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Integrated modeling of digital-motor outcomes and clinical outcome assessments using IRT:
a framework for developing better outcomes for clinical trials in rare neurological diseases

32nd PAGE meeting - 26th June 2024

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Rare diseases, but collectively not rare!

< 1 in 2000 people

7000+ distinct rare disease

300+ million living with rare disease

94% of rare diseases lack an approved treatment

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[1] Nguengang Wakap S et al. *Eur J Hum Genet*. 2020 Feb;28(2):165–73. [2] Austin CP et al. Clinical and Translational Science. 2018;11(1):21–7. [3] Federico A. *Rev Neurol (Paris)*. 2013 Feb;169 Suppl 1:S12-17.

Major bottleneck of therapeutic progress

Small & heterogenous population of patients

Challenge

Understanding the disease progression

Generating robust evidence of drug effects

Need

Optimized clinical outcomes

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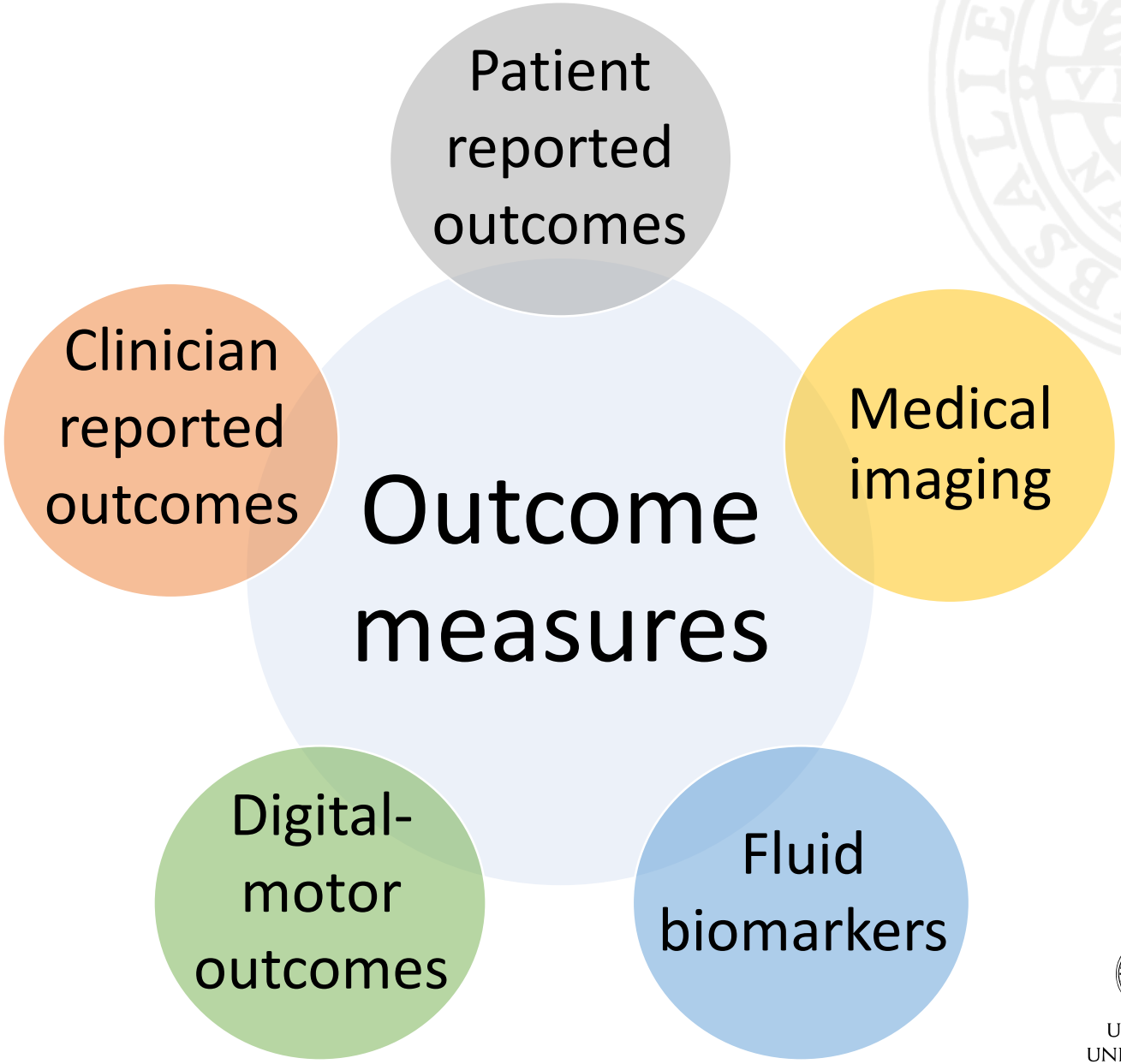
Multiple outcomes to enhance power/ decrease sample sizes in rare disease trials?



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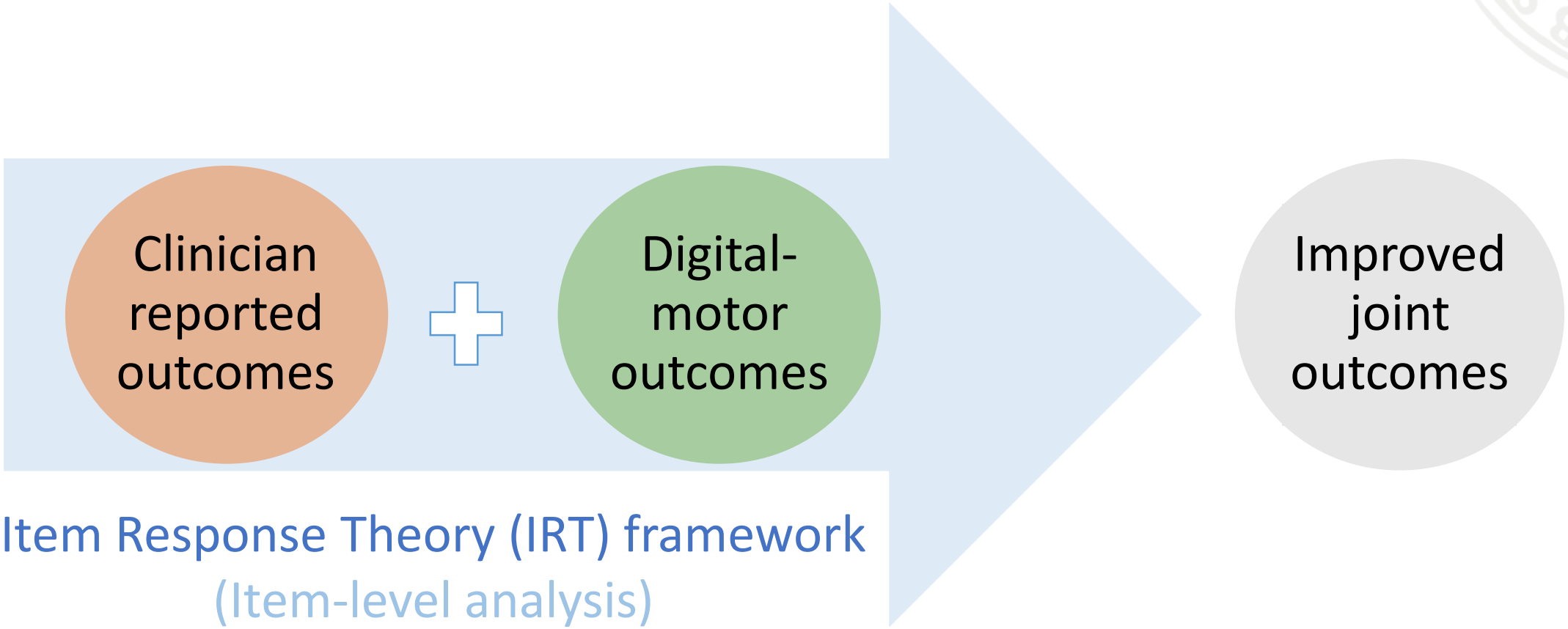
Integrated modeling of digital-motor outcomes and clinical outcome assessments using IRT



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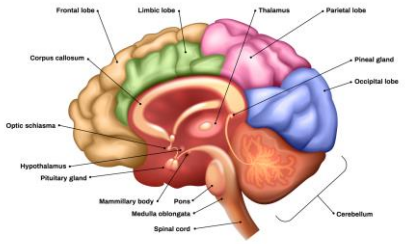
Showcase: Spastic ataxias

