Selected Abstracts Presented at the Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting (Spring 2018)

STUDY	BACKGROUND	DESIGN/METHODS	RESULTS	CONCLUSIONS
CLINICAL SCIENCE/TRIALS				
The efficacy of a Fourth Alemtuzumab Course in RRMS Patients with Disease Activity after Three Prior Courses: Analysis of Care-MS II (Abstract DX06) Barry Singer St. Louis, MO, USA	The two year CARE MS II study evaluated active relapsing MS patients with breakthrough clinical attack on a needle injectable. They were randomized to 2 cycles of alemtuzumab (in year one 12 mg IV daily for 5 days; in year two 12 mg IV daily for 3 days) vs. SC interferon β-1a 44 mcg 3x weekly. In a 4 year extension study patients could receive further courses of 3 days treatment for breakthrough relapse or MRI activity at investigator discretion. This study assessed those who received a fourth course.	Through year 6, 344 of 393 (88%) patients who entered the extension remained in the study. N=62 (16%) received ≥4 courses, and N=49 (12%) received 4 courses. Patients were assessed for 12 months before, and up to 3 years after their fourth alemtuzumab course.	Annualized relapse rate (ARR) decreased from 0.75 in the year prior to course 4, to 0.19 in the year after ($p<0.0001$). ARR remained low at year 3 after course 4 (0.23). EDSS compared to baseline was stable/improved in 53.5% at the time of course 4, vs. 67.5% one year later. Confirmed disability improvement increased from 10% in the year before course 4, to 26.7% in the year after.	In MS patients with breakthrough disease activity despite 3 courses of alemtuzumab treatment, a fourth course of alemtuzumab successfully reduced relapses, and stabilized/improved EDSS.
Continuous remote assessment of multiple sclerosis disability over one year: the UCSF FITRIMS study (Abstract RH26) Valerie A. J. Block San Francisco, CA	Sensitive real world functional outcome measures are needed to advance research, and improve care for MS. This study evaluated continuous remote monitoring in a cohort of MS individuals.	N=95 adults with relapsing or progressive MS were recruited to wear a Fitbit remote monitoring device for one year. They had to be able to walk at least 2 minutes with or without an assistive device. They were assessed at baseline, and at one year for EDSS, timed 25 foot walk (T25FW) and the patient-reported MSWS-12 walking	N=79 (83.2%) MS individuals completed the study. The Fitbit Flex provided valid step rate on average for 3 weeks out of each month per individual. Greater disability was associated with lower STEPS over the year. For those with a baseline STEPS below the median (4,766), odds of disability worsening was 6.7x higher if the initial EDSS was >4, and 9.4x higher if the initial EDSS	Continuous remote activity monitoring over one year is feasible in MS. Low baseline STEPS (<4,766/day) substantially increased risk for clinically meaningful decline at one year. Decreased STEPS was associated with worsening in both clinic-based (T25FW)

		scale. Change in average daily step count (STEPS) was also evaluated.	was >6. A decrease in STEPS over one year was associated with worsening of the T25FW and the MSWS-12 ($p<0.001$).	and patient-reported (MSWS-12) walking disability measures.
Phase 2 multicenter study results of ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody (mAb), in patients with relapsing forms of multiple sclerosis (RMS) (Abstract DX71) Edward J. Fox Round Rock, Texas	Ublituximab is a novel chimeric IgG1 monoclonal that targets a unique CD20 epitope. It is glycoengineered to enhance ADCC and slow activity in "low" CD20 expressing cell lines (a characteristic of rituximab resistance). It may offer benefits over other anti-CD20s with regard to ability to use lower doses, and shorter infusion times.	This 52 weeks phase 2 placebo controlled multicenter study was designed to assess optimal dose and infusion time in relapsing MS. All subjects received 3 ublituximab infusions at days 1 (150 mg), 15 (450 or 600 mg) and week 24 (450 or 600 mg) (placebo subjects were treated post placebo phase).	N=48 subjects were randomized, and N=46 completed 6 months. At week 4 a median 99% B cell depletion was noted, and maintained at week 24 (N=44). No contrast lesions were observed at week 24 (vs. mean 3.8 at baseline). T2 lesion volume was ↓ by 7.67% at week 24; 98% were relapse free at week 24; 83% showed improved or stable EDSS. The most frequent AEs were infusion related reactions, all grades 1 or 2. Rapid infusion as low as one hour of 450 mg was well tolerated.	Final results of the phase 2 trial will be reported at a subsequent meeting. Ongoing phase 3 trials (ULTIMATE I and II) are already under way in relapsing forms of MS vs. teriflunomide.
Obesity at onset impacts the early clinical presentation of multiple sclerosis (Abstract DA07) Farren B.S. Briggs Cleveland, Ohio	Early clinical expression may predict long term MS outcomes. Obesity is linked to risk of MS, but associations with disease outcome are unknown. This study was planned to test whether obesity has negative effects on early clinical MS expression.	N=1,524 people with MS participated in this Accelerated Cure project to collect medical history, socio-demographics, behavioral risk factors, and genotypic data (N=1,054). Outcomes involved age at onset, number of impaired functional domains at onset (based on 31 symptoms), and early relapsing MS activity in the first 2 years. Variables such as age, sex, race, MS phenotype, education level, HLA-DRB1*1501, and comorbidities were accounted for.	Obesity was associated with older age at onset (by 8%), a 17% increase in impaired functional domains ($p=0.04$), a 30% shorter time to second relapse, and 25% more relapses in the first 2 years. Other associations involved smoking and earlier age at onset, 8% increase in impaired functional domains ($p=0.07$), and a 13% increase in early relapse activity ($p=0.06$). HLA-DRB1*1501 was associated with earlier age at onset.	Obesity creates a pro-inflammatory state. In this study it was associated with several initial MS features, including older age at onset, greater involvement of functional domains, and higher early relapse activity.

