

## POINT OF VIEW

# Improving quality, affordability, and equity of multiple sclerosis care

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## Abstract

**Objective:** The prevailing approaches to selecting multiple sclerosis (MS) disease modifying therapies (DMTs) have contributed to exponential increases in societal expenditures and out-of-pocket expenses, without compelling evidence of improved outcomes. Guidance is lacking regarding when and in whom the benefits of preventing MS-related disability likely outweighs the risks of highly effective DMTs (HET) and when it is appropriate to consider DMT costs. Our objective was to develop a standardized approach to improve the quality, affordability and equity of MS care. **Methods:** MS experts partnered with health plan pharmacists to develop an ethical, risk-stratified, cost-sensitive treatment algorithm. We developed a risk-stratification schema to classify patients with relapsing forms of MS as high, intermediate or low risk of disability based on the best available evidence and, when the evidence was poor or lacking, by consensus. DMTs are grouped as highly, modestly or low/uncertain effectiveness and preferentially ranked within groups by safety based on pre-specified criteria. We reviewed FDA documents and the published literature. When efficacy and safety are equivalent, the lower cost DMT is preferred. **Results:** Assignment to the high-risk group prompts treatment with preferred HETs early in the disease course. For persons in the intermediate- or low-risk groups with cost or health care access barriers, we incorporated induction therapy with an affordable B-cell depleting agent. Based on more favorable safety profiles, our preferred approach prioritizes use of rituximab and natalizumab among HETs and interferon-betas or glatiramer acetate among modestly effective agents. **Interpretation:** The risk-stratified treatment approach we recommend provides clear, measurable guidance in whom and when to prescribe HETs, when to prioritize lower cost DMTs and how to accommodate persons with MS with cost or other barriers to DMT use. It can be adapted to other cost structures and updated quickly as new information emerges. We recommend that physician groups partner with health insurance plans to adapt our approach to their settings, particularly in the United States. Future studies are needed to resolve the considerable uncertainty about how much variability in prognosis specific risk factors explain.

## Introduction

The prevailing approach to MS treatment in the US over the past 2 decades has led to an exponential increase in

societal MS treatment expenditures and a sevenfold increase in patient out-of-pocket expenses, without convincing evidence of improved outcomes.<sup>1</sup> We believe a key problem underlying the failure of the current

approach is a lack of standardized care. This creates difficulties for well-intentioned general neurologists to know which disease-modifying treatment (DMT) to give to which person with MS (pwMS) and when; proliferates prescribing of ineffective or low-value DMTs<sup>2</sup>; increases inequities by forcing some pwMS who would benefit from DMTs to go un- or under-treated; and makes measuring quality, let alone improving it, extraordinarily challenging.

Medicare spent an estimated 4.4 billion on interferon-betas, glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod in 2016 alone.<sup>3</sup> This sticker shock has received a lot of attention, but what is even more troubling is that the majority of Medicare recipients are 65 years of age or older. At these ages, several observational studies have found no benefit of treatment with these DMTs,<sup>4–6</sup> and randomized controlled trial (RCT) data to suggest otherwise do not exist.<sup>7</sup> For pwMS under 65, Medicare coverage is only granted to disabled persons, presumably from progressive MS, a form of MS in which most DMTs have failed to demonstrate efficacy.<sup>8,9</sup>

Recognizing that the prevailing US approach was ineffective, unaffordable, and inequitable, we set out to create a new, standardized model of care aimed at improving all three of these metrics in 2012. The cornerstone of our approach is the development of a risk-stratified, cost-sensitive, relapsing MS treatment algorithm that adheres to principles of ethical step therapy.<sup>10</sup> It was designed with extensive input from stakeholders to allow for rapid implementation. It has been successfully implemented in Kaiser Permanente Southern California (KPSC),<sup>11</sup> spread to other KP regions, and has led to substantial reductions in annual relapse rates and DMT expenditures.<sup>11</sup>

## Objective

Our process included several steps. First, we defined the problems to be solved by collecting data on patient outcomes, DMT utilization, and expenditures within our practice. Next, clinical experts partnered with pharmacists employed by the Health Plan to perform literature reviews and summarize evidence regarding risk factors for MS-related disability and the effectiveness and safety of treatments. We then developed an algorithm to guide treatment according to risk. We created a systematic framework that facilitated rapid incorporation of new evidence by pre-specifying the following: evidence-based criteria for classifying DMTs as highly effective (HET), modestly effective (meDMT), or of low/uncertain effectiveness (loDMT); criteria for establishing a preferred treatment hierarchy within each class based on safety profiles; and when to consider differences in DMT costs. Based on the results of these steps, we created a

recommended formulary that can be adapted to other settings. Herein, we provide more detailed information about each of these steps, describe the components of the algorithm, the recommended formulary, and the metrics we use to measure implementation.

