



Review article

An overview of the current state of evidence for the role of specific diets in multiple sclerosis

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ABSTRACT

Background: Surveys of people with multiple sclerosis (MS) report that most are interested in using dietary modifications to potentially reduce the severity and symptoms of their disease. This review provides an updated overview of the current state of evidence for the role of specific diets in MS and its animal models, with an emphasis on recent studies including efficacy and safety issues related to dietary manipulations in people with MS.

Methods: Studies were identified using a PubMed search for each diet in both MS and experimental autoimmune encephalomyelitis, by review of the reference list of papers identified in the search process, and by searching clinicaltrials.gov for ongoing studies. Each study was evaluated and the data was summarized. Each diet was assigned a level of evidence for its use in MS based on the Quality Rating Scheme for Studies and Other Evidence.

Results: Several diets have been explored in people with MS and animal models of MS. Most human trials have been small and non-blinded, limiting their generalizability. Many have also been of short-duration, potentially limiting their ability to find clinically meaningful changes. Presently, insufficient evidence exists to recommend the routine use of any specific diet by people with MS. Clinical trials are ongoing or planned for many diets including the Swank Diet, Wahl's diet, McDougall diet, Mediterranean diet, and intermittent fasting. Results of these studies may help guide clinical recommendations.

Conclusion: There is insufficient evidence to recommend the routine use of any specific diet by people with MS. Some diets touted for MS may have potential negative health consequences. It is important that clinicians inquire regarding dietary manipulations, so they can educate patients on any known efficacy data and potential adverse effects of individual diets. Consultation with a registered dietician is recommended for patients undertaking restrictive diets.

1. Introduction

Multiple Sclerosis (MS), a chronic inflammatory and neurodegenerative central nervous system (CNS) disorder that is presumed to be autoimmune. MS affects people of all ages, races/ethnicities, and sexes, and is thought to be triggered by environmental factors in genetically susceptible individuals. The spread of Westernized diet consumption and resultant adverse effects, such as obesity, are potentially related to the risk of developing MS. Following specific, non-westernized diets may therefore be useful as adjunctive therapies to modify outcomes among people with MS (pwMS). Surveys indicate the vast majority of pwMS are interested in or already implementing dietary modifications

(Brenton and Goldman, 2016; Yadav et al., 2006). Several diets have been suggested for pwMS, and each typically contains multiple aspects that might affect MS risk or course. Many diets have substantial overlap in their emphasis. For example, the Mediterranean, McDougall, calorie restricted and intermittent fasting diets all emphasize intake of vegetables and fruits, which contain many different vitamins and nutrients that may work synergistically to affect MS.

This paper provides an updated overview of current evidence regarding use of specific diets by pwMS. In this article, we focus on human studies examining efficacy and safety issues for each diet. When available, we report data from studies testing individual diets in animal models, which should be interpreted cautiously because no animal

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model fully recapitulates MS and each has limitations. Positive pre-clinical findings are not always replicated in humans and must be interpreted with these limitations in mind. Dietary research is challenging for many reasons; most studies require participants to make major and long-term behavioral modifications and fully adhere to the diet. Further, blinding of subjects is nearly impossible, and a lack of agreement on optimal clinical endpoints exists (Yadav et al., 2016). Many of the studies cited may be limited by confounders including obesity, gender, smoking, medical comorbidities, and exercise habits which have their own effects on MS (Marrie, 2017) (Mowry et al., 2018). It should also be noted that many of the human diet studies reported may not have been of sufficient duration or included sufficient subjects to demonstrate long-term or small effects on MS. With regards to safety, a conservative approach is utilized whereby we report on potential safety concerns regarding the use of these diets, even if rare or unlikely. These side effects may not apply to all pwMS, but we encourage clinicians and patients to be aware of these safety concerns and consider them when implementing dietary modifications.

