Contemporary Concepts in
Multiple Sclerosis

Aaron L. Boster, MD
Systems Medical Chief, Neuroimmunology & Clinical Research
Director, OhioHealth Multiple Sclerosis Center
OhioHealth Physicians Group
Columbus, Ohio
In memory of my mentor, Omar Khan, MD

Your lessons live on in every MS family I treat, every MS fellow I train, every paper I publish and with every learner I teach.
Aaron L. Boster, MD, has a financial interest/relationship or affiliation in the form of:

- **Consultant, Advisor, Speaker** for Biogen; Genentech; Medtronic; Novartis; Genzyme;
- **Grant/Research Support** from Actelion; Roche; Mallenkrodt; Biogen; Teva;

Aaron L. Boster, MD, does not intend to discuss any non–FDA-approved or investigational use of any products/devices.

*When slides are not referenced, this represents Dr. Boster’s personal opinions*
“The Times They Are A-Changing”

1998:
- Don't get in strangers' cars
- Don't meet ppl from internet

2016:
- Literally summon strangers from internet to get in their car
Learning Objectives

1. Incorporate the following terms into your MS lexicon

- Activity
- Breakthrough Activity
- Worsening
- Progression

- Highly Active MS
- NEDA
- CDI
- NEP
- Brain Atrophy Rates

2. Adopt “Topographical Model of MS” into your delivery of MS care

3. Identify breakthrough activity & Highly Active disease

NEDA: No Evidence of Disease Activity; CDI: Confirmed Disability Improvement
NEP: No Evidence of Progression
Updated Terminology For
Multiple Sclerosis Phenotypes
Relapsing MS

Relapse: An acute, or sub-acute episode of new or increasing neurologic dysfunction followed by full or partial recovery, in absence of fever or infection

+/- Activity

+/- Worsening

+/- Progression

(My Opinion) +/− Highly Active

Activity determined by clinical relapse and/or MRI activity (Gad+ T1 lesions; new/unequivocally enlarging T2 lesions assessed at least annually; if assessments not available, activity “indeterminate”).

Activity¹

- Clinical Relapse*
  and/or
- New GEL or new/unequivocally enlarging T2 lesions

*Relapse: An acute, or sub-acute episode of new or increasing neurologic dysfunction followed by full or partial recovery, in absence of fever or infection.
GEL: Gad Enhancing Lesions; DMT: Disease Modifying Therapy

MS Phenotype Modifiers

Worsening

- Documented increase in neurologic dysfunction/disability as a result of relapses or progressive disease

MS Phenotype Modifiers

Progression

- Steadily increasing, objectively documented, neurologic dysfunction independent from relapse

Primary Progressive: Progressive accumulation of disability from onset

Secondary Progressive: Progressive accumulation of disability after initial relapsing course

+/- Activity

+/- Worsening

+/- Progression

---

Activity determined by clinical relapse and/or MRI activity (GELs; new/unequivocally enlarging T2 lesions assessed at least annually; if assessments not available, activity "indeterminate").

Progression measured by clinical evaluation, assessed at least annually.

If assessments are not available, activity and progression "indeterminate."

Stable disease.

Identifying “Highly Active” MS: Common Features

Clinical
- Frequent relapses
- Severe relapses
- Incomplete relapse recovery
- Frequent relapses despite DMT
- Early accrual of impairment

Radiologic
- Heavy T2 lesion burden
- Multiple GELs at onset
- Early brain atrophy
- Continued GEL or NEL burden despite DMT

DMT: disease modifying therapy; GEL: gadolinium enhancing lesion; NEL: New or Enlarged T2 bright lesions

Highly Active MS Defined\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Highly Active MS Defined</th>
<th>Rapidly Evolving Severe MS</th>
<th>High MS Disease Activity</th>
<th>Rapidly Worsening or Fulminant MS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥2 disabling relapses in previous year</td>
<td>≥1 relapse in the previous year on interferon β</td>
<td>Frequent relapses</td>
</tr>
<tr>
<td></td>
<td>≥1 GEL or significant ↑ in T2-lesion load</td>
<td>≥1 GEL or ≥9 T2 lesions on cranial MRI</td>
<td>Resulting in sustained clinical worsening</td>
</tr>
<tr>
<td></td>
<td><em>Licensed indication for natalizumab in many regions of EU</em></td>
<td><em>Licensed indication for fingolimod in many regions of EU</em></td>
<td>Occurring despite DMT and repeated pulses of IVMP</td>
</tr>
</tbody>
</table>

GEL: Gad enhancing lesions; DMT: disease-modifying therapy; IVMP: intravenous methylprednisolone.

