

# IRT Model for EDSS in Multiple Sclerosis

Longitudinal Pharmacometric Analysis of Cladribine Treatment

*Based on Novakovic et al., 2016*

다발성 경화증 EDSS 항목반응이론 모델 | 클라드리빈 치료 효과 분석  
多発性硬化症 EDSS 項目反応理論モデル | クラドリビン治療効果分析

# Presentation Overview

1

## Model Structure

Longitudinal IRT framework with drug effects

2

## Parameter Estimates

Population PK/PD parameters and variability

3

## Random Effects

Correlation structure via Cholesky decomposition

4

## IRT Analysis

Item characteristic curves and information functions

5

## Drug Effects

Symptomatic and disease-modifying mechanisms

6

## Clinical Implications

Key insights for MS treatment optimization

# Clinical Background: Multiple Sclerosis & EDSS

## Multiple Sclerosis (MS)

- Chronic autoimmune disease of the CNS
- Affects ~2.8 million people worldwide
- Progressive neurological disability over time
- Characterized by relapses and remissions
- Cladribine: oral disease-modifying therapy

## EDSS (Expanded Disability Status Scale)

- Gold standard for MS disability assessment
- Composite score from 0 (normal) to 10 (death)
- Based on 8 functional system subscores:
  - Pyramidal, Cerebellar, Brainstem, Sensory
  - Bowel/Bladder, Visual, Mental, Ambulation

## Why Item Response Theory (IRT) for EDSS?

### Traditional Analysis Limitations:

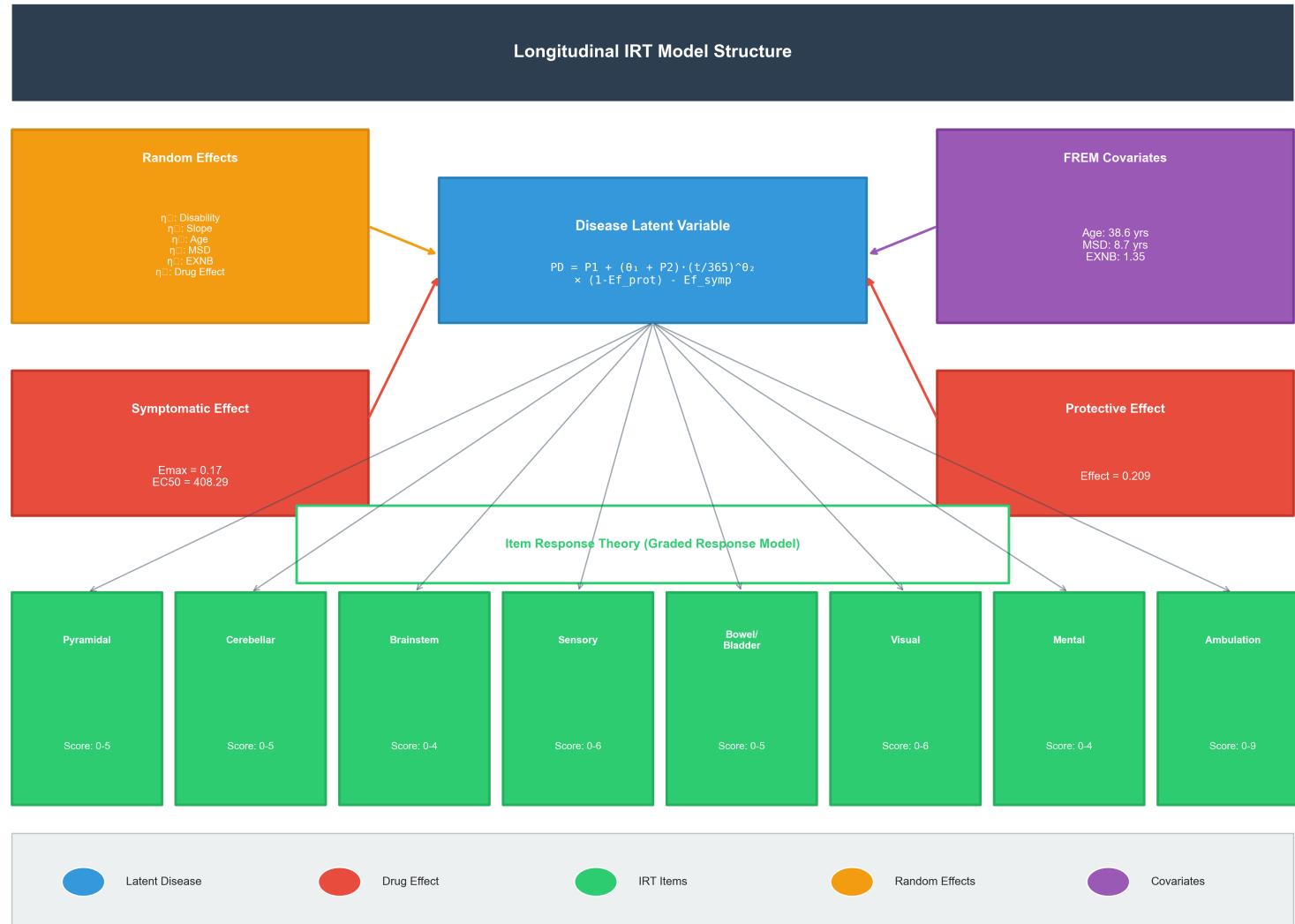
- EDSS is ordinal, not continuous → standard regression inappropriate
- Subscores have different scales (0-4, 0-5, 0-6, 0-9) → not directly comparable
- Floor/ceiling effects mask true disability changes

