REVIEW ARTICLE

Multiple Sclerosis: Systemic Challenges to Cost-Effective Care

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BACKGROUND: Multiple sclerosis (MS) is a progressive autoimmune disorder of the central nervous system characterized by symptoms including reduced mobility, pain, fatigue, and spasticity. MS affects nearly 1 million people in the United States, with significant negative impact on a patient's quality of life, and an average lifetime cost of care in excess of $4 million. The cost-effective management of patients with MS faces several challenges.

OBJECTIVES: To review the challenges to the cost-effective management of patients with MS, and to offer healthcare stakeholders a roadmap to address them.

DISCUSSION: The cost-effective management of patients with MS, which is driven largely by how quickly a patient receives effective medication therapy, is challenged by a paucity of between-office-visit clinical data, variability of provider expertise with magnetic resonance imaging (MRI), MRI machine quality, lack of standards for MRI machines and reports, misaligned financial incentives, the limited number of available Current Procedural Terminology (CPT) codes for brain MRI, the complexity of disease-modifying therapy (DMT) selection, poor patient adherence to treatment plans, poor communication among providers, and a lack of objective measures of disease progression.

CONCLUSION: Insurers, neurologists, researchers, and patient advocacy groups must address the needs of patients with MS holistically. These efforts should include establishing standards for MRI machines and reports, matching patients with MS specialists, aligning financial incentives, including creating a new CPT code for complex brain MRI, streamlining prior authorization processes of DMTs, using technology to gather patient data and improve coordination of care, and developing better measurement tools of disease activity.

KEY WORDS: biomarkers, care coordination, cost-effective, disease-modifying therapy, misaligned incentives, MRI, multiple sclerosis, neurologists, no evidence of disease activity, wearable technologies

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Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disease of the central nervous system that is the most common neurologic disease in young adults.[1] MS is characterized by symptoms related to reduced mobility, pain, fatigue, and spasticity that have a significant impact on the patient's quality of life.[1] As the disease progresses, patients with MS are likely to have declines in standards of living and social withdrawal.[2] According to a 2018 study, the number of cases of MS in the United States is between 800,000 and 1 million, with women being approximately 2.5 times more likely to have MS than men.[3,4]

The average lifetime cost of care of a patient with MS exceeds $4 million.[5] The results of a recent survey by the North American Research Committee on Multiple Sclerosis showed that more than 50% of patients with MS received disease-modifying therapies (DMTs) as part of their treatment plans, representing more than 50% of their annual cost of care[5,6] (**Figure 1**).

The high cost of caring for patients with MS makes developing a new, cost-effective approach to managing patients with MS an important endeavor. In this article, we review certain current systemic challenges to providing cost-effective care for patients with MS as inputs to an initial stakeholder roadmap.

MS is typically first diagnosed in patients aged 20 to 30 years.[7] The classic presentation of MS may include blurred vision with associated eye pain, partial myelitis, focal sensory disturbance, or brainstem syndromes.[7] Other common physical symptoms of MS include changes in gait, fatigue, loss of balance, motor weakness, ataxia, pain, ocular issues, and reduced cognition.[8,9]

The diagnosis of MS is based on clinical findings, medical history, laboratory tests, and magnetic resonance imaging (MRI) of the brain and spinal cord. The revised

