****

 Public Summary Document

Application No. 1582 – Detection of aquaporin-4 (AQP4) and
myelin oligodendrocyte glycoprotein antibody (MOG) antibodies for diagnosis of neuromyelitis optica (NMO) and
myelin oligodendrocyte glycoprotein antibody-related demyelination (MARD)

**Applicant: Royal College of Pathologists of Australasia (RCPA)**

**Date of MSAC consideration: MSAC 79th Meeting, 28-29 July 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

# Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of aquaporin 4 antibody (AQP4-Ab) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab) testing in patients suspected of neuromyelitis optica spectrum disorders (NMOSD) was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health.

# MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported a new MBS item and increased public funding of concurrent testing for the detection of anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies (MOG-Abs) for the differential diagnosis of neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-related demyelination (MARD), as these tests are safe and linked to clinical management consequences that result in cost-effective outcomes. MSAC recommended the descriptor for the MBS item exclude the use of these antibody tests for disease monitoring in either condition.

| **Consumer summary** |
| --- |
| The Royal College of Pathologists Australasia applied for public funding via the Medicare Benefits Schedule (MBS) for an antibody test to see if a patient has neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein (MOG) antibody-related demyelination (MARD). NMOSD and MARD are conditions that affect the central nervous system. They have similar symptoms to multiple sclerosis (MS), but are treated differently. A correct diagnosis is important because some MS treatments are harmful to people who have NMOSD or MARD, and vice versa. These antibody tests allow a doctor to make a more accurate diagnosis and start treating the patient with the correct medicines earlier. This test looks for two types of antibodies: aquaporin-4 antibodies, which indicate that the person has NMOSD; and MOG antibodies, which indicate that the person has MARD. MSAC noted that this test looks for the two types of antibodies at the same time, which gives an answer faster and is more cost-effective than doing one test after another. MSAC noted that the tests are already being done under a generic antibody-testing MBS item number. This application was for a specific MBS item number that has a more appropriate fee.The antibody test can be done on blood (serum) or cerebrospinal fluid (CSF). MSAC recommended doing the test on serum only, as CSF is more difficult to get (it involves putting a needle into the person’s spine) and the test results are less accurate for making a diagnosis.MSAC noted that this test should only be funded for the initial diagnosis of these two conditions, and not for monitoring disease progression or response to treatment. This is because both of the tests do not have sufficient evidence to support the use in disease monitoring. **MSAC’s advice to the Commonwealth Minister for Health**MSAC supported public funding for testing for aquaporin-4 antibodies and MOG antibodies in serum for diagnosis (only) of NMOSD and MARD. MSAC considered that the test is cost-effective, safe and can inform better clinical care for people living with NMSOD and MARD. MSAC noted that this test would only be funded for diagnosing these two conditions, and not for monitoring disease progression or response to treatment. |

# Summary of consideration and rationale for MSAC’s advice

MSAC noted that this application was for a new Medicare Benefits Schedule (MBS) listing initially limited to an antibody test to investigate the presence of NMOSD by detecting anti-aquaporin-4 antibodies (AQP4-Abs) in serum and/or cerebrospinal fluid (CSF). However, given that some patients are negative to AQP-4 but positive to MOG there is a need to differentiate a diagnosis of NMOSD from MARD for therapeutic decision-making which requires separate diagnostic antibody tests; the application expanded during the assessment to include anti-MOG antibody (MOG-Ab) testing in order to reflect the diagnostic criteria used in current clinical practice.

MSAC noted that AQP4-Ab testing is currently claimed under generic MBS item numbers 71119 or 71165, which are non-specific single antibody test descriptors. These items are currently funded at a lower level than these tests are currently billed in order to make a diagnosis of NMOSD. Accordingly, this application seeks a more appropriate fee for this type of low-volume cell-based antibody testing.

MSAC noted that NMOSD is associated with antibodies to AQP4, and MARD is associated with antibodies to MOG, with a small proportion of patients having positivity to both. The advantage of the antibody test in this proposal is that it can detect both antibodies in a combined single test, rather than performing two separate assays. MSAC agreed with the applicant’s pre-MSAC response, which stressed the importance of performing concurrent AQP4-Ab and MOG-Ab testing at initial diagnosis.

MSAC noted the importance of diagnosing NMOSD and MARD early and accurately in order to direct appropriate disease-specific therapy. These conditions present similarly to multiple sclerosis (MS), but may not respond to MS treatments such as natalizumab and can lead to worse outcomes. In the absence of appropriate antibody testing there is a potential for disease misclassification, from which patients may experience adverse effects from incorrect therapy, whilst obtaining no benefit. MSAC agreed with the claim from the Pathology Clinical Committee of the MBS Review Taskforce that the successful listing of AQP4-Ab testing in the target population and setting will lead to more rapid diagnosis and treatment, in order to improve patient outcomes.

MSAC considered the evidence for serum testing to be of an appropriate standard for assessment, but noted the lack of evidence associated with testing using CSF. MSAC considered that lumbar puncture would rarely be performed solely to collect a sample for this antibody test, therefore recommended that the antibody testing be performed on serum only.

MSAC noted the economic evaluation was a cost-utility analysis. MSAC considered that the proposed antibody testing strategy for diagnosing NMOSD is less costly and more effective (dominant) compared with no Ab testing with respect to the other diagnostic strategies and all clinical outcomes assessed.

MSAC agreed with the utilisation estimates provided in the DCAR (10,122 in year 1 with a growth rate of 6–18% each year), but noted that these estimates would also be reduced by restricting the item descriptor to diagnosis (not monitoring) and by concurrent testing of both antibodies (i.e. the test does not needed be repeated for MOG-Ab in those with negative AQP4-Ab results). MSAC considered the financial impact of the proposal to be modest (see Table 16).

MSAC noted that the testing should be restricted to patients presenting with symptoms consistent with NMOSD, MARD or MS with relapses or atypical MS. MSAC considered using the antibody tests are appropriate for initial diagnosis, but not for disease monitoring. MSAC considered that a retest would be appropriate for patients that have tested negative to AQP4-Ab/MOG-Ab but are not responding to MS treatment in order to clarify the diagnosis. Thus, MSAC suggested that the descriptor practice note should be amended to make it clear that a retest for diagnostic purposes is acceptable, but that the test should not be used for monitoring.

MSAC also considered that the proposed item descriptor should state “…patients suspected of having NMSOD or MARD” (i.e. add “or MARD”).

MSAC considered the proposed fee of $50 for concurrent testing of both AQP4-Ab and MOG-Ab to be appropriate.

The MSAC-supported MBS item descriptor is summarised in Table 1.

**Table 1 Revised MBS item descriptor for antibody testing to diagnose NMOSD or MARD**

| **Category PATHOLOGY SERVICES** |
| --- |
| 71XXX |
| *A test to diagnose neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-related demyelination (MARD) by the detection of one or more antibodies in patients suspected of having NMOSD, or MARD, with:* 1. *Recurrent, bilateral or severe optic neuritis; or*
2. *Recurrent longitudinal extensive transverse myelitis (LETM)a; or*
3. *Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or*
4. *Acute brainstem syndrome or*
5. *Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or*
6. *Symptomatic cerebral syndrome with typical NMOSD MRI lesions or*
7. *Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days); or*
8. *Acute disseminated encephalomyelitis; or*
9. *Aseptic meningitis and encephalomyelitis; or*
10. *Patient has poor recovery from multiple sclerosis relapses*

*(Item is subject to rule 26)**Explanatory notes:* *This test is not intended for monitoring purposes**This item is to be requested by a specialist or consultant physician.**This item number should not be used more than 4 times in any 12 month period**Fee: $50.00 Benefit: 75% = $37.50 85% =$42.50* |

Source: MSAC Discussion

# Background

This is the first submission (Department Contracted Assessment Report [DCAR]) for AQP4-Ab and MOG-Ab testing in patients suspected of neuromyelitis optica spectrum disorders (NMOSD). MSAC has not previously considered this application.

The Pathology Clinical Committee – Immunology (PCC-Immunology) of the MBS Review Taskforce recommended the application be made, claiming that the successful listing of AQP4-Ab testing in the target patient population and setting would lead to more rapid diagnosis and treatment, which will ultimately improve patient outcomes[[1]](#footnote-1).

AQP4-Ab testing is currently performed and rebated under a generic MBS item (71119 or 71165).

# Prerequisites to implementation of any funding advice

The National Pathology Accreditation Advisory Council (NPAAC) stated that this test is already conducted in National Association of Testing Authorities (NATA) accredited Australian laboratories and there is an existing quality assurance program (QAP).

# Proposal for public funding

The item descriptor for AQP4-Ab testing proposed in the application is given in Table 2. The item descriptor was proposed by the PCC-Immunology as part of the MBS Review Taskforce process. The meeting of PASC in December 2019 updated the proposed descriptor to include specific symptoms that are indicative of NMOSD. The DCAR stated that the proposed item permits testing of both cerebrospinal fluid (CSF) and serum samples.

