

## REVIEW

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# Reproductive issues and multiple sclerosis: 20 questions

## ABSTRACT

Multiple sclerosis (MS) is commonly diagnosed in young adults during their reproductive years. Consequently, concerns about family planning and MS management related to pregnancy and breastfeeding are often encountered in clinical practice. Pregnancy itself is not harmful for women with MS. However, disease-modifying therapies (DMTs) have implications for reproductive planning, including stopping treatment while trying to conceive and during pregnancy, as well as managing fetal risks. People with MS and their care team must engage in collaborative decision-making before, during, and after pregnancy. Based on the results of a consensus-building initiative, answers are provided to 20 frequently asked questions regarding the management of MS during pregnancy planning, pregnancy, and the postpartum period.

## KEY POINTS

Most women with MS can conceive, have normal pregnancies and deliveries, and breastfeed successfully.

Primary considerations relate to ensuring proper prenatal counseling about cessation of DMT and timing of conception, as well as resumption of DMT.

To engage in collaborative decision-making throughout all stages of pregnancy, clinicians caring for people with MS need to be familiar with pregnancy-related risks associated with MS therapies, as well as the management of MS-related reproductive issues.

**M**ULTIPLE SCLEROSIS (MS), A CHRONIC, inflammatory, neurodegenerative disease, is often diagnosed during patients' child-bearing years. As a result, family planning, contraception, pregnancy, and childbirth are significant concerns. Healthcare for people with MS requires access to information and clinicians who can provide guidance. MS itself is not a barrier to pregnancy, but disease-modifying therapies (DMTs) for MS are associated with varying degrees of risks to the fetus. Many risks are theoretical due to limited fetal safety data, but they require careful consideration by both clinician and patient.

Clinicians at the Cleveland Clinic Mellen Center for Multiple Sclerosis developed a collaborative approach to reproductive health and MS, a summary of which is available on the Mellen Center website.<sup>1</sup> This article, based on the Mellen Center consensus initiative, combines a review of the literature with clinical experience to address 20 frequently asked questions about the management of MS during family planning, pregnancy, and the postpartum period.

## 1: DOES MS IMPACT SEXUAL HEALTH AND FERTILITY?

Sexual dysfunction affects 40% to 80% of women and 50% to 90% of men who have MS,<sup>2</sup> imposing a significant negative impact on quality of life. Targeted symptomatic therapies such as lubricants, sex steroid therapy, prostaglandins, phosphodiesterase 5 inhibitors, or psychotherapy may be utilized. When symptomatic therapies are unsuccessful,

doi:10.3949/ccjm.90a.22066

patients may benefit from further evaluation through gynecologic or urologic specialists.<sup>3</sup>

Conception and fertility rates in people with MS and the general population are comparable. The use of assisted reproductive technology has been reported in some studies to be associated with an increased risk of MS relapse in the first 3 months following unsuccessful cycles.<sup>4</sup> However, a recently published study did not identify this risk.<sup>5</sup>

### ■ 2: WHAT IS THE GENETIC RISK OF MS IN CHILDREN OF PEOPLE WITH MS?

Children of people with MS are approximately 5.77 times more likely to develop MS than people in the general population,<sup>6</sup> though the overall risk remains low at approximately 2%.<sup>7</sup> Although genetic factors contribute to susceptibility to MS, the disorder is complex, with more than 250 identified contributory genes. The development of MS likely also depends on environmental and other factors including exposure to smoking, viral infections, adolescent obesity, vitamin D levels, microbiome, and geographic latitude of residence.<sup>8</sup>

### ■ 3: WHAT ARE THE KEY ISSUES FOR CHOICE OF DMT IN PRECONCEPTION COUNSELING?

The choice of DMT should be based on the patient's level of disease activity, their plans to become pregnant, and the desired timing. Most DMTs are associated with fetal risk; further, the sphingosine 1-phosphate receptor (S1Pr) modulators and natalizumab are associated with a risk of rebound disease activity upon discontinuation.

### ■ 4: WHAT ARE THE RECOMMENDATIONS FOR CONTRACEPTION?

Women with MS of childbearing potential who are using DMT should practice effective birth control regardless of plans to pursue pregnancy. In general, contraceptive methods used in the population at large are safe and effective for women with MS. Potential drug-drug interactions between symptomatic treatments (for MS-related sequelae such as spasticity, urinary dysfunction, and mood dysregulation) and certain contraceptive agents should be considered: for example, modafinil may lessen the efficacy of oral contraceptives by accelerating their metabolism.