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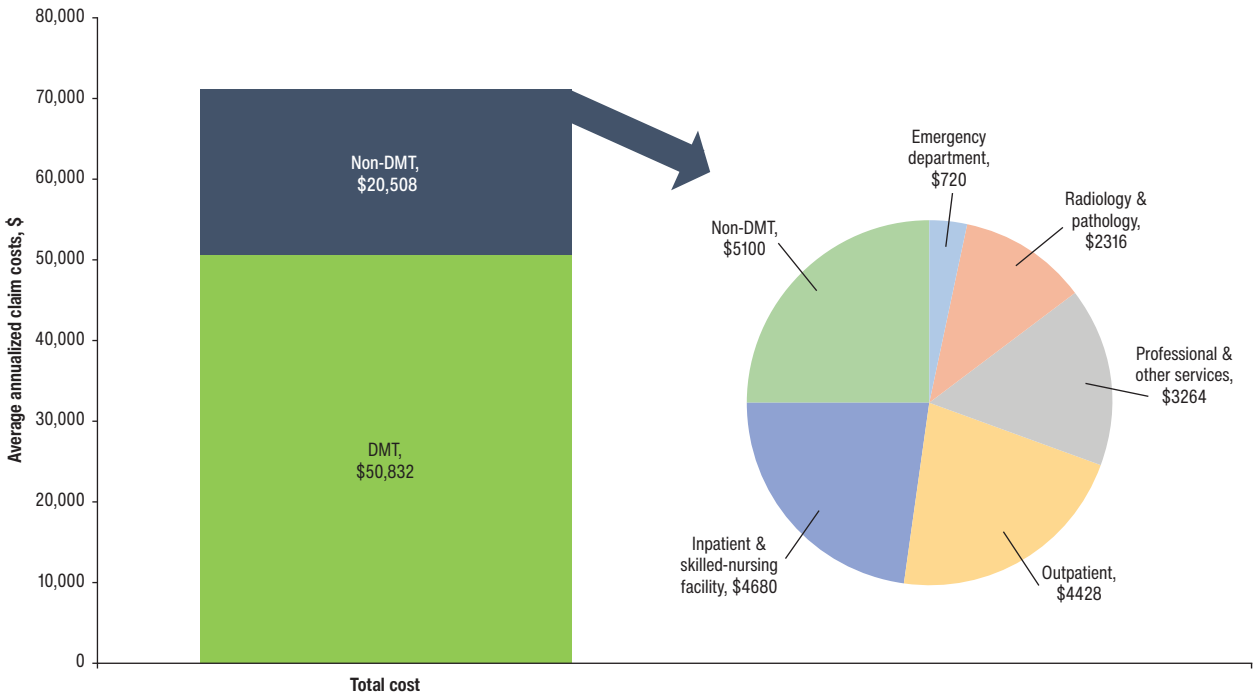
Figure 1 Estimated Annual Claim Costs for Patients with Multiple Sclerosis



NOTE: DMTs made up 71% of the average allowed cost across the insured multiple sclerosis population, whereas the remaining 29% was attributed to inpatient and outpatient care, emergency department visits, durable medical equipment supplies, non-DMT prescription drugs, and other services, including radiology and pathology. DMT indicates disease-modifying therapy.

Source: Milliman. Multiple sclerosis: new perspectives on the patient journey–2019 update. February 2019. www.milliman.com/-/media/milliman/importedfiles/uploadedfiles/insight/2019/ms-patient-journey-2019.ashx. Accessed August 1, 2021.

McDonald criteria, which were published in 2017 by the International Panel on the Diagnosis of Multiple Sclerosis, include specific guidelines to diagnose MS.[10] The McDonald diagnostic criteria apply to individuals who have a typical clinically isolated syndrome, which is defined as a first episode of neurologic symptoms that are typical of an MS relapse in a person who is not known to have MS.[10]

A key principle for diagnosing MS with the revised McDonald criteria is to uncover evidence that demonstrates the presence of lesions in the central nervous system (ie, in the brain and spinal cord) showing "dissemination in space" and "dissemination in time."[10] After providers determine that a patient is meeting the McDonald diagnostic criteria, they must also exclude alternative diagnoses with similar presentation, including other inflammatory diseases, demyelinating or degenerative diseases, infections, neoplasms, migraines, genetic diseases, nutritional deficiencies, and psychiatric diseases.[11]

Notwithstanding the McDonald diagnostic criteria, recent studies indicate significant rates of false-positive diagnoses of MS.[12,13] Kaisey and colleagues reviewed the diagnosis of MS in 241 patients at 2 clinics, and their results showed that 17% and 19% of the patients at each of the clinics were misdiagnosed.[12] The correct diagnoses included migraines (16%) followed by radiologically isolated syndrome (9%), spondylopathy (7%), and neuropathy (7%). The misdiagnosed patients received approximately 110 patient-years of unnecessary DMTs for MS.[12]

