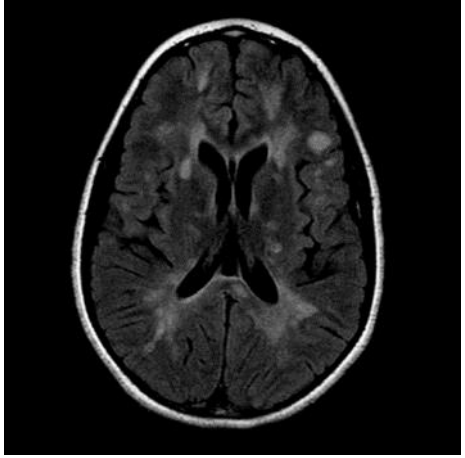


Clinical vs MRI as determinants of treatment efficacy

Oral options

Pediatric challenges

Diagnosis and Treatment of Pediatric MS

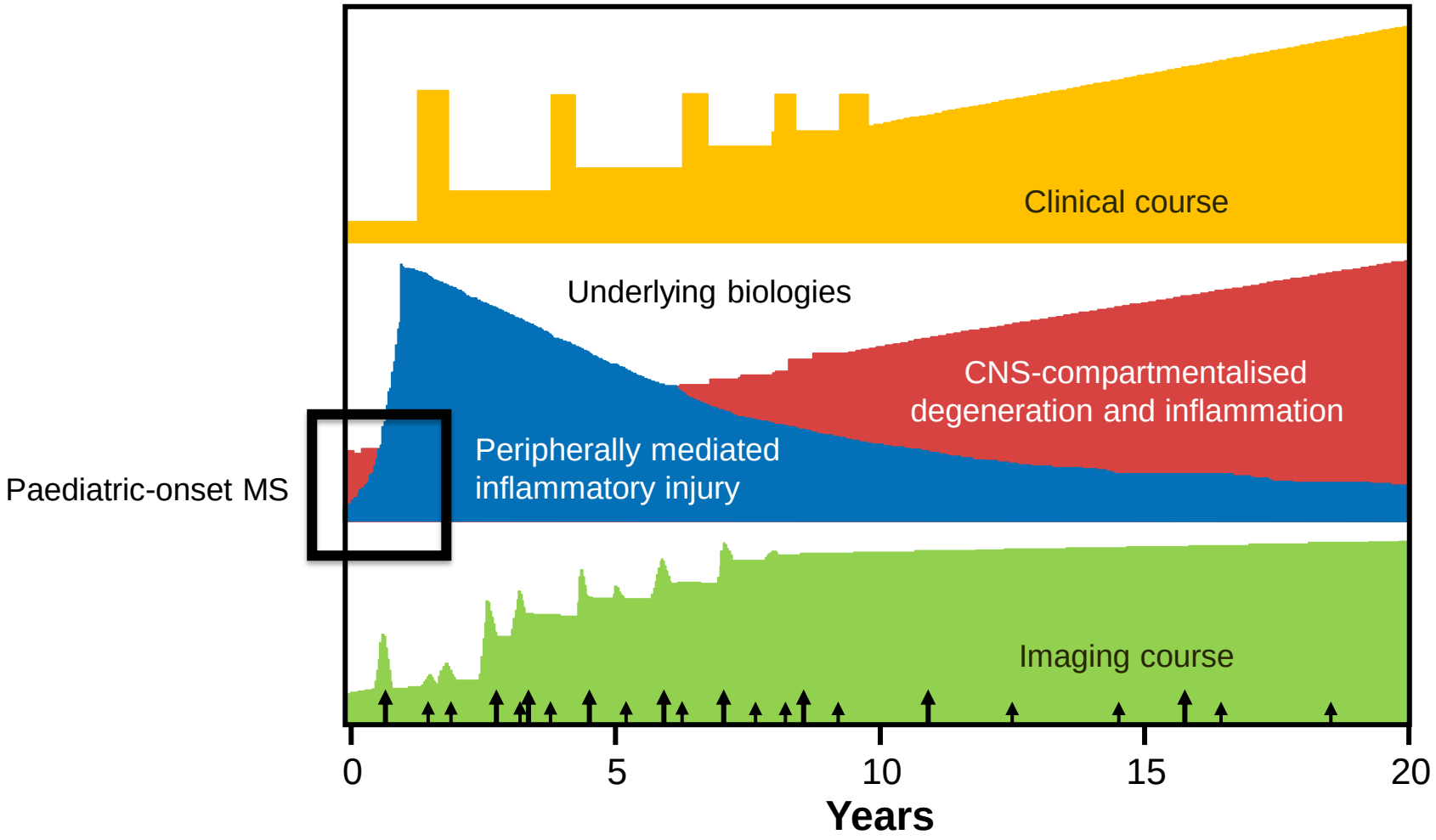
Disclosures

- Dr. Banwell has served as a consultant to Novartis in the capacity of a central MRI reviewer
- Dr. Banwell serves as a non-remunerated member of Advisory boards for Biogen-IDEC, Sanofi, Novartis, and TevaNeuroscience

Objectives

- To review current diagnostic criteria for pediatric MS
- To present current treatment options
- To highlight ongoing clinical trials
- To propose key areas for future priorities for pediatric MS management

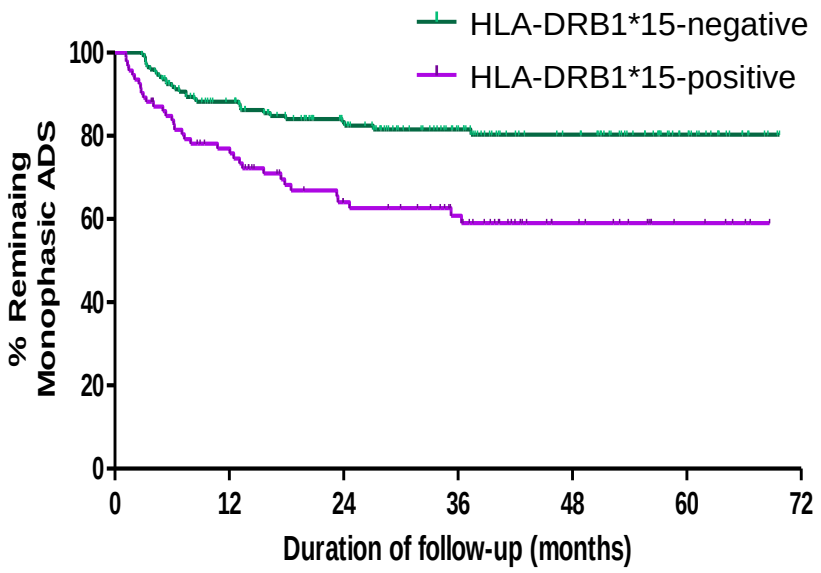
Paediatric-onset MS and adult-onset MS are part of the same disease continuum



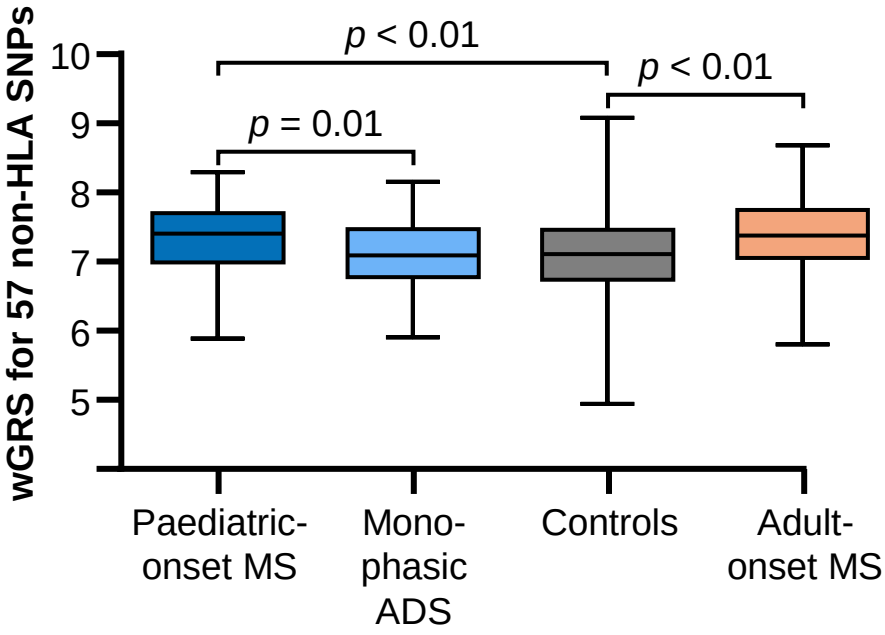
CNS, central nervous system.
Bar-Or A. *Semin Neurol* 2008; 28:29–45.