Men with MS treated with teriflunomide, which carries significant risk of teratogenicity, must practice effective contraception until after the medication is cleared by metabolism (ie, at least 6 months after the

last dose) or by a rapid-clearance protocol. Female partners of men taking teriflunomide must also be counseled on the potential risks of fetal exposure and use of effective contraceptive therapy. Teriflunomide is contraindicated for use during pregnancy and in females of reproductive age not using effective contraception.

Cladribine has been associated with increased embryo lethality in animal studies, and men are thus advised to prevent pregnancy for at least 6 months following treatment with cladribine.<sup>9</sup> Cladribine may cause an increase in nonmotile sperm, leading to reversible infertility.<sup>10</sup>

Alemtuzumab may cause reversible infertility by inactivating mature sperm by binding to CD52, the surface antigen expressed by mature sperm.<sup>11</sup>

### ■ 5: ARE THERE SPECIFIC CARE REQUIREMENTS DURING PREGNANCY?

MS itself does not render a pregnancy “high-risk” or increase the likelihood of congenital malformation or miscarriage. MS may be associated with lower birthweight,<sup>4</sup> although this is usually not clinically significant.

The overall risk of MS relapse decreases during pregnancy, with the relapse rate declining progressively over the 3 trimesters.<sup>12</sup> The patient's recent disease trajectory and her prior DMT pharmacology, efficacy, and latency may influence disease activity during pregnancy. Women with higher relapse rates prior to conception are at increased risk of ongoing disease activity during pregnancy.<sup>12</sup>

### ■ 6: IS IT SAFE TO USE DMT DURING PREGNANCY?

The use of DMT is generally not recommended during pregnancy. Treatment considerations must include the potential benefits and risks to the mother based on her level of disease activity and the likelihood of relapse or worsening disability without DMT. Embryonic or fetal exposure is also associated with risk (Table 1).<sup>1,5,10,11,13–41</sup>

#### Platform injectable therapies

The first DMTs—the “platform therapies,” ie, interferons<sup>13–17</sup> and glatiramer acetate<sup>18,19</sup>—have been associated with low birth weight but not with other significant adverse effects on pregnancy. These treatments are generally stopped before planned conception. However, when benefits outweigh risks, they may be continued in women with MS who are pregnant or wish to become pregnant and whose risk profile is low.

TABLE 1

**Special considerations for use of disease-modifying therapies in pregnancy<sup>a,b</sup>**

Medication	Recommended washout period	Use in pregnancy
<b>Interferons</b> Interferon beta-1a <sup>14,15</sup> Peginterferon beta-1a <sup>16</sup> Interferon beta-1b <sup>13,17</sup>	2 weeks	Use only if benefit outweighs risks
<b>Glatiramer acetate</b> <sup>18,19</sup>	None	Use only if benefit outweighs risks
<b>Fumarates</b> Dimethyl fumarate <sup>28</sup> Diroximel fumarate <sup>29</sup> Monomethyl fumarate <sup>30</sup>	1 week	Not advised
<b>Sphingosine 1-phosphate receptor modulators</b> Fingolimod <sup>32</sup> Siponimod <sup>33</sup> Ozanimod <sup>34</sup> Ponesimod <sup>35</sup>	Fingolimod: 2–3 months Siponimod: 2 weeks Ozanimod: 3 months Ponesimod: 1 week	Spingosine 1-phosphate receptor modulators are not advised Risk for rebound disease activity Consider transition to a B-cell-depleting agent before discontinuing contraception
<b>Cladribine</b> <sup>10</sup>	6 months	Not advised
<b>Teriflunomide</b> <sup>31</sup>	Rapid-elimination procedure required: cholestyramine 8 g every 8 hours orally for 11 days (if not tolerated, reduce dose to 4 g every 8 hours) or activated charcoal powder 50 g every 12 hours for 11 days until a serum concentration below 0.02 mg/L is reached	Not advised; stop treatment and eliminate drug before discontinuing contraception
<b>Natalizumab</b> <sup>21</sup>	2–3 months	Generally not advised Use in special circumstances; high risk for rebound disease activity Consider transition to a B-cell-depleting agent before discontinuing contraception
<b>B-cell-depleting agents</b> Ocrelizumab <sup>22</sup> Ofatumumab <sup>23</sup> Rituximab <sup>24,25</sup> Ublituximab <sup>26</sup>	1–3 months <sup>c</sup>	B-cell-depleting agents are generally not advised; package inserts recommend washout periods of 6 months for ocrelizumab, 6 months for ofatumumab, 6 months for ublituximab, and 12 months for rituximab <sup>c</sup>
<b>Alemtuzumab</b> <sup>27</sup>	4 months	Use not advised

<sup>a</sup>This table reflects our clinical practice and review of combined recommendations of prescribing information and key articles.

