



Australian Government

Department of Health

RATIFIED PICO

Application 1582:

**Antibody testing for neuromyelitis optica
spectrum disorder**

Summary of PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

PPICO criteria for assessing safety and effectiveness of antibody testing in patients suspected of NMOSD (direct evidence)

Component	Description
Patients	<ol style="list-style-type: none"> 1. Patients suspected of having neuromyelitis optica spectrum disorder (NMOSD). For example, those with: <ol style="list-style-type: none"> a) Recurrent, bilateral or severe optic neuritis; or b) Recurrent longitudinal extensive transverse myelitis (LETM)*; or c) Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or d) Acute brainstem syndrome or e) Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or f) Symptomatic cerebral syndrome with typical NMOSD MRI lesions or g) Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) or h) Patient has poor recovery from multiple sclerosis relapse 2. Patients previously diagnosed with NMOSD, who are being monitored or tested for signs of relapse
Prior tests	MRI: Findings of at least one clinical characteristic of NMOSD
Intervention	<ol style="list-style-type: none"> 1. Antibody testing in serum or cerebrospinal fluid using one of a variety of diagnostic substrates (cell, tissue or protein) <ul style="list-style-type: none"> • Concurrent AQP4-Ab and MOG-Ab testing OR • Sequential testing: AQP4-Ab testing followed by MOG-Ab testing in those found –ve for AQP4-Ab 2. Antibody testing (AQP4-Ab OR MOG-Ab) to monitor signs of relapse in those previously diagnosed
Comparator	<p><u>For safety, effectiveness and cost-effectiveness:</u> No AQP4-Ab testing: diagnosis by clinical characteristics alone</p> <p><u>For financial implications:</u> AQP4-Ab +/- MOG-Ab testing under MBS item 71119 or 71165</p>
Outcomes	<p><u>Patient relevant outcomes:</u></p> <p><i>Safety (test related)</i></p> <ul style="list-style-type: none"> • Harm to patient resulting from <ol style="list-style-type: none"> 1. Blood collection (e.g. needle stick injuries) or serum (blood) analysis 2. Consequences of true or false test results <p><i>Effectiveness</i></p> <ul style="list-style-type: none"> • Mortality • Disability rates and severity (e.g. blindness, paraplegia) • Remission and improvement of relapse-associated symptoms. • Annualised relapse rates • Quality of life <p><u>Healthcare system outcomes:</u></p> <ul style="list-style-type: none"> • Cost, cost-effectiveness • Length of hospital stay • Financial implications (financial impact, healthcare resource use, etc)
Research questions	<ol style="list-style-type: none"> 1. What is the direct clinical utility (safety, effectiveness) of AQP4-Ab with/without MOG-Ab testing (either concurrently or sequentially) in patients suspected of having NMOSD, compared to diagnosis by clinical characteristics alone?

Component	Description
	<ol style="list-style-type: none"> 2. What is the direct clinical utility (safety, effectiveness) of monitoring by AQP4-Ab OR MOG-Ab testing in patients previously diagnosed with NMOSD, compared to monitoring by clinical characteristics alone? 3. What is the cost-effectiveness of AQP4-Ab with/without MOG-Ab testing (either concurrently or sequentially) in patients suspected of having NMOSD, compared to diagnosis by clinical characteristics alone? 4. What is the cost-effectiveness of antibody testing (AQP4-Ab or MOG-Ab) compared to monitoring by clinical characteristics alone in previously diagnosed patients? 5. What are the financial implications of AQP4-Ab and/or MOG-Ab testing being performed using a new MBS item number compared to MBS item 71119 or 71165?

AQP4-Ab = aquaporin 4 antibodies; LETM = longitudinal extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder * LETM defined as a spinal cord lesion that extends over 3 or more vertebrae segments (Wingerchuk, D. M. et al. 2015)

PPICO rationale

The Pathology Clinical Committee (PCC) – Immunology, recommended to the Medical Services Advisory Committee (MSAC) that a new Medicare Benefits Schedule (MBS) item be created to investigate the presence of neuromyelitis optica (NMO) by the detection of aquaporin 4 antibodies (AQP4-Abs) in serum and/or cerebrospinal fluid (CSF). Although the NMO test has been in clinical use for 10 years, the PCC recognised that the current MBS item used does not reflect current clinical practice and is funded at a lower level than providers currently bill for NMO testing. Subsequent to the PCC’s recommendations, clinical input has recommended that testing for antibodies against myelin oligodendrocyte glycoprotein (MOG) should also be included as an item on the MBS, to accommodate those individuals who present with clinical symptoms representative of NMO, but who test negative for AQP4-Abs.

POPULATION (and prior testing)

The target population is those suspected of having neuromyelitis optica (NMO)/neuromyelitis optica spectrum disorder (NMOSD).

Neuromyelitis optica (NMO)/Neuromyelitis optica spectrum disorder (NMOSD)

NMO (also known as Devic’s disease) is a rare but severe inflammatory, demyelinating and necrotising, idiopathic, humorally-mediated autoimmune disorder of the central nervous system (CNS) (Jarius, Wildemann & Paul 2014; Sellner et al. 2010). The condition predominantly involves the optic nerves and spinal cord, and is characterised by attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM) (Sellner et al. 2010). There are no clinical features that are disease specific for NMO, as ON and myelitis also occur commonly in typical multiple sclerosis (MS) (Lalan et al. 2012; Sellner et al. 2010). Consequently, it has been assumed for many decades that NMO was a subform of MS, due to considerable overlap in clinical presentation (Jarius, Wildemann & Paul 2014; Trebst, C. et al. 2014).

Advances in identification of a much broader range of CNS symptoms than just NMO has prompted the proposal to refer to the condition as NMO spectrum disorders (NMOSD) (Jarius, Wildemann & Paul 2014), with the International Panel for NMO Diagnosis recommending that the terms NMO and NMOSD should be unified (Wingerchuk, D. M. et al. 2015).

The NMOSD term more broadly encompasses a number of very closely related conditions, and in a 2015 publication (Wingerchuk, D. M. et al. 2015), the International Panel of NMO Diagnosis defined the following NMOSD criteria:

- individuals with limited or inaugural forms of NMO (e.g. first attack LETM or recurrent or bilateral ON) who were at high risk for future attacks;
- those with cerebral, diencephalic and brainstem lesions that occurred in a minority of patients with otherwise typical NMO;
- those with AQP4-Ab positive NMO with coexisting autoimmune disorders (e.g. systemic lupus erythematosus or Sjögren syndrome); and
- those diagnosed with opticospinal MS, an MS phenotype prominent in Asia and distinguished from Western MS.

AQP4-Abs are autoantibodies that bind to the AQP4 water channels, and support the diagnosis of NMOSD from other autoimmune disorders of the CNS, including MS (Sellner et al. 2010). While not everyone with NMOSD has AQP4-Abs, they are present in up to 80% of patients (Jarius, Wildemann & Paul 2014; Mader & Brimberg 2019).

Recent published literature has reported on the presence of serum antibodies against myelin oligodendrocyte glycoprotein (MOG) in AQP4-Ab negative NMOSD individuals (Borisow et al. 2018; Wynford-Thomas, Jacob & Tomassini 2019). The 2015 NMOSD diagnostic criteria has assigned individuals with or without evidence of AQP4-Abs, as well as a subgroup of MOG-Ab positive disorders to the spectrum of NMO disorders (Borisow et al. 2018), although emerging literature has led recommendations that MOG-Abs associated disorders be designated as a separate clinical entity (Borisow et al. 2018; Dos Passos et al. 2018; Ramanathan et al. 2018; Wynford-Thomas, Jacob & Tomassini 2019). The International Panel for NMO consensus diagnostic criteria for NMOSD (Wingerchuk, D. M. et al. 2015) are presented in Table 7 (Appendix A).

The term used to describe the broader population of all MOG-Ab associated disease, is myelin oligodendrocyte glycoprotein antibody related disorder (MARD).

Myelin oligodendrocyte glycoprotein [MOG] antibody-related disorder (MARD)

MARD is an inflammatory, demyelinating CNS disorder, and commonly presents as symptoms of ON and LETM (Borisow et al. 2018), although the condition occurs in the presence of serum MOG-Abs and does not meet the typical criteria for MS or other neuroinflammatory conditions (Wynford-Thomas, Jacob & Tomassini 2019). MARD is considered milder and less frequently relapsing than AQP4-Ab positive NMOSD (Jurynczyk et al. 2017).

For clarity, the terms AQP4-Ab NMOSD and MOG-Ab NMOSD will be used in the document, to refer to individuals testing positive for AQP4-Ab and positive for MOG-Ab, respectively.

Clinical features

The differences and similarities (including clinical features) between AQP4 NMOSD, MARD and MS, are described in Table 1. Figure 1 illustrates the relationship between the known inflammatory demyelinating disorders. There is an overlap of symptoms between MARD and NMOSD, MOG-Ab positive NMOSD forming a subgroup of the total MARD population (Misu T, 2018 #83). It is proposed that only those patients suspected of having NMOSD will be eligible for AQP4-Ab or MOG-Ab testing.

