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|  | Antibody testing for neuromyelitis optica spectrum disorder |
|  |  |
|  | May 2020 |
|  |  |
|  | MSAC application no. 1582  Department Contracted Assessment Report |

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Enquiries about the content of the report should be emailed to [hta@health.gov.au](mailto:hta@health.gov.au).

The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

**MSAC’s advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.**

This report was prepared by Joanne Milverton, Ruchi Mittal, Susan Bellman, Jaqueline Parsons, and Camille Schubert from Adelaide Health Technology Assessment (AHTA). The report was commissioned by the Australian Government Department of Health.

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| Main issues for MSAC consideration |
| --- |
| * *Clinical validity of AQP4 or MOG antibody testing could not be established from the evidence, however as testing is already performed in clinical practice, a satisfactory clinical validity was assumed, and further steps of linked evidence were assessed* * *Patients with NMOSD have worse outcomes than some other demyelinating CNS disorders, and benefit from earlier treatment. AQP4-Ab testing was found to enable earlier diagnosis of NMOSD, and was therefore likely to lead to earlier treatment, in a subset of patients. It was not possible to determine the benefits of MOG-Ab testing from evidence in the literature.* * *The presence of MOG-Abs is not specific to NMOSD, although there is some evidence that patients who are suspected of NMOSD, and who are MOG-Ab positive, may have a worse prognosis than those who are MOG-Ab negative. In extremely rare cases, patients have been found to be positive for AQP4-Ab and MOG-Ab, but the clinical significance of their serostatus is unknown.* * *A delay in correct diagnosis or treatment for NMOSD patients can result in a reduction in quality of life and increased morbidity. In the absence of AQP4-Ab, and therefore non-NMOSD diagnosis, the patient may be misdiagnosed with MS, or treated for symptoms alone. Those who are assumed to have MS, but have true NMOSD will not respond to MS treatment. In NMOSD patients with ON, a delay of days in receiving correct treatment may have severe consequences for patient vision.* * *The economic model (cost-utility analysis) predicted NMOSD-Ab testing 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. This is due to the test facilitating rapid diagnosis and appropriate treatment, reducing relapse and progressed disease, with quality of life benefits, and also cost offsets associated with fewer treatment requirements associated with relapse/progressed disease.* * *NMOSD-Ab testing is currently performed in Australia and claimed under MBS items 71119 and 71165. Net costs to the MBS due to the proposed listing are largely driven by the increase in the number of current services due to proposed listing. Growth rate in the expected number of NMOSD-Ab tests have high impact on the financial implications. Net costs to MBS are also sensitive to the assumption of proportionate claim of services for 71119 and 71165 due to the differences in MBS rebates associated with these items.* |

## Antibody testing for Neuromyelitis Optica Spectrum Disorders

This Departmental contracted assessment report (DCAR) examines the evidence to the support listing of aquaporin 4 antibody (AQP4-Ab) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab) testing on the Medicare Benefits Schedule (MBS). The service would be exclusively used for as a ‘rule-in’ test for the diagnosis of neuromyelitis optica spectrum disorders (NMOSD) and management of those previously diagnosed with NMOSD. Despite considerable overlap in clinical features between NMOSD and other autoimmune disorders of the central nervous system (CNS), including multiple sclerosis (MS), presence of AQP4 and MOG antibodies allows early diagnosis and treatment of NMOSD. Absence of AQP4 or MOG antibodies does not rule out an NMOSD diagnosis, but makes it less likely, as additional clinical features would be required before a clinical diagnosis of NMOSD could be given without antibodies being detected. The target population is people with characteristics of NMOSD or patients diagnosed with MS but who have responded poorly to treatment (and therefore a differential diagnosis of NMOSD is possible).

The Pathology Clinical Committee – Immunology (PCC-Immunology) of the MBS review taskforce claims that the successful listing of AQP4-Ab testing in the target population and setting will lead to more rapid diagnosis and treatment, which will ultimately improve patient outcomes (PCC-Immunology 2018). AQP4-Ab testing is currently performed and rebated under a generic item number. Additionally, clinical input has advised that for those testing negative for AQP4-Ab, MOG-Ab should also be performed. Presence of MOG antibodies can provide a definitive NMOSD diagnosis in AQP4-Ab negative patients suspected of having the disease, thereby reducing the number of patients waiting on the development of further symptoms to provide a clear disease pathway.

Alignment with agreed PICO Confirmation

This contracted assessment of AQP4-Ab and MOG-Ab testing addresses most of the PPICO[[1]](#footnote-1) elements that were pre-specified in the PICO Confirmation that was ratified by the PICO Advisory Subcommittee (PASC). Issues preventing complete alignment with the PPICO elements were related to the comparator and clinical reference standard. Also due to a lack of relevant evidence in the published literature, not all questions regarding testing of MOG-Abs for NMOSD or monitoring with either AQP4-Ab or MOG-Ab could be fully addressed.

The main comparator for the clinical component of this assessment is no antibody testing for NMOSD. In current clinical practice (according to clinical input) in the absence of AQP4-Ab and MOG-Ab testing, diagnosis would be made by a neurologist based on clinical characteristics, including those found on magnetic resonance imaging (MRI). Following clinical input, the comparator (reference standard) chosen for assessing the clinical validity was diagnosis of NMOSD based on the 2015 International Panel for Neuromyelitis optica (NMO) Diagnosis (IPND) (Appendix F).

Studies comparing diagnosis by AQP4-Ab and MOG-Ab testing with the 2015 IPND criteria are inherently flawed. They are at high risk of incorporation bias because the decision based on the comparator (2015 IPND criteria) also partially incorporates the results of the index test (AQP4-Ab testing). In this case, when AQP4-Ab testing is common to both the comparator and the index test there can be an over-estimate of the accuracy of the index test (Roever 2016).

Due to the unreliability of the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of AQP4-Ab and MOG-Ab testing in data presented from the clinical setting, a prognostic evidence section was included (Section B4.2) in the report

The financial implications of a new MBS item for AQP4-Ab and/or MOG-Ab testing has been compared against what is done currently, i.e. AQP4-Ab testing performed using MBS item 71119 or 71165 (Table 15, Section A5).

Proposed Medical Service

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 or MOG is a diagnostic criterion for NMOSD. Their presence allows an early diagnosis of either AQP4-Ab NMOSD or MOG-Ab NMOSD, as distinct from MS, and enables a differential diagnosis of MOG-Ab NMOSD, in those patients who present with clinical symptoms consistent with NMOSD, but who test negative for AQP4-Abs. This is important as the natural history of untreated NMOSD is significantly worse than that of MS, and some treatments used for MS are ineffective in the treatment for NMOSD, with some evidence suggesting they may worsen the disease outcome of individuals with NMOSD. For those patients suspected of having NMOSD, but test negative for AQP4 or MOG antibodies, their management will depend on whether the clinician determines that they are likely to still have NMOSD, or are more likely to have a non-progressive neurological condition (for example non-relapsing ON) or an alternative progressive condition such as MS. Those who are assumed to have MS but truly have NMOSD will not respond to MS treatment, and are likely to develop further clinical features of NMOSD and therefore be clinically diagnosed as having antibody-negative NMOSD after a delay.

The PCC-Immunology recognised that although AQP4-Ab testing has been in clinical practice for approximately 10 years, currently the test is not included as a specific item on the MBS. It is claimed under a MBS generic item number (71119 or 71165) that is funded at a lower level. The PCC-Immunology recommended that a new item number be created so that the fee more appropriately reflects what providers currently bill for the test. Also, as previously mentioned, clinical input has advised that for those testing negative for AQP4-Ab, MOG-Ab testing should also be performed, and therefore the new item number should also incorporate the MOG-Ab testing option.

Proposal for Public Funding

The proposed new item descriptor for AQP4-Ab testing is given in Table 1. The item descriptor was proposed by the PCC-Immunology as part of the MBS Review process. It permits both cerebrospinal fluid (CSF) and serum testing. The proposed item descriptor was presented to PASC along with the PICO Confirmation associated with this assessment (DCAR 1582). PASC updated the proposed descriptor to include specific symptoms that are indicative of NMOSD.

Table 1 Proposed MBS item descriptor for antibody testing to diagnose or monitor NMOSD

| **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:   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. Patient 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 period  Fee: $43.00 Benefit: 75% = $32.20 85% = $36.50 |

AQP4 = aquaporin-4; NMOSD = neuromyelitis optica spectrum disorders

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

Population

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 disease specific for NMOSD, as ON and myelitis also commonly occur in typical MS. The presence of AQP4-Abs supports the differential diagnosis of NMOSD from MS and other autoimmune disorders of the CNS. Although an accurate proportion of AQP4-Ab positive to negative cases of NMOSD in Australia has been difficult to determine, recent studies suggest that as many as 90% of patients with NMOSD are AQP4-Ab positive in this country (Bukhari et al. 2020; Bukhari et al. 2017).

Recent Australian data collected from clinical pathology laboratories suggest that the diagnostic yield of AQP4-Ab seropositivity is between 2.9% and 5.4%. Data from Pathology Queensland indicated that there were 51 AQP4-Ab positive patients identified form 1,596 tested over 5 years (2.9%), while PathWest identified 13 AQP4-Ab positive patients from 240 tested in 2019 (5.4%). In comparison to data found in the literature, the yield in Australia is low, and reflects that a relatively broad population undergoes testing in this country. Amongst those found negative for AQP4-Ab there are likely to be patients with a range of neurological diseases, including NMOSD and MS.

PathWest Laboratory also provided data on MOG-Ab testing. Of 132 patients tested for MOG-Ab in 2019, 21 were found positive (15.9%). However is it not known what proportion of those tested were suspected of NMSOD.

Those with suspected NMOSD who have neither AQP4 or MOG antibodies may have a delay in their clinical diagnosis of NMOSD, or may be misdiagnosed as having MS or another CNS disorder in the interim (until they develop further clinical features which allows diagnosis).

The 2015 NMOSD diagnostic criteria has assigned individuals with MOG-Abs to the NMOSD.

The NMOSD term more broadly encompasses a number of very closely related conditions, and in 2015 the IPND 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.

Treatment for NMOSD is different from MS treatment, which if used can worsen the disease outcome of NMOSD patients.

NMOSD is a rare disease in comparison to MS in Australia. MS was estimated to affect 25,600 people in 2017 and have a prevalence of 103.7/100,000 (MS Australia 2019). Published data suggests that NMO or NMOSD make up approximately 3.7% of all demyelinating CNS disease in Western Australia, although because the study predated the inclusion of AQP4 testing in diagnostic criteria it is likely to be inaccurate (Wu et al. 2008). Patient numbers (clinical expert advice) indicated the prevalence of NMOSD to be between 500 and 600 patients in total in Australia (indicating a prevalence of 2-2.3 per 100,000). This is higher than that estimated by two Australian studies (section B4.1) with a prevalence of NMOSD of between 0.70 and 1.9 per 100,000 patients. The crude NMOSD incidence was estimated to be 0.37 per million per year.

Comparator Details

Following clinical input, the comparator chosen for assessing the clinical validity was diagnosis of NMOSD based on the 2015 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 IPND diagnostic criteria for NMOSD is contained in Appendix F.

The financial implications of a new MBS item for AQP4-Ab and/or MOG-Ab testing have been considered against current practice, i.e. AQP4-Ab testing rebated under MBS item 71165 or 71119.

Clinical management algorithm(s)

The clinical algorithm for historical management can be seen in Figure 4, and for current management in Figure 5 and Figure 6.

The AQP4-Ab and MOG-Ab tests are proposed for use in diagnosing AQP4-Ab NMOSD and MOG-Ab NMOSD. 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.

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 5; Section A6) 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).

* concurrent serum AQP4-Ab and MOG-Ab testing (Figure 6; Section A6)

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.

Key Differences in the Delivery of the Proposed Medical Service and the Main Comparator

The main difference between the proposed medical service (diagnosis by AQP4-Ab and MOG-Ab testing) and comparator (historical NMOSD diagnosis) is AQP4-Ab and MOG-Ab testing. According to the current international clinical recommendations (Wingerchuk et al. 2015), antibody testing should be included in the diagnostic pathway for NMOSD. Historically, diagnosis was based on clinical characteristics alone, and required sufficient development of symptoms to make a definitive NMOSD diagnosis. Testing for AQP4 and MOG-Abs would allow faster time to diagnosis in the current scenario, ameliorating the severity of symptoms with appropriate treatments. In a historical scenario, NMOSD patients are likely to have been treated as though they had a diagnosis of non-classical MS. Evidence in the published literature shows that some MS treatments are not effective and may even be damaging in NMOSD patients. It is therefore thought to be preferential that a differential diagnosis be made as early as possible for these patients.

Clinical Claim

The Applicant (the Royal College of Pathologists Australasia, RCPA) has not submitted a clinical claim. 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.

Approach Taken to the Evidence Assessment

The medical literature was searched on 23rd October 2019 to identify relevant studies and systematic reviews published during the period from the inception of the literature database to the date of the search. Searches were conducted of the literature databases described in Appendix B. Attempts were also made to source unpublished or grey literature. Samples of other sources searched, including clinical trial registries, specialty websites and Health Technology Assessment (HTA) organisations, are also provided in Appendix B. Search terms used for the PubMed biomedical bibliographic citation database are described in Table 13, Section B1.1. A summary of the PPICO criteria can be found in Section A9.

Selection of studies was conducted by two reviewers, with duplicate reviewing performed on a random sample (10%). Studies were excluded if they did not meet the PPICO criteria, such as if the patients were not suspected of having NMOSD, the article did not address pre-specified outcomes, or it provided inadequate data. Studies performed on animals, and articles written in languages other than English were also excluded, unless the English written abstract indicated the article was of higher level evidence, in which case it was included for further consideration. Study profiles of each included study are provided in Appendix C.

Included studies were assessed for quality using an appraisal tool appropriate to the study design. The GRADE of the evidence was determined by appraising the risk of bias within individual studies; appraising the precision, size of effect and clinical importance of the results reported in the evidence base as they related to the pre-specified primary outcomes; rating the overall quality of the evidence per outcome, across studies; and integrating this evidence (across outcomes) for conclusions about the net benefit of AQP4-Ab and MOG-Ab testing in the context of Australian clinical practice.

Due to the absence of direct evidence, a linked evidence approach was taken.

Characteristics of the Evidence Base

Table 2 provides a summary of the key studies that were included in the systematic review. 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). The majority of studies were of moderate to high risk of bias, primarily due to their retrospective observational designs. Characteristics of all included studies are displayed in Appendix C. An additional two studies that were provided by the Department of Health in relation to this Application were included in Appendix H. These articles provide evidence specifically comparing cell-based assay detection methods for AQP4-Abs. These, however, were not counted as part of the analytical validity studies.

Table Features of the key studies included in the linked evidence

|  |  |  |
| --- | --- | --- |
| **Type of Evidence** | **Description** | **Number** |
| Diagnostic performance (Analytical validity) (Section B3) | 🡪 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=2  n=138 |
| Clinical validity  (Section B4) | 🡪 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=23  n=5,756 |
| Clinical Utility (Therapeutic efficacy) (Section B5) | 🡪 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 RCT, cohorts and case series. 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=22  n=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

### Results

#### Safety

The literature search did not identify any studies that directly assessed the safety of AQP4-Ab and MOG-Ab testing in those suspected of NMOSD. The safety (adverse events) associated with NMOSD treatments relevant to the Australian setting are discussed in association with management changes (Section B5.2.4 Safety).

##### Test adverse events

Testing performed on a blood sample is unlikely to result in any 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 samples collected from prior diagnostic investigations such as OCB, which require CSF samples. Therefore, there are not expected to be adverse events as a result of CSF sampling.

##### Adverse events from change in management

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) Of the six primary studies, only one randomised patients to a treatment (eculizumab, ECZ) or placebo, (Pittock et al. 2019)and the others were single armed 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).

Serious adverse event rates were found to range from 0.8 to 13.8% across treatments, ECZ having the highest and RTZ having the lowest serious adverse events rate. 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.

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.

#### Effectiveness

##### Direct effectiveness

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

#### Effectiveness from linked evidence

##### Diagnostic performance

There is no reference standard for diagnostic accuracy for detecting AQP4-Abs in patients suspected of NMOSD. It was understood from the literature, (Prain et al. 2019; Waters et al. 2012) 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 we are able to say whether cell-based assays agree with each other, but not if they are able to give an accurate detection of AQP4-Abs.

Results of the concordance analysis (Table 3), 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 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 3 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

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 PPA for serum and CSF was 100% and 68%, respectively. The NPA was the same for both serum and CSF (100%). Figure 1 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.

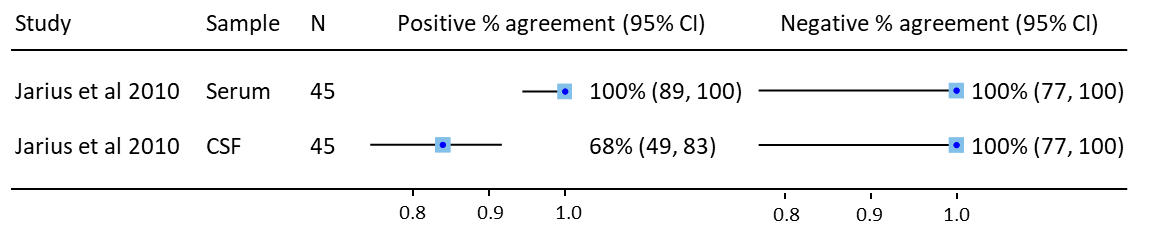


Figure Concordance between assay samples using seruma versus cerebrospinal fluid

CSF = cerebrospinal fluid

a fixed cell-based assay used

##### Clinical validity

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 by clinicians that AQP4-Ab positive is definitive for a diagnosis of NMOSD, therefore making it difficult to determine false positive cases.

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.

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.

This 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

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, when testing was not as strongly emphasised. The association between 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.

###### Therapeutic efficacy (change in management)

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.

Further evidence showed that more patients suspected of NMOSD are diagnosed by the 2015 IPND criteria than by the 2006 criteria (OR [95% 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 of AQP4-Ab testing. Under the 2006 criteria, patients may wait longer for a definitive NMOSD diagnosis because it is likely to require the occurrence of additional clinical features.

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 ⨁⨁⨀⨀)

There was no evidence to determine if MOG-Ab testing impacted on the time to diagnosis for patients suspected of NMOSD.

There were two cross-sectional studies reporting change in management 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 correct diagnosis (0 to 40 years; mean 3.3 ± 6.3 years), and 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)

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.

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[[2]](#footnote-2).

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)

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

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 4.

Table 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

#### Antibody status in the NMOSD population

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 5 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) (see also Section B4.1.5, Table 22). For comparison, the range of proportions in adults with NMO or NMOSD reported in studies from around the world is given in italics in Table 5 (for more detail see Table 22). Data for MS and other CNS conditions is not available.

Table 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

A summary of the balance of benefits and harms for the critical outcomes assessing AQP4-Ab and MOG-Ab testing for NMOSD diagnosis can be seen in Table 68 and Table 69.

#### 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.

On the basis of the evidence profile (summarised in Table 68 and Table 69), **it is suggested that, relative to diagnosis of NMOSD without AQP4-Ab testing, diagnosis with testing and associated treatments has non-inferior safety and superior effectiveness.**

Due to limited evidence**, it is 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**, it is 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 to facilitate development of an economic model in the Australian population.

The applicability issues associated with the clinical evidence identified in the systematic review related to:

1. The diagnostic measures associated with NMOSD-Ab testing. Australian laboratory data suggested that the diagnostic yields identified in published studies were not representative of the Australian population being tested, therefore Australian data will be used in the economic model.
2. The treatment patterns and outcomes associated with identified NMOSD therapies. . However, additional published literature did suggest that Australian treatment patterns were consistent with those already identified.

An extrapolation issue identified was; 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.

Finally, to enable a cost-utility model, there was a transformation issue, as 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 (HSUV) 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 are used for modelled health states no/mild disability and severe disability in the base-case analysis.

### Economic Evaluation

The clinical evaluation suggested that, relative to the no antibody testing, the AQP4-Ab testing has non-inferior safety and superior effectiveness. Therefore a cost-utility analysis was performed for the economic evaluation.

A summary of the key characteristics of the economic evaluation is given in Table 6.

Table Summary of the economic evaluation

|  |  |
| --- | --- |
| **Perspective** | Australian healthcare |
| **Comparator** | No NMOSD-antibody testing |
| **Type of economic evaluation** | Cost-effectiveness, cost-utility, cost-minimisation. |
| **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

The economic model starts with patients presenting with clinical symptoms suggestive of NMO/NMOSD. The decision is between the proposed intervention (pathology testing to investigate the presence of NMOSD by the detection of AQP4-Abs and/or MOG-Abs) to inform ongoing clinical management) vs clinical diagnostic criteria alone to inform ongoing clinical management. Ongoing clinical management (treatment) and disease progression (relapse and disability) is then modelled.

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 multiple sclerosis 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.

Some additional structural assumptions of the model are:

* 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.
* It is assumed that 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) are assumed to have mortality risk similar to the general population. Patients in remission with moderate–severe disability are assumed to 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 are assumed to 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.

The overall expected costs and outcomes, and incremental costs and outcomes per patient associated with the NMOSD-Ab test and comparator in the model, with the base case assumptions, are presented in Table 7.

Table Costs and effectiveness for base-case analysis, AQP4-Ab testing only

|  |  |  |  |
| --- | --- | --- | --- |
| Description | Average cost per patient | QALYs | Relapses |
| NMOSD-Ab testing | $1,271 | 0.1093 | 0.0818 |
| No Ab testing | $1,995 | 0.1060 | 0.1319 |
| Increment (Ab testing – No Ab testing) | –$723 | 0.0034 | –0.0501 |

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

The model estimates that when AQP4-Ab testing is used for the diagnosis of NMOSD (Table 7) it results in an average cost saving of $723 and a gain of 0.0034 additional QALYs, compared with no AQP4-Ab testing i.e., AQP4-Ab testing is dominant (in the South-East quadrant of cost-effectiveness plane) compared with no Ab testing.

Additionally, testing results in 5% fewer relapses than where no Ab-testing is available. This is due to the test facilitating rapid diagnosis and appropriate treatment, such that there is less relapse and progressed disease; resulting in quality of life benefits, and also 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.

The sensitivity analysis results showed 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.

Key sensitivity analyses are presented in Table 8.

Table Key drivers of the economic model

| Description | Method/Value | Increment in cost per QALY (lower value, higher value) (base-case: Dominant, –$72,156) | Impact |
| --- | --- | --- | --- |
| Proportion of patients receiving rituximab | Values changed from 20% to 80% | –$301,756, –$64,292 | 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) | –$259,707, –$52,410 | Dominant across tested range. |

QALY = quality adjusted life-years

Although a number of assumptions were required to develop the model and data inputs were uncertain, particularly given the historical nature of the comparison, the fact that the sensitivity analyses consistently yielded dominant results (resource savings and health outcome benefits) for NMOSD-Ab testing compared with no testing, this would suggest that, despite the limitations or any inaccuracies that may exist in the model, it is unlikely that antibody testing for NMO/NMOSD would not be cost-effective in practice.

### Estimated Extent of Use and Financial Implications

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 is used to estimate the financial implications of a potential listing of NMOSD antibody testing on the MBS.

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 NMOSD-Ab test 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.

The financial implications to the MBS resulting from the proposed listing of NMOSD-Ab testing are summarised in Table 9. It is estimated that the proposed MBS listing of NMOSD-Ab testing will result in net cost to the MBS of $141,000 in first year increasing to $311,000 in the fifth year.

Table 9 Total costs to the MBS associated with NMOSD-Ab testing

| **-** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- |
| **Proposed test** |  |  |  |  |  |
| Number of services | 10,122 | 11,641 | 13,387 | 15,395 | 17,704 |
| Cost to the MBS | $368,230 | $423,465 | $486,984 | $560,032 | $644,037 |
| **MBS services offset** | **-** | **-** | **-** | **-** | **-** |
| Number of services | 9,205 | 10,125 | 11,138 | 12,251 | 13,477 |
| Cost to the MBS | $227,422 | $250,165 | $275,181 | $302,699 | $332,969 |
| **Net cost to the MBS** | **$140,808** | **$173,300** | **$211,803** | **$257,333** | **$311,068** |

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

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 proposed listing. The growth rate in the expected number of NMOSD-Ab tests 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.

### Stakeholder impact summary

There was no public consultation for this Application.

Letters were received from the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) and the Australian and New Zealand Association of Neurologists (ANZAN) during the PICO confirmation development stage. They supported the availability of AQP4-Ab and MOG-Ab testing on the MBS.

# Acronyms and Abbreviations

ABS acute brainstem syndrome

ADS acquired demyelination syndrome

AQP4-Ab/s aquaporin 4 antibody/antibodies (also AQP4-IgG)

ARR annualised relapse rate

AZA azathioprine

CI confidence interval

CNS central nervous system

CSF cerebrospinal fluid

ECZ eculizumab

EDSS expanded disability status scale

ELISA enzyme-linked immunosorbent assay

FACS fluorescence-activated cell sorting

HR-NMO high risk of conversion to NMO

HRQoL health-related quality of life

HTA health technology assessment

ICER incremental cost-effectiveness ratio

IDD inflammatory demyelinating disorder

IIDD idiopathic inflammatory demyelinating disease

IIF indirect immunofluorescence

IVMP intravenous methylprednisolone

LETM longitudinally extensive transverse myelitis

MARD myelin oligodendrocyte glycoprotein antibody-related demyelination

MBS Medicare Benefits Schedule

MMF mycophenolate mofetil

MOG-Ab myelin oligodendrocyte glycoprotein antibody

MRI magnetic resonance imaging

MS multiple sclerosis

MSAC Medical Services Advisory Committee

NMO neuromyelitis optica

NMOSD neuromyelitis optica spectrum disorders

NPA negative percent agreement

NPV negative predictive value

OCB oligoclonal bands

ON optic neuritis

PASC PICO Confirmation Advisory Sub-Committee of the MSAC

PLEX plasma exchange

PPA positive percent agreement

PPV positive predictive value

QALY Quality adjusted life year

QoL quality of life

RDS relapsing acquired demyelinating syndrome

RTX rituximab

T-IIF tissue-based immunofluorescence test

# Section A Context

This Departmental contracted assessment report (DCAR) of aquaporin 4 antibody (AQP4-Ab) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab) testing for the diagnosis and monitoring of neuromyelitis optica spectrum disorders (NMOSD) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The Pathology Clinical Committee (PCC) – Immunology recommended to the MSAC that a new MBS item be created to investigate the presence of AQP4-Ab in serum and/or cerebrospinal fluid (CSF). Although AQP4-Ab testing has been in clinical use for 10 years. The MBS Review Taskforce stated that the AQP4-Ab tests were currently billed through the generic MBS item 71119 and that this was funded at a lower level than providers currently billed for the test. Subsequent to the PCC’s and MBS Review Taskforce recommendations, clinical input has recommended that testing for MOG-Ab should also be included as an item on the MBS, to accommodate those individuals who present with clinical symptoms representative of NMOSD, but who test negative for AQP4-Abs.

Adelaide Health Technology Assessment (AHTA) has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of AQP4-Ab and MOG-Ab testing. This assessment has been undertaken in order to inform MSAC’s decision-making regarding whether the proposed medical service should be re-listed with a specific item number and increased public funding.

Appendix A provides a list of the people involved in the development of this assessment report, including clinical experts that provided input. Clinical guidance was provided from various sources which included private pathology providers, the Royal College of Pathologists Australasia (RCPA), members of the PCC-Immunology (MBS Review Taskforce), and specialists.

The proposed use of AQP4-Ab and MOG-Ab testing for NMOSD in Australian clinical practice was outlined in a PICO Confirmation that was presented to the PICO Confirmation Advisory SubCommittee (PASC) on 6 December 2019. The PICO Confirmation outlining the proposed use of antibody testing for NMOSD in Australian clinical practice was ratified by the PICO Confirmation Advisory SubCommittee (PASC).

## Items in the agreed PICO Confirmation

This contracted assessment of antibody testing for NMOSD addresses most of the PPICO (prior tests, population, intervention, comparator and outcome) elements that were pre-specified in the PICO Confirmation that was ratified by PASC. Accordingly, the approach presented in the PICO Confirmation was followed. There was no direct evidence for antibody testing for diagnosis or monitoring of NMOSD identified in the literature search, therefore the linked evidence approach proposed in the PICO Confirmation was used in the assessment.

Diagnosis by the 2015 International Panel for Neuromyelitis optica (NMO) Diagnosis (IPND) criteria was the accepted clinical reference standard used to assess clinical validity. However, comparison of AQP4-Ab and MOG-Ab testing with the IPND criteria presents the problem of incorporation bias (see Section B4.1.1 for further information), making the calculation of diagnostic accuracy unreliable. A number of other issues also arose in the assessment that make it difficult to rely on diagnostic accuracy measurement of AQP4-Ab testing. These issues are further described in Section B4.1.

Due to the unreliability of the data on sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of AQP4-Ab and MOG-Ab testing in the clinical setting, a prognostic evidence section has been included (Section B4.2). The reasoning is that if testing shows a difference in prognosis between those suspected of NMOSD found positive and negative, then this step can contribute to the linked evidence. Remaining steps of linked evidence were included to show how testing impacts patient management (Section B5.1) and that their health outcomes benefit as a result of management changes (Section B5.2).

A large proportion of the relevant articles identified in the literature search were retrospective case series with before-and-after testing data. The criteria for the comparators in the PICO Confirmation were met primarily in the articles providing evidence for the clinical utility of AQP4-Ab testing.

The majority of evidence identified related to AQP4-Ab testing. There was little evidence related to MOG-Ab testing that met the PICO criteria. Because MOG-Ab can be found across a number of autoimmune conditions, it was often not possible to separate data for those at risk of NMOSD.

There was very little evidence meeting the literature search inclusion criteria for monitoring NMOSD by antibody testing. This question of monitoring has been addressed separately in Section B6.

## Proposed Medical Service

The proposed medical service, is to test for antibodies against aquaporin 4 (AQP4) and against myelin oligodendrocyte glycoprotein (MOG) to identify patients with NMOSD.

AQP4-Ab testing is used to differentially diagnose individuals with NMOSD, from multiple sclerosis (MS) and other autoimmune disorders of the central nervous system (CNS) (Sellner et al. 2010). Despite considerable overlap in clinical features between NMOSD and other autoimmune disorders of the CNS, including MS (Sellner et al. 2010; Trebst et al. 2014), AQP4-Abs are not found in individuals with MS, and AQP4-Ab testing allows early diagnosis and treatment of NMOSD (Mader & Brimberg 2019). The early differential diagnosis of NMOSD is important, as the natural history of untreated NMOSD is significantly worse than that of MS (Sellner et al. 2010), and some treatments that are used for MS are not effective in the treatment of NMOSD. Evidence suggests some MS treatments may even worsen the disease outcome of individuals with NMOSD (Lalan et al. 2012; Mader & Brimberg 2019).

For those patients suspected of having NMOSD, but who do not test positive for antibodies to AQP4 or MOG, their management will depend on whether the clinician determines that they are likely to still have NMOSD, or are more likely to have a non-progressive neurological condition (for example non-relapsing ON) or an alternative progressive condition such as MS. Those who are assumed to have MS but truly have NMOSD will not respond to MS treatment, and are likely to develop further clinical features of NMOSD and therefore be clinically diagnosed as having antibody-negative NMOSD after a delay.

MOG-Ab testing is used to differentially diagnose individuals with MOG antibody-related demyelination (MARD) in individuals who present with clinical symptoms representative of NMOSD, but who test negative for AQP4-Abs. MARD is considered a disorder under NMOSD (Borisow et al. 2018).

The PCC – Immunology recognised, that although AQP4-Ab testing has been in clinical practice for approximately 10 years, currently the test is not listed as a specific item on the MBS (PCC-Immunology 2018). Rather, AQP4-Ab testing is claimed under a MBS generic item number 71119 – ‘antibodies to tissue antigens not elsewhere specified‘ (PCC-Immunology 2018). The PCC-Immunology has proposed that a new item number for AQP4-Ab testing be created, stating that the current MBS item does not reflect current clinical practice and is funded at a lower level than providers currently bill for this testing (PCC-Immunology 2018).

AQP4-Ab and MOG-Ab testing are mainly used by neurologists to diagnose NMOSD and while the tests are predominantly used for diagnosis only, subsequent AQP4-Ab and MOG-Ab testing may be used in already diagnosed individuals, for monitoring disease exacerbations and relapse (Borisow et al. 2018; PCC-Immunology 2018). For MOG-Ab testing, there is no definite consensus regarding regular monitoring, however it has been suggested that re-testing at 6-12 month intervals may be beneficial (Wynford-Thomas, Jacob & Tomassini 2019). As acknowledged in the ratified PICO document, (p. 21 & 23) clinical advice indicated that patients already diagnosed with NMOSD may be monitored by regular antibody testing (AQP4 or MOG) up to four times a year, to ascertain whether there is an increase in antibody presence or activity. However, the PASC considered it unlikely that testing would be done four times in a year, although there is little evidence about this.

AQP4-Ab testing has been supported by the IPND (Wingerchuk et al. 2015) and the European Federation of Neurological Societies (EFNS)(Sellner et al. 2010). IPND stated that the role of MOG-Abs in disease pathogenesis remains undetermined.

Antibody testing for AQP4 and MOG can be performed in serum or CSF, although testing in CSF is not routinely recommended as both antibodies are produced mainly extrathecally and are therefore less frequent in CSF than in serum (Borisow et al. 2018). CSF testing of AQP4-Ab seronegative patients may be considered in selected cases, especially in individuals with additional confounding serum autoantibodies that may lead to uninterpretable or false-positive assay results (Wingerchuk et al. 2015). The PASC (p.11, ratified PICO document) noted that, although testing of serum is preferred to CSF, CSF testing may be used in some clinical situations. 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.

A total of six different serum AQP4-Ab assays are available, and include cell-based assays, tissue based immunofluorescence (T-IIF), enzyme-linked immunosorbent assay (ELISA), and immunoprecipitation measured by either radioimmunoprecipitation assay (RIPA) or fluorescence immunoprecipitation assay (FIPA). The published literature indicates that the most accurate assay type is a cell-based assay (Borisow et al. 2018). Cell-based assays are measured either visually or by flow cytometry (fluorescence-activated cell sorting (FACS)) (Waters et al. 2014).

Cell-based assay kits (Euroimmune®) that test for AQP4-Ab and MOG-Abs concurrently[[3]](#footnote-3) are used in Australia. Dual assays are transfected with cells expressing the AQP4 and MOG protein, and are therefore able to detect both antibody types. By testing for both antibodies at one time, earlier diagnosis and treatment may be available to patients.

## Proposal for Public Funding

AQP4-Ab testing has been occurring in Australia for more than 10 years under MBS items 71119 or 71165, which are non-specific single antibody test descriptors (Table 11). The PCC-Immunology recommended the creation of a new item number so that the fee more appropriately reflects what providers currently bill for the test.

The PCC-Immunology proposed a single item number for “a test to investigate the presence of neuromyelitis optica by detection of aquaporin 4 antibodies”. This was amended to include the updated disease term (NMOSD, which is considered to include the subtype of MARD), and to remove the specification of AQP4, to allow for AQP4-Ab, MOG-Ab and any future antibodies to be tested using the same item number. Advice was provided by PASC 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. The proposed item permits both cerebrospinal fluid (CSF) and serum testing.

Table 1 shows the proposed item descriptor for antibody testing for diagnosis or monitoring of NMOSD.

## Proposed Population

The target population is people suspected of having NMO/NMOSD.

NMO (also known as Devic’s disease) is rare, but severe. It is an inflammatory, demyelinating and necrotising, idiopathic, humorally mediated autoimmune disorder of the 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 MS (Lalan et al. 2012; Sellner et al. 2010). Consequently, it was assumed for many decades that NMO was a subform of MS, due to considerable overlap in clinical presentation (Jarius, Wildemann & Paul 2014; Trebst et al. 2014).

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

The NMOSD term encompasses a number of very closely related conditions, and in a 2015 publication (Wingerchuk et al. 2015), the IPND 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 early differential 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). AQP4 water channels are considered an integral constituent of the blood brain barrier (Jarius, Wildemann & Paul 2014), and are found in high density on the end feet of astrocytes (Bukhari et al. 2017). They are the most abundant water channel in the brain, spinal cord and optic nerve (Mader & Brimberg 2019). In AQP4-Ab positive 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 et al. 2008).

Recent published literature has reported on the presence of serum antibodies against 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 MOG-Abs to the spectrum of NMO disorders. Various terms have been used in the literature to describe the MOG-Abs associated disorder, including MARD (Borisow et al. 2018).

MARD is an acute inflammatory, demyelinating CNS disorder, and presents commonly with 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 relapsing than AQP4-Ab positive NMOSD (Jurynczyk et al. 2017).

MOG-Abs target MOG which 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. This leads to disturbances in the integrity of the blood brain barrier and to CNS inflammation (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).

Treatment for AQP4-Ab NMOSD is different from MS treatment, which can worsen the disease outcome of NMOSD patients (Lalan et al. 2012; Mader & Brimberg 2019). MS medication (e.g. interferon beta, glatiramer acetate, fingolimod, alemtuzumab and natalizumab) has been shown to have no effect, or to cause harm in individuals with AQP4-Ab NMOSD and MARD (Borisow et al. 2018). Due to lack of clinical evidence around treatment for MARD, current treatment protocols for MARD tend to follow those for NMOSD (Illes Z 2016; Wynford-Thomas, Jacob & Tomassini 2019). Treatments for AQP4-Ab NMOSD and MARD include corticosteroids, immunosuppressants (e.g. azathioprine), plasmapheresis, intravenous immunoglobulin and anti-CD20 monoclonal antibody (e.g. rituximab) (Borisow et al. 2018; Trebst et al. 2014; Wynford-Thomas, Jacob & Tomassini 2019).

Those with suspected NMOSD who have neither AQP4 or MOG antibodies may have a delay in their clinical diagnosis of NMOSD, or may be misdiagnosed as having MS in the interim (until they develop further clinical features which allows diagnosis).

### AQP4 and MOG testing in the Australian setting

An accurate proportion of AQP4-Ab positive to negative cases of NMOSD in Australia has been difficult to determine, however, recent studies suggest that as many as 90% of patients with NMOSD are AQP4-Ab positive in this country (Bukhari et al. 2020; Bukhari et al. 2017).

Recent Australian data collected from clinical pathology laboratories suggest that the diagnostic yield of AQP4-Ab seropositivity is between 2.9% and 5.4%. Data from PathQLD indicated that there were 51 AQP4-Ab positive patients identified form 1596 tested over 5 years (2.9%), while PathWest identified 13 AQP4-Ab positive patients from 240 tested in 2019 (5.4%). In comparison to data found in the literature, the yield in Australia is low, and reflects that a relatively broad population undergoes testing in this country. Because of the broad population tested in Australia, there are a large number testing negative for AQP4-Ab (1545 patients (97.1%) and 227 patients (96.6%) from PathQLD and PathWest respectively). Amongst those found negative for AQP4-Ab there are likely to be patients with a range of neurological diseases, including NMOSD and MS.

PathWest also provided data on MOG-Ab testing. Of 132 patients tested for MOG-Ab in 2019, 21 were found positive (15.9%). However is it not known what proportion of those tested were suspected of NMSOD.

NMOSD is a rare disease in comparison to MS in Australia. MS was estimated to affect 25,600 people in 2017 and have a prevalence of 103.7/100,000 (MS Australia 2019). Published data suggests that NMO or NMOSD make up approximately 3.7% of all demyelinating CNS disease in Western Australia, although because the study predated the inclusion of AQP4 testing in diagnostic criteria it is likely to be inaccurate (Wu et al. 2008).

The differences and similarities (including clinical features) between AQP4-Ab NMOSD, MARD and MS, are described in Table 10. Figure 2 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 & Fujihara 2018). **It is proposed that only those patients suspected of having NMOSD will be eligible for AQP4-Ab or MOG-Ab testing.**

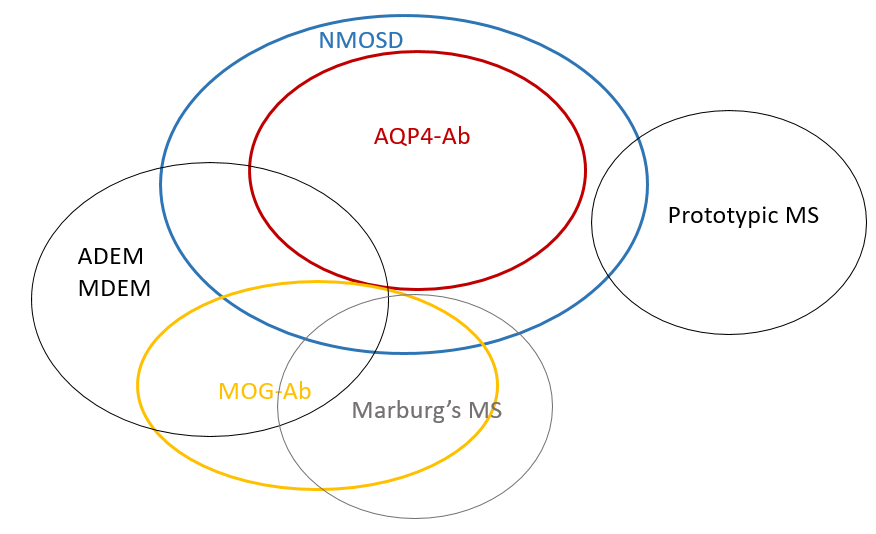


Figure 2 Inflammatory demyelinating diseases of the central nervous system

Source: Adapted from Misu & Fujihara 2018

AQP4-Ab = aquaporin 4 antibodies; ADEM = acute disseminated encephalomyelitisMS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis;

NMSOD is a rare disease. The incidence and prevalence of the NMOSD population is discussed in Section B4.1.

Table 10 Comparison between AQP4-Ab NMOSDa, MARD and MS

|  |  |  |  |
| --- | --- | --- | --- |
| **Comparisons** | **AQP4-Ab NMOSD** | **MARD** | **MS** |
| **Antibody testing** | Serumb antibodies to AQP4 in approximately 80%c of cases | Serumb antibodies to MOG | Rarely serum antibodies to AQP4. MOG (antibodies may be present in Marburg’s disease, also called malignant MSd) |
| **Age** | Age of onset late 30’s 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 |
| **Gender** | More common in womene | Slight predominance in women | More common in women |
| **Ethnicity** | Relatively rare in Europe. Affects non-whites (e.g. Afro-Brazilians (15%), East Asians (up to 48%) and Indians (9%)f | No ethnicity differencesg although some reports indicate higher in Caucasian ethnicityh | More common in Europe compared to NMOSD; ratio 42.7:1 (MS:NMOSD)i |
| **Neurological**  **presentation** | 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 MRI**  **findings** | Brain lesions may initially be absent on MRI at first presentation, but presence of cerebral lesions found in 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**  **findings** | 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 shows lesions more commonly short |
| **Course of disease** | Relapsing disease course | Monophasicj or relapsing disease course | Relapsing or progressing disease course |
| **Type of relapse** | ON; LETM | Commonly ON (more than in NMOSD) | Any type of relapse with phenotype predicted by previous relapse phenotype |
| **Degree of disability** | 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 |
| **Response to interferon beta treatment** | 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; MOG = myelin oligodendrocyte glycoprotein; MRI=magnetic resonance imaging; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis

a the term NMOSD refers to both NMOSD and NMO

b standard specimen for AQP4 and MOG antibody testing is serum

c based on papers byJarius, Wildemann & Paul (Jarius et al. 2014) and Mader & Brimberg (Mader & Brimberg 2019)

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

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

f figures reportedby European Federation of Neurological Societies (Sellner et al. 2010)

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

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

i results based on cohort of 850 patients in North East Tuscany (Sellner et al. 2010)

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

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

**For clarity, the terms AQP4-Ab NMOSD and MOG-Ab NMOSD will be used in the document, from this point on, to refer to individuals testing positive for AQP4-Ab and positive for MOG-Ab, respectively. Also, the report will use the term NMOSD, unless a particular study has separated out the terms into NMO and NMOSD, in which case the specific terms will be used, along with the definitions, as outlined in the particular study. Likewise, the report will use the term AQP4-Ab, rather than NMO-IgG to describe antibodies to aquaporin 4, as the terms are considered synonymous.**

## Comparator Details

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. In the absence of antibody testing, diagnosis would be based on clinical characteristics, including those found on MRI. Diagnosis would be made by a neurologist. 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 (Trebst et al. 2014). 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 core clinical characteristics, with at least one being ON, acute myelitis or area postrema syndrome. Additionally, supportive characteristics in cerebral, spinal cord or optic nerve MRI are required. A description of core and supportive clinical characteristics can be found in Appendix F.

As the main comparator for this assessment is no antibody testing for NMOSD, there is no relevant comparator for the clinical component. The financial implications of a new MBS item for AQP4-Ab and/or MOG-Ab testing will be compared against what is done currently. The Assessment has identified that there are currently mixed practices for claiming an MBS rebate for this test in Australia; most tests are claimed using MBS item 71165 (the antigen tissue being neuron) but some are claimed using MBS item 71119 or 71165 (Table 11). The rebates for these items vary considerably.

Table 11 Current item descriptors for single antibody testing against tissue antigens

| Category PATHOLOGY SERVICES |
| --- |
| Item 71119 Group P4 – Immunology  Antibodies to tissue antigens not elsewhere specified in this Table – detection, including quantitation if required, of 1 antibody.  (see para PN.0.33 of explanatory notes in this Category  Fee: $17.35 Benefit: 75% = $13.05 85% = $14.75 |
| Category PATHOLOGY SERVICES |
| Item 71165 Group P4 – Immunology  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  (Item is subject to Rule 6)  Fee: $34.55 Benefit: 75% = $25.95 85% = $29.40 |

## Clinical Management Algorithm(s)

### Historical clinical management for the 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 3.

When the brain and/or spinal cord MRI detects typical MS lesions, then subsequent diagnostic steps should be made towards this (Illes Z 2016). Presence of 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 incorrect diagnosis, and the 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 cannot be 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 immunoglobulin G (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 to the diagnosis (i.e. MS or NMOSD). Repeat testing or other differential diagnosis is recommended should no diagnosis or confirmation be made (Illes Z 2016).



Figure 3 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 107 for diagnostic criteria from Wingerchuk et al. 2015

### Current clinical management for the proposed 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 4, and for sequential testing, in Figure 5.

When the brain and/or spinal cord MRI detects typical MS lesions, then subsequent diagnostic steps should be made towards this (Illes Z 2016). Presence of CSF-restricted OCB is also a diagnostic mainstay in classical MS (Jarius, Wildemann & Paul 2014).

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 4)

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 testing in the CSF to determine a differential diagnosis of MS or AQP4-Ab NMOSD or MOG-Ab NMOSD.

2) serum AQP4-Ab and MOG-Ab testing (Figure 5)

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 OCB, IgG or AQP4-Ab testing in the CSF to determine a differential diagnosis of MS or AQP4-Ab NMOSD or MOG-Ab NMOSD[[4]](#footnote-4).

If a diagnosis is made, then treatment is prescribed according to the diagnosis (i.e. MS, AQP4-Ab NMOSD or MOG-Ab NMOSD). For those found AQP4-Ab or MOG-Ab positive, correct treatment is likely to start earlier than for those who test negative and need to undergo further testing, or have to wait on symptom development before diagnosis can be made. Repeat testing is recommended should no diagnosis or confirmation be made (Illes Z 2016).

### Clinical management after diagnosis in the identified population

In patients with NMOSD, the correct therapeutic approach has to recognize two distinct clinical situations: treatment of the acute attacks and prevention of the relapses (maintenance treatment) (Bruscolini et al. 2018). As NMOSD takes a relapsing course in most cases, with often incomplete recovery and rapid accumulation of neurological deficits, long-term immunosuppressive treatment (Trebst et al. 2014)

Prednisone, azathioprine (AZA), mycophenolate mofetil (CellCept) and rituximab (RTX) are the first-line drugs used in relapse prevention in NMOSD. The choice of the initial treatment usually depends on availability, costs, co-morbidities, and disease course (Lana-Peixoto & Talim 2019). High-dose intravenous corticosteroids (such as intravenous methylprednisolone (IVMP)), plasmapheresis (PLEX) and intravenous immunoglobulin (IVIG) are the main treatments for acute relapses (Borisow et al. 2018; Trebst et al. 2014; Wynford-Thomas, Jacob & Tomassini 2019).

Due to lack of clinical evidence around treatment for MOG-Ab NMOSD, current treatment protocols tend to follow those for AQP4-Ab NMOSD (Illes Z 2016; Lana-Peixoto & Talim 2019; Wynford-Thomas, Jacob & Tomassini 2019).



Figure 4 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 See Table 107 for diagnostic criteria from Wingerchuk et al. 2015



Figure 5 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 See Table 107 for diagnostic criteria from Wingerchuk et al. 2015

## Key Differences in the Proposed Medical Service and the Main Comparator

The main difference between the proposed medical service (current testing and diagnosis) and comparator (historical diagnosis) is AQP4-Ab testing. According to the current international clinical recommendations (Wingerchuk et al. 2015), AQP4-Ab testing should be included in the diagnostic pathway for NMOSD. Historically, diagnosis was based on clinical characteristics alone, and required sufficient development of symptoms to make a definitive diagnosis. Because of the shorter time taken to reach a diagnosis with antibody testing, the severity of symptoms can be ameliorated with appropriate treatments. Early treatment may also lead to reduced relapse, and better overall health outcomes for NMOSD patients, who are otherwise at risk of accumulating severe disabilities over time.

Clinical input has advised that in the current diagnostic scenario, for those testing negative for AQP4-Ab, MOG-Ab testing should be performed. This test can provide a definitive diagnosis in a proportion of AQP4-Ab negative patients, thereby reducing the number of patients waiting on the development of further symptoms to provide a clear disease pathway.

In the historical scenario, NMOSD patients were likely to have been treated as though they had a diagnosis of non-classical MS. Evidence in the published literature shows that some MS treatments are not effective and may even be harmful in NMOSD patients, and it is therefore preferential that a differential diagnosis be made as early as possible.

## Clinical Claim

The Applicant has not submitted a clinical claim.

## Summary of the PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects the likely future practice with the proposed medical service.

The PPICO that were pre-specified to guide the systematic literature review for direct evidence are presented in Box 1.

A linked evidence approach is used where direct trial evidence of clinical effectiveness of a test is not available, or is inadequate for decision making purposes. An explanation of the linked evidence approach can be found in Section B.2.The PPICO criteria to guide the review for linked evidence are given in Boxes 2 to 4 in Appendix G.

Box 1 Criteria for identifying and selecting studies to determine the safety and effectiveness of antibody testing in patients at risk of NMOSD

| **Component** | **Description** |
| --- | --- |
| Patients | 1. Patients suspected of having neuromyelitis optica spectrum disorder (NMOSD) e.g. those with: 2. Recurrent, bilateral or severe optic neuritis; or 3. Recurrent longitudinal extensive transverse myelitis (LETM)\*; or 4. Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or 5. Acute brainstem syndrome or 6. Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or 7. Symptomatic cerebral syndrome with typical NMOSD MRI lesions or 8. Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) or 9. Patient has poor recovery from multiple sclerosis relapse 10. 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 | 1. Antibody testing in serum or cerebrospinal fluid using one of a variety of diagnostic substrates (cell, tissue or protein)   * 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  1. Antibody testing (AQP4-Ab OR MOG-Ab) to monitor signs of relapse in those previously diagnosed |
| Comparator | For safety, effectiveness and cost-effectiveness: No AQP4-Ab testing: diagnosis by clinical characteristics alone  For financial implications: AQP4-Ab +/- MOG-Ab testing under MBS item 71119 or 71165 |
| Outcomes | Patient relevant outcomes:  *Safety (test related)*   * Harm to patient resulting from   1. Blood collection (e.g. needle stick injuries) or serum (blood) analysis   2. Consequences of true or false test results   *Effectiveness*   * Mortality * Disability rates and severity (e.g. blindness, paraplegia) * Remission and improvement of relapse-associated symptoms. * Long-term stabilisation of disease course by means of relapse prevention. * Annualised relapse rates * Frequency of lesion occurrence * Quality of life   Healthcare system outcomes:   * Cost, cost-effectiveness * Length of hospital stay * Financial implications (financial impact, healthcare resource use, etc.) |
| Research questions | What is the direct clinical utility (safety, effectiveness) of AQP4-Ab and MOG-Ab testing (either concurrently or sequentially) in patients suspected of having NMOSD, compared to diagnosis by clinical characteristics alone?  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?  What is the cost-effectiveness of AQP4-Ab and MOG-Ab testing (either concurrently or sequentially) in patients suspected of having NMOSD, compared to diagnosis by clinical characteristics alone?  What is the cost-effectiveness of antibody testing (AQP4-Ab or MOG-Ab) compared to monitoring by clinical characteristics alone in previously diagnosed patients?  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 = longitudinally extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorders

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

## Stakeholder impact

There was no public consultation for this Application.