<sup>b</sup>Pregnancy testing is recommended before starting or re-dosing for all disease-modifying therapy in women of childbearing potential.

<sup>c</sup>See Question 7 in the article for an in-depth discussion of B-cell-depleting therapies and pregnancy timing.

Based on information in references 1,5,10,11, and 13–41.

**Monoclonal antibodies**

With few exceptions, the use of monoclonal antibodies during pregnancy is not advised. Placental transfer of immunoglobulins begins around the second trimester and increases with gestational age, theoretically lowering the risk of fetal exposure in

the first trimester.<sup>20</sup> Natalizumab may be considered during pregnancy in exceptional circumstances, as in women with severe intrapartum relapses.<sup>12</sup> Its use during the third trimester requires caution because of risk of placental transfer and resulting fetal or infantile pancytopenia.<sup>21</sup> B-cell-depleting therapies

(ocrelizumab, ofatumumab, rituximab, ublituximab)<sup>22–26</sup> can be used prior to pregnancy, but their routine administration is not recommended during pregnancy. Use of alemtuzumab during pregnancy is not advised.<sup>27</sup>

## Oral therapies

None of the currently available oral therapies—fumarates,<sup>28–30</sup> teriflunomide,<sup>31</sup> S1Pr modulators,<sup>32–35</sup> or cladribine<sup>10</sup>—are safe for use during pregnancy.

## 7: HOW LONG BEFORE CONCEPTION SHOULD DMT BE STOPPED?

Washout periods are advised for all DMTs, with consideration of the pharmacokinetics of each medication and the patient's level of disease activity. The pharmacology of the treatment determines recommended minimum washout periods (Table 1). When feasible, the timing of treatment and conception should be coordinated with the aim of keeping DMT washout periods as short as possible to mitigate risk of MS relapse.

Prescribing information approved by the US Food and Drug Administration (FDA) recommends that women continue contraception for 6 months following the last treatment of ocrelizumab,<sup>22</sup> ofatumumab,<sup>23</sup> and ublituximab,<sup>26</sup> and for 12 months following the last treatment of rituximab.<sup>24,25</sup> A pregnancy test should be conducted prior to subsequent dosing of intravenous B-cell–depleting therapies. Ofatumumab is administered by monthly subcutaneous injection, and the FDA-approved prescribing information recommends contraception for 6 months following the last treatment.<sup>23</sup> Ofatumumab is thought to protect against disease activity for 6 to 9 months.<sup>23</sup>

B-cell–depleting therapies infused intravenously may confer prolonged protective effects against MS relapses for 6 to 9 months after administration. Decisions regarding use of B-cell–depleting therapy and pregnancy planning need to consider the patient's degree of disease activity, risks, and individual preferences. When disease is highly active before initiation of B-cell–depleting therapy and it is necessary to minimize time off DMT, the patient may receive a B-cell–depleting therapy and then attempt pregnancy after 1 to 3 months.<sup>36,42,43</sup> The rationale is that based on half-life, these therapies are eliminated 3.5 to 4.5 months after an infusion.<sup>22,24,25</sup> Placental transfer of immunoglobulin G is minimal in the first trimester,<sup>20</sup> so the risk of fetal exposure in the second trimester is low if conception occurs 3 to 6 months after the last dose of B-cell–depleting therapy.<sup>36</sup>

## 8: CAN DISEASE ACTIVITY RETURN WHEN DMT IS PAUSED FOR PREGNANCY?

Women treated with S1Pr modulators or natalizumab prior to conception may have increased risk for rebound disease after medication withdrawal. Annualized MS relapse rates have been shown to be higher throughout pregnancy after fingolimod and natalizumab discontinuation compared with low-efficacy therapies.<sup>12</sup> In women discontinuing natalizumab, relapses during pregnancy and the postpartum year have been reported in up to 67% of patients.<sup>37</sup> Due to the risk of rebound disease activity in people with MS treated with these medications, changing to an alternate therapy such as a B-cell–depleting agent might be considered before discontinuing contraception, especially in women with highly active disease.<sup>44</sup>

