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Item response models for analysing assessments in rare diseases

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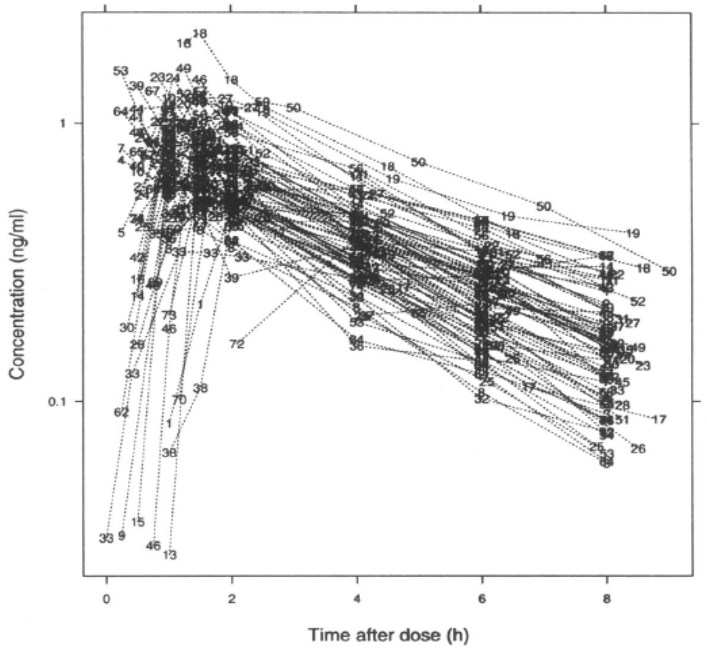
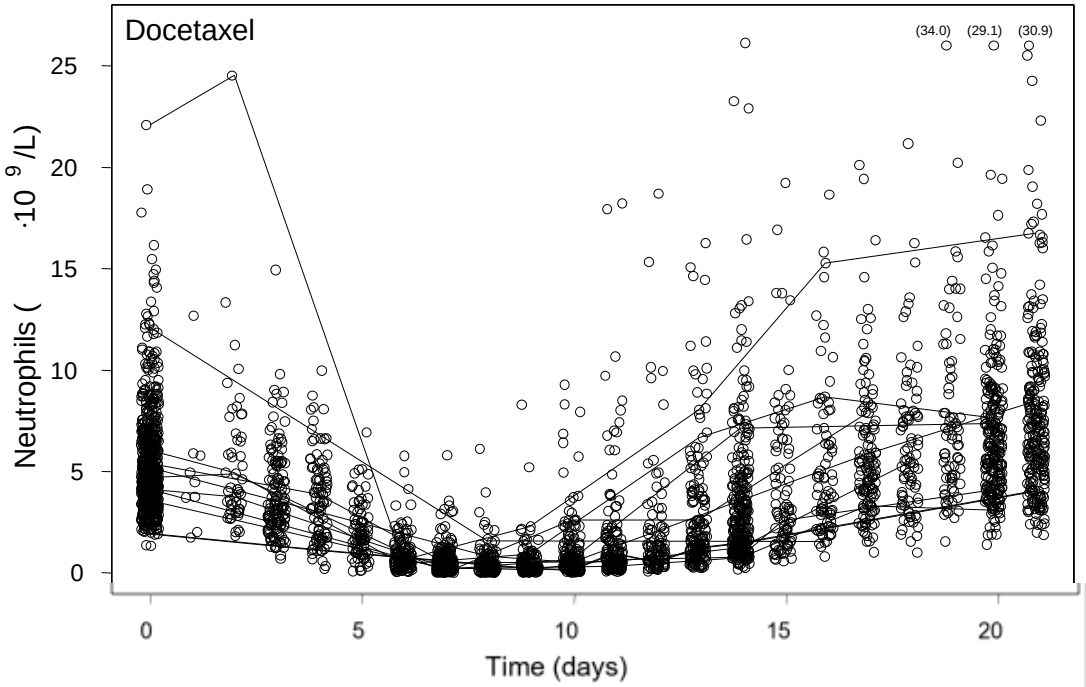
Pharmacometrics

Pharmacokinetics - pharmacodynamics - disease progression

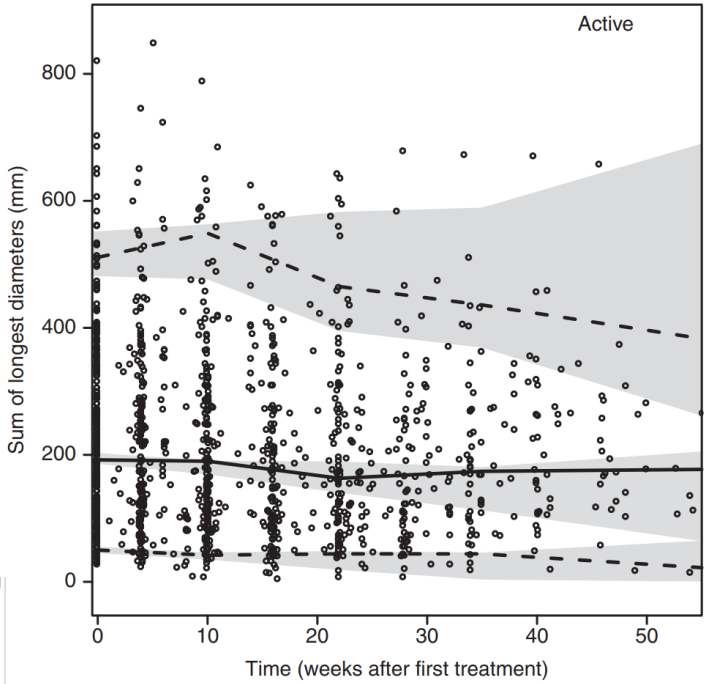
Plasma drug concentration



Neutrophil count

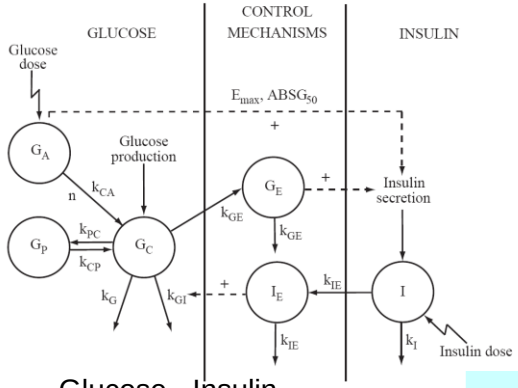


Tumor size (SLD)

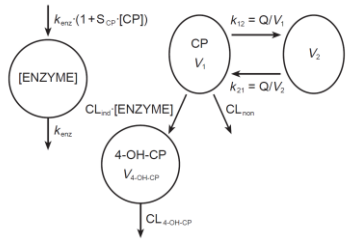


Pharmacometrics

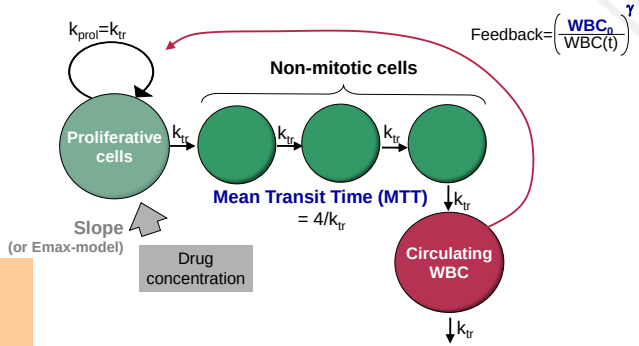
Pharmacokinetics - pharmacodynamics - disease progression



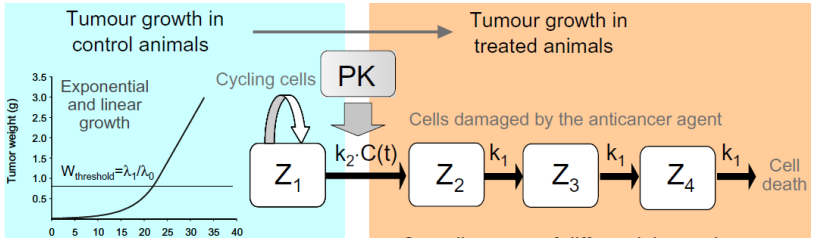
Glucose - Insulin
Silber et al., JCP 2007



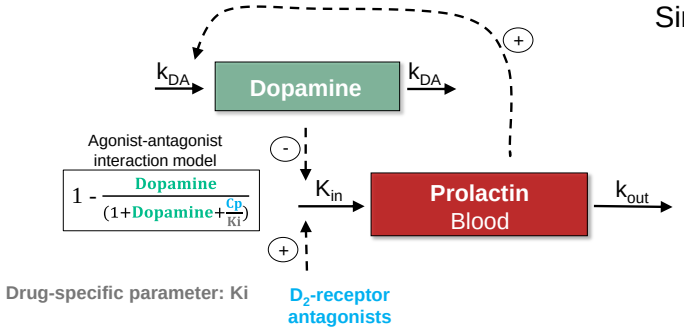
Pharmacokinetics & enzyme induction
Hassan et al., J Clin Pharmacol 1999



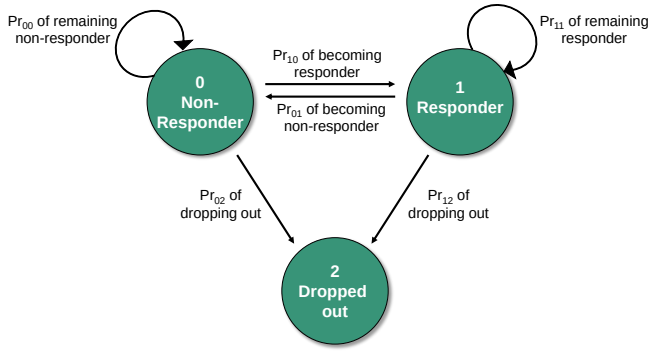
Oncology – Myelosuppression
Friberg et al., JCO 2002



Tumor growth – Xenografts
Simeoni et al., Cancer Res 2004



Schizophrenia – Prolactin elevation
Friberg et al., CPT 2009



Rheumatoid Arthritis – ACR20
Lacroix et al., CPT 2009

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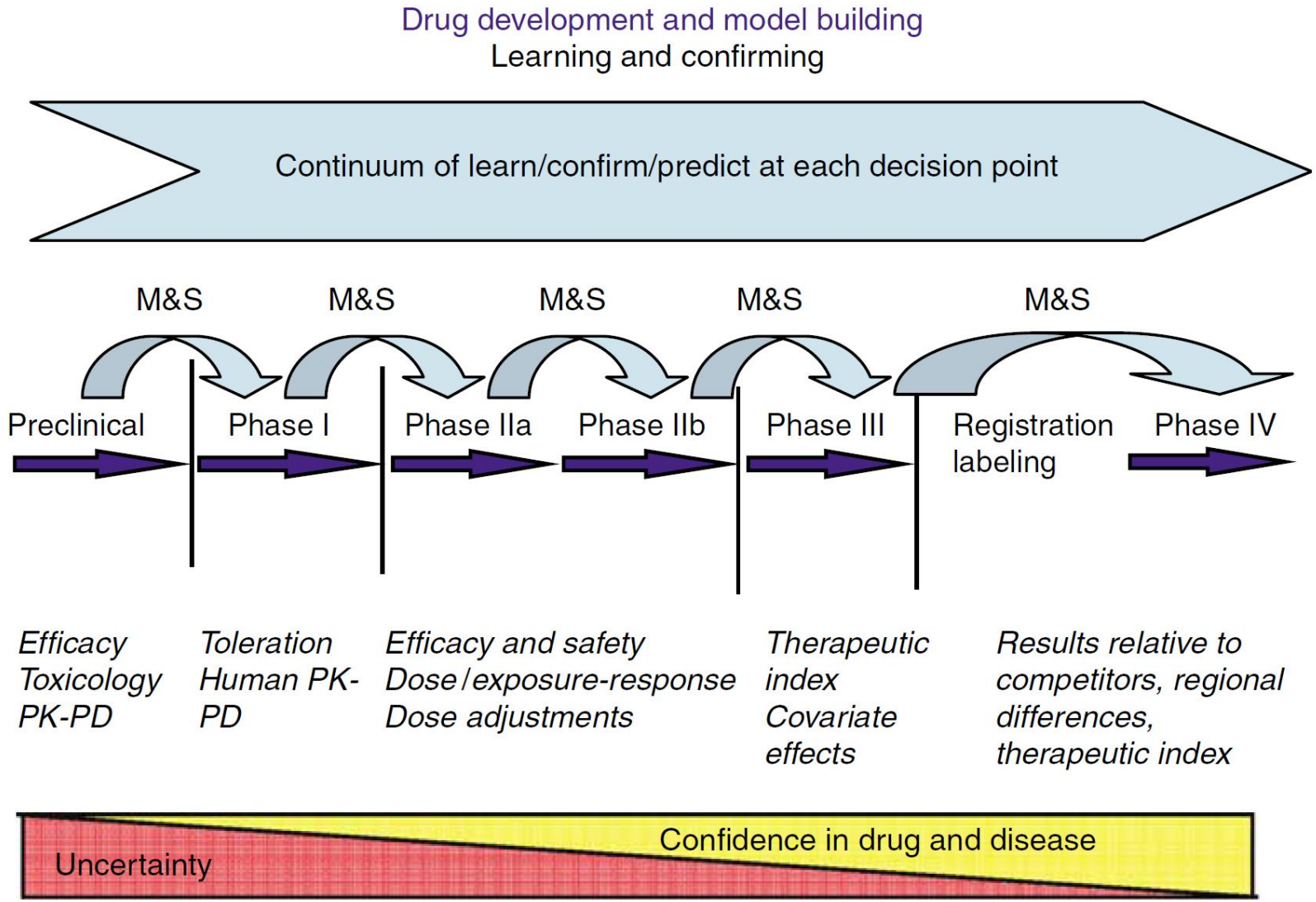


Figure 1 Modeling and simulation (M&S) are performed before each decision point to quantitatively assess risk in moving forward. The drug and disease model is continuously updated to include new information acquired during drug development.

Lalonde et al. Clin Pharmacol Ther 82:21-32 (2007)

ADAS-cog test for Alzheimer's Disease patients

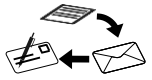
Task Based

Remembering Words — LAKE, CLOCK, FOREST, ANIMAL

Naming Objects

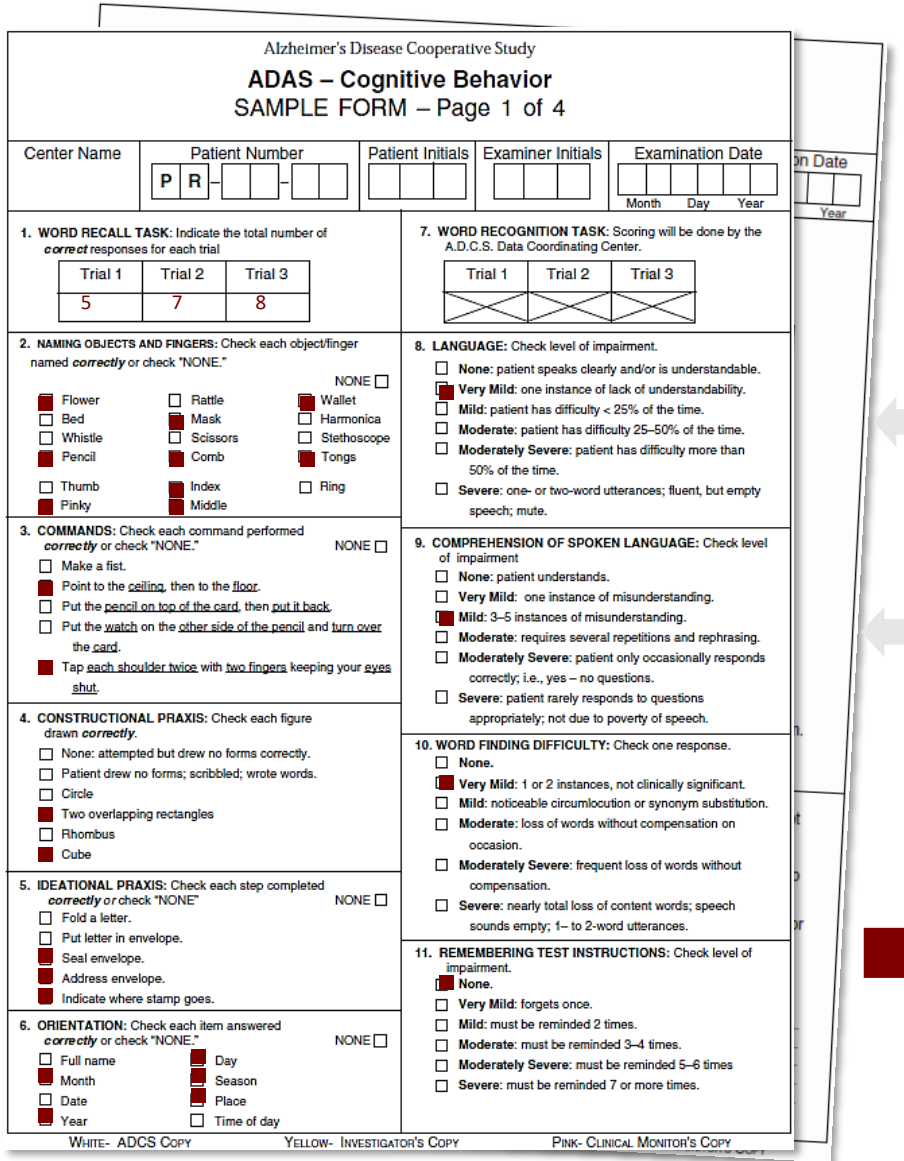
Commands

Construction



Ideational Praxis

Orientation



Alzheimer's Disease Cooperative Study

ADAS – Cognitive Behavior

SAMPLE FORM – Page 1 of 4

Center Name | Patient Number P R – – | Patient Initials | Examiner Initials | Examination Date (Month Day Year)

1. WORD RECALL TASK: Indicate the total number of *correct* responses for each trial

Trial 1	Trial 2	Trial 3
5	7	8

2. NAMING OBJECTS AND FINGERS: Check each object/finger named *correctly* or check "NONE."

NONE ☐

■ Flower	☐ Rattle	■ Wallet
☐ Bed	■ Mask	☐ Harmonica
☐ Whistle	☐ Scissors	☐ Stethoscope
■ Pencil	■ Comb	■ Tongs
☐ Thumb	■ Index	☐ Ring
■ Pinky	■ Middle	

3. COMMANDS: Check each command performed *correctly* or check "NONE." NONE ☐

- ☐ Make a fist.
- ■ Point to the ceiling, then to the floor.
- ☐ Put the pencil on top of the card, then put it back.
- ☐ Put the watch on the other side of the pencil and turn over the card.
- ■ Tap each shoulder twice with two fingers keeping your eyes shut.

4. CONSTRUCTIONAL PRAXIS: Check each figure drawn *correctly*.

- ☐ None: attempted but drew no forms correctly.
- ☐ Patient drew no forms; scribbled; wrote words.
- ☐ Circle
- ■ Two overlapping rectangles
- ☐ Rhombus
- ■ Cube

5. IDEATIONAL PRAXIS: Check each step completed *correctly* or check "NONE" NONE ☐

- ☐ Fold a letter.
- ☐ Put letter in envelope.
- ■ Seal envelope.
- ■ Address envelope.
- ■ Indicate where stamp goes.

6. ORIENTATION: Check each item answered *correctly* or check "NONE." NONE ☐

☐ Full name	■ Day
■ Month	■ Season
☐ Date	■ Place
■ Year	☐ Time of day

7. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.

Trial 1	Trial 2	Trial 3
☒	☒	☒

8. LANGUAGE: Check level of impairment.

- ☐ **None:** patient speaks clearly and/or is understandable.
- ■ **Very Mild:** one instance of lack of understandability.
- ☐ **Mild:** patient has difficulty < 25% of the time.
- ☐ **Moderate:** patient has difficulty 25–50% of the time.
- ☐ **Moderately Severe:** patient has difficulty more than 50% of the time.
- ☐ **Severe:** one- or two-word utterances; fluent, but empty speech; mute.