Letters received from the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) and the Australian and New Zealand Association of Neurologists (ANZAN) during the PICO confirmation development stage were positive regarding the availability of AQP4-Ab and MOG-Ab testing on the MBS.

Points contained in the correspondence from the ANZAN and RANZCO included:

* NMOSD is difficult to distinguish from MS on purely clinical and MRI grounds and there is considerable overlap in clinical features with MS and NMOSD, particularly in the early stages of the condition (e.g. first presentation with ON);
* Testing for AQP4-Ab and MOG-Ab is essential for the early and accurate diagnosis of NMOSD, as the treatment of NMOSD is distinctly different to MS, and current treatment for MS either do not work or can worsen outcomes in NMOSD;
* NMOSD is associated with more frequent relapses than is typically seen in MS, and is also associated with a more rapid accumulation of disability and without treatment, patients are often rendered blind and paraplegic;
* Over recent months, clinical trials have shown positive results with novel treatments for NMOSD in seropositive patients, and a positive AQP4-Ab may be a requisite indication in any future Therapeutic Goods Administration (TGA)/Pharmaceutical Benefits Scheme (PBS) treatment listing.

# Section B Clinical Evaluation

Determination of the clinical effectiveness of an investigative medical service requires either:

* evidence of the effectiveness of antibody testing from high-quality comparative studies evaluating the use of AQP4 and MOG antibody testing in addition to clinical characteristics and subsequent treatment compared to clinical characteristics alone and treatment (direct evidence). Randomised controlled trials (RCTs) provide the highest quality evidence for this comparison. Or, if this is not available:
* evidence of the treatment effectiveness from high-quality comparative studies evaluating the treatment for NMOSD, linked with applicable and high-quality evidence of the accuracy of AQP4 and MOG antibody testing in addition to clinical characteristics to diagnose NMOSD compared to clinical characteristics alone. This is called ‘linked evidence’.

There was no direct evidence to assess the investigative medical service (AQP4-Ab and MOG-Ab testing for NMOSD), therefore a linked evidence approach was utilised, including:

* The diagnostic performance and clinical validity of the investigative medical service (Section B3 and B4).
* The clinical impact of false negatives and false positives (Section B5).
* Impact of repeat testing for monitoring disease status (Section B6).
* The relative safety of performing the test (Section B7).

# Direct Evidence

## Literature Sources and Search Strategies

The medical literature was searched on 23rd October 2019 to identify relevant primary studies and systematic reviews (SRs) published during the period from the inception of the literature database to the date of the search. Because the intervention under investigation has only been in use recently, it was expected to be sufficiently self-limiting with respect to its period of publication. Searches were conducted of the literature databases described in Appendix B. Attempts were also made to source unpublished or grey literature (for example clinical trials not yet published). Samples of other sources searched including clinical trial registries, specialty websites and Health Technology Assessment (HTA) organisations, are also provided in Appendix B. Search terms used for the PubMed platform are described in Table 12.

Studies were excluded if they were not performed in humans. Articles written in languages other than English were excluded unless the English written abstract indicated the article was of higher level evidence than was otherwise identified.

A single literature search was conducted that was deliberately kept broad so as to be sufficient to capture all evidence that includes the new test (i.e. direct evidence of effectiveness, harms, analytical validity and clinical validity (accuracy) and whether there is a change in patient management from the new test). Pearling of relevant reviews was performed to ensure all relevant evidence was captured.

Table Search terms used (PubMed platform)

| Element of clinical question | Search terms |
| --- | --- |
| Prior tests | - |
| Population | “Neuromyelitis optica” OR “Neuromyelitis optica”[MeSH] OR “neuromyelitis optica spectrum disorder” OR “NMO spectrum disorder” OR NMO OR NMOSD OR opticospinal OR ((Devic OR Devic’s) AND (disease OR syndrome OR disorder)) OR opticomyelitis OR MARD OR "myelin oligodendrocyte glycoprotein antibody related disorder" OR (MOG AND (disorder OR syndrome OR encephalitis)) |
| Intervention | “Aquaporin 4”[MeSH] OR aquaporin OR AQP4 OR NMO-IgG OR (MOG AND (igg OR antibody OR ab)) |
| Comparator (if applicable) | - |
| Outcomes (if applicable) | - |
| Limits | Human studies  Published from inception of database to 23/10/2019  Written in English (unless the English abstract indicated a higher level of evidence than was otherwise identified) |

MeSH = medical subject heading

## Results of Literature Search

A PRISMA flowchart provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Figure 6 (Liberati et al. 2009)). Studies were selected independently by two reviewers with a random sample receiving independent assessment.

Disagreements regarding study selection were resolved by discussion and consensus between the reviewers.

A total of 7,601 articles were identified through the literature search and an additional 11 articles were identified through other sources. Following title and abstract screening 1,090 articles were eligible for full-text review. Articles that met the inclusion criteria but were excluded because data could not be extracted or was duplicated elsewhere, or the article could not be retrieved in time to be included are listed by reason for exclusion in Appendix D. All other studies that met the inclusion criteria are listed in Appendix C.

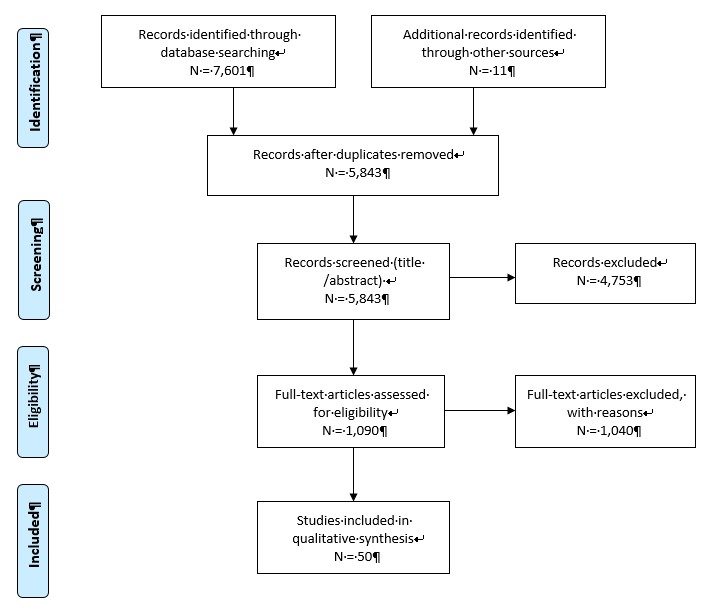


Figure 6 Summary of the process used to identify and select studies for the assessment

A profile of each included study is given in Appendix C. This study profile describes the authors, study ID, publication year, study design and quality (level of evidence and risk of bias), study location, setting, study population characteristics, description of the test (and associated interventions), description of the comparator (and associated interventions), description of the reference standard or evidentiary standard, the source of funding and the relevant outcomes assessed.

## Appraisal of the evidence

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or SRs) included in the review. Some risk of bias items were assessed for the study as a whole, while others were assessed at the outcome level. (Subsections B1.3, B3.3, B4.1.2, B5.1.1)

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results reported in the evidence base as they relate to the pre-specified primary outcomes for this assessment, and determining the assumed baseline risk where relevant. (Subsections B1.6, B3.6, B4.1.5, B5.1.4, B5.2.4)

Stage 3: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. (Evidence profile tables, Appendix D).

Stage 4: Integration of this evidence (across outcomes) for conclusions about the net clinical benefit of the test and associated interventions in the context of Australian clinical practice. (Section B.8)

## Risk of Bias Assessment

Evidence retrieved from the searches was classified according to the NHMRC Dimensions of Evidence which are listed in Table13.

Study quality was evaluated and reported using an appropriate instrument for quality assessment: SRs were evaluated using the AMSTAR 2 checklist (Shea et al. 2017); randomised and non-randomised controlled trials and observational studies were evaluated using the SIGN checklists 2 and 3 (SIGN 2014), studies of diagnostic accuracy were evaluated using QUADAS 2 (Whiting et al. 2011); and case series were evaluated using the Institute of Health Economics (IHE) checklist(IHE 2016).

In addition to the individual studies, the overall body of evidence was assessed using GRADE (Guyatt et al. 2011). For critical health outcomes assessed, a balance sheet of clinical benefits and harms associated with AQP4-Ab testing in the key studies identified was constructed based on the GRADE evidence profile table. The health outcomes pre-specified in the PICO criteria are:

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;
* Long-term stabilisation of disease course by means of relapse prevention;
* Annualised relapse rates;
* Frequency of lesion occurrence;
* Quality of life.

The GRADE outcomes provide a key element in the formation of conclusions from this report.

Table Designations of levels of evidence according to type of research question (including table notes)

|  |  |  |
| --- | --- | --- |
| **Level** | **Intervention 1** | **Diagnostic accuracy 2** |
| I 4 | A systematic review of level II studies | A systematic review of level II studies |
| II | A randomised controlled trial | A study of test accuracy with: an independent, blinded comparison with a valid reference standard,3 among consecutive persons with a defined clinical presentation5 |
| III-1 | A pseudorandomised controlled trial (i.e. alternate allocation or some other method) | A study of test accuracy with: an independent, blinded comparison with a valid reference standard,3 among non-consecutive persons with a defined clinical presentation5 |
| III-2 | A comparative study with concurrent controls: ▪ Non-randomised, experimental trial6 ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence |
| III-3 | A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study7 ▪ Interrupted time series without a parallel control group | Diagnostic case-control study5 |
| IV | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard)8 |

Source: (Merlin, Weston & Tooher 2009)

Explanatory note:

1 Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b) and in the accompanying Glossary.

2 These levels of evidence apply only to studies of assessing the accuracy of diagnostic or screening tests. To assess the overall effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002). The evidence hierarchy given in the ‘Intervention’ column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis/comparator test(s). The evidence hierarchy given in the ‘Screening’ column should be used when assessing the impact of a screening test on health outcomes relative to no screening or opportunistic screening.

3 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

6 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

7 Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

8 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Note C: Each individual study that is attributed a “level of evidence” should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

## Characteristics of the Evidence Base

See Appendix C for details on the individual studies included in the evidence base.

Data were extracted by the evaluators into evidence tables designed specifically for this review. A consensus process was used when there was doubt or disagreement over the inclusion of data. For each study, the extraction table outlined the level of evidence, quality assessment, authors, publication year, location, study design, study population characteristics, type of intervention, inclusion/exclusion criteria, outcomes assessed, funding source and follow-up period.

Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies, including numerator and denominator information, means and standard deviations, medians and inter-quartile ranges. The power of individual controlled studies to detect a clinically important effect was calculated, assuming that α = 0.05.

Meta-analyses of randomised controlled trials and of diagnostic accuracy studies were conducted, where appropriate, and tested for heterogeneity and publication bias. Meta-analyses and all related statistical calculations and testing were undertaken using the biostatistical computer package, Stata version 12.

Where meta-analyses weren’t conducted, a narrative meta-synthesis of the data was undertaken. Differences between clinical outcome measures for intervention and comparator were calculated using online MedCalc[[5]](#footnote-5) statistical software where appropriate, unless published by the study authors.

There was no direct evidence identified in the literature search.

Characteristics of the evidence for the linked approach and the corresponding risk of bias appraisals have been included and discussed with each linked step (sections B3, B4 and B5).

## Outcome Measures and Analysis

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

The diagnostic criteria for NMOSD have evolved over the years, as more is known about the condition. In 1999, (Wingerchuk et al. 1999) proposed NMO diagnostic criteria with three absolute requirements: ON, acute myelitis and no symptoms implicating other CNS regions. However, in 2006 Wingerchuk et al (2006) published revised NMO diagnostic criteria. The earlier diagnostic criteria failed to discriminate NMO from MS by not capturing patients with a disease course highly compatible with NMO, but whose neurologic symptoms or signs implicated CNS regions outside the optic nerves and spinal cord, or whose brain MRI revealed lesions that may meet MS imaging criteria (Wingerchuk et al. 2006). In 2015, Wingerchuk et al (2015) stated that further advances in the specificity of NMO-IgG testing (AQP4-Ab) made the 2006 criteria inadequate for contemporary practice and research. Table 14 compares the NMO diagnostic criteria which have been used in the studies meeting the criteria for this assessment.

Outcome measures and tools used in the identified literature such as expanded disability status scale (EDSS) and annualised relapse rate (ARR) are addressed ahead of each section of this report where they are relevant.

Table 14 Comparison of the Wingerchuk et al NMO diagnostic criteria over the years

| **1999 NMO diagnostic criteriaa** | **2006 NMO diagnostic criteriab** | **2015 NMOSD diagnostic criteriac** |
| --- | --- | --- |
| Diagnosis required *three* absolute criteria (ON, acute myelitis and no evidence of clinical disease outside of the optic nerve or spinal cord), *and*  at least one of three major supportive criterion (1) normal brain MRI at disease onset or not fulfilling MS imaging criteria; (2) spinal cord MRI showing a lesion extending over ≥ 3 vertebral segments, and (3) CSF revealing ≥ 50 WBC/mm3 or ≥ 5 neutrophils/mm3, *or*  two or three minor supportive criteria (bilateral ON, severe residual visual loss, or severe fixed post-attack weakness (MRC grade ≤ 2) in one or more limbs) | Diagnosis required *two* absolute criteria (ON and acute myelitis), *and*  at least two of three supportive criteria (1) contiguous spinal cord MRI lesion extending over ≥ 3 vertebral segments; (2) brain MRI not meeting diagnostic criteria for MS, and (3) NMO-IgG (AQP4-IgG)d seropositive status | Diagnosis criteria for NMOSD *with* AQP4-IgGd   * At least 1 core clinical characteristic (see below) * Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) * Exclusion of alternative diagnoses based on clinical features and laboratory findings and conventional neuroimaging   Diagnostic criteria for NMOSD *without* AQP4-IgG *or* NMOSD with unknown AQP4-IgG status   * At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: * At least 1 core clinical characteristic must be ON, acute myelitis with LETM, or area postrema syndrome * Dissemination in space (2 or more different core clinical characteristics) * Fulfilment of additional MRI requirements, as applicable * Negative tests for AQP4-IgG using best available detection method, or testing unavailable * Exclusion of alternative diagnoses |
|  |  | 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 with NMOSD-typical diencephalic MRI lesions * Symptomatic cerebral syndrome with NMOSD-typical brain lesions |
|  |  | Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status   * Acute ON: 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 * Acute myelitis: required 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 * Area postrema syndrome: requires associated dorsal medulla/area postrema lesions * Acute brainstem syndrome: requires associated periependymal brainstem lesions |

AQP4 = aquaporin-4; CSF = cerebrospinal fluid; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; MRC = Medical Research Council; MRI = magnetic resonance imaging; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; WBC = white blood cells

a Wingerchuk et al., The clinical course of neuromyelitis optica (Devic’s syndrome). Neurology 1999; 53(5): 1107-1114.

b Wingerchuk et al., Revised diagnostic criteria for neuromyelitis optica. Neurology 2006, 66: 1485-1489.

c Wingerchuk et al., International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015; 85: 177-189.

d Theterms NMO-IgG and AQP4-IgG are used interchangeably and are synonymous with AQP4 antibodies

## Results of the Systematic Literature review

## Is it safe?

Summary – How safe is diagnosis by AQP4-Ab with/without MOG-Ab testing in patients suspected of NMOSD compared to diagnosis by clinical characteristics alone?

No conclusions could be drawn based on direct evidence.

There was no relevant direct safety evidence identified in the literature search.

## Is it effective?

Summary – How effective is diagnosis by AQP4-Ab with/without MOG-Ab testing in patients suspected of NMSOD compared to diagnosis by clinical characteristics alone?

No conclusions could be drawn based on direct evidence.

There was no direct evidence identified in the literature search relevant to effectiveness outcomes.

# B2 Linked evidence approach

## Basis for linked evidence

Due to the lack of direct evidence, a linked evidence approach was utilised.

## Steps for linked analysis

To construct a linked evidence analysis, different evidence requirements are required:

* Consideration of the diagnostic performance - does the test measure what it purports to measure? (i.e. the accuracy of testing) and clinical validity of AQP4-Ab testing (Section B3 and B4);
* Consideration of the clinical utility of the diagnostic medical service in terms of:
  + Impact of positive versus negative test results on patient management (i.e. does the information provided by the test change the management that is recommended /received /chosen?), and the contribution and clinical importance of false negatives;
  + Direct impact of each therapeutic option on health outcomes (i.e. do people have better or worse health outcomes resulting from the changes to diagnosis/management?);
* Considerations of the impact of repeat testing (if appropriate) (Section B6);
* Consideration of the relative safety of performing the diagnostic test (Section B5.2.4);

Conclusions linking these steps were made in Section B8.

# B3 Diagnostic performance

## Reference standard

The reference standard is the ’gold’ standard against which the index test is compared for the accuracy. Although there are several different methods for testing for AQP4 and MOG antibodies, none is considered the reference standard. However the IPND recommend testing for AQP4-Abs with cell-based serum assays (microscopy or flow cytometry-based detection) as they optimise autoantibody detection, (Wingerchuk et al. 2015) and recently published data by Prain et al. (2019) and Waters et al. (2012) supports this view. It was considered during the PICO confirmation meeting and decided by PASC that further comparison of assay types was unwarranted. Therefore, this section focuses only on a comparison between different types of cell-based assays.

A comparison of sensitivity and specificity of all various AQP4-Ab serum assay types as provided by Prain et al.(2019) and Waters et al.(2012) is provided in Appendix H.

As no reference standard is applicable for this assessment, diagnostic accuracy using sensitivity, specificity, and positive and negative predictive values were not calculable. Only concordance data (between different cell-based assays) was available to inform diagnostic performance.

## Risk of Bias Assessment

The risk of bias was assessed with the QUADAS-2 checklist for both of the included analytical validity studies identified in the literature search (Jarius et al. 2010 1-7; Waters et al. 2016). Studies were considered to be of low risk of bias if they scored six or seven ☺. They were deemed moderate risk of bias if studies had four or five ☺, and with no more than two ☹. All other scores were considered high risk of bias.

A summary of the risk of bias for each study (risk of bias regarding patient selection, the index test, the reference standard, flow and timing and applicability concerns) can be found in Table 15.

Table 15 Risk of bias (QUADAS-2) of studies for analytical validity

| **Study** | **RISK OF BIAS** | | | | **APPLICABILITY CONCERNS** | | |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient selection** | **Index test** | **Reference standard** | **Flow and timing** | **Patient selection** | **Index test** | **Reference standard** | **RISK OF BIAS** |
| Jarius et al. 2010 | ☺ | ? | ? | ? | ☺ | ☺ | ☺ | Moderate |
| Waters et al. 2016 | ? | ☺ | ? | ? | ☺ | ☺ | ? | High |

Low Risk            High Risk             ? Unclear Risk

QUADAS-2 = A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies

## Characteristics of the Evidence Base

The characteristics of accuracy studies identified in the literature is shown in Table 16. One study by Waters et al. (2016) investigated the detection of serum AQP4-Abs, and compared the diagnostic performance of 21 assays (including live, fixed and flow cytometry cell-based assays) in 15 diagnostic centres in Europe. Of these 21 assays, three were live cell-based assays, 10 fixed commercial cell-based assays (three were run in-house by the manufacturer and seven at other diagnostic centres) and four flow cytometry assays (FACS). A further study (Jarius et al. 2010) investigated testing for AQP4-Abs in CSF with a fixed cell-based assay, and used paired CSF/serum specimens to investigate the diagnostic relevance of CSF compared to serum AQP4-Ab testing in patients from Germany, Austria and Italy. Due to lack of a reference standard for diagnostic accuracy, only a concordance analysis between cell-based assays could be reported.

Table 16 Key features of the evidence comparing the sensitivity and specificity of various cell-based assays

| **Trial/ Study** | **N** | **Level of evidence** | **Risk of bias** | **Patient population** | **Key outcome(s)** | **Result used in meta-analysis** |
| --- | --- | --- | --- | --- | --- | --- |
| Jarius et al. 2010 | 37 NMOSD (31 sero +ve and 14 sero –ve) | III-3 | Moderate | Patients from Germany, Austria and Italy with NMOSD and controls with MS and other neurological diseases | Sensitivity/Specificity of CSF and serum AQP4-Ab cell-based assays | No |
| Waters et al. 2016 | 101 NMO/NMOSD (66 sero +ve and 35 sero –ve) | III-3 | High | Patients with AQP4-Ab positive or negative NMO/NMOSD and controls with MS or other neurological conditions, diagnosed in 15 diagnostic centres in Europe | Sensitivity/Specificity of 21 serum assays including cell-based assays (live, fixed and FACS) | No |

AQP4-Ab = aquaporin 4 antibodies; CSF = cerebrospinal fluid; FACS = fluorescence-activated cell sorting (flow cytometry); MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders

II=a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation

III-1=at study of test accuracy with an independent blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation

III-2=a comparison with reference standard that does not meet the criteria for level II and III-1 evidence

III-3=diagnostic case-control study

IV=study of diagnostic yield (no reference standard)

Two ‘non-systematic’ reviews that reported the sensitivity and specificity of AQP4-Ab detection assays, (including cell-based assays) were identified, but not included.

The first was a review by Ruiz-Gaviria et al. (Ruiz-Gaviria et al. 2015) that included studies comparing the sensitivity and specificity of different assays in the detection of serum AQP4-Abs, but used the Wingerchuk NMO diagnostic criteria (1999 and 2006) as the reference standard. There were no details of critical appraisal of the included studies. The second review, by Waters et al., (2014) searched only the PubMed bibliographic library database to locate studies that compared the sensitivities of serum AQP4-Ab assays, based on ‘positivity in clinically-defined NMO patients’, without further information. In addition, specificity data were based only on results from MS patients.

A further study by Fryer et al. (2014) compared the performance of serum AQP4-Ab assays in patients with NMOSD, but compared the test results with reference to physician-assigned pre-test diagnosis (based on Wingerchuk 2006 criteria). It was also not included in this report.

A full profile of each included study is given in Appendix C. Those studies which technically met the inclusion criteria, but which were not included in the results section or meta-analyses, are listed in Appendix E.

## Outcome Measures and Analysis

Appendix C contains details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

Rather than extracting data from the included studies into classic 2 x 2 tables to assess diagnostic accuracy of the proposed test, the published sensitivity and specificity data were used.

As reported in section B3.1, a reference standard has not been defined, therefore the outcomes of interest reported for diagnostic performance of AQP4-Ab testing in serum and CSF were:

* Positive percent agreement and (PPA)
* Negative percent agreement (NPA)

The estimation of PPA and NPA, rather than sensitivity and specificity, reflects that the estimates are not of accuracy but of agreement (concordance) between the three different serum AQP4-Ab cell-based tests. To determine agreement between the three different serum cell-based tests (live, fixed or FACS) and between serum versus CSF testing, data provided by the studies (positive predictive and negative predictive values) (Waters et al. 2016) and antibody detection data (Jarius et al. 2010) were used and presented in a concordance analysis. A limitation of a concordance analysis is that it can say whether cell-based assays agree with each other, but not if the detection of AQP4-Abs is accurate. However, cell-based assays are already being used in Australia and their accuracy has been deemed sufficient (Prain et al. 2019). There are also differences between the included studies regarding such aspects as population recruitment, storage and handling of samples and testing techniques (refer Appendix H).

## B3.5 Results of the Systematic Literature review

### Is it accurate?

Summary – How accurate is AQP4-Ab testing (serum and CSF) for detecting AQP4-Ab in patients suspected of NMOSD?

There is no reference standard for diagnostic accuracy (analytic validity); therefore test performance in this assessment was limited to the comparison between different types of cell-based assays. The implication of this is that the data identify whether different cell-based assays agree (concord) with each other, but not if they give an accurate detection of AQP4-Abs. That being said, this test is already in use in Australia and is recommended in International guidelines, so its accuracy is deemed sufficient.

Concordance between different serum cell-based assays to detect AQP4-Abs

Based on limited evidence, concordance analysis between three cell-based assay methodologies - live, fixed and FACS - showed that all three assays agreed with each other in the detection of AQP4-Abs. The PPA for all three assays ranged from 96-100%. There was slightly less agreement between the three assays for detecting AQP4-Ab 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 detection of AQP4-Abs negative samples.

Concordance between assays using serum and CSF to detect AQP4-Abs

Based on results of only one study, concordance analysis between serum (fixed cell assay) and CSF samples to detect AQP4-Abs, showed that 32% of sero-positive AQP4-Ab cases were not AQP4-Ab positive in CSF. The PPA for serum and CSF was 100% and 68%, respectively. The NPA of 100% was the same for both serum and CSF. Thus, there were no sero-negative cases identified by CSF, which means the usefulness of CSF sampling as an additional AQP4-Ab test, in sero-negative patients appears questionable. However, clinical advice is that CSF AQP4-Ab testing may still be used in some clinical situations (e.g. a CSF test may be requested to confirm a serum AQP4-Ab negative test).

## B3.6 Concordance analysis

### Concordance between different cell-based assays to detect aqp4-abs

Results of a concordance analysis, using sensitivity and specificity data provided by Waters et al. (2016) and Jarius et al. (2010), are displayed in Table 17. The cell-based assays, live, fixed and flow cytometry assays (FACS), were all investigated.

All three live cell-based assays investigated by Waters et al. (2016) showed a high level of PPA with detection of serum AQP4-Abs in between 97 to 100% of AQP4-Ab seropositive NMO/NMOSD patients. There was also a high level of NPA for all three live cell-based assays (range 96-100%)

Results from two studies (Jarius et al. 2010; Waters et al. 2016) comparing 11 fixed cell-based assays, showed there was a high level of PPA for detection of serum AQP4-Abs in AQP4-Ab seropositive NMO/NMOSD patients, with a pooled PPA of 100% (95% CI 93,100) (refer to Table 14). The NPA for the fixed cell-based assays was lower at 81% (95%CI 76, 86).

For flow cytometry assays (FACS), Waters et al. (Waters et al. 2016) showed that, based on results of four FACS, there was a high level of positive agreement for the detection of serum AQP4-Abs in AQP4-Ab seropositive patients with a pooled PPA of 96% (95% CI 92,98) (refer Table 14). However, the level of negative agreement was lower with a pooled NPA of 85% (95% CI 55, 97) with greater inter-laboratory assay variation, evident by the wider differences in CIs.

Table **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; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; 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

### Concordance between serum and cerebrospinal fluid testing for aqp4-ab detection

One study (Jarius et al. 2010) provided analytical validity data for testing CSF samples compared to serum samples using fixed cell-based assay (Figure 7). An analysis of 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 AQP4-Ab positive in CSF, with a PPA in serum and CSF of 100% and 68%, respectively. These results for testing CSF for AQP4-Abs are 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. The NPA was the same for both serum and CSF.

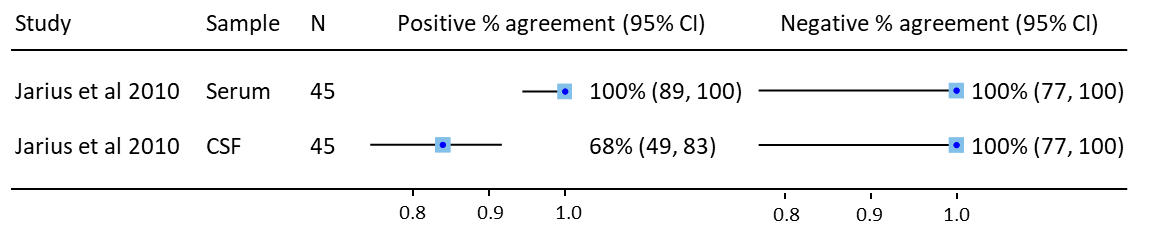


Figure Concordance in assay samples using seruma versus cerebrospinal fluid

CSF = cerebrospinal fluid

a fixed cell-based assay used

## Interpretation of evidence on diagnostic performance

There was only limited evidence found on the diagnostic performance of AQP4-Abs. There were methodological differences between the included studies, such as population recruitment, storage and handling of samples and testing techniques, due to the fact that a number of different diagnostic centres throughout Europe were involved. There was also lack of detail regarding the initial test in the study population that diagnosed NMO/NMOSD. In addition, due to a lack of reference standard, only a concordance analysis could be performed to determine the agreement between cell-based assays, rather than which one was the most accurate at detecting AQP4-Abs.

Overall, all serum cell-based assays tend to agree with each other when detecting AQP4-Abs. The PPA for all three assays (live, fixed and FACS) ranged from 96-100%. There was slightly less agreement between the three assays for not detecting serum AQP4-Abs, where fixed cell (NPA 81%) and FACS (NPA 85%) were less likely to agree with a live cell-based assay (NPA 100%) for negative detection of AQP4-Abs.

CSF performed poorly against serum, agreeing with only 68% of positive samples. It did not detect any additional positive samples in CFS that were negative in serum, questioning its value as an additional test in sero-negative patients. However, as reported in the ratified PICO page 10, clinical advice suggests that CSF AQP4-Ab testing may be used in some clinical situations, for examine if a serum test is negative, a CSF test may be requested as confirmation.

# B4 Clinical Validity

## B4.1 Measures of clinical validity

The clinical validity of a test depends on the prevalence (or pre-test probability) of the target condition or outcome of interest. The key measures used are the positive and negative predictive values, which are the probabilities of disease or absence of disease in a tested individual. These measures are heavily dependent on the prevalence of disease in the study population, and cannot be readily transferred to different populations or pooled to produce a summary estimate.An estimate of the prevalence of the target population in Australia has therefore been provided in this section. The prevalence of NMOSD varies across the globe and is higher in Asian populations, therefore those populations with a higher proportion of those with Asian origins tend to have a correspondingly higher number of individuals with NMOSD.

Ideally, the sensitivity and specificity of diagnosis with the antibody tests in addition to clinical characteristics, compared to diagnosis based on clinical characteristics alone, would be used to determine the PPV and NPV. In this section, sensitivity and specificity were calculated from data extracted from the relevant articles. However, there were several issues that arose with these measures that prevented these data from being reliable. The issues included:

* Incorporation bias – diagnosis by clinical characteristics (2015 IPND criteria) is the clinical reference standard, however the IPND includes the option of AQP-Ab testing which also forms part of the index test (see Section B4.1.1 for explanation);
* It is assumed by clinicians that AQP4-Ab positivity is definitive for a diagnosis of NMOSD. When it is not reported to the contrary, zero cases are assumed for false positive AQP4-Ab results;
* A negative test result for AQP4-Ab does not rule out a NMOSD diagnosis;
* In the literature, a reported patient result of AQP4-Ab negative may also mean status is not available for the purposes of calculating sensitivity;
* There is no clinical reference standard for MOG-Ab testing and so only yield data can be provided for this test.

Due to the unreliability of the sensitivity, specificity, NPV and PPV, evidence for prognosis of AQP4-Ab and MOG-Ab testing has been included (Section B4.2). If testing shows a difference in prognosis between those found positive and negative amongst those tested who are at risk of NMOSD, then this step can contribute to the linked evidence. Prognostic evidence may show that the tests have some validity for separating those at risk from those who are not, however further steps of linked evidence are required to show that those at risk are managed differently from those who are not at risk (Section B5.1) and that their health outcomes benefit as a result (Section B5.2).

### Incidence and prevalence of NMOSD

Two Australian studies (Bukhari et al. 2017; Fabis-Pedrini et al. 2018) were included in this report to investigate the incidence and prevalence of NMOSD. One study by Bukhari et al. (2017) investigated the incidence and prevalence of NMOSD in the Australia and New Zealand population using data from centres managing patients found to have clinical and laboratory features suspicious for NMOSD, and who were tested for AQP4-Abs. The other study by Fabis-Pedrini et al. (2018) investigated just the prevalence of NMOSD in a laboratory-based study using sera or CSF samples from patients suspicious of NMOSD, submitted to the sole pathology laboratory for AQP4-Ab testing in Western Australia, over a three-year period. A control group of patients with definite MS were also included in the study. Both studies used the most recent 2015 diagnostic criteria for NMOSD by Wingerchuk et al. (2015). Critical appraisal to determine the quality of these included studies was not conducted as they are providing only background information. Table 18 summarises results of the two included studies.

Bukhari et al. (2017) estimated the crude incidence and prevalence of NMOSD in Australia to be 0.37 per million per year, and 0.70 per 100,000 patients respectively, based on a capture-recapture analysis (Bukhari et al. 2017). However, the Western Australian study estimated the Australian prevalence for AQP4-Ab positive NMOSD to be 1.9 per 100,000 patients (Fabis-Pedrini et al. 2018). The differences in the prevalence estimated by the two studies could be attributed to the patient selection and study design.

Table 18 Incidence and Prevalence of NMOSD in Australia

| Country | Australia/ New Zealand | Australia (Western Australia) |
| --- | --- | --- |
| Study | Bukhari et al. 2017 | Fabis-Pedrini et al. 2018 |
| Population | Adults/children with clinical/laboratory features suspicious NMOSD  81/170 confirmed NMOSD cases | Patients with possible NMOSD;  Controls (MS cohort)  Caucasian 89.8%  Asian 8.2% |
| Number patients in study | 170 | 196+205 controls |
| Female: Male ratio | 6:1 | NR |
| Age years (range) disease onset | NR | NR |
| Incidence  (95% CI) | 0.33 (0.11, 0.55) /million/year  0.37 (0.35,0.39) **/**million**/**yeara | NR |
| Prevalence per 100,000 (95% CI) | 0.53 (0.45,0.62)  0.70 (0.66,0.74)a | 1.9 (CI NR) |
| n/N (%) +ve AQP4-Ab | 73/171 (43) | 5/196 (2.6)b  MS cohort (0) |
| Assay used | 46% Cell-based | Cell-based |

AQP4-Ab = aquaporin 4 antibodies; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders; NR = not reported; +ve = seropositive

a adjusted based on capture-recapture analysis to identify cases identified in laboratory results that were missed in clinical survey.

b patient selection may have inadvertently allowed patients with low risk of NMOSD being included, contributing to the low frequency of AQP4-Ab positivity.

Further prospective epidemiological studies are warranted to determine the population incidence and prevalence of NMOSD (AQP4-Ab positive and negative) in Australia. Patient numbers (clinical expert advice) indicate the prevalence of NMOSD is higher in Australia than reported by Bukhari et al. (2017), with an estimate of 500 to 600 patients in total (indicating a prevalence of 2-2.3 per 100,000).

The applicant conducted a survey of clinicians and pathology laboratories around Australia on PASC advice. Results indicated a prevalence of 2.9% and 5.4% AQP4-Ab positive NMOSD in the diagnostic cohort suspected of NMOSD in Queensland (includes tests referred by SA Pathology) and Western Australia, respectively. The data from Queensland Health did not specify the number of tests used for patient monitoring and may overestimate the prevalence in the diagnostic population. The crude incidence based on number of positive results provided in the above data is estimated to be around 0.50-0.92 per 100,000. (Refer to section C.X for further details).

## Reference standard

The clinical reference standard for this assessment is clinical diagnosis based on the 2015 IPND criteria. However, this raises some problems when assessing test accuracy.

Studies comparing diagnosis by AQP4-Ab and MOG-Ab testing with the 2015 IPND criteria are inherently flawed. They are at high risk of incorporation bias because diagnosis based on the 2015 IPND criteria incorporates the results of the index test (AQP4-Ab testing). In this case, when AQP4-Ab testing is common to both the reference standard and the index test there can be an over-estimate of the accuracy of the index test (Roever 2016).

It was not always reported whether AQP4-Ab testing had been used as part of the reference diagnostic criteria in the articles identified in the literature, and in these cases the risk of incorporation bias was not clear.

AQP4-Ab and MOG-Ab testing are not able to identify all patients with NMOSD. There are still a proportion of patients who test negative for both antibodies. Ideally, both tests should be used in addition to diagnosis by clinical characteristics as a reference standard to detect all cases.

## Risk of Bias Assessment

There were 12 studies providing evidence for diagnostic accuracy and these were assessed using the QUADAS-2 appraisal tool (Whiting et al. 2011). Of the 12, three were appraised as high risk of bias and the remaining nine were found to be moderate risk of bias. Because of the inherent incorporation bias in the clinical reference standard (diagnosis using the 2015 IPND criteria), all studies were rated high risk of bias for the reference standard (see section B4.1.1 for further information). Patient selection was highly specific according to study inclusion criteria. However, the retrospective study design makes it difficult to judge selection bias if there was report of including consecutive cases. The studies that were rated high for risk of bias either did not fully apply the reference standard to diagnose eligible cases, or included some older cases that had been included by application of the 2006 criteria rather than the 2015 IPND criteria as the reference standard.

Results of the individual domains from study appraisals for diagnostic accuracy studies (level III-3 evidence) are seen in Table 19.

A total of 17 studies provided information on diagnostic yield from patients who were positive or negative for AQP4-Ab and MOG-Ab testing (Table 20). Fifteen of the 17 studies were case series (level IV) and were rated from moderate to high for overall risk of bias using the IHE Checklist for case series (IHE 2014). The remaining two studies (Bouzar et al. 2017; Hamid et al. 2017) were assessed for risk of bias using QUADAS-2. The overall risk of bias for these latter two studies was high. (Individual domain outcomes were not reported for level IV evidence).

Table 19 Risk of bias domains (QUADAS-2) of the included level III-3 diagnostic accuracy studies

|  |  | Risk of bias |  |  | Applicability concerns | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Patient selection | Index test | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Bouzar 2017 | ☹ | ☺ | ☹ | **?** | ☺ | ☺ | **?** |
| Contentti 2017 | ☺ | ☺ | ☹ | ☺ | ☺ | **?** | ☺ |
| Cheng 2016 | ☹ | ☹ | ☹ | **?** | ☺ | ☺ | ☺ |
| Duignan 2018 | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ | ☺ |
| Hacohen 2017 | ☺ | ☺ | ☹ | ☺ | **?** | ☺ | ☺ |
| Hamid 2017 | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ | ☺ |
| Hyun 2017 | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ | ☺ |
| Jain 2016 | **?** | ☺ | ☹ | ☺ | ☺ | ☺ | ☺ |
| Kang 2019 | ☺ | ☺ | ☹ | **?** | ☺ | ☺ | **?** |
| Contentti 2019 | ☺ | ☺ | ☹ | ☺ | **?** | ☺ | ☺ |
| Liu 2019 | **?** | ☹ | ☹ | ☺ | ☺ | ☹ | ☺ |
| Papais 2018 | ☺ | ☺ | ☹ | ☺ | **?** | ☺ | ☺ |

☺ Low Risk; ☹ High Risk; **?** Unclear Risk

## Characteristics of the Evidence Base

See Appendix C for details on the individual studies included in the evidence base.

A summary of the characteristics of studies meeting inclusion criteria for clinical validity accuracy is shown in Table 20. Those studies which technically met the inclusion criteria, but which were not included in the results section or meta-analyses, for various reasons, are listed in Appendix E.

Twelve studies were included for evidence of test accuracy in a clinical setting. Only studies for which data could be extracted to compare patient AQP4-Ab or MOG-Ab test results to a clinical diagnosis using the 2015 IPND criteria were included. The 12 studies were retrospective cohorts with before and after test data, providing level III-3 evidence for diagnostic accuracy. Study populations varied in their initial CNS symptom, and thus were limited in their comparability. However all met one of the 2015 IPND criteria, which would make the patients eligible for AQP4-Ab testing in the Australian setting (See Appendix F for the IPND diagnostic criteria). Populations also varied in size – ranging from 31 to 505 cases. While the location where the studies were conducted also varied, a high proportion were conducted in Asian countries (K= 6 of 12 studies).

The sixteen studies that provided diagnostic yield evidence for AQP4-Abs and MOG-Abs were level IV evidence. All study populations met the Wingerchuk IPND 2015 criteria for test eligibility. Both adults and children were represented in the included studies, with a variety of initial CNS symptoms, including inflammatory conditions or demyelination syndromes, ON or LETM and presenting or suspected NMO/NMOSD. The majority of studies used cell-based assays for antibody testing. Study populations came from a variety of different countries including seven studies from Asia. Study populations ranged in size from 14 to 1,917 participants.

Table Key features of the included studies for clinical validity

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design**  **Level** | **Risk of bias** | **Sample Size** | **Patient population** | **Intervention** | **Comparator** | **Outcomes** |
| (Bouzar et al. 2017)  Algeria. | CS  III-3 | High | 43 | Adults with monophasic or recurrent inflammatory disease affecting the optic nerve and/or spinal cord | AQP4 and MOG antibody testing | NA | Accuracy  Yield |
| (Contentti, CE et al. 2017)  Argentina | CS  III-3 | Moderate | 30 | LETM at presentation; remitted for consideration of NMOSD, MS or other immune -mediated CNS disorder | AQP4-Ab testing; MRI; clinical assessment and diagnosis at follow-up | original diagnosis | Accuracy  Yield |
| (Chen, Q et al. 2018)  China | CS  IV | Moderate | 87 | Patients ≤18 years-old with acute-onset optic neuritis | AQP4-Ab and MOG-Ab testing | NA | Yield |
| (Cheng et al. 2016)  China | CS  III-3 | High | 31 | First event ABS | Diagnosis by clinical criteria (2015) and AQP4 status | diagnosis by clinical criteria (pre 2015 and no AQP4-Ab testing) | Accuracy  Yield |
| (Drulovic et al. 2019)  Serbia | CS  IV | Moderate | 74 | Patients with NMOSD | AQP4-Ab and MOG-Ab testing | NA | Yield |
| (Duignan et al. 2018)  UK | CS  III-3 | Moderate | 371 | Suspected of ADS; AQP4-Ab and MOG-Ab testing requested | Diagnostic assessment following AQP4-Ab and MOG-testing (live sell assays) | NA | Accuracy  Yield |
| (Hacohen et al. 2017)  UK | CS  III-3 | Moderate | 110 | Children attending CNS Inflammatory Demyelination Work Group Centers diagnosed with RDS | AQP4-Ab and MOG-Ab testing; clinical assessment | NA | Accuracy  Yield |
| (Hamid et al. 2017)  UK | CS  III-3 | High | 261 | Patients seen in the clinic over the last 4 years (after the availability of MOG-IgG testing) | AQP4-Ab and MOG-Ab testing | NA | Accuracy  Yield |
| (Hyun et al. 2017)  South Korea | CS  III-3 | High | 505 | Suspected IDD CNS diseases who had available serum samples | AQP4-Ab and MOG-Ab testing | NA | Accuracy  Yield |
| (Houzen et al. 2017)  Japan | CS  IV | Moderate | 14 | Patients with NMOSD  Mean age at onset 45.2 (13-75) | AQP4-Ab and MOG-Ab testing | NA | Yield |
| (Jain et al. 2016)  India | CS  III-3 | High | 64 | LETM of three or more segments of spinal cord on MRI | AQP4-Ab testing by ELISA; MOG-Ab testing; clinical assessment and diagnosis | previous clinical assessment | Accuracy  Yield |
| (Kang et al. 2019)  China | CS  III-3 | Moderate | 51 | Presentation with simultaneous or nearly simultaneous bilateral ON; diagnosis of ON confirmed by using the ONTT | AQP4-Ab (live cell assay) and MOG- Ab testing (fixed cell-based assay) | NA | Accuracy  Yield |
| (Contentti, EC et al. 2019)  Argentina | CS  IV | Moderate | 57 | First episode of clinically acute ON | AQP4-Ab testing; diagnostic categorisation; | NA | Accuracy  Yield |
| (Liu et al. 2019)  China | CS  III-3 | High | 158 | Adult ON | Assessment of visual acuity; MS and NMO diagnosis (by current international criteria) | NA | Accuracy  Yield |
| (Papais-Alvarenga et al. 2018)  Brazil | CS  III-3 | Moderate | 200 | adults with NMO (2006 criteria) and HR-NMO | AQP4-Ab and MOG-Ab testing; application of 2015 diagnostic criteria | NA | Accuracy  Yield |
| (Papais-Alvarenga et al. 2015)  Brazil | CS  IV | Moderate | 1,917 | IIDD | Spectrum of IIDD | None reported | Yield |

ABS = acute brainstem syndrome; ADS = acquired demyelination syndrome; AQP4 = aquaporin 4; AQP4-Ab = aquaporin 4 antibodies; CNS = central nervous system; CS = case series; ELISA = enzyme-linked immunosorbent assay; HR-NMO = high risk of conversion to NMO; IDD = inflammatory demyelinating disorder; IIDD = idiopathic inflammatory demyelinating disease; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; MOG = myelin oligodendrocyte glycoprotein; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MRI = magnetic resonance imaging; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; ONTT = optic neuritis treatment trial; RDS = relapsing acquired demyelinating syndrome

## Outcome Measures and Analysis

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

To assess the diagnostic accuracy of the proposed test, studies were only included if they provided data that could be extracted into a classic 2 x 2 table (Table 21), in which the results of the index test or the comparator were cross-classified against the results of the reference standard[[6]](#footnote-6), and Bayes’ Theorem was applied.

Table 21 Diagnostic accuracy data extraction

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| - | - | **Reference standard** |  | - |
| - | - | *Disease +* | *Disease –* | - |
| **Index test** | *Test +* | true positive | false positive | Total test positive |
| Or comparator | *Test –* | false negative | true negative | Total test negative |
| - | - | Total with disease | Total without disease | - |

In studies from which accuracy data could not be extracted, diagnostic yield data were reported for the number testing positive or negative for AQP4-Ab and MOG-Ab in relevant populations.

## Results of the Systematic Literature review

### Is it accurate?

Summary – 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?

Although the diagnostic accuracy of AQP4-Ab testing compared to diagnosis by clinical characteristics (2015 IPND criteria) could be calculated from 2 x 2 tables using data from relevant publications, the nature of the intervention and issues with the reference standard reduced the usefulness of the diagnostic accuracy outcome.

There were insufficient data in the literature to determine the diagnostic accuracy of MOG-Ab testing for NMOSD compared to diagnosis by clinical characteristics alone.

Prognostic data collected in studies of populations *suspected* of NMOSD due to the presence of one or more relevant symptoms, provided a longitudinal picture of patients tested for AQP4 antibodies. The data indicated that the presence of AQP4 antibodies identifies a group of patients at risk of clinically significant worse outcomes (measured by visual impairment and ARR) amongst those suspected of NMOSD. A similar trend of worse visual outcomes in AQP4-Ab positive compared with negative patients was seen in those *diagnosed* with NMOSD. When assessed by EDSS, prognosis appeared worse for AQP4-Ab positive compared to negative patients *suspected* of NMOSD but there was some inconsistency in the results. (GRADE: VERY LOW ⨁⨀⨀⨀ to HIGH ⨁⨁⨁⨁)

Prognosis of MOG-Ab positive patients also appears to be worse than MOG-Ab negative patients amongst those *suspected* of NMOSD (measured with visual acuity, EDSS and ARR). However, there were fewer studies reporting these outcomes and there was some inconsistency among them. (GRADE: VERY LOW ⨁⨀⨀⨀ to MODERATE ⨁⨁⨁⨀)

There was no clinical reference standard available, but a clinical evidentiary standard of diagnosis by the 2015 IPND criteria was used to assess diagnostic accuracy. Problems associated with the evidentiary standard are discussed in Sections B4.1 and B4.1.1.

### Diagnostic accuracy

Data for 2 x 2 tables were extracted from 12 studies identified in the literature search. The majority of studies were retrospective case series which performed AQP4-Ab testing on patient serum samples identified in clinic databases, or accessed antibody test results from the data. The test results were compared against diagnosis by the 2015 IPND criteria (Table 22). The populations had a range of inclusion criteria, such as first event or history of LETM or acute brainstem syndrome (ABS), inflammatory demyelinating disorder (IDD) or CNS inflammatory disease; however only studies with populations not yet diagnosed with NMOSD were included. In all but two studies, positivity for AQP4-Ab afforded diagnosis of NMOSD with 100% specificity. In one study of adults with ON, patients were not necessarily diagnosed with NMOSD if they were AQP4-Ab positive and the specificity was 63.1% (Liu et al. 2019). Similarly, in a study conducted in children with relapsing acquired demyelinating syndrome (RDS), specificity was 99.02%. Sensitivity across the studies ranged from 25.57% in children with non-MS RDS to 88.24% in adults with ON. AQP4-Ab testing is reported in the IPND to have a mean sensitivity of 76.7% (pooled analysis) and a false positive rate of 0.1% (in a MS clinic cohort) for NMOSD by cell-based assay of serum (Wingerchuk et al. 2015).

Calculation of PPV and NPV was based on a mean pooled prevalence of 34.1% estimated from the rate of NMOSD diagnoses based on the 2015 IPND criteria reported in populations of inflammatory or acquired demyelinating disease (Table 43). By comparison, in Australian data reported by Bukhari et al, 81 out of 170 suspected NMOSD cases were confirmed (48%) (Bukhari et al. 2017). The criteria for suspected NMOSD were more restricted in Bukhari et al than those studies with diagnoses reported in Table 49. These prevalence data are contrasted by prevalence determined from Australian clinical laboratory test data collected by the Applicant. From the laboratory data, prevalence was found to be 2.9% in Queensland (including tests sent from South Australia) and 5.4% in Western Australia, reflecting a broader population undergoing testing than those in the literature. Another aspect influencing rates found in the literature is the retrospective study designs used. The populations in this type of study design tend to be highly selected and may therefore overestimate the prevalence of NMOSD or AQP4-Ab positivity. The rates determined from the Australian laboratory data will be used in the economic analysis.

There was insufficient evidence to extract 2 x 2 table data on MOG-Ab testing compared to the evidentiary standard.

Table Results of key accuracy trials comparing AQP4-Ab testing against a clinical evidentiary standard (clinical diagnosis of NMOSD by the 2015 IPND criteria)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study ID  N | Population tested | Sensitivity  [95%CI] | Specificity  [95%CI] | PPVa  [95%CI] | NPVa  [95%CI] |
| Contentti et al, 2017  N=30 | First event LETM | 64.29% [35.14, 87.24] | 100%  [79.41, 100.00] | 100% | 84.4%  [72.8, 91.6] |
| Cheng et al 2016  N=31 | First event ABS | 85.35% [56.57, 96.20] | 100%  [76.84, 100.00] | 100% | 91.6%  [79.7, 96.8] |
| Liu et al 2019  N=158 | Adults with ON | 88.24%  [63.56, 98.54] | 63.12%  [54.59, 71.08] | 55.3%  [48.4, 62.0] | 91.2%  [73.7, 97.5] |
| Papais-Alvarenga et al 2018 | IDD | 40.87%  [31.70, 50.43] | 100%  [95.75, 100.00] | 100% | 76.6%  [73.7, 79.2] |
| Hamid et al 2017  N=261 | Adult ADS | 72.73%  [64.29, 80.11} | 100%  [97.18, 100.00] | 100% | 87.6%  [84.3, 90.4] |
| Bouzar et al 2017  N=42 | History of ON, LETM or myelitis | 46.15%  [19.22, 74.87] | 100%  [88.06, 100.00] | 100% | 78.2%  [68.5, 85.6] |
| Jain et al, 2016  N=64 | LETM, 3 or more segments | 61.90%  [38.44, 81.89] | 100%  [91.78, 100.00] | 100% | 83.5%  [74.6, 89.7] |
| Contentti et al 2019  N=57 | First episode acute ON | 77.27%  [54.63, 92.18] | 100%  [90.00, 100.00] | 100% | 89.5%  [79.7, 94.8] |
| Hyun et al, 2017  N=505 | CNS inflammatory disease | 87.24%  [82.38, 91.16] | 100%  [98.60, 100.00] | 100% | 93.8%  [91.6, 95.5] |
| Kang et al 2019  N=51 | Bilateral optic neuritis | 64.52%  [45.37, 80.77] | 100%  [83.16, 100.00] | 100% | 84.5%  [77.2, 89.8] |
| Duignan et al 2018  N=237 | Children with ADS | 42.42%  [25.48, 60.78] | 99.02%  [96.50, 99.88] | 95.7%  [84.2, 98.9] | 76.9%  [71.3, 81.7] |
| Hacohen et al 2017  N=48 | Children with RDS (non-MS) | 28.57%  [13.22, 48.67] | 100%  [83.16, 100.00] | 100% | 73.0%  [68.2, 77.4] |

ABS = acute brainstem syndrome; ADS = acquired demyelination syndromes; AQP4-Ab = aquaporin 4 antibodies; CI = confidence interval; CNS = central nervous system; LETM = longitudinally extensive transverse myelitis; NPV = negative predictive value; PPV = positive predictive value; RDS = relapsing acquired demyelinating syndrome

a Calculation were performed using the MedCalc online calculator; and were based on the mean pooled prevalence of 34.1% in patients with inflammatory or acquired demyelinating disease (Table 21).