IRT Solution: Models a latent 'disability' trait that underlies all observed subscores, providing unified disease metric

# Model Structure Overview

## Longitudinal IRT Model Architecture

IRT Model for EDSS in Multiple Sclerosis  
Cladribine Treatment - Novakovic et al., 2016



## Key Points & Discussion

- Central latent variable (PD) represents true underlying disability
- Power model captures non-linear disease progression over time
- Two distinct drug effect mechanisms: symptomatic and protective
- FREM approach incorporates Age, MS Duration, Exacerbation count as covariates
- 8 functional systems linked via IRT graded response model
- Cholesky decomposition ensures valid correlation structure

# Model Structure: Mathematical Framework

## Disease Latent Variable Equation:

$$PD = P_1 + (\theta_1 + P_2) \times (t/365)^{\theta_2} \times (1 - Ef\_prot) - Ef\_symp$$

Where:  $P_1$  = baseline disability ( $\eta_1$ ),  $P_2$  = individual slope ( $\eta_2$ ),  $\theta_1$  = population slope,  $\theta_2$  = power parameter

### Disease Progression

#### *Power Model*

- Slope ( $\theta_1$ ) = 0.093
- Power ( $\theta_2$ ) = 0.710
- Non-linear time course
- Sub-linear progression pattern

### Symptomatic Effect

#### *Emax Model*

- Emax = 0.17
- EC50 = 408.29
- Exposure-dependent
- Immediate effect on symptoms

### Protective Effect

#### *Disease-Modifying*

- Effect = 20.9%
- Exposure-independent
- Slows progression rate
- Long-term benefit

## IRT Link: Connecting Latent Disease to Observed Subscores

Graded Response Model:  $P(X \geq k | \theta) = 1 / (1 + \exp(-a \times (\theta - b_k)))$

- Each functional system has unique discrimination (a) and boundary (b) parameters
- Higher discrimination → item better differentiates disability levels | Boundaries define score thresholds

