



# Differentiation between Parkinson's and Parkinson's-like patients in MDS-UPDRS-based diagnosis using Item Response Theory

Sven C. van Dijkman<sup>1</sup>, Gopichand Gottipati<sup>1</sup>, Elodie L. Plan<sup>1</sup>, Mats O. Karlsson<sup>1</sup>

<sup>1</sup>Pharmacometrics research group, Dept. of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden)

Contact: sven.van.dijkman@farmbio.uu.se

**Problem:** Differentiation between Parkinson's disease (PD) patients and subjects without evidence of dopaminergic deficits (SWEDDs) is currently done by symptomatic evaluation with unreliable sensitivity and specificity<sup>1</sup>

**Solution:** IRT was applied to allow automatic differentiation with 86.3% sensitivity and 62.7% specificity

## Introduction

- There is large inter-rater variability in the sensitivity and specificity of differentiation between PD and PD-like (SWEDD) patients by experts<sup>1</sup>
- A clinical need exists for reliable quantitative measures allowing accurate differentiation and prediction of disease progression and outcome

**Aim:** To analyse the differences between PD and SWEDD, and convert this into a tool for differentiation and prognosis

## Methods

- **Data:** The Parkinson's Progression Marker Initiative (PPMI) study<sup>2</sup> followed healthy volunteers (N=199), Parkinson's patients (N=452) and SWEDDs (N=83) for up to 4 years. At regular intervals (-1.5, 0, 3, 6, 9, 12, 24, 36 and 48 months from baseline) the MDS-UPDRS scale was taken as a measure of disease progression.
- **Data analysis:**
  - An existing<sup>3</sup> IRT model originally developed on the PPMI PD data was applied to the SWEDD cohort
  - Subsequently, one shift was estimated for the distribution of values of each of the 68 questionnaire items compared to the PD cohort
- **Item informativeness analysis:**
  - **Iterative item selection algorithm (ISA):**
    - Calculate sensitivity and specificity using each single separate item
    - Select the item resulting in the largest sum of sensitivity and specificity, and test all other separate additional items
    - Continue until no more improvements can be made
  - **Fisher information (FI):**
    - Calculate likelihood of item scores ( $L_{DV}$ )
    - Request second derivative in NONMEM ( $D_2$ )
    - Calculate  $FI = 0.5 * L_{DV} * D_2$
    - Sum FI over all possible values of DV per item

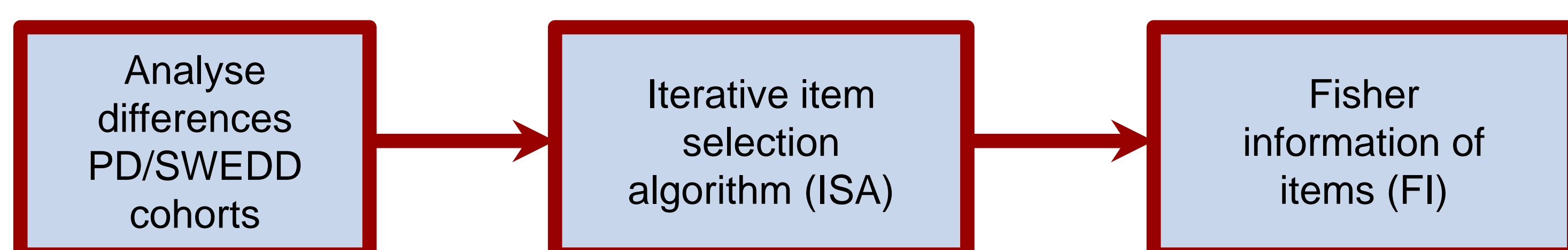


Fig 1. Steps undertaken in the analysis of the data and item informativeness

## Results

- VPCs showed a large improvement in fit of SWEDD data using the shift in item distributions