### Diagnostic Yield

Data on diagnostic yield were tabled according to different populations (all patients, adults and children) and presenting conditions, where the presenting conditions were: 1) inflammatory conditions or demyelination syndromes (including, but not limited to, conditions such as acute brainstem syndrome, idiopathic inflammatory demyelinating disease and acquired demyelination syndromes); 2) ON or LETM and 3) presenting or suspected NMO/NMOSD).

Diagnostic yield from serum AQP4-Ab and MOG-Ab testing in all patients, adults and children with inflammatory conditions or demyelination syndromes is displayed in Table 23. A total of six included studies contained between 31 and 1,917 subjects.

For studies that included patients with inflammatory conditions or demyelination syndromes, the diagnostic yield for AQP4-Ab seropositivity ranged from 34.9% to 45.2%. Only one study (Hyun et al. 2017) reported MOG-Ab testing, which showed that only 4.4% of patients with suspected inflammatory demyelinating CNS diseases were MOG-Ab positive. In adults, the diagnostic yield for positive AQP4-Ab ranged from 14.3% to 73% and for positive MOG-Ab from 7.1% to 11%. One of these studies (Hamid et al. 2017) showed that for adults who tested negative for AQP4-Ab, 42% (15/36) tested positive for MOG-Ab. One study reporting on children showed that over 90% tested negative for AQP4-Ab, and 32% tested positive for MOG-Ab.

Table 23 Diagnostic yield for AQP4-Abs and MOG-Ab in patients, adults and children with inflammatory conditions or demyelination syndromes

| **Study**  **Patients (N)** | **Population** | **AQP4-Ab +ve (%)** | **AQP4-Ab –ve (%)** | **MOG-Ab +ve (%)** | **Double -ve for AQP4 and MOG Ab (%)** |
| --- | --- | --- | --- | --- | --- |
| Cheng et al. 2016  N = 31 | First-event ABS | 14/31 (45.2) | 17/31 (54.8) | NR | NR |
| Hyun et al. 2017  N = 505 | Suspected inflammatory demyelinating CNS diseases | 212/505 (42) | 31/505 (6.1) | 22/505 (4.4) | NR |
| Papais-Alvarenga et al. 2015  N = 1,917 | IIDD | 113/324 (34.9) | 123/324 (38) | NR | NR |
| Bouzar et al. 2017  N = 42 | Adults with monophasic or recurrent inflammatory disease | 6/42a (14.3) | 36/42 (86) | 3/42 (7.1) | 33/42 (78.6) |
| Hamid et al. 2017  N = 132 | Adults with non-MS atypical CNS inflammatory conditions | 96/132 (73) | 36/132 (27) | 15/132 (11)   * 15/36 (42) in AQP4-Ab–ve | 21/132 (15.9) |
| Duignan et al. 2018  N = 237 | Children with ADS | 16/237 (6.8) | 221/237 (93.2) | 76/237 (32) | NR |

+ve = seropositive; -ve = seronegative; ABS = acute brainstem syndrome; ADS = acquired demyelination syndromes; AQP4 = aquaporin 4; AQP4-Ab = aquaporin 4 antibodies; CNS = central nervous system; IIDD =idiopathic inflammatory demyelinating disease; med = median; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders

a all six patients +ve for AQP4-Ab met 2015 Wingerchuk diagnosis criteria (2015) and were all –ve for MOG-Ab

Diagnostic yield from AQP4-Ab and MOG-Ab testing in all patients, adults and children with ON or LETM is displayed in Table 24. The number of subjects included in the studies ranged from 30 to 158.

For studies including all patients with either ON or LETM, the diagnostic yield for AQP4-Ab seropositivity ranged from 20% to 39%. Only one study (Kang et al. 2019) reported MOG-Ab testing and found that 16% of patients with ON tested positive for MOG-Ab, and over a quarter (26%) of patients AQP4-Ab negative were MOG-Ab positive. In adults with ON, between 29.8% and 42.4% were AQP4-Ab positive; one study (Liu et al. 2019) reported nearly a fifth of adults (19.6%) were positive for MOG-Ab. The Australian study by Bukhari et al (2017) 43% (73 of 170 suspected NMOSD cases) were AQP4-Ab positive, whereas 48% (81 of 170 cases) were diagnosed with NMOSD.

For children, one study (Chen, Q et al. 2018) reported that 84% of children with acute onset ON tested negative for AQP4-Ab, 13.3% tested positive for MOG-Ab and 70.7% tested negative for both AQP4-Ab and MOG-Ab.

Table 24 Diagnostic yield for AQP4-Ab and MOG-Ab in patients adults and children with ON or LETM

| **Study**  **Patients N (%)** | **Population** | **AQP4-Ab +ve (%)** | **AQP4-Ab –ve (%)** | **MOG-Ab +ve (%)** | **Double -ve for AQP4 and MOG Ab (%)** |
| --- | --- | --- | --- | --- | --- |
| Bukhari et al. 2017  N = 170 | Patients with severe ON, severe LETM, or other symptoms meeting 2015 IPND criteria for testing | 73/170 (43)a | 97/170 (57) | NR | NR |
| Kang et al. 2019  N = 51  N = 58 controls | Patients with simultaneous BON | 20/51 (39) | 31/51 (61) | 8/51 (16)   * 8/31 (26) in AQP4 –ve | 23/51 (45) |
| Contentti et al. 2017  N = 30 | Patients with LETM | 9/30 (30) | 21/30 (70) | NR | NR |
| Jain et al. 2016  N = 64 | Patients with LETM | 13/64a (20.31) | 5/64b (7.8) | NR | NR |
| Contentti et al. 2019  N = 57 | Adults with first episode of ON | 17/57 (29.8) | 40/57 (70.2) | NR | NR |
| Liu et al. 2019  N = 158 | Adults with ON | 67/158 (42.4) | 91/158 (57.6) | 31/157 (19.6) | 60/157 (38.0) |
| Chen et al. 2018  N = 75 | Children with acute onset ON | 12/75 (16) | 63/75 (84) | 10/75 (13.3) | 53/75 (70.7) |

AQP4-Ab = aquaporin 4 antibodies; BON = bilateral optic neuritis; LETM = longitudinally extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders. NR = not reported; ON = optic neuritis;

a 81 of 170 cases were confirmed to have NMOSD

b serostatus not available for 3 patients

Diagnostic yield from AQP4-Ab and MOG-Ab testing in all patients, adults and children with or suspected of having NMO or NMOSD is displayed in Table 25. The number of subjects in the included studies ranged from 14 to 243.

For studies that included all patients, the diagnostic yield for serum positive AQP4-Ab diagnosed with NMOSD ranged from 57% to 89%. Of those patients who tested negative for AQP4-Ab, between 0% and 29% tested positive for MOG-Ab. Between 7% and 22% of patients were negative for both AQP4 and MOG antibodies. One study (Papais-Alvarenga et al. 2018) reported that for adults with NMO, or at high risk of conversion to NMO, there was a higher yield for AQP4-Ab based on the 2015 (67%) versus 2006 (40.9%) Wingerchuk diagnostic criteria. For those testing positive for MOG-Ab, there were also differences based on the Wingerchuk criteria (0% 2015 criteria versus 7.4% 2006 criteria). In children with NMOSD, between 58 and 69% of children were AQP4-Ab negative, and between 39 and 83% positive to MOG-Ab.

Table 25 Diagnostic yield for AQP4-Ab and MOG-Ab in patients and adults with NMO or NMOSD

| **Study**  **Patients (N)** | **Population** | **AQP4-Ab +ve (%)** | **AQP4-Ab –ve (%)** | **MOG-Ab +ve (%)** | **Double -ve for AQP4 and MOG Ab (%)** |
| --- | --- | --- | --- | --- | --- |
| Drulovic et al. 2019  N = 74 | Patients with NMOSD | 66/74 (89.2) | 7/74 (9.5) | 2/7 (28.6) | 5/74 (6.8) |
| Houzen et al. 2017  N = 14 | Patients with NMOSD | 11/14 (78.6) | 3/14 (21.4) | 0/14 (0) | 3/14 (21.4) |
| Hyun et al. 2017  N = 243 | Patients with NMOSD | 212 (87.2) | 31 (12.8) | 10 (4.1)   * 1/212 (0.5) AQP4+ve * 9/31 (29) AQP4-ve | 53 (21.8) |
| Papais-Alvarenga et al. 2015  N = 200 | Patients with NMO/NMOSD | 113 (56.5) | 87 (43.5) | NR | NR |
| Papais-Alvarenga et al. 2018  N = 115a | Adults with NMO and HR-NMOb | 47/115 (40.9)c  47/70 (67.1)d | 68/115 (59.1)c  23/70 (32.9)d | AQP4-Ab–ve   * 5/68 (7.4)c * 0/70 (0)d | 63/115 (54.8)c  23/70 (32.9)d |
| Duignan et al. 2018  N = 33 | Children with NMOSD | 14 (42.4) | 19 (57.6) | 13 (39.4) | 6 (18.2) |
| Hacohen et al. 2017  N = 28 | Children with NMOSD | 8/26e (30.7) | 18/26e (69.2) | AQP4-Ab –ve  15/18 (83.3) | 3/26e (11.5) |

AQP4-Ab = aquaporin 4 antibodies; HR-NMO = high risk of conversion to NMO; MOG-Ab = myelin oligodendrocyte glycoprotein; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders;

a All 115 met Wingerchuk 2006 criteria and 70/115 (61%) met Wingerchuk 2015 criteria

b HR-NMO Included patients with NMO, LETM, bilateral ON, LETM or bilateral ON plus cerebral or brainstem syndrome

c patients who met the Wingerchuk 2006 diagnostic criteria

d patients who met the Wingerchuk 2015 diagnostic criteria

e calculated using statistical database https://www.statstodo.com/CombineMeansSDs\_Pgm.php

In summary, diagnostic yield for positive AQP4-Ab testing varied widely based on the inclusion criteria of the study (i.e. type of population (all patients vs adults vs children) and their presenting conditions or disease state), and which Wingerchuk NMO/NMOSD diagnostic criteria was used. Data on diagnostic yield for MOG-Ab testing were limited, however in those studies that reported MOG-Ab status, it was evident that some (but not all) individuals who tested negative for AQP4-Ab, were found to test positive for MOG-Ab.

#### Further Australian yield data

Two additional studies that did not meet the inclusion criteria reported test yield data in Australian clinics (Dahan et al. 2020; Fabis-Pedrini et al. 2018). The populations in the studies did not use the 2015 IPND criteria to determine eligibility for testing, however as the data came from Australian settings, they were used in the economic evaluation.

In contrast to Bukhari et al’s (2017) reported AQP4-Ab positive yield (43%) (Table 24), Fabis-Pedrini et al estimated a prevalence of 2.6% of seropositive samples in the diagnostic cohort of 196 consecutive Western Australian patients with a presentation suggestive of NMOSD referred to the PathWest State reference laboratory for diagnostic AQP4-IgG testing during the period from June 2010 to November 2012 (Fabis-Pedrini et al. 2018). Laboratory-based series may not include a uniform clinical population and so the rate of positivity may be less than accurate at the population level.

Another Australian study determined frequency of AQP4-Ab seropositivity (retrospectively) in a cohort of children with central nervous system (CNS) demyelination at the Royal Children’s Hospital, Melbourne (Dahan et al. 2020). Of the 67 children tested for AQP4-Ab, five (7.5%) were diagnosed with NMOSD and only one child was positive for AQP4-Ab (1.5% of the whole cohort and 20% of the NMOSD cases). A total of 12 children (17.9%) in this study were tested for MOG-Ab. Ten children (83.3%) were positive for MOG-Ab, two of these had AQP4-Ab–negative NMOSD. The study concluded that AQP4-Ab seropositivity is rare in children presenting with CNS demyelination overall, but MOG-Ab are present in a significant proportion of children with AQP4-Ab–seronegative NMOSD. The results of this study should be interpreted with caution, as the study sample was very small.

## B4.2 Prognosis or predisposition

Studies that reported the temporal development of symptoms in patients presenting with symptoms of NMOSD, comparing those testing positive and those testing negative by an AQP4-Ab assay, were included in this section. Although the articles included here often documented the treatments patients were given, they did not provide evidence of a treatment effect (even if there was one), reporting only follow-up data on symptoms (articles reporting on treatment effectiveness were included in Section B5.2.4). Studies with similar outcomes for MOG-Ab testing were also included. This type of data can provide evidence for the prognostic effect of AQP4-Ab and MOG-Ab testing. If antibody positivity can predict a different outcome in the tested population, then it is possible that earlier detection will lead to earlier treatment and better outcomes. In this way, prognostic data can provide evidence for a step of the linked evidence (in the absence of reliable diagnostic accuracy data).

### B4.2.1 Characteristics of the evidence base

Prognostic outcomes have been provided by eight case series listed in Table 26. All of the studies were retrospective case series with before and after data (level IV). They were appraised with the appropriate tool and all but two studies were assessed as having moderate risk of bias; Li et al, 2015 (2015) and Zhou et al, 2016 (2016) were found to have low risk of bias.

Four of the level IV studies (Cheng et al. 2016; Contentti, CE et al. 2017; Liu et al. 2019; Zhou et al. 2016) performed AQP4-Ab (or MOG-Ab) testing and diagnosis based on the 2015 IPND criteria (Wingerchuk et al. 2015) and two studies (Cobo-Calvo et al. 2016; Li et al. 2015) performed testing and diagnosis based on the 2006 criteria ((Wingerchuk et al. 2006)). Two other studies (Matsuda et al. 2015; Weinshenker et al. 2006) did not use either the 2006 or the 2015 diagnostic criteria, but assessed before and after symptom severity or relapse rate. Because the outcomes were compared between antibody positive and negative patients (ie test results were not dependent on other criteria), studies that diagnosed patients by the 2006 criteria or symptom severity alone were not excluded.

Studies conducted by Liu et al (2019), Cheng et al (2016) and Cobo-Calvo et al (2016) used a cell-based assay for AQP4-Ab determination. Liu et al and Cobo-Calvo et al also assessed MOG-Ab status by cell-based methods. Contentti et al (2017) used indirect immunofluorescence (IIF) to assess AQP4 antibodies, and the authors acknowledged that more seropositive patients might have been identified if more sensitive methods were used.

There was a minimum follow-up time of 12 months amongst the studies. One of the studies focused on longitudinal outcomes for AQP4-Ab negative patients (Cobo-Calvo et al. 2016).

Table Case series (level IV evidence) included for prognostic outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study ID  Country | Median follow-up | Risk of bias | Population description  N cases | Intervention | Outcomes |
| (Contentti, CE et al. 2017)  Argentina | Mean 34 ± 20.3 months | Moderate | First presentation LETM  N=30 | AQP4-Ab testing and diagnosis (2015 criteria) | Rate of conversion from first event to NMOSD or MS diagnosis  Relapse rate |
| (Cheng et al. 2016)  China | Mean 44.51 ± 14.86 months | Moderate | First event ABS  N=31 | AQP4-Ab testing and diagnosis (2006 and 2015 criteria) | Rate of conversion from first event to NMOSD or MS diagnosis  Relapse rate  Change in EDSS  Risk of developing NMOSD |
| (Cobo-Calvo et al. 2016)  France, Spain | 42.2 (25-79.5) months | Moderate | Monophasic LETM; AQP4-AB -ve  N=56 Adults | MOG-Ab testing and diagnosis (2006 criteria) | Rate of conversion from first event to NMOSD  Rate of conversion from first event to MS  Recurrence rate of LETM after first event |
| (Liu et al. 2019)  China | >12 months | Moderate | ON diagnosis based on the ONTT criteria  N=158 | AQP4-Ab and MOG-Ab testing; diagnosis (2015 criteria) | Rate of conversion from ON diagnosis to NMOSD diagnosis |
| (Li et al. 2015)  China | >12 months | Low | Recurrent or bilateral ON  N=125 | AQP4-Ab testing and diagnosis (2006 criteria) | Rate of conversion to NMOSD or MS  Rate of VA remission |
| (Matsuda et al. 2015)  Japan | Mean 2.8±1.1 years | Moderate | Patients with ON  N=70 | AQP4-Ab and MOG-Ab testing | VA improvement  VA deficit  Annual relapse rate |
| (Weinshenker et al. 2006)  USA | Median 19.3 (range 2.3-74.1) months | Moderate | First episode LETM  N=29 | AQP4-Ab testing | Rate of LETM relapse  Occurrence rate of ON |
| (Zhou et al. 2016)  China | 5 years | Low | First episode ON  N=128 | AQP4-Ab testing and diagnosis (2015 criteria) | Visual recovery  Conversion to NMO  Conversion to MS  Rate of relapsing ON  Rate of legal blindness |

AQP4-Ab = aquaporin 4 antibodies; ABS = Acute brainstem syndrome; EDSS = expanded disability scale; IDD = inflammatory demyelinating disorder; LETM longitudinally extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; ONTT = Optic Neuritis Treatment Trial; RDS = relapsing acquired demyelinating syndromes; VA = visual acuity

One additional study, a systematic review (SR) by Lin, N et al (2017), provided prognostic data for AQP4-Ab testing in patients diagnosed with NMOSD. Visual impairment was compared between AQP4-Ab positive and negative NMOSD patients. The study was moderate for risk of bias (AMSTAR 2), and included cohort studies that were assessed by the authors as moderate to high quality according to the Newcastle-Ottawa Scale. To meet the inclusion criteria patients were diagnosed with NMO by the 1999 or 2006 Wingerchuk criteria and reported any type of visual outcome (Table 27).

Table Systematic review evidence included for prognostic outcomes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study ID  Country | K studies  N cases | Risk of bias | Inclusion criteria  Follow-up | Intervention | Comparator | Outcomes |
| (Lin, N et al. 2017)  Argentina | K=18  N=1198 | Moderate | Cohort studies of NMO patients with AQP4-Ab status | AQP4-Ab testing | No testing | Comparison and meta-analysis of Visual Impairment between seropositive and seronegative patients  Sub group analysis between assay types. |

AQP4-Ab = aquaporin 4 antibodies; NMO = neuromyelitis optica

### B4.2.2 Outcome measures and Analysis

Prognosis results provided were hazard ratios (HR or OR) or simple rates (percentage; %), compared between seropositive and seronegative groups. Outcomes were change in EDSS, change in ARR, rate of visual recovery, and rate of conversion from first event to NMOSD or MS. The EDSS is a scale often used for measuring the level of disability in those with neurological disorders. Kurtzke et al introduced the EDSS in 1983 as an improvement to the sensitivity of measurement of MS disability (Kurtzke JF 1983)[[7]](#footnote-7). It is commonly used in the studies to measure the change in the level of disability over time.

The ARR is another measure commonly used to determine the level of disease severity in neurological disorders in which severe attacks are experienced. A relapse is the worsening of symptoms to a point of increasing disability. Wingerchuk et al. (Wingerchuk et al. 2015) defines a relapse as the recurrence of initial symptoms following an index attack, after a period longer than four weeks. The frequency of attacks is an indicator of disease severity and treatment often aims to reduce the frequency.

A time period between baseline and final measurements was required in the studies so as to allow for development or resolution of symptoms.

### B4.2.3 Results of the systematic literature review

### AQP4-Ab seropositive compared with seronegative patients suspected of having NMOSD

#### Visual impairment

One case series compared the visual acuity (VA) at last follow-up between AQP4-Ab positive and negative patients whose initial presentation was ON (Zhou et al. 2016). Zhou et al reported the number of eyes with VA ≤ 0.1 at final follow-up (5 years) where a VA of < 1 represents a moderate loss of vision. There was a statistically significant greater number of those with a moderate or larger loss in vision for those who were AQP4-Ab positive compared to those who were AQP4-Ab negative. The result was similar for VA ≥ 0.5[[8]](#footnote-8) after 5 years follow-up, in that there was a statistically significant difference between groups, with worse VA occurring in those who were AQP4-Ab positive (Table 28).

Table Visual acuity at the last follow-up

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Population  N tested | Event | AQP4-Ab +ve  N (%) | AQP4-Ab -ve  N (%) | OR [95%CI] P-valuea | Difference  P valueb |
| Zhou et al, 2016 | First episode ON  N=128 patients | VA≤0.1 | 43/80 (53.8) | 38/133 (28.6) | 2.9  [1.63, 5.18]  0.0003 | 0.000 |
| VA≥0.5 | 24/80 eyes (30) | 75/133 eyes (56.4) | 0.33 [0.18,0.60] 0.0002 | <0.01 |

AQP4-Ab = aquaporin 4 antibodies; ON = optic neuritis; OR = odds ratio; VA = visual acuity

a values calculated using MedCalc

b published P-value

Zhou et al (2016) also compared the number of patients with legal blindness in one or both eyes in AQP4-Ab positive and negative patients. There was a statistically significantly higher prevalence of legal blindness in AQP4-Ab positive patients (Table 29).

Table Patients with legal blindness in one or both eyes at the last follow-up

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Population  N tested | Event | AQP4-Ab +ve  N (%) | AQP4-Ab -ve  N (%) | OR [95%CI] P valuea | Difference  P valueb |
| Zhou et al, 2016 | First episode ON  N=128 patients | Legal blindness (1 eye)  Legal blindness (both eyes) | 30/45 (66.7)  13/45 (28.9) | 27/83 (32.5)  11/83 (13.3) | 4.15 [1.92,8.97] 0.0003  2.66 [1.08,6.57] 0.0341 | <0.01  0.036 |

AQP4-Ab = aquaporin 4 antibodies; ON = optic neuritis; OR = odds ratio

a values calculated using MedCalc

b published P-value

#### Conversion to NMOSD diagnosis

Five studies reported on the number of patients who eventually received a diagnosis of NMO or NMOSD following an initial neurological event (Cheng et al. 2016; Contentti, CE et al. 2017; Li et al. 2015; Liu et al. 2019; Zhou et al. 2016). Diagnosis was according to the 2006 or 2015 criteria and therefore was based on the recurrence of neurological events and/or antibody testing. Follow-up periods ranged from 12 months to 5 years. Results are reported in Table 30.

Cheng et al (2016) and Contentti et al (2017) found that 100% of those testing positive for AQP4-ab were diagnosed with NMOSD according to the 2015 criteria compared to 0% to 17.7% of the AQP4-Ab negative groups. Li et al (2015) found that following a diagnosis of bilateral or recurrent ON, 49% of AQP4-Ab positive patients went on to develop NMO according to the 2006 criteria compared to 10.5% of AQP4-Ab negative patients.

In the studies by Zhou et al (2016) and Liu et al (2019), 40% and 22.4% respectively of patients meeting the Optic Neuritis Treatment Trial (ONTT) inclusion criteria[[9]](#footnote-9) or with first event ON went on to develop NMOSD in the AQP4-Ab positive group compared to 1.2% and 2.2% respectively in the negative group. A large proportion of patients in both studies experienced only a single ON event and so did not go on to meet criteria for an NMOSD diagnosis.

In all studies, there was a statistically significant difference in the rate of conversion to NMO or NMOSD between AQP4-Ab positive and negative early event patients, with those testing positive more likely to develop the disease.

Table Rate of conversion to NMO/NMOSD

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Population**  **N tested** | **AQP4-Ab +ve**  **n/N (%)** | **AQP4-Ab -ve**  **n/N (%)** | **OR [95%CI]**  **P-valuea** | **Difference**  **P valueb** |
| Cheng et al 2016 | First event ABS  N=31 | 14/14 (100) | 3/17 (17.7) | 120.14  [5.68,2540.26]  0.0021 | <0.001 |
| Contentti et al 2017 | First presentation LETM  N=30 | 6/6 (100) | 0/21 (0) | 559.00  [10.07,31042.90]  0.0020 | NR |
| Li et al, 2015 | Recurrent or bilateral ON  N=125 | 49/125 (49) | 13/125 (10.5) | 5.55  [2.82,10.93]  < 0.0001 | <0.0001 |
| Liu et al 2019 | ON diagnosis based on the ONTT criteria  N=158 | 15/67 (22.4) | 2/91 (2.2) | 12.84  [2.82,58.37]  0.0010 | <0.001a |
| Zhou et al, 2016 | First episode ON  N=128 | 18/45 (40) | 1/83 (1.2) | 54.67  [6.97,428.97]  0.0001 | <0.01 |

ABS = acute brainstem syndrome; AQP4-Ab = aquaporin 4 antibodies; LETM = longitudinally extensive transverse myelitis; NMO = neuritis optica; NMOSD = neuromyelitis optica spectrum disorders; NR = not reported; ON = optic neuritis OR = odds ratio; ONTT = Optic Neuritis Treatment Trial

a values calculated using MedCalc

b published P-value

One study conducted a survival analysis to compare the risk of developing NMO or NMOSD between AQP4-Ab positive and negative patients (Cheng et al. 2016). The study population included 31 adults attending a Chinese university hospital with first event ABS. Cheng et al used the Kaplan-Meier method to compare the risk of developing NMSOD between AQP4-Ab positive and negative patients. The risk was significantly higher in AQP4-Ab positive patients (log rank 5.23; p = 0.012). The follow-up time for the risk assessment was a mean 44.51 ± 14.86 months.

#### Rate of conversion to MS diagnosis

Four studies compared the number of patients who eventually received a diagnosis of MS following an initial acute neurological event (Cheng et al. 2016; Contentti, CE et al. 2017; Li et al. 2015; Zhou et al. 2016). In all four studies, patients who were AQP4-Ab negative were more likely to receive a diagnosis of MS than those who were AQP4-Ab positive. Three studies found that none of AQP4-Ab positive patients were diagnosed with MS, but results were statistically significant in only two of the four studies (Cheng et al. 2016; Li et al. 2015). Results are given in Table 31.

Table Rate of conversion to MS

| **Study** | **Population**  **N tested** | **AQP4-Ab +ve**  **n/N (%)** | **AQP4-Ab -ve**  **n/N (%)** | **OR [95%CI]**  **P-valuea** | **Difference**  **P valueb** |
| --- | --- | --- | --- | --- | --- |
| Cheng et al 2016 | First event ABS  N=31 | 0/14 (0) | 7/17 (41.17) | 0.048  [0.003,0.942]  0.046 | 0.007 |
| Contentti et al 2017 | First presentation LETM  N=30 | 0/9 (0) | 2/21 (9.5) | 0.411  0.018,9.427]  0.578 | NR |
| Li et al, 2015 | Recurrent or bilateral ON  N=125 | 1/125 (2) | 11/125 (14.5) | 0.084  [0.011,0.658]  0.018 | 0.027 |
| Zhou et al, 2016 | First episode ON  N=128 | 0/45 (0) | 4/83 (4.8) | 0.194  [0.010,3.689]  0.275 | 0.297 |

ABS = acute brainstem syndrome; AQP4-Ab = aquaporin 4 antibodies; LETM = longitudinally extensive transverse myelitis; MS = multiple sclerosis; NR = not reported; ON = optic neuritis; OR = odds ratio

a values calculated using MedCalc

b published P-value

#### Rate of relapse or symptom recurrence

Three studies compared the number of relapses between AQP4-Ab positive and negative patients after a follow-up period (Cheng et al. 2016; Contentti, CE et al. 2017; Weinshenker et al. 2006). The study populations were patients identified with first event ABS or first event LETM. In the ABS population (Cheng et al. 2016), the occurrence of ON or myelitis attacks, or recurrence of ABS symptoms were considered a relapse. Contentti et al reported on the ARR of acute transverse myelitis (ATM), and in Weinshenker et al, the occurrence of transverse myelitis or ON symptoms were considered a relapse. The relapse rate in the three studies (either ARR or percentage patients relapsed) was higher in the AQP4-Ab positive group compared to the seronegative group after the follow-up period. The difference between groups was statistically significant in all three studies. Results are reported in Table 32.

Table Annual relapse rate or patients relapsed

| **Study** | **Population**  **N tested** | **Measure** | **AQP4-Ab +ve** | **AQP4-Ab  -ve** | **Difference**  **P value** |
| --- | --- | --- | --- | --- | --- |
| Cheng et al 2016 | First event ABS  N=31 | Mean ARR ± SDa  (Mean follow-up 44.5 ± 14.86 mo) | 1.05 ± 0.40 | 0.72 ± 0.40 | 0.031 |
| Contentti et al 2017 | First presentation LETM  N=30 | Mean ATM ARR ± SD  (Median follow-up 2.84 ± 1.68 yr) | 1.33 ± 1 | 0.42 ± 0.74 | 0.03 |
| Weinshenker et al, 2006 | First episode LETM  N=29 | Patients relapsed n/N (%)b  (Follow-up - seropositive 14.4 [IQR 11.6-41.2]; seronegative 18.2 [18.2-40.2]) | 6/11 (54.5) | 0/18 (0) | NR  (MedCalc: 0.0005) |

ABS = acute brainstem syndrome; AQP4-Ab = aquaporin 4 antibodies; ARR = annualised relapse rate; ATM = acute transverse myelitis; LETM = longitudinally extensive transverse myelitis; NR = not reported; ON = optic neuritis; SD = standard deviation

a Relapse refers to the occurrence of either ON, LETM or recurrence of ABS symptoms

b Relapse refers to the occurrence of either ON or trans myelitis

#### Change in EDSS

Change in EDSS was assessed in one population of first event ABS patients (Cheng et al. 2016) and one of first presentation LETM patients (Contentti, CE et al. 2017). The mean follow-up times were approximately 44 months and 34 months, respectively. In that period a number of patients experienced relapses and underwent a range of treatments. At baseline, the EDSS was not statistically different between AQP4-Ab positive and negative groups (Table 33).

At follow-up the EDSS was higher (disability was worse) in the AQP4-Ab positive group compared with the negative patients (p < 0.001) in patients with first event ABS (Cheng et al. 2016). Cheng et al used the Kurtz EDSS (Kurtzke JF 1983)7. In the study of first event LETM patients there was no significant difference in EDSS found between groups but no further detail was reported on the follow-up status (Contentti, CE et al. 2017). This result is inconsistent with the majority of results comparing AQP4-Ab positive and negative patients in this review. Contentti et al also used the Kurtz EDSS and in addition defined severe disability (EDSS ≥6) as intermittent or unilateral assistance (braces, canes or crutches) required for walking 100 m with or without resting. The same authors found that limitations of their study were the inconsistent follow-up time and differences in treatments between groups, and the AQP4-Ab assay method (IIF) which may not have identified all seropositive patients.

Table Change in EDSSa at follow-up

| **Study** | **Population**  **N tested** | **AQP4-Ab +ve**  **Median (range)** | **AQP4-Ab -ve**  **Median (range)** | **Difference**  **P value** |
| --- | --- | --- | --- | --- |
| Cheng et al, 2016 | First event ABS  N=31 | Baseline median (range):  3 (2-4) | Baseline median (range):  3 (2-3) | 0.141 |
| Follow-up median (range): 5 (3-7) | Follow-up median (range): 2.5 (1.5-7) | <0.001 |
| Contentti et al 2017 | First presentation LETM  N=30 | Baseline mean (SD):  5.44 (2.08) | Baseline mean (SD):  4.90 (2.10) | NR  (MedCalc: 0.52) |
| Follow-up:  NR | Follow-up: NR | No significant difference |

ABS = acute brainstem syndrome; AQP4-Ab = aquaporin 4 antibodies; EDSS = expanded disability status scale; LETM = longitudinally extensive transverse myelitis; NR = not reported; SD = standard deviation

a The Kurtz EDSS (Kurtzke JF 1983)

### MOG-Ab seropositive compared with seronegative patients suspected of NMOSD

Prognostic data were extracted from a total of three retrospective case series with baseline and follow-up data on patients tested for MOG-Ab (Cobo-Calvo et al. 2016; Liu et al. 2019; Matsuda et al. 2015). Other studies were identified that reported data on MOG-Ab positive and negative patients but they did not meet the criteria for inclusion in this section because they did not compare outcomes between seropositive and seronegative patients at risk of NMOSD.

#### Visual impairment

The retrospective case series by Matsuda et al (2015) compared the VA improvement and residual visual field deficit between MOG-Ab positive and negative patients after a mean follow-up period of 2.8 ± 1.1 years. Of the population of 70 ON patients, 18 were found to be MOG-Ab positive. Visual field was measured using the Goldmann kinetic perimeter method[[10]](#footnote-10) at follow-up. Residual visual field deficit was defined as the presence of any remaining deficits at follow-up that were observed at disease onset. VA improvement was found to be similar between MOG-Ab positive and negative groups. In contrast there was a statistically significant difference in visual field deficit remaining between the groups, which was worse in the MOG-Ab positive patients (p = 0.0015). Results are found in Table 34.

Table Visual acuity and visual field deficit changes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Population  N tested | Event  (follow-up) | MOG-Ab +ve  n/N (%) | MOG-Ab -ve  n/N (%) | OR [95%CI]  P-valuea | Difference  P valueb |
| Matsuda et al, 2015 | ON  N=70 | VA improvement  (Mean 2.8±1.1 years) | 16/18 (88.9) | 37/52 (71.2) | 3.243  [0.663,15.868]  0.146 | No significant difference |
| Residual visual field deficit  (Mean 2.8±1.1 years) | 14/18 (77.8) | 16/52 (30.8) | 7.875  [2.239,27.697]  0.0013 | 0.0015 |

MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; ON = optic neuritis; OR = odds ratio; VA = visual acuity

a values calculated using MedCalc

b published P-value

#### Conversion to NMOSD or MS

Two studies reported on the number of patients with initial neurological episodes that went on to be diagnosed with NMOSD (Cobo-Calvo et al. 2016; Liu et al. 2019). Cobo-Calvo et al reported NMOSD diagnoses in a population of monophasic LETM patients. Liu et al reported the number of NMOSD diagnoses in patients initially diagnosed with ON, based on the ONTT inclusion criteria. The follow-up periods were > 1 year and a median 42.2 (range 25-79.5) months for the studies. The trend was for a higher number of NMOSD diagnoses in MOG-Ab positive compared to negative patients in both study populations, but statistical significance was only reached in the LETM population (Table 35).

Cobo-Calvo et al (2016) also reported the number of MS diagnoses in the study population of 56 monophasic LETM patients. After a median follow-up period of 42 (range 25-79.55) months, only one patient, who was MOG-Ab negative had received a diagnosis of MS. There was no statistical significance in the difference between MOG-Ab positive and negative patients.

Table Rate of conversion to NMOSD

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Population  N tested | Follow-up period | MOG-Ab +ve  n/N (%) | MOG-Ab -ve  n/N (%) | OR [95%CI]  P-valuea | Difference  P valueb |
| (Cobo-Calvo et al. 2016) | Monophasic LETM; AQP4-Ab –ve  N=56 | Median 42.2 (25-79.5) months | 4/13 (30.8) | 2/43 (4.7) | 9.111  [1.441,57.620]  0.0189 | NR |
| (Liu et al. 2019) | ON diagnosis based on the ONTT criteria  N=158c | > 1 year | 2/31 (6.5) | 0/60 (0) | 10.254  [0.477,220.488]  0.1370 | 0.114 |

AQP4-Ab = aquaporin 4 antibodies; LETM = longitudinally extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; ONTT = Optic Neuritis Treatment Trial; OR = odds ratio

a values calculated using MedCalc

b published P-value

c 67 patients who were AQP4-Ab positive were not included in the analysis

#### Change in EDSS

Cobo-Calvo et al (2016) compared the EDSS at baseline and follow-up between MOG-Ab positive and negative monophasic LETM patients. There were 13 MOG-Ab positive and 43 MOG-Ab negative patients in the analysis. There was no difference between the seropositive and seronegative groups at baseline. At follow-up, EDSS had decreased in both groups but there was statistically significant more improvement (lower EDSS) in the MOG-Ab positive group (Table 36).

Table Change in EDSSa at follow-up

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study  N tested | Population | MOG-Ab +ve  Median (range) | MOG-Ab -ve  Median (range) | Difference  P value |
| (Cobo-Calvo et al. 2016) | Monophasic LETM; AQP4-Ab –ve  N=56 | Baseline: 5.5 (3.5-7.0) | Baseline: 4.5 (3.5-8.0) | 0.79 |
| Follow-up: 2 (0-2.5) | Follow-up: 3 (2.0-5.5) | 0.027 |

AQP4-Ab = aquaporin 4 antibodies; EDSS = expanded disability status scale; LETM = longitudinally extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies

a The Kurtz EDSS (Kurtzke JF 1983)

#### Rate of relapse or symptom recurrence

Cobo-Calvo et al and Matsuda et al compared the symptom recurrence rate between MOG-Ab positive and negative patients (Cobo-Calvo et al. 2016; Matsuda et al. 2015). In a population of 56 monophasic LETM patients Cobo-Calvo et al found that there was no difference in the rate of patients who developed recurrent LETM between MOG-Ab positive and negative patients.

Both studies found that the recurrence of ON was higher in those who were MOG-Ab positive compared with those who were negative. In monophasic LETM patients, 30.8% of MOG-Ab positive patients went on to develop recurrent ON compared with 4.7% of MOG-negative patients (p = 0.022) (Cobo-Calvo et al. 2016). Amongst a population of ON patients, the ARR of ON was higher in MOG-Ab positive patients compared to negative patients (p = 0.0005) (Matsuda et al. 2015). Results are reported in Table 37.

Table Rate of symptom recurrence

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Population  N tested | Event  (follow-up) | MOG-Ab +ve  n/N (%) | MOG-Ab -ve  n/N (%) | OR [95%CI]  P-valuea | Difference  P valueb |
| (Cobo-Calvo et al. 2016) | Monophasic LETM  N=56 | Recurrent LETM  (42.2, range 25-79.5 years) | 2/13 (15.4) | 7/43 (16.3) | 0.935  [0.169,5.172]  0.939 | NR |
| Recurrent ON  (42.2, range 25-79.5 years) | 4/13 (30.8) | 2/43 (4.7) | 9.111  [1.441,57.620]  0.019 | 0.022 |
| (Matsuda et al. 2015) | ON  N=70 | ARR of ON  (Mean 2.8±1.1 years) | 0.82 | 0.40 | - | 0.0005 |

ARR = annualised relapse rate; LETM = longitudinally extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibody; NR = not reported; ON = optic neuritis; OR = odds ratio

a values calculated using MedCalc

b published P-value

### AQP4-Ab seropositive compared with seronegative patients diagnosed with NMOSD

#### Visual impairment

One SR (Lin et al. 2017) performed a meta-analysis of visual impairment in NMO patients, comparing outcomes between those testing AQP4-Ab positive and negative. Follow-up periods ranged from 1 year to > 10 years amongst 16 of the 18 included articles that stated this factor. The studies were performed in populations from Asia, the USA and Europe. AQP4-Ab positivity was found to be associated with worse visual impairment when compared with AQP4-Ab negativity using a random effects model (OR 3.16; 95%CI 1.09, 9.19; p = 0.03). Visual impairment measures varied amongst the studies (although not clarified in the SR) and heterogeneity was found to be high (p=0.001, I2=69%). The risk of publication bias was assessed as low by funnel plot.

In a subgroup analysis of AQP4-Ab assay types, only cell-based assays found a statistically significant association between AQP4-Ab positivity and worse visual impairment. ELISA and IIF assays showed a similar trend but a statistically significant association was not found (Table 38).

Table 38 Occurrence of visual impairment at last follow-up in AQP4-AB positive compared with AQP4-Ab negative NMO patients (Lin et al. 2017)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Meta-analysis  K studies | AQP4-Ab +ve  n/N (%) | AQP4-Ab -ve  n/N (%) | ORa  [95% CI] | Difference  P valuea |
| All assay types  K=9 | 299/529 (57) | 46/116 (40) | 3.16  [1.09, 9.19] | 0.03 |
| CBA assays  K=3 | 50/79 (64) | 4/31 (13) | 9.32  [3.01, 28.84] | 0.0001 |
| IIF assays  K=5 | 239/433 (55) | 37/73 (51) | 2.13  [0.25, 17.92] | 0.49 |
| ELISA assays  K=1 | 10/17 (59) | 5/12 (42) | 2.00  [0.45, 8.96] | 0.37 |

AQP4-Ab = aquaporin 4 antibodies; CBA = cell-based assay; ELISA = enzyme-linked immunosorbent assay; IIF = indirect immunofluorescence assay; OR = odds ratio

a published OR and p-value

# B5 Clinical utility

Clinical utility refers to how likely the test is to significantly impact on patient management and health outcomes.

As the intervention (diagnosis with testing) is likely to be more accurate than the comparator (diagnosis without testing), the clinical utility of the test should be evaluated. To determine the safety of a diagnostic test it is important to investigate the impact on patients with false negative and false positive results. If the new test is more accurate but less safe, or less accurate but safer, the impact of change in patient management should be evaluated, as there is a trade-off.

## B5.1 Impact on clinical management (Therapeutic efficacy)

## Risk of Bias Assessment

The risk of bias for studies included to assess therapeutic efficacy was assessed using appraisal checklists for interventional evidence (see Table 10), appropriate to the individual study design. Of seven articles included for change in management evidence, four provided level IV evidence and were appraised using the IHE checklist for case series (IHE 2016). They ranged from low to high risk of bias. Three articles were retrospective cohort design and provided comparative data between patients were who AQP4-Ab positive or negative (level III-3 evidence). They were found to be of low or moderate risk of bias when assessed using the SIGN Checklist 3 for cohort studies (SIGN 2014). Domain scores for the cohort studies are shown in Table 39.Quality appraisal outcomes can be seen in Table 40.

Outcomes were also rated for overall quality across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias (GRADE Evidence profile tables, Appendix D). Clinically critical outcomes are also reported in the GRADE Summary of Findings Table 68 and Table 69.

Table Domain scores for the quality appraisal of cohort studies using the SIGN Checklist 3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Internal validity** | | | | **Overall Assessment** | |
| **Selection of subjects** | **Assessment** | **Confounding** | **Statistical Analysis** | **Applicability** | **Risk of bias** |
| (Akman-Demir et al. 2011) | 3/6 | 5/5 | 0/1 | 0/1 | 2/2 | 10/15  Moderate risk of bias |
| (Hyun et al. 2016) | 4/7 | 4/5 | 1/1 | 1/1 | 1/2 | 12/16  Moderate risk of bias |
| (Li et al. 2015) | 3/4 | 5/5 | 1/1 | 0/1 | 1/2 | 10/13  Moderate risk of bias |

## Characteristics of the Evidence Base

See Appendix C for details on the individual studies included in the evidence base.

Studies that provided evidence on the impact of the test on patient management are characterised in Table 40. Seven studies in all were included, four of which provided level IV evidence and three level III-3 evidence. All studies were conducted in different countries, across four continents. Five of the studies performed retrospective analyses of clinical data. The remaining two studies were surveys, one by authors Beekman et al (2019), who conducted an online survey of the quality of life (QoL) and diagnostic and treatment experiences of NMOSD patients. A second survey was conducted by Jurynczyk et al (2016), in which 12 neurology consultants were asked to diagnose a set of MS and NMOSD cases based on information provided.

The retrospective cohort studies (Akman-Demir et al. 2011) (Hyun et al. 2016; Li et al. 2015) compared management between AQP4-Ab positive and negative patients in populations with neurological symptoms. The multicentre Korean study by Hyun et al included the largest number of patients (n=594), and provided significant data on the time to diagnosis in those diagnosed either with AQP4-Ab testing or without.

Two case series (Hennes et al. 2017; Papais-Alvarenga et al. 2018) compared the number of cases diagnosed using two sets of criteria – 2015 IPND criteria and earlier criteria. They collectively included 410 patients (210 children with acquired demyelination syndrome (ADS) and 200 adults with idiopathic inflammatory demyelinating disease (IIDD)).

Table Key features of studies reporting on change in management

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID**  **Country** | **Study Design**  **Level** | **Risk of bias** | **Sample Size** | **Patient population** | **Intervention** | **Comparator** | **Outcomes** |
| (Akman-Demir et al. 2011)  Turkey | Ret Coh  III-3 | Moderate | 35 | Patients diagnosed with NMO | Seropositive for AQP4-Ab | Seronegative for AQP4-Ab | Time to diagnosis (2006 criteria) |
| (Beekman et al. 2019)  USA | CS  IV | Moderate | 193 | Self-reported, established diagnosis of NMO or NMOSD and ability to read textual content or hear questions audibly and respond to questions. | Role-Physical and Role-Emotional subscales of the Short Form -36 (SF-36) | NA | Change in diagnosis |
| (Hennes et al. 2017)  Europe & Canada | CS  IV | Low | 210 | Children with ADS and a complete data set (including final diagnosis and EDSS after at least 12 months) | AQP4 and MOG-Ab testing; application of new diagnostic criteria | Diagnosis by earlier criteria | Change in diagnosis |
| (Hyun et al. 2016)  Korea | Ret Coh  III-3 | Moderate | 594 | Patients with possible CNS inflammatory diseases | AQP4-AB testing; Diagnosis by 2015 criteria | Diagnosis without AQP4-Ab testing | Time to diagnosis  Change in diagnosis |
| (Jurynczyk et al. 2016)  Europe | CS  IV | High | 12 | Patients specifically selected who had clinical presentations with overlapping features of NMO and MS and to be representative of different clinical dilemmas. | Opinions of 27 clinical experts on diagnosis and treatment based on provided clinical information | NA | Clinician agreement in diagnosis |
| (Li et al. 2015)  China | Ret Coh  III-3 | Low | 125 patients (220 eyes) | Patients with recurrent and bilateral optic neuritis with simultaneous attacks | Seropositive for AQP4-Ab | Seronegative for AQP4-Ab | Time to diagnosis (2006 criteria) |
| (Papais-Alvarenga et al. 2018)  Brazil | CS  IV | Moderate | 200 | Adults patients (≥16 years), with IIDD | AQP4-Ab and MOG-Ab testing; application of 2015 diagnostic criteria | Diagnosis by 2006 criteria | Change in diagnosis |

ADS = acquired demyelination syndrome; AQP4- Ab = aquaporin 4 antibodies; CNS = central nervous system; Coh=cohort; CS=case series; EDSS = expanded disability status scale; IIDD = idiopathic inflammatory demyelinating disease; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MS = multiple sclerosis; NA = not available; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; Ret = retrospective

## Outcome Measures and Analysis

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

The outcomes of interest for assessing the impact of diagnosis with testing on patient management fell into two main categories. The categories were

* outcomes related to the time taken to reach a diagnosis; and,
* outcomes related to change in diagnosis when comparing IPND criteria with earlier criteria.

Evidence in the first category is important in showing the impact of early compared with late NMOSD diagnosis.

Included within the second category were data on the agreement between specialist diagnoses of a set of NMOSD and MS cases. The data were identified in one small survey and used the proportion of observed agreement (p0) to determine the extent of agreement between participants.

## Results of the Systematic Literature review

### Does AQP4-Ab and/or MOG-Ab testing impact on clinical management?

Summary – Does AQP4-Ab with/without MOG-Ab testing in patients suspected of NMOSD, change management, compared to diagnosis by clinical characteristics alone?

There was evidence to show that patients are diagnosed earlier when the AQP4-Ab test is included in the diagnostic regimen, compared to when it is not included (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), but may more closely match the population prevalence that is present in those tested in the Australian clinical setting.

The *earlier* time to diagnosis with testing was supported by evidence showing that *more* patients suspected of NMOSD are diagnosed based on the 2015 IPND criteria than when diagnosis is based on the 2006 criteria. The higher proportion of patients diagnosed by the 2015 criteria is likely to be a result of the greater inclusion of AQP4-Ab testing. Under the 2006 criteria, patients wait longer for a definitive NMOSD diagnosis, as it is likely to require the occurrence of additional clinical features.

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

There was no evidence to determine if MOG-Ab testing impacted on the time to diagnosis for patients suspected of NMOSD.

In a QoL questionnaire, NMOSD patients (over 65% of whom had been given a prior incorrect diagnosis) 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 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). A small cross-sectional study 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.

#### Time to NMOSD diagnosis

One of the largest studies included in this report (N=594) compared the time taken to NMOSD diagnosis based on the IPND 2015 criteria to the time to diagnosis based on the 2006 criteria (Hyun et al. 2016). The study was conducted in Korea and diagnosis was based on the 2015 IPND criteria being met in a retrospective analysis of patient data. The 2015 diagnostic criteria were met by 252 of the 594 patients with CNS inflammatory diseases (CNS ID) reviewed.

The time to diagnosis was almost five times longer in those diagnosed by the 2006 criteria compared to those diagnosed by the 2015 criteria (p<0.001; log rank test). This length of delay in diagnosis is likely to be clinically significant to patients, as it may delay appropriate treatment and allow disease progression that prevents a return to baseline symptom status. This results should be considered with caution, however, as the authors did not indicate the extent to which AQP4-Ab testing contributed to diagnosis for either the group diagnosed by the 2006 or 2015 criteria (Table 41).

Table Time to NMOSD diagnosis with and without AQP4-Ab testing (Hyun et al. 2016)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Population** | **Follow-Up** | **Intervention:  diagnosis based on the 2015 criteria** | **Comparator: diagnosis based on 2006 criteria** | **Difference** |
| Median time to diagnosis | n=252 diagnosed NMOSD cases | Mean (SD) disease duration 9.2 (12.3) years | 11 months  (95% CI 7, 15) | 53 months  (95%CI 28, 78) | p<0.001  (log rank test) |

AQP4-Ab = aquaporin 4 antibodies; CNS ID = central nervous system inflammatory disease; NMOSD = neuromyelitis optica spectrum disorders; SD = standard deviation

Two retrospective studies compared the time it took to meet the 2006 diagnostic criteria between AQP4-Ab positive and negative NMOSD patients (Akman-Demir et al. 2011; Li et al. 2015). This comparison has the potential to show a similar result to the comparison between diagnosis with testing and without testing (Table 41), as patients testing negative for AQP4-Ab are likely to wait longer for a diagnosis than those testing positive. One study reviewed ON patients, approximately 25% of whom were diagnosed with NMO at the time of the study (Li et al. 2015). The second study (identified through pearling) reviewed clinic data on 35 patients diagnosed with NMO (Akman-Demir et al. 2011). The trend was for a longer time to diagnosis for AQP4-Ab negative than AQP4-Ab positive NMO patients; however the difference in both studies was not significant.

The studies did not state whether AQP4-Ab status contributed to the diagnosis, but regardless, testing was performed as part of the study analysis. When considered alongside the results in Table 41 and Table 43, the results from Table 42 (where differences between groups were statistically significant) likely reflect the poorer performance of the 2006 diagnostic criteria when compared to the 2015 IPND criteria, and the heightened awareness of the implication of AQP4-Ab status in the more recent criteria.