# Parameter Estimates Summary

## Population Parameters and Variability

### Parameter Estimates Summary IRT Model - Cladribine in Multiple Sclerosis

#### Disease Progression Parameters

**Slope ( $\theta_1$ )** 0.0930

Disease progression rate

**Power ( $\theta_2$ )** 0.7100

Time-course exponent

$$PD = P_1 + (\theta_1 + \theta_2) \cdot (t/365)^{\theta_2}$$

#### Drug Effect Parameters

**Emax (symptomatic)** 0.170

Maximum symptomatic effect

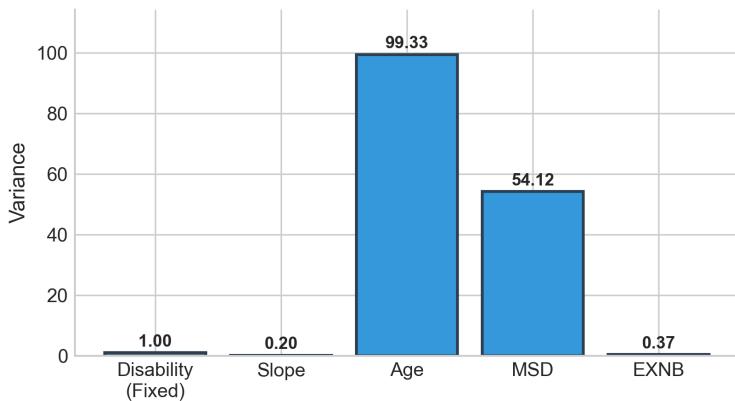
**EC50 (symptomatic)** 408.290

Half-maximal exposure

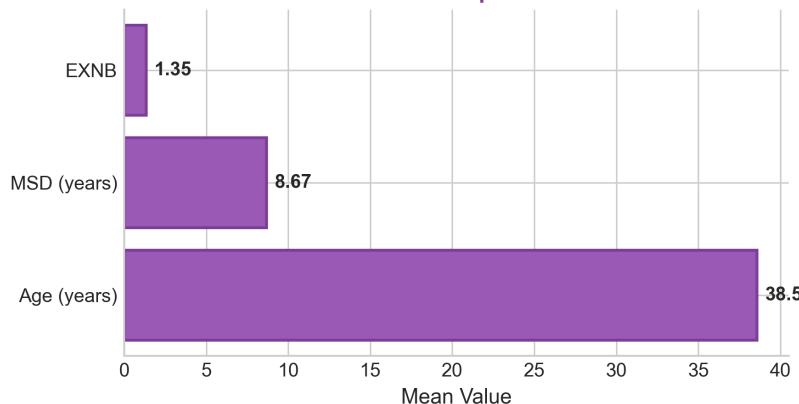
**Protective Effect** 0.209

Disease-modifying fraction

#### Random Effect Variances



#### FREM Covariate Population Means



#### IRT Item Parameters by Functional System



## Key Points & Discussion

- Disease progression slope (0.093) indicates slow accumulation of disability
- Power  $< 1$  (0.71) suggests decelerating progression over time
- Large variance in Age (99.3) reflects patient heterogeneity
- Ambulation has highest discrimination (3.64) - most informative subscore
- Visual has lowest discrimination (0.44) - less reliable indicator
- OFV = 418.626 for model evaluation

# Random Effects Correlation Structure

Cholesky Parameterization of 5x5 Omega Matrix

Random Effects Correlation Matrix (Cholesky Parameterization)



## Key Points & Discussion

- Age-MSD correlation (0.46) is clinically expected and validates the model
- Disability correlates weakly with Age (0.26) and MSD (0.27)
- Slope shows minimal correlation with covariates (good for identifiability)
- Negative EXNB correlations may reflect disease phase transitions
- Overall weak correlations support parameter estimability
- FREM enables covariate effects without traditional covariate modeling

# Random Effects: Clinical Interpretation of Correlations

## Cholesky Parameterization

- Ensures positive-definite covariance matrix
- Correlations estimated as separate parameters
- FREM: Covariates as random effects for correlation

## 5×5 Correlation Structure

Random effects:  $\eta_1$  (Disability),  $\eta_2$  (Slope),  
 $\eta_3$  (Age),  $\eta_4$  (MSD),  $\eta_5$  (EXNB)  
Plus  $\eta_6$  (Drug Emax) - separate block

### Age $\leftrightarrow$ MS Duration

r = 0.458 (Moderate Positive)

Older patients have longer disease duration on average. Expected clinical finding validates model.

