MANAGING MULTIPLE SCLEROSIS

A Guide for Specialty Pharmacy Professionals

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MEDICAL EDUCATION RESOURCES

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SPECIALTY PHARMACY 2019 summit

Learning Objectives

- Review the safety, efficacy, and other attributes of emerging MS therapies
- Discuss recent insights into cost offsets associated with new and emerging MS therapies
- Employ specialty pharmacy management and benefit design strategies for MS therapies to promote appropriate prescribing
- Analyze care pathways and their application to manage economic outcomes in MS

Clinical Update on Current and Emerging MS Treatment Regimens

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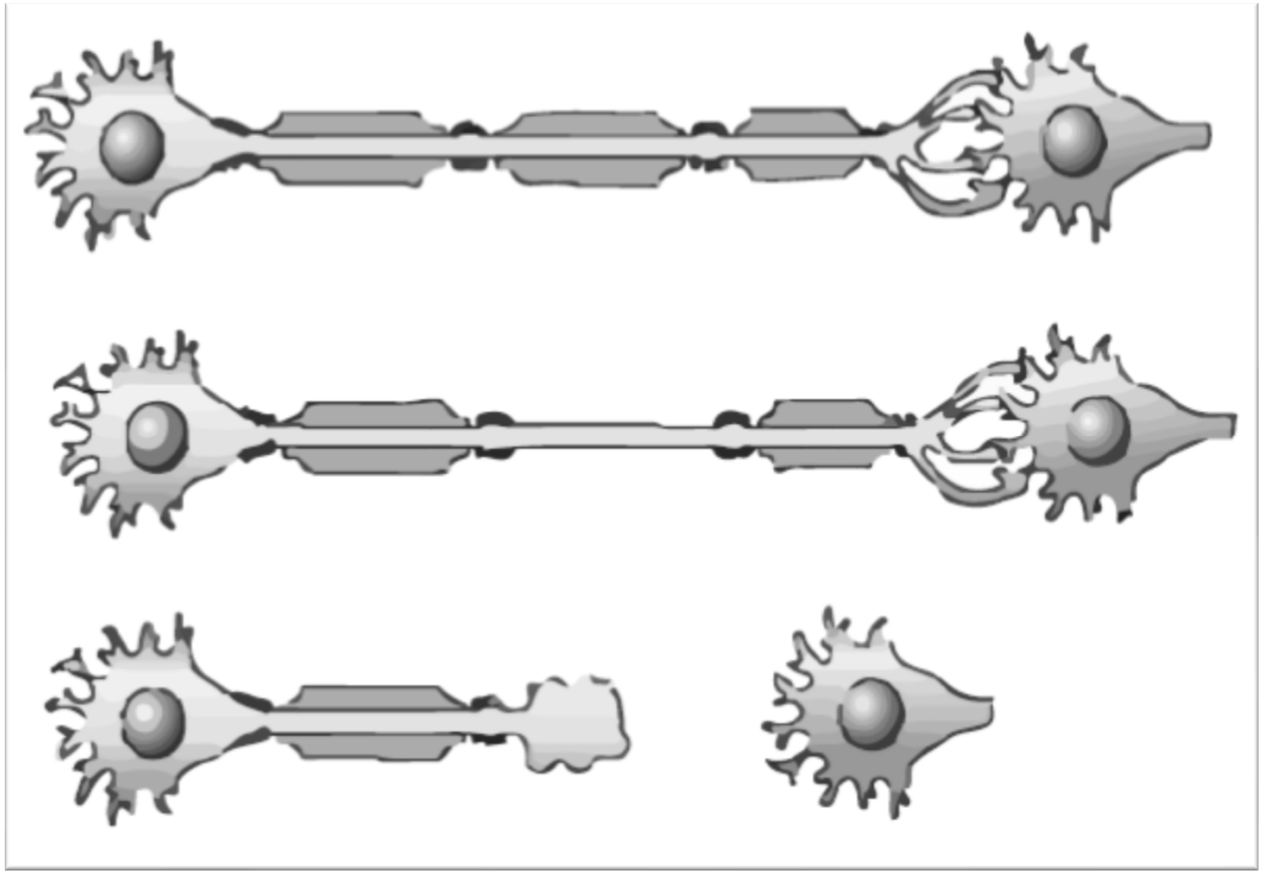
Learning Objective

- Review the safety, efficacy and other attributes of current and emerging multiple sclerosis (MS) therapies

What is Multiple Sclerosis?

- Chronic progressive immune-mediated disease of the CNS
- Associated with demyelination, axonal damage, and subsequent scar or plaque formation
- Associated with significant disability
- Primary etiology unknown, but likely multifactorial



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(12 Suppl):3-9.

MS Epidemiology

- MS affects an estimated 1 million Americans
- It is the most common cause of neurologic disability in 18- to 60-year-old population
- More prevalent in females
- Peak incidence occurs between 20 and 40 years old
- Annual cost in the US estimated to be $6.8 to $11.9 billion

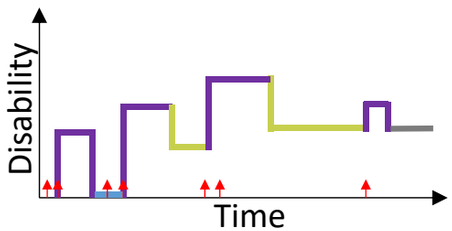
Calabresi PA, Newsome SD. Multiple sclerosis. In: Weiner WJ et al. *Neurology for the Non-Neurologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:192-221; Ascherio A. *Expert Rev Neurother*. 2013;13(12 Suppl):3-9; Whetten-goldstein K, Sloan FA, Goldstein LB, Kulas ED. *Mult Scler*. 1998;4(5):419-25.; Wallin MT, Culpepper WJ, Campbell JD, et al. *Neurology*. 2019;92:e1029-e1040

MS Disease Clinical Subtypes

Radiologically or Clinically Isolated Syndrome (RIS/CIS)

First episode of neurologic symptoms; must last for ≥24 hours; may not evolve into MS

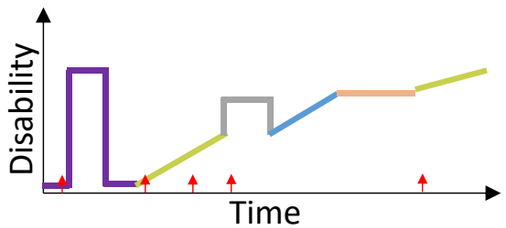
Relapsing-Remitting (RRMS)



- Relapse
- Active without worsening
- Worsening (incomplete recovery from relapse)
- Stable without activity
- New MRI activity

85% of patients diagnosed with **RRMS** at disease onset

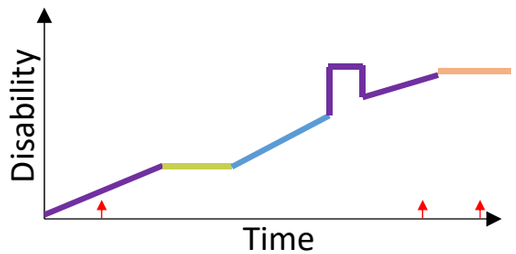
Primary Progressive (PPMS)



- RRMS
- Active (relapse or new MRI activity) with progression
- Active (relapse or MRI activity) without progression
- Not active with progression
- Not active without progression (stable)
- New MRI activity

15% of patients diagnosed with **PPMS** at disease onset

Secondary Progressive (SPMS)

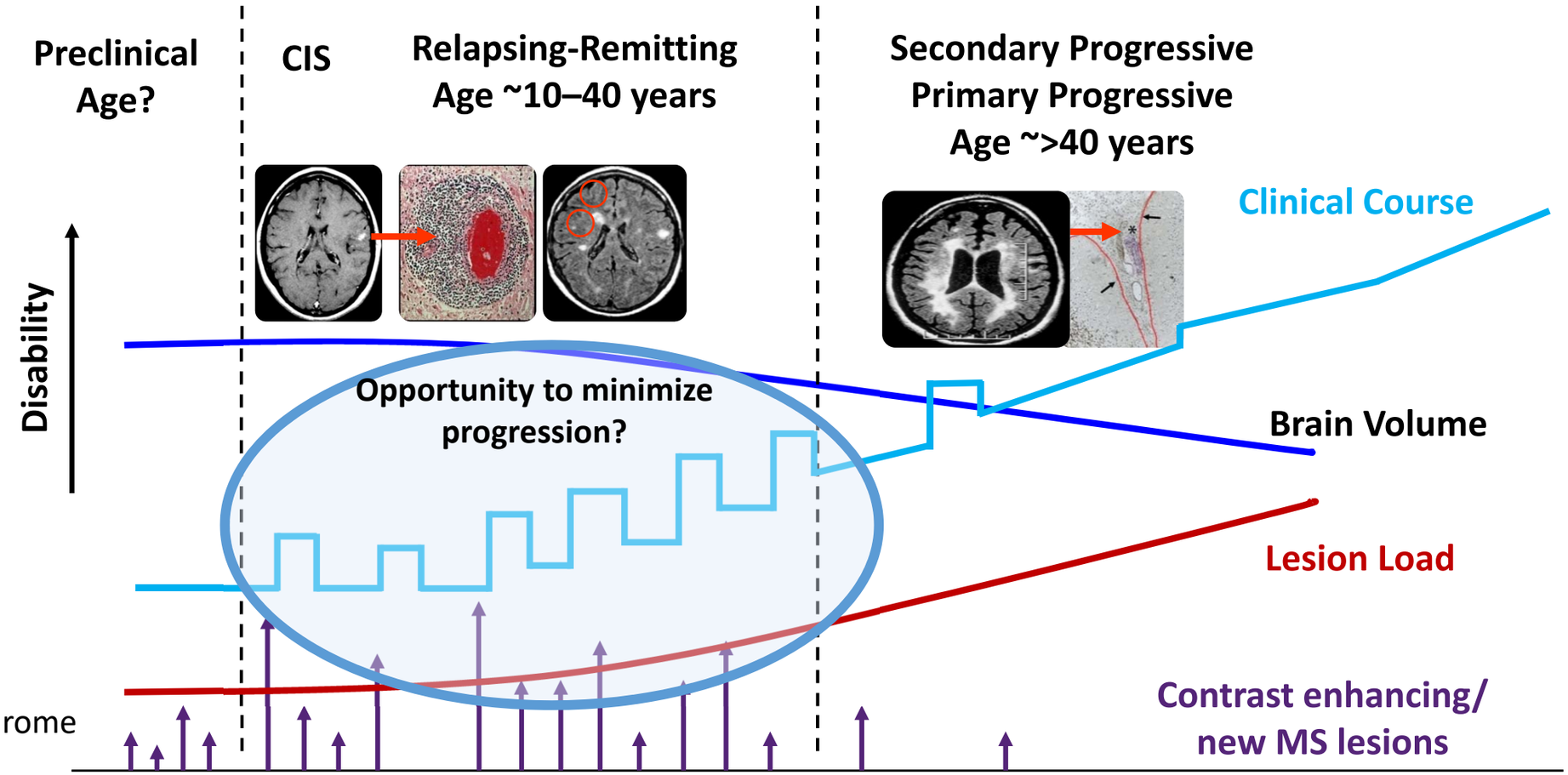


- Active (relapse or new MRI activity) with progression
- Not active without progression (stable)
- Not active with progression
- Active without progression
- New MRI activity

Left untreated, **~50%** of **RRMS** cases transition to **SPMS** within 10 years of diagnosis

Types of MS. National Multiple Sclerosis Society. www.nationalmssociety.org/What-is-MS/Types-of-MS. Accessed February 2019.
Lublin FD, Reingold SC, Cohen JA, et al. *Neurology*. 2014;83(3):278-86.
Definition of MS> National Multiple Sclerosis Society. www.nationalmssociety.org/What-is-MS/Definition-of-MS. Accessed February 2019.

MS Disease Course



CIS: clinically isolated syndrome

Hersh CM, Fox RJ. Multiple Sclerosis. Cleveland Clinic Medical School. https://teachmemedicine.org/cleveland-clinic-multiple-sclerosis. Published June 2014. Accessed February 2019.

MS Presentation

Clinical Presentation

- Can be highly variable and often reflects areas of active inflammation within the CNS
- Presentation can be
  - Focal
  - Multifocal
  - Relapsing
  - Gradually worsening

Notable Presentation Features

- Fatigue
- Imbalance/ataxia
- Optic neuritis
- Transverse myelitis
- Sensory symptoms
- Cognitive/mood symptoms
- Bowel and bladder dysfunction
- Uhthoff's phenomenon (heat intolerance)
- Lhermitte's sign (electrical shocks down the spine)

Milo R, Miller A. *Autoimmun Rev*. 2014;13(4-5):518-24.

Components of the MS Diagnosis

- **Clinical:** symptoms and exam findings suggestive of MS
- **MRI:** objective evidence of CNS white matter lesions disseminated in time and space
- **Lab tests:** blood work to rule out mimics (e.g., antinuclear antibody and neuromyelitis optica)
- **CSF studies:** findings supportive of MS such as cell count, IgG index, and oligoclonal bands
- **Neurophysiology:** evoked potential supportive of MS (e.g., Lhermitte's phenomenon)

Polman CH, Reingold SC, Banwell B, et al. *Ann Neurol*. 2011;69(2):292-302.
Polman CH, Reingold SC, Edan G, et al. *Ann Neurol*. 2005;58(6):840-6.

