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

IVD

For *In Vitro* Diagnostic Use

This Instructions for Use is applicable for:

	Σ	REF	Version
QIAstat-Dx® Meningitis/Encephalitis (ME) Panel	6	691612	Version 1

CE 0197

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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 and differentiated* using the QIAstat-Dx ME Panel: *Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis* (encapsulated), *Streptococcus agalactiae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Streptococcus pyogenes,* Cytomegalovirus, Herpes simplex virus 1, Herpes simplex virus 2, Human herpesvirus 6, Enterovirus, Human parechovirus, Varicella zoster virus and *Cryptococcus neoformans/gattii**.

The QIAstat-Dx ME Panel is indicated as an aid in the diagnosis of specific agents of meningitis and/or encephalitis and results must be used in conjunction with other clinical, epidemiological, and laboratory data. Results from the QIAstat-Dx ME Panel are not intended to be used as the sole basis for diagnosis, treatment, or other patient management decisions. Positive results do not rule out co-infection with organisms not included in the QIAstat-Dx ME Panel. Not all agents of CNS infection are detected by this test. The agent or agents detected may not be the definite cause of the disease. Negative results do not preclude central nervous system (CNS) infection.

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

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

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

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

Intended User

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

Description and Principle

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 16 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)

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

Pathogen	Classification (genome type)
Neisseria meningitidis (encapsulated)	Bacterium (DNA)
Streptococcus agalactiae	Bacterium (DNA)
Streptococcus pneumoniae	Bacterium (DNA)
Streptococcus pyogenes	Bacterium (DNA)
Mycoplasma pneumoniae	Bacterium (DNA)
Cytomegalovirus	Herpesvirus (DNA)
Herpes simplex virus 1	Herpesvirus (DNA)
Herpes simplex virus 2	Herpesvirus (DNA)
Human herpesvirus 6	Herpesvirus (DNA)
Enterovirus	Picornavirus (RNA)
Human parechovirus	Picornavirus (RNA)
Varicella zoster virus	Herpesvirus (DNA)
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 organisms found in the gastrointestinal tract. Most *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].

Mycoplasma pneumoniae

M. pneumoniae is a small bacterium in the class Mollicutes that is characterized by the absence of a peptidoglycan cell wall, which results in resistance to many antimicrobial therapies[20]. *M. pneumoniae* is an important cause of respiratory tract infections and community acquired pneumonia in all age groups. Due to its mild symptoms, it is often referred to as "walking pneumonia"[20]. As *M. pneumoniae* infections are underdiagnosed, estimating the number of *M. pneumoniae*-associated cases and deaths is difficult[21,22]. It is estimated that 25% of *M. pneumoniae* cases involve extra-respiratory conditions, with disease affecting the nervous system (both peripheral and central) the most severe. These cases represent a medical emergency, as central nervous system *M. pneumoniae*-related neuropathies can lead to death or to persistent neurological problems with a significant impact on health and a non-marginal reduction in quality of life[23]. Unfortunately, *M. pneumoniae* is difficult to diagnose because culturing is complicated and slow, and serological tests are only effective in identification when both acute- and convalescent-phase serum are available[23].

Neisseria meningitidis (encapsulated)

N. meningitidis, or meningococcus, is an aerobic, gram-negative diplococcus and a major causative pathogen of bacterial meningitis[24]. 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[25]. The most invasive strains of *N. meningitidis* are usually encapsulated, as the capsule provides resistance to host antibodies and prevents phagocytosis[24,26]. *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[27]. Infections caused by this bacterium can affect individuals of any age, but

the highest incidence is found in infants and adolescents[28]. The case-fatality ratio of meningococcal disease is 10–15%, even with appropriate antibiotic therapy[27]. With the introduction of vaccines, rates of meningococcal disease have been declining in some countries, such as the U.S. and the Netherlands[29,30], but both sporadic and epidemic cases of *N. meningitidis* are still registered in countries where multivalent meningococcal vaccination has not yet been introduced[31].

Streptococcus agalactiae

Group B *Streptococcus* (group B strep, GBS) is a gram-positive coccus. Ten polysaccharide-based serotypes have been identified with 97% of cases attributed to five serotypes (Ia, Ib, II, III, and V)[32,33]. 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[34]. In adults, severe infections can manifest as bacteremia and soft tissue infections[35,36], but GBS is an uncommon cause of bacterial meningitis, mainly occurring in those with underlying conditions, such as immunocompromised state, CSF leakage and endocarditis[37]. Asymptomatic carriage of GBS in gastrointestinal and genital tracts is common[34]. As this bacterium is a leading contributor to worldwide adverse maternal and neonatal outcomes[38], the WHO recommends intrapartum antibiotic administration for women colonized with GBS during pregnancy[39].

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[40]. *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[40,41] and one of the leading causes of bacterial meningitis[40,42]. The WHO estimates that about 1 million children die every year of pneumococcal disease[43]. While the introduction of pneumococcal conjugate vaccines have dramatically reduced the incidence of invasive

pneumococcal disease, including meningitis[44,45,46], non-vaccine serotype pneumococcal meningitis cases are increasing, countering the overall effect of vaccination[46,47,48]. Of concern, significant increases in the prevalence of antibiotic resistance have been observed in non-vaccine serotypes, including resistance to penicillin and erythromycin[48]. Two types of vaccinations for *Streptococcus pneumoniae* are currently available: the pneumococcal conjugate vaccine 13 and the pneumococcal polysaccharide vaccine 23, recommended for children ≤2 and adults ≥65 years, respectively. In addition, vaccinations are recommended for high-risk populations[40].

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[49]. *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[50]. *S. pyogenes* infections of the central nervous system are relatively rare[51], with studies reporting rates of about 1% of all bacterial meningitis cases caused by *S. pyogenes*[52-55], but are associated with elevated mortality and morbidity[54]. 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[54]. Similarly, a Brazilian study reported low incidence of GAS meningitis amongst the pediatric population, but a case fatality rate of 43% between 2003 and 2011[55]. *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[49,50]. Inadequate antibiotic treatment of *S. pyogenes* can lead to the development of acute rheumatic fever[50]. The prevalence of infection is higher in children than adults, but disease in neonates is uncommon[56]. There is currently no vaccine for *S. pyogenes*, but its development has been identified as a priority by the WHO Initiative for Vaccine Research[57].

Cytomegalovirus

CMV, also known as human herpesvirus type 5, is a linear, double-stranded, enveloped DNA virus belonging to the beta subfamily of Herpesviridae[58,59]. CMV is a common human pathogen, infecting at least 50–80% of adults by age 40, transmitted by direct contact with infectious body fluids[60]. CMV infection is generally asymptomatic in healthy individuals or manifests with symptoms including fever, sore throat, fatigue, swollen glands and, occasionally, mononucleosis or hepatitis[60]. However, in immunocompromised individuals and neonates, CMV infection can lead to systemic disease with complications[59]. CMV is the most common cause of congenital infection, and can cause significant morbidity[60,61]. Following primary infection, CMV establishes a state of latency primarily in myeloid cells, from which it can be reactivated by various stimuli including immunosuppression due to therapies or disease[58,59]. While CMV is a rare cause of CNS infection[62,63] immunocompromised patients (e.g. HIV patients with low CD4 counts or transplant recipients) have greater susceptibility to invasive CMV, both from primary infection and reactivation of latent disease[63].

Herpes simplex virus 1 / Herpes simplex virus 2

HSV-1 and HSV-2 are linear, double-stranded, enveloped DNA viruses belonging to the alpha subfamily Herpesviridae[64] and share approximately 50% sequence homology[65]. HSV-1 and HSV-2 can infect the same tissues and cause similar diseases, but each has a predilection for specific sites and diseases. HSV-1 is predominantly, but not exclusively, associated with oral infections, while HSV-2 is mainly associated with genital lesions[66]. In 2020, an estimated 3.8 billion people had HSV-1 infection at any site, and an estimated 519.5 million people were affected by genital HSV-2, representing around 64.2% of the world's population under the age of 50, and 13.3% of people aged 15-49 years respectively[66].

In immunocompromised individuals, HSV infection can lead to severe complications such as encephalitis, meningitis and meningoencephalitis[66,67]. HSV is estimated to cause 11–22% of viral encephalitis[67] and is one of the most common causes of fatal encephalitis worldwide. The

estimated incidence of HSV encephalitis is 2.3 cases/million people annually, and HSV-1 accounts for 95% of all cases[68]. HSV can cause infection either during primary infection or by reactivation of latent virus within the central nervous system[64,69]. HSV-2 can also cause recurrent episodes of meningitis, called Mollaret's meningitis[69]. Rarely, HSV-1 and HSV-2 can be transmitted from mother to infant during delivery, causing neonatal herpes[66].

Given the seriousness of HSV encephalitis and HSV neonatal infections guidelines indicate negative PCR results should be evaluated in conjunction with the entire clinical scenario, including the results of other tests, and should not be used on their own to exclude invasive herpes disease and discontinue therapy[70,71].

Human herpesvirus 6

HHV-6A and HHV-6B are linear, double-stranded viruses belonging to the Roseolovirus genus of the ß-herpesvirus subfamily[72,73]. HHV-6 is ubiquitous, with more than 95% of the population worldwide acquiring seropositivity for HHV-6A, HHV-6B, or both variants by adulthood[74]. HHV-6B infections usually occur during childhood, typically before the age of three, and result in generally mild symptoms such as fever, fussiness, diarrhea, rash and roseola[72,75,76]. HHV-6A is poorly epidemiologically characterized, but it is generally believed to cause infections later in life, with reports linking it both to asymptomatic and symptomatic infections, and with varying seroprevalence worldwide[74].

Like all herpesviruses, HHV-6 establishes lifelong latent infection in their hosts. Unlike other human herpesviruses, HHV-6 can integrate into chromosomes and transmit through Mendelian inheritance, resulting in virus DNA in every nucleated cell in the body. Approximately 1% of the population carries chromosomally integrated HHV-6 (ciHHV-6)[77].

HHV-6 can be reactivated, most commonly in immunosuppressed individuals, and is linked with central nervous system diseases (e.g. encephalitis), hepatitis, pneumonitis and organ rejection[78,79]. However, detection of HHV-6 in CSF can generate a diagnostic challenge, as

detection of latency, sub-clinical re-activation, or chromosomally integrated HHV-6 has been observed frequently [80]. Nonetheless, laboratory identification of HHV- 6 in immunocompromised individuals, patients who undergo allogeneic hematopoietic stem cell transplant, or immunocompetent children with atypical presentations or complications can help reach a final diagnosis, provided that diagnostic results are interpreted within the clinical context of the patient[81, 82].

Enterovirus

Enterovirus is a genus of positive-sense, single-stranded RNA viruses associated with multiple human diseases[83]. Enterovirus can be transmitted via nasopharyngeal secretion[84], and cause a wide range of illnesses in humans, including respiratory, gastrointestinal, and central nervous system illness[84,85]. Symptoms are usually mild and can include fever, runny nose, cough, sneezing and muscle aches[84]. However, individuals who are immunocompromised and children with asthma are at risk of severe symptoms from enterovirus infections[84,85]. Enteroviruses are estimated to cause 1–4% of viral encephalitis cases[86], 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[87]. Enterovirus D68 and Enterovirus A71 (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[88]. In 2014, a nationwide outbreak of Enterovirus D68 in the United States, predominantly in children, lead to >1,300 laboratory-confirmed cases of severe infection[84]. During this outbreak, around 100 patients were diagnosed with acute flaccid myelitis[86], and many of these patients did not fully recover[89].

Human parechovirus

Human parechovirus (HPeV) is a small, non-enveloped RNA virus of the Picornaviridae family. Nineteen genotypes have been identified[90,91], with serological studies showing that >90% of children have been infected with at least one HPeV type by the age of two[92]. HPeV genotype

1 is the most prevalent type, and generally causes mild gastrointestinal and respiratory illness[93], while genotype 3 is typically associated with more severe presentations, such as sepsis-like illness and meningitis, particularly in children under three months of age[91,93]. HPeV is one of the main identified etiological agents of viral meningitis in infants, and while it generally has good survival rates, it is reportedly associated with potential neurodevelopmental impairment that warrants follow-up assessment[94]. Transmission occurs via the faecal-oral route from both asymptomatic and symptomatic infected individuals[91]. HPeV infections are rare in older children and adults[93].

Varicella zoster virus

Varicella zoster virus (VZV), also known as human herpesvirus type 3, is a linear, double-stranded, enveloped DNA virus belonging to the alpha subfamily of Herpesviridae[95,96]. Primary infection causes varicella (chickenpox), during which VZV establishes latent infection in ganglionic neurons[96,97]. In healthy children, varicella is generally mild, self-limiting and uncomplicated, characterized by fever, malaise and pruritic rash progressing from macular to vesicular lesions[97]. Infants, adolescents, adults, immunocompromised individuals and pregnant women are at risk of developing more severe disease and have a higher incidence of complications, including pneumonia, encephalitis and progressive disseminated varicella[96,98]. Reactivation and replication of VZV as a result of increasing age or immunosuppression causes herpes zoster HZ; shingles) in tissues innervated by the involved neurons. HZ is characterized by pain and unilateral rash[95-97], with post-herpetic neuralgia as the most common complication. Other complications include ophthalmic involvement, bacterial superinfection of lesions, cranial/peripheral nerve palsies and visceral involvement, such as meningoencephalitis, pneumonitis, hepatitis and acute retinal necrosis[95–97].

VZV can cause a wide range of different CNS manifestations, including encephalitis, meningitis, cerebellitis, myelitis and Ramsay Hunt syndrome[98]. VZV is estimated to cause 4–14% of viral encephalitis and is the second most common cause of viral meningitis after

enterovirus in developed counties[99]. VZV is highly contagious, and it is transmitted by respiratory droplets, aerosols or direct contact.

Cryptococcus neoformans/gattii

Cryptococcus neoformans and *Cryptococcus gattii* are environmental fungi, and the two etiological agents of *cryptococcosis*[100]. Infection is caused by inhalation of desiccated airborne yeast cells or possibly sexually-produced basidiospores[101–103]. *C. neoformans* has global distribution and is typically found in soil, on decaying wood, in tree hollows or in avian guano[101,102]. In immunocompetent individuals, infections are minimally symptomatic and rapidly cleared[101,104]. In immunocompromised individuals, *C. neoformans* can disseminate from the lungs, cross the blood-brain barrier and result in cryptococcal meningoencephalitis[101]. Symptoms of cryptococcal meningitis include headache, fever, neck pain, nausea, vomiting, photophobia and confusion or changes in behaviour[103]. *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[104]. 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[105].

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[103]. 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%[106]. *C.gattii* infections can affect both immunocompromised and immunocompetent hosts, with varying associated risk factors identified in different regions of the world[107].

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.