Genetic determinants confer increased risk of paediatric-onset MS

Time to MS diagnosis in children following ADS as a function of HLA-DRB1*15 status[1]



Distribution of genetic parameters in patients and controls[2]



DRB1*15-positive children had a greater propensity to be diagnosed with MS (p = 0.0004)[1]

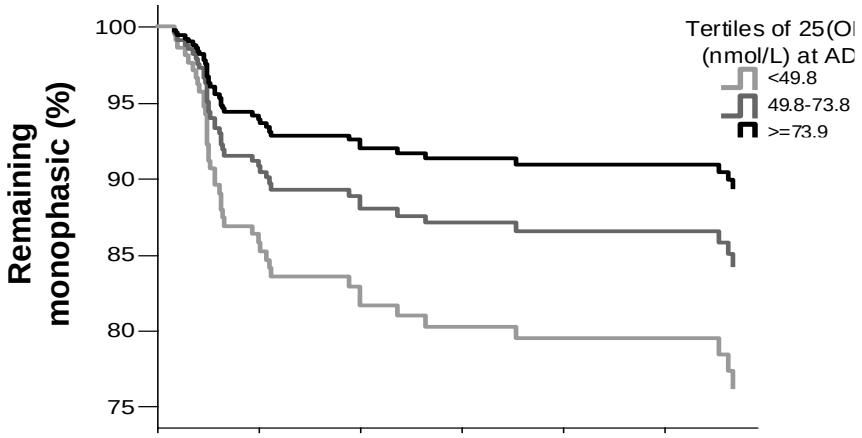
MS risk alleles are associated with paediatric-onset MS but not monophasic ADS[2]

ADS, acquired demyelinating syndrome; HLA, human leukocyte antigen; SNP, single nucleotide polymorphism; wGRS, weighted genetic risk score.

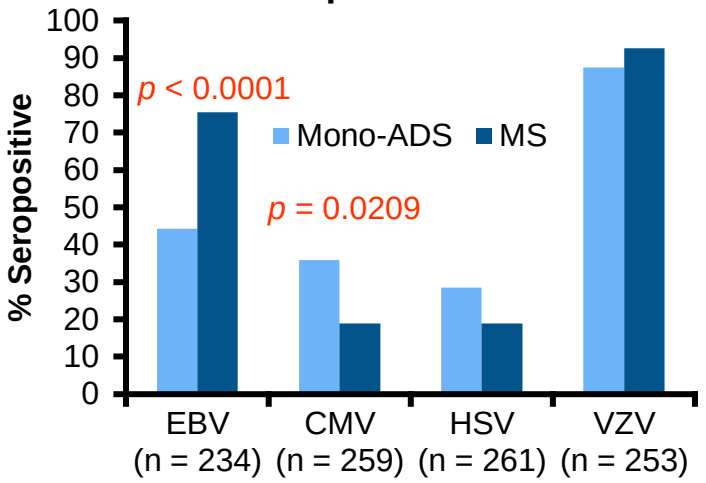
1. Disanto G, *et al. Neurology* 2011; 76:781–786; 2. van Pelt ED, *et al. Neurology* 2013; 81:1996–2001.

Environmental risk factors play a role in paediatric-onset MS

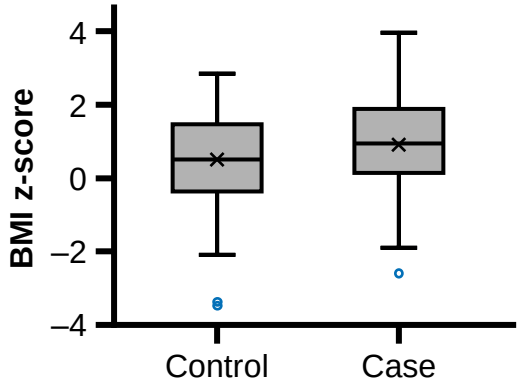
Sunlight and vitamin D[1]



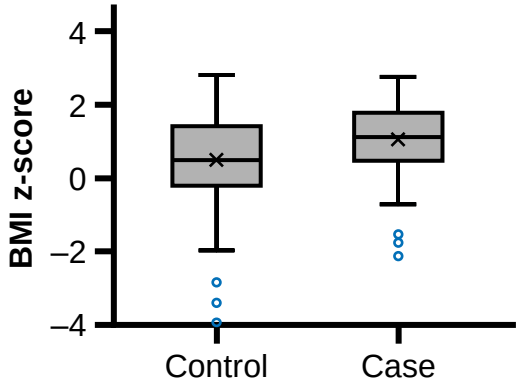
Viral seroprevalence rates[1]



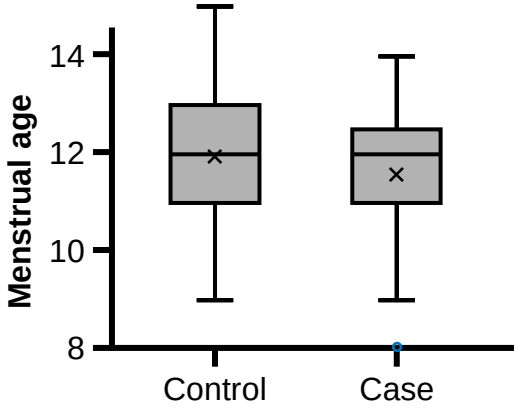
Boys BMI z-scores[2]



Girls BMI z-scores[2]



Girls Menstrual age[2]



ADS, acquired demyelinating syndrome; BMI, body mass index; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; VZV, varicella zoster virus.
1. Speaker's own data, unpublished; 2. Chitnis T, *et al. Ann Clin Transl Neurol* 2016; 3:897–907.

MRI Features that best identify children with MS

Importance	Feature	MS	Non-MS	MS vs non-MS	Sens.	Spec.	PPV	NPV
1	≥ 1 T1 lesion present (Black Hole)	63/71 (89%)	28/251 (11%)	2.3×10^{-22}	0.69 (0.59,0.78)	0.97 (0.93,0.98)	0.89 (0.79,0.95)	0.89 (0.84,0.92)
2	Perpendicular to major axis of corpus callosum	49/71 (69%)	22/253 (9%)	1.9×10^{-20}	0.69 (0.57,0.79)	0.91 (0.87,0.94)	0.69 (0.57,0.79)	0.91 (0.87,0.94)
3	≥ 1 Contrast enhancing lesion	45/64 (70%)	21/233 (9%)	5.6×10^{-19}	0.68 (0.56,0.79)	0.92 (0.87,0.95)	0.70 (0.58,0.81)	0.91 (0.87,0.94)
4	Periventricular lesions N = 0	11/71 (15%)	184/253(73%)	6.5×10^{-14}	0.06 (0.03,0.10)	0.53 (0.45,0.62)	0.15 (0.08,0.26)	0.27 (0.22,0.33)
5	Oligoclonal bands	31/44 (70%)	22/148 (15%)	8.9×10^{-11}	0.58 (0.44,0.72)	0.91 (0.85,0.95)	0.70 (0.55,0.83)	0.85 (0.78,0.90)
6	Anti-MOG antibod						08 (0.04,0.15)	0.73 (0.66,0.79)
7	Intracallosal lesic						48 (0.36,0.60)	0.89 (0.85,0.93)
8	≥ 15 T2 Lesions						48 (0.36,0.60)	0.72 (0.66,0.78)
9	PV N = 2						15 (0.08,0.26)	0.95 (0.92,0.98)
10	Gyral projection						08 (0.03,0.17)	0.89 (0.85,0.93)
11	Other Cerebral white mat						32 (0.71,0.90)	0.66 (0.60,0.72)
12	Infratentorial						52 (0.50,0.73)	0.58 (0.52,0.65)
13	PV N > 3						46 (0.35,0.59)	0.88 (0.84,0.92)
14	Thalamic lesion						15 (0.08,0.26)	0.75 (0.69,0.80)
15	≥ 1 Non-enhancing l						86 (0.75,0.93)	0.46 (0.39,0.53)
16	Juxtacortical						77 (0.66,0.87)	0.62 (0.56,0.68)
17	Internal capsule les						27 (0.17,0.39)	0.83 (0.78,0.88)
18	>9 T2 lesions						51 (0.48,0.72)	0.67 (0.61,0.73)
19	Spine						71 (0.49,0.87)	0.23 (0.16,0.32)
20	Optic nerve T2 hyperintensity	8/13 (62%)	19/34 (56%)	0.73	0.30 (0.14,0.50)	0.75 (0.51,0.91)	0.62 (0.32,0.86)	0.44 (0.27,0.62)
21	PV N = 1	9/71 (13%)	16/253 (6%)	0.082	0.36 (0.18,0.57)	0.79 (0.74,0.84)	0.13 (0.06,0.23)	0.94 (0.90,0.96)
22	Basal ganglia lesion	7/71 (10%)	47/253 (19%)	0.087	0.13 (0.05,0.25)	0.76 (0.71,0.81)	0.10 (0.04,0.19)	0.81 (0.76,0.86)
23	PV N = 3	7/71 (10%)	12/253 (5%)	0.11	0.37 (0.16,0.62)	0.79 (0.74,0.83)	0.10 (0.04,0.19)	0.95 (0.92,0.98)
24	Diencephalic lesion	10/71 (14%)	38/253 (15%)	0.84	0.21 (0.10,0.35)	0.78 (0.73,0.83)	0.14 (0.07,0.24)	0.85 (0.80,0.89)
25	≥ 1 T2 lesion present	67/71 (94%)	151/253(60%)	4.8×10^{-6}	0.31 (0.25,0.37)	0.96 (0.91,0.99)	0.94 (0.86,0.98)	0.40 (0.34,0.47)
26	Optic nerve contrast enhancement	4/11 (36%)	16/32 (50%)	0.44	0.20 (0.06,0.44)	0.70 (0.47,0.87)	0.36 (0.11,0.69)	0.50 (0.32,0.68)