## 9: WHAT IS THE NEXT STEP IF PREGNANCY OCCURS WHILE THE PATIENT IS TAKING A DMT?

If a woman becomes pregnant while taking DMT, the therapy should be discontinued and the pregnancy exposure reported through an appropriate MS pregnancy registry (Table 2).<sup>1,5,10,11,13–41</sup> Follow-up after discontinuation of therapy varies depending on the DMT as follows:

- **Interferon beta or glatiramer acetate:** no additional monitoring required during pregnancy
- **Oral therapies:** referral for early ultrasonography to screen for major malformations
- **Teriflunomide:** rapid-elimination procedure initiated as soon as possible (Table 1) and referral to an obstetrician with expertise in high-risk pregnancies for early ultrasonography to screen for major malformations
- **Cladribine, teriflunomide, or natalizumab:** follow-up with an obstetrician with expertise in high-risk pregnancies.

## 10: HOW ARE RELAPSES MANAGED DURING PREGNANCY?

The patient's obstetrician and neurologist should coordinate management of MS relapses during pregnancy. Mild relapses with nondisabling symptoms or spontaneous improvement might require no intervention. If a relapse warrants intervention, the typical treatment is high-dose corticosteroids, usually intravenous methylprednisolone 1 g daily or oral prednisone 1,250 mg daily for 3 to 5 days. This therapy carries a slightly increased risk for adverse fetal

TABLE 2

**Risks and management recommendations: Fetal exposure to disease-modifying therapies<sup>a</sup>**

Medication	First-trimester exposure recommendations	Exposure risks
<b>Interferons</b> Interferon beta-1a <sup>14,15</sup> Peginterferon beta-1a <sup>16</sup> Interferon beta-1b <sup>13,17</sup>	No additional fetal or neonatal monitoring	With interferons, slight risk of decreased birthweight and increased embryo or fetal death based on animal data
<b>Glatiramer acetate</b> <sup>18,19</sup>	No additional fetal or neonatal monitoring	None
<b>Fumarates</b> Dimethyl fumarate <sup>28</sup> Diroximel fumarate <sup>29</sup> Monomethyl fumarate <sup>30</sup>	Early ultrasonography for major malformations	Dimethyl fumarate: uncertain risk to fetus; animal studies have shown low birthweight, delayed development, delayed ossification, spontaneous abortions, decreased fetal viability, and impaired learning and memory  Diroximel fumarate: based on animal data, may cause fetal harm including skeletal abnormalities, increased mortality, decreased body weight, and neurobehavioral impairment  Monomethyl fumarate: Based on animal data, may cause fetal harm including adverse embryotoxicity, reduction in body weight, and delayed sexual maturation
<b>S1Pr modulators</b> Fingolimod <sup>32</sup> Siponimod <sup>33</sup> Ozanimod <sup>34</sup> Ponesimod <sup>35</sup>	Early ultrasonography for major malformations	All: teratogenic effect likely; risk of neural tube defects, fetal loss and fetal abnormalities  Fingolimod: based on animal studies, increased risk of congenital malformations and embryolethality, fetal growth retardation, and neurobehavioral deficits  Siponimod: based on animal studies, increased risk of congenital malformations and embryolethality, increased incidence of skeletal variations, decreased body weight, and delayed sexual maturation  Ozanimod: based on animal studies, increased risk of congenital malformations and embryolethality, skeletal variations, vascular malformations, and neurobehavioral deficits  Ponesimod: based on animal studies, increased risk of congenital malformations and embryolethality, visceral, cardiac, and skeletal malformations
<b>Cladribine</b> <sup>10</sup>	Follow up with high-risk obstetrician	Risk of congenital malformations and embryolethality based on animal studies
<b>Teriflunomide</b> <sup>31</sup>	Early screening for major and minor malformations; option to follow up with high-risk obstetrician	Highly teratogenic; risk of serious birth defects in fetus; risk of preterm labor; risk of low birthweight
<b>Natalizumab</b> <sup>21</sup>	Screen neonate for liver dysfunction, pancytopenia	Risk of mild to moderate hematologic alterations (pancytopenia with late pregnancy exposure)
<b>B-cell-depleting agents</b> Ocrelizumab <sup>22</sup> Ofatumumab <sup>23</sup> Rituximab <sup>24,25</sup> Ublituximab <sup>26</sup>	Screen neonate for B-cell depletion, pancytopenia	With B-cell-depleting agents, there is a risk of B-cell depletion in fetus or infant with second-trimester and third-trimester exposure  Rituximab: risk of congenital malformations in fetus, and neonatal infections
<b>Alemtuzumab</b> <sup>27</sup>	Monitor thyroid studies	Risk of thyroid disease in mother (autoimmune thyroiditis in up to 40%); risk of low birthweight, preterm birth, preeclampsia; risk of neonatal Graves disease and cognitive impairment

<sup>a</sup>This table reflects our clinical practice and review of combined recommendations of prescribing information and key articles.