The applicant in its pre-ESC response indicated that the proposed MBS fee of $43 is insufficient to adequately fund low-volume AQP4-Ab and MOG-Ab testing using best-practice, cell-based assays, with a fee of at least $50 required to cover the costs of providing testing of both antibodies. The applicant also offered to provide advice from pathology and clinical experts in the field to inform further discussions with the Department if necessary.

**Table 2 Applicant proposed MBS item descriptor for antibody testing to diagnose or monitor NMOSD (*Note, the applicant increased the proposed fee to $50 (in bold font below], in its pre-ESC response*)**

| **Category PATHOLOGY SERVICES** |
| --- |
| **71XXX**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: Recurrent, bilateral or severe optic neuritis; orRecurrent longitudinal extensive transverse myelitis (LETM)a; orArea postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) orAcute brainstem syndrome orSymptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions orSymptomatic cerebral syndrome with typical NMOSD MRI lesions orMonophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) orPatient has poor recovery from multiple sclerosis relapses(Item is subject to rule 26)This item is to be requested by a specialist or consultant physician.Payable not more than 4 times in any 12 month periodFee: ~~$43.00~~ **$50.00** Benefit: 75% = ~~$32.20~~ **$37.50** ~~85% = $36.50~~ **$42.50** |

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

Source: Table 1, p17 of the DCAR

# Summary of public consultation feedback/consumer issues

The DCAR noted that letters were received from two specialist organisations during the development of the PICO confirmation pre-PASC December 2019, which supported the availability of AQP4-Ab and MOG-Ab testing on the MBS. No further consultation feedback was received.

# Proposed intervention’s place in clinical management

**Description of proposed intervention**

The proposed medical service is to test for antibodies against AQP4 and MOG. AQP4 is a water channel protein considered an integral constituent of the blood brain barrier. MOG is a component of the myelin sheath exclusively found in the CNS. The presence of serum antibodies to AQP4 is a diagnostic criterion for NMOSD. The 2015 diagnostic criteria for adult patients with NMOSD stratifies diagnosis into two patient populations – those that are AQP4-IgG positive and those that are AQP4-IgG negative or have unknown status. The AQP4-IgG positive group need only satisfy one “core” clinical criteria compared to more stringent clinical and imaging criteria for the negative group. The proposed intervention may facilitate an earlier diagnosis of NMOSD, as distinct from atypical multiple sclerosis (MS), idiopathic transverse myelitis or idiopathic optic neuritis. This is important as the natural history of untreated NMOSD is significantly worse than that of MS. The earlier detection of NMOSD leads to a specific treatment path with immunotherapy for attack prevention. Moreover, treatments used for MS are ineffective in the treatment for NMOSD and may even contribute to worse disease outcomes in individuals with NMOSD.

Regardless of serostatus, at least one discrete clinical attack of CNS symptoms must occur to establish an NMOSD diagnosis. An NMOSD diagnosis is also partly a diagnosis by exclusion of alternatives and this is explicitly outlined in the 2015 guidelines with a table of red flags signalling the possibility of other diagnoses. For those patients suspected of having NMOSD, but test negative for AQP4 or MOG antibodies, their management will depend on the suspected diagnoses. Those who are assumed to have MS but truly have NMOSD will not respond to MS treatment. They are likely to develop further clinical features of NMOSD and be clinically diagnosed as having antibody-negative NMOSD after a delay.

**Description of medical condition(s)**

The target population is those suspected of having NMOSD.

NMOSD is a rare but severe inflammatory autoimmune disorder of the CNS. 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).

There are no clinical features that are pathognomonic for NMOSD, as ON and myelitis also occur in MS. The presence of AQP4-IgG supports the diagnosis of NMOSD from MS and other autoimmune disorders of the CNS.

**Place in clinical management**

In the absence of antibody testing, diagnosis of NMOSD relies on both the clinical picture (symptoms) and imaging examinations as described by Wingerchuk et al. (2015)[[2]](#footnote-2). The historical management pathway is illustrated in Figure 1.

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 pathways using sequential testing and concurrent testing are illustrated in Figure 2 and Figure 3 respectively.



**Figure 1 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 Diagnostic criteria provided in Wingerchuk et al. 2015

Source: Figure 4, p44 of the DCAR

The DCAR stated that 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:

1. Serum AQP4-Ab testing (Figure 2) followed by MOG-Ab testing in negative cases. 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 indicative of MOG-Ab NMOSD diagnosis. When MOG-Ab testing is negative, additional testing is recommended (e.g., MRI/oligoclonal bands (OCB) testing, immunoglobulin G (IgG) index testing).
2. Concurrent serum AQP4-Ab and MOG-Ab testing (Figure 3). A positive serum test for either AQP4-Ab or MOG-Ab is confirmatory for AQP4-Ab NMOSD or MOG-Ab NMOSD, respectively. Should both serum antibody tests be deemed negative for their respective diagnosis conditions, then additional testing is recommended including oligoclonal bands (OCB), immunoglobulin G (IgG) or AQP4-Ab testing in the cerebrospinal fluid (CSF) to determine a differential diagnosis of MS or AQP4-Ab NMOSD or MOG-Ab NMOSD.

If a diagnosis is made, then treatment is prescribed according to the diagnosis.



**Figure 2 Algorithm for current clinical management of suspected NMOSD patients with sequential AQP4-Ab and MOG-Ab testing**

AQP4-Ab = aquaporin-4 antibody; CSF = cerebrospinal fluid; IgG = immunoglobulin G; MARD = myelin oligodendrocyte glycoprotein 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 Diagnostic criteria provided in Wingerchuk et al. 2015

Source: Figure 5, p46 of the DCAR



**Figure 3 Algorithm for current clinical management of suspected NMOSD patients with concurrent AQP4-Ab and MOG-Ab testing**

AQP4-Ab = aquaporin-4 antibody; CSF = cerebrospinal fluid; IgG = immunoglobulin G; MARD = myelin oligodendrocyte glycoprotein 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 Diagnostic criteria provided in Wingerchuk et al. 2015

Source: Figure 6, p47 of the DCAR

In its pre-ESC response, the Applicant indicated that concurrent AQP4-Ab and MOG-Ab testing, as opposed to either AQP4-Ab testing alone, or sequential testing of AQP4-Ab and MOG-Ab, reflects current clinical best practice in Australia.

# Comparator

The DCAR stated that following clinical input, the comparator chosen for assessing the clinical validity was diagnosis of NMOSD based on the 2015 International Panel for Neuromyelitis optica [NMO] Diagnosis (IPND). According to the IPND, diagnosis of NMOSD *without* AQP4-Ab testing requires identification of two core clinical characteristics, and at least one of the core clinical characteristics has to be ON, acute myelitis or area postrema syndrome. For the diagnosis of NMOSD *with* AQP4-Ab testing, only one of the above-listed core clinical characteristics are required. The diagnostic pathway may vary slightly depending on which symptom/s appear first. Additionally, supportive characteristics in cerebral, spinal cord or optic nerve MRI are required with or without AQP4-Ab testing.

The DCAR stated that the financial implications of a new MBS item for AQP4-Ab and/or MOG-Ab testing were compared against current practice, i.e. AQP4-Ab testing rebated under MBS item 71165 or 71119.

# Comparative safety

No studies were identified that reported direct effectiveness or safety of AQP4-Ab or MOG-Ab testing. Two studies were included that provided evidence on analytical validity, 24 were included on clinical validity, and 21 were included on clinical utility (including 14 on therapeutic effectiveness) [Table 3]. The DCAR stated that the majority of studies were of moderate to high risk of bias, primarily due to their retrospective observational designs.

