# August 2022 Newsletter

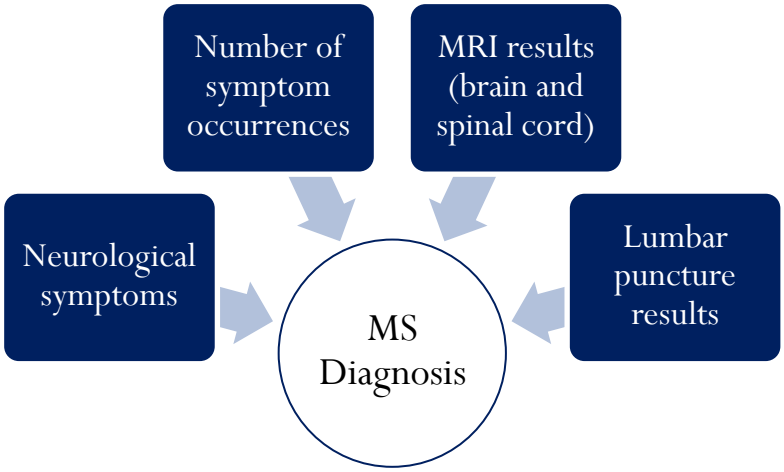
## What are the McDonald Criteria?

It's important to diagnose MS as early as possible, so that treatment can begin and, ideally, prevent the progression of neurological damage and disability. This can be a difficult task because MS symptoms are different in every person and may be mistaken for other medical issues. There is currently no single test that results in a definitive diagnosis of MS. Neurologists use several tools for this purpose, including taking a careful medical history, doing a thorough neurologic exam and performing various tests including magnetic resonance imaging (MRI), lumbar puncture, and blood tests to rule out other conditions. The McDonald criteria are measures aimed at helping doctors diagnose MS more accurately and quickly by guiding them to the most appropriate tests for each individual.

The diagnostic criteria for MS have evolved over time as new health screenings have been developed. The Schumacher criteria were introduced in 1965 as the first internationally recognized method for diagnosing MS. Diagnosis was based on symptoms identified by the physician. In 1983, the Poser Criteria became the new standard where the main requirement for diagnosing MS was finding evidence of damage to the central nervous

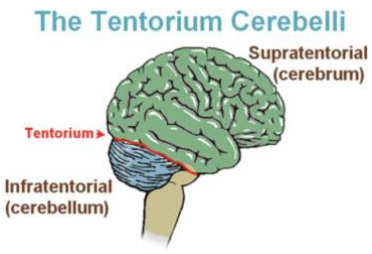
system (the brain and spinal cord) using lumbar puncture and evoked potentials (the new laboratory tests of that era). The Poser criteria defined different levels of certainty in the diagnosis of MS, either definite or probable. The McDonald Criteria (named for neurologist Ian McDonald) were adopted in 2001 and added magnetic resonance imaging (MRI) to the list of tools a neurologist can use to determine a diagnosis of MS. These guidelines were revised in 2005, 2010 and, most recently, in 2017. It's important to note that the revision of the McDonald Criteria over time does not change any MS diagnosis that is based on an earlier version.

According to the 2017 McDonald Criteria, the following information is used to determine a diagnosis of MS:




An exacerbation or relapse of MS is the occurrence of new neurological symptoms or the worsening of old ones. According to the 2017 McDonald Criteria, neurological symptoms are considered for diagnostic purposes if they last at least 24 hours. They must be due to demyelination of the nerves in the brain or spinal cord and not from another cause, like an infection or other illness. Blood tests are used to rule out other conditions. A history of symptoms may also point to past disease activity.

MRI scanning is used to visualize lesions, or damage, in the central nervous system. An individual with MS must have evidence of nerve damage that is "disseminating in space," or appearing in multiple (at least two) locations. These include three areas of the brain (periventricular, juxtacortical or cortical, and infratentorial) and the spinal cord. They must



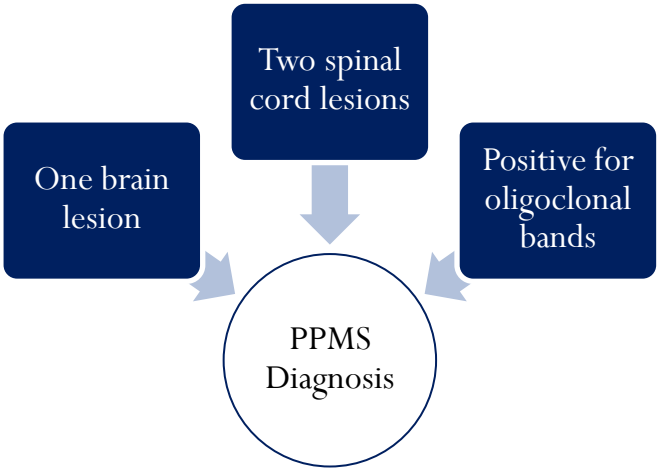
also have evidence of nerve damage that is "disseminating in time," or happening at different points in time. This can be evidenced by a second relapse occurring at least 30 days from the first one, the appearance of new lesions on MRI, or by new inflammatory lesions alongside older ones that are no longer actively inflamed. A contrast agent called gadolinium is often used to make this distinction on MRI. Gadolinium enhancing lesions represent areas of active inflammation.