Diets similar to the Mediterranean diet are associated with lower depression scores and improved cognition scores in people with multiple sclerosis (Abstract N10) Leah Mische Baltimore, MD	People with MS often experience depression, fatigue and cognitive impairment. In the general population, a Mediterranean style diet is reported to improve these symptoms. This study planned to look at MS individuals.	34 people with MS completed a 24 hour dietary recall. Adherence to a Mediterranean style diet was quantified using a well validated scoring approach, to create an overall Mediterranean score ranging from 0 (poor diet quality) to 8 (high diet quality). Neuro-QoL subscales were completed for self-report assessments. Correlations were adjusted for age and sex.	Higher Mediterranean diet scores were associated with less severe depression ($p=0.01$), and cognitive impairment ($p=0.02$).Those in the top dietary quartile had significantly lower depression scores than those in the lowest dietary quartile. Dietary scores were not associated with fatigue.	This cross sectional study suggests adherence to a Mediterranean style diet (high in fruits, vegetables, whole grains, legumes) may be associated with less severe depression and cognitive impairment symptoms in MS.
Potential infectious complications of B-cells depleting therapies-a focus on rituximab in multiple sclerosis (Abstract DX57) Cindy Darius Baltimore, MD	The ramifications of long term therapy with anti-CD20 monoclonal B cell depletion in MS are unknown.	This was a retrospective health records review of all MS patients treated with rituximab by a single provider at Johns Hopkins. The focus was on development of serious infectious complications.	Five of 30 individuals (17%) developed serious infections that led to discontinuation of rituximab. They involved 1) discontinuation after 4 years due to recurrent pneumonia; 2) discontinuation after 1 year due to ringworm and 2 bouts of staph aureus septic arthritis; 3) discontinuation after 2 years due to sinusitis, pneumonia, and ocular herpes simplex keratitis; 4) discontinuation after 2 years due to recurrent urosepsis, sinusitis, and pyrexia; 5) discontinuation after 2 years due to intractable sinusitis and pneumonia with empyema.	B cell depleting therapies are effective in MS, but can be associated with potentially life threatening non-opportunistic infectious complications.

Oligoclonal band number correlates with relapses and progression in multiple sclerosis (Abstract NB03) Christopher Perrone Philadelphia, PA	CSF oligoclonal bands (OCBs) are found in over 90% of MS individuals. They predict that a clinically isolated syndrome is more likely to have MS, and are associated with a worse prognosis. However, only a few small studies have focused on the significance of numbers of bands, and association with clinical and MRI disease markers in 2 year follow up.	This retrospective study evaluated N=1,270 MS individuals on disease modifying therapy for OCB testing. They had to have relapsing MS, and be adherent on a DMT for 2 years of clinical and MRI follow up. There were N=128 such individuals. Primary outcome was steroid treatment relapses and new MRI lesions at 2 year follow up. Secondary outcomes were clinical worsening (independent, cane, walker, wheelchair), and net change in third ventricular width, lateral ventricular width, cortical width.	MS individuals with ≥10 OCBs had significantly more clinical relapses than those with <10 OCBs (p=0.006). They had nearly twice the number of new MRI lesions (p=0.018). Use of a new assistive device was greater for those with ≥10 OCBs (p=0.007). Lateral ventricle width (but not cortical or third ventricle width) increased to a greater extent in these with ≥10 OCBs (p=0.015)	In short term (2 year) follow up ≥10 OCBs were associated with significantly greater relapses (both clinical and MRI), and clinical worsening. Number of OCBs may be an important consideration in MS.
Clinic to in-home telemedicine reduces barriers to care for patients with multiple sclerosis and neuroinflammation (Abstract MC09) Priya Garcha San Francisco, CA	There is an increasing use of telemedicine visits as an alternative to outpatient appointments. The goal of this study was to describe real world use of telemedicine-enabled clinical care in a large MS/Neuroimmunology academic practice, and to quantify its role in alleviating patient burden.	Consecutive adults with MS and other neuroinflammatory disease who presented for routine evaluation at the UCSF Center were enrolled over a 10 month period in 2017 (100 in person visits, 50 telemedicine visits). After the visits, both the patient and their clinician completed questionnaires.	For the televideo visits, the mean age was 51.3 years, EDSS was 4, and visit duration was 37 minutes. Physicians reported that their goals were achieved for 96% of visits, and exam was adequate in 92% of visits. The exceptions were concerns about a cauda equine syndrome, zoster, visual field loss, and subtle clinical worsening. The televideo avoided 2 individuals being sent to the ER. The televideos were conducted at home (80%) or at work (20%). 98% agreed the platform was easy to use, and only 16% felt an in person visit would have been more effective. Travel burden (an	Telemedicine substantially reduced travel and caregiver burden, and provided efficient, convenient and effective follow up.