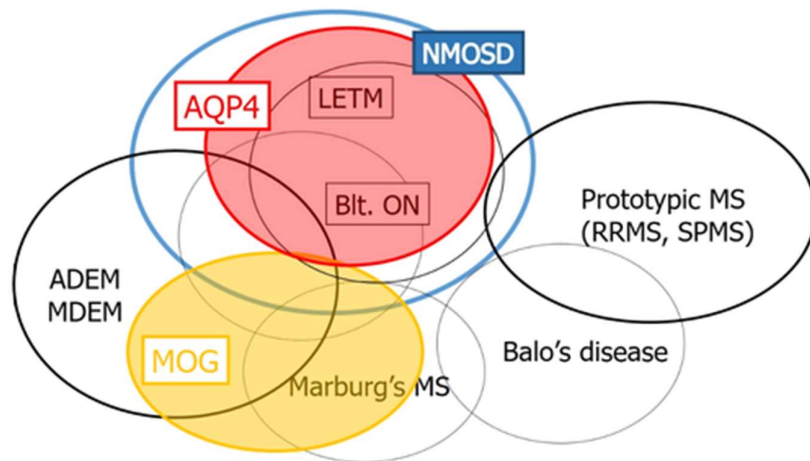


Figure 1 Inflammatory demyelinating diseases of the central nervous system

Source: <https://onlinelibrary.wiley.com/doi/full/10.1111/cen3.12491>

AQP4-Ab = aquaporin4 antibodies; ADEM = acute disseminated encephalomyelitis; Blt ON = bilateral optical neuritis; LETM = longitudinally extensive transverse myelitis; MDEM = multiphasic disseminated encephalomyelitis; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Compared to MS, attacks of ON and myelitis in individuals with AQP4 NMOSD are usually more acute, severe and disabling (Lalan et al. 2012; Sellner et al. 2010). In AQP4 NMOSD, involvement of the spinal cord is not restricted to the maximum two segments (as seen in MS), but extends to at least three segments (Illes Z 2016). The symptoms in NMOSD range from mild sensory disturbances to complete transverse myelitis, with tetraplegia or paraplegia, symmetrical sensory impairment and bladder-bowel dysfunction (Jarius, Paul, et al. 2008; Sellner et al. 2010). In contrast, spinal cord symptoms in MS are milder and asymmetric, caused by acute partial transverse myelitis (Sellner et al. 2010). Visual loss has been shown to be less severe in MS (Sellner et al. 2010). Compared with MS, in AQP4 NMOSD, recovery from attacks is often incomplete (Borisow et al. 2018), and spontaneous remission of neurological dysfunction is rare, with frequent accumulation of irreversible deficits and rapid progression of disability (Jarius, Wildemann & Paul 2014). As the natural history of untreated NMOSD is significantly worse than that of MS, NMOSD requires early recognition and treatment (Sellner et al. 2010).

For AQP4 NMOSD and MARD, while ON and LETM are common symptoms of both conditions, with involvement of the optic nerve, spinal cord and brainstem, histopathological differences have shown inflammation in MARD primarily results in demyelination, while demyelination in NMOSD appears to be secondary following astrocytic damage (Borisow et al. 2018). ON is the most common presenting feature of MARD, occurring in 54-61% of individuals, followed by myelitis, acute disseminated encephalomyelitis (ADEM) or an ADEM-like presentation (Wynford-Thomas, Jacob & Tomassini 2019). By comparison, in individuals with AQP4-Ab NMOSD, the most frequent symptoms at onset are ON in 37-54% and LETM in 30-47% (Borisow et al. 2018). Occurrences of encephalitis and seizures are rare in NMOSD (Borisow et al. 2018). At onset, individuals with MARD are more likely to suffer from simultaneous or rapidly sequential ON and LETM (Borisow et al. 2018), and are considered to have lower risk of further relapses than those individuals with AQP4-Abs NMOSD. Individuals with MARD have better visual and motor outcomes (Wynford-Thomas, Jacob & Tomassini 2019).

Treatment for AQP4 NMOSD is different from MS treatment, and if MS treatment is used, it can worsen the disease outcome of NMOSD patients (Lalan et al. 2012; Mader & Brimberg 2019). Due to

lack of clinical evidence around treatment for MAR, current treatment protocols for MAR tend to follow those for NMOSD (Illes Z 2016; Wynford-Thomas, Jacob & Tomassini 2019). Treatments for NMOSD include corticosteroids, immunosuppressants (e.g. azathioprine), plasmapheresis, intravenous immunoglobulin and anti-CD20 monoclonal antibody (e.g. rituximab) (Borisow et al. 2018; Trebst, C. et al. 2014; Trebst, Corinna et al. 2014; Wynford-Thomas, Jacob & Tomassini 2019). Treatment with MS medications (e.g. interferon beta, glatiramer acetate, fingolimod, alemtuzumab and natalizumab) has been shown to have no or harmful effects in individuals with AQP4-AbNMOSD and MOG-Ab NMOSD (Borisow et al. 2018).

Antibodies and antibody testing

Aquaporin 4 (AQP4) and aquaporin 4 antibodies (AQP4-Abs)

Aquaporin 4 (AQP4) is a water channel expressed in high density on the end-feet of astrocytes, particularly those in close proximity to the blood brain barrier (Bukhari et al. 2017). AQP4 is considered an integral constituent of the blood brain barrier (Jarius, Wildemann & Paul 2014), and belongs to a family of channels that is selectively permeable to water, and is the most abundant water channel in the brain, spinal cord and optic nerve (Mader & Brimberg 2019). The presence of serum antibodies to AQP4 (AQP4-Abs) is a diagnostic criterion for NMOSD, and are not found in serum of healthy individuals and those with MS. Their presence allows an early diagnosis of AQP4 NMOSD (Mader & Brimberg 2019). In AQP4 NMOSD, astrocytes undergo necrosis when exposed to AQP4-Abs (Sellner et al. 2010) and tissue damage has been directly contributed to the presence of AQP4-Abs (Jarius, Aboul-Enein, et al. 2008).

Myelin oligodendrocyte glycoprotein (MOG) and myelin oligodendrocyte glycoprotein antibodies (MOG-Abs)

Myelin oligodendrocyte glycoprotein (MOG) is a component of myelin, exclusively found in the CNS and localised on the surface of the myelin sheath, cell body and processes of oligodendrocytes (Borisow et al. 2018; Ramanathan et al. 2018). While the exact role of MOG is unclear, it is thought to act as a cellular adhesive molecule, involved in the regulation of oligodendrocyte microtubule stability and mediate complement cascade (Wynford-Thomas, Jacob & Tomassini 2019). MOG antibodies (MOG-Abs) target myelin forming oligodendrocytes, leading to disturbances in the integrity of blood brain barrier and to CNS inflammation (Borisow et al. 2018). MOG-Abs have been found in AQP4-Ab negative patients with clinical symptoms of NMOSD (Borisow et al. 2018). The inflammatory condition MAR occurs in the presence of MOG-Abs (Borisow et al. 2018; Dos Passos et al. 2018; Jurynczyk et al. 2017; Wynford-Thomas, Jacob & Tomassini 2019).

Table 1 Comparison between AQP4 NMOSD†, MARD and MS

AQP4 NMOSD	MARD	MS
Serum* antibodies to AQP4	Serum* antibodies to MOG	No serum antibodies to AQP4 or MOG
Age of onset late 30s but can range from childhood to the elderly	Early to mid-30s, but can occur in all decades of life	Age of onset 20-40 years old
More common in women#	Slight predominance in women	More common in women
Relatively rare in Europe. Affects non-whites (e.g. Afro-Brazilians (15%), East Asians (up to 48%) and Indians (9%))	No ethnicity differences^ although some reports indicate higher in Caucasian ethnicity*	More common in Europe 42.7:1 (MS:NMOSD)
ON usually severe with limited recovery (visual loss more severe than MS); transverse myelitis; intractable nausea with hiccups or vomiting	Commonly ON at onset (better visual field outcomes compared to NMOSD ON); other presentations include myelitis, ADEM and ADEM-like events	ON usually with good recovery (visual loss less severe than NMOSD); other neurological systems involved
Brain lesions may initially be absent on MRI at first presentation, but presence of cerebral lesions is not uncommon in 60% of cases	Brain lesions on MRI in approximately 45% at onset. Percentages increase later in course of disease (up to 77%)	Brain lesions present on MRI
Spinal cord MRI shows LETM (≥ 3 vertebral segments)	Abnormal spinal cord MRI in about 50% of cases; lesions more commonly short; in children LETM more common	Spinal cord MRI show lesions more commonly short
Relapsing disease course	Monophasic† or relapsing disease course	Relapsing or progressing disease course
Type of relapse ON; LETM	Type of relapse commonly ON (more than in NMOSD)	Any type of relapse with relapse phenotype predicted by previous relapse phenotype
Repeated attacks are main cause of accumulation of neurological impairment	Disability persists after an attack but may be less severe than NMOSD	Permanent disability is primarily a feature of secondary progression
Worsens with interferon beta treatment	Worsens with interferon beta treatment	Treat with interferon beta

ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin4; AQP4-Abs = aquaporin4 antibodies; LETM = longitudinal extensive transverse myelitis; MARD = myelin oligodendrocyte glycoprotein antibody related disorder; MOG = myelin oligodendrocyte glycoprotein; MRI=magnetic resonance imaging; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis

† the term NMOSD refers to both NMOSD and NMO

*standard specimen for AQP4 and MOG antibody testing is serum

AQP4-Ab negative NMOSD shown to have equal distribution between men and women

^ based on a UK cohort study (Jurynczyk et al. 2017)

* based on paper by Dos Passos et al. 2018(Dos Passos et al. 2018)

‡ monophasic defined as no recurrence, simultaneous or closely related ON and LETM (<30 days)

Reference: Borisow et al. 2018 (Borisow et al. 2018); Dos Passos et al. 2018(Dos Passos et al. 2018); Jurynczyk et al. 2017 (Jurynczyk et al. 2017); Sellner et al. 2010 (Sellner et al. 2010); Wynford-Thomas et al. 2019 (Wynford-Thomas, Jacob & Tomassini 2019)

[Incidence and Prevalence](#)

Neuromyelitis optica spectrum disorders (NMOSD)

Results of a clinic-based survey (that identified cases of AQP4 NMOSD in Australia and New Zealand) showed there were 34 incident cases of AQP4 NMOSD over the period 2010 to 2012, giving a crude incidence of 0.33 (95%CI 0.11, 0.55) per million per year, and 147 prevalent cases giving a crude point prevalence of 0.53 (95%CI 0.45, 0.62) per 100,000 (Bukhari et al. 2017). The peak prevalence age range for women was 40-59 years, and for men was 60-69 years (Bukhari et al. 2017).

