



Brigham and Women's Hospital

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Multiple Sclerosis

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Clinical focus: Multiple Sclerosis, Hospital Neurology

Research Focus: Infections, vaccinations and MS disease
modifying therapy, medical education



Disclosures

- I have served on an advisory board for Neurology Live



Learning Objectives

1. Recognize presenting symptoms of Multiple Sclerosis (MS)
2. Update on disease modifying treatments (DMTs) for MS and implications for the Internist



Outline

- MS epidemiology and symptoms
- MS diagnosis and treatment
- Infections and vaccination considerations



Case of a 32 year old male

CC: Tingling

HPI:

- A 32 year old male presents with three days of tingling.
- The tingling starts in his right foot and then over the course of a day involves both feet. Over the next few days it ascends upwards to below the nipple line.
- He is able to walk around but it feels funny.
- He notes when he bends to pick something up that a shock like sensation runs down his spine.
- Pertinent negatives
 - No recent vaccines
 - No rashes
 - No recent tick or mosquito bite



Case of a 32 year old male, more history

Neurologic history:

- Notable for an episode of “fuzzy vision” in his right eye 10 years prior

Past medical history: none

Social history: prior smoker, social drinker, no drug use

Family history: mother with MS currently requires a wheelchair



Case of a 32 year old male, neurologic examination

Mental status: normal

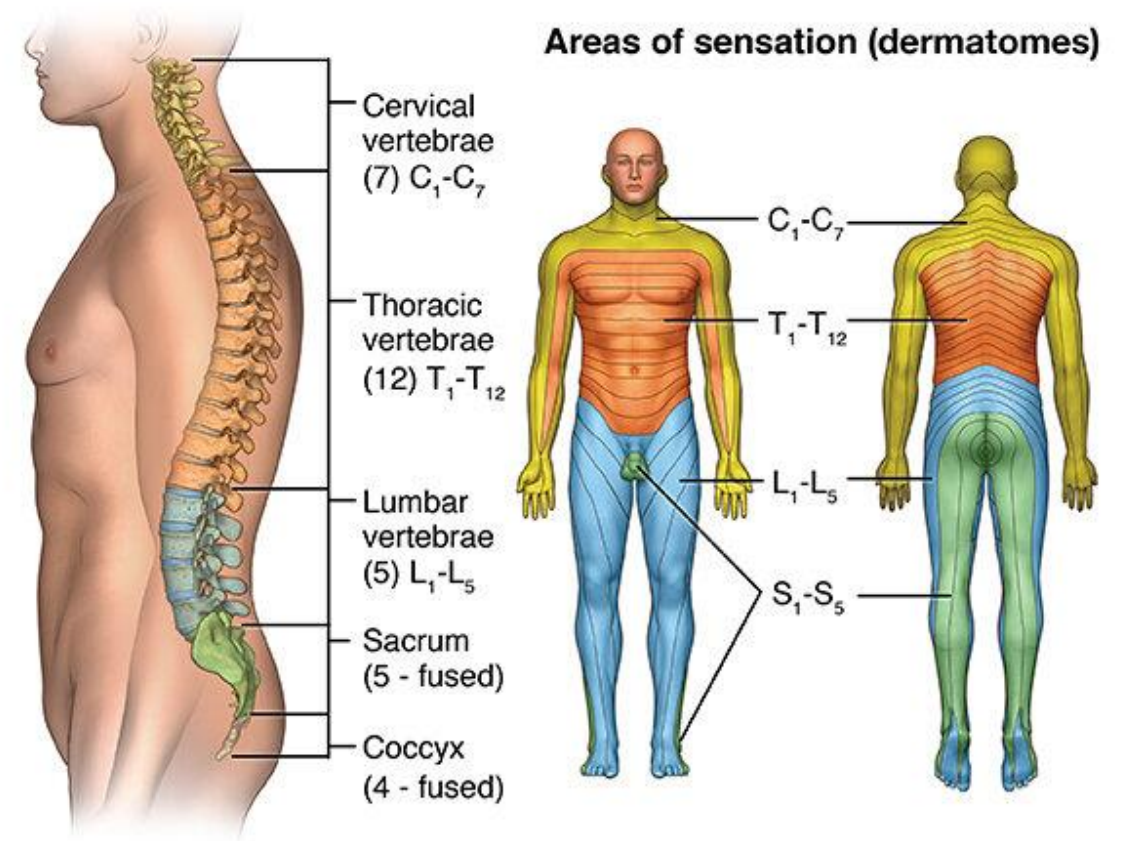
Cranial nerve exam: decreased color vision in the right eye

Motor exam: normal

Sensory exam: decreased vibratory sensation in the feet, sensory level at T4

Reflexes: 3+ throughout; + babinski on the right

Gait: normal



Case of a 32 year old male, differential diagnosis

Differential diagnosis = Localization x Time course

Localization

- CNS- specifically spinal cord due to sensory level, bilateral nature, UMN signs