Risk Factors for Poor Outcomes 5 Years After Diagnosis

Retrospective analysis of 207 RRMS clinic patients

- Examined relative importance of several risk factors to predict worsening (EDSS increase 5 years later)
- Evaluated within 1 year of second attack and ≥ 2 years after first attack

**Risk Factors for Poor Outcomes 5 Years After Diagnosis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>First attack at &gt;40 years of age</td>
<td>30</td>
</tr>
<tr>
<td>&gt;2 attacks in first 2 years from onset</td>
<td>38</td>
</tr>
<tr>
<td>Poor recovery (EDSS &gt;1.5) after second attack</td>
<td>28</td>
</tr>
<tr>
<td>Male gender</td>
<td>24</td>
</tr>
<tr>
<td>Motor symptoms at onset</td>
<td>58</td>
</tr>
</tbody>
</table>

**Regression analysis & KM survival curves suggested:**

1. Poor recovery after 1st 2 attacks best individual predictor of worsening at 5 years after initial diagnosis
2. Having 3-5 individual risk factors associated with higher risk of worsening ($P < .001$)

---

EDSS: Expanded Disability Status Scale.
Limitations to the New MS Phenotypes in Multiple Sclerosis
Limitations of Current MS Phenotypes:
Uncertainties regarding key assumptions

- Is relapsing MS also progressive from onset? (Not encapsulated in “RRMS without activity”)

- Is progressive MS inflammatory throughout the course? (Not encapsulated in “progressive MS without activity”)

Limitations of Current MS Phenotype Descriptions

New Conceptual Models to Understand Multiple Sclerosis
Updated Conceptual Model:
Traditional to “Leaking Swimming Pool”

1. Lublin FD et al. Neurology. 2014;83
Topographical Model of MS; “Leaking Swimming Pool”

Unified visualization of clinical course

1. Water surface = clinical threshold
2. Volume of water = functional reserve
   - Fluid variable across time: periods of depletion, renewal, and decline over long-term
3. Pool Floor = CNS
   - Model reflects relative variation in functional reserve in different parts of CNS

1. Adapted with permission from Krieger et al. Neurology: Neuroimmunooogy & Neuroinflammation. October 2016;3
Inflammatory Activity: “Base Effects”

- Lesions rise up as topographical peaks from pool base
- Water surface depicts clinical threshold
  - 1. clinical attack
  - 2. silent MRI lesion
- Model reflects predilection for ON, TM & brainstem syndromes

1. Adapted with permission from Krieger et al. Neurology: Neuroimmunooogy & Neuroinflammation. October 2016;3
Progression: “Surface Effects”¹

- Progression = slowly dropping water level, representing depletion of functional reserve

- CORE HYPOTHESIS: progression clinically recapitulates the form of prior activity, incrementally exposed above surface (clinical threshold)

- Also explains re-emergence of symptoms with Uhthoff’s phenomenon and pseudo-relapses

¹ Adapted with permission from Krieger et al. Neurology: Neuroimmunooogy & Neuroinflammation. October 2016;3
New Outcome Measures in Multiple Sclerosis
Evolving Clinical Outcome Measures

**Traditional**:  
- Annualized Relapse Rate Reduction  
- Confirmed Disability Progression  
- New T2 bright or GEL  
  “I can make you get worse slower”  
  - Doctor

**Contemporary**:  
- No Evidence of Disease Activity  
- Confirmed Disability Improvement  
- No Evidence of Progression  
- Improved Brain Atrophy Rates

*Traditional clinical outcome measures are still relevant in clinical trials and clinical practice; GEL: Gad Enhancing Lesions*
New Outcome Measures