9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment

- ☐ **None:** patient understands.
- ☐ **Very Mild:** one instance of misunderstanding.
- ■ **Mild:** 3–5 instances of misunderstanding.
- ☐ **Moderate:** requires several repetitions and rephrasing.
- ☐ **Moderately Severe:** patient only occasionally responds correctly; i.e., yes – no questions.
- ☐ **Severe:** patient rarely responds to questions appropriately; not due to poverty of speech.

10. WORD FINDING DIFFICULTY: Check one response.

- ☐ **None.**
- ■ **Very Mild:** 1 or 2 instances, not clinically significant.
- ☐ **Mild:** noticeable circumlocution or synonym substitution.
- ☐ **Moderate:** loss of words without compensation on occasion.
- ☐ **Moderately Severe:** frequent loss of words without compensation.
- ☐ **Severe:** nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.

11. REMEMBERING TEST INSTRUCTIONS: Check level of impairment.

- ■ **None.**
- ☐ **Very Mild:** forgets once.
- ☐ **Mild:** must be reminded 2 times.
- ☐ **Moderate:** must be reminded 3–4 times.
- ☐ **Moderately Severe:** must be reminded 5–6 times
- ☐ **Severe:** must be reminded 7 or more times.

WHITE- ADCS COPY YELLOW- INVESTIGATOR'S COPY PINK- CLINICAL MONITOR'S COPY

Rater Assessed

Ability to Speak

Ability to Understand

• • •

ADAS-cog Score

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Rosen et al. 1984

Types of Clinical Outcome Assessments

Patient-reported outcome (PRO) measures

Reports come directly from the patient

Clinician-reported outcome (ClinRO) measures

Reports come from a trained health-care professional using clinical judgment

Performance outcome (PerfO) measures

A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions

Observer-reported outcome (ObsRO) measures

Reports come from someone other than the patient or a health professional (e.g., a parent or caregiver) who has opportunity to observe the patient in everyday life

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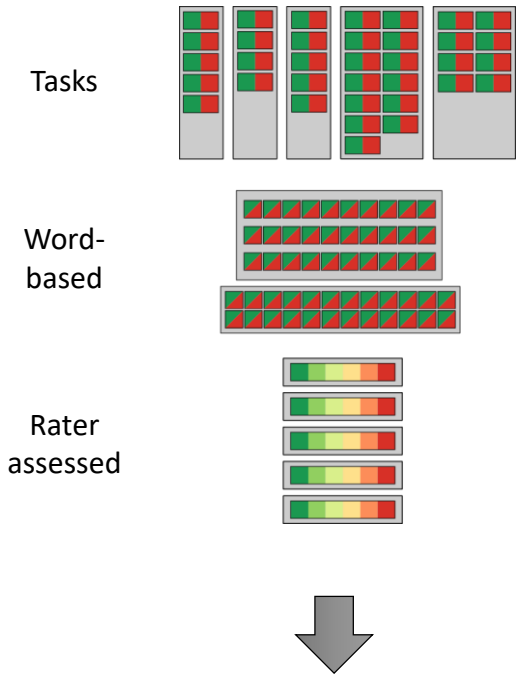
ADAS-Cog in Alzheimer’s Disease

Alzheimer's Disease Assessment Scale - Cognition



Sum

0-70 score range

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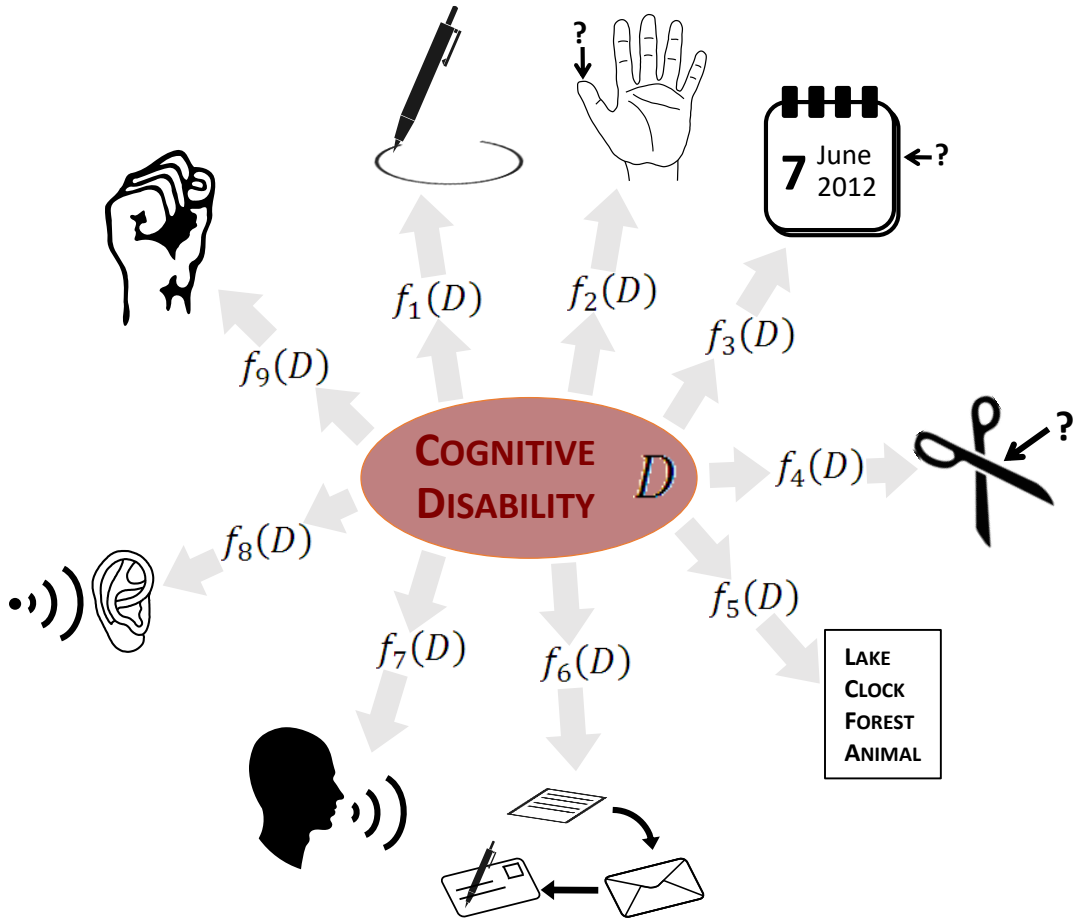
Responses assumed dependent on an underlying Cognitive Disability



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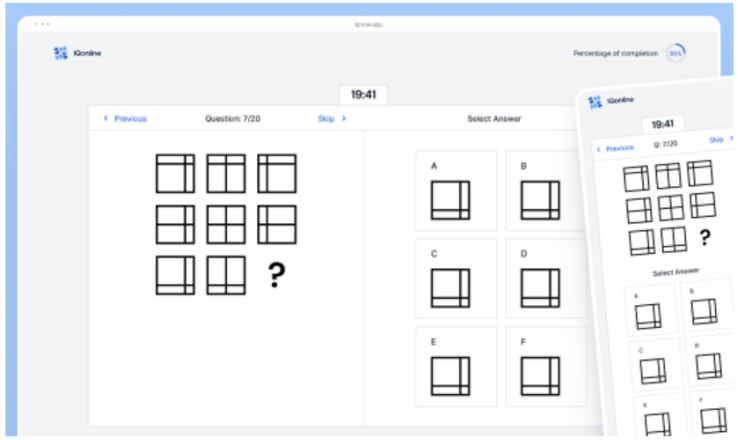
937 people currently taking the test

Official IQ Test

The average IQ score in Europe is 100. Are you ready to test your brain?

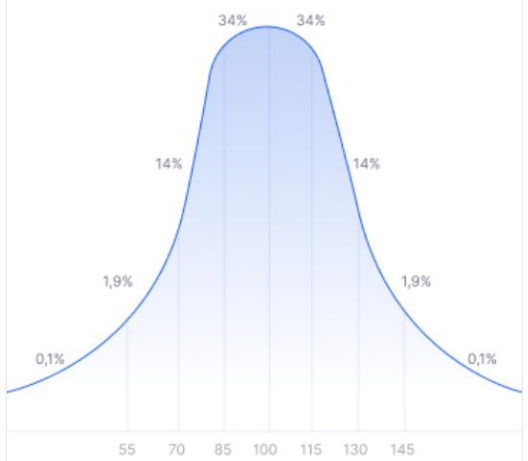
Test My IQ Now!



How does it work?

1 20 questions in 20 minutes

Concentrate and answer our questions, which test your analytical memory, logic, umerical capabilities and



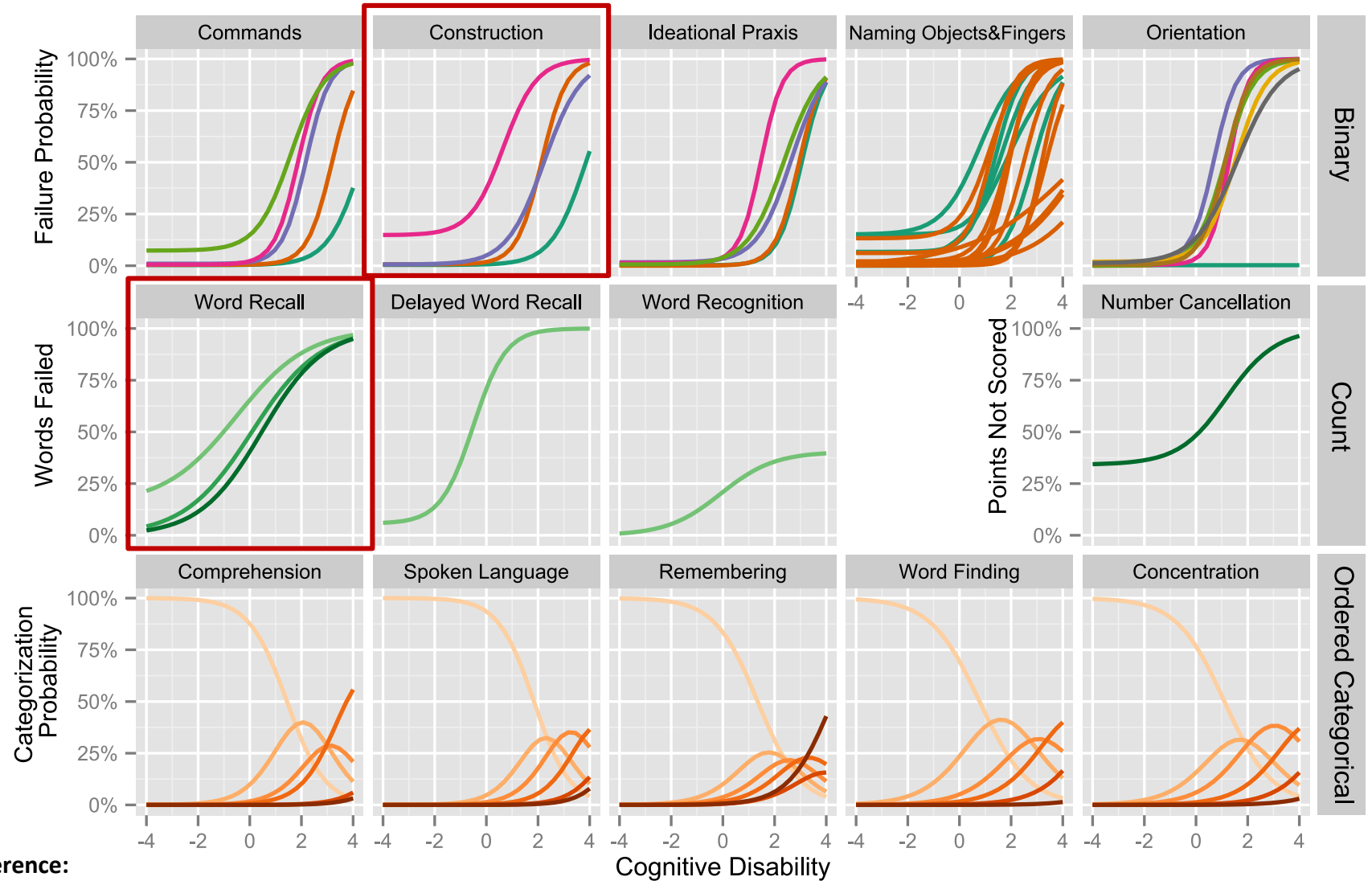
2 Immediate result

Our algorithm estimates your IQ according to the official method and gives you your results as well as a scale to help you understand how you stand in relation to the population.

3 Get your certificate

Get your certificate and performance report so you can share it with your family and friends.

Item Characteristic Curves ADAS-Cog



Reference:

Ueckert et al. Pharm Res 31(2014)

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IRT Analysis of the SARA in ARCAs

Item **R**esponse **T**heory

Item-based analysis

Scale for the **A**ssessment and **R**ating of **A**taxia

Clinical Outcome Assessment (COA)

Autosomal **R**ecessive **C**erebellar **A**taxias

Rare Neurodegenerative Disease (RND)

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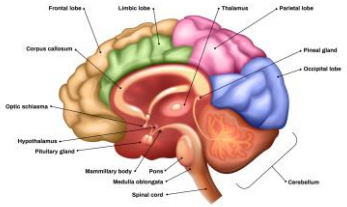
Autosomal Recessive Cerebellar Ataxias (ARCAs)

a heterogenous group of rare and ultra-rare neurodegenerative diseases



Progressive disease

- Loss of coordination & ambulation

Affects the cerebellum and associated tracts

Genetically defined

>200 disease types

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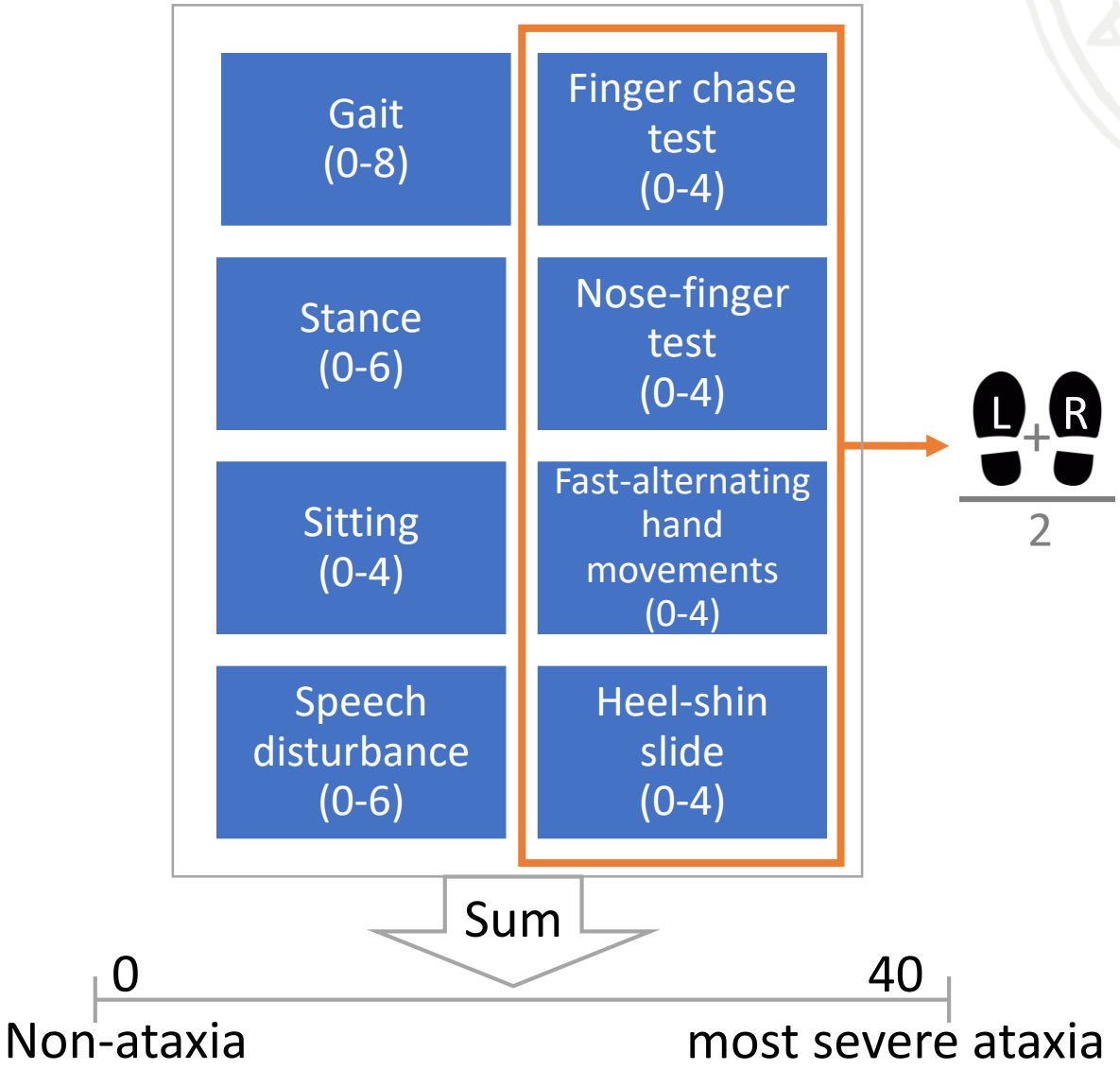
How to measure the ataxia severity?

Scale for the Assessment and Rating of Ataxia (SARA)

- The most widely used outcome measure for ataxias
- Developed in 2004
- Clinician reported outcome (ClinRO)



SARA as a primary outcome measure in treatment trials?

