SPRB™

SPECIALTY PHARMACY REVIEW BOARD™

Assessing the Value of Novel Therapies and Care Management Strategies for **Multiple Sclerosis**

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MEDICAL EDUCATION RESOURCES

This activity is supported by an independent educational grant from Novartis Pharmaceuticals Corporation.

AMCP Academy of Managed Care Pharmacy®

Held in conjunction with AMCP Managed Care & Specialty Pharmacy Annual Meeting 2017.

The Specialty Pharmacy Review Board™

- The educational format of **The Specialty Pharmacy Review Board™** is similar to a mock pharmacy and therapeutics committee review of the clinical data, current guidelines, and economic data of a class of therapeutics
- It includes time for peer-to-peer discussion and debate among the diverse group of faculty members and the audience

Educational Objectives

- At the conclusion of this activity, participants should be able to demonstrate improved ability to:
  - Apply current evidence-based diagnosis and treatment data to optimize clinical outcomes for patients with MS in a managed care setting
  - Evaluate quality standards, health care policy, and benefit designs to enhance clinical and economic outcomes for patients with MS
  - Employ care management strategies to boost adherence to treatment plans and improve overall care coordination for MS
  - Provide accurate and appropriate counsel as part of the managed care treatment team

Assessing the Clinical Benefits of Multiple Sclerosis Therapies in a Managed Care Setting

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Learning Objective

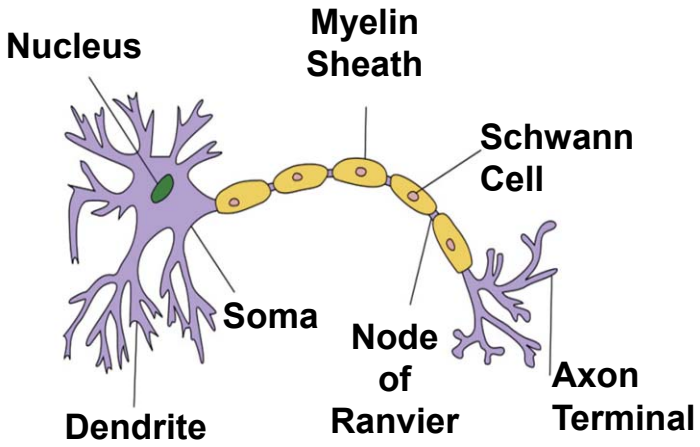
- Apply current evidence-based diagnosis and treatment data to optimize clinical outcomes for patients with multiple sclerosis (MS) in a managed care setting

Outline

- MS Overview (pathogenesis ➡ diagnosis)
- Therapeutic goals in MS
- Review efficacy of current disease modifying treatments (DMT)
- Review side-effect profile and safety monitoring for current DMTs
- Discuss late-stage emerging DMTs
- Acute relapses
- Summary

What Is Multiple Sclerosis?

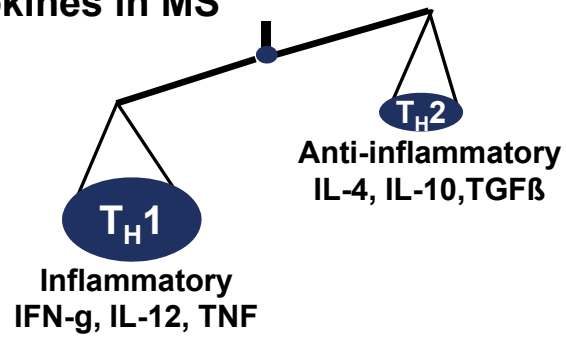
- Chronic progressive autoimmune disease of the central nervous system (CNS)
- Associated with focal areas of inflammation, demyelination, axon transection, neurodegeneration, and subsequent scar or plaque formation
- Often leads to significant disability
  - Median survival in MS population is less than observed in the general population
- Primary etiology unknown, but likely multifactorial
- Risk factors include genetics, viruses, smoking, overweight/obesity, environmental exposures, and low vitamin D



Calabresi PA, Newsome SD. Multiple sclerosis. In: Weiner WJ, et al. *Neurology for the Non-Neurologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010;192-221. Ascherio A. *Expert Rev Neurother*. 2013;13:3-9.

Inflammation and Neuronal Degeneration

Imbalance of Inflammatory Cytokines in MS



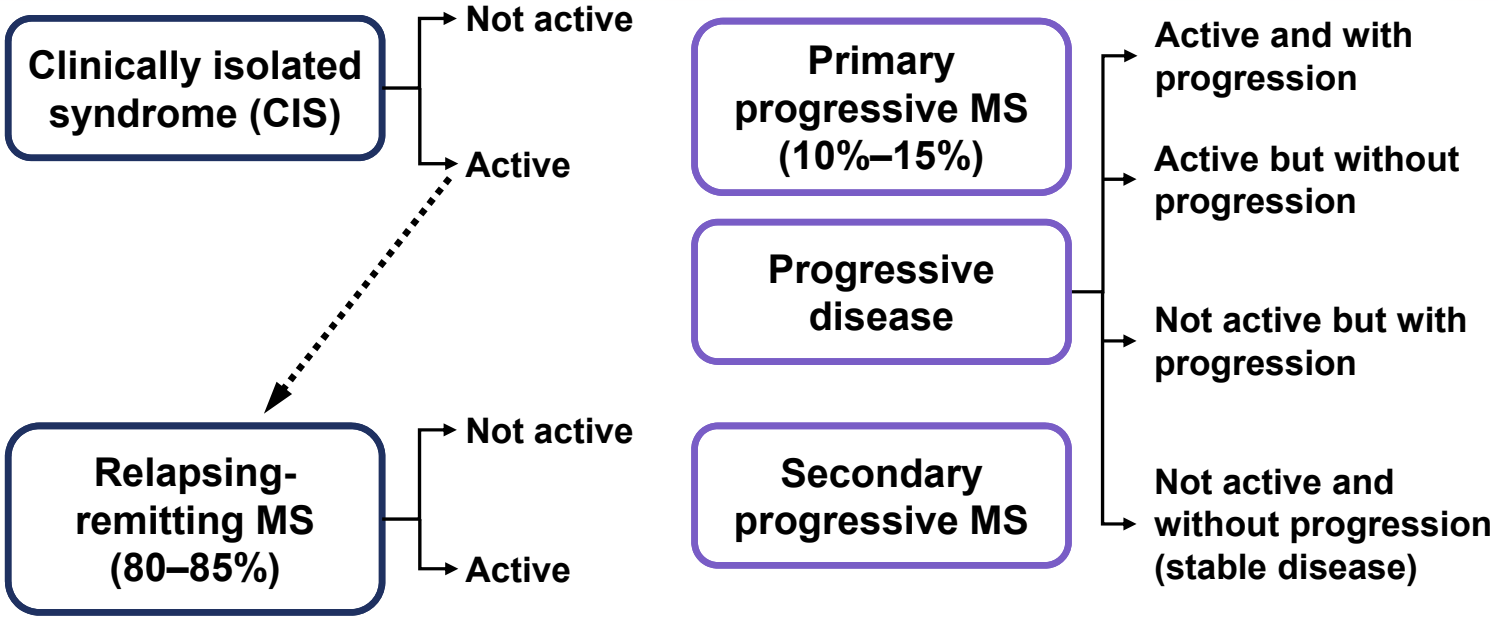
Acute Inflammation → Relapse

Neuronal Degeneration → Disability

- Loss of axons is the main cause of permanent disability in MS
- Axonal damage has been shown to occur in acute inflammatory plaques[1]
- Axonal damage could be the result of cumulative inflammatory damage over time or a parallel degenerative process related to loss of trophic support or an independent axonal degeneration[2]

1. Trapp BD, et al. *N Engl J Med.* 1998;338:278-285. 2. Trapp BD. *Neuroscientist.* 1999;5:48-57.

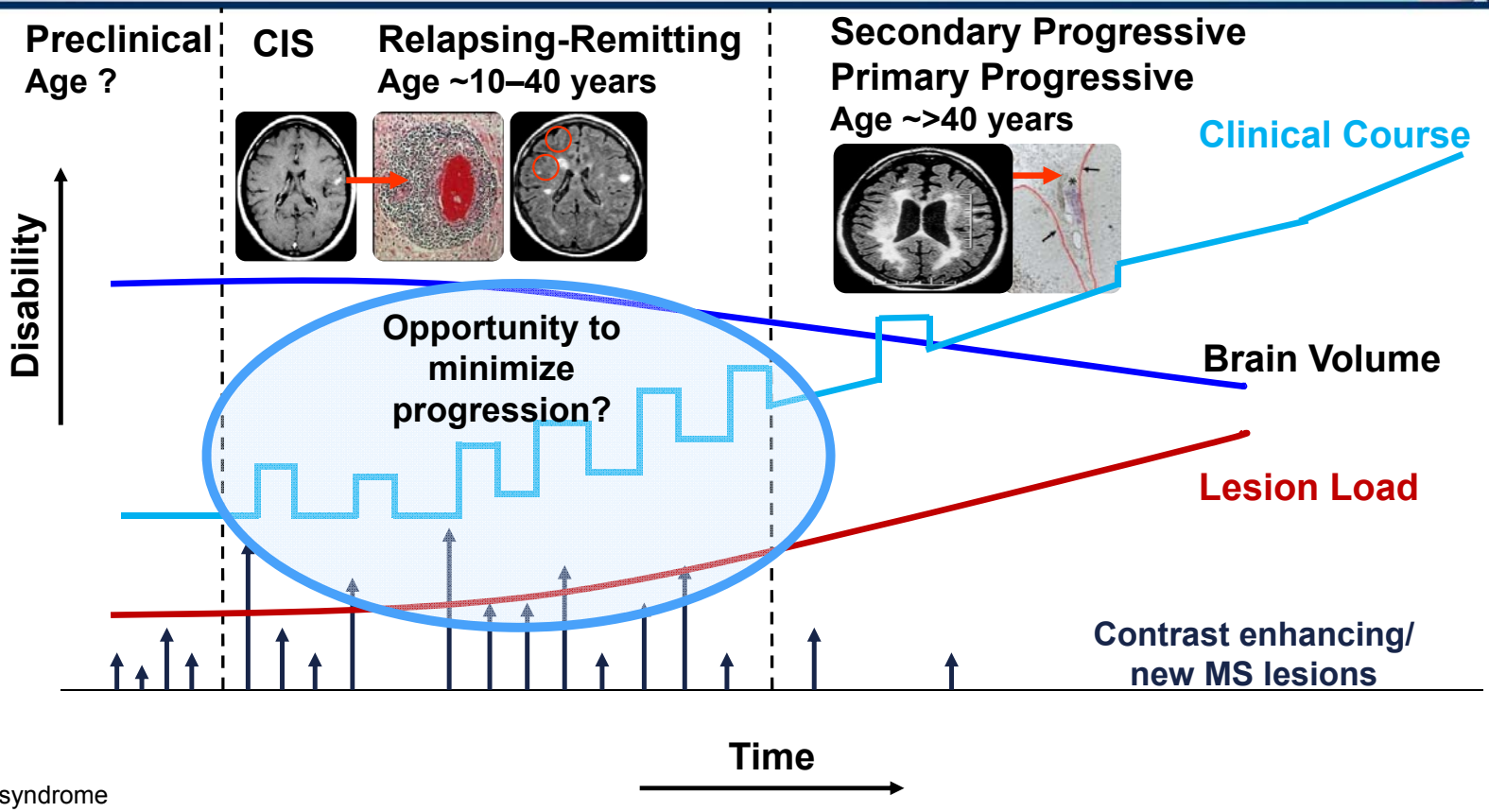
Multiple Sclerosis Disease Subtypes



- Active: Inflammatory activity measured by clinical relapses and/or MRI activity
- Progression: Measured by clinical evaluation
- Radiologically isolated syndrome not included

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

Multiple Sclerosis Disease Course



CIS: clinically isolated syndrome

Slide courtesy of P. Calabresi, MD.

Factors Associated With More Aggressive Multiple Sclerosis

Clinical factors

- Male gender
- Older age at onset
- African American
- Motor involvement
- Cerebellar involvement
- Sphincter involvement
- Frequent relapses
- Poor recovery from relapses
- Multifocal involvement at onset

Paraclinical factors

- MRI high lesion burden at presentation
- 2 gadolinium-enhancing/new T2 lesions or >2 T1-hypointense lesions
- 2 spinal cord lesions
- Brain atrophy
- Low vitamin D

Freedman MS, et al. *Can J Neurol Sci.* 2013;40:307-323.

Common Multiple Sclerosis Symptoms

Primary

- Fatigue
- Weakness
- Numbness/tingling
- Dizziness/vertigo
- Gait difficulties
- Spasticity
- Diplopia (binocular)
- Visual loss
- Cognitive decline
- Mood disorder
- Pain
- Bladder and bowel problems
- Sexual dysfunction

Secondary

- Falls
- Injury
- Bladder infections from urinary retention
- Physical deconditioning

Tertiary

- Vocational changes
- Social isolation
- Change in relationships

National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed February 2017.

Diagnosis of Multiple Sclerosis

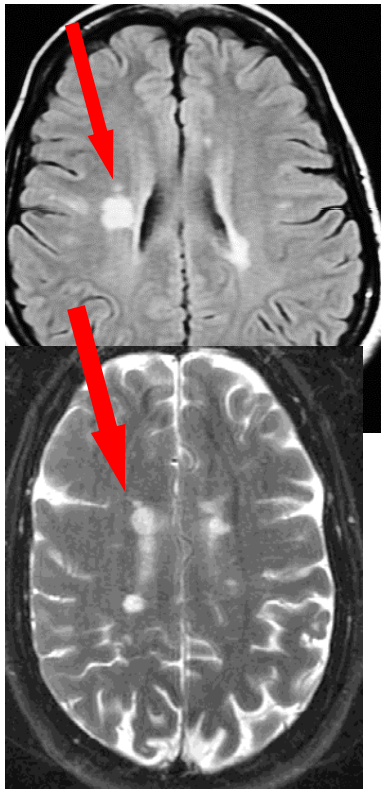
- Based on clinical history, neurologic exam, paraclinical tests (ie, MRI), and exclusion of other possible causes
- Objective evidence of CNS white matter lesions disseminated in time and space
  - Disseminated CNS lesions in time and space can be demonstrated clinically (exacerbations with objective signs on examination, eg, optic neuritis) or by MRI with/without gadolinium
  - Can diagnose MS after a single attack with 2010 McDonald criteria
- CSF in selected patients: cell count, IgG index, and oligoclonal bands
- Blood work obtained to rule out mimics

CSF: cerebrospinal fluid

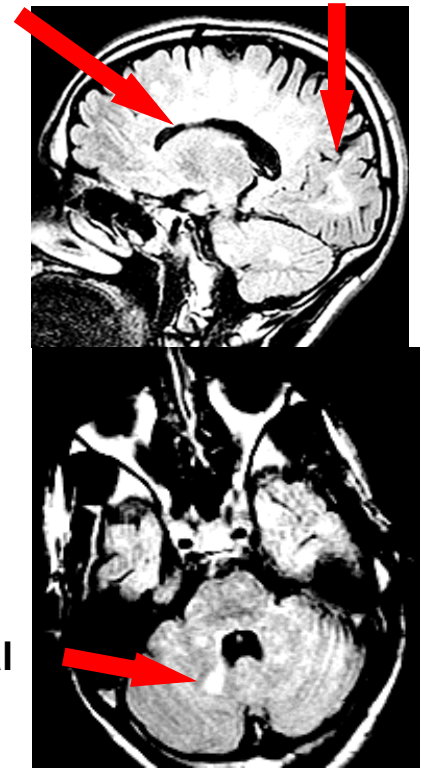
Polman CH, et al. *Ann Neurol*. 2011;69:292-302. Polman CH, et al. *Ann Neurol.* 2005;58:840-846.