In another study, Solomon and colleagues reviewed 110 patients who had been diagnosed with MS from 1 of 4 clinics; according to the study's definition of MS, 46% of these patients had been definitely misdiagnosed, and 54% were probably misdiagnosed with MS.[13] The inappropriate interpretation of symptoms as disease relapses, a lack of objective demonstration that previous symptoms were demyelinating events, and the misinterpretation of MRI results were all identified as contributors to the misdiagnosis of MS.[13]

Solomon and colleagues found that the 4 most common correct diagnoses among the 110 patients diagnosed with MS included migraine, alone or in combination with other diagnoses; fibromyalgia, nonspecific or nonlocalizing neurologic symptoms with abnormal MRI; and conversion or psychogenic disorders.[13] Approximately

33% of the study patients had misdiagnosis durations of more than 10 years, and missed opportunities to make a correct diagnosis were identified in more than 70% of the patients. Furthermore, 70% of the patients received ≥1 DMTs, which might have resulted in adverse events and wasted healthcare expenditures.[13]

The study by Solomon and colleagues also showed that MRI interpretation errors contributed to the misdiagnosis of MS in 60% of the patients.[13] They concluded that "overreliance on the interpretation of MRI abnormalities in patients with atypical syndromes and unverified prior symptoms may be a significant cause of misdiagnosis."[13] If we assume that 50% of misdiagnosed patients are prescribed DMT, a median annual DMT cost of $90,000, and that 800,000 patients are diagnosed with MS in the United States, then a 1% misdiagnosis rate would translate to $360 million in annual spending wasted on DMTs.

Disease-Modifying Therapy

DMTs can reduce the activity and progression of MS. In 2021, more than 20 FDA-approved DMTs were available in the United States, spanning 3 routes of administration, with more than 10 different mechanisms of action (**Table**).[14] DMTs are also expensive; in 2020, the median annual cost for MS DMTs was more than $90,000.[15]

Neurologists consider a myriad of factors when selecting DMT for patients with MS, including the medication's efficacy and safety profiles, the patient's disease course, disease relapse rate and severity, patient preferences, pregnancy risk, comorbidities, monitoring burden, cost, and availability.[16,17] A neurologist at the Cleveland Clinic Mellen Center for Multiple Sclerosis summarized this challenge, stating, "As neurologists, we're faced with having to pick between 18 medications....Many times we're picking somewhat haphazardly what medications people will be starting."[18]

Poor adherence to DMT may have dire consequences. A study by Burks and colleagues of more than 12,000 patients with MS showed that patients who were adherent to their DMTs were 42% less likely to have disease relapse than nonadherent patients.[19] Out-of-pocket (OOP) costs can affect patient adherence.[20] Medicare and many commercial benefit designs expose patients with MS to payment shock when deductibles and total OOP spending amounts reset at the beginning of the plan year. In addition to OOP costs, depression, fear of needles, significant side effects, and the desire to take drug holidays during periods of remission can all negatively affect patients' adherence to therapy.[20] Poor adherence may also make an otherwise effective DMT seem ineffective, resulting in an unnecessary change of therapy.

Neurologists must consider patient preferences (eg, OOP costs, patient biology, and disease progression) when selecting DMTs, as well as navigate formulary, prior authorization, and step-therapy frameworks. Prior authorization processes often involve multiple back and forth communications between prescribers and insurers, which can sometimes require what prescribers view as irrational steps. For example, in the past, patients might have been required to step through ≥2 interferon-based DMTs before insurers agreed to pay for another class of DMT, even though the first interferon chosen was ineffective.[21] Highlighting a need for payers and providers to further cooperate, the results of a 2018 survey of 507 patients with MS showed that the average delay from the time of prescribing until the patient received the prescribed therapy exceeded 8 weeks.[22]

