

# **Retooling for Modern Management of Progressive MS: An Interactive, Case-Based Activity**

A Free, 90-Minute CMEO Live and On Demand Activity

Release Date: Thursday, June 11, 2020

Credit Expiration Date: Friday, June 11, 2021

**[www.cmeoutfitters.com/MScare](http://www.cmeoutfitters.com/MScare)**

**#MScare**

## **FACULTY**

Aaron Miller, MD, FAAN, FANA; Claire S. Riley, MD

## **MODERATOR**

Fred D. Lublin, MD, FAAN, FANA

This continuing education activity is provided by



## INFORMATION FOR PARTICIPANTS

### Statement of Need

The approval of ocrelizumab for primary progressive multiple sclerosis (PPMS) was groundbreaking, and more recently the MS community bore witness to another major breakthrough in MS management when siponimod was approved for secondary progressive MS (SPMS). Additionally, new investigational agents such as MD1003 (high-dose biotin) and masitinib are also being evaluated for treatment of PPMS, and clinical data for both show promise for patients with SPMS.

However, despite these advances, studies have shown that gaps in knowledge and performance exist among neurologists and their care team that pose a barrier to the integration of new and emerging therapies to treat progressive MS in clinical practice.

This CME Outfitters Live and On Demand webcast will include an interactive, case-based panel discussion featuring expert faculty who will discuss the symptoms and clinical features of progressive MS, summarize its immunopathology and the mechanisms of action (MOAs) of new and investigational disease modifying therapies (DMTs), and evaluate the latest clinical evidence on the efficacy and safety of new and emerging therapies for SPMS and PPMS.

### Learning Objectives

**At the end of this CE activity, participants should be able to:**

- Recognize the symptoms and clinical features of progressive MS.
- Summarize the immunopathology of progressive MS and the MOAs of new and investigational DMTs.
- Evaluate the latest clinical evidence of new and emerging therapies for SPMS and PPMS and engage patients in the shared decision-making process.

**The following learning objectives pertain only to those requesting CNE or CPE credit:**

- Recognize the symptoms and clinical features of progressive MS.
- Summarize the immunopathology of progressive MS and the MOAs of new and investigational DMTs.
- Summarize the latest clinical evidence on efficacy and safety of new and emerging therapies for SPMS and PPMS.

### Target Audience

Neurologists, MS specialists, PAs, NPs, nurses, and pharmacists.

### Financial Support

Supported by an educational grant from Novartis Pharmaceuticals Corporation.

## CREDIT INFORMATION

### CME Credit (Physicians)

CME Outfitters, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CME Outfitters, LLC, designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Note to PAs:** PAs may claim a maximum of 1.5 Category 1 credits for completing this activity. NCCPA accepts *AMA PRA Category 1 Credit*<sup>™</sup> from organizations accredited by ACCME or a recognized state medical society.

### CNE Credit (Nurses)

Provider approved by the California Board of Registered Nursing, Provider Number CEP 15510, for 1.5 contact hours.

**Note to Nurse Practitioners:** Nurse practitioners can apply for *AMA PRA Category 1 Credit*<sup>™</sup> through the American Academy of Nurse Practitioners (AANP). AANP will accept *AMA PRA Category 1 Credit*<sup>™</sup> from organizations accredited by the Accreditation Council for Continuing Medical Education. Nurse practitioners can also apply for credit through their state boards.

### CPE Credit (Pharmacists)



CME Outfitters, LLC, is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. 1.5 contact hours (0.15 CEUs)

Universal Activity Number: Live: 0376-0000-20-094-L01-P; Enduring: 0376-0000-20-094-H01-P  
Type: knowledge-based

## Retooling for Modern Management of Progressive MS: An Interactive, Case-Based Activity

### ABIM/MOC Credit

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

**Learning Formats:** Enduring Material

### ABPN MOC Credit

ABPN Diplomates may select any CME activity relevant to their practice to count towards ABPN MOC requirements.

### Royal College MOC

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

### MIPS Improvement Activity

This activity counts towards MIPS Improvement Activity requirements under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Clinicians should submit their improvement activities by attestation via the CMS Quality Payment Program website.

## CREDIT REQUIREMENTS

**Post-tests, credit request forms, and activity evaluations must be completed online** (requires free account activation), and participants can print their certificate or statement of credit immediately (75% pass rate required). This website supports all browsers except Internet Explorer for Mac. For complete technical requirements and privacy policy, visit <https://www.cmeoutfitters.com/privacy-and-confidentiality-policy>.

There is no fee for participation in this activity. The estimated time for completion is 90 minutes. Questions? Please call **877.CME.PROS**.