In a capture-recapture analysis, (which enabled adjustment of prevalence rates in light of laboratory identified cases that had been missed in the clinical survey) an adjusted incidence estimate of 0.37 (95%CI 0.35, 0.39) per million per year gave an estimated total number of AQP4 NMOSD cases of 193, and prevalence of 0.70 (95%CI 0.66, 0.74) per 100,000 (Bukhari et al. 2017). The prevalence of AQP4

NMOSD in the population of Australia and New Zealand with Asian ancestry was a three-fold increase (1.57 (95%CI 1.15, 1.98) per 100,000) compared with the remainder of the population of predominantly European ancestry (0.57 (95%CI 0.50, 0.65) per 100,000) using a capture-recapture analysis (Bukhari et al. 2017).

Patient numbers (provided by clinical input through communications on this document) indicated prevalence is higher in Australia than indicated by Bukhari et al, with an estimate of 500 to 600 patients in total. A conservative estimate of the prevalence of antibody positive NMOSD (AQP4 or MOG) patients in Australia (based on the numbers provided) is in Table 2.

Myelin oligodendrocyte glycoprotein [MOG] antibody-related disorder (MARD)

While the prevalence of MARD varies widely amongst studies, due to differences in study inclusion criteria and detection techniques used, a 2018 review reported that 40% of patients with bilateral or recurrent ON and negative AQP4-Abs were positive for MOG-Ab, and for AQP4-Ab negative LETM, the prevalence of MOG-Ab positivity ranged between 7.4 and 23.2% (Dos Passos et al. 2018).

Table 2 Conservative estimate of NMOSD patient numbers in Australia

Patients	NMOSD	AQP4-Ab +ve	AQP4-Ab -ve	MOG-Ab +ve	MOG-Ab -ve
Proportion	100%	80%	20%	40% of AQP4-Ab -ve	60% of AQP4-Ab -ve
Number	600	480	120	48	72

AQP4-Ab = aquaporin 4 antibodies; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorder

Note: Patient numbers are approximates, based on the following estimates: clinical input that there are 600 NMOSD patients in Australia; 80% of NMOSD patients test positive for AQP-Ab; 60% of AQP4-Ab negative patients test positive for MOG-Ab

PASC noted that, although the numbers diagnosed with AQP4-Ab NMOSD and MOG-Ab NMOSD (much rarer) are small, the population that is tested will be larger, including:

- *patients who are tested despite not meeting the well-established consensus criteria*
- *patients with more severe (atypical) forms of MS (to exclude other conditions)*
- *Patients in whom MS is considered less likely because of their age or ethnicity, for whom the threshold for testing may be much lower.*

PASC considered it critical to establish the number of patients that would be tested, in order to arrive at estimated prevalence figures. This will require further data on utilisation, which should be informed by clinical practice. Utilisation data for current generic AQP4-Ab MBS testing items (71119, 71165) does not show what proportion of testing is for NMOSD.

PASC advised that additional clinical opinion is needed regarding likely incidence or prevalence of NMOSD in Australia.

PASC advised that, because the test is already in widespread use, a survey of laboratories should be able to ascertain how many tests are currently being done. PASC noted this would only be a starting point, because some patients who could be tested may currently be declining testing because of out-of-pocket costs.

In response to PASC advice, the assessment group (that prepared the PICO) has been liaising with the applicant (Royal College of Pathologists of Australasia [RCPA]) about sourcing data from clinicians and pathology laboratories around Australia. This data will be incorporated into the DCAR (Department-contracted assessment report) and will inform the economic analysis.

The applicant (RCPA) has reported it has no capacity to routinely collect diagnostic test data from pathology laboratories, given the labour-intensity associated with this task. However, since the PASC meeting, the applicant has sourced data from Queensland Health (public sector testing; see table directly below) and Sonic HealthCare (see private sector data under 'Sonic HealthCare' heading below). Data will follow from NSW Health, SA pathology and PathWest, which will be provided by the applicant to the assessment group undertaking the DCAR (noting the applicant has elected to progress this application through the DCAR option).

The data to date does not specify the number of tests used for patient monitoring.

Queensland Health (public sector) data

	2015	2016	2017	2018	2019
Total AQP4 requests	1578	1414	1439	1575	1973
Serum	1408	1200	1235	1347	1696
CSF	170	214	204	228	277
Positive Serum	48	31	34	36	63
Positive CSF	3	4	5	4	7

Sonic HealthCare (private sector) data

Figures for Australia-wide private sector testing by Sonic Healthcare indicate a 6% growth in testing over time. A total of 953 unique requests were received by Sonic in 2018; of these, 51 patients had repeat testing once, with five (5) having repeat testing twice.

Clinical opinion remains that monitoring may be useful in some (but not all) patients.

Prior testing

MRI is required to identify the characteristics of NMOSD and MS, as listed by Wingerchuk et al (Wingerchuk, Dean M. et al. 2015). This approach appears to be supported by other literature (Borisow et al. 2018; Di Pauli & Berger 2018; Wynford-Thomas, Jacob & Tomassini 2019). Imaging of the entire central nervous system (cranial and spinal cord MRI) should be performed, irrespective of the primary presenting clinical signs and symptoms.

Analysis of CSF oligoclonal bands (OCBs) is also performed prior to AQP4 or MOG antibody testing, as part of the work-up for MS.

OCBs are defined as having at least two immunoglobulin bands in the CSF, with no corresponding band in the serum. Detection of OCBs requires a lumbar puncture, whereas AQP4 & MOG Ab testing is (usually) done on a blood sample. Certainty is needed around the need to have OCB testing prior to Ab testing. While OCBs are detected in the CSF of the majority of MS patients, the presence of OCBs is not specific to MS: they are also found in a variety of inflammatory and infectious CNS disorders.

Abnormal CSF IgG indexes and OCB patterns have been reported in 70% to 80% of MS patients. At least 1 of these tests has been reported to be positive in 90% of MS patients when both tests are performed. Newer methodologies for OCB detection have been reported to be more sensitive, with sensitivities of 90% to 95% in CSF from MS patients.

Although increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases, this assay is ~95% specific for MS (Mayo Clinic).

Rationale

Diagnosis

The rationale for inclusion of individuals with AQP4 NMOSD is based on the fact that antibodies to AQP4 are not found in serum of healthy individuals and those with MS, and their presence is a diagnostic criterion for NMOSD, allowing an early diagnosis of NMOSD (Mader & Brimberg 2019).

The rationale for inclusion of individuals with MOG-Ab NMOSD is based on the fact that it is possible to identify a subset of patients with antibodies to MOG, who express a clinical phenotype distinct from other similar neuroinflammatory conditions. As previously mentioned, literature has reported the presence of serum MOG-Ab in patients with AQP4-Ab negative NMOSD (Borisow et al. 2018).

Monitoring

For individuals with AQP4-Ab NMOSD, AQP4-Ab testing has been used to monitor patients and identify exacerbations. Use of the test in this way would require *quantitative* validation of AQP4-Ab testing. Recent literature has claimed that AQP4 serostatus and antibody levels may change during the disease course (Borisow et al. 2018) and some sources support AQP4-Ab testing up to four times a year in diagnosed patient, as it may act as a biomarker for disease severity¹. Additionally, monitoring may enable earlier treatment for impending exacerbation than might be otherwise given, and lead to better patient outcomes. However clinical advice has indicated that following diagnosis of NMOSD, further testing for AQP4-Ab has little value for patient management.

Similarly for MOG-Ab NMOSD, MOG serostatus and antibody levels may change during the disease course (Borisow et al. 2018). There is no definite consensus regarding regular MOG-Ab monitoring, however reports suggest that antibodies may increase in relapse and then subsequently become negative (Wynford-Thomas, Jacob & Tomassini 2019). Consequently, it has been argued that there is a role for regular monitoring at diagnosis, as well as throughout the course of MOG-Ab NMOSD, with suggestions that re-test intervals of 6-12 months may be beneficial (Wynford-Thomas, Jacob & Tomassini 2019).

PASC noted that AQP4-Ab testing is used rarely for monitoring (e.g. in patients having plasmapheresis), but there is little evidence to support this; MOG-Ab testing is not considered useful for monitoring (although testing may be repeated to confirm a diagnosis).

PASC therefore advised that use of AQP4-Ab and MOG-Ab testing for monitoring should be evaluated separately from diagnostic use.

INTERVENTION

The intervention of interest is concurrent antibody testing in serum or cerebrospinal fluid (CSF) for the presence of AQP4-Abs and MOG-Abs in individuals suspected of having NMOSD, or sequential AQP4-Ab testing followed by MOG-Ab testing in those individuals found negative for AQP4-Abs.

¹ Sources include the *Referral Template – MBS Review Recommendations to MSAC* (MBS Review Taskforce 2018) and personal communications with Professor S Broadley, Dr P Hissaria and Dr D Langguth

While antibody tests can be divided into tissue-based assays, cell-based assays and protein-based assays (Jarius & Wildemann 2013; Trebst, C. et al. 2014), the International consensus diagnostic criteria for NMOSD recommends testing with cell-based serum assays to ensure optimal autoantibody detection (Wingerchuk, D. M. et al. 2015). Cell-based assays are currently considered gold standard for both AQP4-Abs and MOG-Abs testing (Borisow et al. 2018).