S1Pr = sphingosine 1-phosphate receptor

Based on information in references 1,5,10,11, and 13–41.



outcomes such as cleft palate and low birth weight.<sup>36</sup> Maternal risks include hyperglycemia, hypertension, and fluid overload.

Corticosteroid use should be avoided during the first trimester when possible. If the patient develops a disabling steroid-refractory relapse, then intravenous immunoglobulin therapy<sup>45</sup> or plasmapheresis may be considered. The increased thrombotic risk with intravenous immunoglobulin should be taken into consideration. Nonpharmacologic interventions such as physical therapy can be utilized when deemed appropriate by the patient's care team.

### ■ 11: IS MAGNETIC RESONANCE IMAGING SAFE DURING PREGNANCY?

Despite there being no absolute contraindications to magnetic resonance imaging (MRI) during pregnancy, it is generally avoided. It can be done if clinically indicated, as when findings are critical to clinical decision-making and are expected to impact outcomes. Gadolinium-based contrast should be used with caution, as studies have demonstrated increased risk of stillbirth, neonatal death, and various inflammatory conditions.<sup>46</sup>

### ■ 12: ARE VACCINATIONS SAFE DURING PREGNANCY?

Barring contraindications, the vaccination schedule for the general population is applicable to people with MS.<sup>47</sup> Vaccination updates are best before starting DMT. Any live attenuated vaccines that need to be updated may be administered following delivery and before restarting DMT.

### ■ 13: ARE THERE SPECIFIC REQUIREMENTS FOR LABOR AND DELIVERY?

For most women, there are no MS-specific recommendations for childbirth. Many women can have spontaneous-onset labor and full-term vaginal delivery. Individual factors may need to be considered for women with significant disability, such as planning for assisted delivery methods or cesarean delivery in women with significant motor disability, increased risk of deep vein thrombosis in nonambulatory patients, and increased risk of urinary tract infection in women requiring self-catheterization. The use of any anesthetic is acceptable when clinically indicated,<sup>48</sup> including regional anesthesia as with epidural injections.

### ■ 14: ARE THERE SPECIFIC POSTPARTUM REQUIREMENTS?

Neurologic care generally should resume 4 to 6 weeks postpartum. At that time, breastfeeding plans should be confirmed or revised and resumption of DMT arranged. Women with MS should receive routine obstetric postpartum care, and duration of birth hospitalizations are in the normal range.<sup>49</sup> Patients should be screened for depression and anxiety at follow-up visits. The risk of perinatal depression is higher than in the general population, although the prognosis for recovery at 18 months is similar.<sup>50</sup>

### ■ 15: WHAT IS THE RISK OF RELAPSE AFTER DELIVERY?

Women with MS may be at risk for return of disease activity in the postpartum period. Higher relapse rates before pregnancy are associated with higher postpartum relapse rates. Approximately 13% of women with term or preterm deliveries experience a clinical relapse within 3 months of delivery.<sup>12</sup>

### ■ 16: WHEN SHOULD DMT BE RESUMED?

Breastfeeding plans and timing of DMT resumption should be discussed prior to delivery. When to resume DMT is an individual decision that needs to account for previous disease activity and breastfeeding plans. Resumption of DMT early postpartum should be considered for women with highly active disease before conception or relapse during pregnancy. Women with a low level of disease activity may reasonably defer DMT resumption while they are breastfeeding.

### ■ 17: IS BREASTFEEDING SAFE WITH DMT?

Data are limited concerning the safety of DMT for the breastfed infant, so use of DMT during breastfeeding is generally not advised. The decision to breastfeed and its duration should balance its benefits with the risk of relapse. Notably, the decision to breastfeed requires a delay in DMT resumption that may increase the risk of relapse. The patient's disease characteristics must be considered.