			average of 246 km) was reduced, 11% avoided air travel, and 23% avoided overnight lodging. 39% avoided caregiver time off from work, and 21% avoided child care. Of 49% of employed individuals, 67% avoided taking time off from work. Compared to in clinic evaluations, there was no difference in patient ratings on 6/7 standard quality of care measures; the only difference was in rating of provider's eye contact.	
Vascular disease risk factors and MS progression: a study of brain metabolism (Abstract IM01) Allison Fryman Portland, OR	Mounting evidence supports that vascular disease risk factors (hypertension, hyperlipidemia, obesity, diabetes, heart disease) increases risk for MS disability. Having ≥1 vascular disease risk factor is associated with needing a unilateral assistive device to walk a median of 6 years sooner. There may be a dose response relationship, since a single risk factor increases risk for early gait disability by 51%, while 2 risk factors increase it by 228%. This study looked at how such risk factors affect cerebral blood flow (CBF) and brain metabolism, as measured by MRI and high energy phosphate metabolites in cerebral GM using ^{31}P-MR spectroscopy (MRS).	This is a 3 year observational controlled study with a single site mixed (cross sectional and longitudinal) design with 2 arms. MRI is done at baseline, and then annually. N=60 MS subjects have been enrolled; N=35 have vascular disease risk factors, and N=25 do not. Outcome measures include CBF and blood volume detected by 7T MRI and ^{31}P 7T-MRS, brain atrophy, and clinical impairment, disability, and QoL.	A cross sectional analysis of baseline data on 50 of the 60 enrolled individuals is available. ATP to total phosphate signal ratio is decreased in vascular disease risk factor patients by 4.5% ($p<0.05$). The normalized brain tissue volume was 3.9% less in MS women with vascular risk factors ($p=0.02$). Men showed a similar trend, but were limited by sample size.	This baseline data supports that there is an impaired brain metabolic state in MS subjects with vascular disease risk factors.

Myelin water fraction as a potential marker of progression in primary progressive multiple sclerosis (Abstract DX63) Kimberly Chang Vancouver, Canada	Progressive MS in particular is associated with diffuse injury to normal appearing white matter (NAWM) not detected by conventional MRI. This study evaluated myelin water fraction (MWF) variability and natural history in primary progressive (PP) MS patients vs. healthy controls.	Data was collected as part of a single-site substudy for ORATORIO, a phase 3 PPMS trial looking at ocrelizumab vs. placebo. Only baseline and placebo PPMS data was analyzed. N=41 healthy controls, and N=7 PPMS were scanned at baseline. N=2 PPMS patients randomized to placebo were also scanned at 6, 12 and 24 months, and N=1 at 48 months. MWF and voxel-wise MWFZ-score maps were calculated: MWFZ=(patient MWF – mean controls MWF)/(standard deviation of controls MWF). Severe damage was calculated as % WM voxels with MWF < -4 (damaged regions smaller than 25 voxels were excluded).	Baseline volume of severe damage in PPMS NAWM varied widely, and did not correlate with EDSS. Areas of severe damage extended through NAWM far beyond focal lesions. N=2 PPMS had >8% of WM volume severely affected. N=5 PPMS had small (<80 voxels) isolated patches of severe damage affecting <0.25% of WM volume. Longitudinal studies in the first PPMS patient showed no severe damage at baseline (EDSS=2.5), increasing to 0.09% of WM volume at 24 months (EDSS=3.5). The second PPMS patient had extensive damage at baseline affecting 8.9% of WM volume (EDSS=6.5), increasing to 12.6% at 48 months (EDSS=6.5)	Significant reductions in regional MWF can be detected for individual PPMS patient. PPMS varies in the distribution and extent of severe reductions in regional MWF. MWF Z-scores can detect significant changes in individual patients within 1-2 years of follow up.
Moderate-to-vigorous physical activity is positively associated with the retinal nerve fibre layer thickness in pediatric multiple sclerosis (Abstract DX37) Stephanie A. Grover Toronto, Canada	Previous studies in MS adults reported an association between moderate to vigorous physical activity and RNFL. This study investigated physical activity impact on the RNFL and ganglion cell-inner plexiform layer (GCIPL) in pediatric onset MS.	In this cross sectional study pediatric MS patients were recruited from the Pediatric MS Center at the Hospital for Sick Children in Toronto. They underwent standard visual evaluations including spectral-domain OCT. They filled out the Godin Leisure-Time Exercise Questionnaire, with a calculated health score. Generalized linear models were used to assess associations between moderate to vigorous physical	There were N=27 participants (20 female). 48.1% had a prior optic neuritis. Moderate to vigorous physical activity was positively associated with RNFL thickness (p=0.002) in all eyes. It was also positively associated with GCIPL thickness.	Moderate to vigorous experience was positively associated with RNFL and GCIPL thickness in pediatric MS. This suggests moderate to vigorous physical activity is a modifiable lifestyle factor that may improve anterior visual pathway integrity in pediatric MS.