The diagnostic impact of testing CSF for AQP4-Abs is controversial (Jarius & Wildemann 2013; Trebst, C. et al. 2014), and reportedly does not provide an additional benefit for diagnosing AQP4 NMOSD (Borisow et al. 2018). AQP4-Abs in CSF can be detected in 70% of AQP4-Ab seropositive patients and in none of the AQP4-Ab seronegative patients (Borisow et al. 2018). Cases of clinical NMOSD in which AQP4-Abs was detected in CSF, but not serum have been only rarely reported (Wingerchuk, D. M. et al. 2015). Therefore, serum samples are currently the specimen of choice (Jarius & Wildemann 2013), although CSF testing of AQP4-Abs seronegative patients might be considered in selected seronegative cases (Wingerchuk, D. M. et al. 2015). Like AQP4-Abs, MOG-Abs are produced mainly extrathecally and are therefore less frequent in CSF than in serum (Borisow et al. 2018)

Rationale

Early Diagnosis

Rationale for the testing of AQP4-Abs and MOG-Abs is that *early* correct diagnosis of NMOSD is critical for the effective symptom reduction in this patient group. A *differential diagnosis* of NMOSD is important, as, despite an overlap in symptoms and characteristics with MS, treatment is different to that given for MS. As previously mentioned, MS medications (interferon beta, glatiramer acetate, fingolimod, alemtuzumab, natalizumab) may be ineffective and harmful in individuals with NMOSD (Borisow et al. 2018; Lalan et al. 2012; Mader & Brimberg 2019).

Additionally, clinical decision making with respect to diagnosis and treatment initiation, remains challenging when a patient presents with ON or myelitis only, or with other clinical symptoms such as brainstem encephalitis with intractable hiccups and vomiting (Jarius, Wildemann & Paul 2014). In such cases, testing for AQP4-Ab and MOG-Ab by means of a both highly sensitive and highly specific assay is considered essential (Jarius, Wildemann & Paul 2014).

PASC noted that MOG-Ab assays have much greater variability and some are considered unreliable from a clinical perspective. PASC noted that The Children's Hospital at Westmead (Sydney) has expertise in MOG-Ab testing.

Serum versus CSF samples

The published literature appears to support clinical input in finding that the accuracy of AQP4-Ab testing in CSF is lower than that for serum (Borisow et al. 2018; Jarius & Wildemann 2013; Trebst, C. et al. 2014). Likewise, MOG-Abs are produced mainly extrathecally and are therefore less frequent in CSF than in serum (Borisow et al. 2018). However, testing of CSF appears to be used in some circumstances in the clinical setting, particularly when there is suspicion of NMOSD but serum tests negative for AQP4-Ab. If CSF and serum testing are to be included in the assessment, it may be useful to consider the clinical validity of these tests separately.

PASC noted that, although testing of serum is preferred to CSF, CSF testing may be used in some clinical situations (e.g. if a serum test is negative, a CSF test may be requested as confirmation; in children with MOG-Ab NMOSD who present with acute disseminated encephalomyelitis, a CSF sample will

already be available). The applicant confirmed that the number of CSF tests conducted is small, but agreed it must remain an available option and therefore be evaluated in the assessment.

Therefore, CSF testing should be evaluated in the assessment report.

Cell-based assays versus other assays

The literature on AQP4-Ab testing specify that cell-based assays are more accurate than other tissue-based assay types. Information provided by the Department of Health related to this Application supports this view (Table 3), despite some laboratories in Australia using assays other than cell-based tests. Further comparison of assays may be unwarranted, and the assessment could focus on the safety and effectiveness of cell-based assays.

Table 3 Comparison of sensitivity and specificity of various AQP4-Ab assay types

Assay	T-IIF	ELISA	Euroimmun	Oxford-CBA
NMOSD (Sens) n/N (%)	62/78 (78)	25/42 (60)	34/36 (94)	33/36 (92)
Controls (Spec) n/N (%)	246/247 (99.6)	193/200 (97)	172/172 (100)	152/152 (100)

CBA = cell based assay; ELISA = enzyme linked immunosorbent assay; n/N = number of positive cases/total number of cases; T-IIF = tissue-based indirect immunofluorescence

Note: NMOSD defined by Wingerchuk criteria

Source: Unpublished data provided by Prof S Broadley et al. to the Department of Health

PASC considered it reasonable to restrict the assessment to cell-based assays for AQP4-Ab testing, given this is the reference standard. PASC noted that pathology quality assurance programs (QAP) would ensure that, whatever assay a lab uses, has to meet that standard. Use of alternative tests (e.g. ELISA) would need to be justified.

COMPARATOR

PASC advised that no testing is the appropriate comparator for the economic evaluation; and the assessment of financial implications should compare testing at the proposed higher MBS fee, with testing using the current MBS items (71119 and 71165).

The comparator, for the purposes of determining the clinical utility and cost-effectiveness of AQP4-Ab and/or MOG-Ab testing, is what would be done in the absence of AQP4-Ab and MOG-Ab testing, which is diagnosed based on clinical characteristics, including those found on MRI. This was the standard of care prior to the introduction of AQP4-Ab and/or MOG-Ab testing (i.e. it is a historical comparator).

A differential diagnosis from MS would be based on clinical characteristics alone, and may be more challenging in the absence of AQP4-Ab and/or MOG-Ab testing. The diagnostic pathway may vary slightly depending on which symptom/s appear first. According to Wingerchuk et al (2015) diagnosis of NMOSD without AQP4-Ab testing requires identification of two of the following core clinical characteristics:

- ON;
- Acute myelitis;
- Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting);
- Acute brainstem syndrome;

- Symptomatic narcolepsy or acute diencephalic clinical syndrome (e.g. anorexia with substantial weight loss, hypothermia) with NMOSD-typical diencephalic MRI lesions;
- Symptomatic cerebral syndrome (e.g. encephalopathy, haemiparesis, cortical visual loss) with lowest deficit reached within 3 weeks from onset and associated with NMOSD-typical brain lesions (Wingerchuk, D. M. et al. 2015);

and at least one of the core clinical characteristics has to be ON, acute myelitis or area postrema syndrome.

Additionally, supportive characteristics in cerebral, spinal cord or optic nerve MRI are required, and are as follows:

- Acute ON requiring brain MRI showing normal findings or only nonspecific white matter lesions or long optic nerve lesions with increased T2 signal or gadolinium enhancement of the optic nerve or the chiasm in patients with ON;
- Spinal cord MRI lesion or focal spinal cord atrophy extending over ≥ 3 segments in patients with myelitis;
- Area postrema syndrome requiring associated dorsal medulla/area postrema in patients with area postrema syndrome;
- Periependymal brainstem lesions in patients with acute brainstem syndrome (Wingerchuk, D. M. et al. 2015).

The financial implications of a new MBS item for AQP4-Ab and/or MOG-Ab testing will be compared against what is done currently, i.e. AQP4-Ab testing performed using MBS item 71119 or 71165.

OUTCOMES

PASC advised that the proposed outcomes were appropriate.

Patient-relevant outcomes

Safety (test related):

- Harm to patient resulting from:
 - Blood collection (e.g. needle stick injuries) or serum (blood) analysis;
 - Consequences of true or false test results.

Effectiveness

- Mortality;
- Disability rates and severity (e.g. blindness, paraplegia);
- Remission and improvement of relapse-associated symptoms;
- Annualised relapse rates;
- Quality of life.

Healthcare system outcomes

- Cost, cost-effectiveness;
- Length of hospital stay;
- Financial implications (financial impact, healthcare resource use, etc).

If direct evidence of clinical utility is not identified, a linked evidence approach will be used. The outcomes relevant for a linked evidence approach are shown in Boxes 2 to 4 (Appendix C).

CLINICAL MANAGEMENT ALGORITHMS

PASC noted the algorithms in Figures 3 and 4 are for diagnosis of AQP4-Ab or MOG-Ab NMOSD; and the algorithm in Figure 5 is for monitoring/prediction of/confirmation of relapse. This aligns with PASC's recommendation (above) that diagnosis and re-testing/monitoring need to be evaluated separately.

Historical clinical management algorithm for identified population (comparative situation)

In the absence of antibody testing, diagnosis of NMOSD relies on both the clinical picture (symptoms) and imaging examinations as described above by Wingerchuk et al. (2015). The historical management pathway is illustrated in Figure 2.

When the brain and/or spinal cord MRI detects typical MS lesions, then subsequent diagnostic steps should be made towards this (Illes Z 2016). CSF-restricted oligoclonal bands (OCB) is also a diagnostic mainstay in classical MS (Jarius, Wildemann & Paul 2014). If response to MS treatment is poor, considerations should be given to the possibility of wrong diagnosis, and patient should be investigated for NMOSD as a likely diagnosis.

When brain and/or spinal cord MRI is negative or not typical for MS, and MRI is indicative of NMOSD, treatment is based on acute treatment of relapses, chronic immunosuppression to prevent relapses, and symptomatic therapy (Illes Z 2016).

When a NMOSD diagnosis has not been made, based on brain or spinal cord MRI, additional testing is recommended to determine diagnosis of either NMOSD or MS. CSF-restricted OCB for diagnosis of MS (Jarius, Wildemann & Paul 2014) and the presence of OCB and elevated IgG index may be supportive for diagnosis of MS (Illes Z 2016). Repeated spinal cord MRI is also recommended, where partial T2 hyperintensity(ies) in the spinal cord may support the diagnosis of MS (Illes Z 2016). If a diagnosis is made, then treatment is prescribed according on the diagnosis (i.e. MS or NMOSD). Repeat testing or other differential diagnosis is recommended should no diagnosis or confirmation is made (Illes Z 2016).