No Evidence of Disease Activity (NEDA)
No Evidence of Disease Activity (NEDA)

**NEDA 3**
- No relapses
- No NEL or GEL
- No progression of disability

**Potential Future NEDA:**

**NEDA 5**
- 4 + CSF NF negative

**NEDA 6**
- 5 + No cognitive dysfunction

NEL: New or Enlarged T2 lesion; GEL: Gad Enhancing Lesion; NF: neurofilament

Adapted with permission (david.baker@qmul.ac.uk) Understanding Clinical Trials. https://www.slideshare.net/mstrust/understanding-clinical-trials-55198048
## Predictive Value of 2 years of NEDA3 on progression at 7 years

<table>
<thead>
<tr>
<th></th>
<th>Whole Cohort</th>
<th>NEDA at 7 years</th>
<th>Non-NEDA at 7 years</th>
<th>NEDA at 2 years</th>
<th>Non-NEDA at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>219</td>
<td>17</td>
<td>199</td>
<td>60</td>
<td>158</td>
</tr>
<tr>
<td>Age at 1st visit (mean±SD)</td>
<td>40.2±9.5</td>
<td>42.3±7.7</td>
<td>40.1±9.7</td>
<td>41.9±7.9</td>
<td>39.6±10</td>
</tr>
<tr>
<td>Dz Duration at 1st visit (mean±SD)</td>
<td>6.6±7</td>
<td>9.9±8.9</td>
<td>6.3±6.9</td>
<td>7.3±7.8</td>
<td>6.3±6.7</td>
</tr>
<tr>
<td>EDSS at 1st visit (mean±SD)</td>
<td>1.3±1.1</td>
<td>1.4±0.8</td>
<td>1.4±1.1</td>
<td>1.3±0.8</td>
<td>1.4±1.2</td>
</tr>
</tbody>
</table>

NEDA: no attack, CDP at 2 consecutive semi-annual visits, new T2 or Gd+ DMT at 1st study visit: NONE 48%, IFN-B 36%, GA 15%, CTX 0.5%, NTZ 1%

Rotstein et al. Investigation of NEDA and long-term disability prediction in a seven year longitudinal MS cohort. ECTRIMS 2014 Boston.
**Short Term NEDA: High PPV On Progression 7 Years Later**

<table>
<thead>
<tr>
<th>NEDA Duration</th>
<th>No ½ step EDSS change from baseline at 7 years follow up</th>
<th>No 20% T25FW change from baseline at 7 years follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>72%</td>
<td>75-100%</td>
</tr>
<tr>
<td>2 years</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

- Positive Predictive Value (PPV): proportions of positive results in a statistic that are true positive result
- PPV describe the performance of a diagnostic test. A high result can be interpreted as indicating the accuracy of such a test.

**NEDA:** no attack, Confirmed Disability Progression at 2 consecutive semi-annual visits, new T2 or Gd+ MRI lesions; Rotstein et al. Investigation of NEDA and long-term disability prediction in a 7 year longitudinal MS cohort. ECTRIMS 2014 Boston.
### NEDA Association With Brain Atrophy & Functional Outcomes

**Example in post hoc analysis in RRMS patients**

<table>
<thead>
<tr>
<th>ASSOCIATED OUTCOME MEASURE</th>
<th>NEDA patients</th>
<th>NON-NEDA patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Decrease BPF</td>
<td>-0.15%</td>
<td>-0.28%</td>
<td>0.0055</td>
</tr>
<tr>
<td>PASAT Median Change</td>
<td>2.0</td>
<td>1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T25FW Median Change</td>
<td>0.0 sec</td>
<td>0.20 sec</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>9HPT Median Change</td>
<td>-0.73 sec</td>
<td>-0.24 sec</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDSS Improvement</td>
<td>36.9%</td>
<td>22.6%</td>
<td>0.0001 *</td>
</tr>
</tbody>
</table>