2. Materials and methods

A PubMed search was performed using the terms “multiple sclerosis” and “experimental autoimmune encephalomyelitis (EAE)” AND the name of each diet. No date limitations were applied to the literature searches, which were conducted several times between January 15, 2018 and February 1, 2019. The reference lists of the papers obtained through the PubMed search were reviewed for additional studies and clinicaltrials.gov was queried for ongoing studies. All relevant papers were reviewed. We limited the studies reported to those of specific diets in MS and did not include more generalized studies of dietary quality diet in MS. Each specific diet was assigned a level of evidence for its use in MS based on the Quality Rating Scheme for Studies and Other Evidence modified from the Oxford Center for Evidence-based Medicine for rating of individual studies; available online at <https://www.cebm.net/2016/05/ocbm-levels-of-evidence>; each is listed in the Table. All reported studies performed with humans or animals were previously published and complied with applicable ethical standards (including the Declaration of Helsinki and its amendments, the National Institutes of Health guide for the care and use of Laboratory animals and its amendments, institutional or national research committee standards, and international, national, and institutional guidelines).

3. Results and discussion

Specific Diets (See Table 1)

Table 1
Summary of evidence for specific diets in people with multiple sclerosis.

Diet	Level of Evidence	Safety Concerns
Ketogenic Diet	2	Acute pancreatitis, fatty liver disease, elevated lipid levels, vitamin deficiency
Swank Diet	3	Deficiencies of vitamins A, C and E and folic acid
McDougall Diet	2	Deficiencies of calcium, vitamins B12 and D, and zinc
Caloric Restriction & Intermittent Fasting	2	Reduced bone density, reduced sex hormones, menstrual irregularities
Mediterranean Diet	4	None identified
Wahl's Diet	4	Deficiencies of calcium, and vitamins D and E
Gluten Free Diet	4	Excess heavy metal accumulation
Low Carbohydrate	Insufficient Evidence	
High Fat Diet	4	Obesity, hyperlipidemia, cardiovascular disease
Low Sodium Diet	2	Seizures

Table Legend: Levels of evidence based on the Quality Rating Scheme for Studies and Other Evidence modified from the Oxford Centre for Evidence-based Medicine for rating of individual studies; available online at <https://www.cebm.net/2016/05/ocbm-levels-of-evidence>. Relevant references for level of evidence and safety concerns can be found in the main text of article.

3.1. The ketogenic diet

A ketogenic diet (KD) is a diet low in carbohydrates and high in fat, typically at a macronutrient ratio of ratio of 4 gs of fat to 1 g of protein/carbohydrates. To be undertaken safely, it requires supplementation with vitamins and minerals (Pinto et al., 2018). The KD induces ketone body formation in the liver, which are released into the circulation to be used as energy and may have both anti-inflammatory and neuroprotective effects (Pinto et al., 2018).

In EAE, an animal model of MS, the KD significantly improved motor impairment, memory dysfunction (Kim et al., 2012) and overall clinical severity (Choi et al., 2016). Effects occur through suppression of inflammatory cytokines/chemokines and reactive oxygen species (ROS).

A randomized controlled pilot trial of KD versus fasting-mimicking diet (described later in paper) in 60 RRMS patients over 3 months reported clinically meaningful improvements in health-related quality of life (HRQOL) (Choi et al., 2016). Another study of KD reported colonic biofermentative function impairment in pwMS as being restored by adherence to KD after 6 months (Swidsinski et al., 2017) and reduced expression of pro-inflammatory enzymes and eicosanoids in a subset of patients following the KD (Bock et al., 2018). A prospective observational feasibility trial of KD over 6 months reported that the diet was safe and led to improvements in fatigue and depression (Brenton et al., 2019). Several trials of KD in MS are ongoing. A randomized controlled trial of KD versus intermittent fasting or a vegetarian diet on MRI outcomes in pwMS is recruiting in Germany (NCT03508414). A prospective observational feasibility study of KD over 12 months is currently recruiting (NCT03718247).

Negative effects of the KD can include vitamin deficiencies, weight loss, gastrointestinal side effects (including acute pancreatitis or fatty liver disease), and transient increases in blood lipids (McDonald and Cervenka, 2018).

3.2. The Swank diet

The Swank diet, first proposed in the 1950's as a treatment for pwMS by Roy Swank MD, is a low fat diet limiting saturated fats to less than 15 gs/day and unsaturated fats to less than 40 gs/day. Several vitamins and cod-liver oil are supplemented (Swank and Goodwin, 2003).