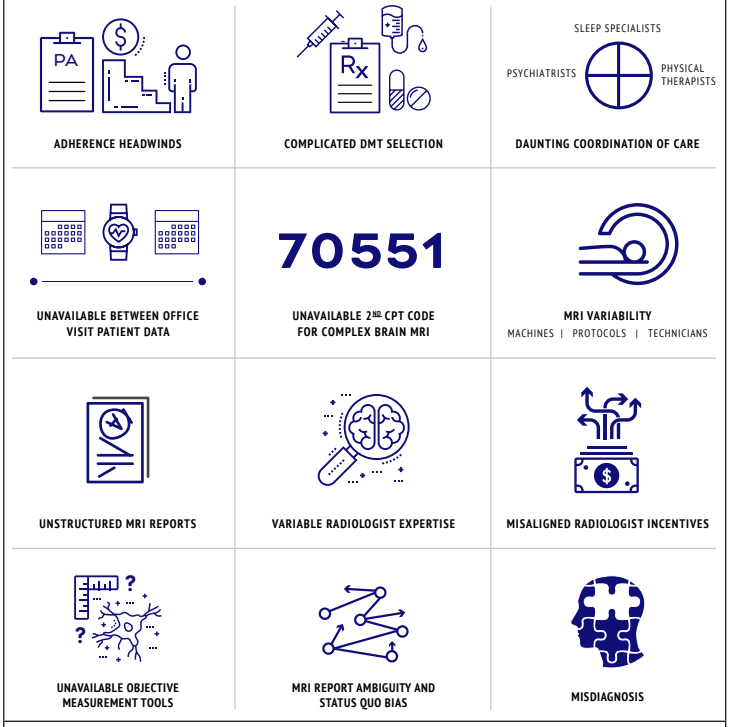
Effective neurologists must coordinate care with several specialty providers for the treatment of the comorbidities of MS, including sleep disorders, gait difficulties, and depression. A study by Sahraian and colleagues showed that 50% of patients with MS had poor sleep quality.[23] Because sleep disorders may trigger relapses in patients with MS, they must be properly managed.[23] In addition to good sleep quality, physical therapy delivers

Table FDA-Approved Disease-Modifying Therapies

Generic drug name	Brand names
Route of administration: Self-injectable (subcutaneous, intramuscular)	
Interferon beta-1a	Avonex, Rebif
Interferon beta-1b	Betaseron, Extavia
Pegylated interferon beta-1a	Plegridy
Glatiramer acetate	Copaxone
Ofatumumab	Kesimpta
Route of administration: Oral	
Teriflunomide	Aubagio
Monomethyl fumarate	Bafiertam
Dimethyl fumarate	Tecfidera
Diroximel fumarate	Vumerity
Fingolimod	Gilenya
Cladribine	Mavenclad
Siponimod	Mayzent
Ponesimod	Ponvory
Ozanimod	Zeposia
Route of administration: Intravenous infusion	
Alemtuzumab	Lemtrada
Mitoxantrone	Novantrone
Ocrelizumab	Ocrevus
Natalizumab	Tysabri

NOTE: Currently, neurologists can choose from more than 20 disease-modifying therapies, with 3 routes of administration.

Figure 2 Systemic Challenges to Cost-Effective MS Care: Clinical, Financial, and Technical



NOTE: The challenges to cost-effective care for patients with MS encompass a patchwork of clinical, financial, and technical elements.

CPT indicates Current Procedural Terminology; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; MS, multiple sclerosis.

favorable outcomes for a variety of motor and nonmotor symptoms in patients with MS, regardless of disability levels.[24] Depression affects 50% of patients with MS, which is 2 to 3 times more prevalent than with patients in the general population, and is associated with increased mortality and decreased quality of life.[25] Neurologists' coordination with these various subspecialists is sometimes made more difficult by the use of disparate practice management technologies across providers with suboptimal interoperability (**Figure 2**).

Simply asking patients about the day-over-day details of symptoms, mood, and physical impairments that occur between office visits (ie, between-visits data) subjects the information to time bias and forgetfulness.[26] Consequently, neurologists need alternative mechanisms to acquire accurate, detailed between-visits data in preparation for their upcoming patient encounters. One mechanism for effectively gathering data between office visits is telephonic or videophonic outreaches by clinicians, during which issues such as mood, fatigue, and DMT tolerance may be discussed, and advice may be provided to the patient; subsequently, insights from these outreaches may be shared with neurologists.