### Disability $\leftrightarrow$ MS Duration

r = 0.273 (Weak Positive)

Longer disease associates with higher baseline disability. Supports progressive nature of MS.

### Disability $\leftrightarrow$ Age

r = 0.265 (Weak Positive)

Age contributes to disability beyond disease duration. May reflect age-related neural reserve decline.

### MS Duration $\leftrightarrow$ EXNB

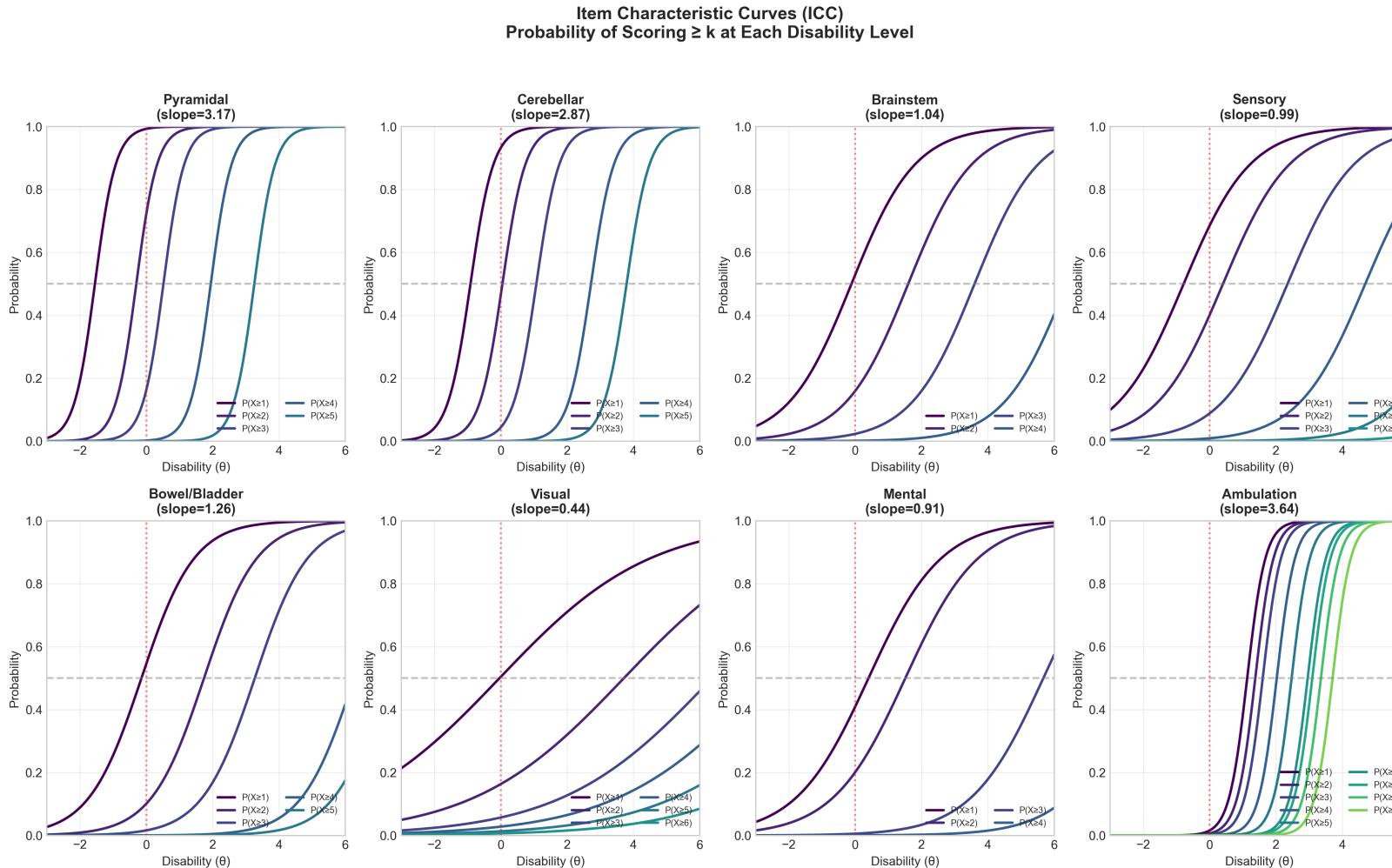
r = -0.115 (Weak Negative)