MacDonald Diagnostic Criteria: 2017 Revision

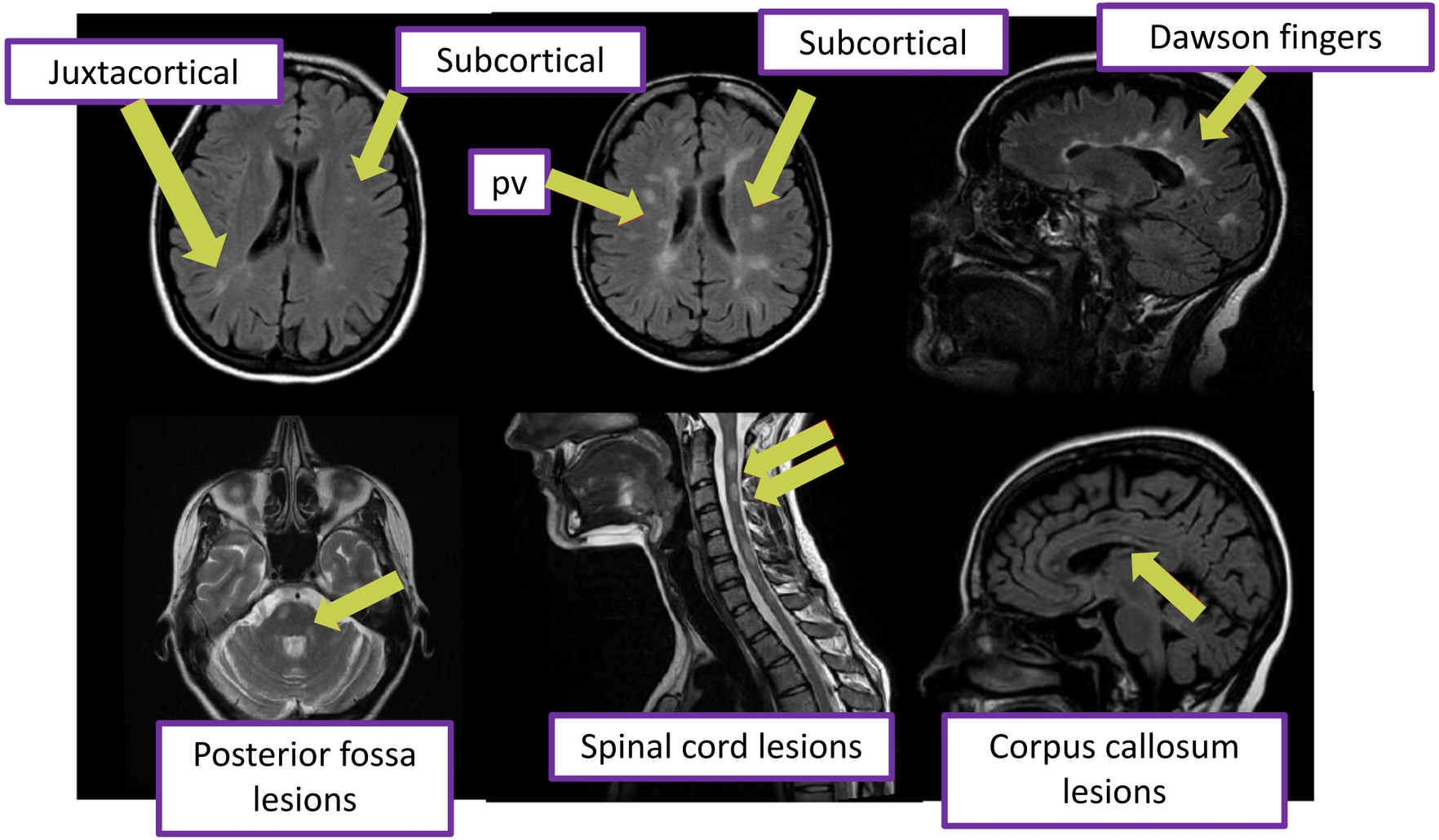
Clinical Presentation	Additional Data Needed for MS Diagnosis
• ≥2 attacks • Objective clinical evidence of ≥2 lesions with reasonable historical evidence of a prior attack	• None; clinical evidence will suffice • Additional evidence (e.g., brain MRI) desirable, but must be consistent with MS
• ≥2 attacks • Objective clinical evidence of 1 lesion	• Dissemination in space demonstrated by MRI **OR** await further clinical attack implicating a different site
• One attack • Objective clinical evidence of ≥2 lesions	• Dissemination in time demonstrated by MRI **OR** second clinical attack or demonstration of CSF-specific oligoclonal bands
• One attack • Objective clinical evidence of 1 lesion (clinically isolated syndrome)	• Dissemination in space demonstrated by MRI or await a second clinical attack implicating a different CNS site **AND** • Dissemination in time, demonstrated by MRI or second clinical attack

• Insidious neurologic progression suggestive of MS	• One year of disease progression and dissemination in space, demonstrated by 2 of the following:
	  • ≥1 T2 lesions in brain, in regions characteristic of MS
	  • ≥2 T2 focal lesions in spinal cord
	  • Positive CSF

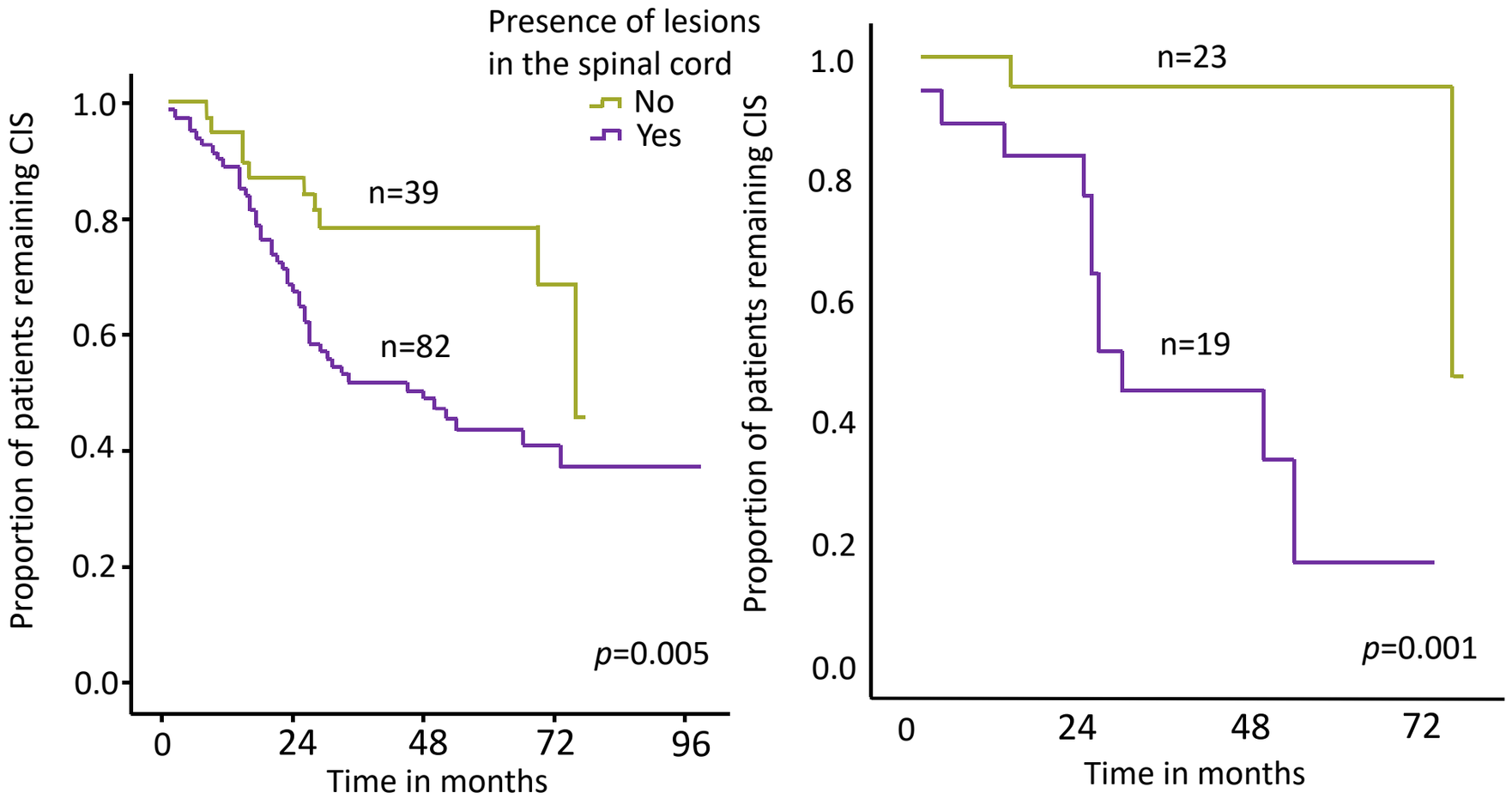
Thompson AJ, Banwell BL, Barkhof F, et al. *Lancet Neurol*. 2017.

MRI Findings Suggestive of MS

Periventricular, Juxta-cortical, Posterior Fossa, and Spinal Cord



Effect of Presence of Spinal Cord Lesions on Time to Conversion From CIS to CDMS



CIS=clinically isolated syndrome; CDMS=clinically definite multiple sclerosis

Sombekke MH, Wattjes MP, Balk LJ, et al. *Neurology*. 2013;80(1):69-75.

Predictors of Disability: Disease Factors

• Clinical Factors[1]

- Younger age at onset
- Longer disease duration
- Higher relapse rate
- More frequent early relapses
- Poor recovery from relapses

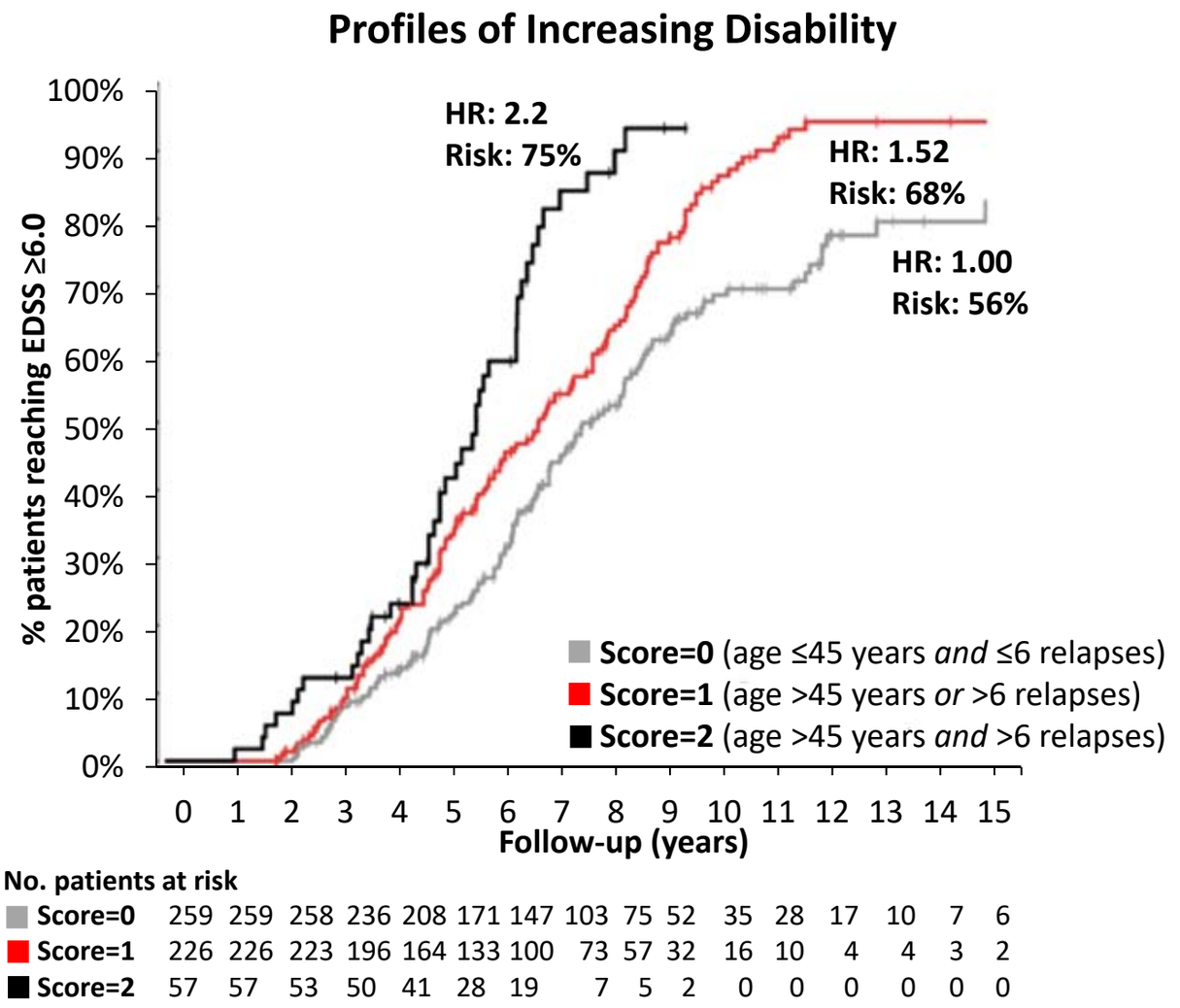
• MS Lesions[2,3]

- Spinal cord lesions
- Diffuse abnormalities in the spinal cord
- Cortical lesions and atrophy

1. Jokubaitis VG, Spelman T, Kalincik T, et al. *Ann Neurol*. 2016;80(1):89-100.
2. KeKearney H, Miszkiel KA, Yiannakas MC, Altmann DR, Ciccarelli O, Miller DH. *Mult Scler*. 2016;22(7):910-20.3.
3. Scalfari A, Romualdi C, Nicholas RS, et al. *Neurology*. 2018;90(24):e2107-e2118..

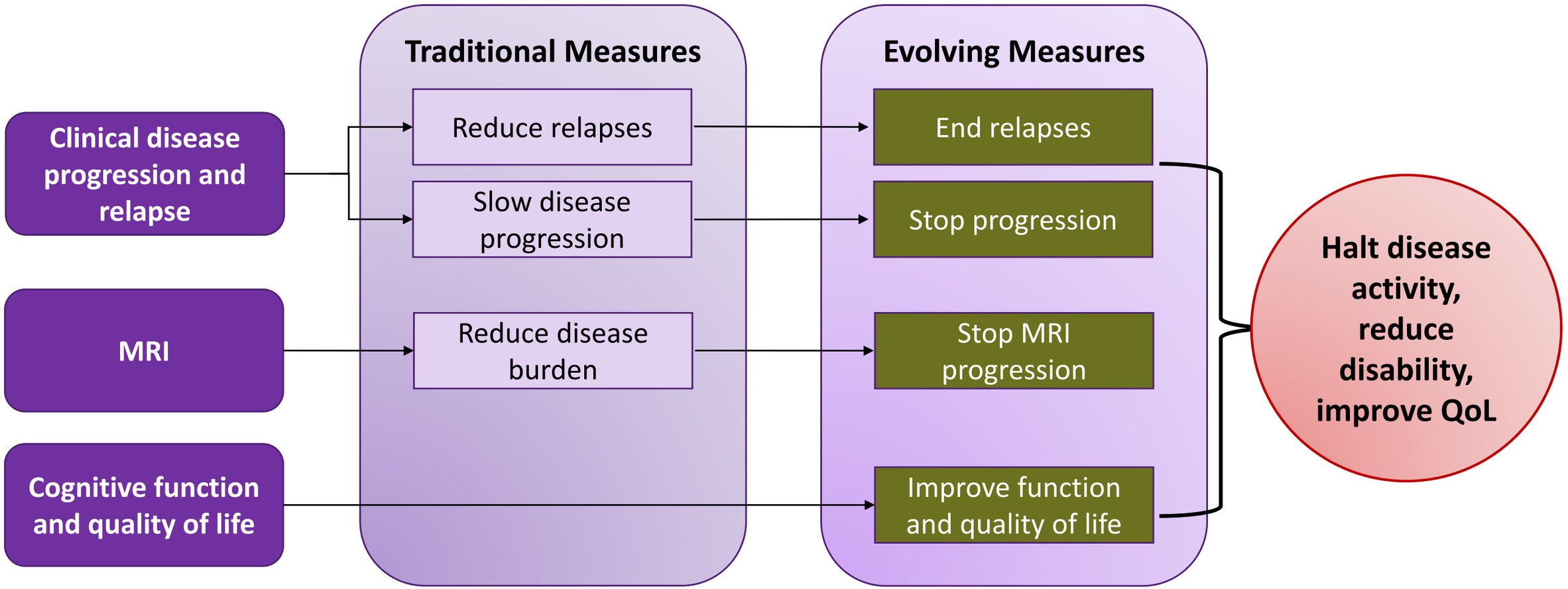
Predicting Disability

- Analysis of demographic, clinical and MRI data from 542 patients with relapsing MS (baseline EDSS: 3.0-4.0) followed for ≥ 2 years
- After 2 years, 63.5% of patients reached EDSS 6.0
- Predictors of disability in patients with disease activity:
  - Number of relapses before reaching EDSS 3.0–4.0
  - Age >45 at baseline
- A composite risk score combining age and number of relapses increased the risk of and shortened the time to EDSS = 6.0



Tomassini V, Fanelli F, Prosperini L, Cerqua R, Cavalla P, Pozzilli C. *Mult Scler*. 2018;:1352458518790397. [Epub ahead of print].

