Advances in Stem Cell Transplant and Neuro-recovery in Multiple Sclerosis

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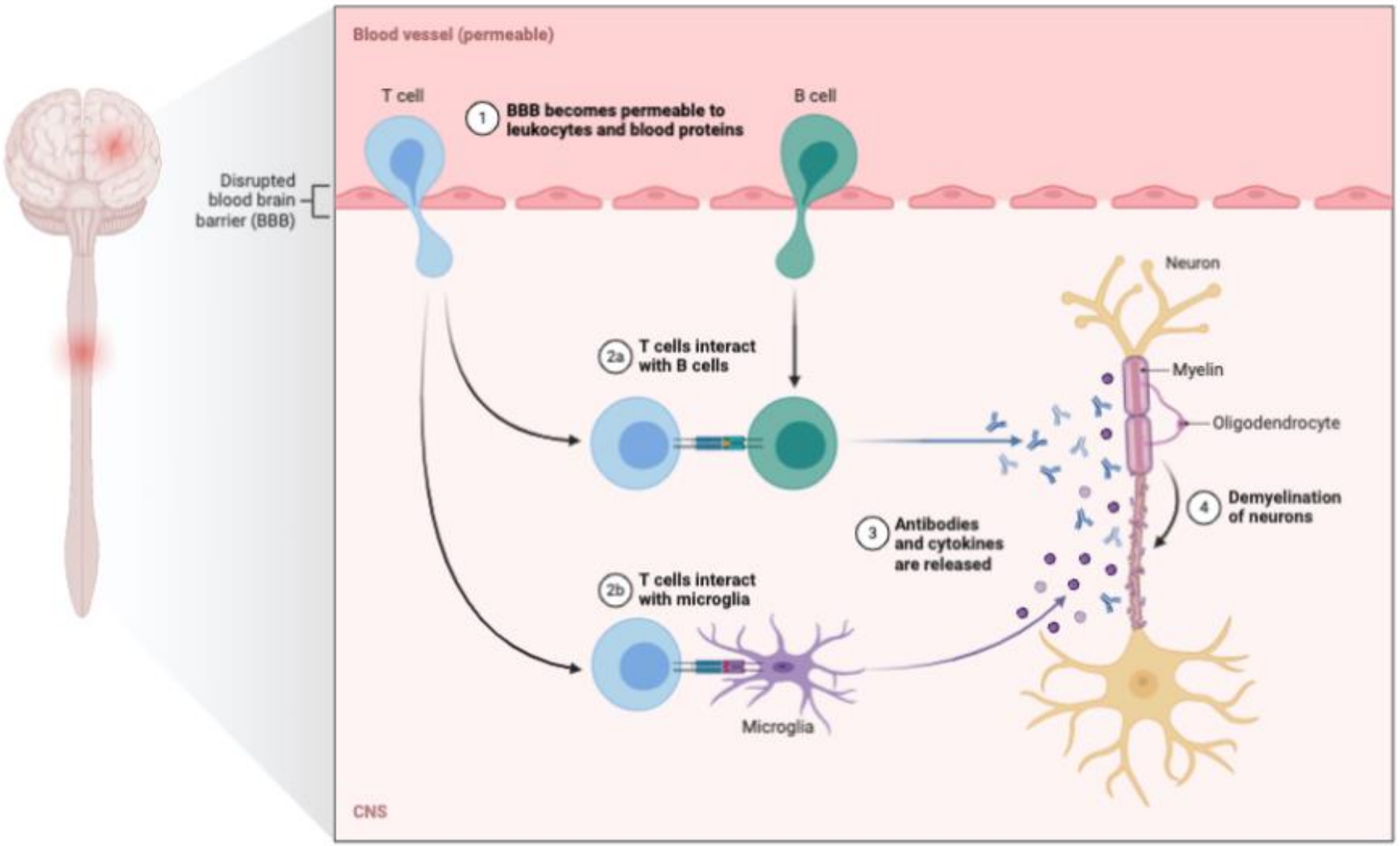
COI:

None to affect this presentation

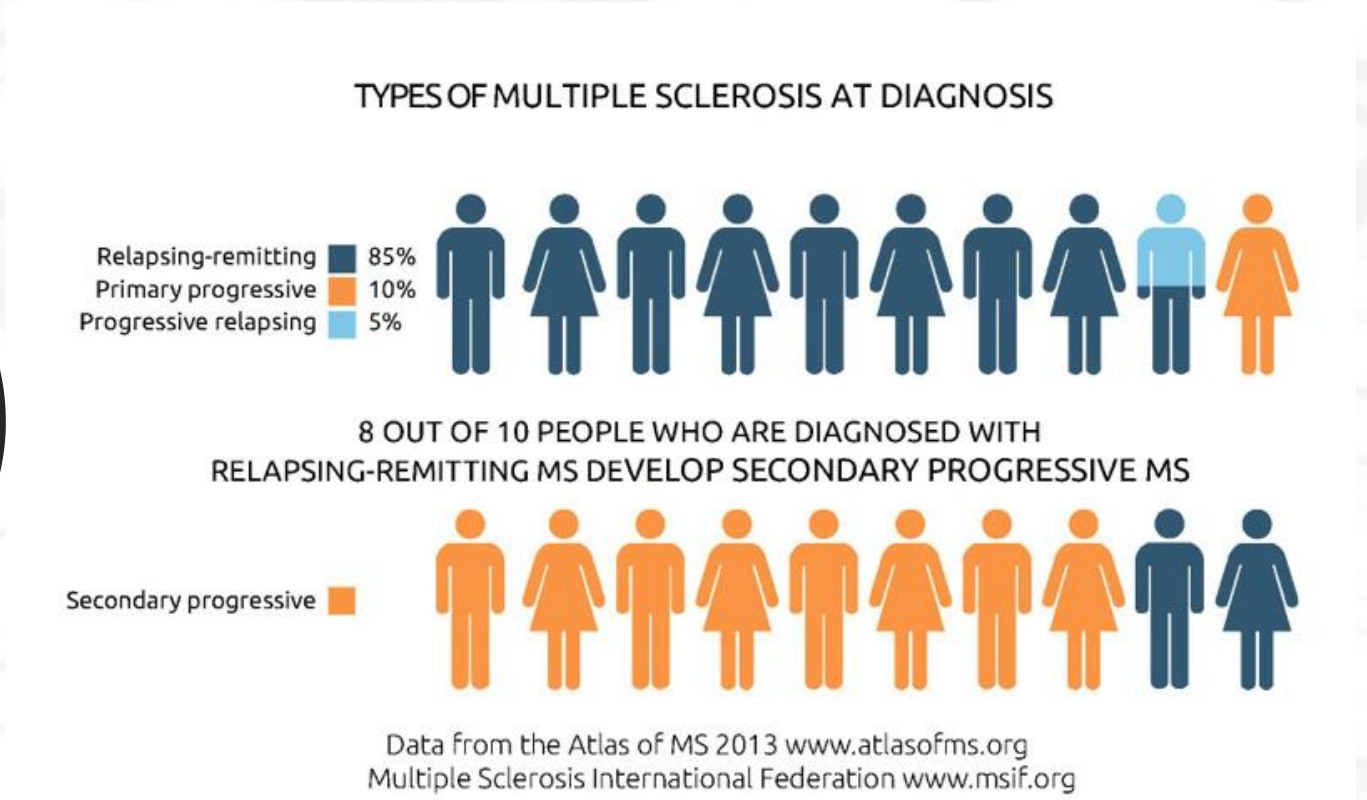
A Quick recap of multiple sclerosis

Pathogenesis of Multiple Sclerosis (MS)

MS is currently classified as an autoimmune disease of the central nervous system (brain, spinal cord, and optic nerves). The disease attacks myelin, the protective covering of the nerves, causing inflammation and damages the myelin (MS Society of Canada, 2020).



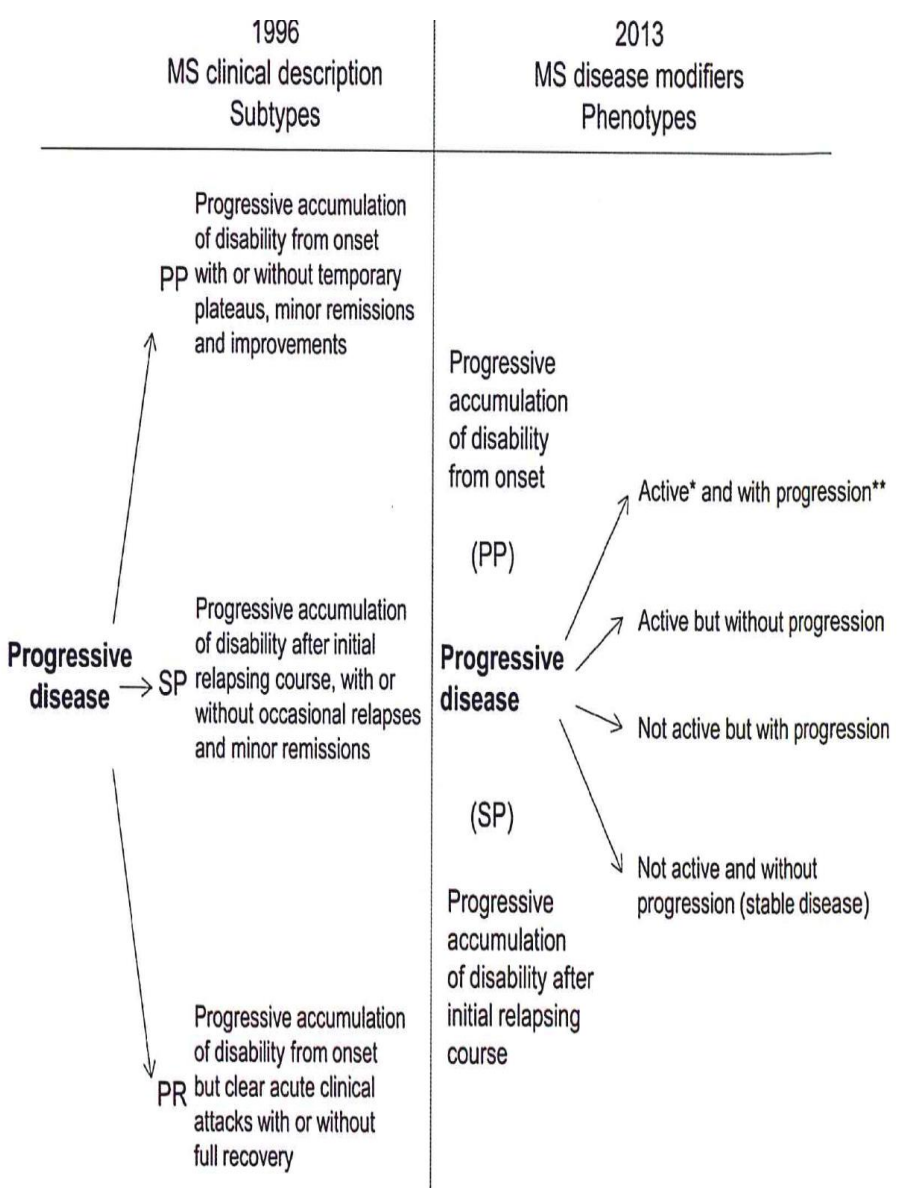
85% of MS is Relapsing-Remitting

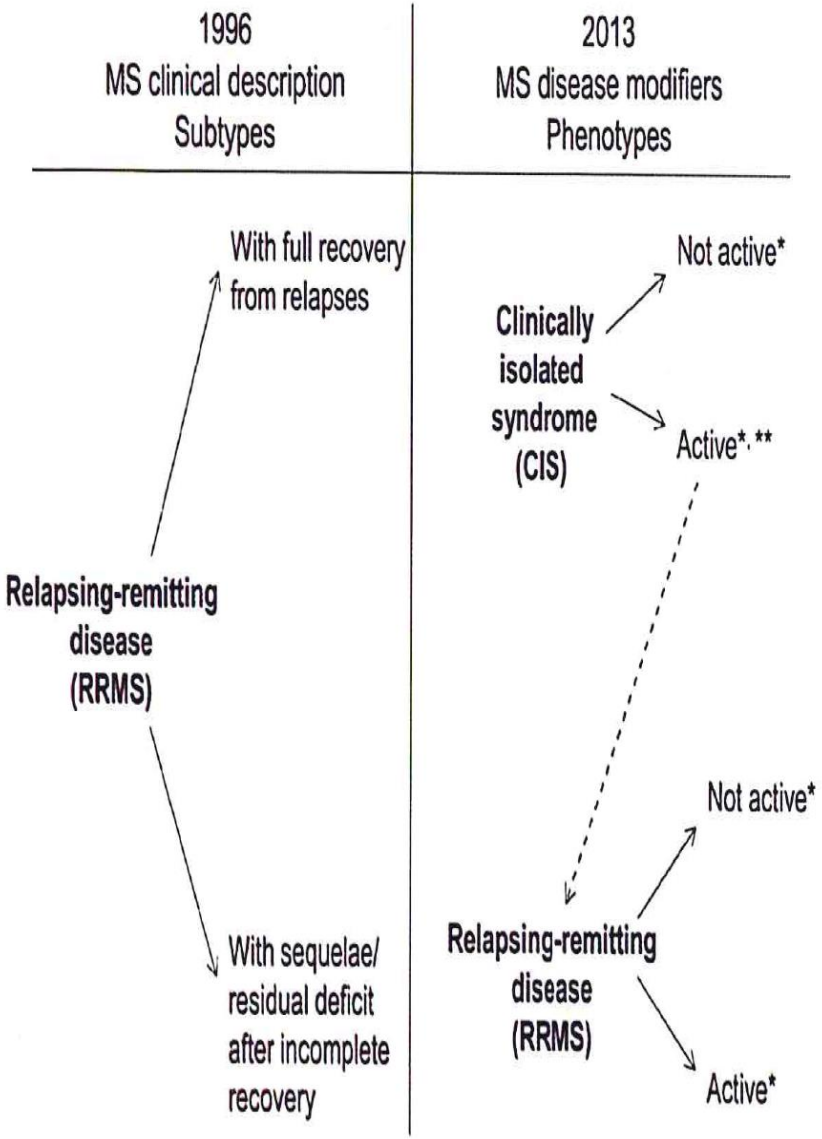


Progression of untreated population

Untreated, about **50%** of people with **RRMS** transition into **SPMS (secondary progressive MS)** within a decade of initial diagnosis.