## FACULTY BIOS & DISCLOSURES

### Fred D. Lublin, MD, FAAN, FANA (Moderator)

Dr. Lublin is the Saunders Family Professor of Neurology at The Icahn School of Medicine at Mount Sinai and Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at that institution.

Dr. Lublin received his medical degree in 1972 from Jefferson Medical College, Philadelphia, PA. He completed his internship in Internal Medicine from the Bronx Municipal Hospital, Albert Einstein Medical Center, and his residency at the New York Hospital, Cornell Medical Center.

As a neuroimmunologist, Dr. Lublin has a special interest in immune functions and abnormalities affecting the nervous system. He has been involved in both basic science and clinical research. He and his colleagues were among the first in the country involved with studies of Interferon beta-1b, which was approved by the Food & Drug Administration in 1993 to treat the relapsing-remitting form of multiple sclerosis. He is currently involved with several new clinical research protocols on promising agents for treating various aspects of MS. He was chairman of the National MS Society (USA) advisory committee on clinical trials of new drugs in MS and the National Multiple Sclerosis Society's Research Programs Advisory Committee. He was a member of the National MS Society National Board of Directors. He is past Chair of the New York City/Southern New York Chapter of NMSS Clinical Advisory Committee. He is a member of the International Medical & Scientific Board of the Multiple Sclerosis International Federation. Dr. Lublin and his colleagues at the National MS Society have re-defined the clinical course definitions of MS, updated in 2014. He has chaired a task force on the ethics of placebo-controlled trials in MS. Dr. Lublin is a member of the international panel that periodically redefines the diagnostic criteria for MS (McDonald Criteria). Dr. Lublin is co-chair of the National Institute of Neurological Diseases and Stroke MS Common Data Element committee and a member of their steering committee. He is a member of the WHO Advisory Group for the Revision of ICD-10 Diseases of the Nervous System working group on demyelinating diseases of the central nervous system. He was a co-chief and founding editor of the journal *Multiple Sclerosis and Related Disorders*.

Dr. Lublin has published numerous scientific articles and is a member of many professional societies and advisory boards. Dr. Lublin has served as a consultant to the National Institutes of Health and to many pharmaceutical/biotech companies in all phases of new drug development and in preparation for presentation to the FDA and their advisory panels. He was the Principal Investigator of the NIH-sponsored multicenter Combination Therapy study in MS. In June of 2019, Dr. Lublin was awarded the June Halper Lifetime Achievement Award from the Consortium of Multiple Sclerosis Centers.

### Aaron Miller, MD, FAAN, FANA

Dr. Miller graduated from Brandeis University in 1964 and received his MD degree from New York University School of Medicine in 1968. Following his residency in neurology at the Albert Einstein College of Medicine, he received additional postdoctoral training in neurovirology and immunology at the Johns Hopkins University School of Hygiene and Public Health and at the Albert Einstein College of Medicine. During this time he was the recipient of a fellowship from the National Multiple Sclerosis Society.

## Retooling for Modern Management of Progressive MS: An Interactive, Case-Based Activity

In March, 2004 Dr. Miller assumed the position of Medical Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at the Icahn School of Medicine at Mount Sinai. For 23 years prior to that, he headed the Division of Neurology at Maimonides Medical Center in Brooklyn, New York, where he continued to serve as co-director of the Multiple Sclerosis Care Center until 2015. Dr. Miller is also a Professor of Neurology at the Icahn School of Medicine at Mount Sinai in New York.

Dr. Miller is currently Chairman of the National Medical Advisory Committee of the National MS Society, having previously served in that position from 2002-2010. He is a past president of the Consortium of MS Centers and was the first president of the Section on Multiple Sclerosis of the American Academy of Neurology. He has participated in numerous clinical trials of new treatments for MS. He has authored two books: *Multiple Sclerosis in Clinical Practice*, with colleagues Dr. Fred Lublin and Dr. Patricia Coyle, and *Neuroimmunology* as part of the *What Do I Do Now?* series with Dr. Tracy DeAngelis, and edited the *Handbook of Relapsing-Remitting Multiple Sclerosis*. He has also published more than 95 articles in peer-reviewed journals, as well as many chapters on MS and other subjects in neurology.

Dr. Miller is also very active with the American Academy of Neurology (AAN). He served as a member of the Board of Directors from 2009 through 2017 and was secretary of the Board from 2013-2017. He completed 10 years as editor of *Continuum*, the bimonthly continuing education publication of the AAN, in 2012, and currently serves as editor of *Continuum Audio*.

Dr. Miller has been cited numerous times by *New York* magazine in its list of top doctors and has been continually included in *Castle Connolly's America's Top Doctors* from 2009-2018.