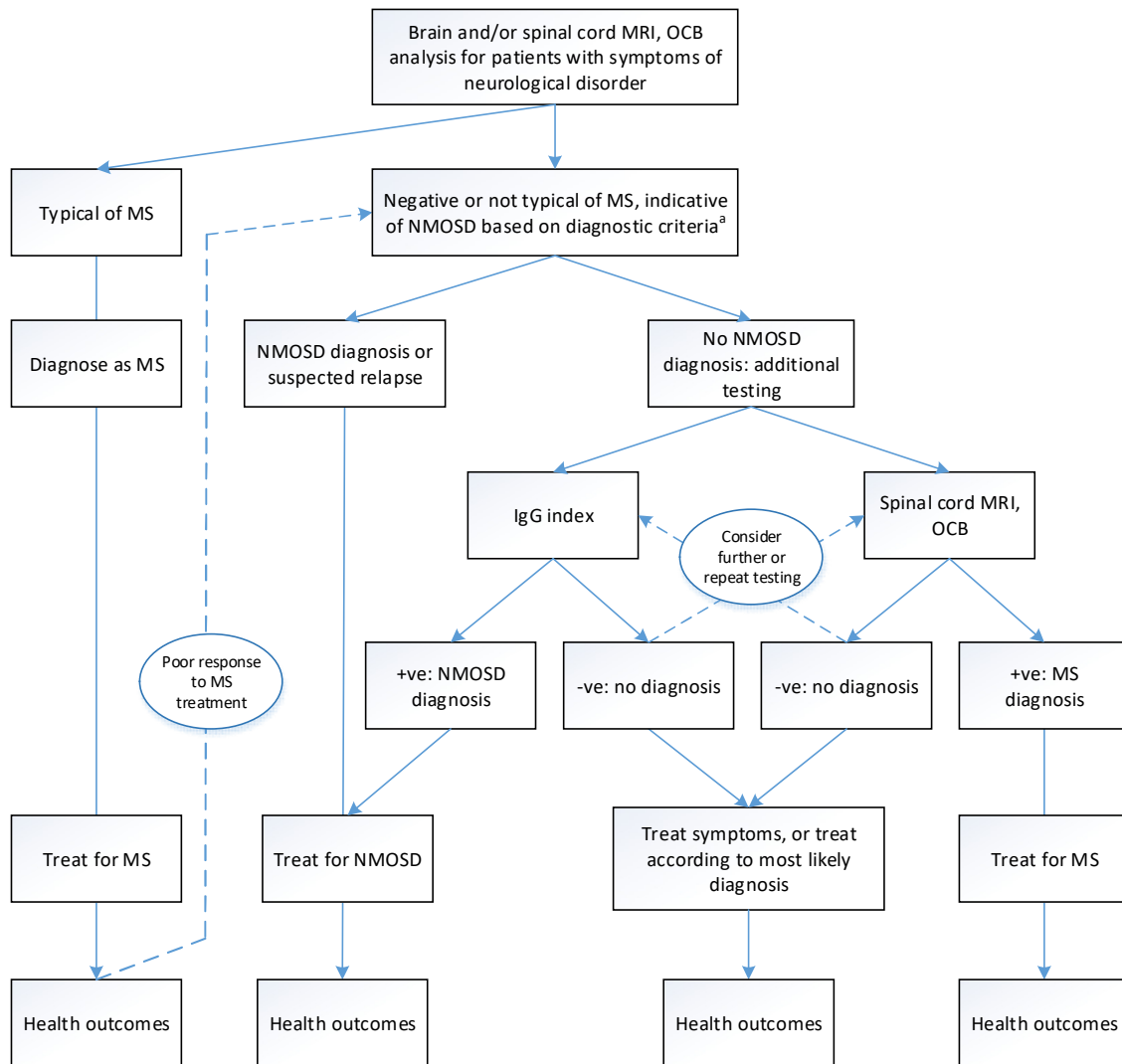


Figure 2: Algorithm for historical clinical management of suspected NMOSD patients

IgG = immunoglobulin G; MRI = magnetic resonance imaging; MS = multiple sclerosis; NMOSD=neuromyelitis optica spectrum disorders; OCB =oligoclonal bands

^a See Table 7 for diagnostic criteria from Wingerchuk et al, 2015

Current clinical management algorithm for identified population

Current standard of care for patients suspected of having NMOSD, is diagnosis based not only on the clinical picture (symptoms) and the imaging examinations, but also on the detection of serum AQP4-Abs and/or MOG-Abs. The current management pathway using concurrent testing is illustrated in Figure 3, and for sequential testing, in Figure 4.

When the brain and/or spinal cord MRI detects typical MS lesions, then subsequent diagnostic steps should be made towards this (Illes Z 2016). CSF-restricted oligoclonal bands (OCB) is also a diagnostic mainstay in classical MS (Jarius, Wildemann & Paul 2014). If reponse to MS treatment is poor, considerations should be given to the possibility of wrong diagnosis, and patient should be investigated for NMOSD as a likely diagnosis.

When brain and/or spinal cord MRI is negative or not typical for MS, and MRI is indicative of NMOSD, there are two diagnostic options:

- serum AQP4-Ab testing (Figure 3)

A positive serum test for AQP4-Abs is confirmatory for AQP4-Ab NMOSD. When serum AQP4-Ab testing is negative, serum MOG-Ab testing is recommended. A positive MOG-Ab test is diagnostic of MOG-Ab NMOSD. When MOG-Ab testing is negative, additional testing is recommended including OCB, IgG index or AQP4-Ab or MOG-Ab testing in the CSF to determine a differential diagnosis of MS or AQP4-Ab NMOSD or MOG-Ab NMOSD.

- serum AQP4-Ab and MOG-Ab testing (Figure 4)

A positive serum test for either AQP4-Ab or MOG-Ab is confirmatory for AQP4-Ab or MOG-Ab NMOSD, respectively. Should both serum antibody tests be negative in patients with these suspected diagnoses, then additional testing is recommended including OCB, IgG or AQP4-Ab testing in the CSF to determine a differential diagnosis of MS or AQP4-Ab or MOG-Ab NMOSD.

If a diagnosis is made, then treatment is prescribed according to the diagnosis (i.e. MS, AQP4-Ab NMOSD or MOG-Ab NMOSD). Repeat testing is recommended should no diagnosis or confirmation be made (Illes Z 2016).

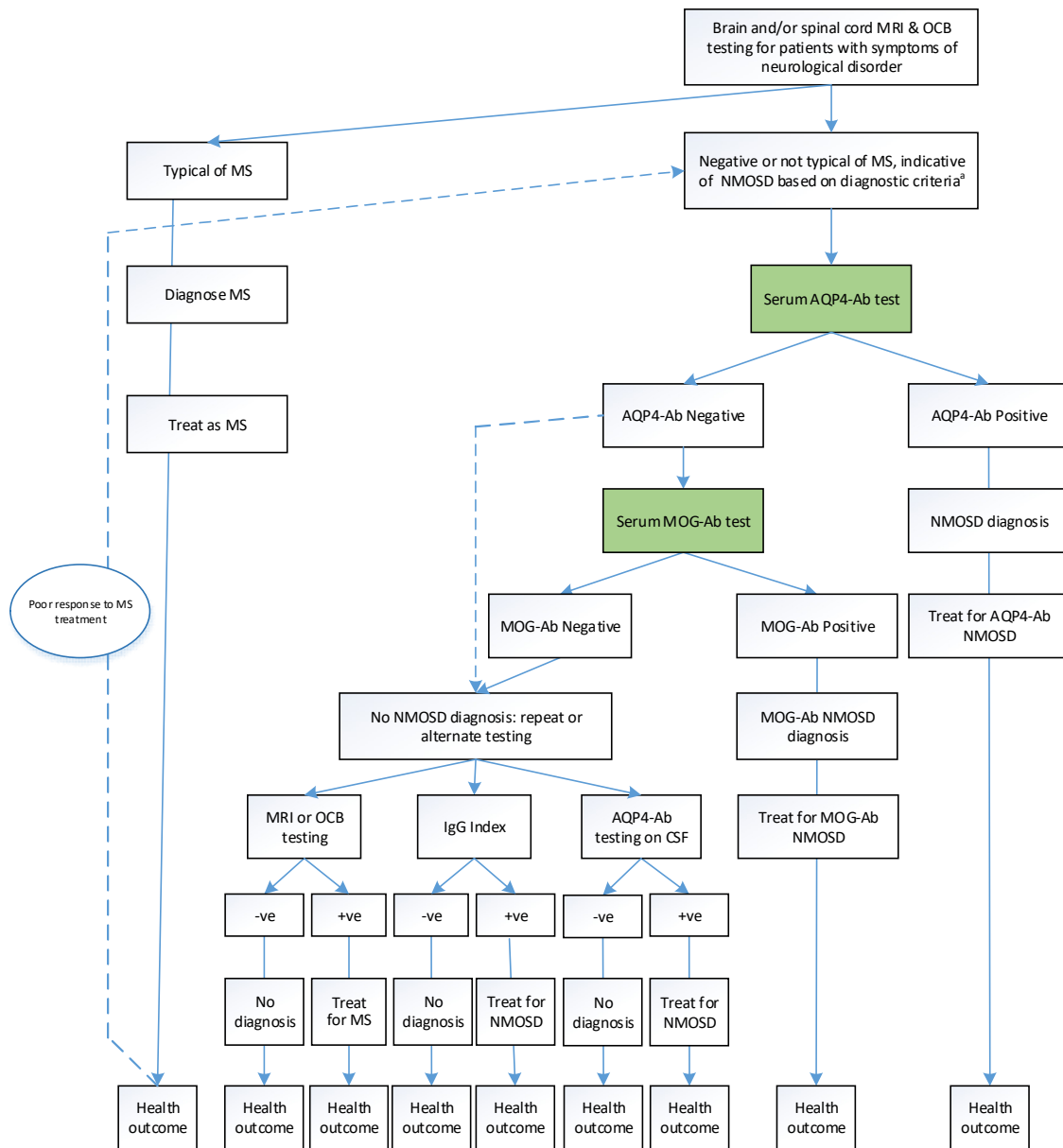


Figure 3: Algorithm for current diagnosis of suspected NMOSD with sequential AQP4-Ab and MOG-Ab testing

AQP4-Ab = aquaporin-4 antibody; CSF = cerebrospinal fluid; IgG = immunoglobulin G; antibody related disorder; MOG-Ab = myelin oligodendrocyte glycoprotein antibody; MRI = magnetic resonance imaging; MS = multiple sclerosis; NMOSD=neuromyelitis optica spectrum disorders; OCB =oligoclonal bands