Typical MRI Features in MS

Periventricular

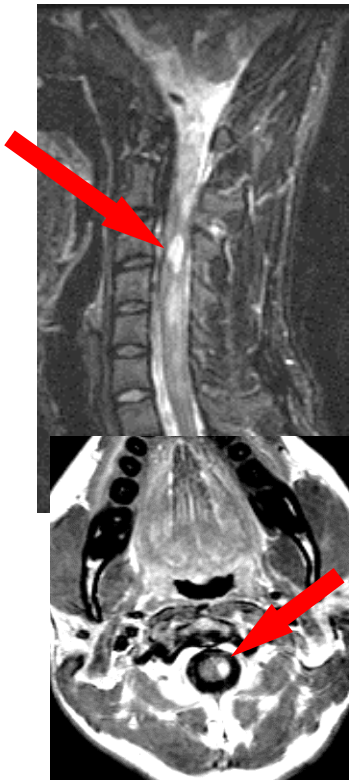


Corpus callosum and juxtacortical



Infratentorial

Spine lesions



Therapeutic Goals in Multiple Sclerosis

- In the absence of a cure for MS, current goals of disease-modifying therapy are to
  - Prevent relapses
  - Prevent development of new or enhancing lesions on MRI
  - Prevent disability
- Additional goals in the management of MS are to
  - Relieve symptoms
  - Maintain well-being
  - Optimize quality of life

Strategies to Attenuate an Immunologically-Mediated Attack

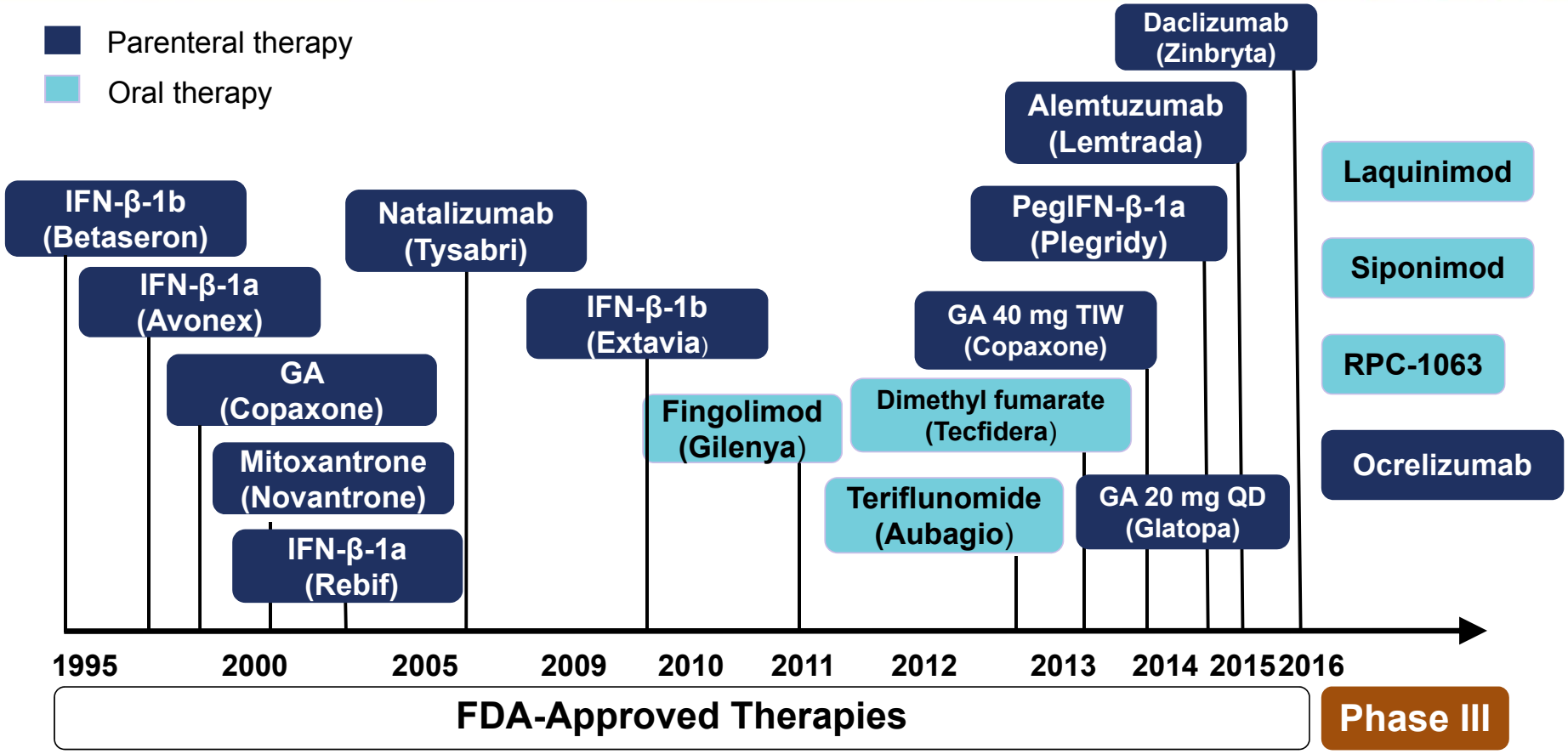
Broad-Spectrum Immunosuppression ⟷ **Antigen-Specific**

Nonselective → **Toxicity**

Selective → **Unknown or multiple antigens**

Slide courtesy of P. Calabresi, MD.

The Evolving Multiple Sclerosis Treatment Landscape



Relapsing-Remitting MS Treatment Algorithm

First Line

Injectable	**Oral**
Interferon β-1a	Dimethyl fumarate
Interferon β-1b	Fingolimod
Peginterferon β-1a	Teriflunomide
Glatirimer acetate	

Second Line
Patients with active disease despite first-line therapy

Natalizumab

Third Line

Alemtuzumab
Daclizumab
Mitoxantrone HCl

Dörr J, Friedemann P. *Curr Treat Options Neurol*. 2015;17:25.

Injectable DMTs: Efficacy

Pivotal Clinical Trials	Agent	Relapses	MRI Activity	12-Week Disability Progression – EDSS
Multiple Sclerosis Collaborative Research Group[1-3]	**IFN β-1a** (Low dose)	ARR: ↓ 18%	Gd+ lesions: ↓50% T2 lesions: no effect	↓ 37%
PRISMS[4,5]	**IFN β-1a** (High dose)	ARR: ↓ 33%	Gd+ lesions: ↓84% T2 lesions: ↓78%	↓ 30%
ADVANCE[6,7]	**Peg IFN β-1a**	ARR: ↓ 36%	Gd+ lesions: ↓86% T2 lesions: ↓67%	↓ 38%
IFNB Multiple Sclerosis Study Group[2,8,9]	**IFN β-1b**	ARR: ↓ 34%	Gd+ lesions: ↓83% T2 lesions: ↓75%	↓ 29% (insignificant Δ from baseline)
Copolymer 1 MS Study Group[10]	**Glatiramer acetate**	ARR: ↓ 29%	Not adequately assessed	Not significant
DECIDE[11, 12]	**Daclizumab vs IFN β-1a**	ARR: ↓ 45%	Gd+ lesions: ↓65% T2 lesions: ↓54%	Not significant

ADVANCE: Efficacy and Safety Study of Peg IFN β-1a in Participants with RMS; ARR: annual relapse rate; DECIDE: Efficacy and Safety of Daclizumab vs Interferon β1a in RRMS; DMTs: disease-modifying therapies; EDSS: Expanded Disability Status Scale; Gd: gadolinium; PRISMS: Prevention of Relapses and Disability by IFN β-1a Subcutaneously in MS

1. Jacobs LD, et al. *Ann Neurol*. 1996;39:285-294. 2. Klawiter EC, et al. *Neurology*. 2009;73:984-990. 3. Simon JH, et al. *Ann Neurol*. 1998;43:79-87. 4. PRISMS Investigators. *Lancet.* 1998;352:1498-1504. 5. EMD Serono. http://www.rebif.com/why-rebif/rebif-efficacy. Accessed September 2016. 6. Calabresi PA, et al. *Lancet Neurol*. 2014;13:657-665. 7. Plegridy Prescribing Information. Biogen Idec Inc. October 2015. 8. IFNB Multiple Sclerosis Study Group. *Neurology*. 1993;43:655-661. 9. Paty DW, Li DK. *Neurology.* 1993;43:662-667. 10. Johnson KP, et al. *Neurology*. 1995;45:1268-1276. 11. Kappos L, et al. *N Engl J Med*. 2015;373:1418-1428. 12. *Neurology Reviews*. 2015 June;23(6):24.

Oral DMTs: Efficacy

Pivotal Clinical Trials	Agent	Relapses	MRI Activity	12-Week Disability Progression-EDSS
FREEDOMS[1]	**Fingolimod**	ARR: ↓ 54%	Gd+ lesions: ↓82% T2 lesions: ↓74%	↓ 32%
TEMSO[2]	**Teriflunomide** (14 mg)	ARR: ↓ 32%	Gd+ lesions: ↓80% Lesion volume: ↓67%	↓ 30%
DEFINE[3]	**Dimethyl fumarate**	ARR: ↓ 53%	Gd+ lesions: ↓90% T2 lesions: ↓85%	↓ 38%

FREEDOMS: Efficacy and Safety of Fingolimod in Patients with RRMS; TEMSO: Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients with MS; DEFINE: Efficacy and Safety of Oral BG00012 in RRMS.

1. Kappos L, et al. *N Engl J Med.* 2010;362:387-401. 2. O'Connor P, et al. *N Engl J Med*. 2011;365:1293-1303. 3. Gold R, et al. *N Engl J Med*. 2012;367:1098-1107.

IV DMTs: Efficacy

Pivotal Clinical Trials	Agent	Relapses	MRI Activity	12-Week Disability Progression-EDSS
AFFIRM[1]	**Natalizumab**	ARR: ↓ 68%	Gd+ lesions: ↓92% T2 lesions: ↓83%	↓ 42%
CARE-MS I[2]	**Alemtuzumab vs IFNβ-1a**	ARR: ↓ 55%	Gd+ lesions: 7% vs 19% T2 lesions: 48% vs 58%	Not significant
CARE-MS II[3]	**Alemtuzumab vs IFNβ-1a**	ARR: ↓ 49%	Gd+ lesions: 9% vs 23% T2 lesions: 46% vs 68%	↓ 42%

AFFIRM: Safety and Efficacy of Natalizumab in the Treatment of MS; CARE-MS I and II: Safety and Efficacy of Alemtuzumab vs. IFNβ-1a in RRMS; ARR: annualized rate of relapse.

1. Polman CH, et al. *N Engl J Med*. 2006;354:899-910. 2. Cohen JA, et al. *Lancet.* 2012;380:1819-1828. 3. Coles AJ, et al. *Lancet*. 2012;380:1829-1839.

Injectable DMTs: Safety and Monitoring

Agent	Minor Side Effects	Major Side Effects	Pregnancy Category	Monitoring
IFNβ-1a (low dose)[1]	Flu-like symptoms, headache, transaminitis, depression	Suicidal ideation, anaphylaxis, hepatic injury, provoke rheumatic conditions, congestive heart failure, blood dyscrasias, seizures, autoimmune hepatitis	C	CBC with differential, LFTs, TFTs, interferon neutralizing antibodies (if clinically warranted), skin surveillance
IFNβ-1a (high dose)[2]	Same as above; injection-site reactions	Same as above; skin necrosis	C	Same as above
Peg IFNβ-1a[3]	Same as above	Same as above	C	Same as above
IFNβ-1b[4,5]	Same as above	Same as above	C	Same as above
Glatiramer acetate[6]	Injection-site reactions; post-injection vasodilatory reaction	Lipoatrophy, skin necrosis, anaphylaxis	B	No specific labs, skin surveillance
Daclizumab[7]	Flu-like symptoms; transaminitis; rash and itching; dry flaky skin; depressed mood	Hepatic injury including autoimmune hepatitis; other immune-mediated disorders; cutaneous events including severe skin reactions	C	Monthly ALT/AST, total bilirubin levels, CBC with differentials

CBC: complete blood count; LFTs: liver function tests; TFTs: thyroid function tests; ALT: alanine amino-transferase; AST: aspartate-aminotransferase

1. IFNβ-1a [prescribing information]. Cambridge, MA: Biogen Idec Inc; 2016. 2. IFNβ-1a [prescribing information]. Rockland, MA: EMD Serono, Inc; November 2015. 3. Pegylated IFNβ-1a [prescribing information]. Cambridge, MA: Biogen Idec Inc; October 2015. 4. IFNβ-1b [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2016. 5. IFNβ-1b [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2015. 6. Glatiramer acetate [prescribing information]. Overland Park, KS: TEVA Neuroscience, Inc; 2015. O'Connor PW, et al. *Handb Clin Neurol*. 2014;122:465-501. 7. Daclizumab [prescribing information]. Cambridge, MA: Biogen Inc. May 2016.

Oral DMTs: Safety and Monitoring

Agent	Minor Side Effects	Major Side Effects	Pregnancy Category	Monitoring
Fingolimod[1]	Lymphopenia (absolute lymphocyte count >200), transaminitis	Bradycardia, heart block, hypertension, risk of infections (herpetic), lymphopenia (absolute lymphocyte count <200), transaminitis, macular edema, skin cancer, reactive airway, PRES, PML	C	First-dose cardiac monitoring, eye and skin examinations, CBC with differential, LFTs, varicella-zoster virus IgG prior to starting medication, PFTs (if clinically indicated)
Teriflunomide[2]	Diarrhea, headache, nausea, hair thinning	Transaminitis, neutropenia, teratogenic (men and women), latent tuberculosis, neuropathy, hypertension, hypersensitivity	X	CBC with differential, LFTs (monthly for first 6 months), PPD prior to starting, wash out (if needed)
Dimethyl fumarate[3]	Flushing, gastrointestinal distress	Transaminitis, lymphopenia, PML	C	CBC with differential, LFTs

CBC: complete blood count; LFT: liver function tests; PFT: pulmonary function tests; PPD: purified protein derivative; PML: progressive multifocal leukoencephalopathy; PRES: posterior reversible encephalopathy syndrome.

1. Fingolimod [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2016. 2. Teriflunomide [package insert]. Cambridge, MA: Genzyme Corporation; June 2016. 3. Dimethyl fumarate [prescribing information]. Cambridge, MA: Biogen Idec Inc; February 2016.

Oral DMTs: Important Treatment Effects

Fingolimod[1]

- 70% to 80% reduction in peripheral lymphocyte counts (ALC 200–600/mm^3 is typical) and 20% neutrophil count; nadir in 2 weeks
- Peripheral counts return to normal 1–2 months after discontinuation
- FDO bradycardia (1:200); mean decrease in heart rate of 13 beats/min
- Higher-risk cardiac patients: cardiology evaluation and admit
- Treatment interruption >12–14 days needs repeat FDO
- Monitor blood pressure over time

Teriflunomide[2]

- Long half-life (18–19 days)
- Slow drug clearance (up to 2 years); use cholestyramine/activated charcoal to quickly eliminate
- Uncommon hepatotoxicity

Dimethyl Fumurate[3]

- 30% reduction in lymphocytes; incidence of infections similar to placebo
- 30% to 40% experience flushing and gastrointestinal distress (symptomatic treatment)
- Chronic lymphopenia and progressive multifocal leukoencephalopathy risk

ALC = absolute lymphocyte count; FDO= first dose observation.

1. Fingolimod [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2016. 2. Teriflunomide [package insert]. Cambridge, MA: Genzyme Corporation; June 2016. 3. Dimethyl fumarate [prescribing information]. Cambridge, MA: Biogen Idec Inc; February 2016.

IV DMTs: Safety and Monitoring

Agent	Minor Side Effects	Major Side Effects	Pregnancy Category	Monitoring
Natalizumab[1]	Headaches, joint pain, fatigue, wearing-off phenomenon	Progressive multifocal leukoencephalopathy, infusion reaction, herpes zoster, other infections, liver failure	C	CBC with differential, LFTs, serum JCV antibody (every 6 months), MRI, natalizumab antibodies (if clinically warranted)
Alemtuzumab[2]	Infusion reactions	Autoimmune thyroid disease, ITP, Goodpasture syndrome, infections (HSV, VZV)	C	Monthly CBC with differential, LFTs, urinalysis with urine cell counts, TFTs every 3 months

ITP: immune thrombocytopenic purpura

1. Natalizumab [prescribing information]. Cambridge, MA: Biogen Idec Inc; May 2016. 2. Alemtuzumab [package insert]. Cambridge, MA: Genzyme Corporation; May 2016.