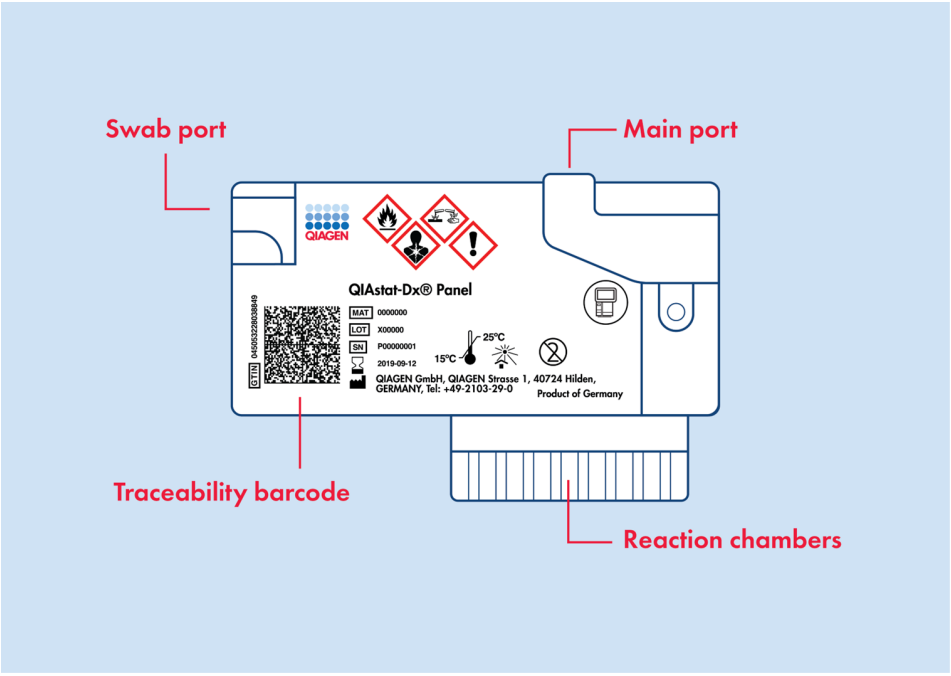


Figure 1. Layout of the QIAstat-Dx Panel Cartridge and its features.

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

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).

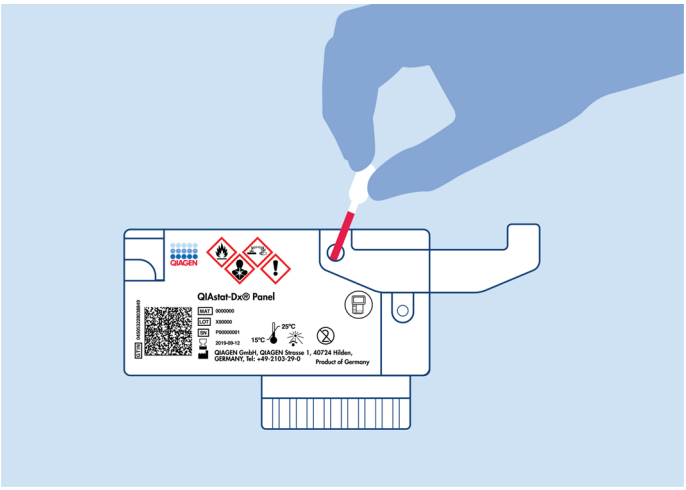


Figure 2. Dispensing sample into the main port.

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).

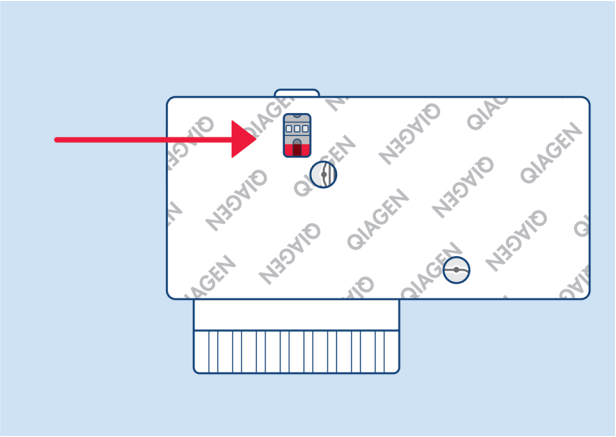


Figure 3. Sample inspection window (red arrow).

4. Scan the sample barcode and QIAstat-Dx ME Panel Cartridge QR code in the QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.

   Important: Do not scan the barcode from the cartridge packaging.

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	
Catalogue no.	**691612**
Number of tests	**6**
QIAstat-Dx ME Panel Cartridge*	6
Transfer pipettes†	6

* 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.

Components of the kit

The principal components of the kit are explained below:

Table 2. Active ingredients

Reagent	Active Ingredient	Concentration (% w/w)
QIAstat-Dx ME Panel Cartridge	Internal Control	40,000-60,000 CFU/cartridge
	Proteinase K	≥0.1%–<1%
	Reverse Transcriptase	20–100 U/cartridge
	dNTPs	1–5 mM
	DNA Polymerase	10–100 U/cartridge
	Target specific primers	100–1000 µM
	Target specific fluorophore labelled detection probe	100–1000 µM

Materials Required but Not Provided

Platform and software

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

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* OR 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 1.0 User Manual* (for use with software version 1.4 or 1.5) OR *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 or Operational Module PRO

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

*DiagCORE® Analyzer instruments running QIAstat-Dx software version 1.4 or 1.5 can be used as an alternative to QIAstat-Dx Analyzer 1.0 instruments.

Warnings and Precautions

Please be aware that you may be required to consult your local regulations for reporting serious incidents that have occurred in relation to the device to the manufacturer and the regulatory authority in which the user and/or the patient is established.

- The QIAstat-Dx ME Panel is for *in vitro* diagnostic use.
- The QIAstat-Dx ME Panel is to be used by laboratory professionals trained in the use of QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.

Safety information

- When working with chemicals, always wear a suitable lab coat, disposable gloves, and protective goggles. For more information, please consult the appropriate safety data sheets (SDSs). These are available online in convenient and compact PDF format at **www.qiagen.com/safety** where you can find, view, and print the SDS for each QIAGEN kit and kit component.
- Observe standard laboratory procedures for keeping the working area clean and contamination-free. Guidelines are outlined in publications such as the Biosafety in Microbiological and Biomedical Laboratories from the European Center for Disease Control and Prevention (**www.ecdc.europa.eu/en/about- us/networks/disease-andlaboratory-networks/erlinet-biosafety**).
- Specimens and samples are potentially infectious. Follow your institution's safety procedures for handling biological samples.Discard sample and assay waste according to your local safety procedures.
- Always wear appropriate personal protective equipment and follow your institution’s safety procedures for handling biological samples. Handle all samples, cartridges, and transfer

pipettes as if they are capable of transmitting infectious agents.

- Handle all samples, cartridges, and transfer pipettes as if they are capable of transmitting infectious agents. Always observe safety precautions as outlined in relevant guidelines, such as the Clinical and Laboratory Standards Institute® (CLSI) Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline (M29), or other appropriate documents provided by local authorities.
- The QIAstat-Dx ME Panel Cartridge is a closed, single-use device that contains all reagents needed for sample preparation and multiplex real-time RT-PCR within the QIAstat-Dx Analyzer 1.0 and the QIAstat-Dx Analyzer 2.0. Do not use a QIAstat-Dx ME Panel Cartridge that is past its expiration date, appears damaged or leaks fluid.
- Dispose of samples, used or damaged cartridges, and transfer pipettes in accordance with all national, state and local health and safety regulations and laws.

Emergency information

CHEMTREC

Outside USA & Canada +1 703-527-3887

Precautions

The following hazard and precautionary statements apply to components of the QIAstat-Dx ME Panel.

Contains: ethanol; guanidine hydrochloride; guanidine thiocyanate; isopropanol; proteinase K; t-Octylphenoxypolyethoxyethanol. Danger! Highly flammable liquid and vapor. Harmful if swallowed or if inhaled. May be harmful in contact with skin. Causes severe skin burns and eye damage. May cause allergy or asthma symptoms or breathing difficulties if inhaled. May cause drowsiness or dizziness. Harmful to aquatic life with long lasting effects. Contact with acids liberates very toxic gas. Corrosive to the respiratory tract. Keep away from heat/sparks/open flames/hot surfaces. No smoking. Avoid breathing dust/-fume/gas/mist/vapors/spray. Wear protective gloves/protective clothing/eye protection/face protection. Wear respiratory protection. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. IF exposed or concerned: Immediately call a POISON CENTER or doctor. Rinse mouth. Do NOT induce vomiting. Remove person to fresh air and keep comfortable for breathing. Wash contaminated clothing before reuse. Store in a well-ventilated place. Keep container tightly closed. Dispose of contents/ container to an approved facility in accordance with local, regional, national and international regulations.

Laboratory precautions

To guard against possible contamination of the specimen and work area standard laboratory safety and cleaning procedures should be used, including the following precautions:

- Samples should be processed in a biosafety cabinet or a similar clean surface ensuring the user's protection. If a biosafety cabinet is not used, a dead air box (e.g., AirClean PCR workstation), a splash shield (e.g., Bel-Art Scienceware Splash Shields), or a face shield

should be used when preparing samples.

- A biosafety cabinet that is used for performing pathogen testing (e.g. culture) should not be used for sample preparation or cartridge loading.
- Prior to processing samples, thoroughly clean the work area using a suitable cleaner such as freshly prepared 10% bleach or a similar disinfectant. To avoid residue buildup and potential damage to the specimen or interference from disinfectants, wipe disinfected surfaces with water.
- Samples and cartridges should be handled one at a time.
- Use clean gloves to remove materials from bulk packaging bags and reseal bulk packaging bags when not in use.
- Change gloves and clean the work area between each sample.
- Discard used cartridges in an appropriate biohazard container immediately after the run has been completed.
- Avoid excessive handling of cartridges after test runs.
- Avoid damaging the cartridge (refer to "Safety information" on page 24 for information about handling of damaged cartridges.
- Use clean gloves to remove materials from bulk packaging boxes, and close bulk packaging when not in use.

Due to sensitive nature of the pathogen detection by QIAstat-Dx Meningitis/Encephalitis Panel and to prevent contamination of the specimen, it is key to follow standard microbiological laboratory practices. Clinical laboratory personnel could be the source of pathogens (e.g. *S. pneumoniae, H. influenzae,* HSV-1, etc.) that are detectable by the QIAstat-Dx Meningitis/Encephalitis Panel.

Contamination of the specimen could happen while the specimen is being collected, transported, or tested. Adherence to best practice sample handling and testing procedures is

recommended to minimize the risk of contamination that could lead to false positive results. Additional precautions may include extra PPE, such as face mask, especially when experiencing signs or symptoms of a respiratory infection or an active herpes sore/fever blister.

Precautions related to Public Health Reporting

State and local public health authorities have published guidelines for notification of reportable diseases in their jurisdictions (e.g., following the Official Journal of the European Union 6.7.2018 L 170/1, the list includes Listeriosis disease, as well as invasive disease caused by *Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae)* to determine necessary measures for verification of results to identify and trace outbreaks and for epidemiological investigations. Laboratories are responsible for following their state or local regulations for submission of clinical material or isolates on positive specimens to their state public health laboratories.

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 24.

Follow recommendations in the Safety Data Sheet (SDS).

Reagent 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. Once the cartridge is removed from the pouch, it should be protected from sunlight. 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 barcode 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 24.

In-use stability

After the cartridge package is opened, sample should be introduced into the QIAstat-Dx ME Panel Cartridge within 30 minutes. Sample-loaded cartridges should be loaded into the QIAstat-Dx Analyzer within 90 minutes.

Do not use if stored outside the specifications, if the packaging has been damaged, or if other signs of deterioration or malfunction are visible.

Specimen Storage and Handling

The QIAstat-Dx ME Panel is for use with CSF. All samples should be treated as potentially hazardous.

The CSF specimen should be collected via lumbar puncture and should not be centrifuged or diluted. CSF specimens should be collected and handled according to the recommended procedures. 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

Specimen collection

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

Protocol

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.

Procedure: 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 691612). QIAstat-Dx ME Panel cartridge identification is supported by a grey-colored bar on the label and an icon indicating a brain (see "Symbols" on page 130).

Handling reagents

- Transfer pipettes provided in the kit are single use. In case transfer pipettes are dropped or contaminated due to user error, use any other commercially available pipette with a minimum volume of 200 µL.

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 introduced into the QIAstat-Dx ME Panel Cartridge within 30 minutes. Sample-loaded cartridges should be loaded into the QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0 within 90 minutes.

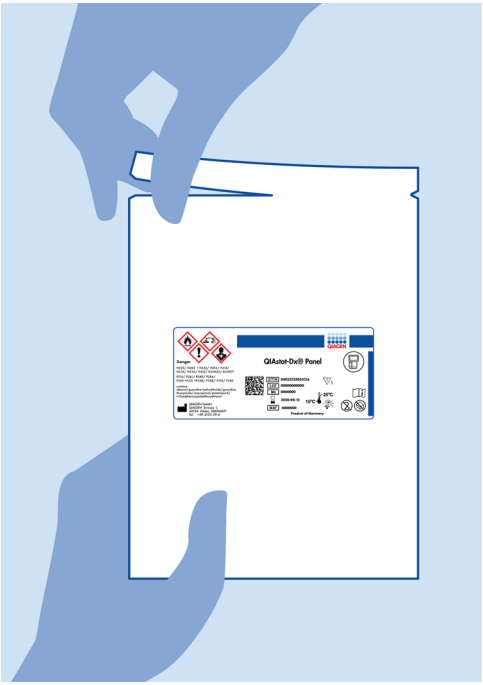


Figure 4. Opening the QIAstat-Dx ME Panel Cartridge.

3. Remove the QIAstat-Dx ME Panel Cartridge from the packaging and position it so that the barcode 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).

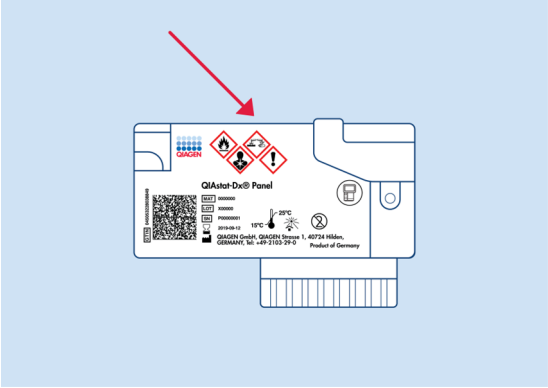


Figure 5. Sample information placement on top of QIAstat-Dx ME Panel Cartridge.

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

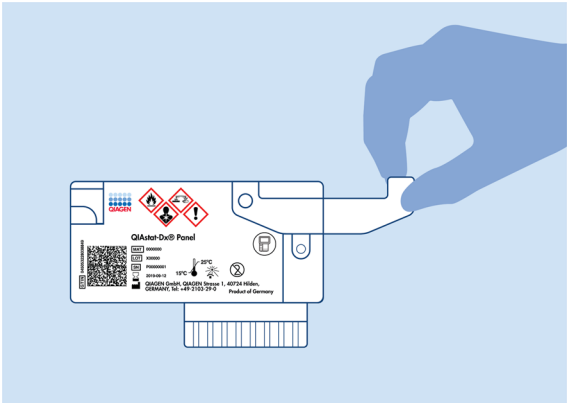


Figure 6. Opening the sample lid of main port.

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.

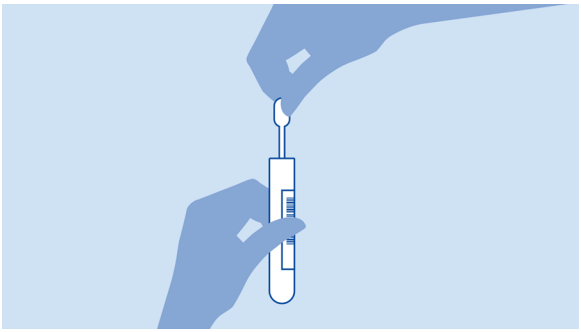


Figure 7. Drawing sample into the supplied transfer pipette.

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).