Read-only wearable technology has the potential to complement between-visit clinician outreaches to patients. In a study by Shema-Shiratzky and colleagues on the use of wearable technology in patients with MS, between-visits data were collected and showed marked changes in multiple domains of community ambulation gait quality, physical activity, and step counts.[27] The study's results show the importance of evaluating issues such as walking characteristics in the clinic, as well as in the real world. The measurements obtained from a wearable device worn for multiple days also provide insights about which clinical tests are truly useful to managing patients with MS.[27]

Supratak and colleagues demonstrated the validity of using accelerometers to track gait remotely in patients with MS.[28] However, deploying wearable devices with accelerometers at scale to track patient motion is challenging. For example, software residing on wearable devices that transmit clinical motion data from the patient may be categorized by the FDA as "mobile medical apps," requiring software manufacturers to embark on potentially time-consuming FDA approval processes.[29] One illustrative example of a mobile medical app listed by the FDA is "use [of] a sensor attached to the mobile platform or tools within the mobile platform itself (e.g., accelerometer) to measure the degree of tremor caused by certain diseases."[29]

MRI Challenges in MS

MRI has become the most important tool for the diagnosis and monitoring of MS.[30] An MRI report is particularly important, because the presence of new lesion activity on MRI is an important marker for the clinical setting, which can be interpreted as a suboptimal clinical response to current therapy.[30] Consequently, an inaccurate or incomplete MRI report can have devastating consequences for the patient. With such responsibility allocated to MRI, one may think there were accordingly strict standards and quality controls that made MRI a commodity service, much like a lipid panel. MRI, however, is far from a commodity service. MRI-produced images may be susceptible to variations in quality that can stem from the competency of the technician overseeing the MRI, the quality and the maintenance of the MRI machine, and/or the specific MRI protocol (ie, the series of imaging sequences) used to create the set of images that will be read by a radiologist.[31]

In addition, the interpretation of the MRI-produced images is subject to a "radiologist effect," which reflects the radiologist's specialty, experience, current reimbursement methodologies, use of structured versus unstructured reporting, and human error, that can affect the accuracy or completeness of the MRI's interpretation.

Wang and colleagues compared neuroradiologists with nonneuroradiologists in the use of brain MRIs to detect new MS plaques.[32] Neuroradiologists performed better than nonneuroradiologists in terms of higher sensitivity, higher negative predictive value, and lower false-negative rates in the detection of new MS.[32]

Herzog and colleagues investigated whether "commodity" fits the MRI paradigm, by conducting a study in which a patient with a history of low back pain and right L5 radicular symptoms had 10 lumbar spine MRIs performed at 10 different MRI imaging centers over a 3-week period.[31] Across the 10 MRI reports, 49 distinct findings were reported "related to the presence of a distinct pathology at a specific motion segment." None of the specific 49 findings was reported in all 10 reports, and only 1 of the 49 findings was present in 9 of the 10 reports. Because of such inconsistencies, Herzog and colleagues concluded that the specific imaging center where the patient's MRI scan is performed, and consequently which radiologist interprets the images and composes the interpretive report, will affect the quality of the information provided to the ordering physician, because of the significant difference in the standards used by radiologists when deciding what to include in diagnostic reports, and at worst, a significant prevalence of interpretive errors.[31] Inevitably, such variability will influence patient treatment plans, because brain MRI reports are significant inputs to neurologists' decision-making.[31]

The risks associated with MRI go beyond the realm of radiologist expertise, imaging center personnel training, machine quality, and selected protocols. These risks are also affected by misaligned financial incentives that are pitting required radiologist time against insurance reimbursement. On the spectrum of required effort, interpreting brain MRIs of patients with MS can be lengthy and/or time-consuming compared with those for patients with other conditions, such as stroke or trauma, particularly if the patient with MS has multiple lesions indicating severe disease, because it is important to track lesion changes accurately over time.

