# The Central Vein Sign in Multiple Sclerosis (CAVS-MS): A North American Imaging in MS (NAIMS) Cooperative Prospective Diagnostic Biomarker Study

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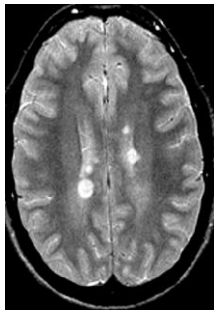
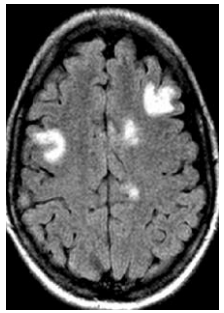
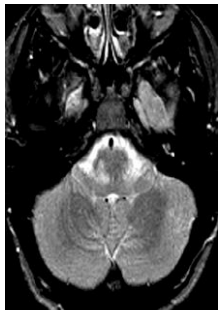
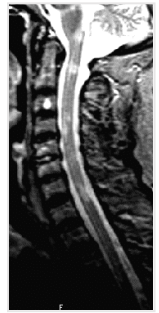
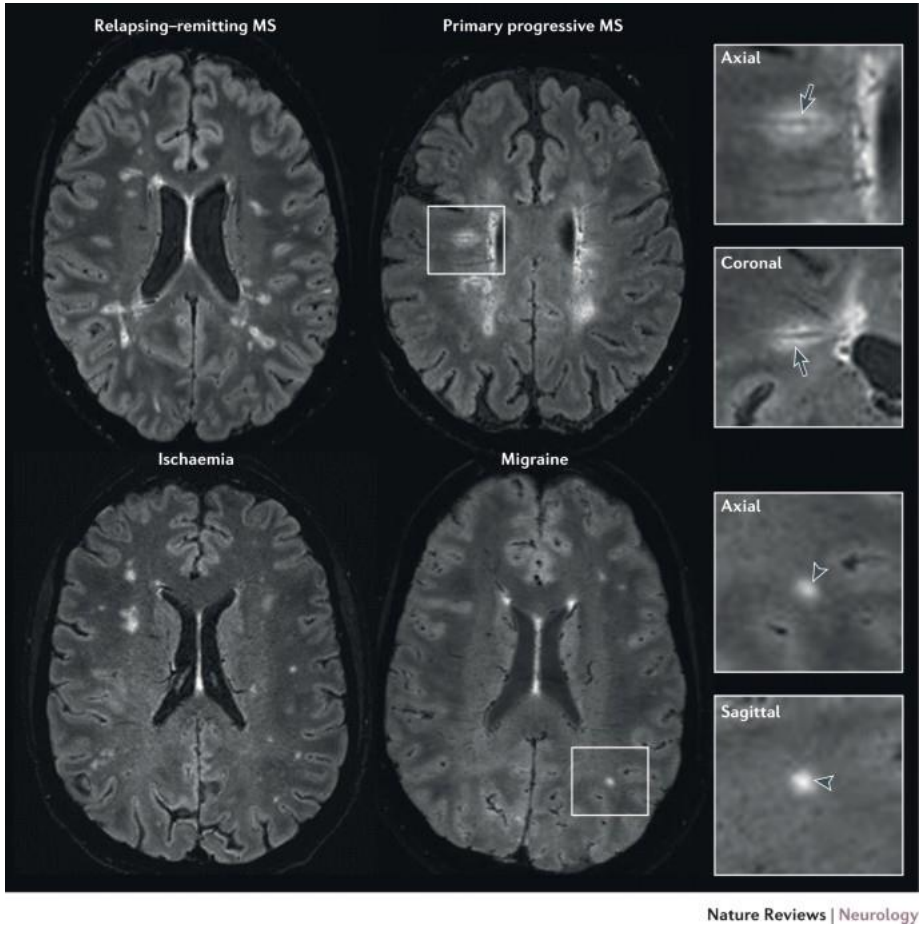
# Background - MRI and Diagnosis of MS