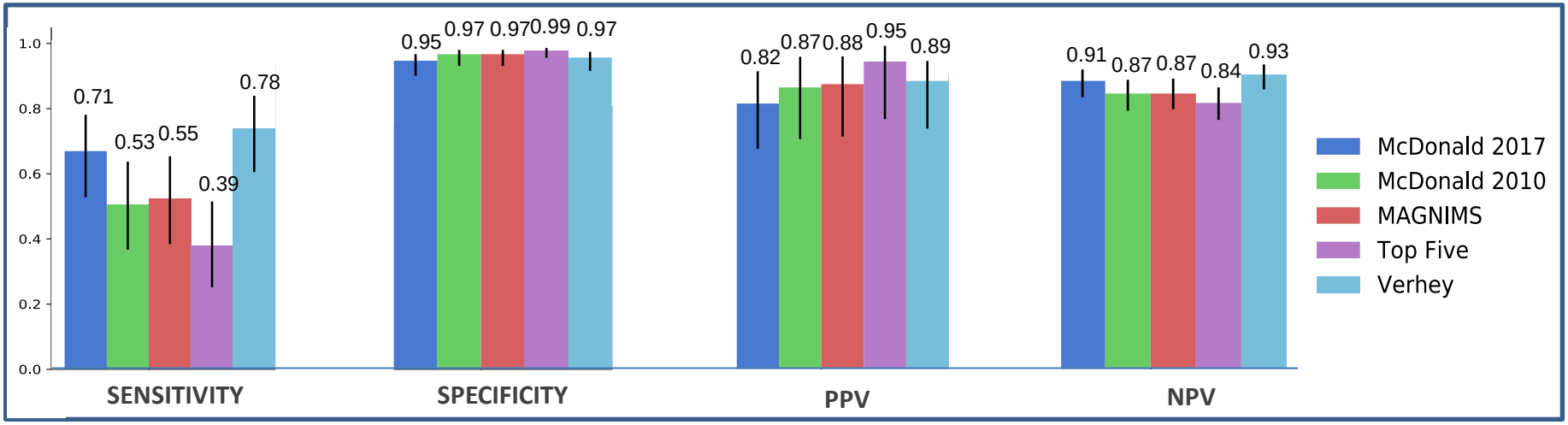
Importance	Feature
1	≥ 1 T1 lesion present (Black Hole)
2	Perpendicular to major axis of corpus callosum
3	≥ 1 Contrast enhancing lesion
4	At least one periventricular lesion
5	Oligoclonal bands
6	Absence of anti-MOG antibodies

MS diagnostic criteria performance in children

McDonald 2017	McDonald 2010	MAGNIMS 2016	Top 5 features	Verhey 2011
DIS: ≥2 T2 lesions: ≥1 PV ≥1 (Cortical/)Juxtacortical ≥1 Infratentorial ≥1 Spinal cord DIT: ≥1 Gd+ ≥1 Gd- Or CSF-OCBs	DIS: ≥2 T2 lesions: ≥1 PV ≥1 Juxtacortical ≥1 Infratentorial ≥1 Spinal cord DIT: ≥1 Gd+ asympto ≥1 Gd- asympto	DIS: ≥2 T2 lesions: ≥3 PV ≥1 (Cortical/)Juxtacortical ≥1 Infratentorial ≥Spinal cord ≥1 Optic nerve DIT: ≥1 Gd+ asympto ≥1 Gd- asympto	DIS: All of: ≥1 Black Hole ≥1 PV ≥1 Gd+ Anti-MOG- DIT: CSF-OCBs	Both of: ≥1 PV ≥1 Black Hole

2017 MS diagnostic criteria perform well in children

McDonald 2017	McDonald 2010	MAGNIMS 2016	Top 5 features	Verhey 2011
Proportion of Participants Meeting Criteria				
MS (36/51) 71%	MS (27/51) 53%	MS (28/51) 55%	MS (20/51) 39%	MS (40/51) 78%
Non-MS (8/160) 5%	Non-MS (4/160) 3%	Non-MS (4/160) 3%	Non-MS (1/160) 1%	Non-MS (5/160) 3%

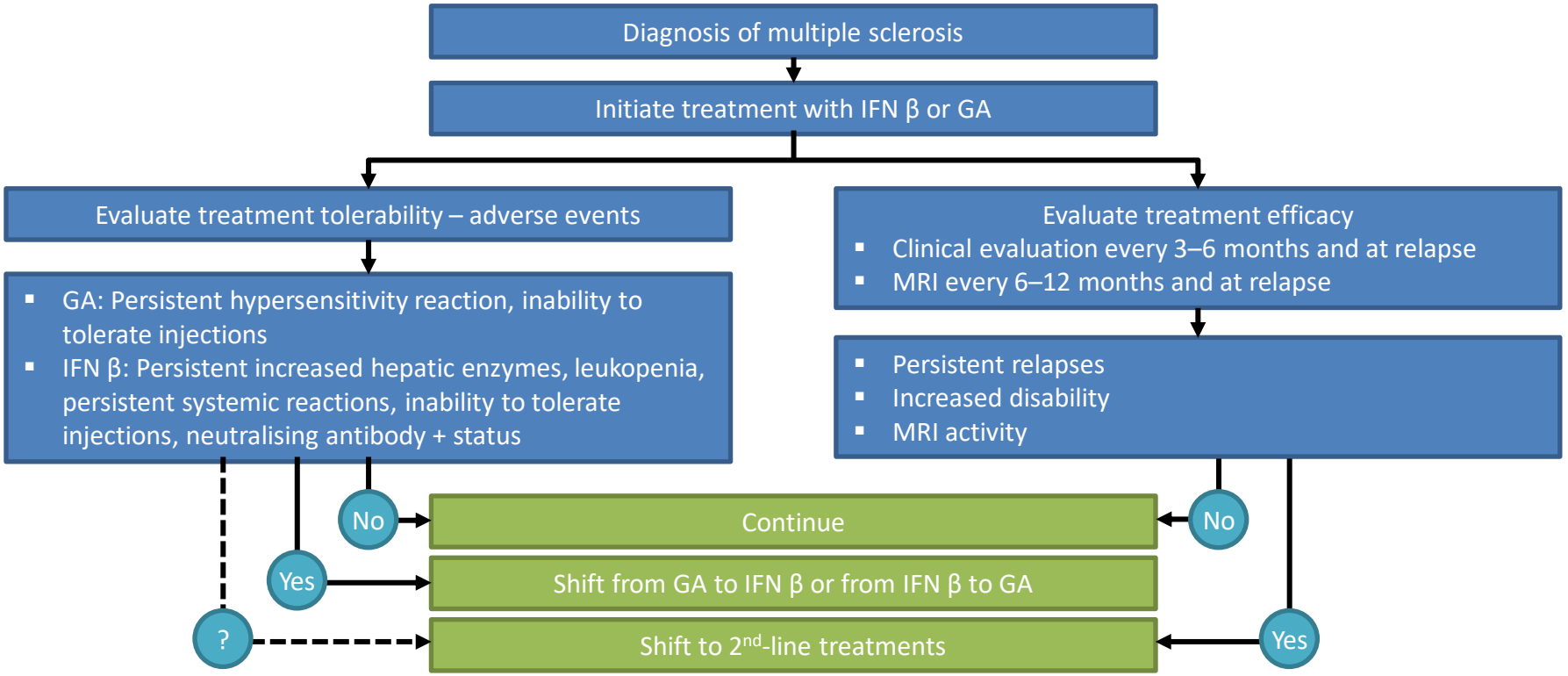


16 available disease-modifying therapies for relapsing forms of MS in the U.S.

Drug class	Brands	Route	FDA approval
beta-interferon	Avonex, Betaseron, Extavia, Plegridy, Rebif	injectable	1996-2014
glatiramer acetate	Copaxone 20/40, Glatopa	injectable	1999
mitoxantrone	Novantrone	intravenous	2000
natalizumab	Tysabri	intravenous	2006/8
fingolimod	Gilenya	oral	2011 (adults 2018 (peds)
dimethyl fumarate	Tecfidera	oral	2013
teriflunomide	Aubagio	oral	2013
alemtuzumab	Lemtrada	intravenous	2014
rituximab	Rituxan	Intravenous	-
daclizumab	Zinbryta	Intravenous	2016
Ocrelizumab	Ocrevus	Intravenous	2017

Slide generously provided by Dr. T. Chitnis, Chair IPMSSG

Current approach to treating children with MS



[a] **There are currently no fully approved therapies for the treatment of paediatric MS. Information regarding off-label use of medications must not be interpreted as a recommendation to prescribe.**
Ghezzi A, *et al. Neurology* 2016; 87:S97–S102.