### Claire S. Riley, MD

Dr. Riley is an attending neurologist and assistant professor of Neurology at Columbia University Irving Medical Center, in New York, NY.

Dr. Riley earned her undergraduate degree from Dartmouth College and a medical degree from Columbia University College of Physicians and Surgeons, in New York. She completed internship in internal medicine and residency in neurology at the Columbia University Medical Center. Dr. Riley completed a two-year clinical fellowship in multiple sclerosis at Columbia University Multiple Sclerosis Clinical Care and Research Center in 2010.

Dr. Riley joined the faculty of the Department of Neurology of Yale University in New Haven, Connecticut, in 2010, where she served as the Clinical Director of the Yale MS Center. She returned to Columbia University as the Director of the Multiple Sclerosis Clinical Care and Research Center in 2012. Under her leadership, the MS Center has flourished and she now serves as the Medical Director of the MS Center, which is part of the larger Columbia Center for Translational and Computational Neuroimmunology.

### Disclosure of Relevant Financial Relationships with Commercial Interests

It is the policy of CME Outfitters, LLC, to ensure independence, balance, objectivity, and scientific rigor and integrity in all of their CE activities. Faculty must disclose to the participants any relationships with commercial companies whose products or devices may be mentioned in faculty presentations, or with the commercial supporter of this CE activity. CME Outfitters, LLC, has evaluated, identified, and attempted to resolve any potential conflicts of interest through a rigorous content validation procedure, use of evidence-based data/research, and a multidisciplinary peer review process. The following information is for participant information only. It is not assumed that these relationships will have a negative impact on the presentations.

Dr. Lublin reports that he receives research support from Actelion Pharmaceuticals; Biogen; Brainstorm Cell Therapeutics Inc; National Institutes of Health (NIH); National Multiple Sclerosis Society (NMSS); Novartis; and Sanofi. He has consulting agreements, serves on advisory boards, or Data and Safety Monitoring Board for Acorda Therapeutics; Actelion Pharmaceuticals/Janssen Pharmaceuticals, Inc.; Apitope; Brainstorm Cell Therapeutics Inc.; Avotres; Biogen; EMD Serono, Inc; GW Pharmaceuticals; Immunic, Inc.; Innate Immunotherapeutics; Jazz Pharmaceuticals, Inc.; Mapi Pharma; MedDay Pharmaceuticals; MedImmune/ Viela Bio; Mylan; Novartis; Orion Biotechnology; Polpharma; The Population Council, Inc.; Receptos, Inc./Celgene Corporation; Roche/Genentech, Inc.; Sanofi/Genzyme Corporation; Teva Pharmaceuticals; and TG Therapeutics. He is a speaker for Sanofi (non-promotional).

Dr. Miller reports he receives research support from F. Hoffmann-La Roche Ltd/Genentech, Inc.; Mallinckrodt; MedDay Pharmaceuticals; Novartis Pharmaceuticals Corporation; and Sanofi/Genzyme Corporation. He serves as a consultant for AbbVie Inc.: Accordant Health Services (Caremark); Adamas Pharmaceuticals, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company/Celgene Corporation; Corrona; EMD Serono, Inc.; F. Hoffmann-La Roche Ltd; Genentech, Inc.; Mallinckrodt; Mapi-Pharma; and Novartis Pharmaceuticals Corporation. He serves on the speakers' bureau for Alexion Pharmaceuticals, Inc. (unbranded disease awareness programs only); Biogen Idec Inc. (unbranded disease awareness programs only); EMD Serono, Inc. (unbranded journal club); and Genentech, Inc. (unbranded disease awareness programs only).

Dr. Riley reports she receives research support from Biogen Idec, Inc. She is a consultant for EMD Serono, Inc.; Genentech, Inc.; Novartis; and TG Therapeutics.

Jeffrey Helfand, DO, MS (peer reviewer) has no disclosures to report.

Mae Ochoa, RPh (peer reviewer) has no disclosures to report.

Alaeddin Abukabda, MS, DMD, PhD (planning committee) has no disclosures to report.

Evan Luberger (planning committee) has no disclosures to report.

Jan Perez (planning committee) has no disclosures to report.

Sharon Tordoff (planning committee) has no disclosures to report.

Disclosures were obtained from the CME Outfitters, LLC staff: No disclosures to report.

## Retooling for Modern Management of Progressive MS: An Interactive, Case-Based Activity

### **Unlabeled Use Disclosure**

Faculty of this CE activity may include discussions of products or devices that are not currently labeled for use by the FDA. The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

### **Activity Slides**

The slides that are presented in this activity will be available to download and print out at the CME Outfitters website: [www.cmeoutfitters.com](http://www.cmeoutfitters.com). Activity slides may also be obtained via fax or email by calling **877.CME.PROS**.