Emerging Multiple Sclerosis Therapies

Agent	Target/ Mechanism of Action	Possible Indication	Route of Administration	Status
Ocrelizumab	Selective anti-CD20 MAb	RRMS PPMS	IV	Phase 3
Ofatumumab	Anti-CD20 MAb	RRMS	IV/SC	Phase 3
Ponesimod	Sphingosine-1-phosphate receptor 1 (S1P1) modulator	RRMS	Oral	Phase 3
Ozanimod	S1P modulator for receptor subtypes 1 and 5	Relapsing MS	Oral	Phase 3
Siponimod	S1P modulator for receptor subtypes 1 and 5	SPMS	Oral	Phase 3
Masitinib	Tyrosine kinase inhibitor	PPMS SPMS	Oral	Phase 3
Anti-LINGO-1	Neuroprotection/remyelination	Relapsing MS	IV	Phase 2

Krieger S, Fabian M. MS Research Update 2016. http://mymsaa.org/publications/msresearch-update-2016/?gclid=CKaQ3Meot84CFZM2aQodgG0LZg. Accessed February 2017.

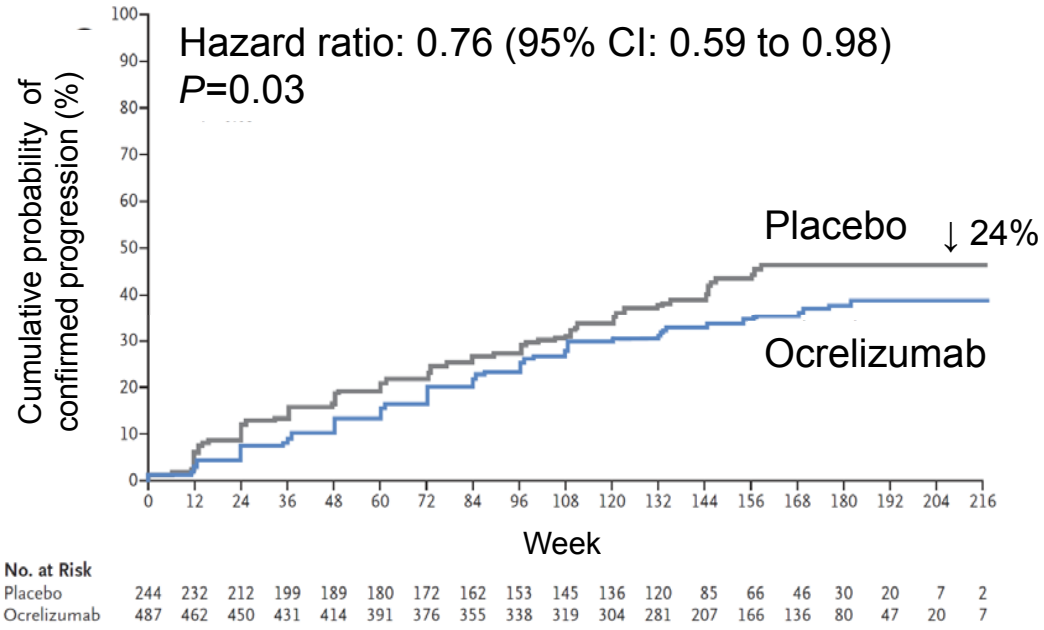
Ocrelizumab vs. Interferon Beta-1a in Relapsing MS: OPERA I and OPERA II Primary Endpoint

	OPERA I			OPERA II		
	Ocrelizumab (N=410)	INF b-1a (N=411)	*P* value	Ocrelizumab (N=417)	INF b-1a (N=418)	*P* value
Primary Endpoint						
Annualized relapse rate (95% CI)	**0.16 (0.12 to 0.20)**	**0.29 (0.24 to 0.36)**		**0.16 (0.12 to 0.20)**	**0.29 (0.23 to 0.36)**	
Rate ratio (95% CI)	**0.54 (0.40 to 0.72)**		**<0.001**	**0.53 (0.40 to 0.71)**		**<0.001**

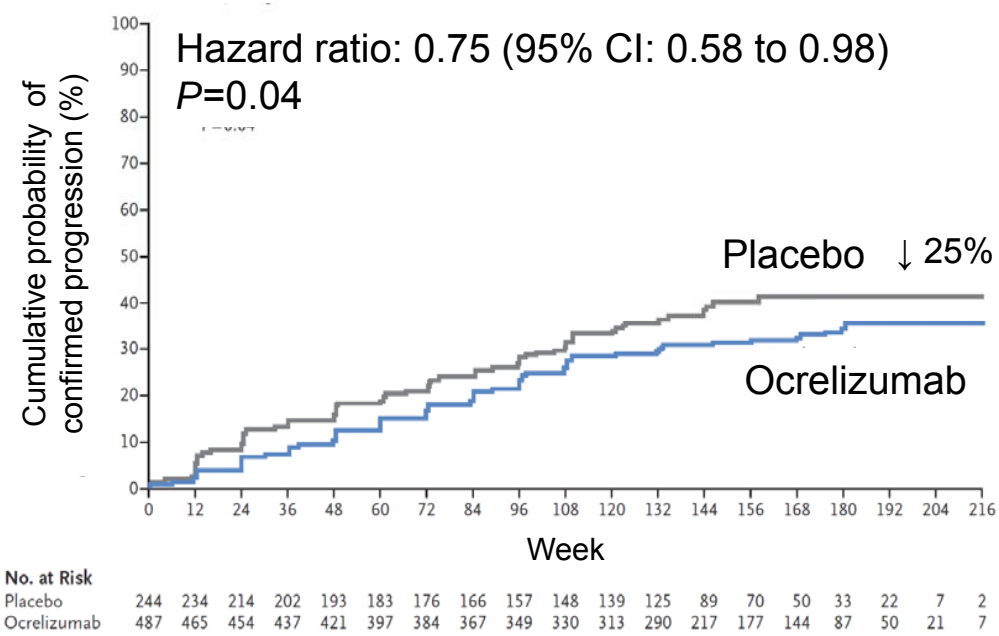
Hauser SL, et al. *N Engl J Med*. 2017;376:221-234.

Ocrelizumab vs. Placebo in Primary Progressive MS: ORATORIO Primary and Key Secondary Endpoints

12-Week Confirmed Disability Progression (Primary Endpoint)



24-Week Confirmed Disability Progression (Key Secondary Endpoint)



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

Ofatumumab

- Phase 2 MIRROR trial (n=232) evaluated 3, 30, and 60 mg Q12W and 60 mg Q4W ofatumumab SC vs placebo
  - Week 0-12 showed 65% contrast lesion reduction
  - Week 4-12 showed ≥90% ↓ (for cumulative doses ≥30 mg)
  - Linear B cell suppression: 32-64 cells/mcL associated with 1 new lesion/year (vs 16 new lesions with placebo)
- Phase 3 trials (ASCLEPIOS I and II) in Relapsing MS began enrolling in September 2016
  - Primary endpoint: annualized relapse rate

Sorensen PS, et al. *Neurology.* 2014;82:573-581; *Neurology.* 2014;82(S17):1.007.

Masitinib: Ongoing Phase 3 Trial

- Blinded, randomized, placebo-controlled, 96 week phase 3 trial to investigate the superiority of masitinib vs. placebo (NCT01433497)
- N=600 patients with primary progressive or relapse-free secondary progressive MS
- Clinical endpoints:
  - Change in MS Functional Composite Score (MSFC)
  - Change in Multiple Sclerosis Quality of Life 54 items (MSQOL-54)
  - Change in Expanded Disability Status Score (EDSS)
- Study is ongoing with results anticipated in 2017

AB Sciences. http://www.ab-science.com/en/human-medicine/masitinib-in-neurodegenerative-disease. Accessed March 2017.

Ozanimod: Phase 3 Trial

- SUNBEAM (NCT02294058)
  - Multicenter, randomized, double-blind, double-dummy, active-controlled study
  - Comparison of the safety, effectiveness and tolerability of two oral doses of ozanimod (0.5 mg and 1 mg) vs. IM injection of interferon beta-1a once a week for at least 12 months
  - N=1346 patients with relapsing MS
  - Both doses of ozanimod demonstrated a significantly lower annual relapse rate (ARR) vs control over 12 months
  - Ozanimod-treated patients also showed fewer brain MRI lesions

Celgene. http://ir.celgene.com/releasedetail.cfm?releaseid=1012395. Accessed March 2017.

Ponesimod: Phase 2 and 3 Trials

- Phase 2b study of 464 patients with relapsing remitting MS investigated orally administered ponesimod (10, 20 and 40 mg) or placebo for 24 weeks
  - The cumulative number of new gadolinium-enhancing (Gd+) lesions detected on MRI scans at Weeks 12 and 24 were significantly reduced in a dose-dependent manner by 43%, 83% and 77% with ponesimod 10, 20 and 40 mg, respectively
  - Annualized relapse rate (ARR) up to week 24 was approximately 0.33, 0.42 and 0.25 in the 10, 20 and 40 mg ponesimod groups, respectively, vs 0.525 in the placebo group
- Phase 3 OPTIMUM Trial (NCT02425644)
  - Multi-center, randomized, double-blind, parallel-group, active-controlled, 3-year superiority study
  - Comparison of the efficacy and safety of ponesimod vs. teriflunomide in 1100 RMS patients
  - The study aims to determine whether ponesimod is more efficacious than teriflunomide in reducing relapses

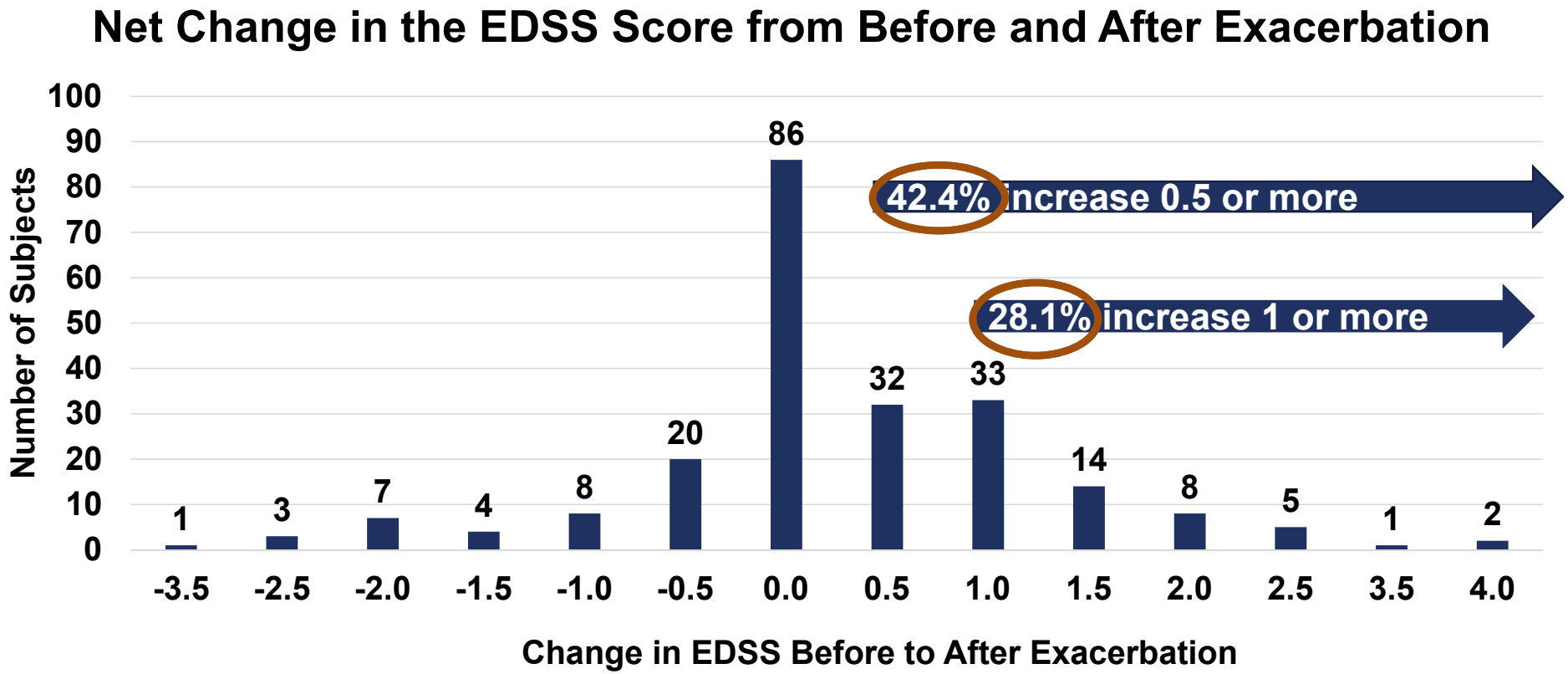
D'Ambrosio D, et al. *Ther Adv Chronic Dis*. 2016;7:18-33.
Actelion. https://www1.actelion.com/en/scientists/development-pipeline/phase-3/ponesimod.page. Accessed March 2017.

Siponimod Phase 3 EXPAND Study

- Secondary Progressive Multiple Sclerosis (SPMS) patients (N=1,651) randomized to 2 mg siponimod or placebo
  - Primary endpoint: Delaying the time to 3-month disability progression as measured by EDSS
  - Secondary endpoints: Delay in time to 6-month confirmed disability progression, time to confirmed worsening of at least 20% from baseline in the timed 25-foot walk test, T2 lesion volume, annualized relapse rate (ARR), safety and tolerability
- EXPAND met its primary endpoint; patients receiving siponimod had a 21% reduced risk of disability progression vs. placebo (*P*=0.013)
  - Secondary endpoints: siponimod-treated patient had 23.4% lower average change in brain volume and reduced lesion volume
  - Siponimod was generally well tolerated; adverse events were similar to those reported with other SP1 receptor modulators

Kappos L, et al. Efficacy and safety of siponimod in secondary progressive multiple sclerosis: results of the placebo controlled, double-blind, phase III EXPAND study. ECTRIMS 206. Abstract 250. September 16, 2016.

Relapses Are Associated With Progression in Disability



EDSS: Expanded Disability Status Scale score

Lublin FD, et al. *Neurology.* 2003;61:1528-1532.

Treating Acute Relapses

- IV corticosteroids = standard of care
  - Methylprednisolone 500 to 1000 mg/d IV for 3 to 5 days
    - May be followed by oral steroid taper
- High-dose oral steroids may be acceptable alternative
  - Phase III randomized OMEGA trial comparing oral and IV steroids
- Plasmapheresis/Plasma exchange for refractory relapse

Berkovich R. *Neurotherapeutics.* 2013;10:97-105.

Summary

- Multiple sclerosis is a common, chronic demyelinating disease of the central nervous system that usually presents in the prime of life
- Ability to treat MS is evolving rapidly and becoming more complicated as additional agents are introduced
- Introduction of effective and generally safe disease-modifying therapies has made a “one size fits all” approach to treatment of relapsing-remitting MS obsolete
- Effective treatment for progressive subtypes of MS remains a significant unmet need
- Goal of treatment is to balance efficacy, safety, and tolerability of therapeutic interventions for each patient

Current Multiple Sclerosis Practice Guidelines

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Learning Objectives

- Aligning multiple sclerosis (MS) therapy coverage decisions with treatment guidelines

MS Treatment Guidelines: Current Status

- Current American Academy of Neurology (AAN) guidelines were issued in 2002 and only included 2 disease-modifying therapies:
  - β-interferon and glatiramer acetate
- There are now more than 16 medications currently approved and widely prescribed for the treatment of MS in the United States with several other agents nearing approval
- Updated AAN guidelines are anticipated in 2017

Current MS Treatment Algorithms Lack Clarity

- There is no single consensus approach to determining access to MS disease modifying therapies (DMTs)
- Treatment guidelines are not necessarily beneficial for developing a health plan's clinical management program
  - Comparative data on available therapies is lacking
  - Current guidelines tend to provide only general statements and do not contain details and/or specific instructions for individualized clinical decisions

Owens G. *Am J Manag Care.* 2013;19:S307-S312.

Which DMT Should Be Used?