Table Mean time to diagnosis (2006 criteria) in AQP4-Ab positive compared AQP4-Ab negative patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Population** | **Follow-Up (disease duration)**  **Mean ± SD (mo)** | **Intervention:  AQP4-Ab positive**  **Mean ± SD (mo)** | **Comparator: AQP4-Ab negative**  **Mean ± SD (mo)** | **Difference**  **P value** |
| (Li et al. 2015) | Recurrent or bilateral ON  N=125a | 41.07±47.06 mo | 19.5±20.51 mo | 27.75±24.27 mo | 0.535 |
| (Akman-Demir et al. 2011) | NMO patients  N=35b | 8.2±6.6 y | 3.8±4.8 y | 4.5±6.7 y | Not significant  (MedCalc: 0.72) |

AQP4-Ab = aquaporin 4 antibodies; mo = months; NMO = neuromyelitis optica; ON = optic neuritis; SD = standard deviation

a note that 24 (49%) AQP4-Ab +ve and 8 (10.5%) AQP4-Ab –ve patients met the 2006 diagnostic criteria

b note that 21 (60%) AQP4-Ab +ve and 14 (40%) AQP4-Ab –ve patients met the 2006 diagnostic criteria

#### Change in diagnosis

A QoL survey conducted by Beekman et al (2019) reported on a number of issues impacting on NMO and NMOSD patients. In the cross-section of 193 patients, 158 had been given a final diagnosis of NMO and 35 of NMOSD. The majority of these patients (65.8%) had received an alternate initial diagnosis, the most common being MS (41.4%) (Table 43). The survey also found that the time to correct diagnosis from initial symptoms ranged from 0 to 40 years (mean 3.3 ± 6.3 years). The mean time it took to receive treatment after a correct diagnosis was reported to be 6 months ± 1.7 years (range 0 – 11 years). One of the concerns for patients was treatments and their future effectiveness, as many had experienced treatments with poor efficacy (n = 48 of 88 respondents; 54.5%) and intolerable side effects (n = 32 of 88 respondents; 36.4%).

Table Proportion of initial diagnoses other than NMOSD

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **All other initial diagnosis (including MS and non-specific ON)**  **N (%)** | **MS initial diagnosis**  **N (%)** | **Non-specific ON initial diagnosis N (%)** |
| (Beekman et al. 2019)  N=193a | 125 (65.8) | 80 (41.4) | 44 (22.7) |

MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis

a In the total cohort 158 patients (82%) were finally diagnosed with NMO and 35 (18.1) with NMOSD.

Three studies compared the number of patients that met the NMOSD 2015 IPND diagnostic criteria with the number of diagnoses by earlier criteria, by retrospective analysis of patient data (Hennes et al. 2017; Hyun et al. 2016; Papais-Alvarenga et al. 2018). One population was of children with ADS, and there were two populations of patients with CNS inflammatory disease (CNS ID or IIDD) One study performed a sub-analysis of AQP4-Ab positive NMOSD patients who met the 2015 criteria (Hyun et al. 2016). The odds ratio (OR) for likelihood of a NMOSD diagnosis was calculated for each study, and reported with results published in the articles in Table 44.

Two of the studies found that a statistically significant higher number of patients were diagnosed with NMOSD by the 2015 IPND criteria than the 2006 criteria, with a further 19.5% to 21.9% of patients receiving a diagnosis with the 2015 criteria. For these two results the OR was statistically significant, indicating an NMOSD diagnosis was 1.76 or 2.48 times more likely using the 2015 criteria compared with the 2006 criteria (which is less likely to include AQP4-Ab testing). Following the same trend, an additional 28% of patients were diagnosed by the 2015 criteria when AQP4-Ab testing was performed compared to when the 2015 criteria were used without testing in a sub-group that had been given a definitive diagnosis of AQP4-Ab positive NMSOD.

The third study, performed in children with ADS, found that there was a 21.9% increase in NMOSD diagnoses 24 months after initial diagnosis, although the OR for this result was not statistically significant. This study was different from the other two in that diagnosis was made within a limited time period (24 months), which may be an indicator of the time taken for symptom development which would lead to a definitive diagnosis in this population.

Table Change in the number of NMOSD diagnoses

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Population** | **Intervention**  **n/N (%)** | **Comparator**  **n/N (%)** | **ORb**  **(95%CI)** | **Differencec**  **P value** |
| (Hyun et al. 2016) | CNS ID  N=594 | **2015 criteria:**  252/594 (42.4) | **2006 criteria:** 136/594 (22.9)a | 2.48  (1.93, 3.19)  P<0.0001 | 116 (19.5%) |
| Definitive NMOSD diagnosis and positive AQP4-Ab status  N=226 | **2015 criteria with testing:**  226/226 (100) | **2015 criteria without testing:** 162/226 (72) | 180  (11.0, 2927)  P=0.0003 | 64 (28%) |
| (Papais-Alvarenga et al. 2018) | IIDD  N=115 | **2015 criteria:** 70/115 (60.1) | **2006 criteria:** 54/115 (47.0) | 1.76  (1.04, 2.97)  P=0.035 | 24 (21.9%) |
| (Hennes et al. 2017) | Children with ADS  N=120 | **Diagnosis of NMOSD after 24 months:**  16/210 (7.6) | **Diagnosed with NMOSD initially:**  12/210 (5.7) | 1.36  (0.63, 2.95)  P=0.435 | 4 (1.9%) |

ADS = acquired demyelination syndrome; AQP4- Ab = aquaporin 4 antibody; CNS ID = central nervous system inflammatory disease; IIDD = idiopathic inflammatory demyelinated disease; NMOSD = neuromyelitis optica spectrum disorders; OR = odds ratio

a Diagnosis by 2006 criteria was only performed on the 252 patients diagnosed with NMOSD by the 2015 criteria

b OR calculated using MedCalc software

c Result published by study authors

#### Clinician agreement in diagnosis

Jurynczyk et al (2016) conducted a survey of 27 neurology consultants who had expertise in the diagnosis of inflammatory demyelinating diseases. The study was designed to examine the challenges presented in diagnosis and management of NMOSD cases in everyday practice. Twelve predetermined anonymous cases were chosen because of their overlapping presentation, and provided to each consultant with clinical details. Clinical opinions on case diagnoses were categorised as MS, NMOSD, indeterminate or other. Observed agreement (p0) was measured between diagnoses.

The authors reported high disagreement among the consultants for diagnosis (p0 = 0.51; Table 45). One of the more consistent outcomes was diagnosis of five cases, which had features of both MS and NMOSD. These were diagnosed more often with MS than NMOSD (61.5% versus 22.9% of consultants), the authors claiming this indicated that MS characteristics overrode NMOSD characteristics in clinical assessment.

Interestingly there was also disagreement between diagnoses of cases which met the 2006 and 2015 diagnostic criteria. Only three of 27 (11%) consultants made their diagnosis exactly according to diagnostic criteria, with 11 (41%) experts making at least one diagnosis other than NMOSD in cases fulfilling the diagnostic criteria.

Table Clinican diagnostic agreement between cases of NMOSD and MS

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Outcome** | **Population** | **Interventiona** |
| (Jurynczyk et al. 2016) | Mean agreement between 27 clinician diagnoses | 12 cases of MS or NMOSD | Mean Po = 0.51  (range between cases = 0.25 - 0.73)  kappa = 0.27 |

MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders;

a Po = observed agreement; kappa = (observed agreement [Po] – expected agreement [Pe])/(1-expected agreement [Pe])

## B5.2 Therapeutic effectiveness

Evidence has been included to show how effective the changes that result from AQP4-Ab and MOG-Ab testing are, compared to diagnosis based on clinical characteristics alone. The evidence falls into four categories:

* Early compared with late treatment for NMSOD
* Effectiveness of treatment in NMOSD patients compared with MS patients
* Disease status before and after treatment for NMOSD patients
* Safety (adverse events) associated with NMOSD treatments relevant in the Australian setting

Because of the volume of evidence identified in the literature search for effectiveness of treatments in NMOSD patients, only the highest level of evidence and most relevant articles have been selected for inclusion.

## Risk of Bias Assessment

Evaluation of studies assessing the health impact due to change in management of NMOSD, involving the therapeutic effectiveness of medication, was performed according to their study design.

One SR and one RCT which also investigated changes in disability, relapse rates and adverse events were assessed with the AMSTAR 2 checklist and SIGN checklist for RCTs, respectively. The SR was considered to be of poor quality evidence with a high risk of bias (Table 47) and the RCT was assessed as being of good quality evidence with a low risk of bias. The cohort studies (including one retrospective) which investigated change in disability, relapse rates and adverse events were assessed using a SIGN checklist for cohort studies, and all were considered to have moderate risk of bias. Domain scores for the cohort studies are shown in Table 46. Case series that investigated such outcomes as changes in disability based on early or late treatment, and adverse events, were assessed with the IHE checklist, with the majority considered to have moderate risk of bias. Table 45 provides a summary of all included primary studies.

Table 46 Domain scores for the quality appraisal of cohort studies using the SIGN Checklist 3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study ID | Internal validity | | | | Overall Assessment | |
| Selection of subjects | Assessment | Confounding | Statistical Analysis | Applicability | Risk of bias |
| (Ashtari et al. 2019) | 1/5 | 4/5 | 1/1 | 1/1 | 2/2 | 9/14  Moderate risk of bias |
| (Huang et al. 2018) | 3/6 | 2/6 | 0/1 | 1/1 | 1/2 | 7/16  Moderate risk of bias |
| (Shaygannejad et al. 2019) | 3/5 | 4/6 | 0/1 | 0/1 | 1/2 | 8/15  Moderate risk of bias |
| (Stellmann et al. 2017) | 2/5 | 3/5 | 0/1 | 1/1 | 2/2 | 8/14  Moderate risk of bias |

## Characteristics of the Evidence Base

One SR (Gao et al. 2019) was identified that evaluated the efficacy of RTX (rituximab) in terms of safety and tolerance, and assessed the treatment efficacies based on relapse rates and disability. The review was assessed as high risk of bias (IV level of evidence). A total of 26 studies were included in the SR; 19 retrospective studies, four prospective studies, and one each of RCT, observational and case-control studies. To meet the inclusion criteria patients had to have NMO, but details of the diagnostic criteria was not provided. The review authors did not provide information on critical appraisal of the included studies or the quality of the evidence.

A further 14 studies (one RCT, four cohorts and nine case-series), provided outcomes related to the impact of patient management changes or the therapeutic effectiveness of medication. The RCT (Pittock et al. 2019) evaluated the efficacy and safety of intravenous eculizumab (ECZ) in patients with AQP4-Ab positive NMOSD, with outcome measures of changes in disability, relapse rate and adverse events. Of the cohort studies, two (Ashtari et al. 2019; Shaygannejad et al. 2019) reported changes in disability and relapse rate with the administration of RTX, one compared the effectiveness of therapy used for NMOSD versus MS (Stellmann et al. 2017) while the other investigated the adverse events associated with intravenous mycophenolate mofetil (MMF).

Three of the included case series investigated plasma exchange (PLEX), with one reporting changes in disability around early versus late PLEX treatment (Bonnan et al. 2018), and the other two reporting the incidence of PLEX-related adverse events (Bonnan et al. 2009; Jiao et al. 2018b). Two case series assessed the effect of early versus late intravenous methyl-prednisolone (IVMP) at prolonging the duration of remission (Lin et al. 2017) and impact on visual recovery associated with ON (Stiebel-Kalish et al. 2019). One case series assessed the impact of AZA treatment on disability and relapse rate (Elsone et al. 2014).

Two other case series investigated adverse events; one associated with MMF (Jiao et al. 2018a), and the other with azathioprine (AZA) combined with prednisone (Bichuetti et al. 2019), while another case series (Mealy et al. 2019) studied the changes in disability in those taking NMOSD-specific immunotherapy.

See Appendix C for details on the individual studies included in the evidence base.

A summary of the trial characteristics of studies providing evidence relating to the health impact from the change in management is provided in Table 47 and Table 48.

Table 47 Systematic review evidence included for clinical utility (therapeutic effectiveness)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study ID  Country | K studies  N cases | Risk of bias | Inclusion criteria  Follow-up | Intervention | Comparator | Outcomes |
| (Gao et al. 2019)  Multiple | K=26  N=577 | High | Patients with NMO irrespective of age, gender, ethnicity and previous treatment  Follow-up range:12 mo to 6.6 yr | Rituximab | Not reported | Changes in EDSS  Change in ARR  Adverse events |

ARR = annualised relapse rate; AQP4-Ab = aquaporin 4 antibody; EDSS = Expanded Disability Status Scale; mo = month; NMO = neuromyelitis optica; yr = year

Table 48 Key features of the included evidence assessing clinical utility (therapeutic effectiveness)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **Country** | **Study Design**  **Level** | **Risk of bias** | **Sample Size** | **Study population** | **Intervention** | **Comparator** | **Outcome** |
| (Pittock et al. 2019)  Multiple | RCT  II | Low | 143 | NMOSD aged ≥18 years with ( 2006 or 2007 criteria), AQP4 IgG +ve, history of 2 or more relapses during the previous 24 months, | IV eculizumab  900 mg/week x 4; maintenance 1200 mg/2 weeks | Matched Placebo | Change in EDSS  Change in ARR  Adverse events |
| (Bonnan et al. 2018)  France | CS  IV | Moderate | 60 | Monophasic or relapsing NMOSD, extensive transverse myelitis or severe ON highly suggestive of NMOSD. | PLEX <20day after attack | PLEX >20 days after attack | Early vs late treatment  Change in EDSS |
| (Lin et al. 2017)  China | CS  IV | Moderate | 32 | Patients with NMOSD who had relapsed with LETM, ON and postrema syndrome | IVMP + early use of Azathioprine (concurrently or within 2 weeks of IVMP) | Azathioprine after IVMP  IVMP alone | Early vs late treatment  Time to next relapse |
| (Elsone et al. 2014) | CS  IV | Moderate | 103 | Patients with AQP4-Ab positive with NMOSD | AZA | None | Change in ARR and EDSS |
| (Stiebel-Kalish et al. 2019)  Israel | CS  IV | Moderate | 27 | AQP4-Ab or MOG-Ab positive patients with first event of ON | IVMP for 3-5 days followed by oral prednisone | IVMP after 4 days  IVMP after 7 days | Early vs late treatment  (< or > 4 or 7 days) |
| (Bonnan et al. 2009)  France | CS  IV | Moderate | 43 | Patients with relapsing NMO or extensive transverse myelitis | PLEX plus steroid treatment | Steroid treatment only | Adverse events |
| (Jiao et al. 2018a) China | CS  IV | High | 109 | NMO or NMOSD with seropositive AQP4-Abs who had received mycophenolate mofetil for six months or longer | MMF: low ≤1000mg/day , moderate 1250mg and 1500mg/day, or high dose 1750mg and 2000mg/day | None | Adverse events |
| (Jiao et al. 2018b)  China | CS  IV | Moderate | 29 | Patients with confirmed NMOSD diagnosed by the 2006 or 2015 IPND criteria | PLEX | None | Adverse events |
| (Mealy et al. 2019)  Multiple | CS  IV | Moderate | 182 | Patients who met 2015 diagnostic criteria for NMOSD and who were AQP4-Ab seropositive and followed for at least one year | NMOSD-specific immunotherapy after early diagnosis | Therapy after late diagnosis | EDSS |
| (Shaygannejad et al. 2019)  Iran | Coh  III-2 | Moderate | 44 | Consecutive NMOSD patients based on 2015 diagnostic criteria | 500 mg rituximab 500mg/ week for 4 weeks (2g in total), followed by (500mg/week every six months | None | Change in EDSS  Change in ARR |
| (Stellmann et al. 2017)  Germany | Ret Coh  III-2 | Moderate | 144 patients, 265 treatments | Patients with NMO diagnosed according to 2006 criteria or with AQP4-Ab positive NMOSD | Therapy in NMOSD patients | Therapy in MS patients | Effectiveness in NMOSD vs MS |
| (Ashtari et al. 2019)  Iran | Coh  III-2 | Moderate | 56 | Patients with NMOSD based on 2015 criteria, aged above 18 years of age, who received the first dose of rituximab in clinic for six months or less before starting the study | Rituximab 4x weekly repeating after 6 and 12 months (500 mg/ dose, 2 gm total in 4 weeks) | None | Change in EDSS  Change in ARR |
| (Bichuetti et al. 2019)  Brazil | CS  IV | Moderate | 158 | Patients with clinical presentation compatible with NMOSD per the IPND criteria (2015) and follow-up > 6 months | Azathioprine + prednisone | None | Adverse events |
| (Huang et al. 2018)  China | Coh  III-2 | High | 90 | Diagnosis by 2006 NMO or 2015 NMOSD criteria, seropositive for AQP4-Abs, ≥ 18 years, more than 2 relapses within 2 years prior to therapy | IV MMF; dose 500mg/day for the first 2 weeks and then 1,000mg/day | None | Adverse events |

ARR = annualised relapse rate; AQP4-Abs = aquaporin 4 antibodies; BCVA = best corrected visual acuity; Coh=cohort; CS=case series; EDSS = Expanded Disability Status Scale; IPND = International Panel for NMO Diagnosis; IV = intravenous; IVMP = intravenous methyl-prednisolone; LETM = longitudinally extensive transverse myelitis; MMF = Mycophenolate mofetil; MOG-Ab = myelin oligodendrocyte glycoprotein antibody; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; PLEX = plasma exchange; Ret = retrospective; RCT=randomised controlled trial

## Outcome Measures and Analysis

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

Outcome measures for therapeutic effectiveness varied according to the category of evidence included (see Section 5.2).

Comparisons of early versus late treatment in NMOSD patients were measured by the impact of treatment on symptoms such as visual impairment or relapse rate.

Change in disease status following treatment was measured using the change in EDSS or change in ARR. These measures of disability and relapse rate have been discussed elsewhere in this report (Section B4.2.2).

The effectiveness of specific treatments for NMOSD compared to MS treatments in NMOSD was reported by way of hazard ratios for attack risk, with effectiveness of interferon-β being the reference point. Interferon-β has been shown previously to be ineffective in the treatment of NMOSD, but is used regularly and with success in MS patients.

Finally, safety of NMOSD treatments was measured in terms of adverse events or serious adverse events.

## Results of the Systematic Literature review

### Does the change in management improve health outcomes?

Summary – 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 versus late treatment, or treatment for NMOSD rather than MS for someone with NMOSD)?

There was a strong to very strong association between early treatment (PLEX, AZA or IVMP) for NMOSD patients and better treatment effectiveness when compared to late treatment. Delay of treatment in three studies led to statistically significantly worse outcomes. Of particular importance for visual outcomes, a study of NMOSD patients with ON found that delay of IVMP treatment, beyond as little as 4 days after an ON attack, led to worse visual deterioration. In other statistically significant results, delay in AZA led to shorter time to relapse, and delay in PLEX led to lower likelihood of complete improvement (measured by EDSS and VA).

Confidence in the association between treatment timing and outcome was moderate to high when assessed by GRADE, but was reduced by the risk of bias in the retrospective observational study designs. (GRADE: LOW ⨁⨁⨀⨀ to MODERATE ⨁⨁⨁⨀)

Specific therapies for NMOSD (PLEX, RTX, and AZA) were more effective overall than standard immunosuppressant therapy (IVMP, glucocorticoids) alone when measured by EDSS or ARR in statistically significant results. ECZ was more effective than placebo when measured by ARR but not by EDSS. MS treatments (interferon beta, glatiramer acetate and mitoxantrone) were not found to be effective in NMOSD patients. The association between better effectiveness and NMOSD treatment was strong and there was moderate confidence in this outcome when assessed by GRADE. (GRADE: LOW ⨁⨁⨀⨀ to HIGH ⨁⨁⨁⨁)

There is a risk of serious side effects associated with NMOSD therapies, including some serious adverse events. However, the risk of side effects is likely to be considered preferable to the risk of the serious clinical impact associated with NMOSD relapse symptoms or attacks. The risk of mortality associated with treatment appears to be very low.

Likely outcomes of AQP4-Ab testing for true positive, true negative, false positive and false negative patients are described in Table 4.

There was insufficient evidence to report on similar outcomes for MOG-Ab testing.

### Early versus late treatment in NMOSD patients

#### Early versus late plasma exchange (PLEX) treatment for NMOSD

PLEX is one of the more commonly used treatments for acute phase NMOSD in Australian patients. One article identified in the literature search assessed the impact of delay in PLEX treatment on improvement for 60 NMSOD patients (Bonnan et al. 2018). Complete improvement was defined as improving to baseline status during follow-up, as determined by EDSS and VA scores.

In the population of 60 NMOSD patients who underwent a total of 115 attacks, it was found that the probability of regaining complete improvement decreased as the delay in receiving PLEX increased after relapse. One quarter of events were disease onset attacks and the majority were in confirmed NMOSD patients. Probability decreased from 50% if PLEX was received at day 0 to 1, to approximately 5% if PLEX was received after day 20. Furthermore, the probability of achieving a good recovery decreased with delay in PLEX, while at the same time, the probability of achieving a poor recovery increased. Both baseline impairment (based on EDSS) and delay in receiving PLEX were associated with the probability of achieving complete improvement.

#### Early versus late azathioprine (AZA) treatment for NMOSD

In one retrospective review of 38 NMOSD patients (Bukhari et al. 2017) impairment was assessed. Outcomes were compared between those who had received AZA at the same time as IVMP or within 2 weeks of an acute phase relapse, with those who had received AZA after IVMP had been tapered to 10mg on alternate days. In a third group only IVMP was given in the acute phase and no AZA was given.

When early and late AZA treatment groups were compared for time to next relapse, patients receiving early AZA experienced a longer time to next relapse than those receiving late AZA (32.74 versus 18.17 months; p = 0.025). Similarly, in a survival analysis, the duration of remission in the early AZA groups a showed longer duration of remission compared to the late AZA group (HR 0.250; 95%CI 0.072, 0.867; p = 0.029).

Multivariate modelling found that receiving treatment at a younger age and history of receiving AZA were associated with better outcomes for patients, whereas older initial age was a risk factor for worse outcomes.

#### Early versus late intravenous methylprednisolone (IVMP) treatment of ON in NMOSD patients

The relationship between time to treatment and visual outcome was investigated in one retrospective study of 27 patients with NMOSD and ON. (Stiebel-Kalish et al. 2019). Patients were either AQP4-Ab or MOG-Ab positive, and had either uni- or bilateral ON. All were treated with IVMP for 3 days followed by oral prednisone. A comparison of best corrected visual acuity (BCVA) at 3 months follow-up after an attack was made between those treated within 7 days and those treated after 7 days.

The primary outcome reported was failure to regain 20/30 vision based on BCVA measurements. Those treated after 7 days had an OR of failure of 10.0 (95%CI 1.39, 71.86) compared to those treated within 7 days (p = 0.01). Additional analyses to determine the optimum threshold for administering treatment found that those treated after 4 days had an OR of 8.33 of failure to regain 20/20 vision when compared to those treated prior to 4 days (p = 0.01). Results are shown in Table 49.

Table Early versus late intravenous methylprednisolone treatment in patients with ON (Stiebel-Kalish et al. 2019)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Population** | **Follow-Up** | **Intervention** | **Comparator** | **Difference** |
| Failure to regain 20/30 vision | NMOSD AQP4-Ab and MOG-Ab ON patients; n=36 | 3 months from treatment start of IVMP | <7 days to treatment: | >7 days to treatment: | OR of failure = 10.0 (96%CI 1.39-71.86); p=0.01 |
| Likelihood of failure to regain 20/20 vision | AQP4-Ab and MOG-Ab positive ON patients; n=36 | 3 months | Treatment <4 days: | Treatment >4 days | OR = 8.33 (95%CI 1.47, 47.22)  P=0.01 |

AQP4-Ab = aquaporin 4 antibodies; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; odds ratio

#### Association of delay in diagnosis with disability (EDSS) associated with any treatment

One recent study (Mealy et al. 2019) looked at the impact of the extent of delay in diagnosis for NMOSD patients on disability measured by EDSS. According to the authors, “patients were started on NMOSD-specific immunotherapy at the time of NMOSD diagnosis confirmation, such that the delay in diagnosis was equivalent to delay in initiation of preventative treatment.” Demographic and clinical data in 182 AQP4-Ab positive patients were analysed for contribution to disability beyond relapse. Disability was measured using the EDSS tool.

Delay in diagnosis/preventative treatment was found to be contribute to a worse EDSS in simple regression analysis (p = 0.033; 95%CI 0.006, 0.140) and by multiple regression modelling (p = 0.006; 95%CI 0.02, 0.15). Other factors found to contribute to disability in the multivariable regression modelling were older age at onset, length of acute T2 myelitis lesion and the presence of symptomatic brain/brainstem lesions. Factors not found to be contributors were the number of inflammatory events, ARR; relapse treatment score (calculated to account for the number of events and type of treatment) and duration of MS modifying treatment in single factor analyses. Multivariable regression results are shown in Table 50.

Table Contributors to NMOSD disability (EDSS) by multivariate analysis (Mealy et al. 2019)

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **P value** | **Coefficienta** | **95% confidence interval** |
| Age at onset | 0.000 | 0.06 | 0.04, 0.08 |
| Delay at diagnosis | 0.006 | 0.09 | 0.02, 0.15 |
| Length of acute T2 myelitis lesion | 0.000 | 0.16 | 0.08, 0.23 |
| Brain/brainstem lesions (normal versus symptomatic) | 0.023 | 0.91 | 0.12, 1.71 |

NMOSD = neuromyelitis optica spectrum disorders; EDSS = expanded disability status scale

a If correlation was greater than 0.6, collinear variables were not included in the multivariate analysis

### Comparison of effectiveness of NMOSD and MS treatments in NMOSD patients

A retrospective cohort study conducted in Germany collected data on 144 patients from 21 regional and university hospitals (Stellmann et al. 2017). Eligible patients had been treated for NMO (2006 criteria) or AQP4-Ab positive or negative NMOSD. Hazard ratios for attack risk were calculated using multivariate analyses and were compared across treatments; RTX, AZA, interferon-β, mitoxantrone and glatiramer acetate. The latter three treatments are commonly used in MS patients; treatment with interferon-β is now ceased for NMOSD (Kim et al. 2012; Tanaka, Tanaka & Komori 2009; Wang et al. 2014). Separate analyses were performed on 127 patients who received 322 treatment episodes with these five treatments.

According to analyses, RTX and AZA were the only treatments to perform better than interferon-β in reducing attacks (RTX: p = 0.034; AZA: p = 0.001). Glatiramer acetate and mitoxantrone were not found to have a statistically significant difference in effectiveness to interferon-β. Predictors of attacks that were found to be statistically significant were seropositivity for AQP4-Ab (p = 0.009) and age at which attack occurred, with frequency decreasing with older age (p = 0.039).

The study evidence favours the treatment of NMOSD with RTX or AZA rather than MS therapies interferon-β or glatiramer acetate. However, the authors commented that sample sizes were too small for strong conclusions to be made. Furthermore, a previous attack under the same treatment was associated with a 1.5 times increase in risk of further attack, but not found to be statistically significant.

### Change in disease status in patients treated for NMOSD

Studies with comparative before and after treatment analyses of EDSS, ARR or relapse frequency were included in this section.

#### Change in EDSS following plasma exchange (PLEX) treatment for NMOSD

Bonnan et al 2009 (Bonnan et al. 2009) assessed the impact of PLEX treatment on a cohort of patients from French West Indies with either NMO or extensive transverse myelitis (ETM). The patients with NMO comprised 79% of the total group of 43 patients. There were 96 spinal attacks in all, 29 of which were treated with PLEX. Change in EDSS was the primary outcome and was compared between patients who received PLEX and patients who received steroid therapy alone for treatment of an attack.

Change in EDSS was measured from peak EDSS at acute phase to residual EDSS. In both treatment groups EDSS was worse at follow-up after the attack. The overall increase in mean EDSS was smaller in those receiving PLEX for an attack compared with those who received only steroid therapy(p < 0.01) (Table 51). There was no statistically significant difference in the treatment groups for baseline EDSS and EDSS at the acute phase.

Table Comparison of change in EDSS between NMOSD atacks treated with steroid or PLEX (Bonnan, M et al. 2009)

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Steroid therapy (n=67)**  **Mean±SD** | **Plasma exchange (n=29) Mean±SD** | **Difference**  **P value** |
| Baseline EDSS | 4.2±2.9 | 3.9±2.9 | 0.84 |
| Acute phase EDSS | 8.0±1.4 | 7.9±1.0 | 0.52 |
| Residual EDSS | 6.8±1.9 | 5.1±2.4 | <0.01 |
| Change in EDSS | 2.6±2.4 | 1.2±1.6 | <0.01 |

EDSS = expanded disability status score; NMOSD = neuromyelitis optica spectrum disorders; PLEX = plasma exchange; SD = standard deviation

#### Change in EDSS following rituximab (RTX) treatment for NMOSD

A recent SR (Gao et al. 2019) performed a review of studies assessing RTX effectiveness in NMOSD patients. Studies were included if they were published in English, and patients were not limited in age, gender, ethnicity or previous treatments. Case studies with one or two patients, reviews and meta-analyses were excluded. Before and after treatment EDSS and ARR data were extracted from the included 26 articles. The majority of articles were retrospective cohorts, one each was a case series, and case controlled in design, three were prospective and one was a randomised controlled trial.

A meta-analysis of 22 articles reporting on change in EDSS found that RTX improved EDSS. A pooled estimate of weighted mean reduction of score of -1.16 (95%CI, -1.36. 0.96; p < 0.0001) was reported. The heterogeneity across studies was moderate (I2 = 15.5%; p = 0.254) There was no correlation between the change in EDSS and age of onset, duration of disease, follow-up time, dose of infusion and AQP4-Ab sero-status.

EDSS was reported in two further studies (Shaygannejad et al. 2019) (Ashtari et al. 2019) identified in the literature search and published after the search date of the meta-analysis.

These two recent primary studies compared EDSS at baseline and last follow-up in NMOSD patients treated with RTX (Ashtari et al. 2019; Shaygannejad et al. 2019). In both studies, NMOSD diagnosis was based on the 2015 IPND criteria.

Ashtari et al conducted a sub-analysis according to AQP4-Ab status (54% were AQP4-Ab positive). Shaygannejad also stratified the results according to AQP4-Ab status and found no difference between groups, however EDSS data were only reported for the whole patient group (Table 52).

Table Change in EDSS reported in recent primary studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **N patients**  **Follow-up** | **Baseline EDSS**  **(Mean±SD)** | **Follow-up EDSS**  **(Mean±SD)** | **Difference**  **P value** |
| (Ashtari et al. 2019) | All patients: 56  1 year | 4.83±1.87 | 2.87±1.63 | NR  (MedCalc: p<0.0001) |
| AQP4-Ab +ve: 30  1 year | 4.94±1.83 | 2.92±1.54 | NR  (MedCalc: p<0.0001) |
| AQP4-Ab –ve: 26  1 year | 4.76±1.93 | 2.84±1.72 | NR  (MedCalc: p=0.0003) |
| (Shaygannejad et al. 2019) | All patients: 46  31.6±7.3 months | 4.1±1.8 | 3.1±1.8 | <0.001 |

AQP4-Ab = aquaporin 4 antibodies; EDSS = expanded disability status scale; NR = not reported; SD = standard deviation

#### Change in EDSS following eculizumab (ECZ) treatment for NMOSD

Authors Pittock et al reported on a double blind, placebo controlled time-to-event randomised controlled trial of ECZ in NMOSD patients (Pittock et al. 2019). Diagnosis was according to 2006 or 2007 criteria, and patients were randomised in a 2:1 ratio to ECZ (n = 96) and placebo (n = 47) respectively. The trial design allowed for continuation until 24 patients had a relapse of NMOSD, however the trial was terminated by the sponsor after the 23 patients relapsed. Twenty of these relapses occurred in the placebo group. Disability was compared between ECZ and placebo groups using the EDSS in a secondary endpoint analysis. Disability was reduced in both groups and the difference between them was not significant (Table 53).

Table Change in EDSS in NMOSD patients randomized to eculizumab or placebo (Pittock et al. 2019)

|  |  |  |  |
| --- | --- | --- | --- |
| **Timeline** | **Eculizumab**  **N=96**  **(Mean±SD)** | **Placebo**  **N=47**  **(Mean±SD)** | **Difference**  **HR (95%CI)** |
| Baseline | 4.00 (1.0–7.0) | 4.00 (1.0–6.5) | NR |
| Follow-up | –0.18±0.81 | 0.12±0.95 | –0.29 (–0.59 to 0.01) |

EDSS = expanded disability status scale; HR = hazard ratio; NMOSD = neuromyelitis optica spectrum disorders; SD = standard deviation

#### Change in ARR following rituximab (RTX) treatment for NMOSD

A SR by Gao et al (2019) performed a review of studies assessing RTX effectiveness in NMOSD patients. Studies were included if they were published in English, and patients were not limited in age, gender, ethnicity or previous treatments. Case studies with one or two patients, reviews and meta-analyses excluded. Before and after treatment EDSS (reported above) and ARR data were extracted from the included 26 articles. The majority of articles were retrospective cohorts, one each was a case series, and case controlled in design, three were prospective and one was a randomised controlled trial.

An analysis of 26 articles reporting on the ARR ratio change, RTX was found to improve the relapse rate. In the random effects model the mean difference in ARR ratio after RTX therapy was -1.56 (95%CI -1.82, -1.29). Heterogeneity was high (I2 = 81.3%; p = 0.000) but in sensitivity analyses no study was found to individually affect heterogeneity, and all studies favoured RTX. As with change in EDSS reported in this SR, there was no correlation with change in ARR with age of onset, duration of disease, follow-up time, dose of infusion and AQP4-Ab sero-status. The authors also reported that 330 of 528 patients receiving RTX (62.9%) reached a relapse free state.

Two recent studies not included in the SR compared ARRs at baseline and last follow-up in NMOSD patients treated with RTX (Ashtari et al. 2019; Shaygannejad et al. 2019). Patients were identified in the same Iranian hospital in both studies, however patients were included from different time periods. NMOSD diagnosis was based on the 2015 IPND criteria.

There was a consistent and statistically significant reduction in ARR from baseline following treatment in both study groups (MedCalc: p<0.0001 for both studies). Ashtari et al conducted a sub-analysis according to AQP4-Ab status (54% were AQP4-Ab positive) that provided a similar result to the whole group analysis. Shaygannejad et al also stratified ARR results according to AQP4-Ab status and found no difference between groups although data were not published for this outcome, however ARR data were only reported for the whole patient group. Published results can be seen in Table 54.

Table Change in ARR from before to after rituximab (RTX) treatment reported in recent primary studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **N patients**  **Follow-up** | **Baseline ARR**  **(Mean±SD)** | **Follow-up ARR**  **(Mean±SD)** | **Difference**  **P value** |
| (Ashtari et al. 2019) | All patients: 56  1 year | 1.43±1.107 | 0.147±0.27 | NR  (MedCalc: p<0.0001) |
| AQP4-Ab +ve: 30  1 year | 1.35±0.85 | 0.10±0.19 | NR  (MedCalc: p<0.0001) |
| AQP4-Ab –ve: 26  1 year | 1.49+±1.25 | 0.17±0.31 | NR  (MedCalc: p<0.0001) |
| (Shaygannejad et al. 2019) | All patients: 46  31.6±7.3 months | 0.26±0.54 | 0 | 0.003 |

ARR = annualised relapse rate; AQP4-Ab = aquaporin 4 antibodies; NR = not reported; SD = standard deviation

#### Change in ARR following eculizumab (ECZ) treatment for NMOSD

A double blind, placebo controlled time-to-event RCT of ECZ in NMOSD patients reported on ARR (Pittock et al. 2019); also reported above for the outcome of EDSS. Diagnosis was according to 2006 or 2007 criteria. The trial design allowed for continuation until 24 patients had a relapse of NMOSD, however the sponsor terminated the trial after the 23 patients relapsed. Twenty of these relapses occurred in the placebo group. ARR was compared between ECZ and placebo groups in an endpoint analysis. The study primary efficacy endpoint was first adjudicated relapse (first physician-determined relapse). A secondary endpoint was the adjudicated ARR (ARR based on physician-determined relapses).

First adjudicated relapse and adjudicated ARR were both significantly higher in the placebo group (both outcomes: p<0.001; Table 55).

Table Difference in first adjudicated and ARR between NMOSD patients randomized to eculizumab (ECZ) or placebo (Pittock et al. 2019)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **Timeline** | **Eculizumab**  **N=96**  **(Mean±SD)** | **Placebo**  **N=47**  **(Mean±SD)** | **Difference**  **HR (95%CI)** |
| Adjudicated ARRa | Baseline (previous 24 months) | 1.94±0.90 | 2.07±1.04 | NR |
| Follow-up | 0.02 (0.01–0.05) | 0.35 (0.20–0.62) | 0.04 (0.01, 0.015)  P<0.001 |
| First adjudicated relapseb | 0 | 3/96 (3%) | 20/47 (43%) | 0.06 (0.02, 0.20)  P<0.001 |

ARR = annualised relapse rate; HR = hazard ratio; NMOSD = neuromyelitis optica spectrum disorders; SD = standard deviation

a Anualised relapse rate based on physician-determined relapses

b First physician-determined relapse

#### Change in ARR and EDSS for AQP4-Ab positive NMOSD patients given Azathioprine (AZA)

Elsone et al (2014) assessed efficacy, tolerability and retention of AZA in a cohort of 103 AQP4-Ab positive NMOSD patients, (Elsone et al. 2014). Efficacy was based on the change in ARR and EDSS. The median follow-up of the whole cohort was 18 months, however using Kaplan-Myer analysis it was estimated that nearly 73%, 58%, 47% and 33% of patients would remain on AZA for longer than one, three, five and ten years, respectively, after initiation of treatment (Elsone et al. 2014). The reasons for treatment discontinuation were mainly attributed to tolerability (due to side effects), death and disease-activity.

Change in ARR and EDSS results are shown in Table 56. There was an improvement in both outcomes, but the difference in ARR was statistically significant (p < 0.00005) but the reduction in EDSS was not.

Table Change in ARR and EDSS from before to after azathioprine (AZA) treatment (Elsone et al. 2014)

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome**  **N patients** | **Baseline (pre-treatment)**  **Median (IQR)** | **Follow-up (post-treatment)**  **Median (IQR)** | **Difference**  **P value** |
| EDSS  N=96 | 6 (3.5–6.5) | 5 (3.5–6.5) | P=0.52 |
| ARR  N=103 | 1.5 (0.6–4.0) | 0 (0–0.27) | p<0.00005 |

ARR = annualised relapse rate; EDSS = extended disability severity scale; IQR = inter-quartile range

### Safety

Adverse events for the most commonly used therapies for NMOSD are reported in this section. Only one study provided comparative evidence for safety. Pittock et al (2019) compared adverse events between patients randomised to either ECZ or placebo. The remaining studies were non-comparative, and reported adverse events in patients receiving treatment only.

#### Plasma Exchange (PLEX)

Bonnan et al (2009) reported on the adverse events occurring in 29 patients receiving PLEX treatment for spinal attack. Eight minor adverse events were reported in seven PLEX sessions. One 84 year old man who experienced extreme brachicardia, and a patient with bacteraemia, ceased treatment sessions early. The adverse events are listed in Table 57.

Table Adverse events in NMOSD patients given plasma exchange (PLEX) (Bonnan et al. 2009)

|  |  |
| --- | --- |
| **Adverse event** | **Patient number**  **n/N (%)** |
| Deep hypofibrinogenaemia (below 0.5 g/L) | 2/29 (6.9) |
| Hematoma at puncture site | 2/29 (3.4) |
| Benign vagal reaction | 1/29 (3.4) |
| Asymptomatic bacteraemia | 1/29 (3.4) |
| Abdominal syndrome | 1/29 (3.4) |
| Extreme bacteraemia | 1/29 (3.4) |

NMOSD = neuromyelitis optica spectrum disorders

A further study by Jiao et al. (Jiao et al. 2018b) reported adverse events in Chinese patients (N=29) with NMOSD who received two to seven sessions of PLEX treatment, on alternate days. A total of 11 of 29 patients (37.9%) experienced adverse events, with nine (18.8%) deemed mild and transient. Two PLEX treatments were prematurely interrupted, one due to life-threatening heparin-related thrombocytopenia and one to catheter-related severe sepsis. There was one death during PLEX treatment, however the study authors did not believe this was a result of PLEX treatment per se.

#### Rituximab (RTX)

The SR by Gao et al 2019 (2019) reported on adverse events reported in the 26 included studies. A total of 95 of 577 patients receiving RTX were recorded as having adverse events, including 22 serious events. The serious adverse events are listed in Table 58. In addition there were five recorded deaths. The causes of death were reported as pneumonia (n = 2); urogenital infection and thrombosis (n = 1); bone marrow transplantation (n = 1), and cardiac and respiratory failure due to extensive myelitis reaching the medulla oblongata (n=1).

Table Serious adverse events in NMOSD patients given rituximab (RTX) (Gao et al. 2019)

|  |  |
| --- | --- |
| **Adverse event** | **Patient number**  **n/N (%)** |
| Severe adverse reaction | 12/577 (2.1) |
| Severe pneumonia | 5/577 (0.87) |
| Transit hyperpyrexia | 2/577 (0.35) |
| Severe allergic reaction | 1/577 (0.17) |
| Urogenital infection | 1/577 (0.17) |
| Seborrheic dermatitis | 1/577 (0.17) |
| Death | 5/577 (0.87) |

NMOSD = neuromyelitis optic spectrum disorders

#### Azathioprine (AZA)

Bichuetti et al (2019) reported on the number of severe side effects in patients receiving AZA therapy. In the study, 100 of 158 NMOSD patients were given AZA, and 11 (11%) suffered severe adverse events that required cessation of therapy. The events are listed in Table 59.

Table Serious adverse events in NMOSD patients given azathiorpine (AZA) (Bichuetti et al. 2019)

|  |  |
| --- | --- |
| **Adverse event** | **Patient number**  **n/N (%)** |
| Gastrointestinal intolerance | 4/100 (4.0 ) |
| Severe infection | 2/100 (2.0) |
| Alopecia | 1/100 (1.0) |
| Liver toxicity | 2/100 (2.0) |
| Allergy/skin reactions | 2/100 (2.0) |

NMOSD = neuromyelitis optica spectrum disorders

#### Mycophenolate mofetil (MMF)

Two studies (Huang et al. 2018; Jiao et al. 2018a) reported on the safety of MMF at different dosing regimens in Chinese patients with NMOSD seropositive for AQP4-Abs. All patients in both studies also received concomitant oral corticosteroids.

The multicentre, open prospective study, by Huang et al. (Huang et al. 2018) evaluated the safety of low dose MMF (500mg/day for the first 2 weeks, followed by 1,000 mg/day after 2 weeks) in 90 patients for a mean duration of 18 months (range 6-40 months). The second study, a case series by Jiao et al. (2018a) included a total of 109 patients and investigated MMF at various doses: low (≤ 1000mg/day N=11), moderate (1,250 and 1,500mg/day N=23) and high (1,750 and 2,000mg/day N=52).

Adverse events included gastrointestinal symptoms, infections and haematological abnormalities. For Huang et al. (Huang et al. 2018) adverse events were documented in 43% (39/90) of patients. Eight patients (9%) discontinued MMF due to intolerable adverse events. Three cases of pneumonia were reported, and two of these patients needed ventilator support. One patient died of acute respiratory distress syndrome, after being diagnosed with “haemorrhagic varicella” (Huang et al. 2018).

Jiao et al (2018a), 19% (21/109) reported adverse effects with MMF treatment over the three dosing regimens, although they were not analysed based on dosing subgroups. A total of five patients (4.6%) receiving MMF 2,000mg/day reported moderate to severe adverse events. For two of the patients, one discontinued MMF in the first two months of treatment, while the other patient had their dose reduced from 2,000mg/day to 1,250mg/day. For the remaining three patients, dosage was lowered from 2,000mg/day to 1,500mg/day. A summary of the reported adverse events from the two studies is presented in Table 60.

While the rate of adverse events was not dissimilar between the two studies, patients with severe events in the study by Jiao et al had the management option of a reduction in dose, rather than cessation of treatment as was the case for those in the study by Huang et al.

Table 60 Adverse events following mycophenolate mofetil (MMF) treatment in those with NMOSD

| **Adverse Event** | **(Huang et al. 2018) N=90a**  **No. with adverse event n (%)** | **(Jiao et al. 2018a) N=109b**  **No. with adverse event n (%)** |
| --- | --- | --- |
| Total | 39 (43) | 21 (19) |
| Gastrointestinal | Total 22 (24)  deranged liver enzymes 18 (20), diarrhoea 2 (2), hyperbilirubinaemia 2 (2) | Total 6 (5.5)  deranged liver enzymes 3 (2.8), diarrhoea and abdominal pain 2 (1.8), constipation 1 (0.9) |
| Infections | Total 21 (23)  respiratory infection 11 (12)  urinary tract infection 5 (6)  Varicella-zoster virus infection 5 (6) | Total 4 (3.7)  herpes simplex infection 2 (1.8)  Varicella-zoster virus infection 2 (1.8) |
| Haematological | Total 10 (11)  leucopenia 4 (4)  anaemia 6 (7) | Total 4 (3.7)  leucopenia and low neutrophil counts 3 (2.8)  thrombocytopenia 1 (0.9) |
| Others | Total 4 (4)  hair loss 2 (2)  rectal cancer 1 (1)  renal insufficiency 1 (1) | Total  hair loss 5 (4.6)  headache 2 (1.8)  chronic dermopathy on hands and nails 1 (0.9) |

NMOSD = neuromyelitis optica spectrum disorders; WBC = white blood cell

a MMF dose was 500mg/day for the first 2 weeks and adjusted to 1,000mg/day for 2 weeks.

b MMF dosewas divided into three treatment groups; low dose (≤1,000mg/day), moderate dose (1,250 and 1,500mg/day) and high dose 1,750 and 2,000mg/day)

All patients in the two studies received oral corticosteroids

#### Eculizumab (ECZ)

A randomised, double-blind, time-to-event trial investigated the safety of ECZ compared to placebo in 143 adults with NMOSD (Pittock et al. 2019). The rate of adverse events per 100 patient years was lower in the ECZ group compared to placebo (745 versus 1,127, respectively). Higher rates of upper respiratory tract infection and headache were reported in the ECZ group than in the placebo group (upper respiratory tract infection 31 versus 19 events per 100 patient-years and headache 55 versus 38 events per 100 patient-years for ECZ and placebo, respectively). The rate of any serious adverse event per 100 patient-years, however, was higher in the placebo group compared to ECZ (27 versus 55 for ECZ and, placebo respectively). No patients in the ECZ group, but two patients in the placebo group discontinued treatment due to adverse events. A summary of serious adverse events associated with ECZ compared to placebo is displayed in Table 61. Although the trial was undertaken with a placebo comparator, patients who were receiving immunosuppressive therapies for relapse prevention (except RTX) were eligible for inclusion. It is unknown therefore, whether the adverse events reported were a consequence of only the ECZ treatment.

Table 61 Serious adverse events following eculizumab (ECZ) treatment compared placebo (Pittock et al. 2019)

| **Serious Adverse Eventa** | **Eculizumab (N=96)** | | | | **Placebo (N=47)** | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **No. of events** | **Events/100 patient-year** | | **No. of patients (%)** | **No. of events** | **Events/100 patient-year** | **No. of patients (%)** |
| Any serious adverse eventb | 46 | 27 | 25 (26) | | 29 | 55 | 13 (28) |
| Deathc | 1 | 1 | 1 (1) | | 0 | 0 | 0 |
| Related to trial agent, as determined by investigatord | 13 | 8 | 9 (9) | | 13 | 24 | 9 (19) |

a Serious adverse events were evaluated during 173 patient-years in eculizumab group and 53 patient-years in the placebo group. Serious adverse event defined as any of the following: death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability; is congenital anomaly/birth defect; or is an important medical event

b Serious adverse events that were reported by more than 1 patient in either group were pneumonia (3 patients receiving eculizumab and 1 patient receiving placebo), cellulitis, sepsis and urinary tract infection (each in 2 patients receiving eculizumab and none receiving placebo)

c Patient died from infectious pleural effusion, which the investigator categorized as probably related to trial agent.

d serious adverse events were those categorised by the investigator as possibly, probably or definitely related to the trial agent or as of unknown relationship and included such events as pneumonia, bronchitis, cellulitis and atrial fibrillation

#### Summary of adverse events of treatments for NMSOD

In Table 62 the number of adverse events and serious adverse events are compared amongst NMOSD treatments, summarising the study results reported earlier in the Safety section. Some studies specified if an adverse event was considered related to the treatment or to other patient circumstances (Pittock et al. 2019; Jiao et al. 2018b). Serious adverse events were defined differently amongst the studies or not defined at all. In the studies by Jiao et al (2018) (Jiao et al. 2018b) and Bonnan et al (2009), patients who ceased treatment due to adverse events are included as serious adverse events in Table 69. Only one study (Pittock et al. 2019) compared events between groups randomised to either treatment ECZ or placebo.

The lowest number of serious adverse events was associated with RTX treatment when compared with the other treatments. The highest number of serious adverse events was associated with ECZ treatment compared to the other treatments, however according to the RCT by Pittock et al those who were randomised to placebo experienced twice the rate of serious adverse events than those who received the intervention. These results should be considered with caution as only selected data has been used to address the Safety section and treatments were only compared indirectly. Moreover, the study sizes are small, limiting confidence in these results.

Table Summary of adverse events reported across NMOSD treatments

| **Study ID** | **Treatment**  **N patients** | **Adverse events**  **n (%)** | **Serious adverse events**  **n (%)** | **Mortality**  **n (%)** |
| --- | --- | --- | --- | --- |
| Bonnan et al, 2009 | PLEX  N=29 | 8 (28) | 2 (7) | 0 |
| Jiao et al, 2018 | PLEX  N=29 | 9 (31) | 2 (7) | 1 (3.4)a |
| Gao et al, 2019 | RTX  N=577 | 96 (16.6) | 22 (3.8) | 5 (0.8) |
| Bichuetti et al, 2019 | AZA  N=100 | NR | 11 (11) | 0 |
| Huang et al, 2018 | MMF  N=90 | 39 (43) | 8 (9) | 1 (1.1) |
| Jiao et al, 2018 | MMF  N=109 | 21 (19) | 5 (4.6) | 0 |
| Pittock et al, 2019 | ECZ: N=96 | 745 per 100 patient years | 13 (13.5)b | 1 (1) |
| Placebo: N=47 | 1127 per 100 patient years | 13 (28)b | 0 |

AZA = azathioprine; ECZ = eculizumab; MMF = mycophenolate mofetil; NMOSD = neuromyelitis optica spectrum disorders; PLEX = plasma exchange therapy; RTX = rituximab

a Death not considered related to treatment

b Only adverse events considered to be related to treatment are reported in Table 69. In total there were 46 adverse events in the ECZ group and 29 in the placebo group.

# B6 Impact of repeat testing/monitoring

There was very little evidence that investigated the clinical validity of retesting or monitoring for AQP4-Abs or MOG-Abs for signs of relapse in patients previously diagnosed with NMOSD. Only two small studies of low quality evidence were identified which considered an association between AQP4-Ab titres and the relapsing course of NMOSD. A retrospective cohort by Chen et al (Chen et al. 2017), examined the influence of AQP4-Ab titres on the probability of relapse in those with NMOSD receiving tacrolimus immunosuppressant treatment. A case series study by Valentino et al. (Valentino et al. 2017) investigated the association of AQP4-Ab titre with disease activity in relapsing NMO in those taking RTX. Both studies were assessed for risk of bias using appropriate assessment tools. Key characteristics of the two studies are reported in Table 63. While several other studies were also initially considered for inclusion, they were later excluded due to such reasons as being unable to extract data (Weinstock-Guttman et al. 2008) and the study not using cell-based assays (Jarius et al. 2008; Kessler et al. 2017; Kim et al. 2011; Yang et al. 2013).