**Table 3 Features of the key studies included in the linked evidence**

| **Type of evidence** | **Description** | **Number** |
| --- | --- | --- |
| Diagnostic performance (Analytical validity) | 🡪 One study compared the diagnostic performance of 21 assays including cell-based assays, in detecting serum AQP4-Abs from 15 diagnostic centres🡪 One study compared the diagnostic performance of cell-based assay testing for AQP4-Abs in CSF versus serum | k=2n=138 |
| Clinical validity | 🡪 Diagnostic accuracy: AQP4-Ab test data were extracted from retrospective cohorts with before and after test data. Study populations were those with CNS symptoms including ADS, ON, LETM and ABS; all were compared with diagnosis by the 2015 IPND diagnostic criteria 🡪 Diagnostic yield: data were obtained from populations with ON or LETM, and with or suspected of having NMO or NMOSD who were tested for AQP4-Ab and/or MOG-Abs🡪 Prognosis: data were obtained from one systematic review and retrospective case series with before and after data. The systematic review compared visual impairment between seropositive and seronegative AQP4-Ab patients. Other study outcomes included rate of conversion from first event to NMOSD, relapse rate of initial symptoms, EDSS and recovery rate from initial symptoms in patients tested for AQP4 and/or MOG-Abs | k=23n=5,756 |
| Clinical utility (Therapeutic efficacy) | 🡪 Change in patient management: studies included adults and/or children diagnosed with NMOSD or other CNS inflammatory diseases who had been tested for AQP4-Abs. The impact of test results on patient management was determined, including time to diagnosis, change in diagnosis and clinician agreement in diagnosis🡪Therapeutic effectiveness: data were obtained from one systematic review and other studies including RCTs, cohort studies and case series studies. The systematic review evaluated the efficacy of rituximab. Other studies provided outcomes related to impact of patient management changes (e.g. early versus late treatment) or therapeutic effectiveness and safety of medication in patients tested for AQP4 or MOG Abs | k=22n=3.166 |

ABS = acute brainstem syndrome; ADS = acquired demyelination syndromes; AQP4-Abs = aquaporin 4 antibodies; CNS = central nervous system; CSF = cerebrospinal fluid; EDSS = expanded disability status scale; IPND = International Panel for NMO Diagnosis; LETM = longitudinally extensive transverse myelitis; MOG-Abs = myelin oligodendrocyte glycoprotein antibodies; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; RCT = randomised controlled trial

Source: Table 2, pp21-22 of DCAR

## Test adverse events

The DCAR stated that testing performed on a blood sample is unlikely to result in any significant adverse effects. It is understood from clinical advice that CSF sampling is not likely to occur for the sole purpose of AQP4-Ab and MOG-Ab testing. Rather, testing of CSF would only occur using existing samples collected from prior diagnostic investigations e.g for OCB analysis, which require CSF samples. Therefore, there are not expected to be additional adverse events as a result of CSF sampling if the proposed antibody tests are not the sole purpose for the lumbar puncture.

## Adverse events from change in management

The DCAR stated that data on adverse events were taken from seven studies that reported on the safety of treatments used in the management of NMOSD. One systematic review of rituximab (RTX) therapy for NMOSD reported on adverse events (Gao et al. 2019[[3]](#footnote-3)). Of the six primary studies, only one randomised patients to a treatment (eculizumab, ECZ) or placebo, (Pittock et al. 2019[[4]](#footnote-4)) and the others were single arm studies or performed a *post-hoc* comparison of treatments. The treatments given for NMOSD in the studies were RTX, ECZ, plasma exchange (PLEX), mycophenolate mofetil (MMF) and azathioprine (AZA).

The DCAR stated that serious adverse event rates were found to range from 0.8% to 13.8% across treatments, ECZ having the highest and RTX having the lowest serious adverse event rates. It was not possible to tell if the events were associated with the treatment in the studies, except where it was specifically stated in one study. For this reason, and because of the non-comparative study designs and small sample sizes, the adverse event data should be considered with caution.

The DCAR stated that there was insufficient evidence meeting the eligibility criteria for any conclusions to be made about the safety of AQP4-Ab or MOG-Ab testing for monitoring disease status in patients diagnosed with NMOSD.

# Comparative effectiveness

There was no direct evidence identified that met the inclusion criteria. A linked evidence approach was undertaken.

## Diagnostic performance

The DCAR stated that there is no reference standard for diagnostic accuracy for detecting AQP4-Abs in patients suspected of NMOSD. It was understood from the literature, and accepted by PASC, that cell-based assays are the best performers for AQP4-Ab and MOG-Ab testing, rather than enzyme-linked immunosorbent assays (ELISA) or indirect immunofluorescence (IIF) assays. Therefore, test performance was limited to a concordance analysis between different types of cell-based assays. The implication of this is that there is evidence about the extent to which the cell-based assays agree with each other, but not if they are able to accurately detect AQP4-Abs.

Results of the concordance analysis (Table 4), based on limited evidence (two studies), suggest that all serum cell-based assays tended to agree with each other when detecting AQP4-Abs. Concordance between three cell-based assay methodologies (live and fixed cell-based assays and fluorescence-activating cell sorting [FACS]) showed that all three assays largely agreed with each other in the detection of AQP4-Abs. The positive percent agreement (PPA) for all three assays ranged from 96-100%. There was lower agreement (expressed as negative percent agreement, NPA) between the three assays for detecting AQP4-Abs negative serum samples, where fixed cell (NPA 81%) and FACS (NPA 85%) were less likely to agree with live cell-based assay (NPA 100%) for a negative AQP4-Ab result.

**Table 4 Concordance between live and fixed cell-based assays and flow cytometry assays using serum samples**

| **Test type** | **N tests compared/** **N NMO/NMOSD cases** | **PPA % Range or Combined (95% CI)**  | **95% CI (lower and upper range)** | **NPA % Range or Combined (95% CI** | **95% CI (lower and upper range)** |
| --- | --- | --- | --- | --- | --- |
| Live CBA | 3/101a  | 97-100 | (91,100) (95,100) | 96-100 | (80,100) (87,100) |
| Fixed CBA | 11/238b | 100 (93,100) | (79,95) (95,100) | 81 (76,86) | (50,81) (77,100) |
| FACS | 4/101a | 96 (92,98) | (84,97) (94,100) | 85 (55,97) | (39,70) (85,100) |

CBA = cell-based assay; FACS = fluorescence-activating cell sorting; NPA = negative percentage agreement; PPA = positive percentage agreement

a Study by Waters et al. 2016

b total includes10 tests and 193 number of cases in study by Waters et al. 2016 and 1 test and 45 number of cases in study by Jarius et al 2010

Source: Table 3, p23 of the DCAR

The DCAR stated that testing of CSF for AQP4-Abs is not as reliable as serum testing, based on results of one study. The concordance between serum and CSF samples to detect AQP4-Abs showed that 32% of cases found to be AQP4-Ab positive in serum were not found to be positive in CSF. The PPAs for serum and CSF were 100% and 68%, respectively. The NPA was the same for both serum and CSF (100%). Figure 4 provides a summary of results. The lack of concordance between detection of AQP4-Abs in serum versus CSF is consistent with Wingerchuk et al. (2015), who reported that cases of AQP4-Ab detection in CSF, when they have not been detected in serum, are rare, and routine CSF testing for AQP4-Ab testing in seronegative patients is not recommended.



**Figure 4 Concordance between assay samples using serum versus cerebrospinal fluid**

CSF = cerebrospinal fluid

a fixed cell-based assay used

Source: Figure 1, p24 of the DCAR

## Clinical validity

The DCAR stated that there were issues associated with the intervention and the clinical reference standard that prevented diagnostic accuracy data from being reliable. The clinical reference standard (diagnosis of NMOSD based in the 2015 IPND criteria) includes or is likely to include the AQP4-Ab test and therefore is at risk of incorporation bias. Issues associated with the test which prevent data collected from the relevant literature being reliable, include the following:

* a negative test result for AQP4-Ab does not rule out a NMOSD diagnosis
* in the literature, a reported patient record of AQP4-Ab negative may also mean serostatus is not available for the purposes of calculating sensitivity
* it was assumed in the DCAR that AQP4-Ab positive is definitive for a diagnosis of NMOSD, therefore making it difficult to determine the effect of identifying false positive cases.

The DCAR stated that yield data for AQP4-Ab testing was determined from retrospective studies of patient cohorts in early stages of disease development. A prevalence of approximately 34% for NMOSD cases was calculated from the yield data for patients having one symptom (for example LETM, ON or acquired brainstem syndrome [ABS]) and meeting the suspected NMOSD PPICO criteria. Prevalence was found to be similar (43%) in one Australian based study, but did not match that determined from Australian data collected from clinical pathology laboratories performing the test. AQP4-Ab and/or MOG-Ab testing is performed in a broader population in Australia, with a prevalence of NMOSD cases of 2.9% for QLD (including tests from SA) and 5.4% for WA, calculated from the tested population.

There is no clinical reference standard for MOG-Ab testing and so its accuracy could not be assessed, and only yield data were reported for this test. In some studies, all patients were tested for MOG-Ab, whereas in others only those testing negative for AQP4-Ab were tested, so it is difficult to compare the outcome across studies.

The DCAR stated that, in the absence of relevant diagnostic accuracy data from the clinical setting, prognostic data have provided a step in the linked evidence. Studies comparing the longitudinal outcomes for patients testing positive or negative for AQP4-Ab indicate that the presence of AQP4 antibodies identifies a group of patients at risk of clinically significantly worse outcomes amongst those *suspected* of NMOSD. Visual impairment, rate of legal blindness, rate of diagnosis with NMO/NMOSD and annualised relapse rate (ARR) were all found to be worse after a minimum follow-up period of 1 year in patients found positive for AQP4-Ab compared to those who tested negative, amongst those who were suspected of NMOSD due to the presence of one or more symptoms.

The DCAR stated that these data were supported by results of a systematic review in which visual outcomes were found to be worse for patients who were AQP4-Ab positive compared to those testing negative, amongst those *diagnosed* with NMO or NMOSD. There were similar but less consistent prognostic data for MOG-Ab testing performed in those suspected of NMOSD, suggesting that those who were MOG-Ab positive had worse outcomes than those testing negative.