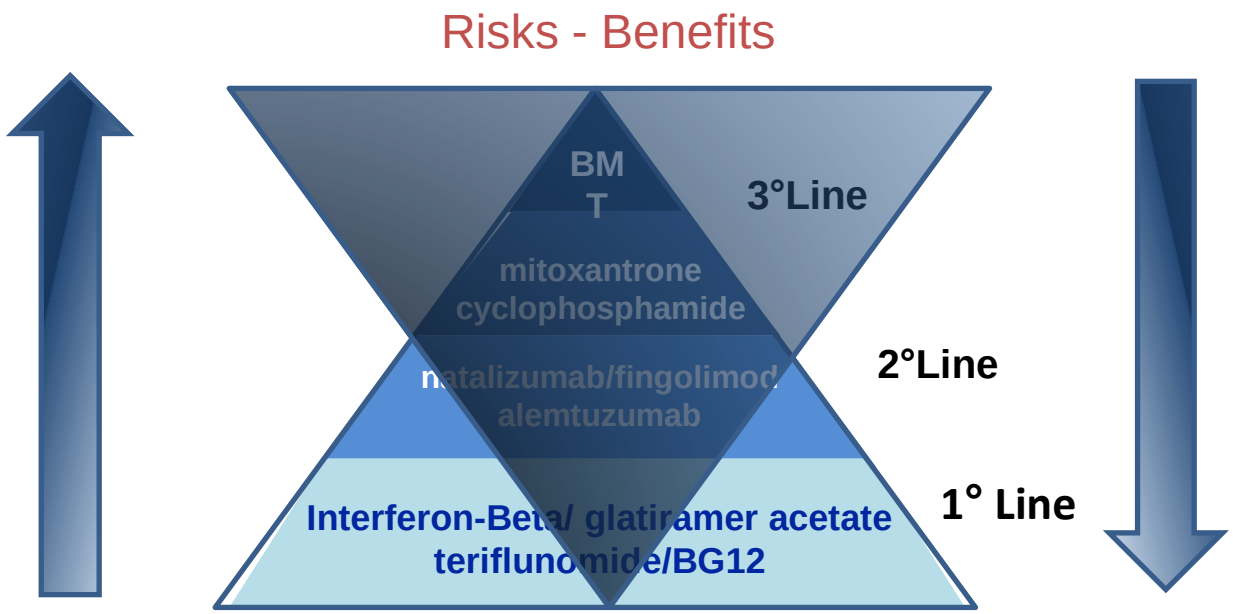
Slide generously provided by Dr. T. Chitnis, Chair IPMSSG

Differing efficacy and side effect profiles in MS DMTs

Drug class	Efficacy – relapse rate reduction	Adverse events
beta-interferon	30-35%	Flu-like sx, ⇧LFTs
glatiramer acetate	30-35%	Injection site reactions
mitoxantrone	55%	Cardiomyopathy, lymphoma
natalizumab	65%	**PML**
fingolimod	55%	Bradycardia, macular edema
dimethyl fumarate	45%	GI upset, flushing, **PML**
teriflunomide	30%	Hair thinning, teratogenicity
alemtuzumab	65-70%	25% autoimmunity, malignancy
rituximab	65%	Infusion reactions
daclizumab	55%	Rash, cutaneous reactions

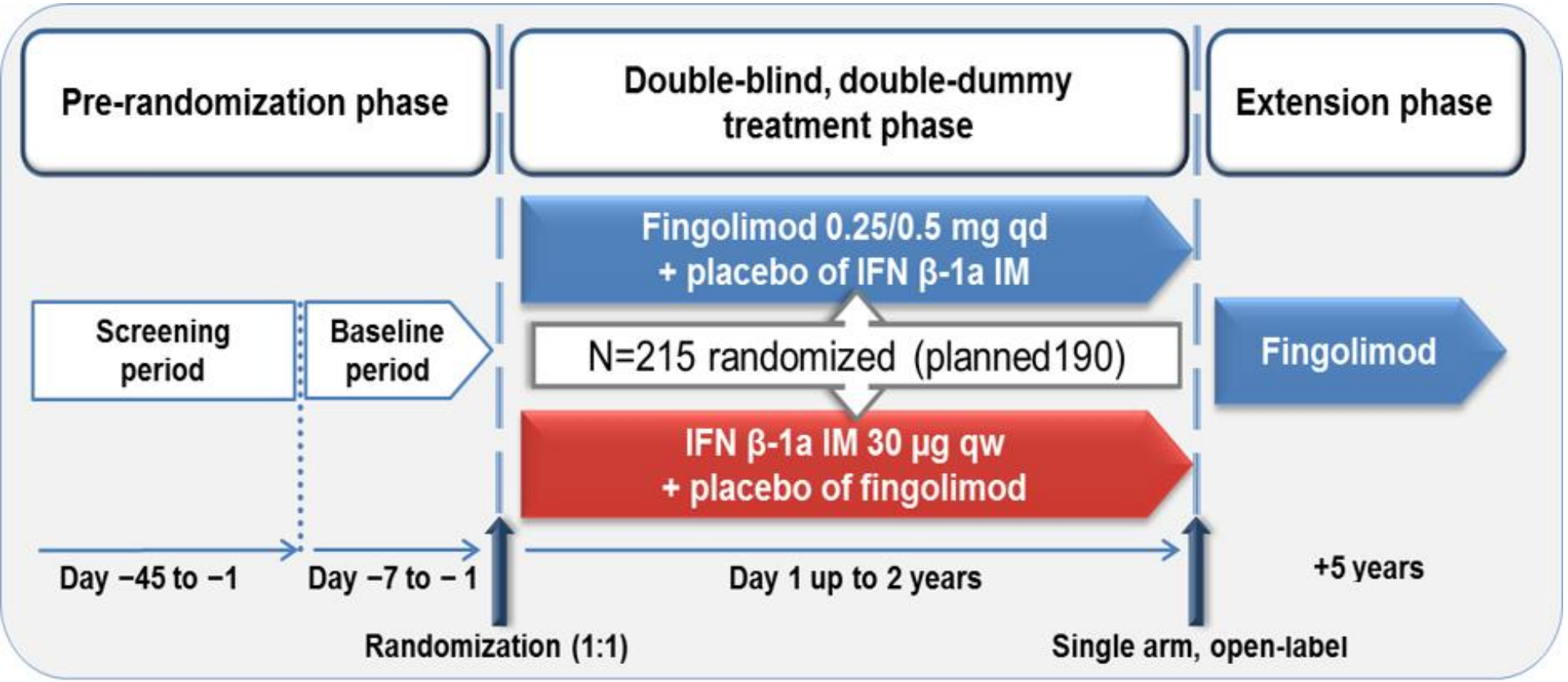
Slide generously provided by Dr. T. Chitnis, Chair IPMSSG

escalation **induction**



Acknowledgment: Angelo Ghezzi

PARADIGMS results



PARADIGMS: baseline characteristics were balanced between treatment arms

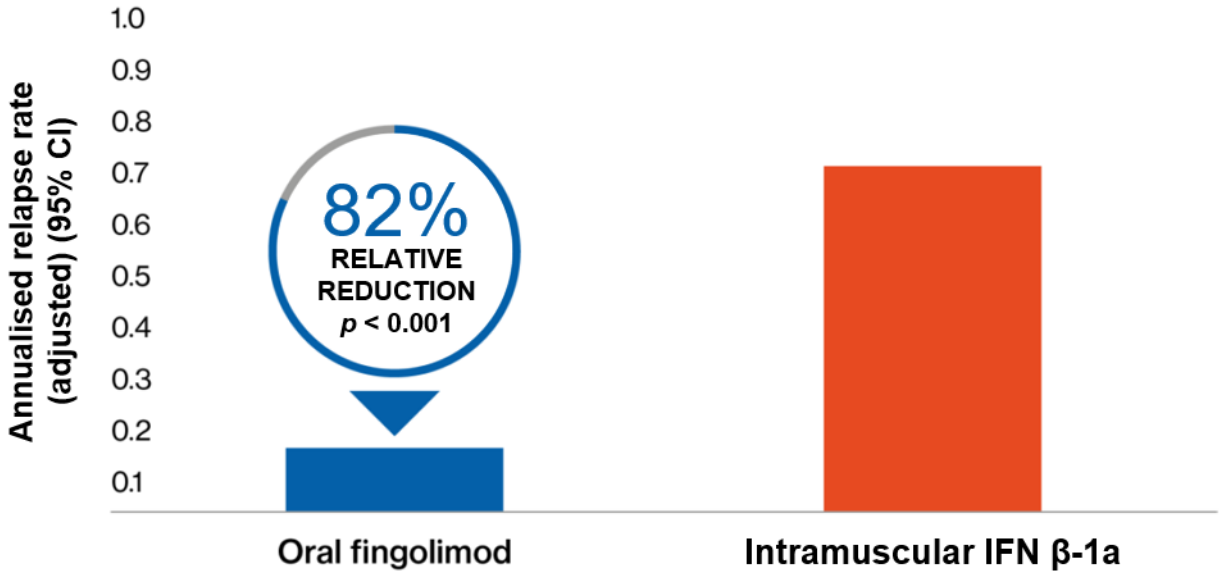
	Fingolimod (N=107)	IFN β-1a (N=108)
Age (years)	15.2 ± 2.0	15.4 ± 1.6
Female, n (%)	70.0 ± 65.4	64.0 ± 59.3
Weight >40 Kg, n (%)	98.0 (91.6)	107.0 (99.1)
Pubertal stage (Tanner score ≥2), n (%)	98.0 (91.6)	105.0 (97.2)
Duration of MS since first symptom (years)	1.9 ± 1.7	2.4 ± 2.1
EDSS score	1.5 ± 1.1	1.6 ± 0.9
Relapses in last year prior to screening	1.5 ± 1.0	1.5 ± 0.9
Number of Gd^+ T1 lesions	2.6 ± 6.0	3.1 ± 6.5
Proportion of patients free of Gd^+ T1 lesions, n (%)	47.0 (44.3)	59.0 (55.1)
Number of T2 lesions	41.9 ± 30.3	45.6 ± 33.9
Volume of Gd^+ T1 lesions (mm^3), median (range)	73 (0–9662)	0 (0–6160)
Volume of T2 lesions (mm^3), median (range)	5245.0 (52–116533)	6197.0 (189–101099)
Volume of T1 hypointense lesions (mm^3), median (range)	484.0 (0–35394)	753.0 (0–46893)
Whole brain volume (cm^3), median (range)	1145.9 (917–1633)	1135.9 (910–1487)