Established DMTs	• DMTs for relapsing MS mostly approved in the 1990s • Include reformulations and generic versions of these substances
Newer DMTs	• DMTs approved for relapsing MS since the 2000s • Typically possess different mechanisms of action from earlier DMTs

- DMT choice based on
  - Disease features (subtype, duration, prognostic profile, clinical/MRI features)
  - Drug features (efficacy, tolerability, dosing/administration, mechanism of action, convenience, risk/benefit ratio, monitoring, access)
  - Patient characteristics (comorbidities, lifestyle, expectations, pregnancy issues, etc)

- Interferon-β and glatiramer acetate remain first-line DMTs for many clinicians
  - Essentially well tolerated with a minimum of serious adverse events (AEs)
  - Effective in reducing clinical attacks and new MRI lesions

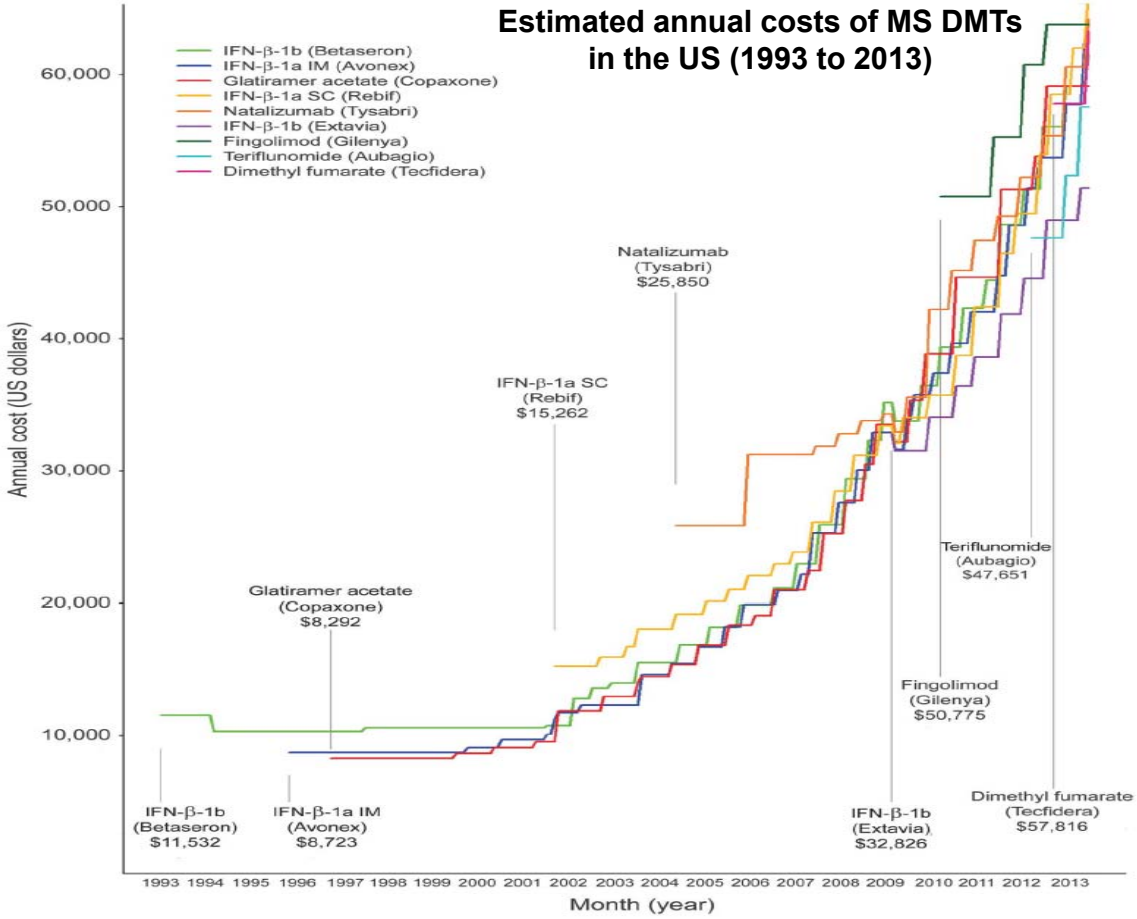
Harrison DM. *Ann Intern Med*. 2014;160:ITC4-1.

Current FDA-Approved DMTs

Route of Administration	Drug	Dosing Frequency	Approval Date
Self-injected	IFNβ-1a • Avonex • Plegridy • Rebif	• Weekly (IM) • Every 2 weeks (SQ) • 3x/week (SQ)	• 1996 • 2014 • 2002
	IFNβ-1b • Betaseron • Extavia	• Every other day (SQ)	• 1993 • 2009
	• Glatiramer acetate	• Daily or 3x/week (SQ)	• 1997
	• Daclizumab	• Every 4 weeks (SQ)	• 2016
Intravenous infusion	• Mitoxantrone • Natalizumab • Alemtuzumab	• Every 3 months • Every 4 weeks • 5 days, then 3 consecutive days, then 12 mo later	• 2000 • 2006 • 2014
Oral	• Teriflunomide • Fingolimod • Dimethyl fumarate	• QD • QD • BID	• 2012 • 2006 • 2013

Access to MS DMTs Complicated by Cost

- High costs of managing MS are receiving scrutiny from managed care organizations and other payers
- With limited price competition, plans must use every lever to drive utilization according to the best pharmacoeconomic analysis available
- Payers often limit the DMTs made available to their insured members as first line agents
- Restrictions on access frequently influences the selection of therapy



Hartung DM, et al. *Neurology*. 2015;84:2185-2192.

Clinical Issues to Consider When Making MS DMT Coverage Decisions

Who should be considered appropriate prescribers?
Is there a difference between new prescriptions and renewals?
Are there guidelines that can be used as the basis for clinical management?
What will the role in therapy be for the newer oral and infusion agents?
Are the interferons approved prior to 2009 and glatiramer acetate still first-line treatments?
Can I have a preferred interferon?
When is it appropriate to switch therapy to another agent?
What is the role of the intravenous agents in therapy?
Are there patients who should not be started on an interferon approved prior to 2009 or glatiramer acetate?
How do we evaluate when a therapy is no longer effective?

Owens G. *Am J Manag Care.* 2013;19:S307-S312.

Plan Strategies to Control Utilization

Tiered formulary
- Generic
- Preferred branded
- Nonpreferred branded specialty
- Non-formulary

Utilization management programs
- Prior authorization
- Step edits

Encouraging appropriate use
- Clinical algorithms/pathways

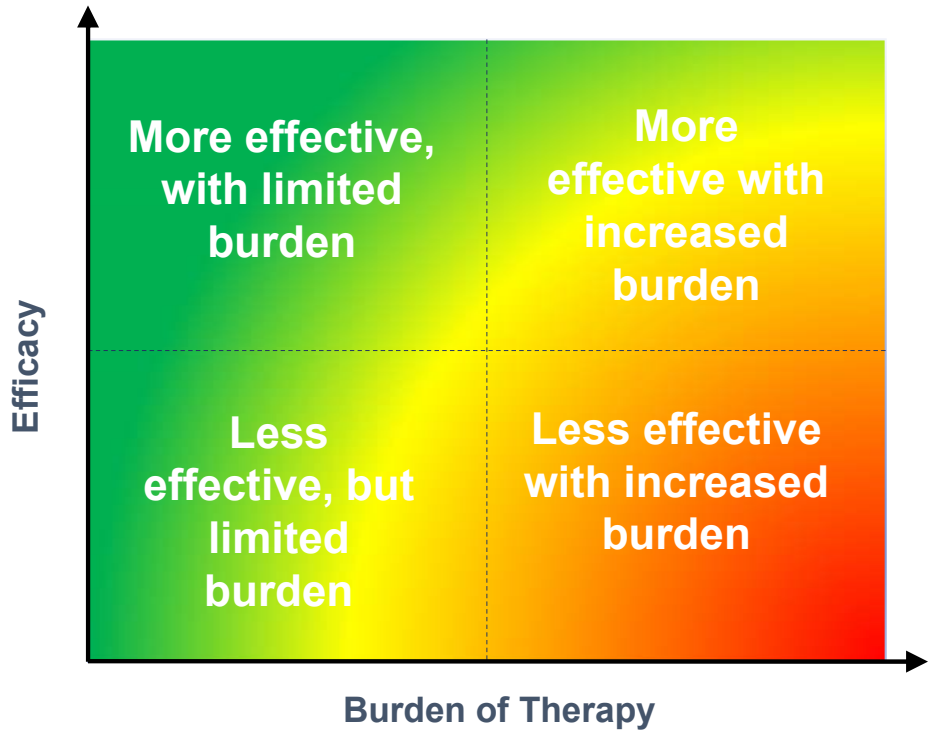
Cost sharing

Cost-effectiveness analysis

Owens G. *Am J Manag Care.* 2013;19:S307-S312.

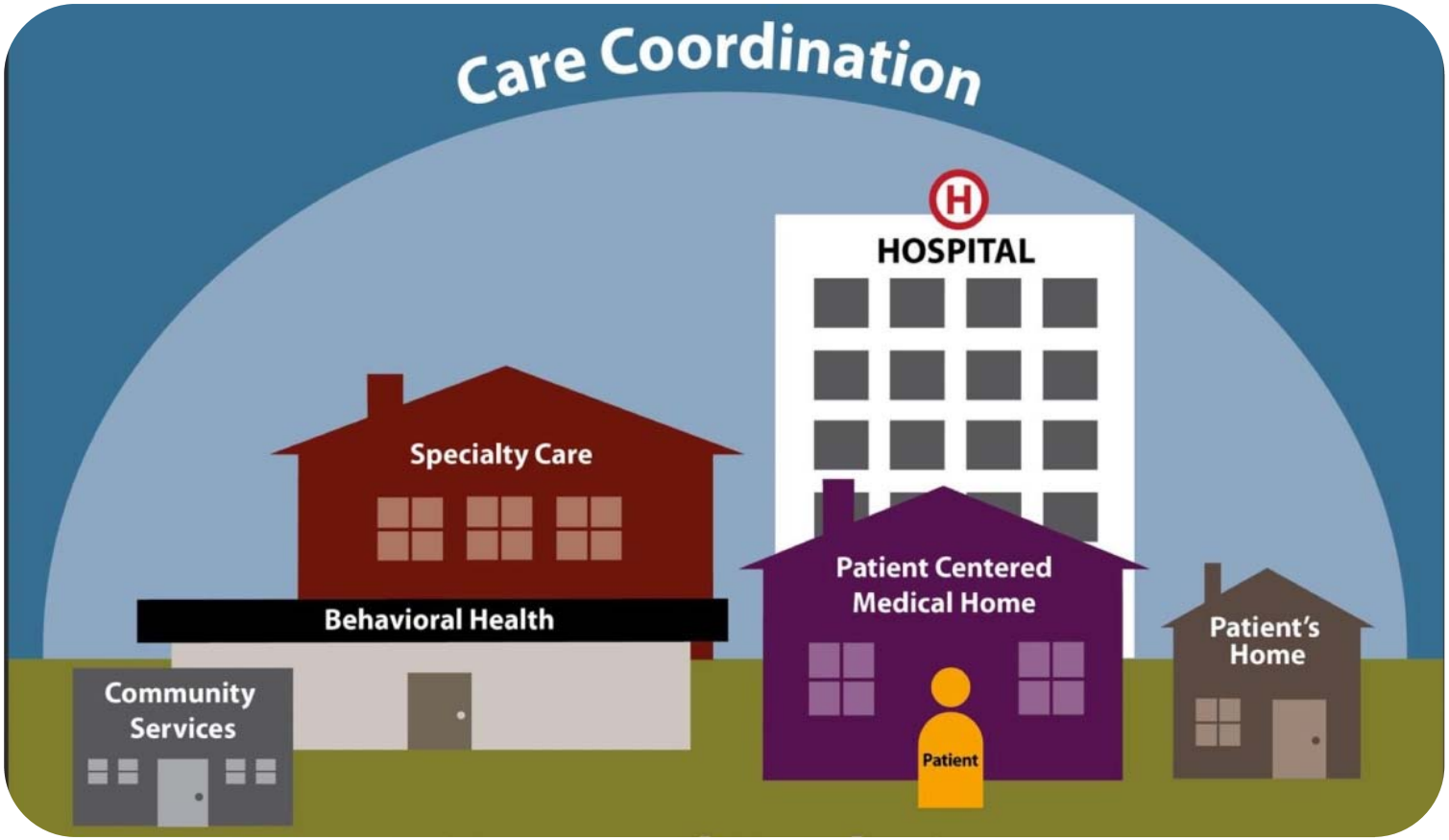
Formulary Decision Making

- P&T decisions typically based on 3 principles
  - Efficacy
  - Cost/value
  - Safety
- Prior to 2009, all MS DMTs were readily available on formulary
  - PA was the primary strategy to manage the category
- Addition of new classes of agents since 2009 has introduced further complexity into the P&T decision-making process
- In the absence of comparative data, committees are seeking to balance efficacy, safety, and burden of therapy in their management of the MS formulary



Owens G. *Am J Manag Care.* 2013;19:S307-S312.

Plan Strategies to Optimize Health Outcomes



Improving Clinical Outcomes for Patients with MS is a Top Priority for Health Plans

Coordinated, multidisciplinary care

- MS patients require lifelong therapy including neurology care, primary care, physical therapy, occupational therapy, and psycho-social counseling

Case management and routine follow up

- Patient education
- Adherence support

Management of comorbidities

- MS patient often require antidepressants, analgesics, antispasmodic agents, anticonvulsants, nonsteroidal anti-inflammatory drugs, and benzodiazepines

Owens G. *Am J Manag Care.* 2013;19:S307-S312.
Treatment and the high cost of MS. https://www.optum.com/resources/library/multiple-sclerosis-complex-costly.html. Accessed February 2017.

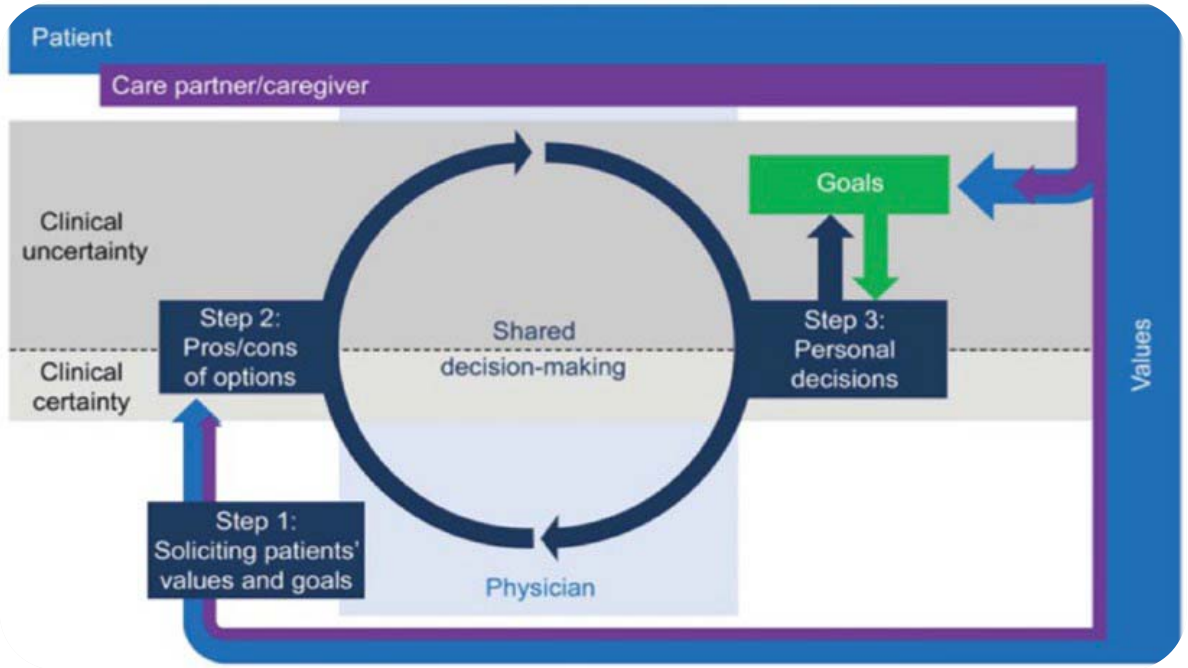
Harnessing Shared Decision-making to Improve Health Outcomes

- Useful in preference-sensitive conditions such as MS
- Guides decision making when a number of available treatment options of similar efficacy exist, but each with differences in risks and benefits

Colligan E, et al. *Mult Scler J*. 2017;23:185-190.

