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QIAstat-Dx®
Meningitis/Encephalitis (ME) Panel Instructions for Use

Σ 6

Version 2

IVD For In Vitro Diagnostic Use

Rx ONLY For prescription use only

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

REF 691621

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R2

Sample to Insight

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Intended Use

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 using the QIAstat-Dx ME Panel: *Enterovirus, Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis* (encapsulated), *Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes*, 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. The agent or agents detected may not be the definite cause of the disease. Negative results do not preclude central nervous system (CNS) infection.

Not all agents of CNS infection are detected by this test and sensitivity in clinical use may differ from that described in the Instructions for Use.

The QIAstat-Dx ME Panel is not intended for testing of specimens collected from indwelling CNS medical devices.

[*] *Cryptococcus neoformans* and *Cryptococcus gattii* are not differentiated.

The QIAstat-Dx ME Panel is intended to be used in conjunction with standard of care culture for organism recovery, serotyping, and antimicrobial susceptibility testing.

Intended User

The QIAstat-Dx ME Panel is intended for *in vitro* diagnostic use by laboratory professionals only.

Description and Principle

Summary and explanation

QIAstat-Dx ME Panel Cartridge description

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 QIAstat-Dx Analyzer 2.0 by pneumatically operated microfluidics and make no direct contact with the actuators. The QIAstat-Dx Analyzer 1.0 and 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.

After the QIAstat-Dx ME Panel Cartridge containing the sample is introduced into the QIAstat-Dx Analyzer 1.0 or 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.

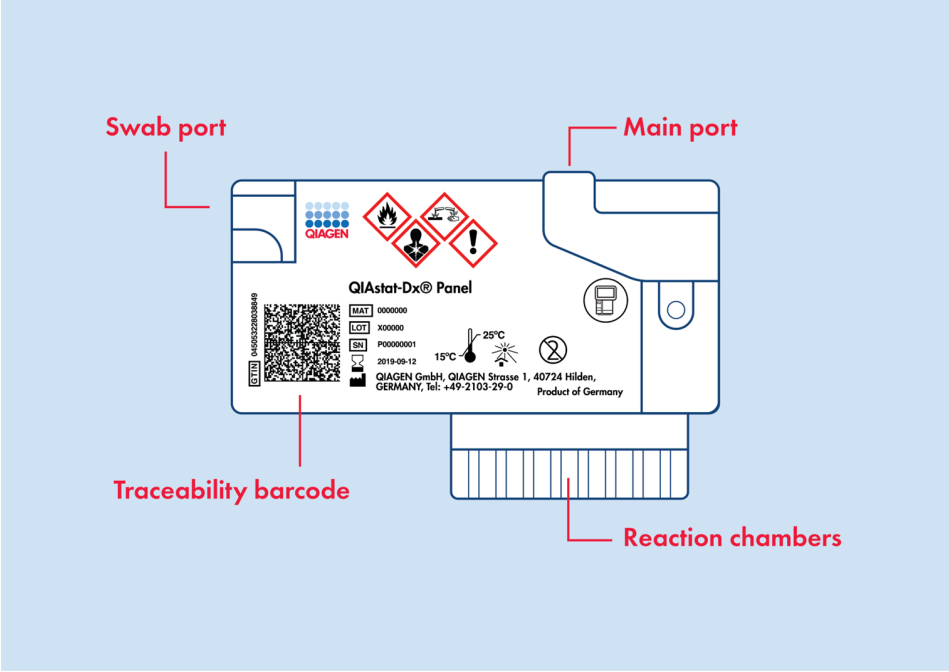


Figure 1. Layout of the QIAstat-Dx Panel Cartridge and its features.

Note: The swab port is not used for the QIAstat-Dx ME Panel assay.

Pathogen information

Meningitis and encephalitis are potentially devastating conditions and can be associated with significant morbidity and mortality[1]. Meningitis is defined as inflammation of the meninges, encephalitis is defined as inflammation of the brain parenchyma, and meningoencephalitis is defined as inflammation at both locations. All these conditions can be caused by bacteria, viruses, or fungi, with encephalitis being more commonly associated with a viral etiology[2]. Clinical presentations are usually nonspecific; as patients often experience headache, altered mental status, and, in the case of meningitis, nuchal rigidity. Early diagnosis is vital, as symptoms can appear suddenly and escalate to brain damage, hearing and/or speech loss, blindness, or even death. As treatment differs depending on the cause of the disease, identification of a specific causative agent is necessary to adjust treatment accordingly.

The QIAstat-Dx ME Panel Cartridge allows detection of 9 bacterial, viral, and fungal pathogenic targets that cause signs and/or symptoms of meningitis and/or encephalitis. Testing requires a small sample volume and minimal hands-on time, and the results are available in less than 80 minutes.

Pathogens that can be detected and identified with the QIAstat-Dx ME Panel are listed in Table 1.

Table 1. Pathogens detected by the QIAstat-Dx ME Panel

Pathogen	Classification (genome type)
Escherichia coli K1	Bacterium (DNA)
Haemophilus influenzae	Bacterium (DNA)
Listeria monocytogenes	Bacterium (DNA)
Neisseria meningitidis (encapsulated)	Bacterium (DNA)

Table 1. Pathogens detected by the QIAstat-Dx ME Panel (continued)

Pathogen	Classification (genome type)
Streptococcus agalactiae	Bacterium (DNA)
Streptococcus pneumoniae	Bacterium (DNA)
Streptococcus pyogenes	Bacterium (DNA)
Enterovirus	Picornavirus (RNA)
Cryptococcus gattii/Cryptococcus neoformans	Yeast (DNA)

Escherichia coli K1

E. coli, a gram-negative bacilli of the order Enterobacterales, is one of the most common organism found in the gastrointestinal tract. Most of the *E. coli* strains are harmless, however, those expressing the K1 capsular polysaccharide can cause extra-intestinal infections[3,4]. *E. coli* strains possessing the K1 capsule are predominant (~80%) among cerebrospinal fluid isolates from neonates with meningitis[5], and they are responsible for ~40% of septicemia and ~80% of meningitis cases in this population, in which they are associated with a mortality rate of 10–15%, and neurological sequelae in 30–50% of cases[6]. The pathogenesis of *E. coli* K1 involves mucosal colonization in the gastrointestinal tract and invasion into the intravascular space[7]. After reaching a threshold level of bacteremia, *E. coli* K1 penetrates the blood-brain barrier (BBB) and invades the central nervous system (CNS)[7]. Once bacteria enter the CNS, it induces the release of pro-inflammatory and toxic compounds, which leads to increased BBB permeability and pleocytosis, resulting in meningitis[8].

Haemophilus influenzae

H. influenzae, is a gram-negative coccobacillus that can be separated into encapsulated strains, of which there are six different serotypes (a through f), each expressing a unique polysaccharide capsule, as well as unencapsulated or non-typable strains[9]. Transmission of *H. influenzae* commonly occurs via respiratory droplets[10]. Historically, *H. influenzae* serotype b

(Hib) was the leading cause of bacterial meningitis among children under 5 years old. However, in countries with Hib conjugate vaccines in national immunization programs, the incidence has decreased over 90%[11–14]. Following implementation of Hib vaccination, non-typeable *H. influenzae* now causes the majority of invasive disease in all age groups[10]. Non-typeable *H. influenzae* can cause ear infections in children and bronchitis but can also result in invasive disease[10]. Serotype b is the most pathogenic in humans and may lead to pneumonia, bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, otitis media, purulent pericarditis and, less commonly, endocarditis and osteomyelitis[10]. Infections with the remaining serotypes lead to similar disease processes[10].

Listeria monocytogenes

L. monocytogenes is a facultatively anaerobic, rod-shaped, gram-positive bacterium[15]. Of the 12 *L. monocytogenes* serotypes identified, over 98% of isolates from human listeriosis belong to four serotypes: 1/2a, 1/2b, 1/2c and 4b[15,16]. Transmission occurs primarily through contaminated food products, which can result in large outbreaks[15], while human-to-human transmission can occur from mother-to-child in utero or at birth[17]. Invasive listeriosis predominantly affects pregnant women, immunocompromised individuals, elderly people and infants, and can cause life-threatening diseases such as septicemia and meningitis[18]. Although the number of infections per year is moderately low, approximately 23,150 cases estimated globally in 2010, the mortality among infected individuals is high, with 5463 deaths estimated globally in 2010, representing 26.6% of all cases[19].

Neisseria meningitidis (encapsulated)

N. meningitidis, or meningococcus, is an aerobic, gram-negative diplococcus and a major causative pathogen of bacterial meningitis[20]. Thirteen serogroups have been identified based on the antigenicity of the polysaccharide capsule; serogroups A, B, C, W, Y, and X are the cause of most cases of invasive disease[21]. The most invasive strains of *N. meningitidis* are usually encapsulated, as the capsule provides resistance to host antibodies and prevents

phagocytosis[20,22]. *N. meningitidis* is carried asymptomatically in the nasopharyngeal mucosa by ~10% of healthy individuals, and transmission occurs by droplet aerosol or secretions from colonized persons[23]. Infections caused by this bacterium can affect individuals of any age, but the highest incidence is found in infants and adolescents[24]. The case-fatality ratio of meningococcal disease is 10–15%, even with appropriate antibiotic therapy[23]. With the introduction of vaccines, rates of meningococcal disease have been declining in some countries, such as the U.S. and the Netherlands[25,26], but both sporadic and epidemic cases of *N. meningitidis* are still registered in countries where multivalent meningococcal vaccination has not yet been introduced[27].

Streptococcus agalactiae

Group B *Streptococcus* (group B strep, GBS) is a gram-positive cocci. Ten polysaccharide-based serotypes have been identified with 97% of cases attributed to five serotypes (Ia, Ib, II, III, and V)[28,29]. GBS can cause life-threatening infections in neonates and immunocompromised adults. In neonates, early-onset (<7 days) and late-onset (7–90 days) disease can manifest as bacteremia, sepsis, pneumonia and meningitis[30]. In adults, severe infections can manifest as bacteremia and soft tissue infections[31,32], but GBS is an uncommon cause of bacterial meningitis, mainly occurring in those with underlying conditions, such as immunocompromised state, CSF leakage and endocarditis[33]. Asymptomatic carriage of GBS in gastrointestinal and genital tracts is common[30]. As this bacterium is a leading contributor to worldwide adverse maternal and neonatal outcomes[34], the WHO recommends intrapartum antibiotic administration for women colonized with GBS during pregnancy[35].

Streptococcus pneumoniae

S. pneumoniae is a gram-positive, encapsulated diplococcus with more than 90 known serotypes identified based on antigenic differences in the capsular polysaccharide[36]. *S. pneumoniae* is a common nasal commensal present in around 20-40% of children and 5-10% of adults, but it is also an important cause of both mucosal disease and invasive disease[36,37]

and one of the leading causes of bacterial meningitis[36,38]. The WHO estimates that about 1 million children die every year of pneumococcal disease[39]. While the introduction of pneumococcal conjugate vaccines have dramatically reduced the incidence of invasive pneumococcal disease, including meningitis[40-42], non-vaccine serotype pneumococcal meningitis cases are increasing, countering the overall effect of vaccination[42-44]. Of concern, significant increases in the prevalence of antibiotic resistance have been observed in non-vaccine serotypes, including resistance to penicillin and erythromycin[44]. Two types of vaccinations for *Streptococcus pneumoniae* are currently available: the pneumococcal conjugate vaccine 13 and the pneumococcal polysacch4aride vaccine 23, recommended for children ≤2 and adults ≥65 years, respectively. In addition, vaccinations are recommended for high-risk populations[36].

Streptococcus pyogenes

S. pyogenes is a gram-positive bacterium, also referred to as Group A *Streptococcus* (GAS), associated with serious diseases that result in high morbidity and mortality[45]. *S. pyogenes* infection can occur through person-to-person transmission (saliva/nasal secretions, skin contact) or directly from the environment through a compromised barrier, such as a skin injury[46]. *S. pyogenes* infections of the central nervous system are relatively rare[47], with studies reporting rates of about 1% of all bacterial meningitis cases caused by S. pyogenes[48-51], but are associated with elevated mortality and morbidity[50]. In a Netherlands study, between 2006 and 2013, GAS caused meningitis in 26 of 1322 patients with community-acquired bacterial meningitis. Of those 26 patients, 5 (19%) died and 11 (52%) of the 21 surviving patients suffered neurologic sequelae[50]. Similarly, a Brazilian study reported low in incidence of GAS meningitis amongst the pediatric population, but a case fatality rate of 43% between 2003 and 2011[51]. *S. pyogenes* infection can cause both localized, non-invasive diseases, such as pharyngitis and impetigo, and invasive diseases, like necrotizing fasciitis and toxic shock syndrome[45,46]. Inadequate antibiotic treatment of *S. pyogenes* can lead to the development of acute rheumatic fever[46]. The prevalence of infection is higher in children than adults, but disease in neonates is uncommon[52]. There is currently no vaccine for *S. pyogenes*,

but its development has been identified as a priority by the WHO Initiative for Vaccine Research[53].

Streptococcus pyogenes is an extremely rare cause of community- acquired meningitis/encephalitis infections in the U.S. and a positive assay result for this analyte should be supported by additional culture evidence.

Enterovirus

Enterovirus is a genus of positive-sense, single-stranded RNA viruses that are associated with multiple human diseases[54]. Enterovirus can be transmitted via nasopharyngeal secretion[55], and cause a wide range of illnesses in humans, including respiratory, gastrointestinal, and central nervous system illness[55,56]. Symptoms are usually mild and can include fever, runny nose, cough, sneezing and muscle aches [55] . However, individuals who are immunocompromised and children with asthma are at risk of severe symptoms from enterovirus infections[55,56]. Enteroviruses are estimated to cause 1–4% of viral encephalitis[57] cases, and they are the most important cause of infant viral meningitis, with studies indicating enteroviruses can account for up to 90% of all cases in which an etiological agent is identified[58]. Enterovirus 68 and enterovirus 71 (sometimes to referred to as non-polio enterovirus) have been implicated in severe secondary neurologic sequelae of infection, including aseptic meningitis, encephalitis, acute flaccid paralysis and acute flaccid myelitis[59]. In 2014, a nationwide outbreak of enterovirus 68 in the United States, predominantly in children, lead to >1,300 laboratory-confirmed cases of severe infection[55]. During this outbreak, around 100 patients were diagnosed with acute flaccid myelitis[57], and many of these patients did not fully recover[60].

Cryptococcus neoformans/gattii

Cryptococcus neoformans and *Cryptococcus gattii* are environmental fungi, and the two etiological agents of *cryptococcosis*[61]. Infection is caused by inhalation of desiccated airborne

yeast cells or possibly sexually-produced basidiospores[62-64]. *C. neoformans* has global distribution and is typically found in soil, on decaying wood, in tree hollows or in avian guano[62,63]. In immunocompetent individuals, infections are minimally symptomatic and rapidly cleared[62,65]. In immunocompromised individuals, *C. neoformans* can disseminate from the lungs, cross the blood-brain barrier and result in cryptococcal meningoencephalitis[62]. Symptoms of cryptococcal meningitis include headache, fever, neck pain, nausea, vomiting, photophobia and confusion or changes in behaviour[64]. *C. neoformans* is the most common opportunistic central nervous system fungal pathogen observed in HIV-positive patients, and cryptococcosis meningitis is considered an indicator of disease in the fulfilment of AIDS[65]. In patients living with HIV, an estimated 220,000 cases of cryptococcal meningitis occur annually, resulting in 181,000 deaths, primarily in sub-Saharan Africa[66].

C. gattii lives in soil and on certain trees, primarily in tropical and subtropical regions across the world, but has also been found in mainland British Columbia, Vancouver Island, the U.S. Pacific Northwest (Oregon and Washington), and California[64]. In studies from Australia, Papua New Guinea, British Columbia, Canada and the U.S. Pacific Northwest, the mortality rate among patients with *C. gattii* infections ranges from 13% to 33%[67]. *C.gattii* infections can affect both immunocompromised and immunocompetent hosts, with varying associated risk factors identified in different regions of the world[68].

Principle of the procedure

Description of the process

Diagnostic tests with the QIAstat-Dx ME Panel are performed on the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0. All of the sample preparation and analysis steps are performed automatically by the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0. Samples are collected and loaded manually into the QIAstat-Dx ME Panel Cartridge.

A transfer pipette is used for sample transfer into the main port (Figure 2).

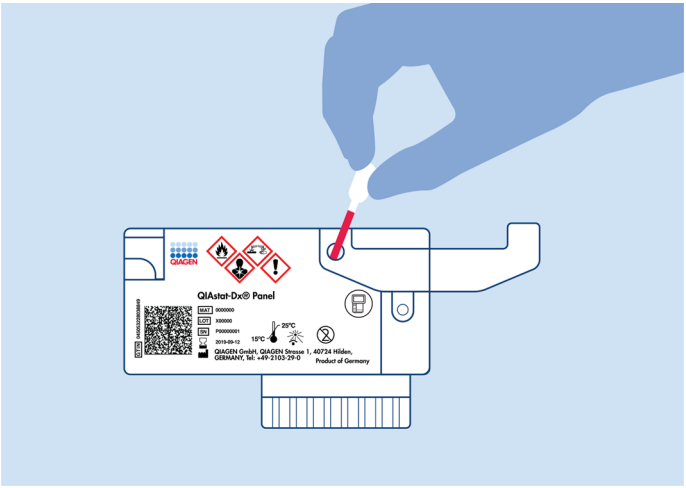


Figure 2. Dispensing sample into the main port.

Sample collection and cartridge loading

The collection of samples and their subsequent loading into the QIAstat-Dx ME Panel Cartridge should be performed by personnel trained in safe handling of biological samples.

The following steps are involved and must be executed by the user:

1. Collect a Cerebral Spinal Fluid (CSF) sample.
2. Write the sample information manually or affix a sample label to the top of a QIAstat-Dx ME Panel Cartridge.
3. Load the CSF sample manually into the QIAstat-Dx ME Panel Cartridge.

   200 µL of sample is transferred into the main port of the QIAstat-Dx ME Panel Cartridge using one of the included transfer pipettes. Use alternative sterile and graduated pipettes in case all six pipettes provided with the kit have been used.

Note: When loading a CSF sample, the user performs a visual check of the sample inspection window (see image below) to confirm that the liquid sample has been loaded (Figure 3).

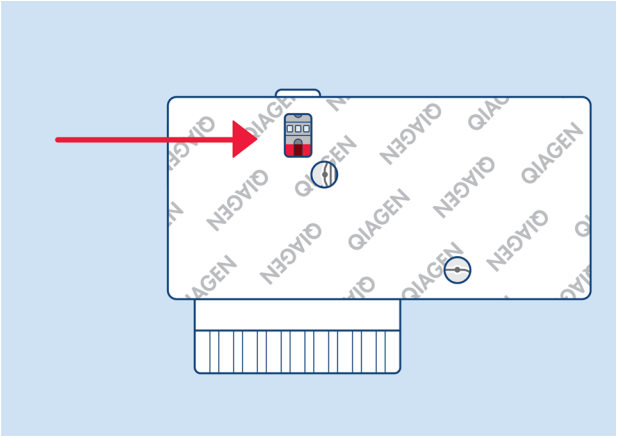


Figure 3. Sample inspection window (red arrow).