*HR 1.9 [95% CI: 1.37-2.68]*

**NEDA:** no relapse, no 3mo CDP EDSS, no Gd+, No N/E T2 lesions over 2 years

**BPF:** Brain Parenchymal Fraction; **PASAT:** paced auditory serial addition task; **T25FW:** timed 25 foot walk; **9HPT:** Nine Hole Peg Test; **EDSS:** Expanded Disability Status Scale; **EDSS improvement:** 3mo sustained decrease of ≥1.0 point. PP1216. Ruddick et al. EFNS European Journal of Neurology 21 (Suppl, 1): 388-713. *Post Hoc Analysis of AFFIRM*
No Evidence of Disease Activity 3

*Example in contemporary RRMS cohort*¹

![Bar chart showing comparison of NEDA proportions between IFN β-1a and Ocrelizumab.]

- **IFN β-1a 44 μg (n=375)**: 25.1%
- **Ocrelizumab 600 mg (n=379)**: 47.5%

**89% improvement vs IFN β-1a**

*P* < 0.0001

NEDA: no protocol-defined relapses, no confirmed disability progression events, no new or enlarging T2 lesions, and no Gd⁺ T1 lesions

Post Hoc analysis of pooled data from FREEDOMS I and FREEDOMS II.
GEL: Gad Enhancing Lesions; BVL: brain volume loss;
1. De Stefano N et al. AAN 2015. Abstract P3.246
No Evidence of Disease Activity 3

Example in Highly Active Patients Subgroup Analysis

Post Hoc Analysis of CARE-MS II trial. NEL: new/enlarging T2 lesion.

- **Freedom From Clinical Disease Activity**
  - IFN β-1a: 33%
  - Alemtuzumab: 61%

- **Freedom From MRI Disease Activity**
  - IFN β-1a: 7.5%
  - Alemtuzumab: 40%

- **Freedom From Demonstrable MS Disease Activity**
  - IFN β-1a: 0%
  - Alemtuzumab: 24%

Post hoc analysis (N = 145)

High disease activity defined as
≥2 relapses in year prior to randomization and ≥1 GEL on baseline MRI

- Relapse-free and absence of ≥1-point increase over baseline on EDSS for ≥6 months for 2 years.
- No new GEL and no NEL for 2 years.
- No clinical or MRI disease activity for 2 years.

No Evidence Of Disease Activity 3
Example in 6yr LTFU of Highly Active Patients Subgroup Analysis

Highly active disease was defined as ≥2 relapses in the year prior to randomization and ≥1 Gd-enhancing T1 lesion at core study baseline; NEDA: defined as absence of MRI disease activity and clinical disease activity (relapses and 6-month confirmed disability worsening, the latter defined as an increase from core study baseline of ≥1.0 EDSS point [or ≥1.5 points if baseline EDSS score=0]). Comi G et al. ECTRIMS 2016, Poster P613.
New Outcome Measures
Confirmed Disability Improvement
Confirmed Disability Improvement (CDI)

Improvement of at least 1 EDSS step maintained for at least 6 months*

*Calculations of CDI only include patients with baseline EDSS > 2.0 Dynamic variable.
“Sustained Improvement in Disability a” (aka CDI)  
*Example in Post Hoc Analysis in Highly Active RRMS cohort*

*≥2 relapses in the year before study entry and ≥1 gadolinium enhancing lesion at study entry, baseline EDSS > 2  
*Defined as EDSS 1 point decrease sustained for 12 weeks.*

Natalizumab Significantly Increases the Cumulative Probability of Sustained Improvement in Physical Disability POST HOC AFFIRM  
F. Munschauer, et. al. Poster #P474 Presented at the World Congress in Treatment and Research in Multiple Sclerosis September 17-20, 2008
Confirmed Disability Improvement:
Example from contemporary RRMS cohort

**Relative improvement: 33%**
Relative risk (95% CI):
1.33 (1.05, 1.68); $P < 0.02$

Proportion of Patients Achieving 12 week CDI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN β-1a 44 μg (n=614)</td>
<td>15.6</td>
</tr>
<tr>
<td>Ocrelizumab 600 mg (n=628)</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Proportion of Patients With CDI for At Least 12 Weeks (Baseline EDSS ≥2.0)

OPERA I & OPERA II
Confirmed Disability Improvement

Example 6 year LTFU in absence of continuous treatment Highly Active RRMS cohort

- CDI (confirmed disability improvement) defined as ≥1-point EDSS decrease among the cohort of patients with baseline EDSS score ≥2.0.

