Managing Clinical and Cost Outcomes in MULTIPLE SCLEROSIS

Expert Insights

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Clinical Update on Current and Emerging MS Treatment Regimens

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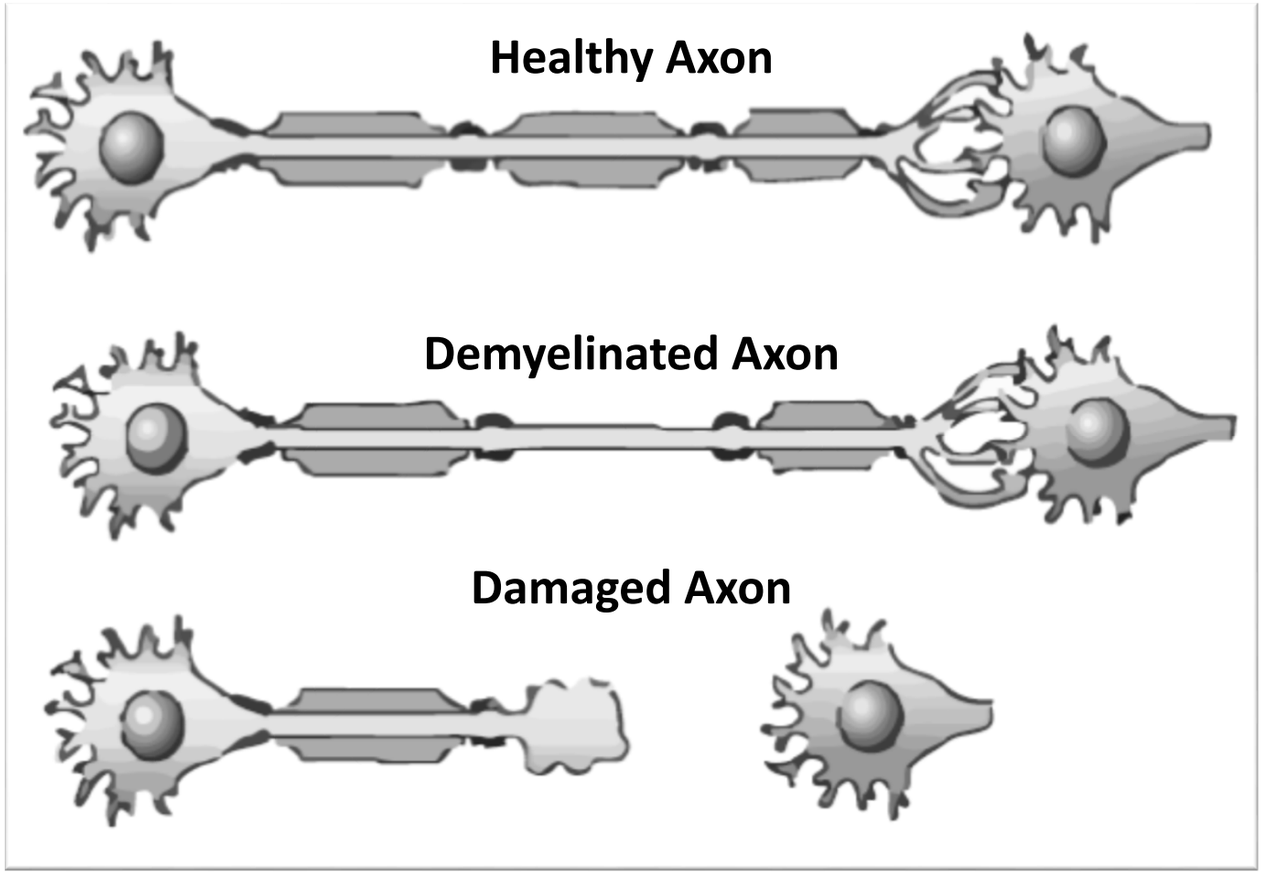
Learning Objective

- 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 Suppl 12:3-9.

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

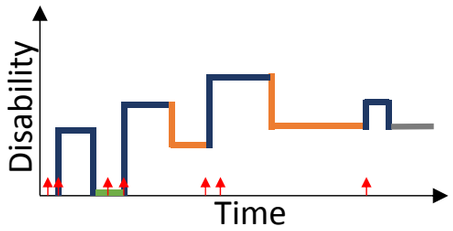
Calabresi PA, Newsome SD. Multiple sclerosis. In: Weiner WJ et al. *Neurology for the Non-Neurologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:192-221. Ascherio, A. *Expert Rev Neurother*. 2013;13 Suppl 12:3-9. Whetten-goldstein K, Sloan FA, Goldstein LB, Kulas ED. *Mult Scler*.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

MS Disease Subtypes

Radiologically or Clinically Isolated Syndrome (RIS/CIS)

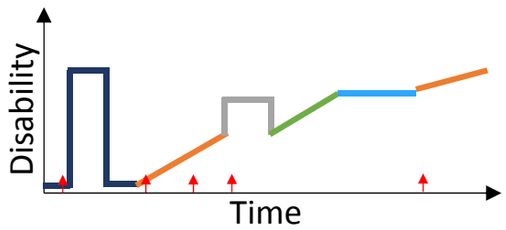
First episode of neurologic symptoms; must last for ≥24 hours; may not evolve into MS

Relapsing-Remitting (RRMS)



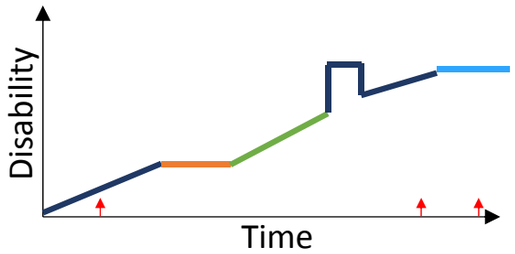
- Relapse
- Active without worsening
- Worsening (incomplete recovery from relapse)
- Stable without activity
- New MRI activity

Secondary Progressive (SPMS)



- 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

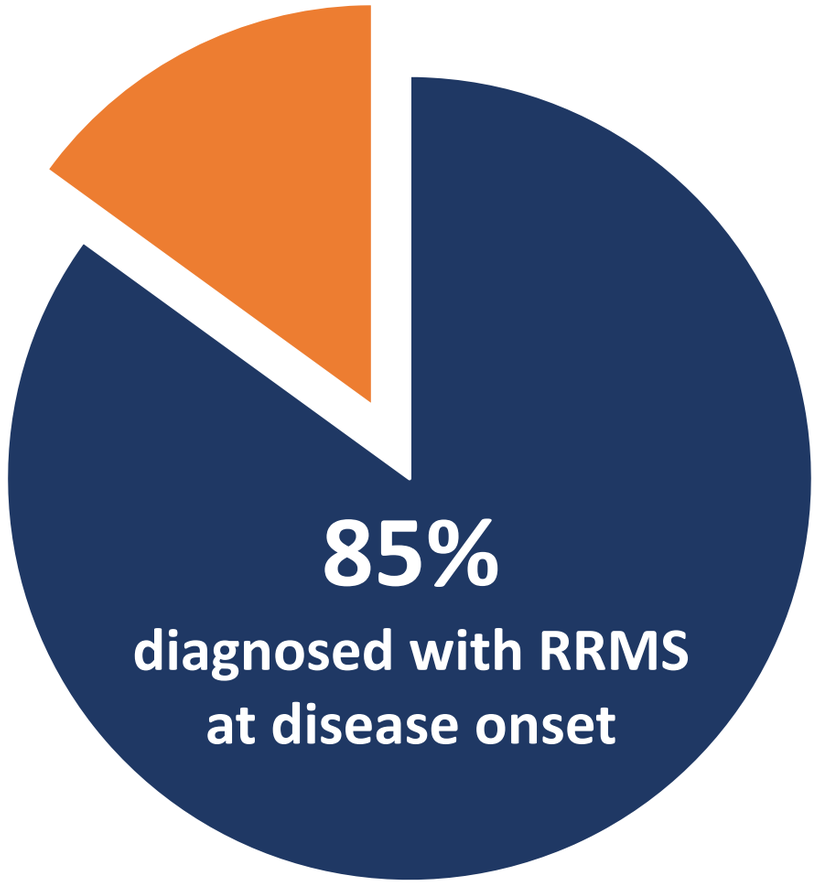
Primary Progressive (PPMS)

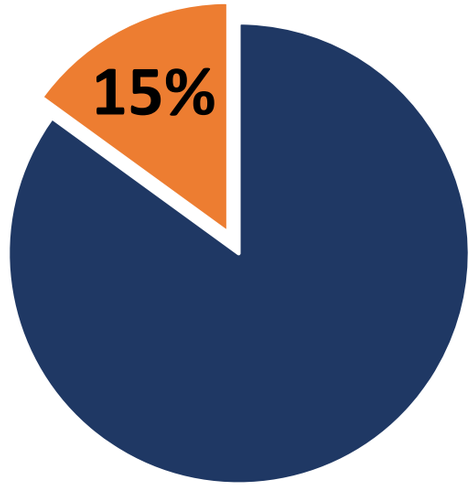


- Active (relapse or new MRI activity) with progression
- Not active without progression (stable)
- Not active with progression
- Active without progression
- New MRI activity

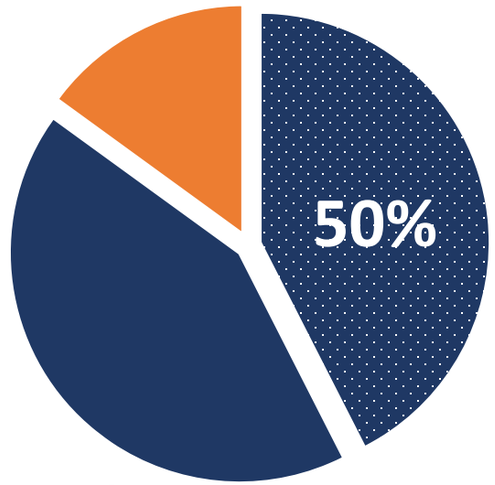
Types of MS. National Multiple Sclerosis Society. www.nationalmssociety.org/What-is-MS/Types-of-MS. Accessed February 2019.
Lublin FD, Reingold SC, Cohen JA, et al. *Neurology*. 2014;83(3):278-286.

Frequency of MS Clinical Subtypes





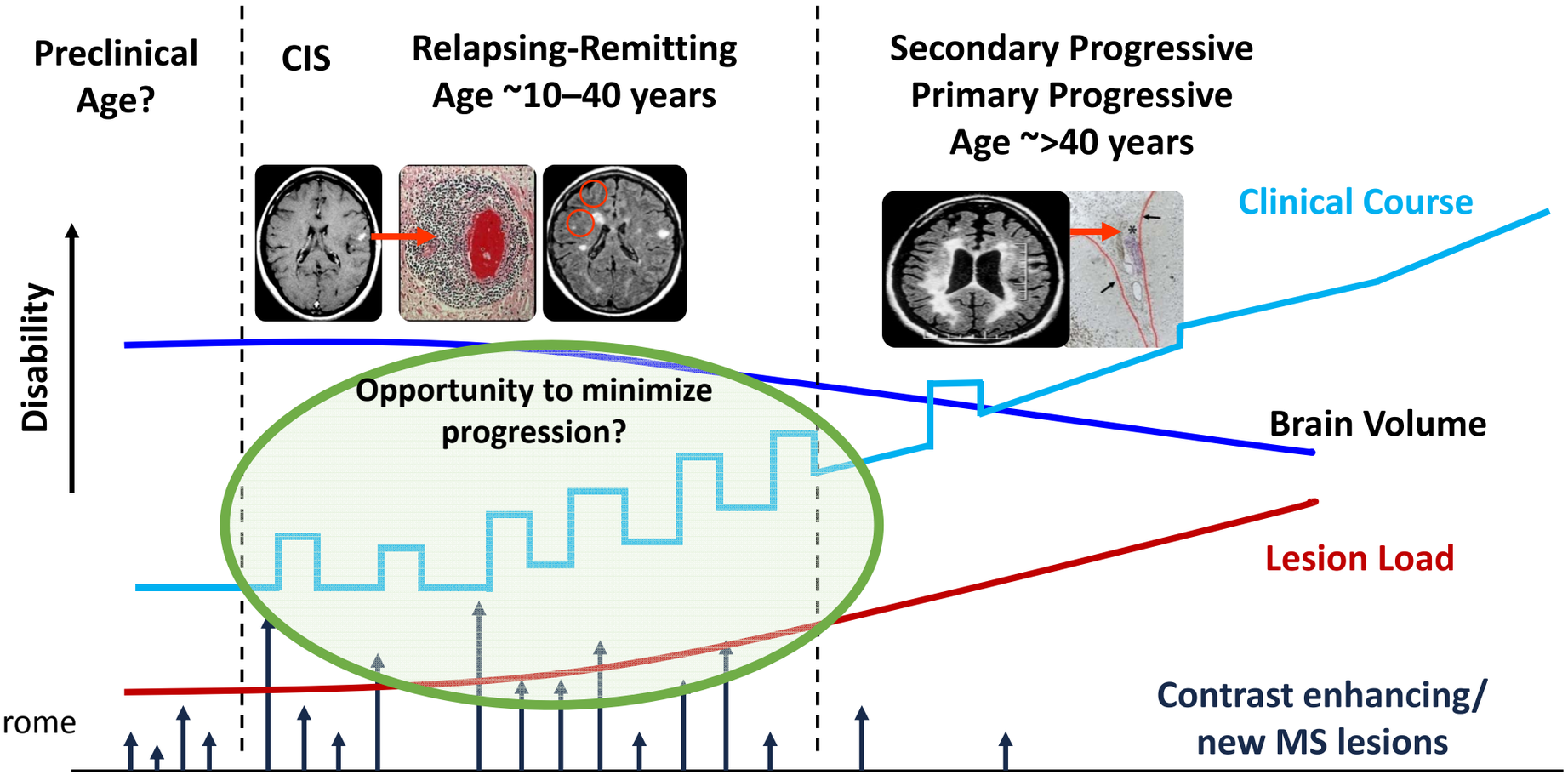
15%
are diagnosed with PPMS at disease onset



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

Types of MS. National Multiple Sclerosis Society. www.nationalmssociety.org/What-is-MS/Types-of-MS. Accessed February 2019.
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):518-524.

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):840-846.

MacDonald Diagnostic Criteria: 2017 Revision

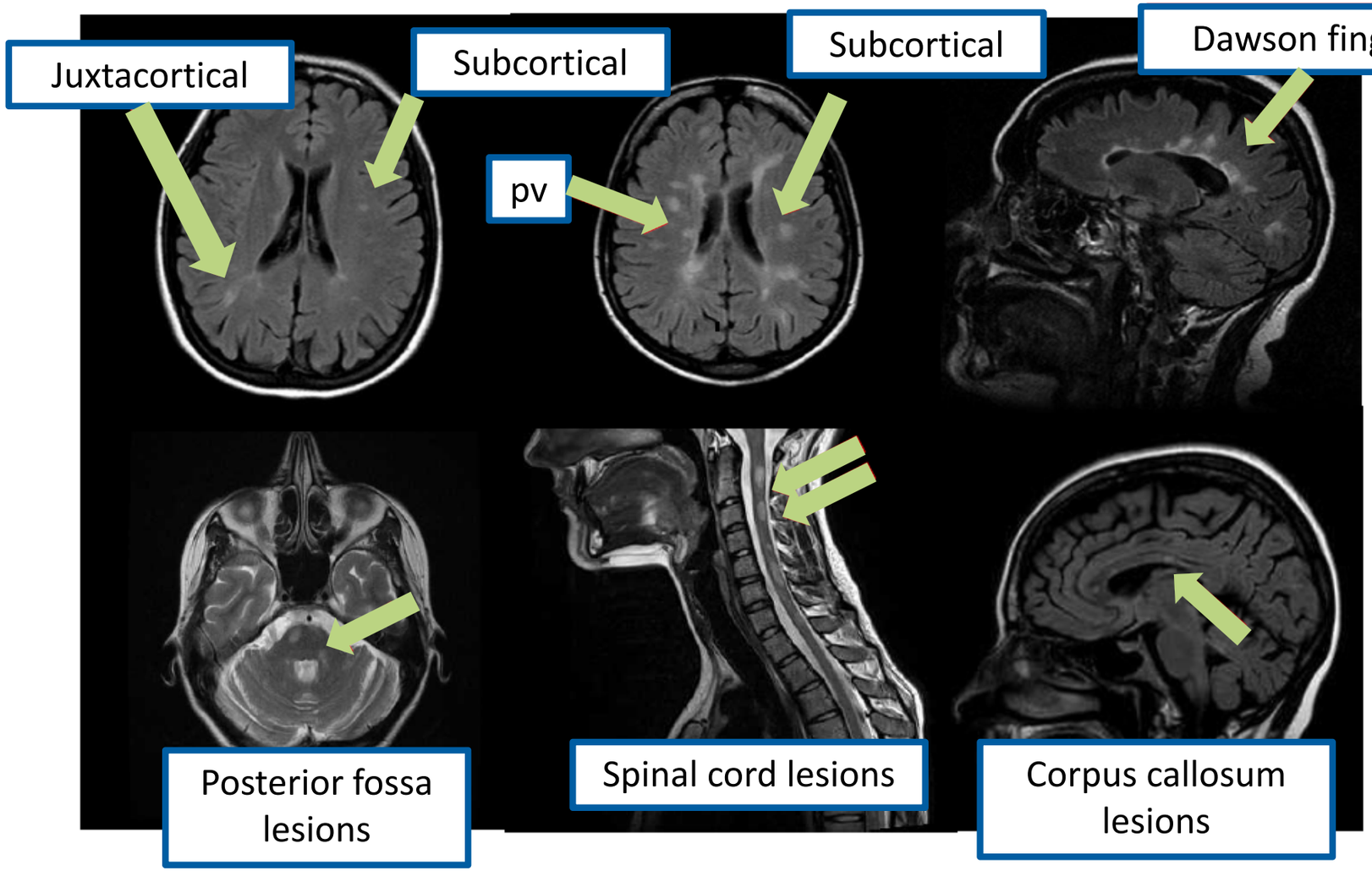
Clinical Presentation	Additional Data Needed for MS Diagnosis
• ≥2 attacks • Objective clinical evidence of ≥2 lesions with reasonable historical evidence of a prior attack	• None; clinical evidence will suffice • Additional evidence (e.g., brain MRI) desirable, but must be consistent with MS
• ≥2 attacks • 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

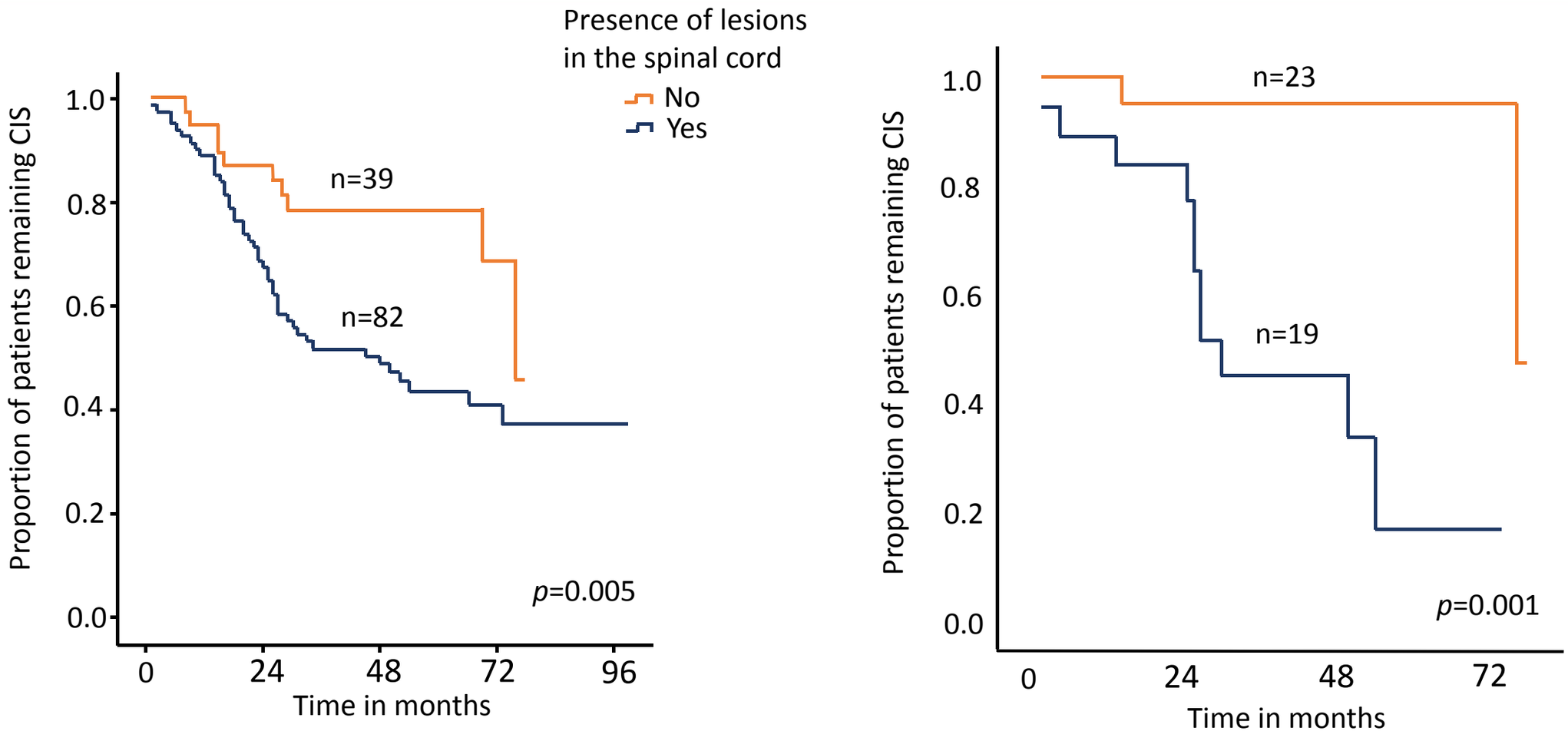
Thompson AJ, Banwell BL, Barkhof F, et al. *Lancet Neurol*. 2017;17:162-173.

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]	MS Lesions[2,3]
• Younger age at onset • Longer disease duration • Higher relapse rate • More frequent early relapses • Poor recovery from relapses	• 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.

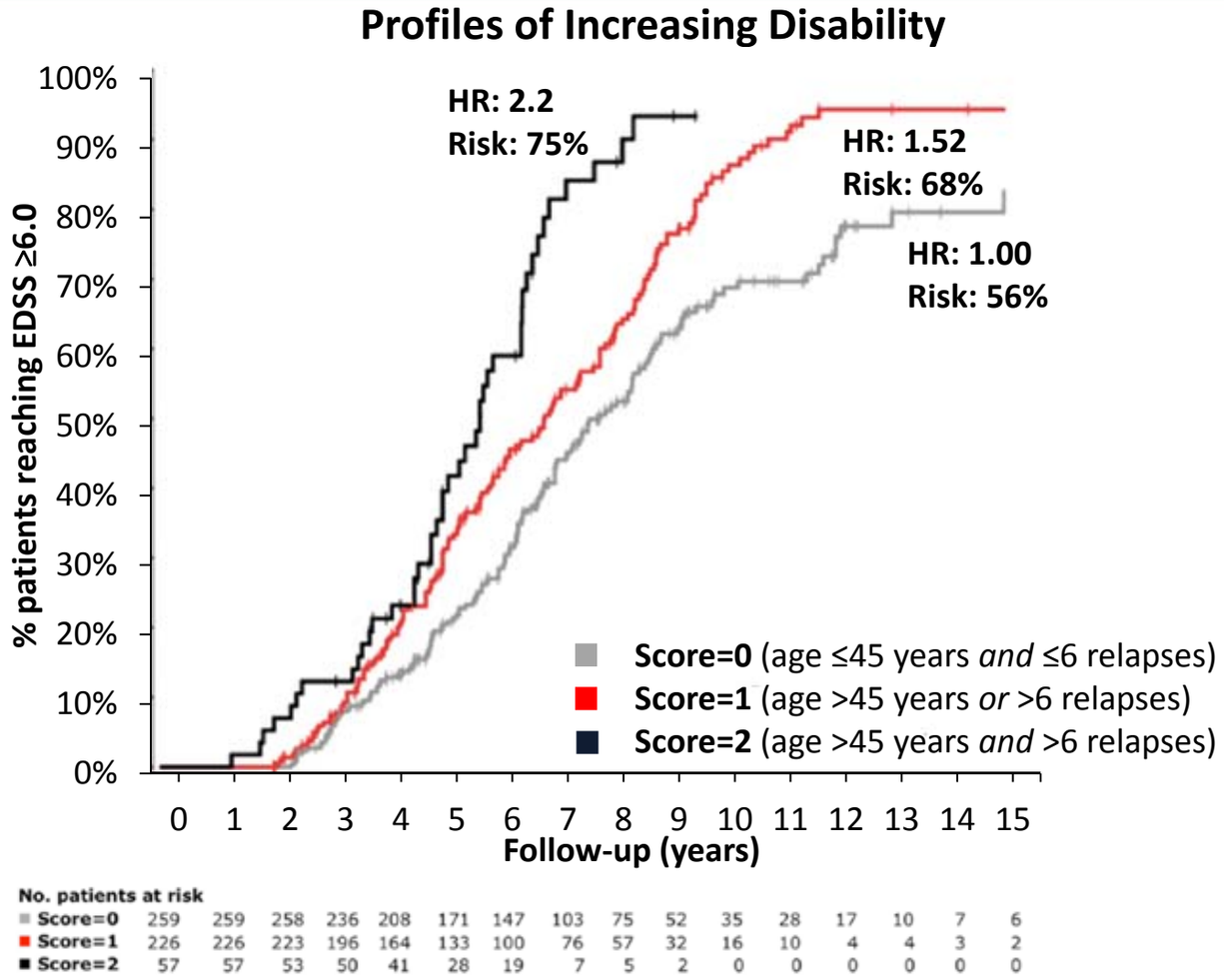
Predictors of Disability: Patient Factors

Ethnicity[1]	• Higher Patient-derived MS Severity Score (P-MSSS) in African-American and Hispanics vs. Caucasians
Gender[2]	• Increased risk in males

1. Ventura RE, Antezana AO, Bacon T, Kister I. *Mult Scler*. 2017;23(11):1554-1557. 2. Jokubaitis VG, Spelman T, Kalincik T, et al. *Ann Neurol*. 2016;80(1):89-100.

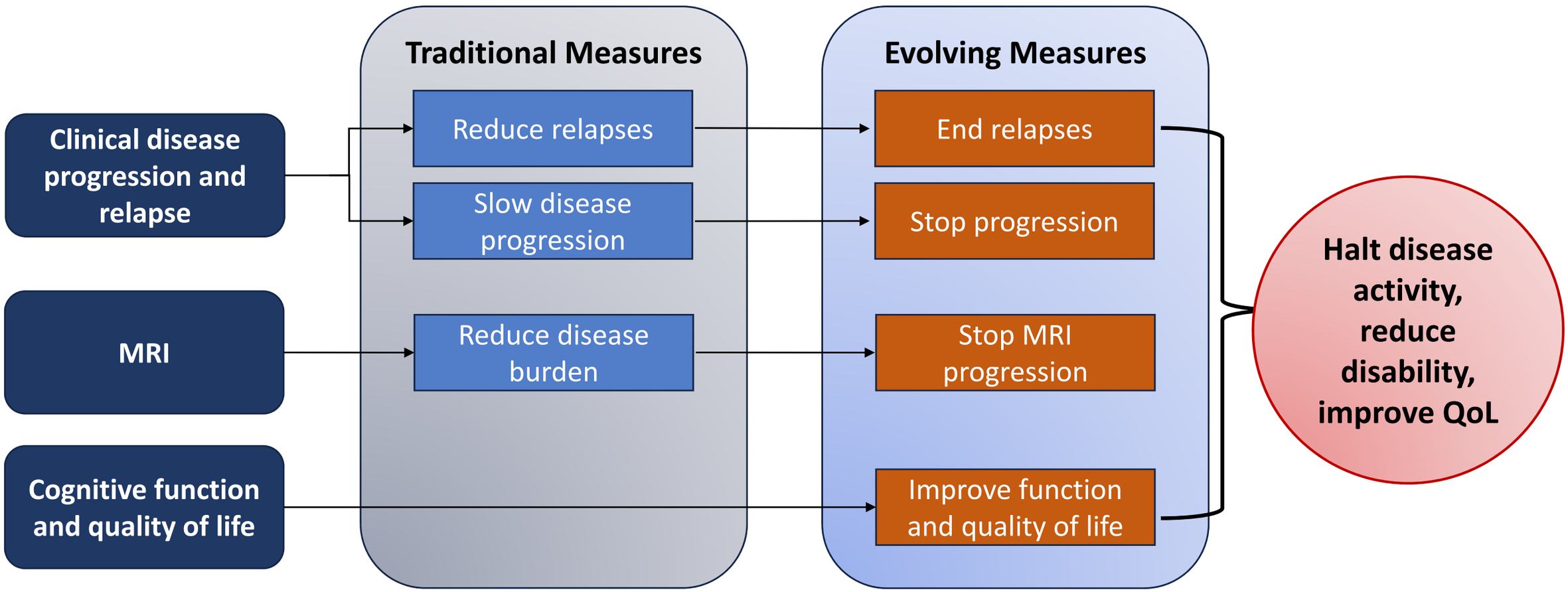
Predicting Disability

- 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].

Treatment Goals in MS



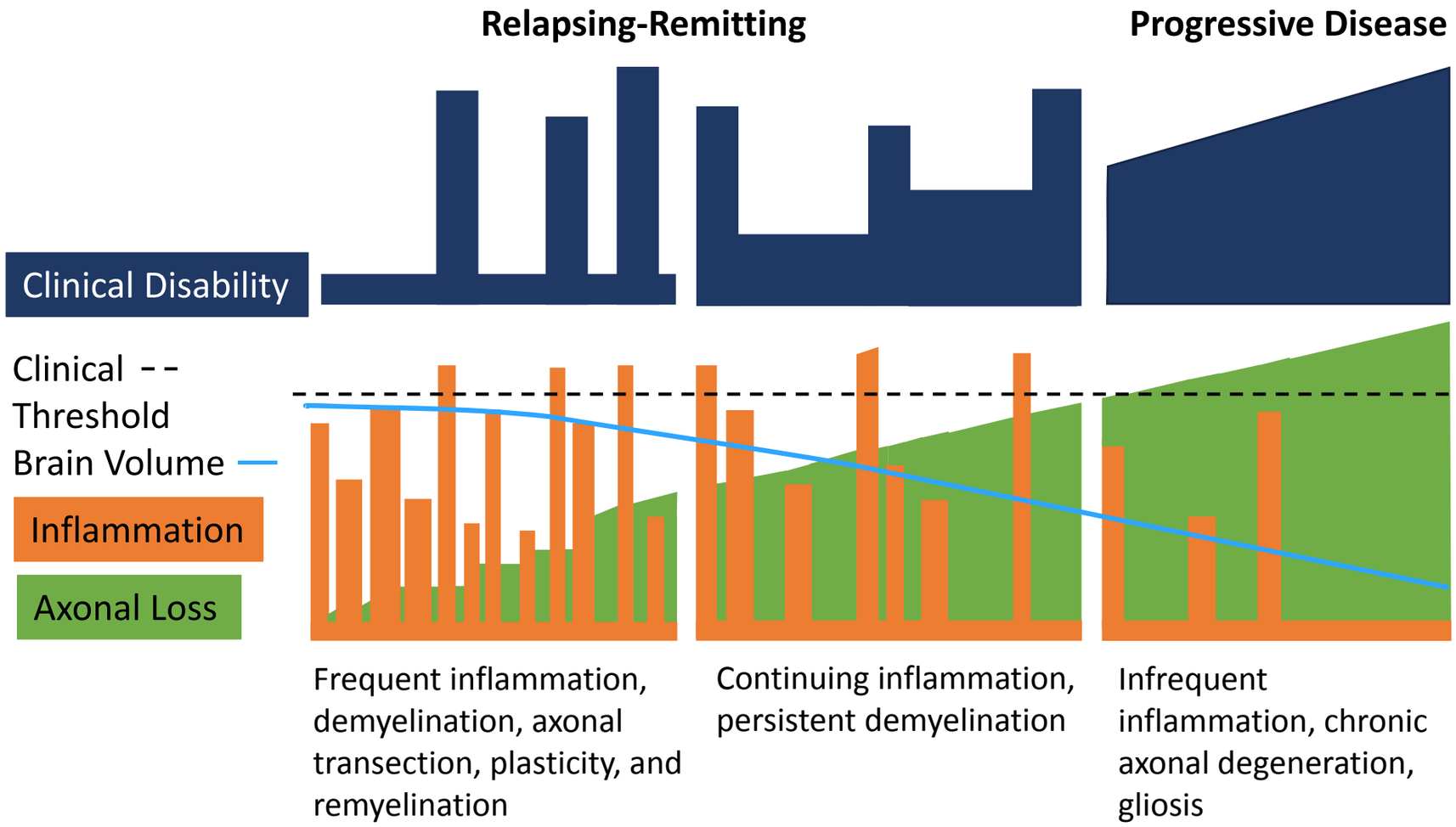
Smith AL, Cohen JA, Hua LH. *Neurotherapeutics*. 2017;14(4):952-960.
Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. *JAMA Neurol*. 2015;72(2):152-158.
Lazibat I, Šamija RK, Rotim K. *Acta Clin Croat.* 2016;55(1):125-133.

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 relapsing–remitting MS
- **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

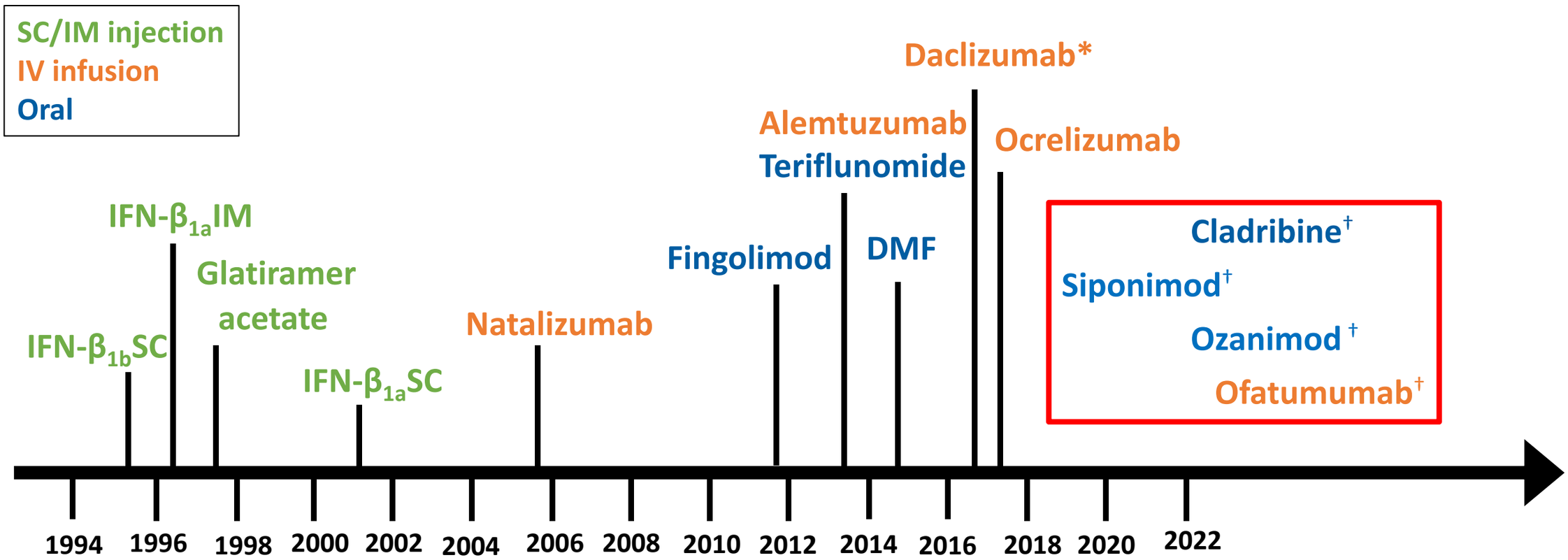
Cerqueira JJ, Compston DAS, Geraldes R, *et al*. *J Neurol Neurosurg Psychiatry* 2018;89:844–850.
Smith AL, Cohen JA, Hua LH. *Neurotherapeutics*. 2017;14(4):952-960.

Importance of Early Treatment



Dendrou CA, Fugger L, Friese MA. *Nat Rev Immunol*. 2015;15(9):545-558.

MS Treatment Landscape Continues to Expand



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

Thompson AJ, Baranzini SE, Geurts J, et al. *Lancet*. 2018;391(10130):1622-1636.

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		✓	✓	

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**
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.

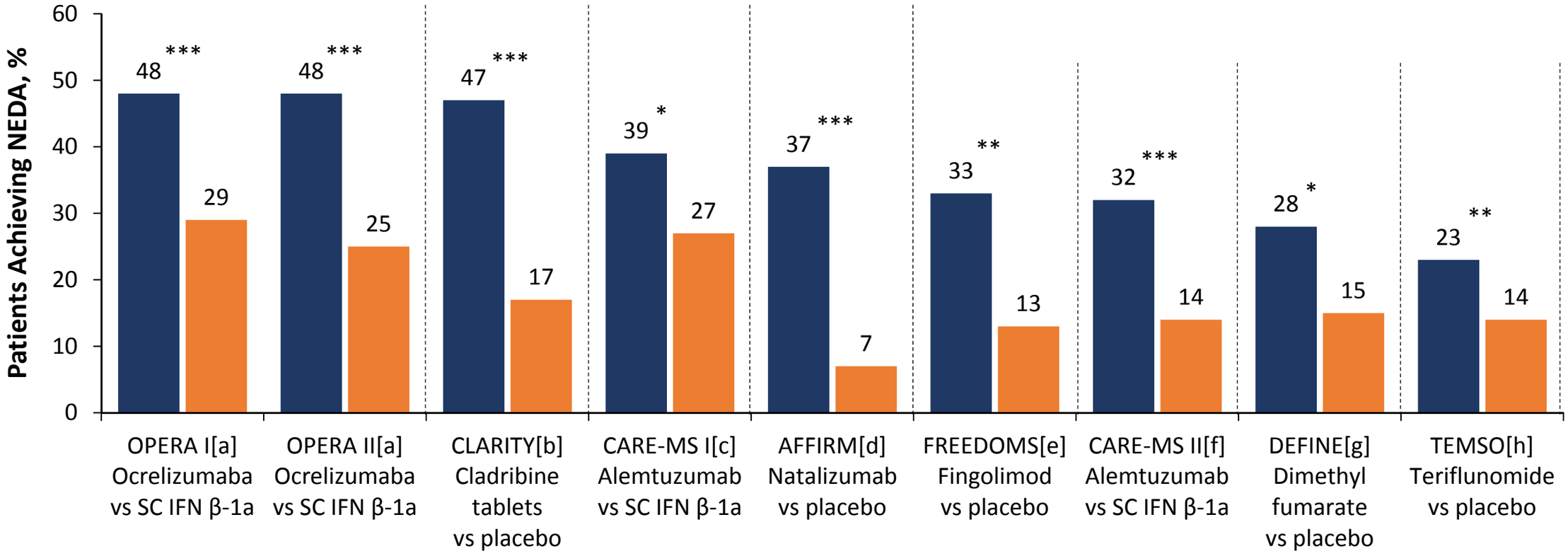
Time to Onset of Clinical Benefit

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**
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.

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



*P<0.5; **P<0.001; ***P<0.0001 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 Suppl 16. Published online February 8, 2016. Accessed February 2019. 2. Giovannoni G, Cook S, Rammohan K, et al. *Lancet Neurol*. 2011;10(4):329-337. 3. Cohen JA, Coles AJ, Arnold DL, et al. *Lancet*. 2012;380(9856):1819-1828. 4. Havrdova E, Galetta S, Hutchinson M, et al. *Lancet Neurol*. 2009;8(3):254-260. 5. Bevan CJ, Cree BA. *JAMA Neurol*. 2014;71(3):269-270. 6. Coles AJ, Twyman CL, Arnold DL, et al. *Lancet*. 2012;380(9856):1829-1839. 7. Giovannoni G, Rhoades RW. *Curr Opin Neurol*. 2012;25 Suppl:S20-27. 8. Freedman 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

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.

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

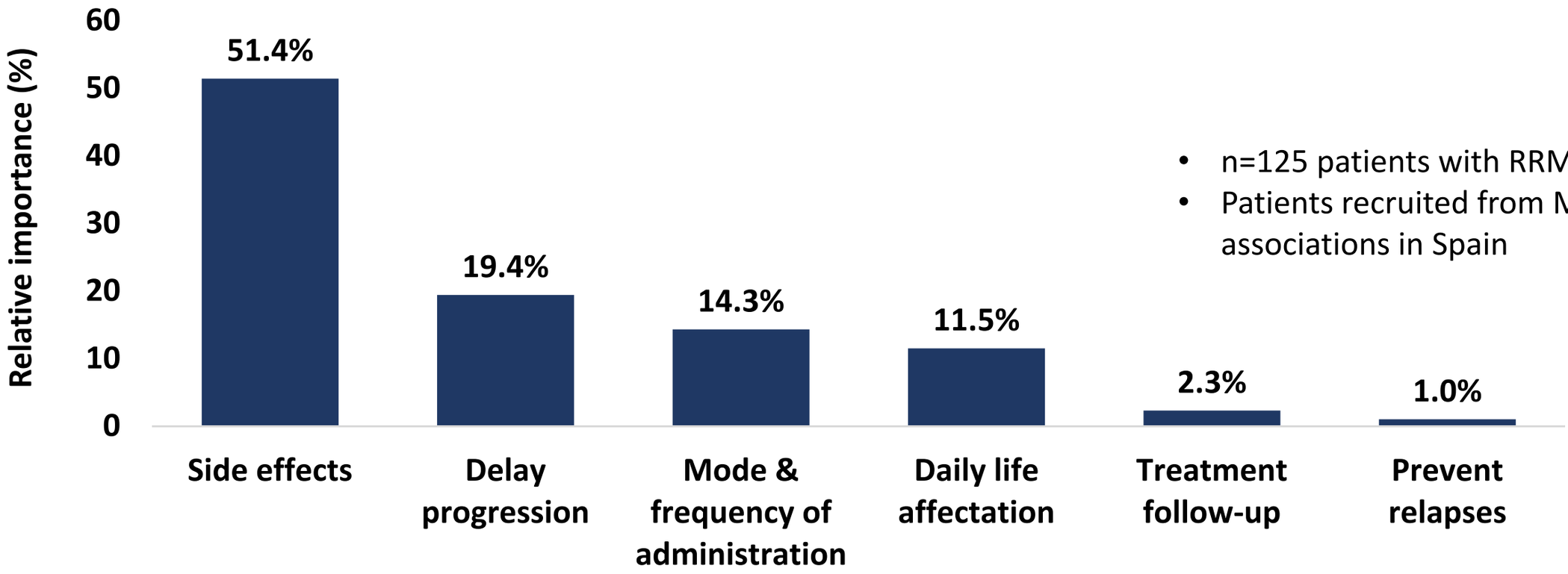
Wingerchuk DM, Weinshenker BG. *BMJ*. 2016;54:i3518.

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*	• 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 (e.g., 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, Arnold DL, et al. *Can J Neurol Sci*. 2013;40(3):307-23.

Patients Prefer DMTs That Minimize Side Effects and Delay Disability Progression

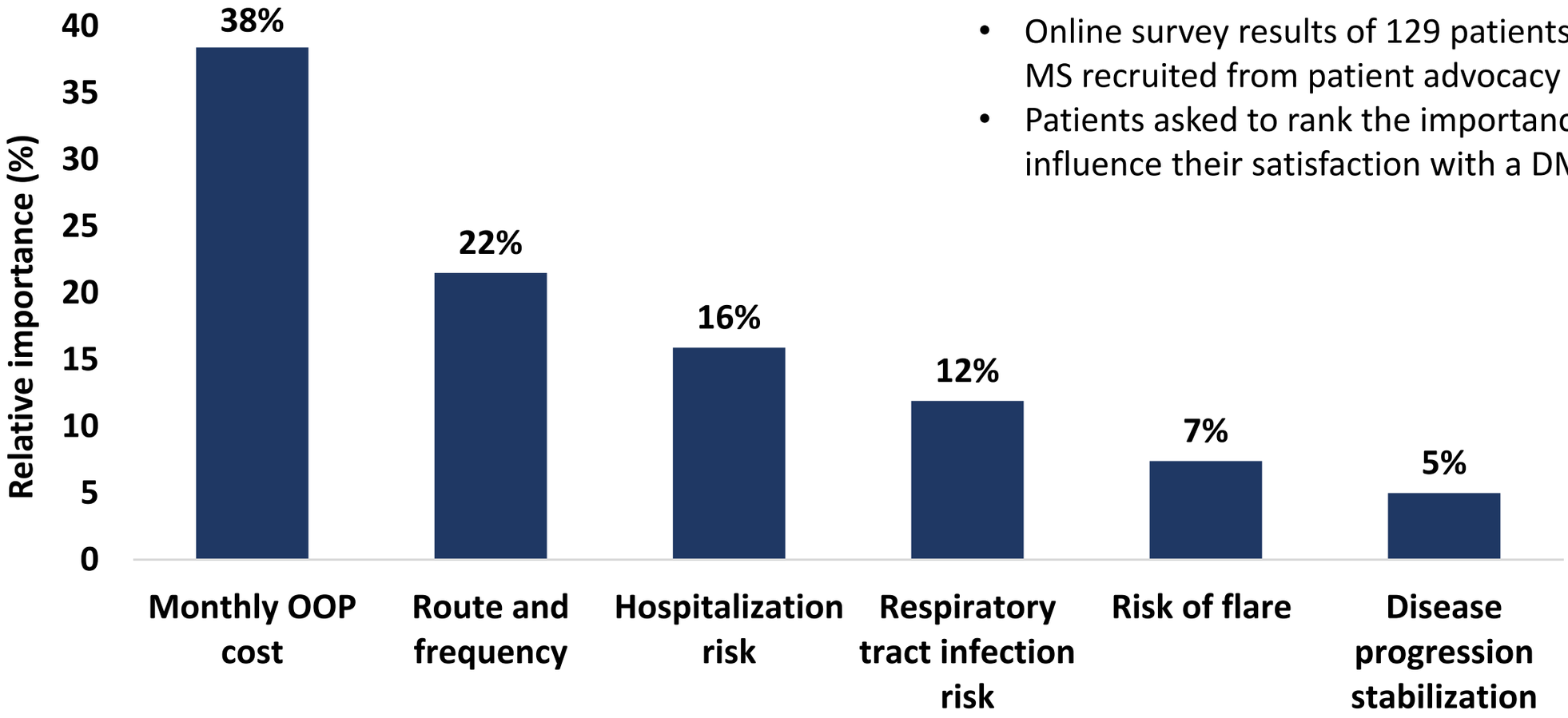


- n=125 patients with RRMS or SPMS
- Patients recruited from MS patient associations in Spain

- 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



- 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.

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):120-126.

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):370-376.

MS Therapies in Late-Phase Development

Agent	Target/ Mechanism of Action	Possible Indication	Administration	Status
Sphingosine-1-Phosphate Receptor Modulators				
Ozanimod	S1P1/S1P5 receptor blocker	RRMS, relapsing MS	Oral	Phase 3
Ponesimod	S1P1 receptor modulator	RRMS	Oral	Phase 3
Siponimod	S1P1/S1P5 receptor blocker	RRMS, SPMS	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
Cladribine	B-cell modulator	RRMS	Oral	NDA submitted
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

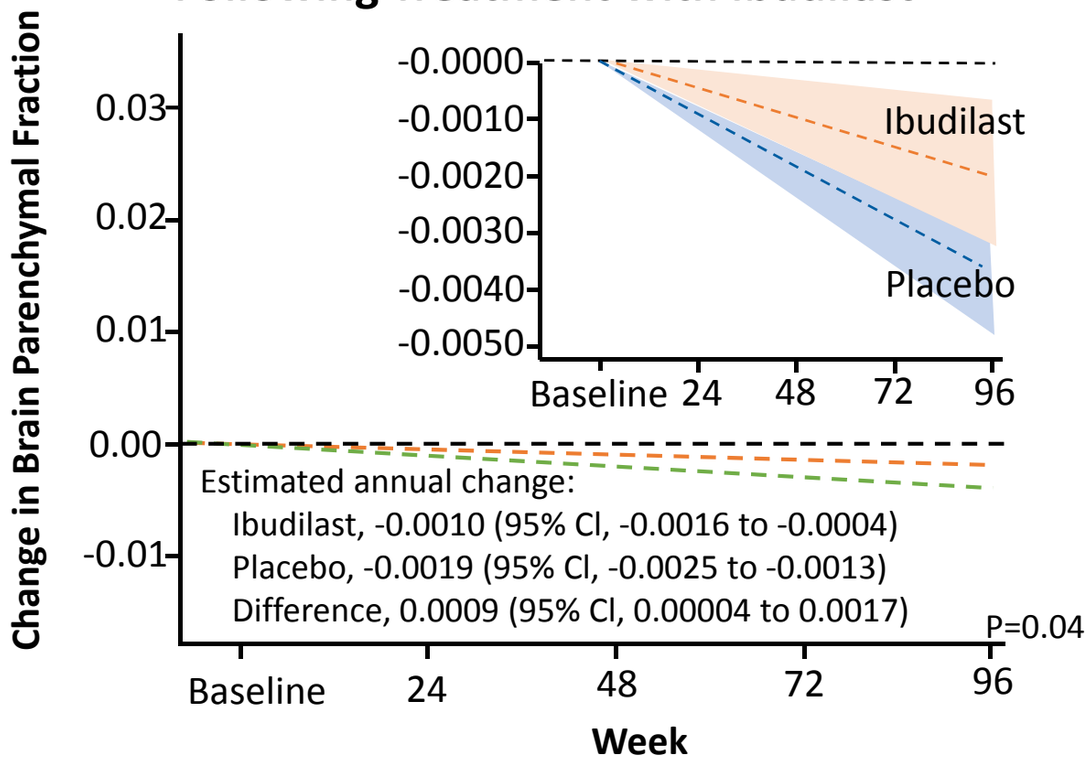
Agent	Target/ Mechanism of Action	Possible Indication	Administration	Status
Anti-LINGO	Remyelination	RRMS, SPMS	IV	Phase 2
Amiloride	Sodium channel blocker	PPMS	Oral	Phase 2
Phenytoin	Sodium channel blocker	PPMS	Oral	Phase 2
Clemastine	Remyelination	RRMS	Oral	Phase 2
Idebenone	Anti-oxidant	PPMS	Oral	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 in 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

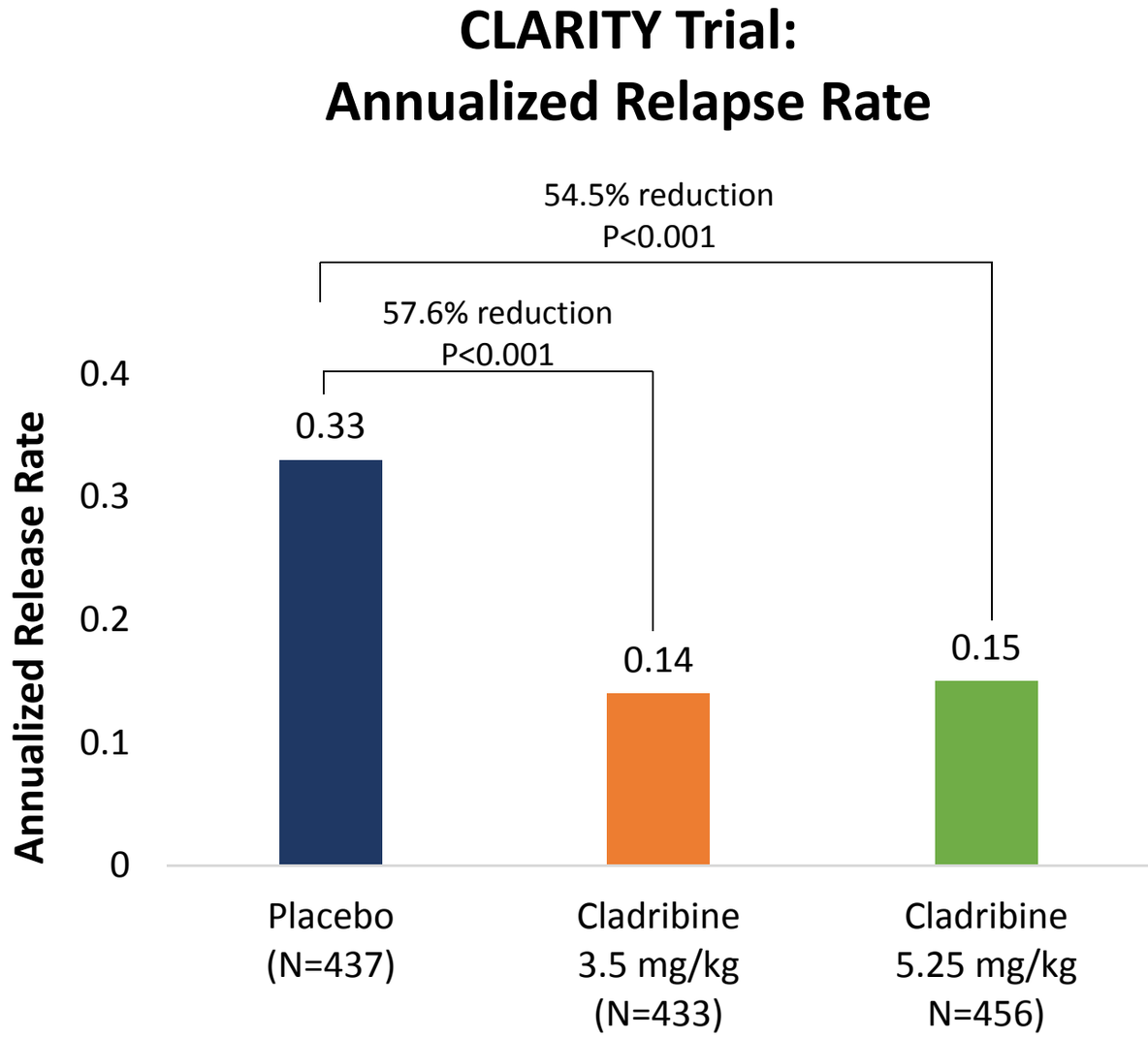
- Gastrointestinal symptoms were the most common adverse events
- Depression was more common with ibudilast vs. placebo, but there were no reports of suicidality or suicide
- Rates of discontinuation of the trial regimen or of the trial were higher with ibudilast vs. placebo

	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.

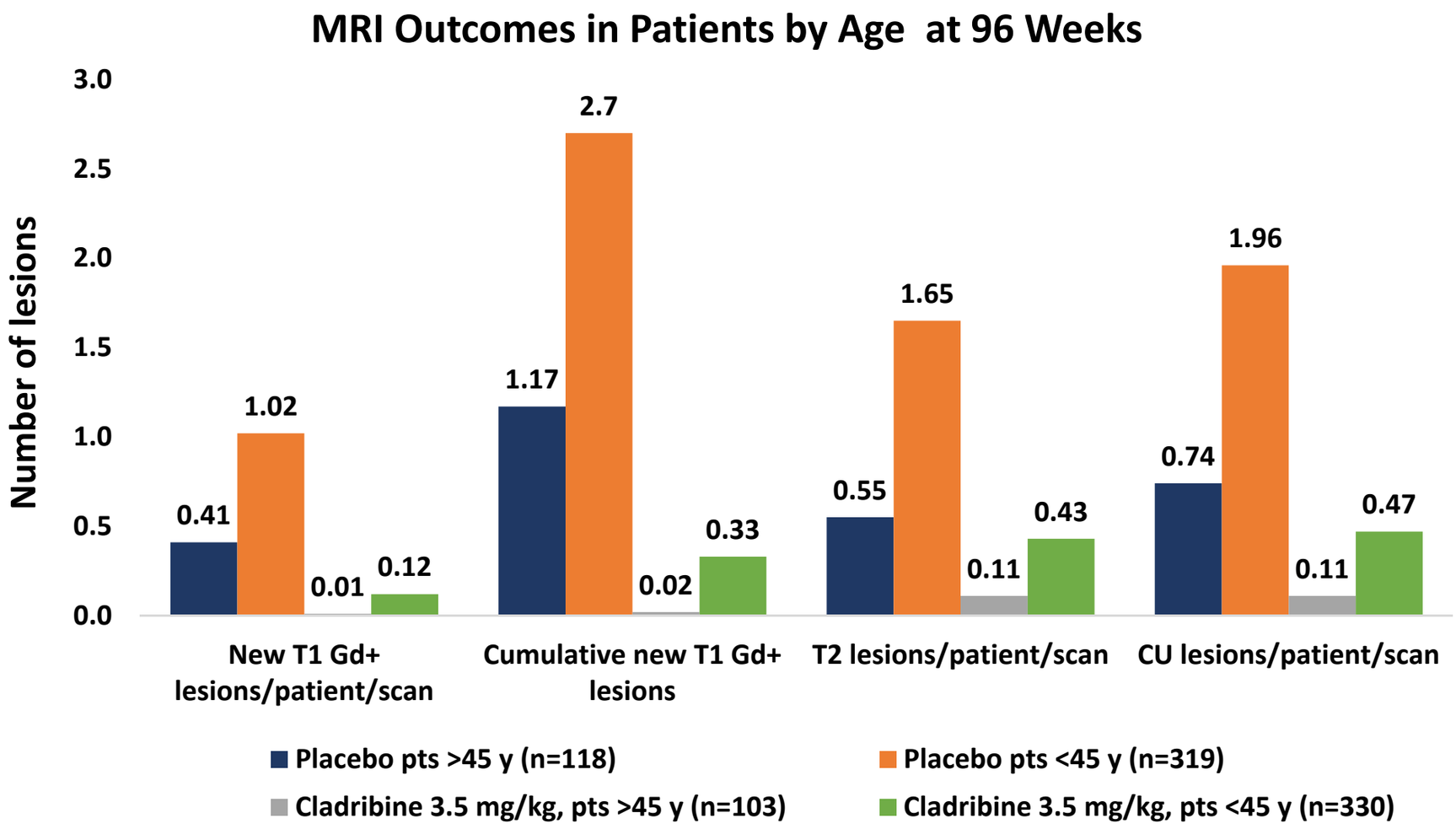
Therapy in Late-Phase Development: Cladribine

- Complete Response letter issued in 2011
  - NDA re-submitted July 2018 with additional safety data
  - Currently approved in the EU
- Phase 3 CLARITY trial demonstrated significantly reduced relapse rates, risk of disability progression, and MRI measures of disease activity at Week 96



Giovannoni G, Comi G, Cook S, et al. *N Engl J Med*. 2010;362(5):416-26.

Therapy in Late-Phase Development: *Post Hoc* Analysis of the CLARITY Data



- **Cladribine (3.5 mg/kg) treatment was associated with**
  - **Reduced relapse frequency**
  - **Reduced number of MRI lesions**
  - **Greater achievement of NEDA**
- **Benefits were seen regardless of patient age**

Giovannoni G, Rammohan K, Cook S, et al. Poster P1204. ECTRIMS Online Library. Published October 12, 2018. Accessed February 2019

Therapy in Late-Phase Development: Siponimod and Ozanimod

Endpoints	Siponimod vs. placebo	Ozanimod vs. IFN-β1a			
	EXPAND Trial[1] (*p* value)	SUNBEAM[2]		RADIANCE[3,4]	
		0.5 mg	1 mg	0.5 mg	1 mg
Reduced 6-month CDP	0.0058	ns	ns	ns	ns
Reduced brain volume loss	0.002	0.06	<0.0001	<0.0001	<0.0001
Reduced increase of T2 lesion volume	<0.0001	<0.00001	<0.0001	<0.00001	<0.0001
Reduced ARR	<0.0001	0.0013	<0.0001	0.0167	<0.0001
No difference in walking scores	--	N/A			

1. Kappos L, Bar-or A, Cree BAC, et al. *Lancet*. 2018;391(10127):1263-1273.
2. Arnold D, Cohen JA, Comi G, et al. Poster P1857. ECTRIMS Online Library. Published October 27, 2017. Accessed February 2019.
3. Comi G, Kappos L, Selmaj KW, et al. Abstract 232. ECTRIMS Online Library. Published October 27, 2017. Accessed February 2019.
4. Cohen JA, Comi G, Selmaj KW, et al. Abstract 280. 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 Suppl 16. 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

Costs Offsets Associated with Emerging MS Therapies

Edmund Pezalla, MD
CEO
Enlightenment Bioconsult, LLC

Learning Objective

- Discuss recent insights into cost offsets associated with new and emerging multiple sclerosis (MS) therapies

Prevalence and Burden of MS

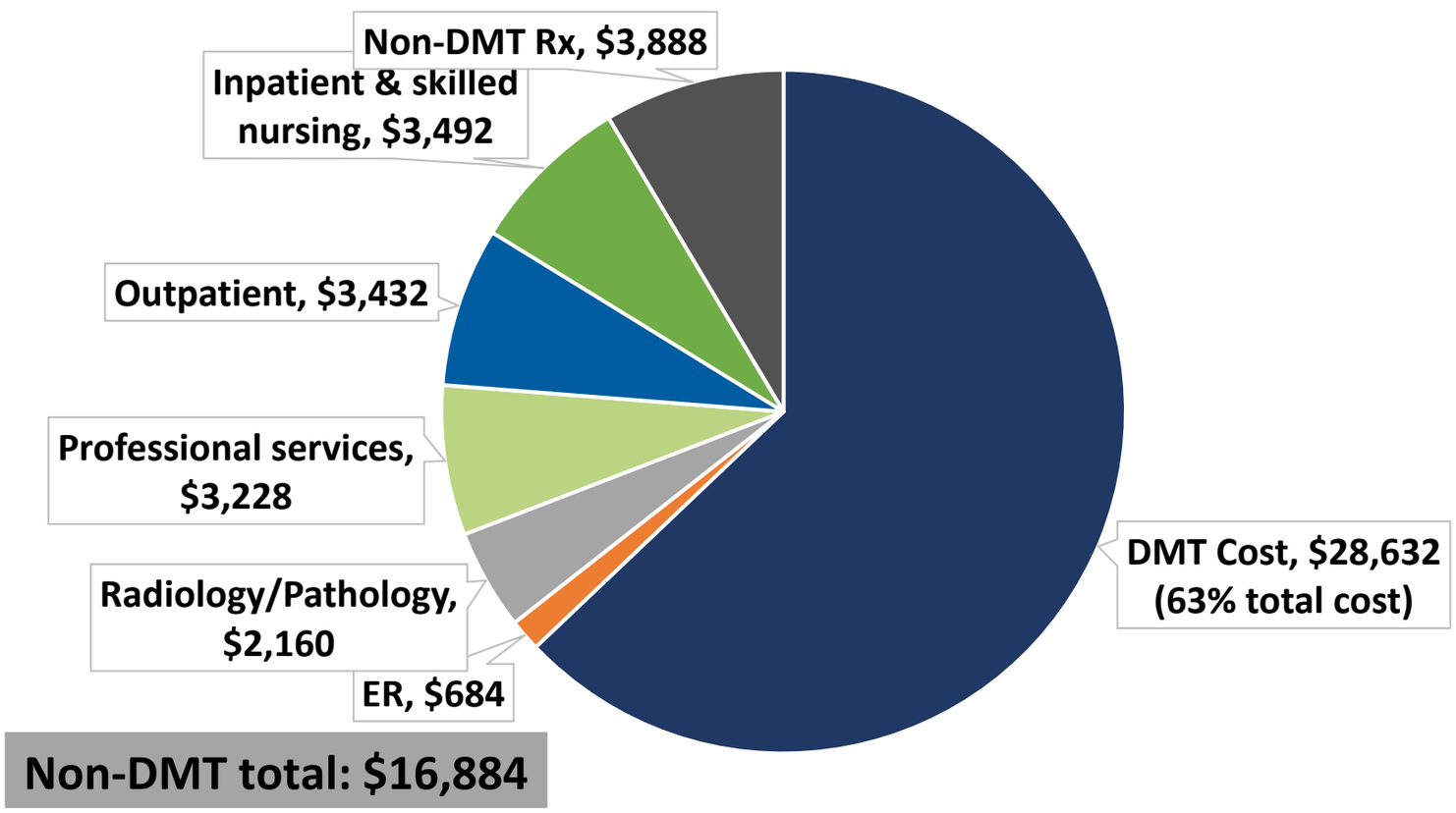
*estimated

- MS affects an estimated 400,000 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

National Multiple Sclerosis Society. MS Prevalence. http://www.nationalmssociety.org/About-the-Society/MS-Prevalence. Accessed February 2019.
Adelman G, et al. *J Med Econ*. 2013;16:639-647.

MS is a Costly Chronic Disease

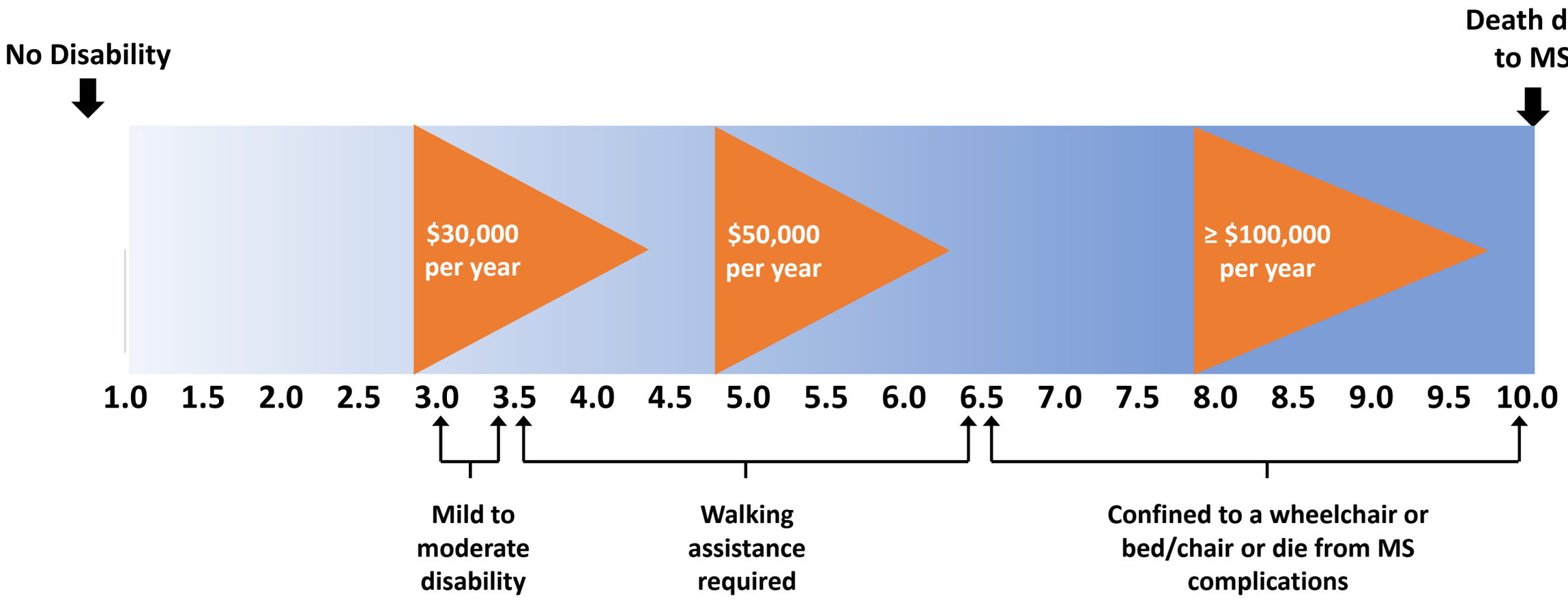
Annual claim costs for MS (per patient)
Total: $45,516



Non-DMT total: $16,884

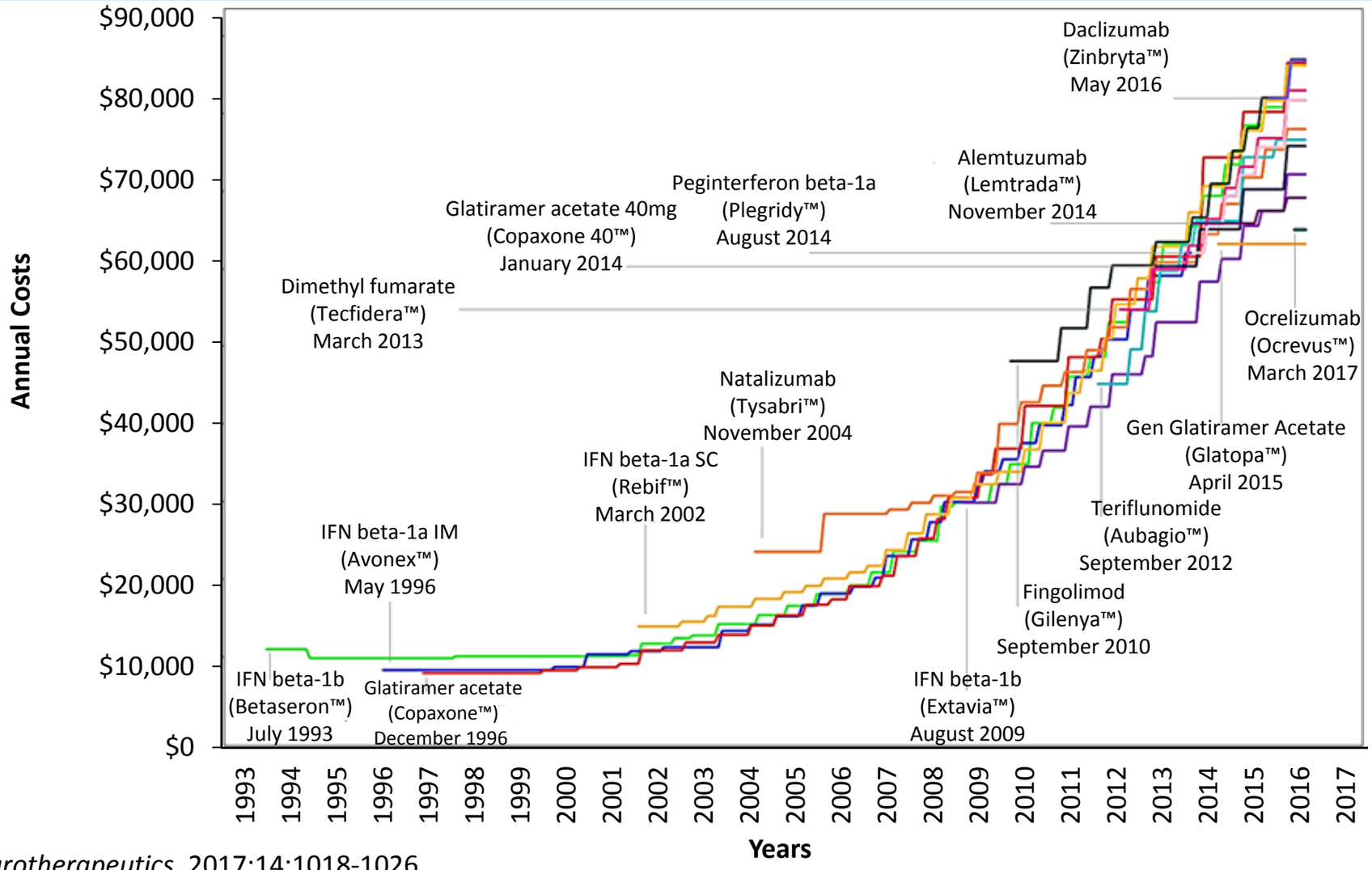
Optum. Six cost drivers of multiple sclerosis. https://www.optum.com/resources/library/ms-cost-drivers.html. Accessed February 2019.

Total MS Costs Rise as Disability Progresses



Owens GM. *Am J Manag Care*. 2016;22:S151-S158.
Optum. Six cost drivers of multiple sclerosis. https://www.optum.com/resources/library/ms-cost-drivers.html. Accessed February 2019.

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



*Pricing estimated from WAC for year of therapy.

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

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%

Express Scripts. Commercial Drug Trend Report. 2017.

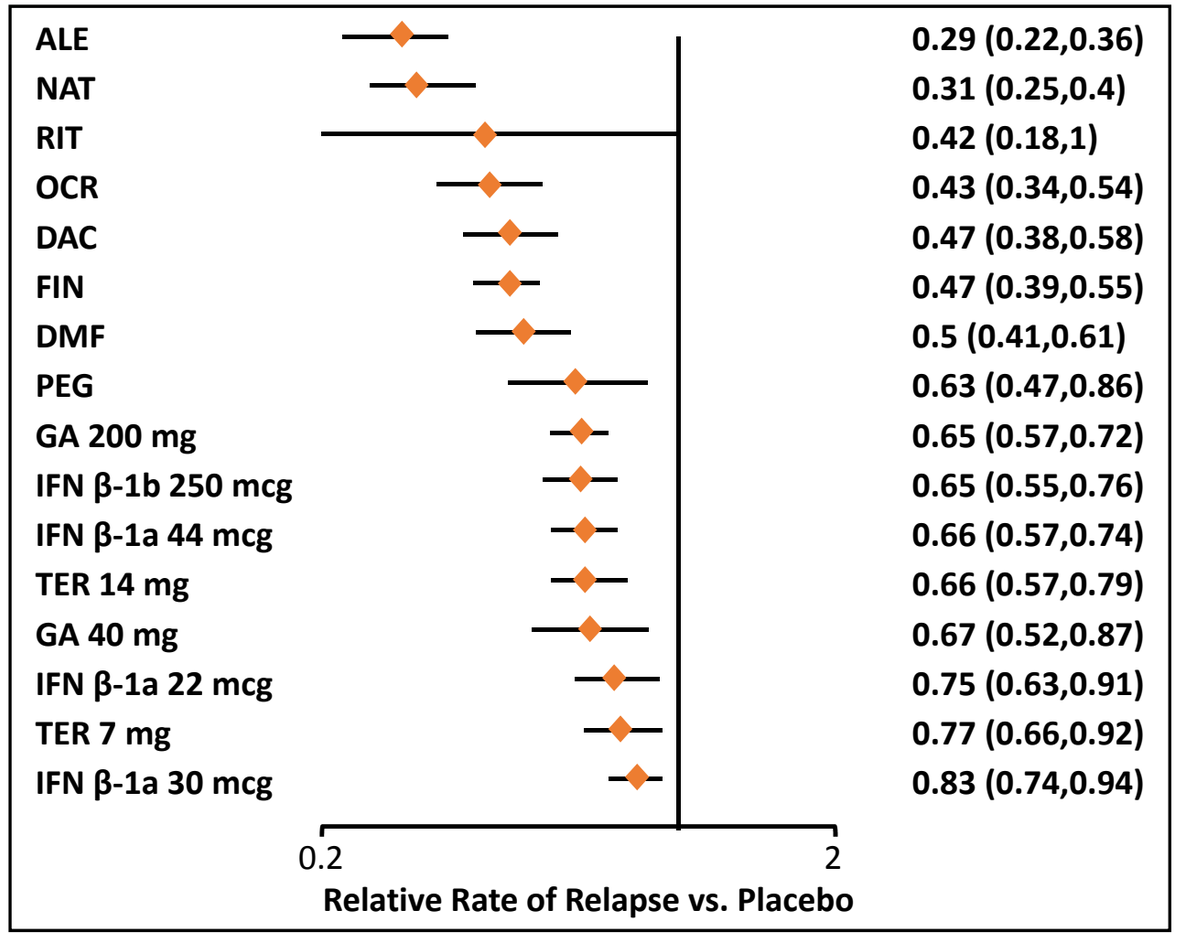
Overall Value of DMTs

- Value in health care: defined as the “efficiency with which interventions deliver outcomes with respect to their costs”
- DMTs have been shown to
  - Reduce relapses
  - Decrease disability
  - Prolong life
  - Improve health-related quality of life
- Reductions in direct medical costs associated with decreased use of outpatient services and reduced number of inpatient hospital stays have the potential to partially offset the cost of DMT therapy

Hartung DM. *Neurotherapeutics*. 2017;14:1018-1026; Nicholas J, et al. *PharmacoEconomics Open*. 2018;2:31–41.

Comparison of Relative Relapse Rates of DMTs Used to Treat MS

- ICER meta-analysis of 113 randomized controlled trials, systematic reviews, and high quality comparative cohort studies of DMTs in patients with RRMS and PPMS
- Participants (n=22,936) in the studies were randomized to one or more DMTs or placebo

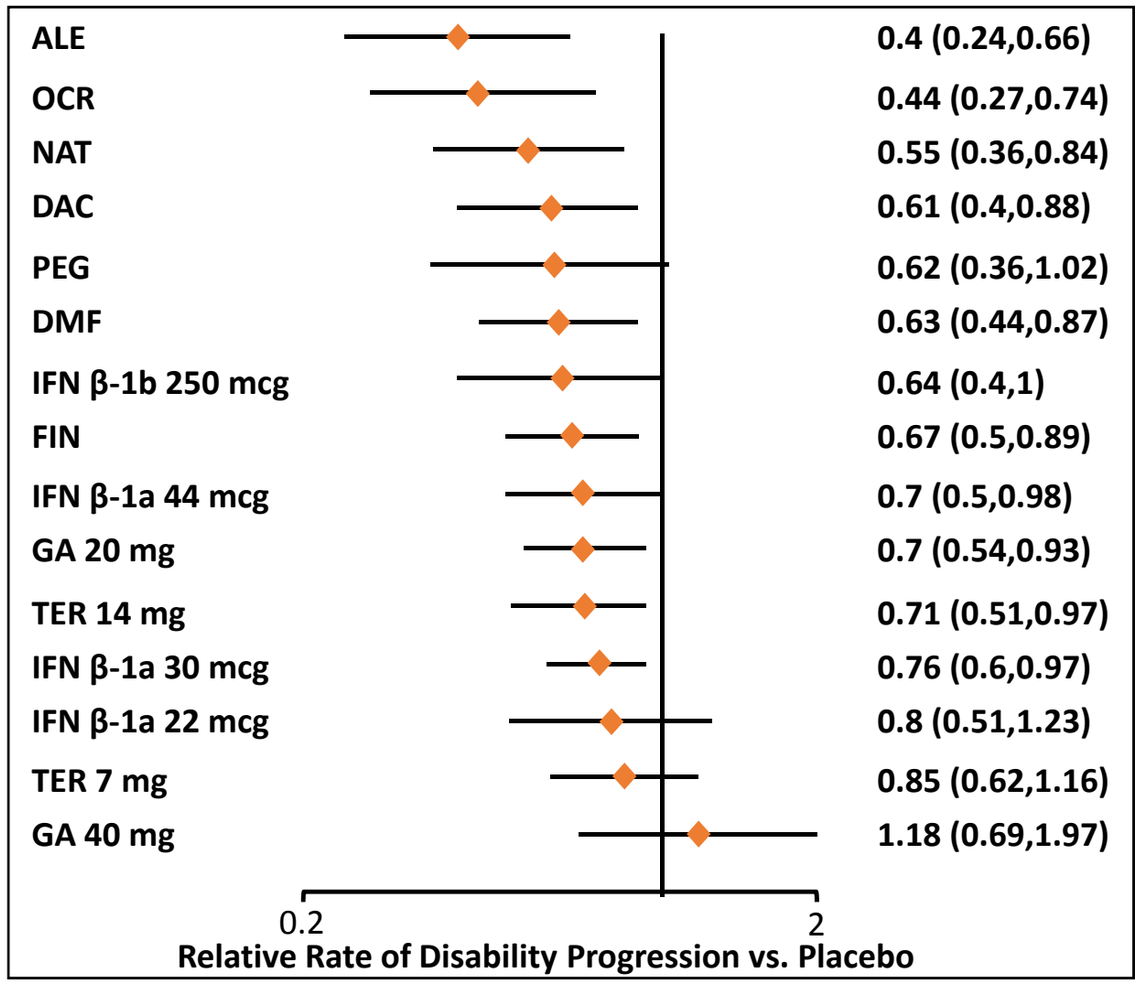


ALE=alemtuzumab; NAT=natalizumab; RIT=rituximab; OCR=ocrelizumab; DAC=daclizumab; FIN=fingolimod; DMF=dimethyl fumarate; PEG=peginterferon; GA=glatiramer acetate; IFN b-1b=interferon beta 1b; IFN b-1a= interferon beta 1a; TER=teriflunomide; mg=milligram; mcg=microgram

Institute for Clinical and Economic Review. Evidence Report: DMTs for RRMS and PPMS. November 2016. file:///C:/Users/K/Desktop/ICER_MS_Report_2016.pdf. Accessed February 2019.

Comparison of the Relative Risk for Disability Progression of DMTs

ICER Meta-Analysis

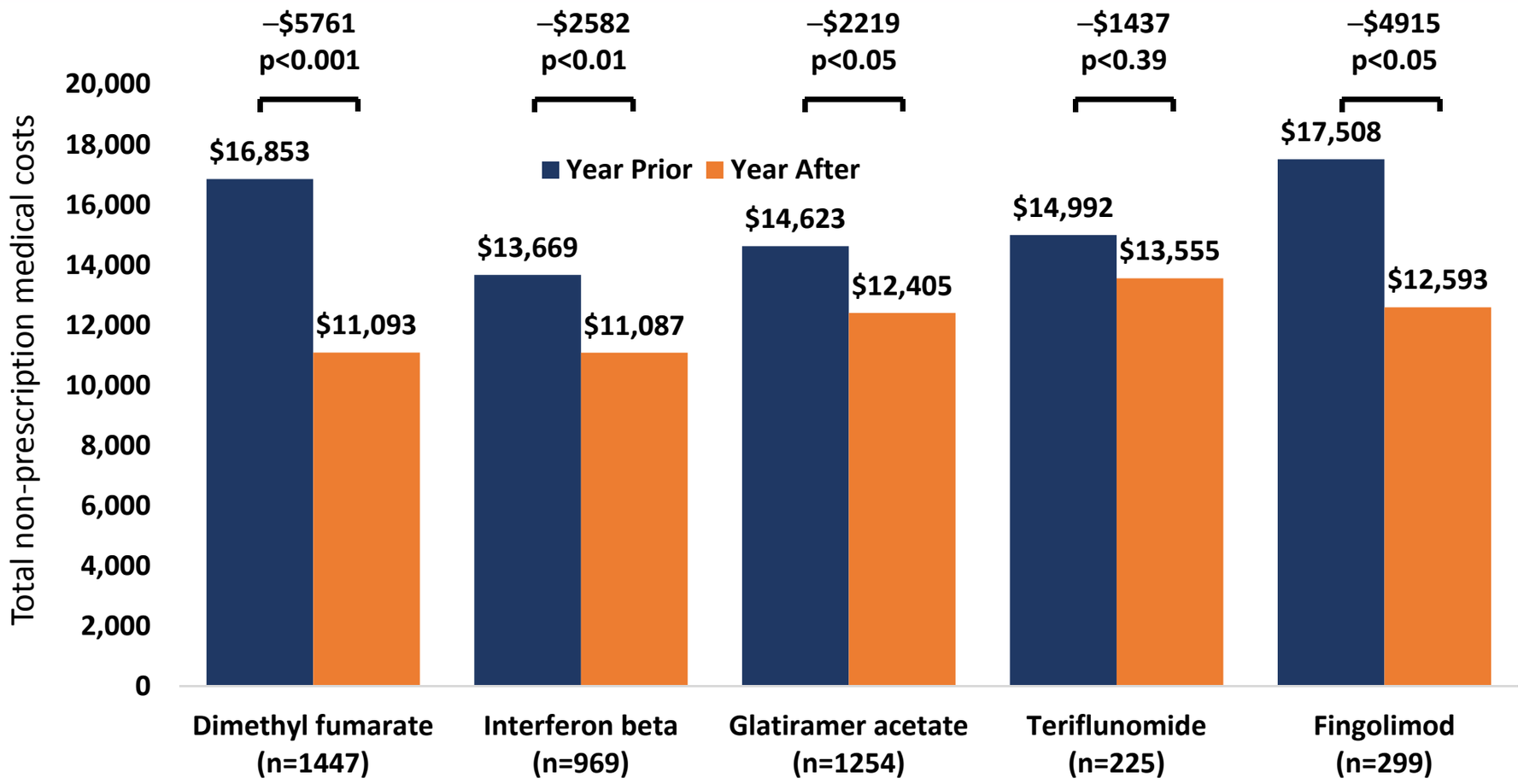


ALE=alemtuzumab; NAT=natalizumab; RIT=rituximab; OCR=ocrelizumab; DAC=daclizumab; FIN=fingolimod; DMF=dimethyl fumarate; PEG=peginterferon; GA=glatiramer acetate; IFN b-1b=interferon beta 1b; IFN b-1a= interferon beta 1a; TER=teriflunomide; mg=milligram; mcg=microgram

Institute for Clinical and Economic Review. Evidence Report: DMTs for RRMS and PPMS. November 2016. file:///C:/Users/K/Desktop/ICER_MS_Report_2016.pdf. Accessed February 2019.

DMT Initiation Was Associated with Reductions in Health Care Resource Utilization

- Analysis of 4194 claims in the 2012-2015 Truven MarketScan Commercial Database
- Hospitalization, ER or urgent care visits in the year after initiating DMT for patients who did not receive a DMT in the previous year



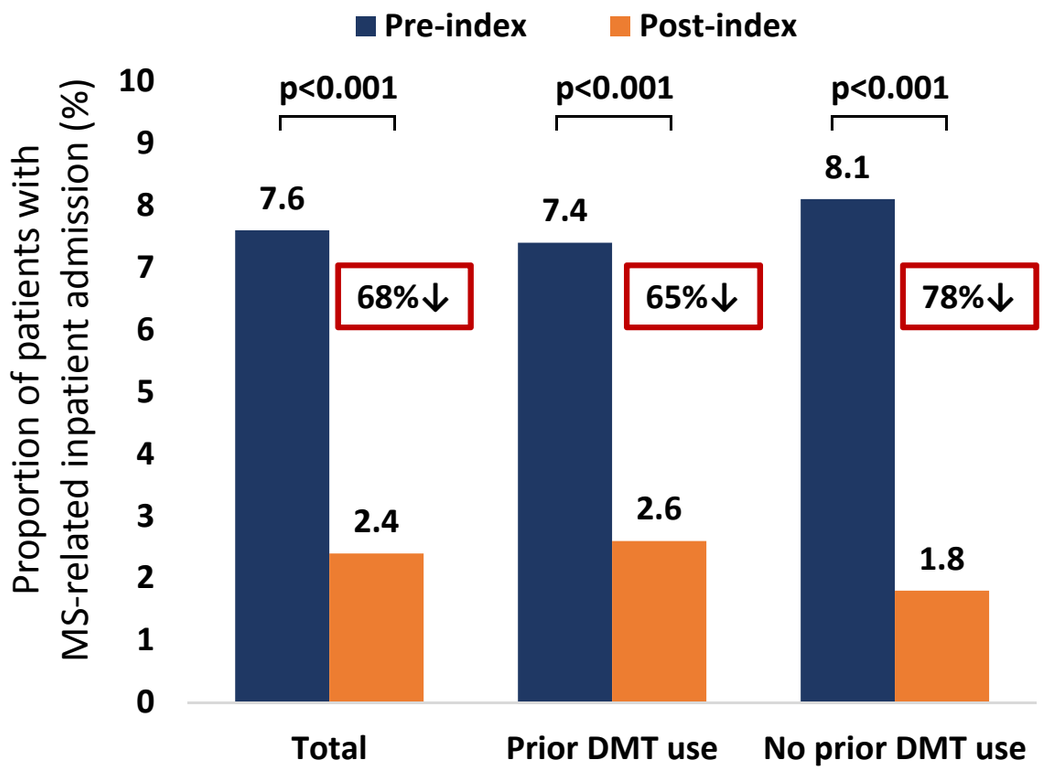
Cost reductions predominantly driven by decreased use of outpatient services and decreased inpatient hospital stays

Nicholas J, et al. *PharmacoEconomics Open*. 2018;2:31–41.

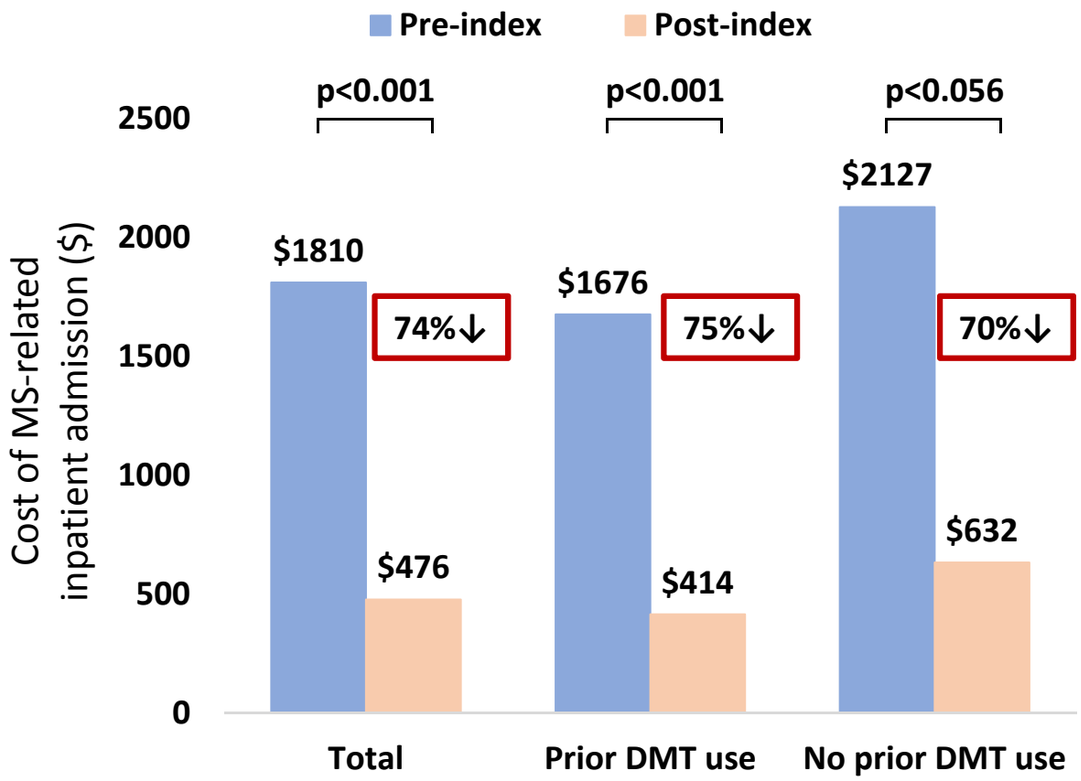
Health Care Use and Costs Were Decreased After Initiation of Treatment with a DMT

Claims Analysis* of Patients with MS (n=1458) Initiated on Natalizumab and Followed for 12 Months

MS-Related Inpatient Utilization



MS-Related Inpatient Costs

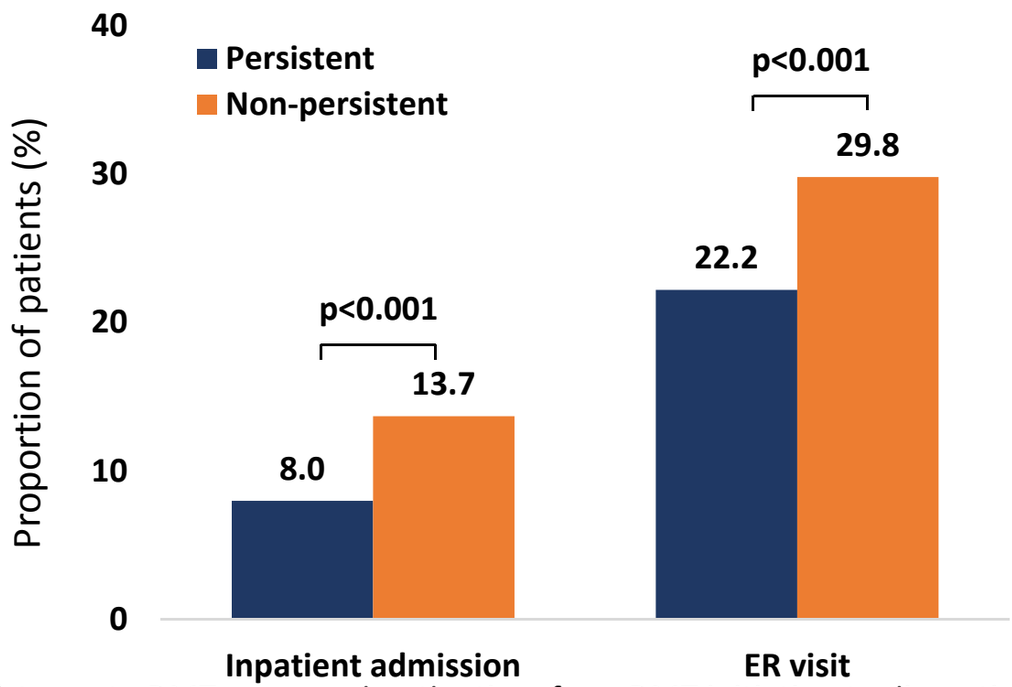


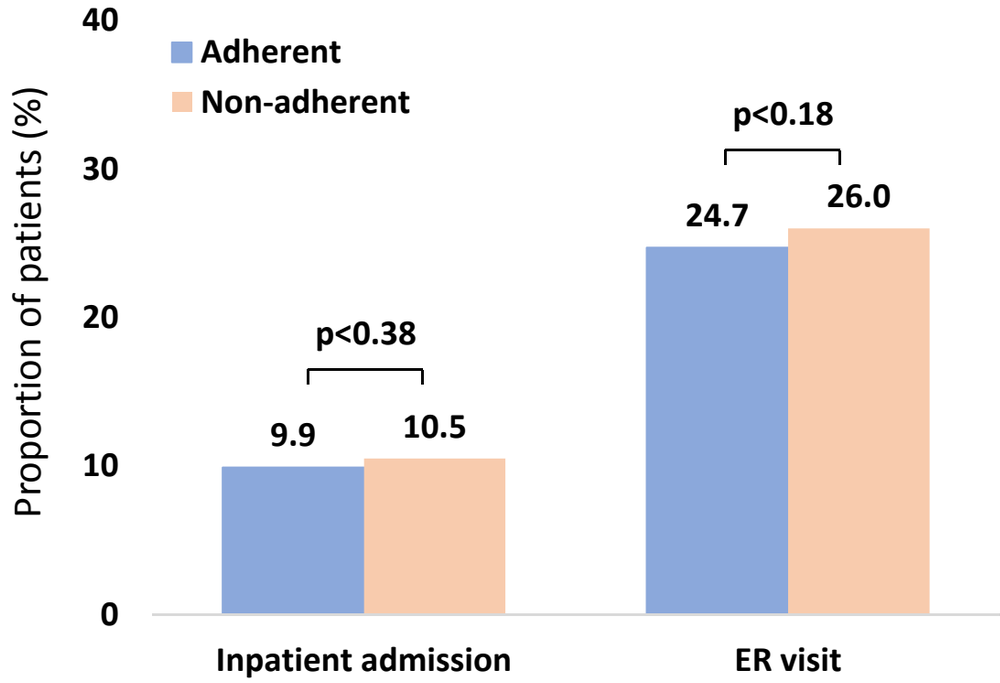
*Truven MarketScan commercial database

Bonafede MM, et al. *ClinicoEconomics Outcomes Res*. 2014:6

Reductions in Resource Use Can Be Dependent on Adherence to DMT Therapy

Truven MarketScan Database Analysis of MS Patients (n=16,218) Who Initiated a DMT and Followed for 1 Year





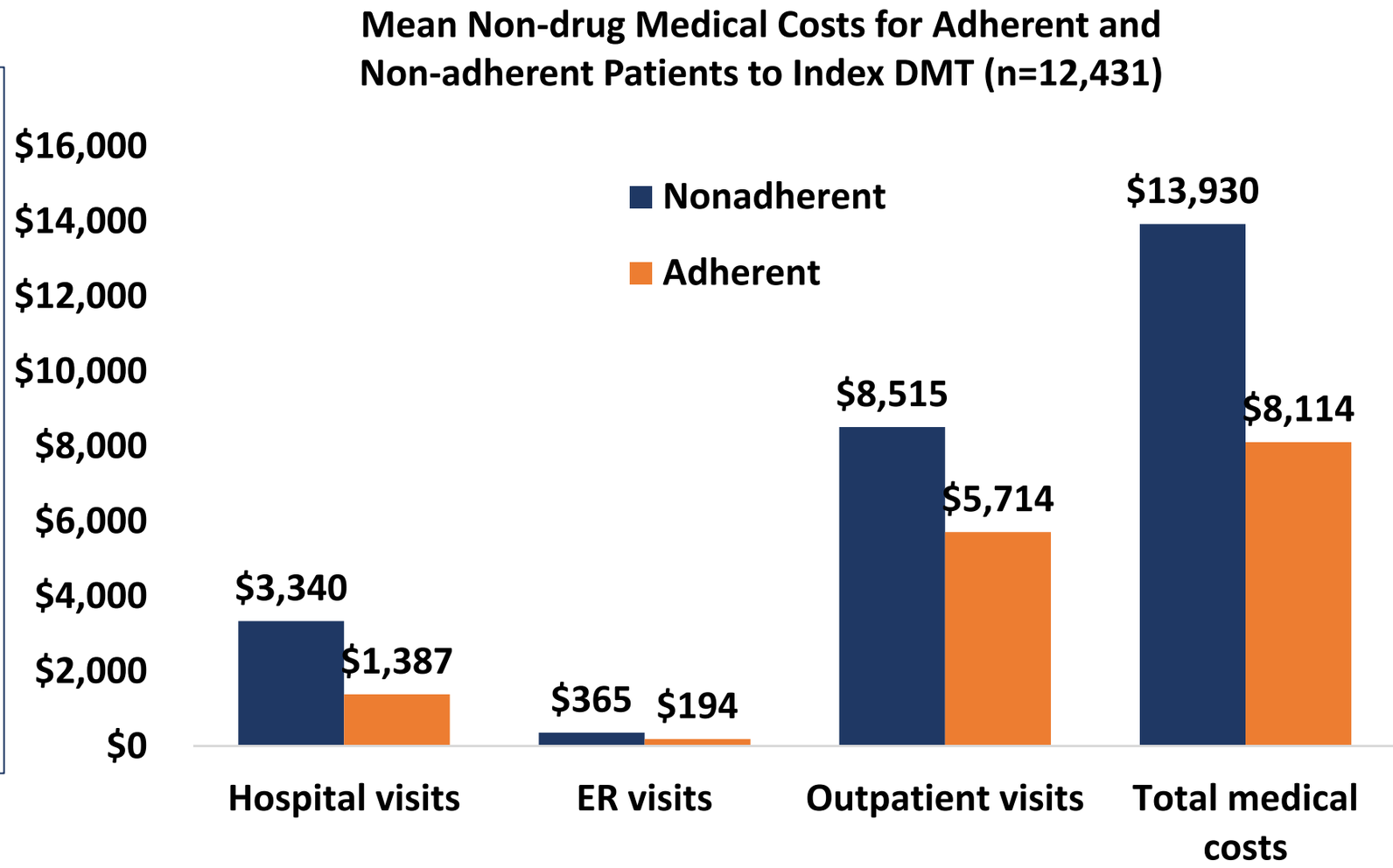
Persistence to DMT measured as the time from DMT initiation to discontinuation (a gap of >60 days without drug 'on hand') or end of 1-year follow-up.
Adherence to DMT measured during the persistence period and operationalized as the medication possession ratio (MPR). Patients with an MPR <0.80 were considered non-adherent.

Persistence and adherence with DMT are associated with decreased likelihoods of inpatient admission or ER visit

Thomas NP, et al. *J Med Econ.* 2016;19:497-505.

Health and Economic Benefits Underscore the Importance of Adherence in MS

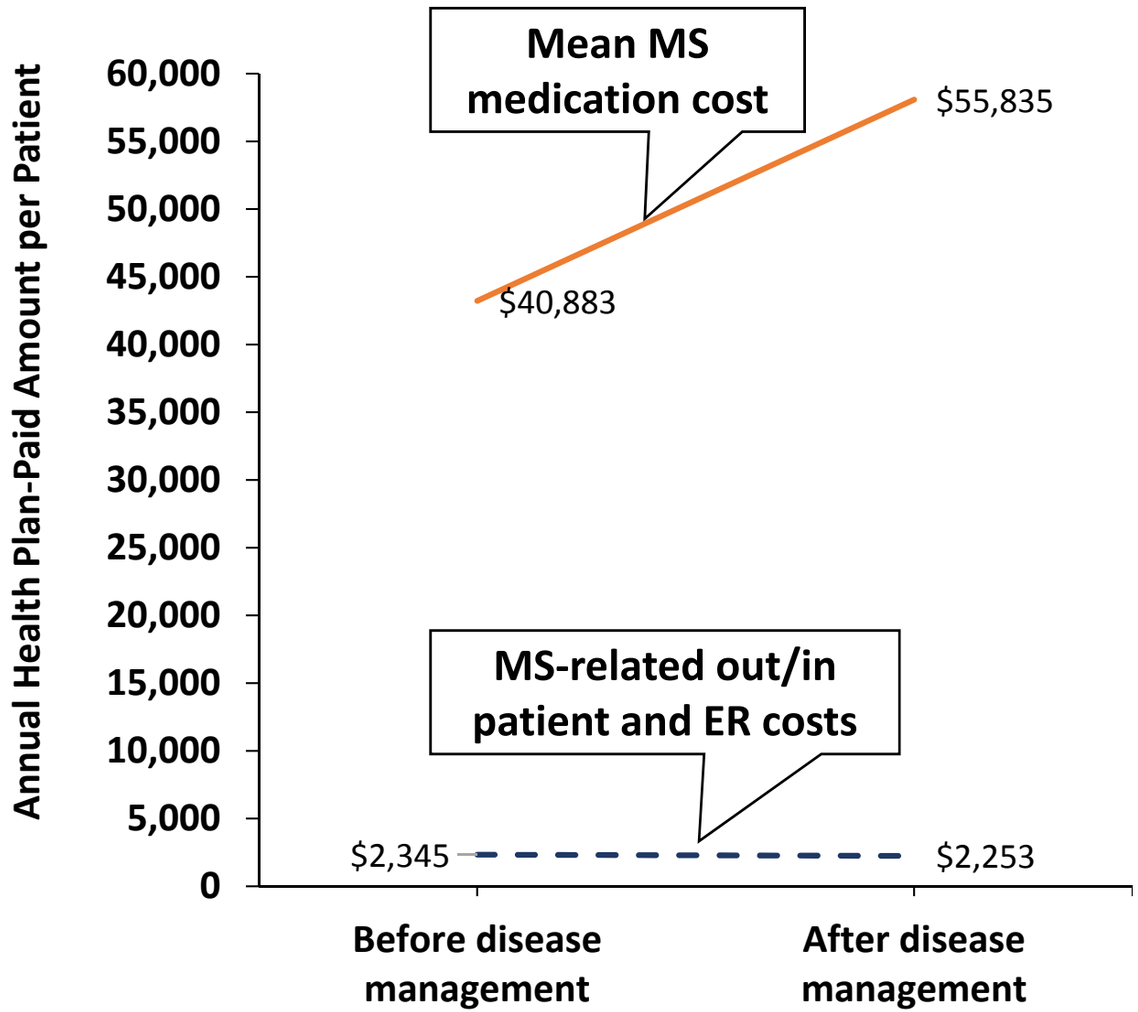
- Analysis of 12,431 claims in the 2008-2015 Truven MarketScan Commercial Database
- Adherence to the index DMT was measured by the 12-month post-index proportion of days covered and compared between oral and injectable DMT initiators
- Relationship between adherence and relapse risk, MS-related health resource utilization, and non-drug medical costs assessed by regression modeling



Burks J, et al. *ClinicoEconomics Outcomes Res*. 2017;9:251-260.

There May Be a Ceiling to the Amount of Benefit Derived From Increased Adherence to DMT Therapy

- Adherence was increased by participation in specialty pharmacy and MS disease management programs
- The increase in spend on DMTs was not offset by savings in health care resource utilization
- **Caveats**
  - Baseline adherence to DMT therapy in this analysis was higher (70%) vs. that observed in the literature (52%-62)
  - High adherence before enrollment may have limited the ability to increase adherence further and subsequently to improve clinical and economic outcomes



Data source: Prescription drug claims, medical claims, and EMR data (2013-2015) for 1 year before and after enrollment in the disease management program for plan members with 24 months of continuous health plan coverage

Groeneweg M, et al. *J Manag Care Spec Pharm.* 2018;24:458-463.

Number Needed to Treat (NNT) to Prevent One Relapse Ranges From 3 to 11 Patients

ICER Meta-Analysis*

- Pooled relapse rate for the placebo group was 0.56 relapses per year
- Assuming this as the background rate, the NNT with a DMT to prevent one relapse ranges from 3 to 11

Drug	NNT
Alemtuzumab	3
Natalizumab	3
Ocrelizumab	4
Fingolimod	4
Dimethyl fumarate	4
Peginterferon β-1a	5
Glatiramer acetate 20 mg	6
Interferon β-1b 250 μg	6
Interferon β-1a 44 μg	6
Teriflunomide 14 mg	6
Glatiramer acetate 40 mg	6
Interferon β-1a 22 μg	8
Teriflunomide 7 mg	8
Interferon β-1a 30 μg	11

*Meta-analysis of 113 trials which randomized 22,936 patients with MS to one or more of DMTs or placebo

Institute for Clinical and Economic Review. Evidence Report: DMTs for RRMS and PPMS. November 2016. file:///C:/Users/K/Desktop/ICER_MS_Report_2016.pdf. Accessed February 2019.

The NNT to Prevent One Disability Progression Ranges From 10 to 24 Patients

ICER Meta-Analysis*

- Pooled risk of sustained disability progression for the placebo group was 0.176
- Assuming this as the background rate, the number needed to treat with a DMT to prevent one patient from sustained disability progression ranges from 10 to 24

Drug	NNT
Alemtuzumab	10
Ocrelizumab	11
Natalizumab	13
Peginterferon β-1a	15
Dimethyl fumarate	16
Interferon β-1b 250 μg	16
Fingolimod	18
Interferon β-1a 44 μg	19
Glatiramer acetate 20 mg	19
Teriflunomide 14 mg	20
Interferon β-1a 30 μg	24
Teriflunomide 7 mg	–
Interferon β-1a 22 μg	–
Glatiramer acetate 40 mg	–

*Meta-analysis of 113 trials which randomized 22,936 patients with MS to one or more of DMTs or placebo

Institute for Clinical and Economic Review. Evidence Report: DMTs for RRMS and PPMS. November 2016. file:///C:/Users/K/Desktop/ICER_MS_Report_2016.pdf. Accessed February 2019.

Summary

- Costs associated with MS are considerable and rise with increasing disability
- Reductions in direct medical costs associated with decreased use of outpatient services and reduced number of inpatient hospital stays have the potential to partially offset the cost of DMT therapy
- DMT initiation is associated with reduction in healthcare utilization and subsequent reductions in MS-related healthcare costs
- Cost offsets may be dependent on patient adherence to their prescribed DMT regimen

Medical and Pharmacy Management Strategies to Enhance MS Patient Outcomes

Learning Objectives

- Employ utilization management and benefit design strategies for multiple sclerosis (MS) therapies to promote appropriate prescribing
- Analyze care management/care pathways and their application to manage economic outcomes in MS

Multiple Sclerosis 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, et al. *Mult Scler*. 2015;21:263-281.

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: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, et al. *J Manag Care Pharm*. 2011;17:S3-S21; National Multiple Sclerosis Society. http://www.nationalmssociety.org/Treating-MS/Comprehensive-Care. Accessed February 2019.

The MS Drug Benefit Must 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:S151-S158.
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 G. *Am J Manag Care.* 2013;19:S307-S312.

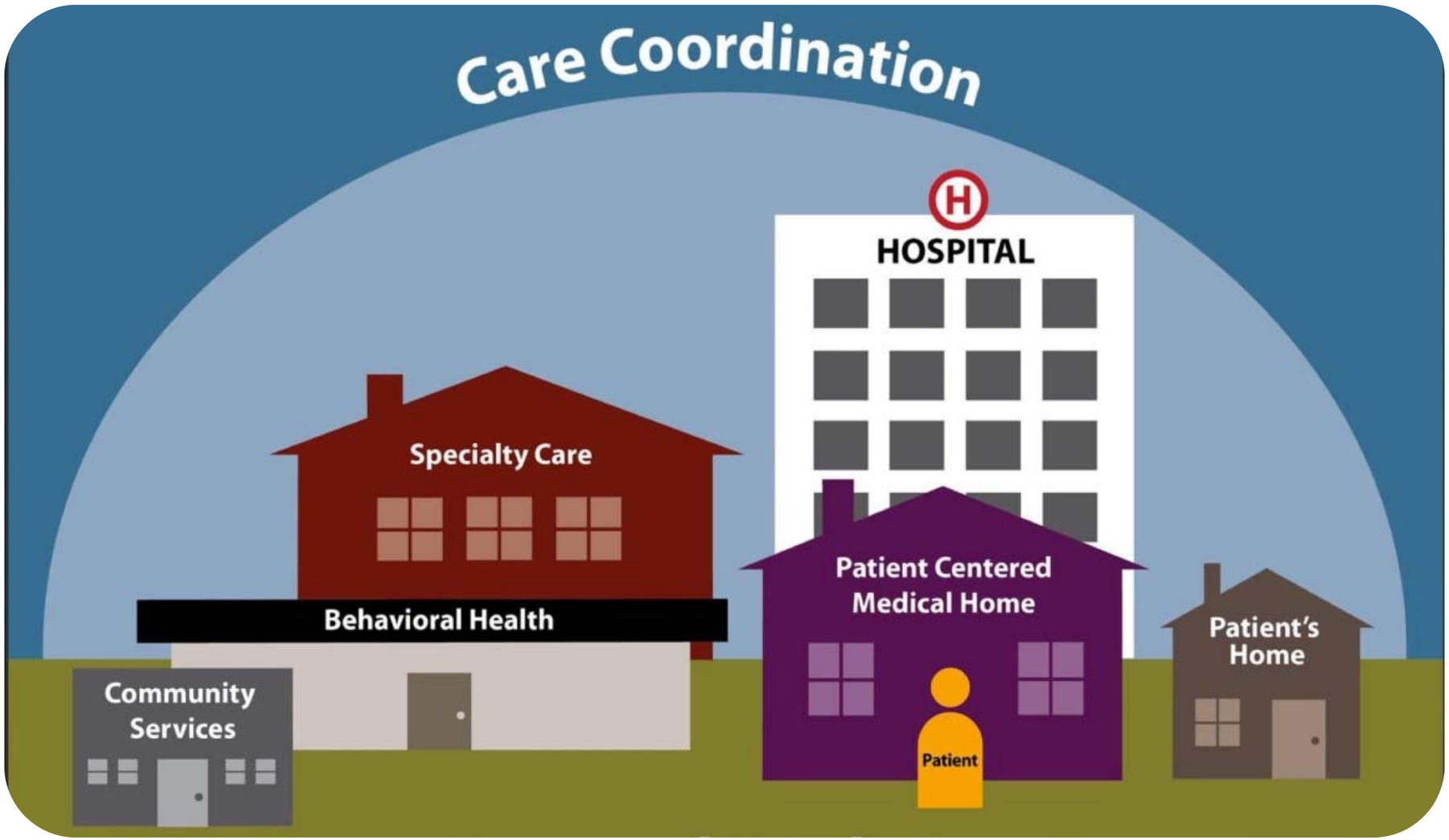
Site of Care Delivery Can Influence Cost and Access

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**

Plan 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 psycho-social counseling

Care management and routine follow up

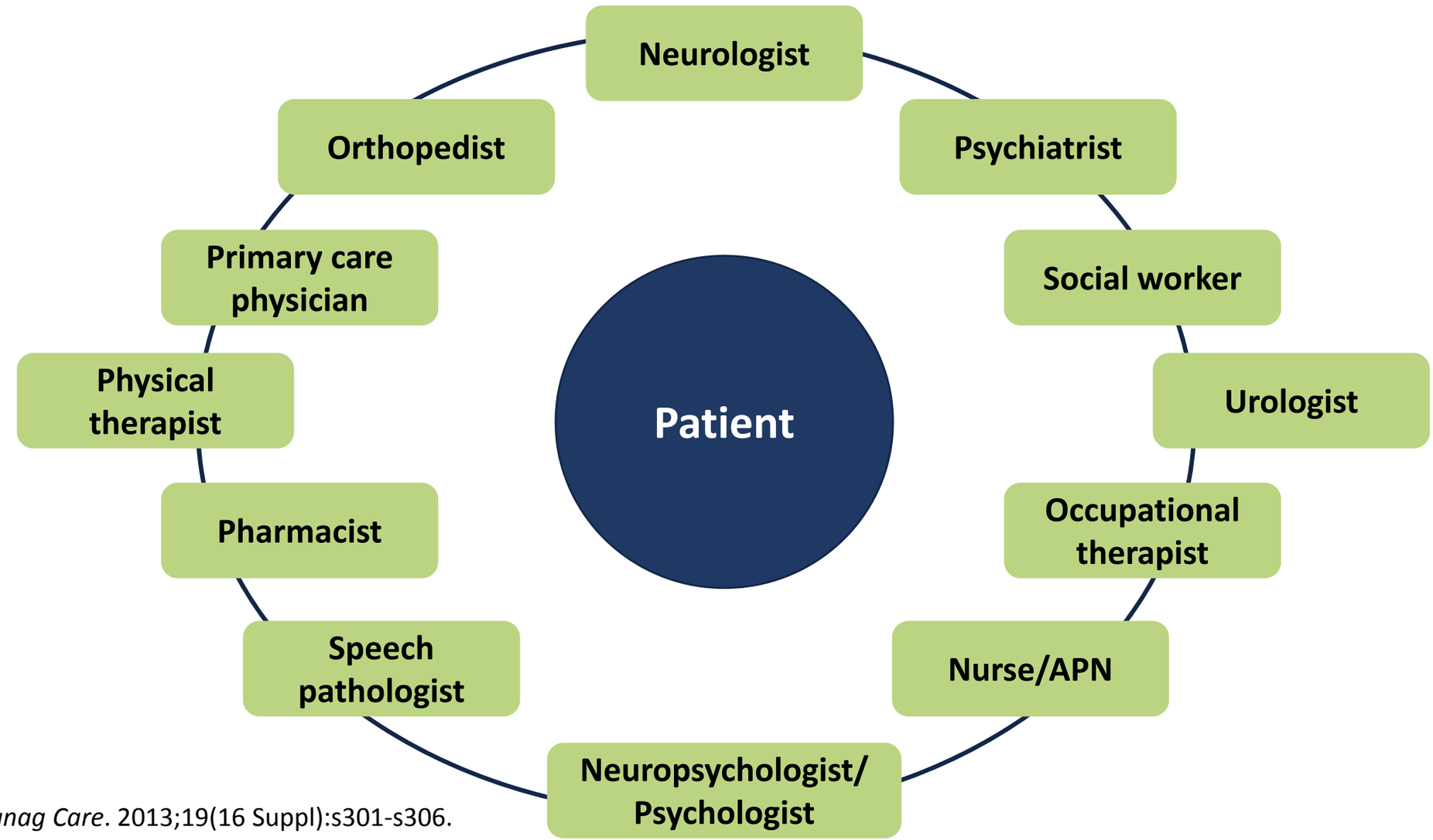
- Patient education
- Adherence support

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

Centers for Medicare and Medicaid Services. 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

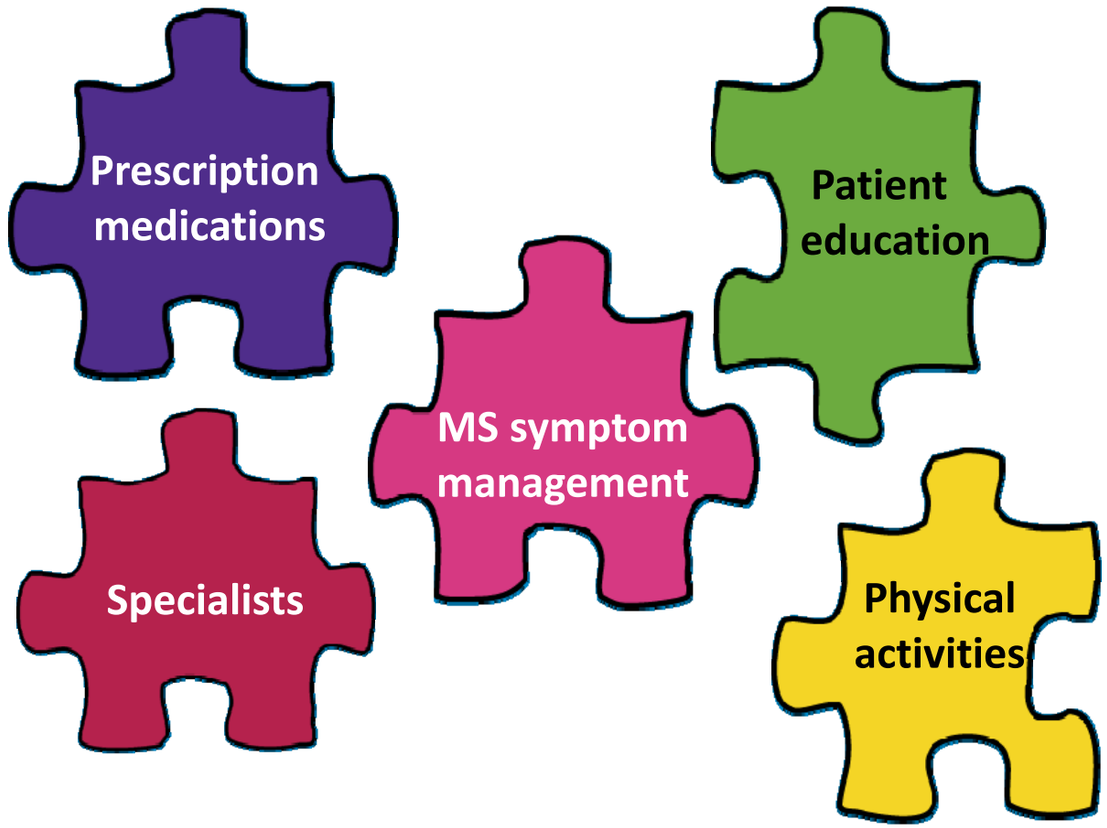
Tertiary Symptoms

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

Compston A, Coles A. *Lancet*. 2008;372:1502-1517.
Tullman MJ. *Am J Manag Care*. 2013;19(2 Suppl):S15-S20.
MS Symptoms. National Multiple Sclerosis Foundation Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed February 2019.

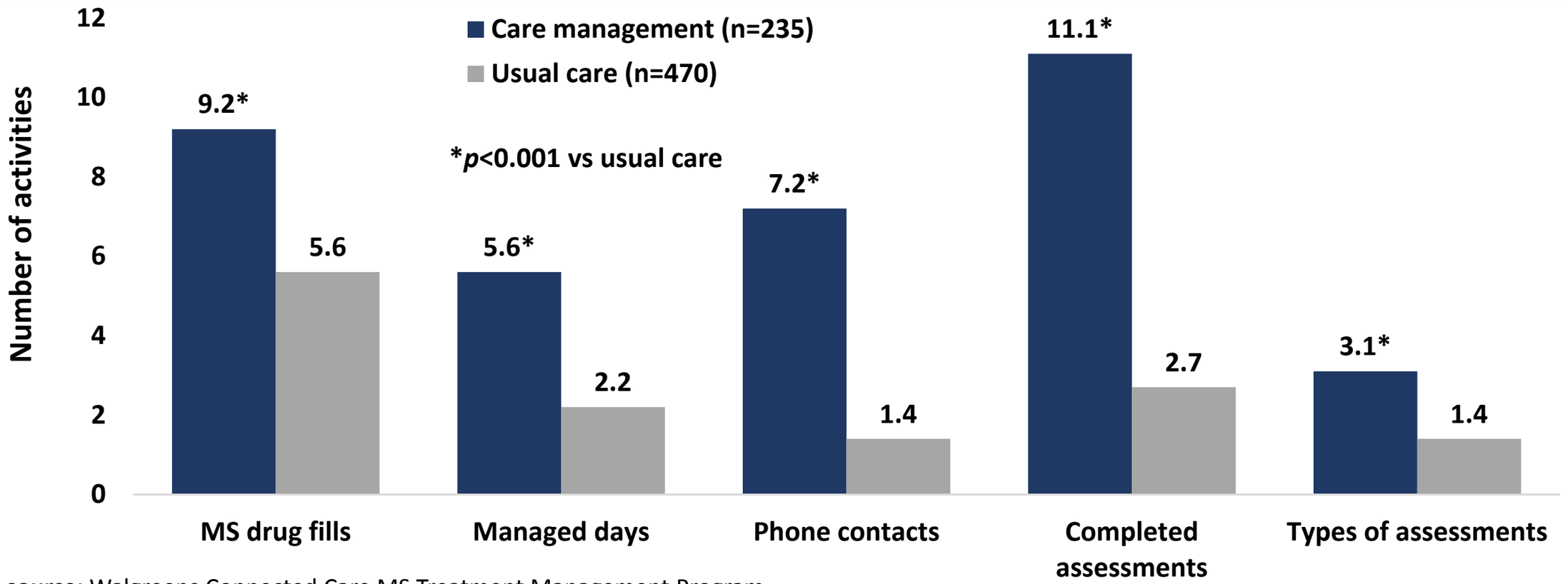
Effective Symptom Management Involves Medication, Rehabilitation and Emotional Support

- 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 Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed February 2019.

Comprehensive Care Management Increased Delivery of Appropriate MS Care



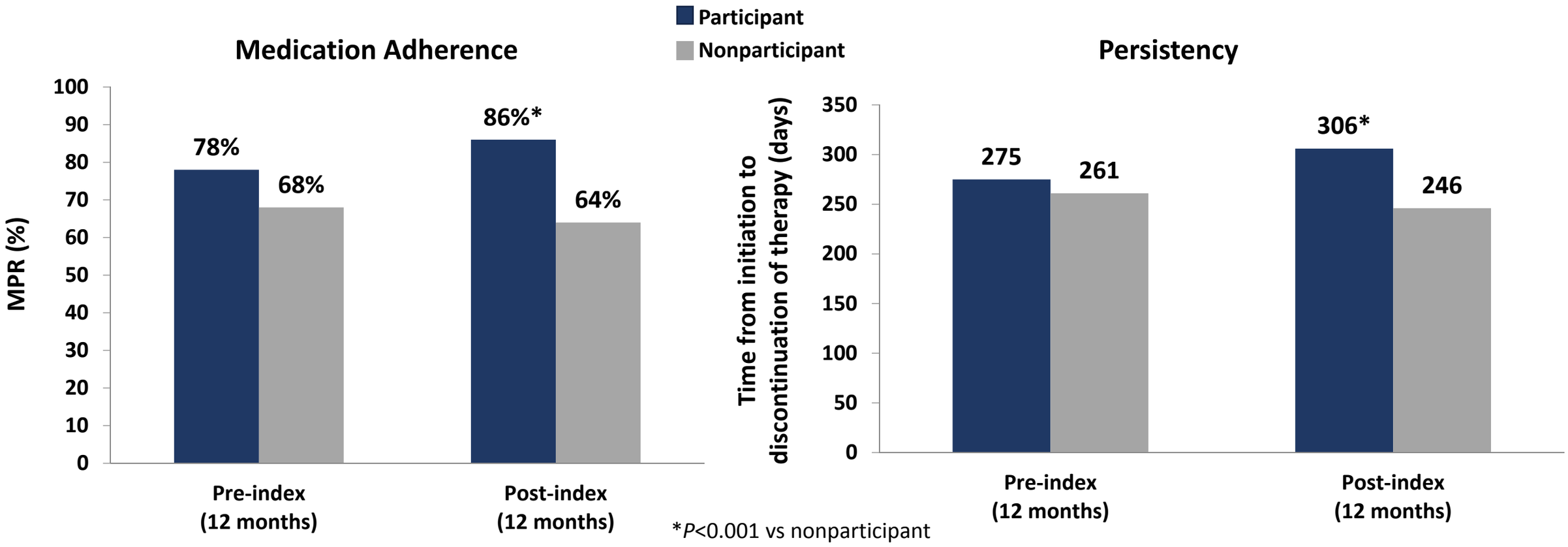
Data source: Walgreens Connected Care MS Treatment Management Program

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, et al. *Int J MS Care*. 2015;17:57-64.

Care Management Improved Adherence and Persistency

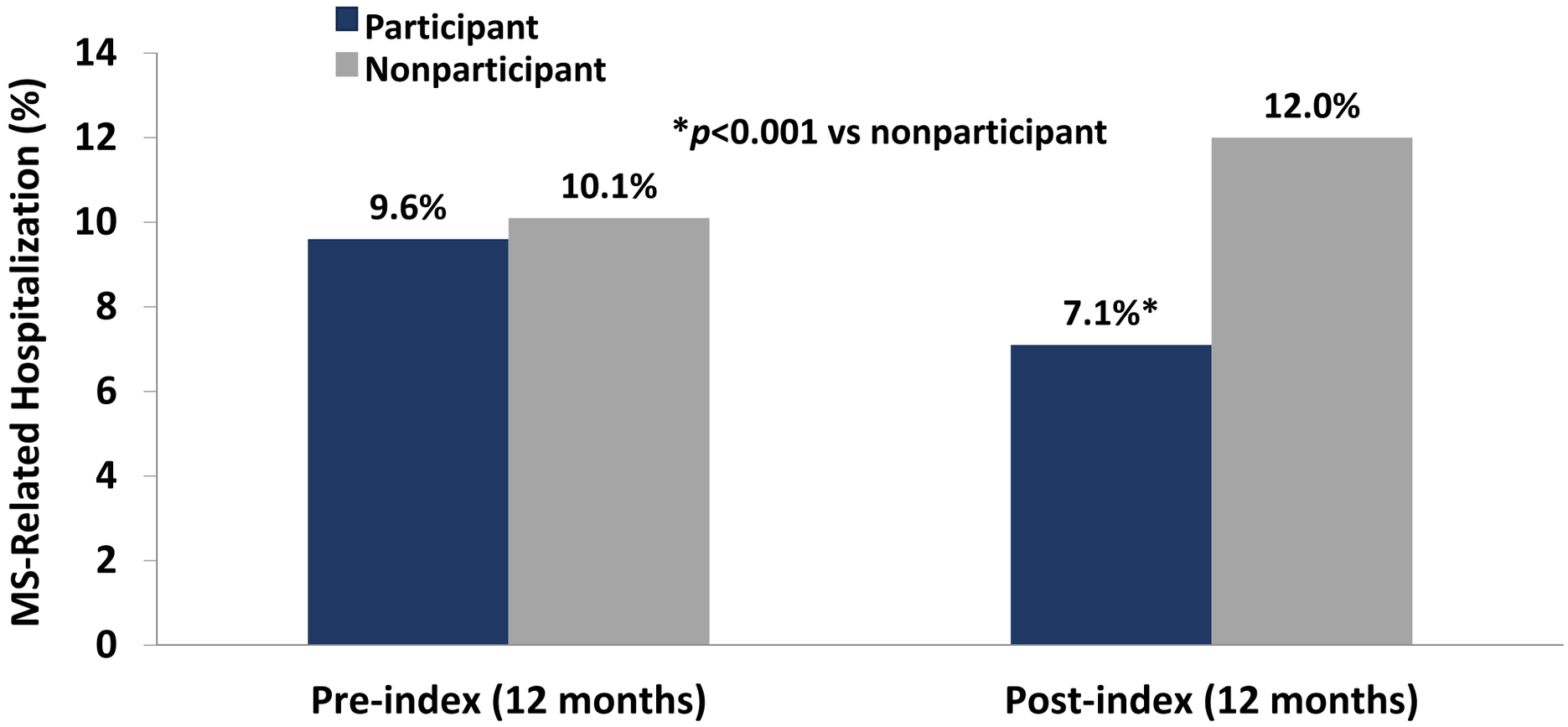


*P<0.001 vs nonparticipant

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, et al. *Mult Scler*. 2010;16:956-963.

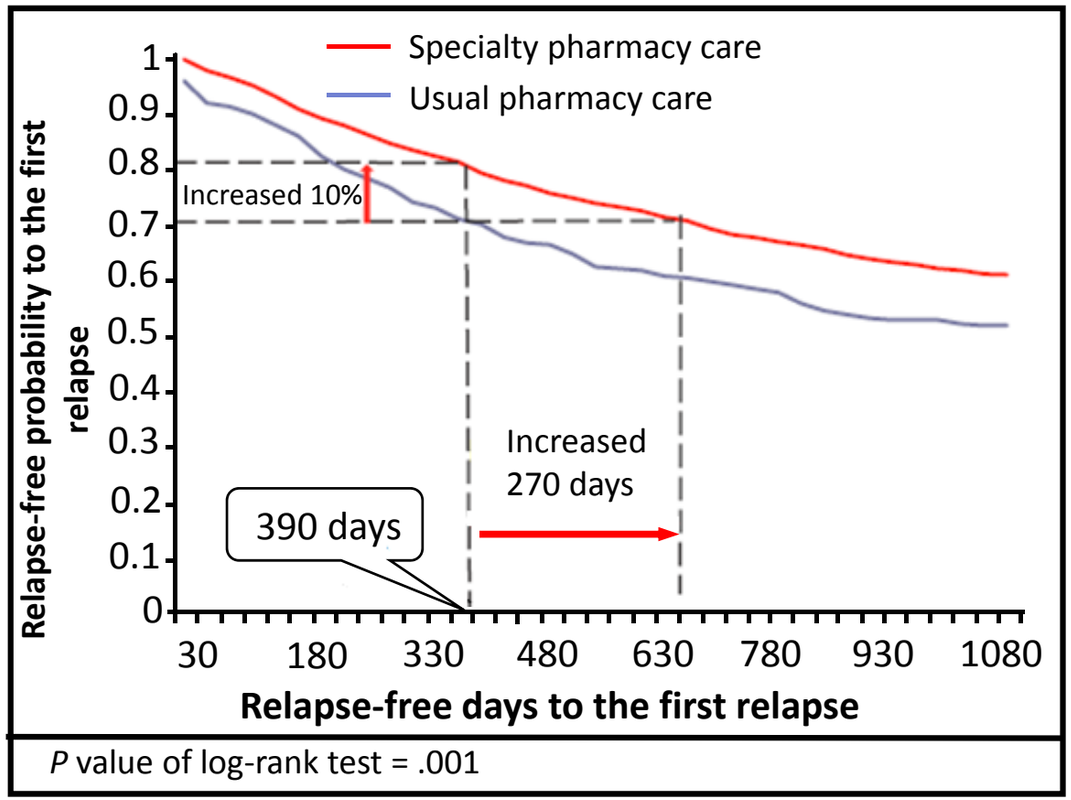
Care Management Reduced Hospitalizations



Tan H, et al. *Mult Scler*. 2010;16:956-963.

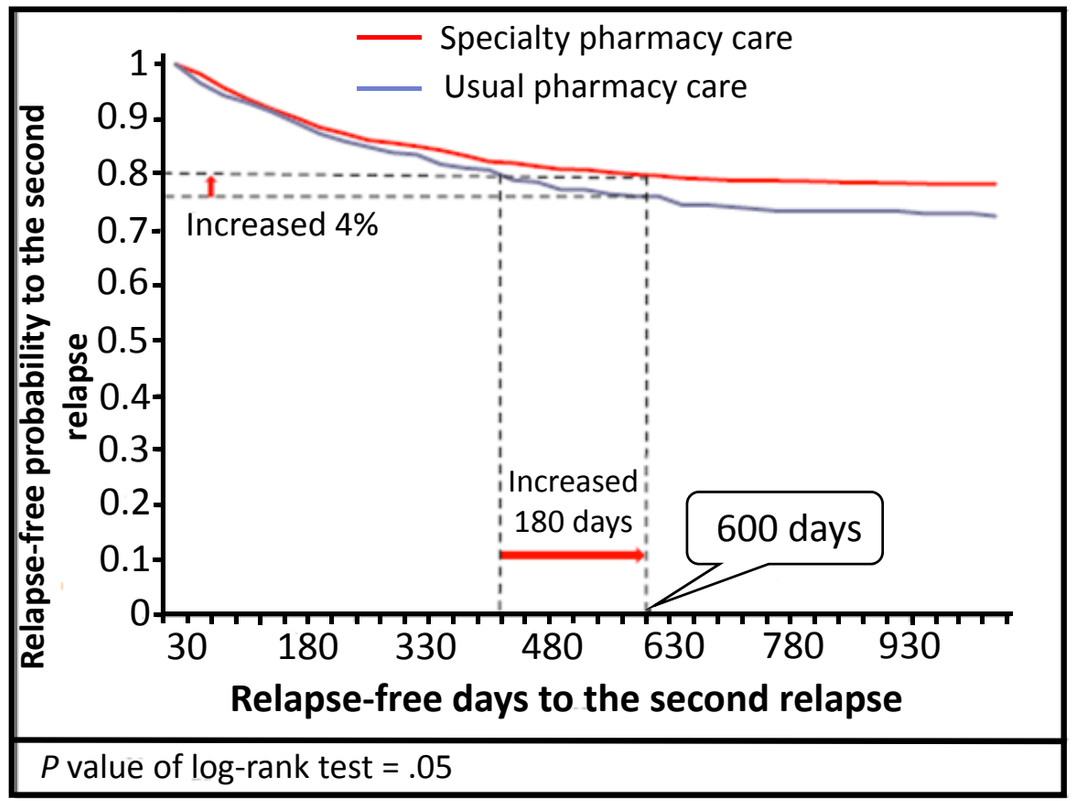
Care Management Implemented Through the Pharmacy Lowered the Risk for Disease Relapse

Time to First MS-Relapse



P value of log-rank test = .001

Time to Second MS Relapse

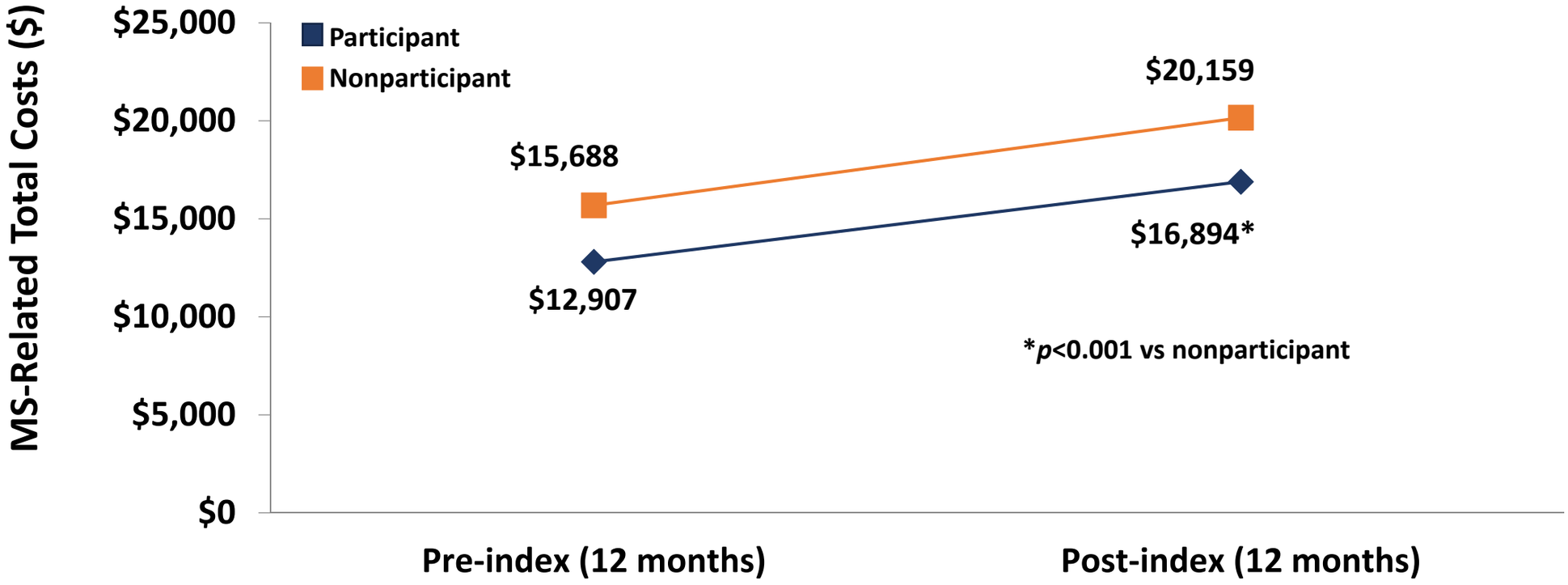


P value of log-rank test = .05

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

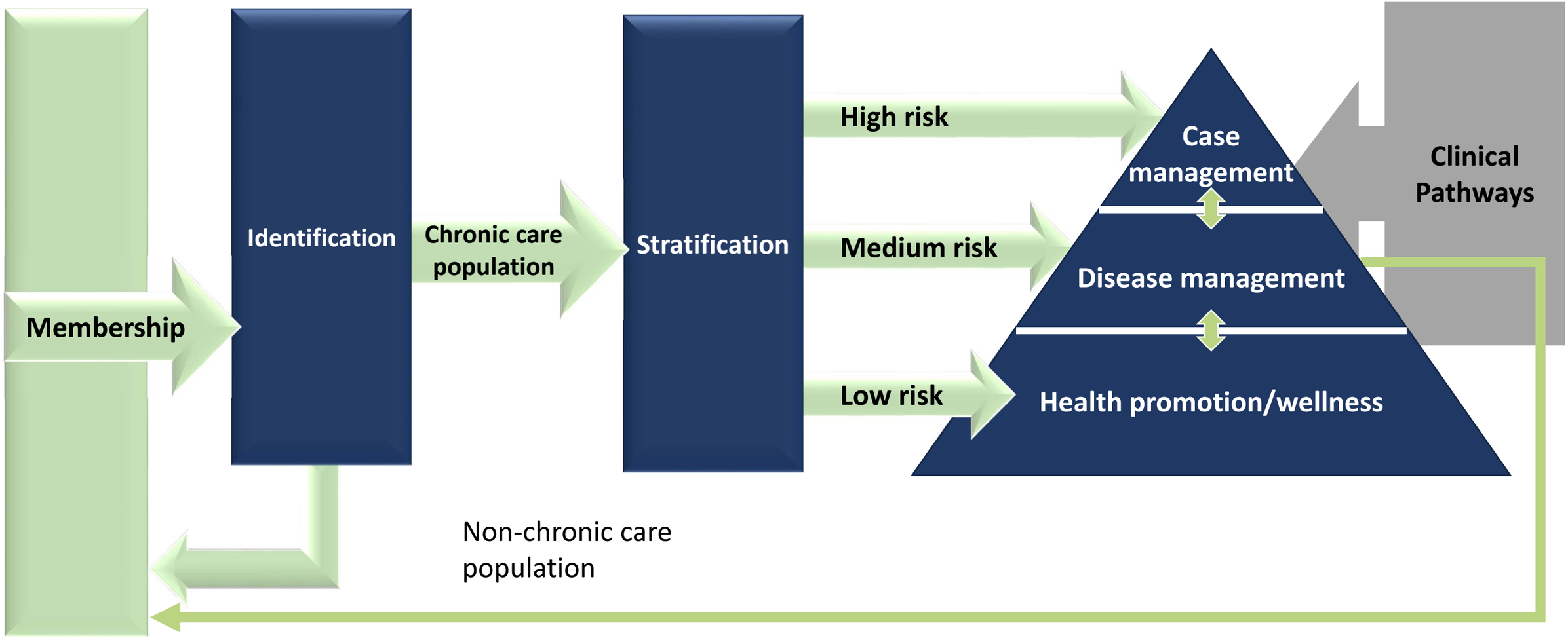
Tang J, et al. *Am Health Drug Benefits*. 2016;9:420-429.

Care Management Reduced Total MS-Related Cost of Care



Tan H, et al. *Mult Scler*. 2010;16:956-963.

In Addition to Chronic Care Management Programs, Clinical Pathways Initiatives Provide an Evidence-based Means of Managing Costs Beyond Increased Member Share



Mattke S, Higgins A, Brook R. *Am J Manag Care*. 2015;21(5):370-6.

Potential Relapsing-Remitting MS Treatment Pathway/Algorithm Example

First Line

Parenteral	**Oral**
Interferon β-1a	Dimethyl fumarate
Interferon β-1b	Fingolimod
Peginterferon β-1a	Teriflunomide
Glatiramer acetate	
Ocrelizumab	

Second Line

Patients with active disease despite first-line therapy

Natalizumab

Third Line

Alemtuzumab
Mitoxantrone HCl

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

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
- Use of care management and/or care pathways can be associated with greater adherence, decreased risk for disease relapse, and lower cost of care