A heterogenous group of rare neurodegenerative diseases



Affects the cerebellum and associated tracts

Lack of coordination

Progressive disease
- Loss of ambulation

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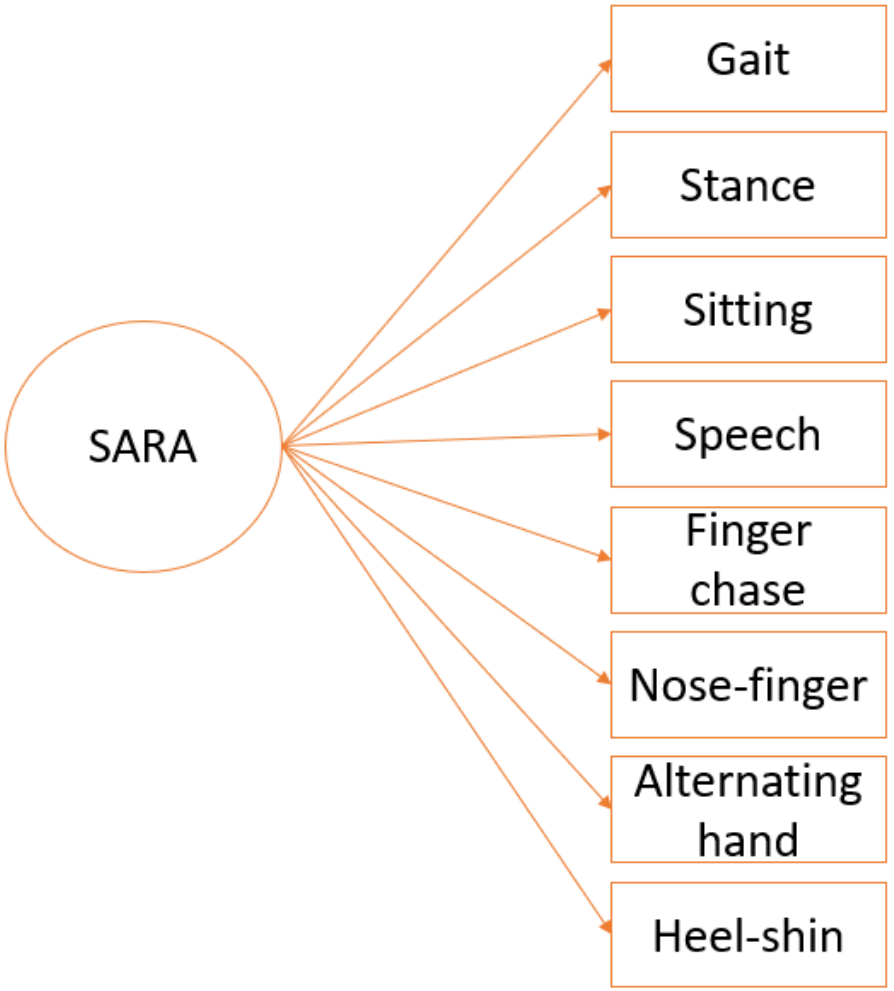
Outcome measures for Ataxia?

Clinician-reported outcome



Item-level analysis using Item Response Theory (IRT) showed SARA adequacy

CPT: Pharmacometrics & Systems Pharmacology

ARTICLE | Open Access

Item performance of the scale for the assessment and rating of ataxia in rare and ultra-rare genetic ataxias

Alzahra Hamdan, Andrew C. Hooker, Xiaomei Chen, Andreas Traschütz, Rebecca Schüle, ARCA Study Group, EVIDENCE-RND consortium, Matthis Synofzik, Mats O. Karlsson

First published: 21 May 2024 | https://doi.org/10.1002/psp4.13162 | Citations: 1

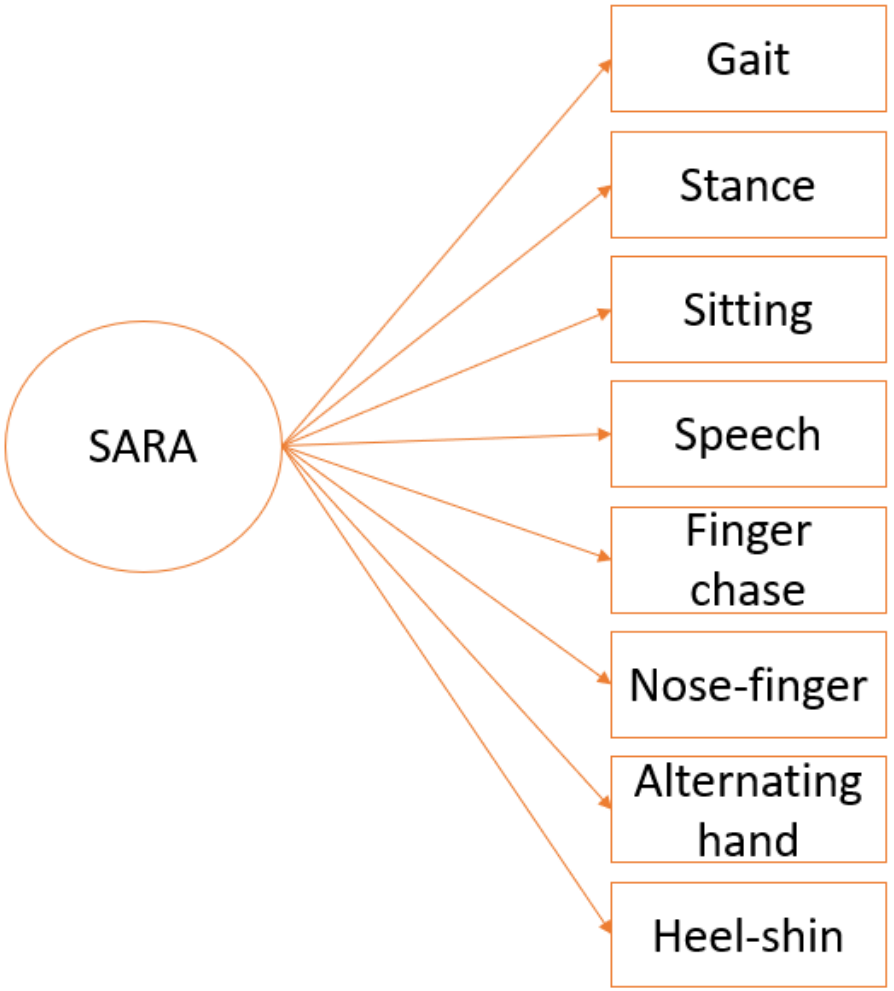
Matthis Synofzik shared last authorship with Mats O. Karlsson.

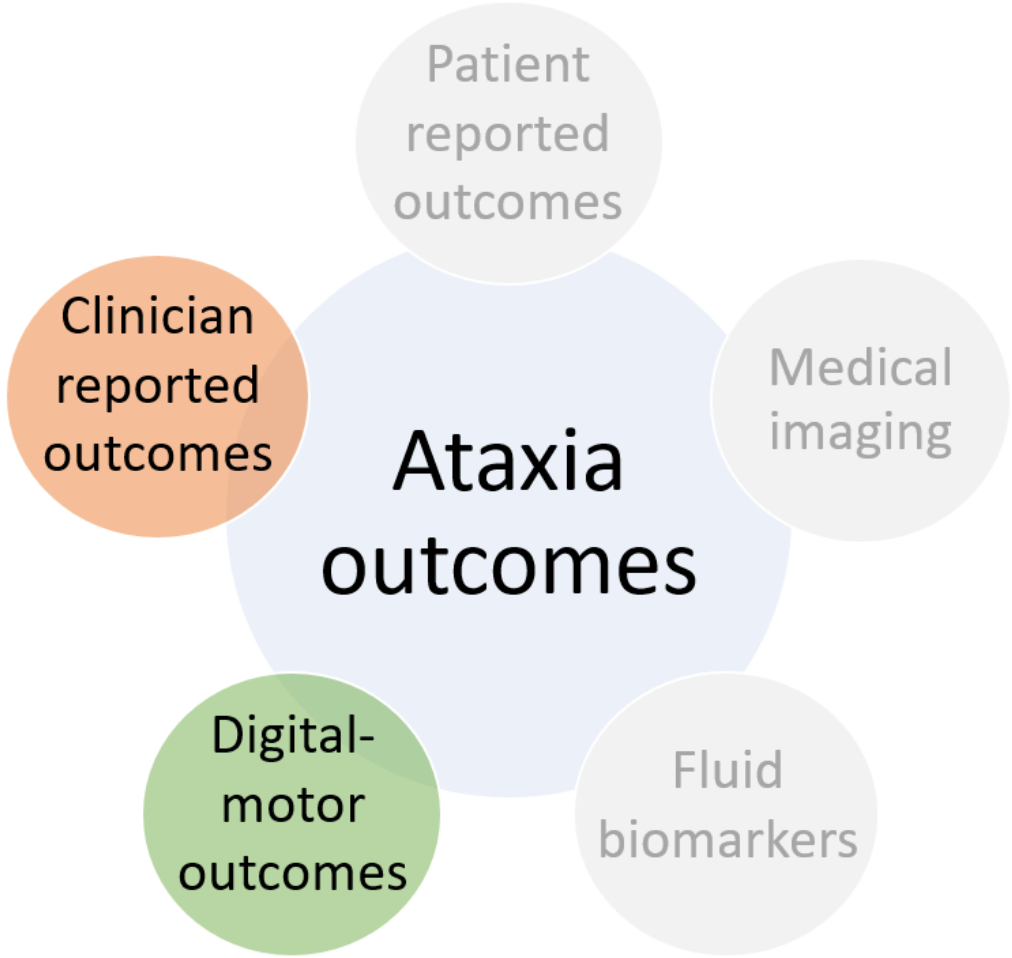
SARA: Scale for the Assessment and Rating of Ataxia

[1] Schmitz-Hübsch T, et al. *Neurology*. 2006;66(11):1717–20. [2] Hamdan A, et al. CPT Pharmacometrics SystPharmacol. 2024;00:1-14. doi:10.1002/psp4.13162

Outcome measures for Ataxia?