No significant differences between the two groups in the baseline level of disability or in the number of relapses before enrolment

Fingolimod is only approved for use in paediatric patients in the US. Fingolimod has received a positive opinion from the EMA CHMP for the treatment of paediatric-onset MS in the EU. Fingolimod is not licensed for paediatric-onset MS in Germany.
Data are presented as mean ± SD, unless specified otherwise.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN, interferon; MS, multiple sclerosis; SD, standard deviation.
1. Chitnis T, *et al. N Engl J Med* 2018; 379:1017–1027.

PARADIGMS: fingolimod significantly reduced annualised relapse rate vs. IFN β-1a IM

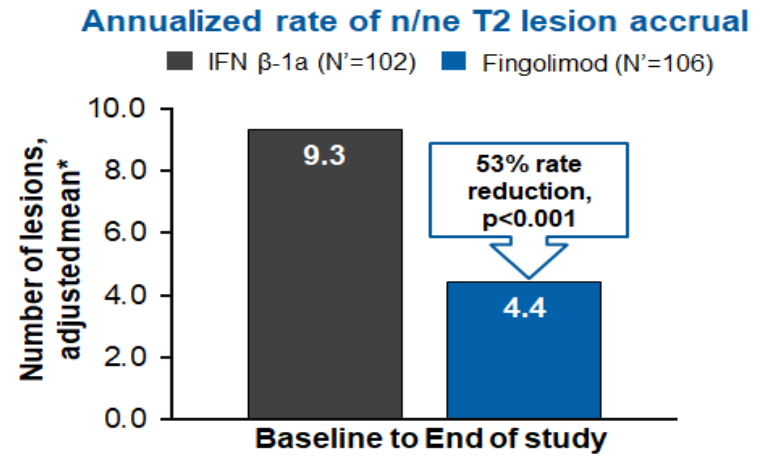
Patients with paediatric-onset MS had an 82% relative reduction in annualised relapse rate when treated with fingolimod vs. patients treated with IFN β-1a:[1]

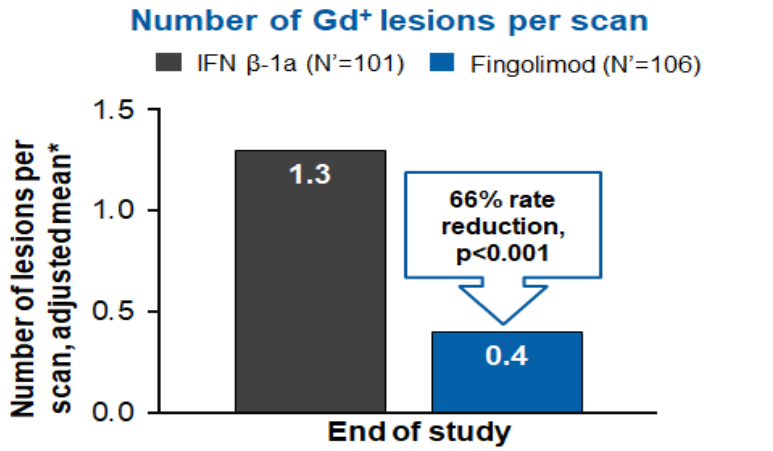


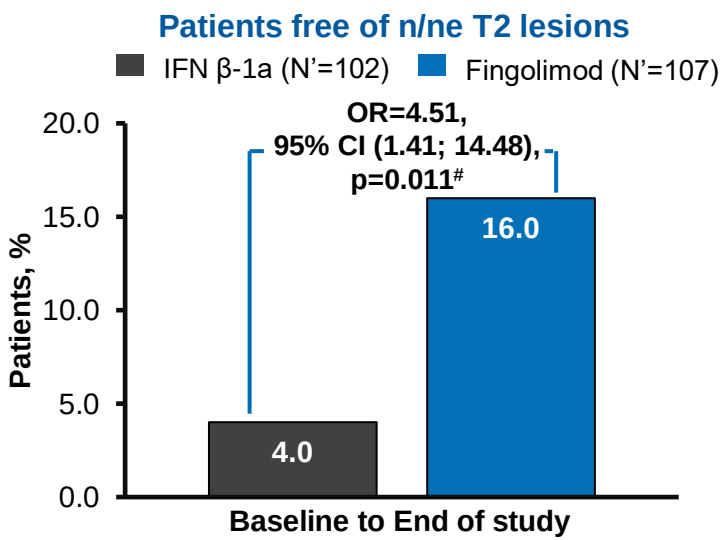
- Time-to-first relapse was significantly delayed with fingolimod vs. IFN β-1a IM ($p < 0.001$)[1]
- 85.7% of patients in the fingolimod group were free of confirmed relapses at Month 24 vs. 38.8% on IFN β-1a IM ($p < 0.001$)[1]

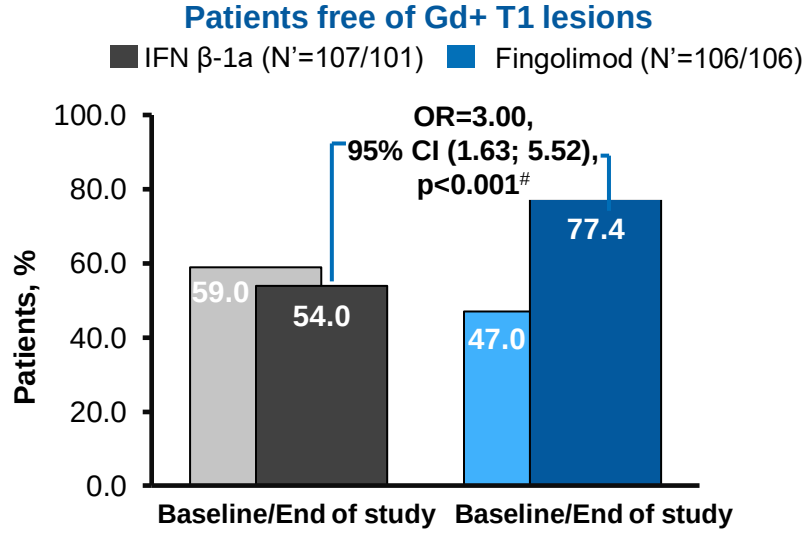
Fingolimod is only approved for use in paediatric patients in the US. Fingolimod has received a positive opinion from the EMA CHMP for the treatment of paediatric-onset MS in the EU. Fingolimod is not licensed for paediatric-onset MS in Germany.
IFN β-1a IM, interferon beta-1a intramuscular.
1. Chitnis T, *et al. N Engl J Med* 2018; 379:1017–1027.