Table 63 Key characteristics of studies that investigated the association between serum titres of AQP4-Abs and relapses of NMOSD/NMO

| **Trial/Study** | **N** | **Level of evidence** | **Risk of bias** | **Patient population** | **Key outcome(s)** |
| --- | --- | --- | --- | --- | --- |
| Chen et al. 2017 | 25 | III-3 | High | Patients with NMOSD who were receiving or had received oral tacrolimus Age at onset (years) median (range) 31 (6-55) | Relapsea-free patients in lowb and highc AQP4-Ab titre groups |
| Valentino et al. 2017 | 7 | IV | Moderate | Patients with relapsing NMO taking rituximab. Median age (years) 35 | Correlation between AQP4-Ab titre and disease activity (relapsed and remission) |

AQP4-Abs = aquaporin 4 antibodies; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders

a relapse defined as a new neurological symptoms and signs lasting > 24 hours with or without a responsible lesion on gadolinium enhancing magnetic resonance imaging (MRI)

b a low titre of AQP4-Ab was defined as the titre in the serum <1:64 or no detectable level

c a high titre of AQP4-Ab was defined as the titre in the serum ≥ 1:64

d relapse defined as patient reported or objectively observed events typical of an acute inflammatory demyelinating event in the central nervous system, with duration of at least 24 hours in the absence of fever or infection, documented by contemporaneous neurologic examination

The retrospective cohort study (Chen et al. 2017) reported an association between serum titres of AQP4-Abs and probability of relapses in those with NMOSD. Included patients were recruited from a single medical centre in China, and were receiving tacrolimus immunosuppressant treatment. A relapse was defined as new neurological symptoms and signs lasting >24 hours, with or without a responsible lesion on gadolinium-enhancing MRI. A high AQP4-Ab titre was defined as ≥1:64 and a low titre as <1:64 or no detectable AQP4-Abs. The study did not state why those particular titres were chosen as the cut-offs for high and low, and so it is difficult to determine how effective they would be in the context of monitoring disease status.

Study results showed that the titre of AQP4-Abs in the serum before tacrolimus treatment appeared to be a factor in predicting relapse after initiation of treatment. Those patients with higher AQP4-Ab titres (≥ 1:64) were more likely to relapse while undergoing tacrolimus treatment, compared to those with lower AQP4-Ab titre (<1:64 or none), with a significant difference in the log-rank test (p=0.028). The influence of the AQP4-Ab titre was also shown in a univariate Cox proportional hazards regression model, where the titre status of AQP-4-Abs before tacrolimus treatment was associated with relapse after treatment (HR 5.665; 95% CI 1.012,31.705, p = 0.048). However, multivariate analysis revealed that the difference did not reach statistical significance (p = 0.061).

The results of this study (Chen et al. 2017) suggest that patients with high titres of AQP4-Abs before the commencement of treatment may have a higher risk of relapse even while receiving treatment. However, these results should be viewed with caution, as the retrospective nature of the study presents many biases particularly around patient selection and detection of outcomes. There was no information regarding number of serum samples per patient, and no indication of the error or variation associated with an antibody titre at any individual time-point. While AQP4-Ab titres may prove to be useful in predicting relapse in those with NMOSD, considerably more high quality, large-scale research is required in this field.

The case series study (Valentino et al. 2017) reported that higher AQP4-Ab levels were observed during and preceding relapses compared to those observed during remission. Study results showed a higher median AQP4-Ab titre at onset of relapse (median titre 320; range 160-640; n=10 samples) and within three months prior to onset of relapse (median titre 320; range 0-640; n=23 samples) compared to samples collected during remission (median titre 80; range 0-1,280; n=261 samples) (p=0.0002). Large variability was observed between AQP4-Ab titres at each sample point. Additionally, based on individual patient data, (Table 64), increases in AQP4-Ab levels did not always lead to clinical relapses.

Table 64 Individual patient data on association between AQP4-Abs increase and clinical relapses(Valentino et al. 2017)

| **Patients** | **Total relapsesa (n)** | **Number of times AQP4-Ab increased/n relapses (%)b** |
| --- | --- | --- |
| All patients (N=7) | 12 | 5/11 (45) |
| Patient 1 | 3 | 2/3 (67) |
| Patient 2 | 1 | 1/1 (100) |
| Patient 3 | 0 | - |
| Patient 4 | 2 | 1/2 (50) |
| Patient 5 | 5 | 1/5 (20) |
| Patient 6 | 1 | - |
| Patient 7 | 0 | - |

AQP4-Ab = aquaporin 4 antibodies;

a relapse defined as patient reported or objectively observed events typical of an acute inflammatory demyelinating event in the central nervous system, with duration of at least 24 hours in the absence of fever or infection, documented by contemporaneous neurologic examination

b Percentage values calculated based on availability of AQP4-Ab data

Based on results of this very small study (Valentino et al. 2017) AQP4-Abs are not considered a useful biomarker for predicting relapses in patients diagnosed with NMO.

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

# B7 Extended assessment of comparative harms

QoL is an outcome of interest listed in the PICO Confirmation for Application 1582. There were no QoL data meeting the inclusion criteria identified in the literature search, and therefore the outcome has not been included in the main clinical section of the report. However, a number of studies did report on health related QoL (HRQoL) for NMOSD patients assessed using standardised questionnaires. The studies were cross-sectional and either non-comparative or compared data between NMOSD and MS patients or with a control population.

### Health related Quality of Life

### Risk of Bias Assessment for Health-related QoL studies

Risk of bias was assessed with the SIGN checklist (SIGN 2014) for cohort studies. The risk of bias for each study is shown in Table 65.

Cohort studies assessed with the SIGN checklist were considered of high quality when 70-100% of the questions were answered ‘yes’ (indicating little or no risk of bias). When 40-69% of questions were answered ‘yes’ it was considered acceptable quality, and less than 40% was considered low quality (relating to significant flaws in key aspects of study design).

Table Studies that investigate the impact of NMOSD on HRQoL

| **Trial/Study**  **N** | **Level of evidence**  **Risk of bias** | **Patient population** | **Key outcome(s)** |
| --- | --- | --- | --- |
| Beekman et al. 2019  N=193 | III-3  Moderate | Self-reported, diagnosis of NMO or NMOSD  Age range (years) 19-76 (mean 49.2±12.8).  158 NMO; 35 NMOSD  (118 +ve for AQP4-Ab; 41 –ve AQP4-Ab; 34 unknown) | Impact of NMOSD on HRQoL using SF-36 |
| Chanson et al. 2011  N=40 | III-3  Moderate | Consecutive patients with NMO  Mean age (years) 45.2 (± SD 9)  (16 +ve for AQP4-Ab) | HRQoL measured by SEP-59a  Fatigue assessed by EMIF-SEPb  Depression evaluated by the EHDc questionnaire |
| Kanamori et al. 2011  N=37 | III-3  Moderate | Consecutive outpatients with NMO or NMOSD  Mean age (years) 50.8 (±SD 14.5)  (35 +ve for AQP4-Ab) | Impact of NMO/NMOSD on pain and HRQoL using SF-BPI  DSS |
| Mutch et al. 2015  N=60 | III-3  Moderate | Patients with NMO/NMOSD and +ve for AQP4-Ab  Median age 49 (range 18-81)  47 NMO; 13 NMOSD | HRQoL using SF-36 |

AQP4-Ab = aquaporin 4 antibodies; DSS = Disability Status Scale; EHD = ‘Echelle d’Humeur Dépressive; HRQoL = health-related quality of life; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; SF-36 = short form-36; SF-BPI = Short Form Brief Pain Inventory

a French version of Multiple Sclerosis QoL-54 Instrument

b French version of the Fatigue Impact Scale

c Depressive Mood Scale

### Results of the systematic literature review

All included HRQoL studies were cross-sectional in design. Three of the studies (Beekman et al. 2019; Kanamori et al. 2011; Mutch et al. 2015) assessed the impact of NMO/NMOSD on HRQoL in adults using the patient-reported short form-36 (SF-36) survey of patient health and daily function, while a further study (Chanson et al. 2011) used a French health-related quality of life self-questionnaire SEP-59. One study (Kanamori et al. 2011) analysed pain and its impact on daily and health related QoL in NMO using the short form Brief Pain Inventory (BPI) and compared the data with those in MS.

The SF-36 consists of 36 questions divided up into 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Each domain is scored on a 0 to 100 basis with a higher score indicating better QoL.

Beekman et al. (Beekman et al. 2019) reported only the role-physical and role-emotional subscales of the SF-36, and Mutch et al. 2015 (Mutch et al. 2015) provided Physical and Mental Component Summary Scores only. Kanamori et al. (Kanamori et al. 2011) used a Japanese version of the SF-36 and compared the scores in NMO and MS with that of the Japanese norm.

Two studies (Beekman et al. 2019; Kanamori et al. 2011) normalised the scoring of each domain to individuals in the general population having a score of 50, while the remaining study (Mutch et al. 2015) reported that SF-36 scores were transformed into the standard 0 to 100 scale using the RAND algorithm, but further information was lacking.

Results of included studies were reported as either means or medians. NMO/NMOSD appeared to have a negative effect on physical functioning when compared to the general population, but wide standard deviations were reported, particularly for the study by Beekman et al. (Beekman et al. 2019) suggesting a wide variation amongst results. The results of emotional health showed greater differences between studies, and only one study (Kanamori et al. 2011) showed a negative effect on emotional health in those with NMO/NMOSD compared to the general population. Another study showed marginal impairment in emotional health (Mutch et al. 2015), and one study (Beekman et al. 2019) reported no impairment in emotional health.

Table 66 provides a summary of the impact of HRQoL in adults with NMO/NMOSD using the SF-36.

Table 66 Impact of HRQoL (physical and emotional functioning) in adults with NMO/NMOSD using Short-Form-36

| **Study** | **Setting**  **Number (N) of patients** | **Impact of NMOSD on QoL using SF-36** | **Results**  **Med or Mean (±SD)** | **Impact of NMOSD on QoL using SF-36** | **Results**  **Med or Mean (±SD)** |
| --- | --- | --- | --- | --- | --- |
| **Beekman et al. 2019** | United States  N=193 | Role physical healthb | Med 27.1 (±39.1) | Role emotional healthb | Med 54.0 (±44.9) |
| **Kanamori et al. 2011** | Japan  N = 37 | Role physical healthc | Mean 33.4 (±19.0) | Role emotional healthc | Mean 37.6 (±17.4) |
| **Mutch et al. 2015** | United Kingdom  N = 60 | Physical Component Summary Scored | Mean 33.9 (±11.0) | Mental Component Summary Scored | Mean 47.8 (±11.6) |

HRQoL = health-related quality of life; Med = median; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; SF-36 = short form-36

a Scores on SF-36 ranging from 0 to 100 (100=highest functioning and better QoL and 0 = lowest functioning and worst QoL).

b The scale is normalised to average US individuals having a score of 50

c Used Second Japanese Version of SF-36 and compared the scores of NMOSD with Japanese norm adjusted to having a score of 50

d Scores were transformed into standard 0 to 100 scale using the RAND algorithm

The study by Chanson et al. 2011 (2011) compared HRQoL between patients with NMO (N=40) and MS (N=431) and general population (N=1,007), and used a French health-related quality of life self-questionnaire (SEP-59), which contained 59 questions grouped into HRQoL subscales of physical and emotional functioning. The questionnaire contained both generic (derived from the SF-36 scale) and MS-specific QoL assessment, allowing comparisons in physical and emotional functioning, with the general population and patients with NMO and MS. Data from the two comparator groups were obtained from previously published papers.

Graphical representation of the results showed that there was significantly worse HRQoL in patients with NMO, compared to the general population, for all domains of physical and emotional functioning. When HRQoL was compared between NMO and MS, there was worse QoL in MS compared to NMO related to cognitive function (cognitive func), but there was worse QoL in NMO compared to MS related to bladder and bowel function (BB func). All other domains appeared to be relatively similar, including the physical health composite score (phys comp) and the mental health composite score (mental comp).

Kanamori et al (2011) used a Japanese version of the short form BPI to investigate pain and its impact on daily life and HRQoL in NMO. The measure consisted of two categories: pain severity and pain-related interference in daily life. The pain severity ranged from 0 (no pain) to 10 (severest pain you can imagine), and the patients rated pain severity in each question for 1) the present pain, 2) worst pain, 3) least pain and 4) average pain. The average score of the four pains (1-4) for each patient obtained from the BPI, was analysed using the Pain Severity Index (PSI). The pain-related inference scale consisted of seven domains: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. The patients rated the interferences in the range of 0 (no interference) to 10 (complete interference). Disability Status Scale (DSS) was also used to rate a patients’ physical disability (0-10) by their walking ability and need for assistance (Kanamori et al. 2011). All scores were compared with the scores of patients with MS.

The PSI score was higher in those with NMO compared with MS (mean 3.6 vs 1.5, respectively), and in the categorised PSI rating, more patients with NMO reported mild, moderate and severe pain, but more patients with MS (52.9%) reported no pain compared to those with NMO (16.2%). The pain-related interference score was higher in NMO than in MS in all domains, with significant differences in walking ability and enjoyment of life. The DSS was also higher in those with NMO compared to those with MS (4.0 vs 3.1). The percentage of patients who reported pain was higher in NMO (83.8%) than in MS (47.1%).

Table 67 provides a summary of the results.

Table 67 Pain and impact on daily life and health related QoL in those with NMO/NMOSD and MS using SF-BPI (Kanamori et al. 2011)

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Results NMO/NMOSD  N=37 | Results MS  N=51 | Mean Difference (SE)  (95% CI)a,c |
| DSS score Mean (SD) | 4.0 (2.1) | 3.1 (1.9) p=0.03 | 0.90 (0.43) (0.05,1.75) |
| PSI score Mean (SD) | 3.6 (2.8) | 1.5 (2.1) p<0.0001 | 2.10 (0.52) (1.06,3.14) |
| Pain-related Inference (0-10) Mean (SD) | | | |
| General activity | 3.3 (3.8) | 2.0 (3.0) | 1.30 (0.73) (-0.14,2.74) |
| Mood | 3.5 (3.3) | 2.4 (3.2) | 1.1 (0.70) (-0.29,2.50) |
| Walking ability | 3.2 (3.8) | 1.6 (2.6) p=0.02 | 1.60 (0.68) (0.24,2.96) |
| Normal work | 3.4 (3.8) | 2.3 (3.4) | 1.10 (0.77) (-0.43,2.63) |
| Relation with other people | 3.0 (3.7) | 1.7 (2.9) | 1.30 (0.70) (-0.10,2.70) |
| Sleep | 3.5 (3.6) | 2.2 (3.1) | 1.30 (0.72) (-0.12,2.72) |
| Enjoyment of life | 3.7 (3.8) | 2.0 (3.0) p=0.02 | 1.70 (0.73 (0.26,3.14) |
| Categorised PSI rating n (%) | | | Difference of proportions (%) (95% CI)b,c |
| None (0) | 6 (16.2) | 27 (52.9) | -36.7 (16.6,52.3) |
| Mild (1-3) | 14 (37.8) | 14 (27.5) | 10.3 (-9.0,29.4) |
| Moderate (4-6) | 9 (24.3) | 8 (15.7) | 8.6 (-7.9,26.1) |
| Severe (7-10) | 8 (21.6) | 2 (3.9) | 17.7 (3.9,33.5) |

DSS = Disability Status Scale; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica syndrome disorders; PSI = Pain Severity Index; SE = standard error; SF-BPI = Short Form Brief Pain Inventory

a Comparison of mean with a t-statistic. Values calculated using MedCalc

b Comparison of proportions with a Chi-squared test. Values calculated using MedCalc

c Differences expressed as NMOSD compared to MS

The study by Chanson et al. (2011) assessed fatigue using the EMIF-SEP, which is the French version of the Fatigue Impact Scale and provides an assessment of the physical, cognitive and social aspects of MS-related fatigue. Scores ranged from 0-100 with the higher values indicating higher fatigue. Depression was evaluated by the ‘Echelle d’Humeur Dépressive or Depressive Mood Scale, and is designed to assess depression in MS, with one point = ‘no sign of depression’ to four points = ‘severe mood disturbances’.

Chanson et al 2001 (2011) reported scores for all dimensions of fatigue were lower in NMO than in MS, but this difference reached the level of statistical significance only for the psychological dimension. The intensity of depression was similar in patients with NMO and MS, but no further information was provided.

In conclusion, all studies investigating the effects of NMO/NMOSD on QoL showed that, for physical functioning, NMO/NMOSD had a negative effect on QoL, compared to the general population. The results were less clear for effects of NMO/NMOSD on emotional functioning QoL, with results showing some, marginal or no impairment in emotional QoL.

In comparison to MS, adults with NMO/NMOSD were more likely to report pain, and the pain was more severe and interfered with daily life, particularly walking ability and enjoyment of life. While there was some evidence that the effect of depression on QoL is the same in both NMO and MS, fatigue is lower in NMO compared to MS; more research is warranted in this area.

# B8 Interpretation of the clinical evidence

It is important to classify the therapeutic profile of diagnosis of NMOSD with antibody testing and associated treatments in relation to diagnosis based on clinical characteristics alone (i.e. whether it is therapeutically superior, inferior or equivalent to the comparator).

On the basis of the evidence profile (summarised in Table 68 and Table 69), **it is suggested that, relative to diagnosis of NMOSD without AQP4-Ab testing, diagnosis with testing and associated treatments has non-inferior safety and superior effectiveness.**

Due to limited evidence**, it is 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**, it is 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.**

### Diagnosis and treatment of NMOSD with AQP4-Ab testing compared to no testing

The critical clinical outcomes of the assessment are summarised in this section and interpreted for the Australian clinical setting.

In the absence of relevant diagnostic accuracy data from a clinical setting, prognostic data indicated that the presence of AQP4 antibodies identifies a group of patients at risk of clinically significantly worse outcomes amongst those suspected of NMOSD. The populations tested in the literature appeared to be more narrowly selected for testing than those who are tested in the Australian setting, based on feedback from clinical experts for this assessment, and articles reporting clinical yield data in Australia. However, this difference is not likely to reduce the prognostic information provided by AQP4-Ab testing. A similar trend for worse outcomes in AQP4-Ab positive compared with negative patients was seen in patients diagnosed with NMO or NMOSD. (Diagnostic accuracy evidence profiles can be found in Table 79. Prognostic evidence profiles can be found in Table 81 and Table 82.) (GRADE: VERY LOW ⨁⨀⨀⨀ to HIGH ⨁⨁⨁⨁)

There was evidence to show that patients are diagnosed *earlier* when the 2015 IPND diagnostic criteria are used compare to when the 2006 criteria are used. This may reflect the impact of increased emphasis of AQP4-Ab test usage in the 2015 criteria (Table 65). This was supported by evidence showing that *more* patients are diagnosed based on the 2015 IPND criteria than when diagnosis is based on the 2006 criteria. The association between 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 ⨁⨁⨀⨀)

There was a strong to very strong association between early treatment (PLEX, AZA or IVMP) for NMOSD patients, and better treatment effectiveness, when compared to late treatment (Table 66). Delay of treatment led to worse clinical outcomes in all three studies contributing to this outcome. For example, in the study of NMOSD patients with ON, delay of IVMP treatment beyond as little as 4 days after an ON attack led to more visual deterioration. Although confidence in the association was moderate when assessed by GRADE, it was reduced by the risk of bias in the retrospective observational study designs. (GRADE: LOW ⨁⨁⨀⨀ to MODERATE ⨁⨁⨁⨀)

Specific therapies for NMOSD (PLEX, RTX, AZA and ECZ) were more effective overall than placebo, standard immunosuppressant therapy (IVMP, glucocorticoids) aloneor MS treatment (interferon beta). In the vast majority of studies, the association was strong and there was moderate confidence in this outcome when assessed by GRADE. (GRADE: LOW ⨁⨁⨀⨀ to HIGH ⨁⨁⨁⨁)

There are side effects associated with NMOSD therapies, including some serious adverse events. However, because of the possibility of serious clinical impact associated with NMOSD relapse symptoms or attacks, side effects of the therapies are likely to be considered preferable. Likely outcomes of AQP4-Ab testing for true positives, true negative, false positive and false negative patients are described in Table 4.

### Diagnosis and treatment of NMSOD with MOG-testing compared to no testing

There was insufficient evidence meeting the inclusion criteria to make any conclusions regarding MOG testing for diagnosis of NMOSD.

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

| **Outcome** | **Number of studies (K)**  **Number of Participants (n)** | **Relative effect (95% CI)** | **Certainty** | **Comments** |
| --- | --- | --- | --- | --- |
|
| Time to diagnosis (months; mean follow-up 9.2 y) | K=1 observational study  N=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 studies  N=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.

Table 69 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 study  N=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 study  N=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 study  N=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 study  N=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 study  N=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 study  N=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 study  N=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 study  N=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 study  N=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 trial  N=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 trial  N=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 |

AZA= azathioprine therapy**;** CI: Confidence interval; EDSS = expended disability severity score; HR = hazard ration; IVMP = intra venous methyl prednisolone therapy; NA = not available; NR = not reported; OR = odds ratio; 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.

# Section C Translation Issues

A cost-effectiveness and cost-utility analyses would be undertaken for the economic evaluation based on the clinical claim of superior effectiveness and non-inferior safety.

## C1 Overview

Multiple forms and sources of evidence are presented in Section B. When considering which aspects of this evidence should be incorporated into an economic model, the following translation considerations have been identified.

Potential applicability issues are:

* Are the diagnostic measures, specifically diagnostic yield associated with NMOSD-Ab testing in the literature applicable to the proposed Australian population?
* Are the treatment patterns and outcomes associated with NMOSD therapies applicable to Australian practice?

The economic analysis also needs to consider that the condition and maintenance treatments are ongoing, therefore a relevant extrapolation issue is;

* How are health resources over time, for long-term maintenance and in treating the attacks?

Conducting the economic analysis as a cost-utility analysis requires the measure of incremental health outcomes in quality-adjusted life years (QALYs)), whereas in Section B treatment efficacy is reported in terms of reducing the number and severity of relapses. In the clinical studies the disease severity and subsequent disability accumulation in NMOSD patients is generally measured on the Expanded Disability Status Scale (EDSS) with scores varying from 0 (no disability) – 10 (death). The transformation issue is:

* What are the health state utility values for patients in the different NMOSD health states? i.e. how are these EDSS scores mapped to health utility index, so that time spent in health states can be translated into QALYs?

## C2 Applicability translation issues

### C2.1 Diagnostic yield in the target population

The economic model will require an estimate of the diagnostic yield of AQP4-Ab and MOG-Ab testing. Section B4.1.5 analysed data on diagnostic yield from serum AQP4-Ab and MOG-Ab testing in adults and children with inflammatory conditions or demyelination syndromes, ON or LETM, or patients diagnosed or suspected of having NMO or NMOSD.

In Table 22, 23 and 24 (section B4.1.5) the diagnostic yields for positive AQP4-Ab and positive MOG-Ab ranged from 6.8% to 89%, and from 0% and 29%, respectively. The diagnostic yield for positive AQP4-Ab testing varied widely depending on the inclusion criteria of the study, and which Wingerchuk NMO/NMOSD diagnostic criteria was used. While the data on diagnostic yield for MOG-Ab testing were limited, in those studies that reported MOG-Ab status, it was evident that some (but not all) individuals who tested negative for AQP4-Ab, were found to test positive for MOG-Ab.

Given the broad range of diagnostic yield results in the published studies, these do not provide a reliable estimate for the Australian economic model. A more applicable and reliable estimate of diagnostic yield in the Australian tested population could be determined using recent Australian laboratory data. The applicant surveyed Australian clinical laboratories to provide current utilisation of AQP4 testing and associated test results in Australia. Out of the four data providers, only two (Pathology Queensland and PathWest Laboratory) provided information regarding number of positive tests in the diagnostic cohort suspected of NMOSD. Table 70 and Table 71 summarise this information.

Table AQP4-Ab test utilisation data provided by Pathology Queensland

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **2015** | **2016** | **2017** | **2018** | **2019** | **Average** |
| **Total AQP4 requests** | **1578** | **1414** | **1439** | **1575** | **1973** | **1596** |
| Serum | 1408 | 1200 | 1235 | 1347 | 1696 | 1377 |
| CSF | 170 | 214 | 204 | 228 | 277 | 219 |
| Positive Serum | 48 | 31 | 34 | 36 | 63 | 42 |
| Positive CSF | 3 | 4 | 5 | 4 | 7 | 5 |
| Yield, serum only | 3.4% | 2.6% | 2.8% | 2.7% | 3.7% | 3.0% |
| **Yield, both serum and CSF** | **3.2%** | **2.5%** | **2.7%** | **2.5%** | **3.5%** | **2.9%** |

Source: Pathology Queensland (also includes tests referred by SA Pathology). Data provided by Dr Greg Bryson through personal communication on 4th February 2020.

AQP4-Ab = aquaporin 4 antibodies; CSF = cerebrospinal fluid

Table Number of AQP4-Ab or MOG-Ab tests referred to PathWest Laboratories in 2019

|  |  |  |
| --- | --- | --- |
| **Description** | **AQP4** | **MOG-Ab** |
| No of patients tested | 240 | 132 |
| No of positives | 13 | 21 |
| Proportion of patients tested positive | 5.4% | 15.9% |
| Repeat testing – number of patients | 27 | 21 |
| Tested once | 213 | 111 |
| Tested twice | 19 | 18 |
| Tested thrice | 8 | 2 |
| Tested four times | - | 1 |
| Total number of NMOSD-Ab tests | 275 | 157 |
| Proportion of tests repeated | 12.7% | 15.9% |
| Proportion of tests positive | 4.7% | 13.4% |

Source: Data provided by Dr Andrew McLean-Tooke, PathWest Laboratories through personal communication on 11/02/2020.

AQP4-Ab = aquaporin 4 antibodies; MOG-Ab = Myelin Oligodendrocyte Glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders

The diagnostic yield of AQP4-Ab seropositivity reported in the literature is contrasted by the lower diagnostic yields determined from Australian clinical laboratory data. From the laboratory data, diagnostic yield was found to be 2.9% in Queensland (including tests sent from South Australia) and 5.4% in Western Australia. This suggests that possibly in Australia a broader population is receiving testing than occurs in the identified studies. Another explanation for the high diagnostic yields in the literature is that retrospective study designs are used: the populations in this type of study design tend to be highly selected and may therefore overestimate the diagnostic yield of NMOSD or AQP4-Ab positivity.

MOG-Ab testing data were only available from PathWest laboratory. 13.4% of the tests (15.9% of the patients) were positive for MOG-Ab (Table 71). Dahan et al had reported that 10/67 (14.9%) children in their study were positive for MOG-Ab (Dahan et al. 2020). However, this study only tested 12 children for the detection of MOG-Ab. The demographics (clinical profile and age) of the patients referred to PathWest Laboratory for MOG-Ab testing is not available, and therefore conclusion regarding the diagnostic yield of MOG-Ab in Australian patients suspected of NMOSD cannot be made with confidence. Of note, the diagnostic yield of MOG-Ab reported above is higher compared with the diagnostic yield of AQP4-Ab, but consistent with the clinical expert advice[[11]](#footnote-11) that the prevalence of MOG-Ab is two-three times the prevalence of AQP4-Ab. This may be attributed to the fact that the presence of MOG-Ab is not proprietary to AQP4-Ab–negative NMOSD, and may be representative of other disorders classified under the MOG antibody-related demyelination (MARD). MOG-Ab positive NMOSD forms only a subgroup of the total MARD population (Misu & Fujihara 2018). Although, it is proposed that only those patients suspected of having NMOSD will be eligible for AQP4-Ab or MOG-Ab testing, a large number of patients with other disorders with symptoms overlapping with NMOSD (such as MARD) may be eligible for testing under the proposed service.

Given the variation reported across studies, and incomplete Australian data, the true diagnostic yield for testing in the proposed Australian population is quite uncertain, however the yield based directly on the available Australian pathology laboratory data are likely the most applicable estimate for the base case economic analysis. That is; an average diagnostic yield of 4.2% for AQP4-Ab positive NMOSD, and alternative values from literature are assessed in sensitivity analyses (2.5% to 89%, lowest and highest values indicated by laboratory data and Section B4.1.5 respectively).

In the absence of any conclusive evidence for MOG-Ab diagnostic yield, it is assumed that one-third of the MOG-Ab positives have NMOSD, that is 5.3% (one-third of 15.9% diagnostic yield calculated from the PathWest data) of the suspected NMOSD patients (or 5.5% of the AQP4-Ab negative cases) will be positive for MOG-Ab. Sensitivity analysis varies the diagnostic yield of MOG-Ab from 2% – 29%.

### C2.2 Treatment patterns

Because treatments will vary between whether a patient is diagnosed or not, determination of treatment patterns relevant to Australia to enable costing is required for the economic model. Treatment options in patients with NMOSD are described in Section A6. None of the drugs used or recommended first-line for NMOSD treatment (relapse or prevention) are currently TGA/PBS[[12]](#footnote-12) indicated specifically for NMOSD in Australia.

With respect to acute relapse management, a clinical survey of NMOSD across Australia and New Zealand reported that 329 attacks occurred in a subgroup of 75 NMOSD patients. Intravenous methyl prednisolone (IVMP) was given in 59% of these attacks and 13% were treated with plasma exchange (Bukhari et al. 2020). This study also indicated that the plasma exchange appears to be more effective treatment for acute attacks.

The National report on the issue and use of IVIG reported that 40 NMOSD patients were treated with IVIG in year 2017–18 (National Blood Authority 2018). If the prevalence of NMOSD is assumed to be 550 patients in Australia that will equate to 7.2% of NMOSD patients receiving IVIG treatment.

With respect to maintenance therapy; a study aimed to determine the frequency of AQP4-Ab seropositivity in an Australian cohort of children with central nervous system demyelination, five children were identified with NMOSD. Rituximab and azathioprine were used as maintenance immunosuppression (and corticosteroids and plasma exchange for treating relapses) (Dahan et al. 2020). Azathioprine is listed on the PBS General Schedule as an immunosuppressant, and there are additional references identifying ‘off-label’ rituximab for NMO being used by Australian public hospitals (Nosadini et al. 2016; O'Connor & Liddle 2013; Wongseelashote, Tayal & Bourke 2018). Therefore inclusion of these agents in the model is appropriate for the Australian context.

Although there is some uncertainty, the treatment pattern in the references above indicate that the treatment of NMOSD in Australian practice is broadly consistent with the treatment patterns described in other studies.

## C3 Extrapolation translation issues

### C3.1 Recurring health resource use

As NMOSD takes a relapsing course in most cases, with often incomplete recovery and rapid accumulation of neurological deficits, both short-term management of relapses and long-term immunosuppressive treatment (potentially ongoing over the patient’s lifetime) is recommended once the diagnosis has been confirmed (Trebst et al. 2014).

The pattern of the various treatments used in NMOSD and hospitalisations are investigated following.

#### Preventive treatment (long-term maintenance)

Although there is consensus that patients with relapsing NMOSD need long-term immunosuppression, the best treatment choice for each individual remains uncertain, and the comparison between these drugs have not yielded a specific superiority of one over another (Bichuetti et al. 2019). Data on the long-term immunosuppressive treatment (more than 5 years) of NMOSD are sparse, all are retrospective, and mainly concern azathioprine ± prednisolone and rituximab.

As azathioprine and rituximab are currently the most widely used preventive and first-line maintenance therapies in NMOSD (Trebst et al. 2014), it is assumed that patients will be treated with either azathioprine ± prednisone or rituximab for maintenance whether in relapse-free state or relapsed.

Relevant studies were sought to identify the proportional use of these drugs used for in immunosuppression in NMOSD. In a retrospective multicentre review of 603 AQP4-Ab NMOSD patients (during 2006–2017) with median disease duration at last follow-up of 8 years, Kim et al reported that 98% of the patients with documented treatment history received immunosuppressive therapy. The first-line treatment was azathioprine, rituximab, mycophenolate mofetil or others in 46%, 20%, 20% and 14% respectively. A retrospective cohort study conducted in Germany collected data on 144 patients from 21 regional and university hospitals (Stellmann et al. 2017). Eligible patients had been treated for NMO (2006 criteria) or AQP4-Ab positive or negative NMOSD. The study identified that 15 different immunotherapy drugs were used to treat patients, of which azathioprine, rituximab and mycophenolate mofetil were the most commonly prescribed immunosuppressants. Study indicated that prescription patterns changed over time with rituximab showing an increase from 24% to 43% of all prescriptions from its first use in 2005 to the cut-off of 2011. This increased use of rituximab may be attributed to better efficacy of rituximab compared with azathioprine (Stellmann et al. 2017).

In a cohort of 206 AQP4-Ab NMOSD patients enrolled in MSBase registry (includes patients from Australia), Kunchok et al reported azathioprine and rituximab as the standard immunosuppressive therapies, with approximately 59% and 41% patients treated with azathioprine and rituximab respectively. Since this study includes Australian patients, these data are used in costing resource use of azathioprine and rituximab. Higher proportionate use of rituximab (60% and 80%) is assessed in the sensitivity analysis.

Initially, azathioprine treatment should be combined with prednisone for three to six months until its maximal therapeutic effect can be reached. One study assessing the long-term efficacy of azathioprine reported that 63% patients receiving azathioprine were on concomitant prednisone (either a tapering dose or low maintenance dose following acute treatment). Concomitant prednisone use was similar in those with and without relapses (Elsone et al. 2014). Therefore, the cost of prednisone is added for 63% of the patients treated with azathioprine.

The base-case analysis in the economic model will assume that all patients in remission/relapse state will have immunosuppressant therapy irrespective of the disease duration. Treatment compliance and discontinuation will not be specifically modelled, however, these are assumed to be implicitly captured in the mean treatment doses.

#### Treatment for relapse/attack

Kleiter et al analyzed the frequency, sequence, and efficacy of therapies used for 871 NMO attacks in 185 patients registered in Neuromyelitis Optica Study Group (NEMOS) (Kleiter et al. 2016). Of the 1,153 treatment courses administered, high-dose intravenous steroids (HD-S) comprised of 70.3% of the treatment courses (n = 810) and apheresis (such as plasma exchange) were used in 20% of all treatment courses. Other therapies included intrathecal steroids, IVIG and various others. The frequency of attacks treated with a second, third, fourth, and fifth treatment course was 28.2%, 7.1%, 1.4%, and 0.5%, respectively. On an average, there were approximately 1.3 treatment courses per attack. Although HD-S was used as first treatment course in 83.6% (median dosage 3g) of all treatments; and was given in 44.7% (median dosage = 6g) of second treatment courses, apheresis (median number of exchanges = 5) were used preferentially at later stages of escalation (75%, and 100% of fourth and fifth treatment courses). The study identified 54 combinations of therapeutic strategies, among which HD-S alone (57.4%), one course of HD-S followed by apheresis (10.1%) and two courses of HD-S alone (7.1%) and plasma exchange alone (6%) were the most common therapeutic strategies. Patients treated with apheresis tend to have had higher EDSS (indicating more sever attacks) and a higher number of preceding attacks at start of the therapy compared with patients receiving other first treatment courses.

An MSBase registry study of 206 AQP4-Ab NMOSD patients reported that most relapses were treated with corticosteroids (76%), and plasma exchange (14%), cyclophosphamide (5%) and IVIG (5%) (Kunchok et al. 2019). Cyclophosphamide use was found to decline over the study time period.

A clinical survey of NMOSD across Australia and New Zealand reported that 329 attacks occurred in a subgroup of 75 NMOSD patients. Corticosteroid (IVMP) was given in 59% of these attacks and 13% were treated with plasma exchange. Recovery data were available for 271 attacks and was full in 30%, partial in 62% and none in 9% (Broadley 2017; Bukhari et al. 2020). This study also indicated that the plasma exchange appears to be more effective treatment for acute attacks.

These studies indicate that intravenous corticosteroids are the first-line treatment for most of the attacks followed by PLEX, IVIG and others. It is assumed that mild attacks would be treated with IVMP (84%) and plasma exchange (16%). Severe attacks are assumed to have 1.3 treatments per attack comprising plasma exchange (75%), IVMP (45%) and IVIG (10%). Sensitivity analysis assumes similar treatment (1.3 treatments/attack) for mild and severe attacks in the ratio as reported in Kunchok et al (76% corticosteroids, 14% plasma exchange and 10% IVIG).

#### Hospitalisations

One study was identified that evaluated comorbidities and health care resource use among patients with highly active NMO (at least two relapses in the last 12-months) compared with other NMO patients and matched non-NMO controls (Ajmera et al. 2018) over a 12-month period. The study reported that nearly 53.7% of patients with highly active NMO had at least one inpatient stay in the 12-month follow-up period, compared with 22.4% of all patients with NMO. The average number of emergency department visits during the follow-up period was 5.2 for patients with highly active NMO versus 2.8 for all patients with NMO.

## C4 Transformation issues

### C4.1 Health state utility values

The impact of NMOSD on health related quality of life (QoL) is discussed in Section B.7. In summary studies investigating the effects of NMOSD on QoL showed that, for physical functioning, NMOSD had a negative effect on QoL, compared to the general population. In comparison to MS, adults with NMOSD were more likely to report pain, and the pain was more severe and interfered with daily life. MS patients scored worse on scale for cognitive function compared with NMOSD, whereas NMO patients scored worse for bladder and bowel function. (Chanson et al 2011). All other domains appeared to be relatively similar across MS and NMOSD, including the composite scores for physical and mental health.

All these outcomes were reported using SF-36 or other health-related questionnaires that cannot be transformed to health state utility values (HSUVs) needed to inform the economic model to measure health outcomes in quality-adjusted life years (QALYs).

One study reported utility of patients with MS or NMOSD in Thailand using the Thai version of EuroQoL Five Dimension with three levels (EQ-5D-3L) instrument. The mean health utility score was reported as 0.41 for both groups. 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 the patients’ scores on Expanded Disability Status Scale (EDSS) (Siritho et al. 2018). The disutilities associated with severe and mild relapses were reported as 0.29 and 0.07 respectively (Aungsumart & Apiwattanakul 2020).

Table Health state utility values mapped with EDSS score for MS and NMOSD

|  |  |  |  |
| --- | --- | --- | --- |
|  | Thai study1 |  | AMSLS2 |
| **EDSS** | **NMOSD** | **MS** | **MS, mean (SD)** |
| 0.0 – 2.5 | 0.56(0.51,0.61) | 0.63(0.58,0.67) | 0.72 (0.20) |
| 3.0 – 5.5 | 0.47(0.41,0.53) | 0.49(0.40,0.59) | 0.54 (0.19) |
| 6.0 – 7.5 | 0.18(0.05,0.31) | 0.17(0.03,0.31) | 0.48 (0.19) |
| 8.0 – 9.5 | −0.15(−0.28,−0.02) | −0.30(−0.46,−0.13) |  |

1 Source: (Aungsumart & Apiwattanakul 2020)

2 Source: (Ahmad et al. 2018). Disease severity was estimated based on the EDSS scores where no disability includes EDSS level 0, mild includes EDSS levels 1 – 3.5, no/mild includes EDSS levels 0-3, moderate includes 4 – 6, and severe includes levels 6.5 – 9.5.

AMSLS = Australian MS Longitudinal Study; HSUV = health state utility value (0=dead, 1= perfect health); EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder

The mean HSUV reported in Thai study appears to be lower than reported in other studies for both MS (Ahmad et al. 2018) and NMOSD (Mealy, MA et al. 2019). Mealy et al reported a mean (SD) EQ-5D-5L score of 0.74 (0.16) for adult patients with NMOSD treated at a US academic neurology clinic. The study found that the EQ-5D scores were better in the NMOSD cohort compared with national MS scores, however NMOSD relapses were likely to be more severe and damaging resulting in higher neurologic disability (Mealy, MA et al. 2019).

The 2017 health economic impact of MS report employed the Assessment of Quality of Life 8 (AQoL-8D) multi-attribute utility instrument to assess quality of life for Australian people with MS who participated in the Australian MS Longitudinal Study (AMSLS) (Ahmad et al. 2018). The overall mean (SD) HSUV in 2016 for people with MS was 0.61 (0.22) compared with the Australian general population with a HSUV of 0.80 (0.19). There was a substantial fall in HSUV between no disability and mild disability for MS patients from mean (SD) 0.81 (0.16) to 0.65 (0.19). HSUVs substantially reduced further for people with moderate (0.54 [0.19]) and severe disability (0.48 [0.19]). HSUV was 0.72 (0.20) when no disability and mild disability groups were combined. Disease severity was estimated based on the EDSS scores where no disability includes EDSS level 0, mild includes EDSS levels 1 – 3.5, no/mild includes EDSS levels 0-3, moderate includes 4 – 6, and severe includes levels 6.5 – 9.5.

Several studies have reported that there is no significant difference in terms of health utility scores between MS and NMOSD (Beekman et al. 2019; Chanson et al. 2011; Siritho et al. 2018). Therefore, HSUVs published in Australian study for MS are used for modelled health states no/mild disability and severe disability in the base-case analysis. HSUVs published in Thai study are assessed in sensitivity analysis (Table 72).

## C5 Relationship of each Pre-Modelling Study to the Economic Evaluation

Table 73 summarises the results of pre-modelling studies and their uses in the economic evaluation.

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

| **Section** | **Pre-modelling study** | **Results used in Section D** | **Results used in Subsection D.6** |
| --- | --- | --- | --- |
| 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 maintenance  Drugs used for treating relapse | AZA, RTX, prednisolone  Corticosteroids, PLEX and IVIG | - |
| Extrapolation |  |  |  |
|  | Identifying the recurring health resource use for maintenance therapy: | AZA: 59%  Prednisolone: 63% of AZA  RTX: 41% | RTX use: 60% and 80% |
|  | Identifying the health resource use for treating future attacks; Mild attack:  Severe attack: | Maintenance therapy +  IVMP (84%), PLEX (16%)  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 disability  Disease with moderate–severe disability  Death | 0.72  0.48  0 | 0.47  0.18  0 |
|  | Identifying Disutility associated with relapses:  Mild relapse  Severe relapse | 0.07  0.29 | - |

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

# Section D Economic Evaluation

## D1 Overview

Table 74 sets out the framework that was used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake in this Section. The clinical evaluation suggested that, relative to the no antibody testing, the AQP4-Ab testing has non-inferior safety and superior effectiveness based on the evidence profile given in Table 74.

It was therefore decided that a cost-utility analyses would be undertaken for the economic evaluation.

Table Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Comparative safety** |  | **Comparative effectiveness** |  |  |
| **-** | **Inferior** | **Uncertaina** | **Non-inferiorb** | **Superior** |
| Inferior | Health forgone: need other supportive factors | Health forgone possible: need other supportive factors | Health forgone: need other supportive factors | ? Likely CUA |
| Uncertaina | Health forgone possible: need other supportive factors | ? | ? | ? Likely CEA/CUA |
| Non-inferiorb | Health forgone: need other supportive factors | ? | CMA | CEA/CUA |
| Superior | ? Likely CUA | ? Likely CEA/CUA | CEA/CUA | CEA/CUA |

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

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

a ‘Uncertainty’ covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

b An adequate assessment of ‘non-inferiority’ is the preferred basis for demonstrating equivalence

The base case of the economic evaluation is generated by a modelled economic evaluation based on inputs sourced from the literature and the systematic review in Section B. Issues associated with translating clinical evidence provided in Section B for use in economic analysis are discussed in Section C.

## D2 Populations and settings

The target MBS population is for patients presenting with clinical symptoms suggestive of NMO/NMOSD. The proposed service is to investigate the presence of NMOSD by the detection of one or more antibodies (AQP4-Abs or MOG-Abs) in the target population. Although AQP4-Ab testing has been in occurring in Australia for approximately 10 years under MBS items 71119 or 71165, which are non-specific single antibody test descriptors (see Section A3). A new item for NMOSD-Ab testing is therefore proposed, as the current MBS items do not reflect current clinical practice and are funded at a lower level than providers currently bill for this testing (PCC-Immunology 2018).

AQP4-Ab and MOG-Ab testing will mainly be used by neurologists predominantly for diagnostic purposes only. Subsequent AQP4-Ab and MOG-Ab testing may be used in already diagnosed individuals for monitoring purposes to identify disease exacerbations and relapse.

Antibody testing for AQP4 and MOG can be performed in serum or CSF although testing in CSF is not routinely recommended. The PASC (p.11, ratified PICO document) noted that, although testing of serum is preferred to CSF, CSF testing may be used in some clinical situations. The applicant confirmed that the number of CSF tests conducted in Australia is small and would not incur any additional costs, as the required CSF sample is usually obtained while conducting other procedures. Therefore, the proposed service is not classified into serum or CSF sample testing in the economic model.

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 diagnosis 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).

## D3 Structure and rationale of the economic evaluation

A summary of the key characteristics of the economic evaluation is given in Table 75.

Table Summary of the economic evaluation

|  |  |
| --- | --- |
| **Perspective** | Australian healthcare |
| **Comparator** | No NMOSD-antibody testing |
| **Type of economic evaluation** | Cost-effectiveness, cost-utility, cost-minimisation. |
| **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: Literature suggests, on average, this is 3.3 years1; therefore 3.5 years (14 full cycles) used in the model base case |
| **Outcomes** | Cost per quality-adjusted life year (QALY) |
| **Methods used to generate results** | Decision tree and Markov model |
| **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) |
| **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

### D3.1 Literature review

A literature search of the PubMed and Embase databases was conducted on 3 December 2019 for published cost-effectiveness analyses of the proposed service. No studies were identified that compared the economic impact of testing for NMOSD-Ab and no-testing for the diagnosis of NMOSD.

One conference abstract was identified that reported the cost-effectiveness of AQP4-Ab detection with cell-based assay compared with Elisa for NMO disease diagnosis in Colombia. Costs, correctly diagnosed cases and relapses averted were compared using a decision-tree model in patients with clinical suspicion of NMO that underwent AQP4-Ab testing for diagnosis. The analysis was undertaken from a third-party payer perspective over a one-year time horizon. AQP4-Ab detection with CBA was identified as a cost-saving diagnostic test, dominant over the ELISA method being more effective (90 additional cases correctly diagnosed and 130 relapses avoided) and less costly (resulting in cost-savings of USD $956 yearly costs per correct diagnosis) (Rosselli et al. 2015). Although this study is not relevant to the proposed economic assessment, it is indicative of the cost-effectiveness of correct diagnosis of NMOSD patients by avoiding relapses.

Another study (identified after the search date) presented the cost effectiveness of rituximab and mycophenolate mofetil for NMOSD in Thailand (Aungsumart & Apiwattanakul 2020). This study was health technology assessment and compared the lifetime costs and outcomes of Thai patients with NMOSD undergoing five different treatment options with azathioprine as the reference, using a Markov model. The Markov model considered three main health states based on the EDSS – patients with no or mild disability (EDSS 0–5.5), patients with moderate to severe disability (EDSS 6–9.5) and deceased NMOSD patients. Two additional health states representing patients temporarily experiencing a mild or severe relapse were also included in the model. The modelled health states reflect natural disease course of patients with NMOSD and relapse classification based on disability score is justified.

Although the studied comparison (cost-comparison of different therapies) in the aforementioned study is different from the one proposed in the current assessment (NMOSD-Ab testing versus no testing), the model structure and some clinical parameters were found appropriate to inform the economic model in the current assessment.

### D3.2 Structure of the economic evaluation

A decision analytic model followed by a Markov analysis is presented which accounts for the diagnostic yield of NMOSD-Ab testing, relapse rates, treatment effect and disease exacerbation in the target population.

The structure of the decision-analytic (Figure 8) is consistent with the clinical management algorithms presented in Figure 3 and Figure 5. In the absence of antibody testing, diagnosis of NMOSD relies on both the clinical picture (symptoms) and imaging examinations as described by IPND 2015 criteria (see section A3). MOG-Ab testing can occur either concurrently or in sequentially with AQP4-Ab testing. It is assumed that only diagnostic yield and cost of testing will vary based on the scenario chosen and the model structure and all other parameters will remain same.

Diagnostic accuracy measures for AQP4-Ab testing are inherently biased as AQP4-Ab testing is included in the diagnostic clinical reference standard (diagnosis by 2015 IPND criteria). There is no clinical reference standard for MOG-Ab testing and so only yield data can be obtained for this test. AQP4-Ab positivity is considered definitive for diagnosis of NMOSD by clinicians. In addition, a negative test result for AQP4-Ab/MOG-Ab does not rule out a NMOSD diagnosis. It is assumed that the patients who test negative for AQP4-Ab/MOG-Ab will face a similar diagnostic challenge and ongoing management of disease pathways irrespective of the modelled arm, therefore the downstream costs and health outcomes of these patients would be equal across the two arms which would offset each other when it come to estimating incremental cost-effectiveness. The Markov analysis therefore only follows patients that would have/do test positive for the AQP4-Ab/MOG-Ab.

NMOSD-Ab testing is used to differentially diagnose individuals with NMOSD, from multiple sclerosis (MS) and other autoimmune disorders of the central nervous system (CNS) (Sellner et al. 2010). Although NMOSD and MS are defined as distinctive disorders, there is a considerable degree of overlap in clinical manifestations and distribution of lesions in the CNS. In the absence of AQP4-Ab testing approximately 65% of the NMOSD cases receive an alternate diagnosis (Beekman et al. 2019), and nearly 43% are diagnosed as MS rather than NMOSD (Jarius et al. 2012).

The structure of the Markov model (Figure 9) is similar to the model presented in study by Aungsumart et al (Aungsumart & Apiwattanakul 2020). The Markov model considered three main health states based on the EDSS score:

1. disease with no or mild disability (EDSS 0–5.5),
2. disease with moderate to severe disability (EDSS 6–9.5), and
3. deceased NMOSD patients.

The model also includes two temporary health states for relapse classified by severity, viz. mild – moderate relapse and severe relapse. Patient in health states one and two can remain in remission (no relapse), temporarily experience a mild or severe relapse or dies due to a severe relapse. Patient with mild disability who suffers severe relapse will progress to health state with moderate to severe disability. Third health state is an absorbing state reflecting disease or age-specific mortality.

Based on the clinical literature, patients who test positive for AQP4-Ab will have a diagnosis and receive immunosuppressive therapy promptly. Subsequently they will have a reduced risk of relapse and associated disability (see Section B5.2.4).

In the absence of testing, diagnosis and therapy initiation depends on the severity and remission of the first relapse and the clinical course. In the absence of testing, only a small proportion of these patients will receive the correct NMOSD treatment initially (Beekman et al. 2019; McCreary et al. 2018). The remaining patients will either receive multiple sclerosis disease modifying treatment (MS-DMT) or no treatment (see Section D.4). MS-DMT are considered to cause more harm in NMOSD patients (Jarius et al. 2012). However, in these patients, given that inappropriate treatment (if received) would not be successful, and the disease would at some stage relapse; it is assumed that these patients will require 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 data in Section B5.1.4.

Although therapeutic evidence in MOG antibody positive patients is limited, they appear to show similar treatment responses to those with AQP4 antibody-positive NMOSD (Misu & Fujihara 2018). Therefore, patients who are MOG-Ab positive will follow the same clinical path as for AQP4-Ab positives.

Resource use and costs for the relevant treatment are based on attack severity with severe attacks requiring expensive and high-dose treatments compared to mild attacks (see Section D.4 for further details). Health utility values are considered to be lower for patients with severe disability and/or experiencing severe relapses (see Section C.4.1).

### D3.3 Time horizon

The model runs over a time horizon equivalent to the mean time to correct NMSOD diagnosis in the longer of the two arms (long enough to capture the effects of delayed diagnosis), with three months (quarterly) model cycles in the Markov component.

There is no conclusive evidence to indicate that treatment effect or disease progression varies consistently over time. The modelled time horizon is required to capture the time where there is a difference in treatment costs and health outcomes between the treatment arms. Given that the correct diagnosis and treatment does occur after a delayed period in the comparator arm, then the time horizon of the model only needs to be until both arms have all patients diagnosed correctly and receiving correct treatment. 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. Thereafter there is no evidence to suggest further incremental costs or outcomes between arms would be expected.

Figure 8 presents the structure of decision analytic model of the economic evaluation and Figure 9 depicts the health states transitions in the Markov modelled analysis.