Shared Decision-making Framework

- Steps in the shared decision-making process
  - Provider elicits the patient's values and preferences about their care
  - Provider facilitates an evidence-based discussion of treatment options
  - Patient and provider arrive at a treatment decision together



Colligan E, et al. *Mult Scler J*. 2017;23:185-190.

Summary

- MS is associated with substantial clinical and economic burdens
- Management of MS has become increasingly complex with the introduction and approval of several safe and effective, but costly therapies
- Coverage decision makers are challenged to find a balance between effectively managing the disease and maximizing the value of high-cost disease-modifying therapies
- Treatment of MS should be individualized, and shared decision-making between patients and health care providers is critical for successful management
- Health care providers and payers need to collaborate to ensure that resources are used optimally to enhance both clinical and economic outcomes

Analyzing the Recent Data to Assess the Value of Multiple Sclerosis Treatment Options

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Baltimore, MD

Learning Objectives

- Review the disease burden of multiple sclerosis (MS)
- Discuss the economic value of disease modifying treatments for patients with MS

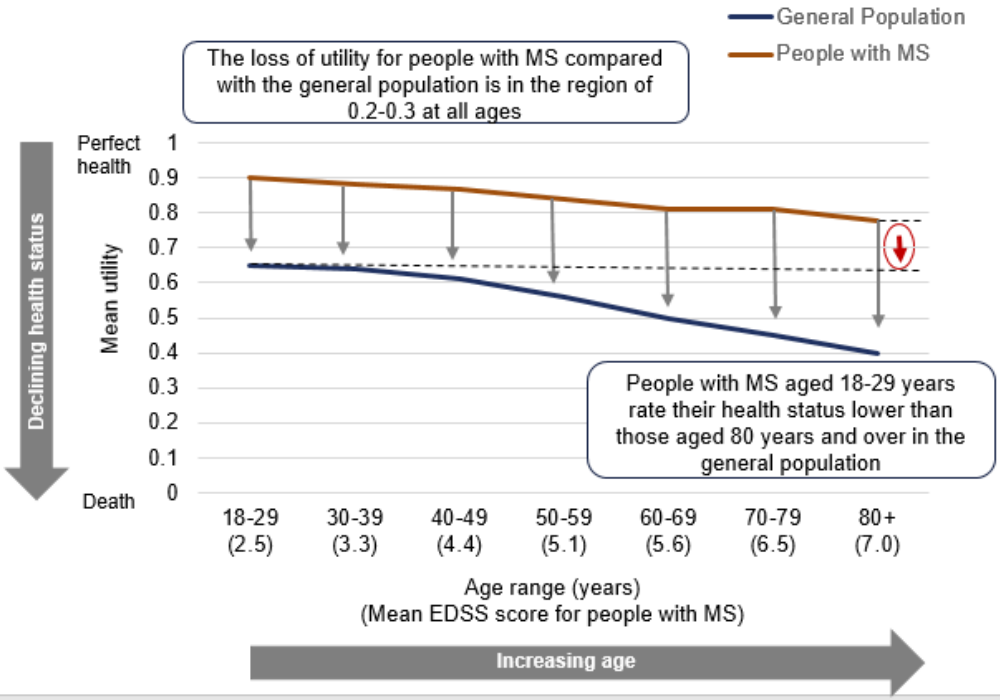
Prevalence and Economic Burden of MS

- MS affects an estimated least 400,000 people in the United States
- Most people diagnosed between age 20 – 50 years
- Affects 2-3x more women than men
- Risk of developing MS: 1 in 1,000
- There is currently no cure

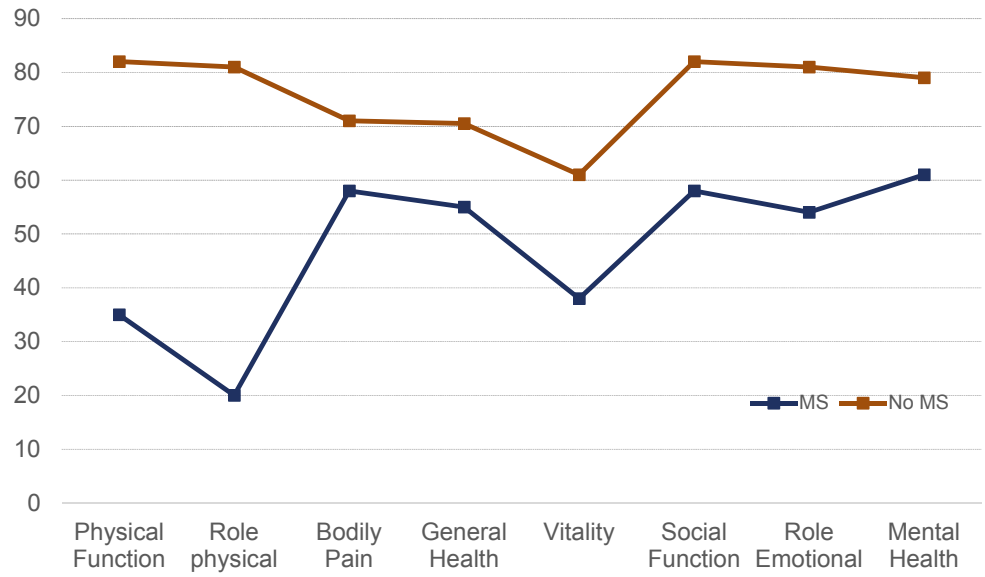
National Multiple Sclerosis Society. MS Prevalence. http://www.nationalmssociety.org/About-the-Society/MS-Prevalence. Accessed February 2017.
Adelman G, et al. *J Med Econ*. 2013;16:639-647.

MS Negatively Affects Health Status and Quality of Life

Health Status



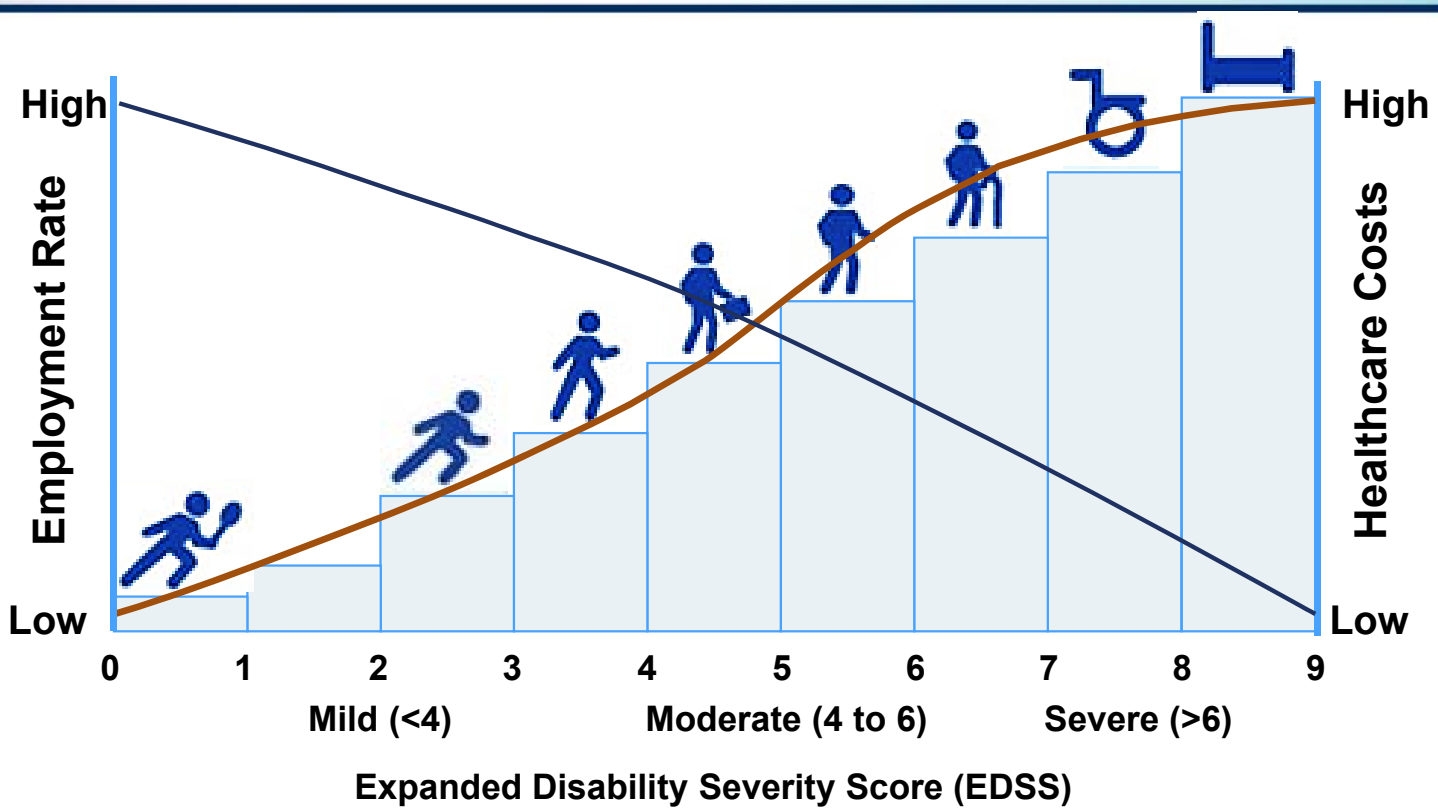
Health-Related Quality of Life*



*Measured with the SF-36.

Kobelt G, Kasteng F. Access to innovative treatments in multiple sclerosis in Europe. The European Federation of Pharmaceutical Industry Associations (EFPIA) 2009. http://www.comparatorreports.se/Access%20to%20MS%20 treatments%20-%20October%202009.pdf. Accessed February 2017.

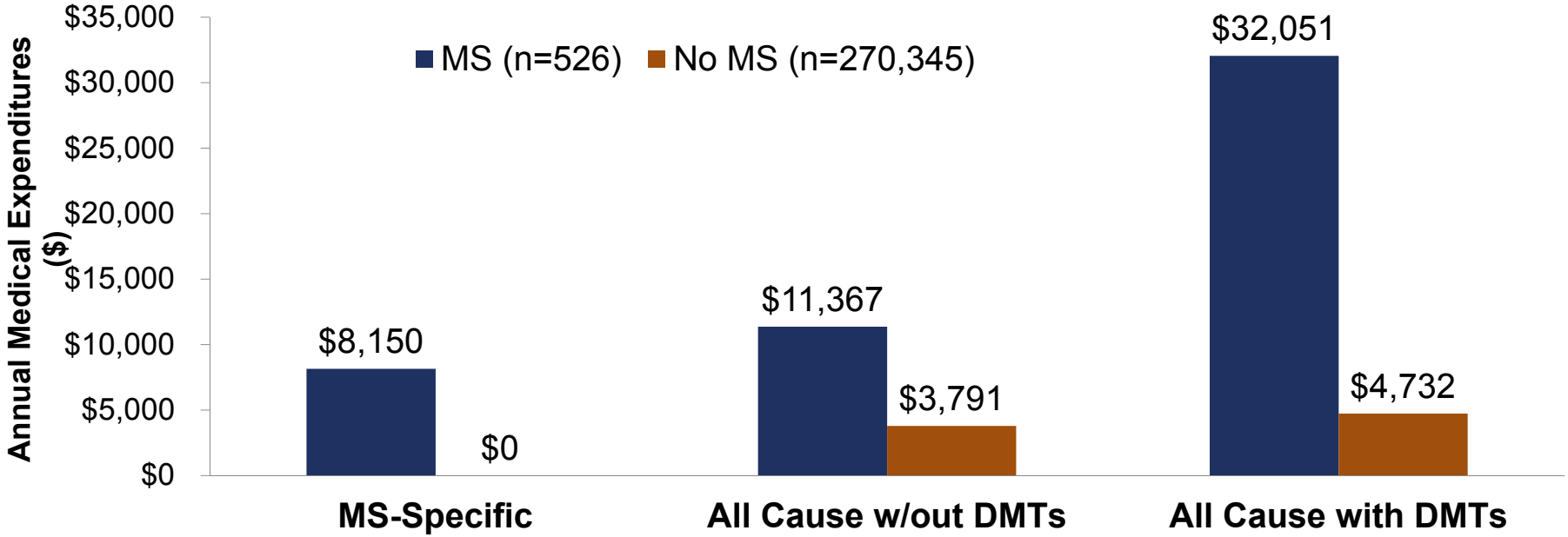
Costs Increase and Productivity Decreases as MS Progresses in Severity



Burks J. *J Manag Care Med*. 2009;12:26-31. http://jmcmpub.org/pdf/12-1/?pdf_page=26. Accessed February 2017; Comi G. *Neurol Sci*. 2006;27:S8-S12; Kobelt G, et al. *Neurology.* 2006;66:1696-1702; Campbell JD, et al. *Mult Scler Relat Disor*. 2014;3:227-236.

MS-specific and All Cause Annual Medical Expenditures

Annual Direct Costs Were $24,327 Higher for the MS population vs the Non-MS Population
(95% CI:$22,320; $26,333)

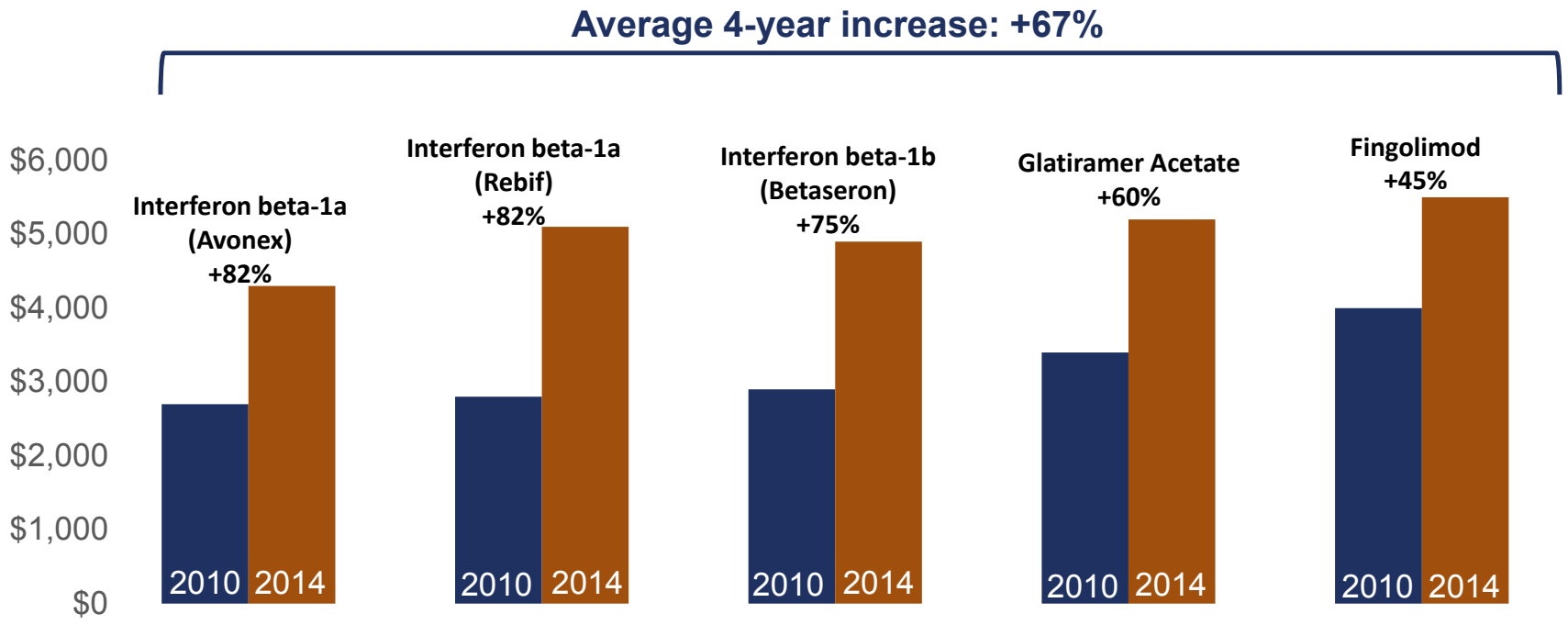


Data from the Medical Expenditure Panel Survey of non-institutionalized MS patients (≥18); 1998 to 2009

DMT=disease modifying therapy

Campbell JD, et al. *Mult Scler Relat Disor*. 2014;3:227-236.