- MRI is a time-tested method of detecting MS-associated lesions and forms an integral part of diagnostic criteria.[1]
- Still, there are significant delays in diagnosis, making refinement and simplification of criteria important.[2]
- Specificity far from perfect: up to 20% of individuals diagnosed with MS do not have the disease.[3]
- Increasing diagnostic sensitivity may have come at the price of decreased specificity.[4]
- >2/3 of misdiagnosed patients are exposed to unnecessary risks associated with DMT[5] and over estimate benefit of treatment in research studies.
- Approximately 50% of patients referred for MS have atypical symptoms, where the diagnostic criteria are not helpful or validated.[6]
- MRI criteria have relatively low specificity for dissemination in space (DIS) (32%) and dissemination in time (DIT).[7]


1. Reich DS. et al. NEJM 2018
2. Kelly S. et al. JNNP 2012
3. Kaisey M. et al. MSARD, 2019
4. Rommer PS. et al. Lancet Neurol 2018
5. Solomon A. et al. Neurology 2016
6. Kelly S. et al. JNNP 2018
7. Filippi M, et al. Lancet Neurol 2018

# Background – Central Vein Sign




NAIMS Criteria

Box 2 | **Radiological definition of a central vein**

A central vein exhibits the following properties on T2*-weighted images:

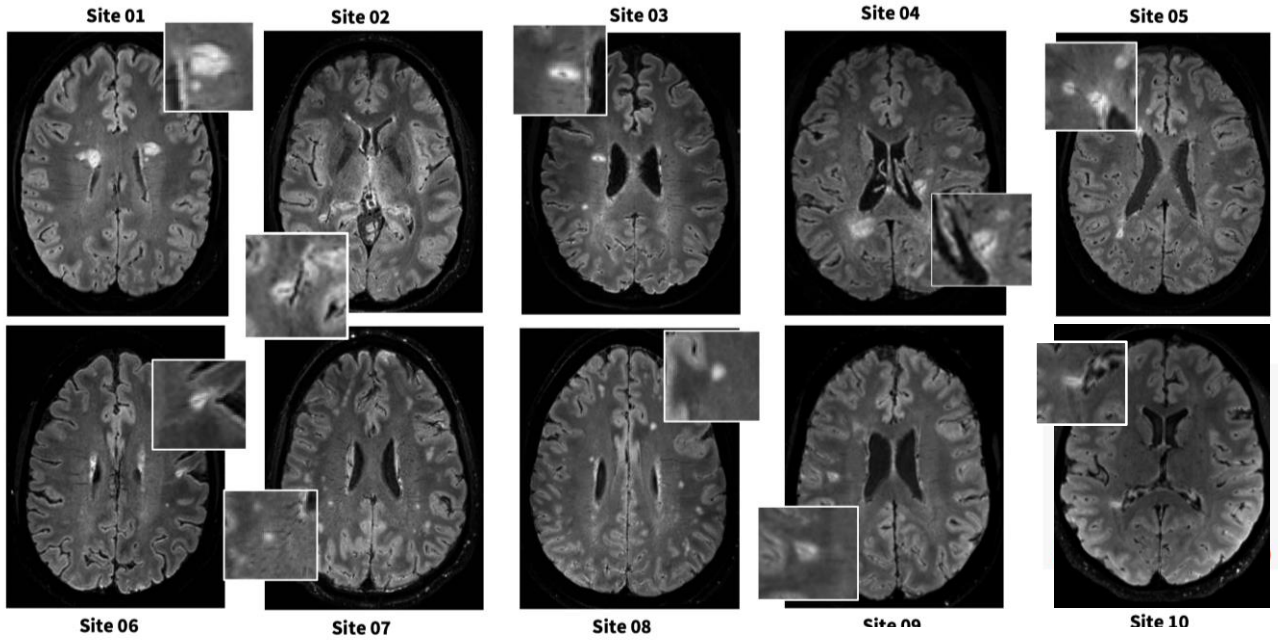
- Appears as a thin hypointense line or small hypointense dot
- Can be visualized in at least two perpendicular MRI planes, and appears as a thin line in at least one plane
- Has a small apparent diameter (<2 mm)
- Runs partially or entirely through the lesion
- Is positioned centrally in the lesion (that is, located approximately equidistant from the lesion's edges and passing through the edge at no more than two places), regardless of the lesion's shape