4. Scan the sample bar code and QIAstat-Dx ME Panel Cartridge QR code in the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.
5. The QIAstat-Dx ME Panel Cartridge is introduced into the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.
6. The test is started on the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.

Sample preparation, nucleic acid amplification, and detection

The extraction, amplification, and detection of nucleic acids in the sample are performed automatically by the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.

1. The sample is homogenized, and cells are lysed in the lysis chamber of the QIAstat-Dx ME Panel Cartridge, which includes a rotor that turns at high speed.
2. Nucleic acids are purified from the lysed sample via binding to a silica membrane in the purification chamber of the QIAstat-Dx ME Panel Cartridge in the presence of chaotropic salts and alcohol.
3. The purified nucleic acids are eluted from the membrane in the purification chamber and are mixed with the lyophilized PCR chemistry in the dried-chemistry chamber of the QIAstat-Dx ME Panel Cartridge.
4. The mixture of sample and PCR reagents is dispensed into the QIAstat-Dx ME Panel Cartridge PCR chambers, which contain lyophilized assay-specific primers and probes.
5. The QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 creates the optimal temperature profiles to carry out effective multiplex real-time RT-PCR and performs real-time fluorescence measurements to generate amplification curves.
6. The QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 software interprets the resulting data and process controls and delivers a test report.

Materials Provided

Kit contents

QIAstat-Dx Meningitis/Encephalitis (ME) Panel	
Catalog no.	**691621**
Number of tests	**6**
QIAstat-Dx ME Panel Cartridge*	6
Transfer pipettes†	6
QIAstat-Dx ME Panel Product Information Card	1

* 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.

Materials Required but Not Provided

Platform and software

The QIAstat-Dx ME Panel is designed for use with the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0. Before beginning a test, make sure the following are available:

- QIAstat-Dx Analyzer 1.0* (at least one Operational Module and one Analytical Module) with software version 1.4 or 1.5.
- *QIAstat-Dx Analyzer 1.0 User Manual* (for use with software version 1.4 or 1.5)
- QIAstat-Dx Analyzer 2.0 (at least one Operational Module PRO and one Analytical Module) with software version 1.6 or later
- *QIAstat-Dx Analyzer 2.0 User Manual* (for use with software version 1.6 or later)
- QIAstat-Dx latest Assay Definition File software for the QIAstat-Dx ME Panel installed in the Operational Module.

Note: Application software version 1.6 or later cannot be installed on QIAstat-Dx Analyzer 1.0.

*Prior to use, ensure that instruments have been checked and calibrated according to the manufacturer's recommendations.

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.
- For prescription use only
- The QIAstat-Dx ME Panel is to be used by laboratory professionals trained in the use of QIAstat-Dx Analyzer 1.0 or 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 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 Centers for Disease Control and Prevention and the National Institutes of Health (**https://www.cdc.gov/labs/BMBL.html**).
- Specimens and samples are potentially infectious. 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.

- 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 or 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 used or damaged cartridges in accordance with all national, state and local health and safety regulations and laws.

Emergency information

CHEMTREC

USA & Canada 1-800-424-9300

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 Centers for Disease Control and Prevention and the National Institutes of Health (**https://www.cdc.gov/labs/BMBL.html**).

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/ physician. Remove person to fresh air and keep comfortable for breathing.

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.
- Use clean gloves to remove materials from bulk packaging boxes, and close bulk packaging when not in use.

Precautions related to Public Health Reporting

National, state, and local public health organizations have published guidelines for the notification of reportable diseases. While the list of reportable conditions varies by state, the Council of State and Territorial Epidemiologists (CSTE) has recommended that state health departments report cases of selected diseases to CDC's National Notifiable Diseases Surveillance System (NNDSS). To date, the notifiable pathogens in the US per CDC included in our QIAstat-Dx ME Panel are:

- *Haemophilus influenzae* (Invasive Disease)
- *Listeria monocytogenes* (Listeriosis)
- *Neisseria meningitidis* (Meningococcal Disease)
- *Streptococcus pneumoniae* (Invasive Disease)
- *Streptococcus pyogenes* (Invasive Disease)
- *Cryptococcus gattii*

Additionally, the following diseases are notifiable:

- Aseptic meningitis (No evidence of bacterial or fungal meningitis)
- Meningitis, other bacterial (bacterial species isolated in CSF other than *Haemophilus influenzae, Neisseria meningitidis, group A Streptococcus*, and *Listeria monocytogenes*)

Pathogens are reportable due to their outbreak potential or impact on public health. 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.

Cartridge Storage and Handling

Store the QIAstat-Dx ME Panel Cartridges in a dry, clean storage space at room temperature (15–25°C). Do not remove the QIAstat-Dx ME Panel Cartridges or the transfer pipettes from their individual packaging until actual use. Under these conditions, the QIAstat-Dx ME Panel Cartridges can be stored until the expiration date printed on the individual packaging. The expiration date is also included in the QIAstat-Dx ME Panel Cartridge bar code and is read by the ME Panel when the cartridge is inserted into the instrument to run a test.

Attention should be paid to the expiration dates and storage conditions printed on the box and labels of all components. Do not use expired or incorrectly stored components.

In the event of cartridge damage please refer to "Safety information" on page 20.

Specimen Handling and Storage

CSF specimens should be collected and handled according to the recommended procedures.

Use freshly collected CSF specimens. If immediate testing is not possible, recommended storage condition for CSF are listed below:

- Room temperature (15–25°C) up to 24 hours
- Refrigerated (2–8°C) up to 7 days

Disposal

Dispose as hazardous waste in compliance with local and national regulations. This also applies to unused products. In case of damaged cartridge please refer to the "Safety information" on page 20.

Follow recommendations in the Safety Data Sheet (SDS).

Procedure

Protocol: Cerebrospinal Fluid Samples

Important points before starting

- Ensure all materials required but not provided are available.
- Select the QIAstat-Dx ME Panel Cartridge (cat.no 691621). QIAstat-Dx ME Panel cartridge identification is supported by a ● colored bar on the label and an icon indicating a brain (see "Symbols" on page 123).

Sample collection, transport, and storage

The CSF specimen should be collected via lumbar puncture and should not be centrifuged.

Loading a sample into the QIAstat-Dx ME Panel Cartridge

1. Thoroughly clean the work area with freshly prepared 10% bleach (or a suitable disinfectant) followed by a water rinse.
2. Open the package of a QIAstat-Dx ME Panel Cartridge using the tear notches on the sides of the packaging (Figure 4).

   Important: After the package is opened, sample should be loaded inside the QIAstat-Dx ME Panel Cartridge and loaded into the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 within 120 minutes.

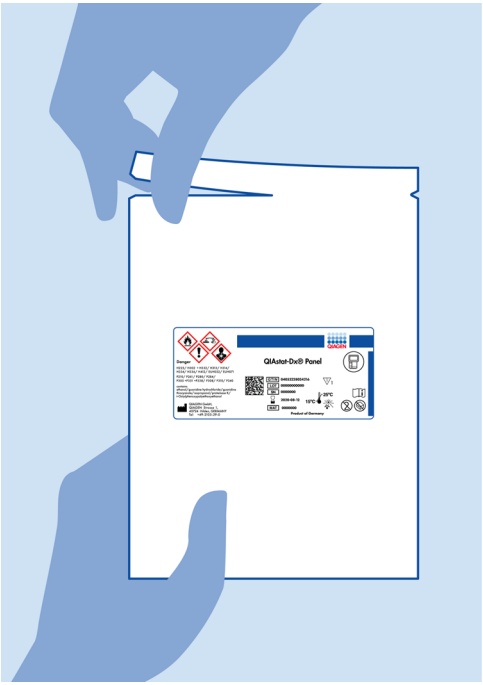


Figure 4. Opening the QIAstat-Dx ME Panel Cartridge.

3. Remove the QIAstat-Dx ME Panel Cartridge from the packaging and position it so that the bar code on the label faces you.
4. Manually write the sample information or place a sample information label on the top of the QIAstat-Dx ME Panel Cartridge. Make sure that the label is properly positioned and does not block the lid opening (Figure 5).

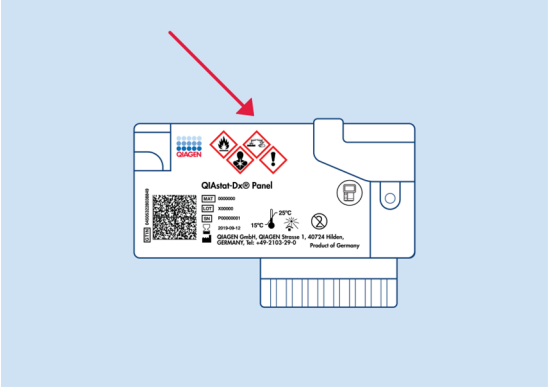


Figure 5. Sample information placement on top of QIAstat-Dx ME Panel Cartridge.

5. Open the sample lid of the main port on the front of the QIAstat-Dx ME Panel Cartridge (Figure 6).

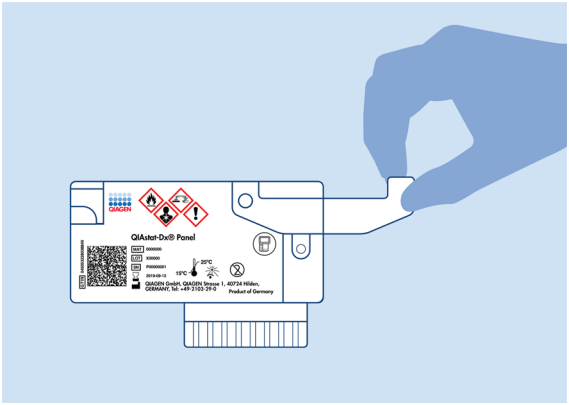


Figure 6. Opening the sample lid of main port.

6. Open the tube with the sample to be tested. Use the supplied transfer pipette to draw fluid up to the second fill line on the pipette (i.e., 200 µL) (Figure 7).

Important: Do not draw air into the pipette. If air is drawn into the pipette, carefully expel the sample fluid in the pipette back into the sample tube and draw up fluid again.

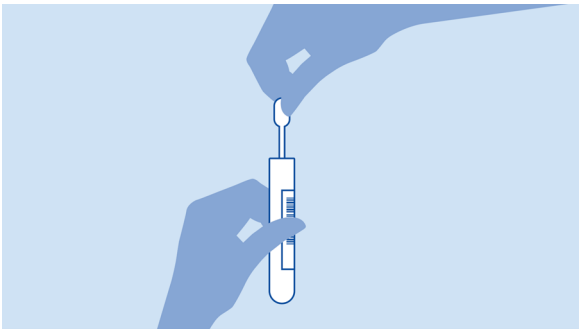


Figure 7. Drawing sample into the supplied transfer pipette.

7. Carefully transfer 200 µL of sample into the main port of the QIAstat-Dx ME Panel Cartridge using the supplied single-use transfer pipette (Figure 8).

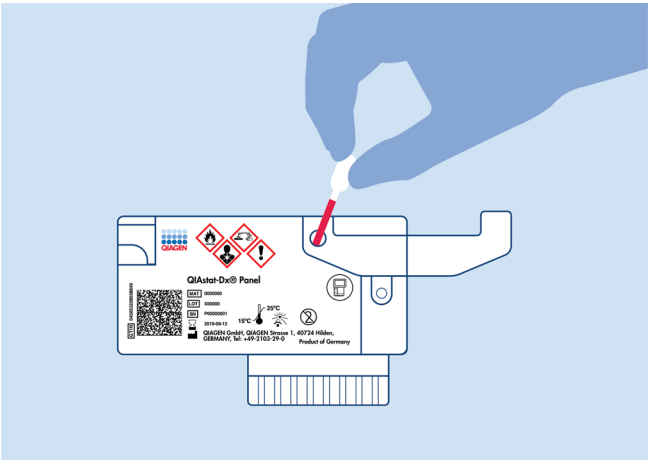


Figure 8. Transferring sample to main port of QIAstat-Dx ME Panel Cartridge.

8. Firmly close the lid of the main port until it clicks (Figure 9).

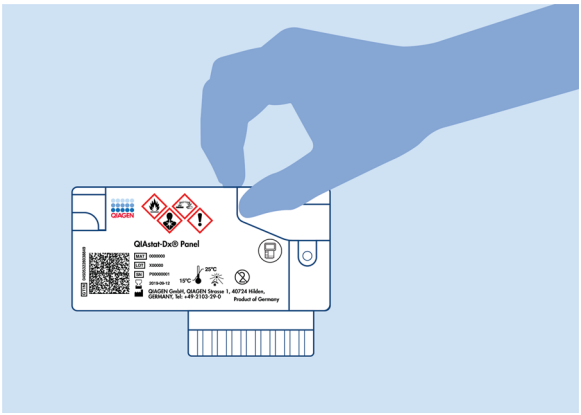


Figure 9. Closing the lid of the main port.

9. Visually confirm that the sample has been loaded by checking the sample inspection window of the QIAstat-Dx ME Panel Cartridge (Figure 10).

   Important: After the sample is placed inside the QIAstat-Dx ME Panel Cartridge, the cartridge must be loaded into the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 within 90 minutes.

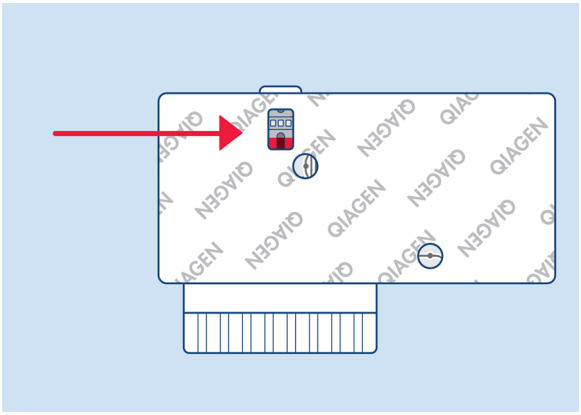


Figure 10. Sample inspection window (red arrow).

Starting the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0

1. Power ON the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 by pressing the **On/Off** button on the front of instrument.

   Note: The power switch on the back of the Analytical Module must be set in the "I" position. The QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 status indicators will turn blue.

2. Wait until the Main screen appears and the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 status indicators turn green and stop blinking.

3. Enter the username and password to log in.

   Note: The Login screen appears if **User Access Control** is activated. If the **User Access Control** is disabled, user name/password is not required and the Main screen will appear.

4. If the Assay Definition File software is not installed on the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0, follow the installation instructions prior to running the test

("Appendix A: Installing the Assay Definition File" on page 115 , for additional information).

Running a test

1. Press **Run Test** in the top-right corner of the touchscreen of the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.
2. When prompted, scan the sample ID bar code on the CSF tube containing the sample, or scan the specimen information barcode located on the top of the QIAstat-Dx ME Panel Cartridge (see step 3) using the integrated front bar code reader of the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 (Figure 11).

   Note: You can also enter the sample ID using the virtual keyboard of the touchscreen by selecting the **Sample ID** field.

   Note: Depending on the selected system configuration, entering the patient ID may also be required at this point.

   Note: Instructions from the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 appear in the Instructions Bar at the bottom of the touchscreen.

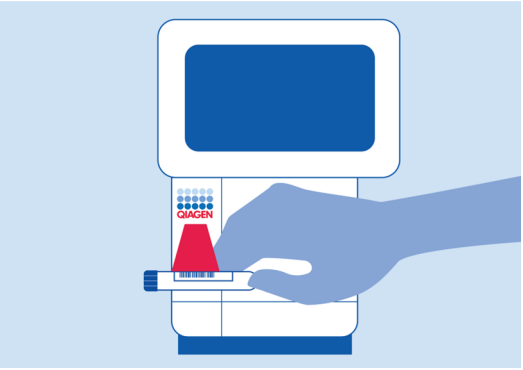


Figure 11. Scanning sample ID bar code.

3. When prompted, scan the bar code of the QIAstat-Dx ME Panel Cartridge to be used (Figure 12). The QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 automatically recognizes the assay to be run based on the cartridge bar code.

   Note: The QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 do not accept QIAstat-Dx ME Panel Cartridges with lapsed expiration dates, previously used cartridges, or cartridges for assays that have not been installed on the unit. An error message is displayed in these cases, and the QIAstat-Dx ME Panel Cartridge will be rejected. Refer to the *QIAstat-Dx Analyzer 1.0 User Manual* or *QIAstat-Dx Analyzer 2.0 User Manual* for further details about how to install assays.

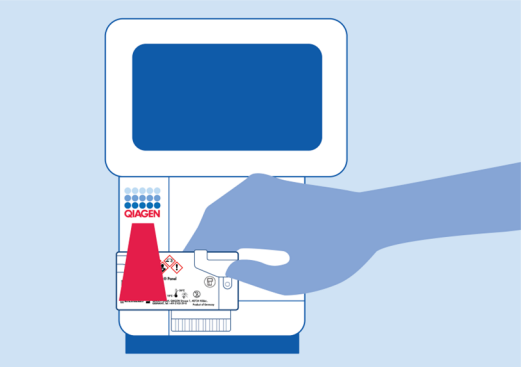


Figure 12. Scanning QIAstat-Dx QIAstat-Dx ME Panel Cartridge bar code.

4. In the Confirm screen, review the entered data and make any necessary changes by selecting the relevant fields on the touchscreen and editing the information.
5. Press **Confirm** if all the displayed data are correct. If needed, select the appropriate field to edit its content, or press **Cancel** to cancel the test (Figure 13).

Figure 13. Confirming data entry.

6. Ensure that both sample lids of the swab port and main port of the QIAstat-Dx ME Panel Cartridge are firmly closed. When the cartridge entrance port on the top of the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 automatically opens, insert the QIAstat-Dx ME Panel Cartridge with the bar code facing to the left and the reaction chambers facing down (Figure 14).

   Note: Do not push the QIAstat-Dx ME Panel Cartridge into the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0. Position it correctly into the cartridge entrance port and the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 will automatically move the cartridge into the Analytical Module.

   Note: The swab port is not used for the QIAstat-Dx ME Panel assay.

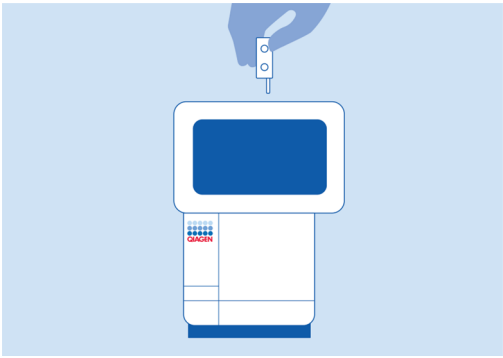


Figure 14. Inserting QIAstat-Dx ME Panel Cartridge into QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.

7. Upon detecting the QIAstat-Dx ME Panel Cartridge, the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 will automatically close the lid of the cartridge entrance port and start the test run. No further action from the operator is required to start the run.

   Note: The QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 will not accept a QIAstat-Dx ME Panel Cartridge other than the one used and scanned during the test setup. If a cartridge other than the one scanned is inserted, an error will be generated and the cartridge will be automatically ejected.

   Note: Up to this point, you can cancel the test run by pressing **Cancel** in the bottom right corner of the touchscreen.

   Note: Depending on system configuration, the operator may be required to re-enter their user password to start the test run.