- Number at risk is the number of patients who remained on study and who had yet to achieve CDI.

High disease activity defined as ≥2 relapses in year prior to randomization and ≥1 GEL on baseline MRI

Confirmed Disability Improvement:
Example in 5-year follow up of Highly Active Patients¹

HIGHER ACTIVELY CARE MS-II: Disability Through Year 5¹

<table>
<thead>
<tr>
<th>Year</th>
<th>≥1-Point Improvement</th>
<th>Stable (≤0.5-point change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y0-2</td>
<td>86.7</td>
<td>26.5</td>
</tr>
<tr>
<td>Y0-3</td>
<td>81.3</td>
<td>58.2</td>
</tr>
<tr>
<td>Y0-4</td>
<td>80.9</td>
<td>61.8</td>
</tr>
<tr>
<td>Y0-5</td>
<td>75.3</td>
<td>25.9</td>
</tr>
</tbody>
</table>

Entire CARE MS-II Cohort: Disability Through Year 5²

<table>
<thead>
<tr>
<th>Years 0–5 (n=325)</th>
<th>≥1-Point Improvement</th>
<th>Stable (≤0.5-point change)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76.6</td>
<td>51.7</td>
</tr>
</tbody>
</table>

Highly Active Disease: >2 attacks in year prior to randomization & ≥1 GEL at core baseline
1. Patients with highly active RRMS Despite Prior Therapy Show Durable Improvement with Alemtuzumab over 5 years. Singer et al. Poster DX17. CMSC 2016
2. Leganke, Boster et al. presentation DX02. CMSC 2016
Confirmed Disability Improvement:
Example in Propensity Matched Switches amongst active* patients from MSBase\(^1\) Registry

• After switch to natalizumab vs. after switch to fingolimod:
  
  • No between-group difference in rate of confirmed disability progression (CDP)
  
  • 2.8 x higher rate of confirmed disability improvement (CDI) observed after switch to natalizumab \((P < .001)\)

*Disease activity defined: patients with RRMS experiencing relapses or disability worsening within the 6 months preceding switch to either natalizumab or fingolimod; CDI: Confirmed Disability Improvement = improve \(\geq 1\) EDSS step for at least 6 months; CDP: Confirmed Disability Progression = worsen \(\geq 1\) EDSS step for at least 6 months

New Outcome Measures

No Evidence of Progression
No Evidence of Progression (NEP)

Measure in Primary Progressive Multiple Sclerosis

NEP = The combined absence of 12-week clinical progression as measured by:

- No 12-week confirmed progression on EDSS
- No 12-week confirmed ≥20% progression on 9HPT
- No 12-week confirmed ≥20% progression on T25FW

9HPT=9-hole peg test; EDSS=Expanded Disability Status Scale; NEP=no evidence of progression; PPMS=primary progressive multiple sclerosis; T25FW=timed 25-foot walk.

1. Adapted from Montalban X, et al. Presented at: ECTRIMS. 2016 (Presentation 167) ORATORIO
No Evidence of Progression (NEP)

Example in Primary Progressive MS

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=230)</th>
<th>Ocrelizumab (n=461)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEP Reference pop</td>
<td>Reference population excluding patients withdrawn for reasons other than efficacy failure or death prior to the Week 120 and without evidence of progression (n=41). Patients withdrawn due to efficacy failure or death are considered as having event.</td>
<td></td>
</tr>
<tr>
<td>NEP</td>
<td>29.1%</td>
<td>42.7%</td>
</tr>
<tr>
<td>No</td>
<td>63.0%</td>
<td>68.6%</td>
</tr>
<tr>
<td>No</td>
<td>38.7%</td>
<td>51.0%</td>
</tr>
<tr>
<td>No</td>
<td>71.3%</td>
<td>82.2%</td>
</tr>
</tbody>
</table>

47% relative increase in NEP with ocrelizumab

Relative risk (95% CI): 1.47 (1.17, 1.84), p=0.0006

Adapted from Montalban X, et al. Presented at: ECTRIMS. 2016 (Presentation 167). ORATORIO
New Outcome Measures
Improved Brain Atrophy Rates
RESULTS:

• Greater decrease of the corpus callosum volume at 6 months (HR 2.74; P = 0.001) was associated with increased cumulative risk of a second clinical attack between months 6 and 48.