## Defining the Problem

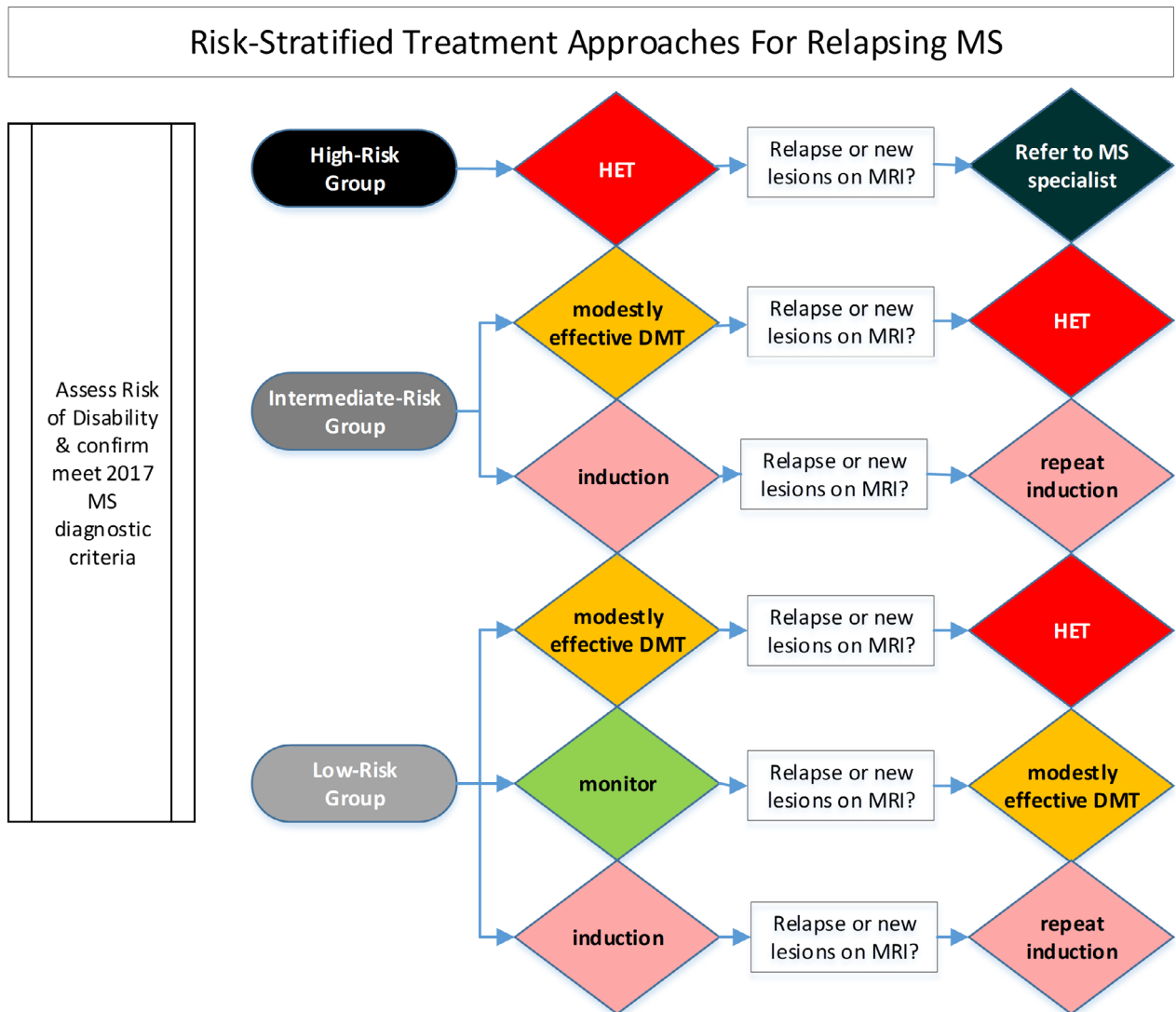
The main gap in the quality of care we identified by examining our data was under-utilization of the HETs, natalizumab, or rituximab, even in RRMS patients with continued disease activity on beta-interferons or glatiramer acetate.<sup>12</sup> In 2009, only 4.9% of DMTs prescribed in KPSC was HETs. Despite early initiation of meDMTs in 87% of our newly diagnosed pwMS, disability outcomes over a mean follow-up time of 3.5 years<sup>12</sup> were no different compared to historical untreated controls.<sup>13</sup> Of the 41.3% with moderate or worse MS-related disability (expanded disability status scale  $\geq 3.0$ ) in our cohort, only 12% of these pwMS were escalated to a HET and only 5.6% prior to the onset of disability.<sup>12</sup> After discussions with KPSC's > 200 neurologists, the main barriers identified were concerns about the rare but serious risks of natalizumab or rituximab treatment and lack of awareness of which factors are associated with poor prognosis in relapsing MS.

## Overarching Treatment Approach

Based on these gap analyses and feedback, we initially chose a risk-stratified approach, as opposed to conventional step or induction therapy, to help clinicians judge in whom and when the risk of MS-related disability outweighed the potential risks of HETs (Fig. 1). As we and others became more familiar with the risks and how to minimize them for rituximab and natalizumab, we loosened the criteria for recommending HET as a first-line treatment and added the option of induction therapy with a B-cell depleting DMT for those in the intermediate or low-risk strata in early 2019.

