	2722 / 2722	100.0 %	99.9%-100.0%
Mycoplasma pneumoniae	85 / 86	98.8%	93.7%-99.8%	2545 / 2545	100.0 %	99.8%-100.0%
***Neisseria meningitidis* (encapsulated)**	89 / 92	96.7%	90.8%-98.9%	2720 / 2721	100.0 %	99.8%-100.0%
Streptococcus agalactiae	100 / 100	100.0 %	96.3%-100.0%	2710 / 2714	99.9%	99.6%-99.9%
Streptococcus pneumoniae	106 / 108	98.1%	93.5%-99.5%	2516 / 2522	99.8%	99.5%-99.9%
Streptococcus pyogenes	87 / 89	97.8%	92.2%-99.4%	2461 / 2461	100.0 %	99.8%-100.0%
Bacteria Overall	748 / 759	98.6%	97.4%-99.2%	21097 / 21119	99.9%	99.8%-99.9%
			Virus			
Cytomegalovirus (CMV)	88 / 92	95.7%	89.3%-98.3%	2718 / 2721	99.9%	99.7%-100.0%
Enterovirus (EV)	118 / 119	99.2%	95.4%-99.9%	2690 / 2695	99.8%	99.6%-99.9%
Herpes simplex virus 1 (HSV-1)	105 / 109	96.3%	90.9%-98.6%	2703 / 2705	99.9%	99.7%-100.0%
Herpes simplex virus 2 (HSV-2)	29 / 31	93.5%	79.3%-98.2%	2780 / 2782	99.9%	99.7%-100.0%

Pathogen	Positive Percent Agreement			Negative Percent Agreement		
	TP/TP+FN	%	95% CI	TN/TN+FP	%	95% CI
Human Parechovirus (HPeV)	89 / 93	95.7%	89.5%-98.3%	2719 / 2720	100.0 %	99.8%-100.0%
Human herpesvirus 6 (HHV-6)	26 / 28	92.9%	77.4%-98.0%	2773 / 2785	99.6%	99.2%-99.8%
Varicella zoster virus	62 / 66	93.9%	85.4%-97.6%	2746 / 2747	100.0 %	99.8%-100.0%
Virus Overall	517 / 538	96.1%	94.1%-97.4%	19129 / 19155	99.9%	99.8%-99.9%
Fungi & Yeast						
***Cryptococcus gattii* / *Cryotococcus neoformans* (not differentiated)**	91 / 91	100.0 %	95.9%-100.0%	2721 / 2723	99.9%	99.7%-100.0%
Fungi & Yeast Overall	91 / 91	100.0 %	95.9%-100.0%	2721 / 2723	99.9%	99.7%-100.0%

Target specific PPA was ≥95% for all QIAstat-Dx ME Panel analytes when assessing performance across prospective, retrospective archived and contrived specimens, except for the PPA of Herpes simplex virus 2 (HSV-2), Human herpesvirus 6 (HHV-6), and Varicella zoster virus which were 93.5%, 92.9% and 93.9%, respectively. The NPA was ≥98.5% for all QIAstat-Dx ME Panel analytes.

Conclusion

The QIAstat-Dx ME Panel demonstrated robust clinical performance characteristics to aid in the diagnosis of specific agents of meningitis and/or encephalitis. Results must be used in conjunction with other clinical, epidemiological, and laboratory data.