   Note: The lid of the cartridge entrance port will close automatically after 30 seconds if a QIAstat-Dx ME Panel Cartridge is not positioned in the port. If this occurs, repeat the procedure starting with step 1.

8. While the test is running, the remaining run time is displayed on the touchscreen.

9. After the test run is completed, the Eject screen will appear (Figure 15) and the **Module status bar** will display the test result as one of the following options:

   - **TEST COMPLETED**: The test was completed successfully.
   - **TEST FAILED**: An error occurred during the test.
   - **TEST CANCELED**: The user canceled the test.

   Important: If the test fails, contact QIAGEN Technical Service.

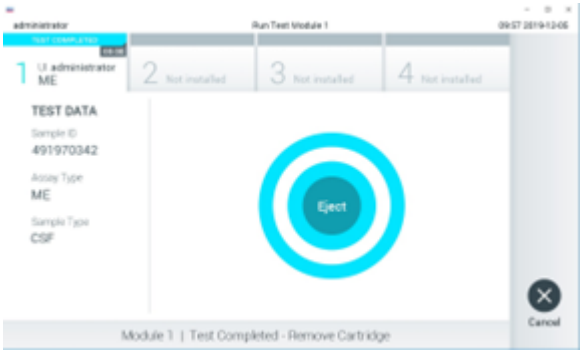


Figure 15. Eject screen display.

10. Press  **Eject** on the touchscreen to remove the QIAstat-Dx ME Panel Cartridge and dispose of it as biohazardous waste in accordance with all national, state, and local health and safety regulations and laws. The QIAstat-Dx ME Panel Cartridge should be removed when the cartridge entrance port opens and ejects the cartridge. If the cartridge is not removed after 30 seconds, it will automatically move back into the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0, and the cartridge entrance port lid will close. If this occurs, press **Eject** to open the lid of the cartridge entrance port again and then remove the cartridge.

Important: Used QIAstat-Dx ME Panel Cartridges must be discarded. It is not possible to re-use cartridges for tests for which the execution was started but then subsequently canceled by the operator, or for which an error was detected.

11. After the QIAstat-Dx ME Panel Cartridge has been ejected, the results Summary screen will appear. To begin the process for running another test, press **Run Test**.

    Note: For further information regarding the use of QIAstat-Dx Analyzer 1.0, refer to *QIAstat-Dx Analyzer 1.0 User Manual*. For further information regarding the use of QIAstat-Dx Analyzer 2.0, refer to *QIAstat-Dx Analyzer 2.0 User Manual*.

Interpretation of Results

Note: Images of the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 screen in this section are meant as an example and may not represent the specific pathogen results provided for the QIAstat-Dx ME Panel.

Viewing results

The QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 automatically interprets and saves test results. After ejecting the QIAstat-Dx ME Panel Cartridge, the results Summary screen is automatically displayed. Figure 16 shows the screen for the QIAstat-Dx Analyzer 1.0.

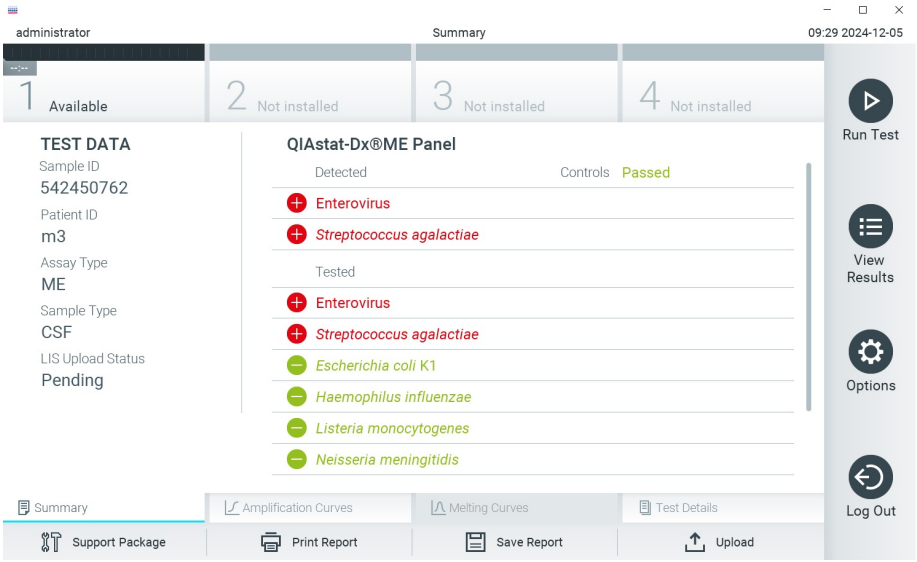


Figure 16. Results Summary screen example showing Test Data on the left panel and Test Summary in the main panel on QIAstat-Dx Analyzer 1.0.

Other tabs with more information are available in this screen (Figure 17). These tabs are explained in the following sections:

- **Amplification curves** ("Viewing amplification curves" on page 43)
- **Melting curves** (this tab is disabled for QIAstat-Dx ME Panel)
- **Test Details** ("Viewing test details" on page 46)

Figure 17 shows the screen for QIAstat-Dx Analyzer 2.0.

Figure 17. Results Summary screen example showing Test Data on the left panel and Test Summary in the main panel on the QIAstat-Dx Analyzer 2.0.

QIAstat-Dx Analyzer 2.0 includes an additional tab:

- **AMR genes**: This is tab is disabled for QIAstat-Dx ME Panel.

Note: From this point forward, example screen shots will be used when referring to the QIAstat-Dx Analyzer 1.0 and/or QIAstat-Dx Analyzer 2.0 where the functions being explained are the same.

The main part of the screen provides the following lists and uses color-coding and symbols to indicate the results:

- The first list, under the heading **Detected**, includes all pathogens detected and identified in the sample, which are preceded by a  sign and are colored red.
- The second list, under the heading **Equivocal** is not used. Equivocal results are not applicable for the QIAstat-Dx ME Panel, therefore, the **Equivocal** list will always be empty.
- The third, under the heading **Tested**, includes all pathogens tested in the sample. Pathogens detected and identified in the sample are preceded by a  sign and are colored green. Invalid pathogens are also displayed in this list.

Note: Pathogens detected and identified in the sample are shown in both the **Detected** and **Tested** lists.

If the test failed to complete successfully, a message will indicate **Failed** followed by the specific Error Code.

The following Test Data is shown on the left side of the screen:

- Sample ID
- Patient ID (if available)
- Assay Type
- Sample Type

Further data about the assay is available, depending on the operator's access rights, through the tabs at the bottom of the screen (e.g., amplification plots and test details).

A report with the assay data can be exported to an external USB storage device. Insert the USB storage device into one of the USB ports of the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 and press **Save Report** in the bottom bar of the screen. This report can be exported later at any time by selecting the test from the **View Result** List.

The report can also be sent to the printer by pressing **Print Report** in the bottom bar of the screen.

Viewing amplification curves

To view test amplification curves of pathogens detected, press the **Amplification Curves** tab (Figure 18).

Figure 18. Amplification Curves screen (PATHOGENS tab).

Details about the tested pathogens and controls are shown on the left and the amplification curves are shown in the center.

Note: If User Access Control is enabled on the QIAstat-Dx Analyzer 1.0 and QIAstat-Dx Analyzer 2.0, the **Amplification Curves** screen is only available for operators with access rights.

Press the **PATHOGENS** tab on the left side to display the plots corresponding to the tested pathogens. Press on the pathogen name to select which pathogens are shown in the amplification plot. It is possible to select single, multiple, or no pathogens. Each pathogen in the selected list will be assigned a color corresponding to the amplification curve associated with the pathogen. Unselected pathogens will be shown in gray.

The corresponding C_T and endpoint fluorescence (EP) values are shown below each pathogen name.

Press the **CONTROLS** tab on the left side to view the controls in the amplification plot. Press the circle next to the control name to select or deselect it (Figure 19).

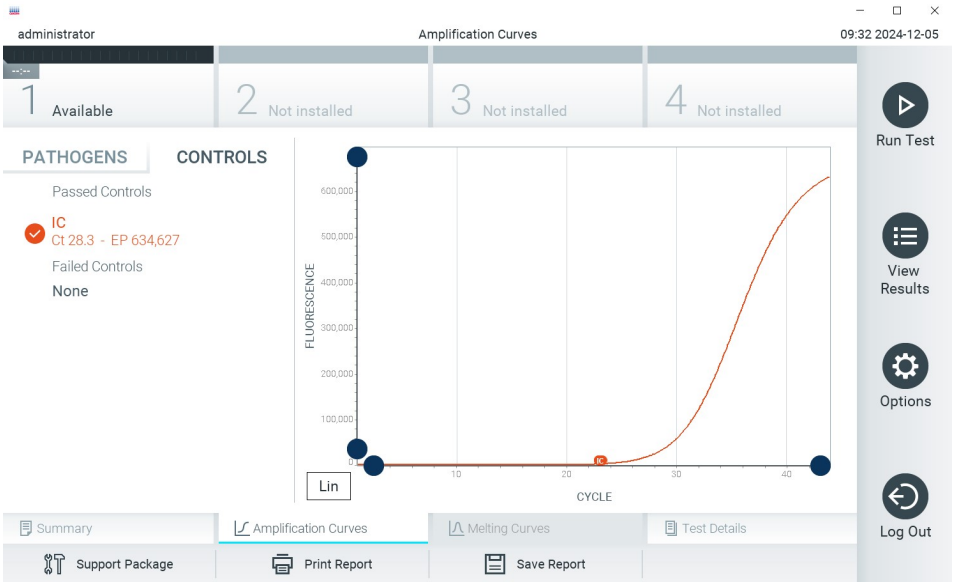


Figure 19. Amplification Curves screen (CONTROLS tab).

The amplification plot displays the data curve for the selected pathogens or controls. To alternate between logarithmic or linear scale for the Y-axis, press the Lin or Log button at the bottom left corner of the plot.

The scale of the X-axis and Y-axis can be adjusted using the **blue pickers** on each axis. Press and hold a blue picker and then move it to the desired location on the axis. Move a blue picker to the axis origin to return to the default values.

Viewing test details

Press **Test Details** in the Tab Menu bar at the bottom of the touchscreen to review the results in more detail. Scroll down to see the complete report.

The following Test Details are shown in the center of the screen (Figure 20):

- User ID
- Cartridge SN (serial number)
- Cartridge Expiration Date
- Module SN
- Test Status (Completed, Failed or Canceled by operator)
- Error Code (if applicable)
- Test Start Date and Time
- Test Execution Time
- Assay Name
- Test ID
- Test Result
    - **Positive** (if at least one meningitis/encephalitis pathogen is detected/identified)
    - **Negative** (if no meningitis/encephalitis pathogen is detected)
    - **Failed** (an error occurred or the test was canceled by the user)

- List of analytes tested in the assay, with C_T and endpoint fluorescence in the event of a positive signal
- Internal Control, with C_T and endpoint fluorescence

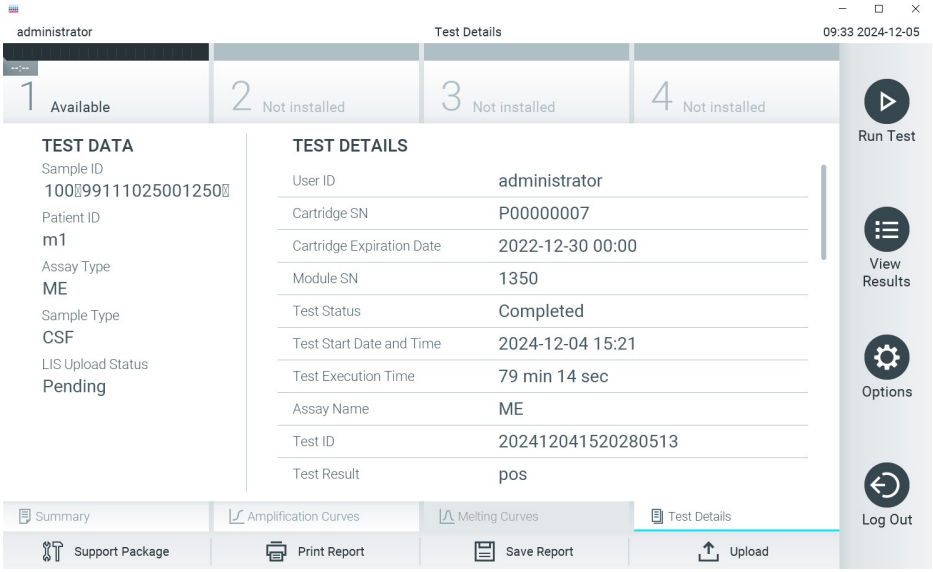


Figure 20. Example screen showing Test Data on the left panel and Test Details in the main panel.

Browsing results from previous tests

To view results from previous tests that are stored in the results repository, press **View Results** on the Main Menu bar (Figure 21).

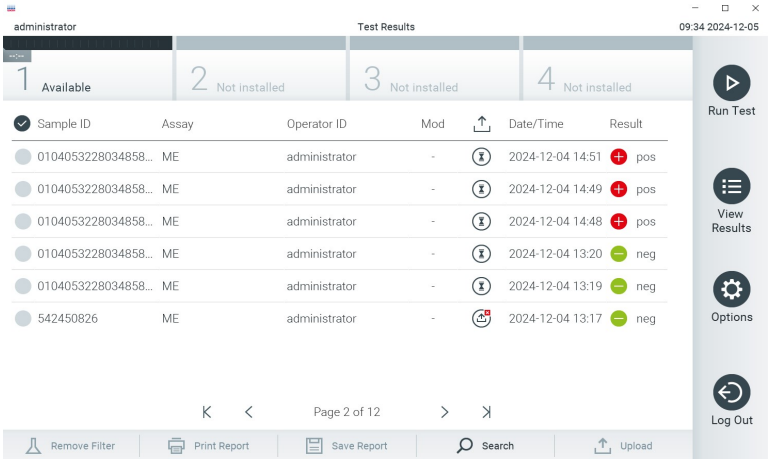


Figure 21. Example View Results screen.

The following information is available for every executed test (Figure 21):

- Sample ID
- Assay (name of test assay which is "ME" for Meningitis/Encephalitis Panel)
- Operator ID
- Mod (Analytical Module on which the test was executed)
- Date/Time (date and time when the test was finished)
- Result (outcome of the test: positive [pos], negative [neg], failed [fail] or successful [suc])

Note: If User Access Control is enabled on the QIAstat-Dx Analyzer 1.0 and QIAstat-Dx Analyzer 2.0, the data for which the user has no access rights will be hidden with asterisks.

Select one or more test results by pressing the gray circle to left of the sample ID. A checkmark will appear next to selected results. Unselect test results by pressing this checkmark. The entire list of results can be selected by pressing the **checkmark** in the top row (Figure 22).

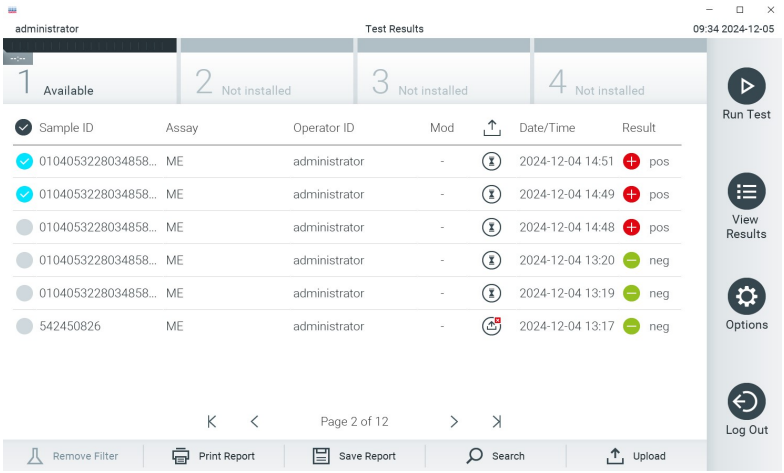


Figure 22. Example of selecting Test Results in the View Results screen.

Press anywhere in the test row to view the result for a particular test.

Press a column headline (e.g., Sample ID) to sort the list in ascending or descending order according to that parameter. The list can be sorted according to only one column at a time.

The Result column shows the outcome of each test (Table 2).

Table 2. Descriptions of the test results in View Results Screen

Outcome	Result	Description	Action
Positive	pos	At least one pathogen is positive	Refer to the Summary Result Screen or Result Printout for pathogen specific results.
Positive with warning	!pos*	At least one pathogen is positive, but the Internal Control failed	Refer to the Summary Result Screen or Result Printout for pathogen specific results.

Table 2. Descriptions of the test results in View Results Screen (continued)

Outcome	Result	Description	Action
Negative	neg	No analytes were detected	Refer to the Summary Result Screen or Result Printout for pathogen specific results.
Failed	fail	The test failed because either an error occurred, the test was canceled by the user, or no pathogens were detected and the internal control failed.	Repeat the test using a new cartridge. Accept the results of the repeat testing. If the error persists, contact QIAGEN Technical Services for further instructions.
Successful	Suc	The test is either positive or negative, but the user does not have the access rights to view the test results.	Login from a user profile with rights to view the results.

Press **Save Report** to save the report(s) for the selected result(s) in PDF format to an external USB storage device.

Select the report type: **List of Tests** or **Test Reports**.

Press **Search** to search the test results by Sample ID, Assay, and Operator ID. Enter the search string using the virtual keyboard and press **Enter** to start the search. Only the records containing the search text will be displayed in the search results.

If the results list has been filtered, the search will only apply to the filtered list.

Press and hold a column headline to apply a filter based on that parameter. For some parameters, such as Sample ID, the virtual keyboard will appear so the search string for the filter can be entered.

For other parameters, such as Assay, a dialog will open with a list of assays stored in the repository. Select one or more assays to filter only the tests that were performed with the selected assays.

The  symbol to the left of a column headline indicates that the column's filter is active.

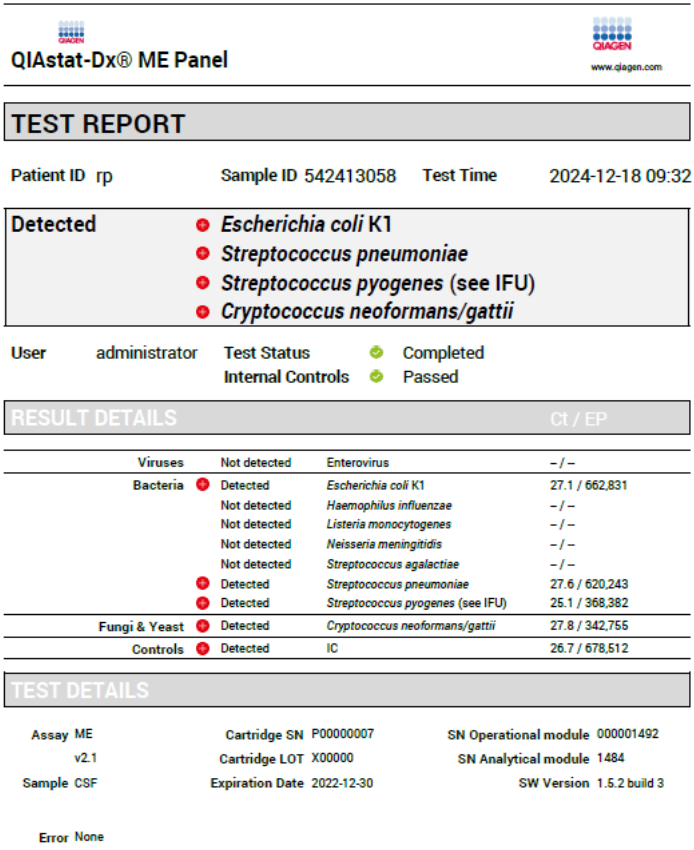
A filter can be removed by pressing Remove Filter in the Submenu bar.