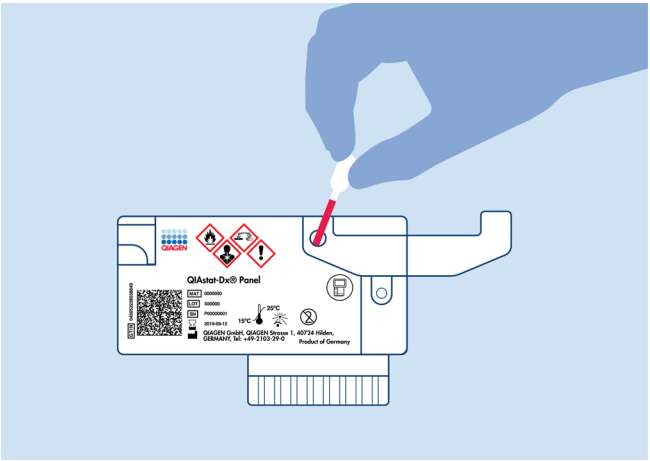


Figure 8. Transferring sample to main port of QIAstat-Dx ME Panel Cartridge.

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

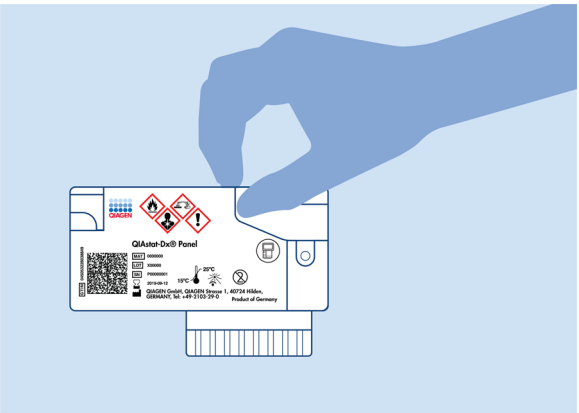


Figure 9. Closing the lid of the main port.

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.

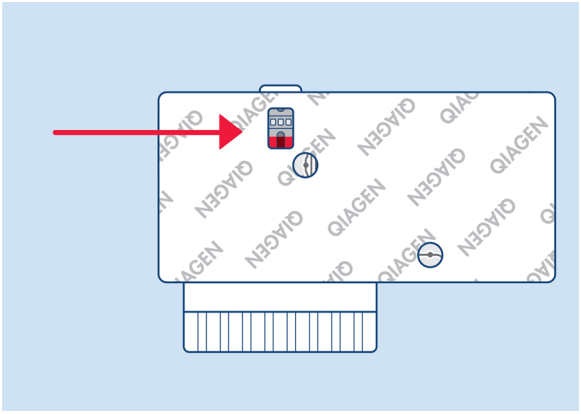


Figure 10. Sample inspection window (red arrow).

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 134 , 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 barcode 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 barcode 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.

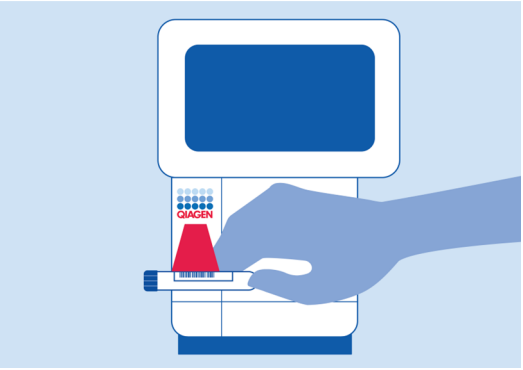


Figure 11. Scanning sample ID barcode.

3. When prompted, scan the barcode 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 barcode.

   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.

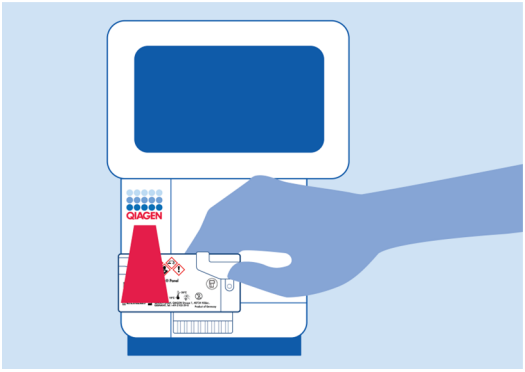


Figure 12. Scanning QIAstat-Dx QIAstat-Dx ME Panel Cartridge barcode.

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).

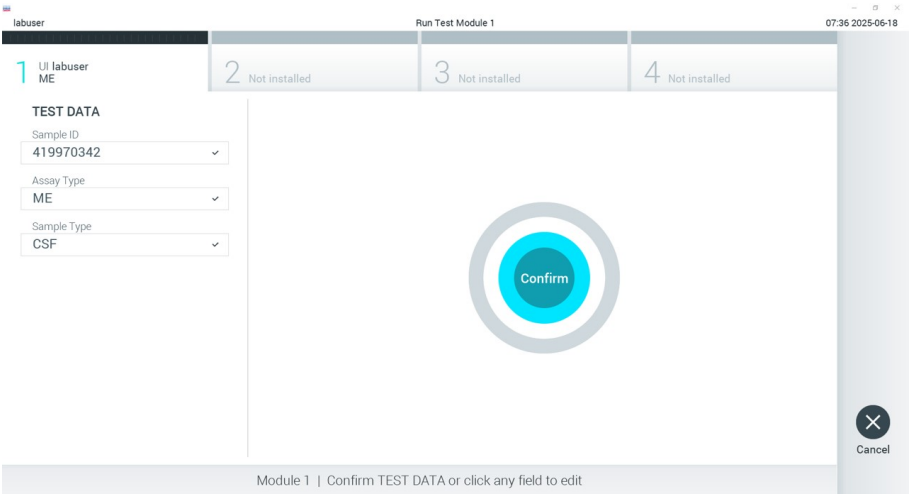


Figure 13. Confirming data entry.

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 barcode 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 instrument. Position it correctly into the cartridge entrance port and the QIAstat-Dx Analyzer instrument will automatically move the cartridge into the Analytical Module.

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

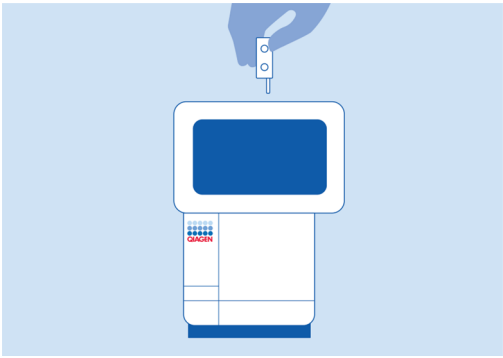


Figure 14. Inserting QIAstat-Dx ME Panel Cartridge into QIAstat-Dx Analyzer 1.0 or QIAstat-Dx Analyzer 2.0.

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.

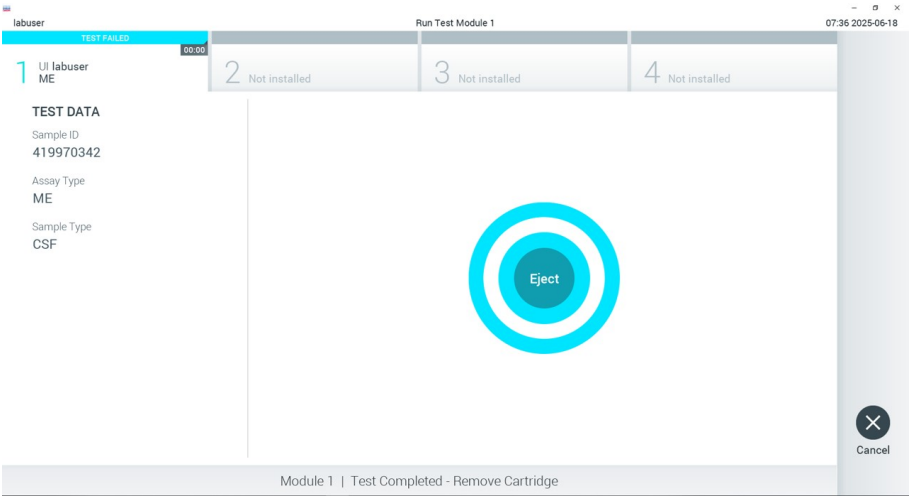


Figure 15. Eject screen display.

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

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 3.

Table 3. 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.

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-DxME Panel.

Viewing results with the QIAstat-Dx Analyzer 1.0 or the QIAstat-Dx Analyzer 2.0

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).

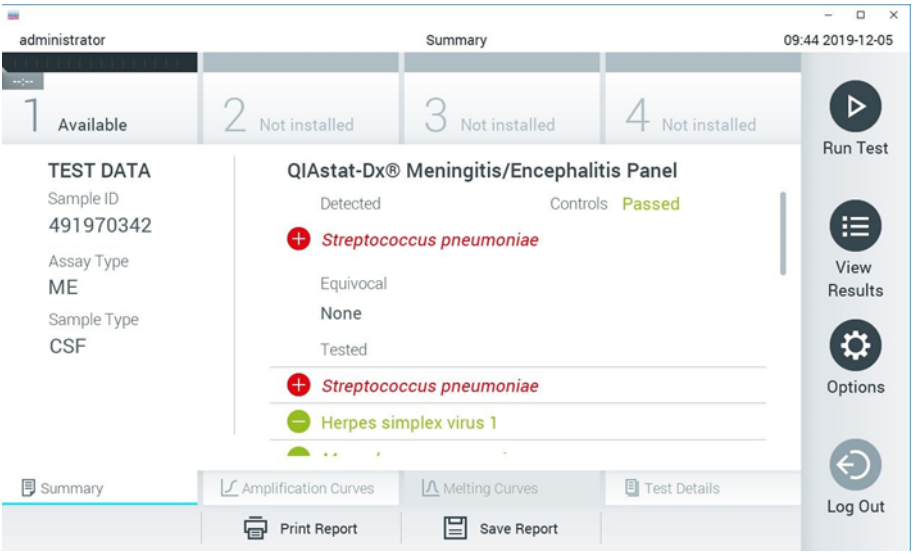


Figure 16. Results Summary screen example showing Test Data on the left panel and Test Summary in the main panel on QIAstat-Dx Analyzer 1.0.

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

- **Amplification curves** ("Viewing amplification curves" on page 49)
- **Melting curves** (this tab is disabled for QIAstat-Dx ME Panel)
- **Test Details** ("Viewing test details" on page 51)

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

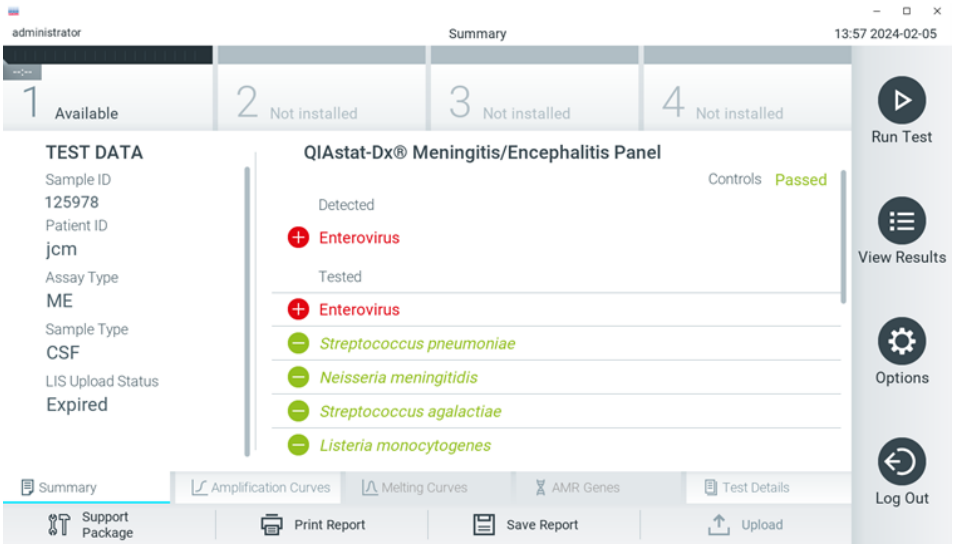


Figure 17. Results Summary screen example showing Test Data on the left panel and Test Summary in the main panel on the QIAstat-Dx Analyzer 2.0.

QIAstat-Dx Analyzer 2.0 includes an additional tab:

- **AMR genes**: This 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 list, 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 red. Pathogens that were tested but not detected 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).

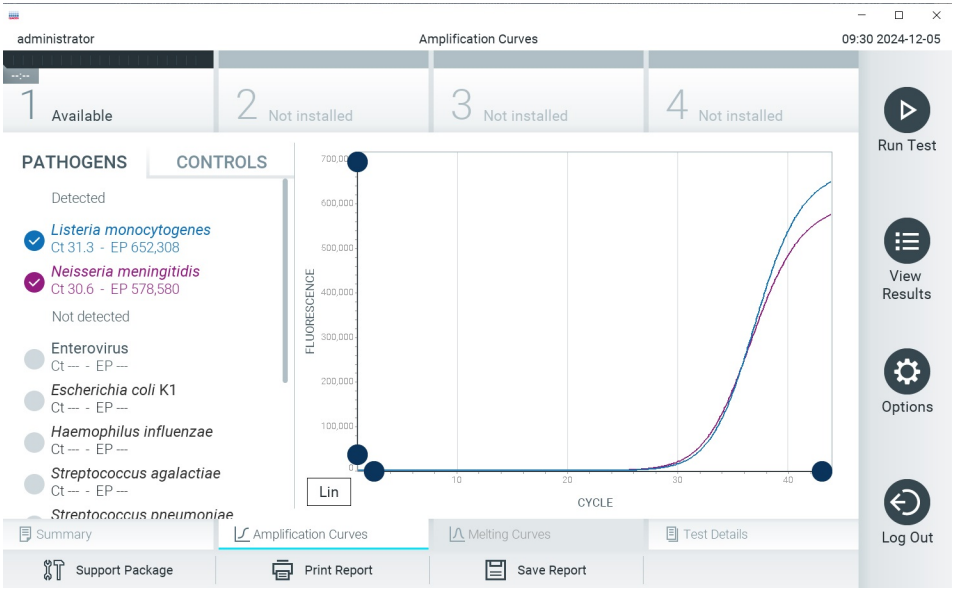


Figure 18. Amplification Curves screen (PATHOGENS tab).

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).

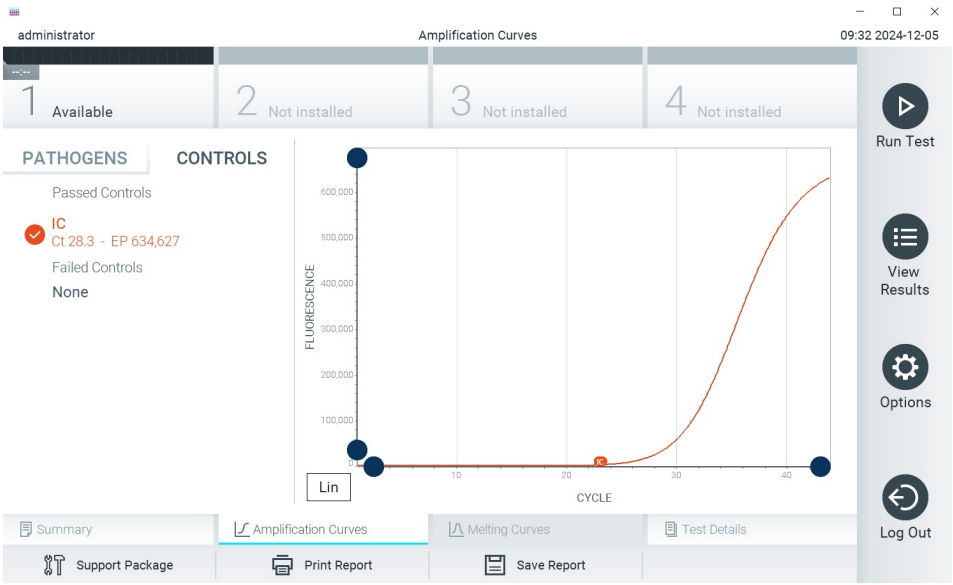


Figure 19. Amplification Curves screen (CONTROLS tab).