Longer disease duration associated with fewer recent exacerbations. Possible transition to progressive phase.

*Note: Weak correlations ( $|r| < 0.3$ ) suggest relatively independent random effects, supporting model identifiability*

# Item Characteristic Curves

Probability of Scoring  $\geq k$  at Each Disability Level



## Key Points & Discussion

- Steeper curves = higher discrimination = better differentiation
- Ambulation shows sharp transitions - excellent disability marker
- Visual shows gradual curves - less sensitive to changes
- Curve spacing indicates boundary (threshold) locations
- Items most informative where curves are steepest
- Can guide selection of endpoints for clinical trials

# IRT Analysis: Clinical Implications of Item Parameters

## High Discrimination Items (slope > 2.5)

- Ambulation (3.64)

Most sensitive to disability changes. Walking ability strongly reflects underlying disease severity.

- Pyramidal (3.17)

Motor function highly informative. Corticospinal tract involvement is a key MS feature.

- Cerebellar (2.87)

Balance and coordination discriminate well between disability levels.

## Lower Discrimination Items (slope < 1.5)

- Visual (0.44)

Optic neuritis often occurs early and may recover. Less reflective of overall progression.

- Mental (0.91)

Cognitive symptoms variable and may not correlate linearly with physical disability.

- Sensory (0.99)

Sensory symptoms fluctuate and are subjective. Less reliable disability indicator.