Retooling for Modern Management of Progressive MS:  
An Interactive, Case-Based Activity



CME Outfitters, LLC,  
is the accredited provider  
for this continuing  
education activity.



---

---

---

---

---

---

CME Outfitters, LLC,  
gratefully acknowledges  
educational grants from  
Novartis Pharmaceuticals  
Corporation in support of this  
CME/CE activity.



The faculty have been informed of  
their responsibility to disclose to  
the audience if they will be  
discussing off-label or  
investigational uses (any use not  
approved by the U.S. Food and  
Drug Administration [FDA]) of  
products or devices.



---

---

---

---

---

---

**Claim ABIM MOC Credit**

3 Things to Do

1. Actively participate in the meeting by **responding to questions** and/or **asking the faculty questions**  
*(It's ok if you miss answering a question or get them wrong; you can still claim MOC)*
2. Complete your post-test and evaluation at the conclusion of the webcast
3. Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation so we can submit your credit to ABIM




---



---



---

**CME for MIPS Improvement Activity**

How to Claim this Activity as a CME for MIPS Improvement Activity

- Actively participate by responding to ARS questions and/or asking the faculty questions
- Complete activity post-test and evaluation at the link provided
- Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation
- Complete the follow-up survey from CME Outfitters in approximately 3 months

**CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity**




---



---



---



**Fred Lublin, MD, FAAN, FANA**

Saunders Family Professor of Neurology  
 Director, The Corinne Goldsmith Dickinson Center for Multiple Sclerosis  
 Icahn School of Medicine at Mount Sinai  
 New York, NY




---



---



---

**Fred Lublin, MD, FAAN, FANA**

Disclosures

- **Research Support:** Novartis; Actelion; Biogen; Sanofi, NMSS, NIH; Brainstorm Cell Therapeutics
- **Consulting Agreements/Advisory Boards/The Data and Safety Monitoring Board (DSMB):** Biogen; EMD Serono; Novartis; Teva; Actelion/Janssen; Sanofi/Genzyme; Acorda; Roche/Genentech; MedImmune/ Viela Bio; Receptos/Celgene; TG Therapeutics; Medday; Atara Biotherapeutics; Polpharma; Mapi Pharma; Innate Immunotherapeutics; Apitope; Orion Biotechnology; Brainstorm Cell Therapeutics; Jazz Pharmaceuticals; GW Pharma; Mylan; Immunic; Population Council; Avotres
- **Speaker:** Sanofi (non-promotional)

**I may discuss unapproved agents that are in the MS developmental pipeline without any recommendation on their use.**




---



---



---



### Aaron Miller, MD, FAAN, FANA

Medical Director  
Corinne Goldsmith Dickinson Center for Multiple Sclerosis  
Professor and Vice-Chair for Education  
Department of Neurology  
Icahn School of Medicine at Mount Sinai  
New York, NY



### Aaron Miller, MD, FAAN, FANA

#### Disclosures

- **Research Support:** F. Hoffmann-La Roche Ltd/Genentech, Inc.; Mallinckrodt; MedDay Pharmaceuticals; Novartis Pharmaceuticals Corporation; and Sanofi/Genzyme Corporation
- **Consultant:** AbbVie, Inc.; Accordant Health Services (Caremark); Adamas Pharmaceuticals, Inc.; Biogen Idec, Inc.; Bristol-Myers Squibb Company/Celgene Corporation; Corrona; EMD Serono, Inc.; F. Hoffmann-La Roche Ltd; Genentech, Inc.; Mallinckrodt; Mapi-Pharma; and Novartis Pharmaceuticals Corporation
- **Speaker's Bureau:** Alexion Pharmaceuticals, Inc. (unbranded disease awareness programs only); Biogen Idec Inc. (unbranded disease awareness programs only); EMD Serono, Inc. (unbranded journal club); and Genentech, Inc. (unbranded disease awareness programs only)



---

---

---

---

---

---



### Claire Riley, MD

Assistant Professor of Neurology  
Medical Director, Columbia University Multiple Sclerosis Center  
Department of Neurology  
Columbia University  
New York, NY



### Claire Riley, MD

#### Disclosures

- **Research Support:** Biogen Idec Inc.
- **Consultant:** EMD Serono, Inc.; Genentech, Inc.; Novartis; and TG Therapeutics



---

---

---

---

---

---





Retooling for Modern Management of Progressive MS:  
An Interactive, Case-Based Activity



---

---

---



Learning Objective **1**

Recognize the symptoms and clinical features of progressive MS.