## Risk Stratification Schema

A validated and accurate prognostic tool for relapsing MS does not exist. Thus, our risk-stratification schema classifies persons with relapsing forms of MS as high-, intermediate-, or low-risk of disability based on the best available evidence or, when the evidence was poor or lacking, by consensus. A comprehensive, systematic review of clinical and demographic predictors of long-term disability in RRMS<sup>14</sup> served as the starting point for the risk-stratification schema. Updated PubMed literature searches and inclusion of commonly encountered MRI characteristics

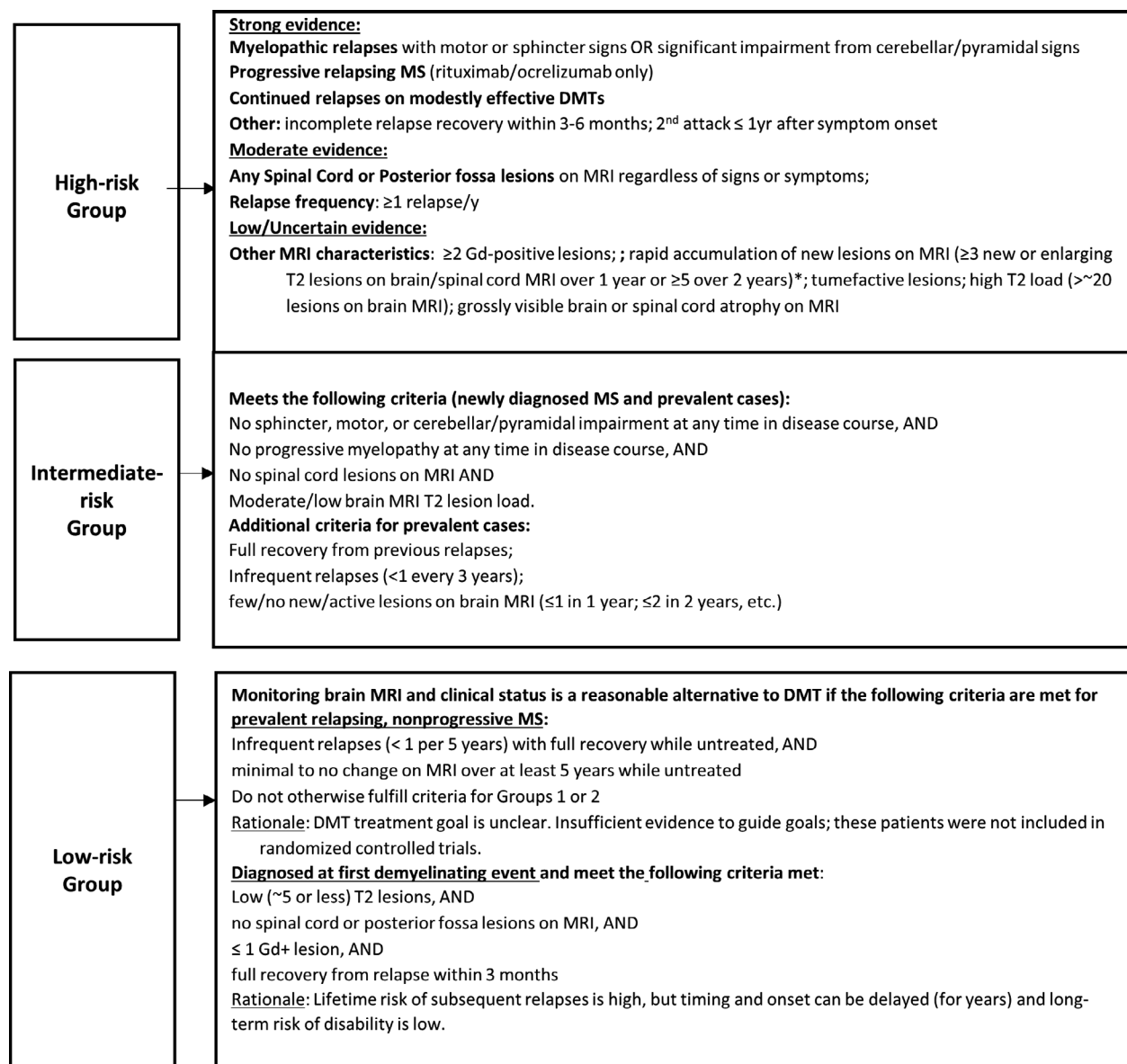


**Figure 1. Recommended risk-stratified treatment approach for relapsing forms of MS.** Depicted is Kaiser Permanente Southern California’s risk-stratified treatment approach. For patients with relapsing forms of MS in the high-risk group, we recommend starting a highly effective disease modifying treatment (HET) as the first line treatment. For the intermediate-risk group, we consider starting a modestly effective disease modifying treatment (meDMT) or induction with rituximab to be in equipoise. For the low-risk group, we consider watchful waiting (green box, monitor), a brief induction with rituximab (1–2 doses) or starting a meDMT to be in equipoise. In all scenarios, we recommend proactive monitoring for relapses and new MRI lesions and escalating treatment without delay if breakthrough disease activity is detected on modestly effective DMTs or new disease activity is detected following induction or during watchful waiting. For patients who have a relapse or new MRI lesions while on a HET, we recommend referral to an MS specialist to weight the severity of these events with the risks of the remaining available HETs before deciding to switch HET or increase dose/dosing interval of the existing HET.

in community-based practice settings (e.g. tumefactive lesions, multiple contrast-enhancing lesions, CEL) were conducted. We also reviewed Food and Drug Administration (FDA) documents to assess whether treatment effectiveness varied by clinical or imaging characteristics to aid in risk-group assignment. The results of this process are summarized in Figure 2.