Clinician-reported outcome





SARA: Scale for the Assessment and Rating of Ataxia

[1] Schmitz-Hübsch T, et al. *Neurology*. 2006;66(11):1717–20. [2] Hamdan A, et al. CPT Pharmacometrics SystPharmacol. 2024;00:1-14. doi:10.1002/psp4.13162

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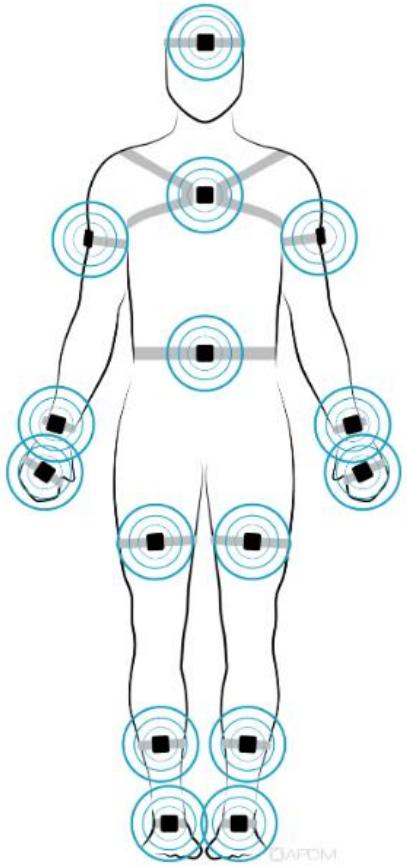
Digital-motor outcomes (DMO) for ataxia

APDM® outcomes
Walking and balance



Q-motor outcomes
Limbs coordination

Grip Lift

postural stability
grip force control

Spiral Drawing

complex movement
fine motor function

Target Pointing

visually directed movement
gross motor function

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[1] Hermle D et al. *Annals of Clinical and Translational Neurology*. 2024;11(5):1097–109. [2] Comprehensive Gait and Balance Analysis - APDM Wearable Technologies. Available from: https://apdm.com/mobility/

Illustration of digital-motor outcomes data

Q-motor: Spiral drawing task

Features

e.g., Efficiency

e.g., Smoothness

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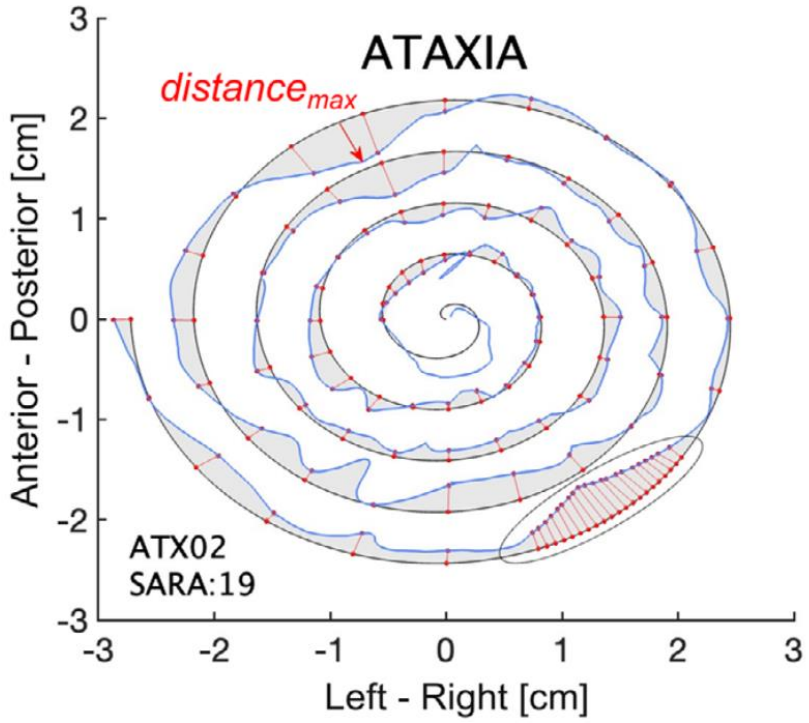
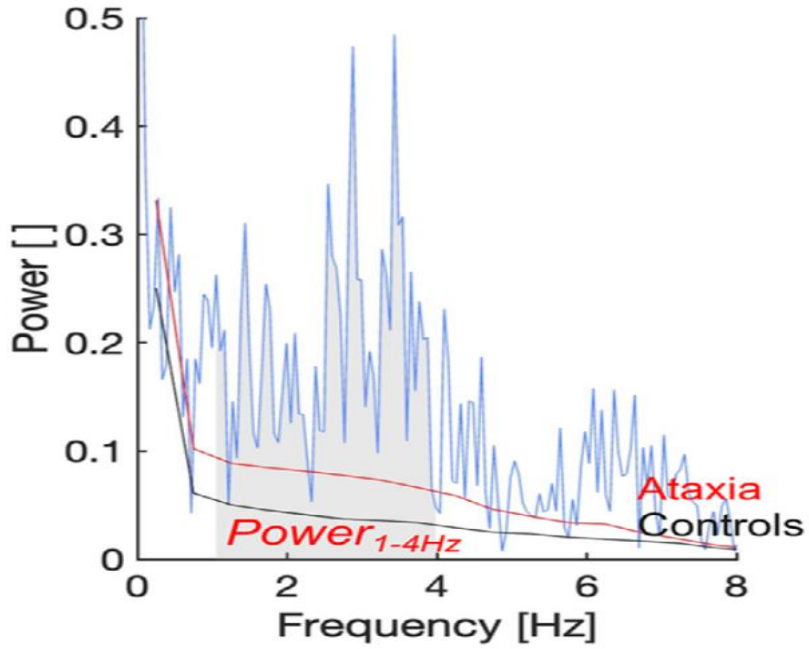
[1] Hermle D et al. *Annals of Clinical and Translational Neurology*. 2024;11(5):1097–109

Illustration of digital-motor outcomes data

Spiral drawing task (Q-motor outcomes)



Feature: Efficiency → **Metric:** Median of the spatial error (from the template)



Feature: Smoothness → **Metric:** Cumulative power in the 1-4 Hz frequency spectrum of drawing speed

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[1] Hermle D et al. *Annals of Clinical and Translational Neurology*. 2024;11(5):1097–109

PROSPAX
NCT04297891

Trial-like data from PROSPAX dataset

- SARA item scores
- Digital-motor measures[1]
  - 9 APDM (lab-based) measures
  - 17 Q-motor measures
- 243 subjects
- 2 genotypes: ARSACS, SPG7 (+healthy controls[2])
- 438 visits[3] (1-2 visits/subject)

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[1] Post-screening; [2] not included in this work ; [3] Available for analysis at the time of presentation

Questions addressed in this work

1. Can we build an integrated IRT model for both continuous and categorical outcomes?
2. Can we increase the precision of individual SARA ataxia severity estimates by adding digital-motor outcomes?
3. Can we reduce the number of measured digital-motor outcomes and select a subset that best supports SARA?

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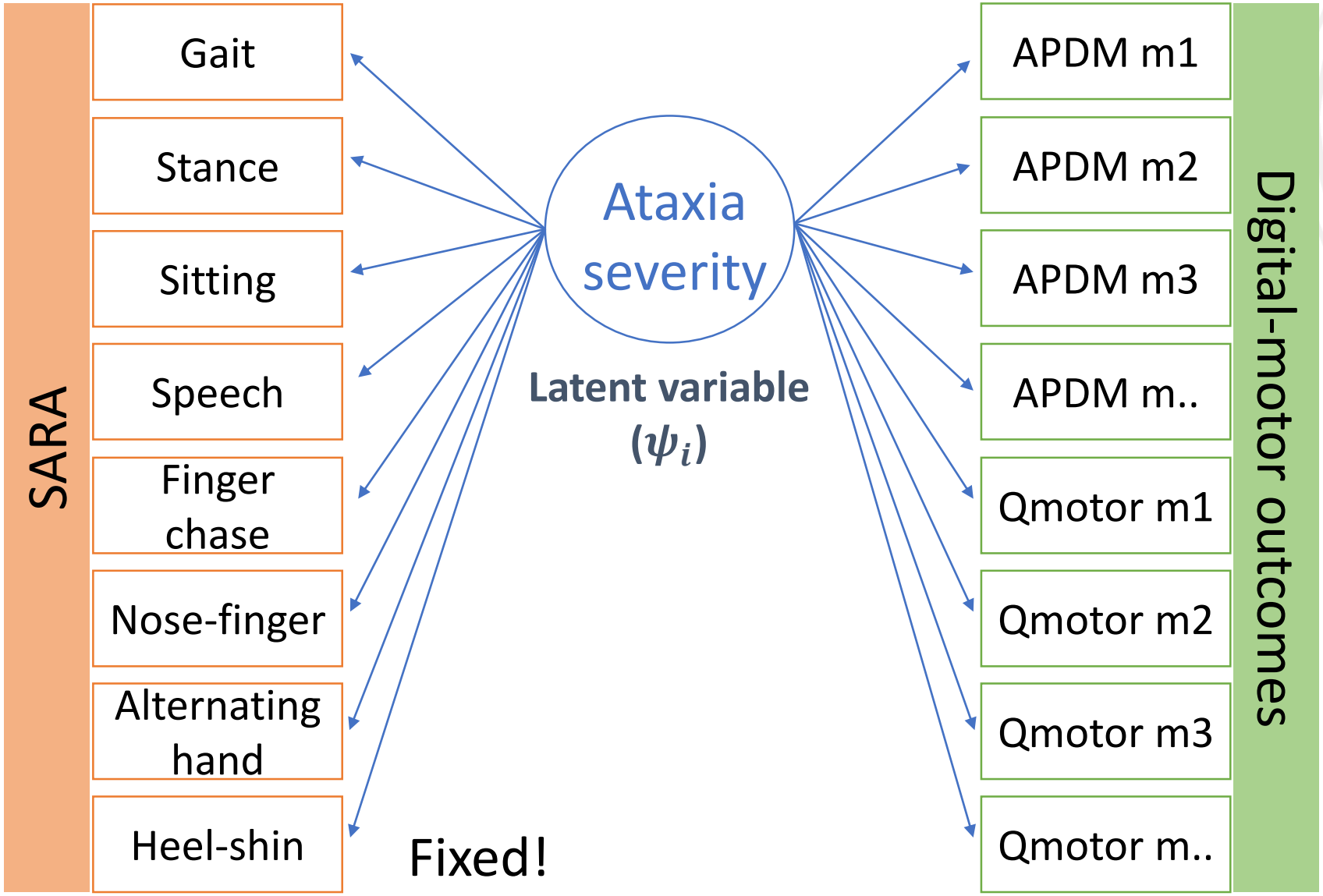
Joint IRT model