Cost Trends of the Five Common DMTs



Hartung DM, et al. *Neurology*. 2015;84:2185-2192.
Brass and Ivory: Life with MS and RA. http://www.brassandivory.org/2010/10/gilenya-priced-at-4000month-30-50.html. Accessed February 2017.
Optum Rx. Multiple sclerosis. https://www.optum.com/content/dam/optum/resources/whitePapers/M53018_G_MS_Insight_Report_ORx_FINAL.pdf. Accessed February 2017.

Determining the Value of DMTs

- Economic evaluation tools include
  - Cost-effectiveness analysis (CEA): Compares the cost and effectiveness of two or more treatments
  - Cost-utility analysis (CUA): A subtype of CEA, applying quality adjusted life years (QALY) as a measure of effectiveness
    - Primary outcome measure in CUA is the incremental cost-effectiveness ratio (ICER)
    - ICER describes difference in cost between two treatments per QALY gained
- A threshold of $50,000/QALY is often used as a socially acceptable standard against which to compare treatments

Joensuu JT, et al. *PLoS One*. 2015;10(3):e0119683.

Interpreting Results of CEA of DMTs: Caveats

- Modeling procedures and data inputs used across CEA of DMTs lacks standardization
- Features of higher quality models include
  - Use of simulations that represent the chronic nature of the disease
  - Inclusion of long-term time horizons, societal perspectives, and QALYs as the primary standards
  - Supplemental evidence with shorter horizons, payer perspectives, and clinical outcomes to inform multiple decision makers
- Actual impact of DMT costs on a particular plan will vary based on drug pricing and other factors affecting drug costs

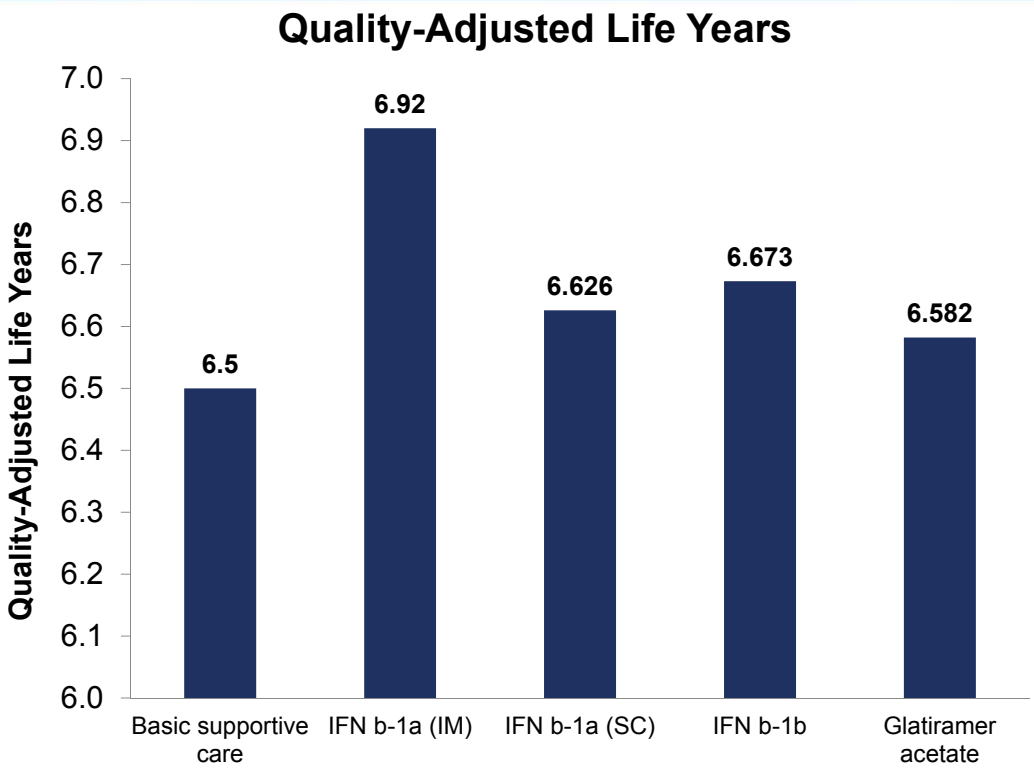
Yamamoto D, Campbell JD. *Autoimmune Dis*. 2012; doi:10.1155/2012/784364.

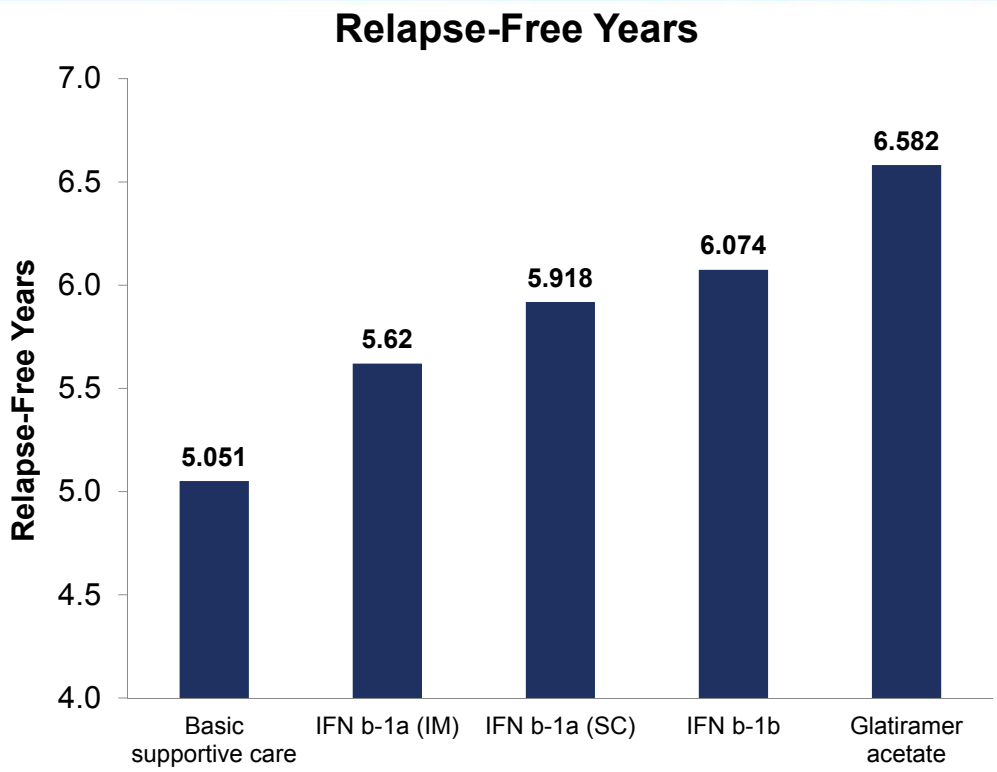
Example 1: Cost-Effectiveness Analysis of Interferons and Glatiramer Acetate

- Markov model used to evaluate cost-effectiveness of DMTs compared to basic supportive therapy without DMT over a 10-year time horizon
- Outcomes were measured as gains in quality-adjusted life-years (QALY) and relapse-free years
- Data obtained from a mail-in survey of > 2,000 MS patients with relapsing MS funded by the National Multiple Sclerosis Society
- DMTs included in the analysis
  - Interferon beta-1a (IM)
  - Interferon beta-1a (SC)
  - Interferon beta-1b
  - Glatiramer acetate

Noyes K, et al. *Neurology*. 2011;77:355-363.

Treatment with DMTs Results in Modest QALY Gains vs Basic Supportive Care Over 10 Years

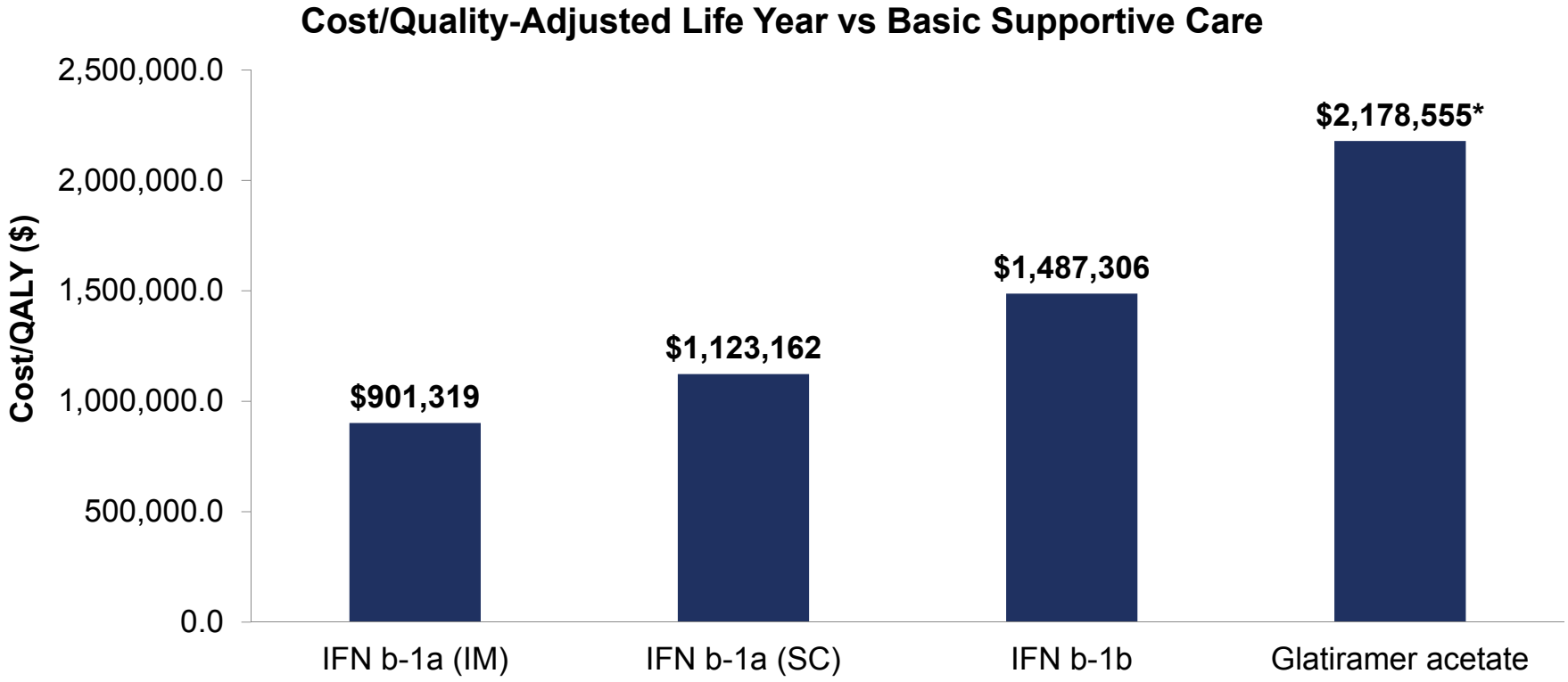




IFN=interferon; b=beta; IM=intramuscular; SC=subcutaneous

Noyes K, et al. *Neurology*. 2011;77:355-363.

Interferons More Cost-effective Than Glatiramer Acetate



**P*<0.05 vs the interferons
IFN=interferon; b=beta; IM=intramuscular; SC=subcutaneous

Noyes K, et al. *Neurology*. 2011;77:355-363.

Example 2: Cost-Effectiveness Analysis of Interferon β-1a vs Fingolimod

- Markov model comparing fingolimod to intramuscular interferon (IFN) beta-1a using a US societal perspective and a 10-year time horizon
- Data sources
  - Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS)]
  - Published studies of MS
- Base-case analysis consisted of a cohort of 37 year-old RRMS patients who had an EDSS score of 0–2.5 and a recent history of relapse
- Outcomes included costs in 2011 US dollars, QALYs, number of relapses avoided, and incremental cost-effectiveness ratios (ICERs)

RRMS = Relapsing–Remitting Multiple Sclerosis; EDSS = Expanded Disability Status Scale.

Lee SD, et al. *J Med Econ*. 2012;15;1088-1096.

Fingolimod Associated with Fewer Relapses and More QALYs Gained vs IFN β-1a

	Fingolimod	IFN β-1a
Cost per patient		
Total costs	$565,598	$505,234
Incremental costs	$60,364	---
Effectiveness measure per patient		
Relapses	4.103	7.314
Relapses avoided	3.211	--
QALYs	6.7663	5.9503
Incremental QALYs	0.816	--
ICER		
Cost per QALY	$73,975 per QALY	Referent
Cost per relapse avoided	$18,799 per relapse	Referent

ICER = incremental cost-effectiveness ratio; IFN = interferon; QALY = quality-adjusted life year.

Lee SD, et al. *J Med Econ*. 2012;15;1088-1096.

Example 3: Cost-Effectiveness Analysis of 6 DMTs

- Markov state transition cohort model used to predict MS disease progression following initiation of a DMT over a 10-year time horizon
  - Expanded Disability Status Scale (EDSS) used to track disease progression
- DMTs included in the analysis:
  - Natalizumab 300 mg every 4 weeks
  - Dimethyl fumarate 240 mg twice daily
  - Peginterferon beta-1a 125 mcg every 2 weeks
  - Fingolimod 0.5 mg once daily
  - Glatiramer acetate 20 mg once daily
  - Interferon beta-1a 44 mcg thrice weekly

Bozkaya D, et al. *J Med Econ*. 2017; 20:297-302.

Clinical Outcomes Over 10 Years

Outcome Measure	NTZ	FIN	DMF	GA	PEG	IFN
Relapses per patient	5.9	6.9	7.7	9.0	8.9	9.0
Relapse-free years gained per patient (undiscounted)	8.5	8.3	8.1	7.8	7.9	7.8
Relapse-free years gained per patient (discounted)	7.3	7.2	7.0	6.8	6.8	6.8
% patients EDSS <6.0	63%	50%	56%	50%	56%	53%
Years spent in EDSS <6.0 per patient (undiscounted)	8.2	7.5	7.8	7.6	7.9	7.7
Years spent in EDSS <6.0 per patient (discounted)	7.2	6.6	6.9	6.6	6.9	6.7

DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FIN = fingolimod; GA = glatiramer acetate; IFN = interferon beta-1a; NTZ = natalizumab; PEG = peginterferon beta-1a

Bozkaya D, et al. *J Med Econ*. 2017; 20:297-302.

Cost-Effectiveness Over 10 Years

Outcome Measure	NTZ vs FIN	DMF vs GA	PEG vs IFN
Incremental cost	-$35,524	-$47,573	-$37,790
Incremental cost per relapse avoided (over 10 years)	NTZ dominant	DMF dominant	PEG dominant
Incremental cost per relapse-free year gained (10 years)	NTZ dominant	DMF dominant	PEG dominant
Incremental cost per progression to (ie, to EDSS ≥6.0) avoided (10 years)	NTZ dominant	DMF dominant	PEG dominant
Incremental cost per progression-free year (EDSS <6.0) gained (10 years)	NTZ dominant	DMF dominant	PEG dominant

- Costs ranged from $561,177 (NTZ) to $616,251 (GA)
- NTZ, DMF, and PEG were more cost-effective (ie, less costly and more effective) than FIN, GA, and IFN for all incremental cost-effectiveness ratios (ICERs)

DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FIN = fingolimod; GA = glatiramer acetate; IFN = interferon beta-1a; NTZ = natalizumab; PEG = peginterferon beta-1a

Bozkaya D, et al. *J Med Econ*. 2017; 20:297-302.