To define the high-risk group, evidence was classified as strong (supported by high-quality studies, consistent

findings and/or large effect sizes), moderate (high-quality studies but mixed results, moderate quality studies or modest effect sizes), or low/uncertain (low-quality studies or case reports only; Fig. 2). The intermediate-risk group was defined by an absence of any high-risk features but with recent clinical or MRI disease activity, and the low-risk group was divided into two commonly encountered scenarios in which the benefits of DMT treatment are uncertain—pwMS with long-standing



**Figure 2. Relapsing multiple sclerosis risk stratification schema.** The classification schema has evolved since 2012 to be more lenient in assigning persons to the high-risk category and more stringent in assigning low-risk status by intention to avoid under-treating patients at risk of MS-related disability. To aide shared decision-making, we clearly label whether the evidence supporting high risk of long-term disability is strong, moderate or low/uncertain as some clinicians or patients may prefer starting a meDMT if high-risk assignment is based solely on factors with low quality evidence. In the low-risk group, we focused on two common clinical scenarios. First was patients with long-standing disease, currently untreated and clinically stable who wish to remain untreated where the treatment goals remain unclear. The rationale being that even small risks of long-term treatments with HETs outweigh their risk of disability, and for meDMTs, their relapses are so infrequent and MRI disease activity quiescent for such long periods of time that these patients were not and are not being included in RCTs. The second scenario was RRMS patients diagnosed at symptom onset (previously called clinically isolated syndrome) without any indicators of a poor prognosis. While the lifetime risk of having subsequent relapses is high, the timing can be delayed for years, and the long-term risk of disability is low. Thus, potentially sparing patients the side effects and expense of meDMT exposure for years.

quiescent clinical and subclinical disease while untreated and those with a first demyelinating event with features suggesting an MS over-diagnosis. We agreed a priori to

err on the side of overtreatment rather than undertreatment, when the evidence of a prognostic factor was low/uncertain. Thus, the algorithm knowingly assigns fewer

people to the low-risk group than natural history studies suggest.<sup>15,16</sup>

### **Classifying DMTs as Highly or Modestly Effective and Designating Preferred Within-Group DMTs**

Because DMT costs can shift rapidly, we first established an ethical process for classifying DMTs based on efficacy and safety profiles, the results of which are summarized in Table 1. To classify DMTs as HETs or meDMTs, we reviewed full FDA documents (appendix), which typically include unpublished subgroup analyses and published studies.<sup>8,9</sup> A DMT is classified as highly effective if it meets at least one of the following two criteria: (1) evidence of superiority to an active comparator in at least one head-to-head RCT; and/or (2) evidence of potency defined as demonstrating a large magnitude of effect in a RCT conducted in a population with highly active disease, or a positive RCT conducted in pwMS who relapsed on meDMTs. Demonstrating efficacy in primary progressive MS (PPMS) or inactive secondary progressive MS (SPMS) patients is also considered evidence of potency, but a negative SPMS or PPMS RCT did not disqualify a DMT as HET if other criteria were met (e.g., natalizumab, fingolimod). We considered only clinical outcomes (first, disability progression, then relapse rate). MRI outcomes were considered as evidence supporting the robustness of a clinical effect and weighed when there was a discrepancy between the effect on disability progression and relapse rate (e.g., intramuscular interferon-beta-1a, teriflunomide).<sup>9</sup> Lower dosed me-too DMTs that were tested only against placebo (peginterferon-beta-1a, glatiramer acetate 40 mg) or lack RCT evaluation (diroximel fumarate) are classified as being of low/uncertain effectiveness. The algorithm does not recommend a fail-first policy, should loDMTs be the lowest cost DMTs because they are potentially less effective than their higher and/or more frequently dosed forerunners. Thus, it would be unclear whether pwMS with breakthrough disease activity on loDMTs should be escalated to a meDMT or accept the risks of HETs.

When assigning preferred DMTs within each group (HET or meDMT), safety was the primary consideration. The DMTs with the least serious toxicities are the preferred agents within each group.

Safety profiles of new classes of drugs are often less favorable in real-world settings than in RCTs for multiple reasons. These reasons include the short duration of RCTs compared to real-world use and exclusion of participants with comorbidities that may increase their risk of drug-related adverse events. Thus, DMTs with long-term safety data demonstrating rare serious adverse events (SAEs), we

considered safer than those with only RCT data. SAEs were defined in accordance with the common terminology criteria for adverse events.<sup>17</sup> We considered safety outcomes in this order: drug-related fatalities, common SAEs, and rare SAEs. We also considered whether successful strategies to minimize risk were in place (e.g., liver function tests, John Cunningham Virus antibody testing). Among DMTs with rare SAEs, those with strategies that avoid almost all SAEs are considered safer than those that only partially decrease the risk of SAEs or those without effective prevention strategies. Secondary considerations included potential for synergistic toxicities should a pwMS switch to another DMT (sequential DMT use, Table 1) prior to complete drug elimination or elimination of effects (e.g. lymphopenia) and complexity of use from the prescribing physician's perspective. This encompasses frequency and complexity of minimizing risk strategies, drug-drug interactions, variable dosing based on genotype (e.g., siponimod), risk of teratogenicity (teriflunomide, fingolimod) or drug cessation relapses with a DMT pregnancy exposure.

### **Affordability: When to Consider DMT Costs**

We considered preferentially ranking one DMT over another based on cost only when efficacy and serious toxicity profiles appeared comparable. Thus, cost can influence within group preferences but not effectiveness group designations. Differences in tolerability are noted, but not considered in the preferential ranking of DMTs. Instead, should the preferred DMT be poorly tolerated, a low threshold for switching to another within-group DMT of similar safety is recommended.<sup>10</sup> The other scenario where we consider DMT costs are pwMS who cannot afford their co-pays. In these scenarios, we are increasingly moving towards rituximab biosimilars using varying dosing regimens depending upon the pwMS's risk profile.