Exporting results to a USB drive

From any tab of the View Results screen, select **Save Report** to export and save a copy of the test results in PDF format to a USB drive (Figure 23 to Figure 24). The USB port is located on the front of the QIAstat-Dx Analyzer 1.0 and QIAstat-Dx Analyzer 2.0. The interpretation of the results in the PDF file is shown on Table 3 below.

Table 3. Interpretation of test results on PDF reports

	Outcome	Symbol	Description
Pathogen result	Detected		Pathogen detected
	Not Detected	No symbol	Pathogen not detected
	Invalid	No symbol	The Internal Control failed there is not valid result for this target and the sample should be retested
Test Status	Completed		The test was completed and the Internal Control and/or one or more targets were detected
	Failed		The test failed
Internal Controls	Passed		The Internal Control passed
	Failed		The Internal Control failed



QIAstat-Dx® ME Panel

www.qiagen.com

TEST REPORT

Patient ID rp Sample ID 542413058 Test Time 2024-12-18 09:32

Detected
- *Escherichia coli* K1
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* (see IFU)
- *Cryptococcus neoformans/gattii*

User administrator Test Status Completed Internal Controls Passed

RESULT DETAILS

				Ct / EP
Viruses		Not detected	Enterovirus	– / –
Bacteria	●	Detected	*Escherichia coli* K1	27.1 / 662,831
		Not detected	*Haemophilus influenzae*	– / –
		Not detected	*Listeria monocytogenes*	– / –
		Not detected	*Neisseria meningitidis*	– / –
		Not detected	*Streptococcus agalactiae*	– / –
	●	Detected	*Streptococcus pneumoniae*	27.6 / 620,243
	●	Detected	*Streptococcus pyogenes* (see IFU)	25.1 / 368,382
Fungi & Yeast	●	Detected	*Cryptococcus neoformans/gattii*	27.8 / 342,755
Controls	●	Detected	IC	26.7 / 678,512

TEST DETAILS

Assay ME v2.1
Sample CSF
Cartridge SN P00000007
Cartridge LOT X00000
Expiration Date 2022-12-30
SN Operational module 000001492
SN Analytical module 1484
SW Version 1.5.2 build 3

Error None

Figure 23. Sample test report.

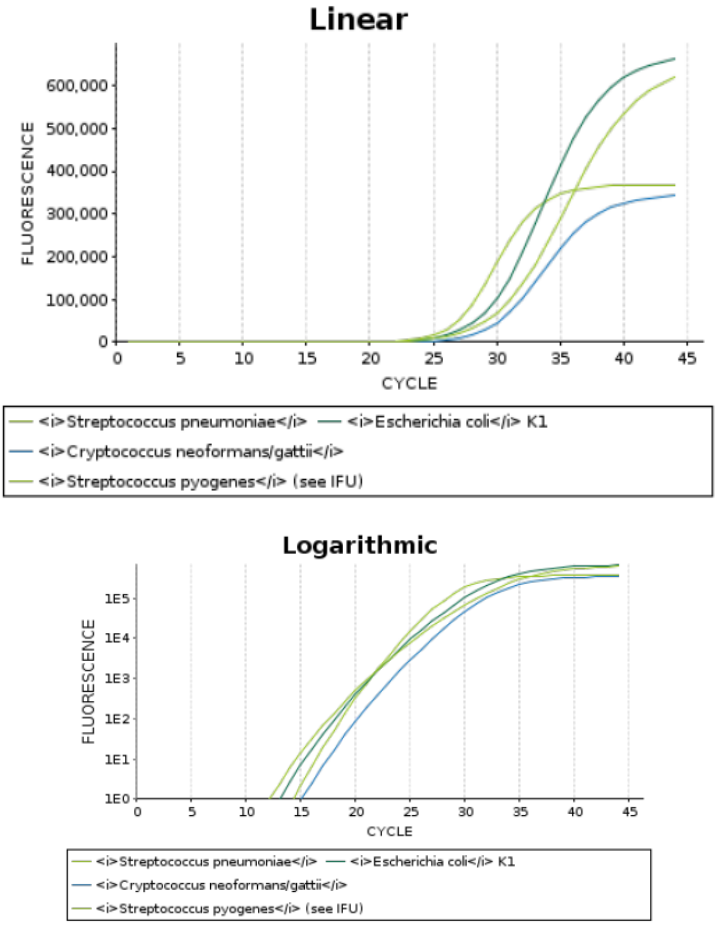


Figure 24. Sample test report showing assay data.

Printing results

Make sure a printer is connected to the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 and the proper driver is installed. Press **Print Report** to send a copy of the PDF test results to the printer.

Result interpretation

A result for a Meningitis/Encephalitis organism is interpreted as **Positive** when the corresponding PCR assay is positive.

Internal control interpretation

The QIAstat-Dx ME Panel Cartridge includes a full process Internal Control, which is titered *Schizosaccharomyces pombe*, a yeast (fungi) that is included in the cartridge in dried form and is rehydrated upon sample loading. This Internal Control material verifies all steps of the analysis process, including sample homogenization, lysis of viral and cellular structures (by means of chemical and mechanical disruption), nucleic acid purification, reverse transcription, and real-time PCR.

A positive signal for the Internal Control indicates that all processing steps performed by the QIAstat-Dx ME Panel Cartridge were successful.

A negative signal of the Internal Control does not negate any positive results for detected and identified targets, but it does invalidate all negative results in the analysis. Therefore, the test should be repeated if the Internal Control signal is negative.

Internal Control results are to be interpreted according to Table 4.

Table 4. Interpretation of Internal Control results

Control result	Explanation	Action
Passed	The Internal Control amplified successfully	The run was completed with success. All results are valid and can be reported. Detected pathogens are reported as positive and undetected pathogens are reported as negative.
Failed	The Internal Control failed	Positively detected pathogen(s) are reported, but all negative results (tested but not detected pathogen[s]) are invalid. Repeat the testing using a new QIAstat-Dx Meningitis/Encephalitis Panel Cartridge.

Quality Control

In accordance with QIAGEN's ISO-certified Quality Management System, each lot of QIAstat-Dx Meningitis/Encephalitis (ME) Panel is tested against predetermined specifications to ensure consistent product quality.

External control information

All external quality control requirements and testing should be performed in accordance with local, state, and federal regulations or accreditation organizations and should follow the user's laboratory standard quality control procedures.

Blank controls are not applicable to the device because it is a single test disposable cartridge. Regular testing of negative and positive external controls is recommended by the company but controls are not provided with the QIAstat-Dx ME Panel.

Limitations

- The QIAstat-Dx ME Panel is intended for professional use only and is not intended for self-testing. The QIAstat-Dx ME Panel is intended for *in vitro* diagnostic use.
- 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. Negative results do not preclude central nervous system (CNS) infection, as not all potential etiological agents are detected by this assay, and pathogens targeted by the QIAstat-Dx ME Panel may be present in lower concentrations below the limits of detection of the system
- 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 QIAstat-Dx Analyzer 2.0.
- 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.
- 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.

- Cross-reactivity with organisms in addition to those listed in the Analytical Specificity section may lead to erroneous results. Although no cross-reactivity was observed with human rhinoviruses in the Analytical Specificity study, neither *in vitro* nor *in silico*, caution should be exercised during specimen collection and testing to prevent contamination with rhinovirus or any other organism associated with respiratory infections.
- *Streptococcus pyogenes* is an extremely rare cause of community- acquired meningitis/encephalitis infections in the U.S. and positive assay result for this analyte should be supported by additional culture evidence.
- Due to the small number of positive prospective and retrospective specimens for certain organisms, performance characteristics for *Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes,* Enterovirus, and *Cryptococcus neoformans/gattii* were established primarily using contrived clinical specimens.
- 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. meningitidi*s will not be detected.

Performance Characteristics

Clinical performance

The clinical performance described in this section was demonstrated using QIAstat-Dx Analyzer 1.0. The QIAstat-Dx Analyzer 2.0 uses the same Analytical Modules as QIAstat-Dx Analyzer 1.0; therefore, 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.

Testing of Prospective Specimens

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 reasons 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 1524 prospective specimens of which 552 (36.2%) were frozen before testing and 972 (63.8%) were tested fresh.

Table 5 provides a summary of demographic information for the 1524 specimens included in the prospective study.

Table 5. Demographic Summary for Prospective Samples for QIAstat-Dx ME Panel Clinical Evaluation

			N	%
Sample Group	**Variable**	**Subgroup**		
Prospective Fresh	Age Group	<1 year	136	14.0
		1-17 years old	87	9.0
		18-44 years old	284	29.2
		45-64 years old	266	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	474	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	174	31.5
		65-84 years old	156	28.3
		≥85 years old	20	3.6
		Unknown	1	0.2
	Gender	Female	271	49.1
		Male	280	50.7
		Not available	1	0.2
Combined	Age Group	<1 year	163	10.7
		1-17 years old	128	8.4

Table 5. Demographic Summary for Prospective Samples for QIAstat-Dx ME Panel Clinical Evaluation (continued)

		N	%
	18-44 years old	417	27.4
	45-64 years old	440	28.9
	65-84 years old	343	22.5
	≥85 years old	31	2.0
	Unknown	2	0.1
Gender	Female	769	50.5
	Male	754	49.5
	Not available	1	0.1

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

All specimens were tested against the FDA-cleared 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 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 *Strepcoccus pyogenes* followed by BDS.

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 prospective data for positive percent agreement and negative percent agreement against the comparator methods are presented by analyte in Table 6.

Table 6. QIAstat-Dx ME Panel Prospective Clinical Performance Summary

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample**	**TP/TP+FN**	**%**	**95% CI***	**TN/TN+FP**	**%**	**95% CI***
Bacteria							
Escherichia coli K1[a]	Prospective Fresh	2 / 3	66.7	20.8–93.9	969 / 969	100.0	99.6–100.0
	Prospective Frozen	0 / 1	0.0	0.0–79.3	551 / 551	100.0	99.3–100.0
	Overall	2 / 4	50.0	15.0–85.0	1520 / 1520	100.0	99.7–100.0
Haemophilus influenzae[b]	Prospective Fresh	0 / 1	0.0	0.0–79.3	970 / 971	99.9	99.4–100.0
	Prospective Frozen	4 / 4	100.0	51.0–100.0	546 / 548	99.6	98.7–99.9
	Overall	4 / 5	80.0	37.6–96.4	1516 / 1519	99.8	99.4–99.9
Listeria monocytogenes[c]	Prospective Fresh	1 / 1	100.0	20.7–100.0	971 / 971	100.0	99.6–100.0
	Prospective Frozen	3 / 4	75.0	30.1–95.4	548 / 548	100.0	99.3–100.0
	Overall	4 / 5	80.0	37.6–96.4	1519 / 1519	100.0	99.7–100.0
Neisseria meningitidis (encapsulated)[d]	Prospective Fresh	1 / 1	100.0	20.7–100.0	971 / 971	100.0	99.6–100.0
	Prospective Frozen	0 / 0	N/A	N/A	551 / 552	99.8	98.0–100.0
	Overall	1 / 1	100.0	20.7–100.0	1522 / 1523	99.9	99.6–100.0

Table 6. QIAstat-Dx ME Panel Prospective Clinical Performance Summary (continued)

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample**	**TP/TP+FN**	**%**	**95% CI***	**TN/TN+FP**	**%**	**95% CI***
Streptococcus agalactiae	Prospective Fresh	2 / 2	100.0	34.2–100.0	970 / 970	100.0	99.6–100.0
	Prospective Frozen	1 / 1	100.0	20.7–100.0	551 / 551	100.0	99.3–100.0
	Overall	3 / 3	100.0	43.9–100.0	1521 / 1521	100.0	99.7–100.0
Streptococcus pneumoniae[e]	Prospective Fresh	1 / 1	100.0	20.7–100.0	845 / 848	99.6	99.0–99.9
	Prospective Frozen	7 / 7	100.0	64.6–100.0	515 / 517	99.6	98.6–99.9
	Overall	8 / 8	100.0	67.6–100.0	1360 / 1365	99.6	99.1–99.8
Streptococcus pyogenes	Prospective Fresh	0 / 0	N/A	N/A	778 / 778	100.0	99.5–100.0
	Prospective Frozen	0 / 0	N/A	N/A	513 / 513	100.0	99.3–100.0
	Overall	0 / 0	N/A	N/A	1291 / 1291	100.0	99.7–100.0
Virus							
Enterovirus (EV)[f]	Prospective Fresh	18 / 20	90.0	69.9–97.2	951 / 952	99.9	99.4–100.0
	Prospective Frozen	4 / 4	100.0	51.0–100.0	548 / 548	100.0	99.3–100.0
	Overall	22 / 24	91.7	74.2–97.7	1499 / 1500	99.9	99.6–100.0
Fungi & Yeast							

Table 6. QIAstat-Dx ME Panel Prospective Clinical Performance Summary (continued)

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample**	**TP/TP+FN**	**%**	**95% CI***	**TN/TN+FP**	**%**	**95% CI***
Cryptococcus gattii / Cryotococcus neoformans (not differentiated)[g]	Prospective Fresh	2 / 5	40.0	11.8–76.9	965 / 967	99.8	99.2–99.9
	Prospective Frozen	2 / 2	100.0	34.2–100.0	550 / 550	100.0	99.1–100.0
	Overall	4 / 7	57.1	25.0–84.2	1515 / 1517	99.9	99.5–100.0

[a] For the prospective fresh *Escherichia coli* K1 discordant sample, no organisms were detected with PCR/BDS. For the frozen Escherichia coli K1 discordant sample no organisms were detected with bacterial culture.

[b] For the prospective fresh *Haemophilus influenzae* discordant sample, no organisms were detected by the SoC bacterial culture and testing with PCR/BDS. Of the three (3) false positive *Haemophilus influenzae* samples, no organisms were detected in one fresh and one frozen by SoC culture and PCR/BDS was also negative. No additional testing results associated with the final frozen false positive sample were available.

[c] For the frozen *Listeria monocytogenes* discordant sample, SoC culture and LDT result was positive.

[d] For the frozen *Neisseria meningitidis* (encapsulated) sample, no organisms were detected by SoC culture and LDT testing with PCR/BDS also returned a negative result for this sample.

[e] Of the five (5) false positive *Streptococcus pneumoniae* samples, no organisms were detected in four (3 fresh and 1 frozen) prospective samples with SoC culture. One prospective frozen sample had no SoC result available. However, an FDA cleared method conducted as part of the study also produced a negative result.

[f] For the prospective fresh Enterovirus discordant samples, no organisms were detected in one sample by two independent SoC LDT assays. The negative result for the second sample returned a negative result with PCR/BDS. For the prospective fresh false positive Enterovirus sample, a negative result was returned when tested with PCR/BDS.

[g] Of the three false negative *Cryptococcus gattii / Cryptococcus neoformans* (not differentiated) results, no organisms were detected in two fresh samples with fungal culture and PCR/BDS. The remaining false negative fresh sample was resulted negative for *Cryptococcus gattii / Cryptococcus neoformans* (not differentiated) with PCR/BDS. Of the two false positive results, no organisms were detected for one fresh sample with PCR/BDS. No organisms were detected in the second fresh sample with SoC fungal culture.

Co-infection summary

The QIAstat-Dx ME Panel detected no multiple organism detections in the prospective study.

Testing of Preselected Archived specimens

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. One hundred and fifty-four (154) archived specimens were excluded from the analysis. A total of 41 evaluable archived specimens were used in the analysis to support the QIAstat-Dx ME Panel performance evaluation and Table 7 provides a summary of demographic information for the archived specimens.

Table 7. Demographic Summary of Evaluable Archived Specimens for QIAstat-Dx ME Panel Clinical Evaluation

Sample	Variable	Subgroup	N	%
Archived	Age Group	<1 year	11	26.8
		1-17 years old	9	22.0
		18-44 years old	12	29.3
		45-64 years old	5	12.2
		65-84 years old	4	9.8
	Gender	Female	19	46.3
		Male	22	53.7

The QIAstat-Dx ME Panel retrospective archived specimen data in positive percent agreement and negative percent agreement against the comparator methods are presented by analyte in Table 8.

Table 8. QIAstat-Dx ME Panel Archived Clinical Performance Summary

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Bacteria						
Escherichia coli K1	2 / 2	100.0	34.2–100.0	39 / 39	100.0	91.0-100.0
Haemophilus influenzae	6 / 6	100.0	61.0-100.0	35 / 35	100.0	90.1-100.0
Listeria monocytogenes	0 / 0	N/A	N/A	41 / 41	100.0	91.4-100.0
Neisseria meningitidis (encapsulated)	3 / 3	100.0	43.9-100.0	38 / 38	100.0	90.8-100.0
Streptococcus agalactiae	9 / 9	100.0	70.1-100.0	32 / 32	100.0	89.3-100.0
Streptococcus pneumoniae	4 / 4	100.0	51.0–100.0	18 / 18	100.0	82.4-100.0
Streptococcus pyogenes	0 / 0	N/A	N/A	23 / 23	100.0	85.7-100.0
Virus						
Enterovirus (EV)	9 / 9	100.0	70.1-100.0	32 / 32	100.0	89.3-100.0
Fungi / Yeast						
Cryptococcus gattii / Cryptococcus neoformans (not differentiated)	8 / 8	100.0	67.6–100.0	33 / 33	100.0	89.6-100.0

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 specimen. This data was used in additional performance calculations outlined in Table 9, Table 10, Table 11, and Table 12.

Table 9. Culture comparison for diagnostic sensitivity and specificity for all clinical samples overall

	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	1113 / 1114	99.9	99.5–100.0
Haemophilus influenzae[b]	4 / 4	100.0	51.0-100.0	1110 / 1113	99.7	99.2–99.9
Listeria monocytogenes[c]	3 / 4	75.0	30.1-95.4	1113 / 1113	100.0	99.7–100.0
Neisseria meningitidis (encapsulated)[d]	2 / 2	100.0	34.2-100.0	1112 / 1115	99.7	99.2–99.9
Streptococcus agalactiae[e]	2 / 2	100.0	34.2-100.0	1114 / 1115	99.9	99.5–100.0
Streptococcus pneumoniae[f]	3 / 3	100.0	43.9-100.0	1107 / 1114	99.4	98.7–99.7
Streptococcus pyogenes[g]	0 / 0	N/A	N/A	1116 / 1117	99.9	99.5–100.0

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

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

Table 9. Culture comparison for diagnostic sensitivity and specificity for all clinical samples overall (continued)

	Sensitivity (compared to culture)			Specificity (compared to culture)		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**

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 Of the three false positive *Neisseria meningitidis* (encapsulated) samples when compared to culture, one returned a negative result with a SoC LDT, an FDA cleared molecular method and the validated PCR/BDS assay. One returned a positive result with an FDA cleared 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, an FDA cleared 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 molecular method therefore PCR/BDS testing was not performed.

f There were seven false positive results when compared with bacterial culture. For two samples there was no PCR/BDS comparator result available. Testing of four 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.

