



## “Unnatural” History: Modeling Disease Progression Using Observational Data

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## Background

- Randomized clinical trials (RCTs) do not provide disease progression rates representative of the general population
  - patient self-selection
  - treatment adherence
  - quality of care
- Treatment effects from observational data may be biased
  - non-randomization
  - patient self-selection

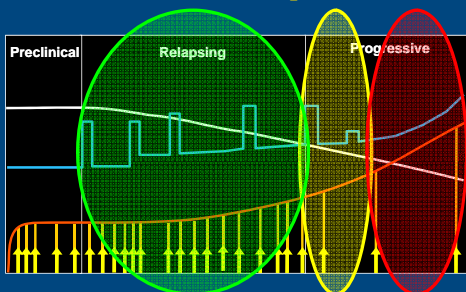
## Study Objective:

- To develop disease progression profiles for treated and untreated individuals with multiple sclerosis using observational data and pivotal trial-based treatment effects

## Multiple Sclerosis (MS) is associated with disability and high expenses

- MS is a autoimmune neurodegenerative condition
- MS is the second most frequent cause of disability in early- to middle-aged adults, after trauma
- Annual direct and indirect costs of MS care can total over \$50,000 (2008 U.S.) per patient

## The Course of Multiple Sclerosis



## Epidemiology of MS

- Chronic demyelinating autoimmune disease of the CNS.
- Peak incidence around age 30.
- Females twice as likely as males to develop MS.
- Estimated US prevalence between 266,000–400,000.



## Data

- 2000-2005 Sonya Slifka Longitudinal MS Survey
  - Representative sample of MS population in the U.S.
  - Information on:
    - MS severity
    - types and extend of disability
    - demographics
    - treatment
- 900 people with relapsing MS
  - Excluded participants:
    - who completed only one interview
    - those with missing information on key information (e.g. disease duration, disease state or demographics)

## Measuring disability in MS patients: Crosswalk from EDSS to Disease States

EDSS CATEGORY	DISABILITY STATUS SCALE
EDSS 0-1.5	1: NO MS SYMPTOMS
EDSS 2-2.5	2: MILD SYMP, NON-LIMITING
EDSS 3-4	3: MILD SYMP, NOT AFFECTING WALKING
EDSS 4.5-5.5	4: PROBLEM W/WALKING, DON'T USE AID 4: 25 FT W/O CANE OR AID
EDSS 6	5: 1-SIDE CANE OR AID FOR 25 FT
EDSS 6.5-7	6: 2-SIDE CANE OR AID FOR 25 FT
EDSS 7.5-8.5	7: ONLY WHEELCHAIR/SCOOTER
EDSS 9-9.5	8: COMPLETELY BED RIDDEN

EDSS = Kurtzke Expanded Disability Status Scale (Kurtzke 1983; Hohol 1995)

## Model Structure

- Disability-based disease states (DSs)
- First-order Markov model with annual cycles for transitions between DSs
- Transition probabilities and relapses estimated with multinomial logit regressions
- Published DMT effects used to modify progressions for individuals on DMT
- 10-year disease progression paths

## Progression Estimation (steps)

- Estimate P & effects of covariates: prior DS, disease duration, recent relapse rate, & demographics
- Set  $T = R_{CT}$
- Re-estimate P applying fixed covariates and T coefficients
- Calculate R, check if  $R = R_{CT}$
- If  $=$ , output P & T to MC simulation
- If  $\neq$ , use numerical algorithm to find T resulting in  $R = R_{CT}$
- Re-estimate P
- Continue iteratively until  $R = R_{CT}$

### Transition probabilities in untreated cohort

DS	2	3	4	5	6	7
2	0.735 (0.678, 0.784)	0.218 (0.175, 0.272)	0.047 (0.028, 0.075)	0 (.)	0 (.)	0 (.)
3	0.211 (0.169, 0.264)	0.666 (0.604, 0.711)	0.103 (0.080, 0.136)	0.019 (0.008, 0.033)	0 (.)	0 (.)
4	0.044 (0.014, 0.088)	0.254 (0.196, 0.323)	0.261 (0.451, 0.338)	0.128 (0.092, 0.180)	0.013 (0.004, 0.036)	0 (.)
5	0 (.)	0.091 (0.028, 0.169)	0.172 (0.112, 0.249)	0.571 (0.364, 0.658)	0.127 (0.089, 0.192)	0.04 (0.019, 0.084)
6	0 (.)	0 (.)	0.132 (0.028, 0.305)	0.276 (0.120, 0.396)	0.525 (0.384, 0.683)	0.115 (0.054, 0.219)
7	0 (.)	0 (.)	0 (.)	0.018 (0.000, 0.070)	0.047 (0.009, 0.107)	0.986 (0.938, 0.978)

### Transition probabilities in mixed cohort

DS	2	3	4	5	6	7
2	0.644 (0.599, 0.688)	0.303 (0.262, 0.344)	0.052 (0.028, 0.072)	0 (.)	0 (.)	0 (.)
3	0.183 (0.156, 0.219)	0.637 (0.598, 0.672)	0.157 (0.122, 0.192)	0.062 (0.012, 0.206)	0 (.)	0 (.)
4	0.027 (0.012, 0.052)	0.222 (0.174, 0.271)	0.54 (0.472, 0.598)	0.195 (0.157, 0.250)	0.025 (0.005, 0.041)	0 (.)
5	0 (.)	0.052 (0.019, 0.103)	0.151 (0.100, 0.225)	0.250 (0.466, 0.618)	0.125 (0.129, 0.267)	0.049 (0.021, 0.090)
6	0 (.)	0 (.)	0.083 (0.024, 0.206)	0.199 (0.115, 0.309)	0.538 (0.301, 0.662)	0.182 (0.092, 0.313)
7	0 (.)	0 (.)	0 (.)	0.012 (0.000, 0.041)	0.043 (0.009, 0.097)	0.946 (0.873, 0.982)

## Study Limitations

- “All models are wrong but some are useful...”
- Limited sample of patients with early & late disease
- Cohort representativeness: Slifka vs. NHIS
- Disability/EDSS as a measure of MS progression
- RCT data quality

## Conclusions

- Treated MS patients had faster disease progression than never untreated
- Patients who forgo treatment have milder, slower progressing forms of MS
- Advantages of correcting for treatment effects in a more representative group of patients:
  - more realistic estimate of natural history and disease progression
  - Improved precision of the estimates

**THANK YOU!**

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