Source: National Multiple Sclerosis Society and NCBI





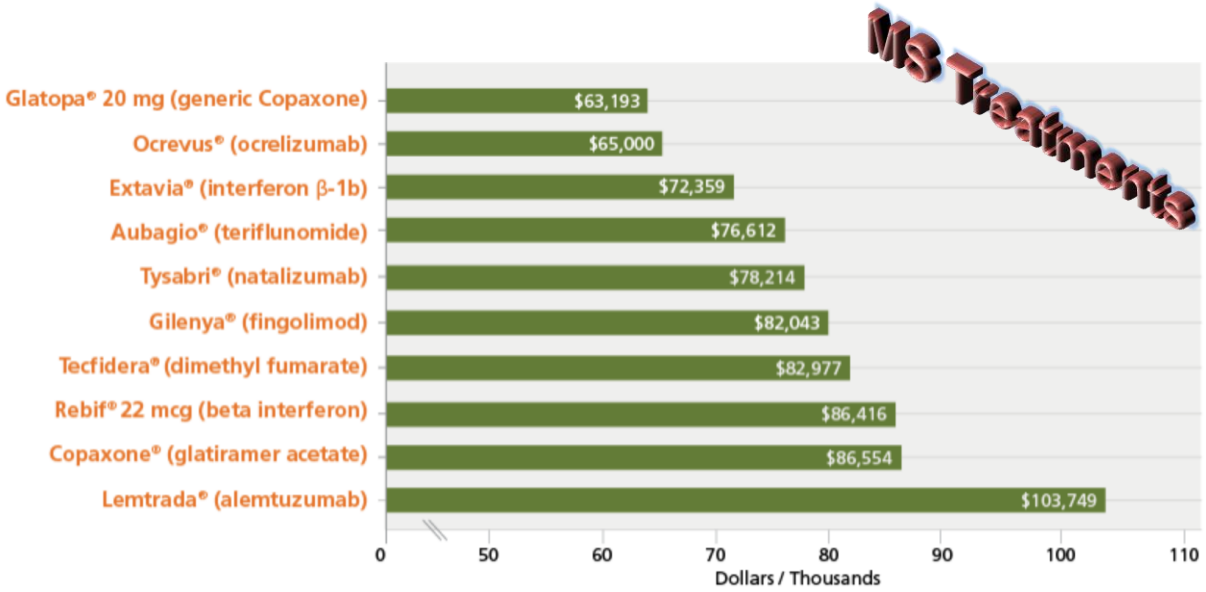
Lublin et al., Neurology 2013

Cost

- Annual cost of $65K USD per patient with disease modifying treatment.

- Proportion of patients with NEDA (no evidence of disease activity: no disability progression, no relapses, no new or enlarging lesions on MRI) is 30-50% in 2 years of treatment, and 18% after 4 years.

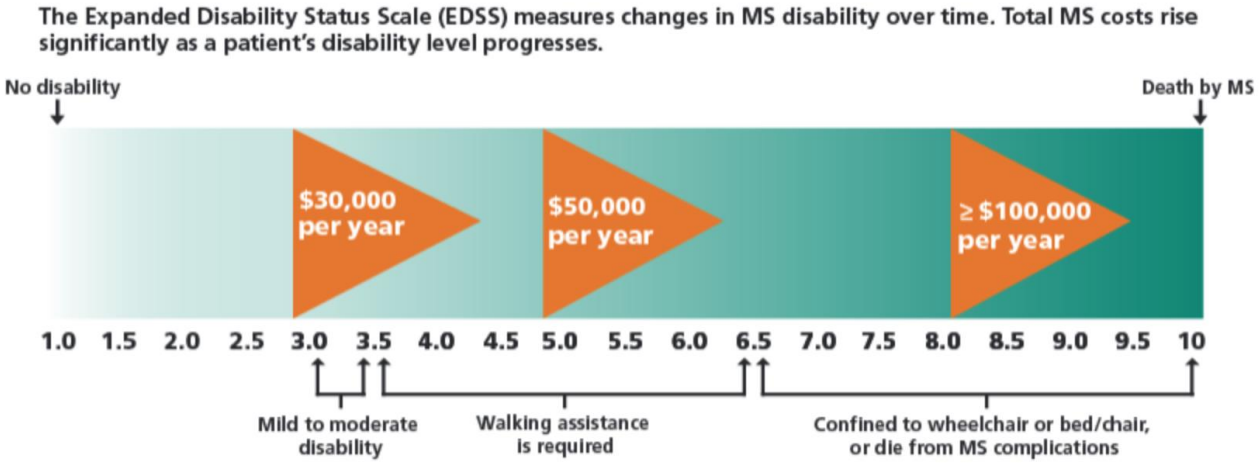
JAMA, Richard K. Burton 2019



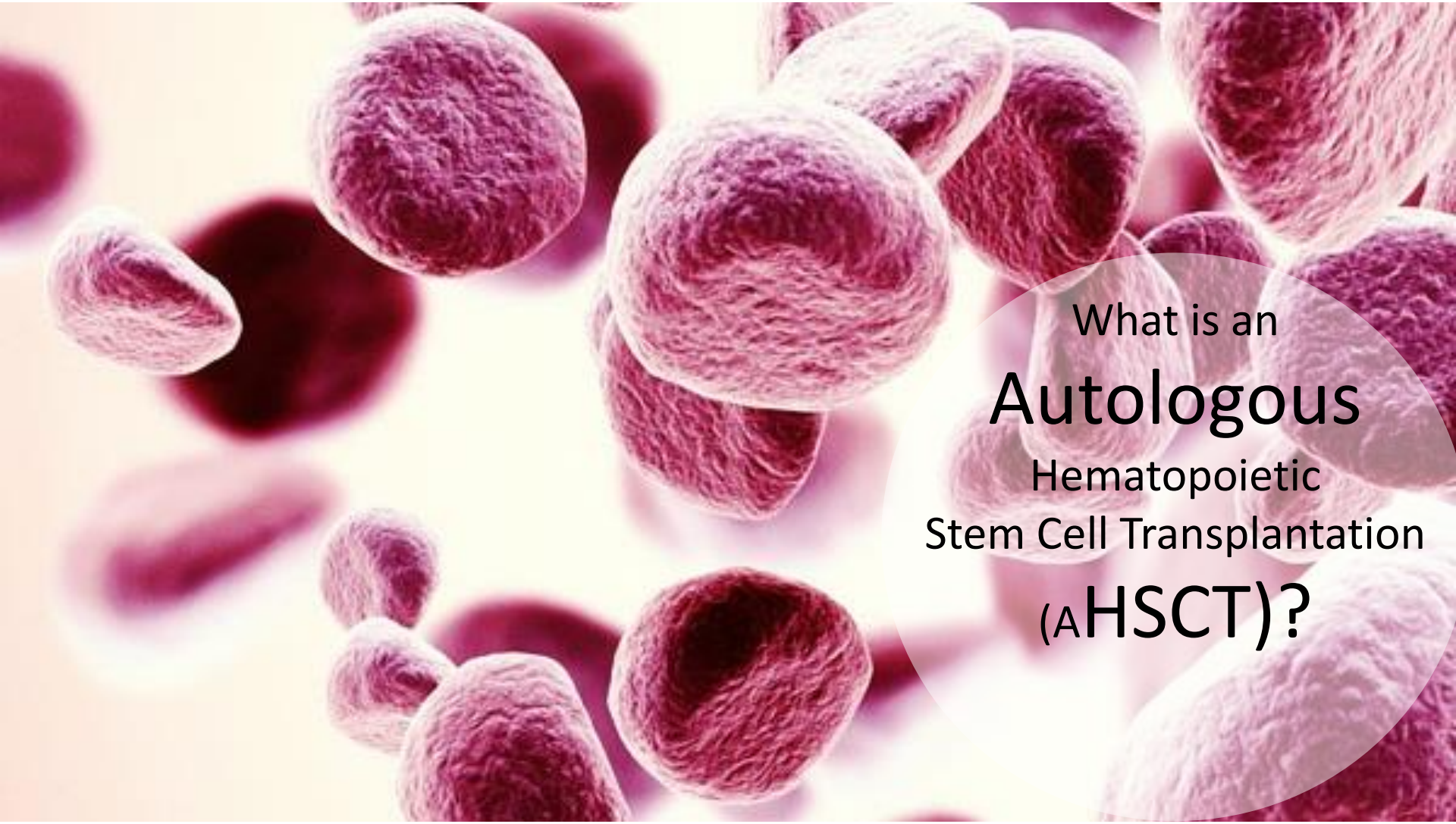
Institute for Clinical and Economic Review. Final Evidence Report – DMTs for RRMS and PPMS. March 6, 2017. [PDF]