An accurate brain MRI interpretation involves the assessment of lesion size, shape, orientation, distribution, location, and signal characteristics on various MRI sequences (eg, unenhanced T1-, T2-, or T2-weighted fluid-attenuated inversion recovery imaging and gadolinium-enhanced T1-weighted images).[33]

One may presume that brain MRIs that require higher levels of effort, such as those for patients with MS, would receive reimbursements commensurate with the additional time expended. Precedents exist for such a reimbursement scheme; for example, a physician office visit for established patients has 5 billable Current Procedural Terminology (CPT) codes (99211-99215) that map increases in expended physician time to increases in reimbursements. However, a brain MRI without contrast has only 1 CPT code (70551).

Without an array of CPT codes for brain MRIs that recognize varied levels of effort, there is not a structural reimbursement mechanism for radiologists to be compensated at higher levels when longer interpretation times are required. The economics of CPT coding motivate radiologists to limit the time they spend interpreting more complex brain MRI scans, such as those of patients with MS.

Misaligned financial incentives are often countervailed by market forces; physicians have an economic need to establish and maintain positive reputations with their patients. When physicians do not deliver quality services to their patients, patients can shift their business elsewhere and, perhaps even more significant, publicize their feelings of dissatisfaction through social media.

The impact of these countervailing market forces on radiologists, however, is weak. Patients typically do not select their radiologists, interact directly with them, or even know their names. Because radiologists have limited contact with patients, radiologists are physically invisible to them, and their role as physicians also remains hidden or invisible to most patients.[34] Consequently, invisible radiologists are relatively immune from negative reputation effects that are driven by patient dissatisfaction and, therefore, may be susceptible to favoring productivity over quality, all things being equal.

The form of a brain MRI report may also affect the quality of care delivered to patients with MS. Some brain MRI reports are delivered to neurologists as unstructured—a collection of sentences requiring a "hunt and peck" review. Other brain MRI reports are structured, containing named sections and familiar, consistent information layouts. Structured reports have 2 hypothetical advantages over unstructured reports. First, structured reports may force radiologists to deliver reports with higher completion rates of important content, including clinical and radiologic data, MRI machine technical parameters, and scan protocols.[35] Second, information in structured reports may be more easily interpreted by the neurologist, reducing the likelihood that key findings are overlooked.[35]

Allesandrino and colleagues tested these hypotheses by studying the differences in content and effectiveness between structured and unstructured brain MRI reports.[35] Their conclusions are an indictment of unstructured reports. Lesion load, the total number of lesions, the number of increased dimensions of new lesions, the presence of cerebral atrophy, the presence of black holes, the presence of lesions suggesting other conditions, the

lesions in critical infratentorial areas, and the presence of pseudotumoral lesions were all more likely to be present in a structured report than in a nonstructured report (P <.0001). Once they read the reports, neurologists could understand lesion load more often when examining structured reports versus unstructured reports (P <.001).[35]

The impact of unstructured reports on neurologists' decision-making may be exacerbated by status quo bias, which is part of the field of behavioral economics pioneered by Nobel laureate Daniel Kahneman.[36] In the context of MS, status quo bias suggests that neurologists are more likely to stay the course regarding DMT decisions when faced with uncertain or unclear MRI reports, even if the reports suggest otherwise.

Implicitly testing status quo bias in an MS setting, Saposnik and colleagues measured neurologists' aversion to risk, ambiguity, and uncertainty.[37] Defining therapeutic inertia in MS as "the lack of treatment escalation when there is clinical-radiological evidence of disease activity," Saposnik and colleagues showed that nearly 70% of the participating neurologists had therapeutic inertia when they faced a need for escalating therapy based on clinical (eg, new relapse) and MRI activity (eg, new T2 and a gadolinium-enhancing T1 lesion) while patients were receiving a DMT.[37] Based on the initial psychographic interviews of the participating neurologists, aversion to ambiguity was the strongest predictor of therapeutic inertia. An unstructured brain MRI report is more ambiguous than a structured report. Consequently, unstructured reports may drive higher rates of therapeutic inertia in DMT assessment, to the detriment of patients with MS.[37]

Neurologists' reliance on the end-to-end process for brain MRI for the diagnosis and measurement of disease progression and DMT efficacy is fraught with peril. The reliability and usefulness of MRI are undermined by the variability and lack of standards in imaging center technology and processes, variability in radiologists' expertise, misaligned financial incentives, lack of standard and structured reporting requirements, and the impact of status quo bias on neurologists driven by ambiguous or incomplete MRI reports.