---

---

---



Learning Objective **2**

Summarize the immunopathology of progressive MS and the MOAs of new and investigational DMTs.



---

---

---



Learning Objective **3**

Evaluate the latest clinical evidence of new and emerging therapies for SPMS and PPMS and engage patients in the shared decision-making process.



---

---

---

### Clinical Case: Andrew

- In 2006, patient presents with numbness in his legs, Lhermitte's sign, dizziness, and double vision
- The patient was started on interferon-beta 1a and his symptoms resolved within 2 months
- Over the next few years, he experienced several episodes of numbness in his legs



CME  
Outitters

---

---

---

### Clinical Case: Andrew

- A 2012 MRI revealed many new small lesions
- In 2014, the patient presented with a feeling of tight compression in his left mid-abdomen, weakness in his legs, and had to stop running a marathon after 5 minutes
- The symptoms resolved but new cervical spinal lesions were noted



CME  
Outitters

---

---

---

### Clinical Case: Andrew

- In 2015, the patient's right foot was getting weak after exercise and he was limping after running 1 mile
- In 2016, the patient was visibly limping and walking with obvious changes in gait after 15 minutes of exercise
- 6 months later, he was unable to go on walks for more than 30 minutes even if he took a break and felt cognitively "less sharp"
- Most recent MRI showed Gd-enhancing lesions



CME  
Outitters

---

---

---

### Phenotypes of MS

- Clinically Isolated Syndrome (CIS)
- Radiologically Isolated Syndrome (RIS)
- Relapsing-remitting (RRMS)
  - About 85% of people are diagnosed with RRMS
- Primary progressive (PPMS)
  - About 15% of people experience this course
- Secondary progressive (SPMS)
  - Most people diagnosed with RRMS will eventually transition to SPMS

Sand JK. *Curr Opin Neurol.* 2015;28(3):193-205.

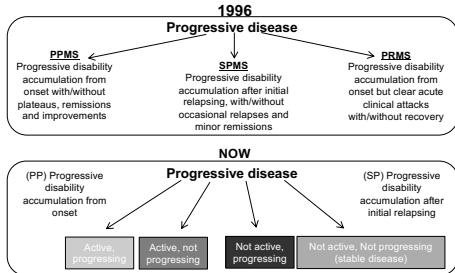
CME  
Outitters

---

---

---

## Phenotype Description for Progressive MS



Lublin FD, et al. *Neurology*. 2014;83(3):278-286.



## Current Diagnostic Criteria for PPMS

- 1 year of disability progression (determined retrospectively or prospectively)
- Two of the following criteria:
  - T2-hyperintense lesions
    - periventricular, infratentorial, or cortical or juxtacortical
  - Two or more spinal T2 hyperintense lesions
  - CSF-specific oligoclonal bands

CSF = cerebrospinal fluid  
Thompson AJ, et al. *Lancet Neurol*. 2018;17(2):162-173.




---



---



---



---



---



---

## Worsening Versus Progression in MS

	Definition	Recommended Evaluation Timeframe
<b>Progressing disease</b>	Accrual of disability, independent of any relapse activity, during the progressive phase of MS (PPMS or SPMS)	Annually by clinical assessment
<b>Worsening disease</b>	Any increase in impairment/disability irrespective of whether it has resulted from residual deficits following a relapse or (increasing) progressive disability during the progressive phase of the illness	Not required

Lublin FD, et al. *Neurology*. 2020 May 29. [Epub ahead of print].



## Predictors of Worsening in MS

- There are currently no available biomarkers that predict MS progression<sup>1</sup>
- Potential predictors of disease worsening<sup>2-4</sup>:
  - Atrophied brain T2 lesion volume
  - Speed of cervical cord atrophy
  - Neurofilament light chain levels
  - Tau protein
  - N-acetylaspartate
  - Chitinase
  - Osteopontin

1. Lublin FD, et al. *Neurology*. 2020 May 29. [Epub ahead of print]. 2. Genovese VA, et al. *Radiology*. 2019;293(2):424-433.  
3. Aymerich FX, et al. *AJNR Am J Neuroradiol*. 2018;39(2):399-404. 4. Ziemssen T, et al. *J. Neuroinflammation*. 2019;16(1):272.




