DETECTION OF ANTI-GLUTAMATE RECEPTOR (NMDA) (REFERENCE – 2014.02.02)

Notice of Assessment

December 2014
1. GENERAL INFORMATION

1.1. Requester: CHU Sainte-Justine
1.2. Application for Review Submitted to MSSS: May 1, 2014
1.3. Application Received by INESSS: July 10, 2014
1.4. Notice Issued: October 31, 2014

Note:
This notice is based on the scientific and commercial information submitted by the requester and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2. TECHNOLOGY, COMPANY, AND LICENCE(S)

2.1 Name of the Technology
Detection of anti-glutamate receptor NMDA (N-methyl-D-aspartate) using indirect immunofluorescence in cerebrospinal fluid (CSF) or in serum

2.2 Brief Description of the Technology, and Clinical and Technical Specifications
The test is designed to detect, in CSF or serum, the presence of autoantibodies directed against membrane antigens of the central nervous system, the N-methyl-D-aspartate (NMDA) receptor,¹ or the anti-glutamate receptor² [Dalmau et al., 2008]. The test is carried out using indirect immunofluorescence on various substrates, rat hippocampal and cerebellar tissue (tissue-based assay), and cell cultures expressing recombinant NMDA receptors (transfected³ HEK²93 cells). Non-transfected cells are used as controls. Tissue-based assays allow the detection of anti-NMDA receptor antibodies as well as other antibodies (e.g., anti-VGKC⁵ and anti-AMPA⁶ receptors). Parallel testing on HEK293 cells (cell-based assay or CBA) provides sensitive, monospecific detection of anti-NMDA receptor antibodies [EUROIMMUN, 2014]. Various kits are available, depending on the substrates used, including a microplate with four biochips combining all the substrates, described below, and a microplate with two biochips with transfected and non-transfected cells as substrates.

1. The NMDA receptor, comprising four postsynaptic transmembrane proteins (tetramers), is generally composed of two RN1 subunits and RN2. It is present in large quantities in the cerebral cortex and hippocampus and is involved in numerous pathophysiological mechanisms such as locomotion, pain perception, memory, and learning. The four proteins form a channel that allows the flow of calcium, sodium, and potassium ions and is normally blocked by magnesium ions, which have binding sites inside the channel. Several molecules, particularly NMDA, can bind to the receptor. When glutamate is released into the synaptic cleft, it can open NMDA receptors, thus allowing calcium molecules to enter postsynaptic dendrites [Lafaix, 2013].
2. Glutamate is the brain’s primary excitatory neurotransmitter, acting on three types of receptors: NMDA, kainate, and AMPA [Monier and Fabien, 2006].
3. Transfection is the process of introducing a fragment of foreign DNA into a eukaryotic cell so that the cell may express a given gene (Futura-Santé. Transfection [website], available at: http://www.futura-sciences.com/magazines/sante/infos/dico/d/genetique-transfection-273/).
   Human embryonic kidney cells (HEK293) were transfected with plasmids expressing rodent NR1, NR2A, or NR2B subunits of the NMDAR [Dalmau et al., 2007]. Plasmid: an extrachromosomal self-replicating structure found in bacterial cells that carries genes for a variety of functions not essential for cell growth (Dorland’s Illustrated Medical Dictionary, 32nd edition, Elsevier).
5. VGKC: voltage-gated potassium channel.
6. AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.
Technique
The test samples (serum diluted to 1:10 in PBS7-Tween or undiluted CSF) are applied to the reagent support using the TITERPLANE™ technique. The biochip slide with the various substrates is then placed on this same support so that it comes into contact with the liquids and allows the individual samples to react simultaneously. The incubation step at room temperature lasts 30 minutes. If a sample is positive, specific IgA, IgG, and IgM antibodies bind to the antigens coupled to the solid phase (biochips). After each incubation step, the biochip slides are washed with PBS-Tween to remove any unbound antibodies or fluorescein-labelled reagents. Bound antibodies are detected with fluorescein-labelled anti-human IgG antibodies and made visible under a fluorescence microscope. Anti-NMDA receptor antibodies show a smooth to fine-granular fluorescence in the cytoplasm of transfected HEK293 cells.8

2.3 Company or Developer
The company EUROIMMUN (Medizinische Labordiagnostika AG) (Germany).

2.4 Licence(s): Not applicable.

2.5 Patent, If Any: Not applicable.

2.6 Approval Status (Health Canada, FDA, other countries)
The Anti-Glutamate Receptor (Type NMDA) IIFT kit (which uses the CBA method) from the company EUROIMMUN is approved by Health Canada (No. 81522).
The FDA has approved EUROIMMUN’s Anti-Glutamate Receptor (Type NMDA) IIFT kit, which uses a CBA with semi-quantitative indirect immunofluorescence technique (k1000179).