Most DMTs are considered unsafe for use during breastfeeding. The exception is glatiramer acetate, recently approved by European Union health authorities for use during breastfeeding<sup>38</sup> based on the rationale that benefits of breastfeeding likely exceed the risk of exposure.

The degree of transfer of DMTs into breast milk

depends on the size of the molecule. Interferon beta are larger than 20 kDa, and glatiramer acetate molecules are 5 to 9 kDa, and the amount of transfer to breast milk is low.<sup>51</sup> B-cell–depleting therapies involve much larger molecules, on the scale of 145 kDa, and their low oral bioavailability limits absorption by the newborn; the relative infant dose is less than 10%.<sup>39</sup> Even so, B-cell–depleting therapies may have clinical implications for the infant such as B-cell depletion and impaired vaccine responses, though this concern remains theoretical.

Natalizumab is detectable in breast milk in small amounts and therefore should also be used with caution.<sup>51</sup> Dimethyl fumarate, S1Pr modulators, cladribine, alemtuzumab, and teriflunomide should not be used during breastfeeding given their risk profiles (Table 2).<sup>36,40</sup>

## 18: HOW SHOULD A RELAPSE BE MANAGED WHILE A PATIENT IS BREASTFEEDING?

Relapses of MS that occur during breastfeeding can be treated as they usually would be. Transfer of methylprednisolone through breastmilk is thought to be minimal and may be further minimized by delaying breastfeeding for 2 to 4 hours after treatment: levels peak approximately 2 hours after infusion and decline rapidly thereafter, falling below the limits of detection 24 hours after infusion.<sup>52,53</sup> For women receiving oral prednisone, the dose ingested by the infant through breastmilk is thought to be negligible, and no adverse effects have been reported in infants breastfed by mothers in general receiving oral corticosteroid treatment.<sup>41</sup>

## 19: IS MRI SAFE DURING BREASTFEEDING?

Gadolinium contrast for MRI studies may be used while breastfeeding when clinically necessary: although small amounts are detectable in breastmilk, there is little gastrointestinal absorption.<sup>54</sup> If there is any concern for potential toxicity, the patient may refrain from breastfeeding or discard breastmilk for 12 to 24 hours after contrast administration.

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## 20: WHAT ARE THE SPECIFIC PREGNANCY AND FERTILITY ISSUES WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT?

Infertility is common in both men and women after autologous hematopoietic stem cell transplant, and gonadal toxicity results from the cytotoxic therapies that comprise the mobilization and conditioning regimens.<sup>55</sup> Therefore, pretreatment counseling regarding the risk of infertility is critical. People with MS may wish to consider fertility preservation such as cryopreservation of sperm, mature oocytes, or fertilized embryos, and referral to an oncofertility specialist may be appropriate. Limited data suggest that infants born to women who have undergone autologous hematopoietic stem cell transplant do not have an increased risk of congenital abnormalities.<sup>55</sup>

## TAKE-HOME MESSAGES

Management of MS is complex and requires individualized treatment, and pregnancy and reproductive issues are often at the forefront of concerns for both women and men of reproductive age. The individual's care team, including the primary care clinician, internist, obstetrician, and neurologist, need to engage in collaborative decision-making before, during, and after pregnancy to optimize the management of MS-related reproductive issues.

## DISCLOSURES

Dr. Carlson discloses fellowship funding (Grant 16696-P-FEL) from Biogen and institutional clinical training award (ICT-1805-31154) from National MS Society. Dr. Ontaneda discloses consulting for Biogen Idec; consulting and research for Genentech; and consulting for Novartis. Dr. Rensel discloses consulting, teaching and speaking, and research for Biogen Idec; private ownership/partnership of Brain Fresh LLC; consulting and independent contracting for Bristol-Myers Squibb; teaching and speaking and research for Genentech/Roche; work as advisor or research panel participant and teaching and speaking for Genzyme; work as advisor or research panel participant for National MS Society; teaching and speaking for Novartis; and work as advisor or research panel participant for EMD Serono. Dr. Cohen discloses consulting for Biogen, Bristol-Myers Squibb, Convelo, EMD Serono, GlaxoSmithKline, Janssen Pharmaceuticals, Mylan Pharma, PSI Pharma Support America; and work as editor for Sage Publishing. Dr. Kunchok discloses consulting for EMD Serono; work as advisor or review panel participant for Genentech and Horizon Therapeutics; and work as editor for the journal *Neurology*.

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