Exclusion criteria for lesions:

- Lesion is <3 mm in diameter in any plane
- Lesion merges with another lesion (confluent lesions)
- Lesion has multiple distinct veins
- Lesion is poorly visible (owing to motion or other MRI-related artefacts)

Sati P. et al. Nat Rev Neurol, 2016

# Pilot CVS Study



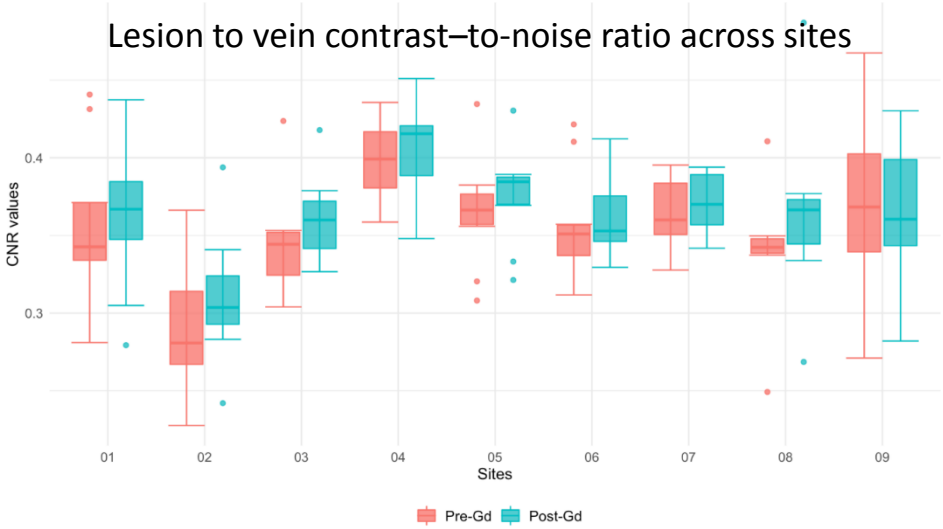

- 92 participants from 10 NAIMS sites
- Clinical or radiological suspicion of MS
- Pre and post contrast 3D T2* EPI
- Generation of FLAIR* on QMENTA

Daboul L. et al. MS VIRTUAL 2020
Martin M. et al. MS VIRTUAL 2020

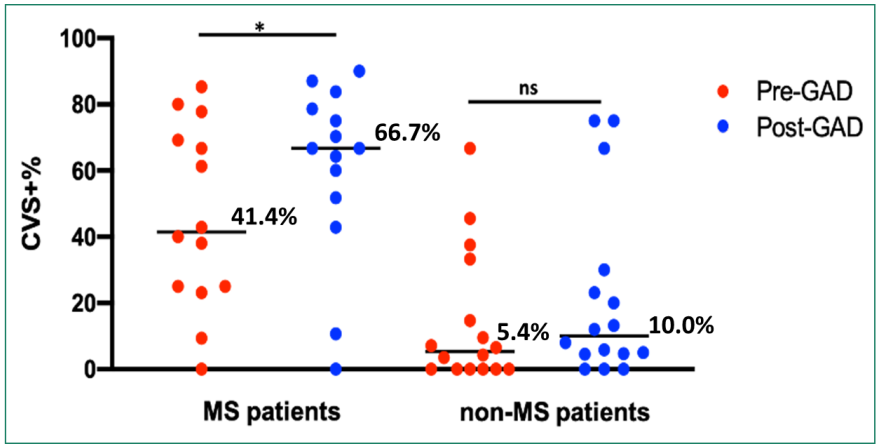
Predicting MS diagnosis using 40% rule:

| | Pre-GAD FLAIR* | Post GAD FLAIR* |
|---|---|---|
| **Sensitivity** | **53.8** | **85.7** |
| **Specificity** | **87.5** | **81.3** |