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

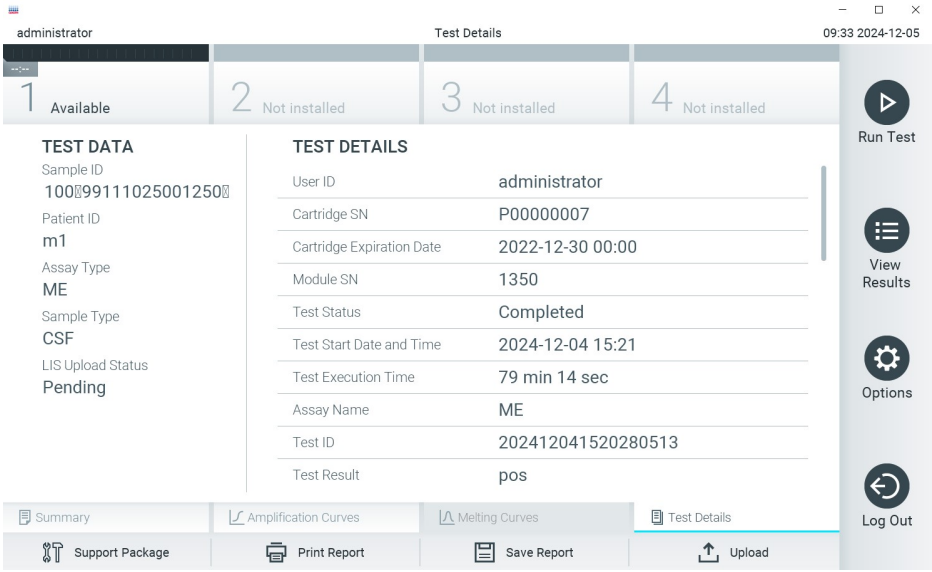


Figure 20. Example screen showing Test Data on the left panel and Test Details in the main panel.

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).

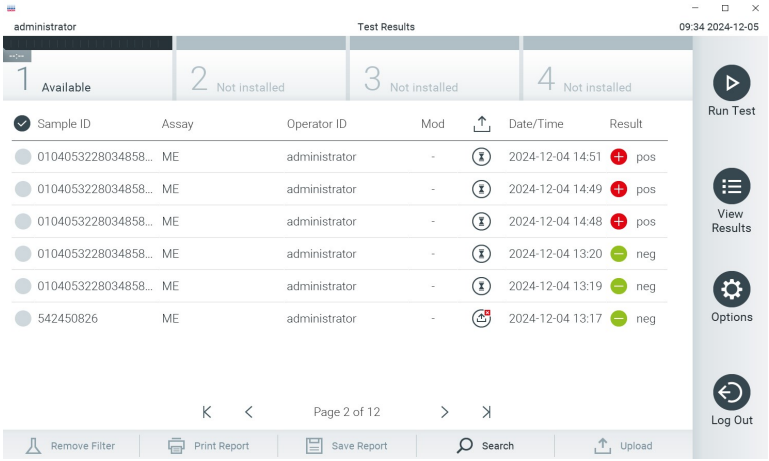


Figure 21. Example View Results screen.

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).

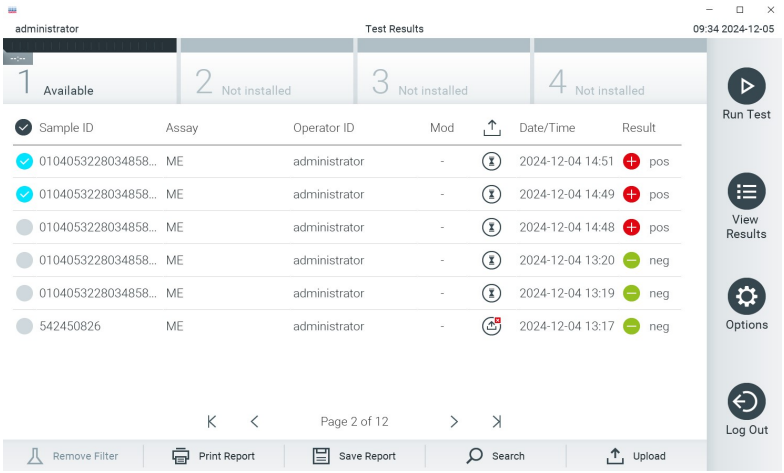


Figure 22. Example of selecting Test Results in the View Results screen.

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 4).

Table 4. 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 4. 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.

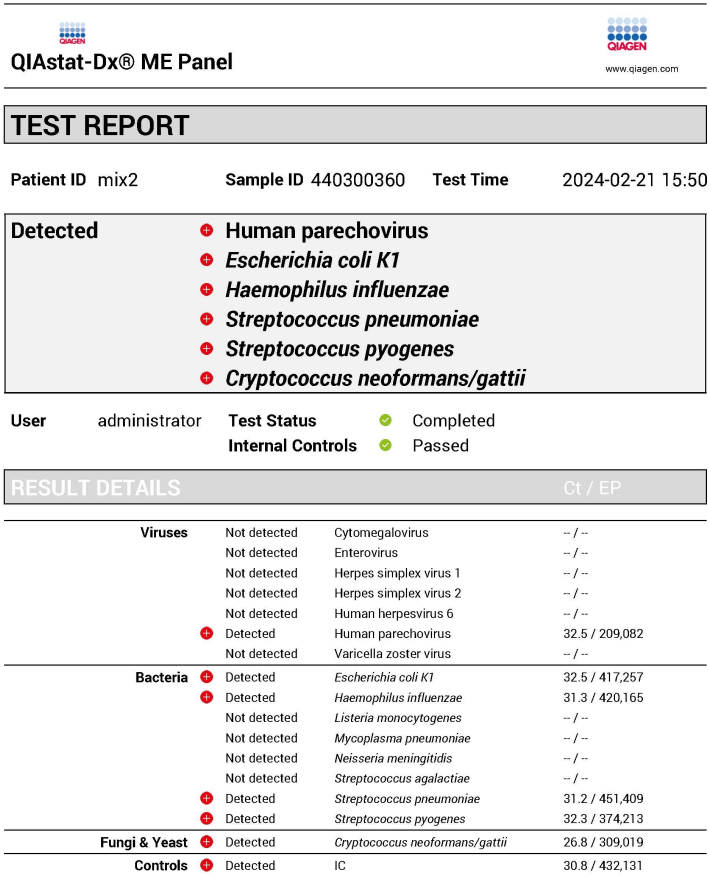
A filter can be removed by pressing Remove Filter in the Submenu bar.

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 5 below.

Table 5. 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 mix2 **Sample ID** 440300360 **Test Time** 2024-02-21 15:50

Detected

- Human parechovirus
- *Escherichia coli K1*
- *Haemophilus influenzae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Cryptococcus neoformans/gattii*

User administrator **Test Status** Completed **Internal Controls** Passed

RESULT DETAILS				Ct / EP
Viruses		Not detected	Cytomegalovirus	-- / --
		Not detected	Enterovirus	-- / --
		Not detected	Herpes simplex virus 1	-- / --
		Not detected	Herpes simplex virus 2	-- / --
		Not detected	Human herpesvirus 6	-- / --
		Detected	Human parechovirus	32.5 / 209,082
		Not detected	Varicella zoster virus	-- / --
Bacteria		Detected	*Escherichia coli K1*	32.5 / 417,257
		Detected	*Haemophilus influenzae*	31.3 / 420,165
		Not detected	*Listeria monocytogenes*	-- / --
		Not detected	*Mycoplasma pneumoniae*	-- / --
		Not detected	*Neisseria meningitidis*	-- / --
		Not detected	*Streptococcus agalactiae*	-- / --
		Detected	*Streptococcus pneumoniae*	31.2 / 451,409
		Detected	*Streptococcus pyogenes*	32.3 / 374,213
Fungi & Yeast		Detected	*Cryptococcus neoformans/gattii*	26.8 / 309,019
Controls		Detected	IC	30.8 / 432,131

Figure 23. Sample test report.

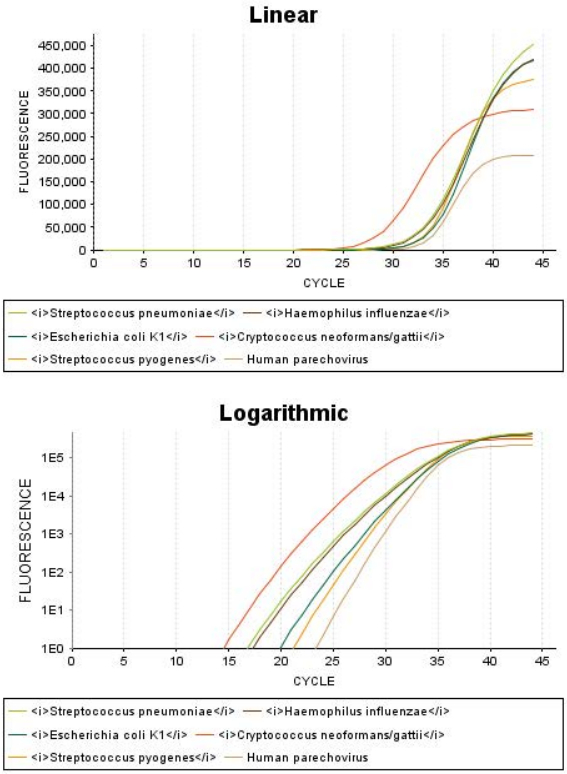


Figure 24. Sample test report showing assay data.

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.

Pathogen result interpretation

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

Limitations

- Results from the QIAstat-Dx ME Panel are not intended to be used as the sole basis for diagnosis, treatment, or other patient management decisions.
- Positive results do not rule out co-infection with organisms not included in the QIAstat-Dx ME Panel. The agent or agents detected may not be the definite cause of the disease.
- Not all agents of CNS infection are detected by this test, and sensitivity in clinical use may differ from that described in the package insert.
- The QIAstat-Dx ME Panel is not intended for testing of specimens collected from indwelling CNS medical devices.
- A negative result with the QIAstat-Dx ME Panel does not exclude the infectious nature of the syndrome. Negative assay results may originate from several factors and their combinations, including sample handling mistakes, variation in the nucleic acid sequences targeted by the assay, infection by organisms not included in the assay, organism levels of included organisms that are below the limit of detection for the assay and use of certain medications, therapies, or agents.
- The QIAstat-Dx ME Panel is not intended for testing of samples other than those described in this Instructions for Use. Test performance characteristics have been established only with CSF.
- The QIAstat-Dx ME Panel is intended to be used in conjunction with standard of care (e.g., culture for organism recovery, serotyping, and antimicrobial susceptibility testing). The results from the QIAstat-Dx ME Panel must be interpreted by a trained healthcare professional within the context of all relevant clinical, laboratory, and epidemiological findings.

- The QIAstat-Dx ME Panel can be used only with the QIAstat-Dx Analyzer 1.0 or 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.
- Accidental contamination of the CSF sample with *Propionibacterium acnes* –a common commensal skin flora organism- can generate an unexpected signal (low positive) for *Mycoplasma pneumoniae* target in the QIAstat-Dx ME Panel. Standard CSF sample handling should prevent this potential contamination.
- Results obtained during co-infection study in the analytical verification show a potential inhibition of HSV1 detection when *S. pneumoniae* is present in the same sample. As this effect was observed even with low concentrations of *S. pneumoniae*, negative results for

*DiagCORE Analyzer instruments running QIAstat-Dx software version 1.4 or 1.5 can be used as an alternative to the QIAstat-Dx Analyzer 1.0.

HSV1 in *S. pneumoniae*-positive samples should be interpreted with caution. The opposite effect (inhibition of *S. pneumoniae* when HSV1 is present in the same sample) was not observed at the highest tested concentration of HSV1 (1.00E+05 $TCID_{50}$/mL).

- Due to the sensitive nature of the pathogen detection by the QIAstat-Dx ME Panel and to prevent contamination of the specimen it is key to follow standard microbiological laboratory practices. Clinical laboratory personnel could be the source of pathogens (e.g. *S. pneumoniae, H. influenzae,* etc.) that are detectable by the QIAstat-Dx ME Panel.
- Contamination of the specimen could happen while the specimen is being collected, transported, or tested. Adherence to best practice sample handling and testing procedures is recommended to minimize the risk of contamination that could lead to false positive results. Additional precautions may include extra PPE, such as a face mask, especially when experiencing signs or symptoms of a respiratory infection.
- Only *E. coli* strains possessing the K1 capsular antigen will be detected. All other *E. coli* strains/serotypes will not be detected.
- Only encapsulated strains of *N. meningitidis* will be detected. Unencapsulated *N. meningitidi*s will not be detected.

Performance Characteristics

Analytical performance

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

Limit of detection

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

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

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

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

Individual LoD values for each QIAstat-Dx ME Panel target is shown in Table 6.

Table 6. Limit of Detection results

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

Table 6. Limit of Detection results (continued)

Pathogen	Strain	Supplier	LoD concentration*	Units	Detection rate
Streptococcus pneumoniae	Serotype 1. NCTC 7465	ATCC	6.22E-01	CFU/ml	29/29
Streptococcus pyogenes	Z472; Serotype M1	ZeptoMetrix	1.80E+03	CFU/ml	30/30
Streptococcus pyogenes	Bruno [CIP 104226]	ATCC	9.10E+01	CFU/ml	31/31
Mycoplasma pneumoniae	PI 1428	ATCC	9.48E+01	CFU/ml	31/31
Mycoplasma pneumoniae	M129	ZeptoMetrix	9.99E+01	CCU/ml	30/30
Cytomegalovirus	AD-169	ZeptoMetrix	2.45E+00	$TCID_{50}/mL$	30/30
Cytomegalovirus	Davis	ATCC	1.00E+01	$TCID_{50}/mL$	30/30
Enterovirus A	Coxsackievirus A16	ZeptoMetrix	3.79E+00	$TCID_{50}/mL$	31/31
Enterovirus A	A6, species A. Strain Gdula	ATCC	1.60E+02	$TCID_{50}/mL$	31/31
Enterovirus B	Coxsackievirus B5	ZeptoMetrix	8.91E+01	$TCID_{50}/mL$	30/30
Enterovirus B	Coxsackievirus A9, species B	ZeptoMetrix	4.36E+01	$TCID_{50}/mL$	28/29
Enterovirus C	Coxsackievirus A17, species C. Strain G-12	ATCC	1.58E+01	$TCID_{50}/mL$	30/30
Enterovirus C	Coxsackievirus A24. Strain DN-19	ATCC	4.99E+00	$TCID_{50}/mL$	30/30
Enterovirus D	EV 70, species D, strain J670/71	ATCC	4.99E+01	$TCID_{50}/mL$	30/31

Table 6. Limit of Detection results (continued)

Pathogen	Strain	Supplier	LoD concentration*	Units	Detection rate
Enterovirus D	Enterovirus D68. Strain US/MO/14-18947	ATCC	5.06E+02	$TCID_{50}/mL$	30/30
HHV-6	HHV-6A. (Strain: GS) Lysate	ZeptoMetrix	3.13E+04	cp/mL	32/32
HHV-6	HHV-6B. (Strain: Z29)	ZeptoMetrix	7.29E+04	cp/mL	30/30
HPeV	Serotype 1. Strain Harris	ZeptoMetrix	1.07E+03	$TCID_{50}/mL$	31/31
HPeV	Serotype 3	ZeptoMetrix	3.38E+01	$TCID_{50}/mL$	30/30
VZV	Ellen	ZeptoMetrix	1.71E+03	cp/ml	30/30
VZV	Oka	ATCC	5.00E-02	$TCID_{50}/mL$	31/31
Cryptococcus neoformans	Serotype D strain WM629, type VNIV	ATCC	2.21E+03	CFU/mL	31/31
Cryptococcus neoformans	*C. neoformans* H99	ATCC	1.64E+02	CFU/mL	31/31
Cryptococcus gattii	Serotype B strain R272, type VGIIb	ATCC	1.32E+04	CFU/mL	30/30
Cryptococcus gattii	A6MR38 [CBS 11545]	ATCC	2.60E+03	CFU/mL	29/29

*The highest LoD is reported.