## Clinical utility

The DCAR stated that there was evidence to show that patients are diagnosed earlier when diagnosis is based on the 2015 IPND criteria compared to those diagnosed by the 2006 criteria. In addition to AQP4-IgG serology status, the 2006 guidelines required both myelitis and optic neuritis for diagnosis of NMO (subsequently relaxed in the 2015 IPND guidelines). The term NMO spectrum disorder (NMOSD) was introduced in 2007 to include AQP4-IgG seropositive patients with limited clinical symptoms but at high risk for future attacks.

### Therapeutic efficacy (change in management)

The DCAR stated that evidence from one study showed that patients are diagnosed earlier using the 2015 IPND criteria compared to those diagnosed by the 2006 criteria (11 versus 53 months). The time to diagnosis was measured retrospectively in patients with central nervous system inflammatory disease, which is broader than the population of interest (those suspected of NMOSD). In more selected populations, this effect may be reduced, but is unlikely to be negated.

The DCAR stated that further evidence showed that more patients suspected of NMOSD are diagnosed by the 2015 IPND criteria than by the 2006 criteria (odds ratio [OR] [95% confidence interval (CI)] of diagnosis range: 1.76 [1.04, 2.94] to 2.48 [1.93, 3.19]). This is possibly because of the more recent emphasis on AQP4-Ab testing.

The DCAR stated that the association between AQP4-Ab testing and earlier diagnosis was strong, but the confidence in the results was reduced by the risk of bias in the retrospective observational study designs. (GRADE: LOW ⨁⨁⨀⨀).

The DCAR stated that there was no evidence to determine if MOG-Ab testing impacted on the time to diagnosis for patients suspected of NMOSD.

The DCAR stated that there were two cross-sectional studies reporting a change in patient management and consequent outcomes of interest. In a quality of life questionnaire, out of 195 NMO and NMOSD patients, 65.8% had been given a prior incorrect diagnosis, MS being the most common (41.4%). Patients were concerned about the amount of time it took to get a correct diagnosis (0 to 40 years; mean 3.3 ± 6.3 years), and to receive an effective treatment. Once a correct diagnosis had been given, the mean time it took to receive treatment was 6 months ± 1.7 years (range 0 – 11 years), indicating that the primary delay to getting treatment was the time taken to diagnosis. In a second, small cross-sectional study, it was found that there was considerable disagreement between specialists when diagnosing patients with suspected NMOSD or MS, at least partly due to the overlapping symptoms between the conditions. It is likely that AQP4-Ab testing may reduce the confusion over diagnoses.

### Therapeutic effectiveness (health benefit from change in management)

The DCAR stated that studies assessing treatments that are likely to be used in the Australian setting were included. Assessment of treatments in NMOSD patients were made using comparisons of early versus late treatment, NMOSD specific treatment versus MS treatment, treatment versus standard immunosuppressant treatment (intravenous methylprednisolone (IVMP) or glucocorticoids alone), or treatment versus placebo.

The DCAR stated that early PLEX treatment resulted in a greater chance of complete improvement, while early AZA treatment led to a longer remission time when compared to delayed treatment. Early IVMP treatment in NMOSD patients with ON resulted in better visual outcomes compared to late treatment. Delay of treatment in all three studies assessing ON treatments led to worse visual outcomes. In the study of NMOSD patients with ON, delay of treatment beyond as little as 4 days after an ON attack led to worse visual outcomes[[5]](#footnote-5).

The DCAR considered that early treatment (PLEX, AZA or IVMP) for NMOSD patients resulted in better treatment effectiveness when compared to late treatment. Although there was a strong to very strong association between early treatment and better outcomes, confidence was reduced by the risk of bias in the retrospective observational study designs and the outcome certainty was moderate when assessed by GRADE. (GRADE: ⨁⨁⨁⨀ MODERATE)

The DCAR considered that therapies for NMOSD (PLEX, RTX, AZA and ECZ) were more effective overall than placebo, standard immunosuppressant therapy (IVMP, glucocorticoids) alone or MS treatment (interferon beta), when assessed by change in expanded disability status scale (EDSS) and annualised relapse rate (ARR). The association between better EDSS and ARR outcomes and NMOSD treatment, compared to interferon beta, was strong and there was moderate certainty in this outcome when assessed by GRADE. One exception to this trend was evidence from a randomised controlled trial (RCT) comparing ECZ treatment to placebo. The study found a very strong association for an improved ARR in ECZ treated patients, but a lower level of association between ECZ and EDSS at follow-up. Change in EDSS, rather than EDSS at follow-up may have detected a difference between groups, as there was improvement in patients given ECZ and placebo in the trial. (GRADE: ⨁⨁⨁⨀ MODERATE)

### Summary of findings for AQP4-Ab testing

The DCAR provided a summary of likely outcomes for tested patients with AQP4-Ab for the diagnosis of NMOSD, who have true positive, true negative, false positive and false negative test results, can be seen in Table 5.

**Table 5 Summary of findings for the linked evidence of AQP4-Ab testing for patients who are suspected of NMOSD**

| Outcomes | Comments |
| --- | --- |
| True positives | Patients are likely to benefit from earlier diagnosis and treatment. Earlier treatment can be effective in reducing disability and relapse rate. There is a risk of serious side effects from treatments. |
| True negatives | Patients are likely to undergo further testing to correctly classify their inflammatory demyelinating disease. |
| False positives | Unlikely to be recognised in a clinical setting. If a false positive result is suspected (for example in a control test) a retest could be considered. |
| False negatives | Patients are likely to be treated as though they are suspected of NMOSD. Effective treatment may be delayed as a diagnosis may not be definitive until further symptoms occur. Delayed treatment may result in worse health outcomes. Alternatively patients may be treated as though they have MS and receive ineffective treatment. |

AQP4-Ab = aquaporin 4 antibodies; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder

Source: Table 4, pp26-27 of the DCAR

## Antibody status in the NMOSD population

The DCAR stated that data provided from Australian laboratories on AQP4 and MOG antibody tests performed did not permit the calculation of the proportion of AQP4-Ab positive and negative, or MOG-Ab positive and negative NMOSD cases. Table 6 provides estimated proportions, based on a single European (Caucasian) study identified that reported AQP4-Ab and MOG-Ab yield in 74 adult NMOSD patients (Drulovic et al. 2019[[6]](#footnote-6)). For comparison, Table 6 also provides the range of proportions in adults with NMO or NMOSD reported in studies from around the world in italics. Data for MS and other CNS conditions are not available.

**Table 6 Estimated proportions of AQP4 and MOG positive and negative adults with demyelinating CNS disorders**

| **CNS Condition** | **AQP4 +ve****MOG -ve** | **AQP4 -ve****MOG +ve** | **AQP4 -ve****MOG -ve** | **AQP4 +ve****MOG +ve** |
| --- | --- | --- | --- | --- |
| NMOSD* Data from single European study of 74 adults
* *Range from global studies*
 | 89.2% of totala*40.9%-89.2% of total* | 28.6% of AQP4 –ve (2.7% of total)a*0%-29% of AQP4 –ve cases* | 71.4% of AQP4 –ve (6.8% of total)a*71%-100% of AQP4 –ve cases* | 0%b*0%Rare cases reported* |
| MS | Approx 0% | Approx 0% | Approx 0% | Approx 0% |
| Neither NMOSD or MS | Approx 0% | Cases are likely but no data available | Cases are likely but no data available | Approx 0% |

AQP4 = aquaporin 4 antibodies; MOG = myelin oligodendrocyte glycoprotein antibodies; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder

a Based on data from Drulovic et al, 2019 (Drulovic et al. 2019)

b Cases are documented but rare

Source: Table 5, p27 of the DCAR

Table 7 and Table 8 present a summary of the balance of benefits and harms for the critical outcomes assessing AQP4-Ab and MOG-Ab testing for NMOSD diagnosis.