PARADIGMS: fingolimod significantly reduced MRI activity vs. IFN β-1a IM







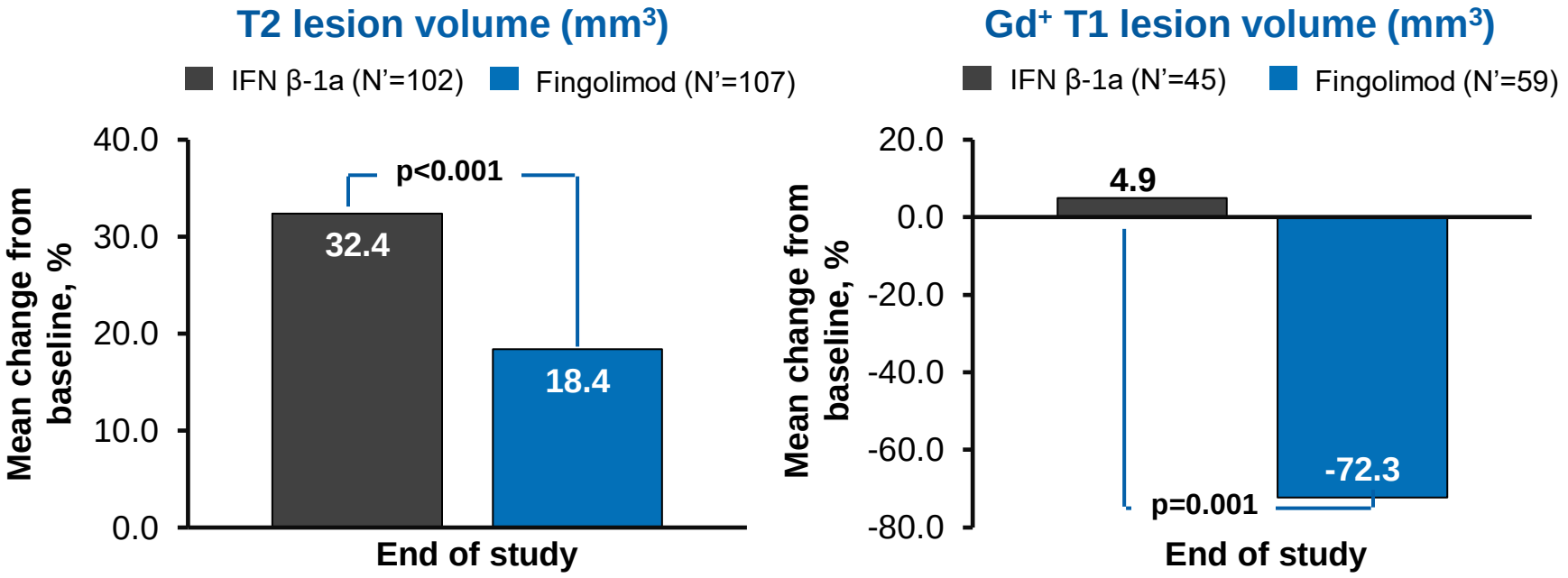


Fingolimod is only approved for use in paediatric patients in the US. Fingolimod has received a positive opinion from the EMA CHMP for the treatment of paediatric-onset MS in the EU. Fingolimod is not licensed for paediatric-onset MS in Germany.

N', number of patients with available results and included in the analysis. *Adjusted mean refers to the adjusted number new/newly enlarging T2 lesions per patient per year/Gd+ T1 lesions per scan. #OR, 95% CI and p values from logistic regression model. EOS was defined as the last assessment taken on or before the final study phase visit. CI, confidence interval; Gd+, gadolinium-enhancing; IFN, interferon; n/ne, new or newly enlarging; OR, odds ratio.

Arnold D, *et al.* AAN 2018; S51.005 (Oral).

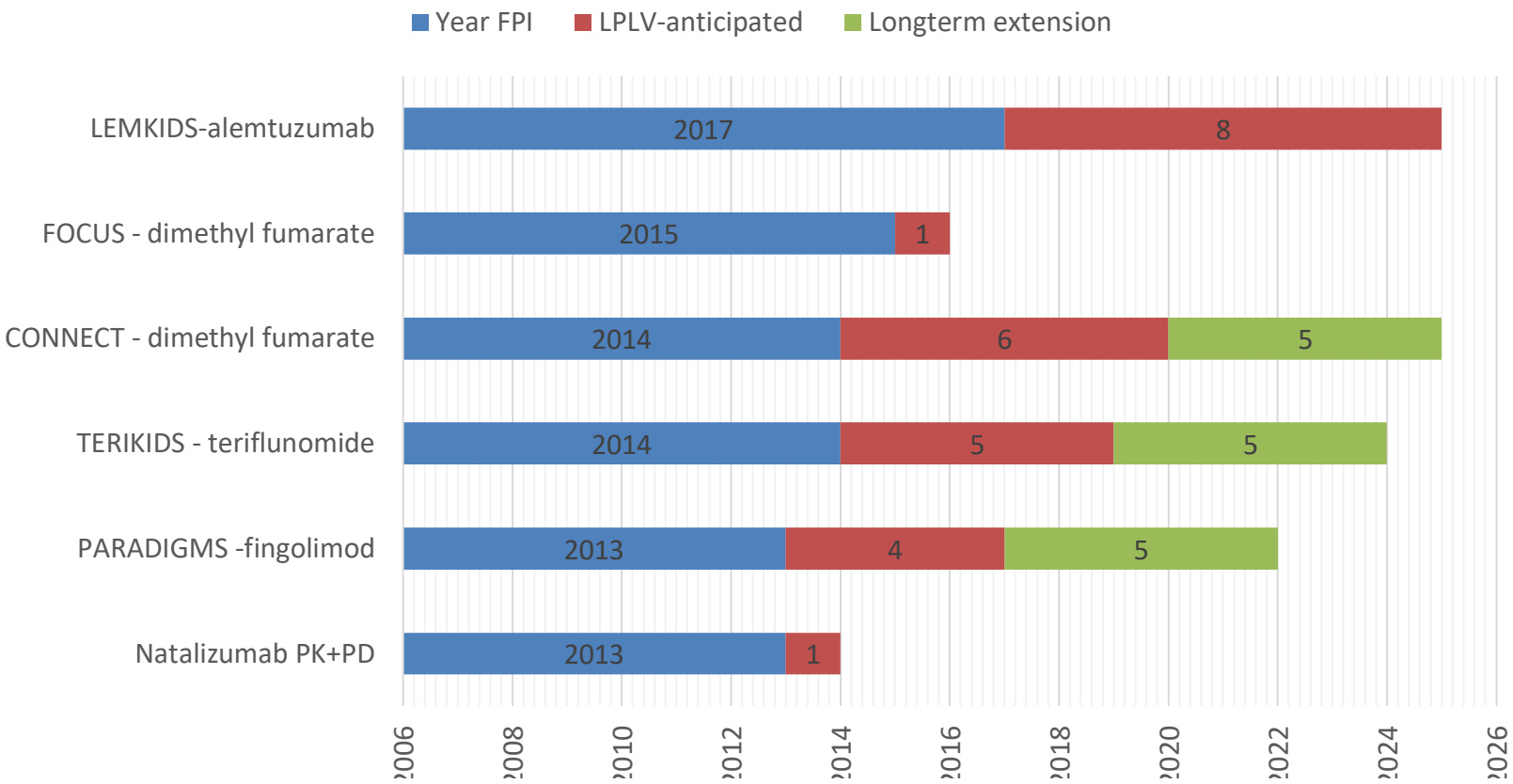
PARADIGMS: fingolimod significantly reduced lesion volume vs. IFN β-1a IM



Fingolimod reduced volume of acute inflammatory lesions compared with IFN β-1a

Fingolimod is only approved for use in paediatric patients in the US. Fingolimod has received a positive opinion from the EMA CHMP for the treatment of paediatric-onset MS in the EU. Fingolimod is not licensed for paediatric-onset MS in Germany.
N', number of patients with available results and included in the analysis. p values are obtained from rank ANCOVA. EOS was defined as the last assessment taken on or before the final study phase visit.
ANCOVA, analysis of covariance; EOS, end of study; Gd+, gadolinium-enhancing; IFN, interferon.
Arnold D, *et al.* AAN 2018; S51.005 (Oral).

Prospective clinical trials in Pediatric MS – May 2017



In addition: Vaccine trial; Betaferon study, Natalizumab (2 studies)