### **Preferred Formulary Recommendations**

Figure 2 shows our preferred formulary recommendations and how to screen patients to choose an appropriate DMT. We recommend that the least expensive of the following injectable DMTs be the preferred meDMT: intramuscular interferon-beta-1a, subcutaneous interferon-beta-1a, interferon-beta-1b, and/or glatiramer acetate 20 mg daily. These DMTs are equivalent in efficacy and SAEs are exceedingly rare with proper laboratory monitoring.<sup>9</sup> If the costs of the lowest priced interferon-beta and daily glatiramer acetate products are comparable, then both products would be considered preferred

**Table 1.** Rationale for effectiveness group assignment and safety considerations for preferred DMTs within Groups.

DMT	Efficacy		Safety			Secondary considerations	
	Superiority in RCT	Potency	Summary of serious risks	Risk mitigation strategies	Long-term use	Sequential DMT toxicities	Complexity of use <sup>1</sup>
<b>Highly effective DMTs</b>							
Natalizumab	Yes	Yes	Common: drug-cessation relapses Rare: PML	Yes	Yes	PML	Moderate Rebound relapses during pregnancy common
Rituximab	Nd	Yes	Hypogammaglobulinemia Rare: serious infections, serum sickness	Yes	Yes	Transient B-cell depletion	Moderate
Ocrelizumab	Yes	Yes	Hypogammaglobulinemia Rare: serious infections, SIRS death, peri-infusion deaths, breast cancer, PML, serum sickness	Partial	No	Transient B-cell depletion	Moderate
Fingolimod	Yes	No	Common: drug-cessation relapses Rare: PRES, seizures, infections, macular edema, lymphoma	Partial	Yes	Transient lymphopenia	High Mild teratogen, rebound relapse during pregnancy
Siponimod	Nd	No	Same as FNG; potentially higher risk of drug cessation relapses due to short half-life and drug-drug interactions	Partial	No	Transient lymphopenia	High
Alemtuzumab	Yes	Yes	Common: auto immune thyroid disease (36.8%), infusion reactions, infections Rare: peri-infusion strokes, malignancies, glomerular nephropathies, autoimmune cytopenias; fatalities from ITP, MI, ICH, HLH, autoimmune hepatitis	Partial	No	Delayed serious toxicities, transient lymphopenia	High
Cladribine	Yes	No	Teratogenicity Common: severe lymphopenia Rare: serious infections, malignancy, pancytopenia	No	Yes	Lymphopenia, neutropenia	Moderate teratogenicity
Daclizumab	Yes	No	Drug-related fatalities, withdrawn	No	No	Na	Na
<b>Modestly effective DMTs</b>							
Glatiramer acetate daily	No	No	Exceedingly rare serious AE	No	Yes	No	Low
Interferon-beta-1b sq	No	No	Rare: serious hepatotoxicity, bone marrow suppression	Yes	Yes	No	Low
Interferon-beta-1a im	No	No	Rare: serious hepatotoxicity, bone marrow suppression	Yes	Yes	No	Low
Interferon-beta-1a sq	No	No	Rare: serious hepatotoxicity, bone marrow suppression	Yes	Yes	No	Low
Dimethyl fumarate	No	No	Rare: PML, gastrointestinal fistulas, hepatotoxicity	No	No	Transient or persistent lymphopenia	Low
Teriflunomide	No	No	Teratogenicity Common: leukopenia and thrombocytopenia Rare: serious infections, hepatotoxicity, peripheral neuropathy	Partial	Yes	Leukopenia and thrombocytopenia	Moderate Highly teratogenic

Abbreviations: AE, adverse event; DMT, disease modifying therapies; HLH, hemophagocytic lymphohistiocytosis; ICH, intracranial hemorrhage; ITP, idiopathic thrombocytopenic purpura; FNG, fingolimod; im, intramuscular; MI, myocardial infarction; na, no longer applicable; PML, progressive multifocal leukoencephalopathy; nd, not done; PRES, posterior reversible encephalopathy syndrome; RCT, randomized controlled trials; SIRS, systemic inflammatory response syndrome; sq, subcutaneous.

<sup>1</sup>Refers to complexity of use from the prescribing clinician's perspective

meDMTs. We do not recommend that dimethyl fumarate, teriflunomide, cladribine, or alemtuzumab be preferred DMTs within their groups even if these are the lowest cost agents because their safety profiles are inferior to other DMTs of similar efficacy. We do not recommend requiring pwMS to first fail fingolimod before allowing access to natalizumab or rituximab as many step therapy coverage programs do.<sup>8,9</sup>

### Rituximab

Including rituximab as a preferred agent was done at a time when other B-cell depleting treatments were not available. The evidence supported rituximab as highly effective,<sup>18,19</sup> but the uncertain safety profile with prolonged use led to cautious and incremental uptake. The clinical challenge we faced was pwMS at high-risk of disability who had already failed multiple meDMTs and finally stabilized on natalizumab but were at increased risk for progressive multifocal leukoencephalopathy. Initially, we switched these pwMS to fingolimod but many still had breakthrough relapses and were then switched to rituximab where disease control was re-established.<sup>20</sup> As our experience has grown, we have seen only rare treatable SAEs associated with rituximab,<sup>21</sup> no increased risk of breast cancer, and no drug-related deaths.<sup>20–23</sup> By the time of FDA approval of its me-too DMTs, ocrelizumab (2017) and ofatumumab (2020), rituximab use had become standard of care in our organization. Because there is no evidence that either me-too DMT is more effective or safer, and both are far more expensive than rituximab, these are non-preferred DMTs. In part, because the manufacturer of rituximab decided not to pursue FDA approval, many US health plans do not cover rituximab for MS.