Lesion to vein contrast–to-noise ratio across sites




Percentage CVS+ Pre and Post GAD




*p=0.0005 p=0.098

*By Wilcoxon Rank Sum Test*

# Scientific Rationale

- The CVS is proposed as a diagnostic biomarker for MS with improved sensitivity and specificity — all in an-easy-to use diagnostic test that can be applied in patients with both typical and atypical disease presentation.
- MS diagnostic criteria are effective in most typical cases, the use of the CVS prospectively may hasten diagnosis even in those presenting with atypical symptoms—meeting a significant unmet need for diagnosis of MS.
- Thus, this study will have significant impact for patients with MS and may also help avoid unnecessary costs and morbidity in those without MS.

# AIMS

- Perform a definitive study with the aim of developing more accurate diagnostic criteria that incorporate CVS.
- To determine if evaluation for CVS hastens accurate diagnosis in individuals presenting with typical initial presentations.
- To determine if CVS improves specificity for MS among individuals presenting with radiological suspicion of MS and atypical symptoms.

# Objectives

**Primary Objective**

- To determine whether CVS allows for an earlier, equally accurate diagnosis of MS in those with a typical first demyelinating events not initially meeting McDonald criteria, and followed over 24 months.

**Secondary Objectives**

- To determine concordance of CVS and McDonald Criteria in those meeting McDonald Criteria at baseline.
- To determine if use of CVS shows specificity for MS among individuals presenting with atypical syndromes over 24-months.
- To determine whether the CVS predicts development of clinical MS in people with radiologically isolated syndrome (RIS).

# Outcomes

- **MRI Outcomes**
  - Select 6 CVS determination (site and central)
  - Select 3* CVS determination (site and central)
  - Proportion of total lesions with central vein (automated)
- **Patient reported Outcomes**
  - Neuro-QoL (short forms)
  - PDDS (patient determined disease steps)
- **Clinical Outcomes**
  - McDonald Criteria 2017 (central and adjudicated by 3 International Panel Members from McDonald 2017)
  - Relapses
  - Cerebrospinal fluid results
  - Blood screening results
- **Economics Outcomes**
  - Estimated health care expenditures using health care recourse utilizations forms

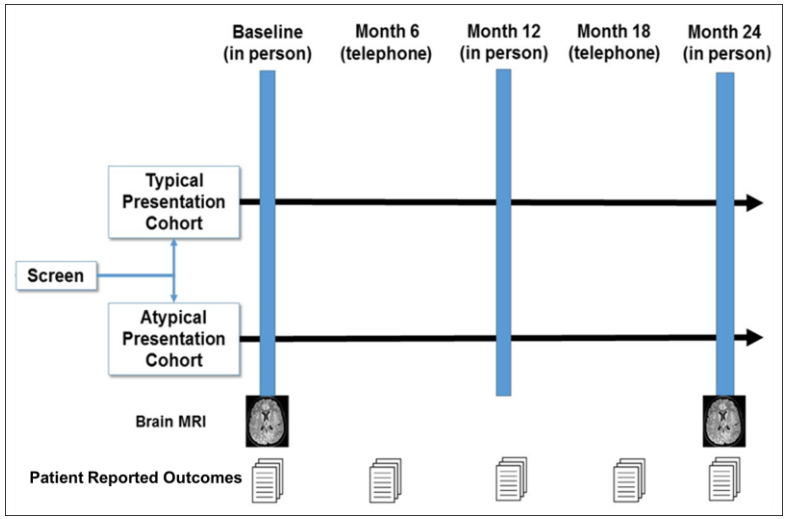
# Sample Estimates, Participants, and Eligibility