Dr.. Swank conducted a prospective, open-label, longitudinal observational study of this diet in 144 pwMS. This study was the longest diet study we found. The study lacked a control group. Adherence to the diet was tracked, with approximately 50% (74/144) being strongly adherent. Comparisons were made between this highly adherent subgroup and the less adherent group (Swank and Goodwin, 2003). Annualized relapse rate (ARR) decreased from an average of 1.0 (in the three years prior to initiation of diet) to 0.3 after 1 year of strong

adherence to the diet and further declined over time. By 14 years of strong adherence, an ARR that remained consistently near or below 0.05 was observed. Though this could be partially explained by the natural history of MS to become less inflammatory over time, as well as regression to the mean, this decline in ARR was greater than expected based on natural history studies for untreated pwMS. Relapses were noted to be more common during dietary non-adherence (Swank, 1970). A 34-year long-term follow-up revealed a survivor rate of 67% in those adherent to the diet versus 21% in those non-adherent to the diet, suggesting a survival benefit with adherence to the Swank diet (Swank and Goodwin, 2003). Major limitations include the lack of a control arm and lack of randomization. A randomized trial of the Swank diet versus the Wahl's diet over 24 weeks to assess effect on fatigue in 100 relapsing pwMS is underway (Wahls et al., 2018) (NCT 02914964).

Persons strictly adherent to the Swank diet may be at risk for vitamin A, C, E, and folate deficiencies (Masullo et al., 2014).

3.3. The McDougall diet

A plant-based, very low fat, vegan diet in which most calories derive from complex carbohydrates has been endorsed by John A. McDougall, MD. The McDougall Diet eliminates all meat and animal-based fat, including fish, dairy, and eggs.

A 12-month study funded by The McDougall Research & Education Foundation randomized 61 relapsing pwMS to the McDougall Diet ($n = 32$) or control ($n = 29$) reported an 80% adherence rate to the McDougall Diet (Yadav et al., 2016). Fatigue, body mass index, and blood lipid levels all improved significantly in the McDougall diet arm. However, after one year no statistical differences were noted in terms of MRI, clinical relapses or changes in disability. Thus, in this small study the McDougall diet did not appear to affect MS disease activity, but may have conferred other health benefits (Yadav et al., 2016). A randomized controlled study of the McDougall Diet in 108 pwMS is currently recruiting (NCT03322982).

Very low fat vegan diets lack some nutrients, including calcium, vitamins B12 and D, and zinc, which should be supplemented (Schüpbach et al., 2017).

3.4. Calorie restriction and intermittent fasting

Calorie restriction (CR) has potential anti-inflammatory and neuroprotective effects. The former are related to effects on circulating cytokines, adipokines, and glucocorticoids (Fontana, 2009; Piccio et al., 2008a), the latter to reduction of oxidative stress and increases in neurotrophic factors, autophagy, and mitochondrial biogenesis (Pani, 2015). Chronic CR is not easily sustainable in humans. Intermittent fasting (IF), an alternative to chronic CR, has similar effects on metabolic and inflammatory markers (Mattson et al., 2017). Different paradigms of IF include alternate-day (every other day) fasting, the 5:2 diet (fast 2 days/week), intermittent energy restriction (IER; reduced caloric intake such as 500 cal/day, 2 days/week), and time-restricted feeding (limiting daily caloric intake to a 4–6 h window).

Rats subjected to severe (66%) CR and then EAE induction did not develop neurological signs of EAE and showed increased plasma ACTH and corticosterone levels, altered immune responses, and impaired interferon (IFN)- γ production (Esquifino et al., 2007, 2004). We showed that 40% CR ameliorated mouse EAE in association with increased corticosterone and adiponectin levels and reduced IL-6 and leptin levels (Piccio et al., 2008a). Alternate day fasting was also beneficial in EAE (Kafami et al., 2010). Our group reported that IF initiated before immunization ameliorated EAE and was associated with increased gut bacterial diversity and enrichment of protective Lactobacilli (Cignarella et al., 2018). A fasting-mimicking diet (FMD; cycles of 3 days of CR followed by 4 days of normal calorie intake) initiated after disease onset ameliorated EAE and was associated with increased

corticosterone and regulatory T (Treg) cells and reduced pro-inflammatory cytokines. FMD promoted remyelination in the cuprizone model (Choi et al., 2016).