Problem

- Concerns about SARA metric properties from regulatory agencies and recent studies
- Modifications to optimize the SARA
- Scarce data evidence and validation
- Analysis based on SARA total score

Aim

Evaluate the **metric properties and performance** of the SARA using **Item Response Theory (IRT)**

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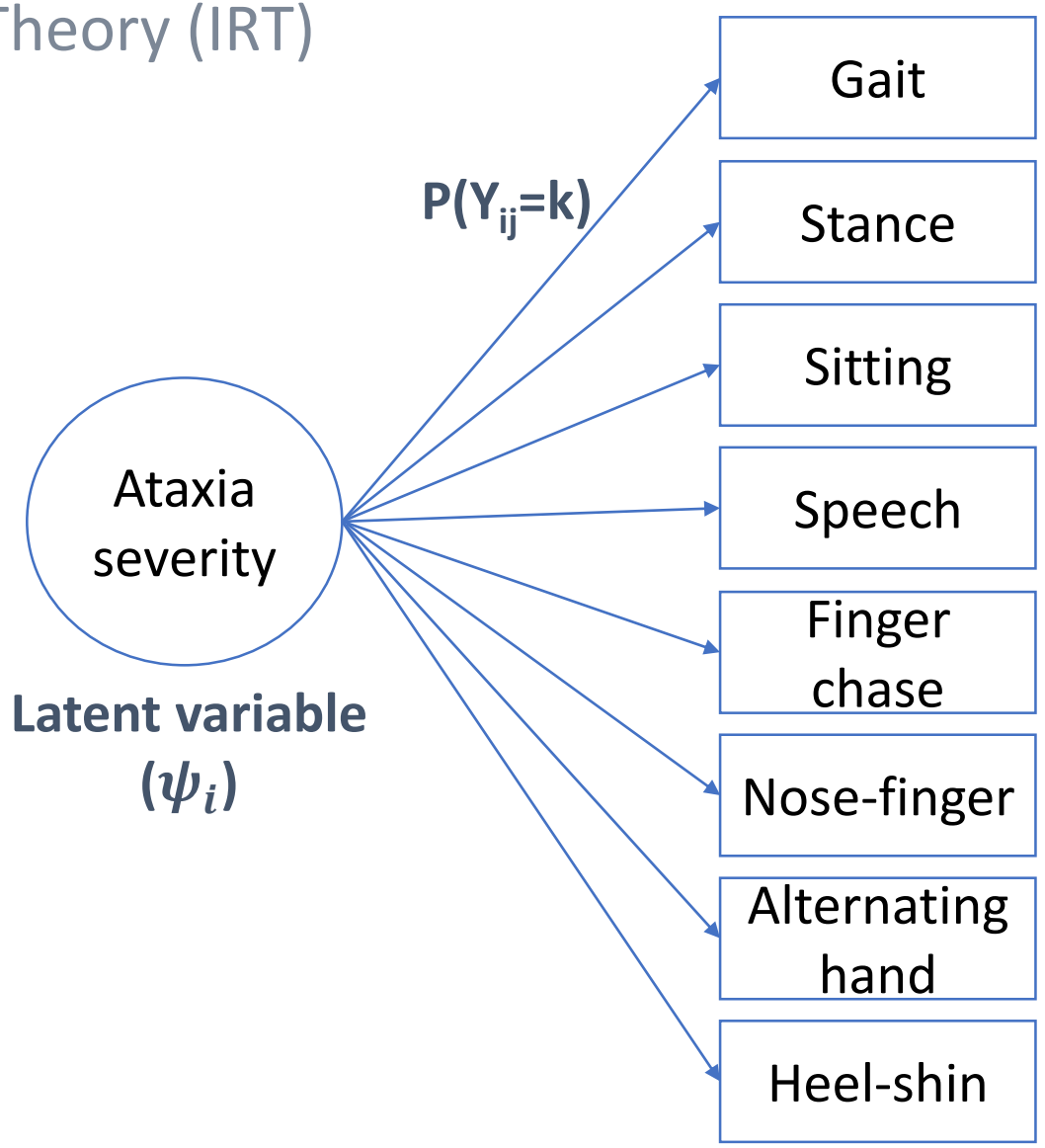
Sub-scores analysis
using Item Response Theory (IRT)

IRT model of SARA



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Sub-scores analysis
using Item Response Theory (IRT)

2-parameters logit functions

$$P(Y_{ij} \geq k) = \frac{e^{(a_j(\psi_i - b_{j,k}))}}{1 + e^{(a_j(\psi_i - b_{j,k}))}}$$

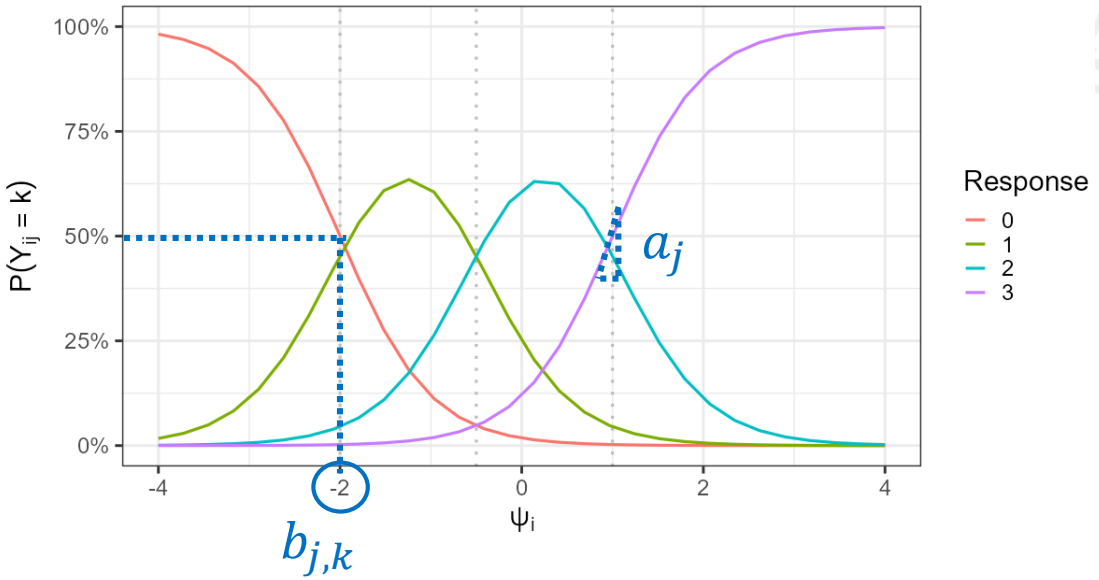
$$P(Y_{ij} = k) = P(Y_{ij} \geq k) - P(Y_{ij} \geq k + 1)$$

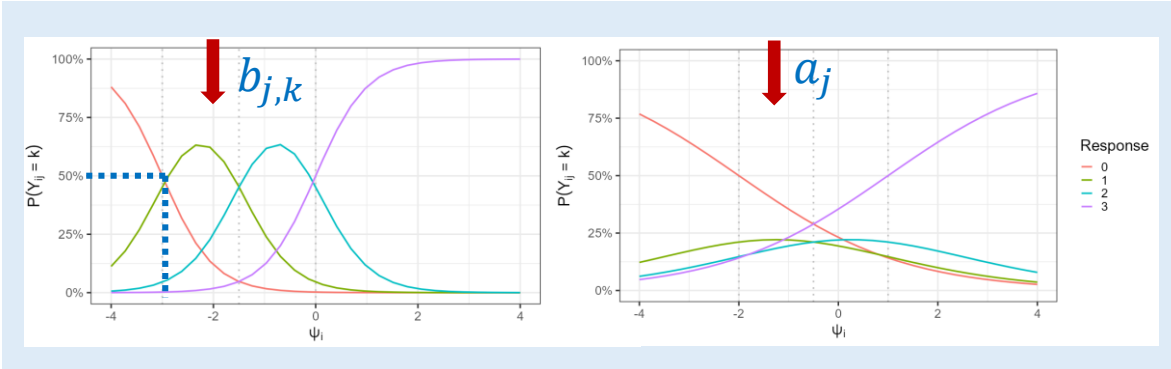
Y_{ij}: observed item score for individual i and item j

k: item response score

- Scale characteristics
  - a_j: Item discrimination
  - $b_{j,k}$: Item difficulty
- Subjects characteristics
  - ψ_i: Latent variable

Item characteristic curves (ICCs)





Dataset

Autosomal Recessive Cerebellar Ataxias Registry

- 990 patients
- 1932 visits
- 69% of patients have genetically defined diagnosis
- 115 ARCA genetic subpopulations
- SARA sub-scores data

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The questions we want to answer in this IRT analysis

- Do all SARA items share one common underlying latent variable?
- What are the characteristics (and performance) of each SARA item?
- Is one IRT model applicable to all ARCA genetic subpopulations?

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The questions we want to answer in this IRT analysis, **and how**

	Methods
Do all SARA items share one common underlying latent variable? (*i.e.*, unidimensional)	• Data correlations • Residuals correlations
What are the characteristics (and performance) of each SARA item?	• Item parameters • Item characteristics curves • Fisher information
Is one IRT model applicable to all ARCA genetic subpopulations?	• Model fit for each subpopulation

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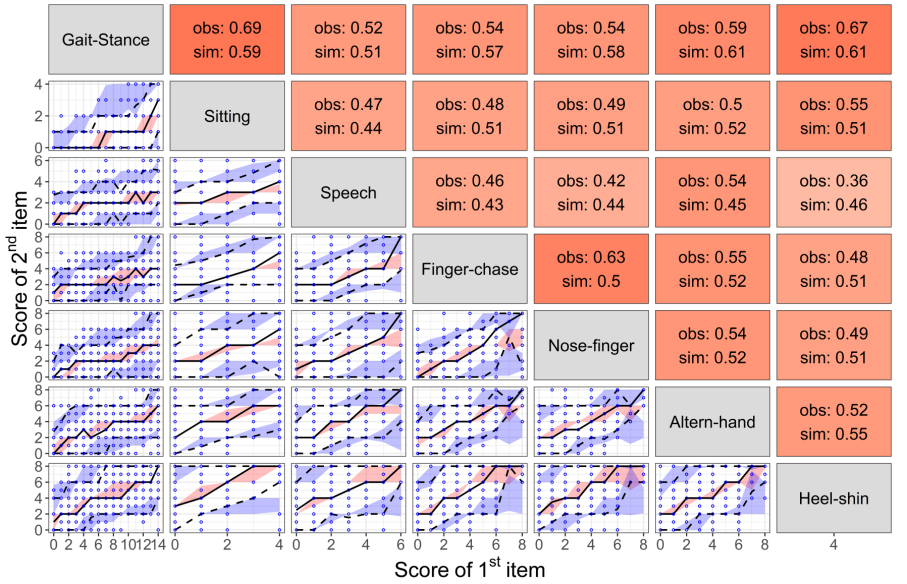
Item-pairs correlations to evaluate SARA dimensionality

Upper matrix

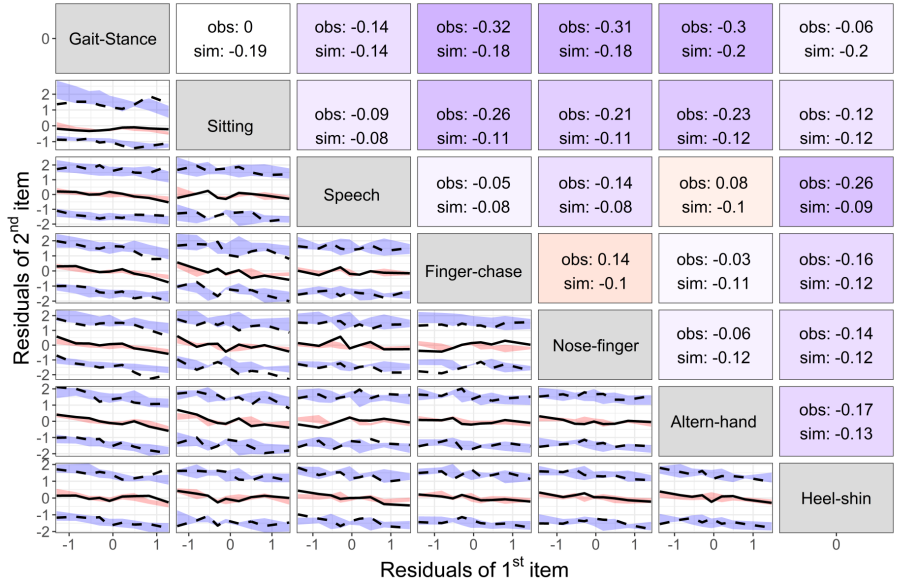
1. Data correlations → before modelling
2. Residual correlations → after modelling
3. Average correlations for 100 simulations

Lower matrix

4. Visual (VPC) diagnostic
   - The 5th, 50th, and 95th percentiles (lines)
   - 95% confidence intervals of the corresponding percentiles (shaded areas)



Item scores



Residuals

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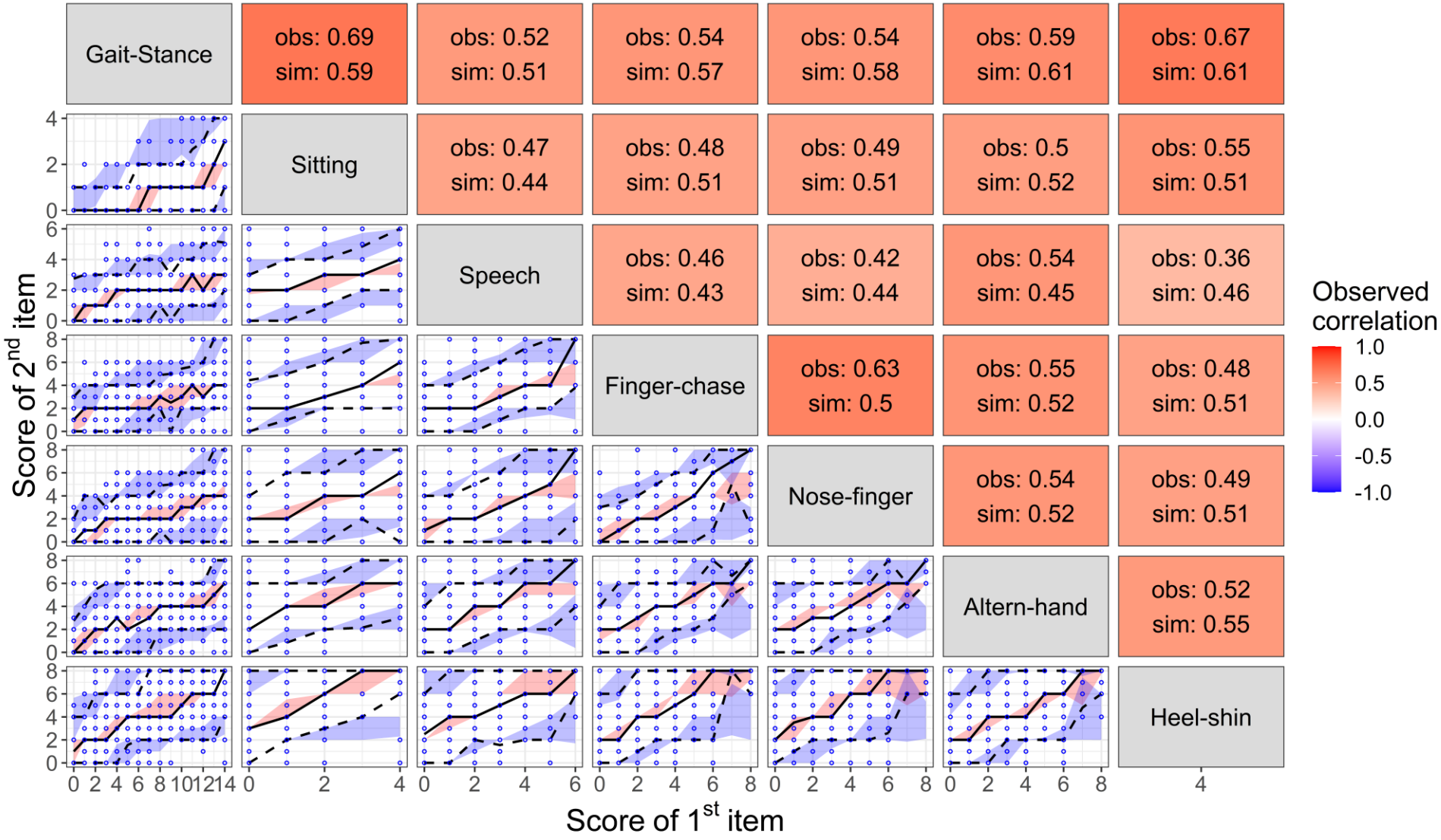
1. High (and similar) levels of correlations indicate unidimensionality
2. Data correlation patterns of simulated datasets mimic the original dataset



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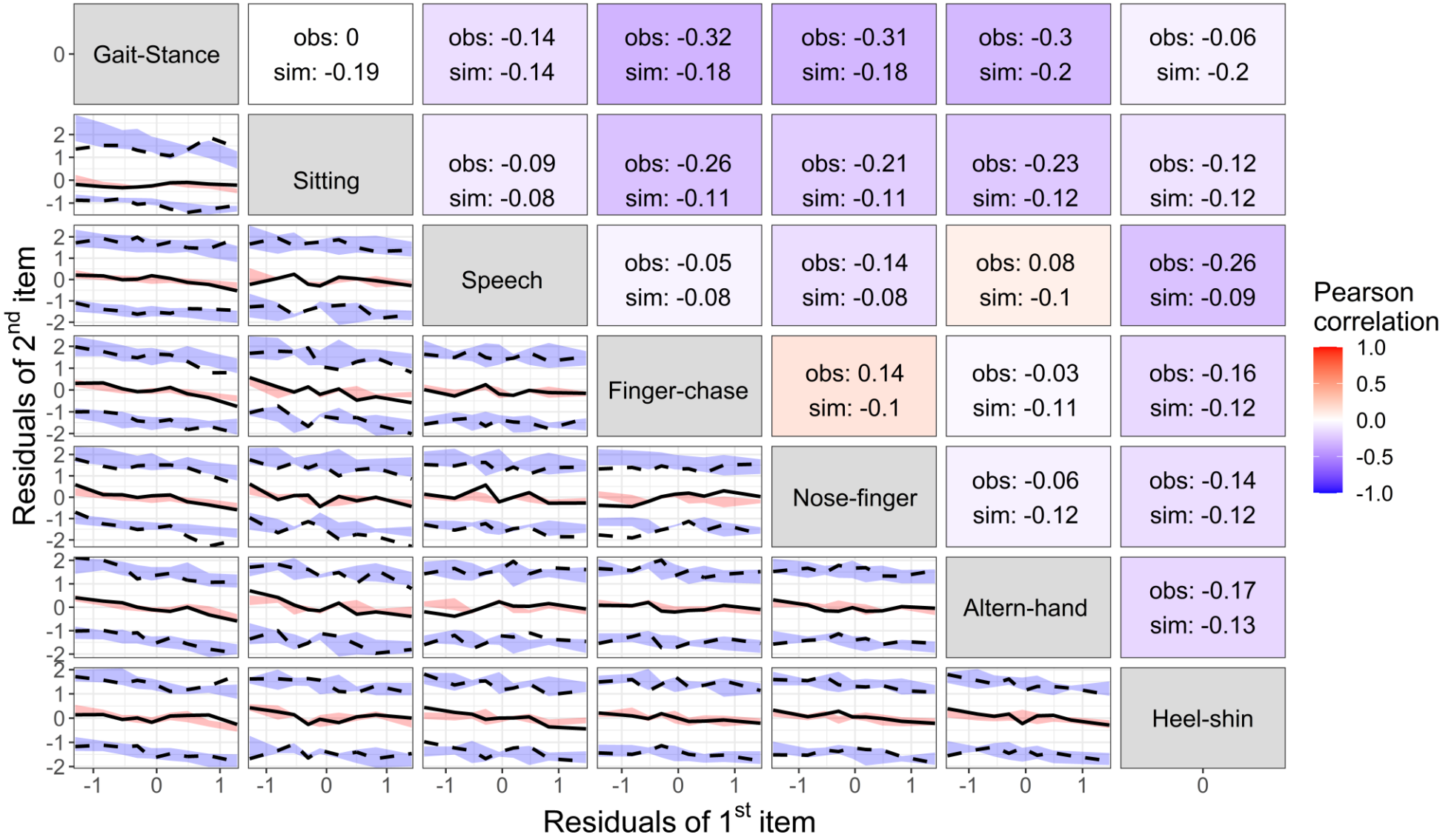
1. Low negative residual correlations indicate a good fit of the unidimensional model
2. Correlation patterns were mimicked in the simulations



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What are the characteristics (and performance) of each SARA item?	• Item parameters • Item characteristics curves • Fisher information
Is one IRT model applicable to all ARCA genetic subpopulations?	• Model fit for each subpopulation