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

Ordered categorical data

$$DMO_{im} = \theta_1 + \theta_2 . \psi_i^{\theta_3} + \varepsilon_{im}$$

Continuous data

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Modeling and assessment workflow

Model selection for each DMO

$$DMO_{im} = f(\psi_{i_{SARA}}) + \varepsilon_{im}$$

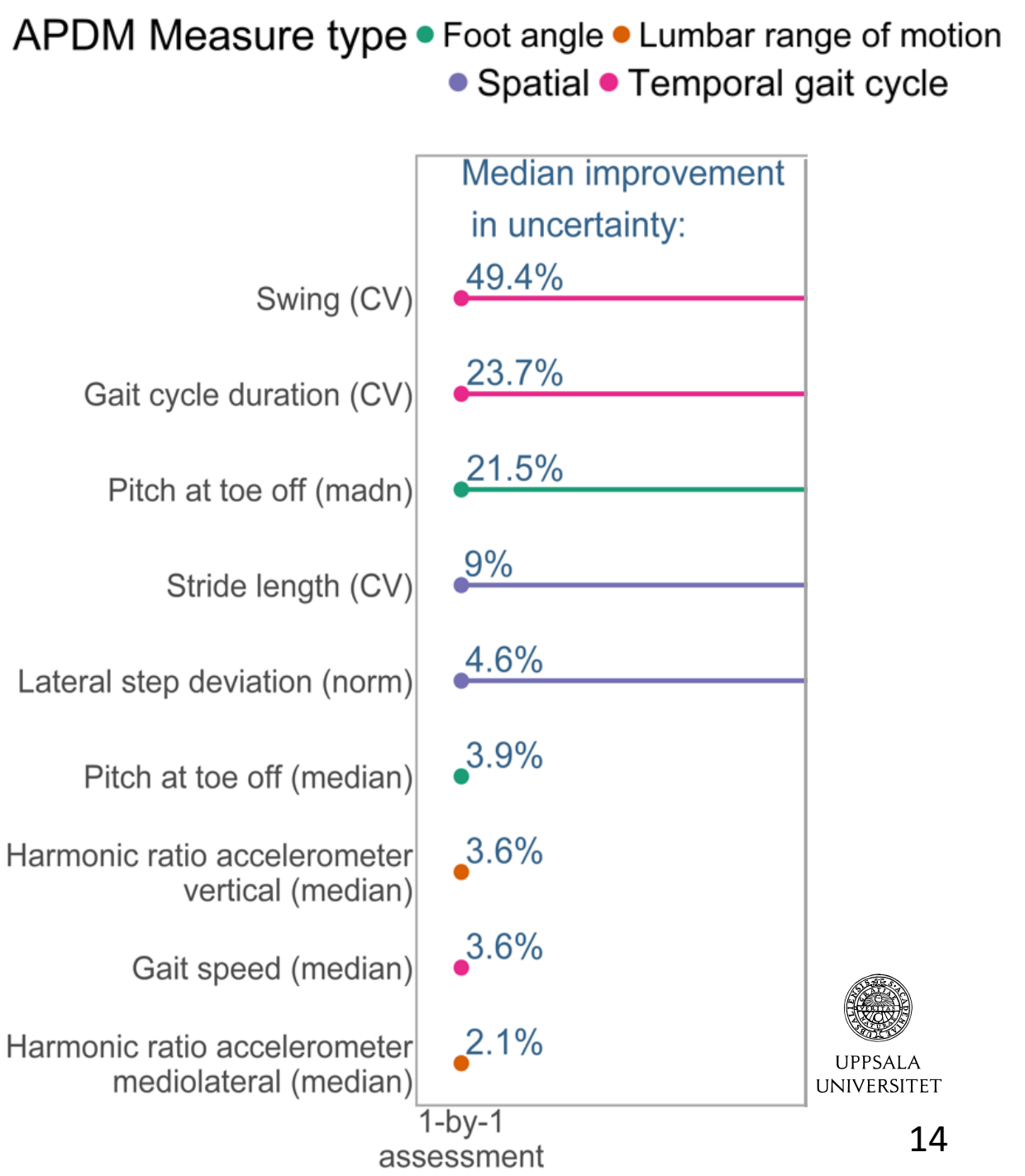
Integrating within the SARA IRT model (1 by 1)

$$SARA_{ij} = h(\psi_i)\,; \quad DMO_{im} = f(\psi_i) + \varepsilon_{im}$$

Selection of best DMO measures (1st round)

DMO: digital-motor outcome
ψ_i : latent variable

i : individual
m : certain DMO measure (1,2, ..M)
j : certain SARA item (1, 2, .. J)