Summary

- The chronic debilitating nature of MS drives increased healthcare resource consumption
- Annual direct medical costs for the MS population are substantially higher vs the non-MS population
- In the absence of head-to-head trials, Markov modeling has been used to assess the cost-effectiveness of DMTs for MS, however, models have weaknesses that limit their current use for health policy and clinical practice decisions

Comparative Analyses for Evidence-based Treatment and Benefit Design Decision Making

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Wellesley, MA

Learning Objective

- Review comparative effectiveness research (CER) and discuss its application as a decision support tool

Why Don’t Patients Receive the “Best” Treatments?

Differing underlying assumptions and study designs make comparison of clinical trial results difficult

Confounding variables include

Presence of comorbidities	Patient age	Health reimbursement system	Year in which costs are determined	Variation in study design

Why Comparative Effectiveness Research (CER)?

- Health care decision-making is often supported by incomplete information
- Lack of head-to-head comparisons of competing treatment alternatives can lead to a “trial and error” approach to decision-making
- If effectively designed and conducted, CER can help fill data gaps
  - Used to compare drug therapies in the absence of head-to-head data
  - Applicable to a wide variety of practice settings and diversity of patients

Brixner DI, Oderda G. *J Manag Care Pharm*. 2012;18(Suppl. 4-a):S3-S4.

How Can CER Change MS Practice?

- Provides prescribers with insights into the advantages and disadvantages of MS Disease Modifying Therapies (DMTs) when head-to-head trial data is unavailable
- Provides payers and benefit design decision makers data to:
  - Inform decisions regarding the level of coverage for current and developing MS therapeutics including
    - Tier status
    - Copayment level
    - Need for prior authorization
  - Drive the use of the most effective treatments

Happe LE. *Am J Manag Care*. 2013;19:S332-S342.

CER Consolidates Evidence From Multiple Sources

- Prospective clinical trials
- Retrospective analyses of health care data including administrative claims databases, electronic health records, patient registries
- Systematic reviews/meta-analyses
- Literature reviews
- Health technology assessment reports
- In-house data analysis

Ahmann A. *Am J Manag Care.* 2011;17(2 suppl):S41-S51.
Malone DC. *Am J Pharm Benefits.* 2010;2:301-303.

CER Analysis of a Commercial Claims Database of DMTs in MS

- Retrospective study of real-world DMT comparative effectiveness in more than 5,000 patients with MS
  - Commercial Claims Database containing administrative claims and eligibility records of 80 million commercially-insured individuals
  - Data collected between January 2012 and September 2014
- **Objective:** Compare annualized relapse rates (ARR) and DMT adherence for MS patients initiating dimethyl fumarate, interferon β, glatiramer acetate, teriflunomide or fingolimod in routine clinical practice

Baseline Patient Demographics

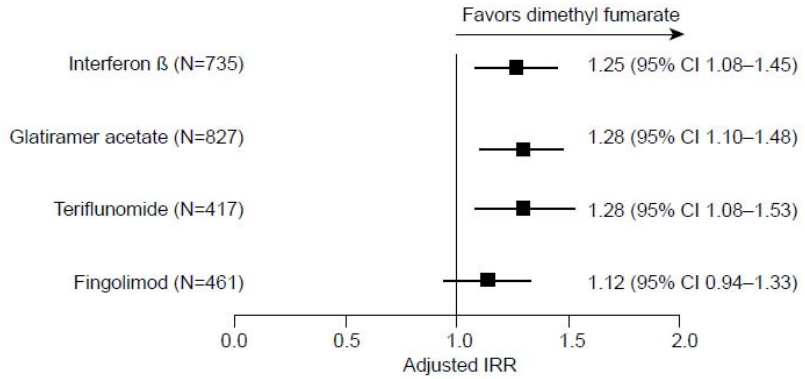
	Dimethyl fumarate (N=2,564)	Interferon β (N=735)	Glatiramer acetate (N=827)	Teriflunomide (N=417)	Fingolimod (N=461)
Age, mean (SD) years	46.8 (9.7)	43.9 (10.8)*	43.5 (10.4)*	49.5 (9.1)*	43.8 (10.1)*
Female, % patients	76.3	78.5	78.7	82.0†	76.6
DMT exposure in pre-index period, % patients					
	70.6	14.6*	17.3*	66.9	65.5†
CCI score, % patients		‡	‡	‡	
0	73.6	69.5	67.0	67.4	78.1
1	11.7	7.9	10.0	11.3	7.8
2	9.6	14.3	13.8	13.7	8.9
≥3	5.1	8.3	9.2	7.7	5.2

*Pairwise comparison with dimethyl fumarate significantly different at p<0.001. †Pairwise comparison with dimethyl fumarate significantly different at p<0.05. ‡CCI scores were significantly different from dimethyl fumarate for interferon β and glatiramer acetate (p<0.0001 for both comparisons) and teriflunomide (p=0.008).
CCI = Charlson Comorbidity Index; DMT = disease-modifying therapy; SD = standard deviation.

Boster A, et al. Presented at the 68th Annual Meeting of the American Academy of Neurology. April 15–21, 2016. Vancouver, Canada.

CER Results: Annualized Relapse Rates and Adherence

In this analysis, Dimethyl Fumarate was Associated with a Lower ARR*[1]



N=2,564
*After adjusting for baseline characteristics, prior DMT exposure, and clinical characteristics.
ARR = annualized relapse rate; CI = confidence interval; IRR = incidence rate ratio.

Adherence to Index DMT** in the Year After DMT Initiation[1]

	Dimethyl fumarate (N=2,564)	Interferon β (N=735)	Glatiramer acetate (N=827)	Teriflunomide (N=417)	Fingolimod (N=461)
Mean PDC	0.70	0.64*	0.62*	0.66†	0.80*
PDC ≥0.8, % patients	57.7	45.3*	44.0*	51.3†	70.5*

PDC=proportion of days covered; defined as the proportion of days within the study period the patient has a prescription claim for a DMT
**Index DMT=dimethyl fumarate
*Pairwise comparison with dimethyl fumarate (P<0.001)
†Pairwise comparison with dimethyl fumarate (P<0.05)

- These results are consistent with previously reported findings of mixed and indirect treatment comparisons[2-4]
- Clinicians should be aware of the importance of real-world data and of differences in real-world CER of available DMTs when making treatment decisions

1. Boster A, et al. Presented at the 68th Annual Meeting of the American Academy of Neurology. April 15–21, 2016. Vancouver, Canada; 2. Bergvall N, et al. *PLoS One.* 2014;9:e88472; 3. Hutchinson M, et al. *Curr Med Res Opin.* 2014;30:613–627; 4. Tramacere I, et al. *Cochrane Database Syst Rev.* 2015;9:CD011381.

Planned Future CER Analyses of MS Therapies

- Four CER studies analyzing therapies used to treat MS or its symptoms have been funded by the Patient-Centered Outcomes Research Institute (PCORI)
  - Studies 1 and 2: safety and efficacy of DMTs prescribed to reduce MS attacks or slow disease progression
  - Study 3: Assess effectiveness of medications used to treat fatigue
  - Study 4: Assess the benefits of treatment and rehabilitation delivered in a traditional clinic vs telehealth

PCORI. http://www.pcori.org/news-release/four-studies-assess-effectiveness-multiple-sclerosis-treatments-receive-19-6-million. Accessed February 2017.

CER in Perspective

- CER results may vary widely
- Use of CER may not directly reduce expenditures for drugs and/or medical technologies in real-world health care settings
- To provide insights on the most effective and cost-effective interventions, cost-effectiveness must be integrated into the CER analysis

Brixner DI, Watkins JB. *J Manag Care Pharm*. 2012 Jun;18(5 Supp A):S06-11.

Summary

- Incomplete data can impact decision-making in health care decisions
- CER can be utilized to generate and/or synthesize data to support health care decision-making
- CER requires valid and feasible data from multiple sources
- The intent of CER is to describe whether a treatment works for the average patient in the average practice
- Decision makers should be aware of the importance of real-world data and of differences in real-world CER of available DMTs when selecting therapy

Maximizing Value for Current and Emerging MS Therapies

Learning Objective

- Evaluate quality standards, health care policy, and benefit designs to enhance clinical and economic outcomes for patients with multiple sclerosis (MS)

Treating Multiple Sclerosis Remains Challenging

- Providers and payers must effectively manage MS while simultaneously maximizing the value of high-cost treatment options
- Challenges include
  - Lack of screening guidelines
  - Significant variation in treatment across practice settings
  - Complex treatment decisions
  - Prolonged treatment durations
  - Rapid introduction of multiple disease-modifying therapies (DMTs)
  - Limited comparative (head-to-head) studies and cost-efficacy data
  - Evolving quality performance measures

"Multiple sclerosis is one of the most difficult problems in clinical medicine."
(J-M Charcot, MD, 1894)

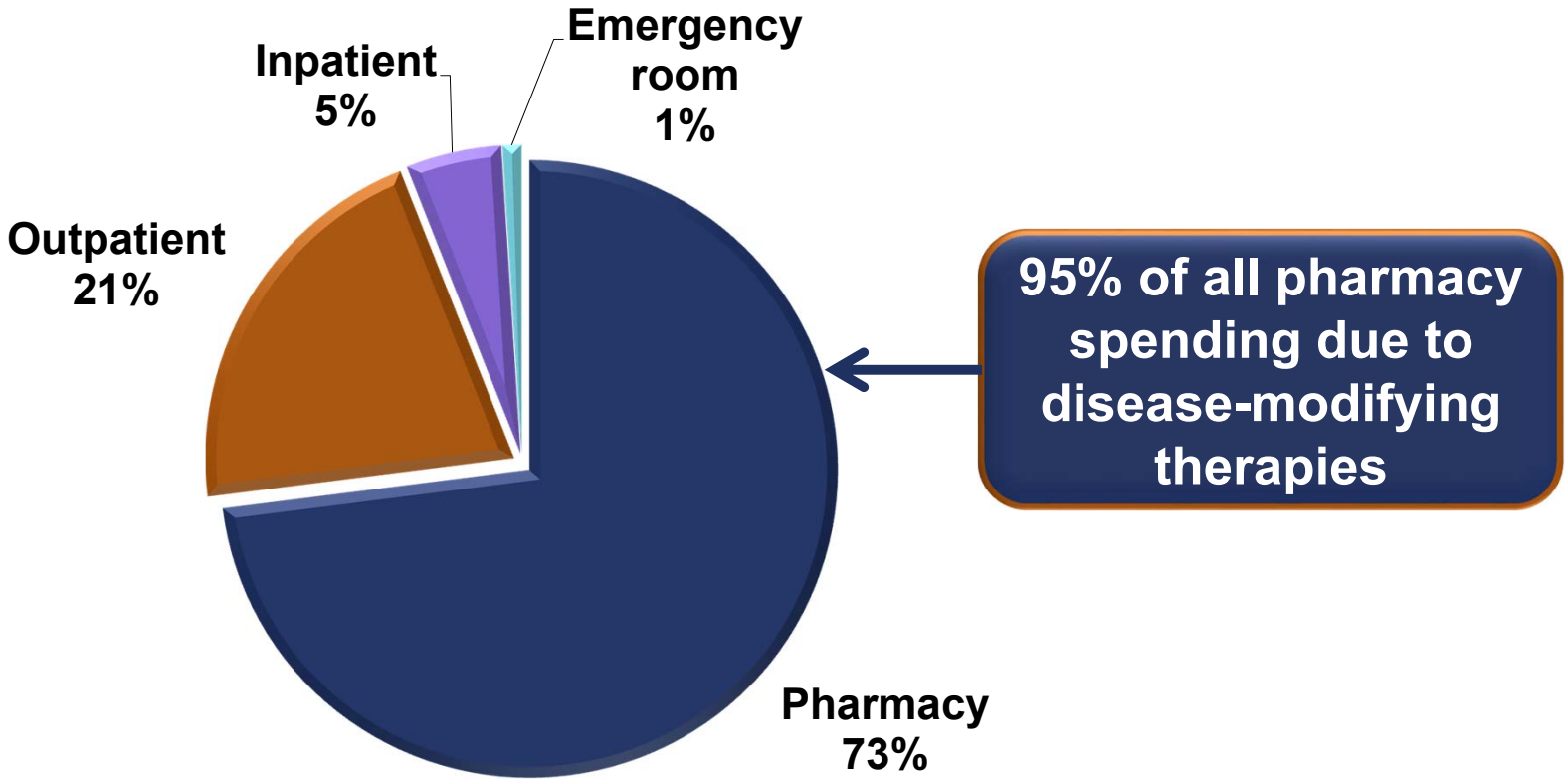
Owens GM. *J Manag Care Pharm*. 2016;22:S151-S158.

Management of Multiple Sclerosis Requires a Coordinated and Comprehensive Approach to Care

Components of MS Care		
Medical intervention	• Modifying disease course • Treating exacerbations • Managing symptoms • Addressing comorbidities	
Rehabilitative services	• Cognitive and vocational rehabilitation • Physical and occupational therapy • Speech therapy	
Mental health support	• Treatment/management of anxiety, depression, and other mood changes	
Long-term care	• Home care • Day care • Assisted living • Nursing home	

Sperandeo K, et al. *J Manag Care Pharm*. 2011;17:S3-S21. National Multiple Sclerosis Society. http://www.nationalmssociety.org/Treating-MS/Comprehensive-Care. Accessed January 2017.

Total Direct Health Care Spending for Multiple Sclerosis



Owens GM, et al. *J Manag Care Pharm*. 2013;19(1 suppl A):S41-S53.

Multiple Sclerosis Drug Benefit Plan Must Be Designed to Optimize Care and Control Costs

Right Drug

- Preferred products
- Efficacy/safety
- Minimal side effects
- Proper duration of therapy

Right Site of Care

- Hospital (in-/out-patient)
- Provider office
- Retail pharmacy/clinic
- Home nursing care
- Home self-administration

Right Cost

- Utilization management
  - Cost sharing
  - Prior authorization
  - Formulary
  - Specialty tiers
- Contracts/rebates

EMD Serono Specialty Digest. 11th ed. 2015.

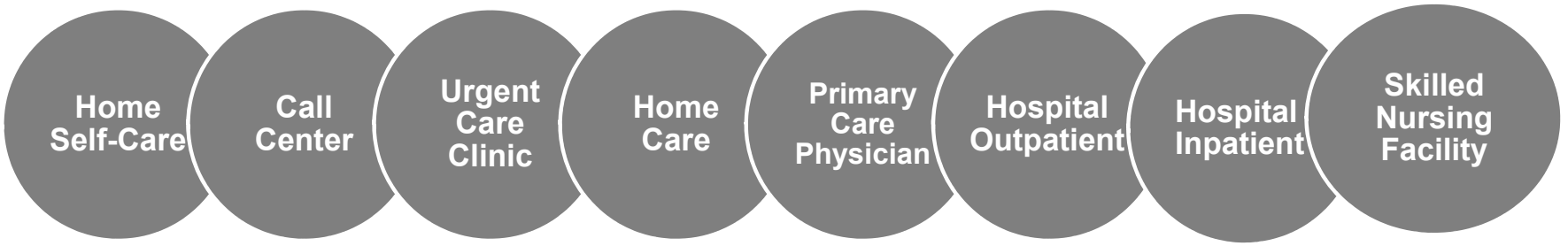
Selecting the “Right” Multiple Sclerosis Drug

- Treatment of MS should be individualized
  - Shared decision-making between patients and health care providers must be preserved
- More than a dozen drugs are FDA approved to treat MS, none of which is curative
  - Multiple unique mechanisms of action
  - Oral, IV, SC, and IM routes of administration
  - Efficacy and safety vary considerably from one individual to another and for any given individual at different points in time
  - Clinicians and patients vary in their tolerance for risk and preference of route-of-administration

Owens GM. *Am J Manag Care.* 2016;22:S151-S158. Multiple Sclerosis Coalition. 2015. http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed January 2017.