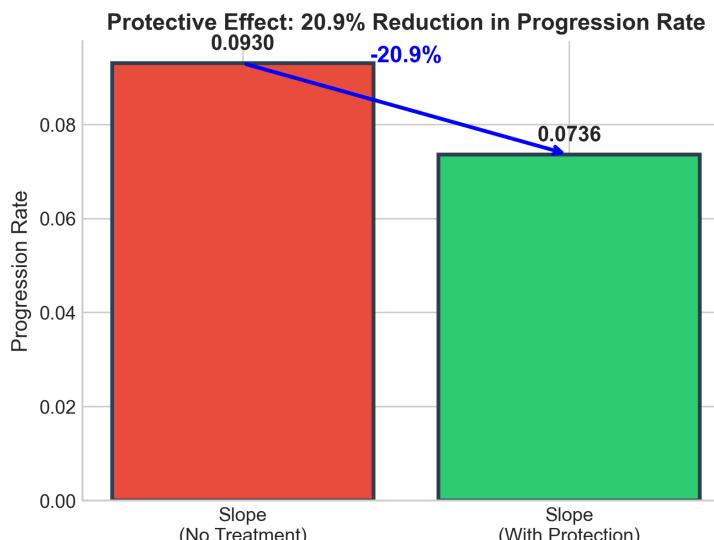
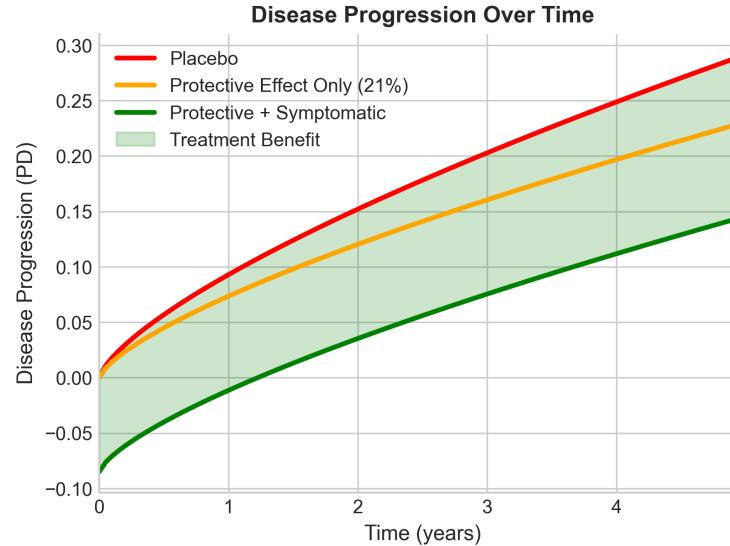
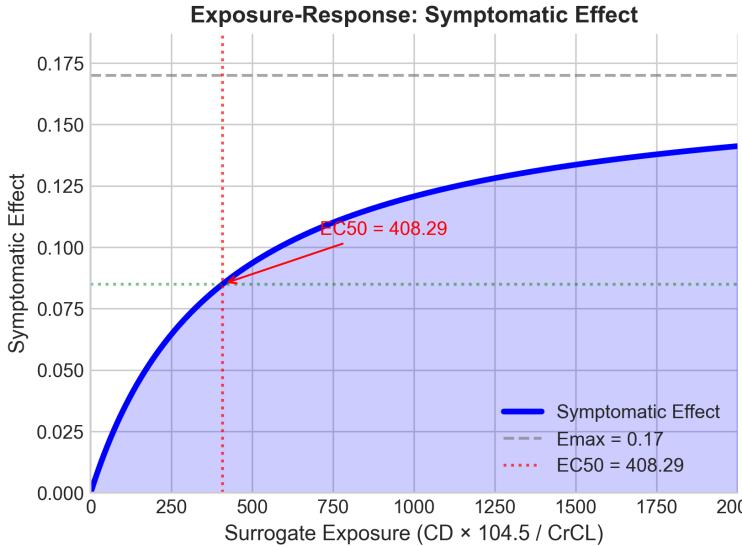
## Clinical & Trial Design Implications

- Trial Endpoints: Consider weighting functional systems by discrimination. Ambulation-focused endpoints may be more sensitive to treatment effects.
- Patient Monitoring: Track high-discrimination items more closely for early detection of progression or treatment response.
- Sample Size: IRT-based analysis can increase power by modeling the latent trait directly, potentially reducing required sample size.
- Precision Medicine: Patients with primarily visual or sensory symptoms may show less response on standard EDSS despite treatment benefit.

# Cladribine Drug Effects

Symptomatic and Disease-Modifying Mechanisms

## Cladribine Drug Effects on Disease Progression



**Drug Effect Summary**

Drug Effect Components:

1. SYMPTOMATIC EFFECT
  - Direct reduction in disability latent variable
  - Exposure-dependent (Emax model)
  - Emax = 0.17, EC50 = 408.3
  - Effect formula:  $Emax \times Exp / (Exp + EC50)$
2. PROTECTIVE (DISEASE-MODIFYING) EFFECT
  - Reduces rate of disease progression
  - Exposure-independent (binary)
  - Reduces slope by 20.9%
  - Effect formula:  $(1 - 0.209) \times slope$

Model Equation:

$$PD = P1 + (\theta_1 + \theta_2) \cdot (t/365)^{\theta_2} \times (1 - Ef\_prot) - Ef\_symp$$

Where  $Ef\_symp$  and  $Ef\_prot$  are active when  $TRT \geq 1$  and  $t > 0$

## Key Points & Discussion

- Emax model: saturable symptomatic effect with exposure
- EC50 = 408.29 guides dosing for optimal symptomatic relief
- Protective effect (20.9%) acts on progression rate, not absolute level
- Combined effects separate over time - greatest benefit long-term
- Model supports both immediate benefit and disease modification claims
- Enables simulation of various dosing regimens