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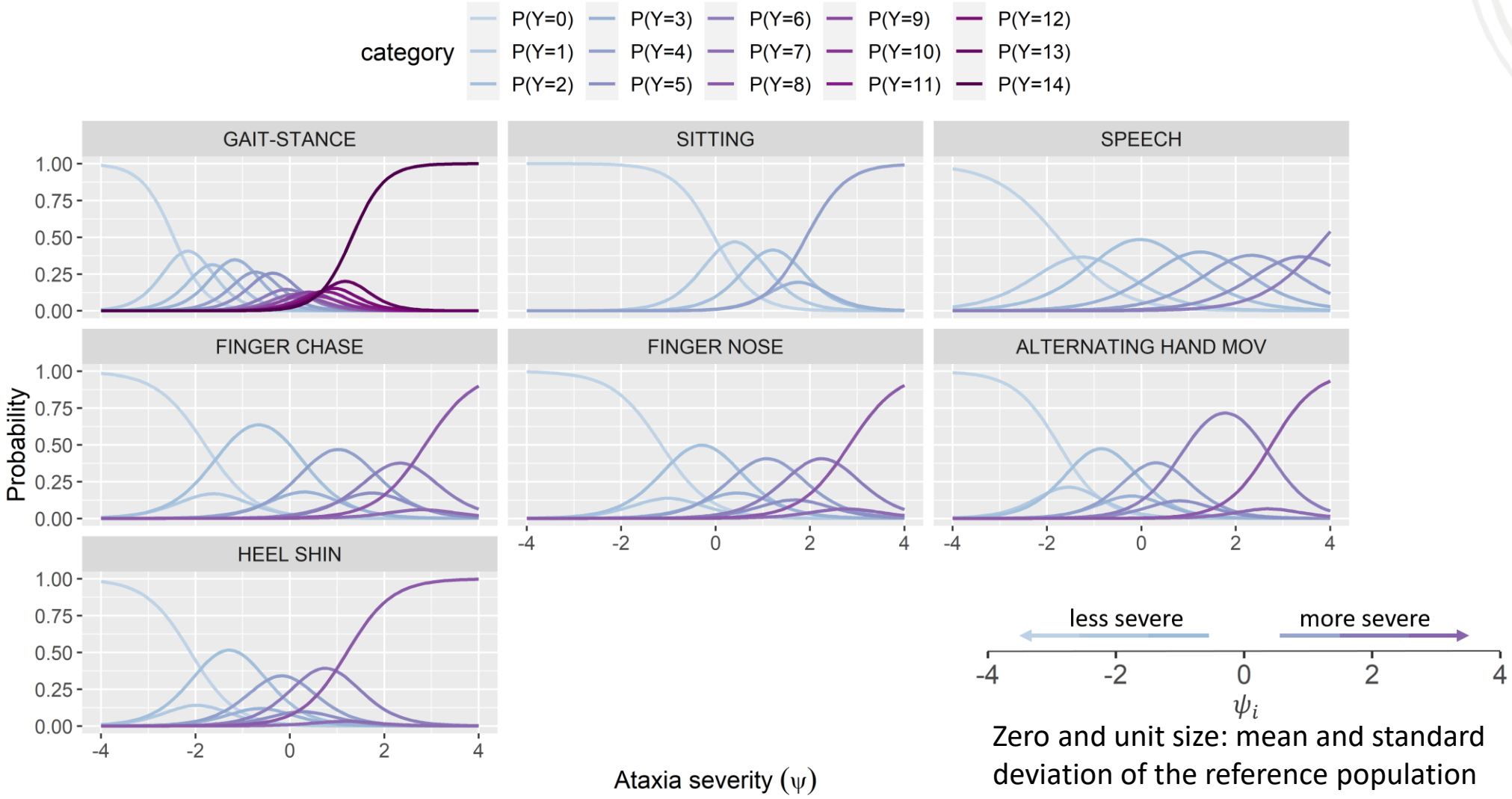
ICCs with separated curves and high discrimination parameters indicate properly designed response categories of SARA



Zero and unit size: mean and standard deviation of the reference population

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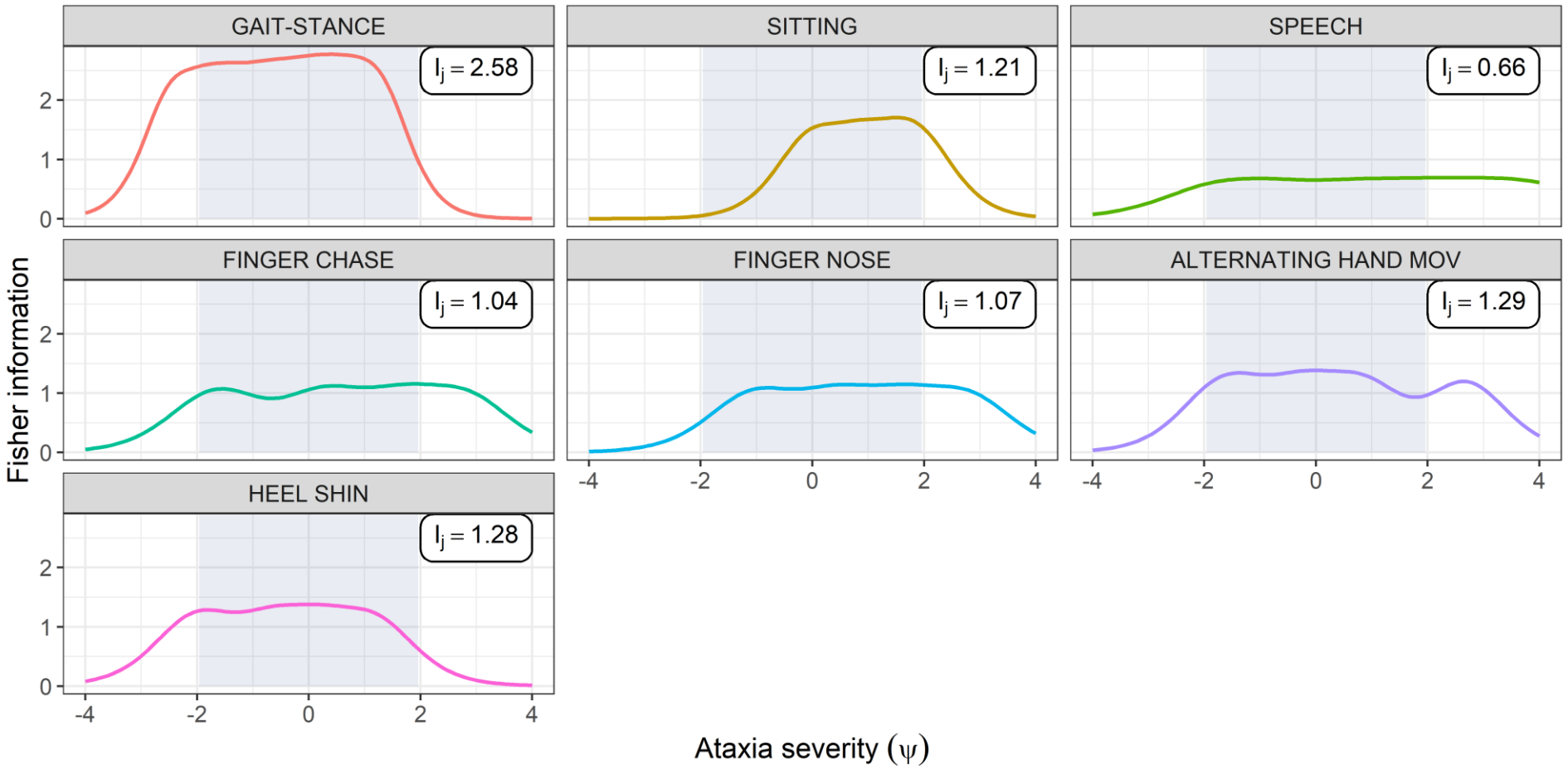
All SARA items are informative with varying importance at different disease severity levels



Shaded areas: the ataxia severity interval for 95% of the studied population

I_j: total item information in the population

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The questions we want to answer in this IRT analysis, **and how**

	Methods
Do all SARA items share one common underlying latent variable?	• Data correlations • Residuals correlations
What are the characteristics (and performance) of each SARA item?	• Item parameters • Item characteristics curves • Fisher information
Is one IRT model applicable to all ARCA genetic subpopulations?	• Model fit for each subpopulation

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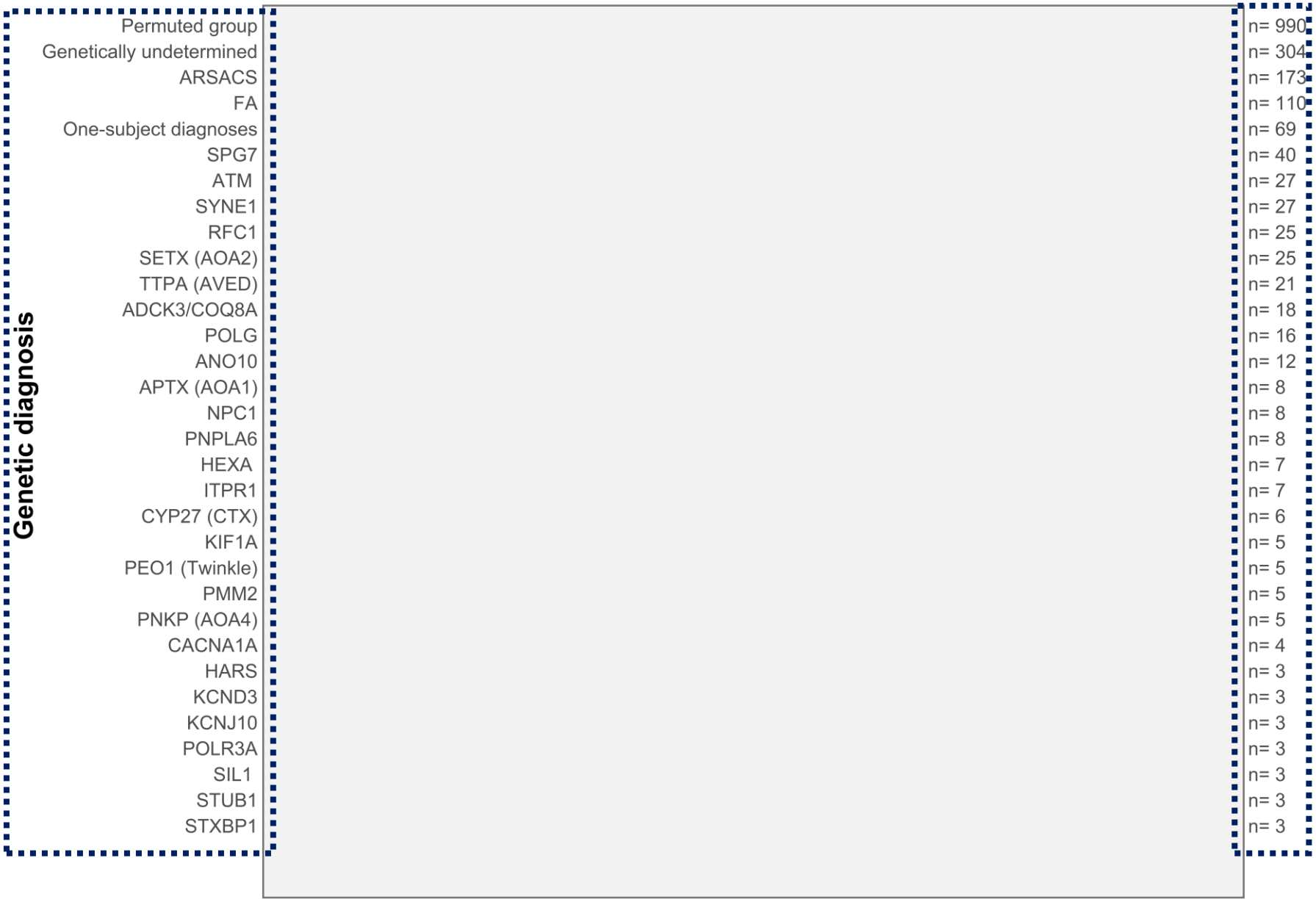
Analysis of ARCA genetic subpopulations



→ Number of subjects in each subpopulation

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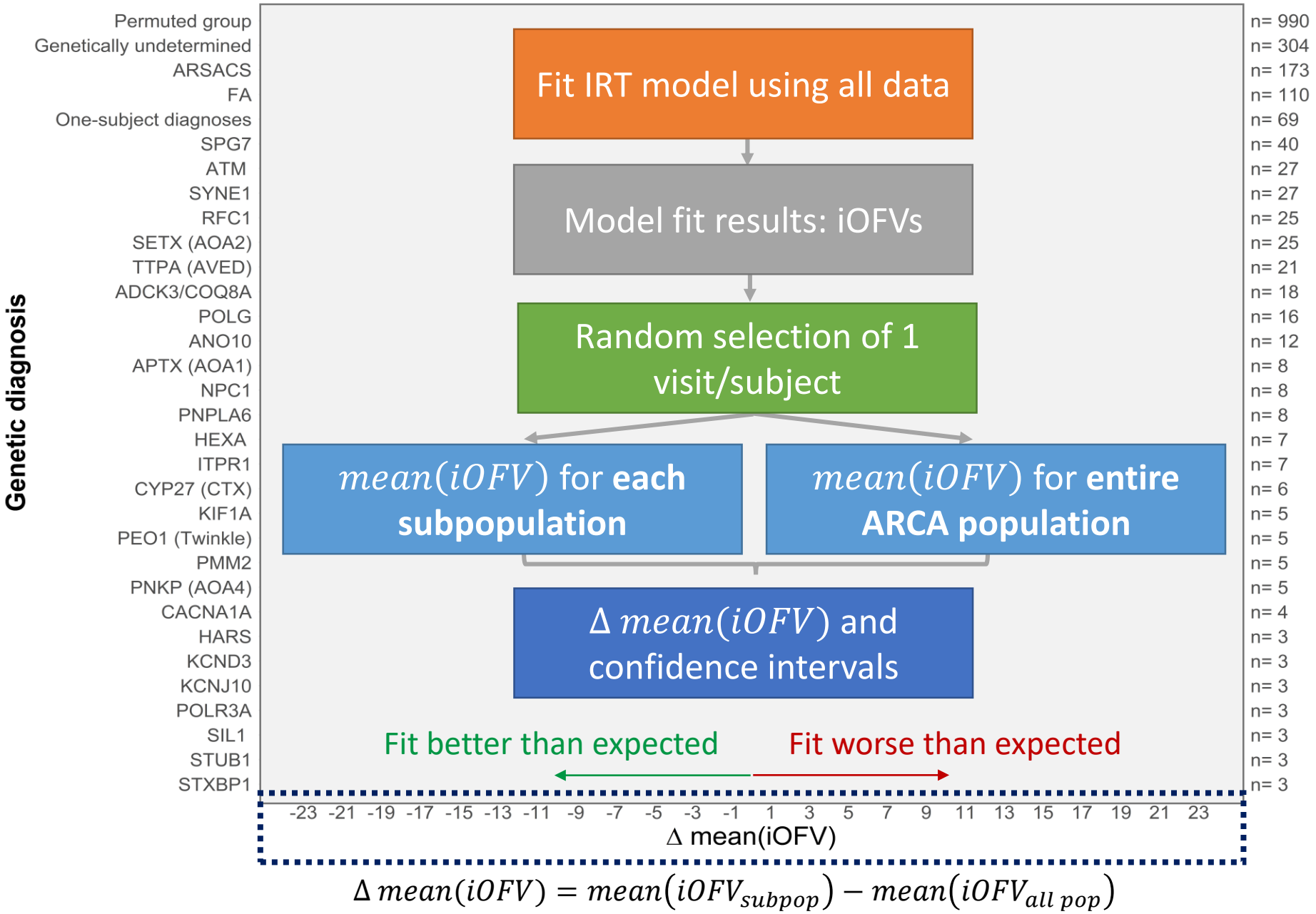
Analysis of ARCA genetic subpopulations



$$\Delta\, mean(iOFV) = mean\left(iOFV_{subpop}\right) - mean\left(iOFV_{all\ pop}\right)$$

iOFV: individual objective function value

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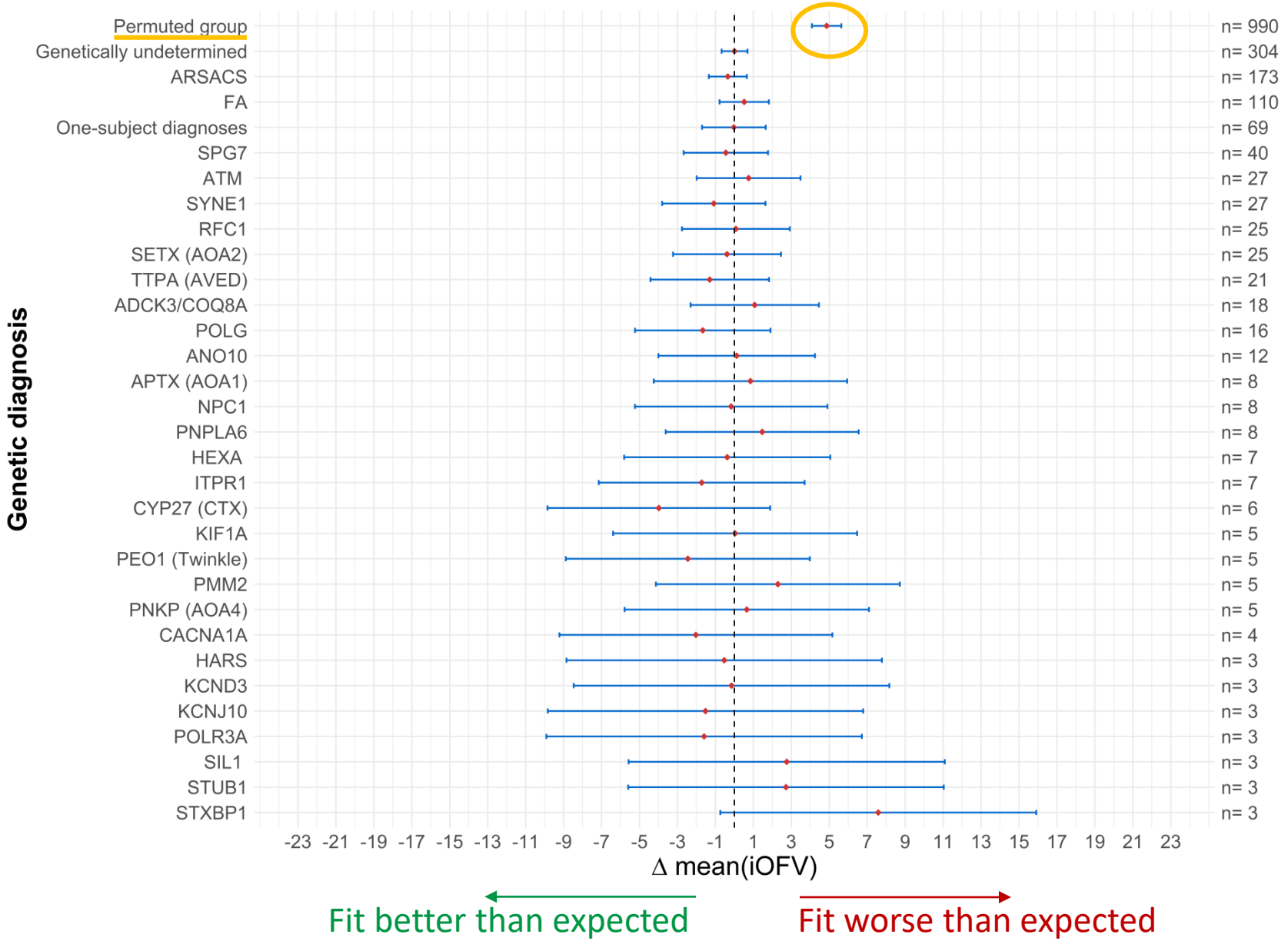
Absence of evidence for differences between ARCA subpopulations



Permuted group:
a hypothetical subpopulation created by permuting the sub-scores of each item across individuals.