Time course

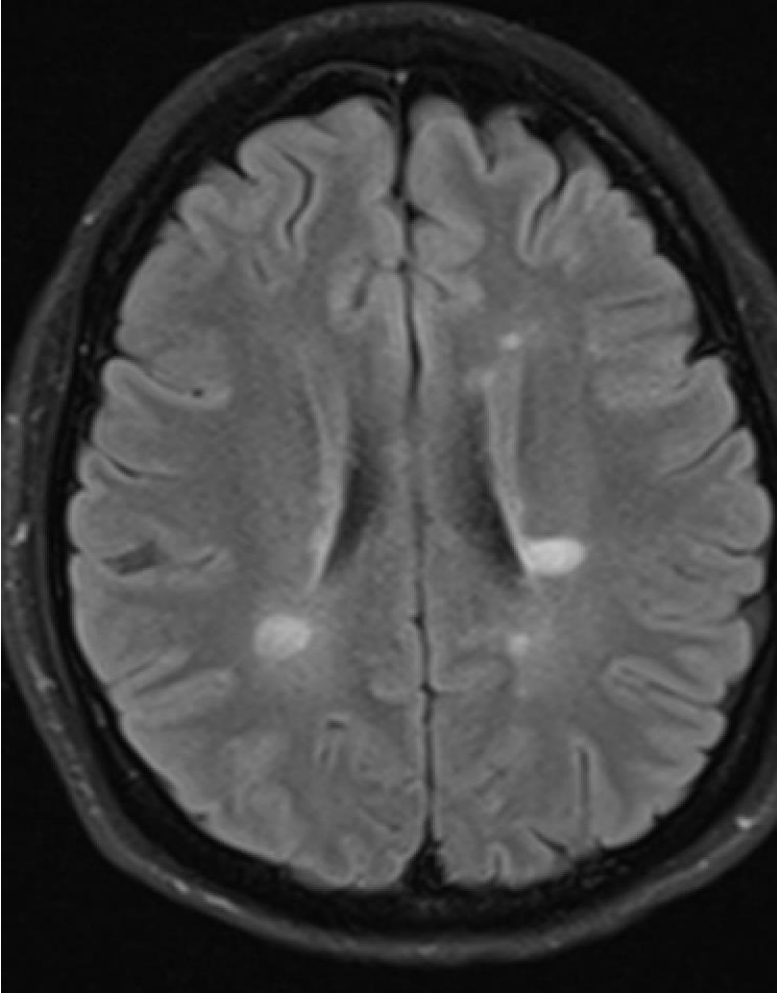
- Subacute- over days

Ddx:

- Demyelinating disease
- Infectious/post-infectious process



Case of a 32 year old male, MRI scans



Notable findings:

MRI brain- multiple
periventricular white
matter lesions

MRI cervical and thoracic
spine- enhancing thoracic
cord lesion

Diagnosis

Based on history, exam, and imaging the patient is diagnosed with:

Relapsing Remitting Multiple Sclerosis

Pertinent features of the case:

- Ascending tingling with **hyperreflexia**
- Shock like sensation with neck flexion-> lhermitte's sign
- Loss of color vision in the right eye-> raises concern for prior optic neuritis



MS introduction and epidemiology

- MS is an autoimmune disease in which the body's immune system attacks myelin in the brain and spinal cord
- Typically affects females>males, in 2:1 ratio
- More common in Whites, but increasing case numbers in African Americans and Hispanics
- Mean age of onset ~28-31 years

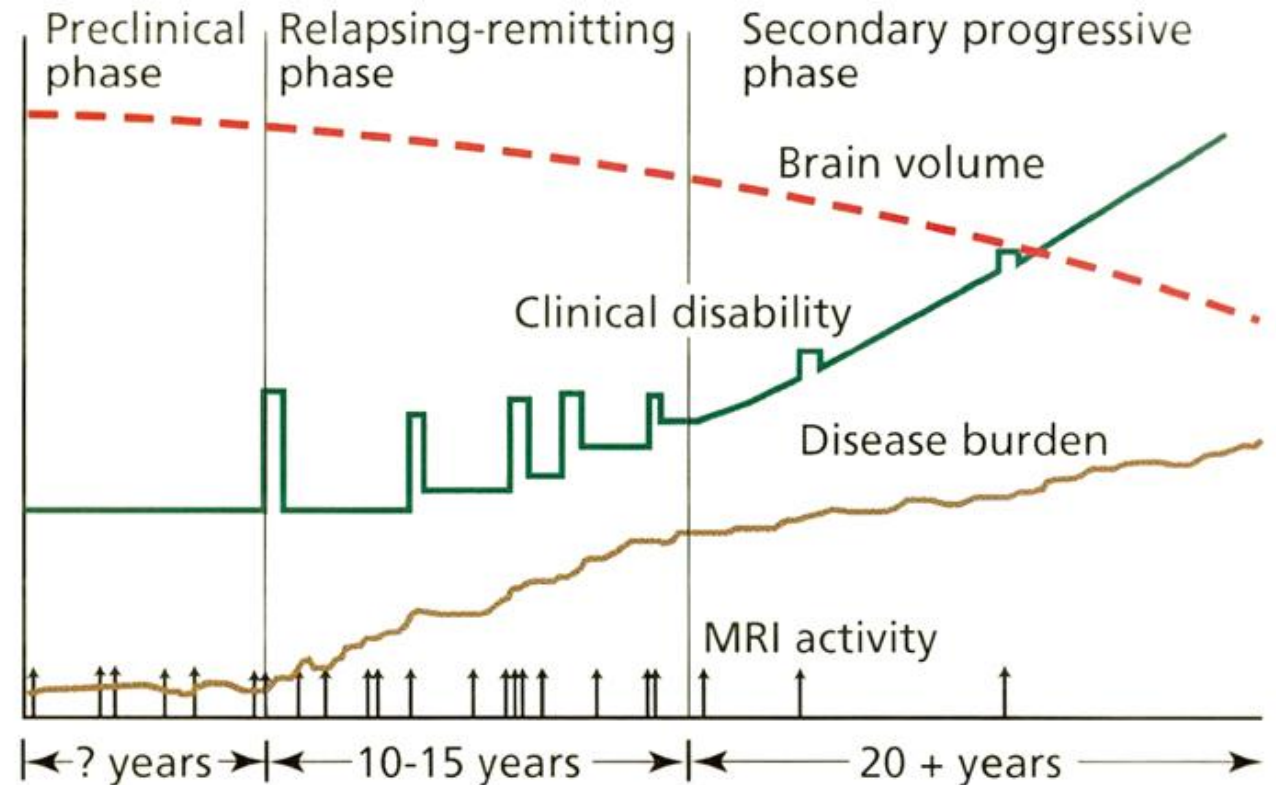


MS introduction and epidemiology

Traditionally broken down into different phenotypes

- RRMS - relapsing remitting MS
- SPMS - secondary progressive MS
- PPMS - primary progressive MS

Recognition that MS is more of a spectrum and that there likely is subclinical progression early on even in RRMS



What causes MS?