Table 10. Culture comparison for diagnostic sensitivity and specificity by sample category

		Sensitivity (compared to culture)			Specificity (compared to culture)		
Pathogen	**Sample**	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Bacteria							
Escherichia coli K1	Archived	1 / 1	100.0	20.7-100.0	10 / 11	90.9	62.3-98.4
	Prospective Fresh	1 / 2	50.0	9.5–90.5	760 / 760	100.0	99.5–100.0
	Prospective Frozen	0 / 0	N/A	N/A	343 / 343	100.0	98.9-100.0
Haemophilus influenzae	Archived	1 / 1	100.0	20.7-100.0	10 / 11	90.9	62.3-98.4
	Prospective Fresh	0 / 0	N/A	N/A	761 / 762	99.9	99.3-100.0
	Prospective Frozen	3 / 3	100.0	43.9–100.0	339 / 340	99.7	98.4-99.9
Listeria monocytogenes	Archived	0 / 0	N/A	N/A	12 / 12	100.0	75.8-100.0
	Prospective Fresh	1 / 1	100.0	20.7–100.0	761 / 761	100.0	99.5–100.0
	Prospective Frozen	2 / 3	66.7	20.8–93.9	340 / 340	100.0	98.9–100.0
Neisseria meningitidis (encapsulated)	Archived	2 / 2	100.0	34.2-100.0	9 / 10	90.0	59.6-98.2
	Prospective Fresh	0 / 0	N/A	N/A	761 / 762	99.9	99.3-100.0
	Prospective Frozen	0 / 0	N/A	NA	342 / 343	99.7	98.4-99.9

Table 10. Culture comparison for diagnostic sensitivity and specificity by sample category (continued)

		Sensitivity (compared to culture)			Specificity (compared to culture)		
Pathogen	**Sample**	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Streptococcus agalactiae	Archived	0 / 0	N/A	N/A	12 / 12	100.0	75.8-100.0
	Prospective Fresh	1 / 1	100.0	20.7-100.0	760 / 761	99.9	99.3-100.0
	Prospective Frozen	1 / 1	100.0	20.7-100.0	342 / 342	100.0	98.9-100.0
Streptococcus pneumoniae	Archived	0 / 0	N/A	N/A	11 / 12	91.7	64.6-98.5
	Prospective Fresh	0 / 0	N/A	N/A	757 / 762	99.3	98.5-99.7
	Prospective Frozen	3 / 3	100.0	43.9-100.0	339 / 340	99.7	98.4-99.9
Streptococcus pyogenes	Archived	0 / 0	N/A	N/A	12 / 12	100.0	75.8-100.0
	Prospective Fresh	0 / 0	N/A	N/A	761 / 762	99.9	99.3-100.0
	Prospective Frozen	0 / 0	N/A	N/A	343 / 343	100.0	98.9-100.0

Fungal culture is considered the gold standard approach for the diagnosis of cryptococcal meningitis, therefore QIAstat-Dx ME Panel performance for detection of *Cryptococcus* was also calculated in comparison to fungal culture performed as a standard of care diagnostic at clinical testing sites. For data that were available, QIAstat-Dx ME Panel performance is summarized in Table 11and Table 12.

Table 11. Performance Evaluation for *Cryptococcus gattii / Cryptococcus neoformans* (not differentiated) with Fungal Culture (when available)

	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)[a]	3 / 3	100.0	43.9–100.0	154 / 156	98.7	95.4–99.6

a There were two false positive samples, one sample which was fungal culture negative, was also tested with the FDA-cleared comparator 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 comparator assay and was also negative on SoC Cryptococcal Antigen test.

Table 12. Fungal Culture comparisonfor diagnostic sensitivity and specificity by sample category

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample type**	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Fungi & Yeast							
Cryptococcus gattii / Cryptococcus neoformans [a] (not differentiated)	Archived	2/2	100.0	34.2–100.0	1/1	100.0	20.7–100.0
	Prospective Fresh	1/1	100.0	20.7–100.0	129/131	98.5	94.6–99.6
	Prospective Frozen	0/0	NA	NA	24/24	100.0	86.2–100.0

Validity of results

The proportion of failed runs in clinical specimens on initial attempt was 2.7% (26/977) for prospective fresh, 1.3% (7/555) for prospective frozen and 1.7% (3/176) for archived and following repeats was 0.3% (3/977) for prospective fresh, 0.4% (2/555) for prospective frozen and 0.0% (0/176) for archived samples, yielding an overall success rate of 97.9%

(1672/1708) before retesting, and of 99.7% (1703/1708) after retesting. The error breakdown due to instrument, invalid results and other run failures is summarized in Table 13. Withdrawn specimens were not included in the validity assessment; however some prospective samples which were excluded from the agreement analysis were included for the validity assessment (3 prospective fresh, 5 prospective frozen and 135 archive specimens).

Table 13. Summary of the Number of Samples with Failed Test Results (Initial and Final)

		Initial Runs		Final Runs (after repeats)	
Sample Type	**Failure Reason**	**N/Total**	**%**	**N/Total**	**%**
Prospective Fresh	Invalid*	0 / 977	0.0	0 / 977	0.0
	Instrument	3 / 977	0.3	0 / 977	0.0
	Other**	23 / 977	2.4	3 / 977	0.3
Prospective Frozen	Invalid	0 / 555	0.0	0 / 555	0.0
	Instrument	1 / 555	0.2	0 / 555	0.0
	Other	6 / 555	1.1	2 / 555	0.4
Archived	Invalid	2 / 176	1.1	0 / 176	0.0
	Instrument	1 / 176	0.6	0 / 176	0.0
	Other	0 / 176	0.0	0 / 176	0.0

*Internal Control failures with at least one analyte detected and the other analytes reported as 'invalid'

** Run failures related to workflow checkpoints.

Testing of contrived specimens

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 the 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 14.

Table 14. QIAstat-Dx ME Panel Contrived Sample Performance Summary

Classification (genome type)	Pathogen	Concentration Level	Frequency of Positive Results	Proportion (%) of Positive Results	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Bacteria	*Escherichia coli K1*	2x LoD	48 / 48	100.0	92.6	100.0
		5x LoD	37 / 37	100.0	90.6	100.0
		Total	85 / 85	100.0	95.7	100.0
	Haemophilus influenzae	2x LoD	57 / 57	100.0	93.7	100.0
		5x LoD	36 / 36	100.0	90.4	100.0
		Total	93 / 93	100.0	96.0	100.0
	Listeria monocytogenes	2x LoD	47 / 49	95.9	86.3	98.9
		5x LoD	38 / 38	100.0	90.8	100.0
		Total	85 / 87	97.7	92.0	99.4
	Neisseria meningitidis (encapsulated)	2x LoD	46 / 48	95.8	86.0	98.8
		5x LoD	39 / 40	97.5	87.1	99.6
		Total	85 / 88	96.6	90.5	98.8
	Streptococcus agalactiae	2x LoD	49 / 49	100.0	92.7	100.0
		5x LoD	39 / 39	100.0	91.0	100.0
		Total	88 / 88	100.0	95.8	100.0
	Streptococcus pneumoniae	2x LoD	55 / 57	96.5	88.1	99.0
		5x LoD	39 / 39	100.0	91.0	100.0
		Total	94 / 96	97.9	92.7	99.4

Table 14. QIAstat-Dx ME Panel Contrived Sample Performance Summary (continued)

Classification (genome type)	Pathogen	Concentration Level	Frequency of Positive Results	Proportion (%) of Positive Results	Lower 95% Confidence Limit	Upper 95% Confidence Limit
	Streptococcus pyogenes	2x LoD	47 / 49	95.9	86.3	98.9
		5x LoD	40 / 40	100.0	91.2	100.0
		Total	87 / 89	97.8	92.2	99.4
Virus	*Enterovirus (EV)*	2x LoD	48 / 49	98.0	89.3	99.6
		5x LoD	39 / 39	100.0	91.0	100.0
		Total	87 / 88	98.9	93.8	99.8
Fungi / Yeast	*Cryptococcus gattii / Cryptococcus neoformans (not differentiated)*	2x LoD	41 / 41	100.0	91.4	100.0
		5x LoD	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 2x LoD and 5x LoD in all tested analytes.

QIAstat-Dx ME Panel performance across all specimen types

The overall target specific PPA and NPA results, when considering all sample types, are reported in Table 15.

Table 15. QIAstat-Dx ME Panel Performance per analyte across all Specimen Types

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample Type**	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Bacteria							
Escherichia coli K1	Prospective Fresh	2 / 3	66.7	20.8–93.9	969 / 969	100.0	99.6–100.0

Table 15. QIAstat-Dx ME Panel Performance per analyte across all Specimen Types (continued)

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample Type**	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
	Prospective Frozen	0 / 1	0.0	0.0–79.3	551 / 551	100.0	99.3–100.0
	Archived	2 / 2	100.0	34.2–100.0	39 / 39	100.0	97.8–100.0
	Contrived	85 / 85	100.0	95.7–100.0	1060 / 1064	99.6	99.0–99.9
Haemophilus influenzae	Prospective Fresh	0 / 1	0.0	0.0–79.3	970 / 971	99.9	99.4–100.0
	Prospective Frozen	4 / 4	100.0	51.0–100.0	546 / 548	99.6	98.7–99.9
	Archived	6 / 6	100.0	61.0–100.0	35 / 35	100.0	90.1–100.0
	Contrived	93 / 93	100.0	96.0–100.0	1052 / 1056	99.6	99.0–99.9
Listeria monocytogenes	Prospective Fresh	1 / 1	100.0	20.7–100.0	971 / 971	100.0	99.6–100.0
	Prospective Frozen	3 / 4	75.0	30.0–95.4	548 / 548	100.0	99.3–100.0
	Archived	0 / 0	N/A	N/A	41 / 41	100.0	91.4–100.0
	Contrived	85 / 87	97.7	92.0–99.4	1063 / 1063	100.0	99.6–100.0

Table 15. QIAstat-Dx ME Panel Performance per analyte across all Specimen Types (continued)

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample Type**	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Neisseria meningitidis (encapsulated)	Prospective Fresh	1 / 1	100.0	20.7–100.0	971 / 971	100.0	99.6–100.0
	Prospective Frozen	0 / 0	N/A	N/A	551 / 552	99.8	99.0–100.0
	Archived	3 / 3	100.0	43.9-100.0	38 / 38	100.0	90.8–100.0
	Contrived	85 / 88	96.6	90. 5-98.8	1061 / 1061	100.0	99.6–100.0
Streptococcus agalactiae	Prospective Fresh	2 / 2	100.0	34.2-100.0	970 / 970	100.0	99.6%-100.0
	Prospective Frozen	1 / 1	100.0	20.7-100.0	551 / 551	100.0	99.3–100.0
	Archived	9 / 9	100.0	70.1-100.0	32 / 32	100.0	89.3–100.0
	Contrived	88 / 88	100.0	95.8-100.0	1058 / 1062	99.6	99.0–99.9
Streptococcus pneumoniae	Prospective Fresh	1 / 1	100.0	20.7-100.0	845 / 848	99.6	99.0–99.9
	Prospective Frozen	7 / 7	100.0	64.6-100.0	515 / 517	99.6	98.6–99.9
	Archived	4 / 4	100.0	51.0-100.0	18 / 18	100.0	82.4–100.0
	Contrived	94 / 96	97.9	92.7-99.4	1053 / 1053	100.0	99.6–100.0

Table 15. QIAstat-Dx ME Panel Performance per analyte across all Specimen Types (continued)

		Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**Sample Type**	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Streptococcus pyogenes	Prospective Fresh	0 / 0	N/A	N/A	778 / 778	100.0	99.5–100.0
	Prospective Frozen	0 / 0	N/A	N/A	513 / 513	100.0	99.3–100.0
	Archived	0 / 0	N/A	N/A	23 / 23	100.0	85.7–100.0
	Contrived	87 / 89	97.8	92.2-99.4	1060 / 1060	100.0	99.6–100.0
Virus							
Enterovirus (EV)	Prospective Fresh	18 / 20	90.0	69.9-97.2	951 / 952	99.9	99.4–100.0
	Prospective Frozen	4 / 4	100.0	51.0-100.0	548 / 548	100.0	99.3–100.0
	Archived	9 / 9	100.0	70.1-100.0	32 / 32	100.0	89.3–100.0
	Contrived	87 / 88	98.9	93.8-99.8	1058 / 1062	99.6	99.0–99.9
Fungi / Yeast							
Cryptococcus gattii / *Cryptococcus neoformans* (not differentiated)	Prospective Fresh	2 / 5	40.0	11.8-76.9	965 / 967	99.8	99.2–99.9
	Prospective Frozen	2 / 2	100.0	34.2-100.0	550 / 550	100.0	99.3–100.0
	Archived	8 / 8	100.0	67. 6-100.0	33 / 33	100.0	89.6–100.0
	Contrived	79 / 79	100.0	95.4-100.0	1071 / 1071	100.0	99.6–100.0

Target specific PPA ≥95% and NPA ≥98.5% was achieved for all QIAstat-Dx ME Panel analytes when assessing performance across prospective, retrospective archived and contrived specimens.

Expected values for all targets

The number and percentage of positive cases, as determined by the QIAstat-Dx ME Panel, calculated by testing site or by age group are present in Table 16. Overall, 1527 specimens were included in the prevalence assessment and the QIAstat-Dx ME Panel detected at least one organism in a total of 65 prospective specimens (4.3% positivity rate).

Table 16. Expected value (EV) (as determined by the QIAstat-Dx ME Panel) summary overall and by site for all targets

Pathogen	Overall	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10	Site 11	Site 12	Site 13
Bacteria														
Escherichia coli K1	2 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haemophilus influenzae	7 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (1.0%)	3 (1.7%)	0 (0.0%)	0 (0.0%)
Listeria monocytogenes	4 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)
Neisseria meningitidis (encapsulated)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Streptococcus agalactiae	3 (0.2%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Streptococcus pneumoniae	17 (1.1%)	2 (2.2%)	0 (0.0%)	3 (2.0%)	1 (0.4%)	2 (4.2%)	1 (1.2%)	3 (2.5%)	0 (0.0%)	1 (0.8%)	1 (0.5%)	3 (1.7%)	0 (0.0%)	0 (0.0%)
Streptococcus pyogenes	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Virus														
Enterovirus (EV)	23 (1.5%)	5 (5.6%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	5 (10.4%)	2 (2.4%)	2 (1.7%)	1 (1.7%)	6 (5.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)

Table 16. Expected value (EV) (as determined by the QIAstat-Dx ME Panel) summary overall and by site for all targets (continued)

Pathogen	Overall	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10	Site 11	Site 12	Site 13
Fungi / Yeast														
Cryptococcus gattii / Cryotococcus neoformans (not differentiated)	6 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.7%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Overall Panel Result														
Negative	1462 (95.7%)	81 (90.0%)	74 (100.0%)	145 (95.4%)	260 (97.7%)	38 (79.2%)	82 (96.5%)	113 (95.8%)	58 (96.7%)	112 (92.6%)	192 (98.5%)	165 (93.8%)	94 (100.0%)	48 (100.0%)
Positive	65 (4.3%)	9 (10.0%)	0 (0.0%)	7 (4.6%)	6 (2.3%)	10 (20.8%)	3 (3.5%)	5 (4.2%)	2 (3.3%)	9 (7.4%)	3 (1.5%)	11 (6.3%)	0 (0.0%)	0 (0.0%)

Table 17. Expected value (EV) (as determined by the QIAstat-Dx ME Panel) summary overall and by age for all targets.

Pathogen	Overall	<1 year	1-17 years old	18-44 years old	45-64 years old	65-84 years old	>85 years old	Unknown
Bacteria								
Escherichia coli K1	2 (0.1%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haemophilus influenzae	7 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	5 (1.1%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Listeria monocytogenes	4 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	1 (0.3%)	1 (3.2%)	0 (0.0%)
Neisseria meningitidis (encapsulated)	2 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Streptococcus agalactiae	3 (0.2%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Streptococcus pneumoniae	17 (1.1%)	3 (1.8%)	0 (0.0%)	3 (0.7%)	7 (1.6%)	4 (1.2%)	0 (0.0%)	0 (0.0%)
Streptococcus pyogenes	1 (0.1%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Virus								
Enterovirus (EV)	23 (1.5%)	12 (7.4%)	3 (2.3%)	5 (1.2%)	1 (0.2%)	1 (0.3%)	0 (0.0%)	1 (50.0%)
Fungi / Yeast								
Cryptococcus gattii / Cryptococcus neoformans (not differentiated)	*6 (0.4%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.2%)*	*5 (1.1%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
Overall Panel Result								
Negative	1462 (95.7%)	145 (89.0%)	124 (96.9%)	407 (97.4%)	419 (94.8%)	336 (98.0%)	30 (96.8%)	1 (50.0%)
Positive	65 (4.3%)	18 (11.0%)	4 (3.1%)	11 (2.6%)	23 (5.2%)	7 (2.0%)	1 (3.2%)	1 (50.0%)

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.

Analytical performance

The analytical performance described in this section was demonstrated using QIAstat-Dx Analyzer 1.0. The QIAstat-Dx Analyzer 2.0 uses the same Analytical Module as QIAstat-Dx Analyzer 1.0; therefore, 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 26 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 18.

Table 18. Limit of detection results

Pathogen	Strain	Supplier	Concentration	Detection rate
Escherichia coli K1	Strain C5 [Bort]; O18ac:K1:H7	ATCC 700973	3.48E+02 CFU/mL	30/30
Escherichia coli K1	NCTC 9001. Serovar O1:K1:H7	ATCC 11775	7.86E+02 CFU/mL	30/30
Haemophilus influenzae	type b (cap)	ATCC 10211	3.16E+02 CFU/mL	32/32
Haemophilus influenzae	Type e [strain AMC 36-A-7]	ATCC 8142	2.54E+03 CFU/mL	30/30
Listeria monocytogenes	Type 1/2b	ZeptoMetrix 0801534	1.86E+03 CFU/mL	21/21
Listeria monocytogenes	Type 4b. Strain Li 2	ATCC 19115	6.64E+03 CFU/mL	30/30
Neisseria meningitidis (encapsulated)	Serotype B. M2092	ATCC 13090	8.28E-02 CFU/mL	31/32
Neisseria meningitidis (encapsulated)	Serotype Y. M-112 [BO-6]	ATCC 35561	1.33E+01 CFU/mL	30/30
Streptococcus agalactiae	Z019	ZeptoMetrix 0801545	1.75E+03 CFU/mL	30/30
Streptococcus agalactiae	G19 group B	ATCC 13813	3.38E+03 CFU/mL	31/31

Table 18. Limit of detection results (continued)

Pathogen	Strain	Supplier	Concentration	Detection rate
Streptococcus pneumoniae	19F	ZeptoMetrix 0801439	7.14E+02 CFU/mL	29/30
Streptococcus pneumoniae	Serotype 1. NCTC 7465	ATCC 33400	6.22E-01 CFU/mL	29/29
Streptococcus pyogenes	Z472; Serotype M1	ZeptoMetrix 0804351	1.80E+03 CFU/mL	30/30
Streptococcus pyogenes	Bruno [CIP 104226]	ATCC 19615	9.10E+01CFU/mL	30/30
Enterovirus A	Coxsackievirus A16	ZeptoMetrix 0810107CF	3.79E+00 $TCID_{50}$/mL	31/31
Enterovirus A	A6, species A. Strain Gdula	ATCC VR-1801	1.60E+02 $TCID_{50}$/mL	30/30
Enterovirus B	Coxsackievirus B5	ZeptoMetrix 0810019CF	8.91E+01 $TCID_{50}$/mL	30/30
Enterovirus B	Coxsackievirus A9, species B	ZeptoMetrix 0810017CF	4.36E+01 $TCID_{50}$/mL	28/29
Enterovirus C	Coxsackievirus A17, species C. Strain G-12	ATCC VR-1023	1.58E+01 $TCID_{50}$/mL	30/30
Enterovirus C	Coxsackievirus A24. Strain DN-19	ATCC VR-583	4.99E+00 $TCID_{50}$/mL	30/30
Enterovirus D	EV 70, species D, strain J670/71	ATCC VR-836	4.99E+01 $TCID_{50}$/mL	30/31
Enterovirus D	Enterovirus D68. Strain US/MO/14-18947	ATCC VR-1823	5.06E+02 $TCID_{50}$/mL	30/30

Table 18. Limit of detection results (continued)

Pathogen	Strain	Supplier	Concentration	Detection rate
Cryptococcus neoformans	Serotype D strain WM629, type VNIV	ATCC MYA-4567	2.21E+03 CFU/mL	31/31
Cryptococcus neoformans	*C. neoformans* H99	ATCC 208821	1.64E+02 CFU/mL	31/31
Cryptococcus gattii	Serotype B strain R272, type VGIIb	ATCC MYA-4094	1.32E+04 CFU/mL	30/30
Cryptococcus gattii	A6MR38 [CBS 11545]	ATCC MYA-4877	2.60E+03 CFU/mL	29/29

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 sub-types, 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 130 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 20).