2.7 Weighted Value
Value of 239.26, including the cost of two slides for each type of sample: serum and CSF ($119.63 per slide).

7. PBS: phosphate-buffered saline.
3. CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

3.1 Targeted Patient Group

 Patients with autoimmune encephalitis with no known common infectious cause (HSV,\(^{10}\) VZV,\(^{11}\) enterovirus).

3.2 Targeted Disease(s)

Clinical signs combining ovarian teratoma with episodes of memory deficits, psychiatric symptoms, decreased level of consciousness or hypersomnia, and signs of central hypoventilation were reported in four women examined by the authors of a study published in 2005 and in five other previously described cases reported in the same study [Vitaliani et al., 2005]. Since then, approximately 419 other patients with this syndrome have been identified, including children and young adults with or without the associated tumour. The exact incidence of the disease is unknown, but it appears to be increasingly common, occurring predominantly in women (80% of cases) [Dalmau et al., 2011].

Most patients with anti-NMDA receptor (anti-NMDAR) encephalitis have intrathecal synthesis of anti-NMDAR antibodies. The main epitope targeted by these antibodies is in the extracellular N-terminal domain of the NR1 subunit [Dalmau et al., 2008]. NMDAR antibodies cause a decrease in the number of NMDA receptors and affect the interneuronal transmission of information. This disorder is most recently called anti-NMDAR encephalitis [Peery et al., 2012; Dalmau et al., 2011 et 2007].

Early clinical signs of the disease, as described by Dalmau et al. [2008], include headaches, fever, or symptoms of nonspecific viral infection. Psychiatric symptoms follow, such as anxiety, restlessness, behaviour problems, paranoid delusions, and visual and auditory hallucinations. Some patients suffer from short-term memory loss or from seizures, which may be associated with psychiatric symptoms. Patient prognosis depends on early diagnosis, appropriate immunomodulatory treatment, and resection of a teratoma, if relevant [Wandinger et al., 2011].

3.3 Number of Patients Targeted

The CHU Sainte-Justine sends 20 to 30 samples each year to Dr. Dalmau’s research laboratory in Spain. The requester estimates that 100 tests will be conducted locally each year.

3.4 Medical Specialties and Other Professions Involved

Neurology, psychiatry, neuro-oncology, microbiology.

3.5 Testing Procedure

CSF samples obtained by lumbar puncture or serum samples obtained by venipuncture.

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10. HSV: herpes simplex virus.
11. VZV: varicella-zoster virus.
4. TECHNOLOGY BACKGROUND

4.1 Nature of the Diagnostic Technology

This test would replace tests being sent outside Quebec. According to the data provided by the MSSS, during the year 2012-2013, 26 tests were sent outside Quebec, either to the United States (Athena Diagnostics or Mayo Medical Laboratories) or to Alberta (Mitogen Advanced Diagnostics in Calgary). The unit cost of the test ranges from $85 to $890.64.

This new test was developed in collaboration with the company EUROIMMUN and Dr. Joseph Dalmau’s research laboratory in Spain.

4.2 Brief Description of the Current Technological Context

Several diagnostic tests help establish a diagnosis of anti-NMDAR encephalitis [Dalmau et al., 2011]:

- Electroencephalogram (EEG): abnormal in most patients, with reduced, unfocused and disorganized activity;
- Magnetic resonance imaging (MRI): abnormal in 50% of cases, most commonly with hyperintensities in T2-weighted sequences in the hippocampus and cerebral cortex;
- Abnormal CSF in 80% of cases at the time of diagnosis, including moderate lymphocytic pleocytosis, normal or slightly elevated protein concentration, and specific oligoclonal bands, present in 60% of patients;
- Screening for anti-NMDAR antibodies in the CSF or serum using the method developed by Dalmau et al. [2007]. These are tissue-based assays and cell-based assays (CBA) using HEK293 cells overexpressing NR1/NR2B heteromers of NMDAR. The presence of antibodies was initially determined by the reactivity of the patient’s serum and CSF. Some authors test for antibodies using cell-based indirect immunofluorescence assays using serum only. Given the qualitative nature of the result, its interpretation depends on the researcher’s experience. Moreover, the serum is often used at low dilutions (<1:100), which can increase the number of false-positive results despite rigorous controls [Lancaster and Dalmau, 2012]. Therefore, as serum screening has limitations, it is necessary to include screening of CSF to establish the diagnosis of anti-NMDAR encephalitis [Gresa-Aribas et al., 2014; Dalmau et al., 2011].

4.3 Brief Description of the Advantages Cited for the New Technology

Tissue-based indirect immunofluorescence assays have the advantage of detecting new antibodies, but this technique can have limitations when several autoantibodies coexist in a single patient [Lancaster et Dalmau, 2012]. When it is performed on CBA, it enables the monospecific detection of anti-NMDAR overexpressing the heteromers of the NMDA receptor NR1 subunit [EUROIMMUN, 2011a].

4.4 Cost of Technology and Options: Not assessed.

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12. Lymphocytic pleocytosis: increase in the number of white blood cells, with a predominance of lymphocytes in the CSF.
5. EVIDENCE

5.1 Clinical Relevance

5.1.1 Other Tests Replaced
This new test would replace tests sent outside Quebec.

5.1.2 Diagnostic or Prognostic Value
 Screening for anti-NMDAR antibodies helps confirm the diagnosis of anti-NMDAR encephalitis and monitor concentrations of these antibodies as the disease progresses. When results are positive, a more extensive clinical investigation, mainly to detect ovarian teratomas or testicular germ cell tumours, is recommended [Wandinger et al., 2011]. Moreover, early diagnosis of anti-NMDAR encephalitis is crucial, as patients treated in the early stages of the disease make a full recovery or show a mild neurological deficit (75% of cases) [Kayser et Dalmau, 2011]. If the outcome is poor (25% of cases), patients may be permanently disabled with severe neurological deficits, or they may die. Based on data for 360 patients who had a clinical follow-up of longer than 6 months, the mortality rate is estimated at 4% (15/360) with a median time of 3.5 months (from 1 to 8 months) between disease onset and death. The majority of deaths occurred in intensive care units as a result of septic shock, cardiac arrest, acute respiratory distress, refractory status epilepticus, or tumour progression [Dalmau et al., 2011]. Mortality was very high for three patients in a case series [Day et al., 2011]. The three patients died after developing complications associated with prolonged hospitalization in intensive care units. The authors agree on the importance of early diagnosis and treatment.

The determination of anti-NMDAR titres is complementary to clinical assessments, since high antibody titres in CSF and serum are associated with poor outcome or the presence of a teratoma, or both. In cases of both good and poor outcome, changes in antibody titres were observed more often in CSF test results than they were in serum test results (p = 0.037) [Gresa-Arribas et al., 2014]. Moreover, the study by Suh-Lailam et al. [2013] showed that, despite the rapid decrease of anti-NMDAR titres in CSF, and despite clinical response to treatment, anti-NMDAR serum titres remained high.

5.1.3 Therapeutic Value
The detection of anti-NMDAR is useful in providing the appropriate immunomodulatory therapy and in assessing the effect of treatment, particularly on the central nervous system [Dalmau et al., 2011]. Irani et al. [2010] reported that a decrease in antibody titres is associated with the administration of immunotherapy less than 40 days after the onset of symptoms in patients without an associated tumour, compared with patients who were not treated or who received treatment after 40 days (p < 0.0001); antibody titres may also decrease with early tumor resection in the case of an associated tumour.

5.2 Clinical Validity
Few studies examined clinical performance in terms of the sensitivity and specificity of tissue-based and cell-based indirect immunofluorescence assays. The only available data were taken from four studies and from data from EUROIMMUN. The literature did not report any direct comparisons of indirect immunofluorescence performance on different substrates (tissue or CBA).
The sensitivity of anti-NMDAR detection in serum and CSF using indirect immunofluorescence on tissue sections and CBA in patients diagnosed with anti-NMDAR encephalitis was tested in two studies13 [Wandinger et al., 2010; Dalmau et al., 2008]. Dalmau et al. [2008] reported that subunit NR1 (target of anti-NMDAR) was identified, in CSF or serum (100%), by the antibodies of all the patients (n = 100). In the second study, the sensitivity also was 100% (n = 66) regardless of the substrate used [Wandinger et al., 2010].