** Highest LoD was obtained in artificial CSF.

Inclusivity (analytical reactivity)

The Inclusivity (analytical reactivity) Study extended the list of pathogen strains tested during the QIAstat-Dx ME Panel Limit of Detection (LoD) Study to confirm the reactivity of the detection

system in the presence of different strains of the same organisms at a concentration near or above the respective Limit of Detection.

A variety of clinically relevant strains of each target organism of the QIAstat-Dx ME Panel (Inclusivity Strains) representing organism 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 187 samples representative of relevant strains, subtypes, serotypes, and genotypes for the different organisms (e.g. a range of different meningitis/encephalitis strains isolated from around the world and in different calendar years) were included in the study (Table 7). All inclusivity strains tested as part of the study were detected by the panel.
- *In silico* analysis: to make assay reactivity predictions of all primers-probe oligonucleotide sequences included in the panel against publicly available sequence databases to detect any possible cross-reaction or unexpected detection of any primer set, *in silico* analysis was performed. In addition, strains not available for *in vitro testing* were included in *in silico* analysis to confirm the predicted inclusivity of the different strains of the same organisms (Table 8). *In silico* analysis confirmed inclusivity (no critical patterns causing a negative impact) for all the existing strains of the QIAstat-Dx ME Panel targets, including all relevant subtypes defined by on-panel organism.

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

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies.

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
***Escherichia coli* K1**	**Strain C5 [Bort]; O18ac:K1:H7**	**ATCC**	**700973**	**1x**
***Escherichia coli* K1**	**NCTC 9001. Serovar O1:K1:H7**	**ATCC**	**11775**	**1x**
Escherichia coli K1	Sc15 02:K1:H6	ATCC	11101	1x
Escherichia coli K1	O-16, F1119-41. Serotype O15:K1:H-	BEI Resources	NR-17674	0.3x
Escherichia coli K1	O-2, U9-41	BEI Resources	NR-17666	1x
Escherichia coli K1	Strain Bi 7509/41; O7:K1:H-	NCTC	9007	1x
Escherichia coli K1	Strain H61; O45:K1:H10	NCTC	9045	0.3x
Escherichia coli K1	0.1285; O18:H7:K1	ZeptoMetrix	0804140	1x
Escherichia coli K1	NCDC F 11119-41	ATCC	23511	3x
Escherichia coli K1	O7:K1:H-	CCUG	28	3x
Haemophilus influenzae	**Type e [strain AMC 36-A-7]**	**ATCC**	**8142**	**1x**
Haemophilus influenzae	**type b (cap)**	**ATCC**	**10211**	**1x**
Haemophilus influenzae	L-378	ATCC	49766	0.1x
Haemophilus influenzae	Non-typeable [strain Rd [KW20]	ATCC	51907	0.3x
Haemophilus influenzae	Non-typeable [strain 180-a]	ATCC	11116	1x
Haemophilus influenzae	Type a [strain AMC 36-A-3]	ATCC	9006	0.1x
Haemophilus influenzae	Type d [strain AMC 36-A-6]	ATCC	9008	0.3x
Haemophilus influenzae	Type f [strain GA-1264]	ATCC	700223	1x
Haemophilus influenzae	Type c [strain C 9007]	ATCC	49699	0.1x
Haemophilus influenzae	Rab Strain	ATCC	31512	0.3x
Listeria monocytogenes	**Type 4b. Strain Li 2**	**ATCC**	**19115**	**1x**

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Listeria monocytogenes	**Type ½b**	**ZeptoMetrix**	**0801534**	**1x**
Listeria monocytogenes	Type 4b	ZeptoMetrix	0804339	1x
Listeria monocytogenes	FSL J2-064	BEI Resources	NR-13237	1x
Listeria monocytogenes	Gibson	ATCC	7644	1x
Listeria monocytogenes	1071/53. Serotype 4b	ATCC	13932	3x
Listeria monocytogenes	Type 1/2a. Strain 2011L-2676	ATCC	BAA-2659	0.3x
Listeria monocytogenes	Serotype 4a	ZeptoMetrix	0801508	1x
Listeria monocytogenes	Serotype 1/2a	ATCC	19111	0.3x
Listeria monocytogenes	Li 23. Serotype 4a	ATCC	19114	1x
***Neisseria meningitidis* (encapsulated)**	**Serotype Y. M-112 [BO-6]**	**ATCC**	**35561**	**1x**
***Neisseria meningitidis* (encapsulated)**	**Serotype B. M2092**	**ATCC**	**13090**	**1x**
Neisseria meningitidis (encapsulated)	79 Eur. Serogroup B	ATCC	23255	0.3x
Neisseria meningitidis (encapsulated)	Serogroup C, M1628	ATCC	13102	0.3x
Neisseria meningitidis (encapsulated)	sequence with variant ctrA gene	IDT	gBlock	0.1x
Neisseria meningitidis (encapsulated)	Serotype B. M997 [S-3250-L]	ATCC	13092	0.1x
Neisseria meningitidis (encapsulated)	Serotype D. M158 [37A]	ATCC	13113	1x

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Neisseria meningitidis (encapsulated)	W135	ATCC	43744	0.1x
Neisseria meningitidis (encapsulated)	Serogroup A, M1027 [NCTC10025]	ATCC	13077	3x
Neisseria meningitidis (encapsulated)	MC58	ATCC	BAA-335	0.3x
Streptococcus agalactiae	**G19 group B**	**ATCC**	**13813**	**1x**
Streptococcus agalactiae	**Z019**	**ZeptoMetrix**	**0801545**	**1x**
Streptococcus agalactiae	MNZ929	BEI Resources	NR-43898	0.3x
Streptococcus agalactiae	Z023	ZeptoMetrix	0801556	0.3x
Streptococcus agalactiae	M-732. Serotype III	ATCC	31475	0.1x
Streptococcus agalactiae	2603 V/R. Serotype V	ATCC	BAA-611	0.1x
Streptococcus agalactiae	Serotype III. Typing strain D136C(3) [3 Cole 106, CIP 82.45]	ATCC	12403	0.3x
Streptococcus agalactiae	3139 [CNCTC 1/82] Serotype IV	ATCC	49446	0.3x
Streptococcus agalactiae	Typing strain H36B – type Ib	ATCC	12401	0.1x
Streptococcus agalactiae	D136C(3). Lancefield's group B | Type III	CCUG	29782	0.3x

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Streptococcus agalactiae	CDC SS700 [A909; 5541], type 1c	ATCC	27591	0.1x
Streptococcus pneumoniae	**19F**	**ZeptoMetrix**	**0801439**	**1x**
Streptococcus pneumoniae	**Serotype 1. NCTC 7465**	**ATCC**	**33400**	**1x**
Streptococcus pneumoniae	DCC1476 [Sweden 15A-25]	ATCC	BAA-661	0.3x
Streptococcus pneumoniae	Diplococcus pneumoniae; Type 3. Strain [CIP 104225]	ATCC	6303	1x
Streptococcus pneumoniae	Serotype 19A. Hungary 19A-6 [HUN663]	ATCC	700673	1x
Streptococcus pneumoniae	Serotype 11A. Type 43	ATCC	10343	0.3x
Streptococcus pneumoniae	Z319; Serotype 12F	ZeptoMetrix	0804016	0.3x
Streptococcus pneumoniae	Serotype 14. VH14	ATCC	700672	1x
Streptococcus pneumoniae	Serotype 5. SPN1439-106 [Colombia 5-19]	ATCC	BAA-341	1x
Streptococcus pneumoniae	Serotype 5. SPN1439-106 [Colombia 5-19]	ATCC	BAA-341	1x
Streptococcus pyogenes	**Z472; Serotype M1**	**ZeptoMetrix**	**0804351**	**1x**
Streptococcus pyogenes	**Bruno [CIP 104226]**	**ATCC**	**19615**	**1x**
Streptococcus pyogenes	C203 -Type 3	ATCC	12384	0.3x
Streptococcus pyogenes	Group a, type 14	ATCC	12972	1x

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Streptococcus pyogenes	Group a, type 23	ATCC	8133	0.3x
Streptococcus pyogenes	Z018; Serotype M58	ZeptoMetrix	0801512	10x
Streptococcus pyogenes	Lancefield's group A / C203 S	ATCC	14289	0.1x
Streptococcus pyogenes	Group a, type 12. Typing strain T12 [F. Griffith SF 42]	ATCC	12353	1x
Streptococcus pyogenes	NCTC 8709 (Type 6 glossy)	ATCC	12203	0.1x
Streptococcus pyogenes	Serotype M1. MGAS 5005	ATCC	BAA-947	100x
Mycoplasma pneumoniae	**M129**	**ZeptoMetrix**	**0801579**	**1x**
Mycoplasma pneumoniae	**PI 1428**	**ATCC**	**29085**	**1x**
Mycoplasma pneumoniae	FH strain of Eaton Agent [NCTC 10119]	ATCC	15531	0.1x
Mycoplasma pneumoniae	UTMB-10P	ATCC	49894	0.3x
Mycoplasma pneumoniae	MAC	ATCC	15492	0.1x
Enterovirus	**A6, species A. Strain Gdula**	**ATCC**	**VR-1801**	**1x**
Enterovirus	**Coxsackievirus A16**	**ZeptoMetrix**	**0810107CF**	**1x**
Enterovirus	A10. M.K. (Kowalik)	ATCC	VR-168	0.1x
Enterovirus	A2 Fl [Fleetwood]	ATCC	VR-1550	0.3x
Enterovirus	A12 – Texas 12	ATCC	VR-170	1x
Enterovirus	Species A, BrCr	ATCC	VR-1775	0.1x
Enterovirus	Species A, Serotype EV-A71 (2003 Isolate)	ZeptoMetrix	0810236CF	1x

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Enterovirus	Tainan/4643/1998	BEI Resources	NR-471	0.1x
Enterovirus	Enterovirus 71. Strain H	ATCC	VR-1432	0.3x
Enterovirus	A7 – 275/58	ATCC	VR-673	0.3x
Enterovirus	**Coxsackievirus A9, species B**	**ZeptoMetrix**	**0810017CF**	**1x**
Enterovirus	**Coxsackievirus B5**	**ZeptoMetrix**	**0810019CF**	**1x**
Enterovirus	Species B, Echovirus 6	ZeptoMetrix	0810076CF	0.3x
Enterovirus	Species B, Serotype CV-B1, Strain Conn-5	ATCC	VR-28	1x
Enterovirus	Species B, Echovirus 9	ZeptoMetrix	0810077CF	0.3x
Enterovirus	Species B, Coxsackievirus B3	ZeptoMetrix	0810074CF	3x
Enterovirus	Echovirus 18. Strain H07218 472	NCTC	0901047v	3x
Enterovirus	Coxsackievirus B4	ZeptoMetrix	0810075CF	1x
Enterovirus	Species B, Serotype E-11	ATCC	VR-41	3x
Enterovirus	Species B, Serotype CV-B2. Strain Ohio-1	ATCC	VR-29	1x
Enterovirus	**Coxsackievirus A17, species C. Strain G-12**	**ATCC**	**VR-1023**	**1x**
Enterovirus	**Species C, Coxsackievirus A24. Strain DN-19**	**ATCC**	**VR-583**	**1x**
Enterovirus	Species C, Coxsackievirus A21. Strain Kuykendall [V-024-001-012]	ATCC	VR-850	0.3x
Enterovirus	Species C, A11-Belgium-1	ATCC	VR-169	0.1x
Enterovirus	Species C, A13 – Flores	ATCC	VR-1488	10x
Enterovirus	Species C, A22 – Chulman	ATCC	VR-182	0.1x
Enterovirus	Species C, A18 – G-13	ATCC	VR-176	0.3x

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Enterovirus	Species C, CV-A21. Strain H06452 472	NCTC	0812075v	0.3x
Enterovirus	Species C, CV-A21. Strain H06418 508	NCTC	0812074v	0.3x
Enterovirus	Species C, A20 IH35	IDT	gBlock	1x
Enterovirus	**Species D, Enterovirus D68. Strain US/MO/14-18947**	**ATCC**	**VR-1823**	**1x**
Enterovirus	**EV 70, species D, strain J670/71**	**ATCC**	**VR-836**	**1x**
Enterovirus	Species D, Enterovirus D68. USA/2018-23089	BEI Resources	NR-51998	1x
Enterovirus	Species D, D68. Strain F02-3607 Corn	ATCC	VR-1197	0.3x
Enterovirus	Species D, Type 68. 2007 Isolate	ZeptoMetrix	0810237CF	1x
Enterovirus	Species D, Enterovirus D68. Strain US/KY/14-18953	ATCC	VR-1825	0.3x
Enterovirus	Species D, Enterovirus D68. Strain Fermon	ATCC	VR-1826	1x
Enterovirus	Species D, Type 68 Major Group (09/2014 Isolate 2)	ZeptoMetrix	0810302CF	1x
Enterovirus	Species D, Enterovirus D68. US/MO/14-18949	BEI Resources	NR-49130	0.3x
Enterovirus	Species D, Enterovirus D68. Strain US/IL/14-18952	ATCC	VR-1824	1x
Cryptococcus gattii	**Serotype B strain R272, type VGIIb**	**ATCC**	**MYA-4094**	**1x**
Cryptococcus gattii	**A6MR38 [CBS 11545]**	**ATCC**	**MYA-4877**	**1x**
Cryptococcus gattii	A1M R265	ATCC	MYA-4138	0.1x
Cryptococcus gattii	R265	BEI Resources	NR-50184	0.1x
Cryptococcus gattii	Alg166	BEI Resources	NR-50195	0.01x