- Assumptions:
  - Sensitivity of baseline McDonald Criteria for determining MS at the end of the study: 70%.
  - >85% of MS lesions have a central vein, the sensitivity of the CVS is >80% (approximately 12% additional sensitivity for MS).
  - Expected discordance rate between McDonald Criteria and CVS: ~20%.
- One-sided hypothesis test assuming a type I error rate of 5% as well as a 20% dropout rate:
  - N=200 for typical presentations
  - 88% power to detect improved sensitivity of the CVS. Since 50% of participants will present with atypical symptoms, the study will need to recruit approximately **400 participants total**.

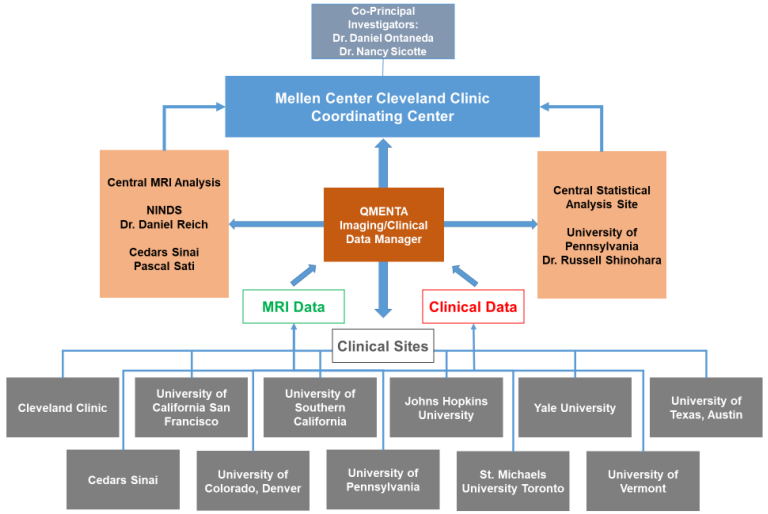
## Inclusion Criteria

Inclusion:
Age 18 to 65 inclusive
Referral to a study academic site for a clinical suspicion of MS
Onset with typical or atypical symptoms
Onset of neurological symptoms within 10 years of screening
Exclusion:
Contraindication to MRI studies
Inability to tolerate MRI
Contraindication to use of gadolinium
Treatment with systemic corticosteroids (last 4w)

## Study Flow Diagram




## Study Structure

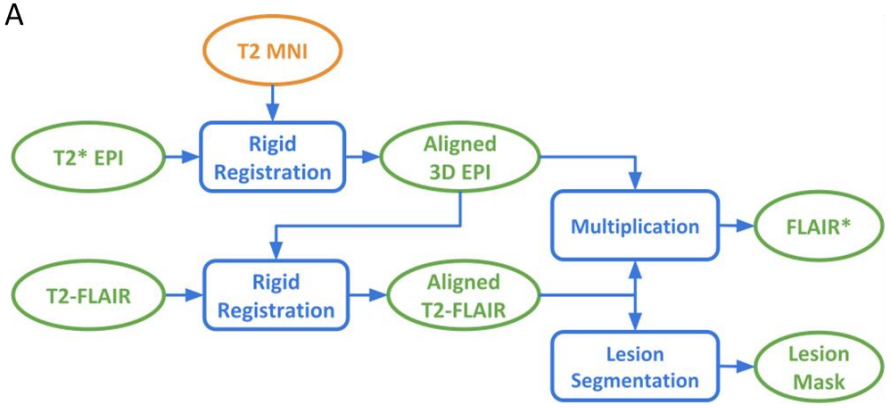


# MRI Acquisition and Harmonization

- Standardized imaging protocol.
- Dummy scan at all sites prior to site activation
- MRI at baseline (first study visit) and month 24 (final study visit).
- Total acquisition time: 34 minutes + 10 minutes patient placement.
- Images uploaded to QMENTA
- QA of images (automated)
- QA by neuroradiology
- Image processing
  - Creation of FLAIR*
  - Lesion segmentation
  - CV annotation