- *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 19).

Table 19. Clinically relevant strains/subtypes detected per pathogen

Pathogen	Clinically relevant strains/subtypes detected
Neisseria meningitidis (encapsulated)	All the encapsulated serotypes (A, B, C, D, E, H, I, K, L, NG, W, W135, X, Y, Z, 29E)
Cryptococcus gattii/ neoformans	All Cryptococcus spp. serotypes: 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)
Listeria monocytogenes	Serotypes 1/2a,1/2b, 1/2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e, 7
Haemophilus influenzae	All encapsulated serotypes (a, b, c, d, e, f) and unencapsulated strains (nontypeable, NTHi) including var. H. aegyptus
Enterovirus	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)
Escherichia coli K1	K1 strains (excluding general E.coli strains)
Rest of On-Panel organism with no biological subclassification (*S. pneumoniae, S. agalactiae, S. pyogenes*)	All genomic sequences available in databases detected

Strains tested for inclusivity are detailed in Table 20.

Table 20. Strains tested for inclusivity

Pathogen	Strain/Serotype	Supplier
Escherichia coli K1	Strain C5 [Bort]; O18ac:K1:H7	ATCC 700973
	NCTC 9001. Serovar O1:K1:H7	ATCC 11775
	Strain Bi 7509/41; O7:K1:H-	NCTC 9007
	NCDC Bi 7509-41 Serotype O7:K1(L):NM	ATCC 23509
	NCDC F 11119-41	ATCC 23511
	O-2, U9-41	BEI Resources NR-17666
	O-16, F1119-41	BEI Resources NR-17674
	Z136 CTX-M-15	ZeptoMetrix 0801905
	Sc15 02:K1:H6	NCTC 11101
	Strain H61; O45:K1:H10	NCTC 9045
Haemophilus influenzae	type b (cap)	ATCC 10211
	Type e [strain AMC 36-A-7]	ATCC 8142
	Non-typeable [strain Rd KW20]	ATCC 51907
	Non-typeable [strain 180-a]	ATCC 11116
	Type a [strain AMC 36-A-3]	ATCC 9006
	Type b [strain Rab]	ATCC 31512
	Type c [strain C 9007]	ATCC 49699
	Type d [strain AMC 36-A-6]	ATCC 9008
	Type f [strain GA-1264]	ATCC 700223

Table 20. Strains tested for inclusivity (continued)

Pathogen	Strain/Serotype	Supplier
	L-378	ATCC 49766
Listeria monocytogenes	Type 1/2b	ZeptoMetrix 0801534
	Type 4b. Strain Li 2	ATCC 19115
	Type 1/2a. Strain 2011L-2676	ATCC BAA-2659
	Type 1/2a. Strain Li 20	ATCC 19111
	Type 4b	ZeptoMetrix 0804339
Neisseria meningitidis (encapsulated)	Serotype B. M2092 [CIP 104218, L. Cunningham]	ATCC 13090
	Serotype Y. M-112 [BO-6]	ATCC 35561
	Serogroup A, M1027 [NCTC10025]	ATCC 13077
	Serogroup C, M1628	ATCC 13102
	Serotype D. M158 [37A]	ATCC 13113
	sequence with variant ctrA gene	IDT (gblock)
	W135	ATCC 43744
	MC58	ATCC BAA-335
	79 Eur. Serogroup B	ATCC 23255
	Serotype B. M997 [S-3250-L]	ATCC 13092
Streptococcus agalactiae	Z019	ZeptoMetrix 0801545
	G19 group B	ATCC 13813
	Serotype III. Typing strain D136C(3) [3 Cole 106, CIP 82.45]	ATCC 12403

Table 20. Strains tested for inclusivity (continued)

Pathogen	Strain/Serotype	Supplier
	2603 V/R. Serotype V	ATCC BAA-611
	type III-ST283	ATCC 31475
	MNZ929	BEI Resources NR-43898
	Typing strain H36B - type Ib	ATCC 12401
	CDC SS700 [A909; 5541], type 1c	ATCC 27591
	3139 [CNCTC 1/82] Serotype IV	ATCC 49446
	Z023	ZeptoMetrix 0801556
Streptococcus pneumoniae	19F	ZeptoMetrix 0801439
	Serotype 1. NCTC 7465	ATCC 33400
	Serotype 4. TIGR4 [JNR.7/87]	ATCC BAA-334
	Serotype 5. SPN1439-106 [Colombia 5-19]	ATCC BAA-341
	Serotype 11A. Type 43	ATCC 10343
	Serotype 14. VH14	ATCC 700672
	Serotype 19A. Hungary 19A-6 [HUN663]	ATCC 700673
	Z319; 12F	Zeptometrix 0804016
	Diplococcus pneumoniae; Type 3. Strain [CIP 104225]	ATCC 6303
	DCC1476 [Sweden 15A-25]	ATCC BAA-661
Streptococcus pyogenes	Z472; Serotype M1	ZeptoMetrix 0804351

Table 20. Strains tested for inclusivity (continued)

Pathogen	Strain/Serotype	Supplier
	Bruno [CIP 104226]	ATCC 19615
	Z018; Serotype M58	ZeptoMetrix 0801512
	Serotype M1. MGAS 5005	ATCC BAA-947
	Lancefield's group A/C203 S	ATCC 14289
	NCTC 8709 (Type 6 glossy)	ATCC 12203
	Group a, type 12. Typing strain T12 [F. Griffith SF 42]	ATCC 12353
	Group a, type 14	ATCC 12972
	Group a, type 23	ATCC 8133
	C203 -Type 3	ATCC 12384
Enterovirus A	Coxsackievirus A16	ZeptoMetrix 0810107CF
	A6, species A. Strain Gdula	ATCC VR-1801
	A10. M.K. (Kowalik)	ATCC VR-168
	Enterovirus 71. Strain H	ATCC VR-1432
	Species A, Serotype EV-A71 (2003 Isolate)	ZeptoMetrix 0810236CF
	Tainan/4643/1998	BEI Resources NR-471
	A2 Fl [Fleetwood]	ATCC VR-1550
	A7 - 275/58	ATCC VR-673
	A12 - Texas 12	ATCC VR-170

Table 20. Strains tested for inclusivity (continued)

Pathogen	Strain/Serotype	Supplier
	EV-A71. Strain BrCr	ATCC VR-1775
Enterovirus B	Coxsackievirus B5	ZeptoMetrix 0810019CF
	Coxsackievirus A9, species B	ZeptoMetrix 0810017CF
	Species B, Serotype CV-B1, Strain Conn-5	ATCC VR-28
	Species B, Serotype CV-B2. Strain Ohio-1	ATCC VR-29
	Coxsackievirus B4	ZeptoMetrix 0810075CF
	Echovirus 6	ZeptoMetrix 0810075CF
	Echovirus 9	ZeptoMetrix 0810077CF
	Coxsackievirus B3	ZeptoMetrix 0810074CF
	Echovirus 18	NCPV 0901047v
	Species B, Serotype E-11	ATCC VR-41
Enterovirus C	Coxsackievirus A17, species C. Strain G-12	ATCC VR-1023
	Coxsackievirus A24. Strain DN-19	ATCC VR-583
	Coxsackievirus A21. Strain Kuykendall [V-024-001-012]	ATCC VR-850
	A11 - Belgium-1	ATCC VR-169
	A13 - Flores	ATCC VR-1488
	A22 - Chulman	ATCC VR-182
	A20 - IH Pool 35	ATCC VR-178

Table 20. Strains tested for inclusivity (continued)

Pathogen	Strain/Serotype	Supplier
	A18 - G-13	ATCC VR-176
	CV-A21. Strain H06452 472	NCTC 0812075v
	CV-A21. Strain H06418 508	NCTC 0812074v
Enterovirus D	EV 70, species D, strain J670/71	ATCC VR-836
	Enterovirus D68. Strain US/MO/14-18947	ATCC VR-1823
	Enterovirus 68. 2007 Isolate	ZeptoMetrix 0810237CF
	Enterovirus D68. Strain US/IL/14-18952	ATCC VR-1824
	D68. Strain F02-3607 Corn	ATCC VR-1197
	Type 68 Major Group (09/2014 Isolate 2)	ZeptoMetrix 0810302CF
	Enterovirus D68. Strain US/KY/14-18953	ATCC VR-1825
	Enterovirus D68. Strain Fermon	ATCC VR-1826
	Enterovirus D68. US/MO/14-18949	BEI Resources NR-49130
	Enterovirus D68. USA/2018-23089	BEI Resources NR-51998
Cryptococcus neoformans	Serotype D strain WM629, type VNIV	ATCC MYA-4567
	H99	ATCC 208821
	Strain, CBS 132	ATCC 32045

Table 20. Strains tested for inclusivity (continued)

Pathogen	Strain/Serotype	Supplier
	Serotype A strain WM148, type VNI	ATCC MYA-4564
	M2092	ATCC 13690
	Serotype AD strain WM628, type VNIII	ATCC MYA-4566
	Serotype A	ZeptoMetrix 0801803
	NIH9hi90	BEI Resources NR-50335
	NIH306	BEI Resources NR-50332
	Var grubiiYL99α	BEI Resources NR-48776
Cryptococcus gattii	Serotype B strain R272, type VGIIb	ATCC MYA-4094
	A6MR38	ATCC MYA-4877
	Serotype B strain WM179, type VGI	ATCC MYA-4560
	Serotype B strain WM161, type VGIII	ATCC MYA-4562
	Serotype C strain WM779, type VGIV	ATCC MYA-4563
	A1M R265	ATCC MYA-4138
	110 [CBS 883]	ATCC 14248
	AIR265	BEI Resources NR-50184

Table 20. Strains tested for inclusivity (continued)

Pathogen	Strain/Serotype	Supplier
	Alg166	BEI Resources NR-50195
	Alg254	BEI Resources NR-50198

All inclusivity strains tested as part of the study were detected by the panel with the exception of five strains. These are detailed in Table 21.

Table 21. Inclusivity Strains Not Detected by the QIAstat-Dx ME Panel

Pathogen	Strain/Serotype
Escherichia coli K1	NCDC Bi 7509-41 Serotype O7:K1(L):NM
Escherichia coli K1	Z136 CTX-M-15
Enterovirus C	CV-A21. Strain H06452 472
Enterovirus C	CV-A21. Strain H06418 508
Streptococcus agalactiae	Serotype III. Typing strain D136C(3) [3 Cole 106, CIP 82.45]

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 22).

Table 22. 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/gatti*
*Cryptococcus depauperatus**	
Cryptococcus wingfieldii	

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

All the organisms on Table 22 were tested in the in vitro analytical specificity study.

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 were prepared by spiking potential cross-reactive organisms into artificial CSF matrix at 10^5 TCID50/mL for viral targets, 10^5 CFU/mL for fungal targets, and 10^6 CFU/mL for bacterial targets, or the highest concentration possible based on the organism stock.

All strains tested for exclusivity are detailed on Table 23. For pathogens marked with *, either quantitative synthetic DNA or inactivated material was used.

Table 23. Pathogens tested for exclusivity

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
On-Panel	Bacteria	*Escherichia coli K1*	Strain C5 [Bort]; O18ac:K1:H7	ATCC 700973
On-Panel	Bacteria	*Haemophilus influenzae*	Type e [strain AMC 36-A-7]	ATCC 8142
On-Panel	Bacteria	*Listeria monocytogenes*	Type 4b. Strain Li 2	ATCC 19115
On-Panel	Bacteria	*Neisseria meningitidis*	Serotype Y. M-112 [BO-6]	ATCC 35561
On-Panel	Bacteria	*Streptococcus pneumoniae*	19F	ZeptoMetrix 0801439
On-Panel	Bacteria	*Streptococcus agalactiae*	Z019	Zeptometrix 0801545
On-Panel	Bacteria	*Streptococcus pyogenes*	Z472; Serotype M1	Zeptometrix 0804351
On-Panel	Virus	Enterovirus A	A6, species A. Strain Gdula	ATCC VR-1801
On-Panel	Virus	Enterovirus B	Coxsackievirus B5	ZeptoMetrix 0810019CF
On-Panel	Virus	Enterovirus C	Coxsackievirus A17, species C. Strain G-12	ATCC VR-1023
On-Panel	Virus	Enterovirus D	Enterovirus D68. Strain US/MO/14-18947	ATCC VR-1823
On-Panel	Yeast	*Cryptococcus neoformans*	WM629 [CBS 10079]	ATCC MYA-4567
On-Panel	Yeast	*Cryptococcus gattii*	Serotype B strain R272, type VGIIb	ATCC MYA-4094
Off-Panel	Virus	Adenovirus A12	Huie	ATCC VR-863
Off-Panel	Virus	Adenovirus C2	Adenoid 6 (NIAID 202-001-014)	ATCC VR-846

Table 23. Pathogens tested for exclusivity (continued)

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
Off-Panel	Virus	Adenovirus D20	A.A	ATCC VR-1090
Off-Panel	Virus	Adenovirus E4	RI-67	ATCC VR-1572
Off-Panel	Virus	Adenovirus F41	Tak	ZeptoMetrix 0810085CF
Off-Panel	Virus	BK polyoma virus	N/A	ATCC VR-837
Off-Panel	Virus	Coronavirus 229E	229E	ATCC VR-740
Off-Panel	Virus	Coronavirus NL63	NL63 (Amsterdam I)	BEI Resources NR-470
Off-Panel	Virus	Coronavirus OC43	OC43	ATCC VR-1558
Off-Panel	Virus	Dengue virus (Type 2)*	New Guinea C	ZeptoMetrix 0810089CFHI
Off-Panel	Virus	Epstein-Barr Virus	B95-8	ZeptoMetrix 0810008CF
Off-Panel	Virus	Hepatitis B virus (HBV)*	N/A	ZeptoMetrix 0810031C
Off-Panel	Virus	Hepatitis C virus (HCV)*	N/A	ZeptoMetrix 0810032C
Off-Panel	Virus	Human herpes virus 7	SB	ZeptoMetrix 0810071CF
Off-Panel	Virus	Human herpes virus 8	N/A	ZeptoMetrix 0810104CF
Off-Panel	Virus	Human Immunodeficiency Virus*	Quantitative Synthetic Human immunodeficiency virus 1 (HIV-1) RNA	ATCC VR-3245SD
Off-Panel	Virus	Human Rhinovirus A1b	2060	ATCC VR-1559
Off-Panel	Virus	Human Rhinovirus A16	11757	ATCC VR-283

Table 23. Pathogens tested for exclusivity (continued)

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
Off-Panel	Virus	Human Rhinovirus B3	FEB	ATCC VR-483
Off-Panel	Virus	Human Rhinovirus B83	Baylor 7 [V-190-001-021]	ATCC VR-1193
Off-Panel	Virus	Influenza A H1N1	A/Florida/3/2006	ATCC VR-1893
Off-Panel	Virus	Influenza A H1N1-2009	A/California/08/2009 (H1N1pdm)	ATCC VR-1895
Off-Panel	Virus	Influenza A H3N2	A/Port Chalmers/1/73	ATCC VR-810
Off-Panel	Virus	Influenza B	B/Virginia/ATCC4/2009	ATCC VR-1784
Off-Panel	Virus	JC polyoma virus	MAD-4	ATCC VR-1583
Off-Panel	Virus	Measles Virus	Edmonston	ATCC VR-24
Off-Panel	Virus	Mumps Virus	Jones	ATCC VR-1438
Off-Panel	Virus	West Nile Virus*	1986	ATCC VR-3274SD
Off-Panel	Virus	Parainfluenza virus 2	Greer	ATCC VR-92
Off-Panel	Virus	Parainfluenza virus 4	N/A	ZeptoMetrix 0810060CF
Off-Panel	Virus	Parvovirus B19	B19	ZeptoMetrix 0810064C
Off-Panel	Virus	Respiratory Syncytial Virus	A2	ATCC VR-1540
Off-Panel	Virus	Rotavirus	RRV (Rhesus Rotavirus)	ZeptoMetrix 0810530CF
Off-Panel	Virus	Rubella Virus	N/A	ZeptoMetrix 0810048CF
Off-Panel	Virus	St. Louis Encephalitis Virus*	Parton	ZeptoMetrix 0810080CFHI
Off-Panel	Virus	*Cytomegalovirus*	Davis	VR-807 ATCC

Table 23. Pathogens tested for exclusivity (continued)

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
Off-Panel	Virus	Herpes simplex virus 1	Macintyre	0810005CF ZeptoMetrix
Off-Panel	Virus	Herpes simplex virus 2	HSV-2. (Strain: MS)	0810006CF ZeptoMetrix
Off-Panel	Virus	Human herpes virus 6	HHV-6B. (Strain: Z29)	0810072CF ZeptoMetrix
Off-Panel	Virus	Human parechovirus	Serotype 3	0810147CF ZeptoMetrix
Off-Panel	Virus	Varicella-zoster virus	Ellen	0810171CF ZeptoMetrix
Off-Panel	Fungi/parasite	*Candida glabrata*	CBS 138	ATCC 2001
Off-Panel	Fungi/parasite	*Candida krusei*	N/A	ATCC 14243
Off-Panel	Fungi/parasite	*Candida lusitaniae*	Z010	ZeptoMetrix 0801603
Off-Panel	Fungi/parasite	*Candida metapsilosis*	MCO429	ATCC 96143
Off-Panel	Fungi/parasite	*Candida orthopsilosis*	MCO471	ATCC 96140
Off-Panel	Fungi/parasite	*Candida viswanathii*	PK 233 [NCYC 997, pK233]	ATCC 20336
Off-Panel	Fungi/parasite	*Candida parapsilosis*	CBS 604	ATCC 22019
Off-Panel	Fungi/parasite	*Candida tropicalis*	Vitek #8935	ATCC 750
Off-Panel	Fungi/parasite	*Cryptococcus albidus*	AmMS 228	ATCC 66030
Off-Panel	Fungi/parasite	*Cryptococcus amylolentus*	NRRY Y-7784	ATCC 56469
Off-Panel	Fungi/parasite	*Cryptococcus laurentii*	CBS 139	ATCC 18803
Off-Panel	Fungi/parasite	*Cryptococcus uniguttulatus*	AmMS 234	ATCC 66033