		activity, and RNFL/GCIPL, with appropriate corrections.		
BASIC SCIENCE				
Metabolomics analysis identifies abnormal bile acid metabolism in multiple sclerosis (Platform Presentation during John Whitaker Research Track. Mike Racke, Chair) Leah Mische Baltimore, MD	Metabolomics allow the detection of abnormalities in multiple metabolic pathways. Bile acids are anti-inflammatory; they directly modulate myeloid cells in the PNS, as well as microglia in the CNS, and influence the gut microbiome. Bile acid therapies have been suggested to help neurodegenerative diseases.	To use nontargeted and targeted metabolomics to determine differences in plasma levels of primary and secondary bile acid metabolites in a discovery cohort of MS (N=50 relapsing MS, N=50 progressive MS) vs. healthy controls (N=50). A validation cohort consisted of N=50 relapsing MS and N=75 healthy controls. The discovery cohort underwent global metabolomics to identify 25 metabolites involved in bile acids. The validation cohort underwent targeted measurement of 15 primary and secondary bile acids to confirm results of the discovery cohort. Pathway deregulation scores (higher scores denote greater abnormality) were compared to individual bile acid levels, adjusted for age and sex, using linear regression.	In the discovery cohort lower levels of multiple primary and secondary bile acids were noted in MS compared to healthy controls. The relapsing MS group showed higher scores for secondary bile acid metabolism ($p=0.002$); the progressive MS group showed abnormalities for both primary and secondary bile acid metabolism compared to healthy controls ($p=0.002$). In the validation cohort scores for primary and secondary bile acid metabolism were higher in progressive MS compared to controls. Multiple glycine and taurine conjugated bile acids were particularly reduced. Multiple bile acids negatively correlated with MS disease duration (after adjustment for age and sex).	Plasma bile acid levels differ between MS and controls. This was more significant for progressive MS, with both primary and secondary bile acids affected. In relapsing MS only secondary bile acids were affected. The targeted analysis showed similar results for progressive MS, with a trend for bile acid levels in relapsing MS. This study identifies potential targets for intervention.

The role of dysregulated lipid metabolism in an EAE model of mice mimicking the Inuit CPT1a mutation (Oral presentation in blocking lipid metabolism in MS – a new class of medications symposium) Ann Morkholt Aalborg, Denmark	It has been proposed that MS is a systemic disease due to abnormal lipid metabolism, with a switch from glucose-based to lipid-based metabolism. Carnitine Palmitoyl Transferase 1 (CPT1) is a key enzyme involved in lipid metabolism. A CPT1a mutation is found in 98% of the Inuit population, leading to a 22% level of CPT1a activity. A CPT1a13 bp deletion is found in 60% of the Hutterites, leading to a 0% level of CPT1a activity. Both these Canadian populations show very low rates of MS: Inuits 1 in 50,000; Hutterites 1 in 1,100; vs. Canadians 1 in 350.	Two CPT1a mice strains were created using CRISPR technology to mimic the Inuit and Hutterite mutations. EAE was studied in these models. The impact of treating EAE with etomoxir, a lipid metabolism blocker that inhibits CPT1, was also studied.	In preliminary studies CPT1a mutations minimalized/ lessened EAE manifestations as demonstrated by lower disease score, greater body weight, and greater grip strength. Etomoxir decreased EAE severity; treatment was associated with a higher proportion of healthy animals, and lower disease score.	Chemical inhibitor of CPT1a by etomoxir appears to treat EAE. Preliminary data based on biologic mutations of CPT1a suggest it may be involved in the pathogenesis of MS.