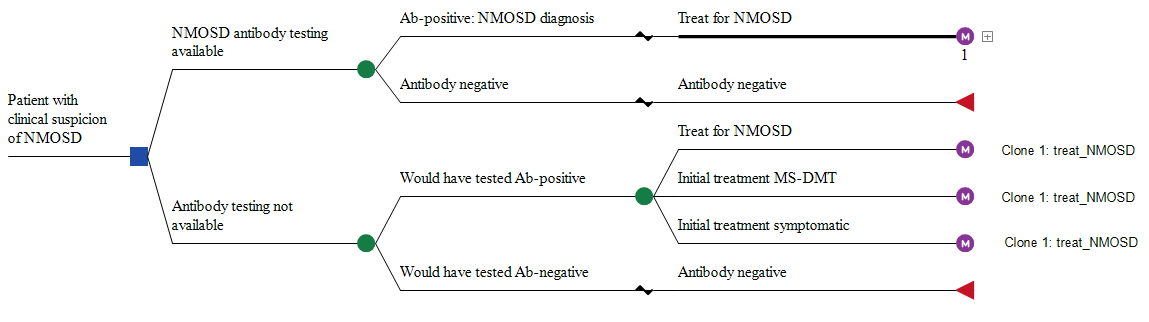


Figure Decision analytic structure of the economic evaluation (also indicating where Markov modelling is initiated)

Ab = antibody; M = Markov modelling process is intiated; MS-DMT = multiple sclerosis disease modifying treatment; NMOSD = neuromyelitis optica spectrum disorder

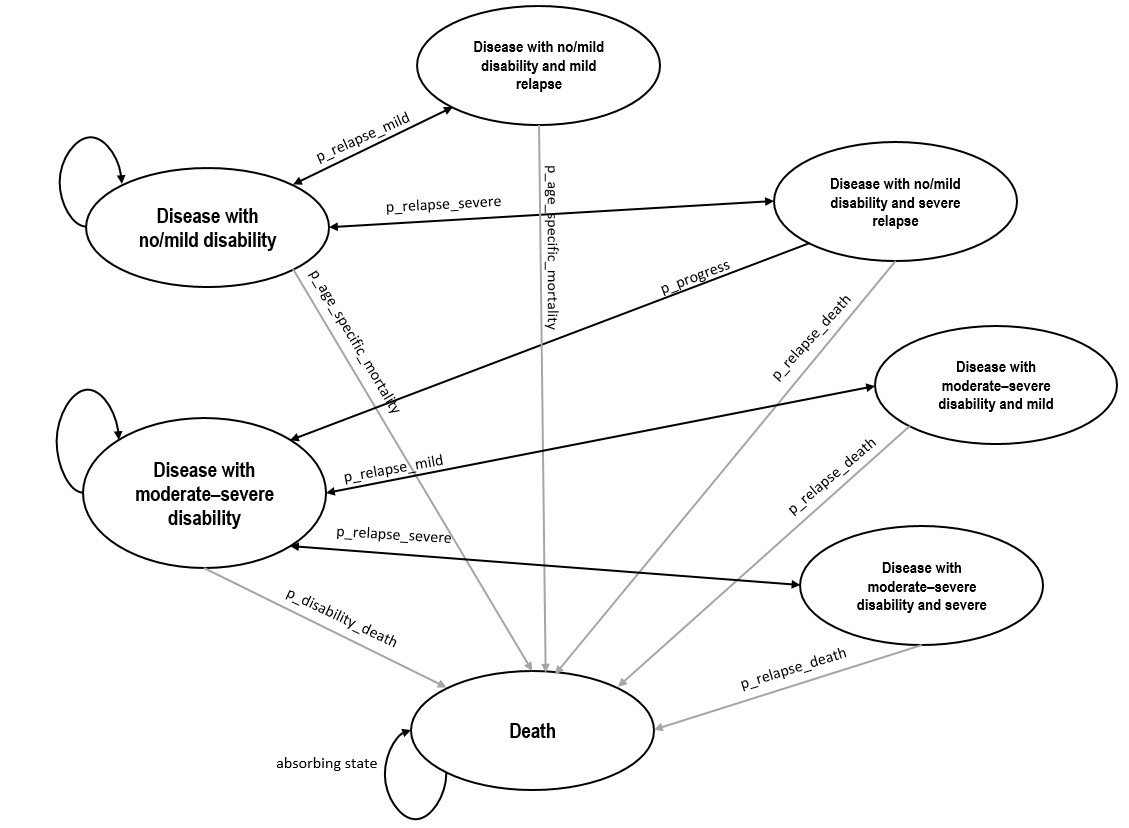


Figure State transition diagram for the Markov component of the economic model

p\_age\_specific mortality = age-specific mortality risk in general population (Australia); \_disability\_death = mortality risk due to disease asscoaited disability; p\_relapse\_death = mortality risk associated with relapse; p\_relapse\_mild = probability of having mild relapse; p\_relapse\_severe = probability of having severe relapse; p\_progress = probability of progressing from temporary health state disease with no/mild disability and severe relapse to health state disease with moderate–severe disability.

Details and justification for the various transition variables used in the model are described in Section D.4, and a summary table of the transition variables with values and/or the sources of these is presented in Table 108, Attachment I.

### D3.4 Assumptions incorporated into the model structure:

A number of assumptions are employed to enable a working model.

Relapses are classified according to the disease severity (mild or severe) and not by the onset type (optic neuritis, transverse myelitis, etc.). A patient undergoing a relapse will require high-dose steroid treatment, single course in mild attack and the multiple courses in a severe attack. NMOSD is not a progressive disease, however disability is accumulated with each relapse due to disease exacerbations. In the real world, patients may improve their EDSS scores, and therefore disability status, but data to support this are insufficient. As most of the NMOSD cases are relapsing, with often incomplete recovery and rapid accumulation of neurological deficits, it is assumed that the patients with moderate to severe disability will not improve enough to have no/mild disability in the model. 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. The temporary health states of mild and severe relapses provide model to account for treatment efficacy and therefore control progression in the disease severity based on the treatment effect.

The probability of relapse (in the absence of treatment) is assumed to be the same for all patient groups, as there is no evidence to the contrary. The probability of relapse (mild/severe) while on treatment is estimated using the treatment effect (relative risk) in the model.

It is assumed that 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 modelled time horizon is set to mean time to correct NMSOD diagnosis in the longer of the two arms.

Patients with no/mild disability (in remission or with mild relapse) are assumed to have mortality risk similar to the general population. Patients in remission with moderate–severe disability are assumed to 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 are assumed to have mortality risk associated with the disease relapse (see Section D.4 for further details).

It is assumed that the patients who test negative for AQP4-Ab/MOG-Ab will have similar diagnostic challenge and ongoing management of disease across each modelled arm. Downstream costs and effectiveness of these patients are considered to offset each other. The Markov analysis therefore only follows patients that would have/test positive for the AQP4-Ab/MOG-Ab. This approach may be incorrect and NMOSD-Ab testing may help in ruling out diagnosis of NMOSD in the patients who test negative. However, evidence related to the conclusive diagnosis and management of patients who test negative is lacking. Limiting the test benefits to the patients who test positive is likely to be a conservative approach and may underestimate the cost-effectiveness of the proposed test.

## D4 Inputs to the economic evaluation

The inputs used to inform costing and transition probabilities are categorised and described throughout this section. A summary table of the transition variables with values and the sources of these is presented in Table 108, Attachment I. All annual probabilities were converted to quarterly cycle lengths using appropriate probability to rate and rate to probability conversion formulas[[13]](#footnote-13). Annual costs of health resources were also adjusted for quarterly cycle lengths.

### D4.1 Patient demographics

There is little detail provided on the demographics of the patients in the studies identified in the systematic review presented in Section B, however most of the studies appear to be in patients who are 12 – 51 years of (mean) age (see Appendix C).

One recently published Australian study (Bukhari et al. 2020) was identified that conducted a clinical survey of possible NMOSD cases across 23 central nervous system (CNS) demyelination clinics in Australia and New Zealand with the aim of outlining the clinical profile of the disease in this region and evaluating the 2015 IPND diagnostic criteria. The key clinical features of NMOSD patients relevant to the economic model are summarised in Table 76.

Table Clinical features of NMOSD patients in Australia and New Zealand1

|  |  |
| --- | --- |
| **Clinical characteristics** | **NMOSD patients (n = 75)** |
| Age at onset (years), median (range) | 40 (13 – 85) |
| Disease duration (years), median (range) | 3.8 (0.1–43.1) |
| Annualised relapse rate, mean (SD) | 0.78 (0.17 – 3.32) |
| EDSS, median (range) | 4 (0–9) |

1Source: (Bukhari et al. 2020)

EDSS = expanded disability status scale; IVMP = intravenous methylprednisolone; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation

It is assumed that the cohort entering the model is 40 years of age and all enter the health state NMOSD with mild disability (EDSS 4.0). Average weight of NMOSD patient in Australia receiving IVIG treatment is reported as 71Kgs (National Blood Authority 2018). In the absence of any other trial data informing the average weight of a NMOSD patient, this value is used to calculate the mean dosage of drugs where required.

### D4.2 Diagnostic yield

The average diagnostic yield of 4.2% for AQP4-Ab positive NMOSD determined from the Australian laboratory data is used in the base-case economic analysis (see Section C2.2) and the values from 2.5% to 73% tested in sensitivity analyses.

It is assumed that 5.3% of the suspected NMOSD patients (that is 5.5% of the AQP4-Ab negative cases) will be positive for MOG-Ab. Sensitivity analysis varies the diagnostic yield of MOG-Ab from 2% – 15%.

### D4.3 Time to diagnosis

Diagnosis is assumed to occur practically immediately on reporting of results (e.g. within a few weeks) following AQP4-Ab testing.

The mean and median times to diagnosis in the assumed *absence of AQP4-Ab testing* reported in Section B5.1.4 range from 3.3 to 4.1 years and 2 to 4.4 years respectively. Therefore, the time to diagnosis in the *absence of NMOSD-Ab testing* is assumed to be 3.3 years (central value in the above ranges) in the base case analysis. The lower and higher values of 2 years and 4.4 years are assessed in the sensitivity analysis.

The length of the delay in diagnosis is likely to be clinically significant, as it may delay appropriate treatment and allow disease progression that prevents a return to baseline symptom status.

There was no evidence to determine if MOG-Ab testing affected the time to diagnosis for patients suspected of NMOSD. It is assumed that the time to diagnosis in the absence of MOG-Ab testing would be similar to time to diagnosis in the absence of the AQP4-Ab testing.

### D4.4 Change in initial diagnosis

In a cross-sectional survey of 193 NMOSD patients assessing the disease impact and quality of life (QoL) of patients, Beekman et al identified that the majority of the study participants (65.8%) had received an alternate diagnosis initially, the most common being MS (41.4%) (see Table 42) (Beekman et al. 2019).

McCreary et al compared treatment outcomes in AQP4-Ab positive patients who met the 2006 NMO diagnostic criteria with patients who met the 2015 IPND criteria for NMOSD. Of the 129 patients included in the study, only seven (5.4%) met the 2006 diagnostic criteria (two core clinical characteristics ON and TM) on initial presentation and rest of the 122 were identified as limited seropositive NMOSD (meeting 2015 criteria with one core clinical characteristic and AQP4-Ab seropositivity, but not 2006) (McCreary et al. 2018).

Based on the evidence above, it is assumed that in the *absence of testing*, 5.4% of the patients will meet the clinical criteria on initial presentation and will be correctly diagnosed as NMOSD, 65.8% of the patients will initially receive an alternate (incorrect) diagnosis and the remaining other patients will have inconclusive/no diagnosis, until the mean time to diagnosis is reached.

### D4.5 Treatment patterns

The therapeutic approach in NMOSD comprises of treatement of attacks and prevention of the relapses. Treatment patterns applicable to the proposed population were investigated in Section C2.2. Based on the evidence it is assumed that rituximab or azathioprine are used as long-term immunosuppressive therapy, and corticosteroids, plasma exchange and IVIG for treating relapses.

In the absence of complete treatment data for patients with an incorrect diagnosis, but identification that most are diagnosed with MS, it is assumed that all of these patients will receive MS –DMT (Beekman et al. 2019), and in this case beta-interferon would be used to treat the patient (Palace et al. 2019). .

Patients with inconclusive/no diagnosis will receive only symptomatic management.

Resource use and costs of these drugs are discussed further.

### D4.6 Treatment efficacy in NMOSD patients

Treatment efficacy in NMOSD patients was measured using the change in symptom scores (EDSS measure) or change in anualised relapse rate (ARR), (see section B5.2.2). Therapies for NMOSD (plasma exchange, azathioprine and rituximab) were identified to be statistically significantly more effective (but with risk of serious side effects) than standard therapy alone when measured by change in EDSS or ARR. MS treatments (beta-interferon, glatiramer acetate and mitoxantrone) were not found to be effective in NMOSD patients (Borisow et al. 2018). The association between better effectiveness and NMOSD treatment was strong, however due to high heterogeneity in the patient selections and retrospective study designs evidence was graded as moderately biased. Furthermore, the significant time variation between attack onset, treatment and assessment adds uncertainty about real benefit.

As no untreated or placebo cohort for estimating hazard ratio was available for these treatment comparisons, either beta-interferon was generally chosen as a reference category (Stellmann et al. 2017) or pre-treatment and post-treatment ARRs and EDSS were compared with no limitation on the previous treatments or the study duration. The ARR for patients using these therapies was reported between 0.1 and 0.9 (Gao et al. 2019; Stellmann et al. 2017). There was insufficient evidence to report on similar outcomes for MOG-Ab testing.

In order to capture the effectiveness of correct diagnosis and treatment received timely in the economic model, comparative treatment effects for immunosuppressive therapies (combined together) and multiple sclerosis disease modifying treatment (MS-DMT) are required with no treatment as the reference standard. Due to the rarity and natural history of NMOSD randomised trials for different treatments are rare and literature for appropriate treatment is mostly retrospective and still evolving. The modelled analysis also requires the value for baseline ARR (pre-treatment) and the change in ARR (post-treatment).

Table 77 summarises the treatment efficacy (change in ARR and/or EDSS) and adverse events reported in Section B5.2.2. Pre-treatment time and post-tretment follow-up varied across these sudies. Only two studies provided ARR in one year before treatment and one-year post-treatment for azathioprine and rituximab (Ashtari et al. 2019; Nikoo et al. 2017). Ashtari et al conducted a prospective observational study for 51 pateints and compared within group differences before and after rituximab treatment (Ashtari et al. 2019). Nikoo et al reported an open-label trial comparing azathioprine and rituximab for 68 patients with NMOSD for one year. Both groups presented statistically significant reduction in ARR and EDSS compared with baseline (Nikoo et al. 2017).

Both of the above studies (Nikoo et al and Ashtari et al) showed the similar baseline ARR (1.30 and 1.35) and follow-up ARR (0.21 and 0.10) for rituximab respectively, however the baseline ARR for azathioprine was reported to be lower (1.0). The patients receiving rituximab had higher baseline EDSS (higher disability) compared with the patients receiving azathioprine in the study by Nikoo et al, indicating patients with higher EDSS are likely to be treated with rituximab than azathioprine. Therefore, the mean baseline ARR is evaluated based on the proportionate use of azathioprine and rituximab in the model.

Table Treatment efficacy of AZA and RTX in patients with NMOSD

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Intervention (reference)** | **Comparator** | **ARR** | **EDSS** | **AEs** | **Additional notes** |
| AZA (Elsone et al. 2014) | Pre-treatment vesus post-treatment phase | Median(IQR)  Pre-Tx: 1.5 (0.6–4.0)  Post-Tx: 0 (0.0–0.27) | NR | Any: 60%  Severe: 3% | N = 103 AQP4-Ab-positive NMOSD patients |
| AZA± prednisone and RTX (McCreary et al. 2018) | Pre-treatment vesus post-treatment | Hazard ratio of relapse (95% CI) during Tx relative to pre-Tx  AZA: 0.60 (0.30–1.22)  AZA+prednisone: 0.40 (0.18–0.91)  RTX: 0.26 (0.12–0.57) | NR | NR | 129 AQP4-Ab NMOSD patients |
| AZA and RTX (Nikoo et al. 2017) | Pre-treatment vesus post-treatment phase | Mean ARR (SD)  Azathioprine:  Pre-Tx: 1.0 (0.38)  1 year Post-Tx follow-up: 0.51 (0.55)  Rituximab  Pre-Tx: 1.30 (0.68)  1 year Post-Tx follow-up: 0.21 (0.42) | Mean (SD) ∆EDSS  Azathioprine:  0.44 (0.54)  Rituximab  0.98 (1.14) | Azathioprine:  Any: 8.5%  Rituximab  Any: 12.1%  Severe: 3.0% | Open, randomized clinical trial, to compare the efficacy of AZA (n=35) and RTX (n=33) as maintenance therapy in NMOSD patients.  This study was included in the meta-analysis by Gao et al for the efficacy of RTX. |
| RTX (Ashtari et al. 2019) | Pre-treatment vesus post-treatment phase | Baseline: 1.35±0.85  Annual follow-up: 0.10±0.19 | Baseline: 4.94±1.83  At annual follow-up: 2.92 ± 1.54 | Severe: 19.6% | Observational prospective study, N=56 |
| RTX (Gao et al. 2019) | Pre-treatment vesus post-treatment phase | Mean ∆ARR: -1.56 (95%CI -1.82, -1.29). | Mean ∆EDSS − 1.16 (95% CI, − 1.36 to − 0.96) | Any: 16.5%  Severe: 3.8% | Meta analysis of 26 studies.  High heterogeneity and no information about baseline and follow-up ARR |

∆ = difference in mean/median values; AQP4-Ab = aquaporin 4 antibody; ARR = annualised relapse rate; AZA = Azathioprine; EDSS = Expanded Disability Status Scale; NMOSD = neuromyelitis optica spectrum disorders; PLEX = Plasma Exchange; RTX = Rituximab; Tx = treatment

Using a large multicentre dataset of 441 AQP4-AB positive NMOSD patients from the UK, USA, Japan and Martinique who collectively experienced 1976 attacks over the median follow-up of 7.1 years, Palace et al applied the mathematical models to predict effects of age, sex, ethnicity and treatment on likelihood of relapse and developing disability at different time points (Palace et al. 2019). The authors identified that immunosuppresants reduced the likelihood of all relapses by 33% (Rate ratio 0.668) whereas MS treatments increased the risk of relapse (Rate Ratio: 1.383) compared with no treatment.

Rate ratio for immunosuppressive therapy reported in this study is found comparable to the other published observational studies (Ashtari et al. 2019; Gao et al. 2019; Nikoo et al. 2017). The rate ratio estimated in this study are not specific to any immunosuppressive therapy or MS-treatment and represent a cohort treated with any of these. Therefore, these values are adapted in the model base-case.

As the treatment pattern are changing over time, for example there appears to be an increasing use of rituximab for immunosuppression, it is possible that the combined treatment efficacy may be higher than predicted by Palace et al. Sensitivity analysis is performed where the treatment efficacy is based on different ratios of azathioprine and rituximab use, and where the change in ARRis based on another randomized clinical trial study (Nikoo et al. 2017).

### D4.7 Risk of acute attacks

Data regarding risk of acute attack (severe relapse) before-treatment and on treatment were searched in the literature. One study conducted a retrospective analysis of treatment outcomes in 138 NMOSD patients treated with azathioprine, mycophenolate mofetil (MMF), or rituximab (Jeong et al. 2016). The primary outcome measures were the ARR, annualized severe relapse rate (ASRR) (EDSS score of ≥ 6), time to first relapse, and time to first severe relapse. The study reported the baseline ASRR for the 36 months prior to therapy as 1.27 for patients in azathioprine group, and 1.01 for both MMF and rituximab group. For the whole cohort the baseline ASRR is estimated to be 1.1 (annual probability: 66.8%). ASRRs in the study showed a reduction of 74.1% (relative risk: 0.32) and 99.8% (relative risk: 0.016) when treated by azathioprine and rituximab respectively.

### D4.8 Mortality rate

Pre-AQP4-Ab testing study have reported a five year mortality rate of 32% (annual probability: 6.2%), however studies post-AQP4-Ab testing have reported a mortality rate of approximately 25% in those with disease duration of less than ten years (annual probability: 2.5%) (Collazo et al. 2018; Wingerchuk & Weinshenker 2003). It is likely that the difference in the mortality rates pre and post test era are not due to the test, but due to an increased understanding of disease epidemiology and subsequently increased/improved treatments (such as rituximab). Therefore, these mortality rates are incorporated in the model to reflect the treatment effect on disease-associated mortality (i.e. as mortality rates associated with inappropriately treated and appropriately treated disease).

Patients with no/mild disability (in remission or with mild relapse) are assumed to have mortality risk similar to the general population (Australian age-specific mortality rates, (Australian Bureau of Statistics 2018)). Patients in remission with moderate–severe disability are assumed to have a mortality risk (2%) associated with disease disability (Aungsumart & Apiwattanakul 2020). Patients with severe relapse (irrespective of disease severity) and patients with moderate–severe disability and mild relapse are assumed to have mortality risk associated with the disease relapse (6.2% for patients receiving no/incorrect treatment and 2.5% for those receiving correct treatment).

### D4.9 Health resource use and costs

Pattern of health resource use was discussed in Section C.3.1. azathioprine ± prednisololne and rituximab are the most commonly used immunosuppressive therapies for ongoing management or prevention of relapses in NMOSD. azathioprine is typically started at 25 mg and increased up to 2.5–3 mg/kg/daily over a few weeks along with 0.5–1 mg/kg/day prednisolone. Prednisolone is then slowly tapered down to a low tolerable maintenance dose or completely once azathioprine is established, usually by six months with median (range) dose of 4.5 (1.25–45) mg daily (Elsone et al. 2014). Rituximab treatment can be initiated using one of two different regimens: either two one-gram infusions of rituximab at an interval of two weeks or four weekly 375 mg/m2 body surface area applications. To prevent infusion-related side effects, all of the patients receive one dose equal to 1 g paracetamol, 100 mg prednisolone, and 4 mg dimethindene maleate intravenously as premedication before initiating rituximab infusion. Re-dosing is considered every six months to maintain B-cell deficiency (Trebst et al. 2014).

For those who are misdiagnosed as MS, the recommended dose for patients with relapsing MS is interferon-beta 44 microgram (12 MIU) given three times per week by subcutaneous injection.

The clinical inputs related to the ongoing management (preventive treatment) of NMOSD are summarised in Table 78 and for treating relapses are presented in Table 79.

Table 78 Therapy dose, duration and use-related inputs for ongoing management of NMOSD

|  |  |  |  |
| --- | --- | --- | --- |
| **Description** | **Regimen** | **Input value** | **Source** |
| Azathioprine (oral) | 2.5 mg/kg/day | 177.5 mg/day a | (Elsone et al. 2014; Lana-Peixoto & Talim 2019) |
| Prednisolone (oral) | 1 mg/kg/day for first 3 months  4.5 mg/day for next 6 months | 71 mg/day  4.5 mg/day | (Elsone et al. 2014) |
| Rituximab (iv injection) | 1 g×2, 6 monthly | 1000 mg/infusion | (Lana-Peixoto & Talim 2019; Trebst et al. 2014) |
| Interferon-beta (sc- injection) | 44 mcg three times/week | 44 mcg | Product information for Rebif 44 b. |

a Average weight of NMOSD patient times the mean dosage (71 kgs × 2.5 mg = 177.5 mg/day).

b <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=interferon>

g = gram; Kg = kilogram; iv = intravenous; mcg = microgram; mg = milligram; NMOSD = neuromyelitis optica; sc = subcutaneous.

The most common drugs to treat NMOSD attacks are IVMP, plasma exchange and IVIG (see section C3.1). Most NMOSD attacks are treated with methylprednisolone (MP) 1g per day intravenously for five consecutive days, in combination with a proton pump inhibitor and thrombosis prophylaxis. If the symptoms persist or the patients condition worsen either plasma exchange (5–7 exchanges), or IVIG (0.4–2g/kg body weight, given over three to five days), are used (Trebst et al. 2014).

Table Therapy dose, duration and use-related inputs for treating relapses in NMOSD

| **Description** | **Input value** | **Source** |
| --- | --- | --- |
| Methylprednisolone (iv) | one gram/day for five days | (Trebst et al. 2014) |
| Plasma exchange | 5–7 exchanges | (Trebst et al. 2014) |
| Intravenous immunoglobulin | 34 gms/patient | (National Blood Authority 2018) |

iv = Intravenous; NMOSD = neuromyelitis optica

Severe adverse events associated with PLEX, RTX and AZA were summarised in Section B5.2.4 (Tables Table 56, Table 57 andTable 58). It is assumed that each of these severe adverse events would incur an associated hospitalisation cost. The costs associated with preventive treatments including drug costs and adverse events are summarised below in Table 80.

Table Annual costs associated with preventive/maintenance therapy

| Description | Cost per unit | Annual cost | Source |
| --- | --- | --- | --- |
| Prednisolone, 25 mg (3 months) | $0.53 | $136 | PBS item 1916W; $15.76 / 30 units |
| Prednisolone, 5 mg (6 months) | $0.24 | $40 | PBS item 1917X; $14.48 / 60 units |
| Total cost, Prednisolone |  | $176 |  |
| Azathioprine, 50 mg | $0.32 | $418 | PBS item 2687K; $32.19 / 100 units |
| Severe adverse events (%) |  |  |  |
| Gastrointestinal intolerance (4%) | $562 | $22 | Non-admitted care Tier 2, 2025 Gastroenetrology |
| Severe infection (2%) | $26,884 | $538 | AR-DRG T60A |
| Liver toxicity (2%) | $10,898 | $218 | AR-DRG H60B |
| Allergy/skin reactions (2%) | $3,198 | $64 | AR-DRG X61A |
| Total cost, Azathioprine ± Prednisolone |  | $1,371 | 63% patients have concomitant prednisolone therapy (Section C3.1) |
| Rituximab 1x 500 mg, 50 ml vial | $1,223 | $9,784 | PBS item 11790M; $2446.03 / 2 units |
| Intravenous methylprednisolone, 44 mg | $8.22 | $75 | PBS item 11739W; $41.09 / 5 units (100mg prior to each infusion, total 4 infusions) |
| Administration cost | $489 | $1,956 | Non-admitted care Tier 2, 2041 Immunology |
| Severe adverse events (%) |  |  |  |
| Severe adverse reaction (2.1%) | $6,442 | $135 | AR-DRG X62A |
| Severe pneumonia (0.87%) | $9,224 | $80 | AR-DRG E62A |
| Transit hyperpyrexia (0.35%) | $2,867 | $10 | AR-DRG T62B |
| Severe allergic reaction (0.17%) | $3,198 | $5 | AR-DRG X61A |
| Urogenital infection (0.17%) | $7,016 | $12 | AR-DRG L63A |
| Seborrheic dermatitis (0.17%) | $251 | $0.43 | Non-admitted care Tier 2, 4045 Dermatology |
| Total cost, Rituximab |  | $12,058 |  |
| Beta-interferon, (44 mcg) | $71 | $11,113 | PBS item 8968B; $854.85 /12 units |
| Administration cost | $489 | $489 | Non-admitted care Tier 2, 2041 Immunology |
| Total cost, beta-interferon |  | $11,602 |  |

AR-DRG = Australian Refined- Diagnosis Related Group; g = gram; Kg = kilogram; mcg = microgram; mg = milligram; NMOSD = neuromyelitis optica; PBS = Pharmaceutical Benefits Scheme

Source: (Independent Hospital Pricing Authority 2020); <http://www.pbs.gov.au/pbs/home;jsessionid=1gj6nvvkqo8l61lok7sjsc9mvl>

In a study evaluating disease burden of highly active NMO, nearly 54% of patients with highly active NMO had at least one inpatient stay in the 12-month follow-up period, compared with 22.4% of all patients with NMO. The average number of emergency department (ED) visits during the follow-up period was 5.2 for patients with highly active NMO versus 2.8 for all patients with NMO (Ajmera et al. 2018). Based on this study, the model assumes that patients with a severe attack will have 5.2 ED visits and patients with mild attack will have 2.8 ED visits. Also, 54% of the patients with severe attack and 22% of the patients with mild attack are assumed to have an inpatient stay. The costs associated with relapse treatments including drug costs and hospital costs are summarised below in Table 81.

Table Costs associated with treating relapses

| Description | Cost per unit | Treatment cost per relapse | Source |
| --- | --- | --- | --- |
| Methylprednisolone (IV) | $8.22 | $220 | PBS item 5264C; $43.98 / 5units |
| Administration cost | $489 | $2,455 | Non-admitted care Tier 2, 2041 Immunology |
| Total cost, methylprednisolone |  | $2,665 |  |
| Plasma exchange | $1,211 | $8,477 | AR-DRG B40Z, Plasmapheresis with neurological disease, sameday |
| IVIG, 34 gms (over five days) | $1,800 | $1,800 | <https://www.blood.gov.au/national-product-list> |
| IVIG administration | $489 | $2,455 | Non-admitted care Tier 2, 2041 Immunology |
| Total cost, IVIG |  | $4,245 |  |
| Symptomatic treatment | $524 | $524 | (Ahmad et al. 2018) |
| Hospitalisation costs |  |  |  |
| Inpatient stay, intermediate – major complexity | $10110 | - | Weighted cost of AR-DRG B67A and B67B based on number of separations |
| Inpatient stay, minor complexity | $1,788 | - | AR-DRG B67C, Degenerative Nervous System Disorders, Minor Complexity |
| Emergency care | $1,124 | - | URG 98, Neurological illness |
| Hospital cost associated with severe attack | $10,110 | $11,277 | 54% of inpatient stay (intermediate – major complexity) + 5.2 times Emergency care |
| Hospital cost associated with mild attack | $1,788 | $3,547 | 22% of inpatient stay (minor complexity) + 2.8 times Emergency care |

AR-DRG = Australian Refined- Diagnosis Related Group; IVIG = intravenous immunoglobulin; IVMP = Intravenous methylprednisolone; PBS = Pharmaceutical Benefits Scheme

Source: (Independent Hospital Pricing Authority 2020); <http://www.pbs.gov.au/pbs/home;jsessionid=1gj6nvvkqo8l61lok7sjsc9mvl>

There are other costs associated with specialist visits, diagnostic imaging and routine pathological testing. These are considered to be same across the modelled arms and are therefore not included.

## D5 Results of the Economic Evaluation

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.

### Incremental costs and effectiveness

#### Base-case analysis

The overall expected costs and outcomes (discounted), and incremental costs and outcomes per patient associated with the AQP4-Ab test and comparator (no testing) in the model, with the base case assumptions, are presented in Table 82. Markov traces for each modelled arm are presented as attachment in the Appendix I.

Table Costs and effectiveness for base-case analysis, AQP4-Ab testing only

| **Description** | **Average cost per patient** | **QALYs** | **Relapses** |
| --- | --- | --- | --- |
| NMOSD-Ab testing | $1,271 | 0.1093 | 0.0818 |
| No Ab testing | $1,995 | 0.1060 | 0.1319 |
| Increment (Ab testing – No Ab testing) | –$723 | 0.0034 | –0.0501 |

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

The base-case analysis suggests that when AQP4-Ab testing is used for the diagnosis of NMOSD (Table 82) it results in an average cost saving of $723 and a gain of 0.0034 additional QALYs, compared with no AQP4-Ab testing. Additionally, it results in 5% fewer relapses than no Ab-testing. This is due to the test facilitating rapid diagnosis and appropriate treatment, such that there is less relapse and progessed disease; resulting in quality of life benefits, and also 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.

The results of the base-case analysis suggest that the AQP4-Ab testing strategy is less costly and more effective (i.e. dominant – in the South-East quadrant of cost-effectiveness plane) compared with no Ab testing, for all clinical outcomes assessed.

#### Scenario analyses

Table 83 summarises the result of scenario analyses performed for AQP4-Ab testing along with either concurrent or sequential MOG-Ab testing.

Table Costs and effcetiveness 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) | |  | |  |  |
| NMOSD-Ab testing | $2,880 | | | 0.2525 | 0.1888 |
| No Ab testing | $4,607 | | | 0.2447 | 0.3047 |
| Increment (Ab testing – No Ab testing) | –$1,727 | | | 0.0078 | –0.1158 |
| Scenario 2 (AQP4-Ab + sequential MOG-Ab testing) a | | |  |  |  |
| NMOSD-Ab testing | $2,923 | | | 0.2525 | 0.1888 |
| No Ab testing | $4,607 | | | 0.2447 | 0.3047 |
| Increment (Ab testing – No Ab testing) | –$1,684 | | | 0.0078 | –0.1158 |

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

When AQP4-Ab and MOG-Ab tests are performed concurrently (Scenario 1, Table 83), it results in a net cost saving of $1,727 with 0.0078 additional QALYs ($214,358 saving per QALY gained) compared with no testing. Additionally, antibody testing results in 11.5% fewer relapses compared with no testing.

When AQP4-Ab and sequential MOG-Ab tests are performed (Scenario 2, Table 83), it results in a net cost saving of $1,684 with 0.0078 additional QALYs compared with no testing. Likewise, antibody testing results in 11.5% fewer relapses compared with no testing.

Overall, the results of scenario analyses suggest that NMOSD-Ab testing strategy is less costly and more effective (dominant) compared with no Ab testing with respect to diagnostic strategies (AQP4-Ab + concurrent/sequential MOG-Ab testing) and all clinical outcomes assessed.

## D6 Sensitivity analyses

Uncertainties in the parameter values chosen for the base-case were discussed in section C and D.4. Univariate sensitivity analyses were performed using the extreme values of these model parameters for base-case model.

The modelled results were robust for all sensitivity analyses. They predict that the proposed NMOSD-Ab test would be dominant (have cost savings and more effectiveness) compared to the hypothetical comparator of no testing across all ranges of tested variables. However, the average cost per patient (and therefore cost-savings) and other clinical outcomes are sensitive to the modelled time-horizon (due to treatment costs and effect being similar after correct diagnosis is received), proportion of patients receving rituximab (due to higher costs associated with rituximab treatment), time to correct diagnosis, and health utility value chosen for the health states no/mild disability and severe disbaility, but nonetheless, testing remained dominant for all alternative inputs tested.

Figure 10 summarises the key sensitivity analyses undertaken for the modelled outcomes.

A graphical trace showing the incremental cost-effectiveness per QALY over varied over the time-horizon range is presented in the Figure 11, Appendix I. Although there is no additional test-driven benefits after 3.3 years (as it is assumed all pateints then have a correct diagnosis and thereafter receive appropriate treatment), some ongoing savings and health outcome benefits associated with the correct diagnosis being provided intially (3.3 years ahead of some patients in the comparator arm) persist over an extended time horizon and the testing strategy remains dominant in the long-term analysis.

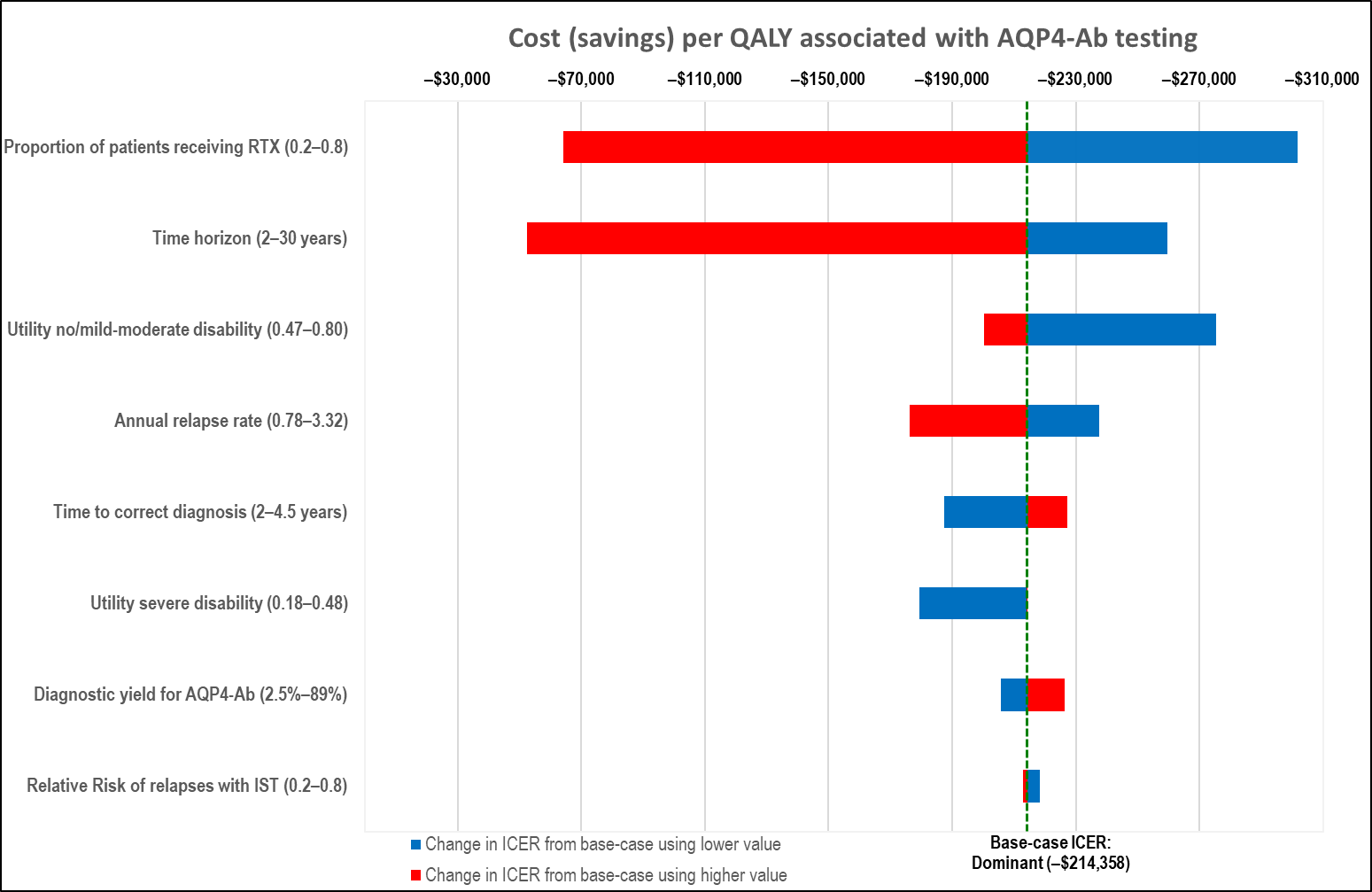


Figure Tornado sensitivity analyses diagram, base-case scenario

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

Although a number of assumptions were required to develop the model and data inputs were uncertain, particularly given the historical nature of the comparison, the fact that the sensitivity analyses consistently yielded dominant results (resource savings and health outcome benefits) for NMOSD-Ab testing vs no testing, this would suggest that, despite the limitations or any inaccuracies that may exist in the model, it is unlikely that Ab testing for NMO/NMOSD would not be cost-effective in practice.

# Section E Financial Implications

## E1 Justification of the Selection of Sources of Data

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 is used to estimate the financial implications of a potential listing of NMOSD antibody testing on the MBS.

Table 84 summarises the data and sources used in the financial analysis.

Table 84 Data and sources used in the financial analysis

| Description | Value used | Source |
| --- | --- | --- |
| Australian demographics | Table 86 | (Australian Bureau of Statistics 2018) |
| Number of AQP4-Ab tests performed in NSW in 2019, public sector | 1,614 | Data provided by NSW Healtha |
| Number of AQP4-Ab tests performed in Queensland in 2015 – 2019, public sector | Table 70 | Data provided by Queensland Healthb |
| Number of AQP4-Ab tests performed in WA in 2019, public sector | 275 | Data provided by PathWest Laboratoryc |
| Number of MOG-Ab tests performed in SA in 2019, public sector | 157 | Data provided by SA Pathologyd |
| Number of AQP4 ± MOG-Ab tests performed by a national private lab in 2019 | 1,014 | Data provided by Sonic Laboratories Australiae |
| Growth rate for AQP4-Ab testing, per annum | 6% – 13% | Data provided by Queensland Healthb and Sonic Laboratoriese |
| Cost of NMOSD-Ab test | $43.00 | Proposed MBS fee, Section A5 |
| Cost of MBS item 71119 | $17.00 | Scheduled fee for MBS item 71119 |
| Cost of MBS item 71165 | $34.55 | Scheduled fee for MBS item 71165 |
| Current proportional usage of MBS items 71165 and 71119, respectively. | 69% and 31% | Assumption based on data provided by various laboratories |
| Proportion of MBS items 71119 and 71165 currently bulk-billed | 99% | Data provided by Department of Health |

a Data provided by A/Prof Steve Reddell, Concord Hospital, NSW through personal communication on 07 February 2020.

b Data provided by Dr Greg Bryson, Pathology Queensland through personal communication on 04 February 2020.

c Data provided by Dr Andrew McLean-Tooke, PathWest Laboratory Medicine through personal communication on 11 February 2020.

d Data provided by Dr Pravin Hissaria, SA Pathology through personal communication on 14 February 2020

e Data provided by Dr Daman Langguth, Sonic Laboratories Australia through personal communication on 04 February 2020.

Source: Cost data sourced from Medicare Benefits Schedule (2020 online version used).

ABS = Australian Bureau of Statistics; AQP4-Ab = aquaporin 4 antibodies; MBS = Medicare Benefits Schedule; MOG-Ab = Myelin Oligodendrocyte Glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders; NSW = New South Wales

The proposed new item is specific for the detection of AQP4-Ab or MOG-Ab for the diagnosis of NMOSD. The proposed service would be provided by both public and private laboratories with appropriate NATA accreditation. For the purpose of this assessment, AQP4-Ab/MOG-Ab testing funded under a mix of MBS items 71119 and 71165 will be used as the financial comparator, however two sensitivity analyses are presented assuming that 100% of existing MBS funding is allocated to each of these items, separately.

## E2 Use and Costs of NMOSD-Ab testing

### E.2.1 Estimated use of the proposed testing

Currently claimed MBS items 71165 and 71119 for NMOSD-Ab testing are generic for antibody testing and therefore the current utilisation of these tests specifically for this purpose cannot be estimated from the MBS statistics data. The applicant (Royal College of Pathologists) collected data from the clinicians and laboratories around Australia (PathWest laboratories in WA, SA Pathology in SA, NSW Health, Queensland Health and Sonic Laboratories Australia) to estimate the current usage of AQP4-Ab/MOG-Ab testing in Australia[[14]](#footnote-14). These tests were referred by specialists and were for both diagnosis and monitoring of AQP4-Ab positive NMOSD. Table 85 summarises the data provided by these laboratories.

Table 85 Current utilisation data for AQP4-Ab tests

| **Source** | **Estimated number of AQP4-Ab tests performed item number used for MBS claims** | **Estimated % of State market** |
| --- | --- | --- |
| Queensland Health | Five year average: 1,596 per year  Pathology Queensland claims AQP4-Ab tests under MBS item 71165.a | State Reference Laboratory, assumed to cover 100% of the testing in Public Sector in Queensland. |
| NSW Health | Public Sector: 1614  NSW Health Pathology claims AQP4-Ab tests under MBS item 71165.b  Sonic Laboratories: 581  Sonic claims AQP4-Ab tests under MBS item 71119.c | Tests performed at Royal Brisbane and Westmead Hospitals; assumed to cover 100% of the testing in Public Sector in NSW.  Private Sector data from Sonic Laboratories. |
| PathWest Laboratories, WA | **AQP4-Ab test**: 275 tests in 2019 (240 patients tested; 213 tested once, 19 tested twice and 8 tested thrice). 13 out of 240 patients tested positive.  **MOG-Ab test**: 157 tests in 2019 (132 unique patients; 111 tested once, 18 twice, 2 tthrice and 1 four times). 21 out of 132 tested positive.  PathWest claims AQP4-Ab tests under MBS item 71165.d | State Reference Laboratory, sole provider of AQP4-Ab testing in WA. |
| SA Pathology, SA | Approximately 3 tests per week (156 per year) referred to Queensland Health  SA Pathology claims AQP4-Ab tests under MBS item 71119.e | State Reference Laboratory; assay not available in-house therefore tests are referred to Queensland. |
| Sonic Laboratories, Australia | 953 unique tests; 51 repeated twice and 5 repeated once. Total number of tests: 1,014.  Sonic claims AQP4-Ab tests under MBS item 71119.c | Around 40% of outpatient serology in the private sector. |

a Personal Communication (email 18/03/2020 from PathQldClients@health.qld.gov.au)

b As per NSW Government Health Pathology website:<http://www.palms.com.au/php/labinfo/info_index.php?tc=AQP4&site=RNSH&tn=Aquaporin%204%20Ab&s=Cerebrospinal%20Fluid&sid=9>

c Personal communication through email, received on 27 September 2019.

d Personal communication through email, received on 19 March 2020

e as per SA Pathology website: <https://www.sapathology.sa.gov.au/wps/wcm/connect/sa+pathology+internet+content+new/content/clinicians/pathology+collection+guide?q=NMO>

AQP4-Ab = aquaporin 4 antibodies; MBS = Medicare Benefits Schedule; MOG-Ab = Myelin Oligodendrocyte Glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders; NSW = New South Wales; SA = South Australia; WA = Western Australia

The information about the number of tests performed in the given time-period provided by these laboratories was used to project the number of NMOSD-Ab tests that are currently performed in Australia using projected 2019 Australian population demographics (Australian Bureau of Statistics 2018) presented in Table 86.

Table 86 Population Estimates, Australia and, state and territories in 2019

|  | **NSW** | **Victoria** | **Queensland** | **WA** | **SA** | **Tasmania** | **ACT** | **NT** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Population in 2018** | 8,089,500 | 6,594,800 | 5,095,100 | 2,621,700 | 1,751,700 | 534,300 | 426,700 | 245,900 |
| **Proportion of AP** | 32% | 26% | 20% | 10% | 7% | 2% | 2% | 1% |

Source: (Australian Bureau of Statistics 2018)

ACT = Australian Capital Territory; AP = Australian population; NSW = New South Wales; NT = Northern Territory; SA = South Australia; WA = Western Australia

Assuming NSW Health, Queensland Health (including SA Pathology) and Western Australia combine to equate to 69% of the total Australian Public Sector Market (based on the State demographics presented in Table 86), total number of AQP4-Ab tests currently performed in the Public Sector will equate to 5,580 (this includes repeat tests).

Assuming Sonic Laboratories Australia (SLA) comprises 40% of the outpatient serology market (clinical expert advice), n=1,014 SLA tests extrapolated to Australia would equate to 2,535 tests annually. Sensitivity analysis assesses this assumption by varying the market share of Sonic Laboratories in the private sector. This is presented in Section E.6.

NMOSD-Ab testing can occur in both serum and in CSF. Utilisation data provided by NSW and Queensland Health indicated that 14% and 18% of the AQP4-Ab tests were performed on CSF, in NSW and Queensland, respectively. However, clinical advice indicated that serum samples are preferred, and ordering of NMOSD-Ab testing on CSF is generally a mistake by clinicians (confusing it with NMDA antibody testing that should be done using CSF)[[15]](#footnote-15).

It was advised during the pre-PASC teleconference that tests requested on CSF would not incur additional costs to the MBS associated with collection procedures, as the CSF sample would be expected to already be available (collected during other relevant procedures/tests). Therefore, the financial estimates are not categorised for serum and CSF testing. Table 87 summarises the steps taken to estimate number of AQP4-Ab tests currently performed in Australia.

Table Estimated number of AQP4-Ab tests currently performed in Australia

|  |  |  |
| --- | --- | --- |
| **Provider** | **Number of tests performed in 2019** | **State / market share** |
| Public Sector |  |  |
| Queensland Health (includes tests referred by SA Pathology) | 1,973 | 27% |
| NSW Health | 1,614 | 32% |
| PathWest Laboratories, WA | 275 | 10% |
| Sub-total | 3,862 | 69% |
| *Public Sector, Australia (extrapolation)* | *5,580* |  |
| Private sector |  |  |
| Sonic Laboratories Australia | 1,014 | 40% |
| *Private Sector, Australia (extrapolation)* | *2,535* |  |
| Estimated number of tests (private + public sector), Australia | 8,115 | includes repeat tests |
| **Estimated number of patients tested (unique tests excluding 10% repeat tests)** | **7,303** |  |

Source: See Table 85 and Table 86.

AQP4-Ab = aquaporin 4 antibodies; MBS = Medicare Benefits Schedule; NSW = New South Wales; SA = South Australia; WA = Western Australia

#### Sequential MOG-Ab testing

PASC informed that MOG-Ab assays have greater variability and, from a clinical perspective, some are considered unreliable. In practice, these tests are mainly ordered together with AQP4-Ab tests for NMOSD diagnosis (advice from A/Prof Steve Reddel and Sonic Laboratories), and therefore it is estimated that approximately a similar number would be performed. Only PathWest provided the number of MOG-Ab tests performed in 2019, however they indicated that AQP4-Ab tests were performed in-house, whilst MOG-Ab tests were sent away to an external laboratory. It is unclear if the number of MOG-Ab tests (n= 157) performed were all for NMOSD (diagnosis/monitoring) or included broader indications for MARD.

The financial analysis assumes that with the proposed listing a small number of laboratories may initially perform/refer sequential MOG-Ab tests due to unavailability of the required resources. It is estimated that approximately 3% (157/5,033) of the additional services currently occur for sequential MOG-Ab tests (assuming all MOG-Ab tests were performed together with AQP4-Ab tests in NSW, Queensland and Sonic) in the estimated number of tests performed in 2019[[16]](#footnote-16). The base case analysis assumes that the sequential MOG-Ab testing will slightly increase to 5% with the proposed MBS listing.

#### Repeat tests (diagnosis/monitoring)

The proposed item descriptor for antibody testing is for diagnosis or monitoring of NMOSD and is restricted to no more than four times in any 12 month period.

A repeat test may be ordered if there is clinical inconsistency to the test result. Clinical advice regarding the use of repeat tests for monitoring is controversial. Some clinicians do not find NMOSD-Ab monitoring useful, while others suggesting that recurrent testing (once a year) is useful to confirm if a patient still has antibodies present, as going from positive to negative may in some cases indicate a reduced requirement for ongoing immunosuppression.

Repeat test rates were informed by PathWest (13% for AQP4-Ab and 16% for MOG-Ab) and Sonic laboratories (6% for AQP4 ± MOG-Ab tests). However, it is unclear what proportion of these repeat tests were for diagnostic or monitoring purposes. Data from other providers did not indicate the number of repeat tests. The base case analysis presented assumes that around 10% of the AQP4-Ab tests currently performed (Table 87) are repeat tests.

#### Growth rate

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–three years. The base case analysis assumes that the MBS listing of NMOSD-Ab test would increase the number of patients tested for AQP4 ± MOG-Ab tests by 20% in the first year of listing, and then an ongoing growth rate of 15% p.a. is assumed over the next four years of listing. Considering NSW and Queensland markets are more mature compared with other states (NMOSD-Ab testing has been available in these states for over 10 years), this may be an overestimate and areas of lower resourcing may show a slower growth rate. Sensitivity analyses are presented assessing the impact of lower and higher growth rates (6 – 25%).

**Estimated use of NMOSD-Ab tests**

The number of patients currently tested for AQP4 ± MOG-Ab tests are estimated to be 7,303 with number of tests equalling 8,115 (accounting 10% of the repeat tests). An additional 3% of the tests performed are assumed to occur as sequential MOG-Ab tests. Repeat tests rates are assumed to be 10% for both for AQP4 ± MOG-Ab tests and sequential MOG-Ab tests. Table 88 presents the projected number of NMOSD tests that would be performed in the first five years of MBS listing. These numbers are estimated by applying growth rates and repeat testing rates on the current estimated utilisation data.

All rows in the Tables below are labelled and referenced using the specified labels in the calculations.