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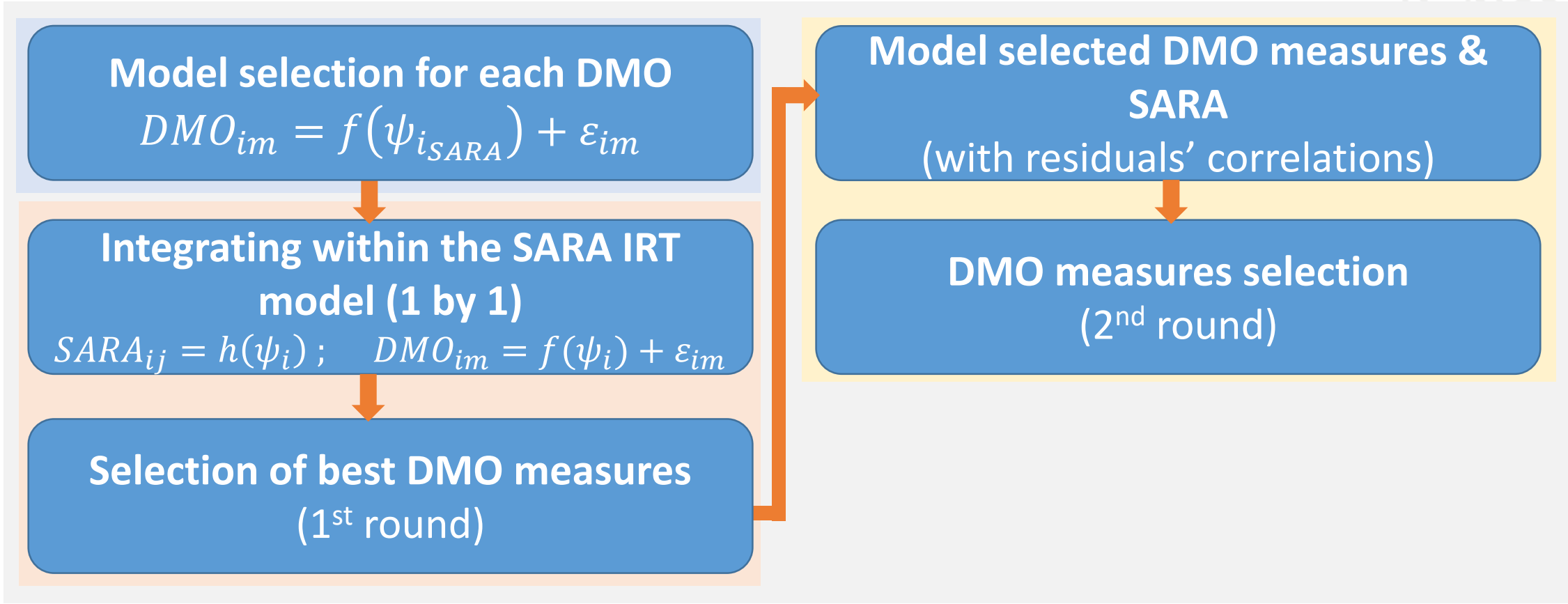
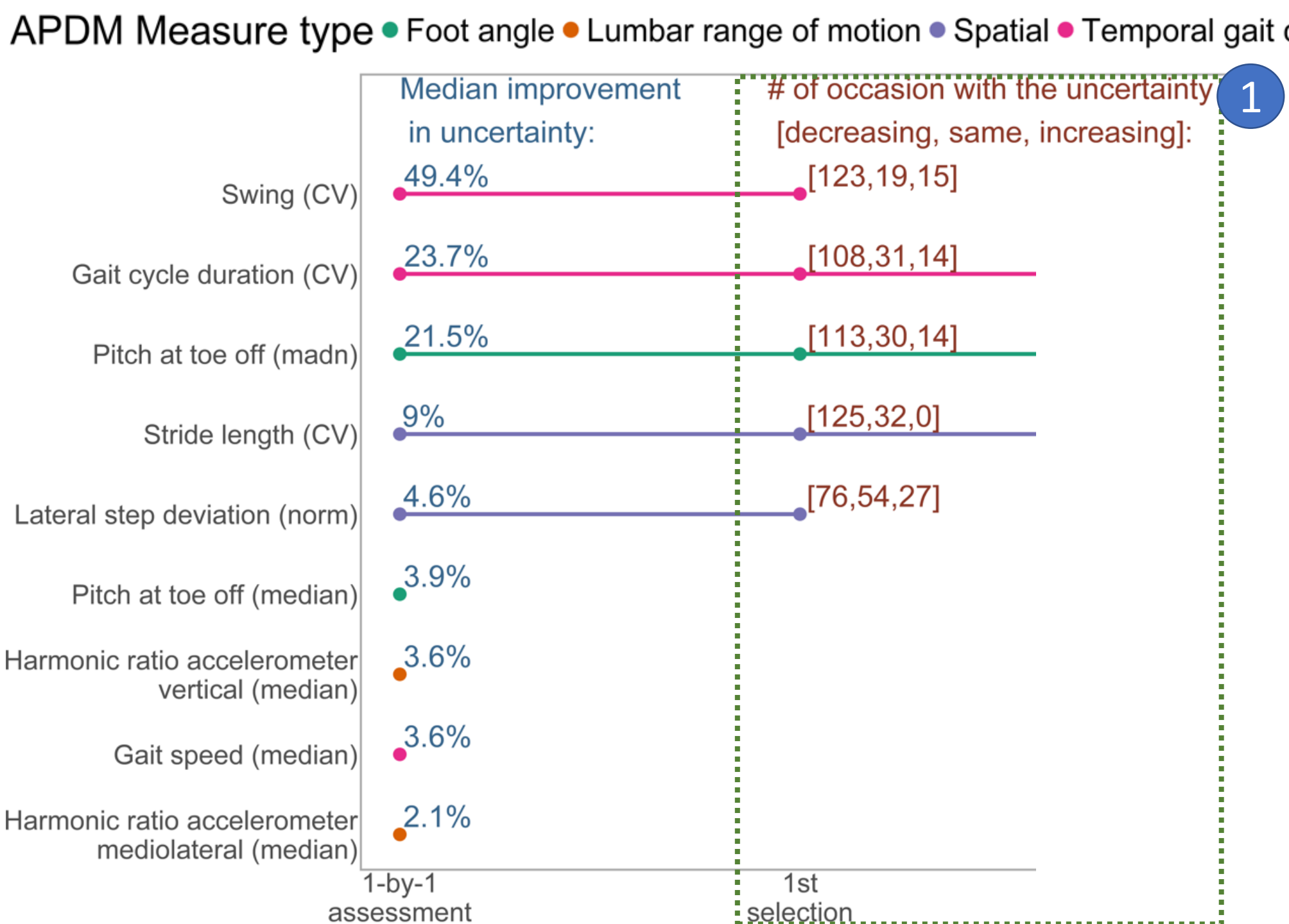
Modeling and assessment workflow





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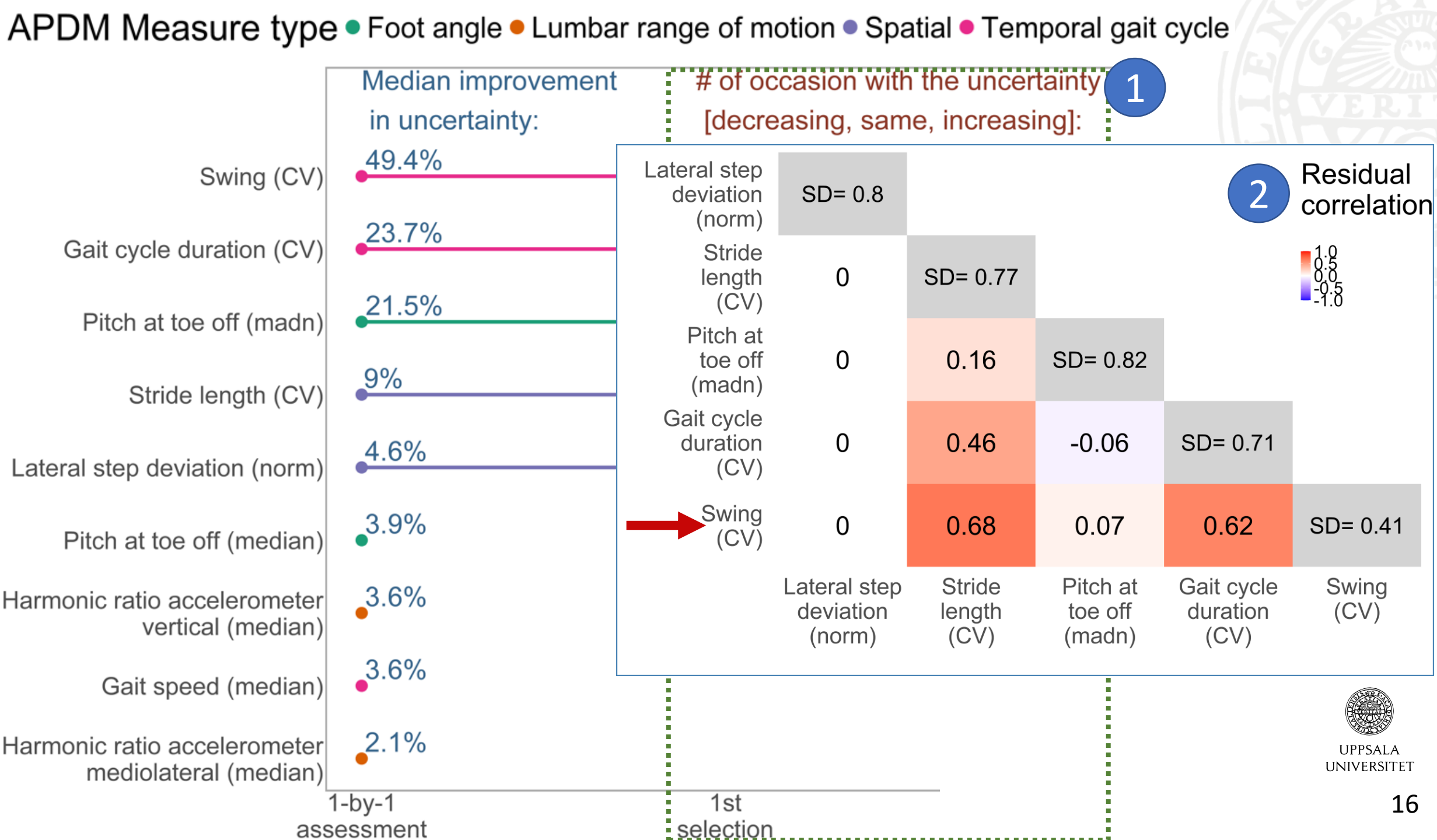