**Table 7 Summary of findings of the relevant critical patient outcomes for change in management with AQP4-Ab testing, relative to no testing**

| **Outcome** | **K studies****N participants** | **Relative effect(95% CI)** | **Certainty** | **Comments** |
| --- | --- | --- | --- | --- |
| Time to diagnosis (months; mean follow-up 9.2 y) | K=1 observational studyN=252  | P<0.001 (log rank test) | ⨁⨁⨁⨀MODERATEa | There was a statistically significant difference in time to diagnosis between those diagnosed based on the 2015 criteria (which has stronger emphasis on testing) (11 months) compared those diagnosed by the 2006 criteria (53 months). The effect was very large, and there is moderate confidence that the effect is true. |
| Number of NMOSD diagnoses based on 2015 compared with 2006 criteria | K=2 observational studiesN=1418 | OR range 1.76 to 2.48  | ⨁⨁⨀⨀LOWa | The odds of receiving a NMOSD diagnosis based on the 2015 IPND criteria were higher than when diagnosed with the 2006 criteria. The 2015 criteria emphasise AQP4-Ab testing for diagnosis whereas the 2006 criteria do not. The effect was large but due to risk of bias, there is low confidence that this is the true effect. |

AQP4-Ab = aquaporin 4 antibodies; CI = confidence interval; NMOSD = neuromyelitis optica spectrum disorders; OR = odds ratio

**Explanations**

a. Retrospective study design at risk of selection bias

**GRADE Working Group grades of evidence (Guyatt et al., 2013)**⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⨁⨁⨁⨀ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⨁⨁⨀⨀ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⨁⨀⨀⨀ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: Table 68, p122 of DCAR

**Table 8 Summary of findings table for relevant critical patient outcomes on the impact of change in management due to AQP4-Ab testing for NMSDO**

| **Outcome** | **K studies****N participants** | **Relative effect****(95% CI)** | **Absolute effect****(95% CI)** | **Certainty** | **Comments** |
| --- | --- | --- | --- | --- | --- |
| **Early treatment compared to late treatment for NMOSD patients** |
| Probability of complete improvement (PLEX received day 0-1 or after day 20) | K=1 observational studyN=60 | P=0.02 | NA | ⨁⨁⨀⨀LOW  | The probability of complete improvement was much higher in the group treated early (50%) compared with those treated late (5%). There was a strong association between early treatment and better outcome. Due to risk of bias, there is low confidence in the effect. |
| Time to next relapse on AZA (months) | K=1 observational studyN=38 | p=0.025 | NA | ⨁⨁⨀⨀LOW  | The time to next relapse on AZA was nearly twice as long in the late (32.74 months) compared to the early treated group (17.17 months). There was a strong association between early treatment and better outcome. Due to risk of bias, there is low confidence in the effect. |
| Duration of remission on AZA (<7 days or >7 days) | K=1 observational studyN=38 | HR 0.250 (0.072, 0.867)P=0.029 | NA | ⨁⨁⨀⨀LOW  | The duration of remission for those who received AZA <7 days from attack was longer compared to those who received AZA >7 days from attack. There was a strong association between early treatment and better outcome. Due to risk of bias, there is low confidence in the effect. |
| Failure to regain 20/30 vision on IVMP (<7 days or >7 days) | K=1 observational studyN=36 | OR 10.0 (1.39, 71.86)p=0.01 | NA | ⨁⨁⨁⨀MODERATE  | The odds of failing to regain 20/30 vision for NMOSD patients with ON were much higher in those who received IVMP >7 days from attack compared to <7 days from attack. There was a very strong association between early treatment and better visual outcome. There is moderate confidence that the effect is true. |
| Likelihood of failure to regain 20/20 vision on IVMP (<4 days or >4 days) | K=1 observational studyN=36 | OR 8.33 (1.47, 47.22)p=0.01 | NA | ⨁⨁⨁⨀MODERATE  | The likelihood of failing to regain 20/20 vision for NMOSD patients with ON was much higher in those who received IVMP >4 days from attack compared to <4 days from attack. There was a very strong association between early treatment and better visual outcome. There is moderate confidence that the effect is true. |
| Impact of early diagnosis on disability in patients on any treatment (EDSS) | K=1 observational studyN=182 | NA | (0.02, 0.15)P=0.006 | ⨁⨁⨀⨀LOW | There was less disability at follow-up in patients with early diagnosis compared with late diagnosis when measured with EDSS. There was a strong association between early diagnosis and better outcome. Due to risk of bias, there is low confidence in the effect. |
| **NMSDO specific treatment compared to MS treatments for NMOSD patients** |
| Likelihood of attack (RTX or interferon beta) | K=1 observational studyN=95 | HR 0.6 (0.4, 1)p=0.034 | NA | ⨁⨁⨀⨀LOW  | The likelihood of attack was lower in NMOSD patients who received RTX compared to those who received standard MS treatment (interferon beta). There was a strong association between RTX therapy and better outcome. Due to risk of bias, there is low confidence in the effect.  |
| Likelihood of attack (AZA or interferon beta) | K=1 observational studyN=76 | HR 0.4 (0.3, 0.7)p=0.001 | NA | ⨁⨁⨀⨀LOW  | The likelihood of attack was lower in NMOSD patients who received AZA compared to those who received standard MS treatment (interferon beta). There was a strong association between RTX therapy and better outcome. Due to risk of bias, there is low confidence in the effect. |
| **Effectiveness of treatment on NMOSD patients** |
| PLEX compared with no PLEX (change in EDSS) | K=1 observational studyN=96 | NA | P<0.01 | ⨁⨁⨀⨀LOW  | NMOSD patients who received PLEX had less deterioration (measured by change in EDSS; 1.22±1.6) than those who received standard therapies alone (2.6±2.4). There was a strong association between PLEX therapy and better outcome. Due to risk of bias, there is low confidence in the effect.  |
| RTX compared with no RTX (weighted mean difference in EDSS) | K=1 SR (22 observational studies)N=NR | NA | -1.16 (1.36, 0.96)p<0.0001 | ⨁⨁⨁⨀MODERATE  | NMOSD patients who received RTX had a better improvement (measured by weighted mean difference in EDSS) than those who received standard therapies alone. There was a strong association between RTX therapy and better outcome, and moderate confidence that this is the true effect. |
| RTX compared with no RTX (weighted mean difference in ARR) | K=1 SR (18 observational studies)N=NR | NA | -1.56 (-1.82, -1.29)P=0.000 | ⨁⨁⨁⨀MODERATE  | NMOSD patients who received RTX had a better improvement (measured by weighted mean difference in ARR) than those who received standard therapies alone. There was a strong association between RTX therapy and better outcome, and moderate confidence that this is the true effect. |
| ECZ compared with no ECZ (EDSS at follow-up) | K=1 randomised controlled trialN=143 | HR -0.29 (-0.59, 0.01)P not significant | NA | ⨁⨁⨁⨀MODERATE | There was a reduction in EDSS in those randomised to both the ECZ and placebo (standard therapies alone) groups. There was no significant difference in the EDSS between groups at follow-up. This result was against the trend of other treatment effects. There was moderate confidence that this is the true effect |
| ECZ compared with no ECZ (ARR at follow-up) | K=1 randomised controlled trialN=143 | HR 0.04 (0.01, 0.015)P<0.001 | NA | ⨁⨁⨁⨁HIGH  | NMOSD patients who were randomised to ECZ had a better outcome (measured by ARR at follow-up) than those randomised to placebo (standard therapies alone). There was a very strong association between ECZ therapy and better outcome, and high confidence that this is the true effect |

ARR = absolute risk reduction; AZA= azathioprine**;** CI: Confidence interval; ECZ = eculizumab; EDSS = expanded disability severity score; HR = hazard ration; IVMP = intravenous methylprednisolone; NA = not available; NMOSD = neuromyelitis optica spectrum disorder; NR = not reported; OR = odds ratio; PLEX = plasma exchange; RTX = rituximab; SR = systematic review

**Explanations**

a. Retrospective study design at risk of selection bias

**GRADE Working Group grades of evidence (Guyatt et al., 2013)**⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⨁⨁⨁⨀ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⨁⨁⨀⨀ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⨁⨀⨀⨀ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: Table 69, pp123-25 of the DCAR

## Impact of repeat testing/monitoring

Due to only limited evidence provided by two studies containing small sample sizes, and of low evidence quality, no conclusion can be drawn regarding the association between the presence of AQP4-Abs and prediction of relapse.

**Clinical claim**

The Applicant did not submit a clinical claim. The DCAR 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.

On the basis of the evidence profile (summarised in Table 7 and Table 8), the DCAR suggested that, relative to diagnosis of NMOSD without AQP4-Ab testing, diagnosis of NMOSD with AQP4-Ab testing and associated treatments has non-inferior safety and superior effectiveness.

Due to limited evidence, the DCAR suggested that, diagnosis of NMOSD with MOG-Ab testing, relative to diagnosis of NMOSD without MOG-Ab testing, has uncertain safety and uncertain effectiveness.

Due to limited evidence, the DCAR suggested that retesting or monitoring of NMOSD with AQP4-AB or MOG-Ab testing, relative to retesting or monitoring of NMOSD without AQP4-Ab or MOG-Ab testing, has uncertain safety and uncertain effectiveness.

## Translation issues

A number of translation issues were identified and have been addressed by the DCAR to facilitate development of an economic model in the Australian population (Table 9):

* Applicability issues:
* The diagnostic measures associated with antibody testing for NMOSD. Australian laboratory data suggested that the diagnostic yields identified in published studies were not representative of the Australian population being tested. Therefore Australian data were used in the economic model.
* The treatment patterns and outcomes associated with identified NMOSD therapies. The evidence suggests that Australian treatment patterns were consistent with those identified in international studies.
* Extrapolation issue:
	+ What are the expected patterns of health resource use that would occur over the long-term, for both maintenance treatment and for treating repeat acute attacks? This was addressed by identifying published articles describing Australian NMOSD treatment.
* Transformation issue:
	+ The health outcomes identified in clinical trials needed to be translated into health states with specified utility values; i.e. EDSS scores mapped to a health utility index to provide health state utility values (HSUVs) in quality-adjusted life years (QALYs). Only one study directly calculated utility values of patients with MS or NMOSD in Thailand using the Thai version of EuroQoL five dimension with three levels (EQ-5D-3L) instrument. No significant difference was identified between MS and NMOSD in terms of health utility score. This study also reported HSUVs for MS and NMOSD mapped to EDSS scores. Several studies have reported that there is no significant difference in terms of health utility scores between MS and NMOSD. Therefore, HSUVs published in Australian study for MS were used for modelled health states no/mild disability and severe disability in the base-case analysis.