Table 1 presents the performance results of cell-based indirect immunofluorescence assays for the detection of anti-NMDAR in a selected patient population diagnosed with anti-NMDAR encephalitis (Studies 1, 3, and 4) and in 6 patients with clinical symptoms of encephalitis of unknown origin selected from a large population of 2,990 patients (Study 2). These data were taken from the manufacturer’s monograph [EUROIMMUN, 2011a]. The capacity of cell-based indirect immunofluorescence assays to detect anti-NMDAR in the serum of these patients was 100% for Studies 1, 3, and 4. Five of the six serum samples (83.3%) of patients fulfilling the diagnostic criteria for anti-NMDAR encephalitis were positive for this type of antibody (Study 2).

The specificity of the methods of analysis (tissue-based and CBA) tested on groups of healthy volunteers or patients in whom suspected autoimmune encephalitis was another type (e.g., anti-VGKC14 receptor and anti-AMPA15 receptor) or in patients with other autoimmune diseases (systemic lupus erythematosus or multiple sclerosis) is 100%, regardless of the type of sample used (CSF or serum) [Gresa-Arribas et al., 2014; Suh-Lailam et al., 201316; EUROIMMUN, 2011a; Wandinger et al., 2010].

Table 1: Results of anti-NMDAR detection in serum using cell-based indirect immunofluorescence assay (EUROIMMUN)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>CONTROLS (N)</th>
<th>N positive (%)</th>
<th>Confidence interval of 95%</th>
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<tr>
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<tr>
<td>Diagnosis of anti-NMDAR encephalitis</td>
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<tr>
<td>Study 1</td>
<td>29</td>
<td>100 HV 18 other AE *</td>
<td>29 (100)</td>
<td>88.1% to 100.0%</td>
</tr>
<tr>
<td>Study 3</td>
<td>8</td>
<td>13 other AE</td>
<td>8 (100)</td>
<td>63.1% to 100.0%</td>
</tr>
<tr>
<td>Study 4</td>
<td>9</td>
<td>13 other AE</td>
<td>9 (100)</td>
<td>66.4% to 100.0%</td>
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<tr>
<td>Total</td>
<td>46</td>
<td></td>
<td>46 (100)</td>
<td></td>
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<tr>
<td>Clinical symptoms of encephalitis of unknown origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Study 2</td>
<td>6</td>
<td></td>
<td>5 (83.3)</td>
<td>35.9% to 99.6%</td>
</tr>
</tbody>
</table>

Abbreviations: AE = autoimmune encephalitis; CBA = cell-based assay; HV = healthy volunteers.

* Anti-VGKC (voltage-gated potassium channels) and anti-AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor encephalitis.

13. The authors of these studies have a stake in the company EUROIMMUN [Wandinger et al., 2010; Dalmau et al., 2008].
14. VGKC: voltage-gated potassium channels.
15. AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.
16. The test kits used in the study by Suh-Lailam et al. [2013] were provide free of charge by the company EUROIMMUN.
Other data on the screening of serum samples (235 patients) and CSF samples (216 patients) from patients with anti-NMDAR encephalitis are available on the website of the company EUROIMMUN. Results show that cell-based indirect immunofluorescence assays have a greater capacity to detect anti-NMDAR in CSF (99.5%) than in serum (85.5%). A positive result was reported in serological tests from a group of 200 healthy volunteers and in CSF tests from a group of 60 patients without neurological abnormalities [EUROIMMUN, 2011b].