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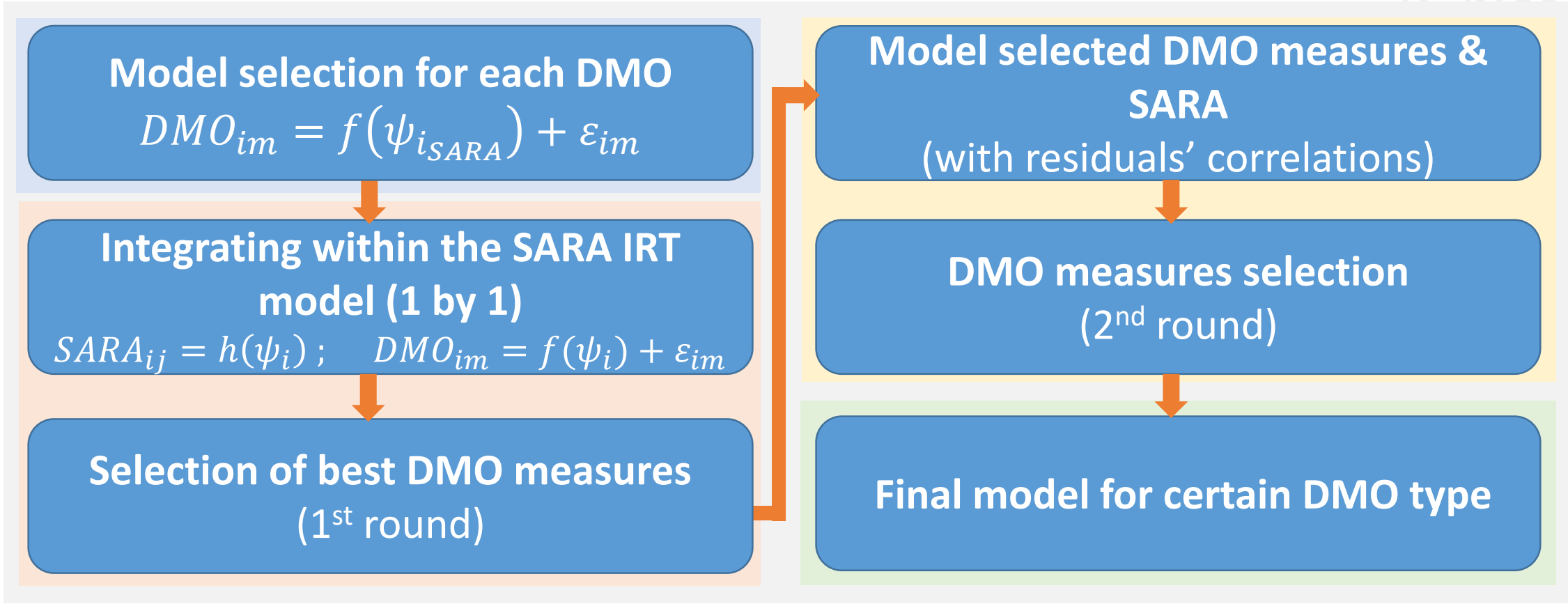
Modeling and assessment workflow



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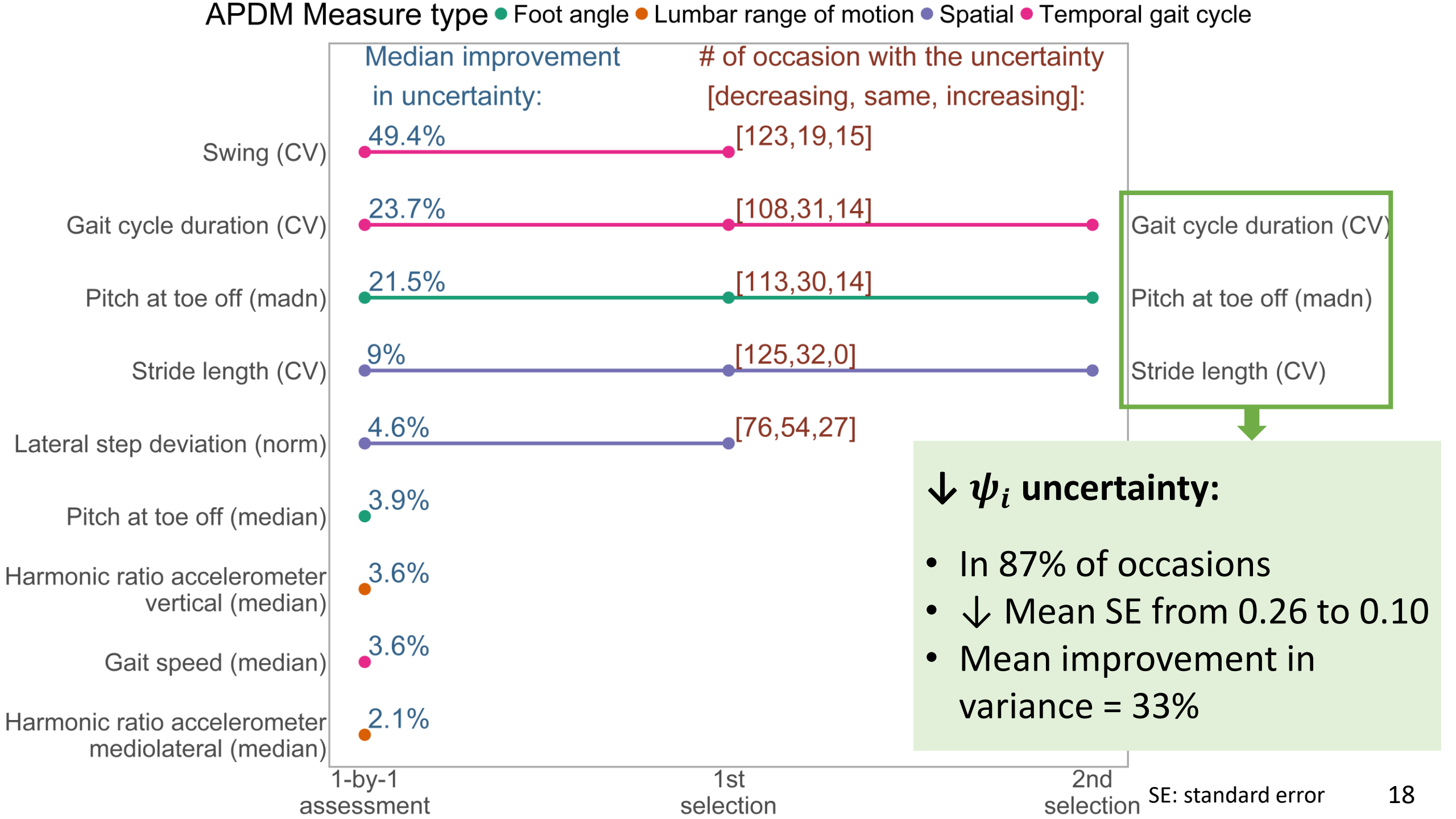
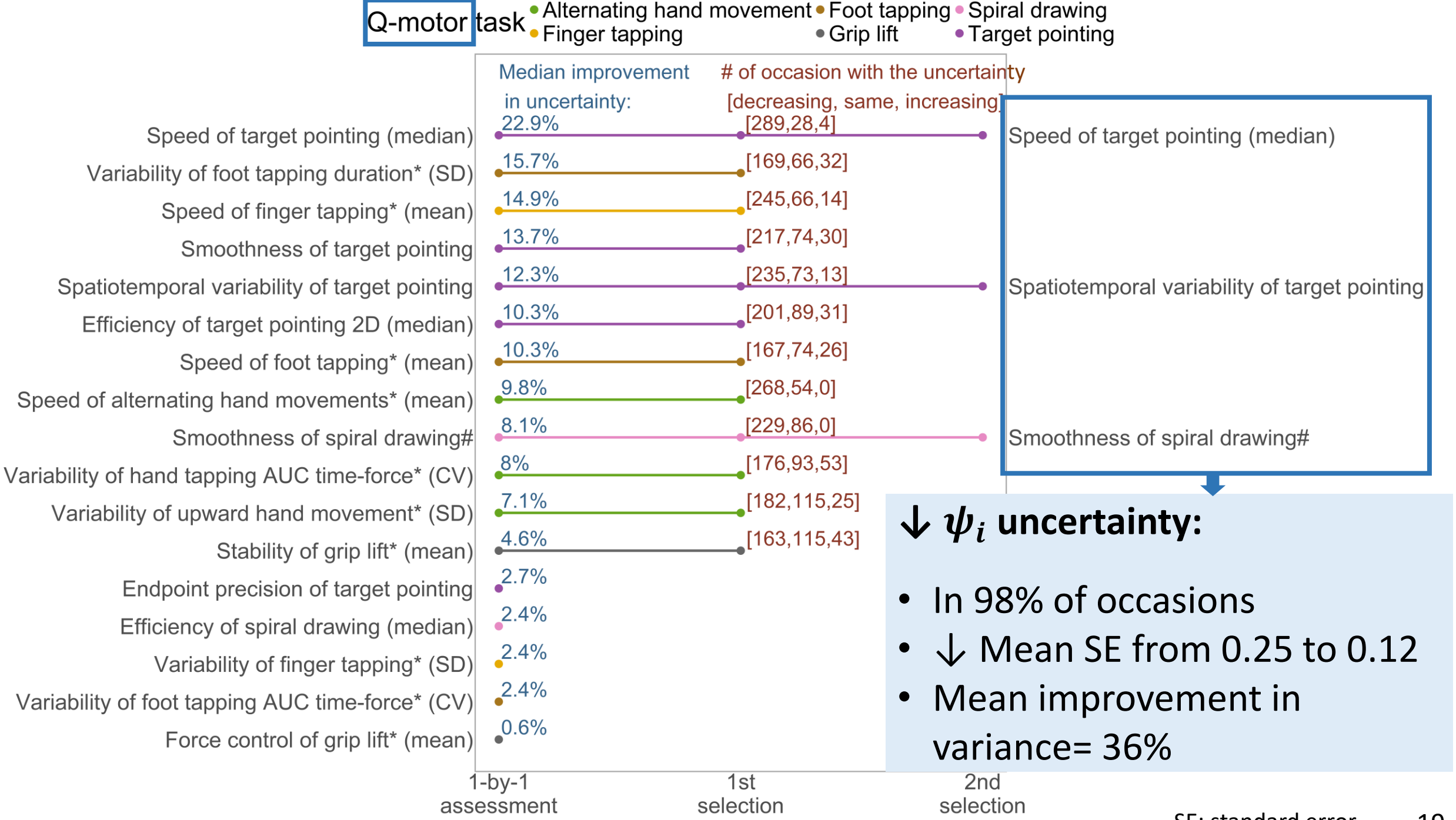