**Table 9 Summary of results of pre-modelling studies and their uses in the economic evaluation**

| **Section** | **Pre-modelling study** | **Results used in base case** | **Results used in sensitivity analysis** |
| --- | --- | --- | --- |
| Applicability  |  |  |  |
|  | Identifying an accurate estimate of diagnostic yield: | AQP4-Ab: 4.2%MOG-Ab: 5.3% | 2.5% – 89%2.0% – 29% |
|  | Identifying treatment patterns:Drugs used for maintenanceDrugs used for treating relapse | AZA, RTX, prednisoloneCorticosteroids, PLEX and IVIG | - |
| Extrapolation |  |  |  |
|  | Identifying the recurring health resource use for maintenance therapy: | AZA: 59%Prednisolone: 63% of AZARTX: 41% | RTX use: 60% and 80% |
|  | Identifying the health resource use for treating future attacks: | Maintenance therapy +Mild attack: IVMP (84%), PLEX (16%)Severe attack: PLEX (75%), IVMP (45%), IVIG (10%) | Same treatment (1.3 treatments/attack) for severe and mild attacks: IVMP (76%), PLEX (14%) and IVIG (10%)a |
| Transformation |  |  |  |
|  | Identifying appropriate health state utility values:Disease with no/mild disabilityDisease with moderate–severe disabilityDeath | 0.720.480 | 0.470.180 |
|  | Identifying disutility associated with relapses:Mild relapseSevere relapse | 0.070.29 | - |

a Source: (Kunchok et al. 2019)

Ab = antibody; AQP4 = aquaporin 4; ARR = annualised relapse rate; AZA = azathioprine; EDSS = expanded disability status scale; IVMP = intravenous methylprednisolone; IVIG = intravenous immunoglobulin; MOG = myelin oligodendrocyte glycoprotein; NMOSD = neuromyelitis optica spectrum disorder; PLEX = plasma exchange; RTX = rituximab

Source: Table 73, p133 of the DCAR

# Economic evaluation

The DCAR performed a cost-utility analysis (CUA) [Table 10].

The DCAR stated that based on the clinical literature, patients who test positive for AQP4‑Ab, or receive a correct diagnosis without testing, receive appropriate immunosuppressive therapy promptly. Subsequently they will have a reduced risk of relapse and associated disability. The remaining patients will initially either receive MS disease modifying treatment (which are harmful in NMOSD) or no treatment. However, it is assumed that these patients will receive ongoing medical attention, and eventually on clinical grounds, the correct diagnosis would be reached (and then correct NMOSD treatment initiated). This event (correct diagnosis and treatment initiation) is modelled to occur at the mean time to NMO/NMOSD diagnosis, based on the clinical data.

**Table 10 Summary of the economic evaluation**

| **Perspective** | Australian healthcare |
| --- | --- |
| **Comparator** | No NMOSD-antibody testing |
| **Type of economic evaluation** | Cost-effectiveness, cost-utility |
| **Sources of evidence** | Systematic review and clinical expert advice |
| **Time horizon** | Until the correct diagnosis is reached and treatment is initiated in both patient arms; 3.5 years (14 cycles) in the base case1 |
| **Outcomes** | Cost per quality-adjusted life year (QALY) |
| **Methods used to generate results** | Decision tree to initial diagnosis, then Markov models for disease pathway |
| **Health states** | Disease with no or mild disability, disease with moderate–severe disability, and death. The model also includes two temporary health states of mild and severe relapse. |
| **Cycle length** | Three months (quarterly): based on average duration of relapse |
| **Discount rate** | 5% for both costs and outcomes |
| **Software packages used** | TreeAge Pro Healthcare 2020® |

1 Time horizon is equivalent to mean time to correct NMSOD diagnosis in the longer of the two arms (long enough to capture the effects of delayed diagnosis).

NMOSD = neuromyelitis optica spectrum disorder

Source: Table 6, p29 of DCAR

The DCAR made some additional structural assumptions for the model:

* Relapses are classified according to the disease severity (mild or severe).
* Patient in health state ‘disease with moderate–severe disability cannot return to health state ‘disease with no/mild disability’, thus indicating a confirmation of disability progression following a severe relapse.
* After the nominated mean time to correct diagnosis, all diagnosed patients will be receiving correct treatment with immunosuppressive therapies, which are considered to have similar treatment efficacy, irrespective of the time on treatment. Therefore, the base case modelled time horizon is to the ‘mean time to correct NMSOD diagnosis’ in the longer of the two arms.
* Patients with no/mild disability (in remission or with mild relapse) have mortality risk similar to the general population. Patients in remission with moderate–severe disability have a mortality risk associated with disease disability. Patients with severe relapse (irrespective of disease severity) and patients with moderate–severe disability and mild relapse have mortality risk associated with the disease relapse.

The base-case analysis assumes that only AQP4-Ab testing is performed. Additional scenario analyses consider the alternative of concurrent or sequential MOG-Ab testing (see Table 12).

The economic results presented in this section are in three parts:

* A revised base case and scenario analyses (different to the DCAR) using 41.4% as the percentage of initial MS misdiagnosis in cases who would have tested seropositive as opposed to 64.8%.
* Sensitivity analyses varying the percentage of initial MS misdiagnosis in cases who would have tested seropositive to illustrate how this drives ICERs in the economic modelling.
* Original sensitivity analyses from the DCAR of other key economic drivers using the higher 64.8% of initial MS misdiagnosis. This likely overestimates the cost-savings from the proposed intervention.

Table 11 presents the overall expected costs and outcomes, and incremental costs and outcomes per patient associated with the AQP4-Ab test for NMOSD and comparator in the model, according to the base case assumptions.

**Table 11 Costs and effectiveness for base-case analysis, AQP4-Ab testing only[[7]](#footnote-7)**

| Description | Average cost per patient | QALYs | Relapses |
| --- | --- | --- | --- |
| -Ab testing for NMOSD | $1,271 | 0.1093 | 0.0818 |
| No Ab testing | $1,591 | 0.1063 | 0.1243 |
| Increment (Ab testing – No Ab testing) | –$320 | 0.0031 | –0.0426 |

Ab = antibody; AQP4 = aquaporin 4; NMOSD = neuromyelitis optica; QALY = quality-adjusted life year

Source: ESC discussion

The DCAR model estimates that AQP4-Ab testing is dominant (less costly and more effective) compared with no Ab testing.

## Scenario analyses

Table 12 summarises the result of scenario analyses performed for AQP4-Ab testing along with either concurrent or sequential MOG-Ab testing. In the pre-ESC response, the applicant highlighted that concurrent testing is supported by this analysis, and used this basis to seek a higher proposed MBS fee of $50 (compared with $43).

**Table 12 Costs and effectiveness for scenario 1 (AQP4-Ab and concurrent MOG-Ab testing) and scenario 2 (AQP4-Ab and sequential MOG-Ab testing)**

| **Description** | **Average cost per patient** | **QALYs** | **Relapses** |
| --- | --- | --- | --- |
| Scenario 1 (AQP4-Ab + concurrent MOG-Ab testing) |  |  |  |
| Concurrent Ab testing for NMOSD | $2,880 | 0.2525 | 0.1888 |
| No Ab testing | $3,675 | 0.2454 | 0.2871 |
| Increment (Ab testing – No Ab testing) | –$795 | 0.0071 | –0.0983 |
| Scenario 2 (AQP4-Ab + sequential MOG-Ab testing) a |  |  |  |
| Sequential Ab testing for NMOSD | $2,923 | 0.2525 | 0.1888 |
| No Ab testing | $3,675 | 0.2454 | 0.2871 |
| Increment (Ab testing – No Ab testing) | –$753 | 0.0071 | –0.0983 |

a Assuming all AQP4-Ab negative patients will undergo sequential MOG-Ab testing.

Ab = antibody; AQP4 = aquaporin 4; MOG = myelin oligodendrocyte glycoprotein; NMOSD = neuromyelitis optica; QALY = quality-adjusted life year

Source: ESC discussion

*Sensitivity analysis of initial MS misdiagnosis*

The proportion of MS misdiagnoses in seropositive or would have tested seropositive NMOSD cases is a key cost driver in the modelling as treatment costs are substantially higher compared to NMOSD treatment for cases initially diagnosed correctly.