Lumbar puncture is another useful diagnostic test that is used to detect the presence of oligoclonal bands. Oligoclonal bands are proteins called immunoglobulins that are usually detected in the cerebrospinal fluid (CSF) of people with MS. Their presence is indicative of inflammation in the central nervous system. According to the 2017 McDonald criteria, testing positive for oligoclonal bands fulfills the criteria for dissemination in time, even if an individual only has evident nerve damage from one time point.

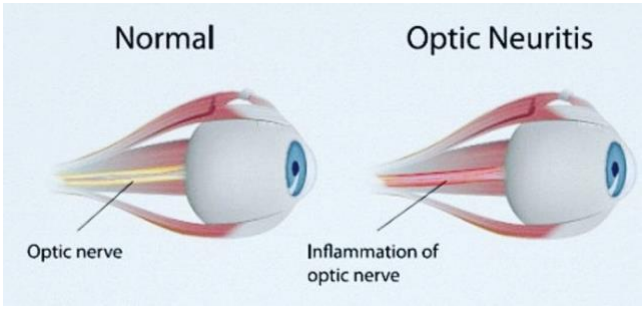
In cases of relapsing remitting MS, a person who has experienced at least two exacerbations and has clear-cut evidence of demyelination in at least two distinct brain areas, can be definitively diagnosed with MS, as they fulfill the requirements for both dissemination in space and time. If an individual has experienced at least two relapses but has evidence of nerve damage in only one brain area, then that individual has fulfilled the criteria for dissemination in time, but not in space. Damage in another brain region must be detected before MS can formally be diagnosed. This can be demonstrated by a subsequent relapse implicating a different brain region, or by an MRI scan. For example, if a person with MS has numbness and tingling, then later develops leg weakness, this can implicate different brain regions just by virtue of their symptoms.


Similarly, someone with lesions in two or more brain regions who experienced only one MS exacerbation fulfills the criteria for dissemination in space, but not in time. New damage occurring over time, evidenced by a new lesion on a subsequent MRI scan or by another relapse, is needed for a formal diagnosis. Alternatively, testing positive for oligoclonal bands can be enough to fulfill the criteria for an MS diagnosis in this case.

Diagnosing MS in individuals that have clinically isolated syndrome (CIS), or primary progressive MS (PPMS) may present additional challenges. Individuals with CIS have typically had one MS relapse and evidence of damage in one brain region (which does not fulfill the criteria for dissemination in space or in time). A formal diagnosis of MS cannot be made without clear evidence of further damage in other brain regions occurring over time or through the presence of oligoclonal bands. PPMS is characterized by worsening disability from the onset of MS symptoms, without relapses or remissions. A diagnosis of PPMS is determined by worsening disability for at least one year **and** at least two of the following:




Optic neuritis is common in people with MS, often occurring as the disease's first symptom. In light of this fact, the optic nerve was proposed as a fifth location to fulfill the criteria for dissemination in space when the McDonald Criteria were last updated. However, the panel performing the review felt there was insufficient evidence to support its inclusion in the guidelines at that time. In their words, "adding optic nerve involvement detected by MRI or visual evoked potentials as a fifth anatomical site led to a minor improvement in sensitivity of predicting development of a second attack." The group went on to state that studies to validate testing related to optic neuritis (for example, MRI, visual evoked potentials, or optical coherence tomography) in support of an MS diagnosis, are a high priority.




Recognizing that everyone's experience is different, research shows that the process of diagnosing MS has improved over time. A 2019 study concluded that MS can be diagnosed more frequently at the first occurrence of MS symptoms using the 2017 McDonald Criteria than the 2010 version. Investigators state that a careful evaluation is essential in atypical cases to avoid misdiagnoses. According to a 2021 study, changes to the diagnostic criteria for MS over the years have resulted in a shorter average time to diagnosis and less disability progression in people with MS. Investigators compared study participants who received an MS diagnosis based on pre-McDonald criteria in 1994 to those diagnosed based on the 2017 guidelines. The latter saw a 77% reduction in time between CIS and their MS diagnosis, and an 82% reduction in time between CIS and starting MS treatment. Over the entire study period (1994 to 2020), participants whose MS treatment began the earliest were 47% less likely to have an Expanded Disability Status Scale (EDSS) score of 3.0 or higher than those whose treatment began later.

Research into MS biomarkers and imaging techniques is essential to ensure that MS diagnostic criteria remain current and reflect new health screenings that may become available in the future. These guidelines should be updated and validated in a variety of populations on an ongoing basis to ensure that the fastest and most accurate MS diagnosis is possible for all. Accelerating research efforts like these, that benefit the MS community, is the heart of ACP's mission.