- Red points: difference in means of iOFVs
- Error bars: 95% confidence intervals (based on pooled two-sampled t-test assuming equal variances)
- n: number of subjects in each group

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Conclusions SARA Score

- Unidimensional- one single latent variable captures data
- SARA is well-performing with high discrimination values
- All items are informative with varying importance at different disease severity levels
- IRT model is applicable across genetic subtypes with no evident item patterns differences

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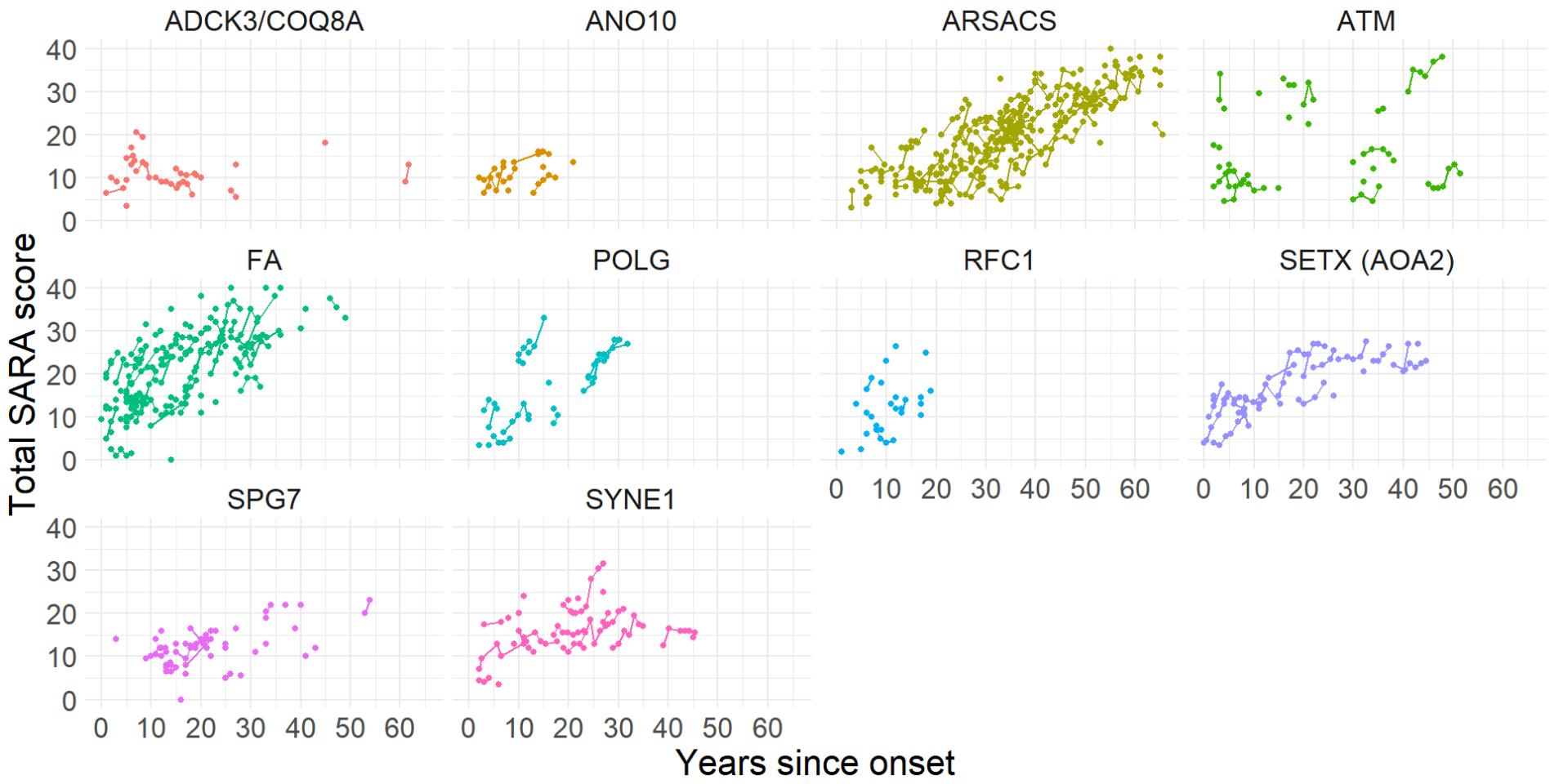
Disease progression in the 10 ARCA subpopulations



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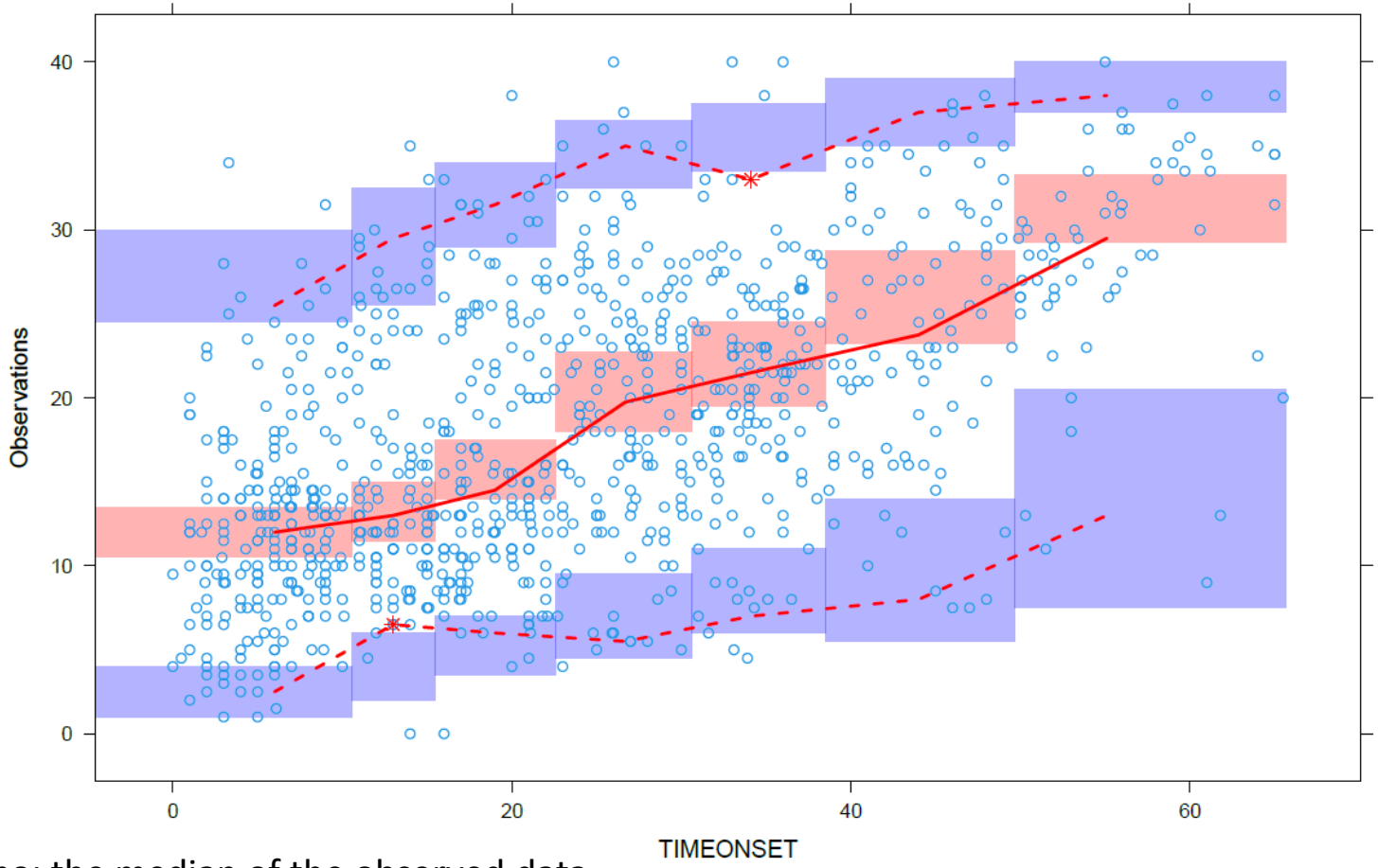
Visual Predictive Check illustrate IRT model goodness of fit to total score data



- **Solid line**: the median of the observed data
- **Dashed lines**: 2.5th and 97.5th percentiles (dashed lines) of the observed data
- **Shaded areas**: 95% confidence intervals for the corresponding percentiles of the simulated data
- **Note**: total scores were calculated as the sum of the individual items score

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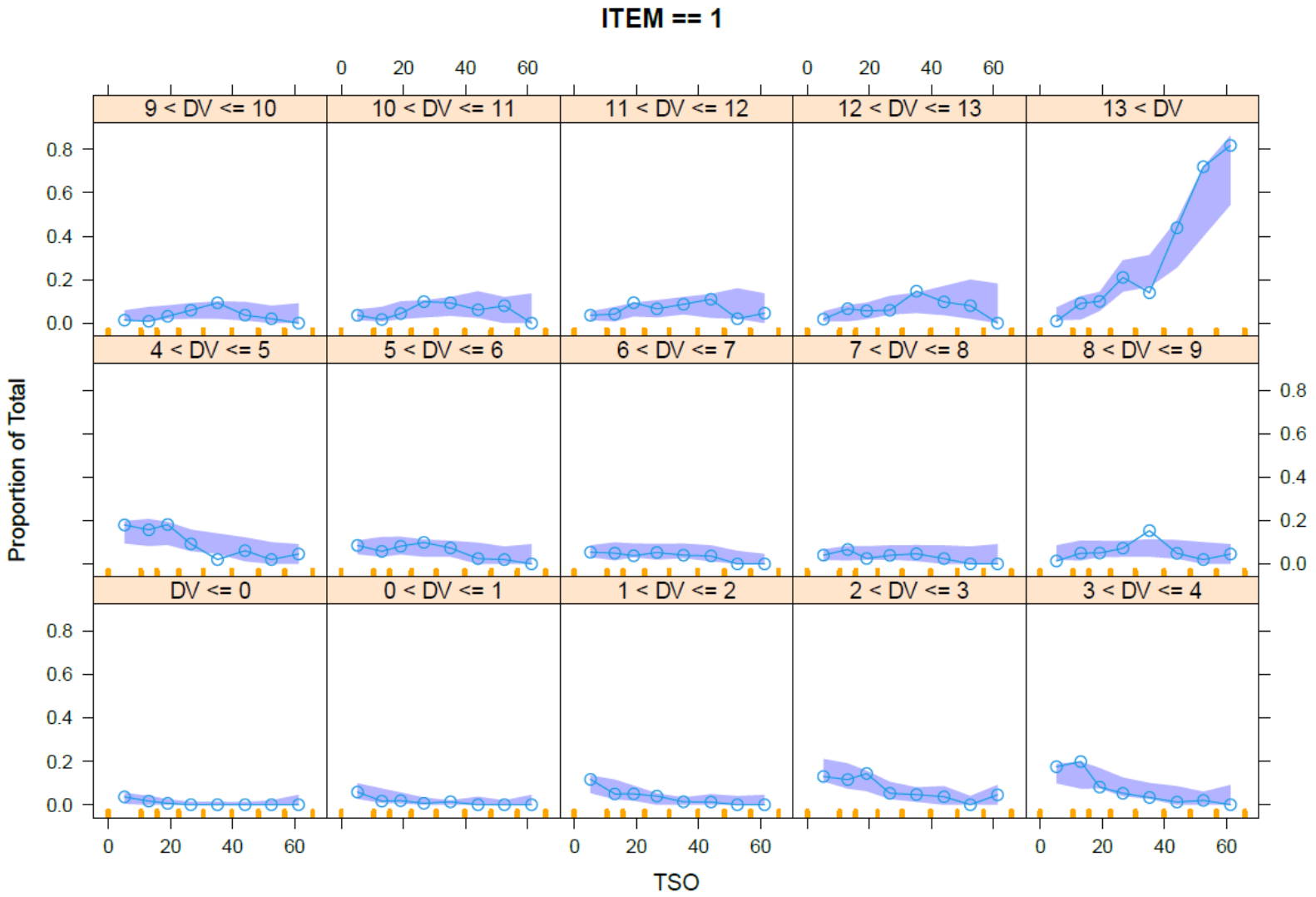
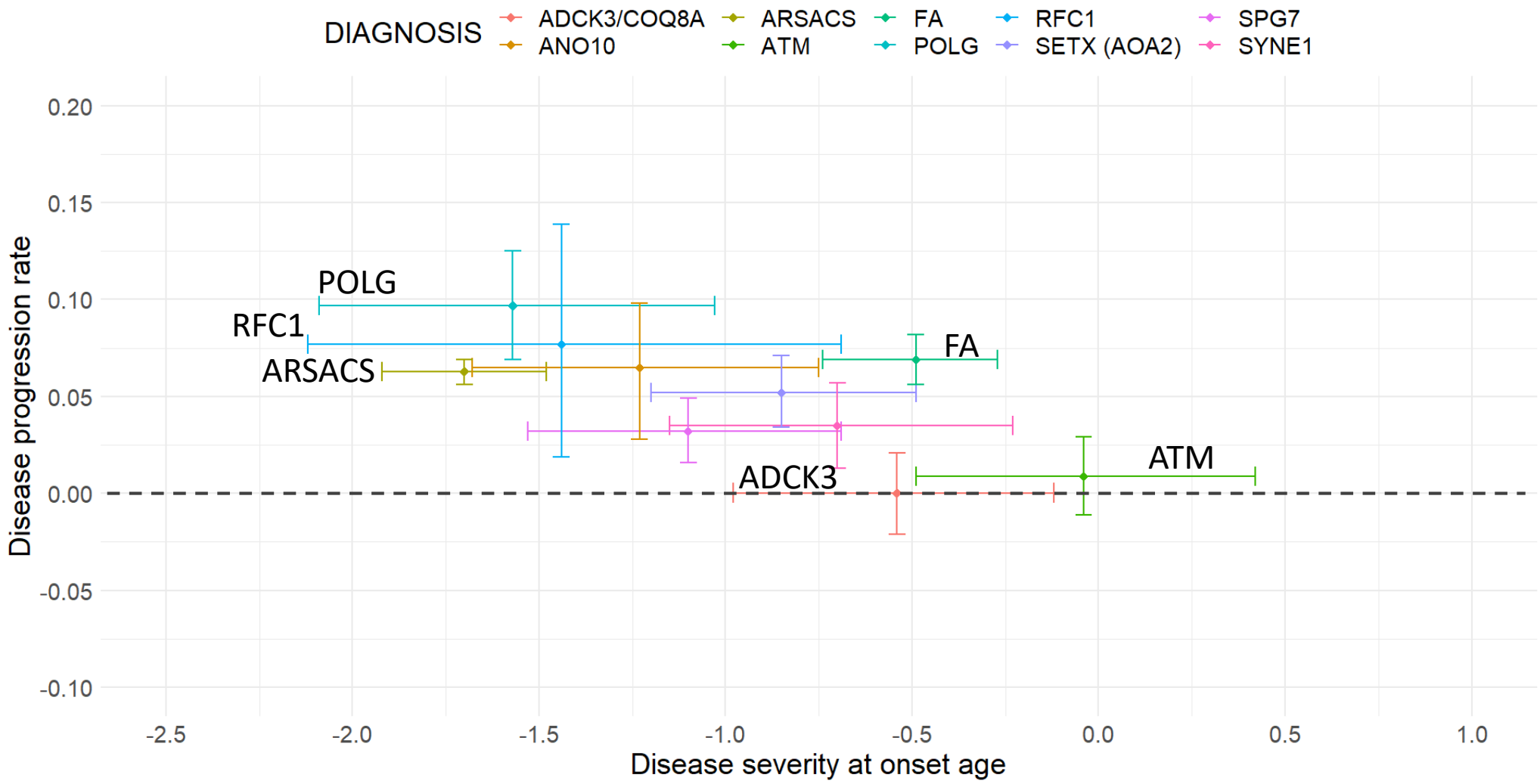
VPC stratified on each item



Model parameter estimates and confidence intervals*



Base-slp IIV correlation: -0.5

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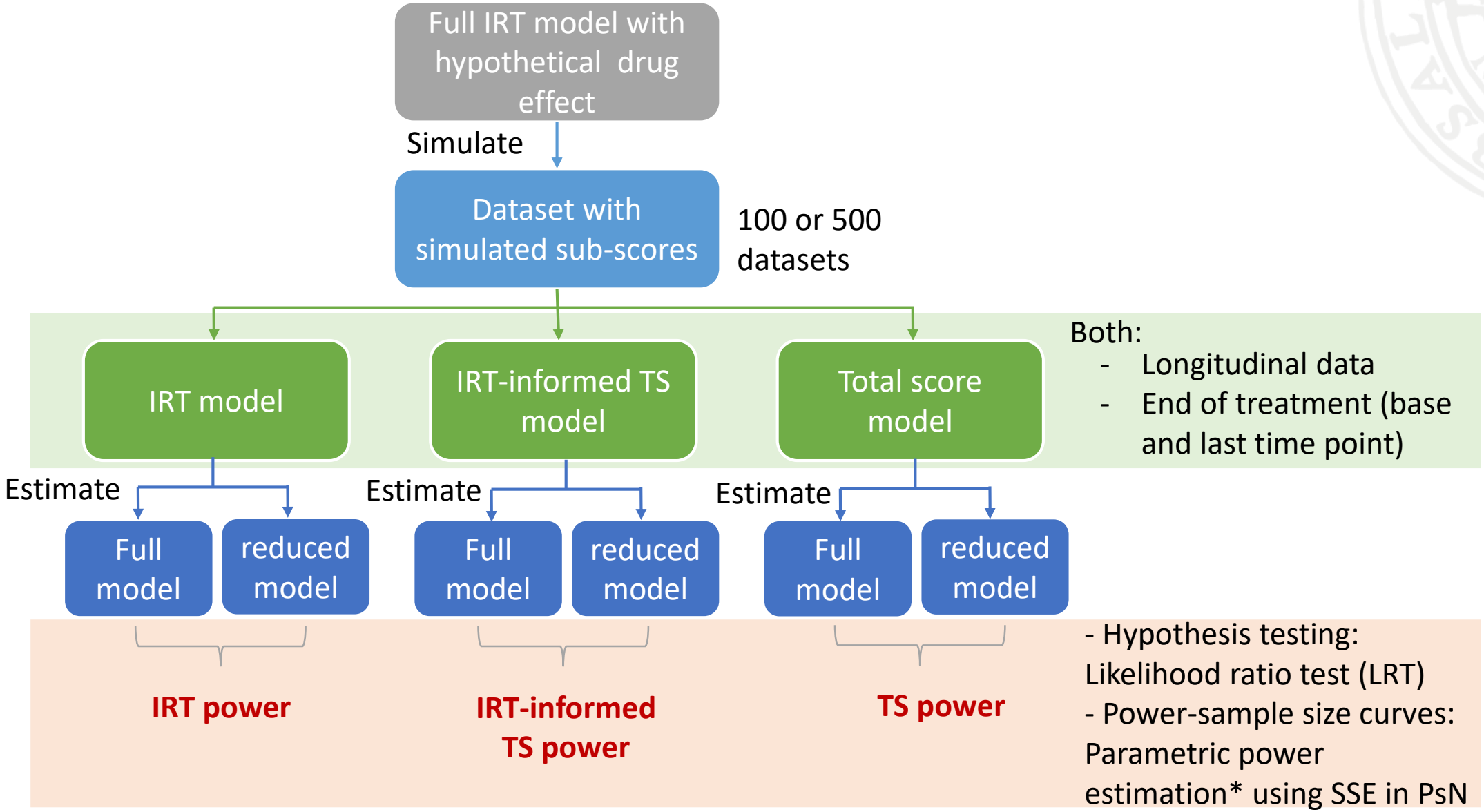
* Computed using sampling importance resampling (SIR) procedure