Table 13 presents sensitivity analyses varying the percentage of MS misdiagnosis in seropositive cases for the base case scenario.

**Table 13 Sensitivity analysis varying rate of MS misdiagnosis for the base case scenario**

|  **% correct diagnosis, MS misdiagnosis, symptomatic treatment** | **Cost** | **QALYs** | **Relapse** | **ICER/QALY** |
| --- | --- | --- | --- | --- |
| *5.4%,* ***80%****, 14.6%* |  |  |  |  |
| Antibody testing not available | $2,229 | 0.1058 | 0.1363368 |  |
| NMOSD antibody testing available | $1,271 | 0.1093 | 0.0817687 |  |
| Increment | -$958 | 0.0036 | -0.0546 | Ab testing Dominant |
| *5.4%,* ***40%****, 54.6%* |  |  |  |  |
| Antibody testing not available | $1,568 | 0.1063 | 0.1238841 |  |
| NMOSD antibody testing available | $1,271 | 0.1093 | 0.0817687 |  |
| Increment | -$297 | 0.0030 | -0.0421 | Ab testing Dominant |
| *5.4%,* ***30%****, 64.6%* |  |  |  |  |
| Antibody testing not available | $1,403 | 0.1064 | 0.1207709 |  |
| NMOSD antibody testing available | $1,271 | 0.1093 | 0.0817687 |  |
| Increment | -$132 | 0.0029 | -0.0390 | Ab testing Dominant |
| *5.4%,* ***20%****, 74.6%* |  |  |  |  |
| Antibody testing not available | $1,238 | 0.1065 | 0.1176577 |  |
| NMOSD antibody testing available | $1,271 | 0.1093 | 0.0817687 |  |
| Increment | $34 | 0.0028 | -0.0359 | $12,022 |
| *5.4%,* ***10%****, 84.6%* |  |  |  |  |
| Antibody testing not available | $1,072 | 0.1067 | 0.1145446 |  |
| NMOSD antibody testing available | $1,271 | 0.1093 | 0.0817687 |  |
| Increment | $199 | 0.0027 | -0.0328 | $74,429 |
| *5.4%,* ***0%****, 94.6%* |  |  |  |  |
| Antibody testing not available | $907 | 0.1068 | 0.1114314 |  |
| NMOSD antibody testing available | $1,271 | 0.1093 | 0.0817687 |  |
| Increment | $364 | 0.0025 | -0.0297 | $143,000 |

Ab = antibody; AQP4 = aquaporin 4; NMOSD = neuromyelitis optica; QALY = Quality-adjusted life year

Source: ESC discussion

The evidence with regards to the percentage of MS misdiagnosis and the percentage of seropositivity in NMOSD cases has uncertainty (as noted in Table 5). The incidence of NMOSD in Australia is such that there will be high variability in the proportion of NMOSD cases initially misdiagnosed as MS in those who would have tested seropositive in the theoretical counterfactual scenario of the comparator.

The percentages of MS misdiagnosis for *all* NMOSD cases referenced in the DCAR are 41.4% and 42.5% from Beekman et al. (2019) and Jarius et al. (2012) respectively. In another retrospective study of 187 patients with NMOSD, 29.4% were initially misdiagnosed with multiple sclerosis.[[8]](#footnote-8) Both the Jarius et al. (2012) and Mealy et al. (2012) studies used the 2006 rather than 2015 diagnostic criteria for NMOSD. The Mealy et al. study was excluded from the DCAR on this basis. It is uncertain if and how this affects the percentage of initial MS misdiagnosis.

The input for the economic model is defined as the percentage of MS misdiagnosis in seropositive cases and not the percentage of MS misdiagnosis in all cases. The base case and scenario analyses do not take into account the proportion of seropositivity in NMOSD cases. Table 14 adjusts the percentage of MS misdiagnosis with the percentage of NMOSD cases that are seropositive, assuming that initial MS misdiagnoses occur equally regardless of the serostatus of those in the no test comparator arm.

**Table 14 Adjusted percentage of MS misdiagnosis in seropositive NMOSD cases**

| **Study** | **Percentage of all cases initially misdiagnosed with MS****(A)** | **Percentage of study population seropositive (B)** | **Adjusted percentage of MS misdiagnosis for seropositive cases (A x B)** |
| --- | --- | --- | --- |
| Beekman et al. (2019) | 41.4% | 61.1% - 78.7% (17.6% unknown status) | 25.3-32.6% |
| Jarius et al. (2012) | 42.5% | 78.3% | 33.3% |
| Mealy et al. (2012) | 29.7% | 78.6% | 23.3% |

MS = multiple sclerosis

Seropositive NMOSD = AQP4-Ab positive NMOSD

Interpreting Table 13 and Table 14 together suggest that the results can vary from dominant (resource saving with health benefits) to a positive ICER.

*Additional sensitivity analyses*

Results from the sensitivity analyses in the DCAR (Table 15 and Figure 5) suggests that the AQP4-Ab testing strategy remains less costly and more effective (dominant) compared with no Ab testing, for alternative model inputs or parameters assessed.

**Table 15 Key drivers of the economic model**

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Proportion of patients receiving rituximab | Values changed from 20% to 80% | Dominant across tested range. However, higher proportions of patients receiving rituximab increase the treatment costs in the intervention arm resulting in lower cost-savings. |
| Time horizon (base-case: 3.5 years, i.e. 14 quarters) | Values changed from 2 to 30 years (8 to 120 quarters) | Dominant across tested range. |

QALY = quality adjusted life-years

Source: Table 8, p30 of the DCAR



**Figure 5 Tornado sensitivity analyses diagram, base-case scenario**

AQP4-Ab = aquaporin 4 antibody; ICER= incremental cost-effectiveness ratio; IST = immunosuppressive therapy; QALY = quality-adjusted life years

Source: Figure 19, p151 of the DCAR

The DCAR noted that a number of assumptions were required to develop the model and data inputs were uncertain, particularly given the historical nature of the comparison, and that the limitations or any inaccuracies may exist in the model. The DCAR stated that, despite this, the fact that the sensitivity analyses consistently yielded dominant results (resource savings and health outcome benefits) for antibody testing for NMOSD compared with no testing, would suggest that it is unlikely that antibody testing for NMO/NMOSD would not be cost-effective in practice. These sensitivity analyses assumed a MS misdiagnosis rate in seropositive cases of 64.8%. Therefore ESC noted that, if the true rate of MS misdiagnosis is closer to the 20-35% range as per Table 14, some of these results may be cost-neutral or have a positive ICER.

In addition, the DCAR stated that there were 5% fewer relapses in patients tested for antibodies compared to the no testing group. The DCAR reasoned that the test may have facilitated rapid diagnosis and appropriate treatment. This has quality of life benefits as well as cost offsets associated with fewer treatment requirements associated with relapse/progressed disease. The savings associated with less relapse/progressed disease outweigh the additional, relatively small, cost of testing.

# Financial/budgetary impacts

The DCAR stated that NMOSD antibody (AQP4-Ab and MOG-Ab) testing is currently performed in Australia, and has been funded under MBS items 71119 or 71165 for more than 10 years. Therefore, a market-based approach was used to estimate the financial implications of a potential listing of NMOSD antibody testing on the MBS (Table 16).

The DCAR stated that market data suggested that a growth rate of 6–18% per annum has been observed in the number of AQP4-Ab tests requested in the last two to three years. The base case analysis assumes that the MBS listing of specified antibody testing for NMOSD would increase the number of patients tested for AQP4 ± MOG-Ab tests by 20% in the first year of listing (due to increased access, additional sequential MOG-Ab testing and lower patient co-payments), and then an ongoing growth rate of 15% p.a. is assumed over the next four years of listing.

**Table 16 Total costs to the MBS associated with antibody testing for NMOSD (applicant proposed fee: $50)**

| **-** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- |
| **Proposed test** |  |  |  |  |  |
| Number of services | 10,122 | 11,641 | 13,387 | 15,394 | 17,704 |
| Cost to the MBS | $428,175 | $492,401 | $566,261 | $651,200 | $748,880 |
| **MBS services offset** | **-** | **-** | **-** | **-** | **-** |
| Number of services | 9,204 | 10,125 | 11,137 | 12,251 | 13,477 |
| Cost to the MBS | $227,422 | $250,165 | $275,181 | $302,699 | $332,969 |
| **Net cost to the MBS** | **$200,753** | **$242,236** | **$291,080** | **$348,501** | **$415,911** |

NMOSD = neuromyelitis optica spectrum disorders; MBS = Medicare Benefits Schedule

The DCAR stated that the net costs to the MBS due to the proposed listing are largely driven by the expected increase in the number of current services due to the proposed listing. The growth rate in the expected number of antibody tests for NMOSD has a high impact on the financial implications. The net costs to MBS are also sensitive to the assumed proportions for which existing AQP4-Ab test services are claimed under items 71119 and 71165, due to the differences in MBS rebates associated with these items.