Table 88 Estimated use of NMOSD-Ab tests for the first five years of MBS listing

| **Row** | **Description** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- |
| A | Estimated number of unique tests for AQP4 ± MOG-Ab (Growth rate 20% in the first year; 15% thereafter) | 8,764a | 10,079 | 11,590 | 13,329 | 15,328 |
| B | Sequential MOG-Ab tests (5%) | 438 | 504 | 580 | 666 | 766 |
| C | Repeat tests (monitoring or diagnostic) (C = 10%\*(A+B)) | 920 | 1,058 | 1,217 | 1,400 | 1,609 |
| **D** | **Estimated number of proposed services (D = A+B+C)** | 10,122 | 11,641 | 13,387 | 15,395 | 17,704 |

a Calculated by applying 20% growth rate to 7,303 unique tests in 2019

Ab = antibody; AQP4-Ab = aquaporin 4 antibodies; MOG-Ab = Myelin Oligodendrocyte Glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders; MBS = Medicare Benefits Schedule

### E.2.2 Estimated costs of NMOSD-Ab tests

The proposed MBS fee for the NMOSD-Ab test is $43. MBS utilisation data for items 71165 and 71119 indicated that approximately 96% of these services occur in outpatient settings with a 99% bulk-billing rate (Table 103, Appendix J). Although these item numbers are not specific to NMOSD-Ab testing, based on the estimated service numbers, NMOSD-Ab test would constitute a significant portion of these claims. It is noted that this data are inconsistent with the clinical advice that suggested that laboratories charged on average fees of $43 and that patients face high co-payments for NMO tests due to MBS rebates being lower than the average fee charged.

It is assumed that with higher rebates, NMOSD-Ab tests will be bulk-billed at similar rates to items 71165 and 71119 (99%) and that similar numbers would be performed in the outpatient testing (96%). The test performed in an outpatient setting will incur an 85% Medicare rebate and the one performed in an inpatient setting incurs 75% Medicare rebate. The MBS rebate and patient co-payment for each NMOSD-Ab test under the proposed listing with a fee of $43 would then be $36.38 and $0.07, respectively. Advice provided in a pre-PASC teleconference was 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.

The base-case analysis assumes that 99% of the current/proposed NMOSD-Ab tests are bulk-billed, but alternative assumptions are tested in Section E.6.

Table 89 summarises the estimated costs to MBS and patient co-payments associated with NMOSD-Ab testing. It is estimated that the NMOSD-Ab testing will cost around $644,000 to MBS annually in the fifth year of the listing.

Table 89 Estimated costs of NMOSD-Ab tests for the first five years, under proposed MBS listing

| **Row** | **Description** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- |
| D | Estimated number of NMOSD-Ab tests (= A+B+C) | 10,122 | 11,641 | 13,387 | 15,395 | 17,704 |
| E | Costs to MBS (= D\*$37) | $368,230 | $423,465 | $486,984 | $560,032 | $644,037 |
| F | Co-payments (= D\*$6) | $670 | $771 | $886 | $1,019 | $1,172 |
| **G** | **Total costs of NMOSD-Ab testing (G = E+F)** | **$368,900** | **$424,236** | **$487,871** | **$561,051** | **$645,209** |

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

## E3 Changes in Use and Cost of Other Medical Services

The number of NMOSD-Ab eligible tests in 2020–21 was estimated to be 10,122 and would grow to 17,704 in 2024–25. The total cost to the MBS is estimated to be $368,000 in 2020–21 and increase to $644,000 in 2024–25. However, this projected cost will likely be offset by the NMOSD-Ab services currently claimed under generic MBS items 71165 and 71119. The scheduled fees for MBS items 71165 and 71119 are $34.55 and $17.35 respectively.

From the data available it is estimated that nearly 69% of the NMOSD-Ab tests happen in public sector, and are claimed under item 71165, except tests performed by SA pathology (see Table 85). The private laboratory, SNL, indicated that they claim these services under item 71119. It is assumed that all tests performed in the public sector are claimed under MBS item 71165 (69%), whilst the private sector claims item 71119 (31%) for the same test. The projected usage of these items for NMOSD-Ab testing is estimated by applying 10% linear growth rate and additional 3% MOG-Ab testing to the number of tests (private + public sector) estimated in Table 87.

Table 90 summarises the number of comparator services offset due to the MBS listing of NMOSD-Ab testing.

Table 90 Estimation of the number of comparator services offset

| **Row** | **Description** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- |
| H | Number of services, current funding scenario | 9,205 | 10,125 | 11,138 | 12,251 | 13,477 |
| I | Number of MBS 71165 offset (I = H\*69%) | 6,329 | 6,962 | 7,658 | 8,424 | 9,267 |
| J | Number of MBS 71119 offset (J = H\*31%) | 2,875 | 3,163 | 3,479 | 3,827 | 4,210 |

MBS = Medicare Benefits Schedule

As discussed in section E.2, approximately 96% of these services occur in outpatient settings with 99% bulk-billing rate. Therefore, the estimated average MBS rebates for each service are $25.26 and $14.68 for MBS items 71165 and 71119, respectively. The respective average co-payments for each service are $0.05 and $0.03. The clinical advice received suggested that patients face higher co-payments for NMO tests due to MBS rebates being lower than the average fee charged ($43). The base-case analysis assumes that 99% of the current NMOSD-Ab tests are bulk-billed, but alternative assumptions are tested in Section E.6.

Table 91 presents the estimated total costs offset by comparator services.

Table 91 Estimated MBS costs-offsets (reduced claims on existing (comparator) services)

| **Row** | **Description** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Number of services offset** |  |  |  |  |  |
| I | MBS 71165 | 6,329 | 6,962 | 7,658 | 8,424 | 9,267 |
| J | MBS 71119 | 2,875 | 3,163 | 3,479 | 3,827 | 4,210 |
|  | ***MBS costs offset*** |  |  |  |  |  |
| K | MBS 71165 (K = I\*$29.26a) | $185,204 | $203,725 | $224,097 | $246,507 | $271,158 |
| L | MBS 71119 (L = J\*$14.68a) | $42,218 | $46,440 | $51,084 | $56,192 | $61,811 |
| M | **Total offsets to MBS** (M = K+L) | **$227,422** | **$250,165** | **$275,181** | **$302,699** | **$332,969** |
|  | ***Co-payment costs offset*** |  |  |  |  |  |
| N | MBS 71165 (N = I\*$0.05) | $338 | $372 | $409 | $450 | $495 |
| O | MBS 71119 (O = J\*$0.03) | $78 | $86 | $95 | $104 | $114 |
| P | **Total offsets to co-payments (P = N+O)** | $416 | $458 | $503 | $554 | $609 |
| Q | **Total costs offset (Q = M+P)** | **$254** | **$313** | **$383** | **$466** | **$563** |

a scheduled fee multiplied by 85% (96%) and 75% (4%) MBS rebate

MBS = Medicare Benefits Schedule

## E4 Financial Implications for the MBS

The financial implications to the MBS resulting from the proposed listing of NMOSD-Ab testing are summarised in Table 92. It is estimated that the proposed MBS listing of NMOSD-Ab testing will result in net cost to the MBS of $141,000 in first year increasing to $311,000 in the fifth year.

Table Total costs to the MBS associated with NMOSD-Ab testing

| **-** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- |
| **Proposed test** |  |  |  |  |  |
| Number of services | 10,122 | 11,641 | 13,387 | 15,395 | 17,704 |
| Cost to the MBS | $368,230 | $423,465 | $486,984 | $560,032 | $644,037 |
| **MBS services offset** | **-** | **-** | **-** | **-** | **-** |
| Number of services | 9,205 | 10,125 | 11,138 | 12,251 | 13,477 |
| Cost to the MBS | $227,422 | $250,165 | $275,181 | $302,699 | $332,969 |
| **Net cost to the MBS** | **$140,808** | **$173,300** | **$211,803** | **$257,333** | **$311,068** |

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

## E5 Financial Implications for Government Health Budgets

There are other downstream benefits of early diagnosis with NMOSD-Ab testing such as reduction in number of additional diagnostic tests, relapses and associated hospitalisations. However, quantification of such cost savings is difficult and is unlikely to be informative given that both AQP4 and MOG-Ab testing are currently being performed in Australia.

Table 93 presents the financial implications to the patients (co-payments) of listing NMOSD-Ab tests. It is estimated that proposed listing will result in a slight increase in cost- to patient due to higher fees compared with currently claimed services.

Table 93 Total costs to private sector associated with MBS listing of NMOSD-Ab tests

| **Row** | **Description** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- |
| D | Estimated number of NMOSD-Ab services | 10,122 | 11,641 | 13,387 | 15,395 | 17,704 |
| F | Co-payments | $670 | $771 | $886 | $1,019 | $1,172 |
|  | Offsets |  |  |  |  |  |
| H | Number of services offset | 9,205 | 10,125 | 11,138 | 12,251 | 13,477 |
|  | Costs offset | $416 | $458 | $503 | $554 | $609 |
|  | Net co-payments | **$254** | **$313** | **$383** | **$466** | **$563** |

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

## E6 Identification, Estimation and Reduction of Uncertainty

NMOSD-Ab testing is currently performed in Australia and claimed under MBS items 71119 and 71165. However, these items are generic for antibody testing and NMOSD-Ab specific usage cannot be determined from the MBS utilisation data. The current usage of NMOSD-Ab testing across Australia was extrapolated from limited laboratory data provided by the applicant. A high growth rate of 20% was applied in the first year with 15% per annum growth in the subsequent four years to estimate cost implications of NMOSD-Ab testing, but these are uncertain. Sensitivity analysis was performed to assess the impact of constant lower (6%) and higher (25%) growth rates.

Base-case analysis assumes that additional 5% of the NMOSD-Ab tests would be claimed for MOG-Ab testing. In practice most of these tests are done together with AQP4-Ab tests with no extra cost. Sensitivity analyses were performed assuming additional NMOSD-Ab test rates (for sequential MOG-Ab testing) to be 2.5% and 10%.

Base-case analysis assumes that Sonic laboratories cover the 40% of the outpatient serology market in Australia. This figure for market share is uncertain and may be higher than assumed. Sensitivity analysis was performed changing the market share of Sonic Laboratories in the private sector (60%–80%).

Current proportionate use of items 71119 and 71165 is estimated to be 31% and 69% based on the items claimed by different laboratories. Sensitivity analysis varies the proportionate use of items 71119 and 71165 as 100%, that is only one item claimed as comparator. This will provide the lower and upper limit of costs offsets by the comparators.

Net costs to the MBS due to the proposed listing are largely driven by the increase in the number of current services due to proposed listing. Growth rate in the expected number of NMOSD-Ab tests have high impact on the financial implications. Net costs to MBS are also sensitive to the assumption of proportionate claim of services for 71119 and 71165 due to the differences in MBS rebates associated with these items.

Results of the sensitivity analyses performed are summarised in Table 94.

Table Sensitivity analyses

| **Description** | **2020–21** | | | | **2021–22** | **2022–23** | | | | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Base-case* |  | | | |  |  | | | |  |  |
| Net costs to MBS | $140,808 | | | | $173,300 | $211,803 | | | | $257,333 | $311,068 |
| *Lower growth rate - 6%a* |  | | | |  |  | | | |  |  |
| Net costs to MBS | $97,848 | | | | $94,622 | $90,292 | | | | $84,703 | $77,677 |
| *Higher growth rate - 25%b* | |  | | |  |  | | | |  |  |
| Net costs to MBS | $156,151 | | | | $229,302 | $324,152 | | | | $446,467 | $603,489 |
| *Sequential MOG tests- 2.5%* | | | | | | |  |  |  |  |  |
| Net costs to MBS | $132,040 | | | | $163,218 | $200,209 | | | | $243,999 | $295,734 |
| *Sequential MOG tests- 10%* | | |  | |  |  | | | |  |  |
| Net costs to MBS | $158,343 | | | | $193,465 | $234,993 | | | | $284,001 | $341,736 |
| Sonic's share in the private sector -60% | | | |  |  |  | | | |  |  |
| Net costs to MBS | $116,536 | | | | $144,684 | $178,121 | | | | $217,747 | $264,607 |
| Sonic's share in the private sector -80% | | |  | |  |  | | | |  |  |
| Net costs to MBS | $104,400 | | | | $130,376 | $161,280 | | | | $197,954 | $241,377 |
| Current share of MBS 71119 - 100% | |  | | |  |  | | | |  |  |
| Net costs to MBS | $98,883 | | | | $127,183 | $161,075 | | | | $201,531 | $249,686 |
| Current share of MBS 71165 - 100% | |  | | |  |  | | | |  |  |
| Net costs to MBS | $233,087 | | | | $274,808 | $323,462 | | | | $380,157 | $446,174 |

*aAssuming growth rate is 6% for each year for both current and proposed services.*

*bAssuming a constant growth rate of 10% for the current services and 25% for the proposed services.*

MBS = Medicare Benefits Schedule

Analysis is also conducted which considers the different financial impact that may occur if bulk-billing is to occur and when the proposed item is claimed in conjunction with Patient episode initiation (PEI) 73928 (fee $5.95). This PEI item provides for collection of the specimen from an approved pathology collection centre. If the patient episode is bulk billed it will be eligible for bulk-billing incentive item 74995 (fee $4.00). PEI and bulk-bill incentive items are claimable for both intervention and comparator per patient episode.

Table 95 presents the net costs to MBS for the co-claimable services (items 73298 and 74995) assuming 99% of the current and proposed services are bulk-billed (as per the utilisation data for items 71119 and 71165).

Table 95 Estimated costs associated with co-claimable services

| **Row** | **Description** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- |
| I | Number of proposed services | 10,122 | 11,641 | 13,387 | 15,395 | 17,704 |
| R | Cost of co-claimable services (= I\*$9.91)a | $100,312 | $115,359 | $132,663 | $152,562 | $175,447 |
| J | Number of services, current funding | 9,205 | 10,125 | 11,138 | 12,251 | 13,477 |
| S | Cost of co- claimable services (= J\*$9.91)b | $91,218 | $100,340 | $110,374 | $121,411 | $133,553 |
| **T** | **Net cost offsets to MBS** **for the co-claimable services** (T = R+S) | $9,094 | $15,019 | $22,289 | $31,151 | $41,894 |

MBS = Medicare Benefits Schedule

Table 96 presents the net costs to MBS for the co-claimable services (items 73298 and 74995) assuming current bulk-billing rate is 0%.

Table 96 Sensitivity analysis, costs associated with co-claimable services

| **Row** | **Description** | **2020–21** | **2021–22** | **2022–23** | **2023–24** | **2024–25** |
| --- | --- | --- | --- | --- | --- | --- |
| I | Number of proposed services | 10,122 | 11,641 | 13,387 | 15,395 | 17,704 |
| U | Cost of co-claimable services (= I\*$9.91)a | $100,312 | $115,359 | $132,663 | $152,562 | $175,447 |
| J | Number of services, current funding | 9,205 | 10,125 | 11,138 | 12,251 | 13,477 |
| V | Cost of co- claimable services (= J\*$5.95)b | $54,768 | $60,245 | $66,269 | $72,896 | $80,185 |
| W | **Net cost offsets to MBS** **for the co-claimable services** (W= U+V) | $45,545 | $55,115 | $66,394 | $79,667 | $95,261 |

MBS = Medicare Benefits Schedule

aEstimated by adding fee for items 73298 ($5.95) and 74995 (99%\* $4.00)

bPatient episode initiation fee ($5.95)

**Appendix A Clinical Experts and Assessment Group**

## Clinical Experts providing input

Name Expertise

Stephen Reddel Neurologist

Andrew McLean-Tooke Pathology

Daman Langguth Clinical Immunologist

Simon Broadley Neurologist

## Assessment group

**Adelaide Health Technology Assessment**

Name Position

Joanne Milverton Senior Health Technology Assessment Analyst

Ruchi Mittal Senior Health Economist

Susan Bellman Senior Health Technology Assessment Analyst

Jaqueline Parsons Team Leader – Special Projects

Camille Schubert Team Leader – Health Economics

**Noted conflicts of interest**

There were no conflicts of interest.

# Appendix B Search strategies

### Bibliographic databases

| Electronic database | Time period searched |
| --- | --- |
| Embase | Inception of database to 23/10/2019 |
| PubMed | Inception of database to 23/10/2019 |
| The Cochrane Library (CDSR, Central, DARE, HTA, HEED) | Inception of database to 23/10/2019 |

### Additional sources of literature (including specialty websites)

|  |  |
| --- | --- |
| Source | Location |
| Australian Clinical Trials Registry | <https://www.australianclinicaltrials.gov.au/> |
| Australian and New Zealand Clinical Trials Registry | [www.anzctr.org.au](http://www.anzctr.org.au) |
| National Institutes of Health | <https://www.nihlibrary.nih.gov/resources> |
| NHMRC- National Health and Medical Research Council (Australia) | <http://www.nhmrc.gov.au/> |
| National Library of Medicine Health Services/Technology Assessment Text | <https://www.ncbi.nlm.nih.gov/books/NBK16710/> |
| National Multiple Sclerosis Society | https://www.nationalmssociety.org/ |
| Royal Australian and New Zealand College of Ophthalmologists | https://ranzco.edu/ |
| Australian and New Zealand Association of Neurologists | https://www.anzan.org.au/ |
|  |  |
| Pearling |  |
| All included articles had their reference lists searched for additional relevant source material |  |

### HTA websites

|  |  |
| --- | --- |
| **AUSTRALIA** |  |
| Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) | <http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/> |
| Centre for Clinical Effectiveness, Monash University | <http://www.med.monash.edu.au/sphpm/divisions/mars/cce.html> |
| Centre for Health Economics, Monash University | <https://www.monash.edu/business/che> |
| **CANADA** |  |
| The Canadian Agency for Drugs And Technologies in Health (CADTH) | <https://www.cadth.ca/> |
| Centre for Health Economics and Policy Analysis (CHEPA), McMaster University | <http://www.chepa.org/> |
| Institute for Clinical and Evaluative Studies (ICES) | <http://www.ices.on.ca/> |
| Saskatchewan Health Quality Council (Canada) | <http://www.hqc.sk.ca/> |
| **FRANCE** |  |
| L’Agence Nationale d’Accréditation et d’Evaluation en Santé (ANAES) | <http://www.anaes.fr/> |
| **GERMANY** |  |
| Institute for Quality and Efficiency in Health Care (IQWiG) | <http://www.iqwig.de/> |
| **THE NETHERLANDS** |  |
| Institute for Medical Technology Assessment (Netherlands) | <http://www.imta.nl/> |
| **NEW ZEALAND** |  |
| New Zealand Health Technology Assessment (NZHTA) | <http://www.otago.ac.nz/christchurch/research/nzhta/> |
| **NORWAY** |  |
| Norwegian Knowledge Centre for the Health Services | <http://www.kunnskapssenteret.no> |
| **SPAIN** |  |
| Andalusian Agency for Health Technology Assessment (Spain) | <http://www.juntadeandalucia.es/> |
| Catalan Agency for Health Technology Assessment (CAHTA) | <http://www.gencat.cat> |
| **SWEDEN** |  |
| Center for Medical Health Technology Assessment | <http://www.cmt.liu.se/?l=en&sc=true> |
| **SWITZERLAND** |  |
| Swiss Network on Health Technology Assessment (SNHTA) | <http://www.snhta.ch/> |
| **UNITED KINGDOM** |  |
| National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) | <https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/> |
| NHS Quality Improvement Scotland | <http://www.nhshealthquality.org/> |
| National Institute for Clinical Excellence (NICE) | <http://www.nice.org.uk/> |
| University of York NHS Centre for Reviews and Dissemination (NHS CRD) | <http://www.york.ac.uk/inst/crd/> |
| **UNITED STATES** |  |
| Agency for Healthcare Research and Quality (AHRQ) | [http://www.ahrq.gov/clinic/techix.htm](http://www.ahrq.gov/) |
| Harvard School of Public Health | <http://www.hsph.harvard.edu/> |
| National Information Centre of Health Services Research and Health Care Technology (US) | <http://www.nlm.nih.gov/hsrph.html> |
| Veteran’s Affairs Research and Development Technology Assessment Program (US) | <http://www.research.va.gov/default.cfm> |

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# Appendix C Studies included in the Systematic Review

Table Profiles of systematic reviews on AQP4-Ab and MOG-Ab testing for diagnosis and monitoring of NMOSD included in the systematic literature review

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID**  **Country** | **Study Design**  **Level of evidence**  **Risk of bias** | **Sample Size (n)**  **Study setting**  **Mean age (y)** | **Inclusion criteria (and population description)** | **Exclusion criteria** | **Intervention** | **Comparator** | **Outcomes** | **Source of funding**  **Conflicts of interest** |
| (Gao et al. 2019)  Multiple | Systematic review  IV  High | 577  Was not reported  41.1 | NMO irrespective of whether they had received treatment before | Case reports and studies that included fewer than 2 patients, review, meta-analysis | Rituximab | Not reported | Therapeutic effectiveness (RTX) | No funding was received  Authors declare that there is no conflict of interest |
| (Lin, N et al. 2017)  Europe and Asia, multiple | Systematic review  I  Moderate | 1198  Hospital clinics  NA | original article of cohort design; NMO defined according to 1999 or 2006 criteria, AQP4-Ab status known; visual outcome was reported; English language articles | literature reviews; abstracts; meeting proceedings | AQP4-Ab testing | No testing | Prognosis | National Natural Science Foundation of China (No. 61302030 and No. 81271322) and the Research Fund of Doctoral Program for Higher Education (No. 220122105110002)  Authors reported that there was no conflicts |

AQP4-Ab = aquaporin 4 antibodies; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; NA = not available; NMOSD = neuromyelitis optica spectrum disorders; NMO = neuromyelitis optica; RTX = rituximab

Table Profiles of primary studies on AQP4-Ab and MOG-Ab testing for diagnosis and monitoring of NMOSD included in the systematic literature review

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID**  **Country** | **Study Design**  **Level of evidence**  **Risk of bias** | **Sample Size (n)**  **Study setting**  **Mean age (y)** | **Inclusion criteria (and population description)** | **Exclusion criteria** | **Intervention** | **Comparator** | **Outcomes** | **Source of funding**  **Conflicts of interest** |
| (Akman-Demir et al. 2011)  Turkey | Case series  IV  Moderate | 35  MS and Myelin Disorders Unit  33.1 | Patients with NMO | Patients with concomitant disease | EDSS | Non reported | Time to diagnosis | Non reported  Non reported |
| (Ashtari et al. 2019)  Iran | Prospective cohort study  III2  Moderate | 56  Kashani Hospital MS clinic, Isfahan University of Medical Science  36.86 | NMOSD based on 2015 criteria ≥18 years; received the first dose of rituximab in clinic for 6 months or less prior to study; MOG-Ab -ve | None reported | RTX 4 x weekly injections repeating the same schedule after 6 and 12 months according to CD19 level in serum. | No comparator was included in study | Change in EDSS  Change in ARR | Isfahan University of Medical Sciences  Authors state that there is no conflict of interest |
| (Beekman et al. 2019)  USA | Comparative study without concurrent controls  III3  Moderate | 193  Patients with NMOSD  49.2 | Self-reported, diagnosis of NMO or NMOSD; ability to respond to questions. | No exclusion criteria were reported | Role-Physical and Role-Emotional subscales of the Short Form -36 (SF-36) | QoL data were compared with data from another published study that examined other autoimmune/inflammatory disorders | Change in diagnosis  QoL | The Guthy-Jackson Charitable Foundation, Alexion Pharmaceuticals, Chugai Pharmaceuticals,Viela Bio and MedImmune  Authors provided information on possible sources of conflict of interest |
| (Bichuetti et al. 2019)  Brazil | Case series  IV  Moderate | 158  Patients from Neuroimmunology Clinic  33 | Clinical presentation compatible with NMOSD by IPND 2015 criteria; follow-up > 6 months | Presence of any infectious syndrome and incomplete medical record | Azathioprine + prednisone | No comparator | Adverse events | Authors reported no financial support was received  Authors declared possible conflict of interest |
| (Bonnan, M. et al. 2018)  France | Case series  IV  Moderate | 60  Medical centre  39 | Monophasic or relapsing NMOSD, LETM or severe ON highly suggestive of NMOSD | Subintrant attack pattern, incomplete clinical data, non-severe attacks defined by acute EDSS <4.0 for spinal cord attacks or visual acuity >20/200. | Plasma exchange (PLEX) | No comparator | Early versus late treatment  Change in EDSS | Authors declared no funding  Author declared no competing interests |
| (Bonnan, M et al. 2009)  France | Case series  IV  Moderate | 43  Hospital ward  34.3 | Relapsing NMO or extensive transverse myelitis | Patients with MS, spinal infarction, granulomatous diseases, infections and tumours | Plasma exchange plus steroid treatment | Steroid treatment only | Adverse events | Not reported  No information was provided |
| (Bouzar et al. 2017)  Algeria | Diagnostic yield study  IV  High | 43  Hospital treatment centre medical files  33 | Patients treated for monophasic or recurrent ID affecting the optic nerve and/or spinal cord | Infectious and systemic disease | AQP4 and MOG antibody testing | NA | Diagnostic accuracy  Yield | Bridge I EDNA (FFG and Euroimmun); “BIG-WIG MS” (Austrian Federal Ministry of Science, Research and Economy)  Stated |
| (Bukhari et al. 2017)  Australia  New Zealand | Diagnostic yield study  IV  Moderate | 170  Patients who were possible cases of NMOSD were identified through a network of 23 clinics | Patients with severe ON, severe LETM, or other symptoms meeting 2015 IPND criteria for testing | Clinical criteria not met, alternate diagnosis apparent | AQP4-Ab testing | NA | Prevalence, incidence  Yield | Funded by ANZ NMO Collaboration, multiple Sclerosis Research Australia, the Brain Foundation Griffith University and the Gold Coast Hospital Foundation  Multiple conflicts reported |
| (Chanson et al. 2011)  France | Comparative study without concurrent controls  III3  Moderate | 40 NMO, 1007 healthy subjects and 431 MS  University Hospitals of Strasbourg and Lille  45.2 | Consecutive patients with NMO, diagnosed according to revised 2006 criteria | No exclusion criteria were reported | SEP-59 the French version of MS QoL; EMIF-SEP the French version of the Fatigue Impact Scale to assess fatigue, and French EHD Depressive Mood Scale to evaluate depression | Results of study were compared with equivalent data in MS and normal subjects derived from previous studies. | QoL | None reported  None reported |
| (Chen, B et al. 2017)  China | Retrospective cohort study  III-2  High | 25  University hospital clinic  31 | NMOSD diagnosis based on 2015 IPND criteria and treated for more than 6 months. with immunosuppressants or immunomodulators | None reported | 2-3 mg/day of oral tacrolimus (1mg/day for children) | NR | Correlation between high and low AQP4-Ab titre and relapse | Kindstar Global company (tested the titres)  Authors declare they have no competing interests |
| (Chen, Q et al. 2018)  China | Diagnostic yield study  IV  Moderate | 87  Hospital ophthalmology department  NA | Patients ≤18 years-old with acute-onset optic neuritis | Uncooperativeness during ophthalmic examinations; unavailability of serum MOG and AQP4 antibodies; refusal to sign the consent form; incomplete clinical data; inability to participate six months of follow-up. | AQP4-Ab and MOG-Ab testing | NA | Yield | National Natural Science Foundation of China, 8130102; Talent Doctor Project at Fudan University, Shanghai, China  It was reported that there were no conflicts to declare |
| (Cheng et al. 2016)  China | Case series  IV  Moderate | 31  University Hospital clinic  31 | Adults tested for NMO-IgG; single clinical episode of ABS; no other neurologic signs or symptoms which suggested the diagnosis of MS or NMO before NMO-IgG testing. | previous or concomitant systemic autoimmune diseases, metabolic etiology, vascular disorders and infections | diagnosis by clinical criteria (2015) and AQP4 status | diagnosis by clinical criteria (pre 2015) and no AQP4-Ab testing | Diagnostic accuracy  Yield  Prognosis | Medical Research Foundation of Guangdong Province (A2014233); Natural Science Foundation of Guangdong Province (2016A030313228)  Reported that there were none |
| (Cobo-Calvo et al. 2016)  France, Spain | Case series  IV  Moderate | 56  data from three European Neuroimmunology Centres  40 | Patients with first episode of LETM and negative for AQP4-Ab | NR | EDSS; AQP4-AB and MOG-Ab testing; OCB; conversion of diagnosis to NMO | Previous clinical characteristics | Prognosis | Association pour la recherche sur la Sclérose en plaques (ARSEP) ; French Agence Nationale de la Recherche (ERA-Net ERARE-2; EDEN project); la Marató de TV3 (AS; 101610), Red Española de Esclerosis Múltiple, Fondo Europeo de Desarrollo Regional (FEDER), Unión Europea, Una forma de hacer Europa (AS; RD12/0032/0002)  Multiple author disclosures reported |
| (Contentti, EC et al. 2019)  Argentina | Diagnostic yield study  IV  Moderate | 57  Department of Neurology and Neuro-ophthalmology patients  35 | Diagnosis with a first episode of clinically acute ON | NR | AQP4-Ab testing; disease progression; diagnostic categorisation | NA | Diagnostic accuracy  Yield | NR  NR |
| (Contentti, CE et al. 2017)  Argentina | Case series  IV  Moderate | 30  Hospital database  38 | Patients attending a hospital with LETM at presentation; data available for at least one year follow-up | compressive or vascular lesions identified by spinal MRI; LETM patients with well-established causes | AQP4-Ab testing; MRI; clinical assessment, diagnosis at follow-up | original diagnosis | Diagnostic Accuracy  Yield  Prognosis | NR  NR |
| (Drulovic et al. 2019)  Serbia | Diagnostic yield study  IV  Moderate | 74  Clinic of Neurology  40 | Patients who fulfilled the 2015 diagnostic criteria | NR | Clinical examination | NA | Yield | Ministry of Education, Science and Technological Development of the Republic of Serbia (Grants no. 175031 and 175087)  Multiple author disclosures were reported |
| (Duignan et al. 2018)  UK | Diagnostic yield study  IV  Moderate | 371  Patients identified through pathology department databases  NA | Suspected of ADS; AQP4-Ab and MOG-Ab testing requested | NR | Diagnostic assessment following AQP4-Ab and MOG-testing (live sell assays) | NA | Diagnostic accuracy  Yield | NR  NR |
| (Elsone et al. 2014)  UK | Case series  IV  Moderate | 103  Patients identified from four tertiary centres | Patients with AQP4-Ab positive with NMO or NMOSD and | NR | AZA | NA | Change in EDSS and ARR | Funded by NHS through the Mational Specialized Commissioning Team  Multiple conflicts stated |
| (Hacohen et al. 2017)  UK | Diagnostic yield study  IV  Moderate | 110  Panel review of clinical assessment data from three centres  NA | children attending CNS Inflammatory Demyelination Work Group Centers diagnosed with relapsing DS | Monophasic ADEM and CIS (even if meeting McDonald criteria after first event) | AQP4-Ab and MOG-Ab testing; clinical assessment | NA | Diagnostic accuracy  Yield | NIHR University College London Hospitals Biomedical Research Centre (OC); NIHR Great Ormond Street Hospital Biomedical Research Centre (YH, CH)  Multiple reported |
| (Hamid et al. 2017)  UK | Diagnostic yield study  IV  High | 261  University hospital clinic that is part of the UK NMOSD service  18 | Patients seen in the clinic over the last 4 years (after the availability of MOG-IgG testing), that could provide clinical information, MRI, and antibody test results. | NR | AQP4-Ab and MOG-Ab testing | NA | Diagnostic accuracy  Yield | It was reported that there was no industry sponsorship  It was reported that there was no conflicts |
| (Hennes et al. 2017)  Europe, multiple | Case series  IV  Low | 210  Medical centres in participating countries  12 | Children with ADS and a complete data set | Diagnosis with other neurological diseases | AQP4 and MOG-Ab testing; application of new diagnostic criteria | Diagnosis by earlier criteria | Change in diagnosis | Grant numbers 14158 and 15918 (Jubilaeumsfonds of the Austrian National Bank); “BIG WIG MS” (Austrian Federal Ministry of Science, Research and Economy).  Multiple affiliations and disclosures reported |
| (Houzen et al. 2017)  Japan | Diagnostic yield study  IV  Moderate | 14  Clinical centres in a Japanese province  45 | Diagnosis with NMOSD | NR | AQP4-Ab and MOG-Ab testing | NA | Yield | No targeted funding reported.  Multiple disclosures reported |
| (Huang et al. 2018)  China | Prospective cohort study  III2  Moderate | 90  Not clearly stated  36 | Patients diagnosed with 2006 NMO or 2015 NMOSD criteria, AQP4-Abs +ve, ≥18 years, more than 2 relapses within 2 years prior to MMF treatment or more than 1 attack in the 1 year prior to treatment | Patients with transaminase and haematological levels beyond the upper limit of normal values or study criteria | IV dose of 500mg/day for the first 2 weeks; adjusted to 1,000mg/day | No comparator | Adverse events | Zhongshan University Clinical Medicine Research  Authors declared that there was no conflict of interest |
| (Hyun et al. 2016)  South Korea | Comparative study with concurrent controls  III2  Moderate | 594  National Cancer Centre registry  33 | Patients with possible CNS inflammatory diseases | patients with known causes including neoplastic, vascular, compressive, infectious, and metabolic etiologies; 34 patients with inappropriate medical records | AQP4-Ab testing; Diagnosis by 2015 criteria | diagnosis without AQP4-Ab testing | Time to diagnosis  Change in diagnosis | No targeted funding reported.  Multiple disclosures reported |
| (Hyun et al. 2017)  South Korea | Diagnostic yield study  IV  High | 505  Neurology Department of the National Cancer Center  NA | Consecutive patients with suspected CNS IDD who had available serum samples | NR | AQP4-Ab and MOG-Ab testing | NA | Diagnostic accuracy  Yield | NR  Multiple reported |
| (Jain et al. 2016)  India | Case series  IV  High | 64  Tertiary care centre  NA | LETM of three or more segments of spinal cord on MRI | NR | AQP4-Ab testing by ELISA; MOG-Ab testing; clinical assessment and diagnosis | previous clinical assessment | Diagnostic accuracy  Yield | Reported as none  Reported that there were no disclosures to declare |
| (Jarius et al. 2010)  Austria, Germany, Italy | Diagnostic case-control study  III3  Moderate | 79.  NR  NA | Patients with NMOSD (AQP4-Ab +ve or -ve); controls with MS and other neurological diseases. | NR | Cerebrospinal fluid samples tested in a cell-based assay. | Serum AQP4-Ab samples. | Test agreement | European Committee for Treatment and Research in Multiple Sclerosis, Bayer Schering Pharma, Merck Serono and German Research Foundation.  Authors declared no competing interests. |
| (Jiao, Cui, Zhang, Zhang, Zhang, et al. 2018)  China | Case series  IV  High | 109  China-Japan Friendship Hospital  51.3 | Patients with NMO or NMOSD and AQP4-Ab +ve who had received MMF for six months or longer | None reported | MMF at different dosages; low ≤1000mg/day; moderate 1250mg/day and 1500mg/day; high 1750mg/day and 2000mg/day | No comparator group | Adverse events | China-Japan Friendship Hospital and Foundation of Capital Characteristic Clinical Application Research  Authors state that they have no conflict of interest |
| (Y. et al. 2018)  China | Case series  IV  Moderate | 29  China-Japan Friendship Hospital  35.5 | Patients with NMOSD receiving PLEX | NR | PLEX No other information was provided | No comparator | Adverse events | Foundation of Capital Characteristic Clinical Application Research and Youth Foundation of China-Japan Friendship Hospital  Authors declared there was no conflict of interest |
| (Jurynczyk et al. 2016)  UK | Case series  IV  High | 12  The Oxford NMO service patients  35 | Patients specifically selected who had clinical presentations with overlapping features of NMO and MS and to be representative of different clinical dilemmas. | NR | Opinions of 27 clinical experts on diagnosis and treatment based on provided clinical information | Previous diagnosis and treatment; diagnosis by 2015 criteria | Clinician agreement in diagnosis | NR  Multiple disclosures reported |
| (Kanamori et al. 2011)  Japan | Comparative study without concurrent controls  III3  Moderate | 37 NMO; 51 MS  Tohoku University Hospital  50.8 | Consecutive patients with NMO or NMOSD diagnosed using 2006 criteria and 58 consecutive patients with MS using 2005 McDonald criteria | Patients with dementia | Short Form-36 (SF-36) Short Form Brief Pain Inventory (BPI) | No comparator was included | QoL | Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare of Japan  Possible conflict of interests were reported |
| (Kang et al. 2019)  China | Diagnostic yield study  IV  Moderate | 51  Ophthalmology department at a Chinese hospital  NA | Presentation with simultaneous or nearly simultaneous bilateral ON; ON confirmed by using the optic neuritis treatment trial criteria (ONTT) (Waschbisch et al. 2013) | Compressive, vascular, toxic, metabolic, infiltrative or hereditary optic neuropathy; hepatitis viral or other systemic infection; other causative ocular diseases | AQP4-Ab (live cell assay) and MOG- Ab testing (fixed cell-based assay) | NA | Diagnostic accuracy  Yield | NR  NR |
| (Li et al. 2015)  China | Case series  IV  Low | 125 patients (220 eyes)  Ophthalmology Department of a university hospital  38.98 | Patients with recurrent and bilateral optic neuritis with simultaneous attacks | Compressive, vascular, toxic, metabolic, infiltrative or hereditary optic neuropathy; hepatitis viral or other systemic infection; other causative ocular diseases; recent ON attack less than 6 months previously. | Well described neuro-ophthalmology testing (including visual acuity) in patients seropositive for AQP4-Ab | Well described neuro-ophthalmology testing (including visual acuity) in patients seronegative for AQP4-Ab | Prognosis  Time to diagnosis | National the 12th Five-Year Plan Science and Technology support project and China Postdoctoral Science Foundation  None declared |
| (Lin, J et al. 2017)  China | Case series  IV  Moderate | 32  The First Affiliated Hospital of Wenzhou Medical University  36.8 | Patients with relapsed LETM, ON and postrema syndrome who could be traced, the date of relapse and treatment | Patients who did not meet the diagnosis criteria, and could not be traced, | Group 1 IV glucocorticoids + azathioprine  Group 2 Azathioprine after IV glucorticoids | IV glucocorticoids | Early versus late treatment  Time to next relapse | Authors did not say whether study was funded  Authors declared no conflict of interest |
| (Liu et al. 2019)  China | Case series  IV  Moderate | 158  Hospital clinic  38 | ON presenting with acute or subacute visual loss; age of ON onset ≥18 years; ≥ two of: ocular pain during eye movement, afferent pupillary defect, abnormal visual evoked response, dyschromatopsia and field defect | Unknown AQP4-Ab or MOG-Ab serum status, existing MS, or NMO prior to the first onset of ON or incomplete clinical and follow-up data. | Assessment of visual acuity; MS and NMO diagnosis according to the current criteria: (1) MS: fulfilling 2017 McDonald criteria; (2) NMO: fulfilling the 2015 IPND | NA | Diagnostic accuracy  Yield  Prognosis | 863 Plan Biological and Medical Technology project “Development of equipments in diagnosis and visual function evaluation for optic neuritis”, China (NO: 2015AA020511)  It was reported that there were none |
| (Matsuda et al. 2015)  Japan | Case series  IV  Moderate | 70  Department of Ophthalmology Department at a University Hospital  43 | MOG-Ab seropositive | NR | AQP4-Ab and MOG-Ab testing | Before and after comparison | Prognosis | Grant-in-Aid for Scientific Research (C), Grant-inAid for Young Scientists (B) (Japan Society for the Promotion of Science); Health and Labour Sciences Research Grants for research on intractable diseases from the Ministry of Health, Labour, and Welfare of Japan.  NR |
| (Mealy, M et al. 2019)  Asia, Europe America, Multiple | Case series  IV  Moderate | 182  Five NMOSD centres worldwide  39.2 | NMOSD diagnosis by 2015 criteria and AQP4-Ab +ve at least one year of records | Patients without a history of myelitis | NMOSD-specific immunotherapy | No comparator was described | Early versus late diagnosis | National Institutes of Health  Authors reported that there was no potential conflicts of interest |
| (Mutch et al. 2015)  UK | Comparative study without concurrent controls  III3  Moderate | 60  Walton Centre NMO clinic (a national referral centre)  49 | Patients with AQP4-IgG positive NMO or NMOSD | No exclusion criteria were reported | Bladder Control Scale; Female Lower Urinary Tract Scale; Male Lower urinary Tract Scale; Bowel Control Scale; Short Form-36 (SF-36); | None reported | QoL | United Kingdom's Department of Health NIHR Biomedical Research Centres funding scheme  All possible conflict of interest has been declared |
| (Papais-Alvarenga et al. 2018)  Brazil | Diagnostic yield study  IV  Moderate | 200  Neurological clinics in Rio de Janeiro  00 | Adults ≥16 years, with confirmed diagnosis of NMO (2006 criteria), LETM, Bilateral ON, or ABS (Wingerchuk et al., 2007), MS and CIS (Polman et al., 2011), non-extensive LETM or ADEM | NR | AQP4-Ab and MOG-Ab testing; application of 2015 diagnostic criteria | NA | Diagnostic accuracy  Yield  Change in diagnosis | NR  It was reported that there were no conflicts |
| (Papais-Alvarenga et al. 2015)  Brazil | Case series  IV  Moderate | 1,917  South American MS centres  32.7 | Confirmed diagnosis of IIDD | Patients still under investigation, those not meeting the criteria for diagnosis, those who lived in cities outside the location of the treatment centre. | Spectrum of idiopathic inflammatory demyelinating disorder | None reported | Yield | Authors reported that they received no funding  Authors declared possible conflict of interests |
| (Pittock et al. 2019)  Europe, South America, Australia, Multiple | Randomized controlled trial  II  Low | 143  70 sites in hospital clinics in 18 countries  36.6 | ≥18 years with diagnosis of NMOSD according to 2006 or 2007 criteria, AQP4 +ve | Previous treatment with MX, RTX or IVIg, prednisone doses greater than 20mg/day, unresolved meningococcal disease or systemic bacterial infections | IV ECZ 900 mg/week x 4; maintenance regimen of 1200 mg / 2 weeks until relapse, trial discontinuation or the end of trial | Matched Placebo | Change in EDSS  Change in ARR  Adverse events | Alexion Pharmaceuticals  Authors provided details of possible conflict of interest |
| (Shaygannejad et al. 2019)  Iran | Prospective cohort study  III2  Moderate | 44  MS and related disorders clinic at Kashani University Hospital in Isfahan  37.2 | Consecutive NMOSD patients based on 2015 diagnostic criteria | Patients with prior or concomitant diseases that prompted the use of rituximab | 500 mg RTX delivered in sodium chloride via IV line for one hour /week x 4 (2g in total); 1g RTX divided for two consecutive weeks (500mg/week every six months | No comparator | Change in EDSS  Change in ARR | Authors reported no funding was received  Authors declared that there was no conflict of interest |
| (Stellmann et al. 2017)  Germany | Retrospective cohort study  III2  Moderate | 144 patients and 265 treatments  NMOSD registry of the German Neuromyelitis Optica Study group (MEMOS)  40.9 | NMO diagnosed according to 2006 criteria or with AQP4-Ab +ve NMOSD | Insufficient baseline or treatment data; with short-term steroid treatments (<60 days) | Therapeutic interventions: alemtuzumab, rituximab, interferon-beta, mitoxantrone, glatiramer acetate | Treatments were compared to each other | Effectiveness for NMOSD vs MS | German Ministry for Education and Research  Possible conflict of interests were documented |
| (Stiebel-Kalish et al. 2019)  Israel | Case series  IV  Moderate | 36  A neuro-ophthalmology and neuroimmunology centre  37 | Diagnosis of NMOSD (2015 criteria) or AQP4-Ab or MOG-Ab associated ON; AQP4-Ab or MOG-Ab positive | ocular causes of poor visual acuity and treatment refusal | treatment after symptom onset | late treatment | Early vs late treatment (< or > 4 or 7 days) | No targeted funding  Multiple disclosures reported |
| (Valentino et al. 2017)  Italy | Case series  IV  Moderate | 7  Regional Referring Centre for Multiple Sclerosis  35 | Patients diagnosed with NMO and positive for AQP4-Abs | Patients with a follow-up period of less than 2 years | AQP4-Ab testing | No comparator reported | Correlation between AQP4-Ab titre and disease activity | Fondazione Italiana Sclerosi Multipla and Fondazione Ricerca Biomedica Onlus  Authors disclosed all possible sources of conflict of interest |
| (Waters et al. 2016)  Europe, multiple | Diagnostic case-control study  III-3  High | 193 patients 92 controls.  15 European diagnostic centres  NA | AQP4-Ab +ve or –ve NMO or NMOSD; control group of patients with clearly defined neurological conditions (e.g. MS). | Patients with unclear diagnoses or diagnoses complicated by related pathologies. | 21 assays including live cell-based assays, fixed commercial cell-based assays (Euroimmum), in-house assays at different diagnostic centres, flow cytometry assays, tissue-based assays using IIF, IH technique and ELISA. | Assayed sera/plasma samples from the included patient group which had previously been coded by Euroimmum AG, Germany. | Test agreement | Eugene Devic European Network project; National Health Service National Specialised Commissioning Group for Neuromyelitis Optica; National Institute for Health Research Oxford Biomedical Research Centre.  Sources of possible conflict of interest were acknowledged. |
| (Weinshenker et al. 2006)  USA | Case series  IV  Moderate | 29  Mayo Clinic and non-Mayo Clinic patients  49.3 | Single episode of LETM and no evidence of ON or recurrent LETM before testing or NMO-IgG | None described | Relapse rate in AQP4-Ab +ve (method was not described) | Relapse rate in AQP4-Ab –ve (method not described) | Prognosis | There was no mention of funding in publication  There was no mention of conflict of interest in publication |
| (Zhou et al. 2016)  China | Case series  IV  Low | 128  Neuro-ophthalmology department of a general Hospital, Beijing  36.8 | ≥18 years ON diagnosis | Unknown serum status of AQP4-Ab; existing MS or NMO prior onset ON; incomplete clinical or follow-up data | SD-optical coherence tomography examinations in AQP4-Ab +ve patients | SD-optical coherence tomography examinations in AQP4-Ab –ve patients | Prognosis | Plan Biological and Medical Technology project  Authors declared no conflict of interest |

ABS = acute brainstem syndrome; ADEM = acute disseminated encephalomyelitis; ADS = acquired demyelination syndrome; ARR = annualised relapse rate; CIS = clinically isolated syndrome; CNS = central nervous system; DS = demyelinating syndromes; ECZ = eculizumab; EDSS = expanded disability status scale; ELISA = enzyme-linked immunosorbent assay; ID = inflammatory disease; IDD = inflammatory demyelinating disorder; IIDD = idiopathic inflammatory demyelinating disease; IIF = indirect immunofluorescence; IgG = immunoglobulin G; IH = immunohistochemistry; IPND = International Panel for NMO Diagnosis; IV = intravenous; IVIg = intravenous immune globulin; LETM = longitudinally extensive transverse myelitis; MMF = mycophenolate mofetil; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MRI = magnetic resonance imaging; MS = multiple sclerosis; MX = mitoxantrone; NA = not available; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; NR = not reported; PLEX = plasma exchange; OCB = oligoclonal bands; ON = optic neuritis; QoL = quality of life; RTX = rituximab; SD = spectrum domain.

# Appendix D Evidence Profile Tables

Table 99 Evidence profile table for the accuracy of AQP4-Ab testing compared to 2015 IPND criteria for diagnosis of NMOSD (prevalence 34%)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  | | --- | --- | | Sensitivity | 0.29 to 0.88 | | Specificity | 0.63 to 1.00 |  |  |  |  |  | | --- | --- | --- | --- | | Prevalence | 34% |  |  | | | | |  |  | | | |  | | |
| **Outcome** | **№ of studies (№ of patients)** | **Study design** | **Factors that may decrease certainty of evidence** | | | | | **Effect per 1,000 patients tested** | | **Test accuracy CoE** | **Importance** |
| **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Publication bias** | **pre-test probability of 34%** | |
| **True positives** (patients with NMOSD) | 12 studies 1684 patients | cross-sectional (cohort type accuracy study) | very serious a,b | NA | not serious | not serious | none | 99 to 299 | | ⨁⨁⨀⨀ LOW | IMPORTANT |
| **False negatives** (patients incorrectly classified as not having NMOSD) | 41 to 241 | | IMPORTANT |
| **True negatives** (patients without NMOSD) | 12 studies 1684 patients | cross-sectional (cohort type accuracy study) | very serious a,b | NA | not serious | not serious | none | 416 to 660 | | ⨁⨁⨀⨀ LOW | IMPORTANT |
| **False positives** (patients incorrectly classified as having NMOSD) | 0 to 244 | | IMPORTANT |

**Explanations**

a. Incorporation bias (AQP4-Ab testing may be included in the clinical reference)

b. A proportion of AQP4-Ab negative patients are known to have NMOSD

**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.

Table 100 Evidence profile table for the prognosis of AQP4-Ab testing in patients suspected of NMOSD or diagnosed with NMOSD

**Question**: AQP4-Ab positive compared to AQP4-Ab negative for prognosis of health outcomes

**Bibliography**: (Cheng et al. 2016; Contentti, CE et al. 2017; Li et al. 2015; Lin, N et al. 2017; Liu et al. 2019; Weinshenker et al. 2006; Zhou et al. 2016)

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies (K)**  **N patients** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **AQP4-Ab positive** | **AQP4-Ab negative** | **Relative (95% CI)** | | **Absolute (95% CI)** | |
| **Visual acuity in those suspected of NMOSD >0.5 at five years follow-up** | | | | | | | | | | | | | | |
| K=1  N=128 | observational studies | serious a | not serious | not serious | not serious | strong association | 24/80 (30.0%) | 75/133 (56.4%) | **OR 0.33** (0.18 to 0.60) | | **26 fewer per 100** (from 38 fewer to 13 fewer-) a | | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Patients suspected with NMOSD with legal blindness in one eye at five years follow-up** | | | | | | | | | | | | | | |
| K=1  N=128 | observational studies | serious a | not serious | not serious | not serious | strong association | 30/45 (66.7%) | 27/83 (32.5%) | **OR 4.15** (1.92 to 8.97) | | **341 more per 1,000** (from 155 more to 487 more) | | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Patients suspected with NMOSD with legal blindness in both eyes at five years follow-up** | | | | | | | | | | | | | | |
| K=1  N=128 | observational studies | serious a | not serious | not serious | not serious | strong association | 13/45 (28.9%) | 11/83 (13.3%) | **OR 2.66** (1.08 to 6.57) | | **156 more per 1,000** (from 9 more to 368 more) | | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Rate of conversion to NMO/NMOSD in patients suspected of NMOSD** | | | | | | | | | | | | | | |
| K=5  N=472 | observational studies | not serious | not serious | not serious | not serious | very strong association | 102/257 (39.7%) | 19/337 (5.6%) | | **OR** range 5.55 to 559.00 | | NA | ⨁⨁⨁⨁ HIGH | IMPORTANT |
| **Rate of conversion to MS diagnosis in patients suspected of NMOSD** | | | | | | | | | | | | | | |
| K=4  N=314 | observational studies | not serious | not serious | not serious | not serious | strong association | 1/193 (0.5%) | 24/246 (9.8%) | | **OR** range 0.05 to 0.41) | | NA | ⨁⨁⨁⨀ MODERATE | IMPORTANT |
| **Rate of relapse in patients suspected of NMOSD** | | | | | | | | | | | | | | |
| K=3  N=90 | observational studies | not serious | not serious | not serious b | not serious | very strong association | ARR (mean range) 1.05 to 1.33  Patients relapsed 6/11 (54/5%) | ARR (mean range) 0.42 to 0.72  Patients relapsed 0/18 (0%) | | NA | | NA | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **Change in EDSS in patients suspected of NMOSD** | | | | | | | | | | | | | | |
| K=2  N=61 | observational studies | not serious | serious c | serious d | very serious e | none | Median (range) 5 (3-7) | Median (range) 2.5 (1.5-7) | | NA | | NA | ⨁⨀⨀⨀ VERY LOW | IMPORTANT |
| **Presence of visual impairment at last follow-up in those diagnosed with NMOSD (follow up: range 1 years to 10 years) (CBA tests only)** | | | | | | | | | | | | | | |
| K=3  N=79 | observational studies | not serious | not serious | not serious | not serious | very strong association | 50/79 (63%) | 4/31 (13%) | **OR 9.32** (3.01 to 28.84) | | **45 more per 100** (from 18 more- to 68 more) a | | ⨁⨁⨁⨁ HIGH | CRITICAL |

**ARR:** Annualised Relapse Rate**; AQP4-Ab:** aquaporin 4 antibodies; **CI:** Confidence interval; **EDSS:** Expanded Disability Status Scale; **MS:** multiple sclerosis; **NA**: not available; **NMO:** neuromyelitis optica**; NMOSD:** neuromyelitis optica spectrum disorders; **OR:** Odds ratio

**Explanations**

aRetrospective study design at risk of selection bias

b. While all studies compared rate of relapse between AQP4-Ab positive and negative patients, two studies reported ARR while the third study reported the percentage of patients who relapsed.

c. There was inconsistency in study results where one study reported a higher EDSS in those AQP4-Ab positive compared to negative patients, but the other study found no significant difference in EDSS between the two groups.

d. Different methods for testing of AQP4-Abs were used for the two studies. One study used cell-based assay and the other used a tissue-based assay.

e. Only one study reported data on outcome measures, therefore a decision regarding imprecision could not be determined for the two studies.