- Complex and incompletely understood
- Likely combination of environmental and genetics
- Risk factors:
 - Smoking
 - Obesity
 - Low vitamin D/low sun exposure
 - Geography- prevalence increases with distance from equator
 - EBV

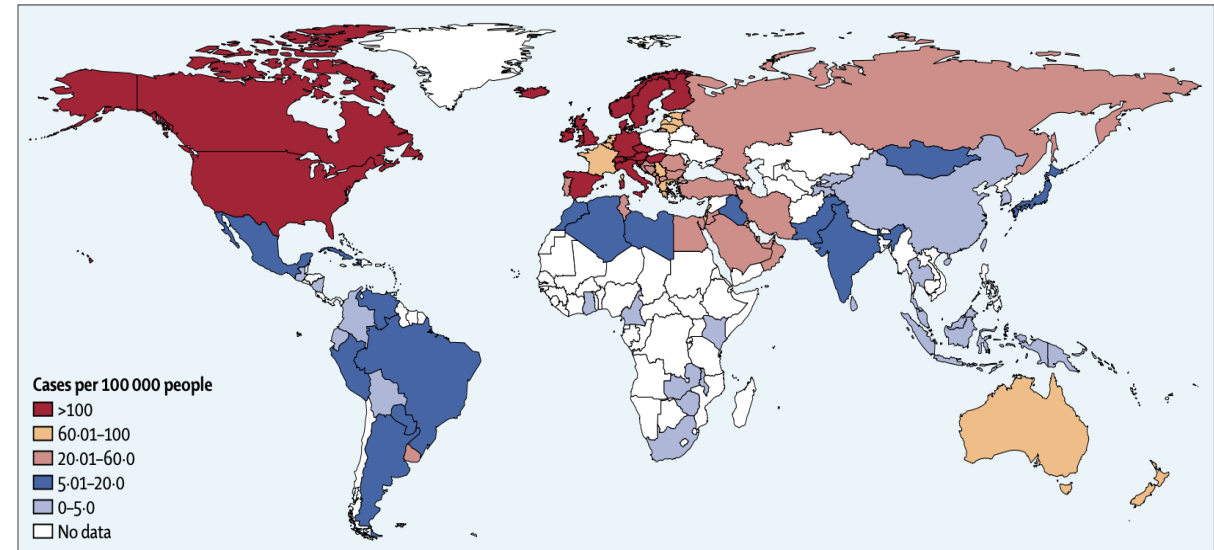


Figure 1: Global prevalence of multiple sclerosis

Source: Reproduced with permission from Atlas of MS 2013, MS International Federation.

Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet*. 2018 Apr 21;391(10130):1622-1636. doi: 10.1016/S0140-6736(18)30481-1. Epub 2018 Mar 23. PMID: 29576504.