# Key issues from ESC for MSAC

| **ESC key issue** | **ESC advice to MSAC** |
| --- | --- |
| Matching populations in the linked evidence steps is uncertain | There is potential for decreased therapeutic effectiveness in patients with milder or more ambiguous spectrum of disease. This could be explored in a sensitivity analysis. |
| Clinical validity estimates are uncertain | There is a range of false negatives and false positives in the literature. Concordance estimates could also be used as proxy for these. |
| Consequences of false positives are uncertain | There are possible negative impacts from false positive results, in that MS-specific treatment or treatment for other conditions is delayed, but these have not been explored. |
| Economic model predicted antibody testing for NMOSD would provide health benefits (gain in quality-adjusted life years and fewer relapses) and cost savings compared with no testing, in the base case and all sensitivity analyses. | The benefits of early testing all hinge on the clinical validity claim. The sensitivity and specificity of test is currently unknown, and: the model does not include false positivesthe model assumes that any false negatives will eventually be corrected and be determined as true positives, but then the advantages of early detection are lost.the model assumes a higher percentage for initial MS misdiagnosis in seropositive cases. A lower percentage may lead to cost-neutral or ICER-positive modelling scenarios.  |
| Financial implications are moderately uncertain | The financial implications are driven by growth rates in testing and the assumptions about offset from current services. There is moderate uncertainty in both of these estimates. |

**ESC discussion**

ESC noted that this application is for a new Medicare Benefits Schedule (MBS) listing for an antibody test to investigate the presence of neuromyelitis optica spectrum disorder (NMOSD) by detecting aquaporin 4 antibodies (AQP4-Abs) in serum and/or cerebrospinal fluid (CSF). AQP4-Ab testing is currently claimed under generic MBS item numbers 71119 or 71165.

ESC noted that no public consultation feedback was received for this application, but letters were received from two specialist organisations during the PICO confirmation development stage, which supported the availability of AQP4-Ab and MOG-Ab testing on the MBS.

ESC considered the proposed MBS item descriptor to be appropriate, and that repeating testing if there is clinical inconsistency with the test result is also appropriate. ESC considered that the current MBS item descriptor appropriately does not include repeat testing for the purposes of monitoring disease activity after diagnosis is confirmed, reflecting the lack of evidence to testing for this purpose. ESC considered that repeat testing should be included in the economic model (this is not included in the current model), but agreed that these costs would likely be insignificant.

ESC noted the limited evidence on clinical validity of AQP4 or myelin oligodendrocyte glycoprotein (MOG) antibody testing, especially on the proportion of tests which are false positives. In general the diagnostic accuracy of AQP4 testing is likely to be overestimated as the clinical reference standard incorporates the AQP4 test result (incorporation bias). Despite the DCAR’s clinical assumption of no AQP4-Ab false positives (i.e. AQP4-Ab seropositivity is considered diagnostic for the condition), there were some estimates of specificity that were less than 100% reflecting that false positive results are possible. The 2015 international consensus guidelines do not directly equate AQP4-Ab seropositivity with diagnosis. ESC considered using concordance estimates as a proxy for the minimum false positive rates could also be appropriate. Although it is clinically accepted that MOG-Ab tests may be positive in conditions other than NMOSD, the lack of a clinical reference standard for MOG-Ab testing meant there was no evidence on diagnostic accuracy. Including MOG-Ab in the diagnostic test pathway, and allowing repeat testing of AQP4, would tend to both increase clinical sensitivity (and decrease the false negative rate), and decrease specificity (and increase the false positive rate). False negative results could cause misdiagnosis with MS and other conditions and could result in delayed diagnosis and treatment of NMOSD as well as a patient incorrectly receiving potentially harmful MS treatments. Conversely, false positive results could cause misdiagnosis with NMOSD and cause delayed diagnosis and treatment of multiple sclerosis (MS) and other conditions, but this possibility was not considered in the DCAR.

ESC noted that the linked evidence approach taken in the DCAR assumed the same spectrum of disease in trials/studies used to estimate therapeutic effectiveness applies to Australian clinical population. However the low rates of AQP4-Ab positivity from the Australian clinical pathology laboratory data suggests broader testing in the Australian clinical population. The potentially broader spectrum of disease which includes milder cases and more ambiguous cases, could mean that the therapeutic effectiveness in the Australian clinical population is lower than that assumed in the DCAR economic model.

ESC noted the decision tree for Markov modelling only follows patients who would have tested positive or do test positive. The antibody negative arms for both testing and no testing are considered to ‘cancel’ each other from ICER calculations. ESC agreed with the assumption that the patients who test negative for AQP4-Ab/MOG-Ab face a similar diagnostic challenge and ongoing management of disease pathways irrespective of the modelled arm. However, false negatives are not explicitly modelled, and ESC therefore considered that the downstream costs and health outcomes of these patients would be equal across the two arms, which would offset each other when estimating incremental cost-effectiveness. The model also assumes that any false negatives will eventually be corrected with repeat testing as disease progresses, but this means the benefits of early detection are lost. ESC noted that the model also assumes that all positive results will be treated appropriately. These assumptions all lead to uncertainty in the modelling.

ESC noted that the economic modelling is dominant, but additional sensitivity analyses suggest a positive ICER is possible. A key driver of costs in the model is the proportion specified for initial misdiagnosis with MS for those who would have tested seropositive.

ESC noted that the net cost to the MBS is sensitive to repeat testing and monitoring, and increasing use from year 1 to 5, making the financial impacts uncertain.

# Other significant factors

Nil.

# Applicant comments on MSAC’s Public Summary Document

The Applicant had no comment.

# Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](http://www.msac.gov.au/)

1. PCC-Immunology 2018, Report from the Pathology-Clinical-Committee-Immunology, Medicare Benefits Schedule Review Taskforce, Department of Health, Commonwealth of Australia, Canberra, Australia. [↑](#footnote-ref-1)
2. Wingerchuk, DM, Banwell, B, Bennett, JL, Cabre, P, Carroll, WM, Chitnis, T, de Seze, J, Fujihara, K, Greenberg, BM, Jacob, A, Jarius, S, Lana-Peixoto, M, Levy, M, Simon, JH, Tenembaum, S, Traboulsee, AL, Waters, P, Wellik, KE & Weinshenker, BG 2015, 'International consensus diagnostic criteria for neuromyelitis optica spectrum disorders', Neurology, vol. 85, no. 2, pp. 177-189. [↑](#footnote-ref-2)
3. Gao, F, Chai, B, Gu, C, Wu, R, Dong, T, Yao, Y & Zhang, Y 2019, 'Effectiveness of rituximab in neuromyelitis optica: a meta-analysis', BMC Neurol, vol. 19, no. 1, Mar 6, pp. 1-7. [↑](#footnote-ref-3)
4. Pittock, S, Berthele, A, Fujihara, K, Kim, HJ, Levy, M, Palace, J, Nakashima, I, Terzi, M, Totolyan, N, Viswanathan, S, Wang, K-C, Pace, A, Fujita, KP, Armstrong, R & Wingerchuk, DM 2019, 'Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder', New England Journal of Medicine, vol. 381, no. 7, pp. 614-625. [↑](#footnote-ref-4)
5. These results could be considered in light of the results of the ONTT, in which patients with ON were randomised within 8 days of symptom occurrence to oral [prednisone](https://www.uptodate.com/contents/prednisone-drug-information?topicRef=5252&source=see_link) (1 mg/kg per day) for 14 days with a four-day taper, intravenous [methylprednisolone](https://www.uptodate.com/contents/methylprednisolone-drug-information?topicRef=5252&source=see_link) (250 mg four times per day for three days) followed by oral prednisone (1 mg/kg per day) for 11 days with a four-day taper, or oral placebo for 14 days. The primary visual outcomes were visual acuity and contrast sensitivity. A summary of results can be found at: <https://www.uptodate.com/contents/optic-neuritis-prognosis-and-treatment> [↑](#footnote-ref-5)
6. Drulovic, J, Martinovic, V, Basuroski, ID, Mesaros, S, Mader, S, Weinshenker, B & Pekmezovic, T 2019, 'Long-term outcome and prognosis in patients with neuromyelitis optica spectrum disorder from Serbia', Multiple Sclerosis and Related Disorders, vol. 36. [↑](#footnote-ref-6)
7. This table is different to table 7 on page 30 of the DCAR. The proportion of MS misdiagnoses was adjusted from 64.8% to 41.4% to reflect rate of MS misdiagnosis rather than overall misdiagnosis. The overall misdiagnosis number includes misdiagnosis with optic neuritis, the costs of which is better approximated with symptomatic treatment rather than misdiagnosis with MS. [↑](#footnote-ref-7)
8. Mealy MA, Wingerchuk DM, Greenberg BM, Levy M. Epidemiology of neuromyelitis optica in the United States: a multicenter analysis. *Arch Neurol*. 2012;69(9):1176-1180. doi:10.1001/archneurol.2012.314 [↑](#footnote-ref-8)