Influence of the Site of Care on Cost and Access to Care

MS Care Continuum

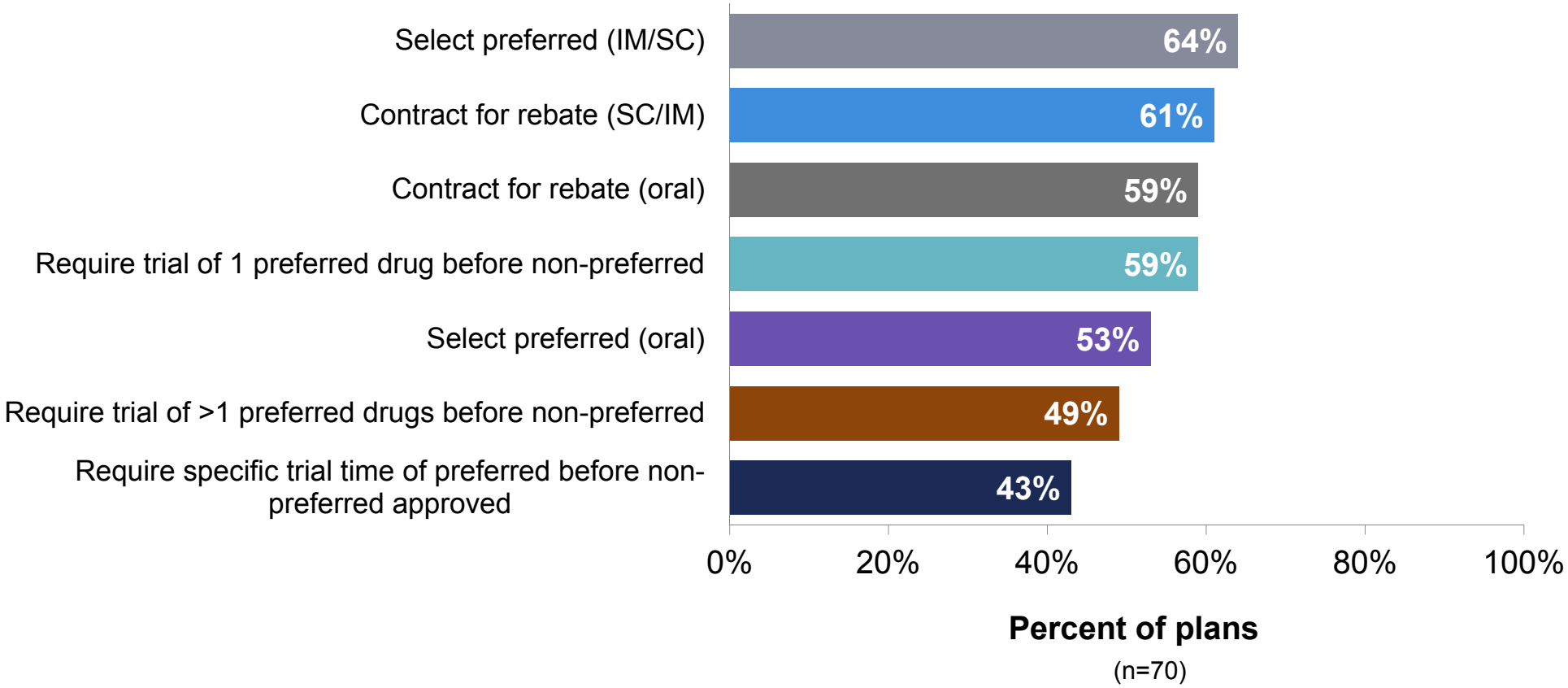


Multiple Sclerosis Represents the 4th Highest Overall Drug Spend by Therapy Class

Therapy Class	Type	PMPY Spend	Trend	
			Utilization	Total
Inflammatory conditions	Specialty	$118.21	11.3%	26.4%
Diabetes	Traditional	$108.80	5.3%	19.4%
Oncology	Specialty	$60.70	11.9%	21.5%
Multiple Sclerosis	**Specialty**	**$58.63**	**-1.3%**	**6.1%**
Pain/Inflammation	Traditional	$51.64	0.6%	1.5%
HIV	Specialty	$39.92	5.5%	21.7%
High cholesterol	Traditional	$38.45	-0.9%	-7.4%
Attention disorders	Traditional	$36.30	5.6%	0.1%
Hypertension/heart disease	Traditional	$34.52	1.5%	-9.1%
Asthma	Traditional	$30.42	3.3%	0.7%

Express Scripts. 2016 Commercial Drug Trend Report.

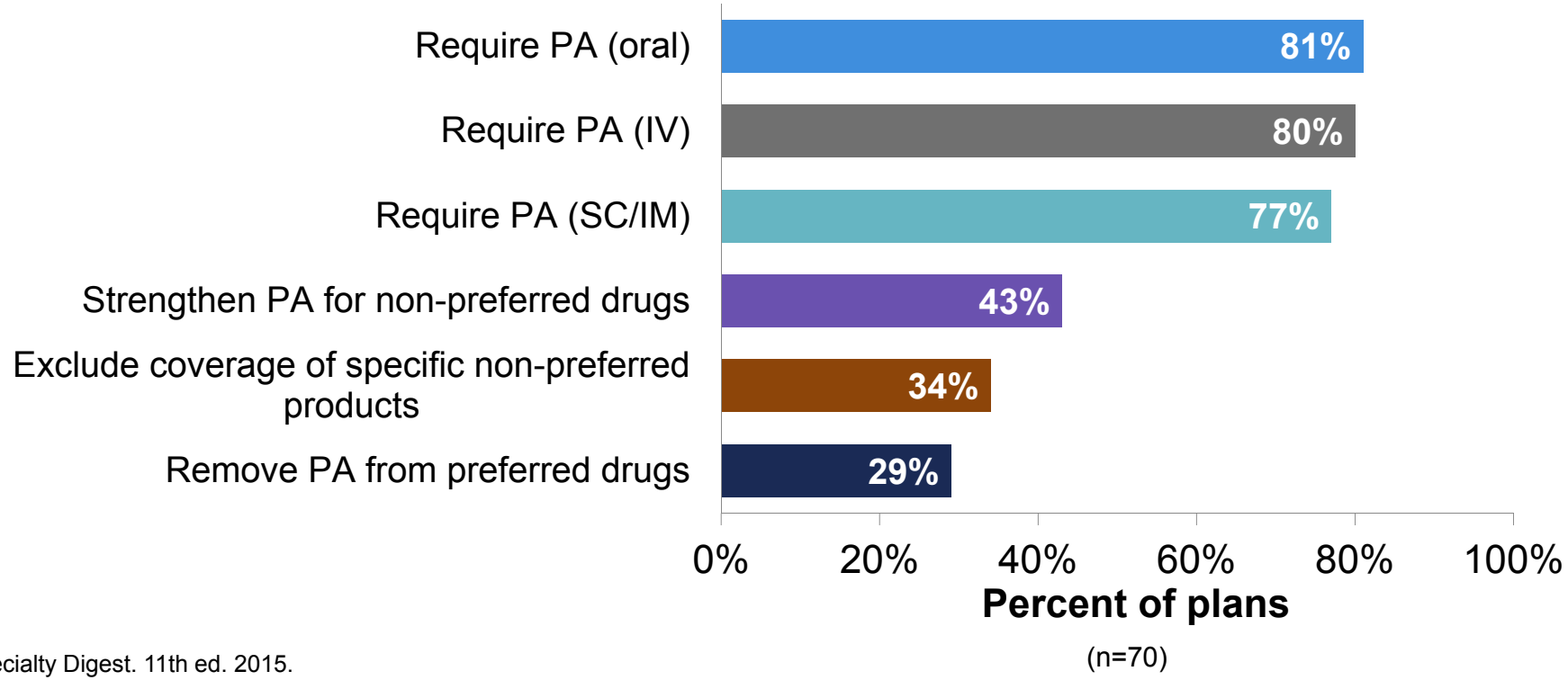
Multiple Sclerosis Disease-Modifying Therapies (DMTs): Preferred Product Strategies



EMD Serono Specialty Digest. 11th ed. 2015.

Multiple Sclerosis DMTs: Utilization Management

Prior Authorization Strategies Implemented by Commercial Plans



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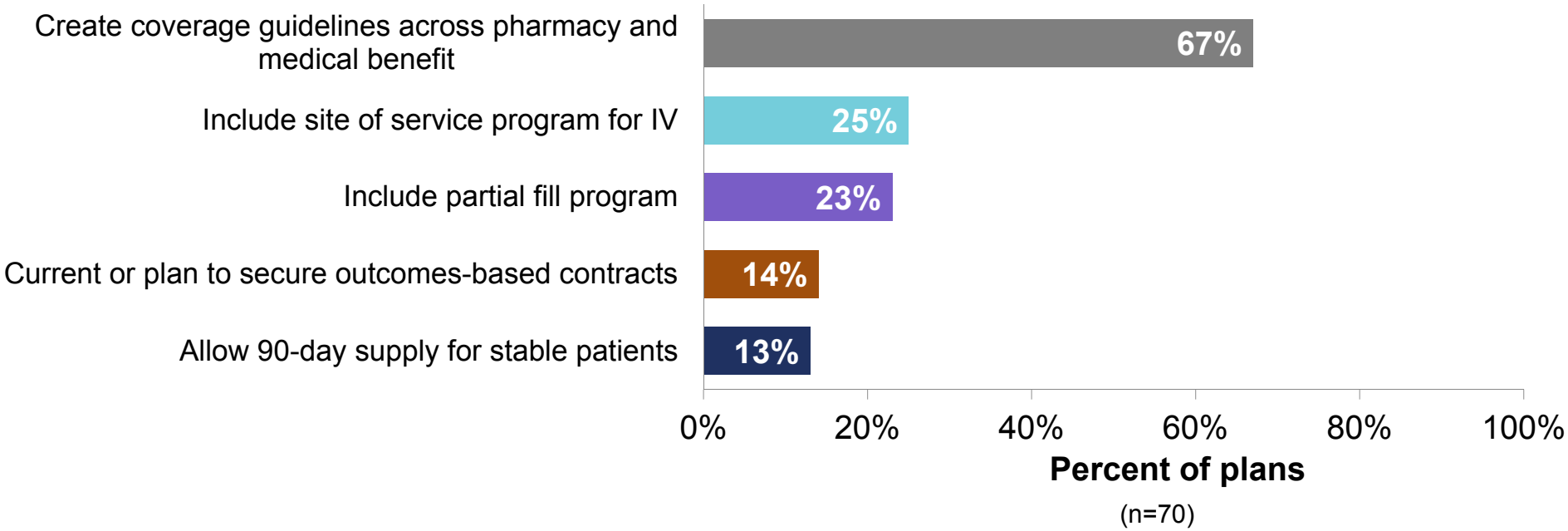
EMD Serono Specialty Digest. 11th ed. 2015.

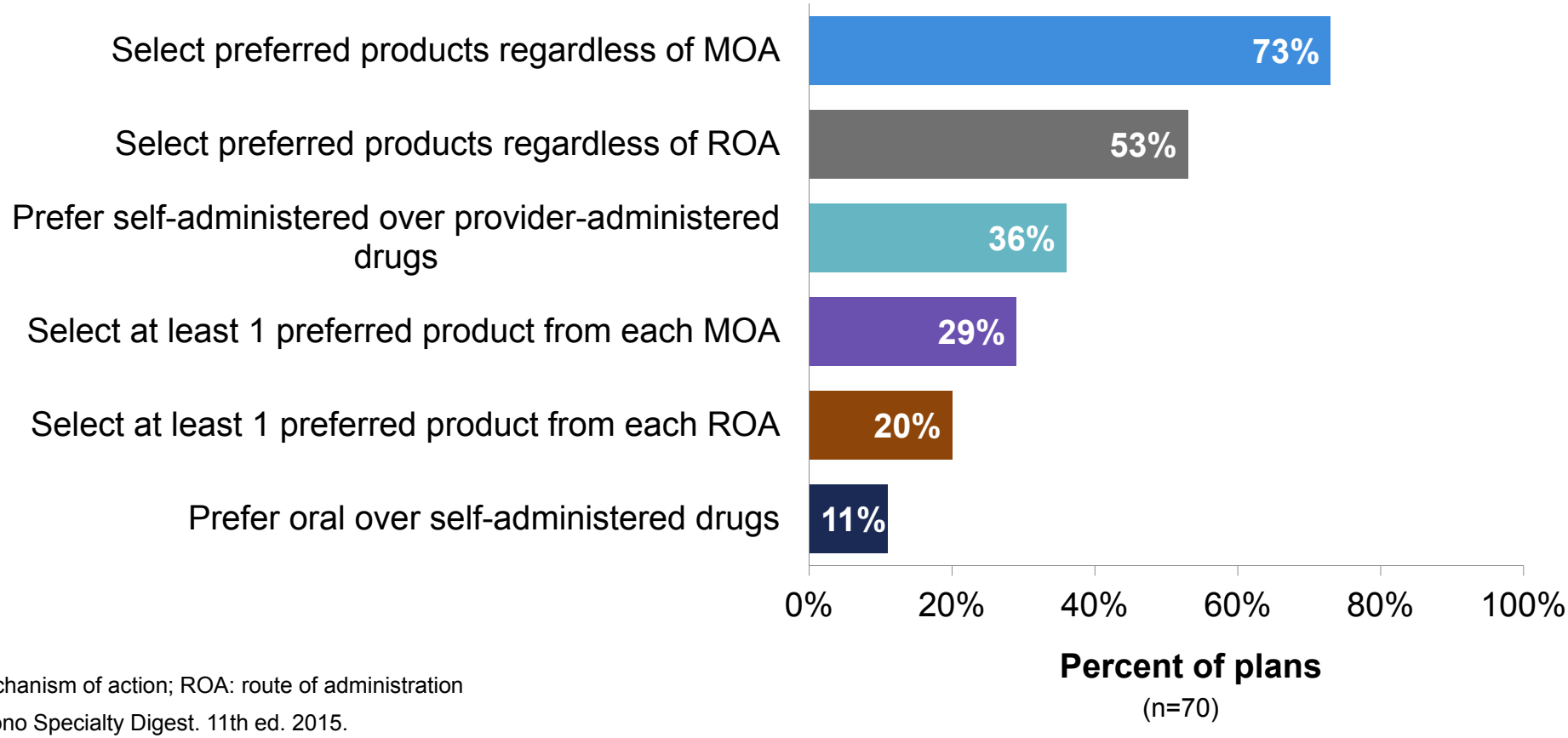
Multiple Sclerosis DMTs: Clinical and Utilization Strategies

Clinical and Utilization Strategies Implemented by Commercial Plans



EMD Serono Specialty Digest. 11th ed. 2015.

Multiple Sclerosis DMTs: Formulary Management



MOA: mechanism of action; ROA: route of administration

EMD Serono Specialty Digest. 11th ed. 2015.

Multiple Sclerosis DMTs: Formulary Tiers

Specialty Tiers	Percent of Plans	Mean Cost Share
Traditional Benefit Design Plans With Specialty Tiers		
Single tier specialty cost share	71%	--
Dollar copay	43%	$102
Coinsurance with maximum OOP	57%	22%
Coinsurance max OOP/Rx amount	--	$217
High-Deductible Plans With Specialty Tiers		
Single tier specialty cost share	74%	--
Dollar copay	32%	$100
Coinsurance with maximum OOP	69%	23%
Coinsurance max OOP/Rx amount	--	$326

EMD Serono Specialty Digest. 11th ed. 2015.

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Biosimilar DMTs for MS

- Currently, no biosimilar DMTs have been approved for MS
- Anticipated biosimilar DMTs for MS include (based on patent expiration)
  - Beta interferons*
  - Natalizumab
  - Mitoxantrone
- Upon approval, these biosimilar competitors may provide less-expensive therapeutic alternatives to the MS community

*Avonex®, Betaseron®,Rebif®, Extavia®

Wells KA. Biosimilars: Approval on the Horizon. http://mymsaa.org/publications/motivator/winter-spring14/feature-story/. Accessed February 2017.

Summary: Putting It All Together

- MS treatment is complicated by the variable natural history of the disease, availability of multiple disease-modifying therapies, and the need for prolonged treatment
- MS therapies represent the third highest specialty drug spend and fourth highest overall drug class spend
- Many drugs are priced similarly with limited ability to mandate switches
- The MS drug benefit must be designed to optimize care and control costs (primarily pharmacy)
- Payers implement several utilization and cost-management strategies to mitigate the financial impact of treatments
- Biosimilar DMTs, when approved, may provide additional cost savings