---



---



---



---

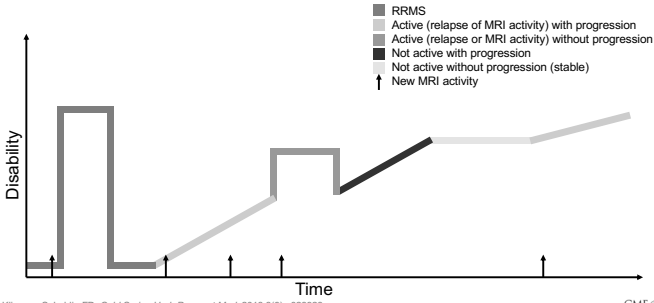


---



---

### Disability Progression in SPMS



Klineova S, Lublin FD. *Cold Spring Harb Perspect Med.* 2018;8(9):a028928.



### Imaging for Diagnosis and Monitoring of MS

**Normal Appearing White Matter**

- New techniques to detect subtle pathological changes
- MTR used to monitor changes in myelin in clinical trials

**Leptomeningeal Infiltrates**

Visible at ultra-high and high field MRI on post-contrast 3D T2-FLAIR

**Cortical Lesions**

- Inclusion in 2017 McDonald criteria
- Association with clinical disability and cognitive impairment
- Association with meningeal inflammation
- Determine neuroprotective effect of treatment

**White Matter Lesions**

- Distinctive lesion features
- Methods to detect slowly expanding lesions on conventional MRI

**Normal Appearing Grey Matter**

- Differences in grey matter atrophy between phenotypes
- Role of deep grey matter and thalamus volume loss in MS
- Relationship between cortical atrophy and cognitive impairment

MTR = magnetization transfer ratio  
 Cortese R, et al. *Theor Adv Neurol Disord.* 2019;12:1756286419859722.




---

---

---



---

---

---

### Pathogenesis of Progressive MS

- Diffuse neurodegeneration (axon, synapse and neuronal damage), diffuse NABT injury, abnormal endothelial tight junction
- Compartmentalized inflammation, microglial activation
- Extensive cortical demyelination

NABT = normal appearing brain tissue  
 Faisner S, et al. *Nat Rev Drug Discov.* 2019;18(12):905-922.



### Pathogenesis of Progressive MS

- Oxidative injury with mitochondrial damage
- Low remyelination and repair capacity, white matter degeneration and loss of myelin trophic support
- High iron deposition
- Glutamate excitotoxicity and astrocyte activation

Faisner S, et al. *Nat Rev Drug Discov.* 2019;18(12):905-922.




---

---

---



---

---

---

## Novel Molecular Targets

- Strategies targeting B- and T-lymphocytes
- Mitochondrion protective strategies
- Anti-inflammatory strategies
- Remyelination strategies

Faisner S, et al. *Nat Rev Drug Discov*. 2019;18(12):905-922.



## Disease Modifying Medications: Categories

### Immunomodulators

Interferon- $\beta$   
Glatiramer Acetate  
Dimethyl Fumarate  
Diroximel Fumarate  
Teriflunomide

- |  |  |
|--|--|
| <b>Pros</b>  | <b>Cons</b>  |
| <ul style="list-style-type: none"> <li>● Safety</li> <li>● Long term experience</li> </ul> | <ul style="list-style-type: none"> <li>● Modest efficacy</li> <li>● Many injectable</li> </ul> |

### Cell-Trafficking Inhibition Agents

Natalizumab  
Fingolimod  
Siponimod  
Ozanimod  
(Ponesimod\*)

- |   |  |
|---|--|
| <b>Pros</b>   | <b>Cons</b>  |
| <ul style="list-style-type: none"> <li>● Greater efficacy</li> <li>● Onset of action quick</li> <li>● Well tolerated</li> </ul> | <ul style="list-style-type: none"> <li>● Opportunistic infections (PML)</li> <li>● Cells still in body</li> <li>● Rebound disease</li> <li>● Long term safety unclear</li> </ul> |

### Cell-Depleting Therapies

Alemtuzumab  
Cladribine  
Ocrelizumab  
Rituximab\*  
(Ofatumumab\*)  
AHST (BMT)

- |   |   |
|---|---|
| <b>Pros</b>   | <b>Cons</b>   |
| <ul style="list-style-type: none"> <li>● Definitive in depleting disease-causing cells</li> <li>● Some are IRT</li> <li>● No rebound disease</li> </ul> | <ul style="list-style-type: none"> <li>● Opportunistic infections</li> <li>● Secondary autoimmunity (alemtuzumab)</li> <li>● Most cumbersome</li> </ul> |

\* Not approved by the FDA for treatment of MS  
IRT = immune reconstitution therapy; PML = progressive multifocal leukoencephalopathy  
Rizvi SA, et al. *Clinical Neuroimmunology: Multiple Sclerosis and Related Disorders*. 2<sup>nd</sup> ed. 2020.