Table 23. Pathogens tested for exclusivity (continued)

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
Off-Panel	Fungi/parasite	*Cryptococcus adeliensis = Cryptococcus adeliae = Naganishia adeliensis*	Cryptococcus adeliae	ATCC 201412
Off-Panel	Fungi/parasite	*Cryptococcus flavescens = Papiliotrema flavescens***	Cryptococcus laurentii var. flavescens (Saito) Lodder et Kregervan Rij	ATCC 10668
Off-Panel	Fungi/parasite	*Cryptococcus wingfieldii = Tsuchiyaea wingfieldii*	OTU 26	Collection Belga CBS 7118
Off-Panel	Fungi/parasite	*Cryptococcus depauperatus = Aspergillus depauperatus = Filobasidiella depauperata*	K [ARSEF 2058, CBS 7842]	ATCC 64866
Off-Panel	Fungi/parasite	*Filobasidium capsuligenum*	ML-186	ATCC 22179
Off-Panel	Fungi/parasite	*Naeglaria fowleri**	Genomic DNA from Naegleria fowleri	ATCC 30174D
Off-Panel	Fungi/parasite	*Toxoplasma gondii*	Haplogroup 2	ATCC 50611
Off-Panel	Fungi/parasite	*Aspergillus fumigatus*	Z014	ZeptoMetrix 0801716
Off-Panel	Fungi/parasite	*Candida albicans*	CBS 562	ATCC 18804
Off-Panel	Fungi/parasite	*Candida dubliniensis*	Z145	ZeptoMetrix 0801915
Off-Panel	Bacteria	*Bacillus cereus*	Z091	ZeptoMetrix 0801823
Off-Panel	Bacteria	*Citrobacter freundii*	[ATCC 13316, NCTC 9750]	ATCC 8090
Off-Panel	Bacteria	*Corynebacterium striatum*	CDC F6683	ATCC 43751
Off-Panel	Bacteria	*Corynebacterium urealyticus*	3 [Garcia strain]	ATCC 43044

Table 23. Pathogens tested for exclusivity (continued)

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
Off-Panel	Bacteria	*Cronobacter (Enterobacter) sakazakii*	CDC 4562-70	ATCC 29544
Off-Panel	Bacteria	*Enterobacter aerogenes*	Z052	ZeptoMetrix 0801518
Off-Panel	Bacteria	*Enterobacter cloacae*	CDC 442-68	ATCC 13047
Off-Panel	Bacteria	*Escherichia coli (non-K1)*	2003-3055	ATCC BAA-2212
Off-Panel	Bacteria	*Escherichia fergusonii*	Z302	ZeptoMetrix 0804113
Off-Panel	Bacteria	*Escherichia hermannii*	CDC 980-72	ZeptoMetrix 0804068
Off-Panel	Bacteria	*Escherichia vulneris*	CDC 875-72	ATCC 33821
Off-Panel	Bacteria	*Haemophilus ducreyi***	DCC1476 [Sweden 15A-25]	ATCC BAA-661
Off-Panel	Bacteria	*Haemophilus haemolyticus*	NCTC 10659	ATCC 33390
Off-Panel	Bacteria	*Haemophilus parahaemolyticus*	536 [NCTC 8479]	ATCC 10014
Off-Panel	Bacteria	*Haemophilus parainfluenzae*	NCTC 7857	ATCC 33392
Off-Panel	Bacteria	*Klebsiella pneumoniae*	NCTC 9633 [NCDC 298-53, NCDC 410-68]	ATCC 13883
Off-Panel	Bacteria	*Listeria innocua*	SLCC 3379	ATCC 33090
Off-Panel	Bacteria	*Listeria ivanovii*	Li 1979	ATCC 19119
Off-Panel	Bacteria	*Morganella morganii*	AM-15	ATCC 25830
Off-Panel	Bacterial targets	*Streptococcus salivarius*	C699	ATCC 13419

Table 23. Pathogens tested for exclusivity (continued)

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
Off-Panel	Bacterial targets	*Streptococcus sanguinis*	DSS-10	ATCC 10556
Off-Panel	Bacterial targets	*Streptococcus pseudopneumoniae*	CDC-SS-1757	ATCC BAA-960
Off-Panel	Bacterial targets	*Mycoplasma genitalium*	M30	ATCC 49895
Off-Panel	Bacterial targets	*Neisseria lactamica*	NCDC A7515	ATCC 23970
Off-Panel	Bacterial targets	*Neisseria mucosa*	AmMS 138	ATCC 49233
Off-Panel	Bacterial targets	*Neisseria sicca*	AMC 14-D-1	ATCC 9913
Off-Panel	Bacterial targets	*Neisseria gonorrhoeae*	Z017	ZeptoMetrix 0801482
Off-Panel	Bacterial targets	*Pantoea agglomerans*	Enterobacter agglomerans	ATCC 27155
Off-Panel	Bacterial targets	*Proprionibacterium acnes*	NCTC 737	ATCC 6919
Off-Panel	Bacterial targets	*Proteus mirabilis*	LRA 08 01 73 [API SA, DSM 6674]	ATCC 7002
Off-Panel	Bacterial targets	*Pseudomonas aeruginosa*	PRD-10 [CIP 103467, NCIB 10421, PCI 812]	ATCC 15442
Off-Panel	Yeast	*Saccharomyces cerevisiae*	NRRL Y-567	ATCC 9763
Off-Panel	Bacteria	*Salmonella bongori*	CIP 82.33	ATCC 43975
Off-Panel	Bacteria	*Salmonella enterica*	CDC K-1891 [ATCC 25928]	ATCC 13076
Off-Panel	Bacteria	*Serratia marcescens*	PCI 1107	ATCC 14756
Off-Panel	Bacteria	*Shigella boydii*	CDC C-123	ATCC 12033

Table 23. Pathogens tested for exclusivity (continued)

On-Panel/Off-Panel	Type	Pathogen	Strain	Source
Off-Panel	Bacteria	*Shigella flexneri*	Z046	ZeptoMetrix 0801757
Off-Panel	Bacteria	*Shigella sonnei*	AMC 43-GG9	ATCC 9290
Off-Panel	Bacteria	*Staphylococcus aureus*	FDA 209	ATCC CRM-6538
Off-Panel	Bacteria	*Staphylococcus capitis*	PRA 360 677	ATCC 35661
Off-Panel	Bacteria	*Staphylococcus epidermidis*	FDA strain PCI 1200	ATCC 12228
Off-Panel	Bacteria	*Staphylococcus haemolyticus*	SM 131	ATCC 29970
Off-Panel	Bacteria	*Staphylococcus hominis*	Z031	ZeptoMetrix 0801727
Off-Panel	Bacteria	*Staphylococcus lugdunensis*	LRA 260.05.79	ATCC 49576
Off-Panel	Bacteria	*Staphylococcus saprophyticus*	NCTC 7292	ATCC 15305
Off-Panel	Bacteria	*Streptococcus anginosus*	NCTC 10713	ATCC 33397
Off-Panel	Bacteria	*Streptococcus bovis*	Z167	ZeptoMetrix 0804015
Off-Panel	Bacteria	*Streptococcus dysgalactiae*	Grouping strain C74	ATCC 12388
Off-Panel	Bacteria	*Streptococcus intermedius*	Z126	ZeptoMetrix 0801895
Off-Panel	Bacteria	*Streptococcus oralis*	Z307	ZeptoMetrix 0804293
Off-Panel	Bacteria	*Streptococcus mitis (tigurinus)*	Clinical Isolate	ZeptoMetrix 0801695
Off-Panel	Bacteria	Streptococcus mutans	LRA 28 02 81	ATCC 35668

* 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 24). Pathogens exhibiting cross-reactivity with the panel, and the lowest concentration where cross reactivity is detected are listed in Table 24.

Table 24. Samples showing cross-reactivity with the panel

QIAstat-Dx ME Target	Potential cross-reactive organism†	Cross reactive concentration
Haemophilus influenzae	*Haemophilus haemolyticus*	≥1.00E+03 CFU/mL
Cryptococcus neoformans/gattii	*Cryptococcus wingfieldii* = *Tsuchiyaea wingfieldii*	≥1.00E+01 CFU/mL
Cryptococcus neoformans/gattii	*Cryptococcus flavescens* = *Papiliotrema flavescens*	≥4.00E+03 CFU/mL
Cryptococcus neoformans/gattii	*Cryptococcus amylolentus*	≥1.00E+01 CFU/mL

† The *in silico* predicted cross-reactivity for Listeria innocua with the *Listeria monocytogenes* assay and *Cryptococcus depauperatus* with *Cryptococcus neoformans/gattii* assay were not confirmed in vitro.

Competitive inhibition

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.

Clinically relevant 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 Percentage Analyte (HPA) does not inhibit the Low Percentage Analyte (LPA) is shown in Table 25.

Table 25. Co-infection Mixes where concentration of the HPA does not inhibit the LPA

	LPA			HPA	
Pathogen	**Concentration**	**Units**	**Pathogen**	**Concentration**	**Units**
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
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
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

Interfering substances

The effect of potentially interfering substances on the detectability of the QIAstat-Dx ME Panel organisms was evaluated. The substances tested in the study (21) 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.

Table 26. Summary of interfering substances tested

Name	Concentration Tested	Interference
Endogenous substances		
Human Blood	10% (v/v)	No
gDNA	20 µg/mL	No
D(+)Glucose	10 mg/mL	No
L-lactate (Na)	2.2 mg/mL	No
Immunoglobulin G (human)	20 mg/mL	No
Albumin (human)	30 mg/mL	No
Peripheral blood mononuclear cells	10,000 cells/µL	No
Exogenous substances		
Chlorhexidine	0.4% (w/v)	No
Ethanol	7% (v/v)	No
Bleach	1% (v/v)	Yes
Bleach	0.1% (v/v)	Yes
Bleach	0.01% (v/v)	No
Acyclovir	69 µg/mL	No
Amphotericin B	5.1 µg/mL	No
Ampicillin	210 µg/mL	No
Ceftriaxone	840 µg/mL	No
Cefotaxime	645 µg/mL	No

Table 26. Summary of interfering substances tested (continued)

Name	Concentration Tested	Interference
Ganciclovir	25 µg/mL	No
Gentamicin	30 µg/mL	No
Meropenem	339 µg/mL	No
Vancomycin	180 µg/mL	No
Voriconazole	11 µg/mL	No
Oseltamivir	0.399 µg/mL	No

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

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, where interference was observed and as such the lowest concentration of the substance causing interference has been determined.

Microbial interference

A microbial interference study was conducted to assess the inhibitory effects of select non-target organisms on the ability to detect the QIAstat-Dx ME Panel target organisms. Challenging concentrations (10^5 units/mL for viral targets and 10^6 CFU/mL for bacterial targets) of non-target organisms were individually mixed with artificial CSF matrix containing spiked targeted QIAstat-Dx ME Panel organisms at 3x LoD. Testing was performed in triplicate. All QIAstat-Dx ME Panel organisms were successfully detected (100% hit rate) when tested in combination with the potentially microbial interferents. See Table 27 for a list of the non-target organisms tested and the result summary.

Table 27. Summary of microbial interferents tested

Name	Supplier	Concentration Tested	QIAstat-Dx ME Panel organisms detection rate (%)	Result
Epstein-Barr virus	ZeptoMetrix, 0810008CF	1E+05 cp/mL	100	No interference
Influenza A H1N1-2009	ATCC, VR-1895	1E+05 CEID50/mL	100	No interference
Cutibacterium acnes	ATCC, 6919	1E+06 CFU/mL	100	No interference
Staphylococcus epidermidis	ATCC, 14990	1E+06 CFU/mL	100	No interference
Escherichia coli (non-K1)	ATCC, 25922	1E+06 CFU/mL	100	No interference
Staphylococcus aureus	ATCC, 29213	1E+06 CFU/mL	100	No interference
Measles Virus	ATCC, VR-24	1E+05 $TCID_{50}$/mL	100	No interference

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 (10^5–10^6 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.

Repeatability and 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.

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 28. Proportion of Correct Repeatability Results

Grouping Variable(s)		Proportion	Percentage (%)	Two-Sided 95% Confidence Limit	
Cryptococcus neoformans/ gattii	1x LoD	60 / 60	100.00	94.04	100.00
	3x LoD	60 / 60	100.00	94.04	100.00
Enterovirus	1x LoD	57 / 60	95.00	86.08	98.96
	3x LoD	60 / 60	100.00	94.04	100.00
Escherichia coli K1	1x LoD	56 / 60	93.33	83.80	98.15
	3x LoD	60 / 60	100.00	94.04	100.00
Listeria monocytogenes	1x LoD	57 / 60	95.00	86.08	98.96
	3x LoD	59 / 60	98.33	91.06	99.96

Table 28. Proportion of Correct Repeatability Results (continued)

Grouping Variable(s)		Proportion	Percentage (%)	Two-Sided 95% Confidence Limit	
Streptococcus agalactiae	1x LoD	60 / 60	100.00	94.04	100.00
	3x LoD	60 / 60	100.00	94.04	100.00
Negative	Negative	60 / 60	100.00	94.04	100.00

Table 29. Proportion of Correct Reproducibility Results

Grouping Variable(s)			Proportion		Two-Sided 95% Confidence Limit	
Target	Concentration	Site	Fraction	Percentage (%)	Lower (%)	Upper (%)
Cryptococcus neoformans/gattii	1x LoD	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
	3x LoD	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	1x LoD	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
	3x LoD	1	30 / 30	100.00	88.43	100.00
		2	30 / 30	100.00	88.43	100.00

Table 29. Proportion of Correct Reproducibility Results (continued)

Grouping Variable(s)			Proportion		Two-Sided 95% Confidence Limit	
Target	Concentration	Site	Fraction	Percentage (%)	Lower (%)	Upper (%)
		3	30 / 30	100.00	88.43	100.00
		All	90 / 90	100.00	95.98	100.00
Escherichia coli K1	1x LoD	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
	3x LoD	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	1x LoD	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
	3x LoD	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	1x LoD	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

Table 29. Proportion of Correct Reproducibility Results (continued)

Grouping Variable(s)			Proportion		Two-Sided 95% Confidence Limit	
Target	Concentration	Site	Fraction	Percentage (%)	Lower (%)	Upper (%)
		All	90 / 90	100.00	95.98	100.00
	3x LoD	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
n/a	Negative	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

In conclusion, reproducibility and repeatability of the tests performed with QIAstat-Dx ME Panel have been demonstrated.

Appendices

Appendix A: Installing the Assay Definition File

The Assay Definition File of the QIAstat-Dx ME Panel must be installed on the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0 prior to testing with QIAstat-Dx ME Panel Cartridges.

Note: Whenever a new version of the QIAstat-Dx ME Panel assay is released, the new QIAstat-Dx ME Panel Assay Definition File must be installed prior to testing.

Note: Assay Definition Files are available at **www.qiagen.com**. The Assay Definition File (.asy file type) must be saved onto a USB Drive prior to installation on the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0. This USB Drive must be formatted with a FAT32 file system.

To import assays into QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0, proceed with the following steps:

1. Insert the USB storage device containing the Assay Definition File into one of the USB ports on the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.
2. Press **Options** > **Assay Management**.

   The Assay Management screen appears in the Content area of the display (Figure 25).

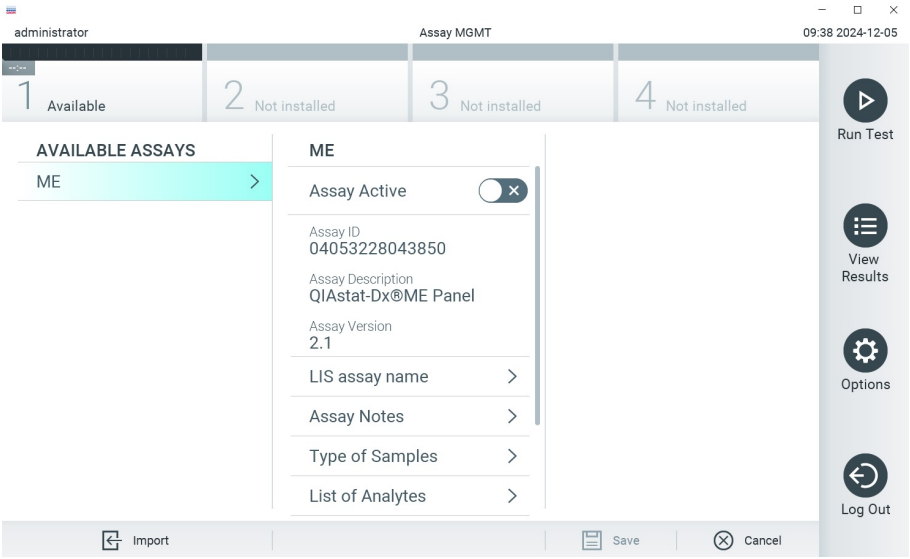


Figure 25. Assay Management screen.

3. Press **Import** located in the bottom left of the screen.
4. Select the applicable assay file to be imported.

   A dialog box will appear to confirm the upload of the file.
5. If a previous version of the QIAstat-Dx ME Panel is installed, a dialog box will appear to override the current version with the new one. Press **Yes** to override.
6. Enable **Assay Active** to activate the assay. (Figure 26).

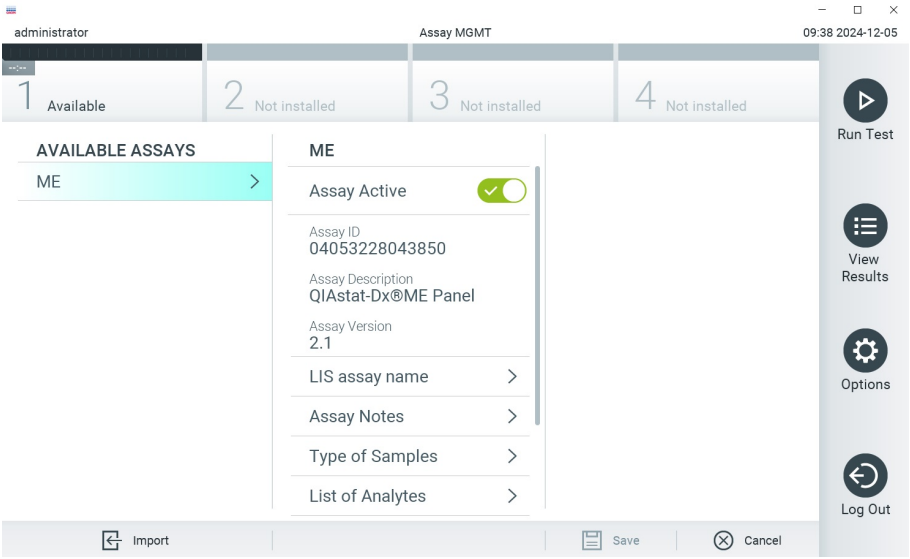


Figure 26. Activating the assay.