### Rituximab or its biosimilars as induction treatment for intermediate- and low-risk strata

As we became more comfortable with the safety profile, risk mitigation strategies, and prolonged efficacy with intermittent rituximab infusions,<sup>24,25</sup> we decided to expand access to rituximab as induction treatment for pwMS in the intermediate- or low-risk groups. This was motivated in part because we have seen an increasing number of pwMS with high out-of-pocket expenses, health care access, or compliance challenges for whom induction therapy with rituximab, rituximab biosimilars, or other affordable B-cell depleting DMTs is the only realistic option. Even without these barriers, some pwMS prefer the convenience of this approach.<sup>26</sup> While RCT evidence supporting rituximab induction therapy is very

limited,<sup>19</sup> we reasoned that while the associated risks of every 6-month infusions likely out-weigh the benefits of B-cell depleting DMTs<sup>27</sup> in the intermediate- or low-risk groups, the risks of infrequent doses probably do not.<sup>19</sup> Rituximab, unlike natalizumab and fingolimod, is also not associated with severe drug-cessation relapses.<sup>24,25</sup> While the potential risks of treating upon return of disease activity remains unclear, for pwMS in the intermediate- and low-risk groups, it is probably low. The safety and efficacy of these treatment strategies are currently being evaluated.

### Measuring Algorithm Implementation

We chose an increase in proportion of pwMS on a HET compared to all DMT-treated pwMS as the main implementation metric of the algorithm because it directly assesses the main quality gap and is easily measured on a quarterly basis. We initially set a target that 60% of DMT-treated pwMS receive a HET based on natural history studies which have shown that over 60% with newly diagnosed relapsing pwMS will develop irreversible physical disability twenty years after symptom onset.<sup>15</sup> We increased the target to 70% in 2019 to account for rituximab use in active PPMS and SPMS patients.<sup>8,9</sup> We also measure the proportion of pwMS on preferred versus non-preferred DMTs quarterly, with a target of  $\geq 90\%$ . Improvement in these two metrics combined corresponded to substantial decreases in annual relapse rates and MS DMT expenditures.<sup>11</sup>

### Controversies and Uncertainties

Rituximab induction therapy is likely to be controversial as the evidence basis for this approach is based primarily on inference. In addition, specific aspects of the risk stratification schema may be controversial as much is based on relatively low-quality studies and/or consensus, particularly the MRI criteria. The significance of tumefactive lesions is uncertain with some case reports of catastrophic outcomes,<sup>28</sup> whereas others suggest no prognostic significance.<sup>29,30</sup> While there is a strong correlation between new T2 lesion formation or CEL and relapses, what number of CEL on a single MRI or new T2 lesions over time confers a worse prognosis remains unknown. To choose cut-points, we reviewed the placebo arm rates of the pivotal RCTs of the interferon-betas and glatiramer acetate, all of which included highly active pwMS.

Similarly, it remains unclear if spinal cord or infratentorial MRI lesions associated only with sensory symptoms or transient diplopia increase the risk of long-term disability, as these symptoms have no prognostic

significance.<sup>10</sup> While referral center-based imaging studies have shown an association between spinal cord or infratentorial lesions and a worse prognosis, these studies did not account for clinical signs or symptoms.<sup>31–36</sup> Further underscoring this uncertainty, we recently showed that 44% of elderly patients with benign/burnt-out MS had spinal cord lesions present on MRIs.<sup>6</sup>

We included high lesion load and presence of brain or spinal atrophy grossly visible on MRI as high-risk features, but these may represent bad outcomes rather than risk factors. These imaging characteristics are strongly correlated with SPMS in cross-sectional studies.<sup>36,37</sup> Detailed measures of brain volume loss and high T2 lesion load predicted disability 10 years later even in DMT-treated pwMS.<sup>38</sup> However, DMTs that slow brain volume loss did so only in those with little loss at baseline but not those with substantial brain volume loss at treatment initiation.<sup>39,40</sup> Thus, it is possible that pwMS with grossly visible brain or spinal cord atrophy are already transitioning to SPMS and DMTs may have marginal benefits, if any.

## Strengths of KPSC's Standardized Approach to MS Treatment

The opinion that a treatment algorithm should be followed that stratifies pwMS by risk of disease activity is becoming increasingly popular among MS specialists.<sup>41,42</sup> It is driven by the availability of HETs, DMTs with significant SAEs, and the simultaneous expansion of MS diagnostic criteria to include milder cases. While some authors have suggested risk-algorithms,<sup>41,42</sup> none have provided sufficient detail to cover the most commonly encountered challenges in clinical practice, none were available in 2012 and none that we are aware of have been systematically implemented.