| MRI sequence Details | | | |
|---|---|---|---|
| **Image Type** | **Scan Time** | **Sequence Details** | **Voxel Size** |
| T1-weighted MPRAGE | 4 min 17 sec | 3D, Sagittal | 1 mm iso |
| T2-weighted FLAIR | 6 min 53 sec | 3D, Sagittal | 1 mm iso |
| T2*-weighted segEPI | 5 min 44 sec | 3D, Sagittal | 0.65 mm iso |
| T1-weighted GRE without contrast | 3 min 34 sec | 3D, Sagittal | 1 mm iso |
| SWI-weighted GRE without contrast | 4 min | 3D, Sagittal | 0.65 mm iso |
| *Contrast Administration* | | *Single dose, 0.1 mmol/kg* | |
| T2*-weighted segEPI with contrast | 5 min 44 sec | 3D, Sagittal | 0.65 mm iso |
| T1-weighted GRE with contrast | 3 min 34 sec | 3D, Sagittal | 1 mm iso |

A

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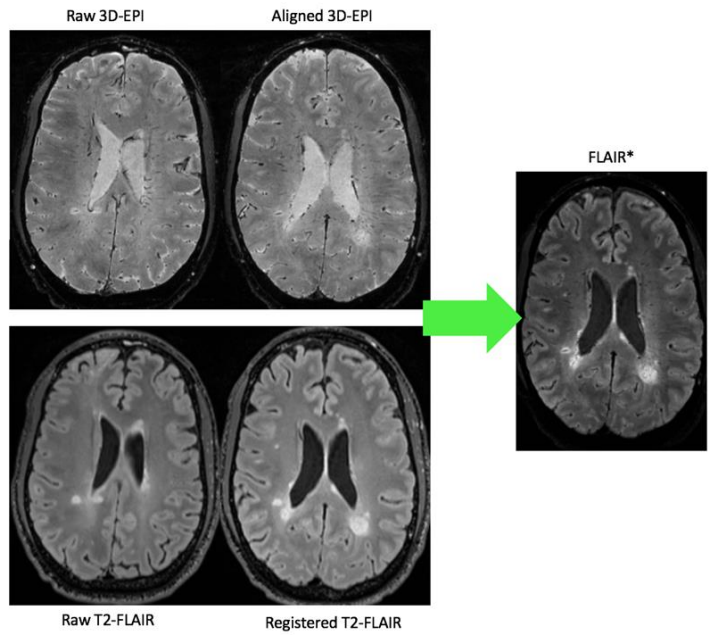
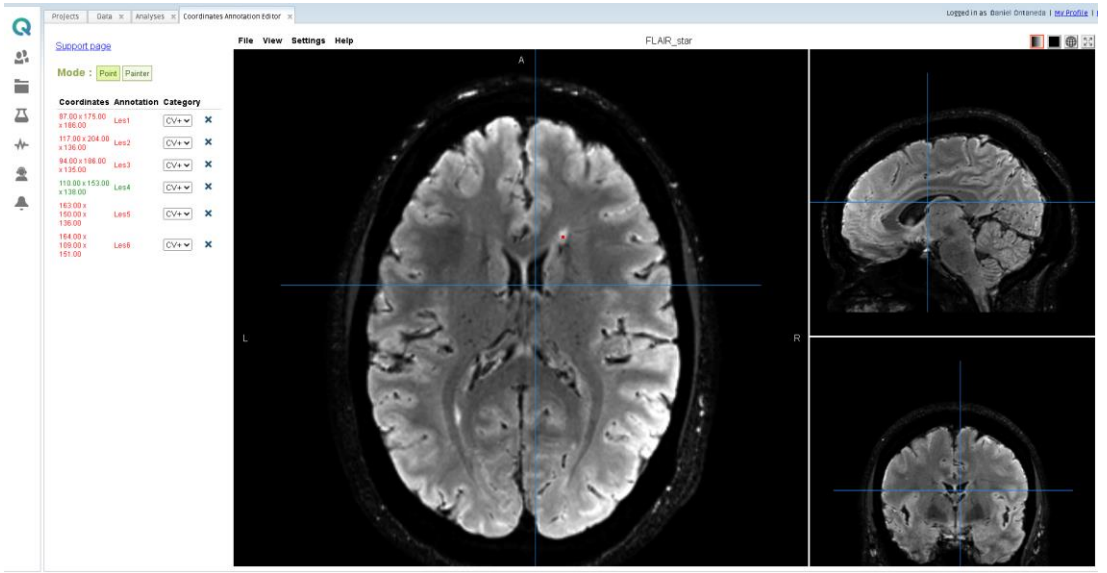
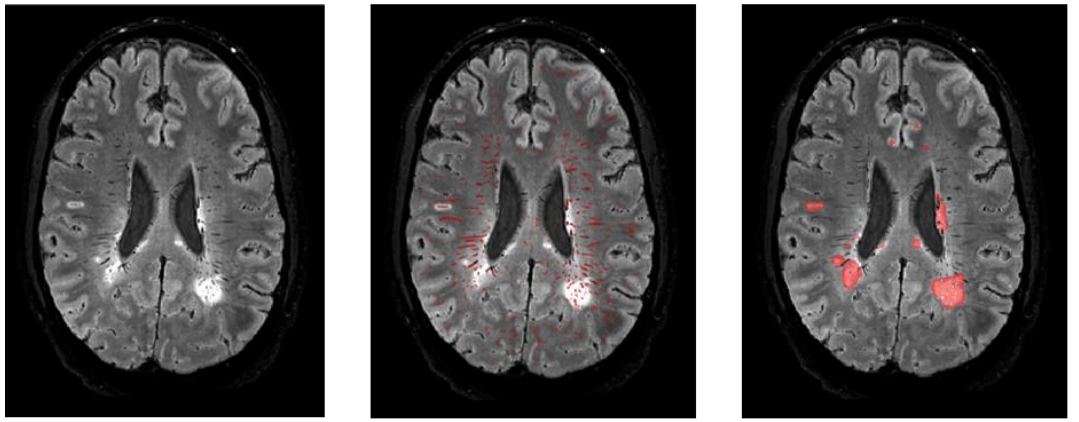


# Analysis Pipeline and CVS Rating/Measures

- Rating of the “Select6” and “Select3*” on scan locally by the site PI at the end of enrollment period.
- Raters are blinded to patient data and will rate only the anonymized scans from their sites.
- Automated lesion detection algorithm: Proportion of automated lesions with central vein will be tested at 30%, 40%, 50%, and 60% as potential thresholds for a positive study.
- A central rater will also rate all study scans using Select6* (identify up to 6 lesions with CVS) and Select3* criteria (identify up to 3 lesions with CVS).



Vein mask (red)

## Expected timeline

- Study start date: July 1, 2020
- Protocol finalized
- Database completed (QMENTA)
- Manuals of operating procedures completed
- Statistical analysis plan completed
- 3 sites activated: 9 participants enrolled, sIRB active
- Diagnosis and onset adjudication panel confirmed
- Neuroradiology panel confirmed
- 12 month enrollment period

## Planned Outcomes

- CVS will reduce misdiagnosis, hasten early diagnosis, and simplify clinical decision-making.
- Incorporation of the CVS into future iterations of the  MS diagnostic criteria.