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Cryptococcus gattii	Alg254	BEI Resources	NR-50198	0.01x
Cryptococcus gattii	Serotype C strain WM779, type VGIV	ATCC	MYA-4563	0.3x
Cryptococcus gattii	110 [CBS 883]	ATCC	14248	0.01x
Cryptococcus gattii	Serotype B strain WM161, type VGIII	ATCC	MYA-4562	0.1x
Cryptococcus gattii	Serotype B strain WM179, type VGI	ATCC	MYA-4560	0.01x
Cryptococcus neoformans	**Serotype D strain WM629, type VNIV**	**ATCC**	**MYA-4567**	**1x**
Cryptococcus neoformans	**C. neoformans H99**	**ATCC**	**208821**	**1x**
Cryptococcus neoformans	var. Grubii.Strain D	ATCC	13690	3x
Cryptococcus neoformans	NIH9hi90	BEI Resources	NR-50335	0.3x
Cryptococcus neoformans	Var grubiiYL99α	BEI Resources	NR-48776	0.1x
Cryptococcus neoformans	Serotype AD strain WM628, type VNIII	ATCC	MYA-4566	0.1x
Cryptococcus neoformans	Serotype A	ZeptoMetrix	0801803	0.1x
Cryptococcus neoformans	NIH306	BEI Resources	NR-50332	0.1x
Cryptococcus neoformans	type strain, CBS 132	ATCC	32045	0.3x
Cryptococcus neoformans	Serotype A strain WM148, type VNI	ATCC	MYA-4564	0.1x

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

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

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

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

Table 7. Inclusivity in vitro test results for all the pathogens tested with the QIAstat-Dx ME Panel Assay. Strains in bold were tested in the LoD studies. (continued)

Pathogen	Strain/ subtype	Supplier	Catalog ID	Times LoD
Varicella zoster virus	**Ellen**	**ZeptoMetrix**	**0810171CF**	**1x**
Varicella zoster virus	**Oka**	**ATCC**	**VR-1832**	**1x**
Varicella zoster virus	Webster	ATCC	VR-916	10x
Varicella zoster virus	Isolate A	ZeptoMetrix	0810172CF	10x
Varicella zoster virus	Isolate B	ZeptoMetrix	0810173CF	1x
Varicella zoster virus	Strain 1700	ZeptoMetrix	0810169CF	10x
Varicella zoster virus	Strain 275	ZeptoMetrix	0810168CF	1x
Varicella zoster virus	Strain 82	ZeptoMetrix	0810167CF	1x
Varicella zoster virus	Strain 9939	ZeptoMetrix	0810170CF	1x
Varicella zoster virus	Isolate D	ZeptoMetrix	0810175CF	1x

Table 8. Inclusivity *in silico* test results

Pathogen	Clinically relevant strains/subtypes detected
S. pneumoniae	No biological subclassification- all genomic sequences available in databases detected
HSV1	No biological subclassification- all genomic sequences available in databases detected
M. pneumoniae	No biological subclassification- all genomic sequences available in databases detected
N. meningitidis	Encapsulated serotypes (A, B, C, D, E, H, I, K, L, NG, W, W135, X, Y, Z, 29E)
C. neoformans/gattii	Serotype A (C. neoformans var neoformans), serotype D (C. neoformans var grubii), serotypes B and C (C. gattii including all VGI, VGII, VGIII, VGIV molecular types)
S. agalactiae	No biological subclassification- all genomic sequences available in databases detected
CMV	No biological subclassification- all genomic sequences available in databases detected

Table 8. Inclusivity in silico test results (continued)

Pathogen	Clinically relevant strains/subtypes detected
HPeV	All Human parechovirus A strains with available 5'-UTR sequence (1, 2, 3, 4, 5, 6, 7, 8, 14, 16, 17, 18, and 19), including echovirus 22 (HPeV 1) and echovirus 23 (HPeV 2). Although there were poliprotein sequences for HPeV A strains 9, 10, 11, 12, 13 and 15, no 5'-UTR sequence were available
L. monocytogenes	Serotypes 1/2a,1/2b, 1/2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e, 7
HHV-6	HHV-6a and HHV-6b
H. influenzae	All encapsulated serotypes (a, b, c, d, e, f) and unencapsulated strains (nontypable, NTHi) including var. *H. aegyptius*
HSV2	No biological subclassification- all genomic sequences available in databases detected
HEV	Coxsackievirus A (CV-A1 through CV-A24), coxsackievirus B (CV-B1 through CV-B6), Echovirus (E-1 through E-33), Enterovirus A (EV-A71, EV-A76, EV-A89 through EV-A92, EV-A119, EV-A120), Enterovirus B (EV-B69, EV-B73 through EV-B75, EV-B79, EV-B80 through EV-B88, EV-B93, EV-B97, EV-B98, EV-B100, EV-B101, EV-B106, EV-B107, EV-B111), Enterovirus C (EV-C96, EV-C99, EV-C102, EV-C104, EV-C105, EV-C109, EV-C116 through EV-C118), Enterovirus D (EV-D68, EV-D70, EV-D94), Poliovirus (PV-1 through PV-3)
S. pyogenes	No biological subclassification- all genomic sequences available in databases detected
E. coli K1	K1 strains
VZV	No biological subclassification- all genomic sequences available in databases detected

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 9).

Table 9. Potential cross-reactions from *in silico* analysis

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

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

In vitro testing results

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

Samples (20 On-Panel and 109 Off-Panel strains) were prepared by spiking potential cross-reactive organisms into artificial CSF matrix at 10^5 $TCID_{50}$/mL for viral targets, 10^5 CFU/mL for fungal targets, and 10^6 CFU/mL for bacterial targets, or the highest concentration possible based on the organism stock.

All strains tested for exclusivity are detailed on Table 10a and Table 10b.

Table 10a. List of On-Panel analytical specificity (exclusivity) pathogens tested

Type	Pathogen	Strain	Source
Bacteria	*Escherichia coli* K1	Strain C5 [Bort]; O18ac:K1:H7	ATCC 700973
	Haemophilus influenzae	Type e [strain AMC 36-A-7]	ATCC 8142
	Listeria monocytogenes	Type 4b. Strain Li 2	ATCC 19115
	Mycoplasma pneumoniae	M129	ZeptoMetrix 0801579
	Neisseria meningitidis	Serotype Y. M-112 [BO-6]	ATCC 35561
	Streptococcus pneumoniae	19F	ZeptoMetrix 0801439
	Streptococcus agalactiae	Z019	Zeptometrix 0801545
	Streptococcus pyogenes	Z472; Serotype M1	Zeptometrix 0804351

Table 10a. List of On-Panel analytical specificity (exclusivity) pathogens tested (continued)

Type	Pathogen	Strain	Source
Virus	Cytomegalovirus	Davis	ATCC VR-807
	Enterovirus A	A6, species A. Strain Gdula	ATCC VR-1801
	Enterovirus B	Coxsackievirus B5	ZeptoMetrix 0810019CF
	Enterovirus C	Coxsackievirus A17, species C. Strain G-12	ATCC VR-1023
	Enterovirus D	Enterovirus D68. Strain US/MO/14-18947	ATCC VR-1823
	Herpes simplex virus 1	Macintyre	ZeptoMetrix 0810005CF
	Herpes simplex virus 2	HSV-2. (Strain: MS)	ZeptoMetrix 0810006CF
	Human herpesvirus 6	HHV-6B. (Strain: Z29)	ZeptoMetrix 0810072CF
	Human parechovirus	Serotype 3	ZeptoMetrix 0810147CF
	Varicella zoster virus	Ellen	ZeptoMetrix 0810171CF
Fungi (Yeast)	*Cryptococcus neoformans*	WM629 [CBS 10079]	ATCC MYA-4567
	Cryptococcus gattii	Serotype B strain R272, type VGIIb	ATCC MYA-4094

Table 10b. List of Off-Panel analytical specificity (exclusivity) pathogens tested

Type	Pathogen	Strain	Source
Bacteria	*Bacillus cereus*	Z091	ZeptoMetrix 0801823
	Citrobacter freundii	[ATCC 13316, NCTC 9750]	ATCC 8090
	Corynebacterium striatum	CDC F6683	ATCC 43751
	Corynebacterium urealyticus	3 [Garcia strain]	ATCC 43044
	Cronobacter (Enterobacter) sakazakii	CDC 4562-70	ATCC 29544
	Enterobacter aerogenes	Z052	ZeptoMetrix 0801518
	Enterobacter cloacae	CDC 442-68	ATCC 13047

Table 10b. List of Off-Panel analytical specificity (exclusivity) pathogens tested (continued)

Type	Pathogen	Strain	Source
	Escherichia coli (non-K1)	2003-3055	ATCC BAA-2212
	Escherichia fergusonii	Z302	ZeptoMetrix 0804113
	Escherichia hermannii	CDC 980-72	ZeptoMetrix 0804068
	Escherichia vulneris	CDC 875-72	ATCC 33821
	*Haemophilus ducreyi***	DCC1476 [Sweden 15A-25]	ATCC BAA-661
	Haemophilus haemolyticus	NCTC 10659	ATCC 33390
	Haemophilus parahaemolyticus	536 [NCTC 8479]	ATCC 10014
	Haemophilus parainfluenzae	NCTC 7857	ATCC 33392
	Klebsiella pneumoniae	NCTC 9633 [NCDC 298-53, NCDC 410-68]	ATCC 13883
	Listeria innocua	SLCC 3379	ATCC 33090
	Listeria ivanovii	Li 1979	ATCC 19119
	Morganella morganii	AM-15	ATCC 25830
	Streptococcus salivarius	C699	ATCC 13419
	Streptococcus sanguinis	DSS-10	ATCC 10556
	Streptococcus pseudopneumoniae	CDC-SS-1757	ATCC BAA-960
	Mycoplasma genitalium	M30	ATCC 49895
	Neisseria lactamica	NCDC A7515	ATCC 23970
	Neisseria mucosa	AmMS 138	ATCC 49233
	Neisseria sicca	AMC 14-D-1	ATCC 9913
	Neisseria gonorrhoeae	Z017	ZeptoMetrix 0801482

Table 10b. List of Off-Panel analytical specificity (exclusivity) pathogens tested (continued)

Type	Pathogen	Strain	Source
	Pantoea agglomerans = *Enterobacter agglomerans*	Beijerinck	ATCC 27155
	Proprionibacterium acnes	NCTC 737	ATCC 6919
	Proteus mirabilis	LRA 08 01 73 [API SA, DSM 6674]	ATCC 7002
	Pseudomonas aeruginosa	PRD-10 [CIP 103467, NCIB 10421, PCI 812]	ATCC 15442
	Salmonella bongori	CIP 82.33	ATCC 43975
	Salmonella enterica	CDC K-1891 [ATCC 25928]	ATCC 13076
	Serratia marcescens	PCI 1107	ATCC 14756
	Shigella boydii	CDC C-123	ATCC 12033
	Shigella flexneri	Z046	ZeptoMetrix 0801757
	Shigella sonnei	AMC 43-GG9	ATCC 9290
	Staphylococcus aureus	FDA 209	ATCC CRM6538
	Staphylococcus capitis	PRA 360 677	ATCC 35661
	Staphylococcus epidermidis	FDA strain PCI 1200	ATCC 12228
	Staphylococcus haemolyticus	SM 131	ATCC 29970
	Staphylococcus hominis	Z031	ZeptoMetrix 0801727
	Staphylococcus lugdunensis	LRA 260.05.79	ATCC 49576
	Staphylococcus saprophyticus	NCTC 7292	ATCC 15305
	Streptococcus anginosus	NCTC 10713	ATCC 33397
	Streptococcus bovis	Z167	ZeptoMetrix 0804015

Table 10b. List of Off-Panel analytical specificity (exclusivity) pathogens tested (continued)

Type	Pathogen	Strain	Source
	Streptococcus dysgalactiae	Grouping strain C74	ATCC 12388
	Streptococcus intermedius	Z126	ZeptoMetrix 0801895
	Streptococcus oralis	Z307	ZeptoMetrix 0804293
	Streptococcus mitis (tigurinus)	Clinical Isolate	ZeptoMetrix 0801695
	Streptococcus mutans	LRA 28 02 81	ATCC 35668
Virus	Adenovirus A12	Huie	ATCC VR-863
	Adenovirus C2	Adenoid 6 (NIAID 202-001-014)	ATCC VR-846
	Adenovirus D20	A.A	ATCC VR-1090
	Adenovirus E4	RI-67	ATCC VR-1572
	Adenovirus F41	Tak	ZeptoMetrix 0810085CF
	BK polyoma virus	N/A	ATCC VR-837
	Coronavirus 229E	229E	ATCC VR-740
	Coronavirus NL63	NL63 (Amsterdam I)	BEI Resources NR-470

Table 10b. List of Off-Panel analytical specificity (exclusivity) pathogens tested (continued)

Type	Pathogen	Strain	Source
	Coronavirus OC43	OC43	ATCC VR-1558
	Dengue virus (Type 2)*	New Guinea C	ZeptoMetrix 0810089CFHI
	Epstein-Barr Virus	B95-8	ZeptoMetrix 0810008CF
	Hepatitis B virus (HBV)*	N/A	ZeptoMetrix 0810031C
	Hepatitis C virus (HCV)*	N/A	ZeptoMetrix 0810032C
	Human herpes virus 7	SB	ZeptoMetrix 0810071CF
	Human herpes virus 8	N/A	ZeptoMetrix 0810104CF
	Human Immunodeficiency Virus*	Quantitative Synthetic Human immunodeficiency virus 1 (HIV-1) RNA	ATCC VR-3245SD
	Human Rhinovirus A1b	2060	ATCC VR-1559
	Human Rhinovirus A16	11757	ATCC VR-283
	Human Rhinovirus B3	FEB	ATCC VR-483
	Human Rhinovirus B83	Baylor 7 [V-190-001-021]	ATCC VR-1193
	Influenza A H1N1	A/Florida/3/2006	ATCC VR-1893
	Influenza A H1N1-2009	A/California/08/2009 (H1N1pdm)	ATCC VR-1895
	Influenza A H3N2	A/Port Chalmers/1/73	ATCC VR-810
	Influenza B	B/Virginia/ATCC4/2009	ATCC VR-1784
	JC polyoma virus	MAD-4	ATCC VR-1583

Table 10b. List of Off-Panel analytical specificity (exclusivity) pathogens tested (continued)

Type	Pathogen	Strain	Source
	Measles Virus	Edmonston	ATCC VR-24
	Mumps Virus	Jones	ATCC VR-1438
	West Nile Virus*	1986	ATCC VR-3274SD
	Parainfluenza virus 2	Greer	ATCC VR-92
	Parainfluenza virus 4	N/A	ZeptoMetrix 0810060CF
	Parvovirus B19	B19	ZeptoMetrix 0810064C
	Respiratory Syncytial Virus	A2	ATCC VR-1540
	Rotavirus	RRV (Rhesus Rotavirus)	ZeptoMetrix 0810530CF
	Rubella Virus	N/A	ZeptoMetrix 0810048CF
	St. Louis Encephalitis Virus*	Parton	ZeptoMetrix 0810080CFHI
Fungi (Yeast)	*Candida albicans*	CBS 562	ATCC 18804
	Candida dubliniensis	Z145	ZeptoMetrix 0801915
	Candida glabrata	CBS 138	ATCC 2001
	Candida krusei	N/A	ATCC 14243
	Candida lusitaniae	Z010	ZeptoMetrix 0801603
	Candida metapsilosis	MCO429	ATCC 96143
	Candida orthopsilosis	MCO471	ATCC 96140

Table 10b. List of Off-Panel analytical specificity (exclusivity) pathogens tested (continued)

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

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

** Highest concentration possible due to stock restrictions.

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

except for the pathogens shown in the table below (Table 11). Pathogens exhibiting cross-reactivity with the panel, and the lowest concentration where cross reactivity is detected are listed in Table 11.

Table 11. Samples showing cross-reactivity with the QIAstat-Dx ME Panel

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

Co-infections

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

Co-infections testing demonstrated that when at least two QIAstat-Dx ME Panel pathogens of different concentrations are simultaneously present in one sample all targets can be detected by the assay. A summary of the final co-infection mixes whereby the High Positive Analyte does not inhibit the Low Positive Analyte is shown in Table 12.