• Greater lateral ventricle volume enlargement at 6 months (HR 2.43; P = 0.002) was associated with increased cumulative risk of a second clinical attack between months 6 and 48.

• Greater lateral ventricle volume enlargement at 6 months (HR 4.70; P = 0.001) was associated with increased risk of confirmed disability progression over 48 months.
Reduction in Brain Atrophy Rates
*Example in contemporary RRMS cohort*

**OPERA II**

**Percentage Change in Brain Volume From Baseline to Week 96**

<table>
<thead>
<tr>
<th>Week</th>
<th>IFN β-1a 44 μg</th>
<th>Ocrelizumab 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>-0.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>48</td>
<td>-0.8</td>
<td>-1.2</td>
</tr>
<tr>
<td>96</td>
<td>-1.2</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

23.8% reduction in rate of brain volume loss vs IFN β-1a  
*P*=0.0001

EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; IFN, interferon; ROW, rest of the world.
Reduction in Brain Atrophy Rates

Example in contemporary PPMS cohort

![Graph showing the reduction in brain atrophy rates with Ocrelizumab compared to Placebo. The graph illustrates the mean percent change from Week 24 in brain volume (mean, 95% CI).]

**Relative Difference:** 17.5% vs placebo

\[ p = 0.02 \]

**ITT population.** \( p \)-value based on mixed-effect model repeated measure adjusted at Week 120 for week 24 brain volume, geographic region (United States vs ROW), and age (≤45, >45).

CI=confidence interval; ITT=intent-to-treat; MRI=magnetic resonance imaging.

Normalization of Brain Atrophy Rates in the Absence of Continuous Treatment

Example Alemtuzumab 6 year LTFU in RRMS population

BPF=brain parenchymal fraction

*Alemtuzumab vs SC IFNB-1a, P=0.0121.

[P1181] Alemtuzumab Durably Slows Brain Volume Loss Over 6 Years in the Absence of Continuous Treatment in Patients With Active RRMS Who Were Treatment-Naïve (CARE-MS I) or Had an Inadequate Response to Prior Therapy (CARE-MS II) Traboulsee A et al. ECTRIMS 2016, Poster P1181.
Reduced Rates of Brain Atrophy
Example: 5yr LTFU in RRMS cohort

CONCLUSIONS

- In this cohort of relapsing MS patients treated with natalizumab beyond 5 years in STRATA, annualized MRI disease activity burden remained extremely low.
- The mean rate of PBVC in this cohort is comparable with the estimated yearly rate of brain volume loss in healthy controls (0.1%–0.3%), measured using a variety of techniques.11
- These data suggest that with respect to MRI surrogate markers of brain tissue damage and disease activity/observed during the phase 3 trials are well maintained with long-term treatment.

1. Incorporate the following terms into your MS lexicon

   • Activity
   • Breakthrough Activity
   • Worsening
   • Progression

   • Highly Active MS
   • NEDA
   • CDI
   • NEP
   • Atrophy Rates

2. Adopt “Topographical Model of MS” into your delivery of MS care

3. Identify Breakthrough Activity & Highly Active disease

NEDA: No Evidence of Disease Activity; CDI: Confirmed Disability Improvement
NEP: No Evidence of Disease Progression
Take Home Points

- **Revised MS phenotypes** and new **Topographical Model** of MS provide **more accurate language** to describe the heterogeneous behavior of MS disease activity.

- Certain demographic, radiographic and clinical factors may aid in identifying patients at higher risk for faster worsening. Understanding the definitions of **breakthrough disease activity** and **highly active disease** aids in early identification.

- Contemporary outcome measures should **impact our expectations** of MS disease modifying therapies.