Annual DMT's cost

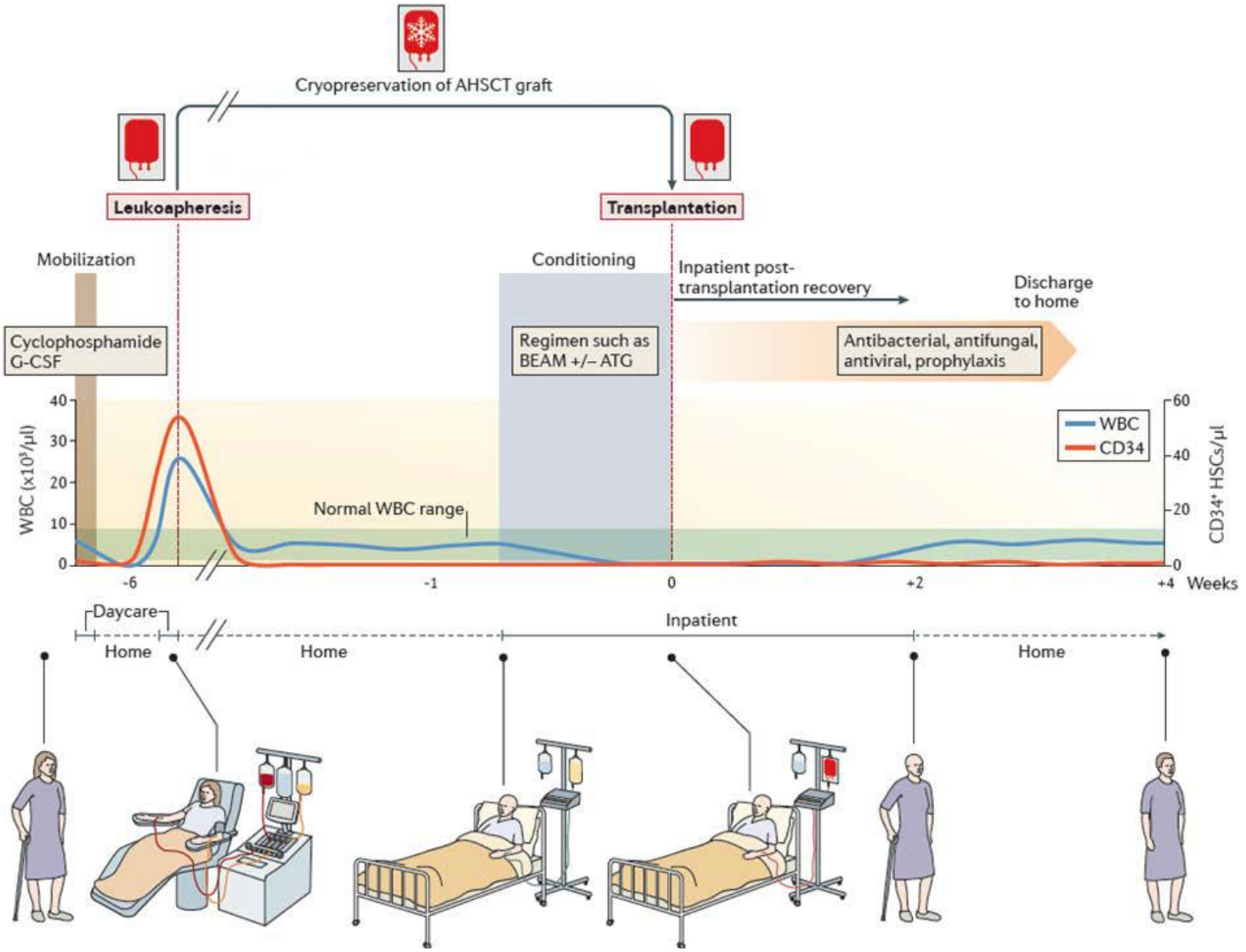
Cost of MS based on disability



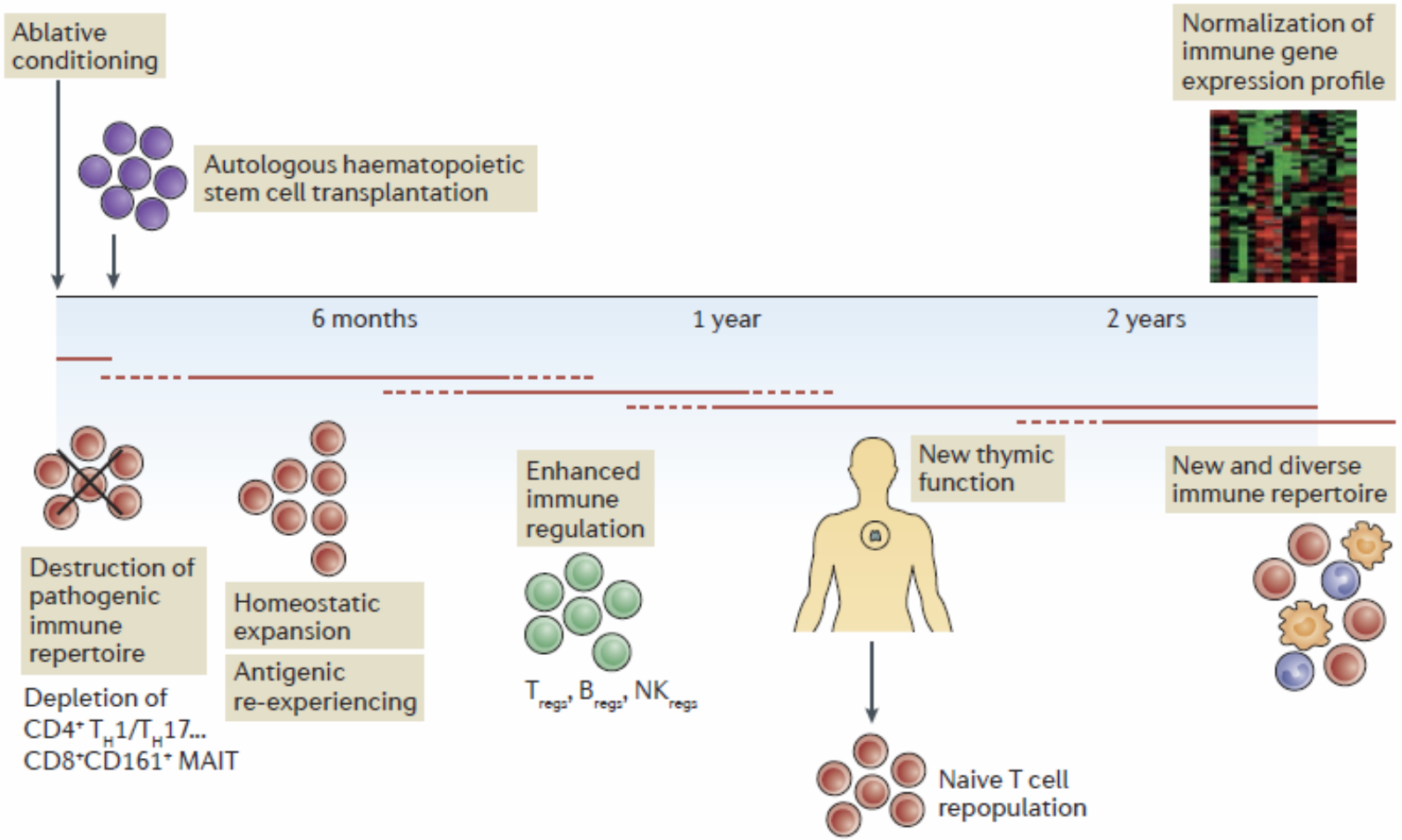
Sources: Expanded Disability Status Scale: Multiple Sclerosis Trust. At: https://www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss
Costs: *American Journal of Managed Care*. Economic Burden of Multiple Sclerosis and the Role of Managed Care Organizations in Multiple Sclerosis Management. May, 2016.


What is an
Autologous
Hematopoietic
Stem Cell Transplantation
(AHSCT)?

Autologous Hematopoietic Stem Cell Transplant-BEAM regimen



Immune Reconstitution Following HSCT



Resetting the Immune system

As a part of an autologous hematopoietic stem cell transplant, the patient's immune system is decimated after collection, so that it will rebuild itself afterwards.

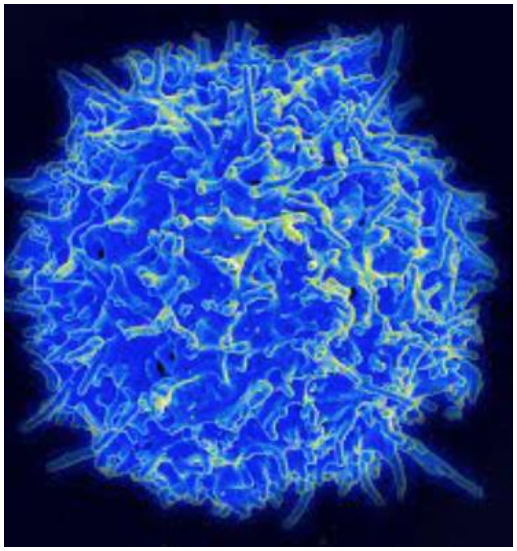
A reconstitution of both T- and B-cells is needed to re-establish self-tolerance

Establishing a New Immune Database

Post-transplant, it is shown that **the targets for T-cell receptors are different** and more diverse when compared to the same “database” these T-cells had to work with prior to the procedure.

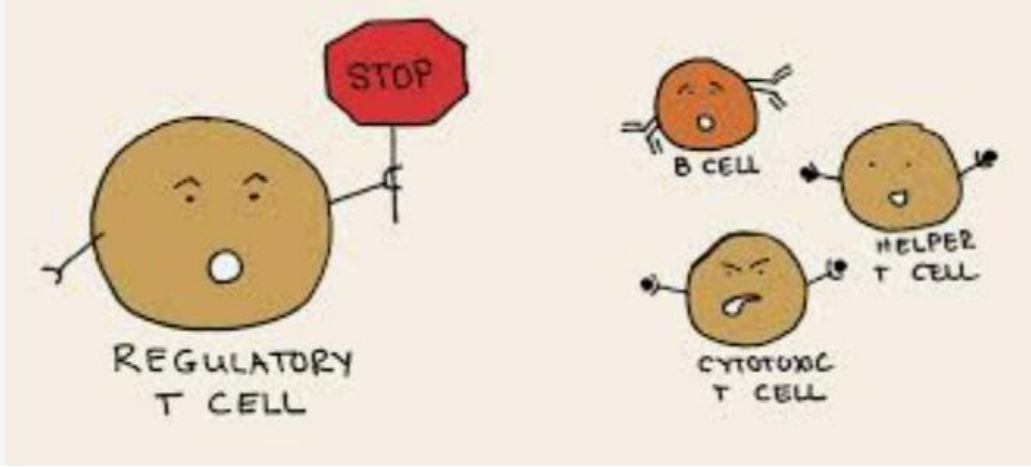
This is likely due to a reactivation of the thymus, as the balance again shifts to naïve T-cells in the periphery.

In this way, the mature memory of lymphocytes no longer includes the self-destructive targets it used to have that produced autoimmune disease



Reinstatement of Normal Immune Regulation

In most autoimmune disease, there is a deficiency in T_{reg} cells. However, with the reactivation of the thymus, T_{reg} cells appear to return to normal numbers and helps to maintain prolonged autoimmune remission.



First multicenter trial

HSCT vs. DMT

Concept

-Burt et al., Bone Marrow Transplant 1995

Preclinical

-Burt et al., Blood 1998 and 1999

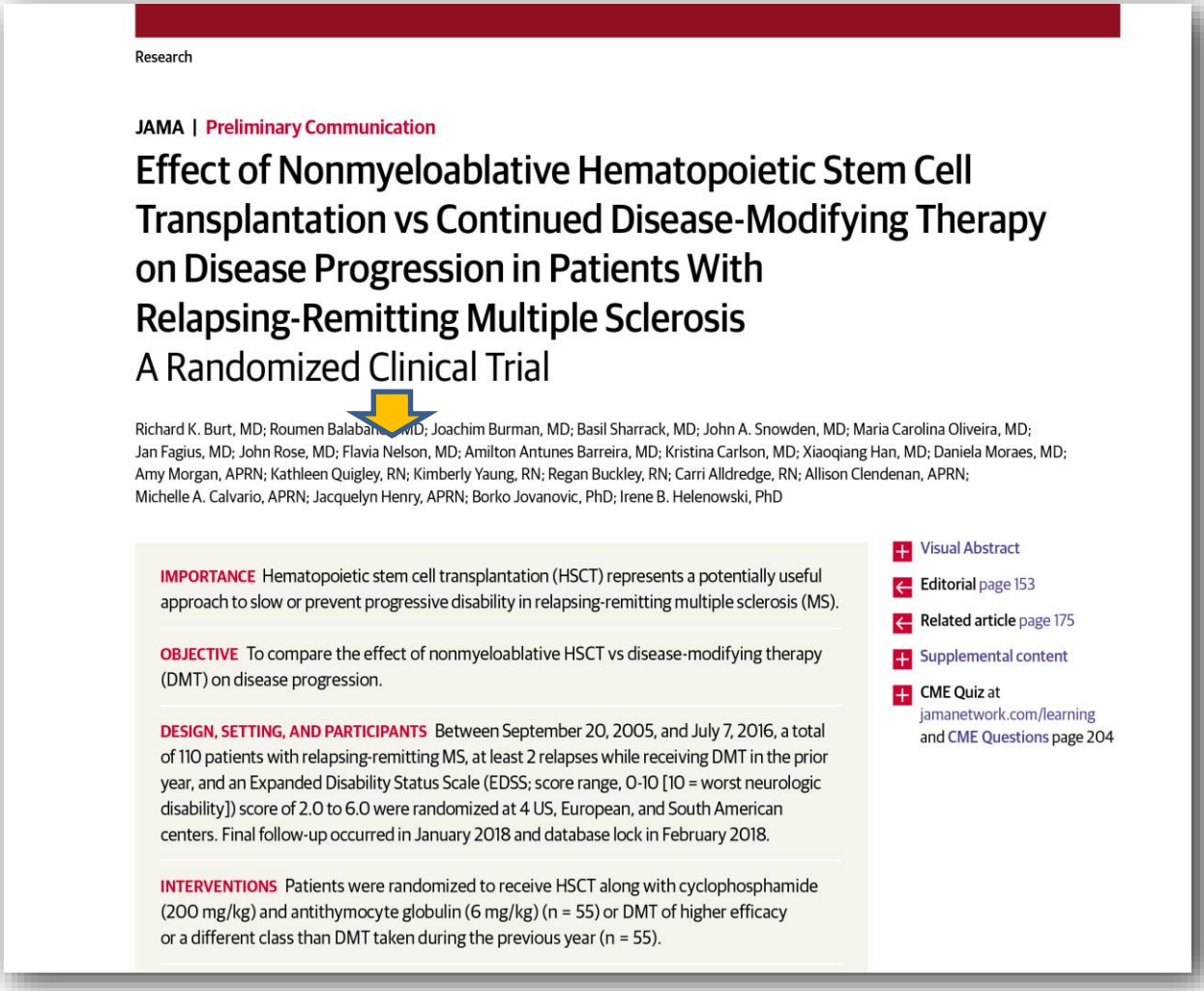
Clinical

-Burt et al., Blood 1998, 2003 (failure in 2nd progressive MS), and 2007

-Burt et al., Lancet Neurol 2009 (Lemtrada 2nd autoimmune)

MIST trial

-Burt et al., JAMA 2019



Research

JAMA | Preliminary Communication

Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis

A Randomized Clinical Trial

Richard K. Burt, MD; Roumen Balabanov, MD; Joachim Burman, MD; Basil Sharrack, MD; John A. Snowden, MD; Maria Carolina Oliveira, MD; Jan Fagius, MD; John Rose, MD; Flavia Nelson, MD; Amilton Antunes Barreira, MD; Kristina Carlson, MD; Xiaoqiang Han, MD; Daniela Moraes, MD; Amy Morgan, APRN; Kathleen Quigley, RN; Kimberly Yaung, RN; Regan Buckley, RN; Carri Alldredge, RN; Allison Clendenan, APRN; Michelle A. Calvario, APRN; Jacquelyn Henry, APRN; Borko Jovanovic, PhD; Irene B. Helenowski, PhD

IMPORTANCE Hematopoietic stem cell transplantation (HSCT) represents a potentially useful approach to slow or prevent progressive disability in relapsing-remitting multiple sclerosis (MS).

OBJECTIVE To compare the effect of nonmyeloablative HSCT vs disease-modifying therapy (DMT) on disease progression.

DESIGN, SETTING, AND PARTICIPANTS Between September 20, 2005, and July 7, 2016, a total of 110 patients with relapsing-remitting MS, at least 2 relapses while receiving DMT in the prior year, and an Expanded Disability Status Scale (EDSS; score range, 0-10 [10 = worst neurologic disability]) score of 2.0 to 6.0 were randomized at 4 US, European, and South American centers. Final follow-up occurred in January 2018 and database lock in February 2018.

INTERVENTIONS Patients were randomized to receive HSCT along with cyclophosphamide (200 mg/kg) and antithymocyte globulin (6 mg/kg) (n = 55) or DMT of higher efficacy or a different class than DMT taken during the previous year (n = 55).