## Progressive MS Therapeutic Landscape

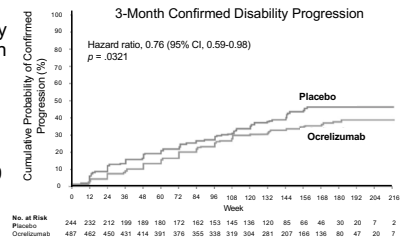
PPMS	SPMS with Activity
Ocrelizumab	Alemtuzumab
	Cladribine
	Dimethyl Fumarate
	Diroximel Fumarate
	Fingolimod
	Glatiramer Acetate
	Interferons
	Ocrelizumab
	Ofatumumab*
	Ozanimod
	Natalizumab
	Siponimod
	Teriflunomide

\* Not approved by the FDA for treatment of MS  
Olek M, Nowry E. Pathogenesis and epidemiology of multiple sclerosis. UpToDate Website.  
<https://www.uptodate.com/contents/pathogenesis-and-epidemiology-of-multiple-sclerosis>. Updated February 17, 2020. Accessed July 11, 2020.



## Clinical Efficacy - Ocrelizumab

- ORATORIO trial (N = 732)
- 3-month confirmed disability progression was 32.9% with ocrelizumab versus 39.3% with placebo (24% relative risk reduction)
- Mean change in volume of T2 lesions was  $-0.39 \text{ cm}^3$  with ocrelizumab and  $+0.79$  with placebo ( $p < .0001$ )

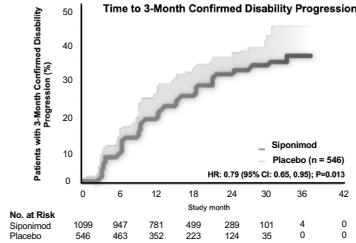


Montalban X, et al. *N Engl J Med*. 2017;376(3):209-220.



## Clinical Efficacy - Siponimod

- EXPAND trial (N = 1651)
- Proportion of patients on siponimod with 3-month confirmed disability progression was 26% versus 32% for those on placebo (21% relative risk reduction)
- Mean change in volume of T2 lesions was 183.9 mm<sup>3</sup> with siponimod and 879.2 with placebo ( $p < .01$ )

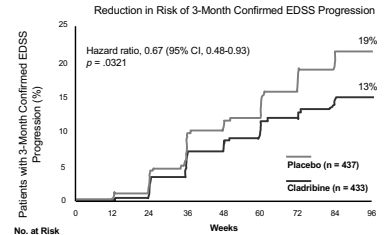


Kappos L, et al. *Lancet*. 2018;391(10127):1263-1273.



## Clinical Efficacy – Cladribine

- CLARITY trial (N = 1326)
- 3-month confirmed EDSS disability progression was 13% with cladribine versus 19% with placebo (33% relative risk reduction)
- Mean number of active T2 lesions per scan was 0.38 with cladribine and 1.43 with placebo ( $p = .001$ )

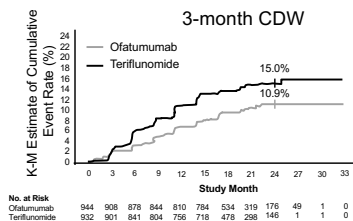


EDSS = Expanded Disability Status Scale  
Giovannoni G, et al. *N Engl J Med*. 2010;362(5):416-426.



## Clinical Efficacy: Ofatumumab\*

- ASCLEPIOS I and II  
● N = 927, N = 954, respectively
- 3-month CDW disability progression was 10.9% with ofatumumab versus 15.0% with teriflunomide (34.4% relative risk reduction)
- Mean number of active T2 lesions per scan was 0.72 and 0.64 with ofatumumab and 4.00 and 4.15 with teriflunomide in ASCLEPIOS I and II, respectively ( $p < .001$ )



\* This agent is not currently approved by the FDA for treatment in MS. Regulatory review expected in September 2020.  
CDW = confirmed disability worsening  
Hauser SL, et al. *ECTRIMS* 2019. Abstract No. 336.



## Clinical Case: Mary

- 45-year-old patient with endometriosis but otherwise healthy
- In 2013, Mary developed left optic neuritis and her brain MRI showed multiple white matter lesions and was prescribed interferon-beta 1a
- In 2014, she began to drag her right leg and reported difficulty walking long distances because of weakness and fatigue. Her symptoms improved but did not resolve completely.