Epstein-Barr Virus

EBV has been suspected to play a role in MS development

 | **REPORT** | MULTIPLE SCLEROSIS



Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

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↓ 437,811 💬 1,211

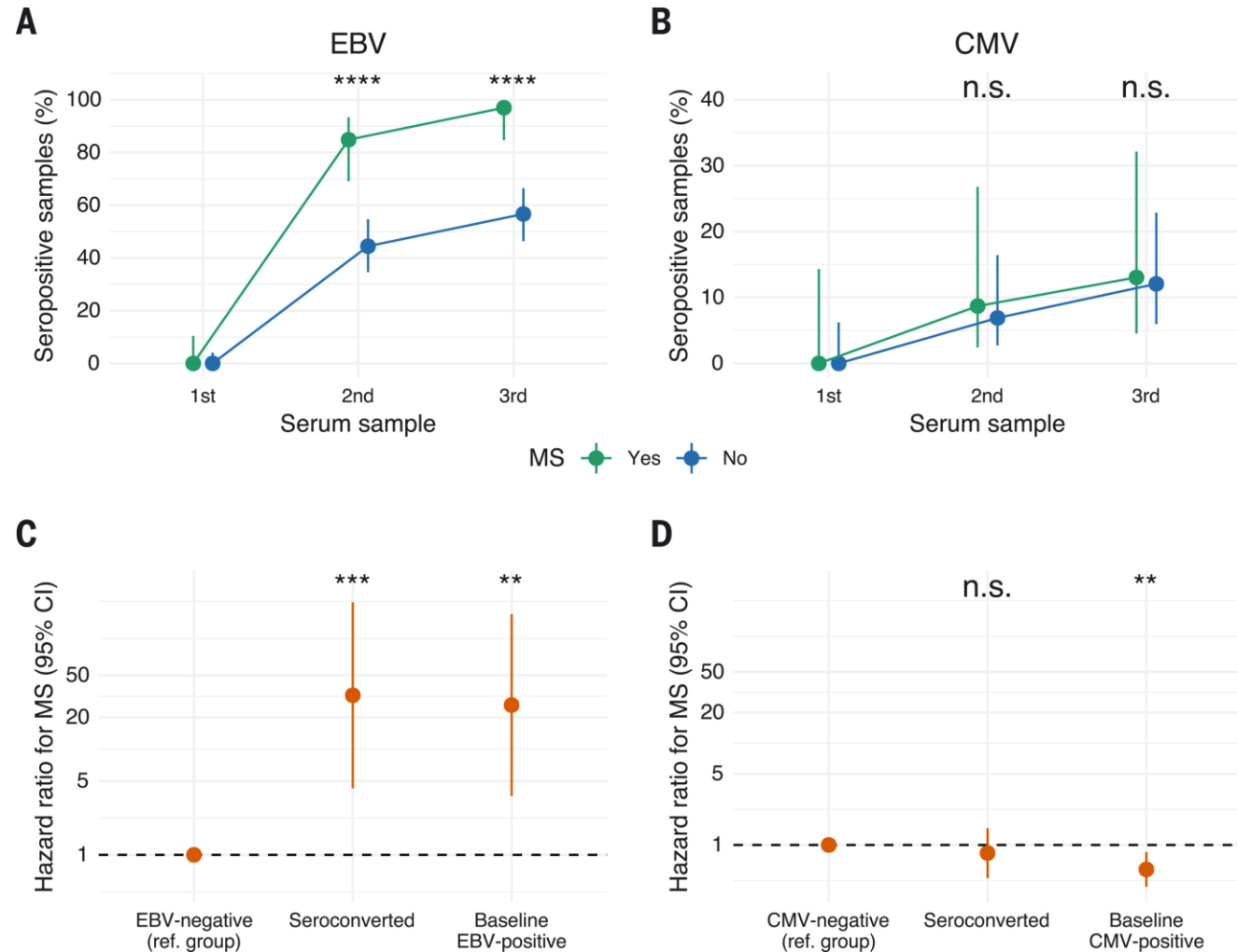


Epstein-Barr Virus

Paper by Ascherio et al in collaboration with the US military

Used serum samples of US active duty members prior to MS disease onset to determine EBV status, and relation between EBV infection and MS onset

EBV infection confirmed a 32 fold increased risk of MS



MS signs and symptoms:

In general symptoms consistent with demyelination present subacutely (over the course of hours to days) and persist for > 24 hours

- If acute onset consider vascular event
- If chronic and progressive the differential diagnosis is broad and includes metabolic and sometimes genetic etiologies



MS signs and symptoms:

Optic neuritis

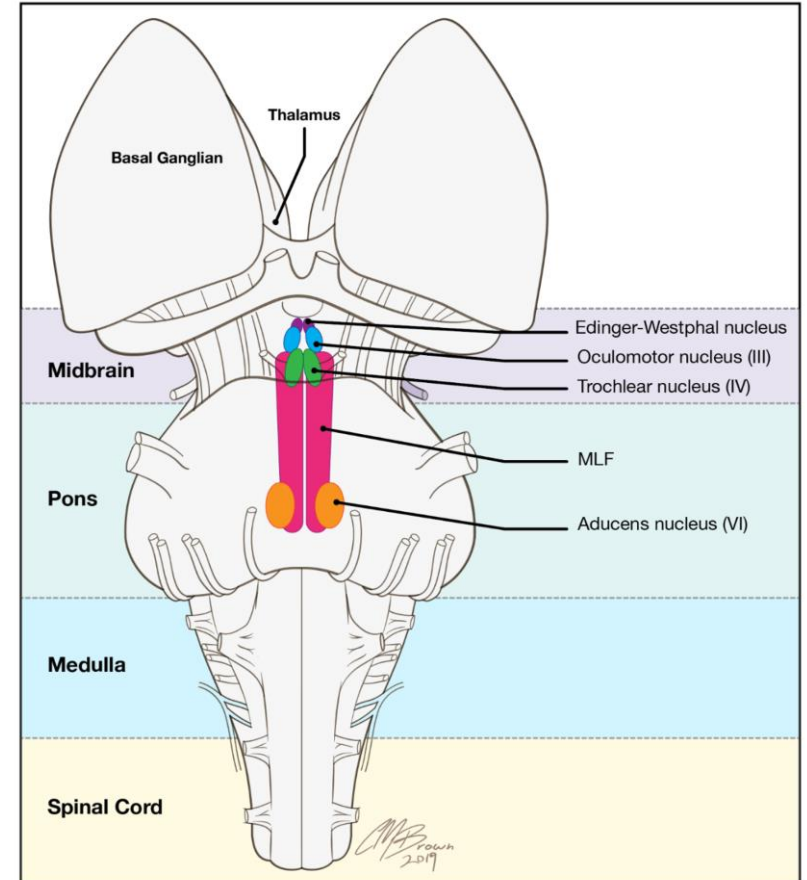
- Definition
 - Inflammation of the optic nerve
- Presentation/exam
 - Pain with eye movements
 - Visual acuity loss, typically mild
 - Color vision loss
 - Red desaturation
 - Described often as a visual blurriness, or a film over the eye
 - Symptoms come on over a few days, and tend to improve over a few weeks
 - Typically occurs in one eye



MS signs and symptoms:

Diplopia

- Binocular
 - Double vision which occurs with both eyes open
 - Closing one eye resolves the double vision
- Common in MS due to involvement of the medial longitudinal fasciculus



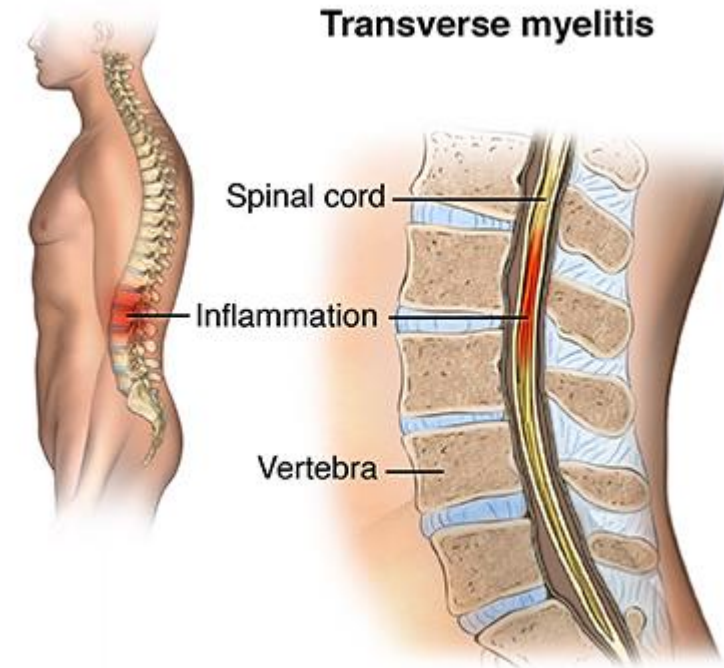
MS signs and symptoms:

Transverse myelitis

- Ascending numbness and weakness
- Bowel/bladder involvement
- Spasticity
- Lhermitte's- shock like sensation with neck flexion

Exam:

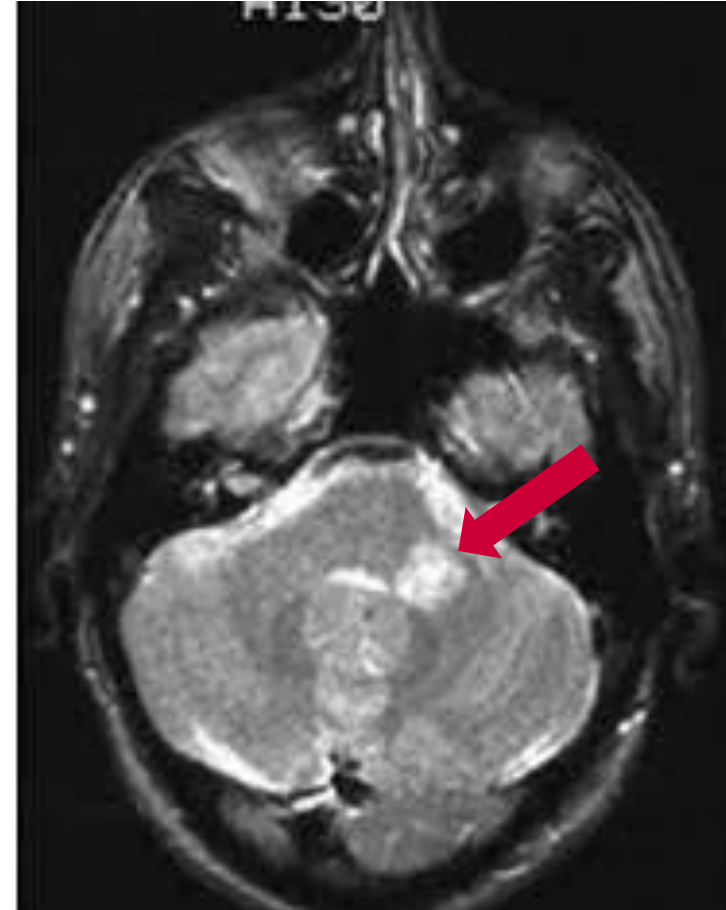
- Common to have sensory deficits
- Weakness if severe
- Reflexes brisk, other UMN signs



MS signs and symptoms:

Cerebellar syndrome

- Imbalance
- Impaired coordination
- Dizziness/vertigo

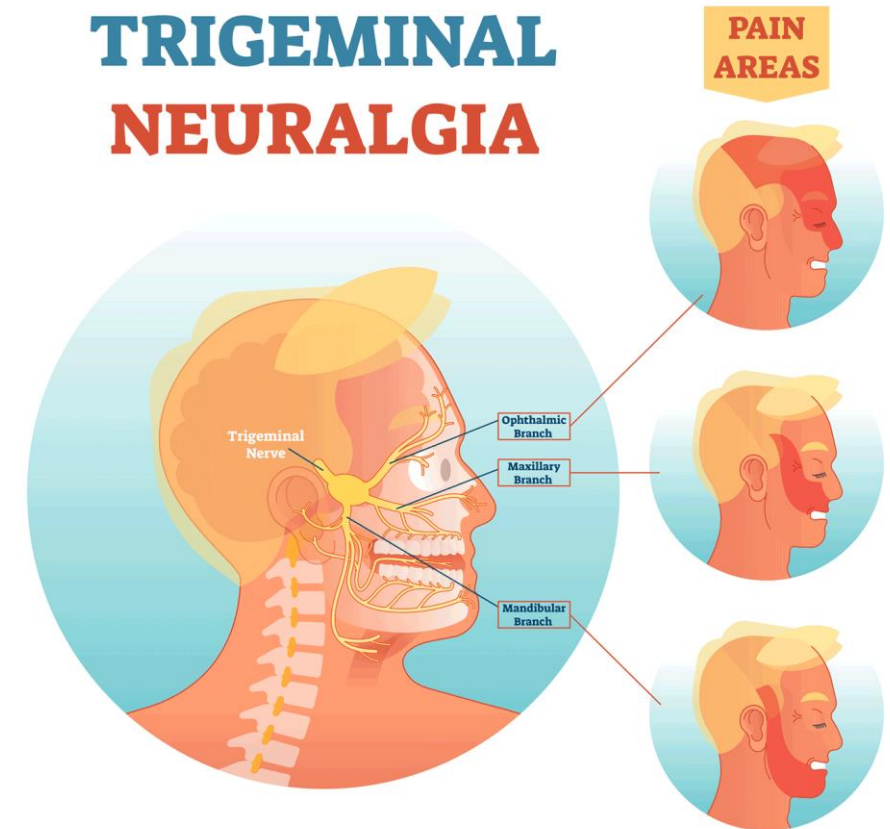


<https://dizziness-and-balance.com/disorders/central/ms.htm>

MS signs and symptoms:

Cranial neuropathy

- Trigeminal neuralgia:
 - CN V is the most common cranial nerve affected in MS
 - Severe lancinating pain in the distribution of the trigeminal nerve
 - Stimulation (ie tooth brushing) may trigger severe pain



MS signs and symptoms:

Other common symptoms (many of these are non-specific and not diagnostic)

Fatigue

- Most common symptom, and worst MS symptom in majority of MS patients

Uthoff phenomena

- Transient worsening of neurologic symptoms with heat

Cognitive changes

- Most common in attention and executive function



Making the diagnosis of relapsing remitting MS (RRMS):