Visual Abstract

Editorial page 153

Related article page 175

Supplemental content

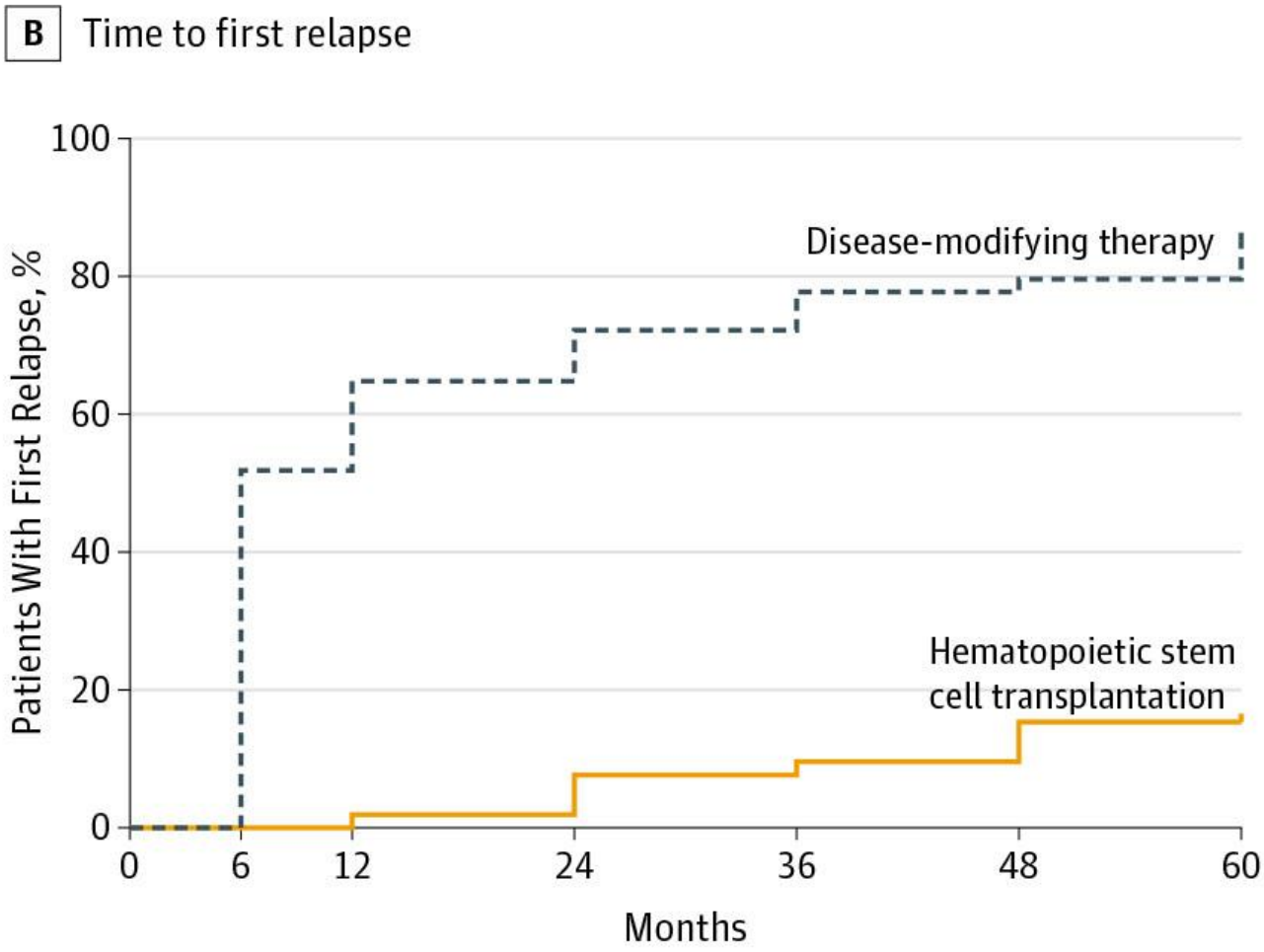
CME Quiz at jamanetwork.com/learning and CME Questions page 204

MIST trial

1st year evaluation (98):

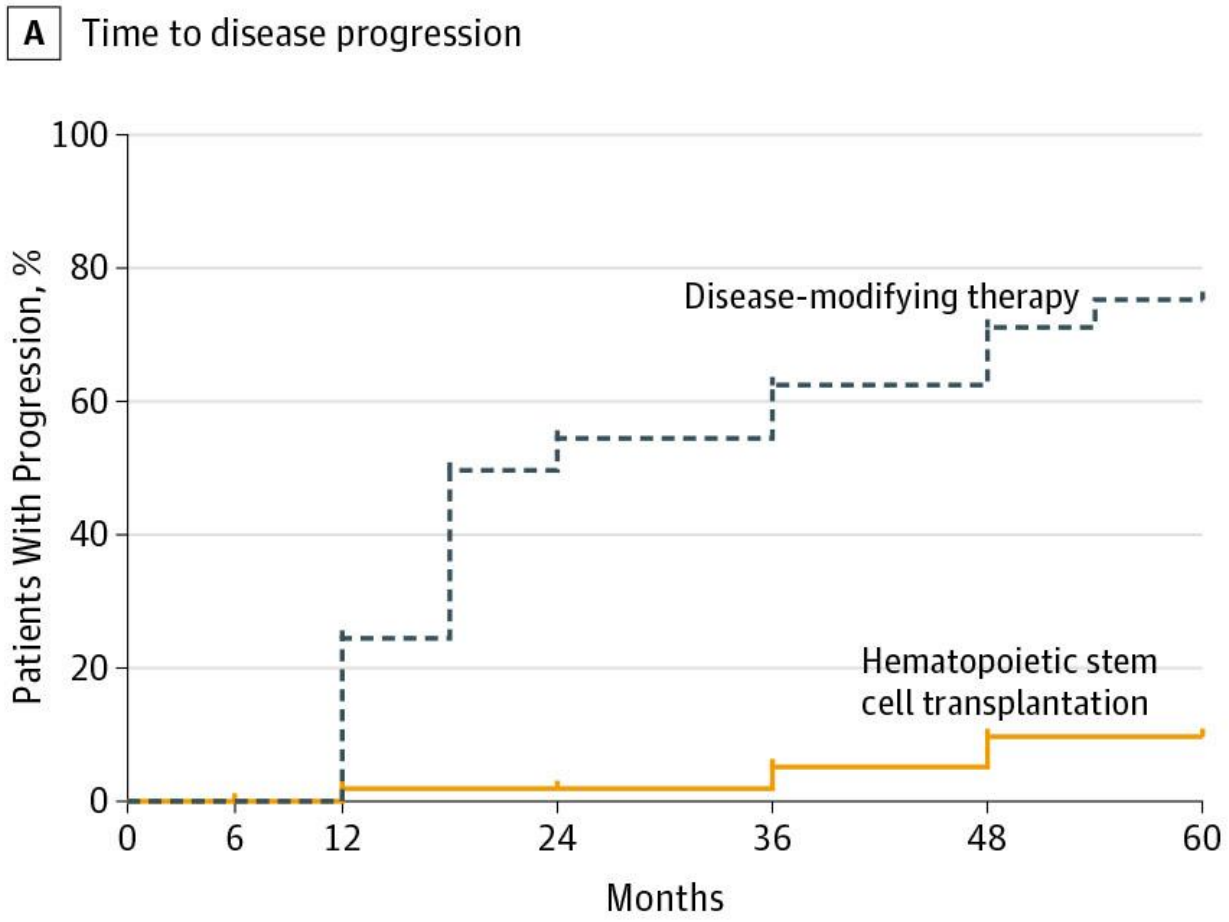
- **36 (69%) of 52 patients relapsed in the DMT group compared with 1 (2%) of 51 patients who relapsed in the HSCT group.**
- EDSS scores **improved** from **3.38 to 2.36** in the HSCT group
- EDSS **worsened** from 3.31 to 3.98 in the DMT group.
- Disease progression occurred in 3 patients in the HSCT group and 34 patients in the DMT group.
- DMT group: mean time 25-ft walk **worsened** from 5.59 seconds at baseline to 7.96 s, whereas in the HSCT group, mt 25-ft walk **improved** from 6.48 s to 6.01 s.
- There were no deaths during the study
- No patients who received HSCT developed non-hematopoietic grade 4 toxicities

Burt et al., JAMA 2019



Burt et al., JAMA 2019

RESULTS
MIST
PRIMARY
ENDPOINT



Burt et al., JAMA 2019

Disease progression by year

- For the HSCT group, the proportion of patients with disease progression was:

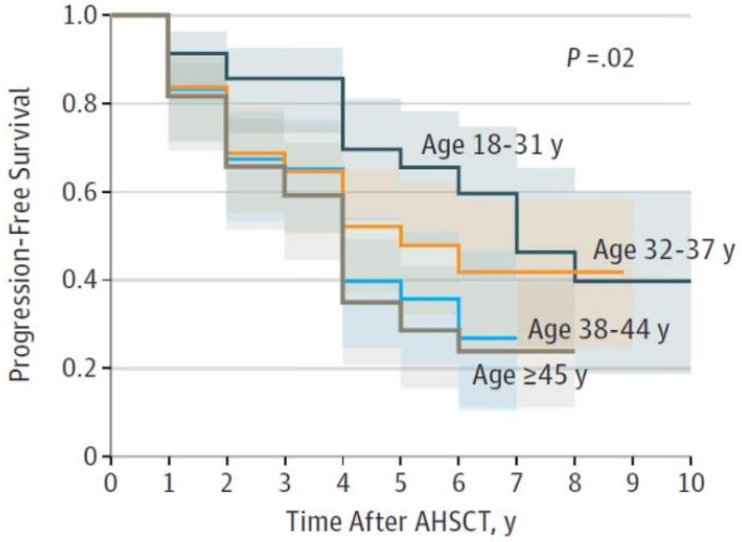
1.92% (95% CI, 0.27%-12.9%) at 1 year and 2 years,
5.19% (95%CI, 1.26%- 20.1%) at 3 years,
9.71% (95% CI, 3.0%-28.8%) at 4 and 5 years

- For the DMT group, the proportion of patients with disease progression was:

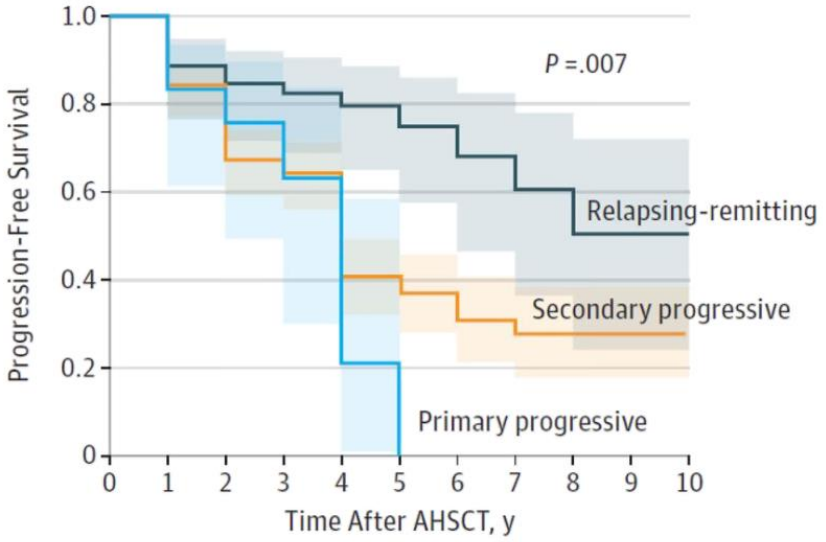
24.5% (95% CI, 14.7%-39.1%) at 1 year,
54.5% (95%CI,40.7%-69.4%) at 2 years,
62.5% (95%CI, 48.3%-76.7% at 3 years,
71.2% (95%CI, 56.8%-84.2%) at 4 years, and
75.3% (95% CI, 60.4%-87.8%) at 5 years.