5.3 Analytical (or Technical) Validity

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>PRESENCE</th>
<th>ABSENCE</th>
<th>NOT APPLICABLE</th>
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<tbody>
<tr>
<td>Repeatability</td>
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<tr>
<td>Reproducibility</td>
<td>X</td>
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<td>Analytical sensitivity</td>
<td>X</td>
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<tr>
<td>Analytical specificity</td>
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<td>Matrix effect</td>
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<td>Concordance</td>
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<tr>
<td>Correlation between test and comparator</td>
<td>X</td>
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<tr>
<td>Other, depending on type of test</td>
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</table>

Reproducibility/Precision

The manufacturer’s monograph indicates that six different serum samples were used to test the intra-assay (10 parallel tests) and inter-assay reproducibility of cell-based indirect immunofluorescence assay on 5 series (tested in duplicate). Interlot reproducibility was tested on three different serum samples and three different lots. The intensity of the specific fluorescence is expressed as a numeric value. All serum samples were tested according to fluorescence intensity levels of 0 (no specific fluorescence), 1 (very weak positive reaction visible), 2 (weak positive reaction visible), and 3 (specific positive reaction very visible). In all cases, the deviation in fluorescence intensity level did not exceed ± 1 level for all samples tested [EUROIMMUN, 2011a].

Sensitivity of Measurement in Paired Samples of Serum and CSF

Results for the sensitivity of CSF for the detection of anti-NMDAR using indirect immunofluorescence vary from those of serum. Gresa-Arribas et al. [2014] tested the sensitivity of tissue-based and cell-based indirect immunofluorescence assays on paired samples (serum and CSF) from 250 patients. The samples were taken the same day from patients randomly selected from a cohort of 577 cases of anti-NMDAR encephalitis from around the world. Test results had been positive for anti-NMDAR in CSF and serum in a previous study [Titulaer et al., 2013]. Results of the test conducted by Gresa-Arribas et al. [2014] show a sensitivity of the method on CSF of 100% (98.5 to 100%) compared with that of serum (91.6% [87.5 to 94.7%] for tissue-based immunofluorescence and 86.8% [82 to 90.7%] for cell-based immunofluorescence). The difference in sensitivity of the test in both types of samples is significant (p < 0.0001). These results confirm the importance of detecting anti-NMDAR in CSF; serum sample tests are not sufficient. As reported by Dalmau et al. [2008], antibody titres are higher in CSF than in serum for 53 paired samples.
Suh-Lailam et al. [2013] reported the results of their observations for 20 paired samples (CSF and serum) tested with a cell-based indirect immunofluorescence assay over a period of 24 hours. They obtained 14 positive results (paired CSF and sera) and 6 discordant results (4 positive CSF and negative sera and 2 negative CSF and positive sera). Serum antibody levels were significantly higher than in CSF ($p = 0.02$).

**Reference Range**
Anti-NMDAR (IgG) serum levels were analyzed using a cell-based indirect immunofluorescence assay on 120 serum samples from healthy adult donors. All serum samples were negative. The reference range was determined to be an antibody titre equivalent to $1: < 10$ [EUROIMMUN, 2011a].

**Cross-Reactivity**
Cross-reactivity was tested on 29 serum samples from patients with autoimmune encephalitis, 1 sample from a patient with cerebellar degeneration, and 1 sample from a patient with retinopathy. The method used was a cell-based indirect immunofluorescence assay. Samples that were positive for anti-GluR2, anti-VGKC, and anti-zic4 (cerebellar degeneration) were negative for the glutamate receptor (type NMDA) [EUROIMMUN, 2011a].

**Interference**
Results of tests using cell-based indirect immunofluorescence assays were not affected by concentrations of up to 500 mg/dL of hemoglobin, 2000 mg/dL of triglycerides, and 40 mg/dL of bilirubin [EUROIMMUN, 2011a].

**Correlation**
Correlation between cell-based indirect immunofluorescence assays and the immunoprecipitation method (Spearman’s rank correlation: $r = 0.86; p < 0.0001$) [Irani et al., 2010].

5.4 **Recommendations from Other Organizations**
Recommendations from official organizations are not yet available. However, a panel of three international experts (Austria, Spain, United States) proposed a decision algorithm for the diagnosis of anti-neuronal antibodies, including anti-NMDAR [Höftberger et al., 2012]. The diagnostic approach includes tissue-based indirect immunofluorescence assays on CSF or serum for the detection of these antibodies. Based on the results obtained, there are three possible scenarios:

- If the results are positive, confirmation of the presence of anti-NMDAR using cell-based indirect immunofluorescence assays is indicated.
- When the clinical presentation is strongly suggestive of anti-NMDAR encephalitis, or in cases of uncertain results in serum samples using tissue-based indirect immunofluorescence assays, diagnostic confirmation must be obtained by a repeated measurement with this same method on CSF or with a cell-based indirect immunofluorescence assay.
- If the cell-based indirect immunofluorescence assay is used to detect these antibodies without the use of the tissue-based method, results must be interpreted with caution and according to the clinical context.