No disease specific biomarker available

2017 McDonald Criteria:

Evidence of **dissemination in space** (lesions involving multiple characteristic areas of MRI; OR clinical relapses implicating different areas of the CNS)

AND

Evidence of **dissemination in time** (lesions that are both contrast and non contrast enhancing simultaneously, or evidence of new lesions on MRI, or a new clinical relapse over time)

*** update as of 2017, criteria for dissemination in time can also be met by presence of CSF specific oligoclonal bands



Making the diagnosis of primary progressive MS (PPMS)

2017 McDonald Criteria:

1 year of disability progression

AND

Two or more of the following:

- T2 hyperintense lesions on brain MRI consistent with MS
- At least 2 T2 hyperintense lesions in spinal cord
- Presence of CSF oligoclonal bands



Source: <https://radiologyassistant.nl/neuroradiology/spine/myelopathy>

Relapses

- **Relapse:** neurologic symptoms that are new or worsening of prior MS symptoms not due to fever/infection and last at **least 24 hours**
- **Pseudorelapse:** recrudescence of prior MS symptoms that last for longer than 24 hours mimicking an MS relapse
 - Triggers: fever, infection, or stress
 - Workup: laboratory testing- CBC, BMP, LFTs, U/A, +/- cxray, viral panel



Relapses

- **Relapse triggers**
 - Systemic infection (bacterial and viral)
 - Stress (epidemiologic studies in times of war)
 - Postpartum and IVF
- **Not associated with relapses: VACCINES (except yellow fever vaccine)**
 - COVID vaccine
 - Hepatitis B vaccine
 - Flu vaccine
 - HPV vaccine
 - Pneumococcus vaccine
 - Shingles vaccine

Source; Kalincik T. Multiple Sclerosis Relapses: Epidemiology, Outcomes and Management. A Systematic Review. Neuroepidemiology. 2015;44(4):199-214



What if a patient has a relapse?

- Manage acutely with STEROIDS!
 - Then consider escalation or change in disease modifying therapy
- **Dose 1g IV methylprednisolone daily for 3-5 days**
 - Equivalent of 1250mg PO prednisone (25, 50mg tablets)
- PO dose likely non inferior both in terms of efficacy and side effects
- For refractory cases consider plasma exchange



QUESTION 1:

Which of the following clinical presentations is most concerning for new onset demyelinating disease?

- A. 32 year old female presents with intermittent right hand tingling that is worse at night, provoked by typing and lasts one to two hours before self-resolving
- B. 65 year old male with coronary artery disease and hypertension presents with acute onset of vision loss in the left eye
- C. 40 year old female presents with pain on eye movements that progresses to blurriness in the left eye over a few days
- D. 50 year old male with diabetes who presents with numbness and tingling in his feet for three years that has progressed up to his ankles over the past year



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MS, disease modifying therapies

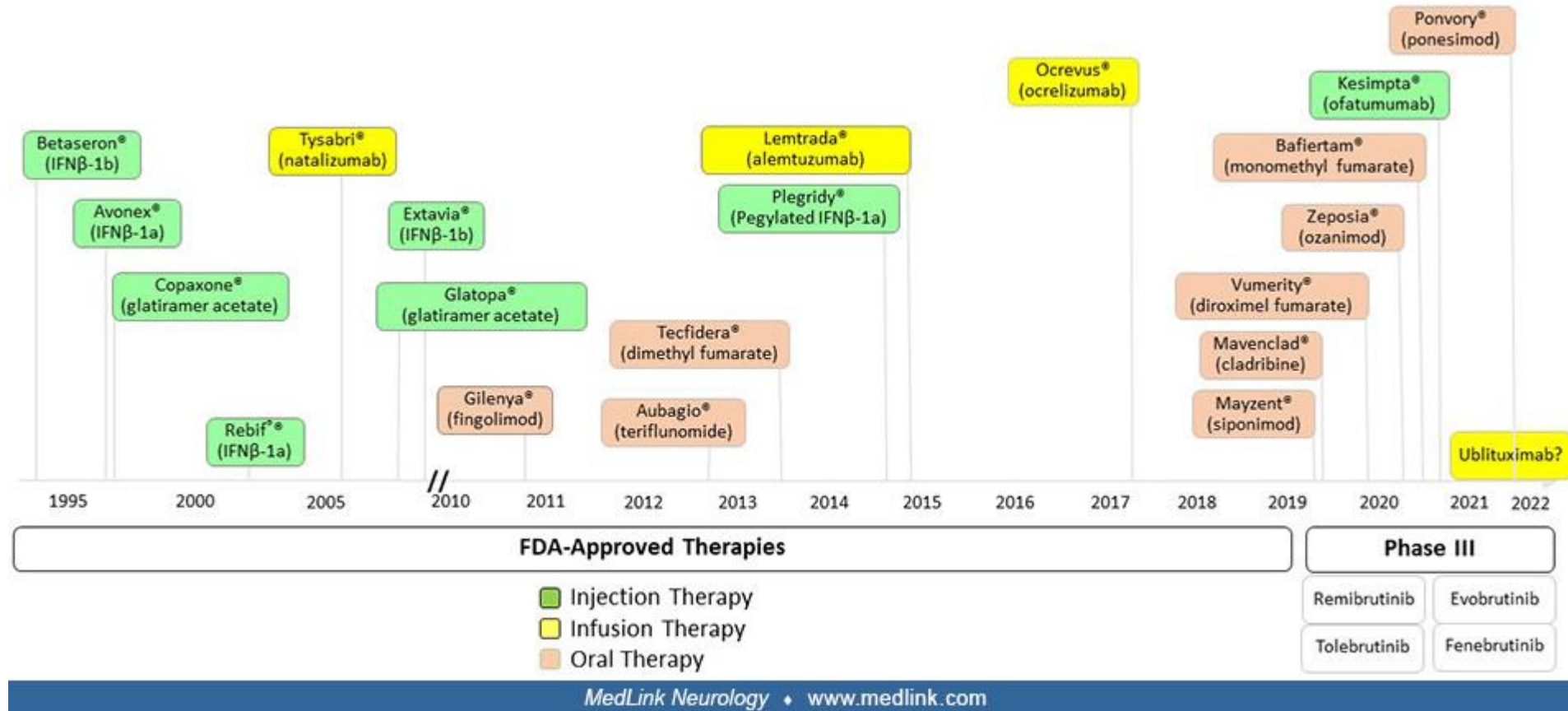
Goals of MS treatment

1. Prevent new clinical symptoms or relapses
2. Prevent new MRI lesions or contrast enhancing lesions (clinically silent relapses)
3. Prevent disability progression