Long Term MS Progression-Free Survival after AHCT

By age



By MS subtype

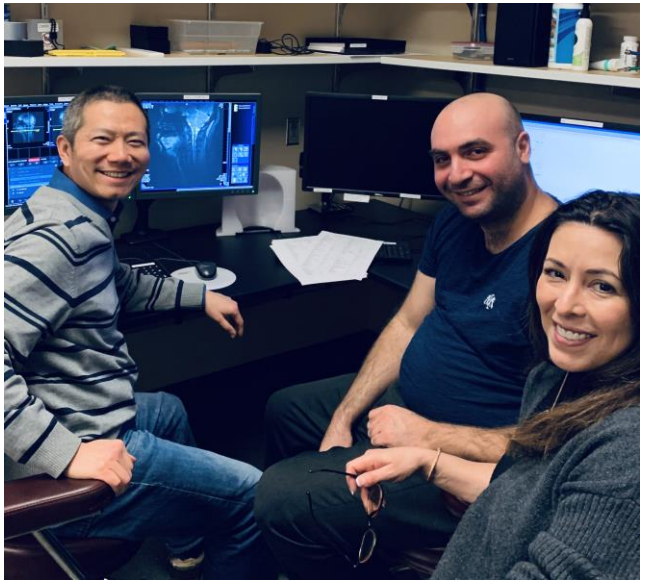


Probability of EDSS Progression-Free Survival after autologous hematopoietic cell transplantation
EBMT CIBMTR Analysis: 25 centers, 281 patients; AHCT between 1995-2006. Median follow-up 6.6 years

ASTCT

Muraro PA et al., JAMA Neurology (74) 2017

MRI OUTCOMES



MRI results

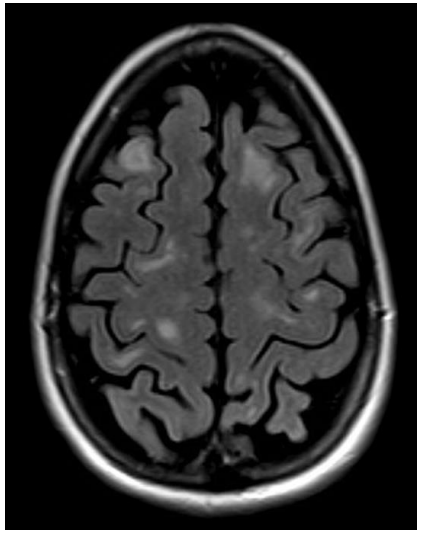
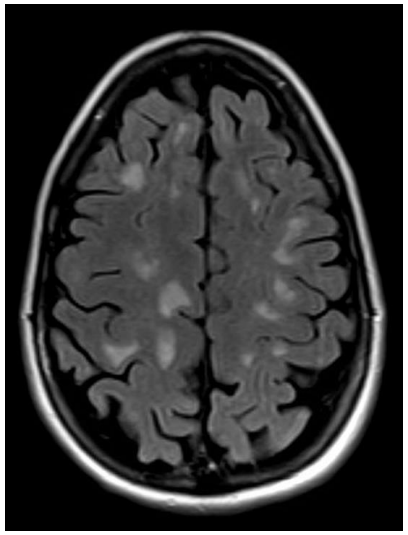
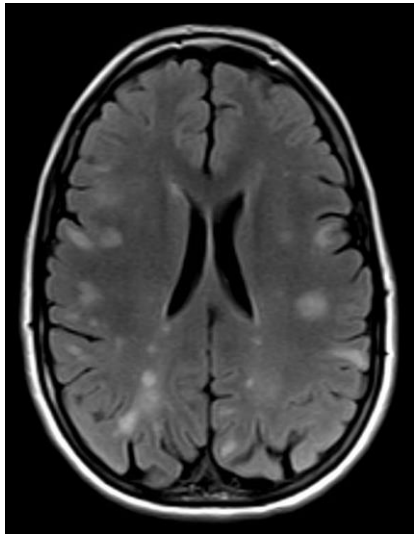
The MIST trial was the first to incorporate centralized MRI analysis that included T2 lesion volume (T2LV) estimation, rather than lesion number.

- MRI results showed that in the AHSCT arm, mean T2LV **decreased** by 24.4% at month 6 (16.2 cm^3 to 12.81 mm^3), and by 31.7 % (to 12.33 cm^3) at year 1, compared with pre-HSCT baseline.
- In the DMT arm, mean T2LV **increased** by 29% from baseline (12.54 cm^3 to 14.04 cm^3) at month 6, and by 34.3% (to 15.14 cm^3) at year 1.
- This is the first reported significant decrease in T2LV in a phase III clinical trial.

Burt et al., JAMA 2019

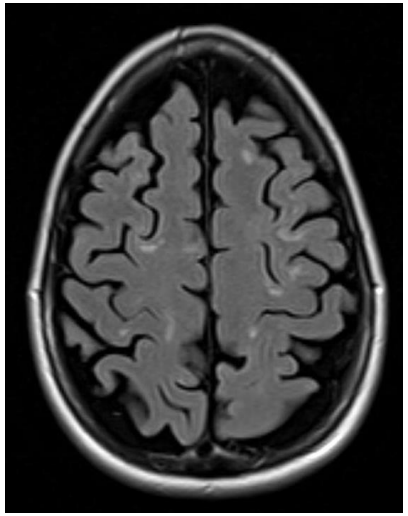
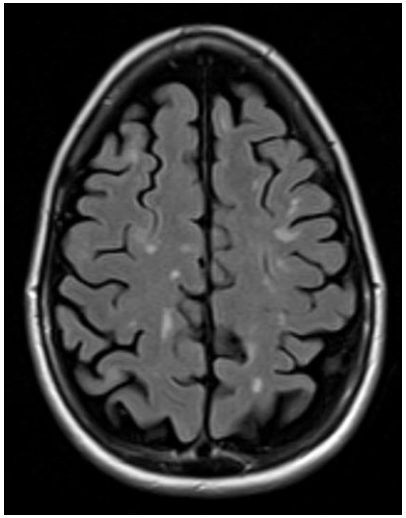
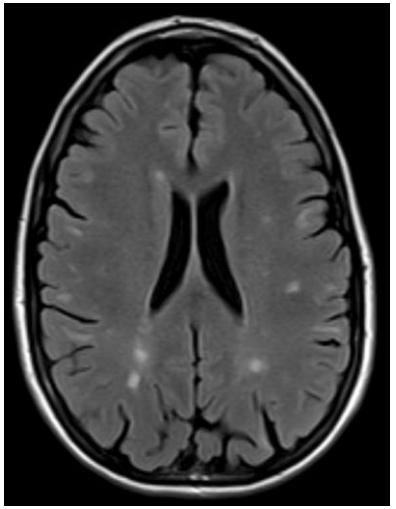
Patient 1

Before HSCT

Baseline T2LV = 30.273 cm^3

After HSCT

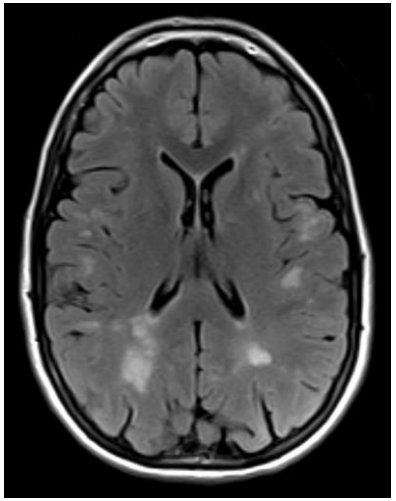
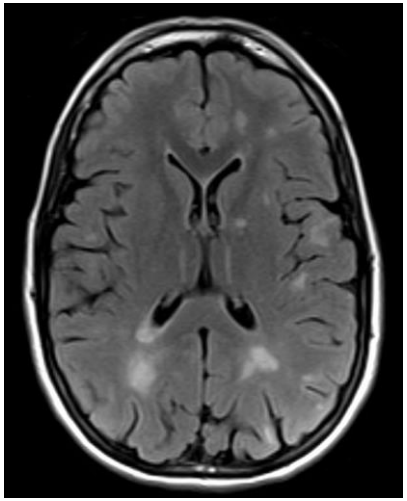
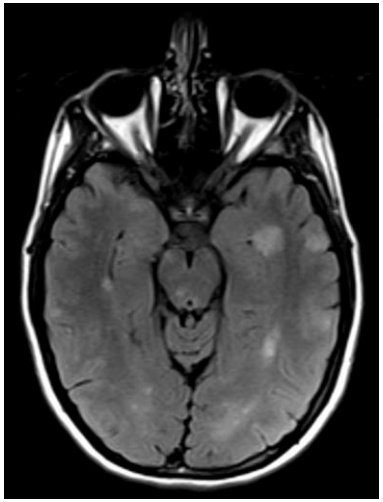




5y Post HSCT T2LV = 8.055c^3

Reduction in T2LV = 73.4%

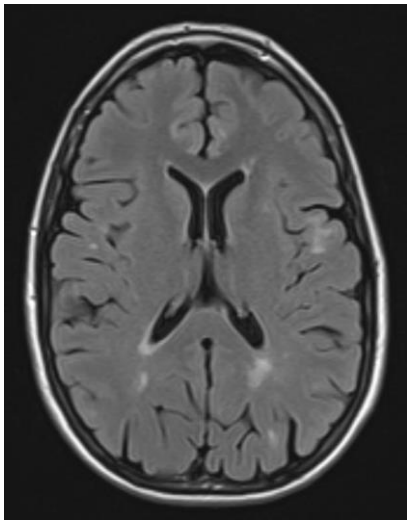
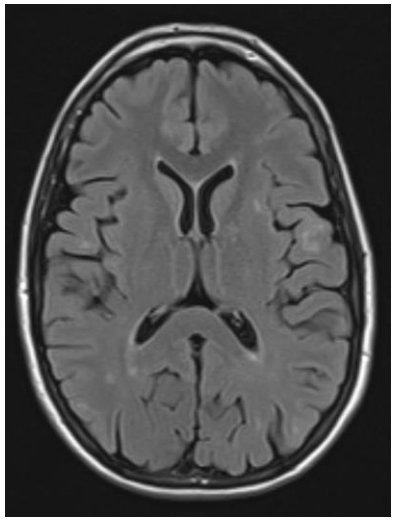
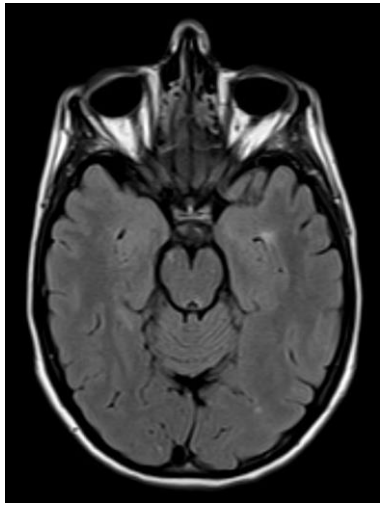
Patient 1

Before HSCT

T2LV Baseline : 30.273 cm^3

After HSCT

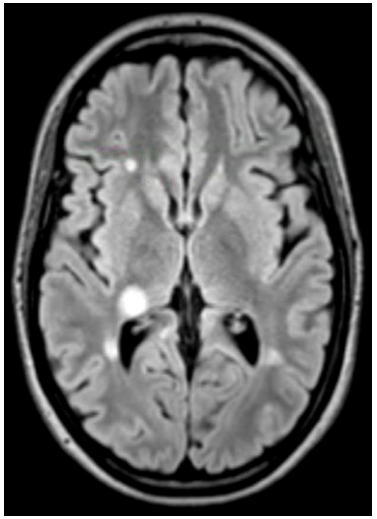
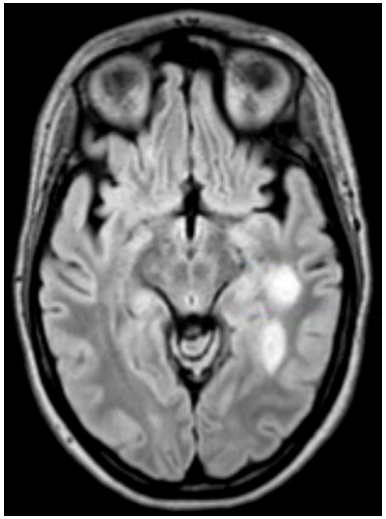
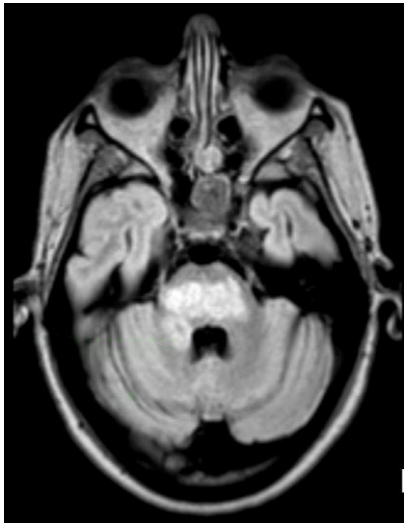




5y Post HSCT: 8.055 cm^3

T_{2LV} Reduction: 73.4%

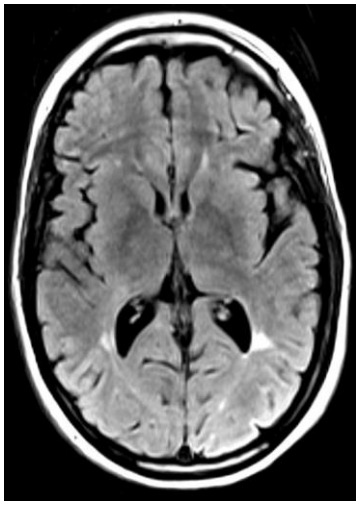
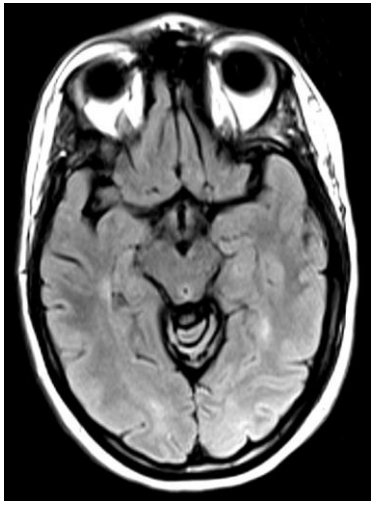
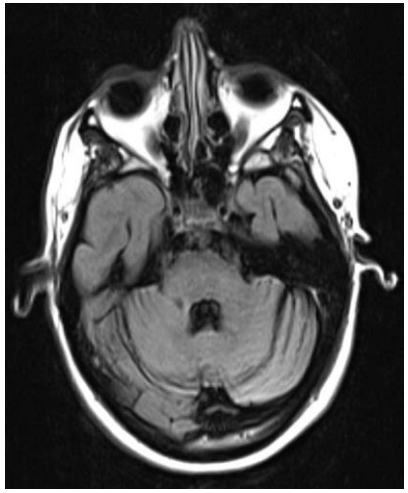
Patient 2