Table 12. Co-infection mixes tested where concentration of the High Positive Analyte does not inhibit the Low Positive Analyte

Low Positive Analyte		High Positive Analyte	
Pathogen	**Concentration**	**Pathogen**	**Concentration**
Escherichia coli K1	3.30E+02 cfu/mL	*Haemophilus influenzae*	1.00E+06 cfu/mL

Table 12. Co-infection mixes tested where concentration of the High Positive Analyte does not inhibit the Low Positive Analyte (continued)

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

Table 12. Co-infection mixes tested where concentration of the High Positive Analyte does not inhibit the Low Positive Analyte (continued)

Low Positive Analyte		High Positive Analyte	
Pathogen	**Concentration**	**Pathogen**	**Concentration**
VZV	1.62E+02 cp/mL	*Neisseria meningitidis*	1.00E+06 cfu/mL
Neisseria meningitidis	3.99E+01 cfu/mL	VZV	1.00E+06 cp/mL
Enterovirus	4.80E+02 $TCID_{50}$/mL	*Streptococcus pyogenes*	1.00E+06 cfu/mL
Streptococcus pyogenes	1.71E+03 cfu/mL	Enterovirus	1.00E+05 $TCID_{50}$/mL
HPeV	1.01E+02 $TCID_{50}$/mL	Cytomegalovirus	1.00E+02 $TCID_{50}$/mL
Cytomegalovirus	3.00E+01 $TCID_{50}$/mL	HPeV	1.00E+05 $TCID_{50}$/mL
HPeV	1.01E+02 $TCID_{50}$/mL	Enterovirus	1.00E+05 $TCID_{50}$/mL
Enterovirus	4.80E+02 $TCID_{50}$/mL	HPeV	1.00E+05 $TCID_{50}$/mL
HHV-6	9.39E+04 $TCID_{50}$/mL	HSV1	1.00E+05 $TCID_{50}$/mL
HSV1	2.67E+02 $TCID_{50}$/mL	HHV-6	1.00E+05 $TCID_{50}$/mL
Streptococcus agalactiae	5.25E+03 cfu/mL	HSV2	1.00E+05 $TCID_{50}$/mL
HSV2	3.78E+01 $TCID_{50}$/mL	*Streptococcus agalactiae*	1.00E+06 cfu/mL

Reproducibility

For the reproducibility assessment, a multi-site scheme was followed by testing both negative and positive samples at three different study sites with varying workflow variables, such as sites, days, instruments, operators and cartridge lots that could have an impact on the precision of the system. Negative samples consisted of artificial CSF. Positive combined samples consisted of artificial CSF spiked with a representative panel of pathogens covering all types of organisms targeted by the QIAstat-Dx ME Panel (i.e. RNA virus,DNA virus, gram

(+) bacteria, gram (-) bacteria and yeast) at the limit of detection (1x LoD) and at 3x LoD. For each site, testing was performed across 5 non-consecutive days per mix with 6 replicates per day per mix (leading to a total of 90 replicates per target, concentration, and site), a minimum of 9 different QIAstat-Dx Analyzers per site, and at least 3 operators on each testing day.

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

Table 13 summarizes the results for 3x LoD and 1x LoD concentrations where it is observed that the detection rate for all targets was 100% and ≥98%, respectively. All negative samples returned a negative call 100% of the time.

Table 13. Proportion of true positive Reproducibility Results at 1x LoD and 3x LoD

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

Table 13. Proportion of true positive Reproducibility Results at 1x LoD and 3x LoD (continued)

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

Table 13. Proportion of true positive Reproducibility Results at 1x LoD and 3x LoD (continued)

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

Table 13. Proportion of true positive Reproducibility Results at 1x LoD and 3x LoD (continued)

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

Repeatability

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

Table 14 summarizes the results for 3x LoD and 1x LoD concentrations where it is observed that the detection rate for all targets was >98% and ≥93%, respectively. All negative samples returned a negative call 100% of the time.

Table 14. Proportion of true positive Repeatability Results at 1x LoD and 3x LoD

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

Carryover

A carryover study was performed to evaluate the potential occurrence of cross-contamination between consecutive runs when using the QIAstat-Dx ME Panel on the QIAstat-Dx Analyzer 1.0. Pathogenic CSF samples with alternating high-positive (10^4–10^6 organism/mL) and

negative samples, were conducted on two QIAstat-Dx Analyzer 1.0 instruments. No carryover between samples was observed in the QIAstat-Dx ME Panel, demonstrating that the system design and recommended sample handling and testing practices are effective in preventing unexpected results due to carryover or cross-contamination between samples.

Interfering substances (analytical specificity)

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

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

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

The results of interfering substances testing are provided in Table 15.

Table 15. Summary of interfering substances testing results

Substance tested	Concentration tested		Result
	Endogenous substances		
Human Blood	10	% (v/v)	No Interference

Table 15. Summary of interfering substances testing results (continued)

Substance tested	Concentration tested		Result
	Endogenous substances		
gDNA	20	µg/mL	**Interference**
	2.0	µg/mL	No Interference
D(+)Glucose	10	mg/mL	No Interference
L-lactate (Na)	2.2	mg/mL	No Interference
Immunoglobulin G (human)	20	mg/mL	No Interference
Albumin (human)	30	mg/mL	No Interference
Peripheral blood mononuclear cells	10,000	cells/µL	No Interference
	Exogenous substances		
Chlorhexidine	0.4	% (w/v)	No Interference
Ethanol	7	% (v/v)	No Interference
Bleach	1	% (v/v)	**Interference**
	0.1	% (v/v)	**Interference**
	0.01	% (v/v)	No Interference
Acyclovir	69	µg/mL	No Interference
Amphotericin B	5.1	µg/mL	No Interference
Ampicillin	210	µg/mL	No Interference
Ceftriaxone	840	µg/mL	No Interference
Cefotaxime	645	µg/mL	No Interference
Ganciclovir	25	µg/mL	No Interference
Gentamicin	30	µg/mL	No Interference
Meropenem	339	µg/mL	No Interference

Table 15. Summary of interfering substances testing results (continued)

Substance tested	Concentration tested		Result
	Endogenous substances		
Vancomycin	180	µg/mL	No Interference
Voriconazole	11	µg/mL	No Interference
Oseltamivir	0.399	µg/mL	No Interference
	Non-target microorganisms		
Epstein-Barr virus	1.00E+05	cp/mL	No Interference
Influenza A H1N1-2009	1.00E+05	$CEID_{50}$/mL	No Interference
Cutibacterium acnes	1.00E+06	CFU/mL	No Interference
Staphylococcus epidermidis	1.00E+06	CFU/mL	No Interference
Escherichia coli (non-K1)	1.00E+06	CFU/mL	No Interference
Staphylococcus aureus	1.00E+06	CFU/mL	No Interference
Measles virus	1.00E+05	$TCID_{50}$/mL	No Interference

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

Clinical performance

The clinical performance shown below 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.

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 1526 prospective specimens of which 553 (36.2%) were frozen before testing and 973 (63.8%) were tested fresh (Table 16).

Table 16. 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	8.9
		18-44 years old	284	29.2
		45-64 years old	267	27.4
		65-84 years old	187	19.2
		≥85 years old	11	1.1
		Unknown	1	0.1
	Gender	Female	498	51.2
		Male	475	48.8

Table 16. Demographic summary for prospective samples for QIAstat-Dx ME Panel clinical evaluation (continued)

			N	%
Prospective Frozen	Age Group	<1 year	27	4.9
		1-17 years old	41	7.4
		18-44 years old	133	24.1
		45-64 years old	175	31.6
		65-84 years old	156	28.2
		≥85 years old	20	3.6
		Unknown	1	0.2
	Gender	Female	271	49.0
		Male	281	50.8
		Not available	1	0.2

Residual CSF specimens were tested with the QIAstat-Dx ME Panel and two types of comparator methods (an FDA-cleared/CE-marked molecular comparator and two validated end point PCRs followed by bidirectional sequencing (BDS) for selected targets). All targets were compared to the FDA-cleared/CE-marked molecular method except *Streptococcus pneumoniae, Streptococcus pyogenes and Mycoplasma pneumoniae* which were compared against two validated end point PCRs followed by bidirectional sequencing for selected targets (Table 17). The standard of care testing varied across all sites but included bacterial culture, PCR, FDA-cleared/CE-marked 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 bi-directional sequencing for selected targets.

All specimens were tested against the FDA cleared/CE-marked molecular comparator however, the number of specimens tested against each set of two validated end point PCRs

followed by bidirectional sequencing for selected targets were lower due to CSF volume constraints. A total of 1524 prospectively collected specimens were evaluated against an FDA-cleared molecular comparator. A total of 1372 prospectively collected specimens were evaluated against validated end point x 2 PCR for *Mycoplasma pneumoniae* followed by BDS. A total of 1373 prospectively collected specimens were evaluated against validated end point x 2 PCR for *Streptococcus pneumoniae* followed by BDS. A total of 1291 prospectively collected specimens were evaluated against validated end point x 2 PCR for *Streptococcus pyogenes* followed by BDS.

Table 17. Comparator Methods for the Clinical Evaluation of QIAstat-Dx ME Panel

Targets	Comparator method
Escherichia coli K1	FDA-cleared/CE-marked molecular test
Haemophilus influenzae	
Listeria monocytogenes	
Neisseria meningitidis (encapsulated)	
Streptococcus agalactiae	
Streptococcus pneumoniae	Validated end point x2 PCR followed by BDS
Streptococcus pyogenes	
Mycoplasma pneumoniae	
Human herpesvirus 6	FDA-cleared/CE-marked molecular test
Enterovirus	
Human parechovirus	
Cryptococcus gattii/Cryptococcus neoformans (Not Differentiated)	
Cytomegalovirus	
Herpes simplex virus 1	
Herpes simplex virus 2	
Varicella zoster virus	

Several analytes in the QIAstat-Dx ME Panel were of low prevalence and were not encountered in sufficiently large numbers during the prospective study to adequately demonstrate clinical performance. To supplement the results of the prospective clinical study, an evaluation of frozen archived positive retrospective specimens was performed. The specimens selected for testing had previously tested positive for one of the QIAstat-Dx ME Panel targets using the clinical laboratory standard of care method. The archived specimen testing was mixed with the prospective specimen testing at the clinical sites to ensure blinding. A total of 195 retrospective archived specimens were enrolled onto the study. Fifty-five (55) archived specimens were excluded from the analysis. A total of 140 evaluable archived specimens were used in the analysis to support the QIAstat-Dx ME Panel performance evaluation and Table 18 provides a summary of demographic information for the archived specimens.

Table 18. Demographic Summary of Evaluable Archived Specimens for QIAstat-Dx ME Panel Clinical Evaluation

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

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

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

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

The QIAstat-Dx ME Panel positive percent agreement and negative percent agreement against the comparator methods for clinical specimens (prospective and archived) are presented by analyte in Table 19.

Table 19. QIAstat-Dx ME Panel clinical specimens performance

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
			Overall			
Overall	222 / 260	85.4%	80.6%-89.2%	25712 / 25736	99.9%	99.9%-99.9%
			Bacteria			
Escherichia coli K1	4 / 6	66.7%	30.0%-90.3%	1658 / 1658	100.0%	99.8%-100.0%
Haemophilus influenzae	10 / 11	90.9%	62.3%-98.4%	1650 / 1653	99.8%	99.5%-99.9%

Table 19. QIAstat-Dx ME Panel clinical specimens performance (continued)

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Listeria monocytogenes	4 / 5	80.0%	37.6%-96.4%	1659 / 1659	100.0%	99.8%-100.0%
Mycoplasma pneumoniae	0 / 0	N/A	N/A	1482 / 1482	100.0%	99.7%-100.0%
Neisseria meningitidis (encapsulated)	4 / 4	100.0%	51.0%-100.0%	1659 / 1660	99.9%	99.7%-100.0%
Streptococcus agalactiae	12 / 12	100.0%	75.8%-100.0%	1652 / 1652	100.0%	99.8%-100.0%
Streptococcus pneumoniae	12 / 12	100.0%	75.8%-100.0%	1463 / 1469	99.6%	99.1%-99.8%
Streptococcus pyogenes	0 / 0	N/A	N/A	1401 / 1401	100.0%	99.7%-100.0%
Bacteria Overall	46 / 50	92.0%	81.2%-96.8%	12624 / 12634	99.9%	99.9%-100.0%
			Virus			
Cytomegalovirus (CMV)	3 / 5	60.0%	23.1%-88.2%	1656 / 1659	99.8%	99.5%-99.9%
Enterovirus (EV)	31 / 33	93.9%	80.4%-98.3%	1630 / 1631	99.9%	99.7%-100.0%
Herpes simplex virus 1 (HSV-1)	10 / 12	83.3%	55.2%-95.3%	1652 / 1652	100.0%	99.8%-100.0%
Herpes simplex virus 2 (HSV-2)	29 / 36	80.6%	65.0%-90.2%	1627 / 1628	99.9%	99.7%-100.0%
Human Parechovirus (HPeV)	4 / 8	50.0%	21.5%-78.5%	1655 / 1656	99.9%	99.7%-100.0%
Human herpesvirus 6 (HHV-6)	25 / 30	83.3%	66.4%-92.7%	1628 / 1634	99.6%	99.2%-99.8%

Table 19. QIAstat-Dx ME Panel clinical specimens performance (continued)

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Varicella zoster virus (VZV)	62 / 71	87.3%	77.6%-93.2%	1593 / 1593	100.0%	99.8%-100.0%
Virus Overall	164 / 195	84.1%	78.3%-88.6%	11441 / 11453	99.9%	99.8%-99.9%
			Fungi & Yeast			
Cryptococcus gattii / Cryptococcus neoformans (not differentiated)	12 / 15	80.0%	54.8%-93.0%	1647 / 1649	99.9%	99.6%-100.0%
Fungi & Yeast Overall	12 / 15	80.0%	54.8%-93.0%	1647 / 1649	99.9%	99.6%-100.0%

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

The QIAstat-Dx ME Panel positive percent agreement and negative percent agreement against the comparator following discrepant resolution is presented by analyte in Table 20.

Table 20. QIAstat-Dx ME Panel clinical specimens performance after discrepant resolution

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
			Bacteria			
Escherichia coli K1	4 / 4	100.0%	51.0%-100.0%	1660 / 1660	100.0%	99.8%-100.0%
Haemophilus influenzae	10 / 10	100.0%	72.2%-100.0%	1651 / 1654	99.8%	99.5%-99.9%

Table 20. QIAstat-Dx ME Panel clinical specimens performance after discrepant resolution (continued)

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

Table 20. QIAstat-Dx ME Panel clinical specimens performance after discrepant resolution (continued)

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

Clinical sensitivity and specificity determined against culture

The performance measure of sensitivity and specificity was calculated only for bacterial and fungi analytes for which the gold-standard CSF culture results was available in the standard of care for the clinical prospective and archived specimens. This data was used in additional performance calculations outlined in Table 21.

Table 21. Bacterial or Fungal Culture comparison for diagnostic sensitivity and specificity for all clinical samples.