A study comparing pwMS observing one month of Ramadan fasting with non-fasting controls reported no differences in relapses or disability at a 6-month follow up (Saadatnia et al., 2009), while another study reported Ramadan fasting in pwMS improved HRQOL (Etemadifar et al., 2016). An uncontrolled pilot study ($n = 43$) of semi-vegetarian CR over 6 months found no significant clinical changes, but noted reduction of circulating levels of gelatinase matrix metalloproteinase 9 (Riccio et al., 2016). A controlled study of FMD versus KD in 60 RRMS patients over 6 months concluded that both diets were feasible, safe, and potentially increased HRQOL (Choi et al., 2016). A randomized controlled pilot study of continuous daily CR versus intermittent CR over 8 weeks in 36 pwMS concluded that CR diets are safe, feasible, and may improve emotional health (Fitzgerald et al., 2018). Our group reported a pilot study of IER in 16 actively relapsing pwMS being treated with steroids who were then randomized to IER or regular diet for 15 days. IER was safe, well-tolerated, and significantly reduced leptin levels without significantly affecting adiponectin levels (Cignarella et al., 2018). We are currently performing a randomized controlled pilot study of IER (2 days/week) versus an improved Western diet (with supplemented vegetables) over 12 weeks in 60 relapsing pwMS (NCT03539094) to explore IER effects on peripheral blood inflammatory markers and gut microbiota. A randomized study in 111 relapsing pwMS comparing IF to vegetarian diet or KD on MS lesions is recruiting in Germany (NCT03508414).

Negative effects of IF and CR depend on the degree of restriction, but may include reduction of bone mass, and decreased levels of sex hormones with effects on libido and/or menstrual cycles (Most et al., 2017).

3.5. The Mediterranean diet

The Mediterranean diet is rich in olive oil, fruits, vegetables, nuts and whole grains with moderate intake of fish, poultry, and wine and low intake of dairy products, red meats, and sweets (Mente et al., 2009). Beneficial effects of the Mediterranean diet have been attributed to increased consumption of polyphenols, flavonoids, and tannins. A rat EAE model supplementing dry olive leaf extract, rich in polyphenols, reported reduced EAE severity and reduced production of IFN- γ and IL-17 (Miljković et al., 2009).

The dietary habits of 480 incident MS cases in the Nurses Health Studies were examined using multiple patient questionnaires, including the Alternate Mediterranean Diet index and found no association between adherence to a Mediterranean Diet and risk of developing MS after adjusting for age, BMI, smoking status, and vitamin D intake (Rotstein et al., 2018). An Australian case-control study of 252 clinically isolated syndrome (CIS) cases and 446 controls examined environmental risk factors for demyelination. Subjects were divided into two main dietary patterns, "healthy" and "Western." The "healthy" diet was similar to a Mediterranean diet, being high in poultry, fish, eggs, vegetables, and legumes, though without an emphasis on olive oil consumption, while the "Western" diet was high in meat and high-fat dairy, and low in whole grains, nuts, and fruit. After adjusting for factors known to increase risk of MS, a one-standard deviation increase in the "healthy" pattern score was found to be associated with a 25% reduced risk of CIS (Black et al., 2018). An Iranian case-control interview-based study (70 pwMS and 142 controls) reported that higher consumption of fruits and vegetables typical of the Mediterranean diet was significantly associated with reduced MS risk (Sedaghat et al., 2016). An Iranian case-control retrospective dietary recall study (75 pwMS and 75 controls) reported that diets high in red meat, animal fat, hydrogenated fats, and sugars and low in vegetables were associated with a nearly doubled risk of developing MS compared with vegetarian or traditional Iranian diets (Jahromi et al., 2012). A randomized

controlled pilot study of a modified Mediterranean Diet in 30 pwMS has been completed, but results are not yet published (NCT02986893).

We did not identify any negative health consequences of the Mediterranean diet.

3.6. The Paleolithic diet and Wahl's elimination diet

The Paleolithic diet, intended to mimic the diet of human ancestors prior to the agricultural revolution, involves consumption of non-domesticated meats, vegetables, fruits, and legumes and avoidance of highly processed foods, dairy, eggs, and gluten. Published clinical trials of the Paleolithic diet in pwMS are limited to the Wahl's diet, which is a modified Paleolithic diet (Bisht et al., 2014).