MS Treatment Goals



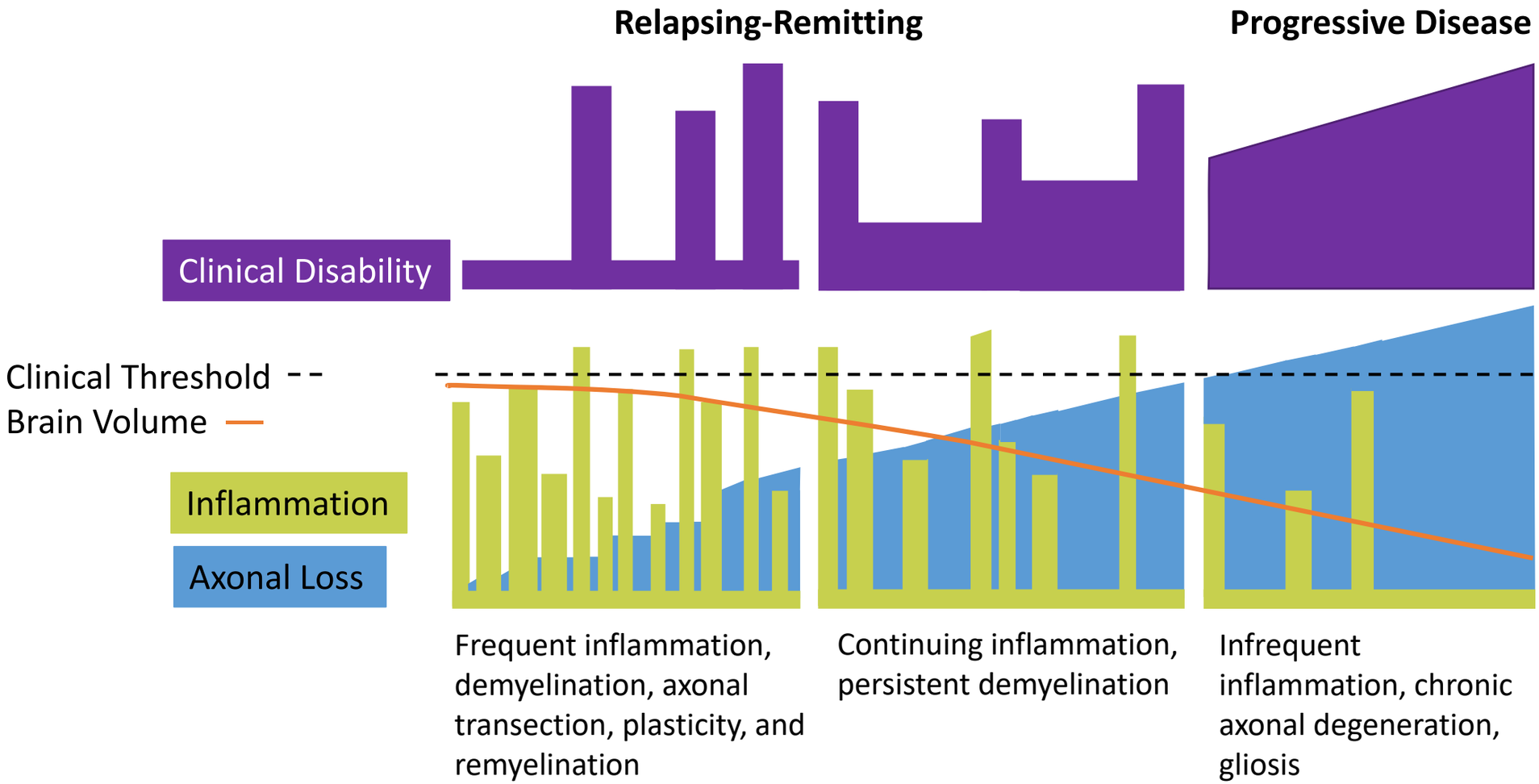
Smith AL, Cohen JA, Hua LH. *Neurotherapeutics*. 2017;14(4):952-960.
Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. *JAMA Neurol*. 2015;72(2):152-8.
Lazibat I, Šamija RK, Rotim K. *Acta Clin Croat.* 2016;55(1):125-33.

Approach to MS Treatment

- **Early treatment:** start treatment within 12 months after symptom onset if MRI is positive
- **Early treatment with DMTs:** may limit disability and attenuate secondary progression and in patients with active RRMS
- **Treat-to-target:** a common treatment goal is to minimize and/or stop disease activity; currently, however, there is minimal evidence that this approach improves outcomes

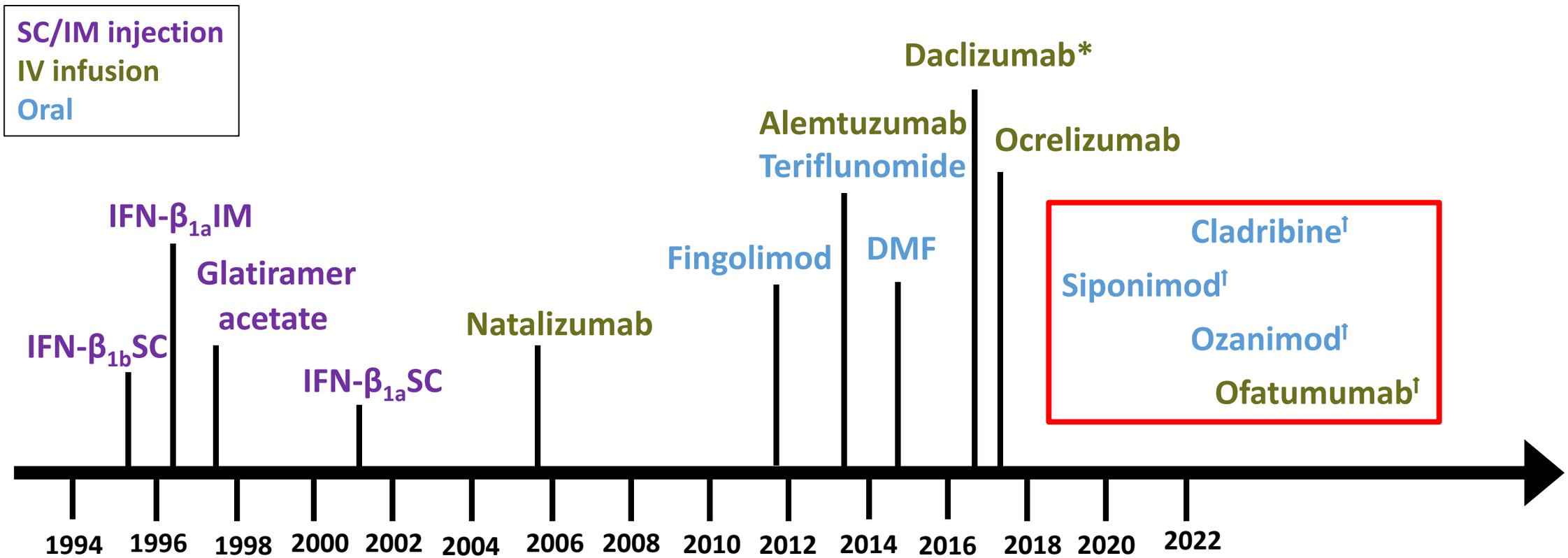
Cerqueira JJ, et al. *J Neurol Neurosurg Psychiatry*. 2018;89:844–850; Smith AL, Cohen JA, Hua LH. *Neurotherapeutics*. 2017;14(4):952-960.

Importance of Early Treatment



Dendrou CA, Fugger L, Friese MA. *Nat Rev Immunol*. 2015;15(9):545-58.

MS Treatment Landscape Continues to Expand



*Daclizumab: withdrawn March 2018 due to reports of AEs including inflammatory encephalitis and meningoencephalitis.
†In development.

Thompson AJ, Banwell BL, Barkhof F, et al. *Lancet Neurol*. 2017.

FDA Indications for Currently Available DMTs

Agent	Approval	CIS	RRMS	PPMS	SPMS
Interferon β-1b (Betaseron; Extavia)	1993	✓	✓		
Interferon β1-a (Avonex)	1996	✓	✓		
Glatiramer acetate (Copaxone)	1996	✓	✓		
Interferon β-1a (Rebif)	1996		✓		
Mitoxantrone (Novantrone)	2000		✓		✓
Alemtuzumab (Lemtrada)	2001		✓		
Natalizumab (Tysabri)	2004		✓		
Fingolimod (Gilenya)	2010		✓		
Teriflunomide (Aubagio)	2012		✓		
Dimethyl fumarate (Tecfidera)	2013		✓		
Peginterferon β-1a (Plegridy)	2014		✓		
Ocrelizumab (Ocrevus)	2017		✓	✓	
Siponimod (Mayzent)	2019	✓	✓		✓
Cladribine (Mavenclad)	2019		✓		✓

Clinical Benefit of Widely Used DMTs: Annual Relapse Rate (ARR)

Agent	Trial/Duration	ARR Reduction vs. Placebo
IFN-β1b 250 µg qod SC	3 years	34% ↓
IFN-β1a 30 µg/wk	2 years (stopped early)	18%-21% ↓
IFN-β1a 44 µg SC tiw	PRISMS/2 years	33% ↓
IFN-β1a 125 µg q2w	ADVANCE/48 weeks	35% ↓
Glatiramer acetate 20 mg	2 years	29% ↓
Glatiramer acetate 40 mg tiw	GALA/ 1 year	34% ↓
Natalizumab	AFFIRM/2 years	**68% ↓**
Alemtuzumab 12 or 24 mg/day	CARE MS I-II/2 years	**55%, ↓ 49% ↓ vs IFN-β1a**
Ocrelizumab	OPERA I-II/96 weeks	**46% and 47% ↓ vs IFN-β1a**
Fingolimod 5 mg	FREEDOMS I-II/2 years TRANSFORMS/1 year	**54% ↓** **48% ↓ vs IFN-β1a**
Siponimod 2 mg	EXPAND/3 years	**55% ↓**
Cladribine 3.5 to 5.25 mg/kg	CLARITY/96 weeks	**58% ↓**
Teriflunomide 14 mg po/day	TOWER/>48 weeks TEMSO/108 weeks	36% ↓ 31% ↓
Dimethyl fumarate	DEFINE, CONFIRM/ 2 years	49% ↓ 44% ↓

Bold: >50% reduction vs. placebo/comparator.

Smith AL, Cohen JA, Hua LH. *Neurotherapeutics*. 2017;14(4):952-960; Cladribine [prescribing information]. Rockland, MA: EMD Serono; March 2019; Siponimod [prescribing information]. E. Hanover, NJ: Novartis; March 2019.

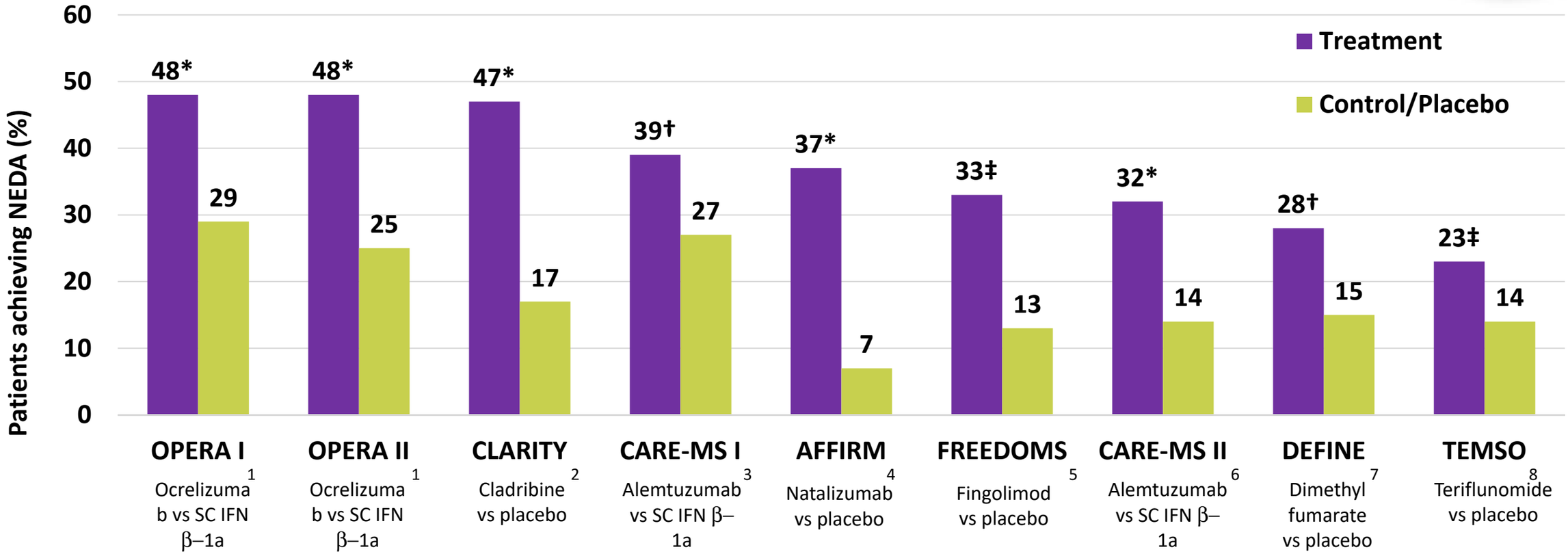
Time to Onset of Clinical Benefit

Agent	Trial/Duration	Onset of Effect
IFN-β1b 250 µg qod SC	3 years	**3 weeks**
IFN-β1a 30 µg/wk	2 years (stopped early)	< 26 weeks
IFN-β1a 44 µg SC tiw	PRISMS/2 years	**≤ 2 months**
IFN-β1a 125 µg q2w	ADVANCE/48 weeks	≤ 12 weeks
Glatiramer acetate 20 mg	2 years	---
Glatiramer acetate 40 mg tiw	GALA/ 1 year	≤ 6 months
Natalizumab	AFFIRM/2 years	**≤ 4 weeks**
Alemtuzumab 12 or 24 mg/day	CARE MS I-II/2 years	≤ 3 months
Ocrelizumab	OPERA I-II/96 weeks	**≤ 8 weeks**
Fingolimod 5 mg	FREEDOMS I-II/2 years TRANSFORMS/1 year	**≤ 60 days**
Siponimod 2 mg	EXPAND/3 years	**< 3 months**
Cladribine 3.5 to 5.25 mg/kg	CLARITY/96 weeks	**< 3 months**
Teriflunomide 14 mg po/day	TOWER/>48 weeks TEMSO/108 weeks	≤ 12 weeks
Dimethyl fumarate	DEFINE, CONFIRM/ 2 years	≤ 6 months

Bold: ≤ 2 months onset of efficacy on MRI or relapse rate

Smith AL, Cohen JA, Hua LH. *Neurotherapeutics*. 2017;14(4):952-960; Cladribine [prescribing information]. Rockland, MA: EMD Serono; March 2019; Siponimod [prescribing information]. E. Hanover, NJ: Novartis; March 2019.

No Evidence of Disease Activity (NEDA) Rates in Phase 3 Trials



*p<0.0001; ‡p<0.001; †p<0.5 vs. comparator

NEDA defined as no relapses, no 3-month CDP, no new T1 Gd+ lesions, and no new enlarging or enlarged T2 lesions on MRI

1. Traboulsee A, et al. Abstract PL02.004. *Neurology*. 2016;86 (16 Suppl). Published online February 8, 2016. Accessed February 2019; 2. Giovannoni G, Cook S, Rammohan K, et al. *Lancet Neurol*. 2011;10(4):329-37; 3. Cohen JA, Coles AJ, Arnold DL, et al. *Lancet*. 2012;380(9856):1819-28; 4. Havrdova E, Galetta S, Hutchinson M, et al. *Lancet Neurol*. 2009;8(3):254-60; 5. Bevan CJ, Cree BA. *JAMA Neurol*. 2014;71(3):269-70; 6. Coles AJ, Twyman CL, Arnold DL, et al. *Lancet*. 2012;380(9856):1829-39; 7. Giovannoni G, Rhoades RW. *Curr Opin Neurol*. 2012;25 (Suppl):S20-7; 8. Freeman MS. *Ther Adv Chronic Dis*. 2013;4(5):192-205.

Injectable DMTs: Safety and Monitoring

Agent	Minor Side Effects	Serious Side Effects	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	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	Same as above
Peg IFNβ-1a[3]	Same as above	Same as above	Same as above
IFNβ-1b[4,5]	Same as above	Same as above	Same as above
Glatiramer acetate[6]	Injection-site reactions; post-injection vasodilatory reaction	Lipoatrophy, skin necrosis, anaphylaxis	No specific labs, skin surveillance

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; March 2016. 2. IFNβ-1a [prescribing information]. Rockland, MA: EMD Serono, Inc; November 2015. 3. Pegylated IFNβ-1a [prescribing information]. Cambridge, MA: Biogen Idec Inc; July 2017. 4. IFNβ-1b [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; August 2018. 5. IFNβ-1b [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2018. 6. Glatiramer acetate [prescribing information]. Overland Park, KS: TEVA Neuroscience, Inc; January 2018.

IV DMTs: Safety and Monitoring

Agent	Minor Side Effects	Serious Side Effects	Monitoring
Natalizumab[1]	Headaches, joint pain, fatigue, wearing-off phenomenon	Boxed warning for PML, infusion reaction, herpes zoster, other infections, liver failure	CBC with differential, LFTs, serum JCV antibody (every 6 months), MRI, natalizumab antibodies (if clinically warranted)
Alemtuzumab[2]	Infusion reactions	Boxed warning for autoimmunity, infusion reactions, stroke, and malignancies; autoimmune thyroid disease, ITP, Goodpasture syndrome, infections (HSV, VZV)	Monthly CBC with differential, LFTs, urinalysis with urine cell counts, TFTs every 3 months
Ocrelizumab[3]	Upper respiratory tract infections and infusion reactions	Severe infusion reactions, reactivation hepatitis, opportunistic infections, malignancies	Hepatitis panel, CBC with differential, LFTs, PPD or Tb spot/QuantiFERON prior to starting

ITP: immune thrombocytopenic purpura

1. Natalizumab [prescribing information]. Cambridge, MA: Biogen Idec Inc; April 2018; 2. Alemtuzumab [package insert]. Cambridge, MA: Genzyme Corporation; January 2019; 3. Ocrelizumab [prescribing information]. Genentech, Inc. November 2018.

Oral DMTs: Safety and Monitoring

Agent	Minor Side Effects	Serious Side Effects	Monitoring
Fingolimod[1]	Lymphopenia (absolute lymphocyte count >200), transaminitis	Bradycardia, heart block, hypertension, risk of infections (herpetic, cryptococcal), lymphopenia (absolute lymphocyte count <200), transaminitis, macular edema, skin cancer, reactive airway, PRES, PML, cryptococcal meningitis, rebound	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, nausea, hair thinning	Boxed warning for hepatotoxicity and risk of teratogenicity, transaminitis, lymphopenia, teratogenic (men and women), latent tuberculosis, neuropathy, hypertension	CBC with differential, LFTs (monthly for first 6 months), PPD or Tb spot/QuantiFERON prior to starting, wash out (if needed)
Dimethyl fumarate[3]	Flushing, gastrointestinal distress	Transaminitis, leukopenia, PML	CBC with differential, LFTs
Siponimod[4]	Headache; edema; dizziness; diarrhea; increased LFTs	PML; increased risk of infections; macular edema; bradyarrhythmia and atrioventricular conduction delays; respiratory effects; liver injury; hypertension	First dose monitoring for bradycardia and blood pressure response (6 hours); monitor for infections during treatment
Cladribine[5]	Upper respiratory tract infections, headache, decrease lymphocyte count	Increased risk of infection, leukopenia, hematologic toxicity, bone marrow suppression, graft-vs.-host disease, and liver toxicity	Lymphocyte counts should be monitored before, during, and after treatment

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; January 2019; 2. Teriflunomide [package insert]. Cambridge, MA: Genzyme Corporation; November 2016; 3. Dimethyl fumarate [prescribing information]. Cambridge, MA: Biogen Idec Inc; December 2017; 4. Siponimod [prescribing information]. East Hanover, NJ: Novartis Pharmaceutical Corp.; March 2019; 5. Cladribine [prescribing information]. Rockland, MA: EMD Serono; March 2019.

Patient Factors Influencing Initial Choice of MS Therapy

Disease Activity

- Inactive
- Active
- Highly active
- Rapidly evolving
- Severe

Drug-related Issues

- Tolerability
- Safety profile
  - Immunosuppression
  - PML risk
- Monitoring frequency
- Drug effects
  - Drug-drug interactions

Patient Profile

- Adherence
- Comorbidities
- Personal factors
  - Pregnancy
  - Travel
  - Work
  - Other

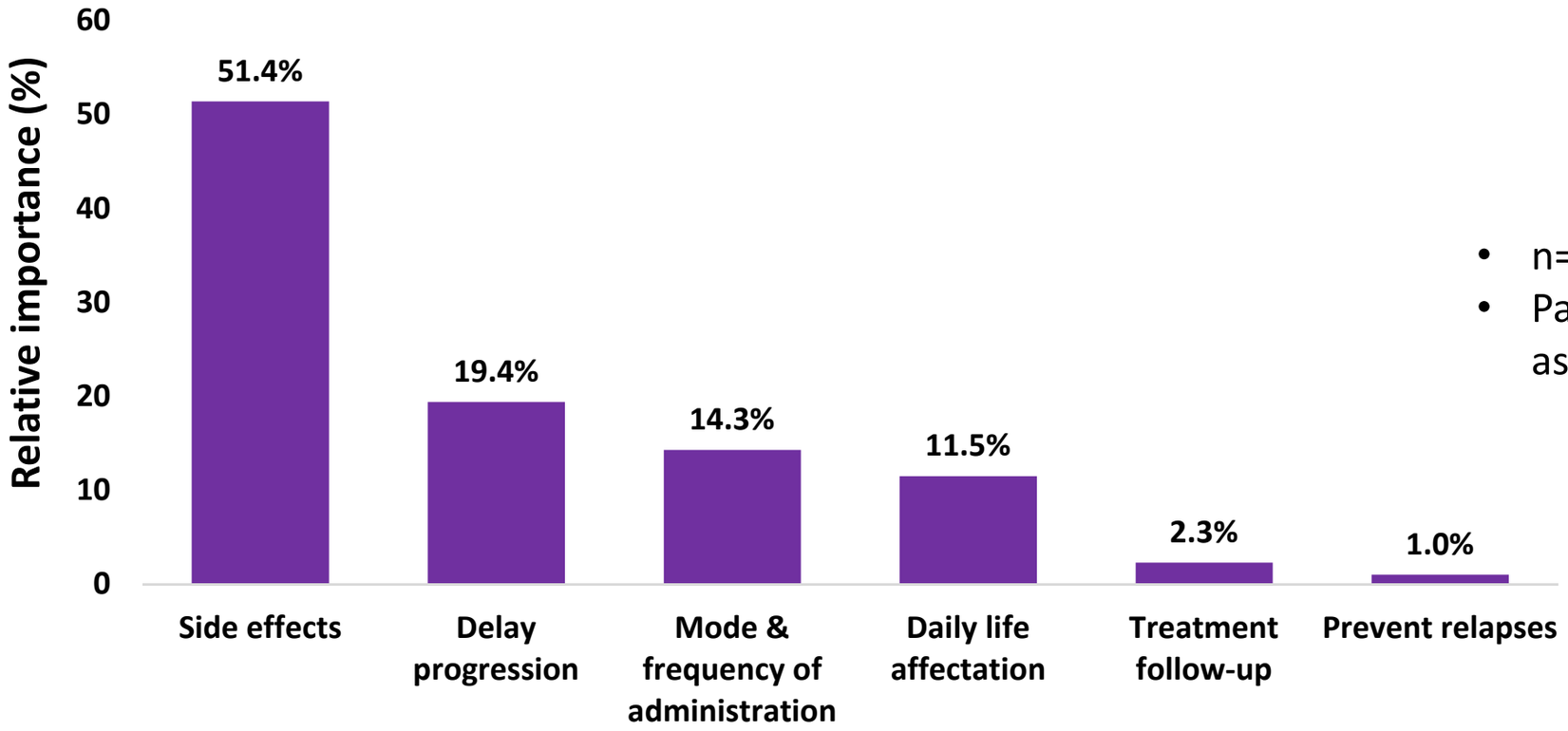
Wingerchuk DM, Weinshenker BG. *BMJ*. 2016;54:i3518.

Factors Influencing a Decision to Switch the DMT

Line of Therapy	Factor Influencing a Switch
First-line DMT to another first line (lateral switch) *1st line: IFN; GA; teriflunomide; DMF*	• Tolerability/safety issues • Suboptimal efficacy with suboptimal response but still a low risk for imminent progression
First-line to a second-line DMT (i.e., escalation) *2nd line: fingolimod; natalizumab; alemtuzumab; ocrelizumab; cladribine; siponimod*	• Suboptimal response to first-line DMT with a moderate-higher risk for progression (as opposed to low risk) • RRMS patients transitioning to the secondary progressive phase with evidence of relapses or MRI activity
Second-line to a third-line or higher DMT (i.e., these are the patients who moved to a higher risk for progression and the first- and second-line DMTs would not be able to change the risk) *3rd line/higher: mitoxantrone; cyclophosphamide; experimental therapy (eg, cladribine)*	• RRMS patients continuing to experience relapses on a second-line therapy • Progressive forms of MS with relapses and/or active MRI despite treatment • Safety issues (e.g., patients on natalizumab at high risk of developing progressive multifocal leukoencephalopathy)
Second-line to a first-line DMT	• Tolerability/safety issues should the patient maintain the second-line agent AND the perception that the disease is under good control and the patient's risk for imminent progression has been reduced

Freedman MS, Selchen D, Prat A, Giacomini PS. Can J Neurol Sci. 2018;45(5):489-503.

Patients Prefer DMTs That Minimize Side Effects and Delay Disability Progression

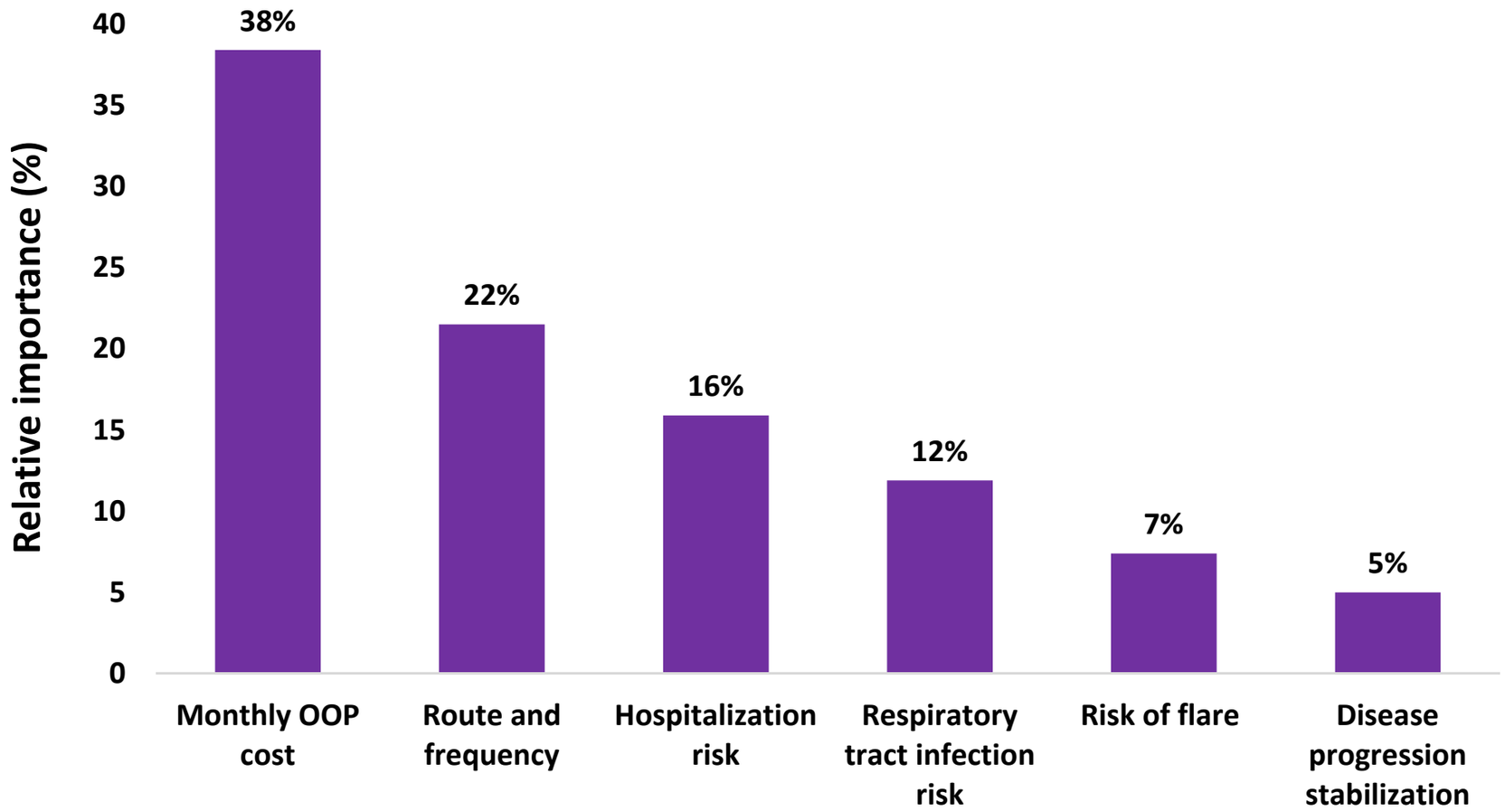


- n=125 patients with RRMS or SPMS
- Patients recruited from MS patient associations in Spain

- Preferences measured using a discrete choice experiment
- Multilinear regression used to evaluate the association between preferences for each attribute and patients' demographic and clinical characteristics

Garcia-dominguez JM, Muñoz D, Comellas M, Gonzalbo I, Lizán L, Polanco sánchez C. *Patient Prefer Adherence.* 2016;10:1945-1956.

Monthly OOP Cost Also Influences Patient Perceptions of DMTs



OOP=out-of-pocket

- Online survey results of 129 patients prescribed DMT for MS recruited from patient advocacy groups in the US
- Patients asked to rank the importance of attributes that influence their satisfaction with a DMT

Hincapie AL, Penm J, Burns CF. *J Manag Care Spec Pharm*. 2017;23(8):822-830.

Choice of DMT Autoinjector May Influence Adherence and Treatment Outcomes

- Ease of administration of a DMT may enhance patient adherence to therapy[1]
- Patient satisfaction with the autoinjector used to administer a DMT has been associated with improved adherence[2]
- Providing patients with autoinjector options may have a favorable impact on adherence[1]

1. Wray S, Hayward B, Dangond F, Singer B. *Expert Opin Drug Deliv.* 2018;15(2):127-135.
2. Pozzilli C, Schweikert B, Ecari U, Oentrich W. *J Neurol Sci*. 2011;307(1-2):120-6.

Introduction of Generic DMTs: Glatiramer Acetate

- Generic glatiramer acetate (GA) is available in 2 dosage forms[1]
  - 20 mg administered daily
  - 40 mg administered 3x/week
- Three-times-weekly dosing elicited a 50% reduction in mean annualized rate of injection-related adverse events compared to the daily 20 mg dose version[2]
- In addition to potential cost advantage, patient preference for three-times-weekly dosing may reduce reluctance to initiate a generic DMT

1. FDA Approves Another New Generic Form of 40mg Copaxone. National MS Society. https://www.nationalmssociety.org/About-the-Society/News/FDA-Approves-Another-New-Generic-Form-of-40mg-Copa. Published February 15, 2018. Accessed February 2019.
2. Wolinsky JS, Borresen TE, Dietrich DW, et al. *Mult Scler Relat Disord*. 2015;4(4):370-6.

MS Therapies in Late-Phase Dev

Agent	Target/ Mechanism of Action	Possible Indication	Administration	Status
Sphingosine-1-Phosphate Receptor Modulators				
Ozanimod	S1P1/S1P5 receptor blocker	RRMS, relapsing MS	Oral	NDA filed
Ponesimod	S1P1 receptor modulator	RRMS	Oral	Phase 3
Monoclonal Antibodies				
Ofatumumab	Anti-CD20 B cell modulator	RRMS	IV/SC	Phase 3
Rituximab	Anti-CD20 B cell modulator	RRMS, SPMS	IV	Phase 2
Ublituximab	Anti-CD20 B cell modulator	Relapsing MS	IV	Phase 3

Garry T, Krieger S, Fabian, M. MS research update. MSAA website: https://mymsaa.org/publications/msresearch-update-2018/. Accessed February 2019.

MS Therapies in Late-Phase Development (cont'd)

Agent	Target/ Mechanism of Action	Possible Indication	Administration	Status
Other Strategies				
ALKS 8700	Prodrug of monomethyl fumarate	RRMS	Oral	Phase 3
Laquinimod	Immunomodulator	RRMS, Progressive MS	Oral	Phase 3
Evobrutinib	Bruton tyrosine kinase inhibitor (B cell signal inhibition)	Relapsing MS	Oral	Phase 2
Ibudilast	Inhibits cyclic nucleotide phosphodiesterase, macrophage migration inhibitory factor, and Toll-like receptors	Progressive MS	Oral	Phase 3 (fast track designation)
Masitinib	Protein kinase inhibitor of mast cells	PPMS, SPMS	Oral	Phase 3
Biotin	Vitamin involved in fat metabolism	SPMS, PPMS	Oral	Phase 3
Lipoic acid	Antioxidant	SPMS	Oral	Phase 2/3
Simvastatin	HMG-CoA reductase inhibitor	SPMS	Oral	Phase 3

Garry T, Krieger S, Fabian, M. MS research update. MSAA website: https://mymsaa.org/publications/msresearch-update-2018/. Accessed February 2019.

Novel Therapeutic Strategies

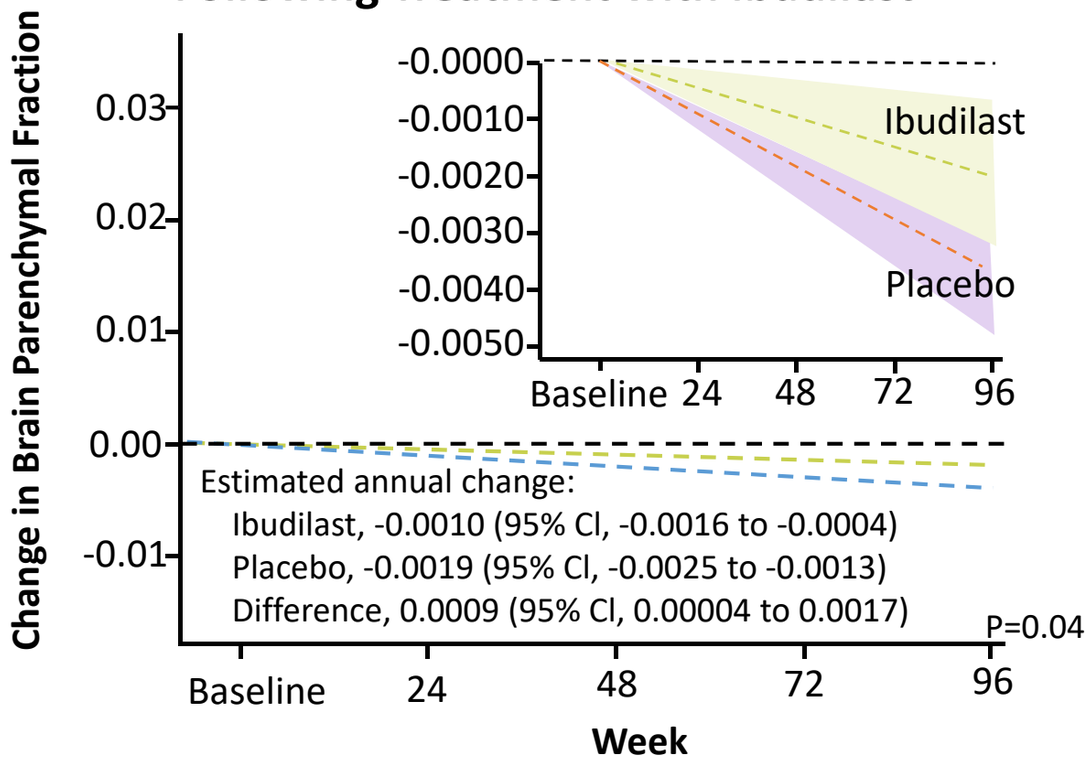
Agent	Target/ Mechanism of Action	Possible Indication	Administration	Status
Anti-LINGO	Remyelination	RRMS, SPMS	IV	Phase 2
Amiloride	Sodium channel blocker	PPMS	Oral	Phase 2
Phenytoin	Sodium channel blocker	PPMS	Oral	Phase 2
Clemastine	Remyelination	RRMS	Oral	Phase 2
Idebenone	Anti-oxidant	PPMS	Oral	Phase 1/2
MIS416	Therapeutic vaccine	PPMS, SPMS	Injection	Phase 1/2
ATL1102	Antisense oligonucleotide	RRMS	Oral	Phase 2
ATA188/190	Autologous T cell immunotherapy	PPMS, SPMS	IV	Phase 1

Garry T, Krieger S, Fabian, M. MS research update. MSAA website: https://mymsaa.org/publications/msresearch-update-2018/. Accessed February 2019.

Therapy in Late-Phase Development: Ibudilast for PMSS and SPMS

- **Ibudilast**: A small molecule that can cross the BBB with potential beneficial effects in progressive MS
- **Design**: 96-week, randomized, placebo controlled phase 2 study (n=255)
- **Primary endpoint**: rate of brain atrophy, as measured by the brain parenchymal fraction
- **Results**: ibudilast was associated with slower progression of brain atrophy than placebo

Change in Whole Brain Atrophy Following Treatment with Ibudilast



Change was measured according to the mean brain parenchymal fraction between baseline and week 96. The inset shows the same data on an enlarged y axis, with shaded areas indicating 95% confidence intervals of the estimated slope.

Fox RJ, Coffey CS, Conwit R, et al. *N Engl J Med*. 2018;379(9):846-855.

Therapy in Late-Phase Development: Safety of Ibudilast

- Gastrointestinal symptoms were the most common adverse events
- Depression was more common with ibudilast vs. placebo, but there were no reports of suicidality or suicide
- Rates of discontinuation of the trial regimen or of the trial were higher with ibudilast vs. placebo

	Ibudilast (n=120)	Placebo (n=126)	P value
Any adverse event (AE)	92%	88%	0.26
Trial withdrawal due to AE	8%	4%	0.21
Serious AE	16%	19%	0.46

Fox RJ, Coffey CS, Conwit R, et al. *N Engl J Med*. 2018;379(9):846-855.

Therapy in Late-Phase Development: Ozanimod

Endpoints	Ozanimod vs. IFN-β1a			
	SUNBEAM[1]		RADIANCE[2,3]	
	0.5 mg	1 mg	0.5 mg	1 mg
Reduced 6-month CDP	3.8% ns	2.9% ns	6.5% Ns	7.6% Ns
Reduced brain volume loss	12% 0.06	33% <0.0001	25% <0.0001	27% <0.0001
Reduced increase of T2 lesion volume	25% <0.00001	48% <0.0001	34% <0.00001	42% <0.0001
Reduced ARR	0.24 0.0013	0.18 <0.0001	0.22 0.0167	0.17 <0.0001
No difference in walking scores	N/A			

1. Arnold D, Cohen JA, Comi G, et al. Poster P1857. ECTRIMS Online Library. Published October 27, 2017. Accessed February 2019.
2. Comi G, Kappos L, Selmaj KW, et al. Abstract 232. ECTRIMS Online Library. Published October 27, 2017. Accessed February 2019.

Therapy in Late-Phase Development: Ofatumumab

Phase 2b MIRROR Study[1]	3 mg q12w	30 mg q12w	60 mg		Placebo
			q12 w	q4w	
Number	34	32	34	64	67
Cumulative new Gd+ lesions (0-12 w)	33	30	33	63	67
Mean cumulative new enlarging T2 lesions (4-12 w)	0.36	0.11	0.09	0.08	0.83

- 90% reduction of new Gd+ lesions with depletion to 32 CD19+ cells/mL
- Repletion to LLM CD19+ by study week 48

Phase 3[2]

- Identical randomized, double blind/double dummy, parallel **ASCLEPIOS I** and **ASCLEPIOS II** trials
- 20 mg ofatumumab SC q4w vs. active control with teriflunomide 14 mg po
- Primary endpoint: ARR
- n=900 patients with RRMS (18-55 years)

1. Bar-or A, Grove RA, Austin DJ, et al. *Neurology*. 2018; 90:e1805-e181
2. Hauser SL, Bar-or A, Cohen J, et al. Abstract S16.005. *Neurology*. 2017; 88 (16 Suppl). Presented April 24, 2017 at American Academy of Neurology.

Therapy in Late-Phase Development: Ublituximab

Phase 2 Study Design

- n=48 patients with RRMS followed for 48 wk
- Day 1
  - Placebo vs. ublituximab 150 mg over 1 of 4 infusion durations
- Day 15
  - Placebo vs. ublituximab 450 mg over 1 of 3 infusion durations
- Day 24
  - Placebo vs. ublituximab 450 mg over 1 of 2 infusion durations
- Primary endpoint: B cell depletion (Week 4)

Results

- Median B cell depletion: 99%
- Maintained at Weeks 24 and 48
- T2 lesions vs. baseline:
  - Week 24: 7.3% ↓
  - Week 48 10.6% ↓
- T1-Gd+ lesions reduced to 0 at Week 24 and sustained at Week 48
- ARR: 0.07 at Week 48
- 93% of patients relapse free at Week 48
- Safety
  - Most common AE: IRR
  - 1 SAE related to treatment

Fox E, et al. Abstract 229. ECTRIMS Online Library. Published October 11, 2018. Accessed February 2019.

Summary

- MS is a chronic progressive immune-mediated disease of the CNS and is associated with significant disability
- The clinical presentation can be highly variable between patients
- Treatment with disease modifying therapies should be initiated within 12 months of symptom onset to slow disease progression and minimize disability
- Multiple safe and effective DMTs are available with several more in late phase development
- Patient preference should be considered when selecting a DMT

Specialty Pharmacy Management Strategies to Enhance MS Patient Outcomes

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Learning Objective

- Employ utilization management and benefit design strategies for multiple sclerosis (MS) therapies to promote appropriate prescribing

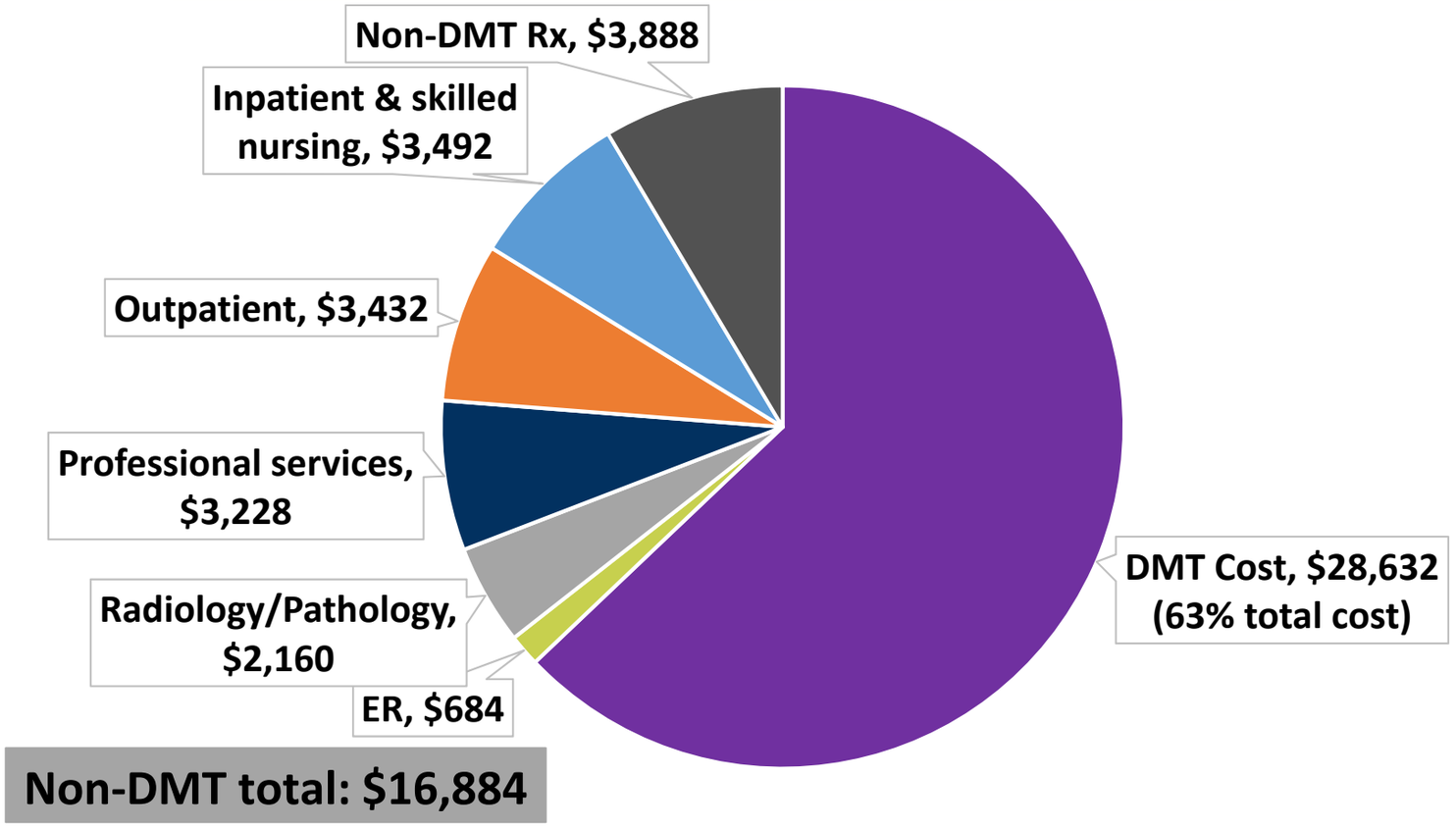
Prevalence and Burden of MS

- MS affects an estimated 900,000 people in the United States
- Because the majority of cases are diagnosed between 20 – 50 years of age, MS can have a significant negative functional, financial, and psychosocial impact during the prime of a patient's life
- Costs associated with MS are considerable and rise with increasing disability
- There is currently no cure

MS Prevalence. National Multiple Sclerosis Society website. http://www.nationalmssociety.org/About-the-Society/MS-Prevalence. Accessed February 2019.
Adelman G, Rane SG, Villa KF. *J Med Econ*. 2013;16(5):639-47.

MS is a Costly Chronic Disease

Annual claim costs for MS (per patient)
Total: $45,516



Non-DMT total: $16,884

Six cost drivers of multiple sclerosis. Optum website. https://www.optum.com/resources/library/ms-cost-drivers.html. Accessed February 2019.

MS Requires Lifelong Care

- Majority of people with MS live with the disease for more than 20 years
- Common chronic comorbidities (eg, hypertension, diabetes, heart disease, depression, anxiety, lung disease) can impact MS progression, mortality, and quality of life
- MS disease and symptom control and treatment of comorbid conditions requires lifelong care management

Marrie RA, Cohen J, Stuve O, et al. *Mult Scler.* 2015;21(3):263-81.

Managing MS Remains a Challenge

Multiple sclerosis is one of the most difficult problems in clinical medicine*

- Providers and payers must effectively manage MS while simultaneously maximizing the value of high-cost treatment options
- Ongoing challenges:
  - Significant variation in treatment across practice settings
  - Complex treatment decisions
  - Prolonged treatment duration
  - Continual introduction of novel disease-modifying therapies (DMTs) and biosimilars
  - Limited head-to-head and cost-efficacy data
  - Evolving quality performance measures

*Jean-Martin Charcot, MD—the “Father of Neurology” (1894)

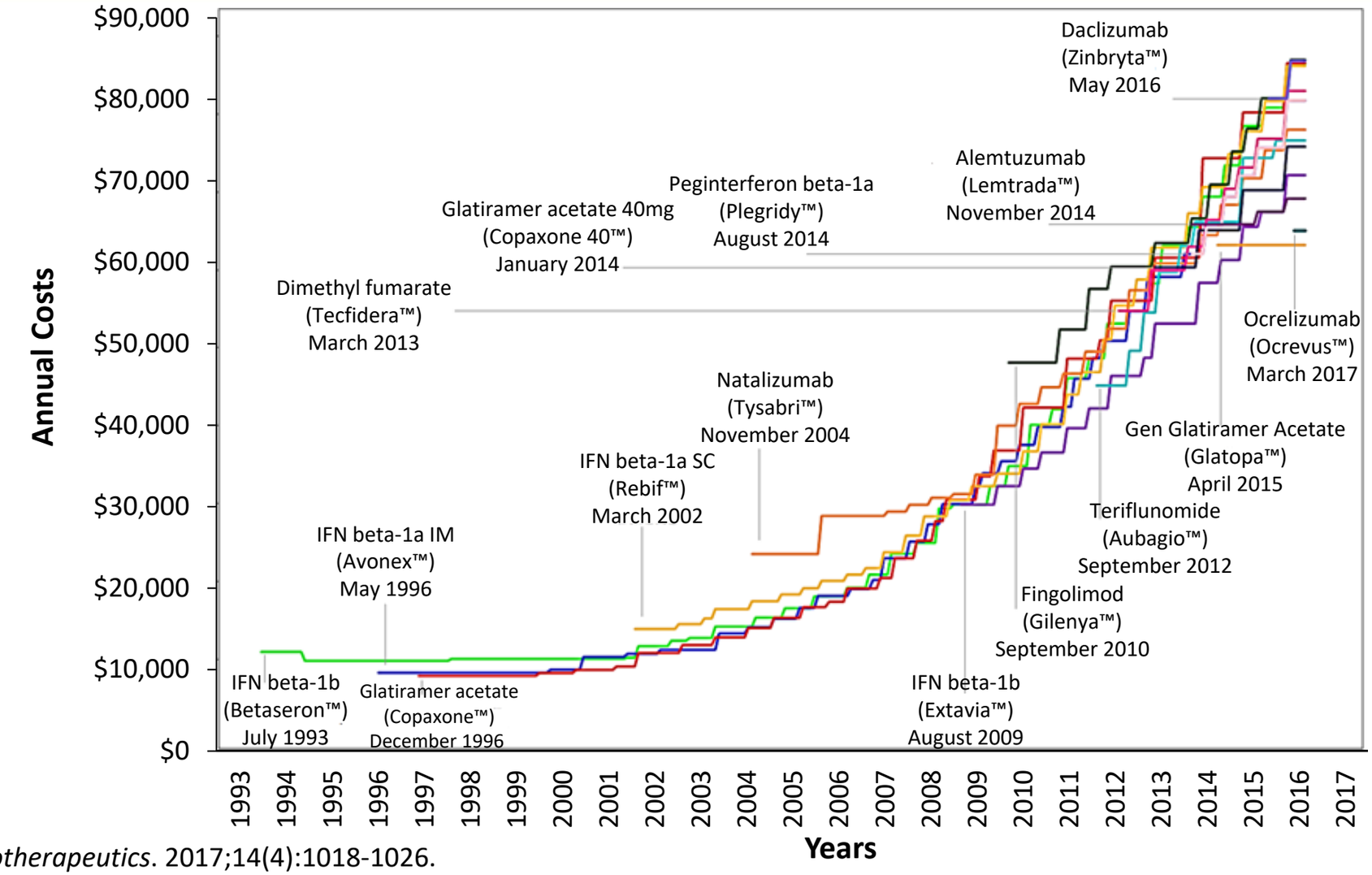
Owens GM. *J Manag Care Pharm*. 2016;22(6 Suppl):S151-S158.

MS Management Requires Coordinated Multidisciplinary 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, Nogrady L, Moreo K, et al. *J Manag Care Pharm*. 2011;17(9 Suppl):S3-S21;
Comprehensive Care. National Multiple Sclerosis Society website. http://www.nationalmssociety.org/Treating-MS/Comprehensive-Care. Accessed February 2019.

Cost of Existing DMTs Have Risen, Matching Prices Set by the Most Recent Competitor*



Hartung DM. *Neurotherapeutics*. 2017;14(4):1018-1026.

*Pricing estimated from WAC for year of therapy.

MS Drug Spend Ranks Among the Highest in Commercial Plans

Therapy Class	Type	PMPY Spend	Trend	
			Utilization	Total
Inflammatory conditions	Specialty	$157.49	3.9%	15.3%
Diabetes	Traditional	$116.23	4.2%	2.1%
Oncology	Specialty	$70.66	4.3%	17.4%
Multiple Sclerosis	**Specialty**	**$60.20**	**-3.4%**	**3.0%**
HIV	Specialty	$26.82	2.5%	13.7%
Pain/Inflammation	Traditional	$44.06	-2.1%	-15.0%
Attention disorders	Traditional	$36.12	2.9%	-0.3%
Asthma	Traditional/Specialty	$33.40	2.6%	0.7%
Hypertension/heart disease	Traditional	$31.41	0.6%	-7.1%
High cholesterol	Traditional	$26.82	0.3%	-30.6%

2017 Drug Trend Report. Express Scripts. http://lab.express-scripts.com/lab/drug-trend-report/~/media/2b56ec26c9a04ec2bcca0e9bf1ea8ff1.ashx. Accessed February 2019.

The MS Drug Benefit Should Be Designed to Optimize Care and Manage 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. 14th Edition. 2018. https://online.flippingbook.com/view/567745/. Accessed February 2019.

Selecting the “Right” MS Drug

- Treatment should be individualized using shared decision making between the provider and patient
- None of the approved MS therapies is curative
- Clinicians and patients vary in their tolerance for risk and preference of route-of-administration
  - Multiple mechanisms of action
  - Oral, IV, SC, and IM routes of administration
  - Variable efficacy and safety

Owens GM. *Am J Manag Care.* 2016;22(6 Suppl):S151-S158.
The use of disease modifying therapies in multiple sclerosis. Multiple Sclerosis Coalition. 2018. http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed February 2019.

Plan Strategies to Manage 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 GM. *Am J Manag Care*. 2013;19(16 Suppl):s307-12.

Site-of-Care Delivery Can Influence Cost and Access

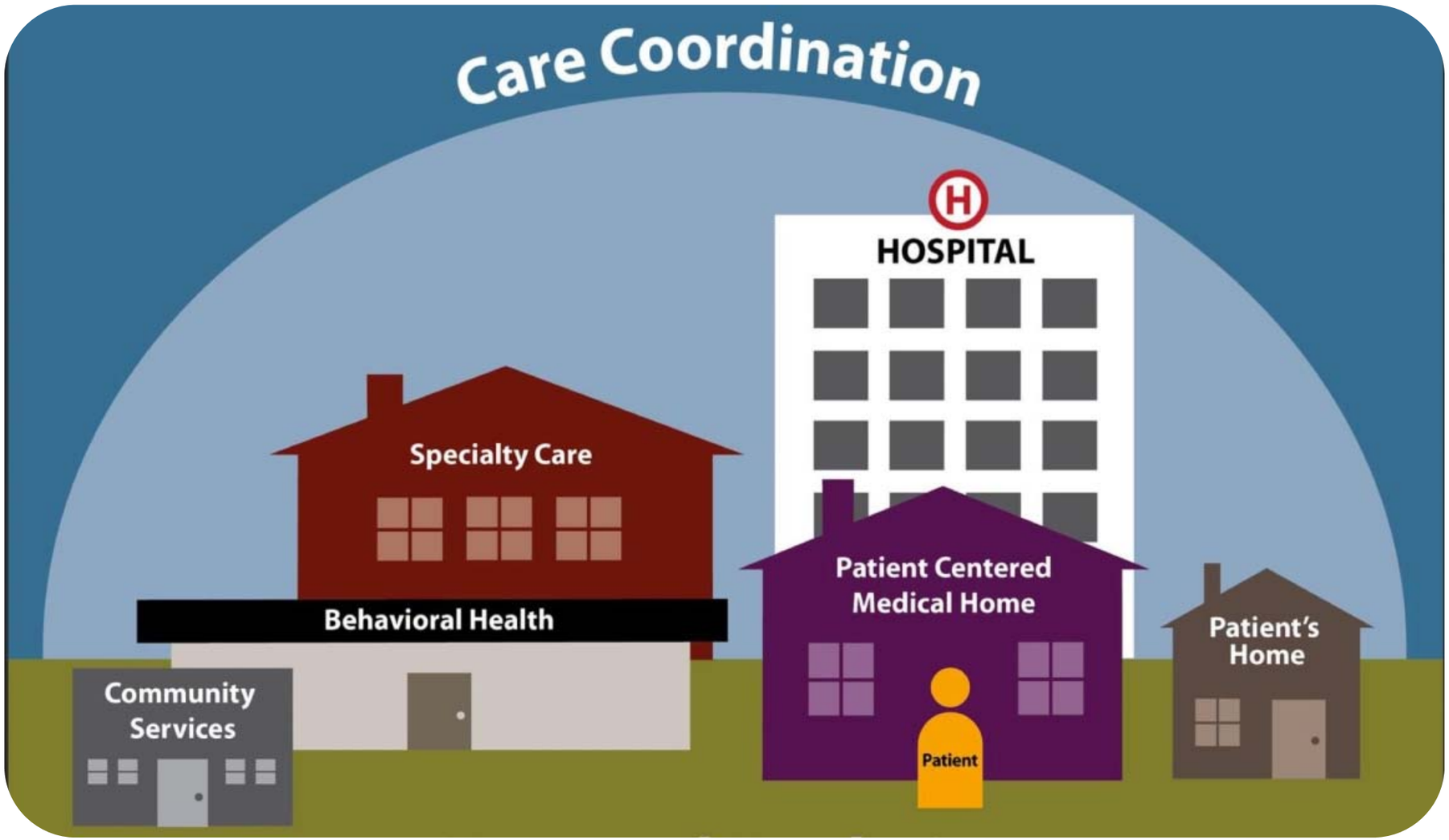
MS Care Continuum

- Home Self Care
- Call Center
- Urgent Care Clinic
- Home Care
- Primary Care Physician
- Hospital Outpatient
- Hospital Inpatient
- Skilled Nursing Facility

Ease of Access

Cost of Care

Strategies to Optimize Health Outcomes



Strategy to Improve Clinical Outcomes for Patients with MS

Coordinated, multidisciplinary care

- Lifelong therapy, including neurology care, primary care, physical therapy, occupational therapy, and psychosocial counseling

Care management and routine follow up

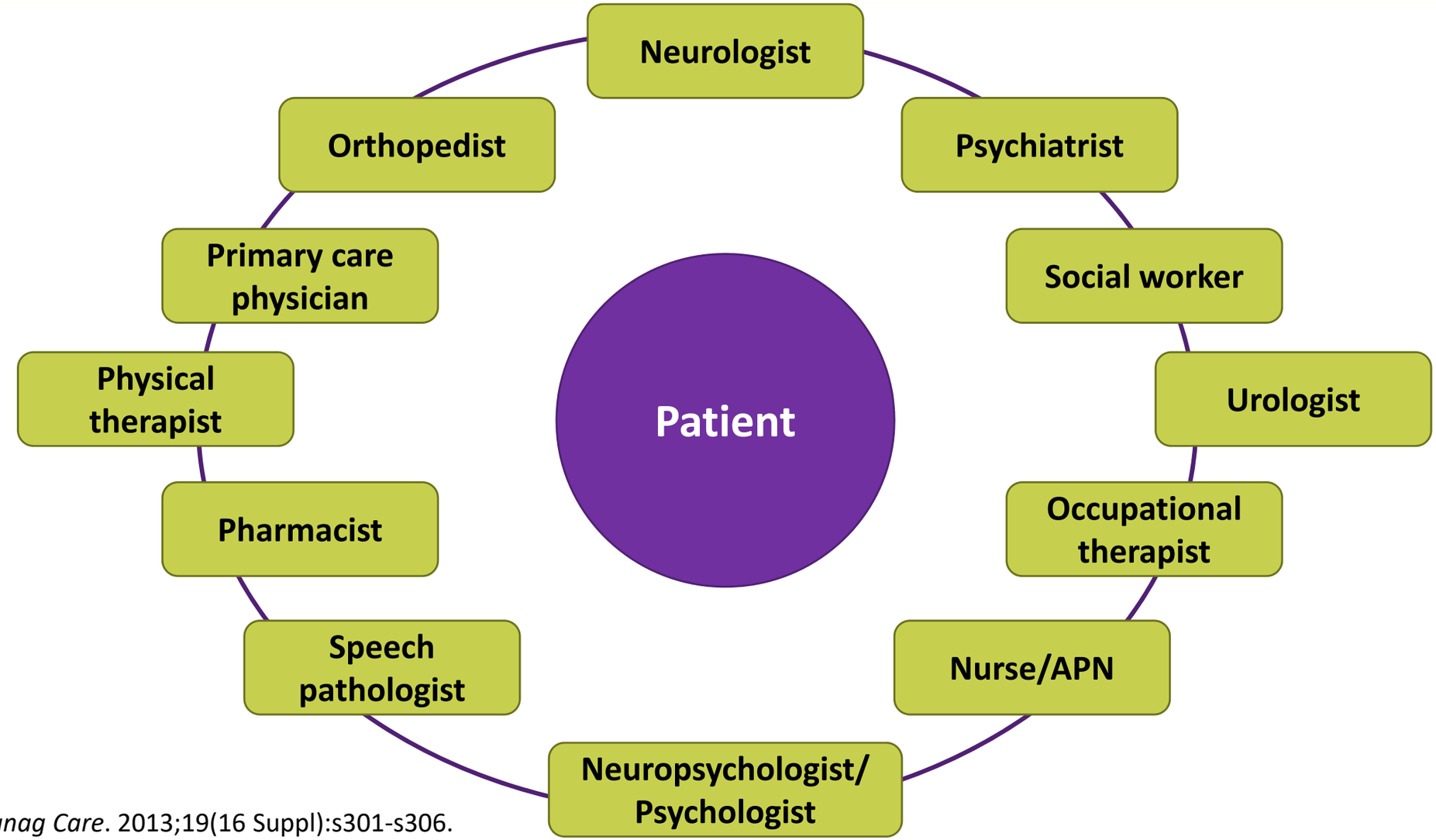
- Patient education
- Adherence support

Screening for and management of symptoms

- Fatigue, depression, cognitive impairment, ataxia/tremor, spasticity, bowel/bladder dysfunction

Goodell S, Bodenheimer T, Berry-Millet R. What are the keys to successful care management? In: Care management of patients with complex health care needs. Robert Wood Johnson Foundation. https://www.rwjf.org/content/dam/farm/reports/issue_briefs/2009/rwjf49853. Accessed February 2019.

Members of the Multidisciplinary Care Team



Perrin RA. *Am J Manag Care*. 2013;19(16 Suppl):s301-s306.

What is Care Management?

- **Care management**: A set of activities intended to improve patient care and reduce the need for medical services by enhancing *coordination of care*
- **Goal:** Improve coordination of care, reducing the rate of functional decline and improving health in the most cost-effective manner
- **Components:** Includes services to enhance continuity of care, coordination across providers, and development of comprehensive care plans

Schurrer J, O'Malley A, Wilson C, et al. Evaluation of the Diffusion and Impact of the Chronic Care Management Services: Final Report. Centers for Medicare and Medicaid Services website. https://innovation.cms.gov/Files/reports/chronic-care-mngmt-finalevalrpt.pdf. Accessed February 2019.

Keys to Successful Care Management

Success Factor	Description
Communication	• Health care team explains information clearly, tries to understand the patient's experience, and provides viable treatment/management options
Care coordination	• Organization of care activities between a multidisciplinary team of providers facilitates delivery of appropriate health care services
In-person encounters	• Face-to-face interaction is ideal • Telephone and/or electronic encounters are an efficient approach to follow up • Preferred patient communication style is often dependent on age
Personnel	• Trained care managers are a critical part of the multi-disciplinary care team
Physician involvement	• Physician involvement ensures patient and caregiver engagement
Informal caregivers	• MS patients with physical or cognitive functional decline often require the assistance of informal caregivers to actively participate in care management
Coaching	• Patients and their caregivers must be taught how to recognize early signs of worsening disease

Goodell S, Bodenheimer T, Berry-Millet R. What are the keys to successful care management? In: Care management of patients with complex health care needs. Robert Wood Johnson Foundation. https://www.rwjf.org/content/dam/farm/reports/issue_briefs/2009/rwjf49853. Accessed February 2019.

MS Care Management Involves Effective Symptom Management

Primary Symptoms

- **Brainstem:** Diplopia; nystagmus; vertigo
- **Cerebellum:** Ataxia; tremor
- **Cerebrum:** Cognitive impairment; depression
- **Optic nerve:** Optic neuritis; vision loss
- **Spinal cord:** Bladder and bowel dysfunction; weakness; spasticity
- **Other:** Fatigue; pain; temperature sensitivity

Secondary Symptoms

- **Neurogenic bladder:** Urinary tract infection
- **Inactivity:** Loss of muscle tone; poor posture; decreased bone density
- **Immobility:** Pressure sores

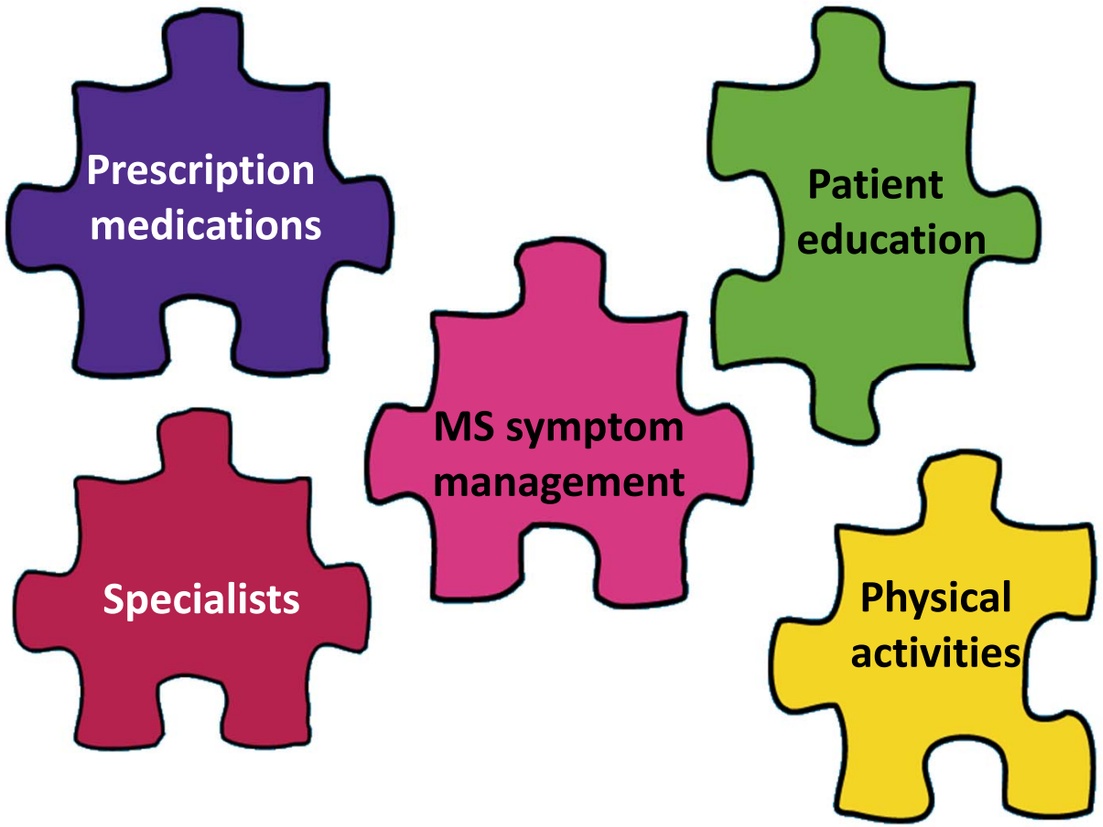
Tertiary Symptoms

- **Social isolation**
- **Depression**
- **Lost work/personal productivity**

Compston A, Coles A. *Lancet*. 2008;372(9648):1502-17.
Tullman MJ. *Am J Manag Care*. 2013;19(2 Suppl):S15-S20.
MS Symptoms. National Multiple Sclerosis Foundation website. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed February 2019.

Effective Symptom Management Involves Medication, Rehabilitation and Emotional Support

- Successful MS management includes:
  - Early identification, prioritization, and treatment of primary MS symptoms
  - Individualized MS therapy
  - Treatment of comorbid conditions
  - Coordinated, multidisciplinary care



MS Symptoms. National Multiple Sclerosis Foundation website. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed February 2019.

Care Management Can Foster Improved Adherence to Treatment

- Patient motivation and readiness for treatment is key to adherence
- Factors that negatively affect readiness include:
  - Lack of knowledge about MS/denial of illness
  - Lack of support (medical team, family, caregivers)
  - Unrealistic expectations of treatment outcomes
  - Cost of medical care/treatment
  - Side effects
  - Cultural factors
  - Distrust of medical community and/or prescription medications

Remington G, Rodriguez Y, Logan D, Williamson C, Treadaway K. *Int J MS Ca*re. 2013;15(1):36-45.

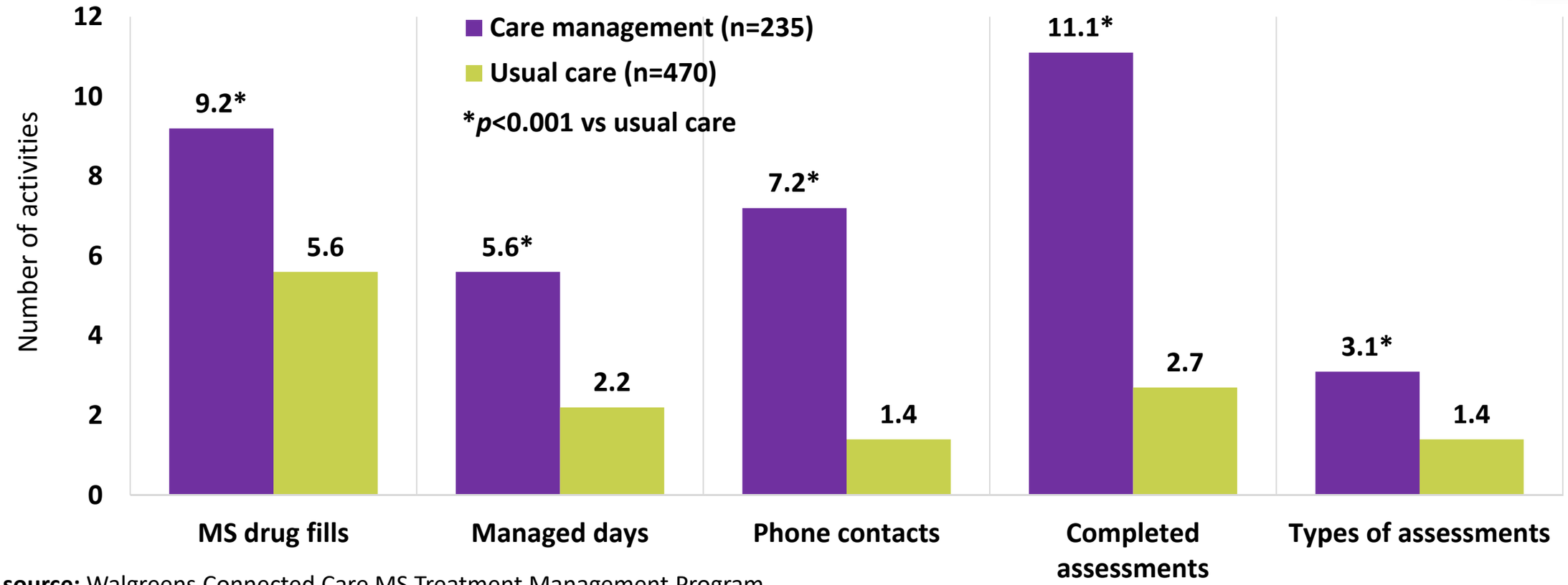
Care Management: A Strong Patient-Clinician Relationship Can Foster Improved Adherence

- The clinician-patient relationship is a crucial factor affecting adherence, especially as treatment continues over the long term
- Clinicians can work with each patient to set expectations regarding
  - Disease diagnosis and prognosis
  - Benefits expected from treatment interventions
  - Strategies to overcome barriers to achieving a specific health outcome (including adherence)

Bubalo J, Clark RK, Jiing SS, et al. *J Am Pharm Assoc* (2003). 2010;50(3):394-406.

Does Care Management Improve Outcomes?

Comprehensive Care Management Increased Delivery of Appropriate MS Care



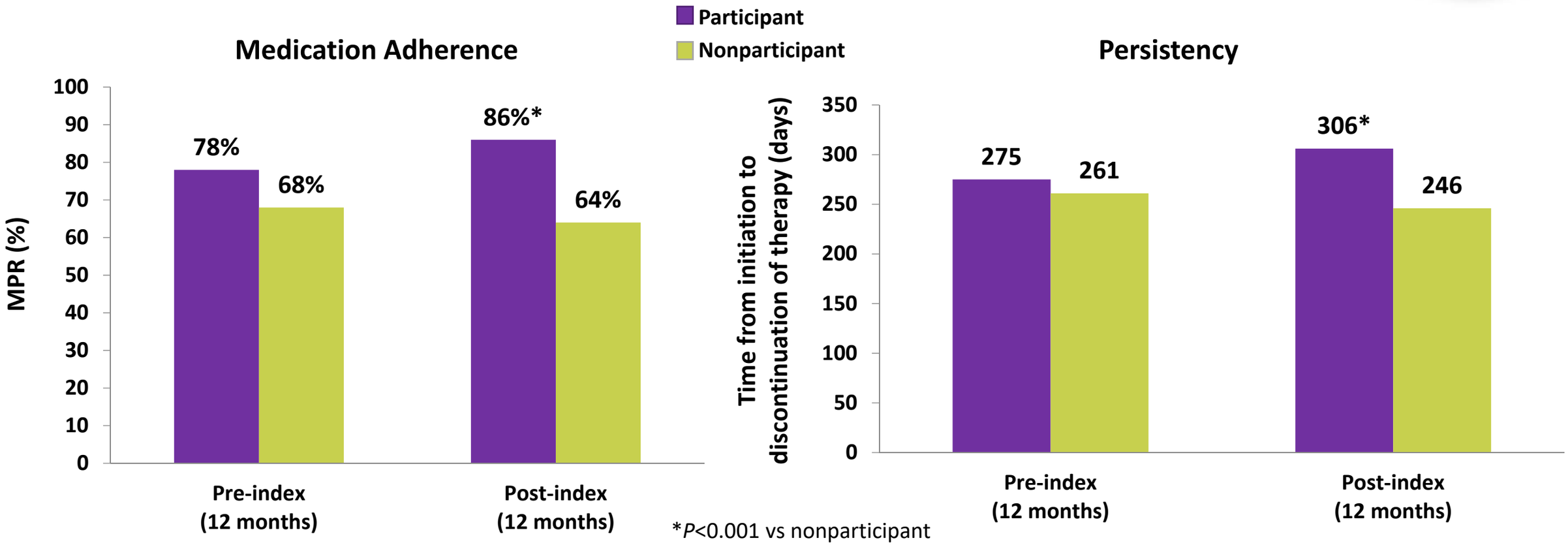
Data source: Walgreens Connected Care MS Treatment Management Program

Intervention: Patients received services beyond standard medication fulfillment, including individualized therapy management; education about disease progression, dosing and administration, and managing adverse effects; adherence support and assistance; recommendations regarding supportive care; and advice about overall health and wellness.