# Cladribine: Dual Mechanism Drug Effects

## Symptomatic Effect

$$Ef_{symp} = Emax \times \text{Exposure} / (\text{Exposure} + EC50)$$

- Emax = 0.17 (17% maximum reduction)
- EC50 = 408.29 (half-maximal exposure)
- Exposure-dependent: higher dose → greater effect
- Direct reduction in disability latent variable
- Rapid onset, dependent on drug levels
- Surrogate exposure:  $CD \times 104.5 / CrCL$

## Protective (Disease-Modifying) Effect

$$\text{Progression} \times (1 - Ef_{prot}) \text{ where } Ef_{prot} = 0.209$$

- 20.9% reduction in progression rate
- Exposure-INDEPENDENT (binary effect)
- Slows the underlying disease process
- Cumulative benefit over time
- Active when  $TRT \geq 1$  and time > 0
- Mechanism: lymphocyte depletion

## Clinical Significance & Therapeutic Implications

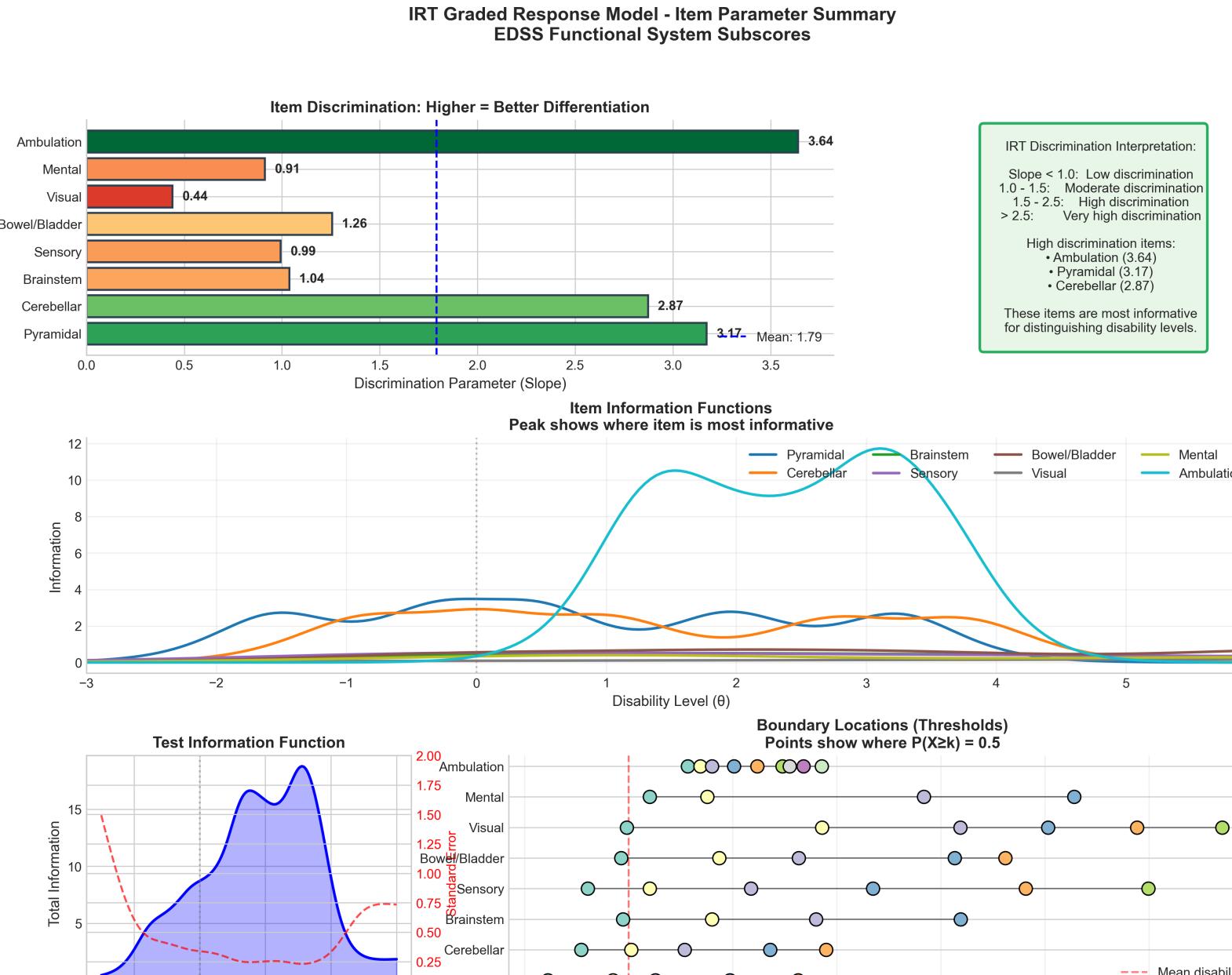
### Dual Mechanism Advantage:

- Symptomatic effect provides immediate benefit patients can perceive (improved daily function)
- Protective effect provides long-term disease modification (delayed disability progression)
- Combined effect: both symptom relief AND slower progression trajectory
- Model enables prediction of long-term outcomes from short-term exposure data

**Key Insight:** The protective effect (20.9%) compounds over time - a patient treated for 5 years accumulates substantial disability reduction vs. placebo

# IRT Item Parameter Analysis

Discrimination, Information, and Boundary Thresholds



## Key Points & Discussion

- Test Information Function peaks around  $\theta = 2-3$  (moderate disability)
- Less precision at extremes (very low or very high disability)
- Ambulation boundaries span wide  $\theta$  range (0-9 score range)
- Item information curves show where each subscore is most useful
- Standard error inversely related to information
- Results support IRT as superior to simple sum scoring

# Summary: Key Findings & Clinical Implications

## Disease Model

Power function progression  
Slope = 0.093, Power = 0.71  
Non-linear, sub-linear course

## Drug Effects

Dual mechanism: Symptomatic (Emax)  
+ Protective (20.9% rate reduction)  
Both contribute to efficacy

## IRT Insights

Ambulation most informative ( $a=3.64$ )  
Visual least informative ( $a=0.44$ )  
Consider weighted endpoints

## Correlations

Age-MSD:  $r=0.46$  (expected)  
Weak inter-correlations support  
model identifiability

## Population

Mean age: 38.6 years  
Mean MS duration: 8.7 years  
Mean exacerbations: 1.35

## Model Fit

OFV = 418.626  
Laplacian estimation  
241 obs, 3 subjects (simulated)

Conclusion: IRT-based longitudinal modeling provides mechanistic insights into cladribine's dual action,  
enabling optimized dosing strategies and more sensitive clinical trial endpoints for MS treatment.

# References & Further Reading

## Primary Reference:

- Novakovic AM, et al. (2016). Longitudinal Item Response Theory Model for EDSS in Multiple Sclerosis. *CPT: Pharmacometrics & Systems Pharmacology*.

## IRT Methodology:

- Samejima F. (1969). Estimation of latent ability using a response pattern of graded scores. *Psychometrika Monograph Supplement*, 34(4).
- Ueckert S, et al. (2014). Modeling composite assessment data using item response theory. *CPT: Pharmacometrics & Systems Pharmacology*.

## NONMEM & Pharmacometrics:

- Beal S, Sheiner LB, Boeckmann A, & Bauer RJ. (2009). NONMEM User's Guides. Icon Development Solutions.
- Karlsson MO & Holford N. (2008). A Tutorial on Visual Predictive Checks. PAGE Meeting.

## Multiple Sclerosis & EDSS:

- Kurtzke JF. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*.
- Thompson AJ, et al. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurology*.

## Cladribine:

- Giovannoni G, et al. (2010). A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *NEJM*.