A multimodal intervention including the Wahl's diet, multiple dietary supplements, an exercise program, neuromuscular electrical stimulation, massage, and meditation was studied in an uncontrolled pilot study of 10 people with SPMS over 12 months, reporting 60% adherence to the multimodal intervention and improved self-reported fatigue in 7 of 9 subjects (Bisht et al., 2014). Other small ($n = 19$ – 20 progressive pwMS), uncontrolled pilot studies of the multimodal intervention over 12 months by these same investigators reported improved self-reported HRQOL and fatigue in 11/20 subjects (Bisht et al., 2015) and improvements in anxiety, depression, and executive functioning (Lee et al., 2017) with no overall change in balance or gait (Bisht et al., 2017). A randomized controlled pilot trial of the Wahl's diet without the other multimodal interventions in 17 relapsing pwMS reported improvement in fatigue and HRQOL in the 65% of pwMS who completed the 3-month trial (Irish et al., 2017). A randomized trial of the Wahl's diet versus the Swank diet over 24 weeks to assess effect on fatigue in 100 relapsing pwMS is underway (Wahls et al., 2018) (NCT 02,914,964).

PwMS following a strict Paleolithic diet are at risk for deficiencies of Vitamins E and D and calcium (Masullo et al., 2014).

3.7. Gluten free diet

Gluten-free diets (GFD) are devoid of gluten, a composite that is found in wheat, barley, and rye. GFD is a treatment for Celiac disease, a systemic autoimmune disorder of gluten intolerance, which can co-occur, with other autoimmune disorders. The role of gluten in MS has recently been reviewed and collectively, the evidence does not support an increased prevalence of Celiac Disease in pwMS (Thomsen et al., 2019).

A small ($n = 21$) rat EAE study of GFD from birth to day 40 post-immunization for EAE found that rats on GFD had worse EAE outcome and earlier onset of motor impairment (Di Marco et al., 2004).

The Paleolithic and Wahl's elimination diets, when followed strictly, are both gluten free diets (please see above). An uncontrolled pilot study of 42 relapsing pwMS found no effect of GFD on relapses or disability over 2 years (Liversedge, 1977). A prospective study of GFD in 72 pwMS with a median follow-up of 4.5 years reported a lower ARR rate, less MRI activity, and a lower EDSS in the 50% of patients who were adherent to the GFD versus the 50% of patients who were non-adherent to the diet (Rodrigo, 2017). There was no randomization or true control group in this study. A 6-month trial examining the effects of GFD on blood brain barrier integrity in CIS is underway (NCT03451955).

Strict adherence to GFD may lead to heavy metal bioaccumulation as a result of increased consumption of heavy metal-rich foods such as rice and shellfish, though whether this has any clinical effects is unknown (Raehsler et al., 2017).

3.8. Low carbohydrate diets

We found no published studies reporting on the use of low-carbohydrate, low-sugar, or the Atkins diet in animal models or pwMS.

3.9. High fat diet

Dietary fats come in several varieties with diverse effects on human health. Unsaturated fats derived from fish oils or plant-based sources, are a major component of several diets discussed earlier. One subset, polyunsaturated fatty acids, including omega-3 and omega-6 supplements, are potentially beneficial in animal models and pwMS (Evans et al., 2018). Saturated fats, common in westernized diets, derive mainly from animal fats. High consumption of saturated fats will be considered below.

EAE studies report consumption of excess fat may enhance autoimmune inflammation and influence EAE severity and pathology (Piccio et al., 2008b; Timmermans et al., 2013). Administration of long-chain fatty acids, which are commonly found in processed food typical of the Western diet, exacerbated EAE severity by expanding Th1 and Th17 cells in the small intestine (Haghikia et al., 2015).

Epidemiological studies suggest a positive correlation with long term high consumption of saturated animal fat and MS incidence and severity (Alter et al., 1974; Swank et al., 1952). An observational study of 219 children with demyelinating syndromes found an association between fat intake and risk of subsequent relapse. In particular, increased intake of saturated fat was associated with more MS disease activity, with each 10% increase in saturated fat, tripling the relapse risk (Azary et al., 2018).

Consumption of a diet high in saturated fats can lead to obesity, cardiovascular disease, hyperlipidemia, and type 2 diabetes, which could negatively impact both overall health and MS course in pwMS (Marrie et al., 2015).