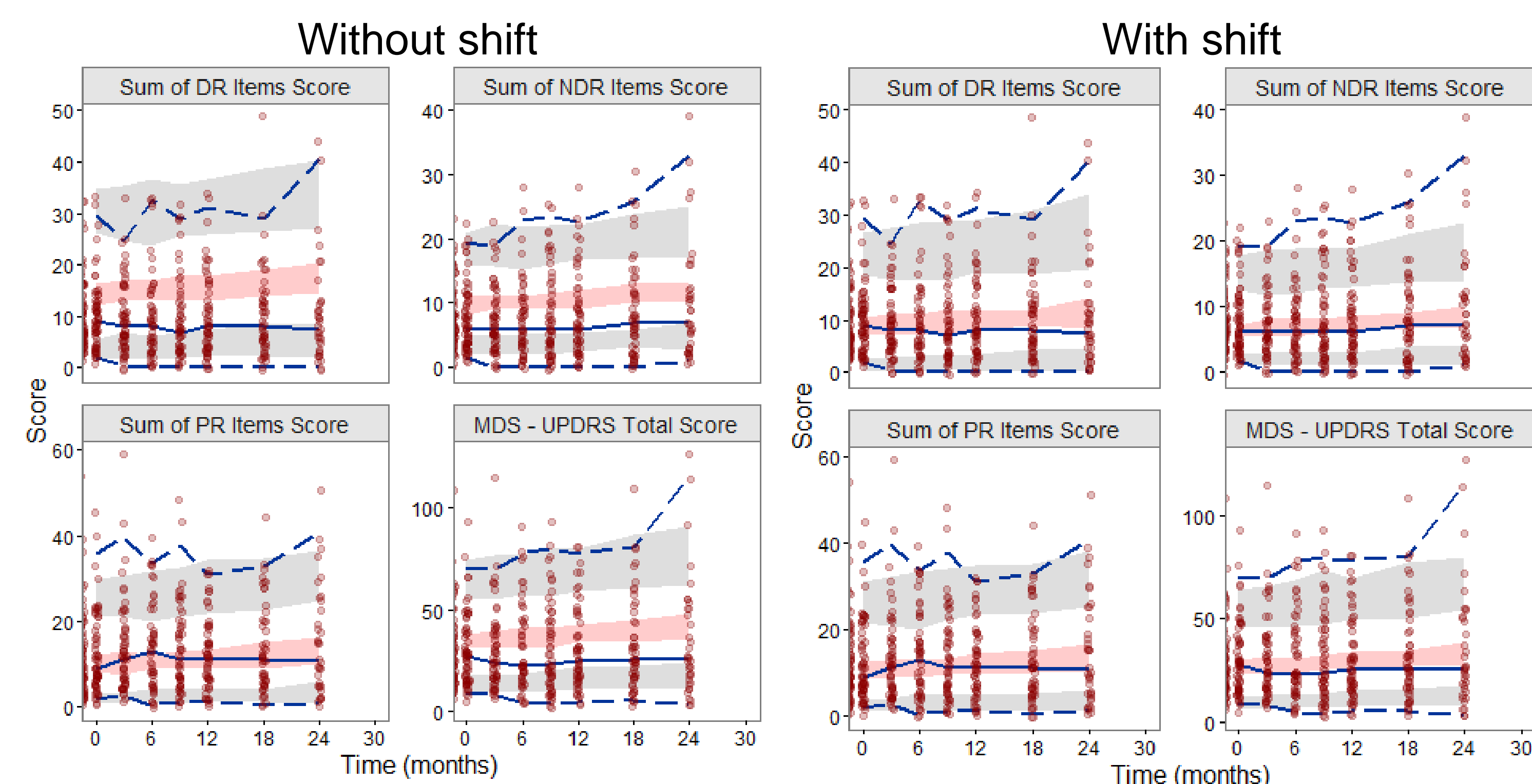


Fig 2. Visual predictive check for total MDS-UPDRS score without (left) and with (right) shift. Full and interrupted lines: median and 95% CI of data. Red and grey areas: median and 95% prediction interval of models. Red dots: individual data.

- Using the shift, and based on only screening ( $t=-1.5$ ) and baseline ( $t=0$ ) data, differentiation could be performed with 86.3% sensitivity and 62.7% specificity
- ISA selected 14 items with 94.9% sensitivity and 57.8% specificity
  - Patient reported: 2
  - Non-handed, non-patient reported: 2
  - Handed (left/right-hand side of body), non-patient reported: 10
- FI revealed which items were most informative regarding disease status & progression, many of which did not coincide with those selected by ISA, which relate to differentiation informativeness:

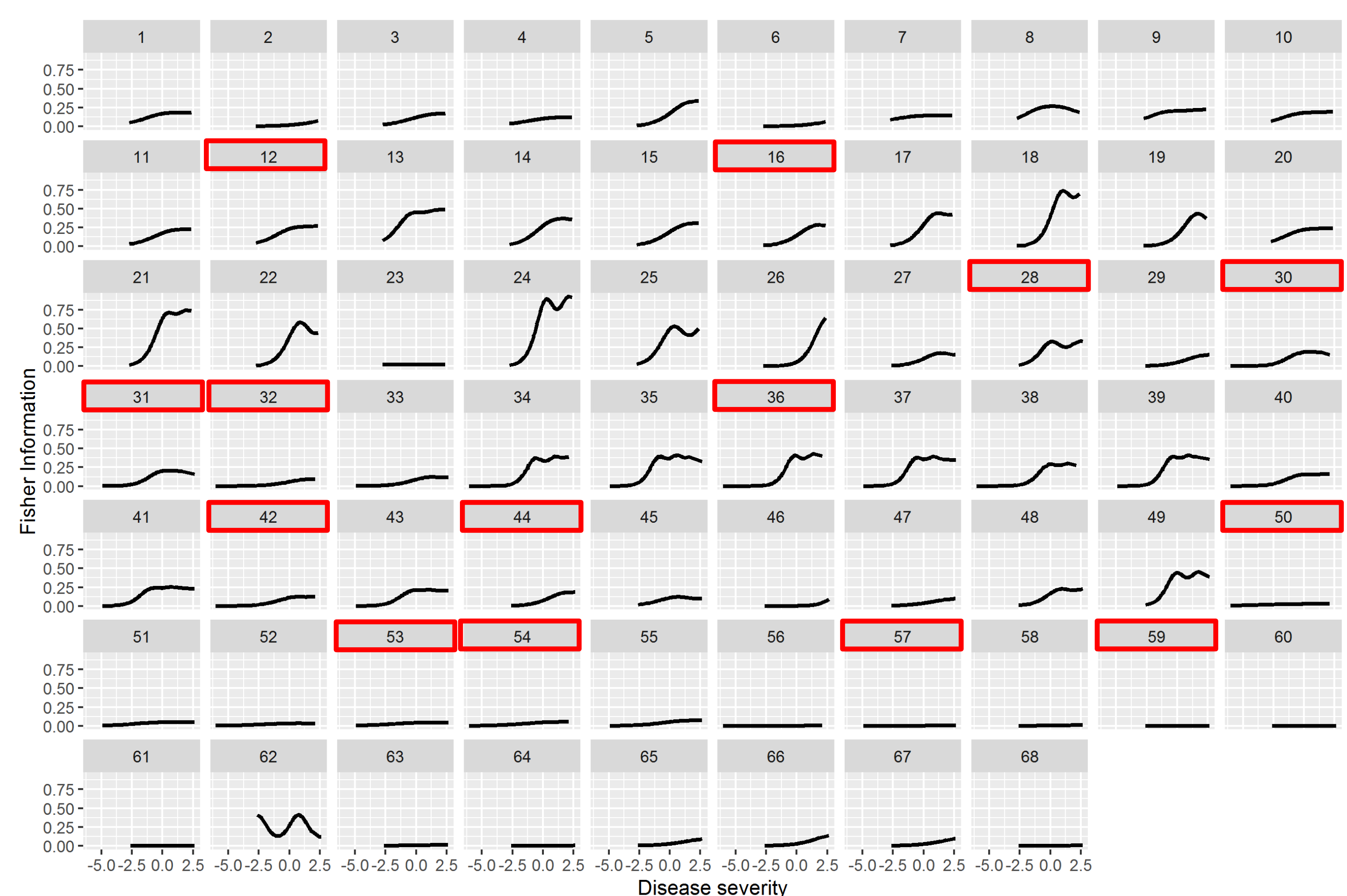


Fig 3. Fisher information (y-axis) depending on disease severity (x-axis) for each item. Red boxes: items selected by ISA for their differentiation informativeness

## Conclusions & Future Perspectives

- The current setup allows differentiation at a similar level of sensitivity and specificity as clinicians, but with higher reliability
- Performance of the IRT models is under improvement, eventually allowing their incorporation into a user-friendly tool for the application of these models in the clinic

<sup>1</sup> Bajaj et al. Accuracy of clinical diagnosis in tremulous parkinsonian patients: a blinded video study. J Neurol Neurosurg Psychiatry. 2010;81:1223–8

<sup>2</sup> Data used in the preparation of this work were obtained from the Parkinson's Progression Markers Initiative (PPMI) database ([www.ppmi-info.org/data](http://www.ppmi-info.org/data)).

<sup>3</sup> PAGE 24 (2015) Abstr 3596 [[www.page-meeting.org/?abstract=3596](http://www.page-meeting.org/?abstract=3596)]