Clinical trial simulations and power/sample size calculations



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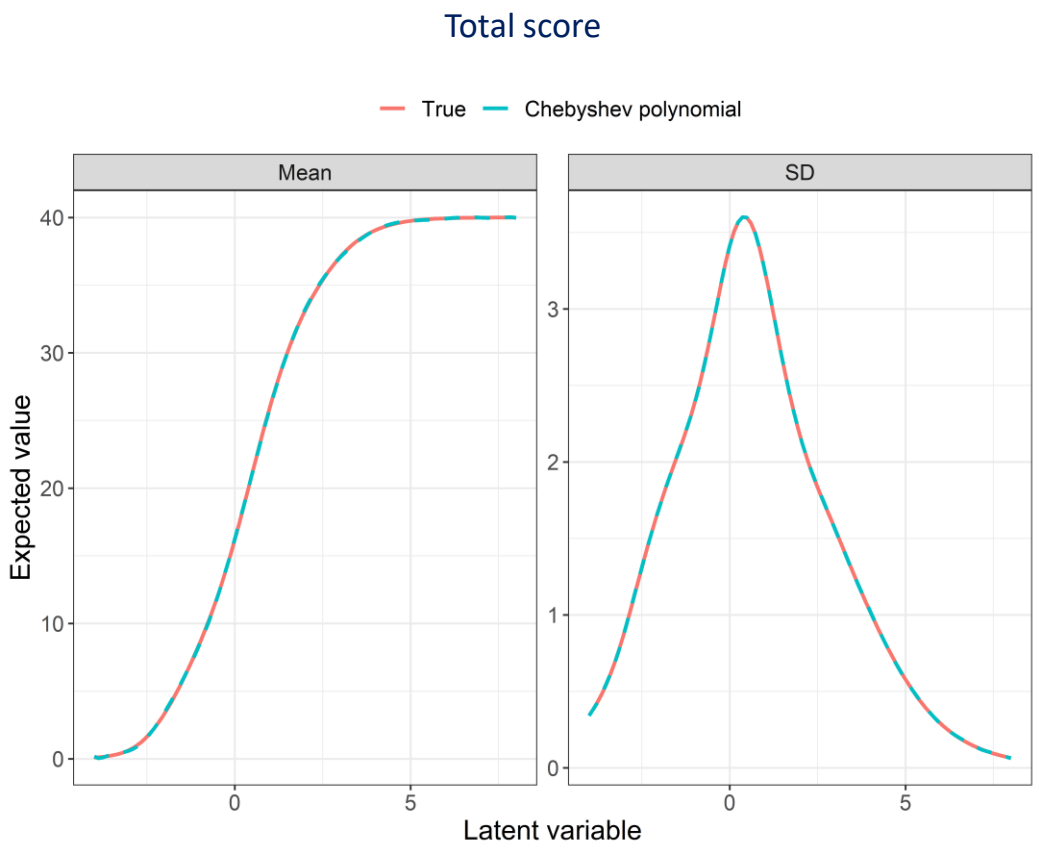
* Ueckert et al., JPKPD 43:223-234 (2016)

IRT-informed link function for SARA scores



$$\Psi_{ij} = h(\Theta, \eta_i, t_{ij}, X_i)$$
$$Y_{ij} = pn_1(\Psi_{ij}) + \varepsilon_{ij} \cdot pn_2(\Psi_{ij})$$
$$\eta_i \sim N(0, \omega^2)$$
$$\varepsilon_{ij} \sim N(0, 1)$$

- **h()** function is the disease progression function on the latent variable
- ψ: latent variable
- **Y:** total score
- **Pn:** polynomial functions describing the theoretical expectations of mean and variance. (derived from the base IRT model)

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ARSACS- sample size for 80% power

5-year study with disease-modifying treatment
Visits every 6 month

Drug effect	Analysis	Sample size (treatment+control, 1:1) for 80% power			
		Early pop. 0-10 yr	Intermed. pop. 10-20 yr	Late pop. 20-30 yr	Heterogenous pop. 0-30 yr after onset
50% inhibition	Tot score	200	130	130	100
	IRT	134	122	118	94
	IRT-inf	178	160	150	114
	IRT EoT	258	222	222	174
	IRT-inf EoT	302	264	284	222
100% inhibition	Tot score	56	40	32	30
	IRT	40	34	30	26
	IRT-inf	52	42	40	32
	IRT EoT	82	58	58	50
	IRT-inf EoT	94	68	74	58

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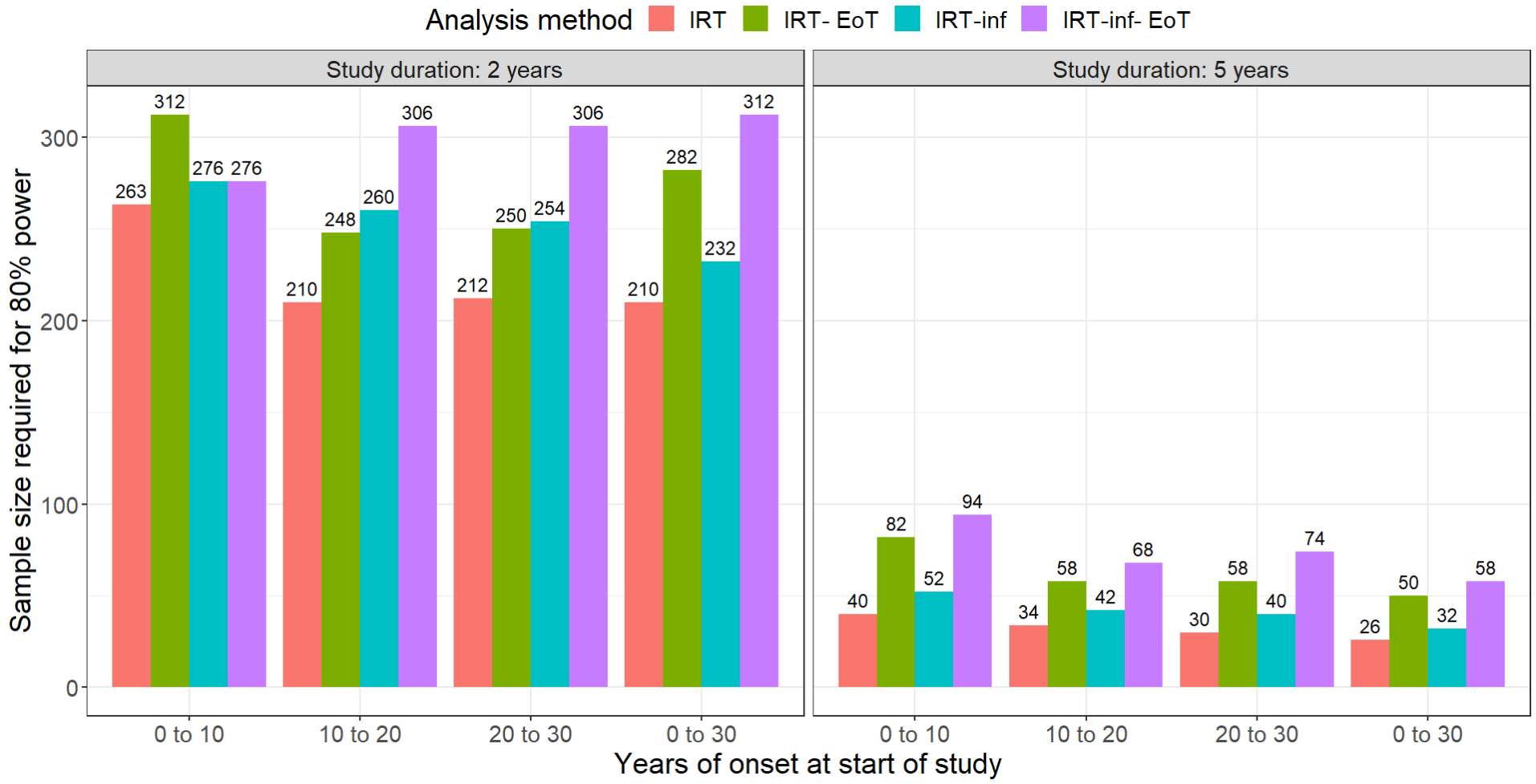
100% inhibition

ARSACS- Comparison of sample sizes across different: Study durations & Analysis methods



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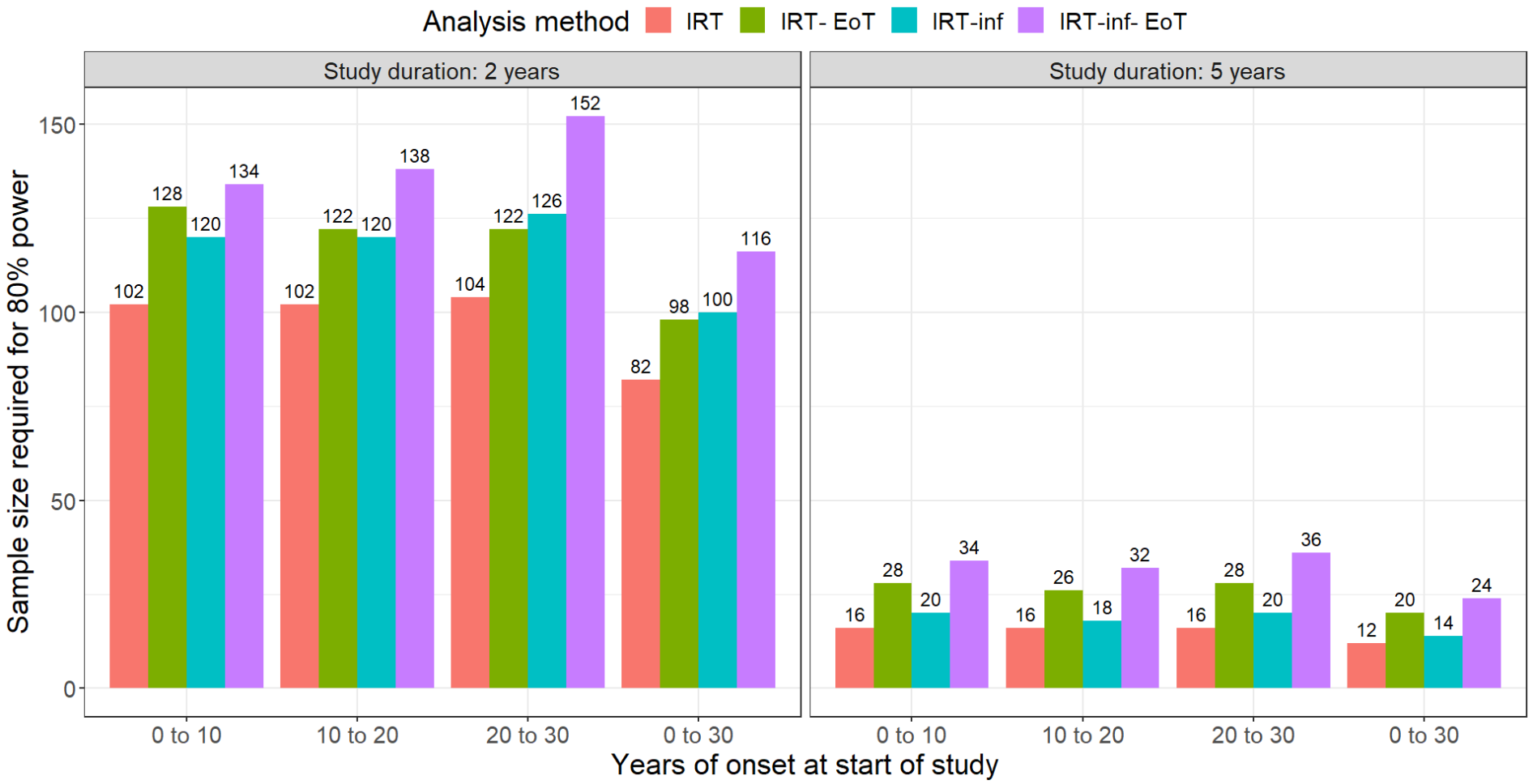
100% inhibition

POLG- Comparison of sample sizes across different: Study durations & Analysis methods



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Progressive Supranuclear Palsy (PSP)

- Neurodegenerative
  - Unknown cause
- Symptoms include:
  - Problems with walking, balance and eye movements
  - Cognitive impairment
  - Speech impairment
  - Difficulty swallowing

Data description PSPRS

Progressive Supranuclear Palsy Rating Scale

Study	#patients	Mean #visits	Mean study duration (yr)	Mean disease duration (yr)	#arms	Mean age (yr)	Study type
Abbvie	377	4.3	1	3.2	3	69	interv
Biogen	161	2.8	1	1.5	1	69	interv
Prospera	44	4.1	1	3.3	2	67	interv
Tauros	138	5.7	1.2	3.4	2	68	interv
Describe PSP	127	2.4	2.8	1.1	1	70	observ
ProPSP	132	2.6	1.6	4.3	1	69	observ

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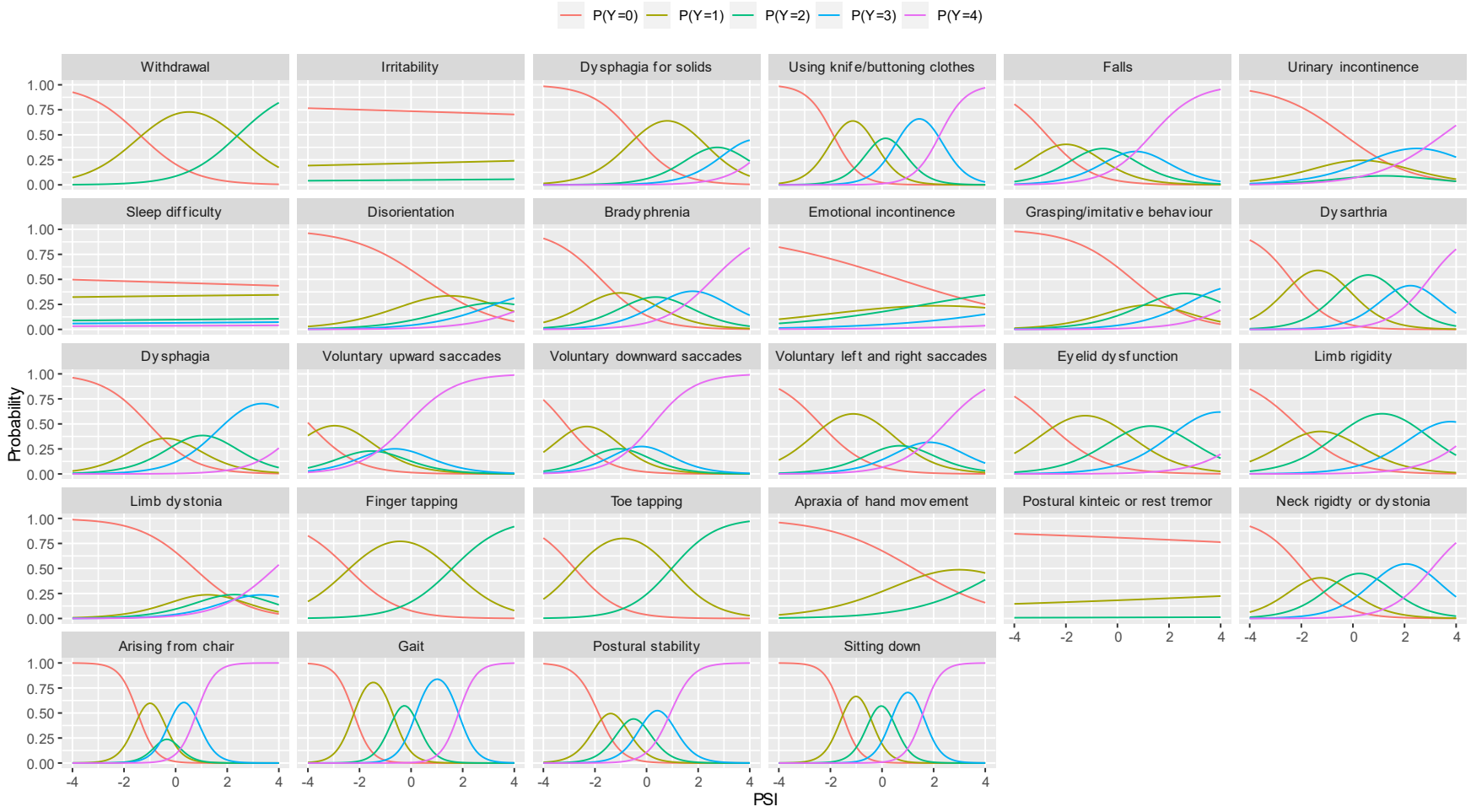
Item Characteristic Curves for PSPRS - Progressive Supranuclear Palsy Rating Scale



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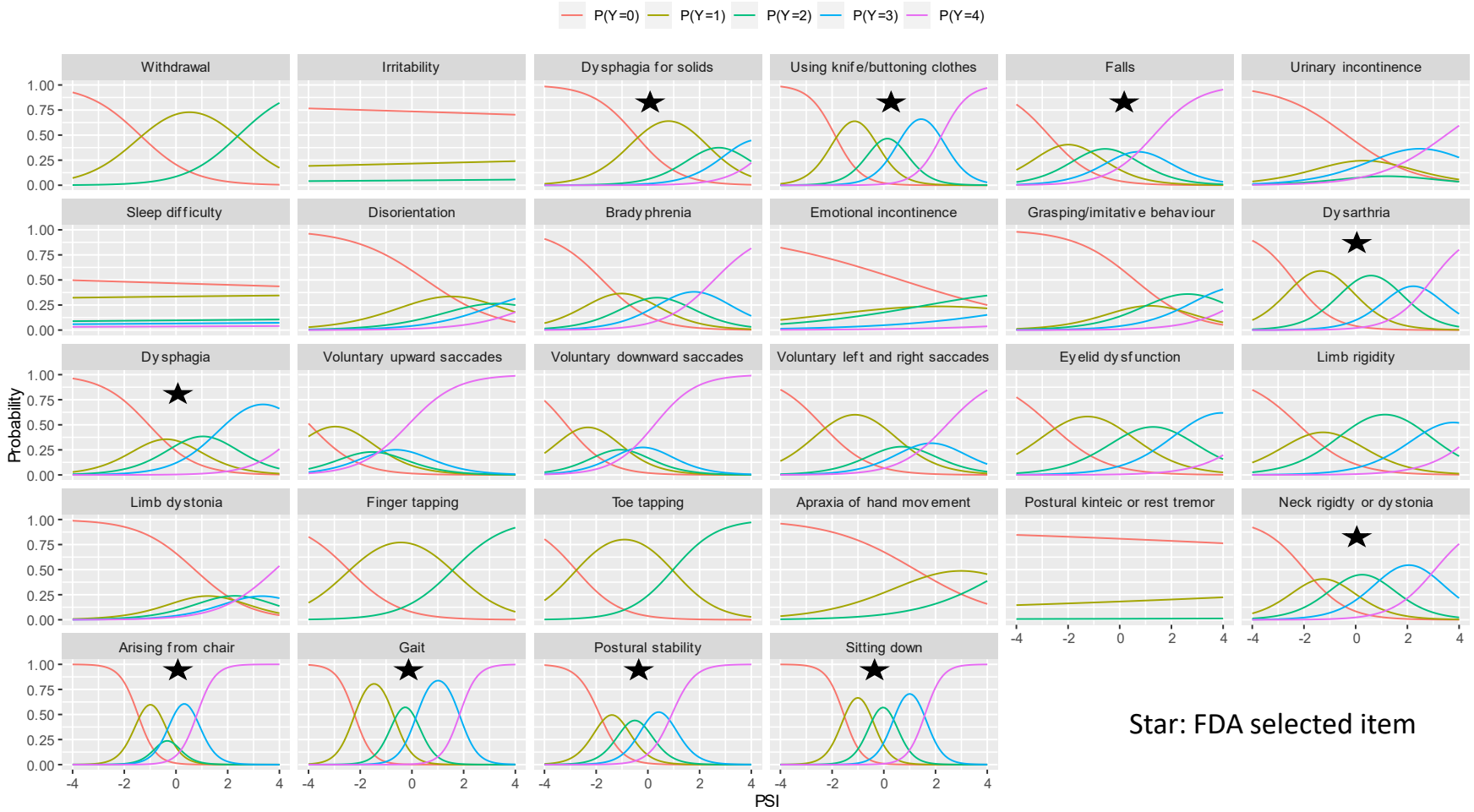
Item Characteristic Curves for PSPRS - Progressive Supranuclear Palsy Rating Scale



Star: FDA selected item

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PSP Ranking Scale items ranked by information content

★ : FDA selected item

	ITEM	Information content	Discrimination parameter	Number of categories
★	28	2.16	2.97	5
★	25	1.99	2.86	5
★	26	1.91	2.93	5
★	27	1.4	2.29	5
★	4	1.05	1.98	5
★	12	0.48	1.32	5
	24	0.43	1.21	5
★	15	0.41	1.24	5
★	5	0.39	1.14	5
★	13	0.35	1.1	5
★	3	0.34	1.19	5
	16	0.34	1.08	5
	9	0.33	1.03	5
	14	0.29	1.07	5
	21	0.28	1.17	3
	18	0.26	0.96	5
	17	0.24	0.93	5
	20	0.21	1.01	3
	1	0.21	0.97	3
	19	0.19	0.93	5
	11	0.17	0.85	5
	6	0.16	0.75	5
	8	0.12	0.71	5
	22	0.08	0.6	3
	10	0.02	0.33	5
	23	0.001	0.07	3
	2	0.001	0.04	3
	7	0.001	0.03	5