Figure 3 outlines the current challenges and potential solutions for treating patients with MS.

Value- or Outcomes-Based Payment Models

Today, most doctors, including neurologists, are working under fee-for-service payment models that do not directly reward them for cost-effectiveness, outcomes, or the speed at which they help patients arrive at effective treatment plans. Related, quality measures for MS are relatively nascent. Consequently, it is challenging to compare quality across neurologists and accordingly reward outstanding work.

The American Academy of Neurology has developed a quality measurement set for MS that includes 6 measures aimed at improving the delivery of care and outcomes for patients with MS, including MRI and DMT monitoring; bladder, bowel, and sexual dysfunction screening; cognitive impairment screening; fatigue screening; and appropriate physical activity counseling.[38] However, these are process measures, not outcomes-focused measures.

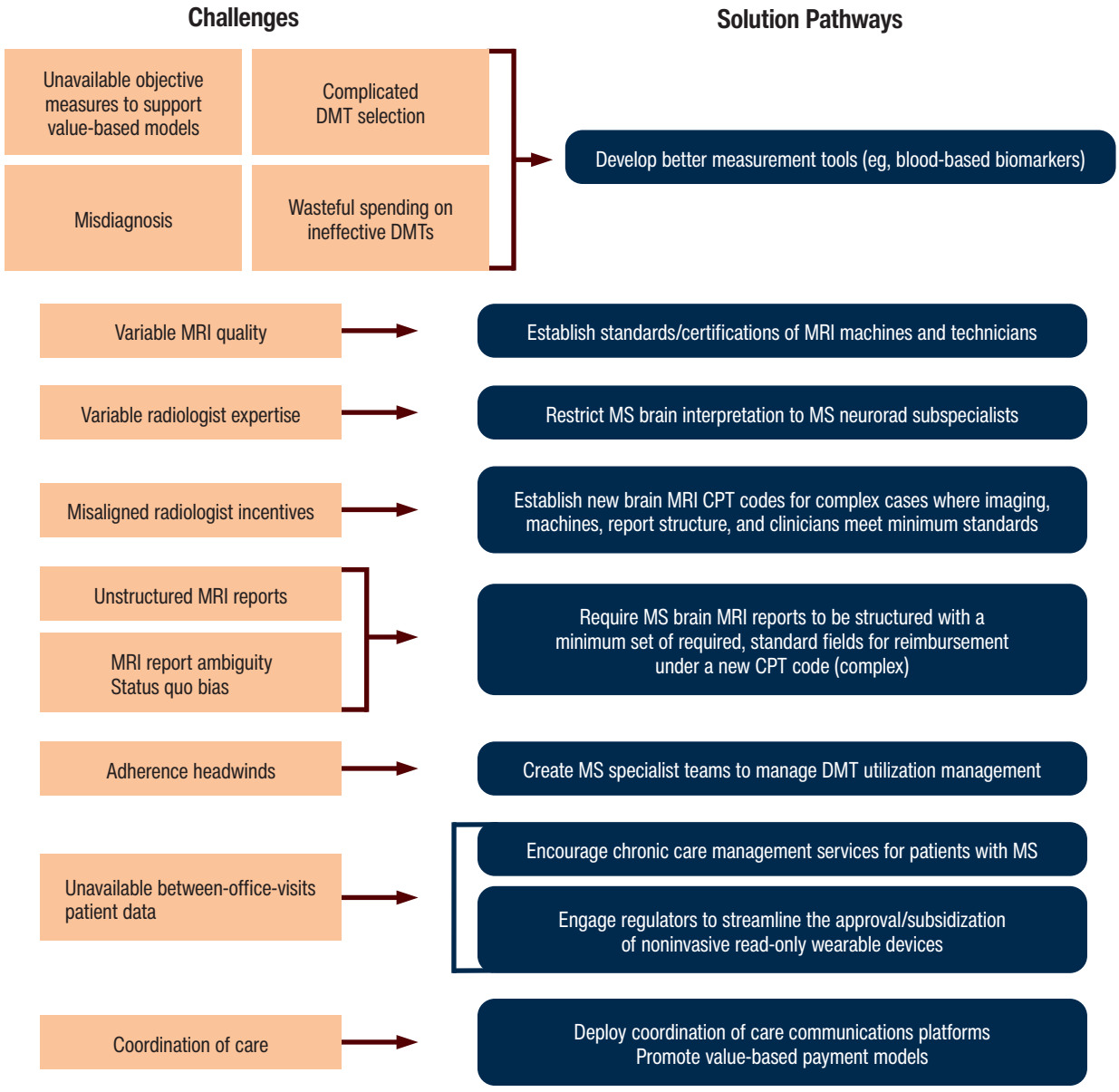
A potential measure of therapeutic efficacy that may be used in randomized clinical trials is the concept of no evidence of disease activity (NEDA). NEDA includes measures of clinical relapses, disability progression, MRI activity, and brain volume loss.[39] Although NEDA has been widely used in randomized clinical trials, the long-term implications of NEDA remain largely unknown, and its use has not shifted over to clinical practice.[39] Research in rheumatoid arthritis may foreshadow the development of standardized, objective quality measures for MS.[40,41] In recent years, a clinically valid blood-based multibiomarker test for disease activity in rheumatoid arthritis was introduced to the market.[40,41]