The European Autoimmunity Standardisation Initiative (EASI) published a general practice
The guideline was created to provide family physicians with the necessary information regarding various autoimmune diseases, such as autoimmune encephalitis, to ensure better care for patients with the disease, including refer patients to medical specialists. The authors indicate that the cell-based indirect immunofluorescence assay is the best diagnostic method for anti-NMDAR encephalitis, and that these antibodies may be present in CSF when serum screens are negative [Shoenfeld and Meroni, 2012].

6. ANTICIPATED OUTCOMES OF INTRODUCING THE TEST

6.1 Impact on Material and Human Resources
Not assessed.

6.2 Economic Consequences of Introducing Test Into Quebec's Health Care and Social Services System
Not assessed.

6.3 Main Organizational, Ethical, and Other (Social, Legal, Political) Issues
Not assessed.

7. IN BRIEF

7.1 Clinical Relevance
The clinical relevance of anti-NMDAR encephalitis is recent. Screening for anti-NMDAR should be considered if signs of encephalitis develop (neuropsychiatric symptoms, seizures, abnormal movements, dysautonomia) with sudden onset, which occurs mainly at a young age and primarily in women. Tests for anti-NMDAR antibodies with indirect immunofluorescence on serum and CSF are useful to:

- confirm the clinical diagnosis of anti-NMDAR encephalitis and the autoimmune origin of neurologic disorders;
- help detect a tumour syndrome, if relevant. CSF is more informative than serum for the detection of anti-NMDAR in paraneoplastic autoimmune encephalitis;
- monitor the concentrations of these antibodies as the disease progresses, and assess the effects of treatment;
- determine antibody titres, which complement clinical and biological assessments.

7.2 Clinical Validity
Available results show good clinical performance of tissue-based and cell-based indirect immunofluorescence assays for the detection of anti-NMDAR antibodies. However, according to the evidence found in the literature, no direct comparisons were made of the performance of indirect immunofluorescence on different substrates (tissue-based and cell-based assay) or with any other technique.
7.3 Analytical Validity
Data from the company EUROIMMUN and from several validation studies suggest good analytical performance of cell-based indirect immunofluorescence assay for the detection of anti-NMDAR antibodies in serum. The analytical validity of indirect immunofluorescence has not been assessed, either for cell-based assays on CSF or for tissue-based assays on CSF or serum.

7.4 Recommendations from Other Organizations
No official organization has produced recommendations on the clinical relevance of screening for anti-NMDAR antibodies in serum and CSF using indirect immunofluorescence. According to a decision algorithm developed by a group of experts, tissue-based assays are the most appropriate method for the diagnosis of anti-NMDAR, followed by CBA to confirm the presence of these antibodies [Höftberger et al., 2012]. Cell-based assays may be used as first-line tests, and the results must be interpreted according to clinical context.
8. INESSS NOTICE IN BRIEF
Detection of anti-glutamate receptor (NMDA)

<table>
<thead>
<tr>
<th>Status of the Diagnostic Technology:</th>
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<tbody>
<tr>
<td>☒ Established</td>
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<tr>
<td>☐ Innovative</td>
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<tr>
<td>☐ Experimental (for research purposes only)</td>
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<tr>
<td>☐ Replacement for technology: __________________, which becomes obsolete</td>
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<tr>
<th>INESSS Recommendation:</th>
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<tbody>
<tr>
<td>☒ Include test in the Index</td>
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<tr>
<td>☐ Do not include test in the Index</td>
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<tr>
<td>☐ Reassess test</td>
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<tr>
<th>Additional Recommendation:</th>
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<tr>
<td>☐ Draw connection with listing of drugs, if companion test</td>
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<tr>
<td>☐ Produce an optimal use manual</td>
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<td>☐ Identify indicators, when monitoring is required</td>
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**Note**
This test has several advantages. It enables:
- the diagnosis of a rare disease;
- more effective monitoring of the disease;
- appropriate therapy.

Making the test available in Quebec would provide a faster turnaround time than sending the samples outside Quebec.
REFERENCES