Sample size calculation - PSP

- Parallel group study, 1:1 randomization placebo:active treatment
- 1 year study, 5 visits/patient, no dropout
- Treatment effect: 50% progression inhibition
- Disease progression rate as estimated from interventional studies
- 80% power

Total number of subjects				
	scale	PSPRS	FDA	FDA rescore
model				
IRT model (item level data)		36	36	40
IRT-informed model (total score data)		50	48	50
Linear mixed effects model (total score data)		62	76	84

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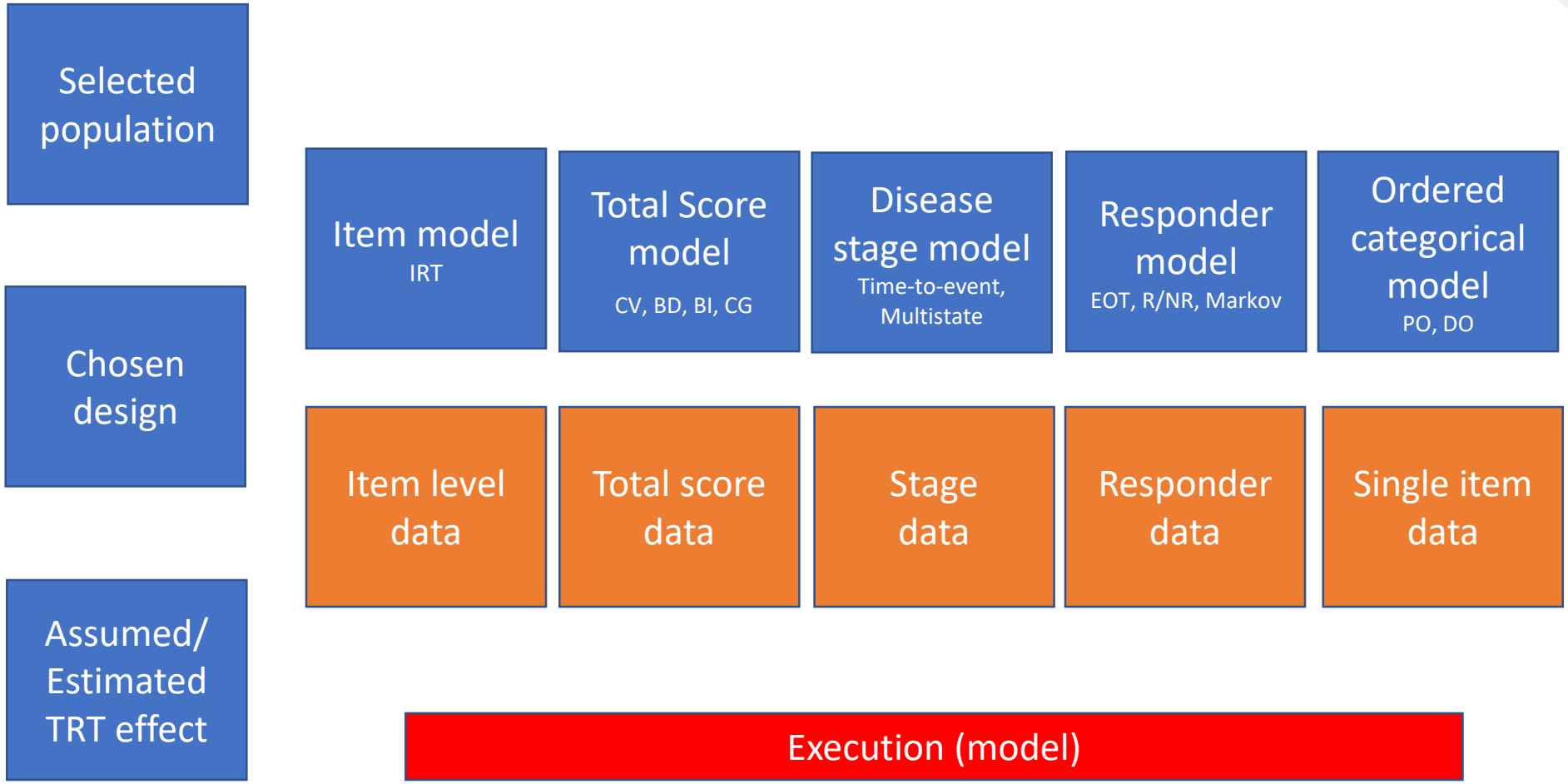
Understand relation between endpoints

An IRT model can inform trial choices of population, instrument, design and analysis



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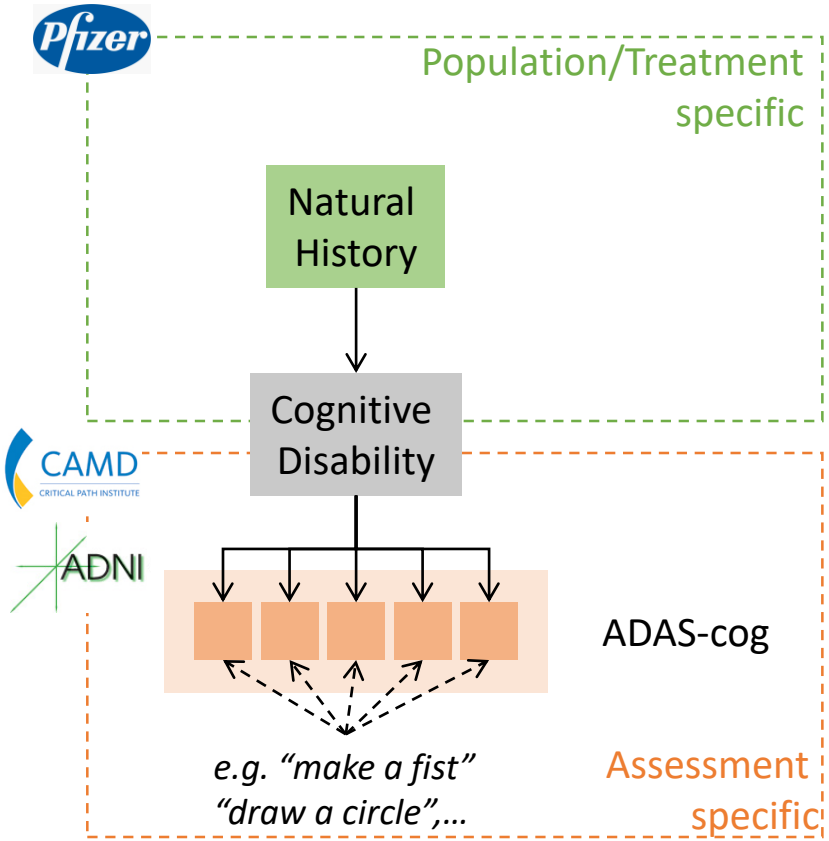
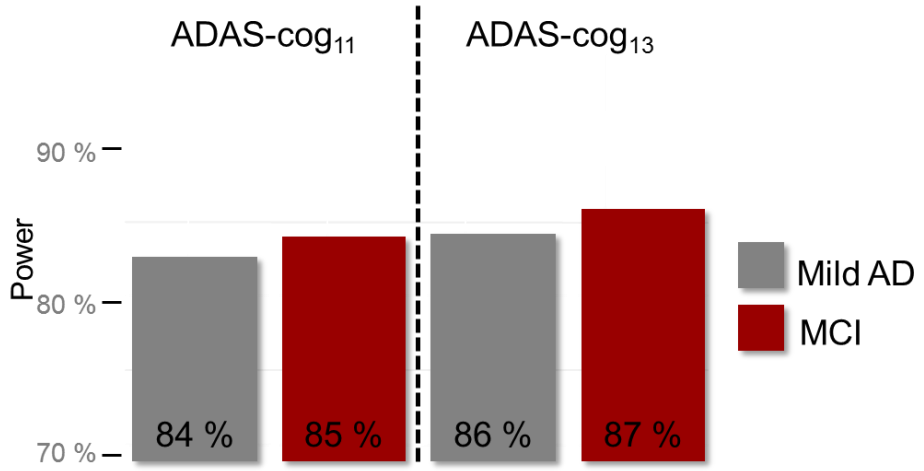
Separately determined ICCs
Example: Alzheimer's Disease



+ Utilize data from public or in-house clinical trial databases

+ Study influence of patient population & assessment variant independent from another



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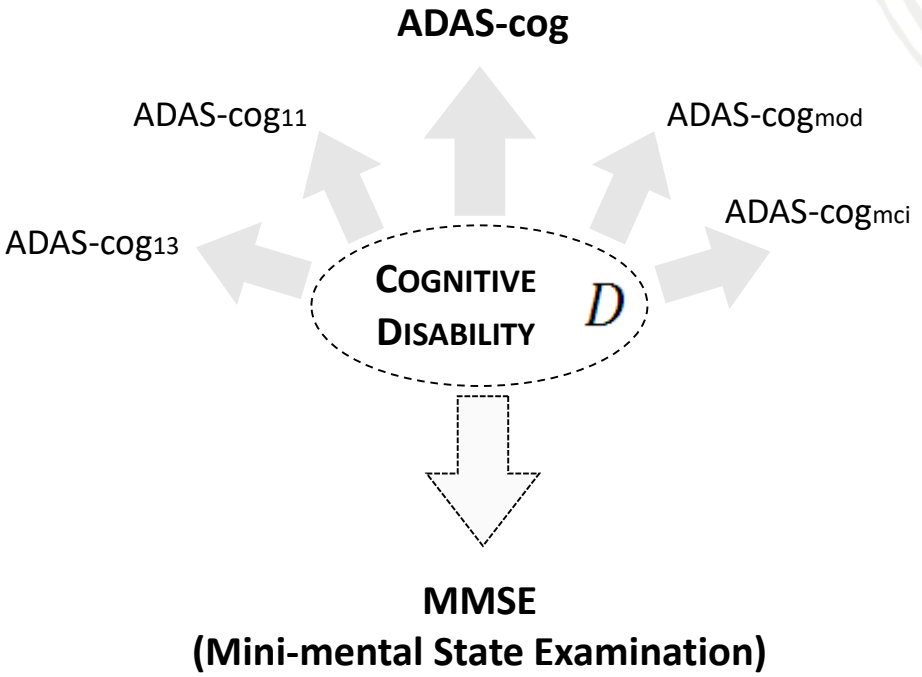
Reference:
Ueckert et al. Pharm Res 31(2014)

Item information

	Component	Information	% Total
1	Delayed Word Recall	4.79	33.6
2	Word Recall	3.81	26.7
3	Orientation	1.64	11.5
4	Word Recognition	1.40	9.8
5	Naming O&F	0.82	5.7
6	Number Cancellation	0.37	2.6
7	Construction	0.29	2.0
8	Word Finding	0.20	1.4
9	Ideational Praxis	0.18	1.3
10	Concentration	0.18	1.2
11	Remembering	0.16	1.1
12	Comprehension	0.16	1.1
13	Commands	0.15	1.1
14	Spoken Language	0.10	0.7

90 %



<u>Reduced tests options:</u>

Screening tests

Trial conduct with limited tests

Trial conduct with individualized dynamic testing

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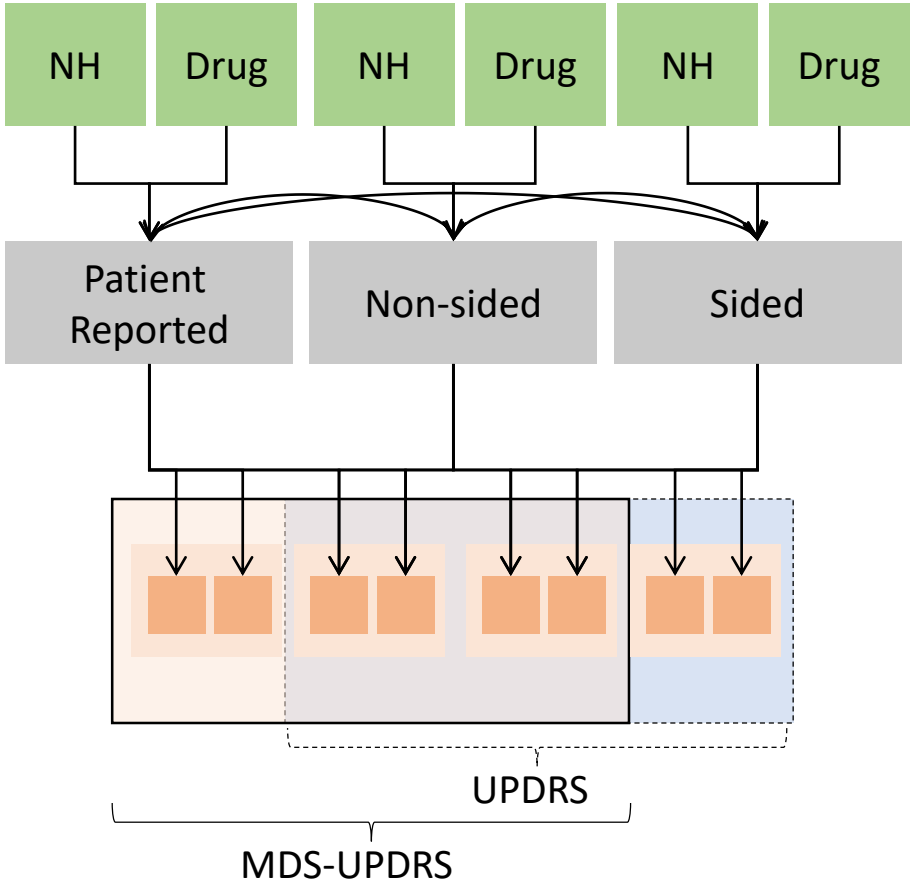
Example: Parkinson's Disease



- Model links established (UPDRS) and novel endpoint (MDS-UPDRS)
  - Leverage historic data
  - Comparison with older compounds
  - Joint framework for complete disease severity range
- Also done in AD for MMSE (often used for screening & diagnosis) & ADAS-cog (regulatory accepted endpoint)
  - Utilize all collected data
  - Leverage clinical routine data
  - Predict clinical endpoint from screening

References:

Gottipati et al. AAPSJ(2017)

Gottipati et al. PAGE 25 (2016) Abstr 5990

Jönsson et al PAGE (2017) Abstr 7236

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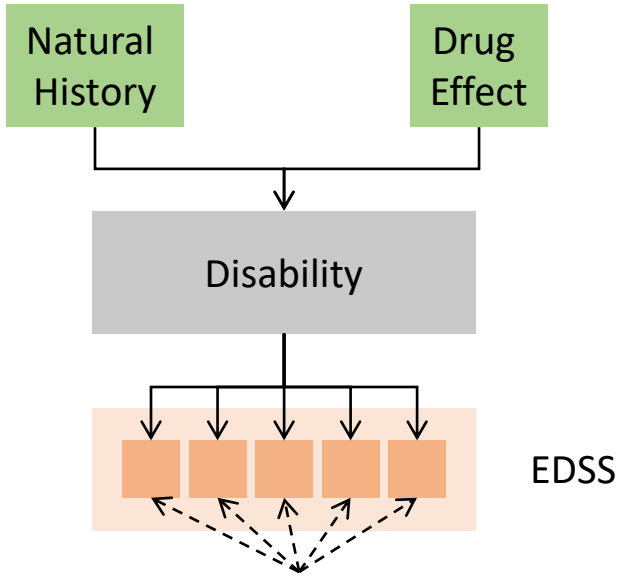
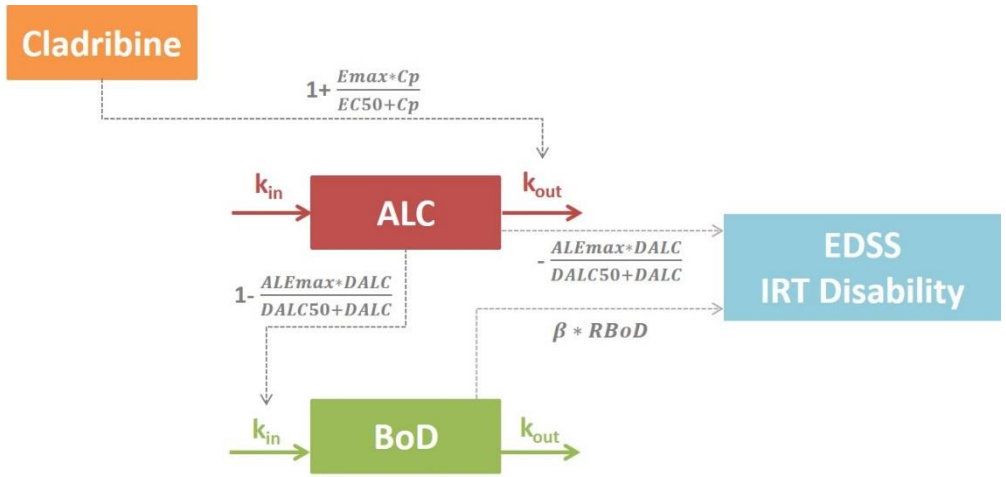
Biomarker – endpoint models
Multiple Sclerosis

1st generation model



2nd generation model



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References:
Novakovic A et al., AAPSJ 19(1): 172-179 (2017)
Novakovic A et al., J Clin Pharmacol 58(10): 1284-94 (2018)

IRT model based subpopulation identification

- Parkinson Progression Markers Initiative (PPMI) Database:


Unified Parkinson's Disease Rating Scale

PD workbook
THE WEMOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

I. Mentation, Behavior and Mood

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living
(for both "on" and "off")

5. Speech
0 = Normal.

De Novo Parkinson's Disease Subjects	Subjects With Scans Without Evidence of Dopaminergic Deficit (SWEDD)
(n = 423)	*(n = 64)*
Diagnosed ≤ 2 years	*Consented as Parkinson's patients*
***Not** taking any medications for Parkinson's disease*	