Although there is not a similar blood-based biomarker test to measure MS disease activity as of this writing, research in this area is ongoing.[42] Several biomarkers, including neurofilament light chain, osteopontin, and C-X-C motif chemokine ligand 13, are being investigated, as well as other biomarkers in combination, to survey the complex, heterogeneous nature of MS and the diverse pathways involved.[43] The deployment of blood-based biomarker tests for the measurement of MS disease activity would be a much-needed supplement to brain MRI reports, support the development of standardized quality and outcome measures for MS, and help transition neurologists to value-based care payment models in which they take on financial risk for patient outcomes.

Given the high cost of DMTs, bringing pharmaceutical manufacturers into a value- or outcomes-based framework is another important element of a new, holistic approach to managing patients with MS cost-effectively, but the unavailability of an objective measure of DMT success is an impediment.

Gray and Kenney surveyed representatives of pharmaceutical companies, payers, and industry consultants to understand the barriers to adopting an outcomes-based contracting paradigm for DMTs for MS.[44] Under this paradigm, drug manufacturers would compensate payers in some fashion for purchased DMTs that did not deliver the required outcomes.[44] Not surprisingly, there was skepticism among the study participants related to the value of the MRI data in outcomes-based contracts; however, the respondents were receptive to the use of

Figure 3 Challenges and Solution Roadmap for Managing Patients with Multiple Sclerosis



NOTE: Stakeholders must collaborate to develop a holistic solution. These elements may provide a good starting point for discussion and resolution.
CPT indicates Current Procedural Terminology; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; MS, multiple sclerosis.

blood-based clinical biomarkers that were measurable, clearly defined, objective, and realizable in a relatively short period of time to measure MS disease activity as an outcomes-based contract end point. Subject to the patients' adherence to therapy, the reaction to the use of such biomarkers was viewed more favorably and more objectively than the use of MRI, physician observation, or patient-reported symptoms.[44]

Conclusion

Successful, cost-effective management of MS is a complicated endeavor requiring coordination of care among providers, insurers, and patients. It is further affected by patient barriers to best therapies, poor medication adherence, variability in MRI interpretation and provider MS expertise, lack of standards for MRI machines and reports, misaligned financial incentives, lim-

ited number of available CPT codes for brain MRI, complexity of DMT selection and prior authorization processes, scarcity of objective disease measurement tools, lack of widely adopted MS-specific quality and outcomes measures, and providers' access to between-visits patient clinical data outside of office visits. The MS care paradigm requires a comprehensive analysis and a new approach. Neurologists, insurers, researchers, and patient advocacy groups must lead this effort.

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