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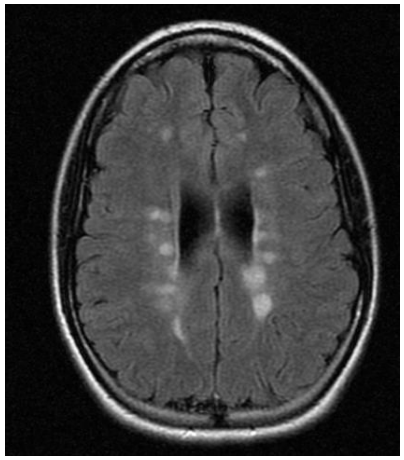
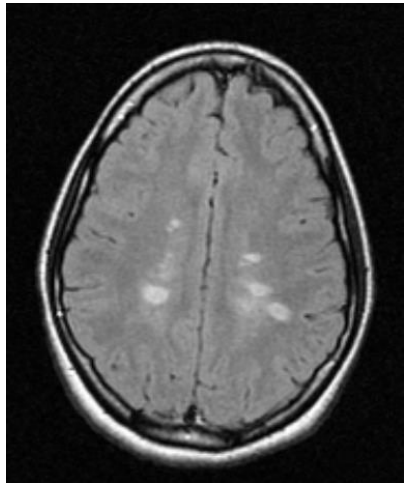
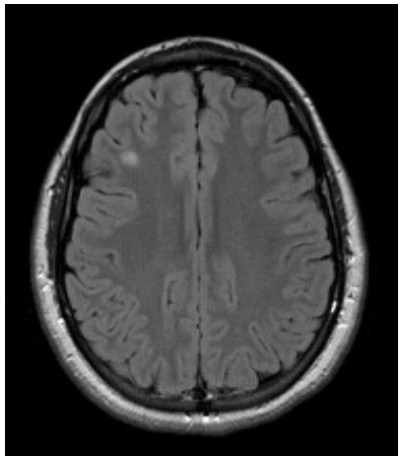
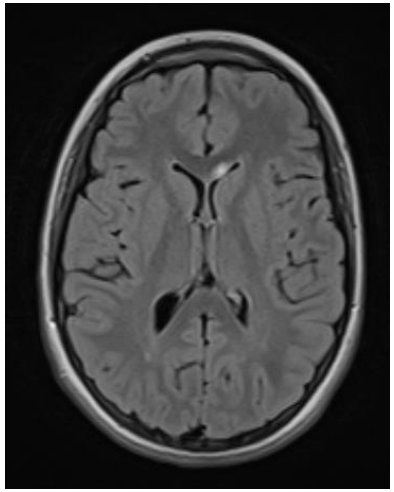
Can baseline MRI predict clinical disease course?



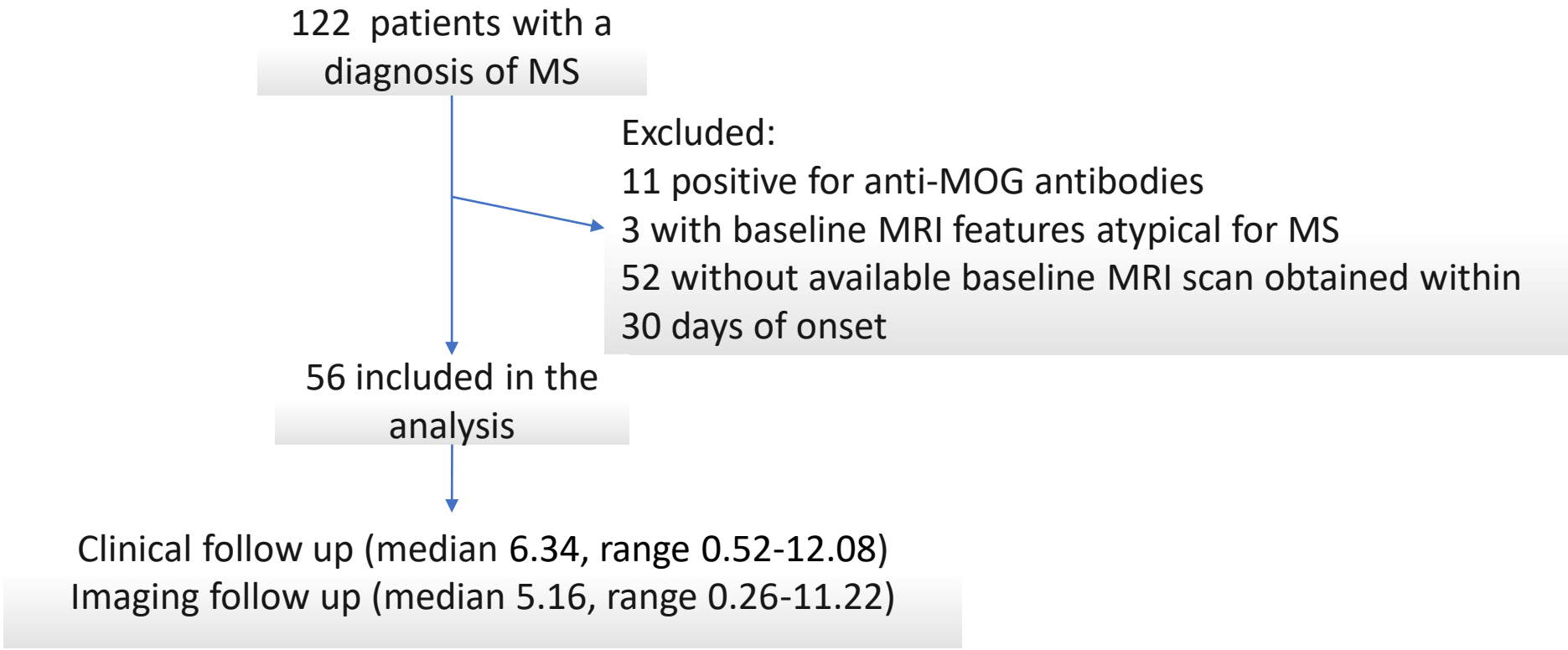


Which patient will have the highest disease activity?





Study cohort



Inception study cohort

Participants N	**56**
Age at first clinical attack (median, range)	14.25 (1.9-17.86)
Sex F:M	42:14
Length of clinical follow up (median, range)	6.34 (0.52-12.08)
N of scans	483
Treatment with DMT (ever treated) List n of DMT	Variable
EDSS at two years from onset (median, range)	1 (0-7.5)* only 5 patients with EDSS>4 (4 with EDSS 4.5, 1 with EDSS 7.5)
ARR at two years (median, range)	1 (0.5-2)
Relapse observed in (N, %)	39 (70%)
Time to first relapse (median, range)	0.94 years, (0.09 – 6.00)
First measured brain volume (z-score; median, range)	-0.41, (-2.8 – 1.8)

Baseline features

Age at onset	Brainstem lesions
Sex	Peri 4th ventricle lesions
Lesions present	Basal ganglia lesions
Lesions count	Diencephalic lesions
Periventricular lesions	Spinal lesions
Periventricular lesions = 1	Presence of discrete lesions
Periventricular lesions = 2	Sole presence of well defined lesions
Periventricular lesions = 3	Black holes
Periventricular lesions >3	Lesion enhancement
Juxtacortical lesions	Perpendicular lesions
Thalamic lesions	Tumefactive lesions
Cerebellar lesions	Oligoclonal bands
Cerebellar peduncle lesions	Anti-EBNA titre

Can baseline features predict a **high frequency of attacks** in the **first two years**?

All MRI features most typical for MS had high sensitivity in identifying patients with greater ARR, but very poor specificity

Relapses divided into high (top tertile, >= 3 attacks) and low (bottom two tertiles)

None of the features considered had PPV greater than 0.4

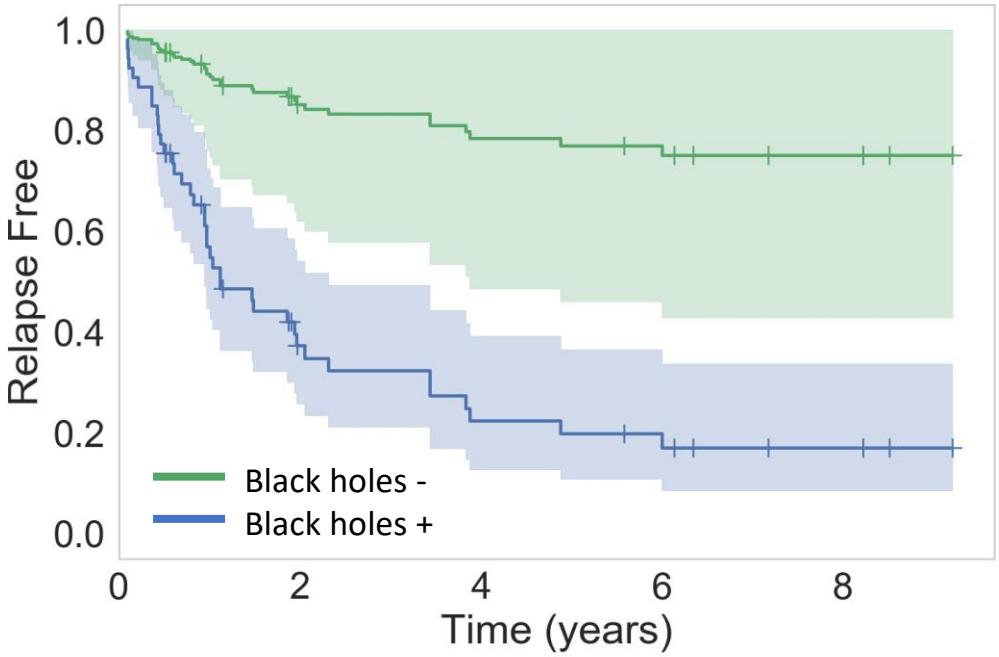
	sensitivity	specificity	NPV	PPV
McDonald 2010 DIT	1	0.44	1	0.33
Enhancing Lesions	1	0.33	1	0.3
McDonald 2010 DIS	1	0.23	1	0.26
Black holes	1	0.09	1	0.23
Sqrt T2 Lesions count	1	0.01	1	0.24

Baseline lesion count did not predict relapses

Can baseline features predict the the **time to second attack**?

	Hazard Ratio	% positive	p (uncorrected)
Black Holes	6.17	93	0.073
McDonald 2001 DIS	3.93	82	0.023
Periventricular lesion	3.39	91	0.095
McDonald 2017 DIS	3.04	88	0.067
Sqrt T2 Lesions count	1.36	-	0.079

Survival Curve: Black Holes at Baseline



Standard Cox proportional hazards model including time to first relapse

Absence of black holes in a small proportion of patients predicts long time to relapse

Can baseline features predict the probability of having **gad enhancing lesions at any follow up scan**?

- Binomial mixed effects model predicting odds ratio for observing an enhancing lesion on a follow-up scan
- Remote EBV and OCB are not predictors since they are present in nearly all
- The total n of lesions does predict likelihood of new Gd+ lesions

	Odds Ratio	**% positive**	**p (uncorrected)**
Black Holes	12.21	93	0.022
Gyral Projections	7.61	7	0.001
Non-enhancing lesion	7.31	90	0.015
McDonald 2017 DIS	3.08	88	0.011
Sqrt T2 Lesions count	1.63	-	0.007

Can baseline features predict the probability of having **new T2 lesions** at **any follow up scan**?

- Binomial mixed effects model predicting odds ratio as before
- Remote EBV and OCB are not predictors since they are present in all
- The total n of lesions is a significant, but very weak predictor

	Odds Ratio	**% positive**	**p (uncorrected)**
Black Holes	5.81	93	0.006
Cerebellar Lesions	2.35	43	0.016
MAGNIMS DIS	2.13	86	$< 10^{-4}$
McDonald 2010 DIS	1.53	88	0.355
Sqrt T2 Lesions count	1.03	-	$< 10^{-4}$

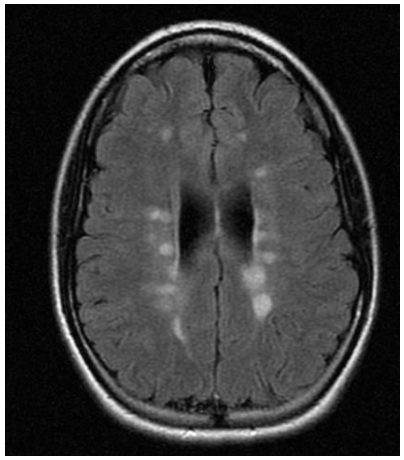
Can baseline features predict brain atrophy at two years?

- Linear model (equivalent to *t*-test or regression) predicting change in brain volume *z*-score over first two years post onset
- McDonald 2017 DIT was strongest predictor, followed by the presence of an enhancing lesion at baseline
- Baseline T2 lesion count did not predict

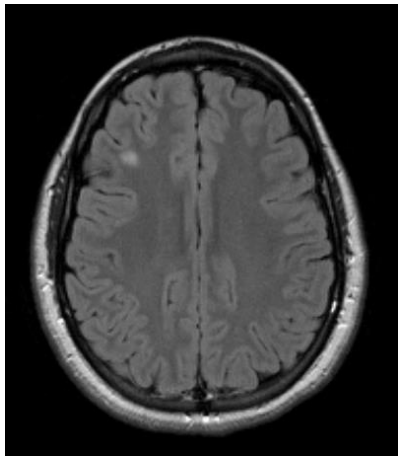
	Change in z	**% positive**	**p (uncorrected)**
Gryal Projections	-0.25	7	0.168
Internal Capsule Lesions	-0.16	27	0.233
Enhancing lesion	-0.13	74	0.207
McDonald 2010 DIT	-0.13	66	0.217
Sqrt T2 Lesions count	-0.01	-	0.813

Can baseline MRI predict clinical disease course?

17 year old
6 relapses
> 15 lesions

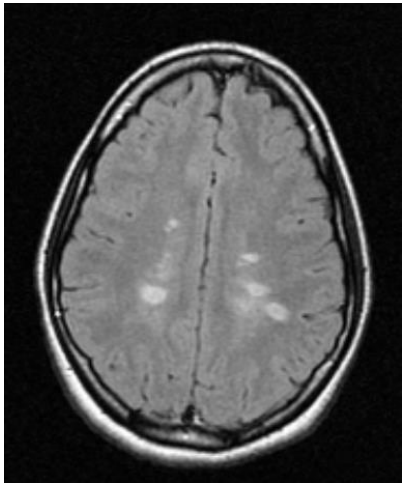


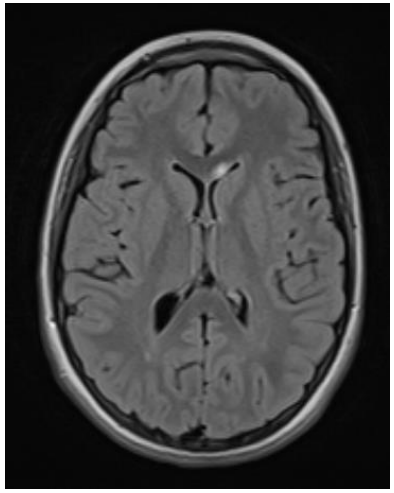
NO



16 year old
4 relapses
4 lesions

15 year old
1 relapse
>15 lesions





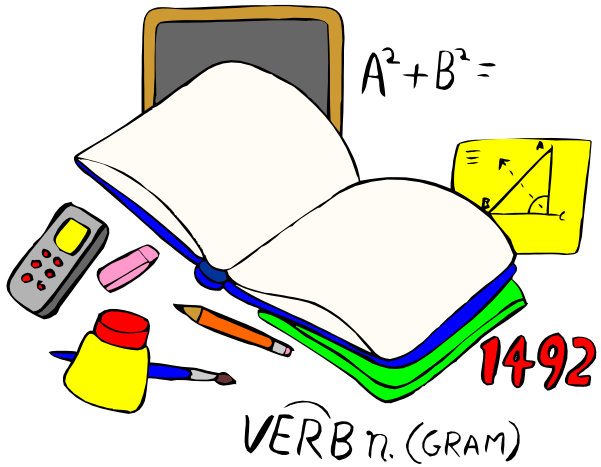
12 year old
1 relapse
3 lesions

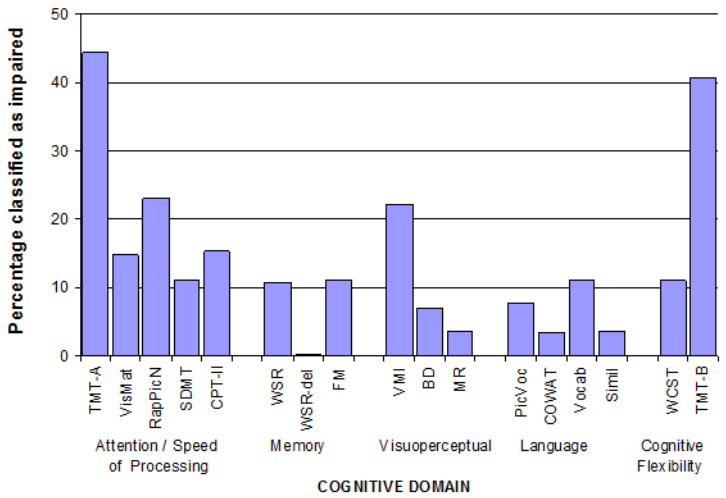
Living with MS

- Goal is to optimize care so that all patients can participate in the same activities as peers
- Modifications can facilitate engagement in activities such as recreational or competitive sports (cooling jacket, fatigue management)
- Avoid heavy backpacks!
- Medication “holiday” when patient is on holiday

Going to school with MS

- Goal is to limit absenteeism (optimize treatment efficacy to reduce relapses)
- Manage fatigue (modafinil, energy conservation strategies)
- Mood affects motivation (treat depression and anxiety)
- Neuropsychiatric evaluation provides insight into cognitive deficits as well as strategies to best address areas of strength
- Optimize 504 plan (school accommodations)





Wellness as a Treatment

Exercise

Pediatric MS patients engage in less vigorous activity
(Yeh et al)

Vitamin D

Decreased 25(OH) D is a risk factor for MS, treatment with vitamin D may reduce relapses (limited evidence)

Weight Loss

Increased BMI, particularly in adolescent, is a risk factor
Adiopose tissue is an inflammatory reservoir
Chitnis et al, Ann Clin Transl Neurol. 2016

Emotional Health

Depression, anxiety and addition contribute substantially to QoL

Future Priorities

- Phase 4 analyses of ongoing trials will inform on longer-term safety and sustained efficacy
- Need for real-world monitoring to inform on the impact of treatment on the full spectrum of pediatric MS
- Need to evaluate sequential therapies and their risk:benefit ratio and outcome
- Imperative to evaluate impact of early-life treatment on key variables such as future fertility, pregnancy outcomes, infection risk including PML

Current Considerations for Care

- Clinical and MRI features confirm that the onset of MS in childhood and adolescence is associated with high disease activity
  - *Should high(er) efficacy agents be first-line therapy?*

- Can we change longterm outcome?
  - *Can new therapies alter the lifetime risk of secondary disease progression and accrual of disability?*