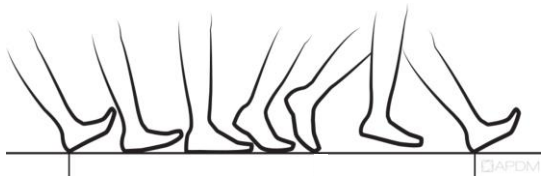
SE: standard error



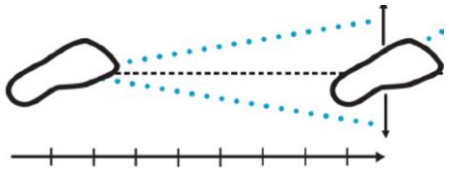
** non-dominant side of the body # Cumulative power in the 1-4 Hz frequency spectrum*

SE: standard error

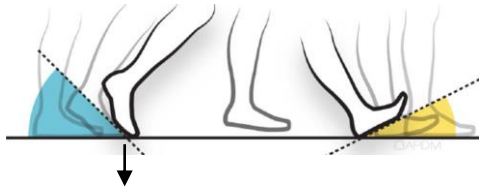
SARA-APDM-Qmotor model



Gait cycle duration (CV)



Stride length (CV)



Pitch at toe off (madn)

APDM DMO measures

Spiral Drawing

complex movement
fine motor function

Target Pointing

visually directed movement
gross motor function

- Smoothness of spiral drawing (cumulative power)

- Speed of target pointing (median)
- Spatiotemporal variability of target pointing

Q-motor DMO measures

1. APDM measures
2. Q-motor measures

Model selection for each DMO
$DMO_{im} = f(\psi_{i_{SARA}}) + \varepsilon_{im}$

Integrating within the SARA IRT model (1 by 1)
$SARA_{ij} = h(\psi_i)\,; \quad DMO_{ij} = f(\psi_i) + \varepsilon_{im}$

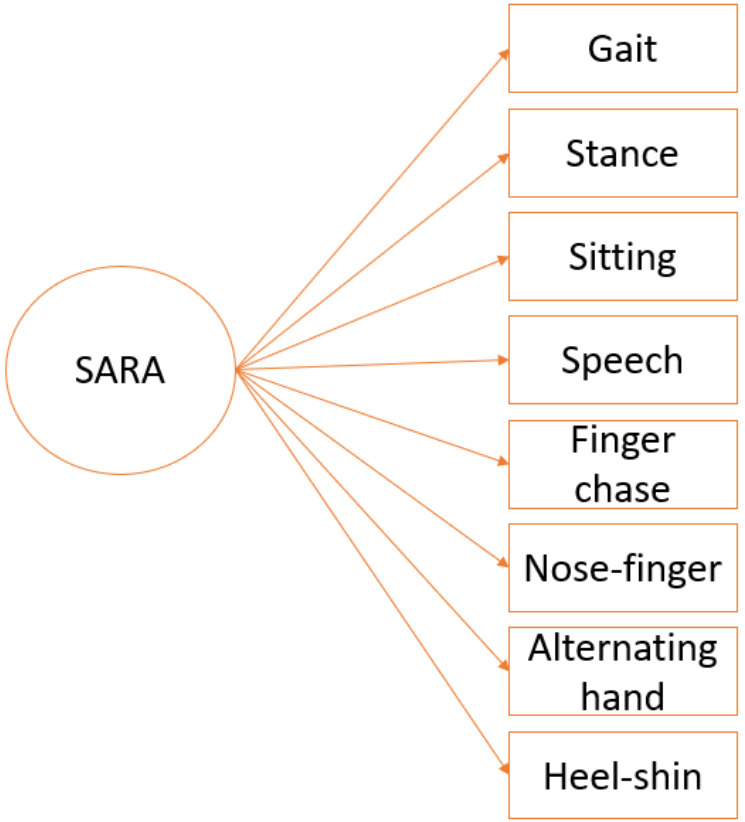
Selection of best DMO measures (1st round)

Model selected DMO measures & SARA (with residuals' correlations)

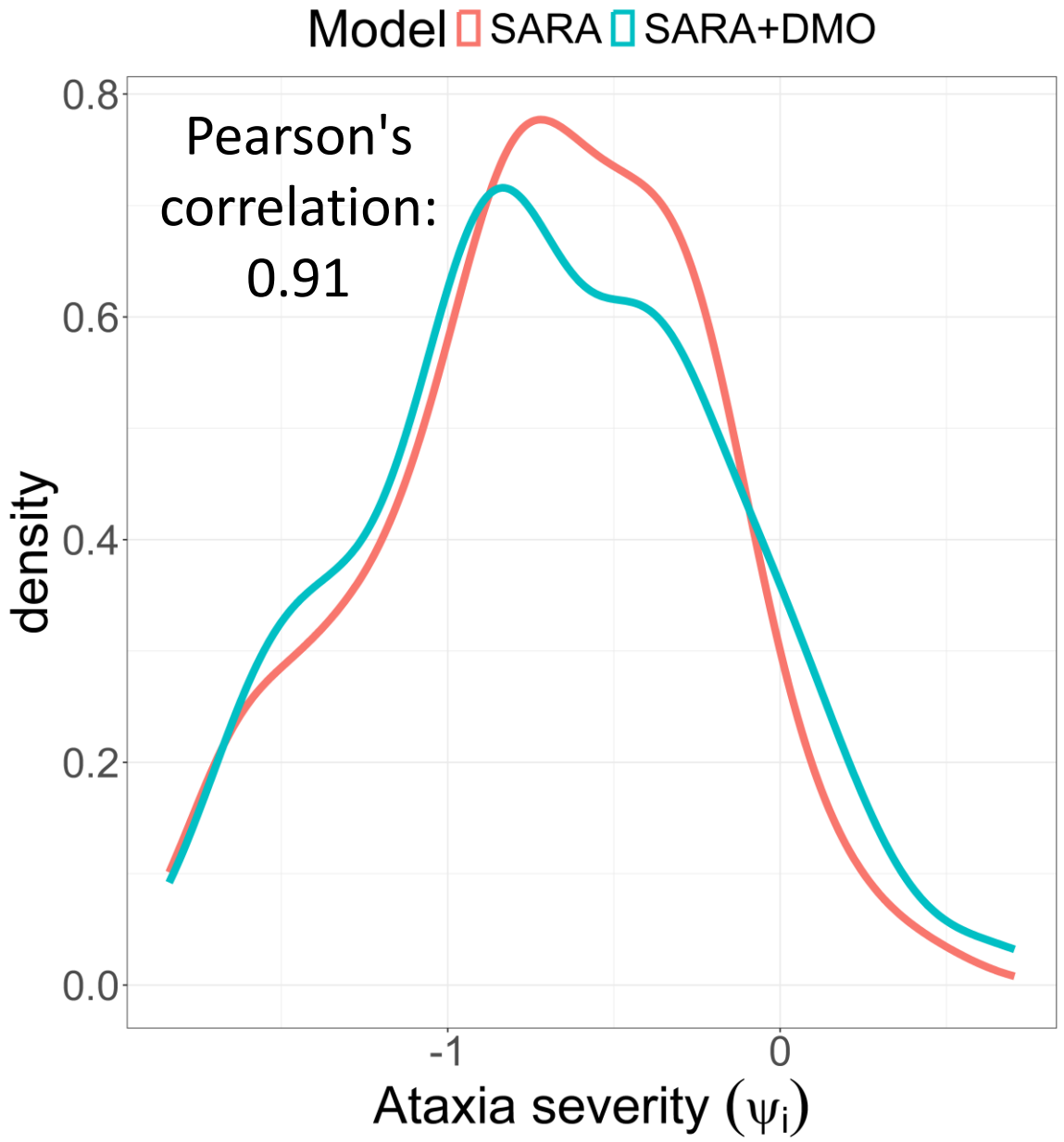
DMO measures selection (2nd round)