3.10. Sodium

Westernized diets also include increased salt (NaCl) intake. Although serum sodium level is tightly regulated, high salt diets can cause higher sodium osmolality within lymphoid and other tissues (Kleinewietfeld et al., 2013; MacHnik et al., 2009). High salt concentrations induce the serum/glucocorticoid-regulated kinase (SGK1), which then leads to increased Th17 cells (Hernandez et al., 2015; Kleinewietfeld et al., 2013; Wu et al., 2013). Mechanisms by which excess sodium could potentially influence MS involve not only Th17 T-cell induction, but also inhibition of regulatory T-cell function (Hernandez et al., 2015), shifting human monocytes toward a pro-inflammatory phenotype (Hucke et al., 2016), altering development of CD4 T-cells producing GM-CSF and IFN- γ (Éliás et al., 2016), and altering the gut microbiome (Wilck et al., 2017). High concentrations of NaCl increase development of follicular T helper (Tfh) cells in humans. Tfh cells are important for development of B-cells and of lymphoid tissue, including ectopic lymphoid tissues. Presence of ectopic lymphoid tissues, which are found in the CNS of some MS patients, is associated with worse MS outcomes (Howell et al., 2011). EAE studies reported worse clinical course in mice fed a high sodium diet associated with enhanced Th17 cell function (Wilck et al., 2017; Wu et al., 2013).

Several groups have examined sodium intake on clinical and imaging measures in pwMS with inconclusive results. An observational study of 122 pwMS found medium to high sodium intake was positively correlated with relapse rate and conferred three-fold greater risk of developing new MRI lesions after 2 years (Farez et al., 2015). In contrast, studies in the pediatric population did not show an association between sodium intake and risk of MS development or relapse rate in pwMS or CIS (McDonald et al., 2016; Nourbakhsh et al., 2016). Data from BENEFIT, a multi-center, international randomized clinical trial of 465 adult CIS patients were used to analyze sodium intake at various time points in the study, as determined by 24-h urine sodium excretion. Over 5 years, there was no association between sodium intake and conversion to MS or MRI activity (Kathryn C. Fitzgerald et al., 2017a). No clinical trial prospectively testing reduction of salt intake in MS has been published. A controlled study examining the effects of high versus

low salt diet on immune cell subsets in pwMS is currently recruiting (NCT02282878).

Extreme salt restriction, to the point of hyponatremia, can be associated with seizures and other neurological disorders (Diringer, 2017). However, in general, evidence indicates that less salt intake is more healthful than excessive salt.”

4. Conclusions

This review is intended to facilitate patient discussions and improve patient care by equipping clinicians with knowledge regarding safety and efficacy of specific dietary manipulations among pwMS.

A growing body of literature including epidemiological, preclinical, observational and small clinical studies suggests the potential importance of diet as an environmental factor impacting MS onset, clinical course, symptomatology, and HRQOL (Bisht et al., 2015; Choi et al., 2016; Fitzgerald et al., 2017b; Hadgkiss et al., 2015). Dietary changes might also improve MS by reducing inflammation and promoting neuroprotection through various mechanisms discussed herein.

In our opinion, a balanced diet appears to be optimal for general health. However, there is currently insufficient evidence to recommend any specific diet for widespread use by pwMS. The collective data suggest that certain dietary modifications, such as decreased consumption of animal products, saturated fats, salt, and processed foods coupled with a preference for consumption of whole grains, and increased consumption of legumes, vegetables, and fruit may promote general health and lead to patient-perceived, often clinically meaningful, improvement of symptoms like fatigue and HRQOL (Bisht et al., 2015; Choi et al., 2016; Fitzgerald et al., 2017; Hadgkiss et al., 2015).

Numerous clinical trials are presently ongoing or planned, including studies of intermittent fasting and the Swank, Wahls, McDougall, and Mediterranean diets. Results of these studies may help guide future clinical recommendations. For patients considering significant dietary manipulations or restrictive diets, we recommend consultation with a dietician to take into account individual medical comorbidities and avert nutritional deficiencies.

Declaration of Competing Interest

Dr. Evans has been a paid consultant for: Biogen, Teva, Genzyme/Sanofi, & Genentech/Roche. Dr. Evans has been a paid speaker for Genzyme/Sanofi and Novartis.

Dr. Cross has been a paid consultant for: Biogen, Celgene, EMD-Serono, Genentech/Roche, & Novartis, and has received research funding from EMD Serono and Genentech/Roche.

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