Our current medications are most effective for goals 1 and 2

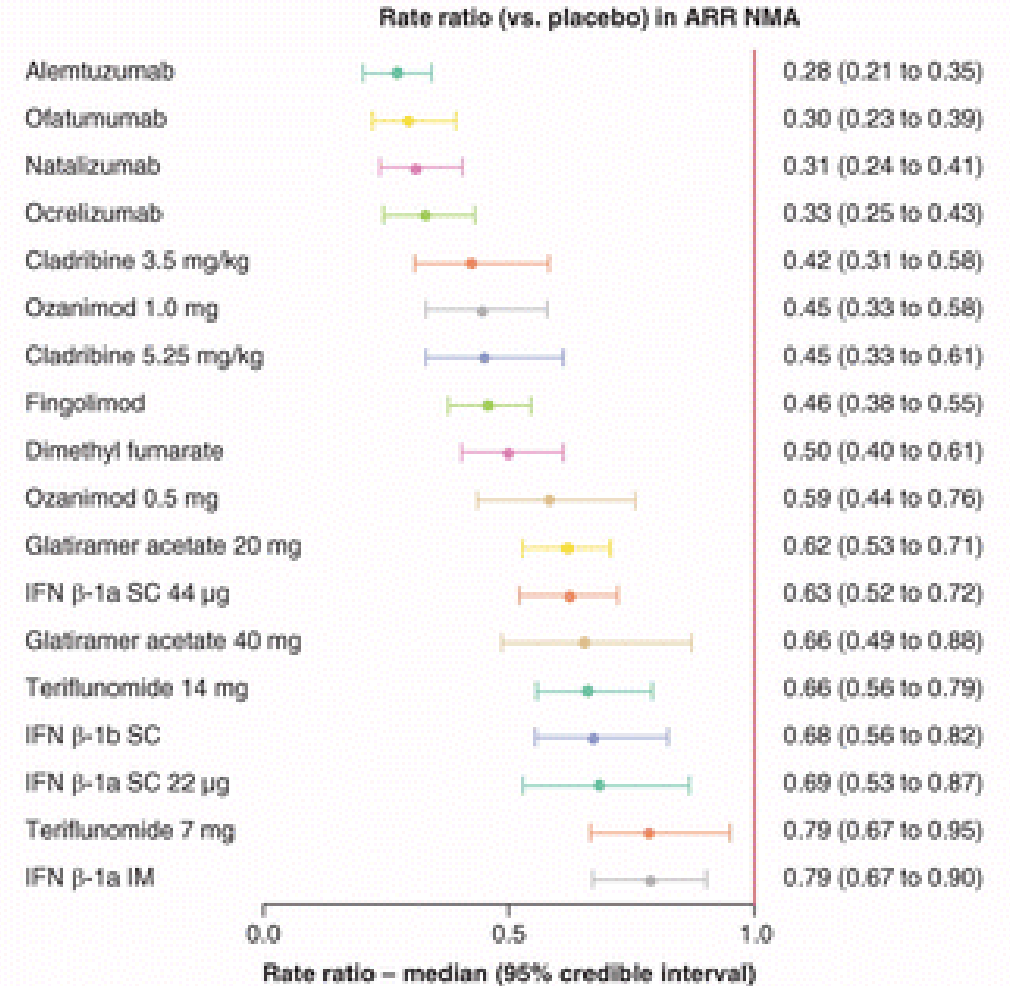


Treatments



How do we decide what disease modifying therapy (DMT) to start?

- Lower efficacy: injectables
- Medium efficacy: oral medications
- Higher efficacy: infusions, anti-CD 20 therapy
- Data suggests that **higher efficacy therapy earlier on leads to better long term outcomes**



Samjoo IA, Worthington E, Drudge C, Zhao M, Cameron C, Häring DA, Stoneman D, Klotz L, Adlard N. Efficacy classification of modern therapies in multiple sclerosis. J Comp Eff Res. 2021 Apr;10(6):495-507. doi: 10.2217/ceer-2020-0267. Epub 2021 Feb 23. PMID: 33620251.



DMT mechanism of action and side effects

Teriflunomide

- Mechanism
 - Pyrimidine synthesis inhibitor
- Side effects
 - Transaminitis
 - Lymphopenia
 - Rarely- neuropathy, hypertension
- Monitoring
 - **Monthly LFTs** x 6 months on initiation
 - Q 6 mo CBC with differential and LFTs
 - **Teratogenic**
 - **T spot prior to initiation**



DMT mechanism of action and side effects

Dimethyl fumarate, diroximel fumarate, monomethyl fumarate

- Mechanism
 - Anti-inflammatory, anti-oxidant
- Side effects
 - Transaminitis
 - Lymphopenia
 - GI upset
 - Flushing
- Monitoring
 - Q 6 mo CBC with differential and LFTs



DMT mechanism of action and side effects

Sphingosine-1-phosphate receptor modulators (end in – IMOD, ie fingolimod, siponimod, ozanimod)