Our risk-stratified treatment algorithm provides relevant clinical context in real-time, something that is difficult to capture when relying only on rigorously defined evidence ratings for effectiveness but not safety,<sup>43</sup> network meta-analyses, or quality-adjusted life years (QALY) analyses.<sup>8,9</sup> Our systematic framework for classifying DMTs by effectiveness and establishing within-group rankings allows for real-time updates of preferred DMT rankings as new drugs or evidence become available. For example, upon FDA approval of daclizumab and alemtuzumab, no external guidance existed for whom and when the risk of MS disability outweighed these DMTs' substantial risks of SAEs. According to our framework, we classified both DMTs as HETs, but strongly recommended to never use daclizumab as SAEs were substantially higher than natalizumab or rituximab without improved efficacy. Alemtuzumab did appear somewhat more effective than other

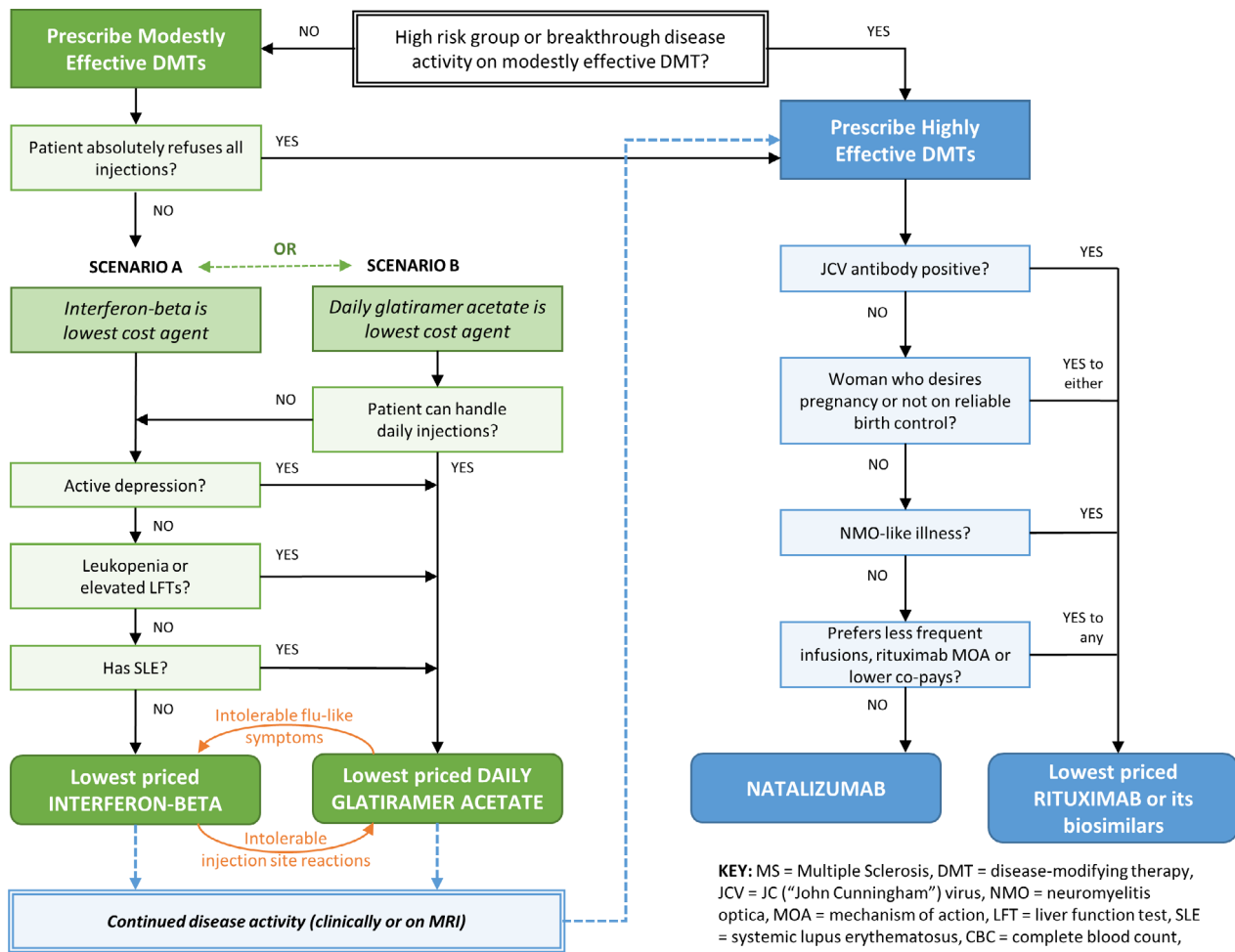
HETs, but with then 13%<sup>9</sup> and now ~50% SAEs,<sup>44</sup> we recommended use only in pwMS with active inflammation on at least two safer HETs (i.e., as a third- or fourth-line agent). Subsequently, daclizumab has been withdrawn from the market due to drug-related deaths, and alemtuzumab's already unfavorable safety profile has expanded to include multiple types of drug-related fatalities.<sup>44</sup>

By designing and implementing a standardized approach to MS treatment and defining metrics of success, we have taken necessary steps toward improving equity. High out-of-pocket healthcare expenses disproportionately affect Blacks and Hispanics in the United States,<sup>45</sup> which is likely to contribute to delays in initiating and maintaining pwMS of Color on DMTs. To what extent barriers to timely and appropriate MS care explain their apparently worse outcomes later in the disease course compared to US Whites<sup>46,47</sup> has not been studied. Our standardized care path considers affordability of health care coverage, out-of-pocket expenses, and barriers to use of certain DMTs, like jobs where pwMS lose pay when they need frequent infusions or psychosocial stressors at home, and work that make adding in daily pills or regular injections unrealistic. By incorporating risk-stratification, we aim to ensure access to a DMT that is most likely to control disease activity while simultaneously minimizing risks. By providing quarterly audit and feedback on these metrics, pwMS who may be on suboptimal DMTs can be assessed prior to the onset of permanent disability, and physicians can do their part to curb costs so that their patients' premiums do not rise, potentially leaving them unable to afford healthcare coverage entirely.

