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# Literature Review

## Introduction

Medical error is the third leading cause of death in the United States. Misdiagnosis is a large contributor to this as it can prevent sick patients from receiving timely treatment, while exposing other patients to unnecessary and excessive treatment that often weakens their immune system and can lead to early death. When it comes to Multiple Sclerosis (MS), which affects around 900,000 people in the U.S. alone, it is estimated that the frequency of misdiagnosis is about 50% of the time. The discovery of a patient's false diagnosis often takes years, with 50% of patients carrying a misdiagnosis for at least 3 years, 33% for ten years or longer, and more than 5% for over 20 years. Due to the fact that doctors often begin MS disease-modifying therapy (DMT) as soon as they suspect MS, 31% of patients suffer from "unnecessary morbidity as a direct result of misdiagnosis" (Solomon et. al) of MS.

Multiple Sclerosis (MS) is a chronic neurological disorder. It is an autoimmune disorder which means the immune system for MS patients would mistakenly attack healthy cells instead of pathogens such as bacteria and viruses. Multiple Sclerosis affects people differently, some will have mild symptoms and others will have worsening symptoms that lead to increased disability over time.

Usually manifest from a relatively young age, MS symptoms usually begin between the ages of 20 and 40. MS patients typically have a normal life expectancy. Pathologically speaking, the MS immune system attacks myelin and the nerve cell bodies of the central nervous system. Myelin is a mixture of protein and fatty acids that makes the myelin sheath which covers and protects nerve fibers (axons). The individual symptoms of MS patients would vary depending on the severity of the attacks and the size of the plaques (patches of scar-like tissues that have sizes

from the head of a pin to a golf ball). MS has a wide range of symptoms including Muscle weakness, vision problems, mental or physical fatigue, mood, and cognitive changes.

Currently, there are no single tests to diagnose MS, different tests are used to confirm or rule out MS. Besides medical history examination, physical and neurological examination, MRI scan, and spinal cord are often used to look for MS characteristic lesions. Additionally, optic coherence tomography (OCT), cerebrospinal fluid tests, and evoked potential tests are commonly used for MS diagnosis. There is no cure for MS, but treatments can reduce the number and severity of relapses and delay long-term disease progressions. Clinically different symptoms will be managed by various treatments. Currently, much research on MS is being conducted, topics including finding new biomarkers for MS that can help diagnose and monitor MS, genetic and environmental risk factors, gut microbiome and diet, MS risk factors such as race and gender, etc. (National Institute of Health (NIH))

Diagnosing Multiple Sclerosis is a complex task due to the nature of the disease; overlapping symptoms with other diseases, a lack of specific diagnostic tests, variable presentation, and nonspecific symptoms are some of the many ongoing obstacles to proper diagnosis.

In 2017, the McDonald criteria utilized by clinicians and providers to aid in the differential of MS were revised. These revisions were only meant to be applicable to a specific subset of patients, however, several clinicians have unknowingly inappropriately applied McDonald criteria to “patients for whom they were not intended” (Solomon MD et. al). These revisions were based on a study performed on primarily white patients under the age of 50 with low co-illness rates, indicating that “application of the criteria should be approached cautiously” (Solomon MD et al.) for patients who do not fall within this demographic. Similarly, a study of 110 patients across the United States revealed that 85% of misdiagnoses were female patients and 15% were male patients, indicating that gender may play a role in misdiagnosis as well.

A study found that 89% of patients who were referred to an MS subspecialty center based primarily on an abnormal MRI were *not* later diagnosed with MS, but may have already started

treatment. The McDonald criteria, amongst other factors such as overlapping symptoms of related diseases, has consequently led to “misinterpretation and overreliance on MRI abnormalities of nonspecific neurologic symptoms” (Solomon, MD et al). Although MRI’s and other imaging technologies are helpful in aiding healthcare systems in providing an accurate diagnosis, identifying the cause of cortical lesions is extremely challenging as there are several common diseases that may present similarly on an MRI scan. As of 2024, there is still no specific biomarker for Multiple Sclerosis that has been identified exclusively of other diseases. It is a huge responsibility on a clinician to be able to differentiate subtle and near-invisible differences in lesions caused by MS and others caused by vascular disease, diabetes mellitus, tobacco use, and small vessel ischemic disease, which may all present in similar ways. There are suggestions that tiny hair-like veins on lesions, known as the Central Vein Sign (CVS), are as close to a biomarker for MS as we have gotten. However, AI has proven to be a lot better at identifying these tiny veins in imaging, and it may prove useful to clinicians to use AI tools in order to catch this. This opens up the possibility of reduced time of diagnosis and a personalized treatment plan for MS patients.

**Artificial Intelligence in Medical Space**

The medical space has benefited tremendously from the introduction of artificial intelligence. These applications can take a variety of forms ranging from disease outbreak prediction models to image enhancement techniques for noisy medical imaging data such as Magnetic Resonance Imaging (MRI) data. Some of the main image artifacts that cause distortions in MR images include motion corruption and the Gibbs ringing artifact. Motion corruption is caused by slight movements made by the patient while the MRI scan is underway. The Gibbs ringing artifact is caused by the truncation of data that requires a higher sampling frequency to observe. Research has shown that the effect of the Gibbs ringing artifact can be reduced in post-processed utilizing deep learning-based networks (Chen). Currently, a smoothing filter is applied to MR images to mitigate the effects of the Gibbs artifact, but the technique fails to reproduce the features lost from the artifact (Muckley).

Image enhancement is just one way that artificial intelligence is revolutionizing the medical space. Another significant utilization of AI is the employment of neural network models

to recognize patterns amongst visual-based medical data. Studies have shown the convolutional neural networks (CNNs) have shown notable promise in their ability to process this data and detect subtle patterns indicative of diseases (Pinto). These models tend to have better diagnostic results on diseases whose symptoms typically manifest in a uniform manner. Given that multiple sclerosis (MS) tends to present somewhat uniquely for every patient, larger databases are required to train models that have the capability to detect MS in its multitude of presentations Another complication that MS poses is that the treatment plan is often burdensome on the patient. The subsequent effect is that the cost of false positives associated with MS is higher than other diseases. Since the probability of detection ($P_D$) and the probability of false alarms ($P_{FA}$) have a direct relationship, lowering $P_D$ causes $P_{FA}$ to increase. Despite this, progress has been made in leveraging AI to help diagnose MS. Researchers work around MS's numerous presentations by creating multiple databases that separate the data collected from common early symptoms such as movement impairment, cognitive decline etc. (Cartwright).

**Conclusion**

The high misdiagnosis rates of Multiple Sclerosis, coupled with the complexities involved in accurately diagnosing the disease, highlight the need for new solutions to support healthcare professionals. This project aims to investigate the ongoing challenges and limitations of current diagnostic methods for MS, including the exploration of the latest research on potential biomarkers. Additionally, it seeks to combine the capabilities of artificial intelligence in detecting subtle patterns in medical imaging and data, which can assist clinicians in reducing misdiagnosis rates. Exploring AI's potential to enhance diagnostic accuracy and offer effective and personalized treatment plans for patients would no doubt be helpful in advancing the integration of new technologies into clinical practice.

**Citations:**

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