**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.

Table 101 Evidence profile table for the prognosis of MOG-Ab testing for patients at risk of NMOSD

**Question**: MOG-Ab positive compared to MOG-Ab negative for prognosis of health outcomes

**Bibliography**: (Cobo-Calvo et al. 2016; Liu et al. 2019; Matsuda et al. 2015)

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies (K)**  **N patients** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **MOG-Ab positive** | **MOG-Ab negative** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Improvement in visual acuity (follow up: mean 2.8 years)** | | | | | | | | | | | | |
| K=1  N=70 | observational studies | Seriousa | not serious | not serious | not serious | none | 16/18 (88.9%) | 37/52 (71.2%) | **OR 3.243** (0.663 to 15.868) | **177 more per 1,000** (from 91 fewer to 264 more) | ⨁⨁⨀⨀ LOW | IMPORTANT |
| **Difference in visual field deficit (follow up: mean 2.8 years)** | | | | | | | | | | | | |
| K=1  N=70 | observational studies | Seriousa | not serious | not serious | not serious | very strong association | 14/18 (77.8%) | 16/52 (30.8%) | **OR 7.875** (2.239 to 27.697) | **470 more per 1,000** (from 191 more to 617 more) | ⨁⨁⨁⨀ MODERATE | CRITICAL |
| **Conversion to NMOSD diagnosis (follow up: range 1 years to 80 months)** | | | | | | | | | | | | |
| K=2  N=214 | observational studies | Seriousa | not serious | not serious | serious b | none | 6/44 (13.6%) | 2/103 (1.9%) | **OR** range 9.11 to 10.25 | NA | ⨁⨀⨀⨀ VERY LOW | IMPORTANT |
| **Change in EDSS (follow up: median 42.2 months)** | | | | | | | | | | | | |
| K=1  N=56 | observational studies | Seriousa | not serious | not serious | not serious | none | Median (range) 2 (0-2.5) | Median (range) 3 (2.0-5.5) | NA | NA | ⨁⨁⨀⨀ LOW | IMPORTANT |
| **Rate of relapse (follow up: range 2.8 years to 42.2 months)** | | | | | | | | | | | | |
| K=2  N=126 | observational studies | not serious | not serious | serious c | serious a | none | ARR ON 0.82  Patients relapsed LETM 2/13 (15.4%)  Patients relapsed ON 4/13 (30.8%) | ARR ON 0.40  Patients relapsed LETM 7/43 (16.3%)  Patients relapsed ON 2/43 (4.7%) | NA  **OR** 0.935 (0.169,5.172)  **OR** 9.111 (1.441,57.620) | NA | ⨁⨀⨀⨀ VERY LOW | IMPORTANT |

**ARR:** Annualised Relapse Rate**; CI:** Confidence interval; **EDSS:** Expanded Disability Status Scale; **LETM**: longitudinally extensive transverse myelitis; **MOG-Ab:** myelin oligodendrocyte glycoprotein; **NMOSD:** neuromyelitis optica spectrum disorders; **ON:** optic neuritis; **OR:** Odds ratio

**Explanations**

aRetrospective study design at risk of selection bias

b. There was a wide confidence interval around the calculated odds ratio, and the clinical course would differ if the upper versus the lower boundary of the confidence interval represented the truth.

c. While both studies compared rate of relapse between MOG-Ab positive and negative, one study reported ARR while the other reported the percentage of patients who relapsed.

**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.

Table 102 Evidence profile table for the change in management due to AQP4-Ab testing compared to no testing for diagnosis of NMOSD

**Question: Diagnosis using AQP4-Ab testing compared to Diagnosis without testing for management of NMOSD patients**

**Bibliography**: (Akman-Demir et al. 2011; Hennes et al. 2017; Hyun et al. 2016; Li et al. 2015; Papais-Alvarenga et al. 2018)

| **Certainty assessment** | | | | | | | **№ of patients** | | | | **Effect** | | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies (K)**  **N patients** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Diagnosis using AQP4-Ab testing** | | **Diagnosis without testing** | | **Relative (95% CI)** | **Absolute (95% CI)** | |
| **Time to diagnosis (follow up: mean 9.2 years; assessed with: months)** | | | | | | | | | | | | | | | |
| K=1  N=252 | observational studies | serious a | not serious | not serious | not serious | very strong association | 11 months | 53 months | | P<0.001 (log rank test) | | | NA | ⨁⨁⨁⨀ MODERATE | CRITICAL |
| **Mean time to diagnosis (2006 criteria) for AQP4-Ab positive compared to negative patients (follow up: range 41 months to 8 years)** | | | | | | | | | | | | | | | |
| K=2  N=160 | observational studies | serious a | not serious | not serious | serious b | none | Range 19.5 (SD 20.51) to 45.6 (SD 57.6) months | Range 27.75 (SD 24.27) to 54 (SD 80.4) months | | no significant difference | | | NA | ⨁⨀⨀⨀ VERY LOW | IMPORTANT |
| **Number of NMOSD diagnoses based on 2015 compared with 2006 criteria** | | | | | | | | | | | | | | | |
| K=2  N=709 | observational studies | serious a | not serious | not serious | not serious | strong association | 322/709 (45.4%) | | 190/709 (26.8%) | | OR range  1.76 to 2.48 | not estimable | | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Number of NMOSD diagnoses after compared with before 24 months** | | | | | | | | | | | | | | | |
| K=1  N=120 | observational studies | serious a | not serious | not serious | not serious | none | 16/210 (7.6%) | | 12/210 (5.7%) | | OR 1.36 (0.63 to 2.95) | 19 more per 1,000 (from 20 fewer to 95 more) | | ⨁⨀⨀⨀ VERY LOW | IMPORTANT |

AQP4-Ab = aquaporin 4 antibody**;** CI **=** Confidence interval; NA = not available; OR = odds ratio

**Explanations**

a. Retrospective study design at risk of selection bias

b. Wide ranges for follow-up time and outcome

**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.

Table 103 Evidence profile table for the impact of change in management due to early compared to late diagnosis and/or treatment for NMOSD patients

**Question: Early treatment compared to late treatment for NMOSD patients**

**Bibliography**: (Bonnan, M. et al. 2018; Lin, J et al. 2017; Mealy, M et al. 2019; Stiebel-Kalish et al. 2019)

| **Certainty assessment** | | | | | | | **№ of patients** | | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies (K)**  **N patients** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **early treatment** | **late treatment** | | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Probability of complete improvement (assessed with: PLEX received day 0-1 or after day 20)** | | | | | | | | | | | | | |
| K=1  N=60 | observational studies | serious a | not serious | not serious | not serious | strong association | 50% | 5% | | P=0.02 | NA | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Time to next relapse on AZA (assessed with: months)** | | | | | | | | | | | | | |
| K=1  N=38 | observational studies | serious a | not serious | not serious | not serious | strong association | 18.17 months | | 32.74 months | p=0.025 | NA | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Duration of remission on AZA** | | | | | | | | | | | | | |
| K=1  N=38 | observational studies | serious a | not serious | not serious | not serious | strong association | NA | | NA | HR 0.250  (0.072, 0.867)  P=0.029 | NA | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Failure to regain 20/30 vision on IVMP (assessed with: <7 days compared with > 7 days)** | | | | | | | | | | | | | |
| K=1  N=27 | observational studies | serious a | not serious | not serious | not serious | very strong association | NA | NA | | OR 10.0  (1.39, 71.86)  p=0.01 | NA | ⨁⨁⨁⨀ MODERATE | CRITICAL |
| **Likelihood of failure to regain 20/20 vision on IVMP (assessed with: < 4 days compared with > 4 days)** | | | | | | | | | | | | | |
| K=1  N=27 | observational studies | serious a | not serious | not serious | not serious | very strong association | NA | NA | | OR 8.33  (1.47, 47.22)  p=0.01 | NA | ⨁⨁⨁⨀ MODERATE | CRITICAL |
| **Association of delayed diagnosis on disability for patients on any treatment (assessed with EDSS)** | | | | | | | | | | | | | |
| K=1  N=182 | observational studies | serious a | not serious | not serious | not serious | strong association | NA | NA | | NA | (0.02, 0.15)  P=0.006 | ⨁⨁⨀⨀ LOW | CRITICAL |

AZA= azathioprine therapy**;** CI: Confidence interval; EDSS = expended disability severity score; HR = hazard ration; IVMP = intravenous methyl prednisolone therapy; NA = not available; 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.

Table 104 Evidence profile table for the impact of change in management due to NMSDO specific treatment compared to MS treatments for NMOSD patients

**Question: NMOSD treatment compared to MS treatment for NMOSD patients**

**Bibliography**: (Lin, J et al. 2017)

| **Certainty assessment** | | | | | | | **№ of patients** | | **Relative Effect**  **(95% CI)** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies (K)**  **N patients** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **NMOSD treatment** | **MS treatment** |
| **Likelihood of attack (assessed with: RTX compared with Interferon beta)** | | | | | | | | | | | |
| K=1  N=127 | observational studies | serious a | not serious | not serious | not serious | strong association | NA | NA | HR 0.6 (0.4, 1)  p=0.034 | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Likelihood of attack (assessed with: AZA compared with interferon beta)** | | | | | | | | | | | |
| K=1  N=127 | observational studies | serious a | not serious | not serious | not serious | strong association | NA | NA | HR 0.4 (0.3, 0.7)  p=0.001 | ⨁⨁⨀⨀ LOW | CRITICAL |
| **Likelihood of attack (assessed with: GLAT compared with interferon beta)** | | | | | | | | | | | |
| K=1  N=127 | observational studies | serious a | not serious | not serious | not serious | none | NA | NA | HR 1.5 (0.8, 2.6)  p=0.188 | ⨁⨀⨀⨀ VERY LOW | IMPORTANT |
| **Likelihood of attack (assessed with: Mitox compared with interferon beta)** | | | | | | | | | | | |
| K=1  N=127 | observational studies | serious a | not serious | not serious | not serious | none | NA | NA | HR 0.9 (0.5, 1.6)  p=0.639 | ⨁⨀⨀⨀ VERY LOW | IMPORTANT |

AZA = azathioprine therapy**; CI:** Confidence interval; GLAT = Glatiramer acetate therapy; HR = hazard ratio; mitox = mitoxantrone; MS = multiple sclerosis; NA = not available; NMOSD = neuromyelitis optica spectrum disorders; RTX = rituximab therapy

**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.

Table 105 Evidence profile table for the impact of change in management due to treatment compared to no treatment for NMOSD patients

**Question: Effectiveness of treatment on NMOSD patients**

**Bibliography**: (Bonnan, M et al. 2009; M et al. 2009; Pittock et al. 2019)

| **Certainty assessment** | | | | | | | **№ of patients** | | | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies (K)**  **N patients** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Treatment** | | **no treatment** | | **Relative (95% CI)** | **Absolute (95% CI)** |
| **PLEX compared with no PLEX (assessed with change in EDSS)** | | | | | | | | | | | | | | |
| K=1  N=96 | observational studies | serious a | not serious | not serious | not serious | strong association | 1.2 (SD 1.6) | | 2.6 (SD 2.4) | | NA | P<0.01 | ⨁⨁⨀⨀ LOW | CRITICAL |
| **RTX compared with no RTX (assessed with weighted mean difference in EDSS)** | | | | | | | | | | | | | | |
| K=22  N=531 | observational studies | serious a | not serious | not serious | not serious | very strong association | NA | | NA | | NA | -1.16  (1.36, 0.96)  p<0.0001 | ⨁⨁⨁⨀ MODERATE | CRITICAL |
| **RTX compared with no RTX (assessed with weighted mean difference in ARR)** | | | | | | | | | | | | | | |
| K=18  N=484 | observational studies | serious a | not serious | not serious | not serious | very strong association | NA | | NA | | NA | -1.56  (-1.82, -1.29)  P=0.000 | ⨁⨁⨁⨀ MODERATE | CRITICAL |
| **ECZ compared with no ECZ (assessed with EDSS at follow-up)** | | | | | | | | | | | | | | |
| K=1  N=143 | randomised trials | not serious | not serious | not serious | not serious | none | -0.18 (SD 0.81) | | 0.12 (SD 0.96) | | HR -0.29  (-0.59, 0.01)  P not significant | NA | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **ECZ compared with no ECZ (assessed with ARR at follow-up)** | | | | | | | | | | | | | | |
| K=1  N=143 | randomised trials | not serious | not serious | not serious | not serious | strong association | 0.02 (SD 0.01-0.05) | 0.35 (SD 0.20-0.62) | | HR 0.04  (0.01, 0.015)  P<0.001 | | NA | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **ECZ compared with no ECZ (assessed with first adjudicated relapse)** | | | | | | | | | | | | | | |
| K=1  N=143 | randomised trials | not serious | not serious | not serious | not serious | strong association | 3% | 43% | | HR 0.06  (0.02, 0.20)  p<0.001 | | NA | ⨁⨁⨁⨁ HIGH | CRITICAL |

CI: Confidence interval; ECZ = eculizumab therapy; EDSS = expanded disability severity score; HR = hazard ratio; NA = not available; NMOSD = neuromyelitis optica spectrum disorders; PLEX = plasma exchange therapy; RTX = rituximab therapy

**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.

# Appendix E Excluded Studies

Studies which met the inclusion criteria but from which relevant data could not be extracted, full-text articles which were not available, and articles which duplicated data from within studies were excluded and listed in Table 85

Table Articles meeting eligibility criteria but excluded, by reason

|  |
| --- |
| **Could not extract relevant data** |
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# Appendix F IPND diagnostic criteria for NMOSD

Table 107 Diagnostic criteria for NMOSD (Wingerchuk et al. 2015)

|  |
| --- |
| **Diagnostic criteria for NMOSD with AQP4-IgG**  1. At least 1 core clinical characteristic  2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)  3. Exclusion of alternative diagnosis |
| **Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status**  1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:  a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome  b. Dissemination in space (2 or more different core clinical characteristics)  c. Fulfillment of additional MRI requirements, as applicable  2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable  3. Exclusion of alternative diagnoses |
| **Core clinical characteristics**  1. Optic neuritis  2. Acute myelitis  3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting  4. Acute brainstem syndrome  5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions  6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions |
| **Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status**  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  2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments of focal spinal cord atrophy in patients wth history compatible with acute myelitis  3. Areas postreme syndrome: requires associated dorsal medulla/area postrema lesions  4. Acute brainstem syndrome: requires associated periependymal brainstem lesions |

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 et al. 2015).

# Appendix G PPICO criteria for linked evidence

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

|  |  |
| --- | --- |
| **Component** | **Description** |
| Patients | 1. Patients suspected of having neuromyelitis optica spectrum disorder (NMOSD) e.g. those with: 2. Recurrent, bilateral or severe optic neuritis; or 3. Recurrent longitudinal extensive transverse myelitis (LETM)\*; or 4. Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or 5. Acute brainstem syndrome or 6. Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or 7. Symptomatic cerebral syndrome with typical NMOSD MRI lesions or 8. Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) or 9. Patient has poor recovery from multiple sclerosis relapses 10. 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 | 1. 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)  * Serum * CSF  1. Antibody testing (AQP4-Ab or MOG-Ab) of serum to monitor for signs of relapse in previously diagnosed patients? |
| Reference standard | None available |
| Comparator (evidentiary standard) | Diagnosis by clinical characteristics alone (including MRI) |
| Outcomes | * Sensitivity * Specificity * Need for re-testing * Reliability * Reproducibility * PPV * NPV * Diagnostic yield |
| Research question | 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?  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? |

AQP4-Ab = aquaporin 4 antibodies; CSF = cerebrospinal fluid; LETM = longitudinal extensive transverse myelitis; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorders (includes MARD); NPV = negative predictive value; PPV = positive predictive value

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

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

|  |  |
| --- | --- |
| **Component** | **Description** |
| Patients | 1. Patients suspected of having neuromyelitis optica spectrum disorder (NMOSD) e.g. those with: 2. Recurrent, bilateral or severe optic neuritis; or 3. Recurrent longitudinal extensive transverse myelitis (LETM)\*; or 4. Area postrema syndrome (otherwise unexplained hiccups or nausea/vomiting) or 5. Acute brainstem syndrome or 6. Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD MRI lesions or 7. Symptomatic cerebral syndrome with typical NMOSD MRI lesions or 8. Monophasic neuromyelitis optica (no recurrence; simultaneous or closely related optic neuritis and LETM within 30 days) or 9. Patient has poor recovery from multiple sclerosis relapses 10. 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 | 1. 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 2. 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 | * 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 | Do AQP4-Ab with/without MOG-Ab testing in patients suspected of NMOSD change management, compared to being diagnosed by clinical characteristics alone?  Does monitoring by AQP4-Ab or MOG-Ab testing in patients previously diagnosed with NMOSD change management compared to monitoring by clinical characteristics alone? |

AQP4-Ab = aquaporin 4 antibodies; LETM = longitudinal extensive transverse myelitis; MARD = MOG antibody related disorder; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorders (includes MARD)

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

Box : 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 | 1. Patients diagnosed with NMOSD or those testing negative for AQP4-Ab and MOG-Ab  2. Previously diagnosed NMOSD patients confirmed to be relapsing or those who had no increase in AQP4-Ab or MOG-Ab titre |
| Intervention | 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 | * 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 | 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)?  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? |

AQP4-Ab = aquaporin 4 antibodies; MARD = MOG-antibody related disorder; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; NMOSD = neuromyelitis optica spectrum disorders (includes MARD)

# Appendix Sensitivity and specificity of various AQP4-Ab assays

Prain et al. (Prain et al. 2019), compared different assays (cell-based, tissue-based and immunosorbent) for serum AQP4-Ab testing. As summarised in the table below, both fixed and live cell-based assays were the most sensitive assays, with sensitivity of 94% and 92%, respectively. The tissue-based indirect immunofluorescence and immunosorbent assay, ELISA were less sensitive (78% and 60%, respectively). A high level of specificity was shown for all serum assay types, especially the live cell-based assay, tissue-based indirect immunofluorescence and fixed cell-based assay (100%, 99.7% and 99.5%, respectively). The immunosorbent assay, ELISA showed the least sensitivity (60%) and specificity (97%) for serum AQP4-Ab testing. This recent data are also consistent with earlier data published by Waters et al. (Waters et al. 2012) (also provided by the Department) who in 2012, reported that three cell-based serum assays were more sensitive than a tissue-based assay and ELISA immunosorbent assay, but all were highly specific. Of particular note, however was that the overall sensitivities results reported in the 2012 paper, (Waters et al. 2012) were considerably lower than results of the more recent 2019 study (Prain et al. 2019), possibly due to the advances in detection technology over the years.

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

| **Prain et al 2019** | | | | | |
| --- | --- | --- | --- | --- | --- |
| Assay | T-IIF | ELISA | Euroimmun® Fixed-CBA | Oxford Live-CBA | |
| Case Sensitivity (n/N) (%) | | | | | |
| NMOSD  [95% CI] | 62/78 (78)  [69-87] | 25/42 (60)  [45-73] | 34/36 (94)  [82-99] | 33/36 (92)  [78-97] | |
| Control Specificity (n/N) (%) | | | | | |
| Controls  [95% CI] | 346/346 (99.7)  [98-100] | 255/264 (97)  [94-98] | 214/215 (99.5)  [97-100] | 201/201 (100)  [98-100] | |
| **Waters et al 2012** | | | | | |
| Assay | T-IIF | ELISA | Euroimmun® Fixed-CBA | Oxford –CBAa | FACS |
| Case Sensitivity (n/N) (%) | | | | | |
| NMOSD/NMO | 29/60 (48) | 36/60 (60) | 41/60 (68) | 44/60 (73) | 46/60  (77) |
| Control Specificity (n/N) (%) | | | | | |
| Controls | 86/86 (100) | 86/86 (100) | 86/86 (100) | 86/86  (100) | 86/86  (100) |

AQP4-Ab = aquaporin-4 antibodies; CBA = cell-based assay; ELISA = enzyme linked immunosorbent assay; FACS = fluorescence-activated cell sorting; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; n/N = number of positive cases/total number of cases; T-IIF = tissue-based indirect immunofluorescence.

Figures in italicised bold represent the cell-based assays.

a Publication did not state whether this was a live cell-based assay

Reference: Prain et al. (Prain et al. 2019); Waters et al. 2012 (Waters et al. 2012)

Misu, T & Fujihara, K 2018, 'Neuromyelitis optica spectrum and myelin oligodendrocyte glycoprotein antibody-related disseminated encephalomyelitis', *Clnical and experimental Neuroimmunology*, no. 10, pp. 9-17.

Neuromyelitis optica (NMO) is characterized by severe optic neuritis and transverse myelitis. The relationship of NMO to multiple sclerosis (MS) has long been debated. With the discovery of an NMO-specific autoantibody to aquaporin 4 (AQP4), the clinical, radiological, and laboratory findings have clarified the differences between NMO and MS, and NMO spectrum disorders (NMOSD) have been proposed as the unifying term for the entire clinical entity including brain syndromes. Pathological studies in NMO showed loss of immunoreactivity to AQP4 and glial fibrillary acidic protein, but a relative preservation of myelin basic protein, especially at the lesions with perivascular deposition of immunoglobulins and complements. AQP4 antibody-positive NMOSD is now considered an autoimmune astrocytopathic disease. In addition, the definite diagnosis should be made initially from the therapeutic viewpoint, because there have been several AQP4 antibody-positive NMOSD cases exacerbated by disease-modifying drugs for MS. In recent years, the antibody against myelin oligodendrocyte glycoprotein (MOG) has been studied for its association with other types of acute demyelinating diseases, such as acute or multiphasic disseminated encephalomyelitis, optic neuritis, NMOSD and brainstem or cerebral cortical encephalomyelitis. Recent brain biopsied MOG antibody-positive case reports have suggested the dominance of humoral immunity, but it is not well elucidated whether the cellular immune responses against MOG could develop perivenous inflammatory demyelination like classical acute disseminated encephalomyelitis pathology. In the present review, we focus on two distinct diseases, aquaporin 4 antibody-related NMOSD and MOG antibody-related diseases, both of which were recently differentiated from MS by means of the disease-specific autoantibodies and the distinct pathophysiologies.

# Appendix Additional information for economic analysis

### Summary of inputs to the model

Table Summary of inputs used in the model

|  |  |  |  |
| --- | --- | --- | --- |
| Variable name | Description | Source | Value |
| ARR | Annual relapse rate | (Nikoo et al. 2017) | 1.123 |
| ASRR | Annualised severe relapse rate | (Jeong et al. 2016) | 1.10 |
| cost\_Ab\_Test | Cost of NMOSD-Ab testing, proposed | PICO confirmation | $43.00 |
| cost\_AZA | Cost associated with azathioprine and severe adverse events | Calculated, Section D.4 | $1,371 |
| cost\_IVIG | Cost of intravenous immunoglobulin | Calculated, Section D.4 | $4,245 |
| cost\_IVMP | Cost of methylprednisolone (iv) | Calculated, Section D.4 | $2,665 |
| cost\_Mild\_Relapse | Annual cost of treating mild relapse | Calculated, Section D.4 | ($3547/4) + prop\_IVMP\_mild \* cost\_IVMP + prop\_PLEX\_mild\*cost\_PLEX |
| cost\_MST | Annual cost of MS therapy | Calculated, Section D.4 | $11,602 |
| cost\_PLEX | Cost of plasma exchange | Calculated, Section D.4 | $8,477 |
| cost\_RTX | Cost associated with rituximab and adverse events | Calculated, Section D.4 | $12,058 |
| cost\_Severe\_Relapse | Annual cost of treating severe relapse | Calculated, Section D.4 | ($11,277/4) + 1.3\*(prop\_IVMP\_severe\*cost\_IVMP + prop\_PLEX\_severe \* cost\_PLEX + prop\_IVIG \* cost\_IVIG) |
| cost\_symptomatic\_Tx | Cost of symptomatic treatment | (Ahmad et al. 2018) | $524 |
| diag\_yield\_AQP4 | Diagnostic yield for AQP4-Ab | Section C2.1 | 4.2% |
| diag\_yield\_MOG | Diganostic yield for MOG-Ab in AQP4 -ves | Section C2.1 | 5.5% |
| disutil\_mild\_relapse | Disutility after mild relapse | (Aungsumart & Apiwattanakul 2020) | 0.07 |
| disutil\_severe\_relapse | Disutility after severe relapse | (Aungsumart & Apiwattanakul 2020) | 0.29 |
| onsetAge | Age at onset (years) | (Bukhari et al. 2020) | 40 |
| p\_alt\_diagnosis | Proportion of patients misdiagnosed | (Beekman et al. 2019) | 65.8% |
| p\_diagnosed\_noTest | Proportion of patients diagnosed with NMOSD at baseline without antibody testing | (McCreary et al. 2018) | 5.4% |
| p\_dis\_death | Probability of death due to disability | (Aungsumart & Apiwattanakul 2020) | probtoprob(0.02;1/4) |
| p\_progress | probability of transitioning from mild health state to severe health state | (Aungsumart & Apiwattanakul 2020) | probtoprob(0.190;1/4) |
| p\_relapse | Risk of annual relapse, no treatment | Calculated | 1–exp(–ARR\*1/4) |
| p\_relapse\_death\_noTest | risk of death in the absence of test (no/incorrect treatment) | (Wingerchuk & Weinshenker 2003) | probtoprob(6.2%;1/4) |
| p\_relapse\_death\_Test | risk of death when testing available (correct treatment) | (Collazo et al. 2018) | probtoprob(2.5%;1/4) |
| p\_relapse\_IST | risk of relapsing when on Immuno suppressive Tx | Calculated | p\_relapse\*RR\_relapse\_IST |
| p\_relapse\_MST | risk of relapse when on MS Tx | Calculated | p\_relapse\*RR\_relapse\_MST |
| p\_relapse\_severe | Probability of transitioning to severe disability health state | Calculated | 1-exp(-ASRR\*1/4) |
| p\_relapse\_severe\_IST | Risk of severe relapse under IST | Calculated | p\_relapse\_severe \* (prop\_AZA\*0.32 + prop\_RTX\*0.016) |
| prop\_IVIG | Proportion receiving IVIG | Section C3.1 | 10% |
| prop\_IVMP\_mild | Proportion treated with IVMP | Section C3.1 | 84% |
| prop\_IVMP\_severe | Proportion treated with IVMP in severe attack | Section C3.1 | 45% |
| prop\_PLEX\_mild | Proportion treated with PLEX in mild relapse | Section C3.1 | 16% |
| prop\_PLEX\_severe | Proportion treated with PLEX in severe attack | Section C3.1 | 75% |
| prop\_RTX | Proportion of patients receiving rituximab: 41% | Section C3.1 | 41% |
| RR\_relapse\_IST | Relative risk of relapses with immunosuppressive treatment | (Palace et al. 2019) | 0.668 |
| RR\_relapse\_MST | Relative risk of relapses with MS treatment | (Palace et al. 2019) | 1.383 |
| time\_to\_diagnosis | Time to correct diagnosis in the comparator arm (years) | Section D.4 | 3.3 |
| u\_Mild\_State | Utility of patients with NMOSD (no/mild-moderate disability) | (Ahmad et al. 2018) | 0.72/4 |
| u\_Severe\_State | Utility of patients with NMOSD (severe disability) | (Ahmad et al. 2018) | 0.48/4 |

ARR = annualised relapse rate; ASRR = annualised severe relapse rate; AZA = azathioprine; iv = intravenous; IVIG= intravenous immunoglobulin; IVMP = intravenous methyl prednisolone; IST = immunosuppressive therapy; NMOSD = neuromyelitis optica; PLEX = plasma exchange; RR = relative risk; RTX = rituximab

## 

### Markov traces for nodes with Markov initiation (base-case analysis)

#### NMOSD-Ab testing available - Treat for NMOSD

Table NMOSD-Ab testing available - treat for NMOSD

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Stage  (quarters) | Disease with no or mild disability  (%) | Disease with moderate-severe disability  (%) | Disease with no/mild disability and mild relapse  (%) | Disease with no/mild disability and severe relapse  (%) | Disease with moderate – severe disability and mild relapse  (%) | Disease with moderate – severe disability and severe relapse (%) | Death  (%) | Cost | Cumulative Cost | QALY | Cumulative QALY | Relapse | Cumulative Relapse |
| 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | $2,267 | $2,267 | 0.3573 | 0.3573 | 0.1625 | 0.1625 |
| 1 | 0.8363 | 0.0000 | 0.1558 | 0.0077 | 0.0000 | 0.0000 | 0.0002 | $2,074 | $4,341 | 0.1737 | 0.5310 | 0.1347 | 0.2972 |
| 2 | 0.8624 | 0.0004 | 0.1303 | 0.0064 | 0.0000 | 0.0000 | 0.0005 | $2,068 | $6,409 | 0.1718 | 0.7027 | 0.1372 | 0.4343 |
| 3 | 0.8576 | 0.0007 | 0.1344 | 0.0066 | 0.0001 | 0.0000 | 0.0007 | $2,039 | $8,448 | 0.1696 | 0.8723 | 0.1348 | 0.5691 |
| 4 | 0.8577 | 0.0010 | 0.1336 | 0.0066 | 0.0001 | 0.0000 | 0.0010 | $2,015 | $10,463 | 0.1675 | 1.0398 | 0.1332 | 0.7024 |
| 5 | 0.8571 | 0.0012 | 0.1337 | 0.0066 | 0.0001 | 0.0000 | 0.0012 | $1,990 | $12,452 | 0.1654 | 1.2051 | 0.1316 | 0.8339 |
| 6 | 0.8566 | 0.0015 | 0.1336 | 0.0066 | 0.0002 | 0.0000 | 0.0015 | $1,965 | $14,418 | 0.1633 | 1.3684 | 0.1299 | 0.9639 |
| 7 | 0.8561 | 0.0018 | 0.1335 | 0.0066 | 0.0002 | 0.0000 | 0.0018 | $1,941 | $16,359 | 0.1613 | 1.5297 | 0.1283 | 1.0922 |
| 8 | 0.8556 | 0.0021 | 0.1334 | 0.0066 | 0.0003 | 0.0000 | 0.0021 | $1,917 | $18,276 | 0.1592 | 1.6889 | 0.1267 | 1.2189 |
| 9 | 0.8550 | 0.0024 | 0.1333 | 0.0066 | 0.0003 | 0.0000 | 0.0024 | $1,893 | $20,169 | 0.1572 | 1.8462 | 0.1252 | 1.3441 |
| 10 | 0.8545 | 0.0026 | 0.1332 | 0.0066 | 0.0004 | 0.0000 | 0.0027 | $1,870 | $22,039 | 0.1553 | 2.0014 | 0.1236 | 1.4677 |
| 11 | 0.8539 | 0.0029 | 0.1332 | 0.0066 | 0.0004 | 0.0000 | 0.0030 | $1,847 | $23,886 | 0.1533 | 2.1548 | 0.1221 | 1.5897 |
| 12 | 0.8534 | 0.0032 | 0.1331 | 0.0066 | 0.0005 | 0.0000 | 0.0033 | $1,824 | $25,710 | 0.1514 | 2.3062 | 0.1205 | 1.7103 |
| 13 | 0.8528 | 0.0035 | 0.1330 | 0.0066 | 0.0005 | 0.0000 | 0.0036 | $1,801 | $27,511 | 0.1495 | 2.4557 | 0.1190 | 1.8293 |
| 14 | 0.8523 | 0.0037 | 0.1329 | 0.0065 | 0.0005 | 0.0000 | 0.0040 | $1,779 | $29,290 | 0.1476 | 2.6033 | 0.1176 | 1.9469 |

#### NMOSD-Ab testing not available - Treat for NMOSD

Table NMOSD-Ab testing not available - Treat for NMOSD

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Stage  **(quarters)** | Disease with no or mild disability  **(%)** | Disease with moderate-severe disability  **(%)** | Disease with no/mild disability and mild relapse  **(%)** | Disease with no/mild disability and severe relapse  **(%)** | Disease with moderate – severe disability and mild relapse  **(%)** | **Disease with moderate – severe disability and severe relapse (%)** | Death  **(%)** | **Cost** | **Cumulative Cost** | **QALY** | **Cumulative QALY** | **Relapse** | **Cumulative Relapse** |
| 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | $2,224 | $2,224 | 0.3573 | 0.3573 | 0.1625 | 0.1625 |
| 1 | 0.8363 | 0.0000 | 0.1558 | 0.0077 | 0.0000 | 0.0000 | 0.0002 | $2,074 | $4,298 | 0.1737 | 0.5310 | 0.1347 | 0.2972 |
| 2 | 0.8624 | 0.0004 | 0.1303 | 0.0064 | 0.0000 | 0.0000 | 0.0005 | $2,068 | $6,366 | 0.1718 | 0.7027 | 0.1372 | 0.4343 |
| 3 | 0.8576 | 0.0007 | 0.1344 | 0.0066 | 0.0001 | 0.0000 | 0.0007 | $2,039 | $8,405 | 0.1696 | 0.8723 | 0.1348 | 0.5691 |
| 4 | 0.8577 | 0.0010 | 0.1336 | 0.0066 | 0.0001 | 0.0000 | 0.0010 | $2,015 | $10,420 | 0.1675 | 1.0398 | 0.1332 | 0.7024 |
| 5 | 0.8571 | 0.0012 | 0.1337 | 0.0066 | 0.0001 | 0.0000 | 0.0012 | $1,990 | $12,409 | 0.1654 | 1.2051 | 0.1316 | 0.8339 |
| 6 | 0.8566 | 0.0015 | 0.1336 | 0.0066 | 0.0002 | 0.0000 | 0.0015 | $1,965 | $14,375 | 0.1633 | 1.3684 | 0.1299 | 0.9639 |
| 7 | 0.8561 | 0.0018 | 0.1335 | 0.0066 | 0.0002 | 0.0000 | 0.0018 | $1,941 | $16,316 | 0.1613 | 1.5297 | 0.1283 | 1.0922 |
| 8 | 0.8556 | 0.0021 | 0.1334 | 0.0066 | 0.0003 | 0.0000 | 0.0021 | $1,917 | $18,233 | 0.1592 | 1.6889 | 0.1267 | 1.2189 |
| 9 | 0.8550 | 0.0024 | 0.1333 | 0.0066 | 0.0003 | 0.0000 | 0.0024 | $1,893 | $20,126 | 0.1572 | 1.8462 | 0.1252 | 1.3441 |
| 10 | 0.8545 | 0.0026 | 0.1332 | 0.0066 | 0.0004 | 0.0000 | 0.0027 | $1,870 | $21,996 | 0.1553 | 2.0014 | 0.1236 | 1.4677 |
| 11 | 0.8539 | 0.0029 | 0.1332 | 0.0066 | 0.0004 | 0.0000 | 0.0030 | $1,847 | $23,843 | 0.1533 | 2.1548 | 0.1221 | 1.5897 |
| 12 | 0.8534 | 0.0032 | 0.1331 | 0.0066 | 0.0005 | 0.0000 | 0.0033 | $1,824 | $25,667 | 0.1514 | 2.3062 | 0.1205 | 1.7103 |
| 13 | 0.8528 | 0.0035 | 0.1330 | 0.0066 | 0.0005 | 0.0000 | 0.0036 | $1,801 | $27,468 | 0.1495 | 2.4557 | 0.1190 | 1.8293 |
| 14 | 0.8523 | 0.0037 | 0.1329 | 0.0065 | 0.0005 | 0.0000 | 0.0040 | $1,779 | $29,247 | 0.1476 | 2.6033 | 0.1176 | 1.9469 |

#### NMOSD-Ab testing not available - Initial treatment MS-DMT

Table NMOSD-Ab testing not available - Initial treatment MS-DMT

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Stage  **(quarters)** | Disease with no or mild disability  **(%)** | Disease with moderate-severe disability  **(%)** | Disease with no/mild disability and mild relapse  **(%)** | Disease with no/mild disability and severe relapse  **(%)** | Disease with moderate – severe disability and mild relapse  **(%)** | **Disease with moderate – severe disability and severe relapse (%)** | Death  **(%)** | **Cost** | **Cumulative Cost** | **QALY** | **Cumulative QALY** | **Relapse** | **Cumulative Relapse** |
| 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | $5,096 | $5,096 | 0.3538 | 0.3538 | 0.3365 | 0.3365 |
| 1 | 0.6613 | 0.0000 | 0.2571 | 0.0814 | 0.0000 | 0.0000 | 0.0002 | $4,347 | $9,442 | 0.1680 | 0.5217 | 0.2239 | 0.5604 |
| 2 | 0.7703 | 0.0042 | 0.1700 | 0.0538 | 0.0000 | 0.0000 | 0.0017 | $4,520 | $13,962 | 0.1666 | 0.6884 | 0.2570 | 0.8174 |
| 3 | 0.7296 | 0.0055 | 0.1981 | 0.0627 | 0.0011 | 0.0003 | 0.0028 | $4,386 | $18,348 | 0.1639 | 0.8522 | 0.2415 | 1.0589 |
| 4 | 0.7389 | 0.0082 | 0.1876 | 0.0594 | 0.0014 | 0.0004 | 0.0040 | $4,355 | $22,703 | 0.1616 | 1.0139 | 0.2423 | 1.3012 |
| 5 | 0.7316 | 0.0103 | 0.1900 | 0.0601 | 0.0021 | 0.0007 | 0.0052 | $4,291 | $26,994 | 0.1593 | 1.1732 | 0.2377 | 1.5389 |
| 6 | 0.7298 | 0.0126 | 0.1881 | 0.0595 | 0.0026 | 0.0008 | 0.0065 | $4,239 | $31,233 | 0.1570 | 1.3302 | 0.2350 | 1.7739 |
| 7 | 0.7262 | 0.0147 | 0.1877 | 0.0594 | 0.0032 | 0.0010 | 0.0078 | $4,183 | $35,416 | 0.1547 | 1.4849 | 0.2317 | 2.0056 |
| 8 | 0.7232 | 0.0169 | 0.1867 | 0.0591 | 0.0038 | 0.0012 | 0.0091 | $4,129 | $39,545 | 0.1525 | 1.6374 | 0.2286 | 2.2342 |
| 9 | 0.7200 | 0.0190 | 0.1860 | 0.0589 | 0.0043 | 0.0014 | 0.0104 | $4,076 | $43,621 | 0.1503 | 1.7877 | 0.2255 | 2.4597 |
| 10 | 0.7169 | 0.0212 | 0.1851 | 0.0586 | 0.0049 | 0.0015 | 0.0117 | $4,023 | $47,644 | 0.1481 | 1.9358 | 0.2225 | 2.6822 |
| 11 | 0.7138 | 0.0232 | 0.1843 | 0.0584 | 0.0054 | 0.0017 | 0.0131 | $3,971 | $51,614 | 0.1460 | 2.0817 | 0.2195 | 2.9016 |
| 12 | 0.7107 | 0.0253 | 0.1835 | 0.0581 | 0.0060 | 0.0019 | 0.0145 | $3,919 | $55,533 | 0.1438 | 2.2256 | 0.2165 | 3.1181 |
| 13 | 0.7076 | 0.0273 | 0.1827 | 0.0578 | 0.0065 | 0.0021 | 0.0159 | $3,255 | $58,788 | 0.1418 | 2.3673 | 0.2135 | 3.3317 |
| 14 | 0.7045 | 0.0293 | 0.1820 | 0.0576 | 0.0070 | 0.0022 | 0.0174 | $1,723 | $60,511 | 0.1419 | 2.5092 | 0.1030 | 3.4347 |

#### NMOSD-Ab testing not available - Initial treatment Symptomatic

Table NMOSD-Ab testing not available - Initial treatment Symptomatic

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Stage  **(quarters)** | Disease with no or mild disability  **(%)** | Disease with moderate-severe disability  **(%)** | Disease with no/mild disability and mild relapse  **(%)** | Disease with no/mild disability and severe relapse  **(%)** | Disease with moderate – severe disability and mild relapse  **(%)** | **Disease with moderate – severe disability and severe relapse (%)** | Death  **(%)** | **Cost** | **Cumulative Cost** | **QALY** | **Cumulative QALY** | **Relapse** | **Cumulative Relapse** |
| 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | $1,730 | $1,730 | 0.3552 | 0.3552 | 0.2433 | 0.2433 |
| 1 | 0.7550 | 0.0000 | 0.1859 | 0.0589 | 0.0000 | 0.0000 | 0.0002 | $1,361 | $3,091 | 0.1700 | 0.5252 | 0.1844 | 0.4277 |
| 2 | 0.8108 | 0.0030 | 0.1404 | 0.0444 | 0.0000 | 0.0000 | 0.0013 | $1,427 | $4,518 | 0.1683 | 0.6935 | 0.1954 | 0.6232 |
| 3 | 0.7940 | 0.0045 | 0.1508 | 0.0477 | 0.0006 | 0.0002 | 0.0023 | $1,388 | $5,907 | 0.1658 | 0.8594 | 0.1896 | 0.8128 |
| 4 | 0.7947 | 0.0066 | 0.1476 | 0.0467 | 0.0008 | 0.0003 | 0.0033 | $1,375 | $7,282 | 0.1636 | 1.0229 | 0.1879 | 1.0007 |
| 5 | 0.79117023 | 0.00843411 | 0.14775758 | 0.04676981 | 0.00122464 | 0.00038764 | 0.004256 | 1355.687686 | 8637.256714 | 0.1612636 | 1.1841673 | 0.1852738 | 1.1860196 |
| 6 | 0.78867653 | 0.01031385 | 0.14710248 | 0.04656245 | 0.00156816 | 0.00049637 | 0.00528016 | 1338.168456 | 9975.42517 | 0.1590162 | 1.3431835 | 0.1828789 | 1.3688985 |
| 7 | 0.78594013 | 0.01215842 | 0.14663883 | 0.04641569 | 0.00191766 | 0.000607 | 0.00632228 | 1320.500837 | 11295.92601 | 0.1567953 | 1.4999788 | 0.1804557 | 1.5493542 |
| 8 | 0.78326844 | 0.01398747 | 0.14613005 | 0.04625464 | 0.00226062 | 0.00071555 | 0.00738322 | 1303.124553 | 12599.05056 | 0.1546039 | 1.6545828 | 0.1780746 | 1.7274288 |
| 9 | 0.78058722 | 0.01579567 | 0.1456333 | 0.04609741 | 0.00260069 | 0.0008232 | 0.00846251 | 1285.931178 | 13884.98174 | 0.1524409 | 1.8070237 | 0.1757182 | 1.903147 |
| 10 | 0.77791325 | 0.0175847 | 0.14513478 | 0.04593961 | 0.00293689 | 0.00092962 | 0.00956115 | 1268.94288 | 15153.92462 | 0.1503059 | 1.9573296 | 0.1733902 | 2.0765372 |
| 11 | 0.77524251 | 0.01935427 | 0.14463761 | 0.04578224 | 0.00326953 | 0.00103491 | 0.01067893 | 1252.152069 | 16406.07669 | 0.1481987 | 2.1055283 | 0.1710894 | 2.2476265 |
| 12 | 0.772576 | 0.02110467 | 0.14414104 | 0.04562506 | 0.00359855 | 0.00113905 | 0.01181563 | 1235.558395 | 17641.63508 | 0.1461189 | 2.2516472 | 0.1688157 | 2.4164422 |
| 13 | 0.76991351 | 0.022836 | 0.14364525 | 0.04546813 | 0.003924 | 0.00124207 | 0.01297105 | 1767.331684 | 19408.96677 | 0.1440662 | 2.3957134 | 0.1665689 | 2.5830112 |
| 14 | 0.76725547 | 0.02454842 | 0.14315021 | 0.04531143 | 0.0042459 | 0.00134396 | 0.0141446 | 1755.190545 | 21164.15731 | 0.1434724 | 2.5391858 | 0.1104319 | 2.693443 |

### Sensitivity analyses (time-horizon)

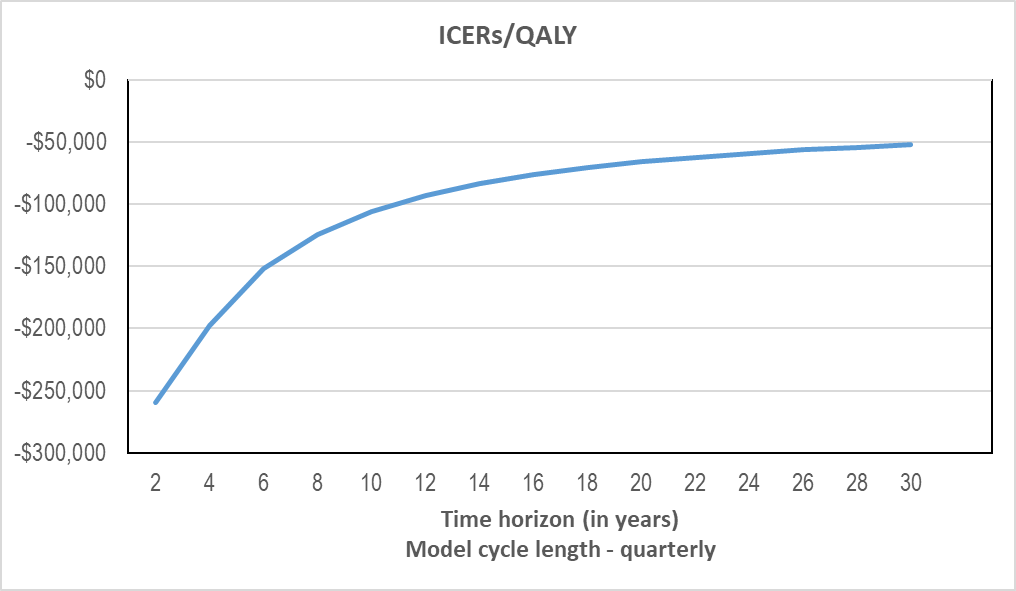


Figure Sensitivity analyses, ICERs per QALY over the varied modelled time-horizon

ICER = incremental cost-effectiveness ratio

# Appendix Additional information for financial analysis

Table MBS utilisation data for comparator items, 2014–15 to 2018–19

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **2014/2015** | **2015/2016** | **2016/2017** | **2017/2018** | **2018/2019** |
| **71119** | In Hospital | Number of Services | 5,152 | 5,453 | 5,930 | 6,543 | 6,805 |
| Bulk Billing Rate | 2.9% | 2.2% | 1.3% | 1.8% | 2.0% |
| Out of Hospital | Number of Services | 140,983 | 148,548 | 143,466 | 157,149 | 163,274 |
| Bulk Billing Rate | 98.9% | 99.1% | 99.1% | 99.2% | 99.2% |
| Total | Number of Services | 146,135 | 154,001 | 149,396 | 163,692 | 170,079 |
| Bulk Billing Rate | 95.5% | 95.7% | 95.3% | 95.3% | 95.3% |
| **71165** | In Hospital | Number of Services | 3,724 | 3,496 | 4,234 | 4,470 | 4,406 |
| Bulk Billing Rate | 2.4% | 2.4% | 1.2% | 1.8% | 1.7% |
| Out of Hospital | Number of Services | 124,483 | 145,221 | 145,278 | 158,823 | 168,751 |
| Bulk Billing Rate | 98.3% | 98.7% | 98.8% | 99.0% | 99.4% |
| Total | Number of Services | 128,207 | 148,717 | 149,512 | 163,293 | 173,157 |
| Bulk Billing Rate | 95.5% | 96.4% | 96.0% | 96.4% | 97.0% |

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1. Prior tests, Population, Intervention, Comparator, Outcomes [↑](#footnote-ref-1)
2. 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-2)
3. Clinical advice provided through personal communications with Professor S Broadley and Dr D Langguth [↑](#footnote-ref-3)
4. While cases that are positive for both AQP4-Ab and MOG-Ab have been noted in the literature they are extremely rare and will not be considered as a separate group in this assessment. [↑](#footnote-ref-4)
5. [MedCalc statistical software](https://www.medcalc.org/calc/comparison_of_means.php) [↑](#footnote-ref-5)
6. Armitage, P, Berry, G & Matthews, JNS 2002, *Statistical methods in medical research*, fourth edn, Blackwell Science, Oxford.

   Deeks, JJ 2001, 'Systematic reviews of evaluations of diagnostic and screening tests', in M Egger, G Davey Smith & DG Altman (eds), *Systematic Reviews in Healthcare: Meta-Analysis in Context*, second edn, BMJ Publishing Group, London, pp. 248–282. [↑](#footnote-ref-6)
7. The EDSS includes eight functional systems (pyramidal; cerebellar; brainstem; sensory; bowel and bladder; visual; cerebral or mental; other or miscellaneous) which are scored for impairment and an overall disability status scale. Scoring is defined in steps (10 steps in all), each of which represent worse disability than the previous. EDSS step 0 represents normal neurological examination regardless of symptoms whereas step 10 represents death due to MS. EDSS step 5 requires ambulation for 200 metres without aid, but disability is severe enough to impair full daily activities (Kurtzke JF 1983). [↑](#footnote-ref-7)
8. Decimal notation was used for visual acuity in the case series by Zhou et al, 2016. A visual acuity of 0.5 is equivalent to 6/12 or 20/40 using Snellen fractions, where the numerator = distance which was conducted. (source: <https://www.nidek-intl.com/visual_acuity.html>) [↑](#footnote-ref-8)
9. The inclusion criteria for the Optic Neuritis Treatment Trial (ONTT) were (1) initiated with ON, presenting with acute or subacute visual loss; (2) age of ON onset ≥18 years; (3) at least two of the following conditions: ocular pain during eye movement, afferent pupillary defect, abnormal visual evoked response, dyschromatopsia and field defect. [↑](#footnote-ref-9)
10. The Goldmann kinetic perimetry test is a common test for visual field, and is performed by an experienced perimetrist. Specialised equipment and adjustable light stimuli are used to test the extent of the visual field. [↑](#footnote-ref-10)
11. Personal communication with Prof Stephen Reddel, email received on 7 February 2020. [↑](#footnote-ref-11)
12. TGA = Therapeutic Goods Administration; PBS = The Pharmaceutical Benefits Scheme [↑](#footnote-ref-12)
13. p(t) = 1 − e−rt; and r(t) = –ln(1-p) × (1/t); where p is the probability, r is the rate and t is the cycle length [↑](#footnote-ref-13)
14. Data provided by Dr Greg Bryson (Pathology Queensland), Dr Daman Langguth (Sonic Laboratories Australia), A/Prof Steve Reddell (NSW Health), Dr Andrew McLean-Tooke (PathWest Laboratory Medicine, WA) and Dr Pravin Hissaria (SA Pathology, SA) through personal communications; emails received between 4–11 February 2020, respectively. [↑](#footnote-ref-14)
15. Clinical expert advice by A/Prof Stephen Reddel received on 7th February 2020 through personal communication. [↑](#footnote-ref-15)
16. Total number of tests performed by QLD (1,973), NSW (1,614), Sonic (1,014) and PathWest (AQP4-Ab- 275; MOG-Ab 157) equates to 5,033. 157 MOG-Ab tests forms 3% of 5,033 total tests performed. [↑](#footnote-ref-16)