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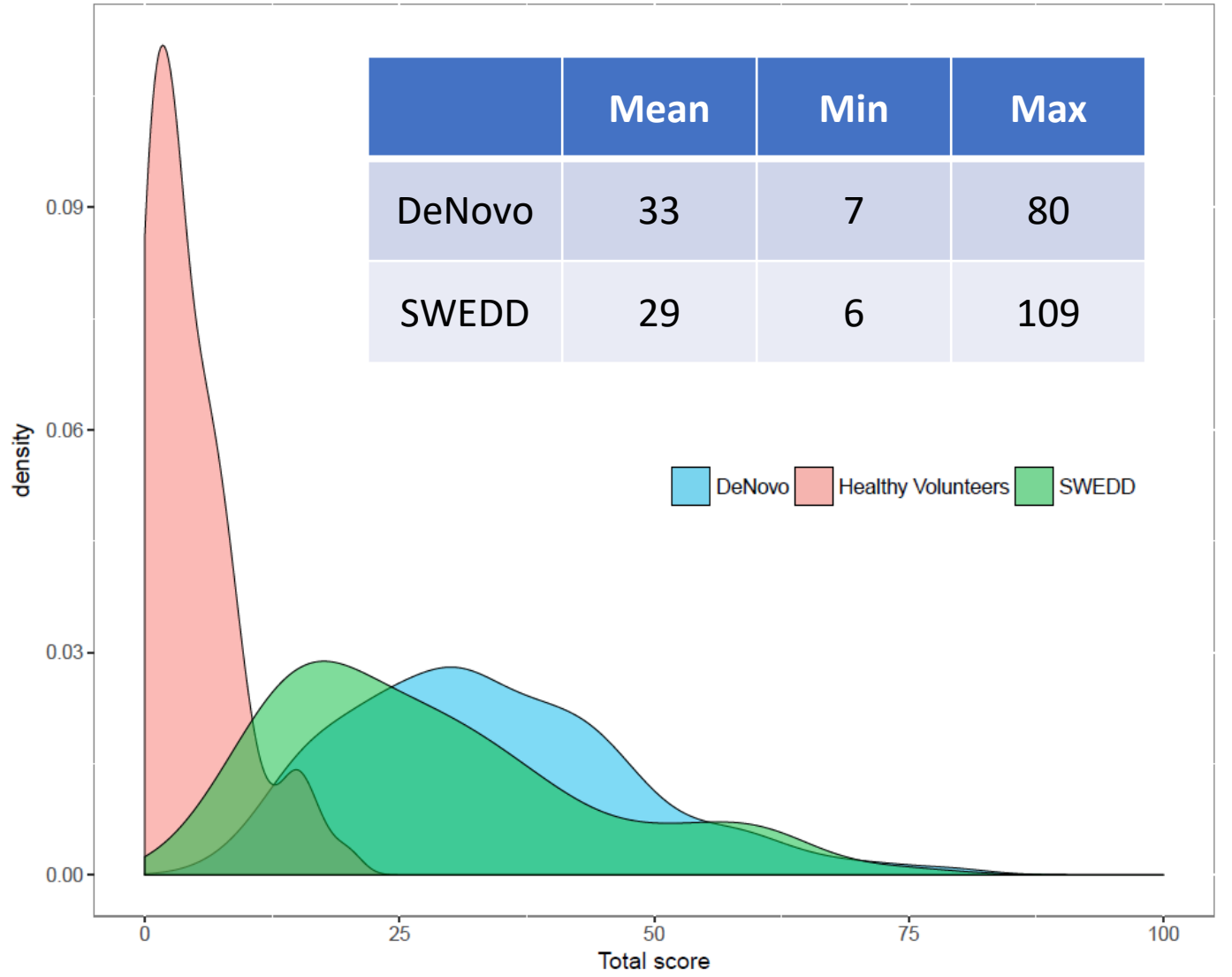
MDS-UPDRS total score

	Mean	Min	Max
DeNovo	33	7	80
SWEDD	29	6	109



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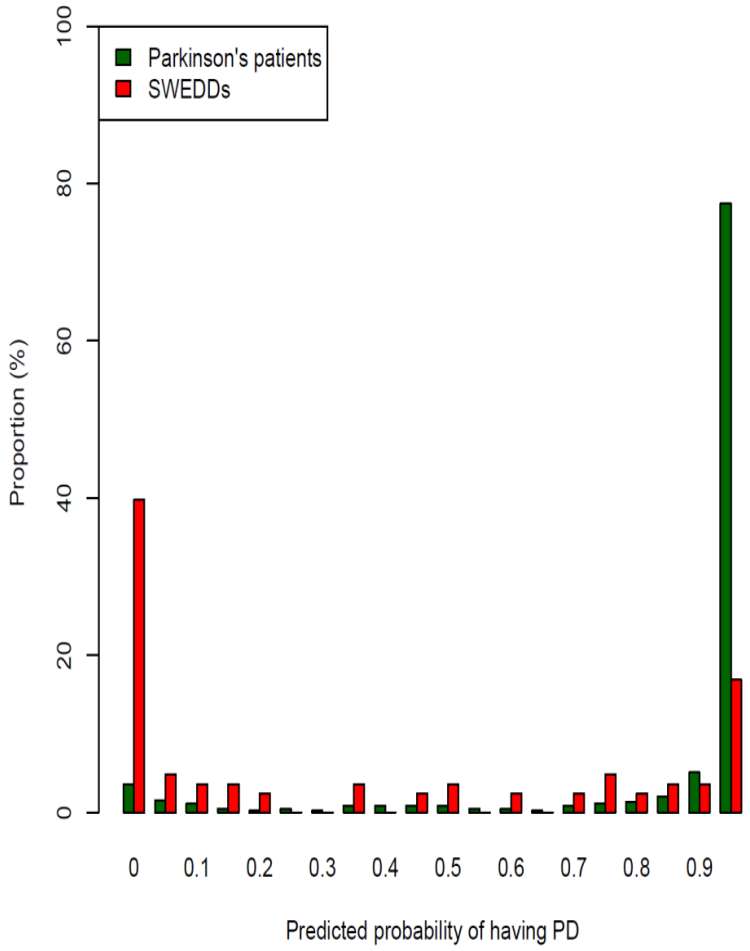
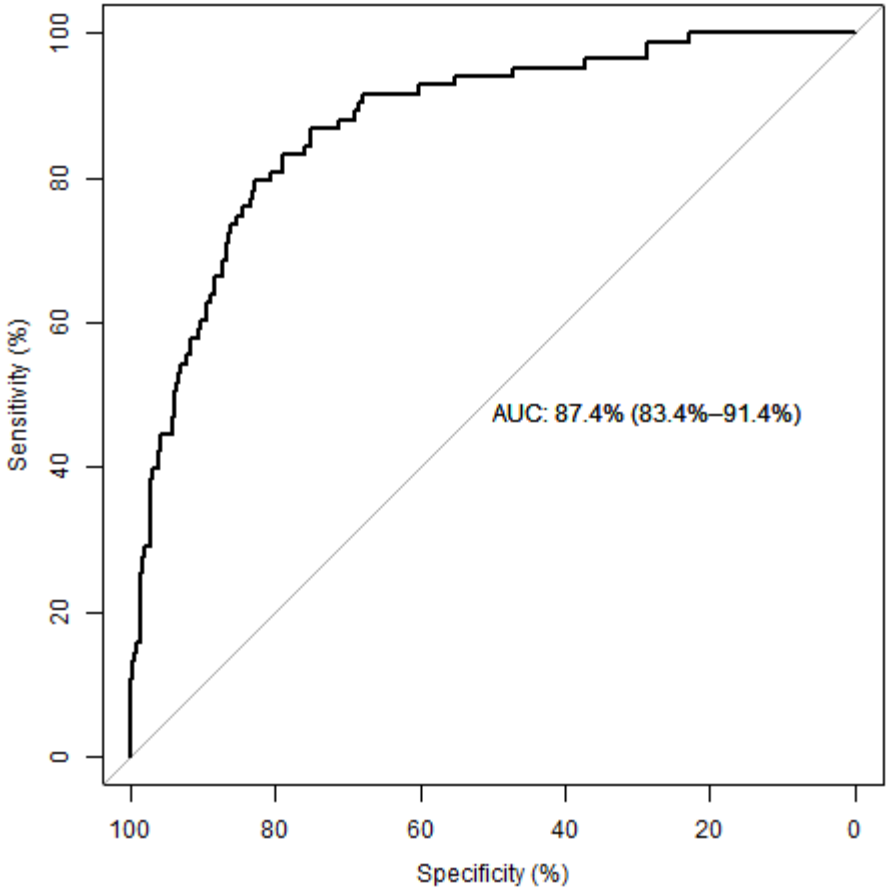
Item Response Model-based patient classification





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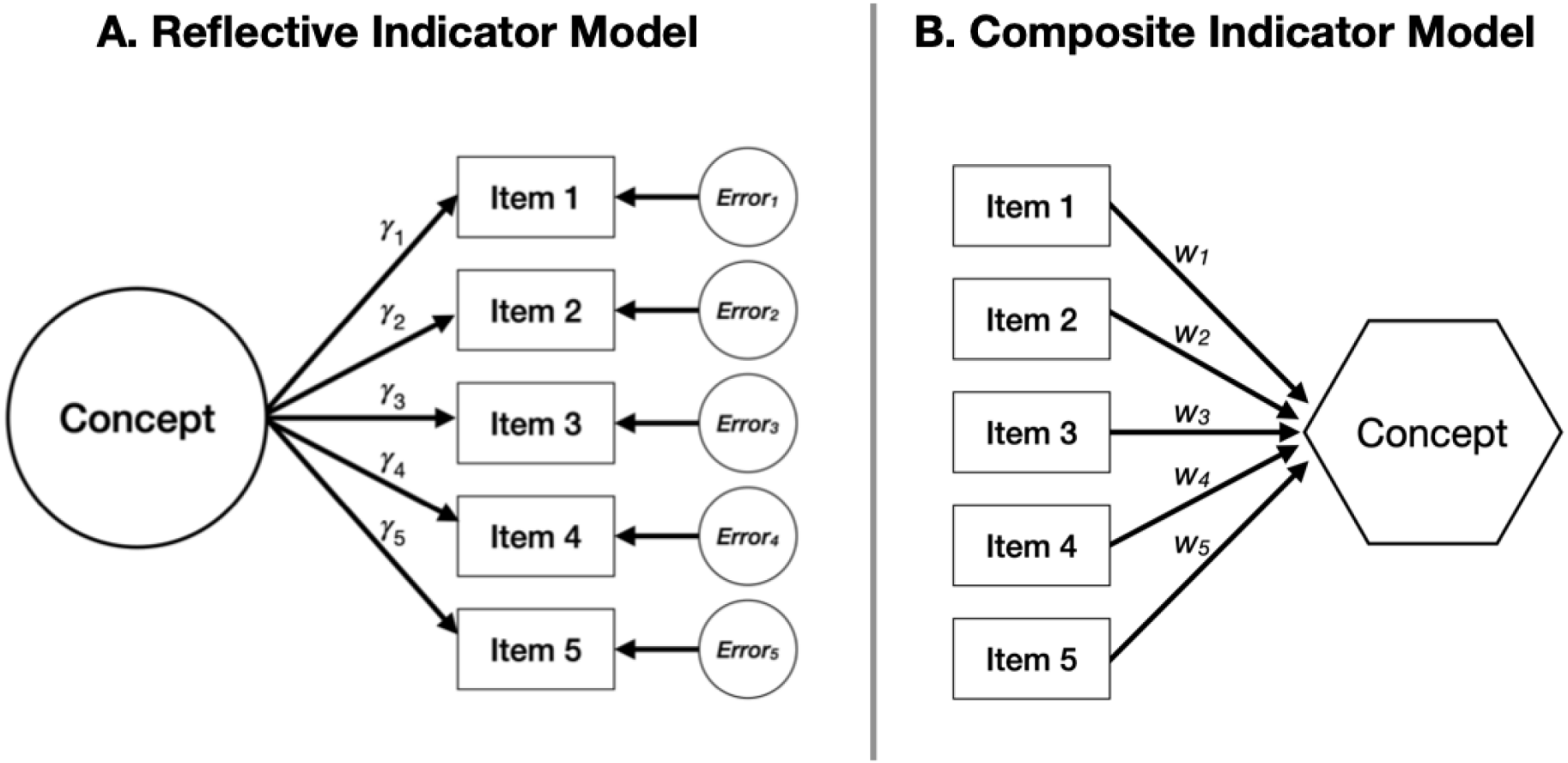
Differentiation and prognosis of healthy subjects, SWEDDs and Parkinson's patients using a multi-dimensional item response theory model.
S.C. van Dijkman, S. Ueckert, E.L. Plan, M.O. Karlsson. Journal of the Neurological Sciences, Volume 381, Supplement, 15 October 2017, Pages 97-98
https://doi.org/10.1016/j.jns.2017.08.317



Note: In panel A, the concept within a circle is conceptualized as a latent variable; the smaller circles represent measurement error that contributes to the responses of each item; γ denotes the causal effect of the concept on the item response. In panel B, the concept within a hexagon is conceptualized as a composite variable; w indicates the weight (may or may not be equally weighted) used for the item response in computing the calculated composite score that represents the concept.

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments, FDA Draft guidance, June 2022

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Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

New onset sensory or motor neuropathy involving cranial nerves	**No 0**	Yes +8
Lupus headache Severe, persistent headache (may be migrainous but must be nonresponsive to narcotic analgesia)	**No 0**	Yes +8
Proteinuria >0.5 g/24 hours	**No 0**	Yes +4
Pyuria >5 WBC/high-power field; exclude infection	**No 0**	Yes +4
Low complement CH50, C3, or C4 decreased below lower limit of normal for lab	**No 0**	Yes +2
High DNA binding Increased above normal range for lab	**No 0**	Yes +2
WBC <3 x 10^9/L Exclude drug causes	**No 0**	Yes +1

0 points

Authors recommend a cutoff of 3 or 4 to define active disease and the need to increase therapy (see Evidence for details)

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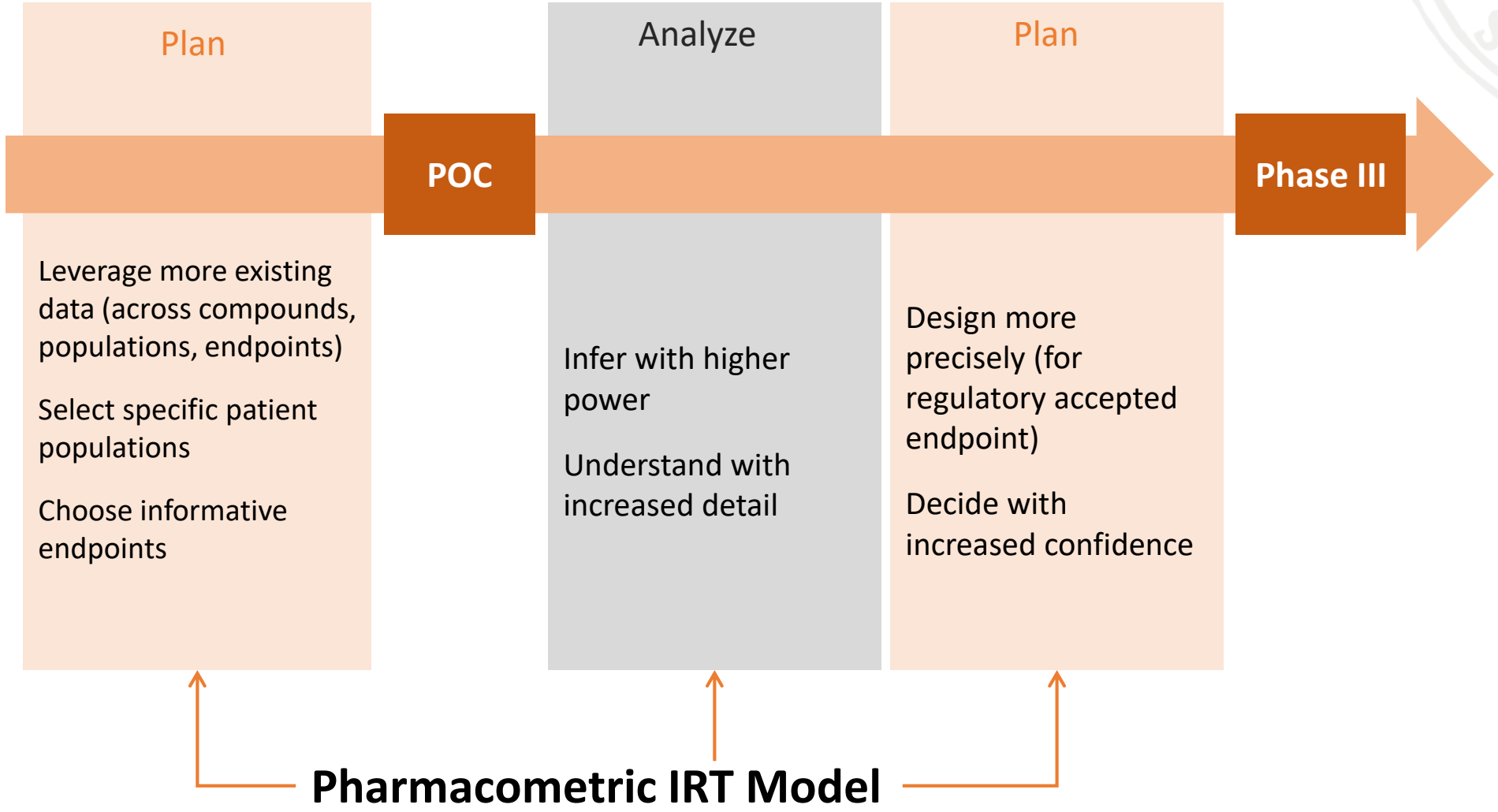
Potential of IRT modeling in clinical drug development



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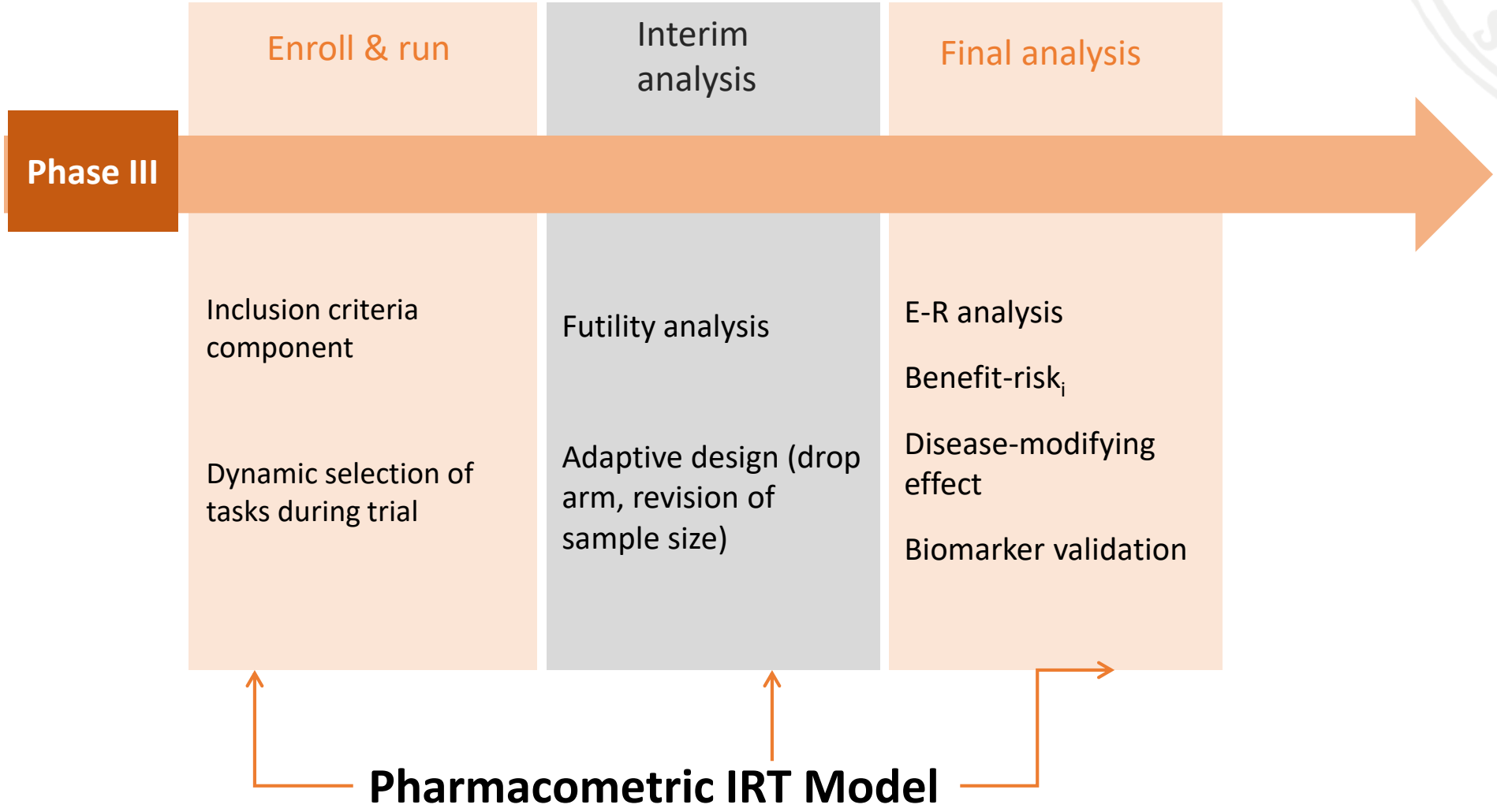

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