7. To assign the active assay to a user, perform the following steps:

   a. Press **Options** > **User Management**.

   b. Select the user who should be allowed to run the assay.

   c. From the **User Options** list, select **Assign Assays**.

   d. Enable the assay and press **Save**.

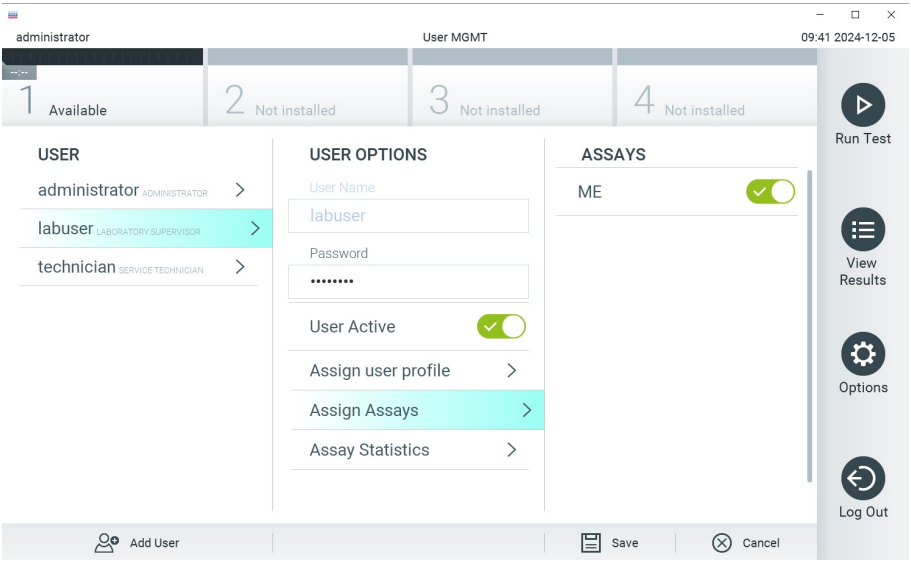


Figure 27. Assigning the active assay

Appendix B: Glossary

Amplification curve: Graphical representation of the multiplex real-time RT-PCR amplification data.

Analytical Module (AM): The main QIAstat-Dx Analyzer 1.0 hardware module, in charge of executing tests on QIAstat-Dx Meningitis/Encephalitis (ME) Panel Cartridges. It is controlled by the Operational Module. Several Analytical Modules can be connected to one Operational Module.

QIAstat-Dx Analyzer 1.0: The QIAstat-Dx Analyzer 1.0 consists of an Operational Module and an Analytical Module. The Operational Module includes elements that provide connectivity to the Analytical Module and enables user interaction with the QIAstat-Dx Analyzer 1.0. The Analytical Module contains the hardware and software for sample testing and analysis.

QIAstat-Dx Analyzer 2.0: The QIAstat-Dx Analyzer 2.0 consists of an Operational Module PRO and Analytical Module. The Operational Module PRO includes elements that provide connectivity to the Analytical Module and enables user interaction with the QIAstat-Dx Analyzer 2.0. The Analytical Module contains the hardware and software for sample testing and analysis.

QIAstat-Dx ME Panel Cartridge: A self-contained disposable plastic device with all pre-loaded reagents required for the complete execution of fully automated molecular assays for the detection of meningitis/encephalitis pathogens.

IFU: Instructions For Use.

Main port: In the QIAstat-Dx ME Panel Cartridge, inlet for transport medium liquid samples.

Nucleic acids: Biopolymers, or small biomolecules composed of nucleotides, which are monomers made of three components: a 5-carbon sugar, a phosphate group and a nitrogenous base.

Operational Module (OM): The dedicated QIAstat-Dx Analyzer 1.0 hardware that provides the user interface for 1–4 Analytical Modules (AM).

Operational Module PRO (OM PRO): The dedicated QIAstat-Dx Analyzer 2.0 hardware that provides the user interface for 1–4 Analytical Modules (AM).

PCR: Polymerase Chain Reaction.

RT: Reverse Transcription.

User: A person who operates the QIAstat-Dx Analyzer 1.0 / QIAstat-Dx Analyzer 2.0 / QIAstat-Dx ME Panel Cartridge in the intended way.

Appendix C: Disclaimer of Warranties

EXCEPT AS PROVIDED IN QIAGEN TERMS AND CONDITIONS OF SALE FOR THE QIAstat-Dx ME Panel Cartridge, QIAGEN ASSUMES NO LIABILITY WHATSOEVER AND DISCLAIMS ANY EXPRESS OR IMPLIED WARRANTY RELATING TO THE USE OF THE QIAstat-Dx ME Panel Cartridge INCLUDING LIABILITY OR WARRANTIES RELATING TO MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR INFRINGEMENT OF ANY PATENT, COPYRIGHT, OR OTHER INTELLECTUAL PROPERTY RIGHT ANYWHERE IN THE WORLD.

Troubleshooting Guide

In case of damaged cartridge, please refer to "Safety information" on page 20. For technical assistance and more information, please see our Technical Support Center at **www.qiagen.com/Support** (for contact information, visit **www.qiagen.com**). For issues that may occur with the QIAstat-Dx Analyzer, please refer to the corresponding User Manuals which are also available at **www.qiagen.com**.

Symbols

The following symbols appear in the instructions for use or on the packaging and labeling:

Symbol	Symbol definition
	Contains reagents sufficient for <N> reactions
	Prescription Use only
	Use by
	In vitro diagnostic medical device
	Catalog number
	Lot number
	Material number (i.e., component labeling)
	Global Trade Item Number
	Unique Device Identifier
	Contains

Symbol	Symbol definition
	Component
	Number
Rn	R is for revision of the Instructions for Use and n is the revision number
	Temperature limitation
	Manufacturer
	Consult instructions for use
	Protect from light
	Do not reuse
	Caution
	Serial number

Symbol	Symbol definition
	Do not use if package is damaged
	Flammable, risk of fire
	Corrosive, risk of chemical burn
	Health Hazard, risk of sensitization, carcinogenicity
	Risk of harm
	Brain icon present on the QIAstat-Dx ME Panel Cartridge

References

1. Meningitis and Encephalitis Fact Sheet. **www.ninds.nih.gov/disorders/patient-caregiver-education/fact-sheets/meningitis-and-encephalitis-fact-sheet**
2. Meningitis. **www.cdc.gov/meningitis/index.html**
3. Makvana S, Krilov LR. Escherichia coli Infections. Pediatr Rev. 2015;36(4):167-171. doi:10.1542/pir.36-4-167
4. Mushtaq N, Redpath MB, Luzio JP, Taylor PW. Treatment of experimental Escherichia coli infection with recombinant bacteriophage-derived capsule depolymerase. J Antimicrob Chemother. 2005;56(1):160-165. doi:10.1093/jac/dki177
5. Robbins JB, McCracken GH Jr, Gotschlich EC, Orskov F, Orskov I, Hanson LA. Escherichia coli K1 capsular polysaccharide associated with neonatal meningitis. N Engl J Med. 1974;290(22):1216-1220. doi:10.1056/NEJM197405302902202
6. Alkeskas A, Ogrodzki P, Saad M, et al. The molecular characterisation of Escherichia coli K1 isolated from neonatal nasogastric feeding tubes. BMC Infect Dis. 2015;15:449. Published 2015 Oct 26. doi:10.1186/s12879-015-1210-7
7. Xie Y, Kim KJ, Kim KS. Current concepts on Escherichia coli K1 translocation of the blood-brain barrier. FEMS Immunol Med Microbiol. 2004;42 (3):271- 279. doi:10.1016/j.femsim.2004.09.001
8. CDC bacterial meningitis: **www.cdc.gov/meningitis/bacterial.html**
9. Musher DM. Haemophilus Species. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 30;
10. CDC (for clinicians): **www.cdc.gov/hi-disease/clinicians.html**

11. Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases: Haemophilus Influenzae type b. Atkinson, W et al. eds. 13th ed. Washington DC: Public Health Foundation, 2015;

12. Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev. 2000;13(2):302-317. doi:10.1128/CMR.13.2.302

13. WHO position paper on Hib vaccination: **www.who.int/wer/2013/wer8839.pdf?ua=1**

14. Koelman DLH, van Kassel MN, Bijlsma MW, Brouwer MC, van de Beek D, van der Ende A. Changing Epidemiology of Bacterial Meningitis Since Introduction of Conjugate Vaccines: 3 Decades of National Meningitis Surveillance in The Netherlands. Clin Infect Dis. 2021;73(5):e1099-e1107. doi:10.1093/cid/ciaa1774

15. CDC (for healthcare professionals): **www.cdc.gov/listeria/technical.html**

16. Liu D. Identification, subtyping and virulence determination of Listeria monocytogenes, an important foodborne pathogen. J Med Microbiol. 2006;55 (Pt 6):645- 659. doi:10.1099/jmm.0.46495-0

17. Murray PR, et al. Medical Microbiology. 8th Edition. 2016. Elsevier Inc. [Page 210–213];

18. WHO. **www.who.int/news-room/fact-sheets/detail/listeriosis**

19. de Noordhout CM, Devleesschauwer B, Angulo FJ, Verbeke G, Haagsma J, Kirk M, Havelaar A, Speybroeck N. The global burden of listeriosis: a systematic review and meta-analysis. Lancet Infect Dis. 2014 Nov;14(11):1073-1082. doi: 10.1016/S1473-3099(14)70870-9. Epub 2014 Sep 15. PMID: 25241232; PMCID: PMC4369580.

20. Rouphael, NG, Stephens DS. Neisseria meningitidis: biology, microbiology, and epidemiology. Methods Mol Biol. 2012;799:1-20. doi:10.1007/978-1-61779-346-2_1

21. Harrison OB, Claus H, Jiang Y, et al. Description and nomenclature of Neisseria meningitidis capsule locus. Emerg Infect Dis. 2013;19 (4):566- 573. doi:10.3201/eid1904.111799

22. Uria MJ, Zhang Q, Li Y, et al. A generic mechanism in Neisseria meningitidis for enhanced resistance against bactericidal antibodies. J Exp Med. 2008;205(6):1423-1434. doi:10.1084/jem.20072577

23. CDC. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, et al. eds: **www.cdc.gov/vaccines/pubs/pinkbook/mening.html**

24. Caugant DA, Maiden MC. Meningococcal carriage and disease–population biology and evolution. Vaccine. 2009;27 Suppl 2(4):B64-B70. doi:10.1016/j.vaccine.2009.04.061

25. CDC meningococcal surveillance: **www.cdc.gov/meningococcal/surveillance/index.html**

26. Koelman DLH, van Kassel MN, Bijlsma MW, Brouwer MC, van de Beek D, van der Ende A. Changing Epidemiology of Bacterial Meningitis Since Introduction of Conjugate Vaccines: 3 Decades of National Meningitis Surveillance in The Netherlands. Clin Infect Dis. 2021;73(5):e1099-e1107. doi:10.1093/cid/ciaa1774

27. GBD 2019 Meningitis Antimicrobial Resistance Collaborators. Global, regional, and national burden of meningitis and its aetiologies, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2023;22 (8):685-711. doi:10.1016/S1474-4422(23)00195-3

28. Slotved HC, Kong F, Lambertsen L, Sauer S, Gilbert GL. Serotype IX, a Proposed New Streptococcus agalactiae Serotype. J Clin Microbiol. 2007;45 (9):2929- 2936. doi:10.1128/JCM.00117-07

29. Madrid L, Seale AC, Kohli-Lynch M, et al. Infant Group B Streptococcal Disease Incidence and Serotypes Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S160-S172. doi:10.1093/cid/cix656

30. CDC (for clinicians): **www.cdc.gov/groupbstrep/clinicians/index.html**

31. Raabe VN, Shane AL. Group B Streptococcus (Streptococcus agalactiae). Microbiol Spectr. 2019;7 (2):10.1128/microbiolspec.GPP3- 0007- 2018. doi:10.1128/microbiolspec.GPP3-0007-2018

32. CDC signs and symptoms: **www.cdc.gov/groupbstrep/about/symptoms.html**

33. van Kassel MN, van Haeringen KJ, Brouwer MC, Bijlsma MW, van de Beek D. Community-acquired group B streptococcal meningitis in adults. J Infect. 2020;80(3):255-260. doi:10.1016/j.jinf.2019.12.002

34. Seale AC, Bianchi-Jassir F, Russell NJ, et al. Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children. Clin Infect Dis. 2017;65(suppl_2):S200-S219. doi:10.1093/cid/cix664

35. WHO recommendation (2015): **apps.who.int/iris/bitstream/handle**

36. ECDC factsheet: **www.ecdc.europa.eu/en/pneumococcal-disease/facts**

37. CDC clinical features: **www.cdc.gov/pneumococcal/about/symptoms-complications.html**

38. CDC. **www.cdc.gov/pneumococcal/about/facts.html**

39. WHO **www.who.int/teams/health- product- policy- and- standards/standards- and-specifications/vaccine-standardization/pneumococcal-disease**

40. Iwata S, Takata M, Morozumi M, et al. Drastic reduction in pneumococcal meningitis in children owing to the introduction of pneumococcal conjugate vaccines: Longitudinal analysis from 2002 to 2016 in Japan. J Infect Chemother. 2021;27 (4):604-612. doi:10.1016/j.jiac.2020.11.019

41. Lodi L, Ricci S, Nieddu F, et al. Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Severe Invasive Disease Caused by Serotype 3 Streptococcus Pneumoniae in Italian Children. Vaccines (Basel). 2019;7 (4):128. Published 2019 Sep 24. doi:10.3390/vaccines7040128

42. González-Diaz A, Càmara J, Ercibengoa M, et al. Emerging non-13-valent pneumococcal conjugate vaccine (PCV13) serotypes causing adult invasive pneumococcal disease in the late- PCV13 period in Spain. Clin Microbiol Infect. 2020;26 (6):753- 759. doi:10.1016/j.cmi.2019.10.034

43. Løchen A, Croucher NJ, Anderson RM. Divergent serotype replacement trends and increasing diversity in pneumococcal disease in high income settings reduce the benefit of expanding vaccine valency. Sci Rep. 2020;10(1):18977. Published 2020 Nov 4. doi:10.1038/s41598-020-75691-5

44. Lo SW, Gladstone RA, van Tonder AJ, et al. Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole-genome sequencing study. Lancet Infect Dis. 2019;19(7):759-769. doi:10.1016/S1473-3099(19)30297-X

45. Kanwal S & Vaitla P. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2020;

46. CDC Diseases Caused by Group A Strep (for clinicians): **www.cdc.gov/groupastrep/diseases-hcp/index.html**

47. Randhawa E, Woytanowski J, Sibliss K, Sheffer I. Streptococcus pyogenes and invasive central nervous system infection. SAGE Open Med Case Rep. 2018;6:2050313X18775584. Published 2018 May 31. doi:10.1177/2050313X18775584

48. Koelman DLH, van Kassel MN, Bijlsma MW, Brouwer MC, van de Beek D, van der Ende A. Changing Epidemiology of Bacterial Meningitis Since Introduction of Conjugate Vaccines: 3 Decades of National Meningitis Surveillance in The Netherlands. Clin Infect Dis. 2021;73(5):e1099-e1107. doi:10.1093/cid/ciaa1774

49. O'Loughlin RE, Roberson A, Cieslak PR, et al. The epidemiology of invasive group A streptococcal infection and potential vaccine implications: United States, 2000-2004.

Clin Infect Dis. 2007;45(7):853-862. doi:10.1086/521264

50. Lucas MJ, Brouwer MC, Bovenkerk S, Man WK, van der Ende A, van de Beek D. Group A Streptococcal meningitis in adults. J Infect. 2015;71:37–42

51. De Almeida Torres RSL, Fedalto LE, de Almeida Torres RF, et al. Group A streptococcus meningitis in children. Pediatr Infect Dis J 2013; 32(2): 110–114

52. Efstratiou A & Lamagni T. In: Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center 2016

53. WHO Group A Streptococcus Vaccine Development Technology ROADMAP: **www.who.int/immunization/research/development/group_a_streptococcus/en**

54. Royston, Léna, and Caroline Tapparel. "Rhinoviruses and Respiratory Enteroviruses: Not as Simple as ABC." Viruses vol. 8,1 16. 11 Jan. 2016, doi:10.3390/v8010016

55. CDC. **www.cdc.gov/non-polio-enterovirus/about/ev-d68.html**

56. Messacar, Kevin et al. "The Emergence of Enterovirus-D68." Microbiology spectrum vol. 4,3 (2016): 10.1128/microbiolspec.EI10- 0018- 2016. doi:10.1128/microbiolspec.EI10-0018-201661.

57. Bookstaver PB, et al. J Cent Nerv Syst Dis 2017;9:1179573517703342

58. de Crom, S C M et al. "Enterovirus and parechovirus infection in children: a brief overview." European journal of pediatrics vol. 175,8 (2016): 1023- 9. doi:10.1007/s00431-016-2725-763.

59. Robinson CP, Busl KM. Crit Care Explor 2020;2:e0107

60. Messacar, Kevin et al. "Acute flaccid myelitis: A clinical review of US cases 2012-2015." Annals of neurology vol. 80,3 (2016): 326-38. doi:10.1002/ana.2473065.

61. Kwon-Chung KJ, et al. Cold Spring Harb Perspect Med 2014;4:a019760

62. Maziarz, Eileen K, and John R Perfect. "Cryptococcosis." Infectious disease clinics of North America vol. 30,1 (2016): 179-206. doi:10.1016/j.idc.2015.10.006

63. Bose, Indrani et al. "A yeast under cover: the capsule of Cryptococcus neoformans." Eukaryotic cell vol. 2,4 (2003): 655-63. doi:10.1128/EC.2.4.655-663.2003

64. Clinical Overview of Cryptococcosis, CDC (**www.cdc.gov/cryptococcosis/hcp/clinical-overview/index.html** accessed December 2024)

65. Góralska, Katarzyna et al. "Neuroinfections caused by fungi." Infection vol. 46,4 (2018): 443-459. doi:10.1007/s15010-018-1152-2

66. Rajasingham, Radha et al. "Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis." The Lancet. Infectious diseases vol. 17,8 (2017): 873-881. doi:10.1016/S1473-3099(17)30243-8

67. C. gattii Infection Statistics, Fungal Disease, CDC, (**archive.cdc.gov/www_ cdc_ gov/fungal/diseases/cryptococcosis-gattii/statistics.html** accessed December 2024)

68. Chen SC, Meyer W, Sorrell TC. Cryptococcus gattii infections. Clin Microbiol Rev. 2014;27(4):980-1024. doi:10.1128/CMR.00126-13

Contact Information

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Document Revision History

Revision	Description
R1, December 2024	Initial release.
R2, June 2025	Inclusion of QIAstat-Dx Analyzer 2.0 and Operational Module OMPro throughout the document Removed old references to DiagCORE Analyzer instruments Updated Interpretation of Results to include ME figure for Results Summary screen on Analyzer 2.0 Inserted performance note in Clinical and Analytical performance sections regarding the demonstration of data using Analyzer 1.0 Updated Contact Information

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