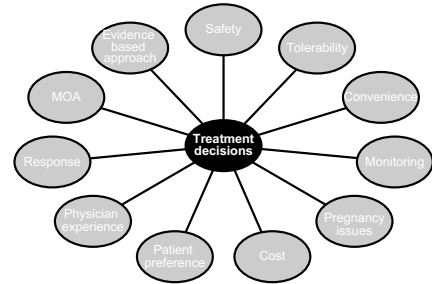
### Clinical Case: Mary

- Mary continued to report episodes of worsening balance, unsteady gait, and lower extremity weakness, and began using a cane intermittently in 2016 and regularly in 2017
- Patient did not return for appointments until 2020 where a neurological examination found moderately severe spastic paraparesis, mild dysmetria, and clumsy, rapid alternating movements in her arms
- Most recent MRI in 2020 showed non-enhancing lesions compared to prior MRI in 2010



CME Outlines

### Making Treatment Decisions Considering the Benefits and Risks



Ross AP. Am J Manag Care. 2013;19(16Suppl):s301-306.

CME Outlines

---



---



---



---



---



---

### Shared Decision-Making in MS



CME Outlines

### Ultimately, the Patient Must Choose

- Patient-Related Considerations**
- Occupation
  - Lifestyle
  - Travel
  - Vaccinations
  - Monitoring availability
  - Pregnancy
  - Ability to use various formulations (i.e., fear of injections)

- Medication-Related Considerations**
- Adverse events
  - Risk vs benefit
  - Treatment goals
  - Severity of disease



CME Outlines

---



---



---



---



---



---

### Engaging Patients in Shared Decision-Making

- Treatment selection must be individualized and based on patient- and disease-specific factors
- Careful consideration of the benefits and risks and communication between physician and patient is necessary to optimize outcomes



### Engaging Patients in Shared Decision-Making

- MS Topography App<sup>1</sup>: Disease simulation application that encourages clinician-patient discussion
- Decision aids: Tools that foster patient involvement in preference-sensitive healthcare decision-making
- 9-Item Shared Decision-Making Questionnaire (SDM-Q-9)<sup>2</sup>: Brief assessment measuring patient and/or clinician perceived involvement in decision-making

1. Krieger SC, et al. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(5):e279.; 2. Kriston L, et al. *Patient Educ Couns*. 2010;80(1):94-99.



---

---

---

---

---

---

### SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Combine diagnostic features and clinical picture to diagnose progressive MS
- Integrate most recent clinical data and mechanism of action of novel and available therapeutic agents into the treatment paradigm of patients with progressive MS
- Engage patients in the treatment decision-making process



### To Receive Credit

To receive CME/CE credits for this activity, participants must complete the post-test and evaluation online.

**[www.cmeoutfitters.com/tst36645](http://www.cmeoutfitters.com/tst36645)**

Participants can print their certificate or statement of credit immediately.

---

---

---

---

---

---



### Claim ABIM MOC Credit

1. Complete your post-test and evaluation at the conclusion of the webcast
2. Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so we can submit your credit to ABIM.



---

---

---

### CME for MIPS Improvement Activity

How to Claim this Activity as a CME for MIPS Improvement Activity

- Actively participate by responding to ARS questions and/or asking the faculty questions
- Complete activity post-test and evaluation at the link provided
- Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation
- Complete the follow-up survey from CME Outfitters in approximately 3 months

**CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity**



---

---

---

### Additional Resources

Visit **www.cmeoutfitters.com** for clinical information and certified educational activities



---

---

---



CONTINUING MEDICAL EDUCATION

After the live webcast, this activity will be available as a web archive at **www.cmeoutfitters.com**



---

---

---

# Attendance Form for Groups

Please complete and FAX to **614.929.3600**

Activity Title and Faculty:

## Retooling for Modern Management of Progressive MS: An Interactive, Case-Based Activity

with Fred D. Lublin, MD, FAAN, FANA (Moderator); Aaron Miller, MD, FAAN, FANA; Claire S. Riley, MD

Site/Institution Name: \_\_\_\_\_

Practice Setting:  Office-based  Hospital  Clinic  Managed Care  Small Group Practice (less than 5)  
 Large Group Practice (more than 5)  Other: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ ZIP: \_\_\_\_\_

Site Coordinator: \_\_\_\_\_ Phone: \_\_\_\_\_

Fax: \_\_\_\_\_ Email: \_\_\_\_\_

Completion Date: \_\_\_\_\_ We participated in: \_\_\_\_\_

Attendee Name (please print)	Please Circle Discipline							Other: _____
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	
_____	MD	DO	PA	NP	RN	Pharm	Other: _____	

Please FAX completed form to 614.929.3600 and use additional sheets as necessary.  
Questions? Call 877.CME.PROS. Thank you for participating in this continuing education activity!