^a See Table 7 for diagnostic criteria from Wingerchuk et al, 2015

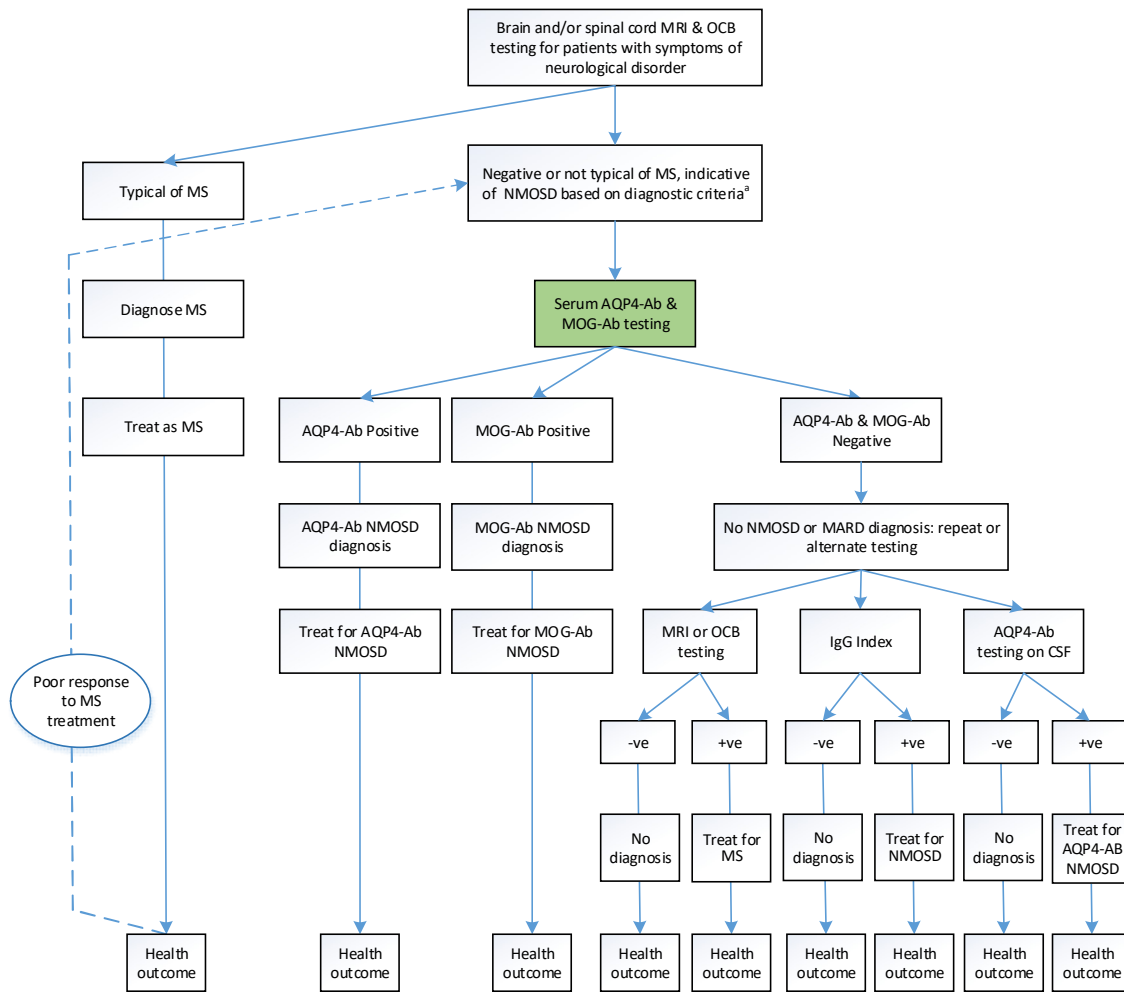


Figure 4: Algorithm for current diagnosis of suspected NMOSD with concurrent AQP4-Ab and MOG-Ab testing

AQP4-Ab = aquaporin-4 antibody; CSF = cerebrospinal fluid; IgG = immunoglobulin G; antibody related disorder; MOG-Ab = myelin oligodendrocyte glycoprotein antibody; MRI = magnetic resonance imaging; MS = multiple sclerosis; NMOSD=neuromyelitis optica spectrum disorders; OCB =oligoclonal bands

^a See Table 7 for diagnostic criteria from Wingerchuk et al, 2015

Current and historical management pathway for previously diagnosed patients who are at risk of relapse

A third clinical algorithm (Figure 5) is proposed for patients who have been previously diagnosed with NMOSD. Clinical advice indicates that this population may be monitored by regular AQP4-Ab (or MOG-Ab) testing, up to four times per year, to ascertain whether there is an increase in antibody presence or activity. An increase in AQP4-Ab (or MOG-Ab) titre may be an indication of exacerbation of symptoms, or relapse. Early recognition of the signs of relapse may enable earlier treatment than would be given based on symptoms and signs of disease alone. Earlier treatment may prevent worsening of symptoms or even full-blown relapse.

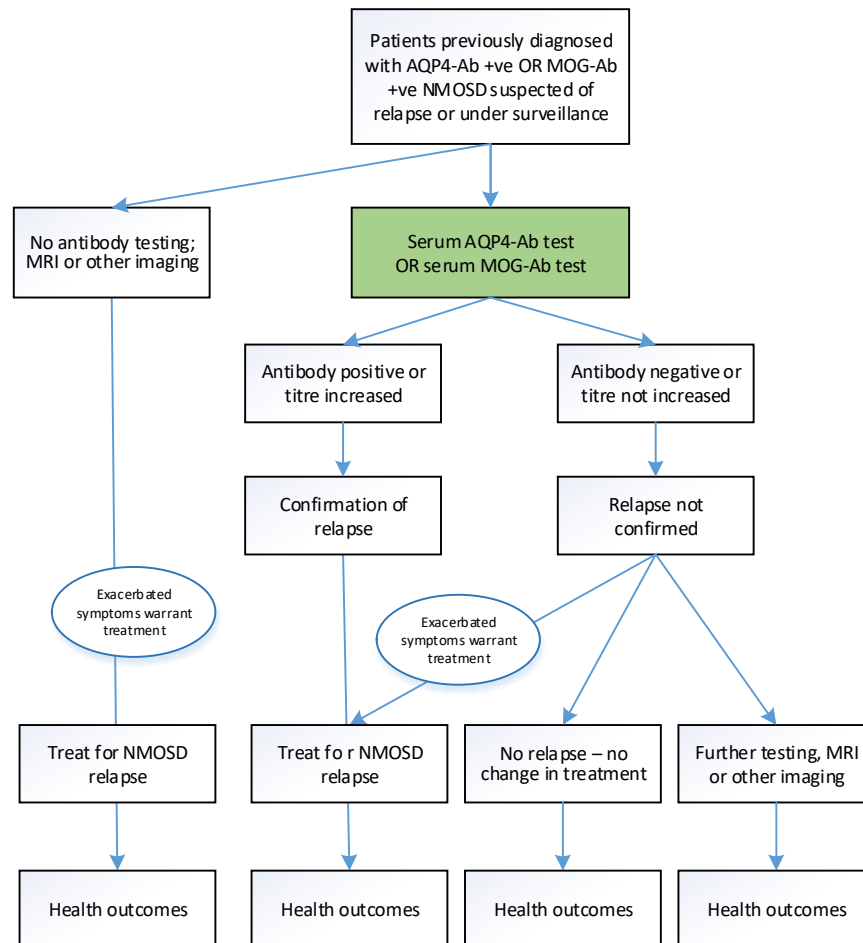


Figure 5 Current (with AQP4-Ab testing) and historical (without AQP4-Ab testing) pathways for management of patients previously diagnosed with NMOSD.

AQP4-Ab = aquaporin-4 antibody; MRI = magnetic resonance imaging; NMOSD=neuromyelitis optica spectrum disorders

PROPOSED ECONOMIC EVALUATION

PASC advised that the economic evaluation should be a cost-effectiveness/cost-utility analysis.

It is expected that AQP4-Ab testing with/without MOG-Ab testing will have non-inferior safety and superior effectiveness to clinical diagnosis alone for the diagnosis of NMOSD. As shown by Table 4, the appropriate type of economic evaluation would therefore be a cost-effectiveness analysis or cost-utility analysis.

Table 4 Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator					
		<u>Superior</u>		<u>Non-inferior</u>	<u>Inferior</u>		
Comparative safety versus comparator	<u>Superior</u>	CEA/CUA		CEA/CUA		Net clinical benefit	CEA/CUA
						Neutral benefit	CEA/CUA*
						Net harms	None [^]
	<u>Non-inferior</u>	CEA/CUA		CEA/CUA*	None [^]		
	<u>Inferior</u>	Net clinical benefit	CEA/CUA	None [^]	None [^]		
		Neutral benefit	CEA/CUA*				
Net harms		None [^]					

CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

[^] No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Proposed MBS item descriptor/s and MBS fees (if relevant)

(If the MBS is not relevant, please make that statement in this section, and provide alternative proposed funding source and price information)

AQP4-Ab testing has been occurring in Australia for more than 10 years under MBS item 71119 or 71165 (see Table 6). The Pathology Clinical Committee (PCC) recommended that a new item number be created so that the fee more appropriately reflects what providers currently bill for the test.

The PCC proposed a single item number for “a test to investigate the presence of neuromyelitis optica by detection of aquaporin4 antibodies”. This was amended to include the updated disease term (NMOSD, which is considered to include the subtype of MARF), and removal of the specification of AQP4, to allow for AQP4-Ab, MOG-Ab and any future antibodies to be tested using the same item number. The proposed new item descriptor is shown in Table 5. PASC has advised that the item descriptor should restrict requesting to a specialist or consultant physician. Advice was provided in a pre-PASC teleconference that if both AQP4-Ab and MOG-Ab testing occur at the same time, there would be no additional cost, compared to testing for only one antibody.

There is currently some inconsistency regarding whether MARF is classified as a subgroup of NMOSD or as a distinct nosology.

PASC advised that a single MBS item (allowing either or both antibody tests) would be preferable. It is unclear if this will cover both diagnosis and any re-testing/monitoring. Although testing is not generally used for monitoring, re-testing may be done in some situations. PASC considered it unlikely that testing would be done four times in a year; however, there is little evidence/information about this. Evidence provided by the DCAR may clarify the effectiveness of testing in these scenarios.