Before HSCT

Baseline T2LV at = 41,995 cm^3

After HSCT

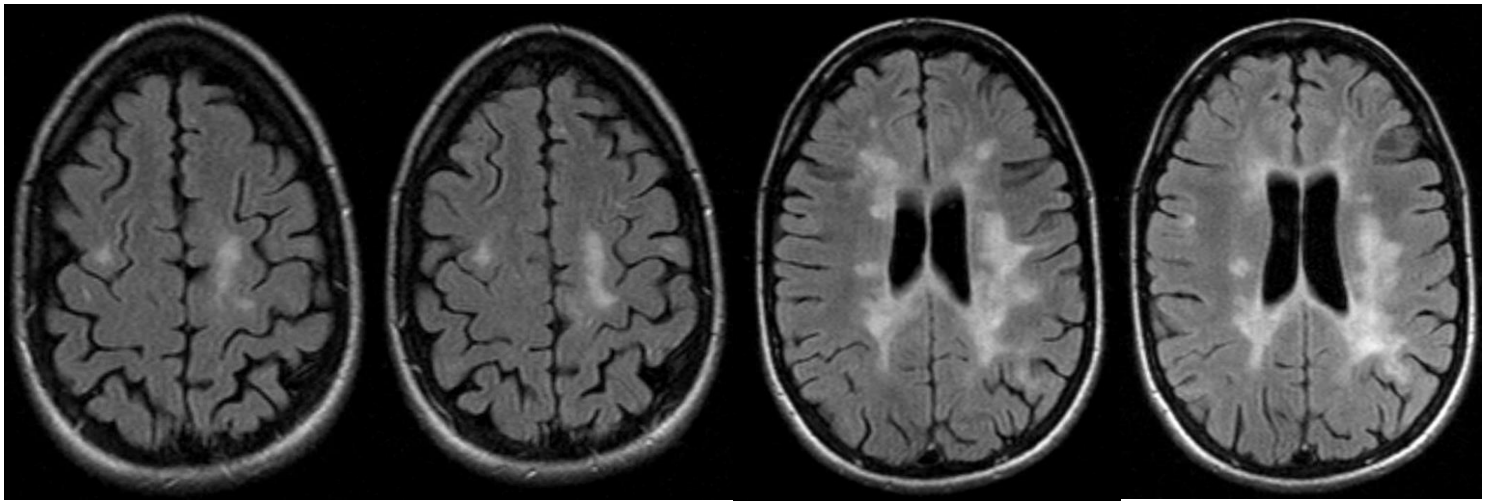




5y Post HSCT = 8.913 cm^3

Reduction in T2LV = 78.5%

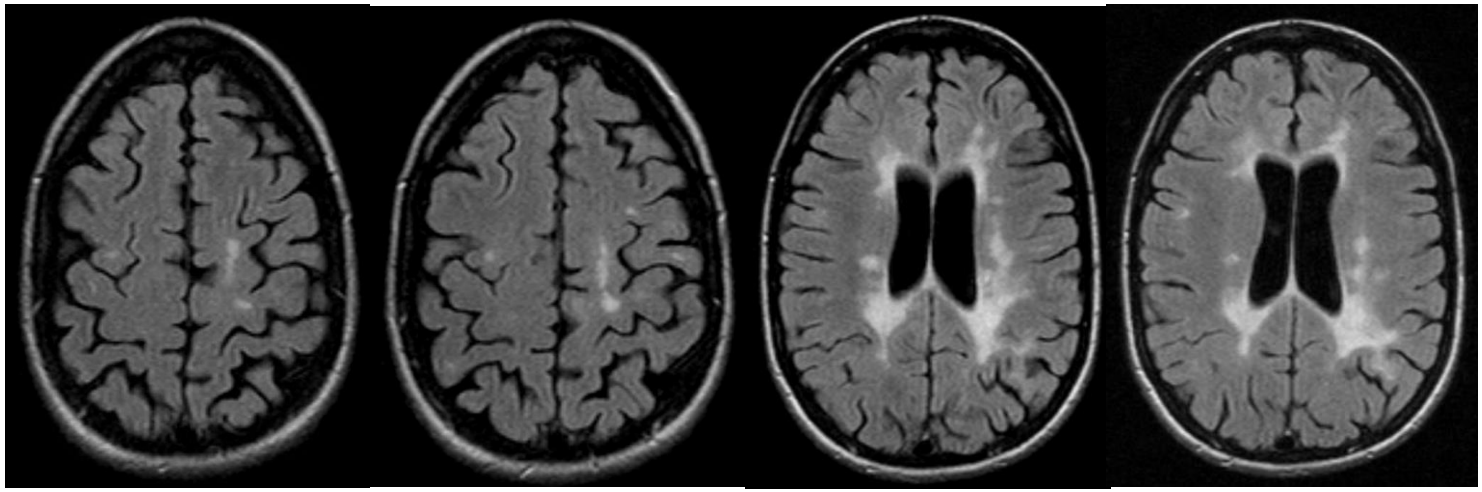
Patient 3

Before HSCT



Baseline T2LV: 71.802 cm^3

After HSCT



2y Post HSCT T2LV: 45.247 cm^3

T2LV Reduction 37 %

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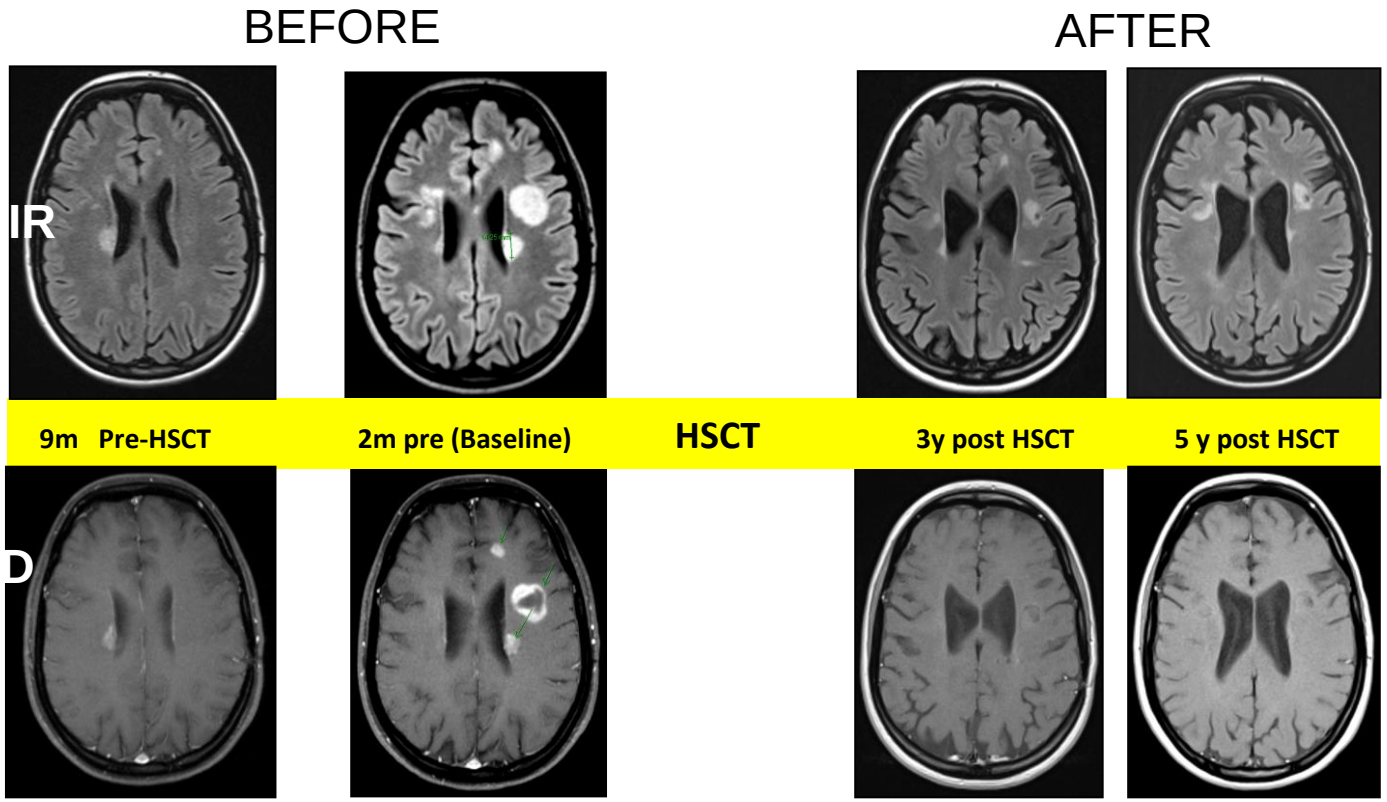
LESION EVOLUTION



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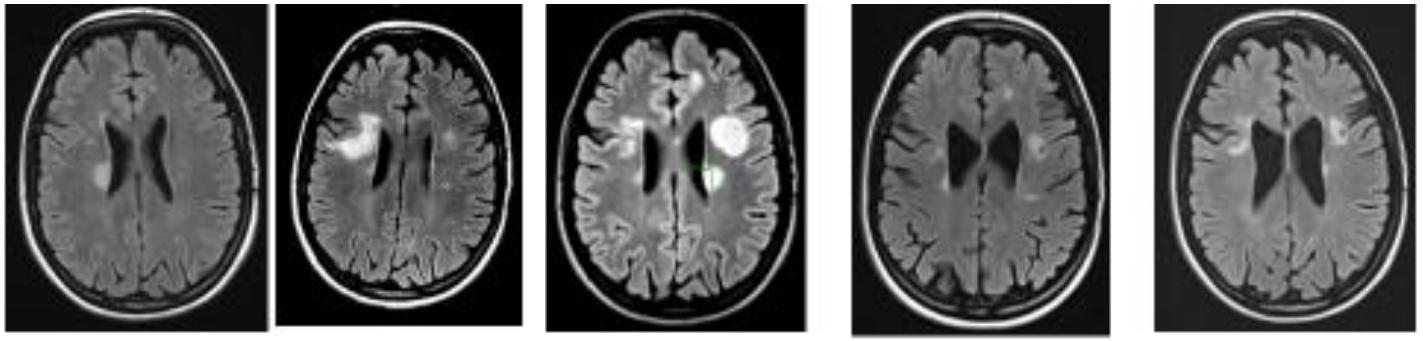
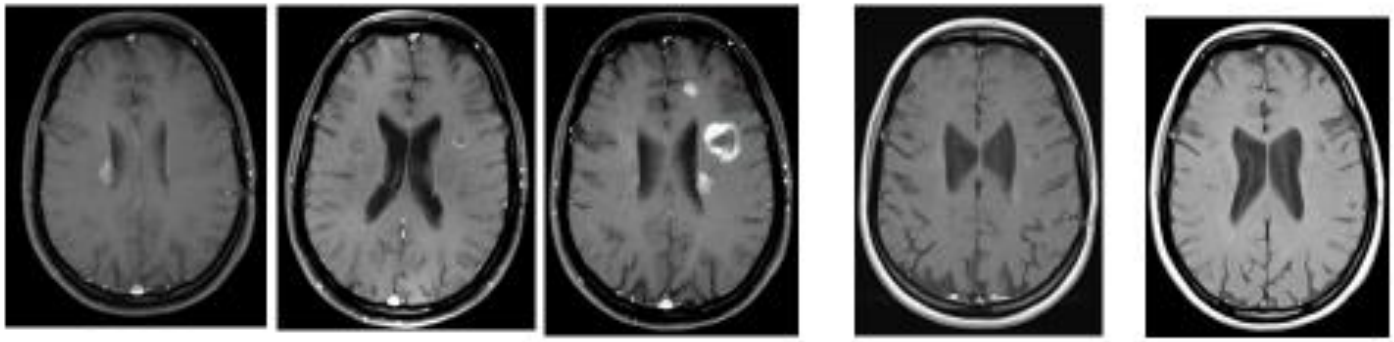


Patient D.B

9m Pre-HSCT | 5m Pre-HSCT | 2m pre-HSCT(Baseline) | 3 years post transplant | 5 years post transplant



Time	9m pre	5m pre	3m pre	2m pre	6m post	1y post	2y post	3y post	4y post	5y Post
T2LV (cm^3)	13.437	18.948	20.779	41.995	8.913	6.938	6.945	6.709	6.568	6.52
Enhancing Lesions	5	4	6	15	0	0	0	0	0	0

Adverse effects MIST trial

In the HSCT:

- **16 upper respiratory tract infections.**
- **6 urinary tract infections.**
- **7 dermatomal varicella zoster reactivations.**
- **1 Idiopathic thrombocytopenic purpura.**

Neverthless, complications were not exent in the DMT group.

- The rate of infection per patient per year was 0.19 in the HSCT group and 0.23 in the DMT group.

Burt et al., JAMA 2019

MRI endpoints in AHSCT clinical trials

- In the randomized phase II clinical trial **ASTIMS,** the primary outcome was T2 lesion number, the study compared AHSCT (n9) vs. Mitoxantrone (n12) in MS.
- Results showed a significant decrease in T2 lesion number in the AHSCT arm. Over the 4-year period, the median number of new T2 MRI lesions was 2.5 in AHSCT vs 8 in Mitoxantrone (rate ratio, 0.21; 95% CI, .1-.48; p= .00016).
- Secondary endpoints showed no gadolinium enhancing lesions in the AHSCT arm over the same period vs. at least 1 gad lesion in 56% of patients treated with Mitoxantrone.
- ARR was 0.19 in AHCT vs. 0.6 in the Mitoxantrone arm, (rate ratio 0.36, 95% CI 0.15-0.88; p = .026).