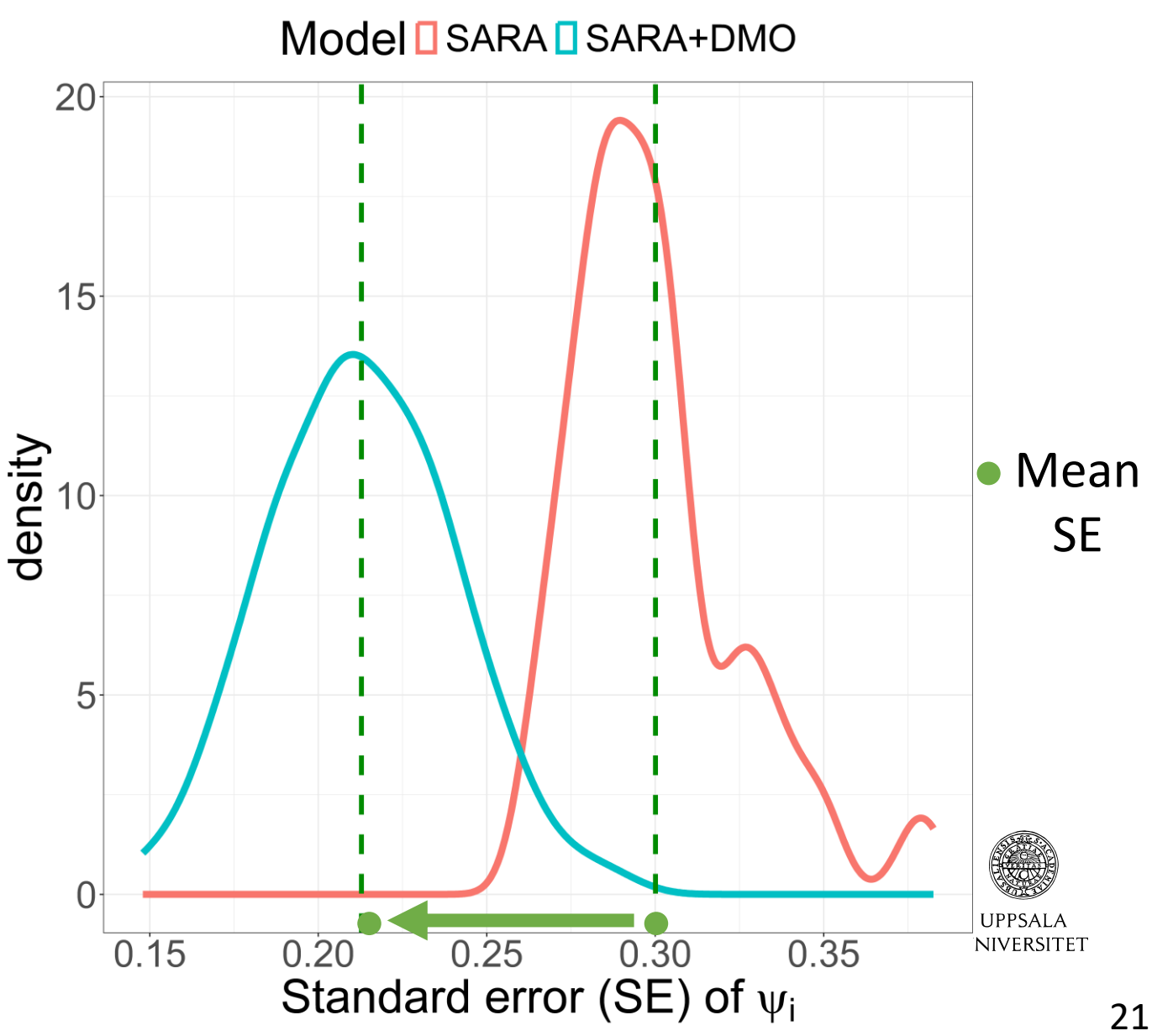
Final model for certain DMO type

SARA-APDM-Qmotor integrated model

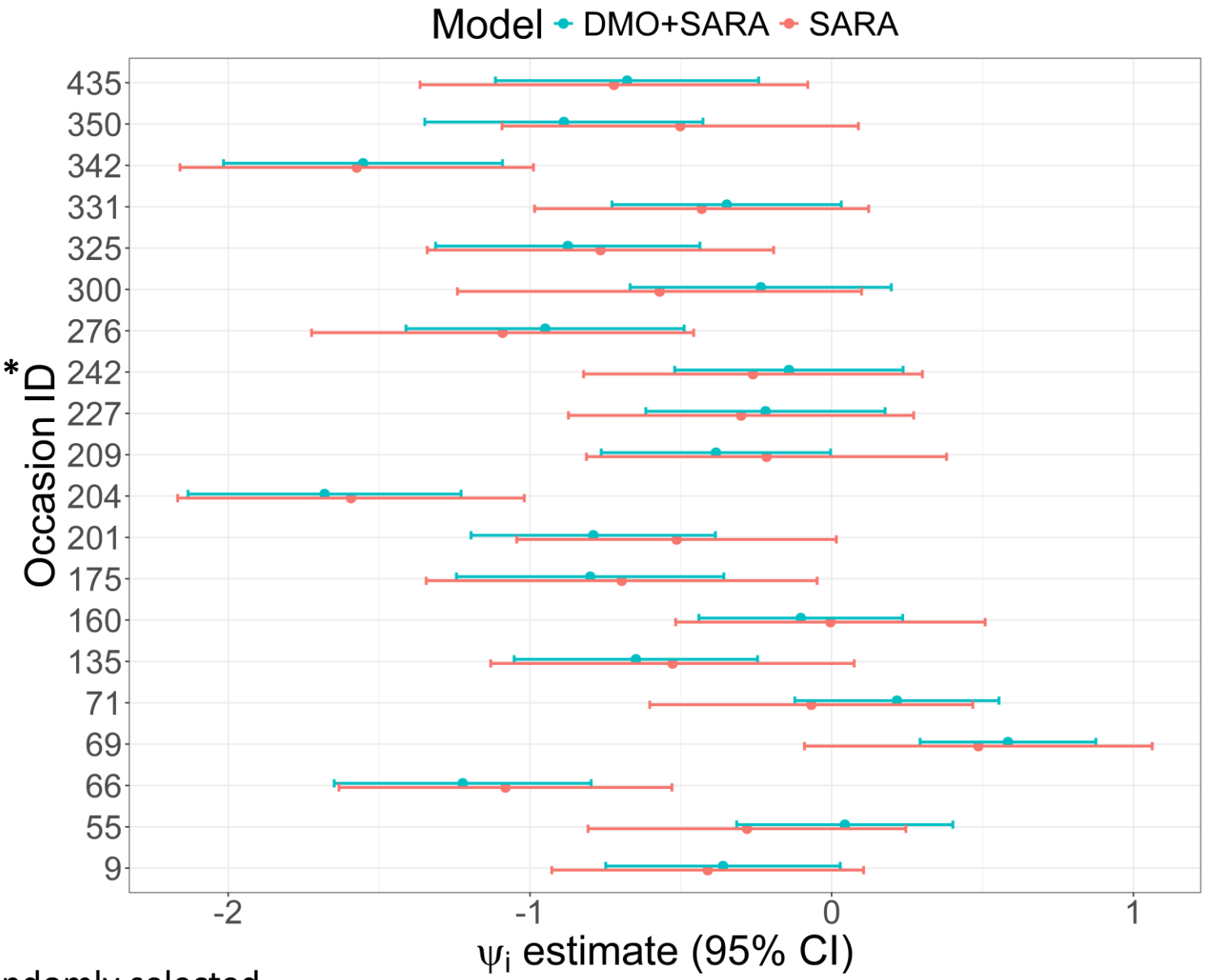


SARA-APDM-Qmotor integrated IRT model





DMOs Reduce the individual estimates uncertainty



Mean (SD) improvement in individual variance: 49% (10%)

Sample size can decrease with up to 49%#, depending on the design and analysis

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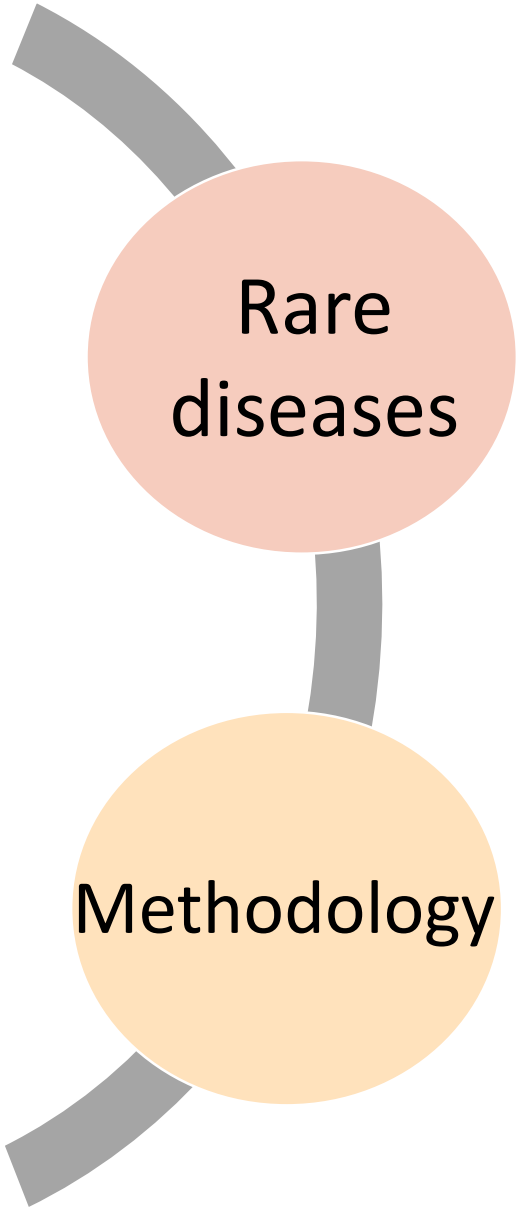
* Randomly selected

assuming a t-test evaluation

Study contributions



Digital-motor outcomes improve the SARA assessment of ataxia severity:

- **Reduce uncertainty**

Positive expectations:

- Improve power
- Enhance feasibility of n-of-1/ n-of-few trials

Joint IRT framework for modeling:

- Multiple outcomes with both categorical and **continuous** data

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- Rebecca Schüle

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