PASC advised that the population should be defined in the item descriptor, to prevent leakage to testing at the higher MBS fee in other populations.

PASC advised the item descriptor should restrict requesting to a specialist or consultant physician.

PASC advised that the preferable outcome would be for the item descriptor to be test agnostic. However, the evaluation will need to assess the performance of available non-cell-based assays against that of cell-based assays, which are currently considered to be the reference standard.

The applicant agreed with PASC that the item descriptor should be test agnostic, to allow for future developments in testing.

The applicant re-stated that the item should allow for the possibility of monitoring, subject to the evidence-based evaluation. Private sector figures provided by Sonic Healthcare indicate the number of re-tests in a calendar year account for approximately 61/953 (6%) of all tests.

Table 5 Proposed item descriptor for antibody testing for diagnosis (or monitoring, depending on evidence) of NMOSD

Category PATHOLOGY SERVICES	
71XXX	<p>A test to investigate the presence of neuromyelitis optica spectrum disorder (NMOSD) by the detection of one or more antibodies in patients suspected of having NMOSD:</p> <ul style="list-style-type: none"> a) Recurrent, bilateral or severe optic neuritis; or b) Recurrent longitudinal extensive transverse myelitis (LETM)*; or c) Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or d) Acute brainstem syndrome or e) Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or f) Symptomatic cerebral syndrome with typical NMOSD MRI lesions or g) Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) or h) Patient has poor recovery from multiple sclerosis relapses <p>(Item is subject to rule 26)</p> <p>This item is to be requested by a specialist or consultant physician.</p> <p>Payable not more than 4 times in any 12 month period</p> <p>Fee: \$43.00 Benefit: 75% = \$32.20 85% = \$36.50</p>

Table 6 Current item descriptors for single antibody testing against tissue antigens

Category PATHOLOGY SERVICES	
Item 71119	Group P4 – Immunology
<p>Antibodies to tissue antigens not elsewhere specified in this Table – detection, including quantitation if required, of 1 antibody.</p> <p>(see para PN.0.33 of explanatory notes in this Category)</p> <p>Fee: \$17.35 Benefit: 75% = \$13.05 85% = \$14.75</p>	
Category PATHOLOGY SERVICES	
Item 71165	Group P4 – Immunology
<p>Antibodies to tissue antigens (acetylcholine receptor, adrenal cortex, heart, histone, insulin, insulin receptor, intrinsic factor, islet cell, lymphocyte, neuron, ovary, parathyroid, platelet, salivary gland, skeletal muscle, skin basement membrane and intercellular substance, thyroglobulin, thyroid microsome or thyroid stimulating hormone receptor) - detection, including quantitation if required, of 1 antibody</p> <p>(Item is subject to Rule 6)</p> <p>Fee: \$34.55 Benefit: 75% = \$25.95 85% = \$29.40</p>	

[Consultation feedback](#)

PASC noted the letters of support in the consultation feedback.

[Next steps](#)

Upon ratification of PICO 1582, the application can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage. The applicant has elected to progress this application through a DCAR (Department-contracted assessment report).

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Appendix A: diagnostic criteria for NMOSD

Note: These figures will need to be redacted from the PICO confirmation prior to being distributed publicly.

Table 7 Diagnostic criteria for NMOSD (Wingerchuk, Dean M. et al. 2015)

Diagnostic criteria for NMOSD with AQP4-IgG <ol style="list-style-type: none">1. At least 1 core clinical characteristic2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)3. Exclusion of alternative diagnoses^a
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status <ol style="list-style-type: none">1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:<ol style="list-style-type: none">a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndromeb. Dissemination in space (2 or more different core clinical characteristics)c. Fulfillment of additional MRI requirements, as applicable2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable3. Exclusion of alternative diagnoses^a
Core clinical characteristics <ol style="list-style-type: none">1. Optic neuritis2. Acute myelitis3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting4. Acute brainstem syndrome5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)
Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status <ol style="list-style-type: none">1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

AQP4= aquaporin-4; IgG=immunoglobulin G; LETM=longitudinally extensive transverse myelitis lesions; NMOSD=neuromyelitis optica spectrum disorders

^a See Wingerchuk et al (2015) for recommendations regarding interpretation of clinical and serologic testing
Please note: Figure 1, 2 and 3 referenced in (Wingerchuk, Dean M. et al. 2015).

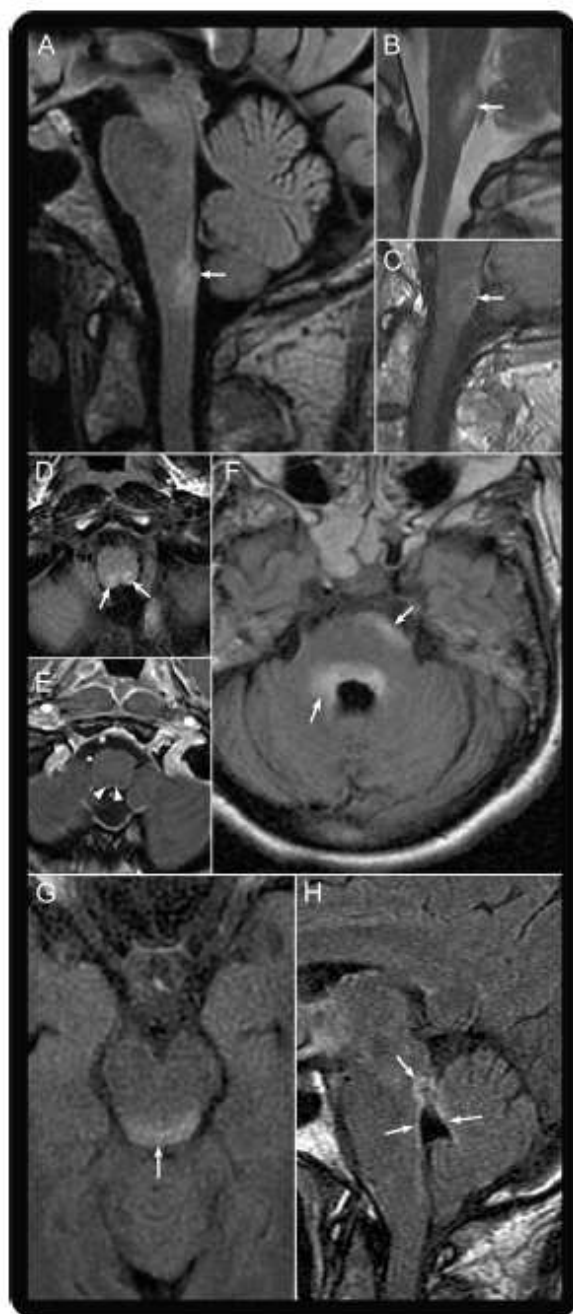
Figure 1 Spinal cord and optic nerve MRI patterns in neuromyelitis optica spectrum disorder



Spinal cord imaging in the context of acute myelitis in neuromyelitis optica spectrum disorders (NMOSD) usually reveals a longitudinally extensive transverse myelitis (LETM) lesion extending over 3 or more vertebral segments. Sagittal T2-weighted MRI of the thoracic spinal cord (A) demonstrates a typical LETM lesion involving most of the thoracic spinal cord (arrows). LETM lesions have a predilection for the central cord, as shown by axial T2-weighted (B; arrowhead) and T1-weighted MRI with gadolinium (C; arrowhead). Cervical LETM may extend into the medulla, a characteristic NMOSD pattern demonstrated in D (arrows; sagittal T2-weighted MRI) and E (arrows; sagittal T1-weighted MRI with gadolinium). Acute LETM lesions can be associated with intrasional hypointensity as shown by sagittal T1-weighted MRI (F; arrow); in this example, a rim of gadolinium enhancement surrounds the hypointense region. Chronic sequelae of LETM may include longitudinally extensive segments of spinal cord atrophy as shown by T2-weighted MRI using sagittal (G; the 2 arrowheads indicate the atrophic segment and the top arrow indicates the normal diameter of unaffected cervical spinal cord) and axial planes (H; arrowhead shows an atrophic spinal cord). Fast spinecho fat-suppressed T2-weighted MRI in the axial (I) and coronal (J) planes shows increased signal throughout most the length of the left optic nerve, especially its posterior portion (arrows). Axial T1-weighted MRI with gadolinium shows enhancement of the optic chiasm (K; arrows). These images are from 2 different patients experiencing acute optic neuritis in the setting of NMOSD.