## Conclusion

Since the initial inception of our risk-stratified algorithm in 2012, there is growing real-world evidence that increasing utilization of HETs reduces the risk of long-term disability,<sup>48</sup> and that HETs continue to be underutilized even at academic MS Centers.<sup>49</sup> Existing insurance policies and current physician prescribing patterns contribute to this problem, as neither carefully consider pwMS's underlying risks of disability. Many health insurers set formularies based on opaque price negotiations, often requiring failing multiple agents of equivalent efficacy before approving access to a more effective treatment.<sup>8,9</sup> Physicians in turn, often prioritize convenience of treatments over efficacy or safety,<sup>48</sup> and many accept gifts or payment from drug manufacturers that clearly influence prescribing practices.<sup>50,51</sup> Certain countries restrict access to DMTs that do not meet standard thresholds for QALYs or other cost-effectiveness measures,<sup>52</sup> but QALYs





**Figure 3. Recommended MS Formulary.** Depicted are our recommendations for how to incorporate DMT prices into MS formularies. For persons in the high-risk group, natalizumab is the preferred DMT, despite high prices, among patients who test antibody negative for the John Cunningham virus (JCV) as long as women of childbearing potential are on reliable birth control and the other depicted conditions are met. If these conditions are not met, we recommend treatment with the lowest priced product among rituximab and its biosimilars. The oral HET, fingolimod (not depicted) or its generics, is reserved only for patients who absolutely refuse intravenous infusions, because of its inferior safety and efficacy profiles compared to rituximab and natalizumab. In patients where the risk stratification schema prompts initiating a meDMT, we recommend starting the lowest priced DMT among the multiple formulations of interferon-betas or daily glatiramer acetate products. In Scenario A, an interferon-beta product (with the exception of interferon-beta-1a every 2 weeks) is substantially lower in price than other interferon-betas and daily glatiramer acetate products and should be the first meDMT tried unless there are contraindications to interferon-beta products as depicted. Beta-interferons can worsen active depression and are associated, albeit rarely, with lupoid reactions. In Scenario B, a daily glatiramer acetate product is substantially lower in price than interferon-betas and should be the preferred meDMT, particularly in treatment naïve patients, unless the patient cannot handle daily injections in which case the lowest priced interferon-beta should be started. In both Scenario A and B, we recommend a low threshold for switching should the preferred agent be poorly tolerated. Should the lowest priced interferon-beta be similar in price to the lowest price glatiramer acetate, then both DMTs could be designated as preferred.

inadequately account for a pwMS’s underlying risk of disability, resulting in all-or-none coverage policies.

The risk-stratified treatment approach we recommend provides clear, measurable guidance in whom and when to prescribe HETs, when to prioritize lower cost DMTs and how to accommodate pwMS with cost or other barriers to DMT use. It can be adapted to other cost structures and updated quickly as new information emerges.

Our overall approach, to be somewhat liberal in assigning high-risk status prompting treatment with relatively safe HETs early in the disease course, will likely lead to better long-term outcomes. FDA analyses have already shown that MS DMTs appear less effective in older relapsing pwMS or those with higher levels of disability at treatment initiation,<sup>2,4,5,8,9</sup> underscoring the importance of treating high-risk pwMS early, before disability

accumulation. Future studies are needed to resolve the considerable uncertainty about how much variability in prognosis specific risk factors explain, particularly MRI characteristics available in real-world practice settings.

We recommend that physician groups partner with health insurance plans to adapt our approach to their settings, particularly in the United States. Meaningful, measurable targets should be agreed upon including HET use, patient outcomes, and DMT expenditures. Prescribing physicians should strive to adhere to the mutually agreed upon preferred formularies, and health plans should provide audit and feedback, minimize prior authorization requirements, eliminate fail-first policies, eliminate fingolimod as the only first-line HET, and increase out-of-pocket-cost-free access to rituximab or its biosimilars, particularly for those patients at high risk of disability.

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## Authors' Contributions

Annette Langer-Gould's contributions include treatment algorithm design, data review, data analysis, and drafting and revising the manuscript for content, including study concept and interpretation of data. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Shilpa Klocke contributed to the treatment algorithm design, data review, data analysis, and revising the manuscript for content.

Brandon Beaber contributed to the treatment algorithm design and revising the manuscript for content.

Sonu M. Brara contributed to the treatment algorithm design and revising the manuscript for content.

Allen Scott Nielsen contributed to the treatment algorithm design and revising the manuscript for content.

Julie DeBacker contributed to the treatment algorithm design and revising the manuscript for content.

Oluwasheyi Ayeni contributed to the treatment algorithm design and revising the manuscript for content.

## Conflicts of Interest

A. Langer-Gould receives grant support and awards from the Patient Centered Outcomes Research Institute and the National MS Society. She currently serves as a voting member on the California Technology Assessment Forum,

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix