Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value

Public Meeting – February 16, 2017

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

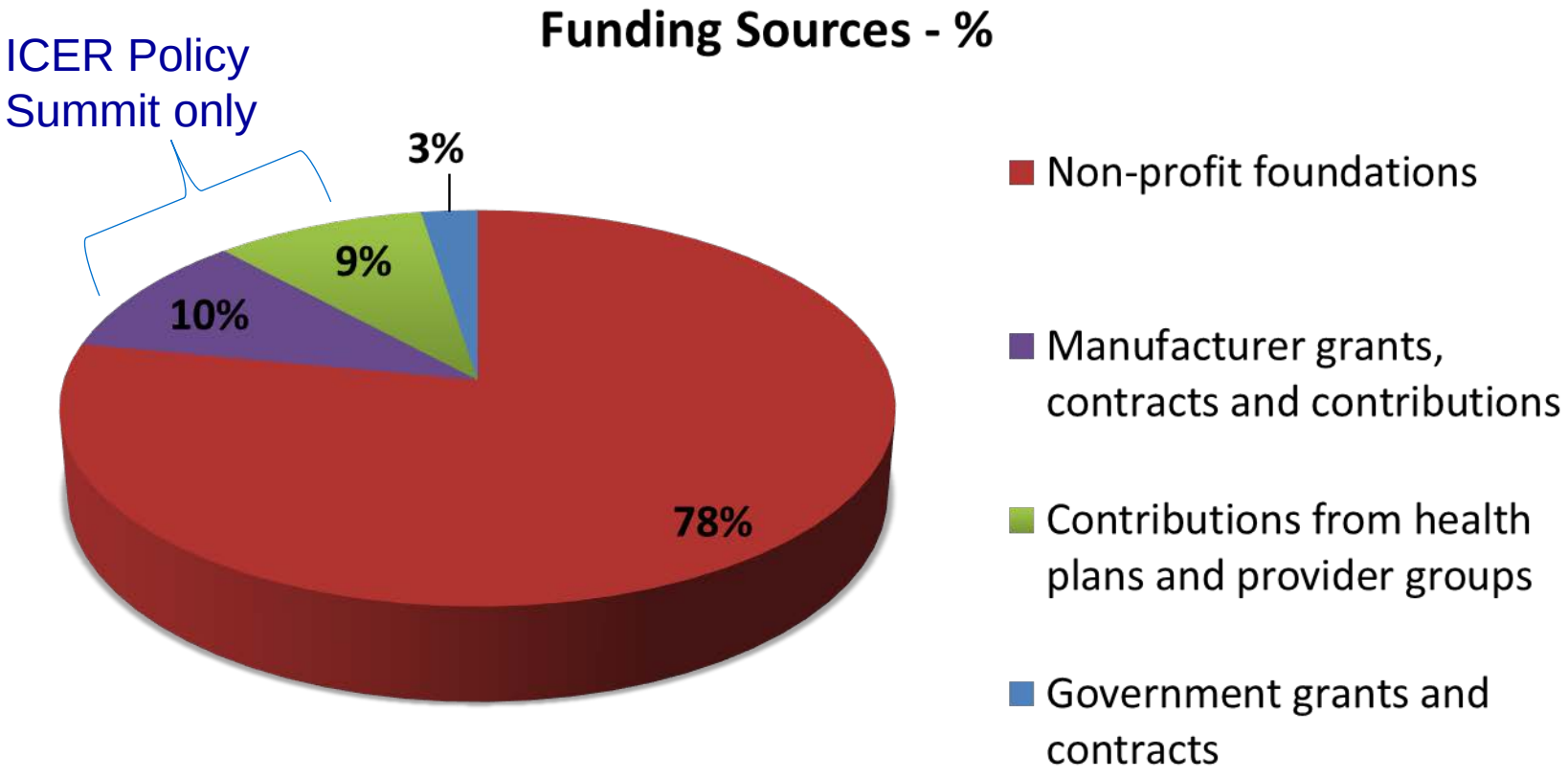
Welcome and Introduction

- California Technology Assessment Forum (CTAF)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2017

ICER Policy Summit only



Welcome and Introduction

- Why are we here today?

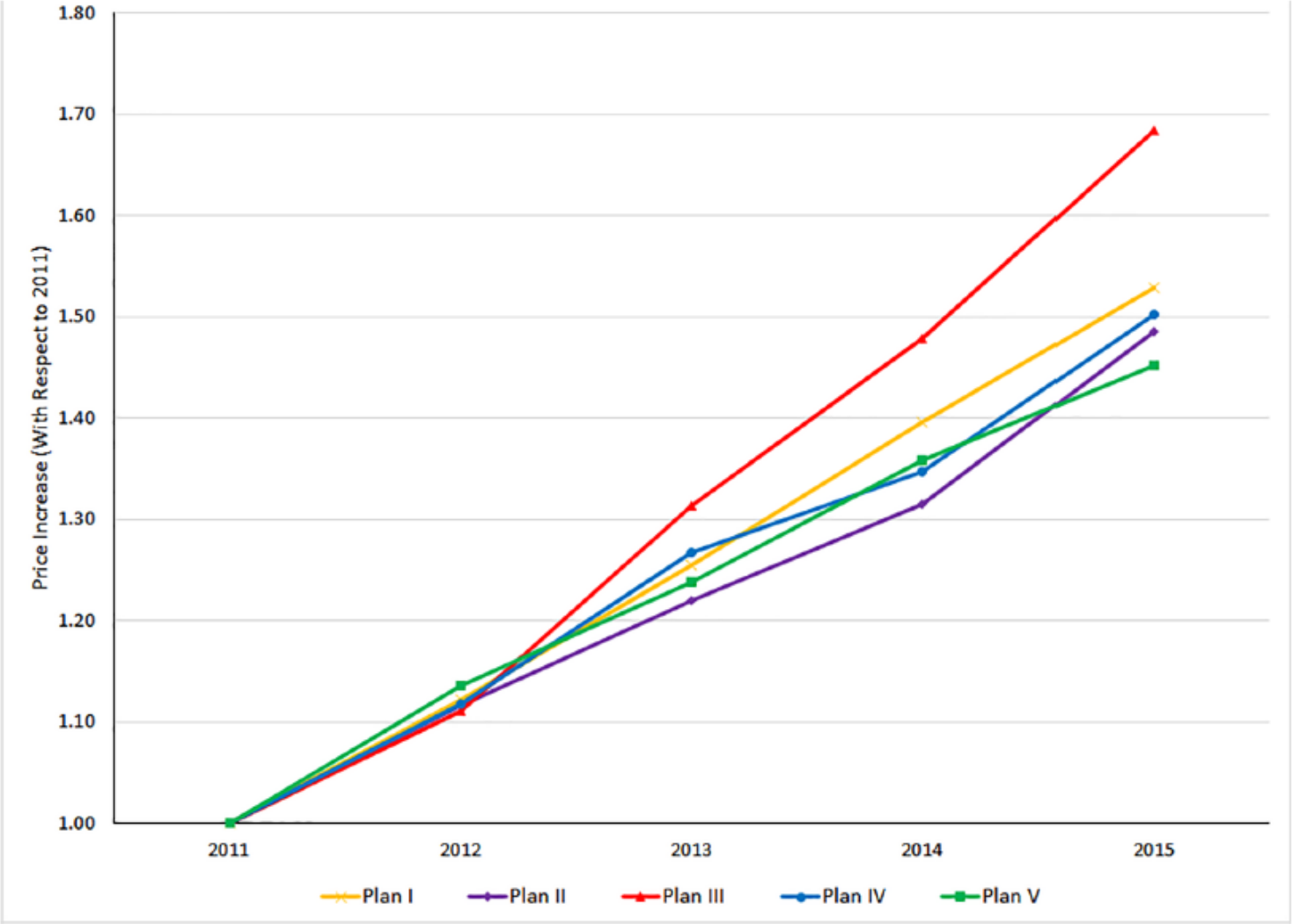
  -- *National Multiple Sclerosis Society, 2016**

  - "Multiple sclerosis (MS) medications have transformed the treatment of relapsing MS over the last 20 years."

  - "Yet, many people living with MS cannot access the medications they need. Continually escalating prices are creating significant barriers to treatment, including higher costs, increased stress, and a greater burden for those who already live with a chronic, life-altering condition."

*http://www.nationalmssociety.org/Treating-MS/Medications/Make-MS-Medications-Accessible

Relative Price Increase Net of Rebates for MS Drugs: 2011-2015



Source: Examination of Health Care Cost Trends and Cost Drivers Pursuant to G.L. c. 12C, § http://www.mass.gov/ago/docs/healthcare/cc-market-101316.pdf

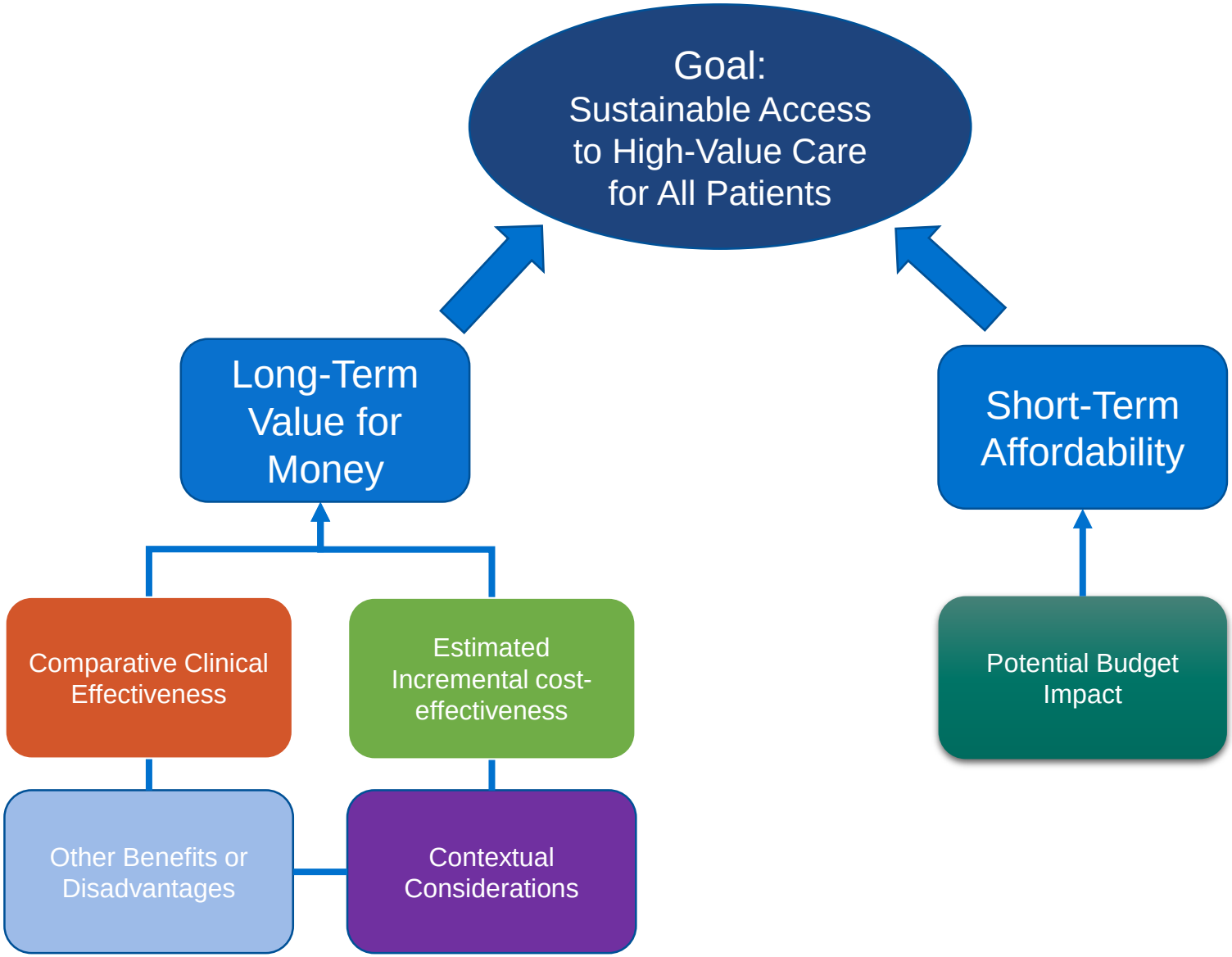
Welcome and Introduction

- Why are we here today?
  - “People with MS report high and rapidly escalating medication prices, increasing out-of-pocket costs, confusing and inconsistent formularies, and complex approval processes that stand in the way of getting the treatments they need.”
  - “It is time for change.”

Welcome and Introduction

How was the ICER report on MS treatments developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff and UCSF evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Clinical expert report reviewer
  - David E. Jones, MD
    Associate Professor of Medicine, University of Virginia
- How is the evidence report structured to support CTAF voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Estimated Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Welcome and Introduction

What is the agenda for the day?

9:30 am: Welcome and Opening Remarks

9:45 am: Presentation of the Evidence

- **Evidence Review**: Jeffrey A. Tice, MD, University of California, San Francisco
- **Comparative Value**: Marita Zimmermann, MPH, PhD, University of Washington

10:45 am: Manufacturer Comments and Discussion

11:45 am: Patient, Clinician, and Public Comments and Discussion

12:15 pm: Lunch

1:00 pm: CTAF Deliberation and Votes

2:15 pm: Break

2:30 pm: Policy Roundtable

3:45 pm: Reflections and Wrap Up

4:30 pm: Meeting Adjourned

Wifi Network and PW: Nile

Meeting Materials: https://tinyurl.com/ctaf-feb16

Evidence Review

Jeffrey A. Tice, MD

Professor of Medicine

University of California, San Francisco

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Contributors

- **Anne Loos, MA**, Senior Research Associate, ICER
- **Shanshan Liu, MS, MPH**, Research Associate, ICER
- No conflicts of interest to disclose

Background: Multiple Sclerosis (MS)

- Chronic, immune-mediated disease of CNS
- 400,000 Americans affected
  - Diagnosis in 20's and 30's
  - Progressive disability in prime years of productivity
  - Women:men ~3:1
  - African Americans more rapid disease
- Relapsing-remitting MS ~ 85-90% at diagnosis
- Primary progressive MS ~10-15% at diagnosis
  - No FDA approved medications

MS in Context: Patient Perspective

- Primary goal is to remain independent, balanced by risk for adverse events
- Some have strong preference for oral agents; others equally comfortable with injectable medications
- Their provider should be allowed to choose the best medication based on their individual disease history and personal characteristics without restriction
- Economic burdens are underappreciated: lost wages from missed work, transition to part-time work, high out of pocket costs of medications and medical equipment

DMTs for MS

Drug	Mechanism	Year approved
Interferons, GA	Immune modulation	1993-2002
Natalizumab	Anti-integrin α4β1/ α4β7 mAb	2004
Fingolimod	Sphingosine 1 receptor modulator	2010
Teriflunomide	Pyrimidine synthesis inhibitor	2012
Dimethyl fumarate	Multifactorial	2013
Alemtuzumab	Anti-CD52 mAb	2014
PegInterferon	Immune modulation	2014
Daclizumab	Anti-CD25 mAb	2016
Ocrelizumab	Anti-CD20 mAb	2017?
Rituximab	Anti-CD20 mAb	?

Topic in Context: DMTs and Cost

- $28 billion annually in US
- Rising list price for DMTs
- Interferon β-1a (Avonex) and GA (Copaxone)
    - 1996: $8,500 per year
    - 2013: $61,000 per year
    - 35% annual increase in price
  - Natalizumab
    - 2004: $26,000 per year
    - 2013: $64,000 per year
    - 16% annual increase in price

Hartung et al, Neurology, 2015

Key Outcomes

- MS Relapses
- Confirmed disability progression (CDP)
  - Change in Expanded Disability Status Score (EDSS)
- MRI findings
- Patient-reported outcomes
  - Fatigue
  - Mood disorders / depression
  - Quality of life (QOL)
  - Function

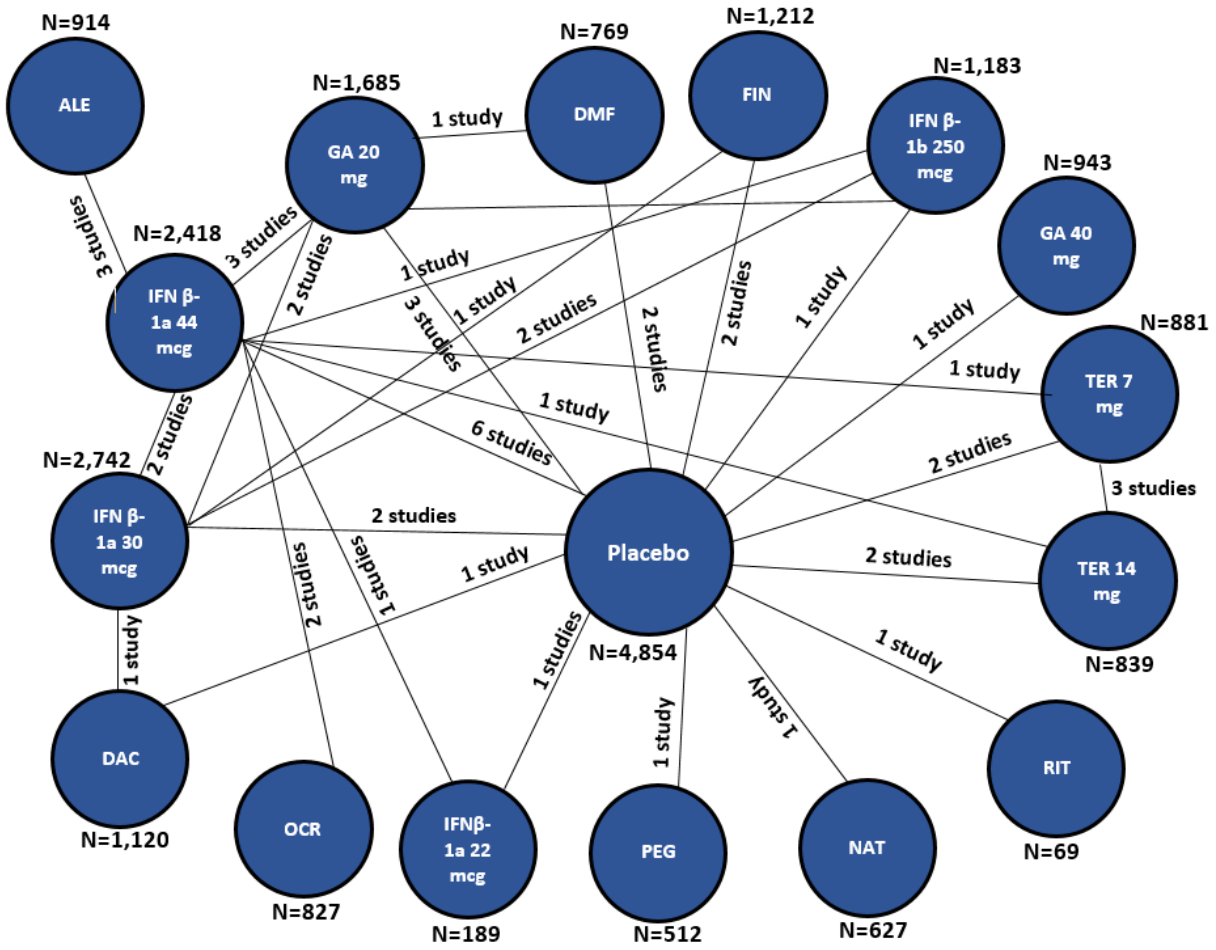
MS Coalition Survey for ICER

Decision-making Factor	Important / Very Important
Delay disability	94%
Prevent relapse / MRI lesions	94%
Continue working / usual activities	90%
Doctor recommends therapy	86%
Health plan restrictions	69%
Risk of PML	68%
Out of pocket costs	66%
Dosing frequency	58%
Monitoring / blood tests	44%

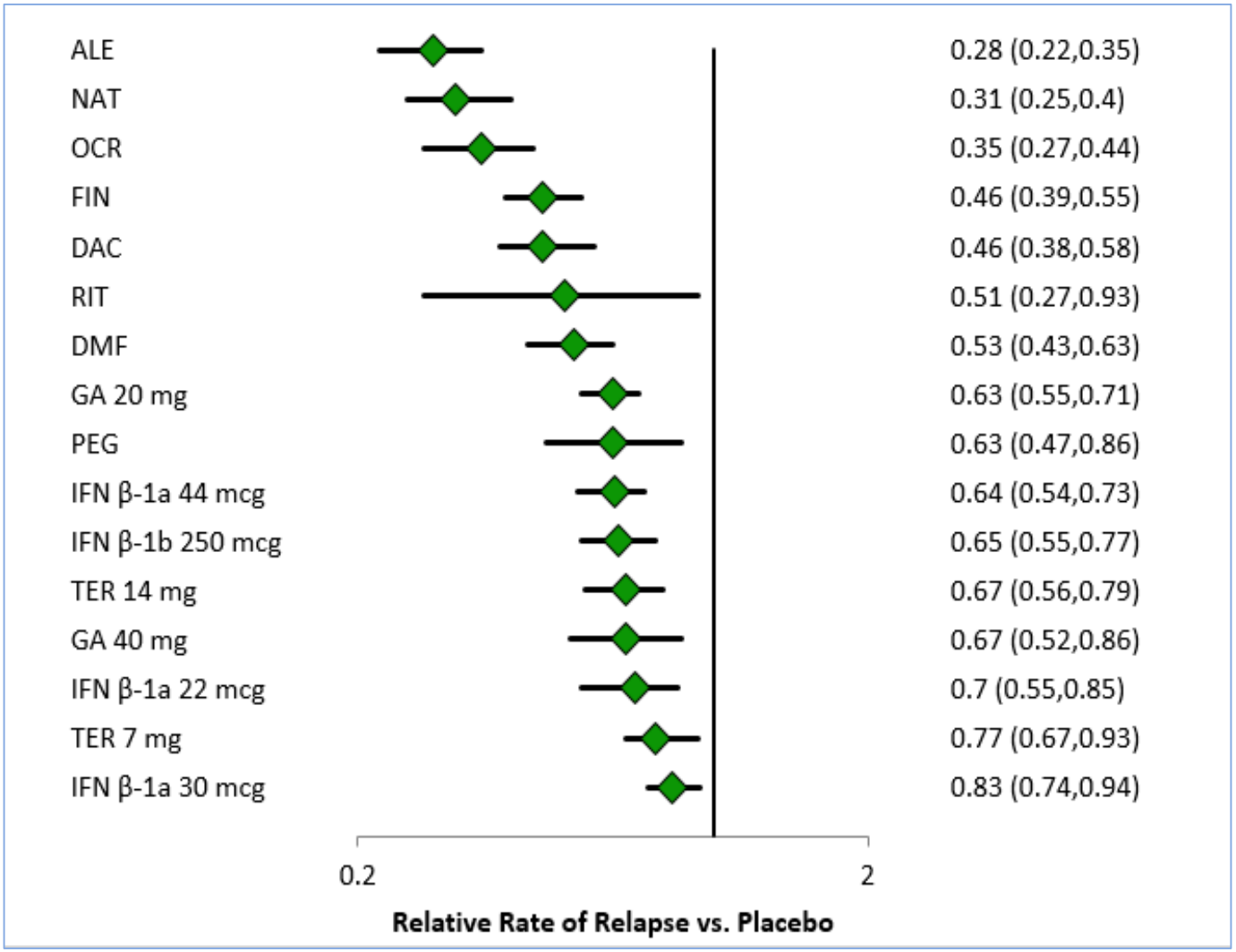
Online Questionnaire: N=15,793

Results:
Network Meta-Analysis (NMA) for RRMS

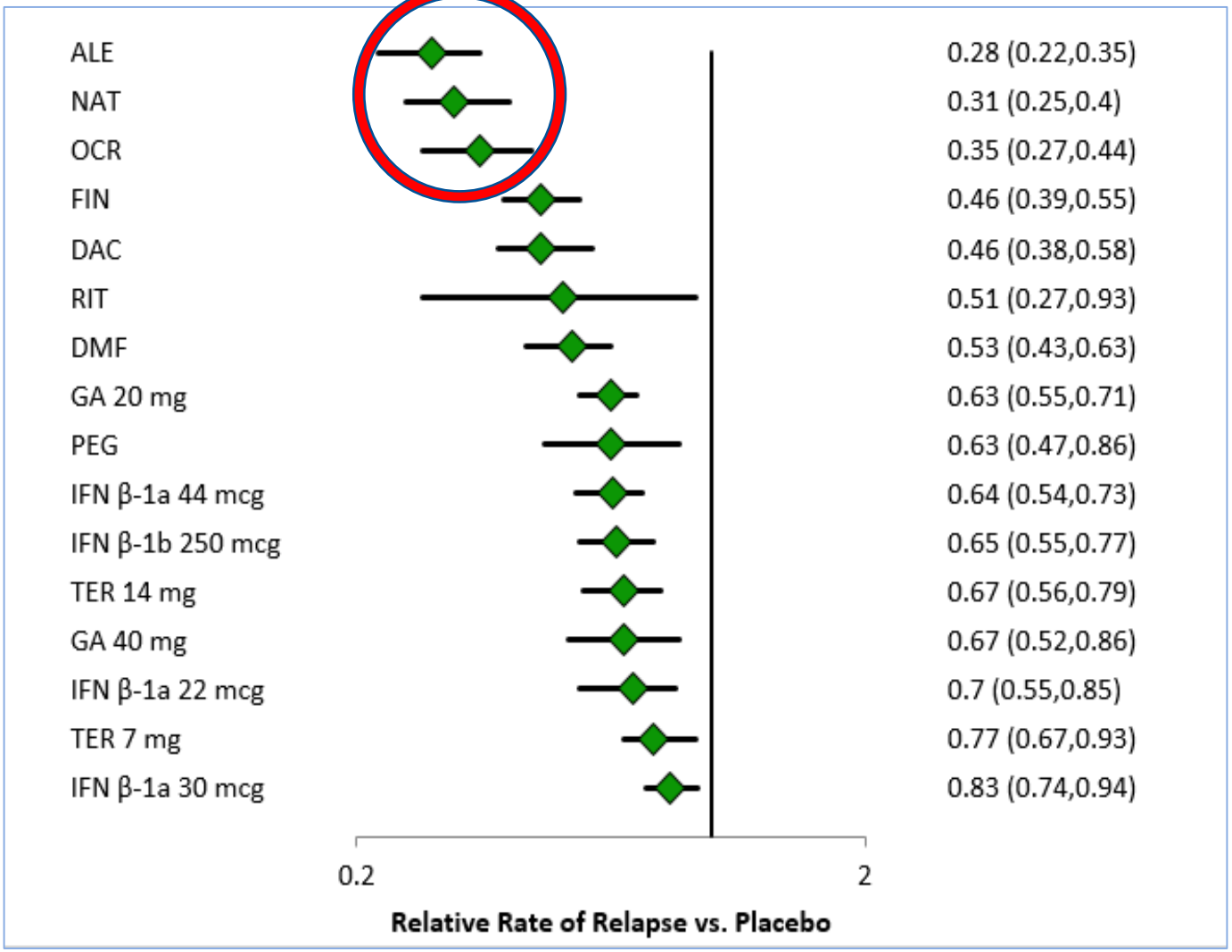
Network Diagram for Relapse Rates



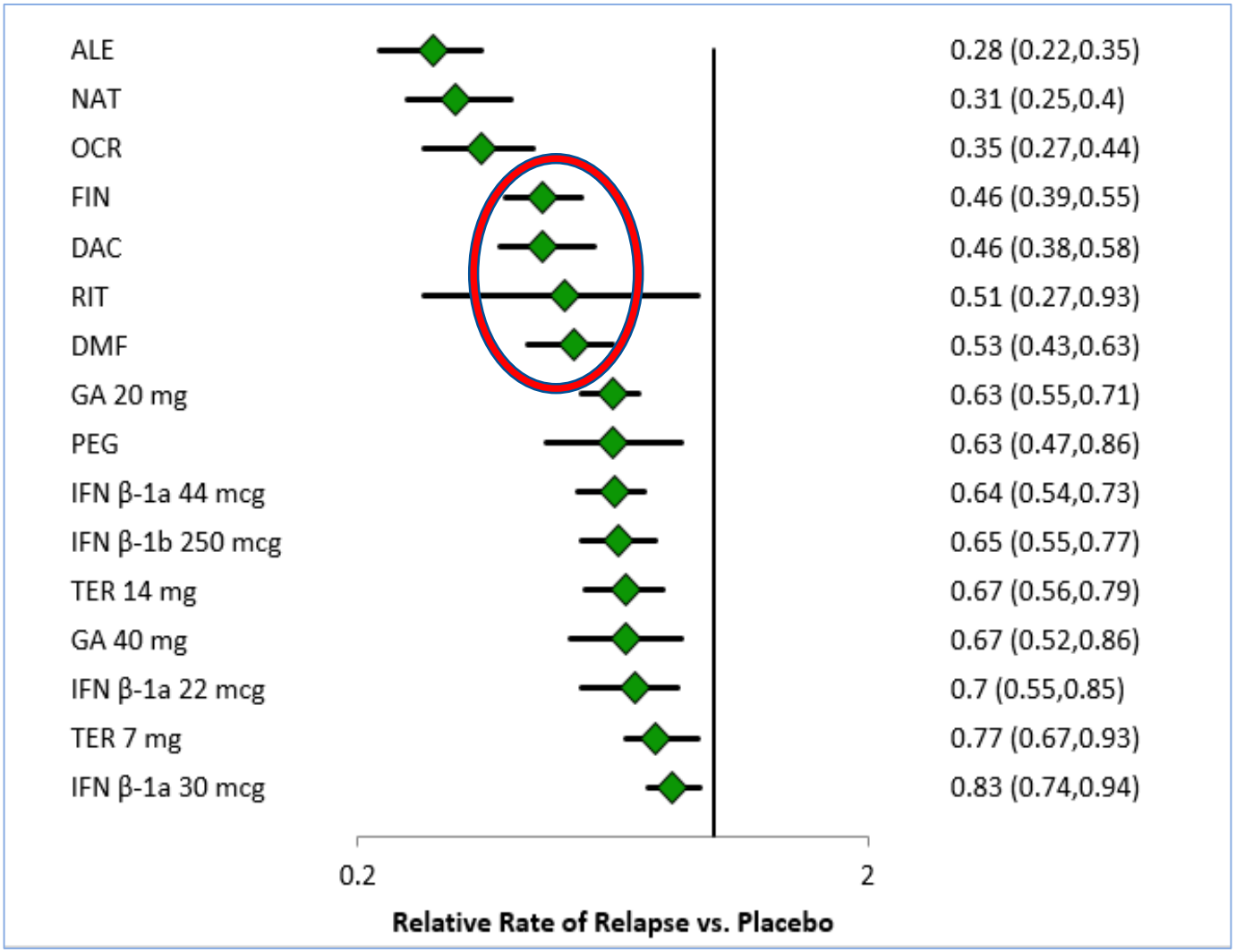
Results: Annualized Relapse Rate



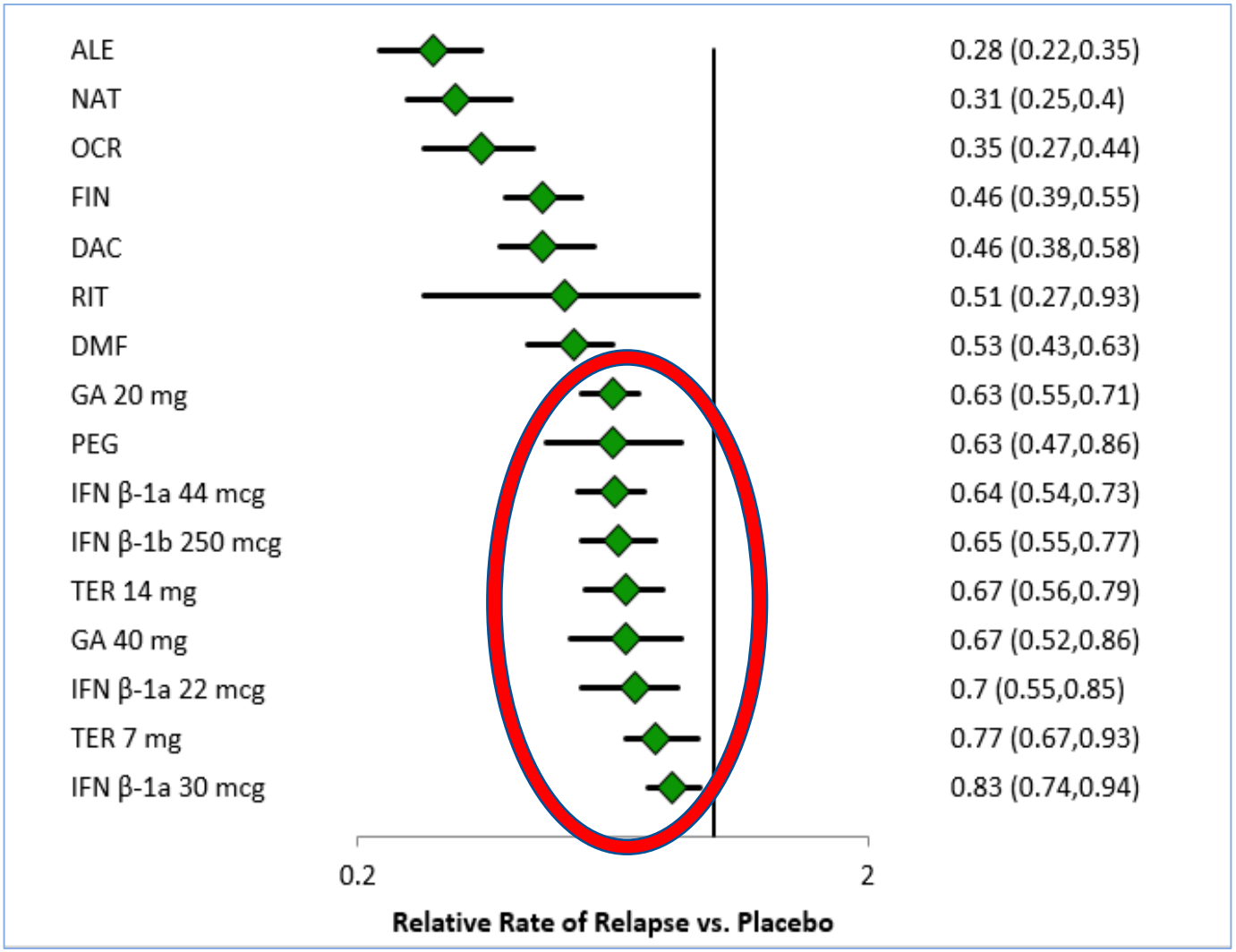
Results: Annualized Relapse Rate



Results: Annualized Relapse Rate



Results: Annualized Relapse Rate

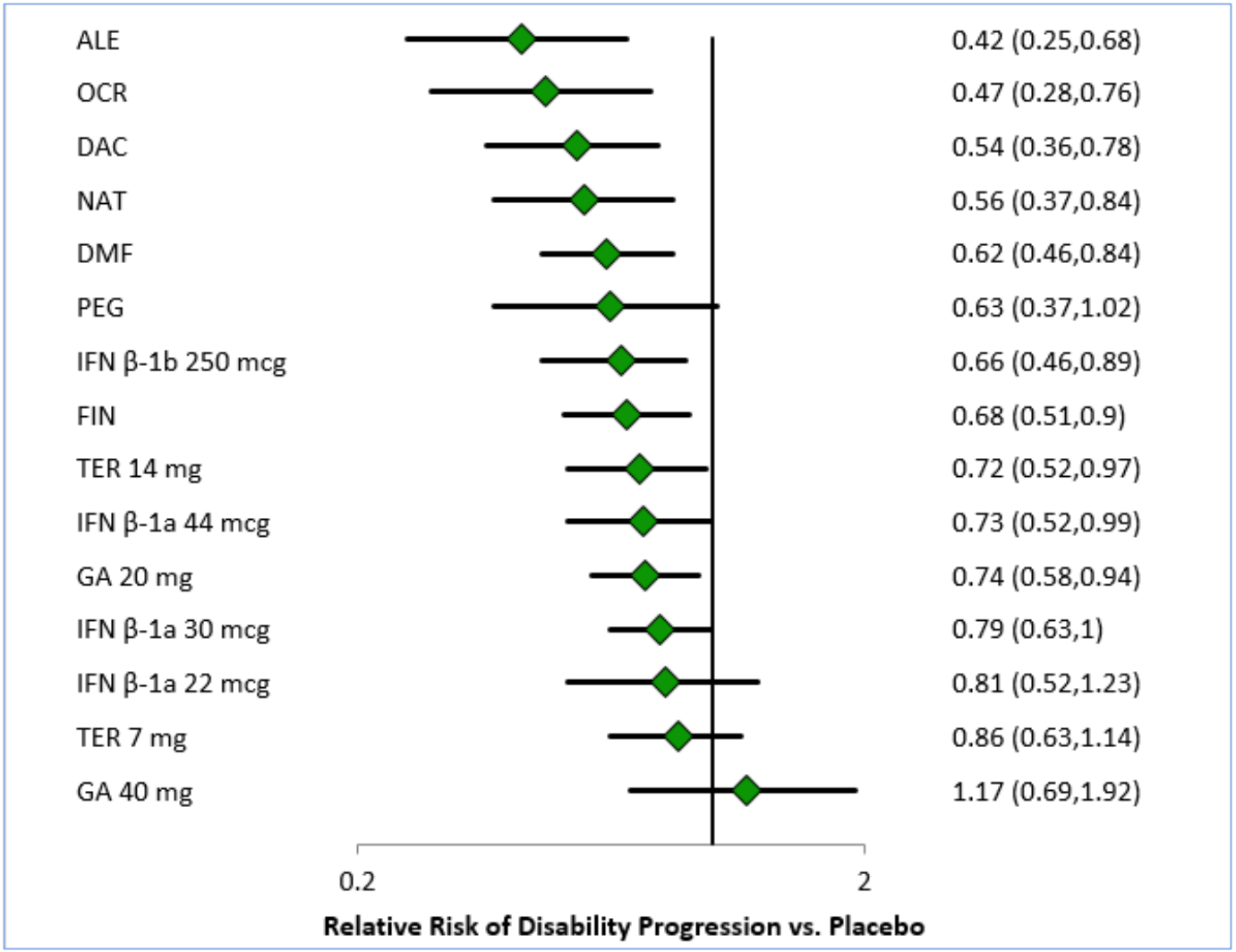


Robustness of Relapse Rate NMA

- Very similar to prior NMAs
- No significant changes with adjustment for baseline characteristics, direct meta-analysis results, or subgroup analyses based on quality of studies, size of studies, definition used for MS (a surrogate for older versus more recent studies), prior treatment with DMTs, or length of follow-up.

Results:
NMA for Confirmed Disability Progression

Results: Disability Progression



Limitations of the NMA

- Differences in patient populations in trials over time (earlier trials with higher relapse rates in placebo groups; different criteria for diagnosis of MS; different national composition)
- Differences in trial design (length of follow-up, definitions of relapses and disability progression)
- Differences in the quality of trials
- No evidence for effect modification in sensitivity analyses accounting for these factors

MRI Outcomes

- Steady evolution in MRI technology and the techniques used to assess MS in the CNS
- Meta-analyses demonstrate that MRI findings parallel the effects of DMTs on relapse rates, but not disability progression
- Lack of standard technique precludes NMA of MRI outcomes across trials

Patient-Reported Outcomes

- At least 13 different quality of life / treatment satisfaction / fatigue / depression scales reported, but none consistently
- Significant short term decreases during relapses
- Long term QOL correlates with disability progression
- No NMA because no standard measure used across trials

Harms of the DMTs

- The most effective DMTs have highest risk of life-threatening adverse events
- Natalizumab
  - PML incidence: 11/1000 for JC virus +
- Alemtuzumab
  - Autoimmune disease: up to 50% at 6 years
- Black Box Warnings: natalizumab, alemtuzumab, daclizumab, rituximab, teriflunomide
- REMS: natalizumab, alemtuzumab, daclizumab, (fingolimod – lifted in December 2016)
- Ocrelizumab: unknown as not FDA approved

Other Harms

- Serious AEs in RCTs
  - Generally not significantly different from comparator
- New harms observed
  - Alemtuzumab: severe B-cell mediated CNS disease (n=2) Lancet Neurology 2017
  - Dimethyl fumarate: liver injury added to label 2017 (n=14)

Other Benefits or Disadvantages

- Route of administration
  - Subcutaneous injection daily to every other week
  - Daily oral
  - Office infusion monthly to annually
- The value of choice: multiple mechanisms
- Increased productivity within family, community, and work
- Reductions in caregiver burden

Limitations of the Evidence Base

- Trials too short: minimum of 5 years recommended to evaluate disability progression
- Preferred outcome (CDP confirmed at 24 weeks) not always reported
- MRI technology evolving: no standard measure used across trials
- Patient reported outcomes insufficient
  - No standard measure
  - Not consistently measured / reported

Comparative Effectiveness vs. IFN/GA

Drug	ICER rating
Injectable Agents	
Daclizumab (Zinbryta)	C+
Oral Agents	
Fingolimod (Gilenya)	C+
Teriflunomide 7 mg (Aubagio)	C
Teriflunomide 14 mg (Aubagio)	C
Dimethyl fumarate (Tecfidera)	C+
Infused Agents	
Natalizumab (Tysabri)	B+
Alemtuzumab (Lemtrada)	B+
Ocrelizumab (Ocrevus)	B+
Rituximab (Rituxan)	P/I

Comparative Effectiveness:

Interferon β-1a Avonex (30 mcg IM qW) vs. Rebif (44 mcg SC TIW)

- NMA
  - Relapses: Rebif 0.77 (0.65-0.68)
  - CDP: Rebif 0.92 (0.65-1.27)
- Evidence Trial (head to head)
  - Relapses: Rebif 0.84 (CI NR, p=0.093)
  - CDP: Rebif 0.70 (0.39-1.25)
  - MRI Rebif better (p<0.001 on 3 measures)
- B+ Moderate certainty of small to substantial net health benefit

PPMS

Placebo-controlled Trials in PPMS

- OLYMPUS: Rituximab. Good-quality study
  - Significant reduction in T2 lesion volume (primary endpoint)
  - No significant reduction in disability progression
- ORATORIO: Ocrelizumab. Good-quality study.
  - Significant reduction in disability progression
    - HR 0.75, 95% CI 0.59-0.98
  - Also significant reductions in T2 lesion volume, brain volume loss, but not QOL (SF-36)
  - Fewer SAEs, but more malignancies

Drug	ICER rating
Ocrelizumab (Ocrevus)	B+
Rituximab (Rituxan)	P/I

Comparative Value

Marita Zimmermann, MPH, PhD

Josh Carlson, MPH, PhD

University of Washington

Department of Pharmacy

Pharmaceutical Outcomes Research and Policy Program

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Disclosures

- Josh Carlson has served as a consultant to Genentech and Sandoz.
- Marita Zimmermann has severed as a consultant to Genentech.

Objective

The primary aim of this analysis was to estimate the lifetime cost-effectiveness of various DMTs for patients initiating treatment for 1) RRMS and 2) PPMS.

Methods in Brief

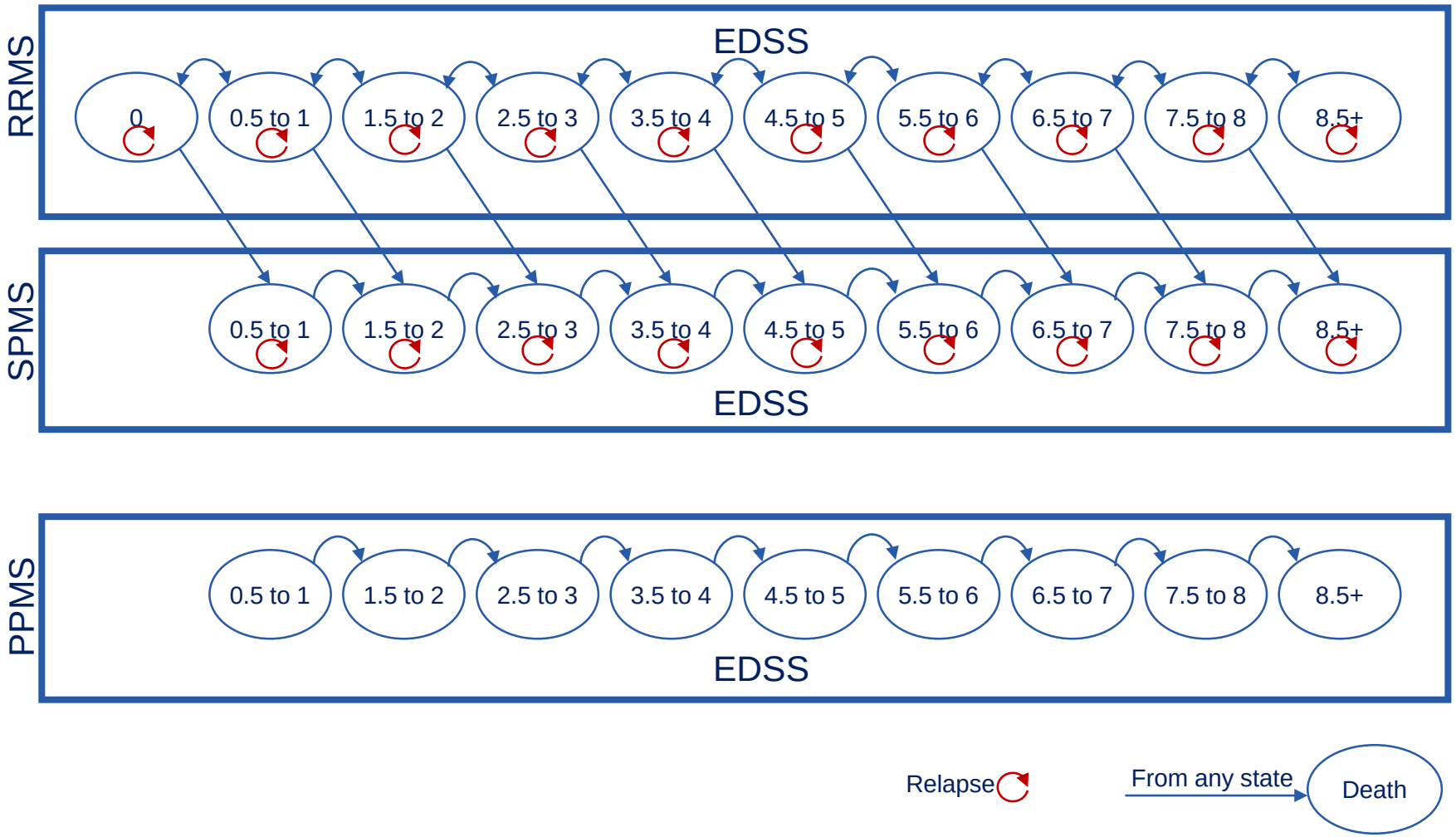
Overall Approach

- We modelled the natural history of RRMS, secondary-progressive MS (SPMS), and PPMS using probabilities from the published literature
- Treatment effects for progression and relapses were based on the NMAs described earlier, and were applied to the natural history model.
- Used a lifetime horizon with 1-year cycles
- Mean age of onset: 29 for RRMS[1], 42 for PPMS[2]
- Lines of therapy:
  - RRMS transitioned to aggregate second-line then supportive care
  - PPMS transitioned to supportive care
- Comparators
  - Generic glatiramer acetate 20 mg
  - Supportive care

ICER

[1] Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. *BMJ open.* 2014;4(1):e004073.
[2] Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of primary progressive multiple sclerosis. *Neurology.* 2009;73(23):1996-2002.

Model Structure



DMTs included

- Daclizumab
- Glatiramer acetate (20 mg only)
- Interferon β-1a
- Peginterferon β-1a
- Interferon β-1b
- Dimethyl fumarate
- Fingolimod
- Teriflunomide
- Alemtuzumab
- Natalizumab
- Ocrelizumab (health outcomes only)

Key Model Assumptions

- Supportive care costs and mortality risks for the different EDSS-defined disease stages were assumed to be the same for patients with 1) RRMS and 2) SPMS or PPMS.
- Patients receiving DMTs were assumed to stop treatment when their EDSS score reached 7 or above.
- Second-line treatment was evenly distributed across natalizumab, fingolimod, alemtuzumab, daclizumab, and dimethyl fumarate. In the case that the first-line DMT was one of these, the second line treatment was distributed equally over the remaining DMTs.

Treatment Discontinuation

Derived from trials in disability progression NMA

DMT	Annual Discontinuation Probability
Interferon β-1a 30 mcg (Avonex)	5.3%
Interferon β-1b 250 mcg (Betaseron)	4.1%
Interferon β-1b 250 mcg (Extavia)	4.1%
Glatiramer Acetate 20 mg (Copaxone)	5.2%
Glatiramer Acetate 20 mg (Glatopa)	5.2%
Interferon β-1a 22/44 mcg (Rebif)	6.9%
Peginterferon β-1a 125 mcg (Plegridy)	7.4%
Daclizumab 150 mg (Zinbryta)	6.6%
Fingolimod 0.5 mg (Gilenya)	7.5%
Teriflunomide 7/14 mg (Aubagio)	15.5%
Dimethyl Fumarate 240 mg (Tecfidera)	13.3%
Natalizumab 20 mg (Tysabri)	4.9%
Alemtuzumab 12 mg (Lemtrada)	1.9%
Ocrelizumab (Ocrevus)	4.6%
Second-line (assumption)	10%

Utility Scores by Health State

EDSS State	Annual Utility, RRMS[1]*	Annual Utility, SPMS/PPMS[1]*
0	0.8752	--
1	0.8342	0.7905
2	0.7802	0.7365
3	0.6946	0.6509
4	0.6253	0.5816
5	0.5442	0.5005
6	0.4555	0.4118
7	0.3437	0.3000
8	0.0023	-0.0413
9	-0.1701	-0.2138
Death	0	0
*Varied ± 20% in sensitivity analysis		

[1] Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;6998:1-11.

Adverse Events

Derived from trials used in NMA.

Severe AE	Cost		Disutility		Rates
	Per Event	Utilization	Per Event	Source	
Lymphopenia	$126.38	blood count; 1 specialist visit	0	Jakubowiak 2016	1% IFN β-1a 22/44 mcg
ALT increased	$284.30	2 specialist visits; 4 liver function tests	0	Mauskopf 2016	1% TER
Cholelithiasis	$4,476.85	DRG 446	0.005	Cook 1994	1% IFN β-1a 22/44 mcg
Influenza	$5,687.24	DRG 194	0.016	Mauskopf 2016	1% IFN β-1a 22/44 mcg
Serious infection	$11,176.56	DRG 177	0.005	Jakubowiak 2016	1% DMF
Trigeminal neuralgia	$7,829.06	DRG 073	0.44	Tölle 2006	1% IFN β-1a 22/44 mcg
Depression	$3,884.28	DRG 881	0.56	Mauskopf 2016	1% IFN β-1a 22/44 mcg
PML	$23,444.88	ICD diagnosis code 046.3	0.4	Campbell 2013	0.03% NAT

Drug Costs – 'Real World' Estimates

We estimated net prices by comparing the four-quarter (i.e., 4Q15 – 3Q16) rolling averages of both net prices* and list (WAC) prices per unit to arrive at an average discount from WAC, by drug.

Drug Name and Labeled Dose	WAC Package Cost	Discount Applied to WAC	Annual Net Acquisition Cost	
			Year 1	Subsequent years
Interferon β-1a 30 mcg (Avonex)	$6,287 / 4EA	20%	$65,654	$65,654
Interferon β-1b 250 mcg (Betaseron)	$6,648/ 14EA	35%	$60,958	$56,328
Interferon β-1b 250 mcg (Extavia)	$5,947 / 15EA	35%	$50,899	$47,033
Glatiramer Acetate 20 mg (Copaxone)	$7,114 / 30EA	15%	$73,571	$73,571
Glatiramer Acetate 20 mg (Glatopa)	$5,194 / 30EA	35%	$41,075	$41,075
Interferon β-1a 22/44 mcg (Rebif)	$6,629 / 0.5ml 12EA	15%	$73,454	$73,454
Peginterferon β-1a 125 mcg (Plegridy)	$6,287 / 1ml	10%	$73,760	$73,760
Daclizumab 150 mg (Zinbryta)	$6,833 / 1ml	5%	$77,900	$77,900
Fingolimod 0.5 mg (Gilenya)	$6743 / 30EA	10%	$73,839	$73,839
Teriflunomide 7/14 mg (Aubagio)	$5,877 / 28EA	10%	$68,951	$68,951
Dimethyl Fumarate 240 mg (Tecfidera)	$6,820 / 60EA	10%	$74,679	$74,679
Natalizumab 20 mg (Tysabri)	$6,000 / 15ml	5%	$74,304	$74,304
Alemtuzumab 12 mg (Lemtrada)	$20,749 /1.2ml	5%	$98,562	$59,137

ICER

*Source: SSR Health, LLC

Model Results

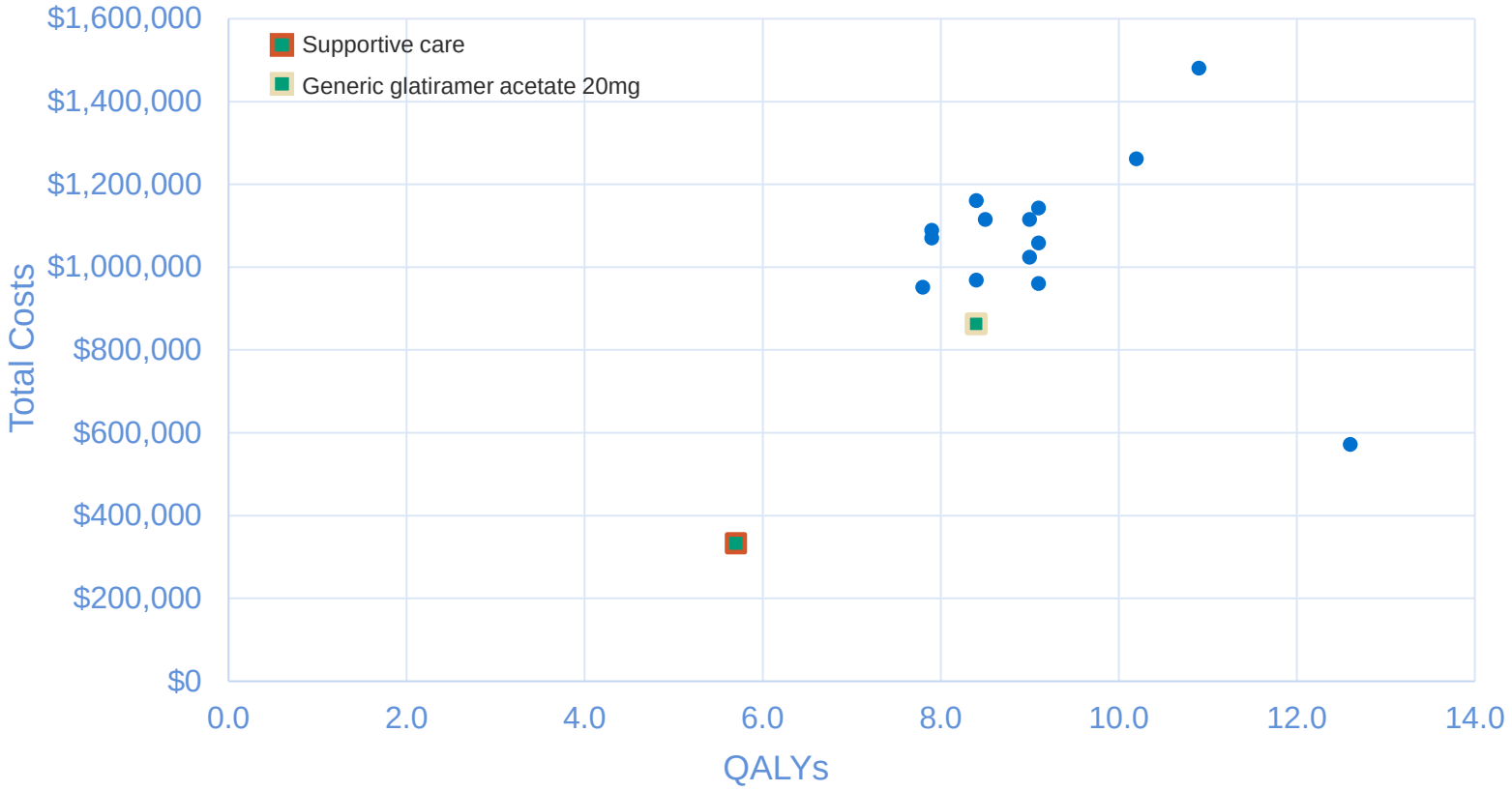
Results

Drug	Cost	Relapses	Life-Years	QALYs
RRMS				
Supportive Care	$333,273	16.4	21.4	5.7
Teriflunomide 7 mg	$951,141	14.8	21.9	7.8
Interferon β-1a 22 mcg (Rebif)	$1,088,892	14.6	21.9	7.9
Interferon β-1a 30 mcg (Avonex)	$1,069,959	15.6	22.0	7.9
Teriflunomide 14 mg	$968,663	14.8	22.0	8.4
Glatiramer acetate 20 mg (Copaxone)	$1,160,237	14.3	22.0	8.4
Glatiramer acetate 20 mg (Glatopa)	$862,912	14.3	22.0	8.4
Interferon β-1a 44 mcg (Rebif)	$1,114,885	14.5	22.1	8.5
Dimethyl fumarate	$1,023,958	14.3	22.2	9.0
Fingolimod	$1,114,879	13.5	22.2	9.0
Interferon β-1b 250 mcg (Betaseron)	$1,057,932	14.8	22.2	9.1
Interferon β-1b 250 mcg (Extavia)	$959,939	14.8	22.2	9.1
Peginterferon β-1a	$1,142,597	14.8	22.2	9.1
Natalizumab	$1,261,612	12.3	22.4	10.2
Daclizumab	$1,480,080	13.0	22.7	10.9
Ocrelizumab	-	12.8	22.7	11.0
Alemtuzumab	$571,971	10.8	23.1	12.6
PPMS				
Supportive Care	$264,334	N/A	15.6	2.7
Ocrelizumab	-	N/A	16.1	3.3

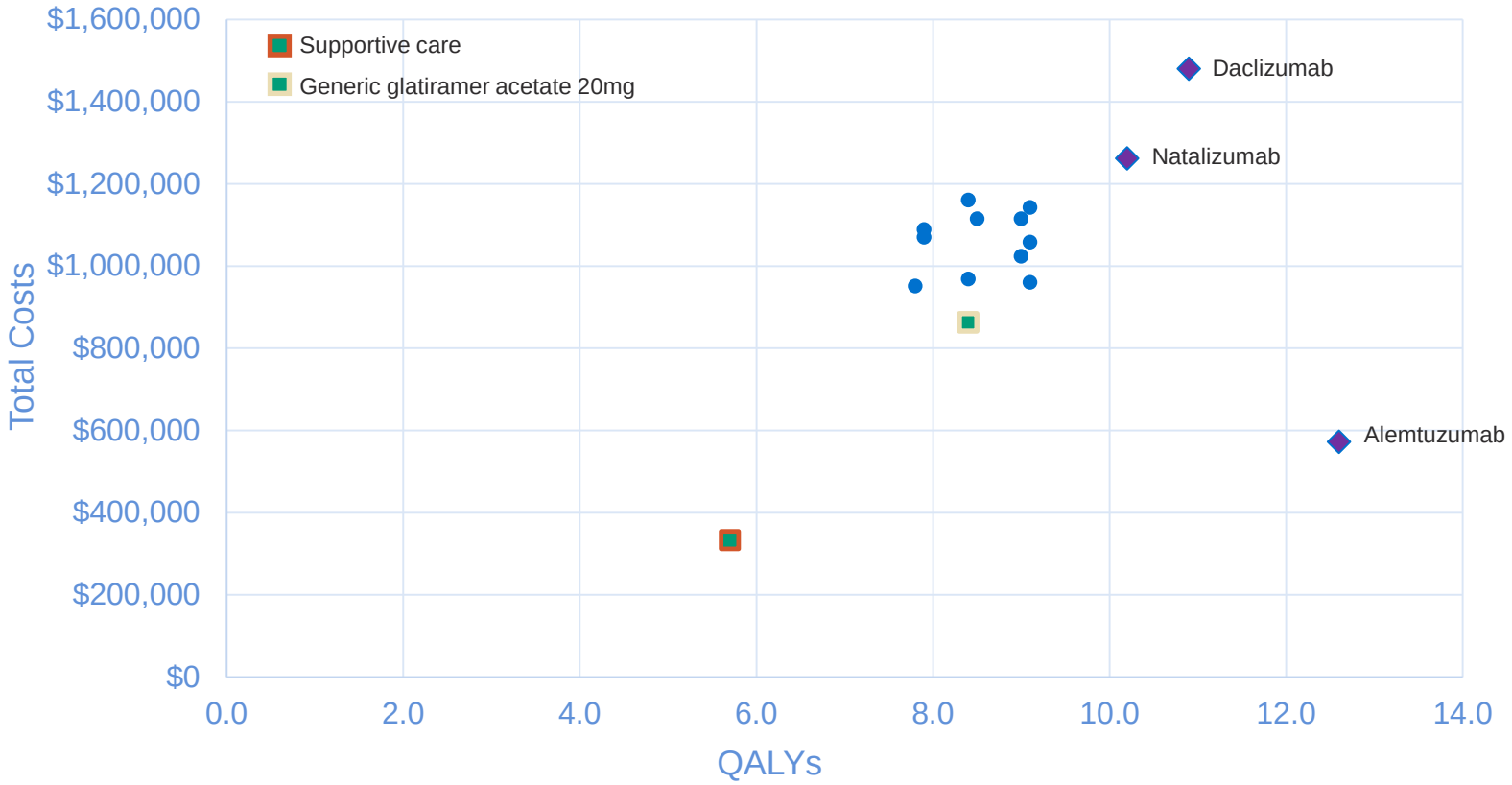
Annual discount rate of 3% applied to costs, life-years, and QALYs

ICER

Results - QALYS

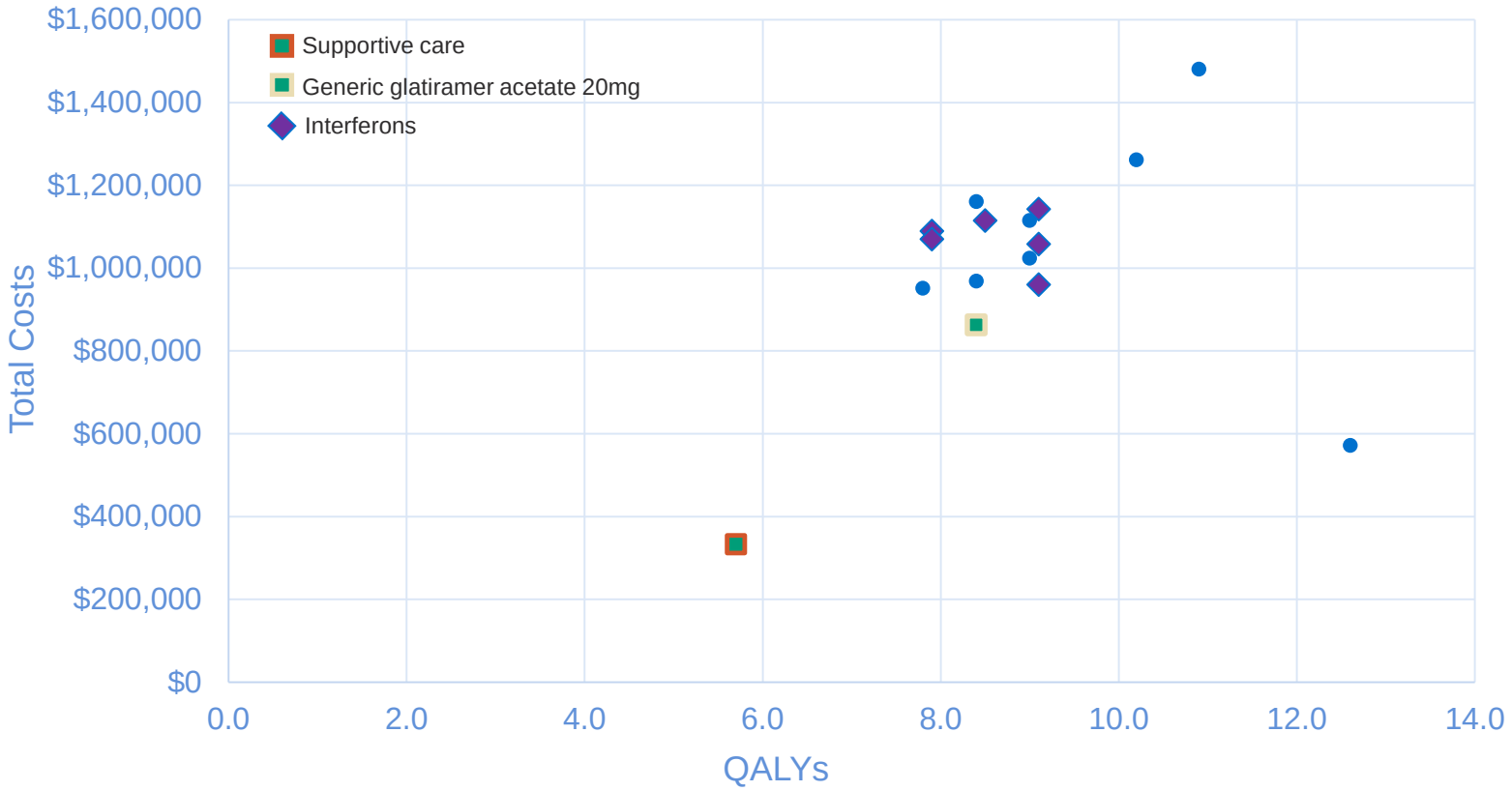


Results - QALYS



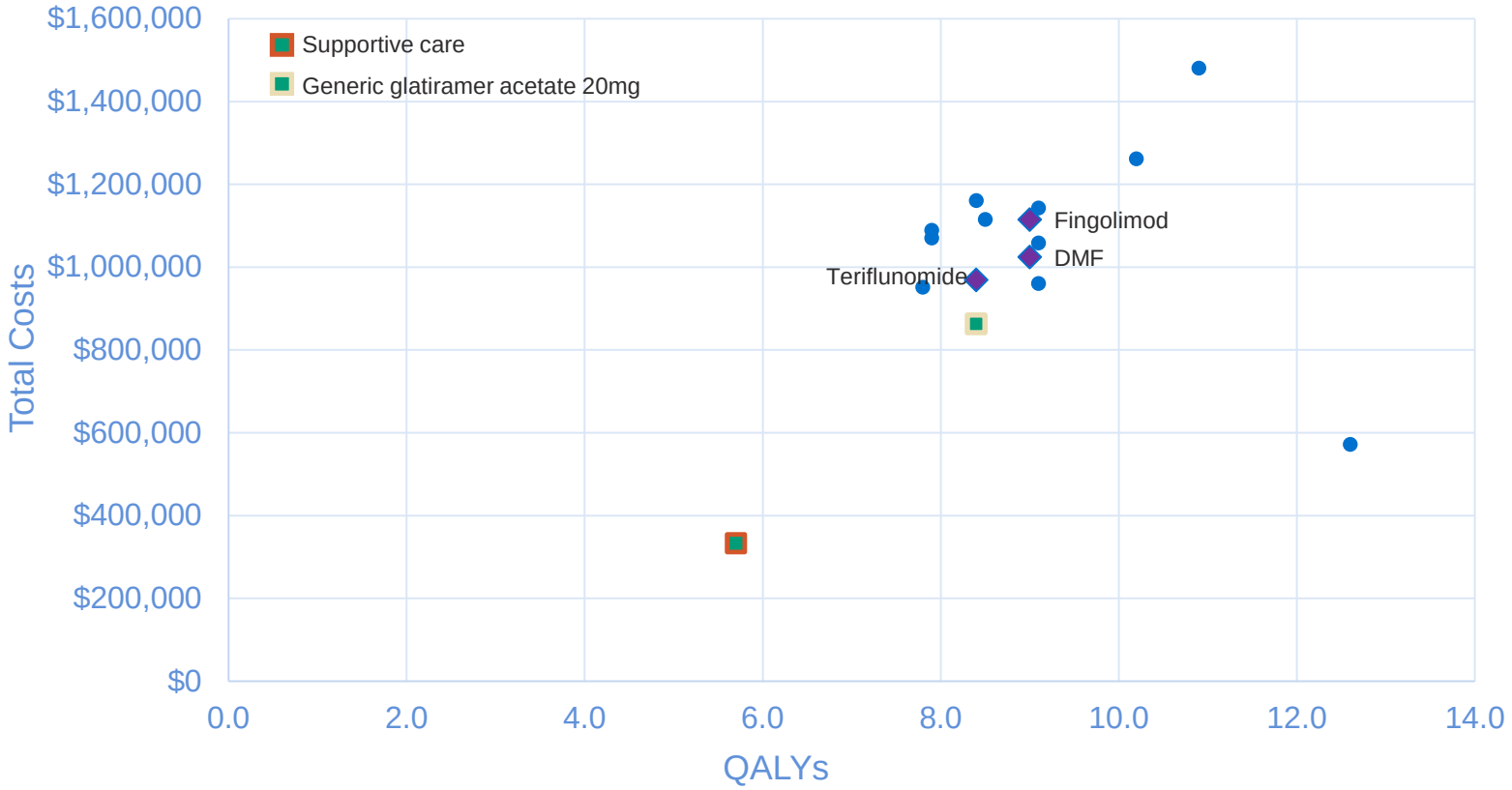
DMT	ICER vs supportive care	ICER vs generic glatiramer acetate
Daclizumab	$222,782	$254,908
Natalizumab	$208,978	$232,405
Alemtuzumab	$34,659	Dominant

Results - QALYS



DMT	ICER vs supportive care	ICER vs generic glatiramer acetate
Interferon β-1a 22 mcg	$341,359	Dominated
Interferon β-1a 44 mcg	$284,135	$10,366,948
Interferon β-1a 30 mcg	$331,381	Dominated
Interferon β-1b (Betaseron)	$214,355	$298,148
Interferon β-1b (Extavia)	$185,369	$148,335
Peginterferon β-1a	$238,321	$417,814

Results - QALYS



DMT	ICER vs supportive care	ICER vs generic glatiramer acetate
Fingolimod	$238,970	$463,009
Dimethyl fumarate	$211,444	$298,242
Teriflunomide 14mg	$236,954	Dominated

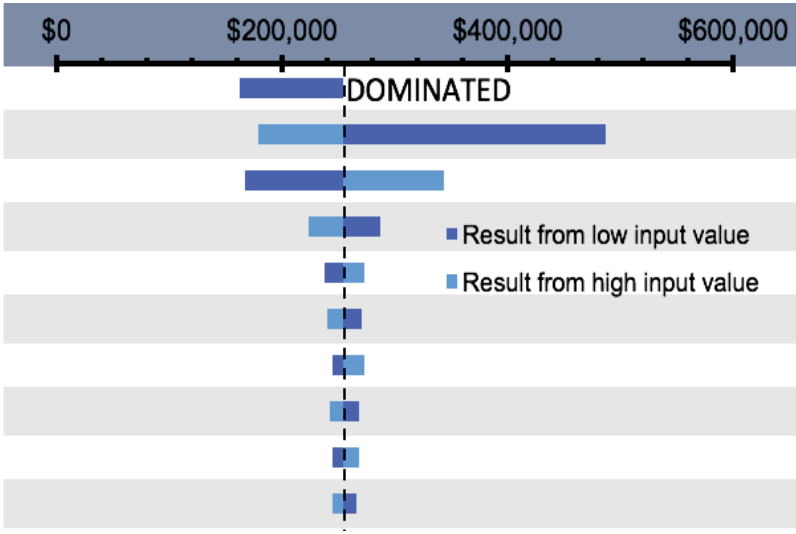
ICER

Results - Relapses

DMT	Cost / Relapse Avoided Compared to Supportive Care	Cost / Relapse Avoided Compared to Glatiramer Acetate 20 mg (Glatopa)
Interferon β-1a 30 mcg (Avonex)	$954,935	DOMINATED
Teriflunomide 7 mg	$410,754	DOMINATED
Interferon β-1b (Betaseron)	$468,100	DOMINATED
Interferon β-1b (Extavia)	$404,801	DOMINATED
Peginterferon beta-1a	$514,656	DOMINATED
Teriflunomide 14 mg	$400,198	DOMINATED
Interferon beta-1a 22 mcg (Rebif)	$430,998	DOMINATED
Interferon beta-1a 44 mcg (Rebif)	$418,760	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$407,877	DOMINATED
Glatiramer acetate 20 mg (Glatopa)	$261,230	--
Dimethyl fumarate	$332,580	$3,269,010
Fingolimod	$276,100	$313,627
Daclizumab	$344,719	$475,000
Natalizumab	$228,597	$196,062
Alemtuzumab	$43,178	DOMINANT

Sensitivity Analysis: Illustrative Example

Cost per Additional QALY for Daclizumab Compared to Generic Glatiramer Acetate 20 mg for RRMS



Parameter	Low Value	High Value
Relative Risk, Progression, DAC	0.36	0.78
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
WAC, DAC	5467	8200
WAC, GA 20 mg (Glatopa)	4155	6233
Discount, GA 20 mg (Glatopa)	0.28	0.42
Annual Utiity, RRMS, EDSS 2	0.62	0.94
Rate Ratio, Relapse, DAC	0.38	0.58
Annual Utiity, RRMS, EDSS 0	0.70	1.05
Age at beginning treatment, RRMS	23	35
Annual Utiity, RRMS, EDSS 1	0.67	1.00

Results were sensitive to relative risks for progression and DMT acquisition costs.

Probabilistic Results

Probability of Each DMT Costing Less than $150,000 per QALY Compared to Supportive Care and Generic Glatiramer Acetate 20 mg

DMT	Compared to Supportive Care	Compared to Glatiramer Acetate 20 mg (Glatopa)
Teriflunomide 7 mg	0.0%	4.4%
Interferon β-1a 22 mcg (Rebif)	0.1%	2.2%
Interferon β-1a 30 mcg (Avonex)	0.0%	1.5%
Teriflunomide 14 mg	0.0%	**12.8%**
Interferon β-1a 44 mcg (Rebif)	0.0%	3.2%
Glatiramer acetate 20 mg (Copaxone)	0.0%	--
Glatiramer acetate 20 mg (Glatopa)	**11.1%**	--
Fingolimod	0.2%	7.4%
Interferon β-1b 250 mcg (Betaseron)	5.0%	**27.9%**
Interferon β-1b 250 mcg (Extavia)	**20.9%**	**52.6%**
Dimethyl fumarate	0.6%	**21.4%**
Peginterferon β-1a	0.8%	**11.0%**
Daclizumab	1.5%	7.0%
Natalizumab	3.6%	**19.6%**
Alemtuzumab	**99.9%**	**99.3%**

Other scenario/sensitivity analyses

- NMA results with 24-week only data
  - Many changes but non-influential for daclizumab
- Higher AE rates
  - Minimal changes
- Indirect costs
  - ↑ Costs
  - Non-influential changes
- Remove EDSS 7 stopping rule
    - ↓ Relapses, ↑ Costs, ↑ QALYs
    - Non-influential changes

Limitations

- Lack of 24-week data for all DMTs
- Natural history data out of date
- Lack of consensus on treatment sequencing
- Limited data for PPMS

Summary

- DMTs of interest in this evaluation uniformly and substantially improved health outcomes compared to best supportive care, but demonstrated mixed results compared to generic glatiramer acetate.
- Alemtuzumab consistently demonstrated improved health outcomes and good value compared to both supportive care and generic glatiramer acetate 20 mg.
- In most cases, cost-effectiveness ratios were well above commonly accepted willingness-to-pay thresholds in the U.S. healthcare system.

Appendix Slides

EDSS Distribution of Populations of RRMS and PPMS Patients Entering the Model

EDSS State	RRMS												PPMS
	CONFIRM[1] (n)				DEFINE[2] (n)			OPERA I & II[3] (n)	TOWER & TEMSO[4] (% of n)	CARE II[5] (% of n)	TOTAL		ORATORIO[3] trial
0	13	15	15	18	21	29	24	51	5%	3%	280	4.4%	0.1%
1	78	85	84	77	105	109	104	312	20%	21%	1385	21.8%	0.3%
2	11	94	94	96	112	116	146	504	30%	28%	1805	28.4%	26.5%
3	98	105	99	99	97	82	85	389	21%	25%	1540	24.3%	27.3%
4	50	47	42	46	56	56	42	244	17%	16%	940	14.8%	15.7%
5	13	12	11	14	16	16	14	145	7%	7%	396	6.2%	29.9%
6								10			10	0.2%	0.1%
7												0%	0.0%
8												0%	0.0%
9												0%	0.1%
Total n	263	358	345	350	407	408	415	1655	1493	666	6355		

[1] Fox 2012
[2] Gold 2012
[3] Genentech Data on File.
[4] Sanofi Genzyme. Teriflunomide US adaptation for AMCP dossiers.
[5] Sanofi Genzyme Data on File.

ICER

Natural History ARR by EDSS States, Base Case and Sensitivity Analysis Values

EDSS State	Relapse Rate, RRMS		Relapse Rate, SPMS		Relapse Rate, PPMS	Scenario SA[1]*		Scenario SA[3]	
	Base case[1,2†]	Range for One-Way SA	Base case[1,2†]	Range for One-Way SA		Relapse Rate, RRMS	Relapse Rate, SPMS	Relapse Rate, RRMS	Relapse Rate, SPMS
0	0.71	0.57-0.85				1.26		0.261	
1	0.73	0.58-0.88	0.00	0.00-0.10	0	1.32	0	0.237	0
2	0.68	0.54-0.82	0.47	0.38-0.56	0	1.32	0.91	0.46	0.315
3	0.72	0.58-0.86	0.88	0.70-1.06	0	1.35	1.64	0.495	0.602
4	0.71	0.57-0.85	0.55	0.44-0.66	0	1.36	1.05	0.67	0.515
5	0.59	0.47-0.71	0.52	0.42-0.62	0	1.43	1.27	0.181	0.16
6	0.49	0.39-0.59	0.45	0.36-0.54	0	1.18	1.1	0.15	0.139
7	0.51	0.41-0.61	0.34	0.27-0.41	0	1.23	0.82	0.156	0.104
8	0.51	0.41-0.61	0.34	0.27-0.41	0	1.23	0.82	0.156	0.104
9	0.51	0.41-0.61	0.34	0.27-0.41	0	1.23	0.82	0.156	0.104

*** Rates based on observational data**

† Rates based on trial data

[1] Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;6998:1-11.

[2] Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. *Acta neurologica Scandinavica.* 1982;65(4):248-266.

[3] Hernandez L, Guo S, Kinter E, Fay M. Cost-effectiveness analysis of peginterferon beta-1a compared with interferon beta-1a and glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;19(7):684-695.

Annual Probability of Moving Between EDSS States, RRMS

		EDSS State at End of Year[1]									
		0	1	2	3	4	5	6	7	8	9
EDSS State at Start of Year	0	0.311	0.289	0.312	0.07	0.016	0.001	0	0	0	0
	1	0.178	0.231	0.419	0.127	0.039	0.004	0.001	0	0	0
	2	0.06	0.13	0.493	0.215	0.088	0.011	0.002	0	0	0
	3	0.019	0.055	0.299	0.322	0.241	0.044	0.013	0.003	0.004	0
	4	0.005	0.017	0.127	0.251	0.411	0.121	0.048	0.014	0.007	0
	5	0.001	0.004	0.033	0.096	0.252	0.295	0.211	0.085	0.023	0
	6	0	0.001	0.009	0.034	0.123	0.257	0.329	0.19	0.056	0.001
	7	0	0	0.003	0.013	0.057	0.169	0.309	0.257	0.189	0.004
	8	0	0	0	0	0	0	0	0	0.995	0.005
	9	0	0	0	0	0	0	0	0	0	1

[1] Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain : a journal of neurology.* 2010;133(Pt 7):1914-1929.; Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *The New England journal of medicine.* 2012;367(12):1087-1097.; Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *The New England journal of medicine.* 2012;367(12):1098-1107.; Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;6998:1-11.

Annual Probability of Conversion from RRMS to SPMS

Initial RRMS EDSS State	Probability of transitioning to SPMS[1]*	Range for SA
0	0	0-0.003
1	0.003	0.002-0.004
2	0.032	0.026-0.038
3	0.117	0.094-0.140
4	0.210	0.168-0.252
5	0.299	0.239-0.359
6	0.237	0.190-0.284
7	0.254	0.203-0.305
8	0.153	0.122-0.184
9*	1.000	0.900-1.000

***In a cycle when a transition from RRMS to SPMS occurs we assumed a 1 level increase in EDSS, except in the case of RRMS EDSS 9, where transition was directly to SPMS 9.**

[1] Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain : a journal of neurology.* 2010;133(Pt 7):1914-1929.; Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;6998:1-11.

Annual Probability of Moving Between EDSS States, SPMS

		EDSS State at End of Year[1]								
		1	2	3	4	5	6	7	8	9
EDSS State at Start of Year	1	0.769	0.154	0.077	0	0	0	0	0	0
	2	0	0.636	0.271	0.062	0.023	0.008	0	0	0
	3	0	0	0.629	0.253	0.077	0.033	0.003	0.005	0
	4	0	0	0	0.485	0.35	0.139	0.007	0.018	0
	5	0	0	0	0	0.633	0.317	0.022	0.026	0.002
	6	0	0	0	0	0	0.763	0.19	0.045	0.002
	7	0	0	0	0	0	0	0.805	0.189	0.006
	8	0	0	0	0	0	0	0	0.926	0.074
	9	0	0	0	0	0	0	0	0	1

[1] Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain : a journal of neurology.* 2010;133(Pt 7):1914-1929.; Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;6998:1-11.

Mortality Multipliers of All-Cause General Population Mortality

EDSS State	Mortality Multiplier[1]*	Range for SA
0	1.00	0.80-1.20
1	1.43	1.15-1.72
2	1.60	1.28-1.92
3	1.64	1.31-1.96
4	1.67	1.34-2.01
5	1.84	1.47-2.21
6	2.27	1.82-2.73
7	3.10	2.48-3.72
8	4.45	3.56-5.34
9	6.45	5.16-7.74
*Calculated using the equation: Multiplier = $0.0219*EDSS^3-0.1972*EDSS^2+0.6069*EDSS+1$		

[1] Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *Journal of insurance medicine (New York, NY).* 1997;29(2):101-106.

Treatment Effect Parameters

Treatment	Relative Risk Disability Progression (Increasing EDSS and RRMS to SPMS)		Rate Ratio for Relapse Rate (for RRMS/SPMS)	
	Base Case	Range for SA	Base Case	Range for SA
Alemtuzumab (Lemtrada)	0.42	0.25-0.68	0.28	0.22-0.35
Daclizumab (Zinbryta)	0.54	0.36-0.78	0.46	0.38-0.58
Dimethyl Fumarate (Tecfidera)	0.62	0.46-0.84	0.53	0.43-0.63
Fingolimod (Gilenya)	0.68	0.51-0.9	0.46	0.39-0.55
Glatiramer acetate 20 mg (Glatopa)	0.74	0.58-0.94	0.63	0.55-0.71
Glatiramer acetate 20 mg (Copaxone)	0.74	0.58-0.94	0.63	0.55-0.71
Interferon β-1a 30 mcg (Avonex)	0.79	0.63-1	0.83	0.74-0.94
Interferon β-1a 22 mcg (Rebif)	0.81	0.52-1.23	0.7	0.55-0.85
Interferon β-1a 44 mcg (Rebif)	0.73	0.52-0.99	0.64	0.54-0.73
Interferon β-1b 250 mcg (Betaseron)	0.66	0.46-0.89	0.65	0.55-0.77
Interferon β-1b 250 mcg (Extavia)	0.66	0.46-0.89	0.65	0.55-0.77
Natalizumab (Tysabri)	0.56	0.37-0.84	0.31	0.25-0.4
Ocrelizumab (Ocrevus) (RRMS)	0.47	0.28-0.76	0.35	0.27-0.44
Ocrelizumab (Ocrevus) (PPMS)[1]	0.75	0.58-0.98	N/A	
Peginterferon β-1a (Plegridy)	0.63	0.37-1.02	0.63	0.47-0.86
Teriflunomide 7 mg (Aubagio)	0.86	0.63-1.14	0.77	0.67-0.93
Teriflunomide 14mg (Aubagio)	0.72	0.52-0.97	0.67	0.56-0.79

[1] Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *New England Journal of Medicine.* 2017;376(3):209-220.

Supportive Care, Indirect, and Relapse Costs

EDSS State	Annual Direct Costs (2016 $)[1]	*Annual Indirect Costs (2016 $)[1]**
0	$2,825	*$10,711*
1	$4,856	*$14,653*
2	$6,887	*$18,595*
3	$8,917	*$22,537*
4	$10,948	*$26,480*
5	$12,979	*$30,422*
6	$15,010	*$34,364*
7	$17,041	*$38,306*
8	$19,071	*$42,249*
9	$21,102	*$46,191*

Average relapse cost (per event):
$2,692 in direct costs
$2,339 in indirect costs

[1] Extrapolated from Figure 2 of Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: A cross-sectional study in the United States. *Neurology.* 2006;66:1696-1702.
* Used in sensitivity analysis only

Lab and Utilization Costs

Category	Cost*	Variable name	Source
Infusion cost (1st hour), CPT 96365	$70		Source: physician fee schedule 2016[1]
Infusion cost/hr (2+ hours), CPT 96366	$19		Source: physician fee schedule 2016[1]
Complete blood count, CPT 85025	$14	c_blood	Source: lab fee schedule 2016[2]
Serum Creatinine, CPT 80053	$19	c_creatinine	Source: lab fee schedule 2016[2]
Urinalysis, CPT 81000	$6	c_urine	Source: lab fee schedule 2016[2]
Thyroid, CPT 84436+84479	$25	c_thyroid	Source: lab fee schedule 2016[2]
Liver, CPT 80076	$15	c_liver	Source: lab fee schedule 2016[2]
MRI, CPT 70543	$495	c_MRI	Source: physician fee schedule 2016[1]
ECG, CPT 93000	$17	c_ecg	Source: physician fee schedule 2016[1]
ALT, CPT 84460	$10	c_ALT	Source: lab fee schedule 2016[2]
CD4 lymphocyte, CPT 86360	$87	c_cd4	Source: lab fee schedule 2016[2]
PML, ICD diagnosis code 046.3	$23,445		HCUP costs, 2012 data, accessed on July 6, 2015 by AbbVie, adjusted to 2016 USD using multiplier 1.0363629[1]
Hospital stay for disorders of the biliary without complications, DRG 446	$4,477		Source: physician fee schedule 2016[1]
Inpatient stay for depression, DRG 881	$3,884		Source: physician fee schedule 2016[1]
Hospital stay for influenza/pneumonia, DRG 194	$5,687		Source: physician fee schedule 2016[1]
Serious infection, DRG 177	$11,177		Source: physician fee schedule 2016[1]
Cranial nerve disorder, DRG 073	$7,829		Source: physician fee schedule 2016[1]
Specialist visit, CPT 99215	$112	c_office	Source: physician fee schedule 2016[1]
*varied ± 20% in sensitivity analysis			

[1] Center for Medicare and Medicaid Services. 2016 National Physician Fee Schedule Relative Value File January Release. 2016.
[2] Center for Medicare and Medicaid Services. 2016 Clinical Diagnostic Laboratory Fee Schedule 2016.
[3] Abbvie. Data on File.

ICER

DMT Administration Costs

DMT	Administration instructions	Annual administration cost*	
		Year 1	Subsequent years
Alemtuzumab	Infusion over 4 hours; 5 infusions year 1, 3 infusions subsequent years	$634	$380
Ocrelizumab (PPMS)	Infusion of 300 mg given over 150 minutes (4.35 infusions per year)	$427	$427
Ocrelizumab (RRMS)	Dose 1: infusion of 300 mg given over 150 minutes (2 infusions year 1) Dose 2+: For each cycle, it is necessary to prepare two infusion bags. Infusions of bag 1 and bag 2 given over 240 minutes (2 infusions year 1, 2.17 infusions subsequent years)	$450	$275
Natalizumab	Infusion over 1 hour, 13.04 infusions per year	$910	$910
***Varied ±20% in sensitivity analysis**			

DMT monitoring costs

Product Name	Monitoring instructions	Implemented as (annual)	Annual monitoring cost†		
			Year 1	Subsequent years	After discontinuation
Alemtuzumab	blood, urine, CD4 lymphocyte, and serum cr, (prior to treatment initiation and at monthly intervals thereafter), A test of thyroid function, such as thyroid stimulating hormone (TSH) level (prior to treatment initiation and every 3 months thereafter); must continue for 4 years after your last infusion	N/A	$0*	$0*	$0*
Daclizumab	Test transaminase levels and total bilirubin monthly, follow monthly for 6 months after the last dose	12*c_liver annual 6*c_liver after discontinuation	$180	$180	$90
Fingolimod	First Dose Monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of observation period required. LFT every 6 months, CBC test every 2 months	2*c_liver +6*c_blood +2*c_ecg +c_office year 1 2*c_liver +6*c_blood subsequent	$262	$116	N/A
Glatiramer acetate 20 mg (Copaxone)	None	N/A	$0	$0	N/A
Glatiramer Acetate 20 mg (Glatopa)	None	N/A	$0	$0	N/A
Interferon β-1a 30 mcg (Avonex)	Blood cell counts and liver function tests are recommended at regular intervals (1, 3,and 6 months) and then periodically (2x/yr) thereafter	3*(c_blood+c_liver) year 1 2*(c_blood+c_liver) subsequent	$88	$59	N/A
Interferon β-1a 22/44 mcg (Rebif)	blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) and then periodically (2x/yr) thereafter	3*(c_blood+c_liver) year 1 2*(c_blood+c_liver) subsequent	$88	$59	N/A
Interferon β-1b 250 mcg (Betaseron)	Blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) and then periodically (2x/yr) thereafter	3*(c_blood+c_liver) year 1 2*(c_blood+c_liver) subsequent	$88	$59	N/A
Interferon β-1b 250 mcg (Extavia)	Blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) and then periodically (2x/yr) thereafter	3*(c_blood+c_liver) year 1 2*(c_blood+c_liver) subsequent	$88	$59	N/A
Dimethyl Fumarate	Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy; CBC every 6 months	6*c_blood	$29	$29	N/A
Natalizumab	MRI every 6 months CBC+ LFT every month	2*c_MRI +12*c_liver	$1,171	$1,171	N/A
Ocrelizumab (RRMS)	None	N/A	$0	$0	N/A
Ocrelizumab (PPMS)	None	N/A	$0	$0	N/A
Peginterferon β-1a	CBC and liver function every 6 months	2*(c_blood+c_liver)	$59	$59	N/A
Teriflunomide	CBC and LFTs within 6 months prior to starting teriflunomide. ALT level (not a full LFT panel) monthly for 6 months after starting therapy.	c_blood +c_liver +6* c_ALT year 1	$88	$0	N/A

*All monitoring costs paid by manufacturer

ICER

Results – Scenario, no 2nd line

Drug	Cost	Relapses	Life-Years	QALYs	ICER	
RRMS					vs. supportive care	vs. generic GA
Supportive Care	$333,273	16.4	21.4	5.7	--	--
Teriflunomide 7mg	$665,537	15.9	21.5	6.2	$659,163	Lower costs, lower QALYs
Teriflunomide 14mg	$670,593	15.9	21.6	6.7	$343,314	Lower costs, lower QALYs
Interferon beta-1a 22mcg (Rebif®)	$890,229	15.4	21.7	6.8	$498,451	DOMINATED
Interferon beta-1a (Avonex®)	$899,034	16.3	21.7	7.0	$439,012	DOMINATED
Dimethyl fumarate	$743,487	15.5	21.8	7.3	$266,020	DOMINATED
Interferon beta-1a 44mcg (Rebif®)	$906,938	15.3	21.8	7.3	$357,396	DOMINATED
Glatiramer acetate 20mg (Copaxone®)	$985,481	15.1	21.8	7.5	$367,827	DOMINATED
Glatiramer acetate 20mg (Glatopa™)	$688,156	15.1	21.8	7.5	$200,145	--
Fingolimod	$898,122	14.4	21.8	7.7	$290,414	$1,221,854
Peginterferon beta-1a	$914,038	15.7	21.9	7.8	$272,000	$623,928
Interferon beta-1b (Betaseron®)	$898,787	15.5	22.0	8.2	$224,281	$281,473
Interferon beta-1b (Extavia®)	$800,794	15.5	22.0	8.2	$185,417	$150,522
Natalizumab	$1,080,329	13.1	22.2	9.1	$218,668	$238,655
Ocrelizumab	--	13.7	22.4	10.0	--	--
Daclizumab	$1,386,270	13.6	22.6	10.3	$227,489	$244,468
Alemtuzumab	$440,283	11.4	23.0	12.1	$16,826	DOMINANT

Results – Scenario, all 2nd line

Drug	Cost	Relapses	Life-Years	QALYs	ICER	
RRMS					vs. supportive care	vs. generic GA
Supportive Care	$333,273	16.4	21.4	5.7	--	--
Teriflunomide 7mg	$948,338	15.2	21.8	7.4	$375,543	DOMINATED
Interferon beta-1a 22mcg (Rebif®)	$1,085,338	14.9	21.8	7.6	$401,605	DOMINATED
Interferon beta-1a (Avonex®)	$1,068,039	15.8	21.9	7.6	$380,346	DOMINATED
Teriflunomide 14mg	$965,537	15.1	21.9	7.8	$296,232	DOMINATED
Interferon beta-1a 44mcg (Rebif®)	$1,111,119	14.8	22.0	8.1	$326,515	DOMINATED
Glatiramer acetate 20mg (Copaxone®)	$1,156,926	14.6	22.0	8.1	$340,255	DOMINATED
Glatiramer acetate 20mg (Glatopa™)	$865,186	14.6	22.0	8.1	$219,736	--
Dimethyl fumarate	$1,031,486	14.8	22.0	8.4	$264,174	$748,059
Fingolimod	$1,118,498	13.9	22.0	8.5	$282,950	$714,680
Peginterferon beta-1a	$1,138,434	15.1	22.1	8.7	$270,648	$493,008
Interferon beta-1b (Betaseron®)	$1,057,500	15.0	22.2	8.8	$233,849	$284,368
Interferon beta-1b (Extavia®)	$960,959	15.0	22.2	8.8	$202,677	$141,617
Natalizumab	$1,267,442	12.6	22.3	9.8	$228,294	$240,691
Ocrelizumab	--	13.1	22.6	10.6	--	--
Daclizumab	$1,483,749	13.2	22.6	10.7	$231,437	$242,543
Alemtuzumab	$555,463	11.0	23.1	12.4	$33,026	DOMINANT

Results – Scenario, 10% discontinuation

Drug	Cost	Relapses	Life-Years	QALYs	ICER	
RRMS					vs. supportive care	vs. generic GA
Teriflunomide 7mg	$999,395	14.8	21.9	7.7	$333,209	DOMINATED
Interferon beta-1a 22mcg (Rebif®)	$1,033,631	14.6	21.9	8.0	$308,691	DOMINATED
Interferon beta-1a (Avonex®)	$993,762	15.4	22.0	8.0	$286,547	DOMINATED
Glatiramer acetate 20mg (Copaxone®)	$1,055,030	14.5	22.0	8.4	$270,247	DOMINATED
Glatiramer acetate 20mg (Glatopa™)	$838,484	14.5	22.0	8.4	$189,166	--
Interferon beta-1a 44mcg (Rebif®)	$1,051,477	14.6	22.0	8.4	$265,454	$6,113,234
Teriflunomide 14mg	$1,029,219	14.7	22.0	8.5	$253,026	$2,391,198
Interferon beta-1b (Betaseron®)	$960,623	14.8	22.1	8.8	$203,886	$300,667
Interferon beta-1b (Extavia®)	$896,200	14.8	22.1	8.8	$182,949	$142,077
Fingolimod	$1,059,927	13.7	22.1	8.9	$228,324	$432,648
Peginterferon beta-1a	$1,081,894	14.8	22.2	9.0	$230,373	$420,493
Dimethyl fumarate	$1,077,157	14.2	22.2	9.1	$217,383	$317,691
Natalizumab	$1,096,684	13.3	22.3	9.5	$199,996	$225,225
Daclizumab	$1,112,417	14.0	22.3	9.5	$203,267	$235,665
Ocrelizumab	--	13.6	22.4	10.0	--	--
Alemtuzumab	$807,245	13.4	22.4	10.2	$105,249	DOMINANT
PPMS					vs. supportive care	vs. generic GA
Ocrelizumab	$677,193	--	16.0	3.2	$897,603	--

Manufacturer Public Comment and Discussion

Speakers

Name	Title	Company
Mark Rametta, DO, FACOI, FACP	Medical Director, US Medical Affairs, Neurology	Bayer
Terrie Livingston, PharmD	Senior Director, US Medical	Biogen
Kathleen Hawker, MD	VP, Neurology and Immunology US Medical Affairs	EMD Serono
Peter S. Chin, MD, MSHS	Group Medical Director, Neuroscience	Genentech
Norman Putzki, MD	VP & Head of Medical Business Unit, Neuroscience	Novartis
Laura Saltonstall, MD, MBA	Senior Medical Director, US Medical Affairs	Sanofi-Genzyme
Scott Kolodny, MD	Sr. Global Medical Director, MS	Teva Pharmaceuticals

Public Comment and Discussion

Kathleen Costello, MS
National MS Society

Vice President, Healthcare Access

Conflicts of interest:

- No personal conflicts declared

The National MS Society receives less than 25% of its overall funding through contributions from pharmaceutical companies.

Jeffrey English, MD; MS Center of Atlanta

Director of Clinical Research

Conflicts of interest:

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000
- Manufacturer support of research in the clinical area of this meeting

The MS Center of Atlanta has conducted research for:

- Biogen
- EMD Serono
- Genzyme
- Genentech
- Teva
- Novartis

Dr. English has served on Advisory Boards, performed group and independent consulting, and has been a speaker for the following companies in the previous year:

- Biogen
- EMD Serono
- Genzyme
- Genentech
- Teva

Edward Fox, MD, PhD
Central Texas Neurology Consultants
Director

Conflicts of interest:

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000
- Manufacturer support of research in the clinical area of this meeting in which you are participating

Dr. Fox has been compensated for advisory, consultant, and/or speaker's bureau positions by:

- Acorda
- Bayer
- Biogen
- EMD Serono
- Roche Genentech
- Novartis
- Sanofi-Genzyme

Dr. Fox has received research support from:

- Acorda
- Biogen
- Chugai
- EMD Serono
- Roche Genentech
- Novartis
- Sanofi-Genzyme
- Teva

Lunch
Meeting will resume at 12:45 pm

Voting Questions

Test Voting Question

Q1. Which President wore a lock of Abraham Lincoln's hair to his own inauguration?

A. Theodore Roosevelt

B. Franklin D. Roosevelt

C. Dwight Eisenhower

D. William H. Taft

Oral Agents for RRMS
Clinical Evidence
Dimethyl Fumarate vs. Teriflunomide

Q1. For patients with relapsing-remitting multiple sclerosis (RRMS), is the evidence adequate to demonstrate that the net health benefit of **dimethyl fumarate (Tecfidera®, Biogen Inc.)** is greater than that of **teriflunomide 14 mg (Aubagio®, Sanofi-Genzyme, Inc.)**?

Yes No

Oral Agents for RRMS
Clinical Evidence
Fingolimod vs. Teriflunomide

Q2. For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of **fingolimod (Gilenya®, Novartis, Inc.)** is greater than that of **teriflunomide 14 mg**?

Yes No

Oral Agents for RRMS
Clinical Evidence
Dimethyl Fumarate vs. Fingolimod

Q3. For patients with RRMS, is the evidence adequate to distinguish the net health benefit between **dimethyl fumarate** and **fingolimod**?

Yes No

Emerging Agents for RRMS
Clinical Evidence
Daclizumab vs. Dimethyl Fumarate / Fingolimod

Q4. For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of **daclizumab (Zinbryta®, Biogen Inc. and AbbVie Inc.)** is greater than that of **dimethyl fumarate or fingolimod**?

Yes No

Emerging Agents for RRMS
Clinical Evidence
Daclizumab vs. Generic Glatiramer Acetate 20 mg

Q5. For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of **daclizumab** is greater than that of **generic glatiramer acetate 20 mg (Glatopa®, Sandoz, Inc.)**?

Yes No

Emerging Agents for RRMS
Clinical Evidence
Ocrelizumab vs. Generic Glatiramer Acetate 20 mg

Q6. For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of **ocrelizumab (Ocrevus®, Roche Genentech Inc.)** is greater than that of **generic glatiramer acetate 20 mg**?

Yes No

Emerging Agents for RRMS
Clinical Evidence
Rebif vs. Avonex

Q7. For patients with RRMS, is the evidence adequate to demonstrate that that the net health benefit of treatment with **interferon β-1a 44 mcg (Rebif®, EMD Serono Inc.)** is greater than that of treatment with **interferon β-1a 30 mcg (Avonex®, Biogen Inc.)**?

Yes No

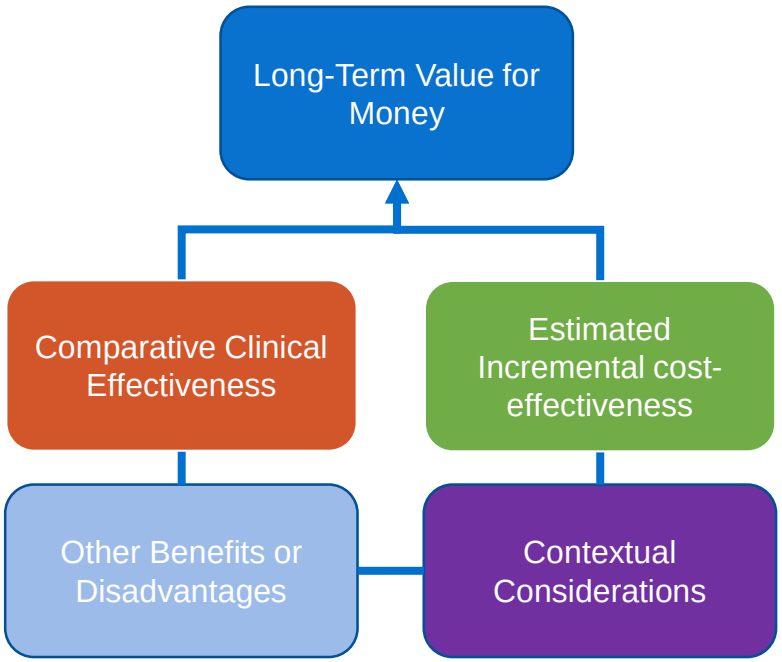
Emerging Agents for RRMS: Long-Term Value for Money Daclizumab vs. Generic Glatiramer Acetate 20 mg

Q8. Given the available evidence for patients with RRMS, what is the long-term value for money of treatment with **daclizumab** versus treatment with **generic glatiramer acetate 20 mg?**

A. Low

B. Intermediate

C. High



Emerging Agents for PPMS
Clinical Evidence
Ocrelizumab vs. Best Supportive Care

Q9. For patients with primary progressive multiple sclerosis (PPMS), is the evidence adequate to demonstrate that the net health benefit of treatment with **ocrelizumab** is greater than that of **best supportive care**?

Yes No

Oral Agents for RRMS
Clinical Evidence
Dimethyl Fumarate vs. Fingolimod

Q3a. For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of **dimethyl fumarate** is greater than that of **fingolimod**?

Yes No

Oral Agents for RRMS
Clinical Evidence
Dimethyl Fumarate vs. Fingolimod

Q3b. For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of **fingolimod** is greater than that of **dimethyl fumarate**?

Yes No

Break
Meeting will resume at 2:30 pm

Policy Roundtable

Policy Roundtable

Name	Title	COI Declaration
Sara Alvarez, PharmD, BCPS	Manager of Pharmacoeconomic Evaluations, UnitedHealthcare	**UHC Employee**
Peter Chin, MD, MSHS	Group Medical Director for Neuroscience, USMA, Genentech Inc.	**Genentech Employee**
David Jones, MD	Assistant Professor of Neurology, UVA; MS Section Chair, AAN	**Honoraria**: Biogen, Genentech (<$5k each) **Salary Support**: Consortium of MS Centers (CMSC), Biogen (PI of clinical trial) **Board Position**: CMSC, Can Do MS
Annette Langer-Gould, MD, PhD, MS	Research Scientist, Kaiser Permanente Department of Research and Evaluation; MS Specialist, Los Angeles Medical Center	None
Bari Talente, JD	Executive Vice President, Advocacy, National MS Society	None
Philip Posner, PhD	MS Patient	None
John Yao, MD, MPH, MBA, MPA, FACP	Staff Vice President of Medical Policy and Technology Assessment, Anthem	**Anthem Employee**

CTAF Panel Reflections

Summary and Closing Remarks

Adjourn