	Sensitivity (compared to culture)			Specificity (compared to culture)		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
			Bacteria			
Escherichia coli K1[a]	2 / 3	66.7%	20.8%-93.9%	1125 / 1126	99.9%	99.5%-100.0%
Haemophilus influenzae[b]	4 / 4	100.0%	51.0%-100.0%	1122 / 1125	99.7%	99.2%-99.9%
Listeria monocytogenes[c]	3 / 4	75.0%	30.1%-95.4%	1125 / 1125	100.0%	99.7%-100.0%
Mycoplasma pneumonia[e]	0 / 0	N/A	N/A	1129 / 1129	100.0%	99.7%-100.0%
Neisseria meningitidis (encapsulated)[d]	2 / 2	100.0%	34.2%-100.0%	1124 / 1127	99.7%	99.2%-99.9%
Streptococcus agalactiae[e]	2 / 2	100.0%	34.2%-100.0%	1126 / 1127	99.9%	99.5%-100.0%
Streptococcus pneumoniae[f]	3 / 3	100.0%	43.9%-100.0%	1118 / 1126	99.3%	98.6%-99.6%
Streptococcus pyogenes[g]	0 / 0	N/A	N/A	1128 / 1129	99.9%	99.5%-100.0%
			Fungi & Yeast			

Table 21. Bacterial or Fungal Culture comparison for diagnostic sensitivity and specificity for all clinical samples. (continued)

	Sensitivity (compared to culture)			Specificity (compared to culture)		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Cryptococcus gattii / Cryptococcus neoformans (not differentiated) [h]	3 / 3	100.0%	43.9%-100.0%	155 / 157	98.7%	95.5%-99.6%

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

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

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

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

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

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

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

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

Co-infection summary

Amongst the 1667 non-withdrawn specimens with a valid QIAstat-Dx result, 245 specimens (14.7%) reported positive results for at least one analyte while the remaining 1422 (85.3%) were negative. In total 6 positive specimens shown multiple detections. Each multiple detections contained two organisms and they are summarized in Table 21.

Table 22. Co-infections combinations as Determined by the QIAstat-Dx ME Panel

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

QIAstat-Dx ME Panel Tests Success Rate

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

Contrived samples testing

Contrived specimen testing was required for all targets on the panel as there were insufficient positive specimens obtained from both prospective and archived collection efforts. Contrived specimens were prepared by spiking five different quantified strains representative of the genetic diversity of 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 23.

Table 23. QIAstat-Dx ME Panel contrived sample performance summary

Pathogen	Concentration Level	Frequency of Positive Results	Proportion (%) of Positive Results	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Escherichia coli K1	2xLoD	48 / 48	100.0%	92.6%	100.0%
	5xLoD	37 / 37	100.0%	90.6%	100.0%
	Total	85 / 85	100.0%	95.7%	100.0%
Haemophilus influenzae	2xLoD	57 / 57	100.0%	93.7%	100.0%
	5xLoD	36 / 36	100.0%	90.4%	100.0%
	Total	93 / 93	100.0%	96.0%	100.0%
Listeria monocytogenes	2xLoD	47 / 49	95.9%	86.3%	98.9%
	5xLoD	38 / 38	100.0%	90.8%	100.0%
	Total	85 / 87	97.7%	92.0%	99.4%
Mycoplasma pneumoniae	2xLoD	46 / 46	100.0%	92.3%	100.0%
	5xLoD	39 / 40	97.5%	87.1%	99.6%
	Total	85 / 86	98.8%	93.7%	99.8%
Neisseria meningitidis (encapsulated)	2xLoD	46 / 48	95.8%	86.0%	98.8%
	5xLoD	39 / 40	97.5%	87.1%	99.6%
	Total	85 / 88	96.6%	90.5%	98.8%
Streptococcus agalactiae	2xLoD	49 / 49	100.0%	92.7%	100.0%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	88 / 88	100.0%	95.8%	100.0%

Table 23. QIAstat-Dx ME Panel contrived sample performance summary (continued)

Pathogen	Concentration Level	Frequency of Positive Results	Proportion (%) of Positive Results	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Streptococcus pneumoniae	2xLoD	55 / 57	96.5%	88.1%	99.0%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	94 / 96	97.9%	92.7%	99.4%
Streptococcus pyogenes	2xLoD	47 / 49	95.9%	86.3%	98.9%
	5xLoD	40 / 40	100.0%	91.2%	100.0%
	Total	87 / 89	97.8%	92.2%	99.4%
Cytomegalovirus (CMV)	2xLoD	46 / 50	92.0%	81.2%	96.8%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	85 / 89	95.5%	89.0%	98.2%
Enterovirus (EV)	2xLoD	48 / 49	98.0%	89.3%	99.6%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	87 / 88	98.9%	93.8%	99.8%
Herpes simplex virus 1 (HSV-1)	2xLoD	50 / 52	96.2%	87.0%	98.9%
	5xLoD	45 / 47	95.7%	85.8%	98.8%
	Total	95 / 99	96.0%	90.1%	98.4%
Human Parechovirus (HPeV)	2xLoD	46 / 48	95.8%	86.0%	98.8%
	5xLoD	39 / 39	100.0%	91.0%	100.0%
	Total	85 / 87	97.7%	92.0%	99.4%
Cryptococcus gattii / Cryptococcus neoformans (not differentiated)	2xLoD	41 / 41	100.0%	91.4%	100.0%
	5xLoD	38 / 38	100.0%	90.8%	100.0%
	Total	79 / 79	100.0%	95.4%	100.0%

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

QIAstat-DxME Panel performance across all specimen types

The results for all target pathogens obtained during clinical specimens testing in the prospective and retrospective studies after discordant resolution and contrived samples testing combined, is summarized in Table 24.

Table 24. QIAstat-Dx ME Panel Performance per analyte across all specimen types

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Overall Panel	1356 / 1388	97.7%	96.8%-98.4%	42947 / 42997	99.9%	99.8%-99.9%
Bacteria						
Escherichia coli K1	89 / 89	100.0%	95.9%-100.0%	2720 / 2724	99.9%	99.6%-99.9%
Haemophilus influenzae	103 / 103	100.0%	96.4%-100.0%	2703 / 2710	99.7%	99.5%-99.9%
Listeria monocytogenes	89 / 92	96.7%	90.8%-98.9%	2722 / 2722	100.0%	99.9%-100.0%
Mycoplasma pneumoniae	85 / 86	98.8%	93.7%-99.8%	2545 / 2545	100.0%	99.8%-100.0%
Neisseria meningitidis (encapsulated)	89 / 92	96.7%	90.8%-98.9%	2720 / 2721	100.0%	99.8%-100.0%
Streptococcus agalactiae	100 / 100	100.0%	96.3%-100.0%	2710 / 2714	99.9%	99.6%-99.9%
Streptococcus pneumoniae	106 / 108	98.1%	93.5%-99.5%	2516 / 2522	99.8%	99.5%-99.9%
Streptococcus pyogenes	87 / 89	97.8%	92.2%-99.4%	2461 / 2461	100.0%	99.8%-100.0%

Table 24. QIAstat-Dx ME Panel Performance per analyte across all specimen types (continued)

	Positive Percent Agreement			Negative Percent Agreement		
Pathogen	**TP/TP+FN**	**%**	**95% CI**	**TN/TN+FP**	**%**	**95% CI**
Bacteria Overall	748 / 759	98.6%	97.4%-99.2%	21097 / 21119	99.9%	99.8%-99.9%
Virus						
Cytomegalovirus (CMV)	88 / 92	95.7%	89.3%-98.3%	2718 / 2721	99.9%	99.7%-100.0%
Enterovirus (EV)	118 / 119	99.2%	95.4%-99.9%	2690 / 2695	99.8%	99.6%-99.9%
Herpes simplex virus 1 (HSV-1)	105 / 109	96.3%	90.9%-98.6%	2703 / 2705	99.9%	99.7%-100.0%
Herpes simplex virus 2 (HSV-2)	29 / 31	93.5%	79.3%-98.2%	2780 / 2782	99.9%	99.7%-100.0%
Human Parechovirus (HPeV)	89 / 93	95.7%	89.5%-98.3%	2719 / 2720	100.0%	99.8%-100.0%
Human herpesvirus 6 (HHV-6)	26 / 28	92.9%	77.4%-98.0%	2773 / 2785	99.6%	99.2%-99.8%
Varicella zoster virus (VZV)	62 / 66	93.9%	85.4%-97.6%	2746 / 2747	100.0%	99.8%-100.0%
Virus Overall	517 / 538	96.1%	94.1%-97.4%	19129 / 19155	99.9%	99.8%-99.9%
Fungi & Yeast						
Cryptococcus gattii / Cryotococcus neoformans (not differentiated)	91 / 91	100.0%	95.9%-100.0%	2721 / 2723	99.9%	99.7%-100.0%
Fungi & Yeast Overall	91 / 91	100.0%	95.9%-100.0%	2721 / 2723	99.9%	99.7%-100.0%

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

virus which were 93.5%, 92.9% and 93.9%, respectively. The NPA was ≥98.5% for all QIAstat-Dx ME Panel analytes.

Conclusion

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

Summary of Safety and Performance

The summary of safety and performance section can be downloaded from the Eudamed website at the following location:

www.ec.europa.eu/tools/eudamed/#/screen/searchdevice

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Troubleshooting Guide

In case of damaged cartridge, please refer to "Safety information" on page 24. 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
	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
	Component

Symbol	Symbol definition
	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
	Do not use if package is damaged

Symbol	Symbol definition
	Flammable, risk of fire
	Corrosive, risk of chemical burn
	Health Hazard, risk of sensitization, carcinogenicity
	Risk of harm
EC REP	Authorized representative in the European Community
	Brain icon present on the QIAstat-Dx ME Panel Cartridge

Contact Information

For technical assistance and more information, please see our Technical Support Center Centre at **www.qiagen.com/Support**, call 1-800-362-7737, or contact one of the QIAGEN Technical Service Departments or local distributors (see back cover or visit **www.qiagen.com**).

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).

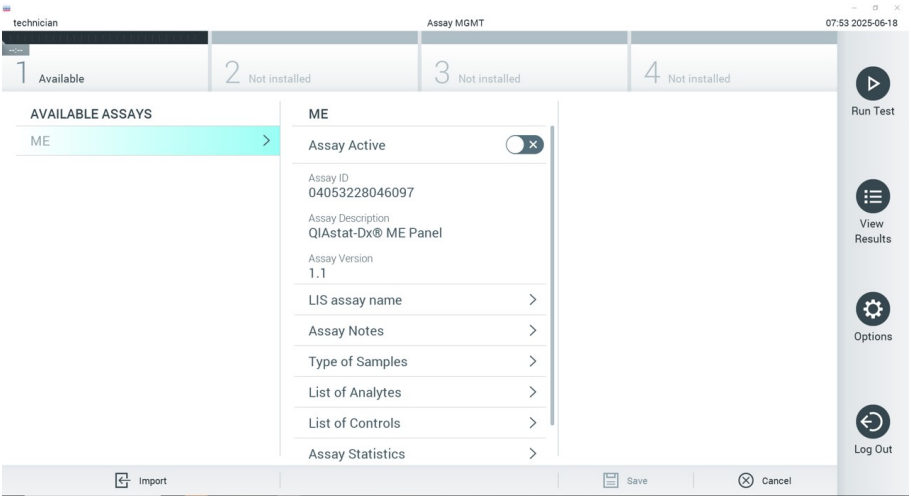

Figure 25. Assay Management screen.

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).

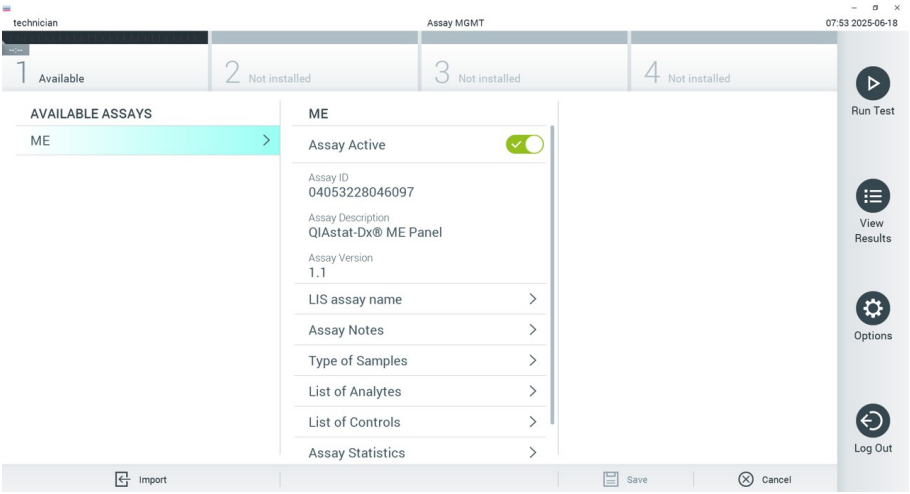

Figure 26. Activating the assay.

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**.

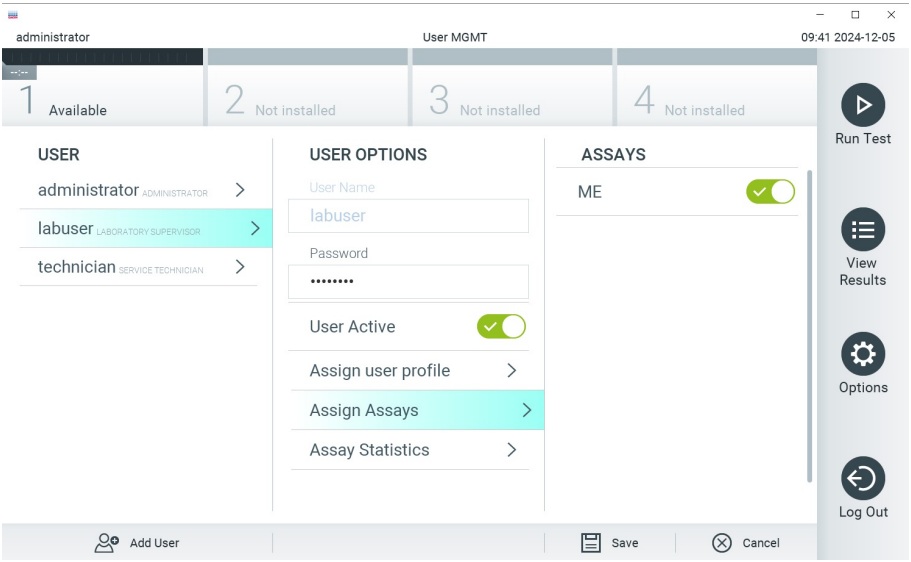

Figure 27. Assigning the active assay

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 or the Analyzer 2.0 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 or Operational Module PRO.

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.

Ordering Information

Product	Contents	Cat. no.
QIAstat-Dx Meningitis/Encephalitis (ME) Panel	For 6 tests: 6 individually packaged QIAstat-Dx Meningitis/Encephalitis (ME) Panel Cartridges and 6 individually packaged transfer pipettes.	691612
Related Products		
QIAstat-Dx Analyzer 1.0	1 QIAstat-Dx Analytical Module, 1 QIAstat-Dx Operational Module, and related hardware and software to run molecular diagnostic QIAstat-Dx assay cartridges.	9002824
QIAstat-Dx Analyzer 2.0	1 QIAstat-Dx Analytical Module, 1 QIAstat-Dx Operational Module PRO, and related hardware and software to run molecular diagnostic QIAstat-Dx assay cartridges.	9002828

For up-to-date licensing information and product-specific disclaimers, see the respective QIAGEN kit Instructions for Use. QIAGEN kit Instructions for Use are available at **www.qiagen.com** or can be requested from QIAGEN Technical Services or your local distributor.

Document Revision History

Revision	Description
R1, June 2025	Initial release.

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