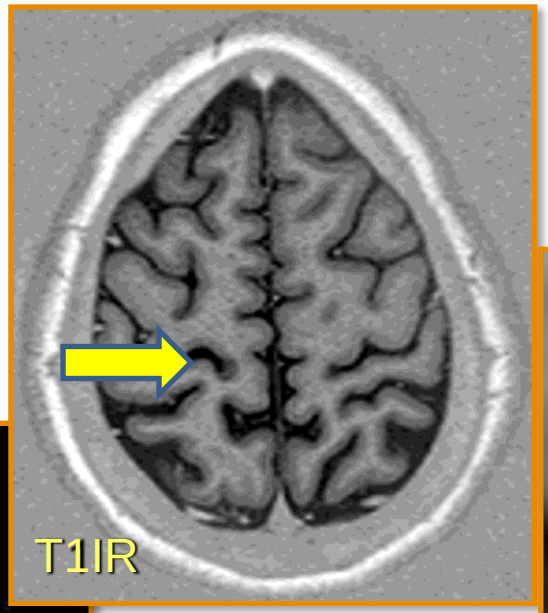
Cohen et al ., bbmt.2019.

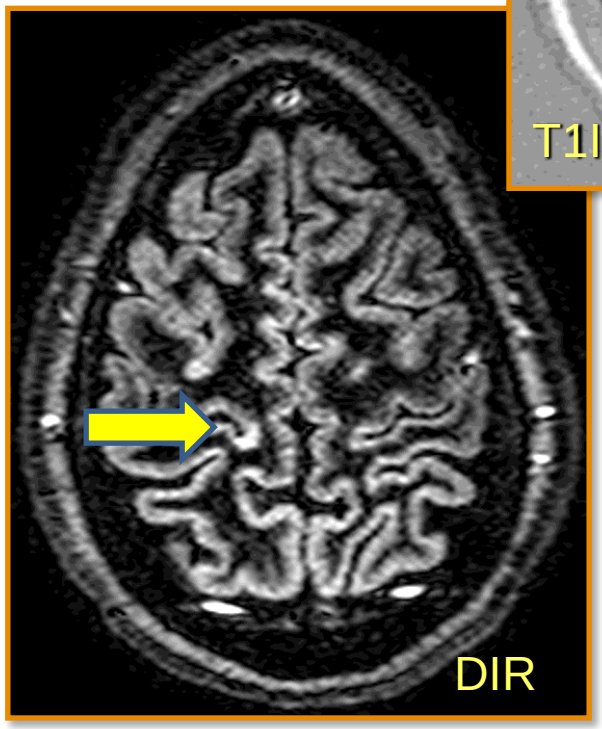
Not evaluated in BEAT MS: evidence of repair by MRI

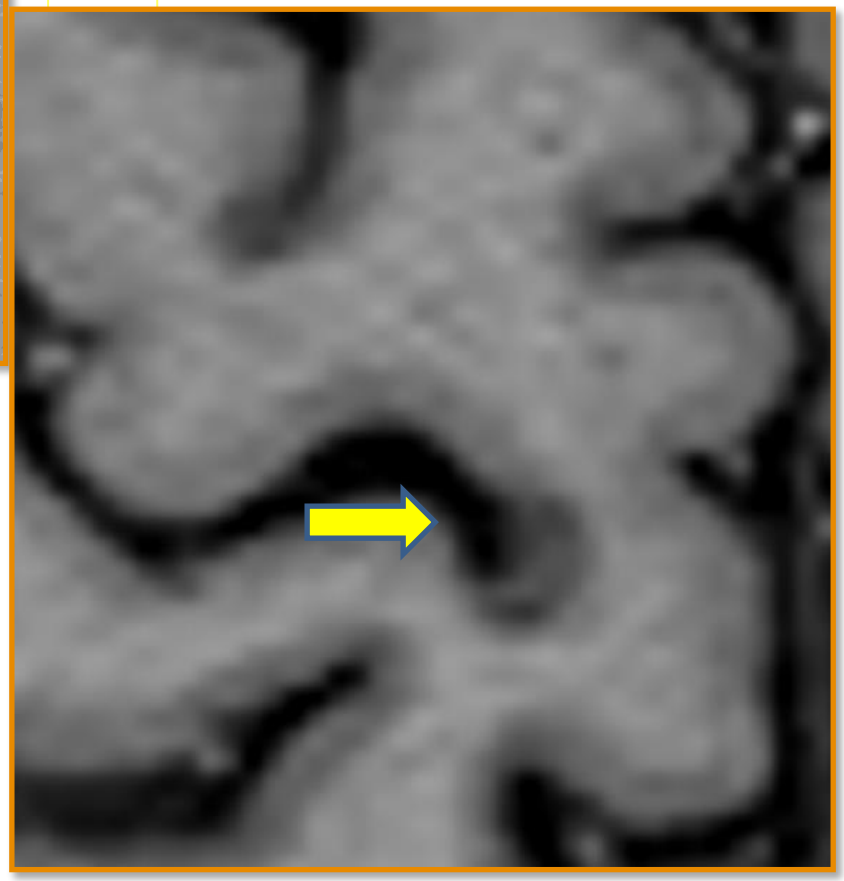
- Repair sub-study (University of Minnesota-CMRR ONLY)
- Repair protocol will include:
- Double inversion recovery (DIR): detects cortical gray matter lesions
- Diffusion Tensor Imaging (DTI): detects white matter tract damage and axonal diameter
- RAFF 4, T1 and T2ρ: detection of NAWM with loss of neuronal cells and their axons, decreased levels of myelin even in NAWM, and altered iron content.
- Functional MRI to evaluate cognition (information processing speed)

Cortical Pathology at 3T

Cortical pathology part of 2017 Mc Donald criteria

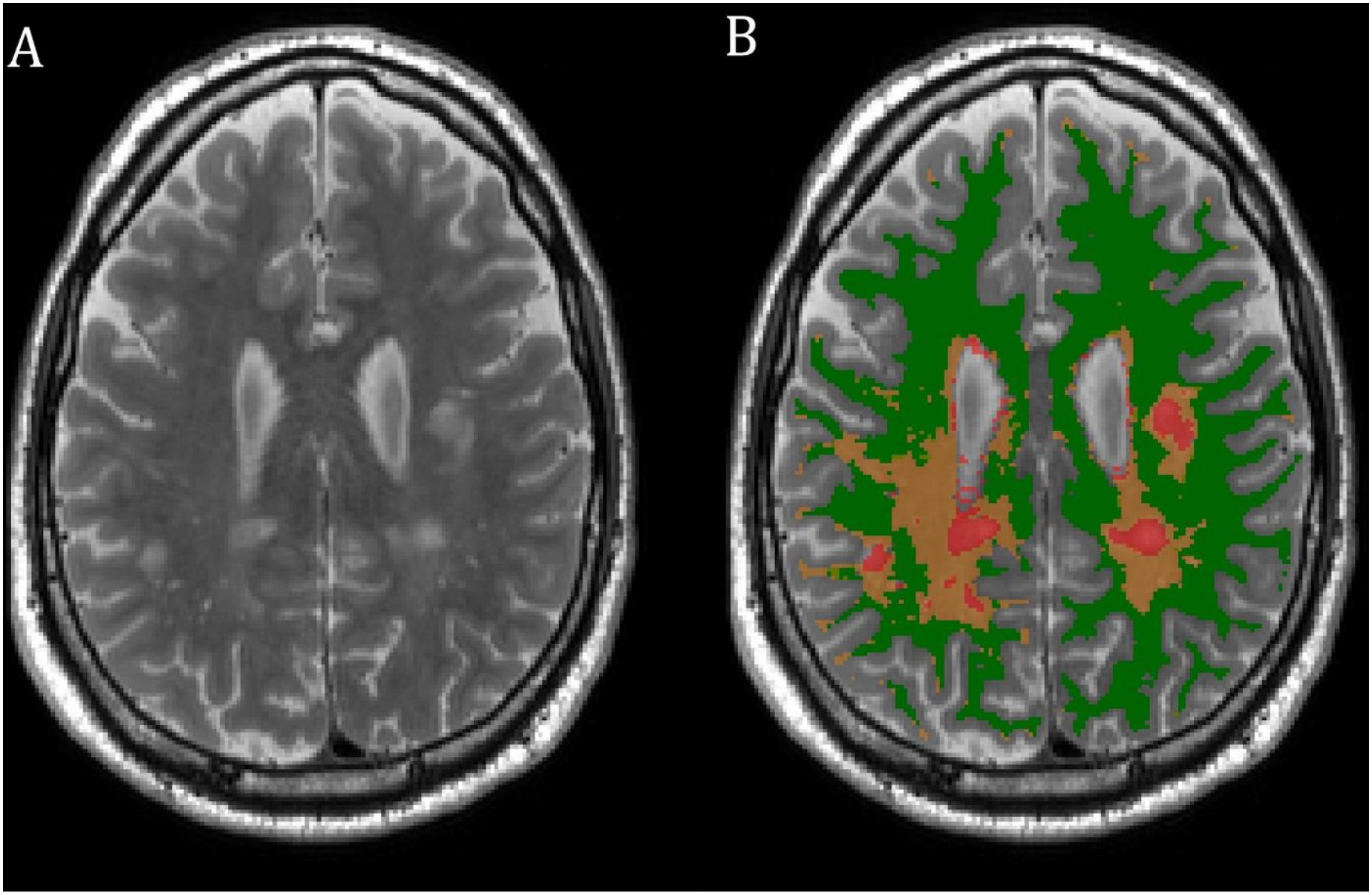






Nelson et al. AJNR 28:1645, 2007

Raff 4 (at 4T): Detects damage to normal appearing white matter (green)



NEDA (No evidence of disease activity)

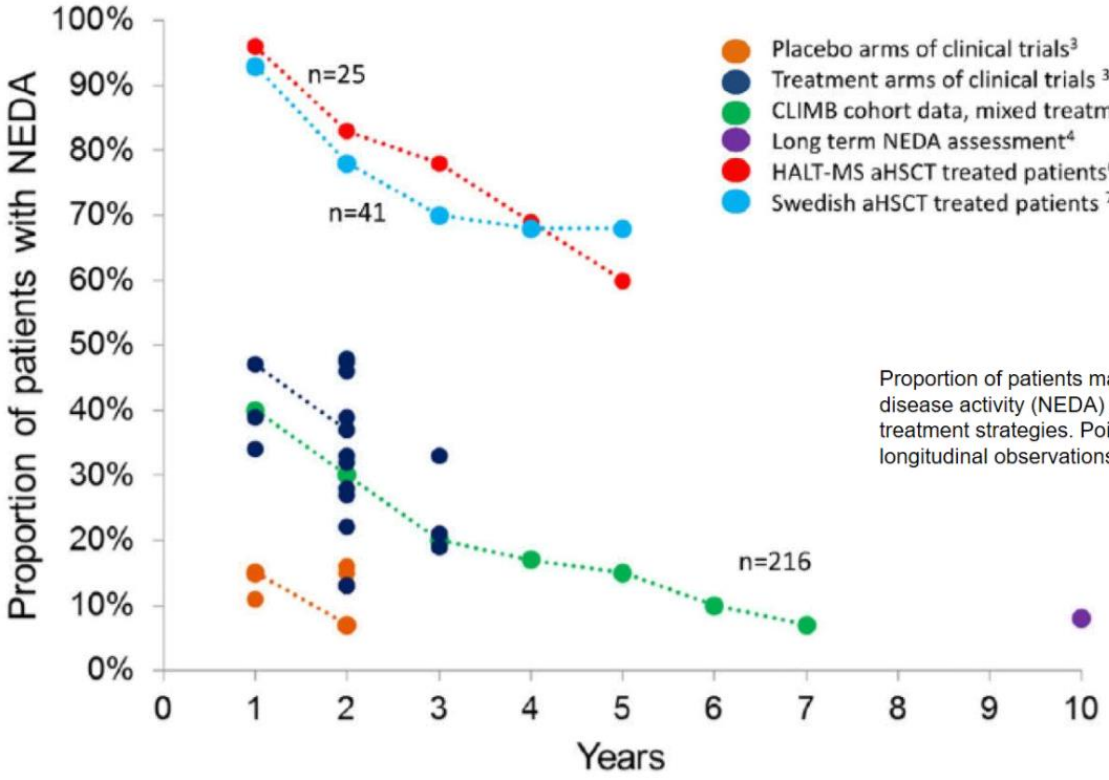
- Metanalyses data from AHSCT studies showed important findings regarding NEDA 3:

1 no relapses
2 no disability progression,
3 no MRI metrics of disease activity

- In studies of AHCT (n = 66) compared with DMTs (n = 216), AHSCT resulted in NEDA rates of **78% to 83% at 2 years and 60% to 68% at 5 years**.

- In contrast, studies of conventional MS DMTs, including those considered to be high efficacy, reported NEDA rates of **13% to 46% at 2 years**.

Comparison of NEDA status after various treatments



Proportion of patients maintaining the no evidence of disease activity (NEDA) status over time under different treatment strategies. Points connected by a line represent longitudinal observations in the same study.

ASTCT

Sormani MP, et al., MS Journal, Feb 2017

Position Statement

Autologous Hematopoietic Cell Transplantation for Treatment- Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation (ASBMT)

Jeffrey A. Cohen[1,*], Laura E. Baldassari[1], Harold L. Atkins[2], James D. Bowen[3], Christopher Bredeson[2], Paul A. Carpenter[4], John R. Corboy[5], Mark S. Freedman[6], Linda M. Griffith[7], Robert Lowsky[8],Navneet S. Majhail[9], Paolo A. Muraro[10], Richard A. Nash[11], Marcelo C. Pasquini[12], Stefanie Sarantopoulos[13],Bipin N. Savani[14], Jan Storek[15], Keith M. Sullivan[13], George E. Georges[4]

- Multiple sclerosis is a chronic, disabling, immune-mediated, demyelinating and degenerative disease of the central nervous system. Approved disease-modifying therapies may be incompletely effective in some patients with highly active relapsing disease and high risk of disability.

- The use of immunoablative or myeloablative therapy followed by AHCT has been investigated in retrospective studies, clinical trials, and meta-analyses/systematic reviews as an approach to address this unmet clinical need.

- **On behalf of the American Society for Blood and Bone Marrow Transplantation (ASBMT), a panel of experts in AHCT and MS convened to review available evidence and make recommendations on MS as an indication for AHCT.** A review of recent literature identified 8 retrospective studies, 8 clinical trials, and 3 meta-analyses/systematic reviews. In aggregate, these studies indicate that AHCT is an efficacious and safe treatment for active relapsing forms of MS to prevent clinical relapse, magnetic resonance imaging-detectable lesion activity, and worsening dis- ability and to reverse disability without unexpected adverse events.

- **Based on the available evidence, the ASBMT recommends that treatment-refractory relapsing MS with high risk of future disability be considered a "standard of care, clinical evidence available" indication for AHCT.**

Cohen et al ., https://doi.org/10.1016/j.bbmt.2019.

BEAT-MS TRIAL

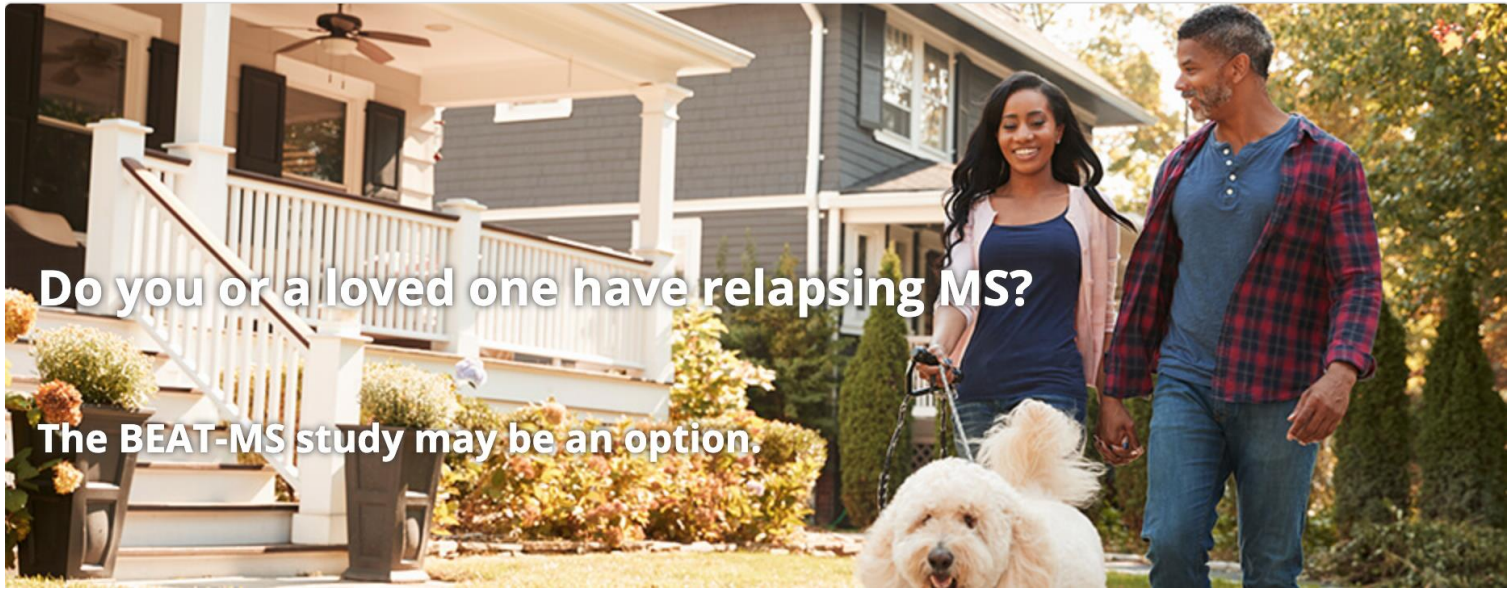
Use of Stem Cells Transplantation for treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

beat-ms

A clinical study for relapsing multiple sclerosis

BEAT-MS is currently enrolling study participants

HOME | ABOUT RELAPSING MS | ABOUT BEAT-MS | AM I ELIGIBLE? | STUDY LOCATIONS



Beat-ms: study design

- This is a multi-center prospective rater-blinded randomized controlled trial sponsored by the Immune Tolerance Network and the National Institute of Health of 156 participants comparing the treatment strategy of myeloablative and immunoablative therapy followed by autologous hematopoietic stem cells transplant (**AHSCT**) vs. the treatment strategy of best available therapy (**BAT**) for treatment-resistant relapsing multiple sclerosis.
- Participants will be randomized on a 1:1 ratio.
- The study will be conducted at sites in the United States and in the United Kingdom (pending)
- Total study duration target is 108 months (9 years):
- Enrollment phase target is 36 months (3 years).
- Study participation phase will be 72 months (6 years).

Study objectives

- To compare efficacy, safety, immunologic effects, and **cost-effectiveness** of **AHSCT** vs **BAT** over 72 months in RRMS and continue MS disease activity despite treatment with DMTs

- The primary efficacy objective is to compare the occurrence of MS relapse or death from any cause.

- Secondary and exploratory efficacy objectives will compare disease activity assessed clinically and by **MRI**, worsening and improvement in **clinical disability**, and neurodegeneration measured by MRI and **neurofilament light chain (NfL).**

- Overall safety and specific safety outcomes will be compared.

- As exploratory objectives, self-reported health status, quality of life, cost-utility and differences in immune signatures will be compared.

Beat MS vs. MIST (Use of DMT)

Both trials allow DMT selection to be done by the primary treating neurologist.

Beat MS : Best available therapy arm

- High efficacy drugs: Ocrelizumab (and other anti CD20/19)

Natalizumab, Alemtuzamab, Cladribine.

MIST: Best available therapy arm:

- No high efficacy drugs were used (not available at the time), except for Natalizumab, Fingolimod, Interferons, GA, Teriflunomide, Dimethyl Fumarate.

Of note: Patients failing a particular DMT were NOT allowed to continued on it

The first transplant in the beat MS trial was performed by Cleveland clinic in 2019

Actress Selma Blair was diagnosed with the autoimmune disease in 2018.
Blair, told reporters her condition had improved as a result of a stem cell transplant.

The **second** transplant was performed at University of Minnesota.
The patient is doing very well and back at her job as an elementary school teacher

Conclusion

- AHSCT studies in MS have evolved over the past 15 years, demonstrating improvement in efficacy achieving NEDA **(REMISSION)** safety and patient selection.
- MRI outcomes have been incorporated into recent AHSCT studies and are key to support NEDA **(REMISSION)** in MS
- MRI metrics after HSCT in the MIST trial support the brain's ability to repair.
- **Better MRI metrics need to be evaluated before and after AHSCT, in order to detect remyelination, preserved axonal and myelin integrity, effect on cortical lesions and brain volume.**
- Evaluation of cognition pre and post AHSCT (by functional MRI) may show improvement in clinical outcomes and provide further evidence of brain plasticity in MS.

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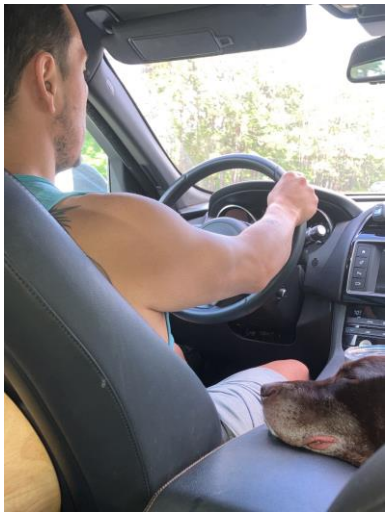
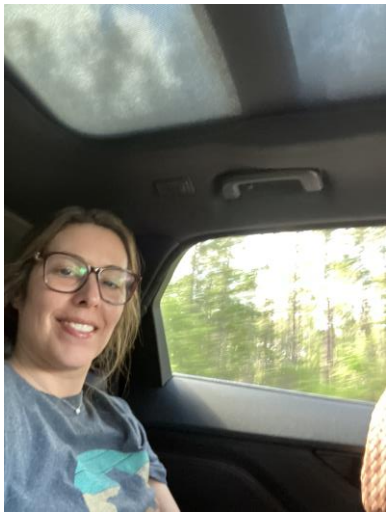
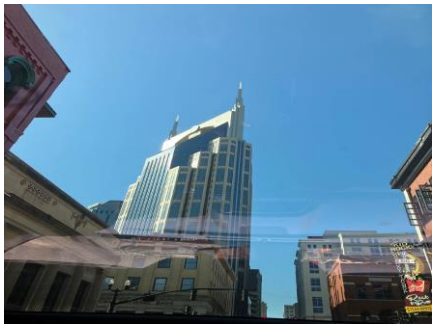
- Kristina Hayes
- Ainy Saeed
- Joel Joshua
- Alicia Archibeque

From Minneapolis to Miami: 1800 miles (with 4 dogs…)



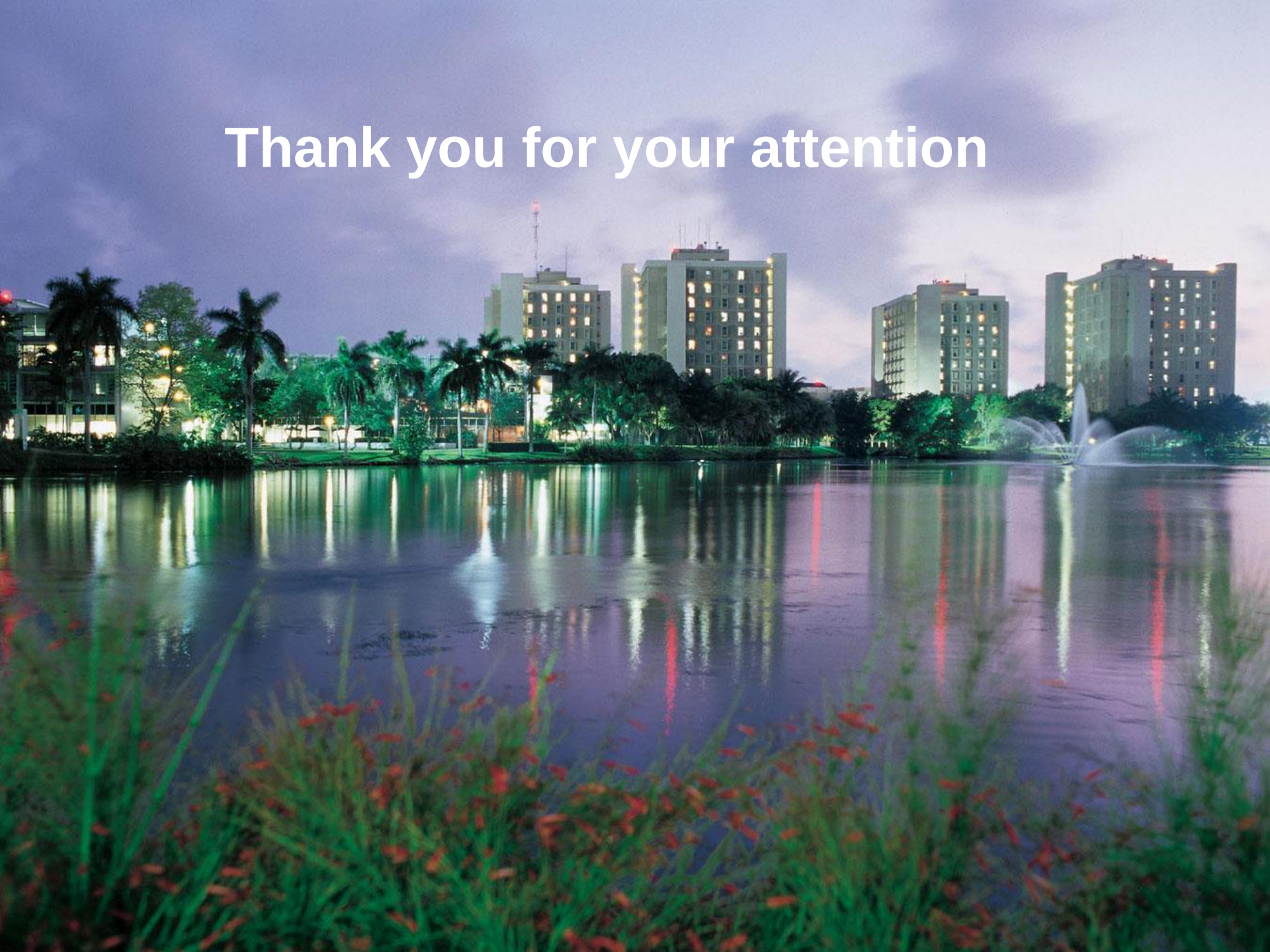


Iowa



Nashville

Atlanta


Thank you for your attention