Outcomes assessed: Clinical services received and adherence at 12 months

Duchane J, Clark B, Staskon F, Miller R, Love K, Duncan I. Int *J MS Care*. 2015;17(2):57-64.

Care Management Improved Adherence and Persistency

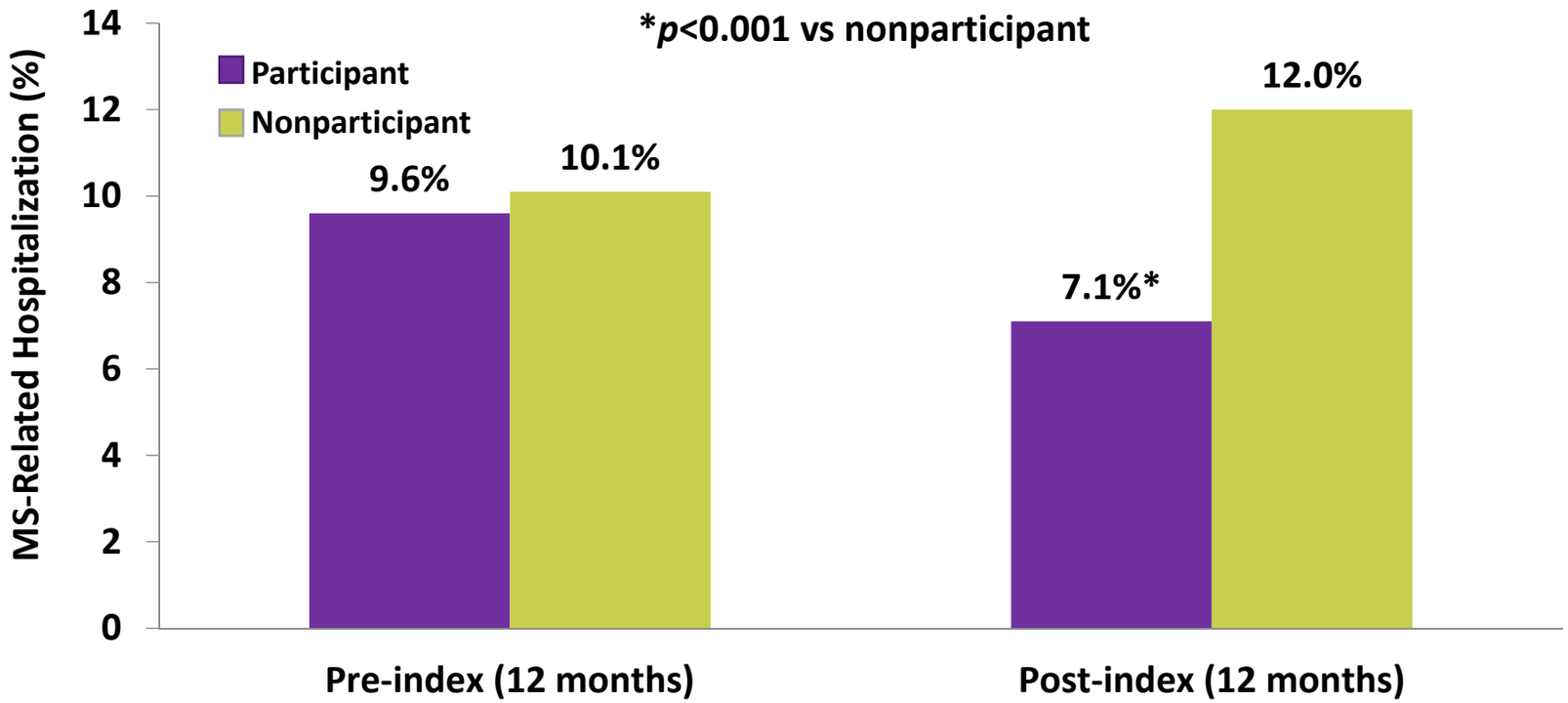


*P<0.001 vs nonparticipant

Data source: Retrospective claims analysis of MS patients ≥18 years (n=3993) from the HealthCore Integrated Research Database (January 2004-April 2008)
Intervention: Regular phone calls by nurses to provide a liaison to the pharmacy, medical information, adherence support, AE management, and refill reminders
Outcomes assessed: Adherence and persistence; MS-related hospitalization; total MS-related cost of care during the 12 months post-index period

Tan H, Yu J, Tabby D, Devries A, Singer J. *Mult Scler*. 2010;16(8):956-63.

Care Management Reduced Hospitalizations



Data source: Retrospective claims analysis of MS patients ≥18 years (n=3993) from the HealthCore Integrated Research Database (January 2004-April 2008)
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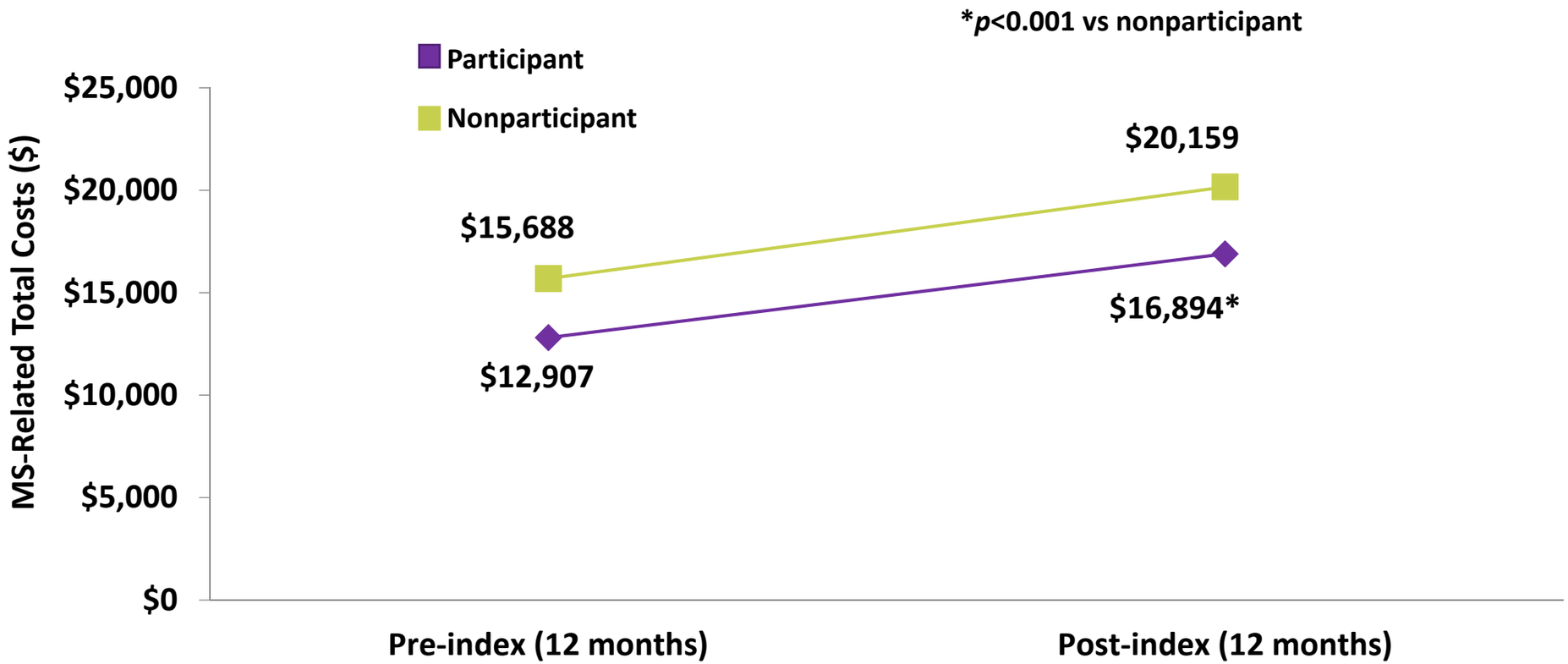
Tan H, Yu J, Tabby D, Devries A, Singer J. *Mult Scler*. 2010;16(8):956-63.

Care Management Reduced Total MS-Related Cost of Care

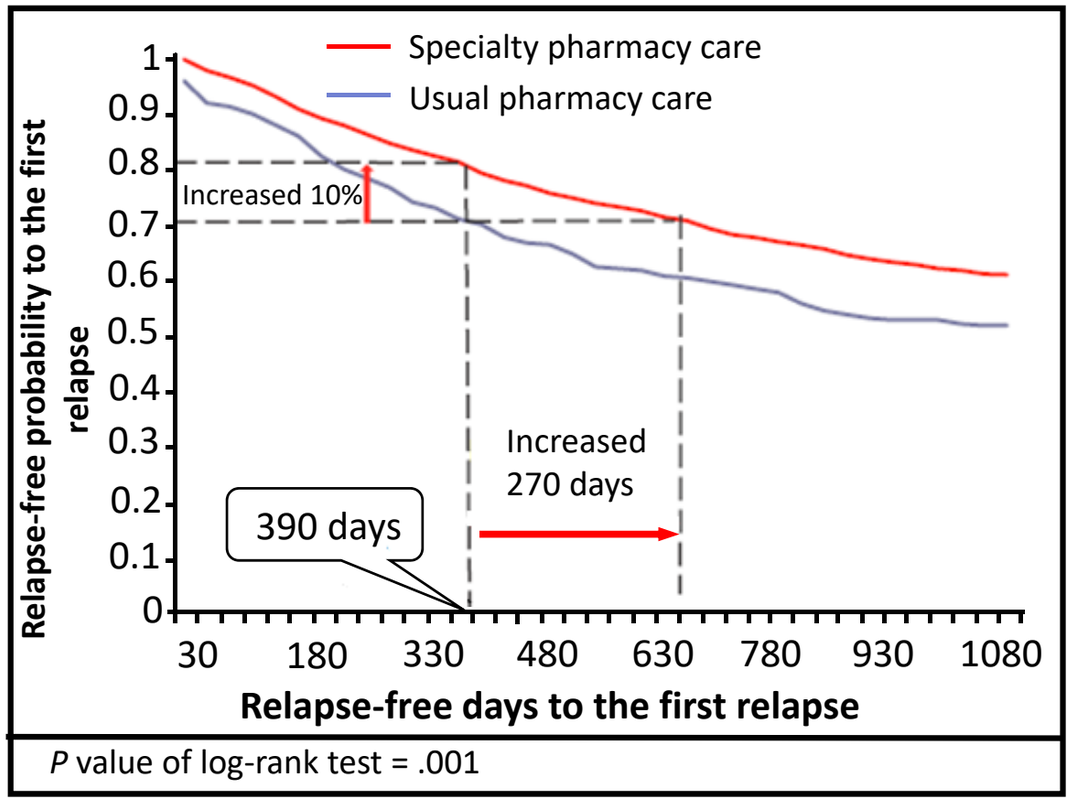


Data source: Retrospective claims analysis of MS patients ≥18 years (n=3993) from the HealthCore Integrated Research Database (January 2004-April 2008)
Intervention: Regular phone calls by nurses to provide a liaison to the pharmacy, medical information, adherence support, AE management, and refill reminders
Outcomes assessed: Adherence and persistence; MS-related hospitalization; total MS-related cost of care during the 12 months post-index period

Tan H, Yu J, Tabby D, Devries A, Singer J. *Mult Scler*. 2010;16(8):956-63.

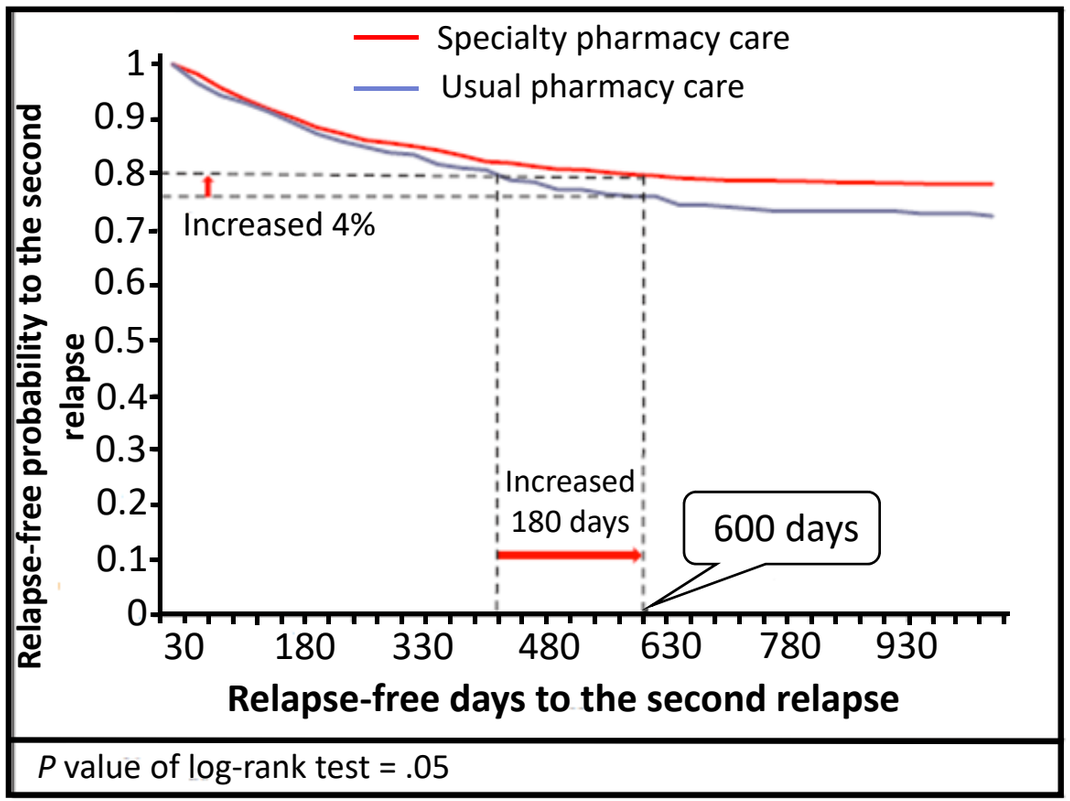
Care Management Implemented Through Specialty Pharmacy Lowered the Risk for Disease Relapse

Time to First MS-Relapse



P value of log-rank test = .001

Time to Second MS Relapse



P value of log-rank test = .05

Data source: Retrospective claims analysis of MS patients ≥18 years (n=1731) from an integrated national PBM pharmacy and medical database (2006 - 2009)
Intervention: Specialty pharmacy vs. community pharmacy care
Outcomes assessed: Time to first and second relapse and total number of relapses

Tang J, Bailey J, Chang C. et al. *Am Health Drug Benefits*. 2016;9(8):420-429.

Summary

- Management of MS can be complex and requires lifelong care, ideally delivered by a coordinated multidisciplinary team
- Coverage decision makers are challenged to find a balance between effectively managing the disease and maximizing the value of high-cost DMTs
- Treatment of MS should be individualized, and shared decision making between patients and healthcare providers is critical for successful management
- Care management is associated with greater adherence, decreased risk for disease relapse, and lower cost of care