- Mechanism
 - Trap lymphocytes in lymph nodes
- Side effects
 - Macular edema especially in diabetics
 - Bradycardia, qTC prolongation
 - **HSV/VZV**
 - **Cutaneous malignancies**
 - Lymphopenia (to be expected, consider changing medication when ALC <200)
- Monitoring
 - Q 6 mo CBC with differential and LFTs
 - Some require first dose monitoring; if miss more than 2 weeks, first dose monitoring needs to be repeated



DMT mechanism of action and side effects

Natalizumab (Tysabri)

- Mechanism:
 - Humanized monoclonal antibody against alpha 4-beta-1 integrin on white blood cells; stops WBC from entering CNS
- Side effects:
 - Infections
 - **PML** (progressive multifocal leukoencephalopathy), rare brain infection caused by the JC virus
 - HSV/VZV
- Monitoring:
 - JCV inhibition assay from serum



DMT mechanism of action and side effects

Anti-CD 20 monoclonals:

- Rituximab (chimeric anti-CD 20, IV)
- Ocrelizumab (humanized anti-CD 20, IV)
- Ofatumumab (humanized anti-CD 20, subcutaneous injection)
- Ublituximab (chimeric anti-CD 20, IV)
- Infusion reactions
 - Hypogammaglobulinemia
 - Infections: URIs, UTIs, **Hep B reactivation**
- **Monitoring:**
 - Hep B serologies prior to initiation; CD19, CD 20 counts and immunoglobulins



QUESTION 2:

Your patient with RRMS is started on natalizumab. She is also interested in alternative treatment options.

Which of the following supplements can she take to better control her disease?

- A. alpha lipoic acid
- B. vitamin D
- C. magnesium
- D. coenzyme q 10
- E. high dose biotin



ANSWER 2:

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- C. magnesium
- D. coenzyme q 10
- E. high dose biotin



ANSWER 2: MS supplements

- **Vitamin D**
 - Low vitamin D associated with development of MS and worse outcomes
 - Recommend 2,000 – 5,000 IU daily
 - Goal vitamin D level 40-60 ng/mL
- **Alpha lipoic acid**
 - 600mg daily, can be helpful for nerve pain
- **Magnesium**
 - 200-400mg daily, for muscle cramps/spasticity, can also be helpful for migraine
- **Coenzyme q 10**
 - 500mg daily, can help with MS related fatigue and mood
- **High dose biotin**
 - Small studies suggested improved outcomes in progressive MS, refuted by larger studies
 - Some patients find helpful
 - Impacts thyroid tests



MS and infections

- COVID-19 infection
- Vaccine considerations



MS and COVID-19 infection

- MS is itself not a risk factor for severe COVID-19
- Certain DMTs (specifically anti-CD20 therapies) may be associated with more severe COVID-19
- COVID-19 infection can worsen MS symptoms
- Patients on DMT
 - If COVID-19 positive should be offered **monoclonal or oral antiviral** if available
 - **Pre-exposure prophylaxis** should be considered if available for highest risk patients (those on anti-CD20 therapies and sphingosine-1-phosphate receptor modulators)



MS and vaccination

- Non-live vaccines are safe in MS patients on DMT
- Live vaccines are not recommended for MS patients during treatment
- Patients on certain medications may have attenuated responses to vaccines
 - This is mainly a consideration for patients on anti-CD20 therapies and sphingosine-1-phosphate receptor modulators)



MS and vaccination

The following vaccinations (all non-live) should be recommended for pwMS

- **Hepatitis B**
 - anti-CD 20 therapies if not immune
- **Zoster Vaccine Recombinant**
 - Adults >18 years old if immunocompromised (anti-CD 20 therapies, cladribine, DMF, S1P, alemtuzumab, natalizumab) OR adults > 50 years old
- **HPV vaccine**
 - consider extra dose in those <26 years on moderate/high efficacy therapy
- **RSV vaccine**
 - if adult > 75 years old, or 60—74 years old and at increased risk
- **Pneumococcus vaccine**
 - Recommended for adults >18 years old if immunocompromised (anti-CD 20 therapies) OR adults > 65 years old
- **Seasonal flu/Covid vaccine**
 - all patients



Summary/Take Home Points

- MS commonly presents with optic neuritis, brainstem syndrome or transverse myelitis, that is subacute and lasts >24 hours
- **There are many new and effective treatments for MS**
 - Important side effects for family practitioners/internists to be aware of
 - Lymphopenia/transaminitis- oral medications (teriflunomide, fumarates, S1P receptor modulators)
 - Macular edema, cutaneous malignancy, cardiac side effects- S1P receptor modulators
 - PML- natalizumab
 - Hepatitis B reactivation- anti-CD 20 therapies (rituximab, ocrelizumab, ofatumumab, ublituximab)
 - Hypogammaglobulinemia and infection risk- anti-CD 20 therapies
- Though patients on certain DMTs may have attenuated responses to vaccination, **non-live vaccines are safe** in MS patients and do not cause relapses or disease worsening



Consider treatment for COVID-19 in MS patients on immunotherapy

References:

Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, Ascherio A. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science*. 2022 Jan 21;375(6578):296-301. doi: 10.1126/science.abj8222. Epub 2022 Jan 13. PMID: 35025605.

Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, de Seze J, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Rammohan KW, Selmaj K, Traboulsee A, Sauter A, Masterman D, Fontoura P, Belachew S, Garren H, Mairon N, Chin P, Wolinsky JS; ORATORIO Clinical Investigators. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med*. 2017 Jan 19;376(3):209-220. doi: 10.1056/NEJMoa1606468. Epub 2016 Dec 21. PMID: 28002688.

Samjoo IA, Worthington E, Drudge C, Zhao M, Cameron C, Häring DA, Stoneman D, Klotz L, Adlard N. Efficacy classification of modern therapies in multiple sclerosis. *J Comp Eff Res*. 2021 Apr;10(6):495-507. doi: 10.2217/cer-2020-0267. Epub 2021 Feb 23. PMID: 33620251.

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Thank you! Please feel free to contact me at seconway@bwh.harvard.edu for further questions