Reference Wingerchuk et al. 2015(Wingerchuk, D. M. et al. 2015)

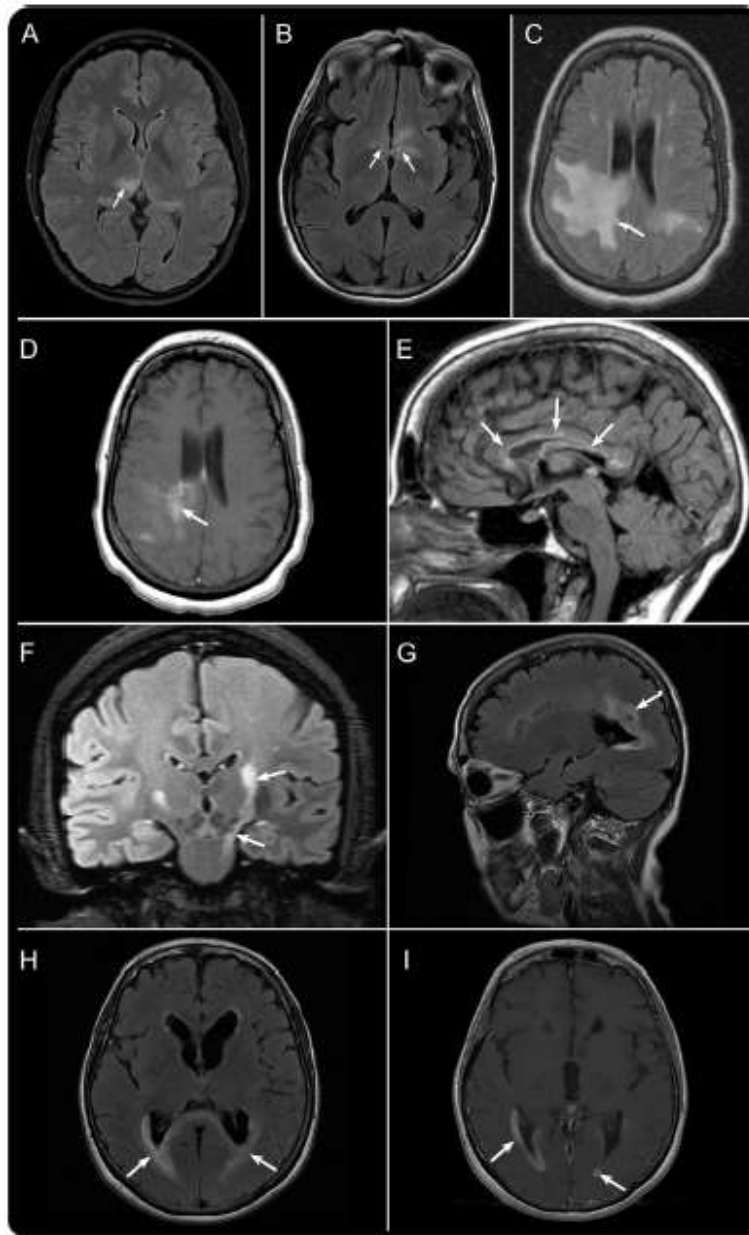
Figure 2 Dorsal medulla, area postrema, and other brainstem lesions in neuromyelitis optica spectrum disorder



Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI shows a lesion in the dorsal medulla (A; arrow). Sagittal T2-weighted (B) and T1-weighted MRI with gadolinium (C) each demonstrate an acute lesion (arrows) associated with area postrema clinical syndrome. Axial T2-weighted FLAIR (D; arrows) and T1-weighted MRI with gadolinium (E; arrowheads) show dorsal medulla involvement in a patient with acute area postrema clinical syndrome. Axial T2-weighted FLAIR MRI shows periependymal lesions involving the pons (F; arrows) and dorsal midbrain (G; arrow). Sagittal T2-weighted FLAIR MRI shows increased signal surrounding the fourth ventricle (H; arrows).

Reference Wingerchuk et al. 2015(Wingerchuk, D. M. et al. 2015)

Figure 3 Diencephalic and cerebral lesions in neuromyelitis optica spectrum disorder



A variety of brain lesion patterns are associated with neuromyelitis optica spectrum disorder. Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI from 2 patients demonstrates lesions involving the right thalamus (A; arrow) and the hypothalamus (B; arrows). Axial T2-weighted FLAIR MRI shows an extensive subcortical white matter lesion (C; arrow) that enhances after gadolinium administration on T1-weighted sequences (D; arrow). Chronic longitudinally extensive and linear corpus callosum lesions are depicted on sagittal T2-weighted FLAIR MRI (E; arrows). Coronal T2-weighted FLAIR MRI shows longitudinal involvement of the corticospinal tract extending to the cerebral peduncle and pons (F; arrows). Acute perilependymal cerebral lesions from one patient are depicted using sagittal (G; arrow) and axial (H; arrows) T2-weighted FLAIR MRI and axial T1-weighted MRI with gadolinium (I; arrows).

Reference Wingerchuk et al. 2015(Wingerchuk, D. M. et al. 2015)

Appendix B PPICO criteria for linked evidence

PPICO criteria for the linked evidence approach (if direct evidence not identified)

Box 2: PPICO criteria for assessing the clinical validity of antibody testing in patients with symptoms of NMOSD (linked evidence)

Component	Description
Patients	<ol style="list-style-type: none"> Patients suspected of having neuromyelitis optica spectrum disorder (NMOSD) - e.g. those with: <ol style="list-style-type: none"> Recurrent, bilateral or severe optic neuritis; or Recurrent longitudinal extensive transverse myelitis (LETM)*; or Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or Acute brainstem syndrome or Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or Symptomatic cerebral syndrome with typical NMOSD MRI lesions or Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) or Patient has poor recovery from multiple sclerosis relapses Patients previously diagnosed with NMOSD who are being monitored or tested for signs of relapse
Prior tests	MRI: findings of at least one clinical characteristic of NMOSD
Intervention	<ol style="list-style-type: none"> AQP4-Ab and MOG-Ab concurrent testing OR sequential testing (AQP4-Ab followed by MOG-Ab testing in those found -ve for AQP4-Ab) using a variety of diagnostic substrates (cell, tissue or protein) <ul style="list-style-type: none"> Serum CSF <u>Antibody testing (AQP4-Ab or MOG-Ab) of serum to monitor for signs of relapse in previously diagnosed patients?</u>
Reference standard	None available
Comparator (evidentiary standard)	Diagnosis by clinical characteristics alone (including MRI)
Outcomes	<ul style="list-style-type: none"> Sensitivity Specificity Need for re-testing Reliability Reproducibility PPV NPV Diagnostic yield
Research question	<p>What is the clinical validity of AQP4-Ab with/without MOG-Ab testing (either concurrently or sequentially) in patients suspected of NMOSD, compared to being diagnosed by clinical characteristics alone?</p> <p>What is the clinical validity of AQP4-Ab or MOG-Ab monitoring in patients previously diagnosed with NMOSD compared to those monitored by clinical characteristics alone?</p>

AQP4-Ab = aquaporin 4 antibodies; CSF = cerebrospinal fluid; LETM = longitudinal extensive transverse myelitis; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder; NPV = negative predictive value; PPV = positive predictive value
 * LETM defined as a spinal cord lesion that extends over 3 or more vertebrae segments (Wingerchuk, D. M. et al. 2015)

Box 3: PPICO criteria for assessing the impact on patient management of antibody testing in patients with symptoms of NMOSD (linked evidence)

Component	Description
Patients	<ol style="list-style-type: none"> Patients suspected of having neuromyelitis optica spectrum disorder (NMOSD) - e.g. those with: <ol style="list-style-type: none"> Recurrent, bilateral or severe optic neuritis; or Recurrent longitudinal extensive transverse myelitis (LETM)*; or Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or Acute brainstem syndrome or Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or Symptomatic cerebral syndrome with typical NMOSD MRI lesions or Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) or Patient has poor recovery from multiple sclerosis relapses Patients previously diagnosed with NMOSD who are being monitored or tested for signs of relapse
Prior tests	MRI: Findings of at least one clinical characteristic of NMOSD
Intervention	<ol style="list-style-type: none"> AQP4-Ab and MOG-Ab concurrent testing or sequential testing (AQP4-Ab testing followed by MOG-Ab testing in those testing –ve for AQP4-Ab) in serum or cerebrospinal fluid, using currently available assays Antibody testing (AQP4-Ab OR MOG-Ab) of serum to monitor for relapse in those previously diagnosed, using currently available assays
Comparator	No AQP4-Ab OR MOG-Ab testing: diagnosis by clinical characteristics alone, including tests to exclude other related diagnoses
Outcomes	<ul style="list-style-type: none"> Time to diagnosis or commencement of therapy Change in treatments recommended or received by patient Number of additional tests performed/avoided (e.g. further investigations after an AQP4-Ab or MOG-Ab test result vs investigations in the absence of antibody testing) Change in specialist referrals Change in diagnosis
Research question	<p>Do AQP4-Ab with/without MOG-Ab testing in patients suspected of NMOSD change management, compared to being diagnosed by clinical characteristics alone?</p> <p>Does monitoring by AQP4-Ab or MOG-Ab testing in patients previously diagnosed with NMOSD change management compared to monitoring by clinical characteristics alone?</p>

AQP4-Ab = aquaporin 4 antibodies; LETM = longitudinal extensive transverse myelitis; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder

* LETM defined as a spinal cord lesion that extends over 3 or more vertebrae segments (Wingerchuk, D. M. et al. 2015)

Box 4: PICO criteria for assessing the therapeutic effectiveness (impact of the change in patient management) of antibody testing in patients with symptoms of NMOSD (linked evidence)

Component	Description
Patients	<ol style="list-style-type: none"> 1.. Patients diagnosed with NMOSD or those testing negative for AQP4-Ab and MOG-Ab 2. Previously diagnosed NMOSD patients, confirmed as relapsing or those who had no increase in AQP4-Ab or MOG-Ab titre
Intervention	<ol style="list-style-type: none"> 1. Management changes resulting from AQP4-Ab and MOG-Ab concurrent testing or sequential testing (AQP4-Ab testing followed by MOG-Ab testing in those testing –ve for AQP4-Ab) in serum or cerebrospinal fluid using a currently available assay (e.g. earlier diagnosis, changes in treatment, avoiding unnecessary testing) 2. Management changes resulting from antibody testing (AQP4-Ab or MOG-Ab) in serum using a currently available assay (e.g. earlier treatment, changes in treatment)
Comparator	No management changes (management based on other diagnostic evidence only)
Outcomes	<ul style="list-style-type: none"> • Health impact due to diagnosis and differences between early diagnosis vs late diagnosis • Health impact due to treatments received and differences between early treatment vs late treatment • Quality of life • Psychological health • Patient acceptability, satisfaction and convenience
Research question	<p>How effective are the changes which result from AQP4-Ab with/without MOG-Ab testing compared to diagnosis based on clinical characteristics alone (e.g. how effective is early vs late treatment, or treatment for NMOSD rather than MS for someone with NMOSD)?</p> <p>How effective are changes which result from AQP4-Ab or MOG-Ab testing compared to monitoring based on clinical characteristics alone (e.g. how effective is early vs late treatment) for those previously diagnosed with NMOSD?</p>

AQP4-Ab = aquaporin 4 antibodies; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorder