

# The importance of natural history and biomarker studies in the ataxias - Using data from the European Friedreich Ataxia Consortium for Translational Studies (EFACTS)

*Jörg B. Schulz*

*Department of Neurology*

*RWTH Aachen*

Leptokaria May 20th, 2023

# The EFACCTS Registry

European Friedreich's Ataxia Consortium for Translational Studies

EFACCTS  
Clinical Sites:  
17 sites in  
11 countries



Country	Institute/Hospital	Principal Investigator
Austria	Medizinische Universität Innsbruck	Prof. Dr. Sylvia Bösch
Belgium	Université libre de Bruxelles	Dr. Gilles Naeije
Czech Republic	Motol University Hospital, Prague	Prof. Dr. Martin Vyhálek
France	Hôpital Pitié Salpêtrière, Paris	Prof. Dr. Alexandra Durr
	Hôpitaux Universitaires de Strasbourg	Prof. Dr. Mathieu Anheim
Germany	Universitätsklinikum RWTH Aachen	Prof. Dr. Jörg B. Schulz Prof. Dr. Kathrin Reetz
	Universitätsklinikum Bonn	Prof. Dr. Thomas Klockgether
	Klinikum der Universität München	Prof. Dr. Thomas Klopstock
	Universitätsklinikum Tübingen	Prof. Dr. Ludger Schöls
Greece	National and Kapodistrian University of Athens	Prof. Dr. Georgios Koutsis
Ireland	Tallaght University Hospital, Dublin	Prof. Dr. Richard Walsh Prof. Dr. Sinead Murphy
Italy	Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan	Prof. Dr. Caterina Mariotti
	Ospedale Pediatrico Bambino Gesù, Rome	Prof. Dr. Enrico Bertini
Netherlands	Radboudumc, Nijmegen	Prof. Dr. van de Warrenburg
Spain	Sant Joan de Déu Children's Hospital, Barcelona	Prof. Dr. Francesc Palau
	Hospital Universitario La Paz, Madrid	Prof. Dr. Francisco Rodríguez
United Kingdom	University College London	Prof. Dr. Paola Giunti

# The EFACTS Registry

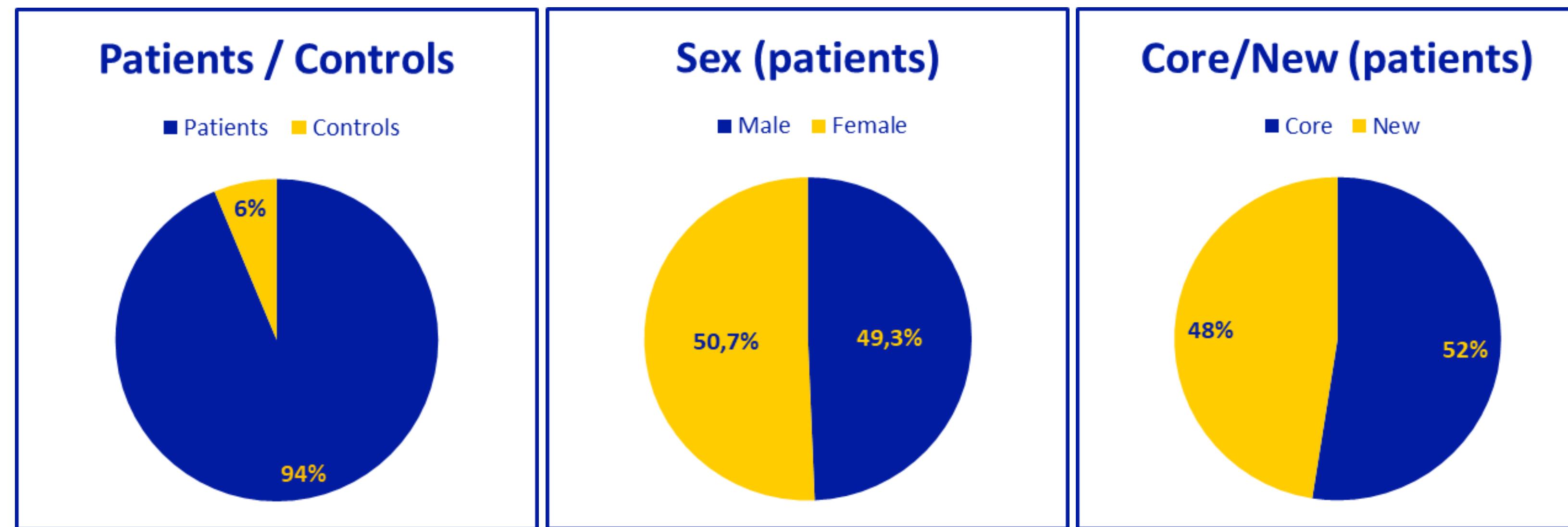
## Demographic Data

Status 05 May 2023:

**1143 FRDA patients**  
**76 control subjects**

**579 female patients**  
**564 male patients**

**600 core patients \***  
**543 new patients**



(\* Core patients recruited before 01 May 2013, new patients afterwards)

# The EFACTS Registry

## Age Distribution

### All Patients

192	<18 y at BL
74	<18 y 2023

### Core Patients

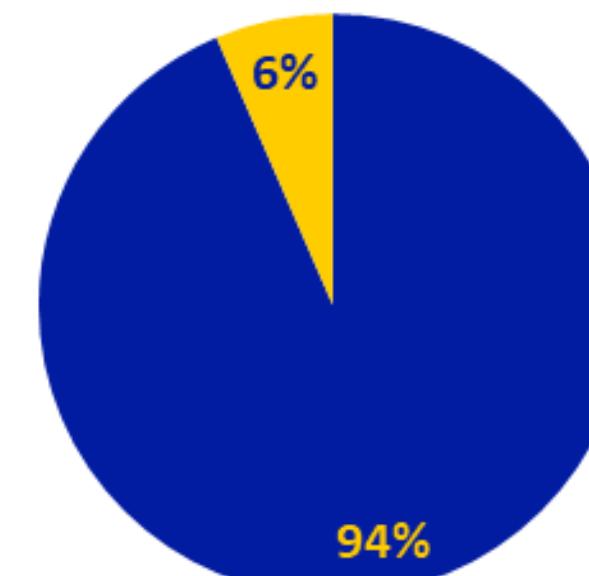
59	<18 y at BL
3	<18 y 2023

### New Patients

133	<18 y at BL
71	<18 y 2023

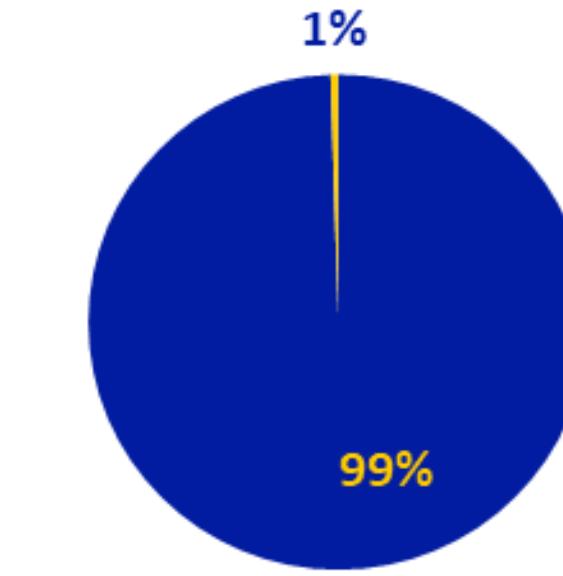
#### Underage patients (all patients)

■ ≥18y 2023 ■ <18 y 2023



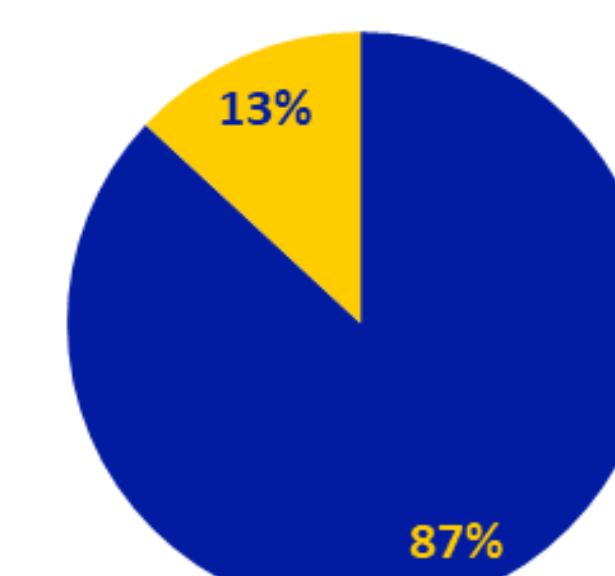
#### Underage patients (core)

■ ≥18y 2023 ■ <18 y 2023



#### Underage patients (new)

■ ≥18y 2023 ■ <18 y 2023

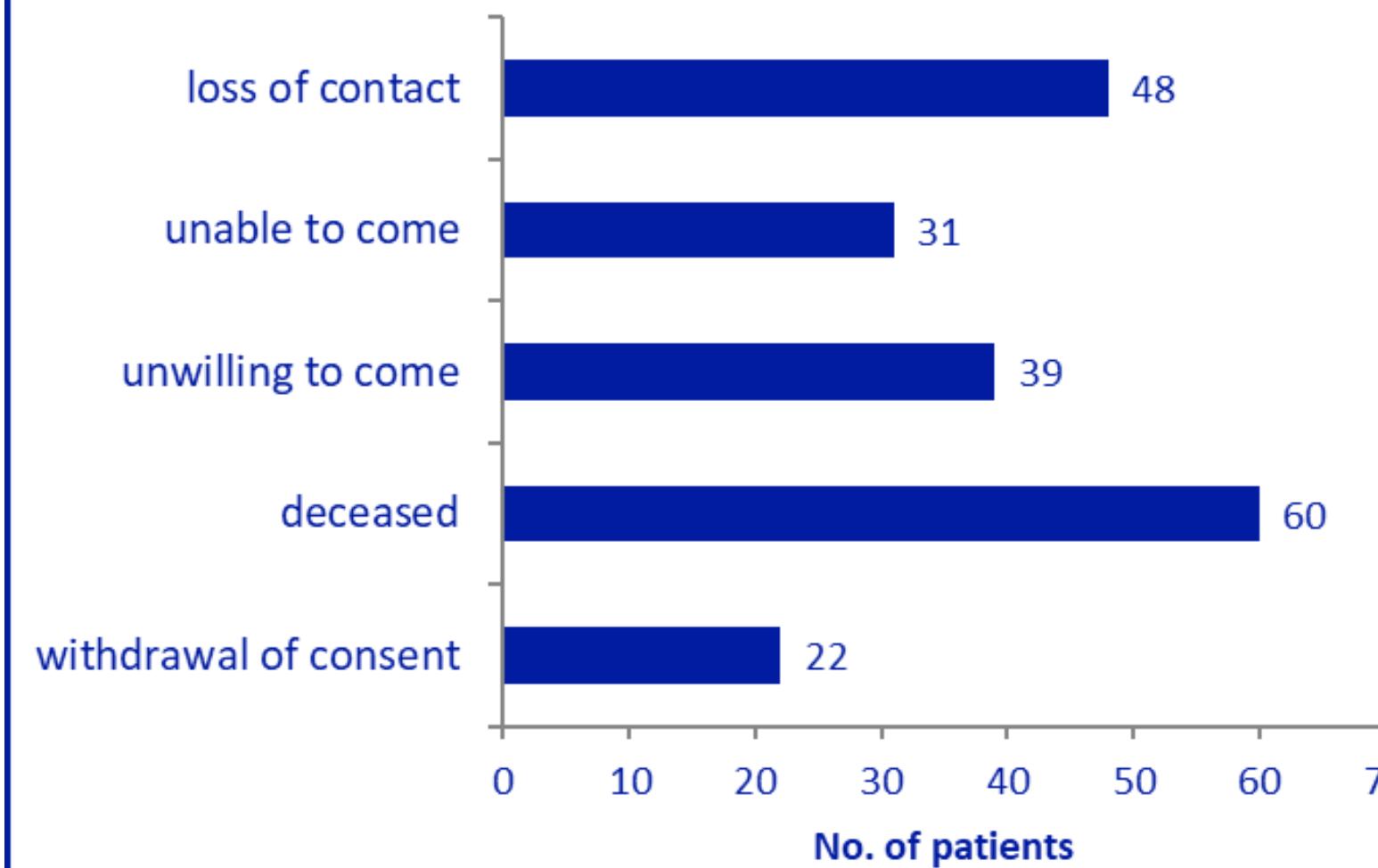


# The EFACTS Registry

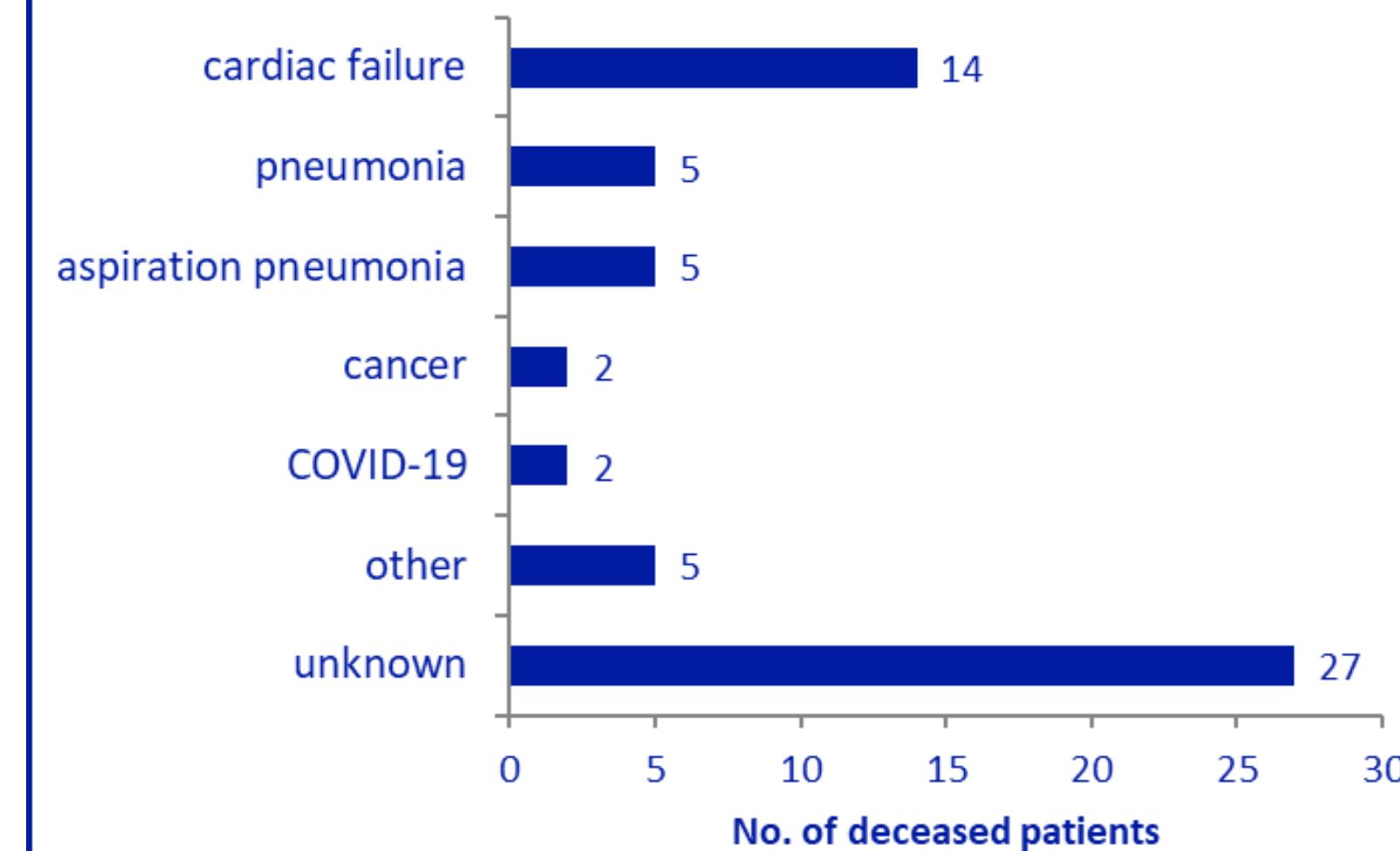
## Terminations

Status 05 May 2023: **200 terminations**

**Reasons for terminations**

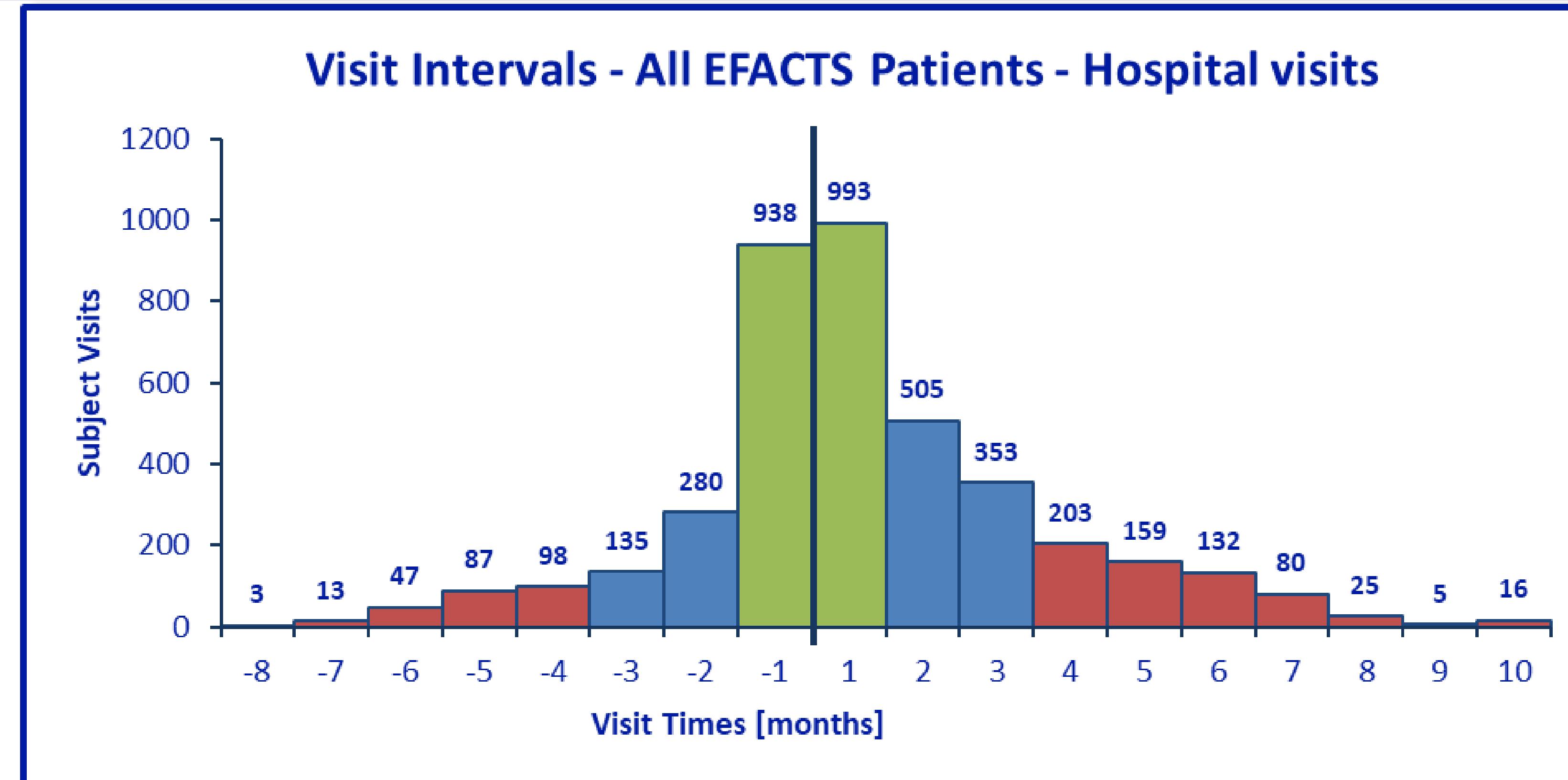


**Cause of death**



# The EFACTS Registry

## Visit Intervals

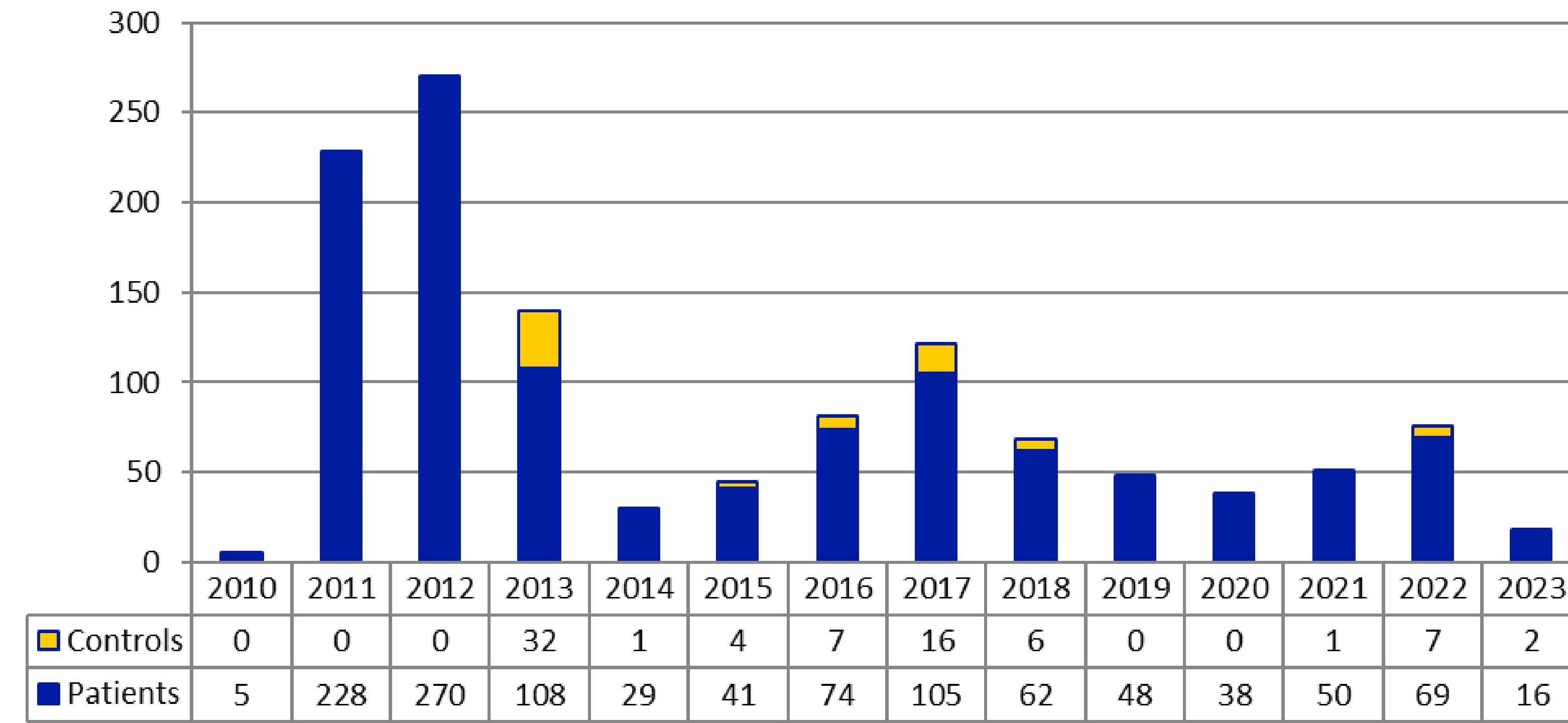


<b>1 month interval:</b>	<b>47.4 %</b>
<b>3 month interval:</b>	<b>31.3 %</b>
<b>&gt; 3 month interval:</b>	<b>21.3%</b>

# The EFACTS Registry

## Visit Numbers

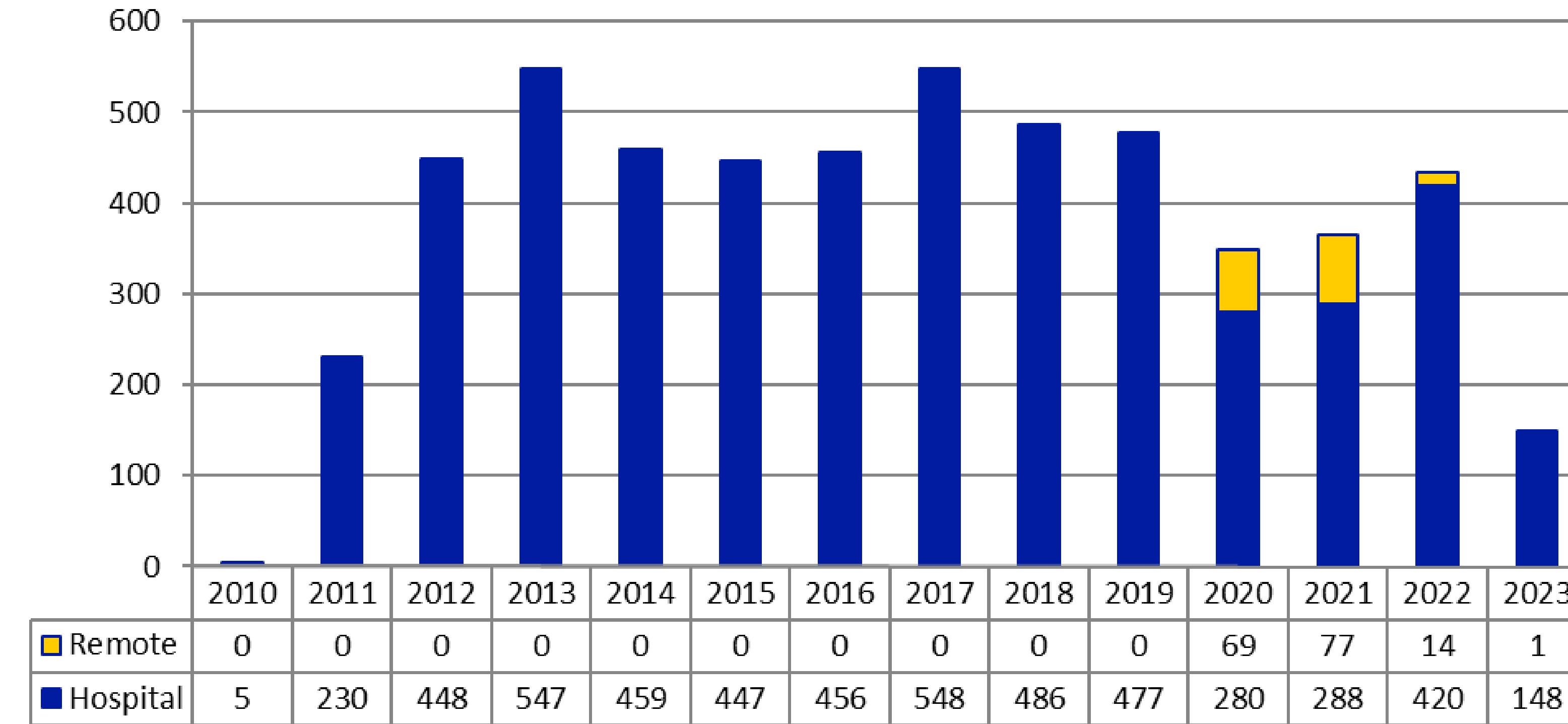
### EFACTS Recruitment



# The EFACTS Registry

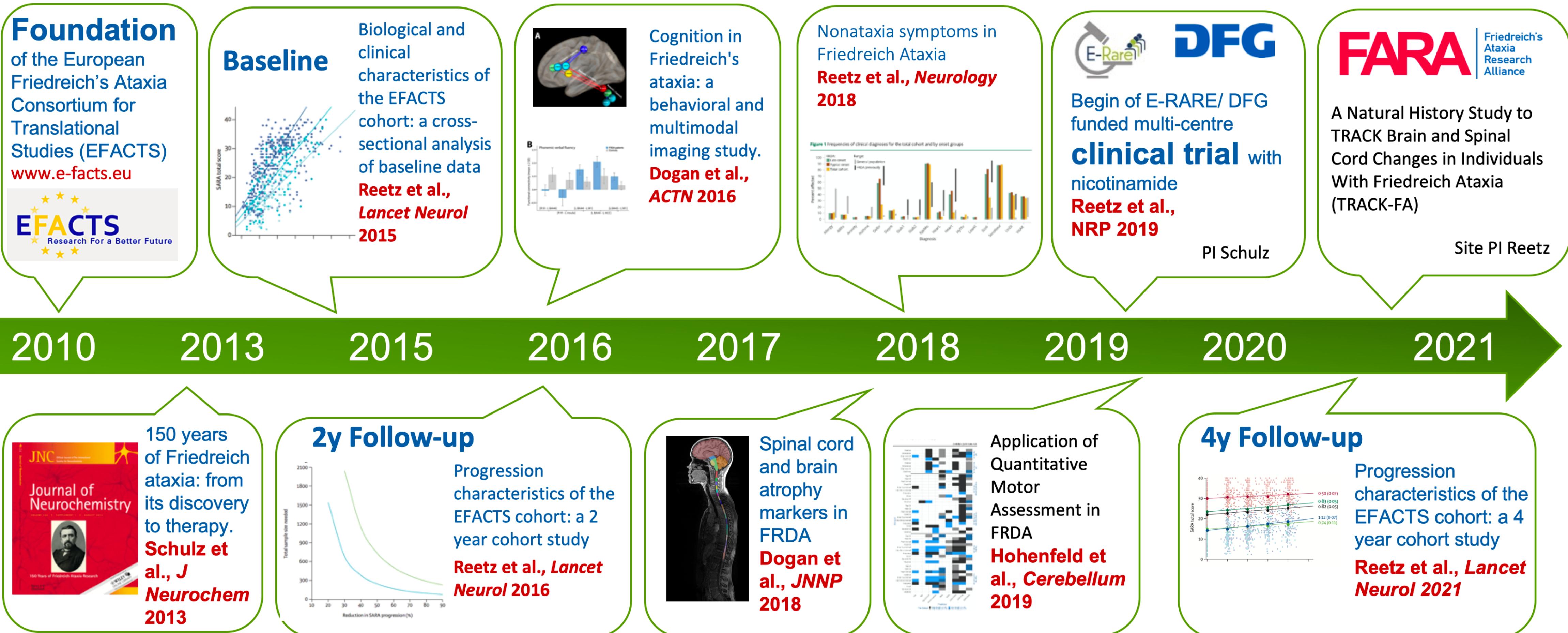
## Visit Numbers

### EFACTS Hospital and Remote Visit Numbers

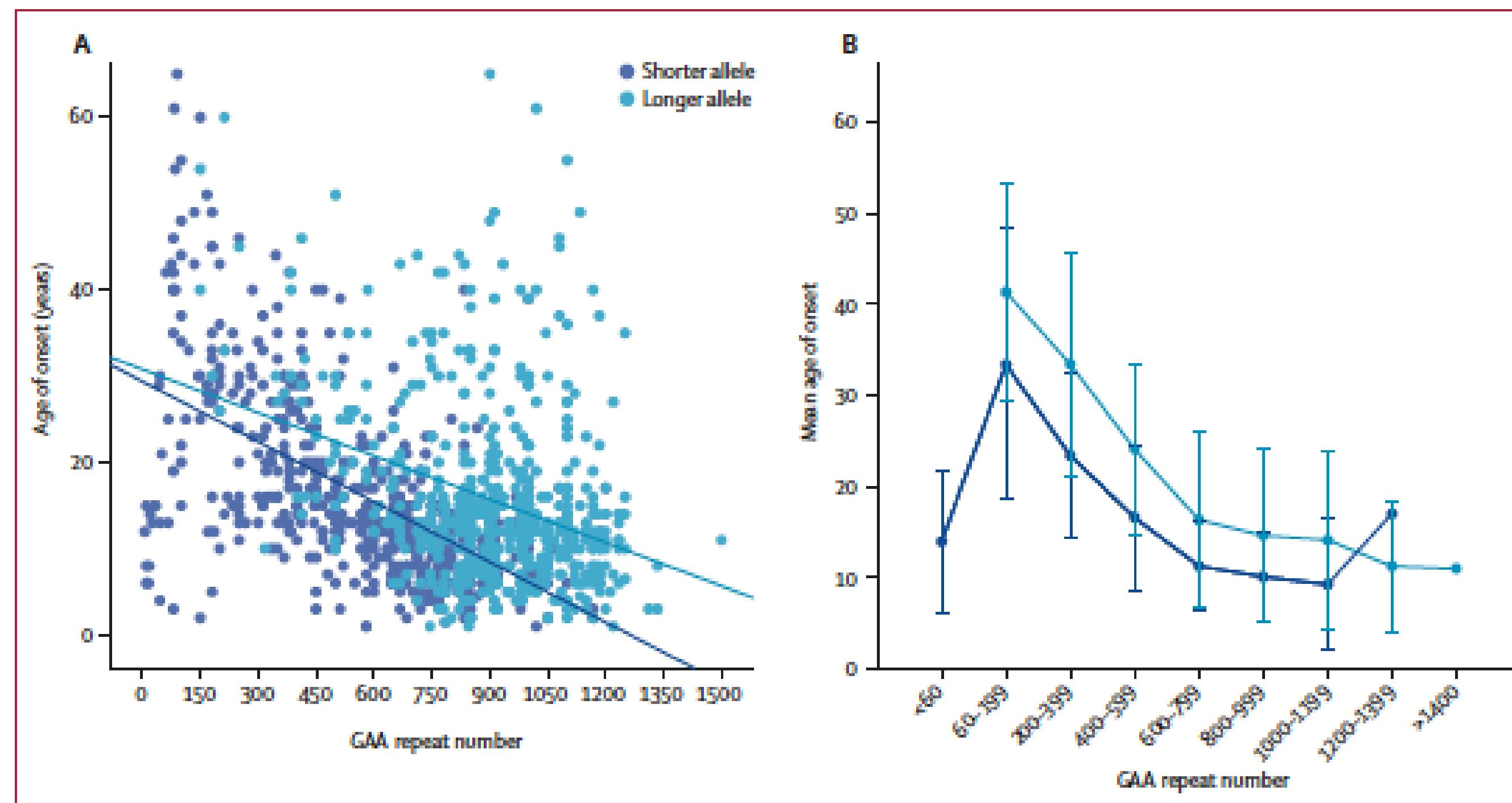


# The EFACTS Registry

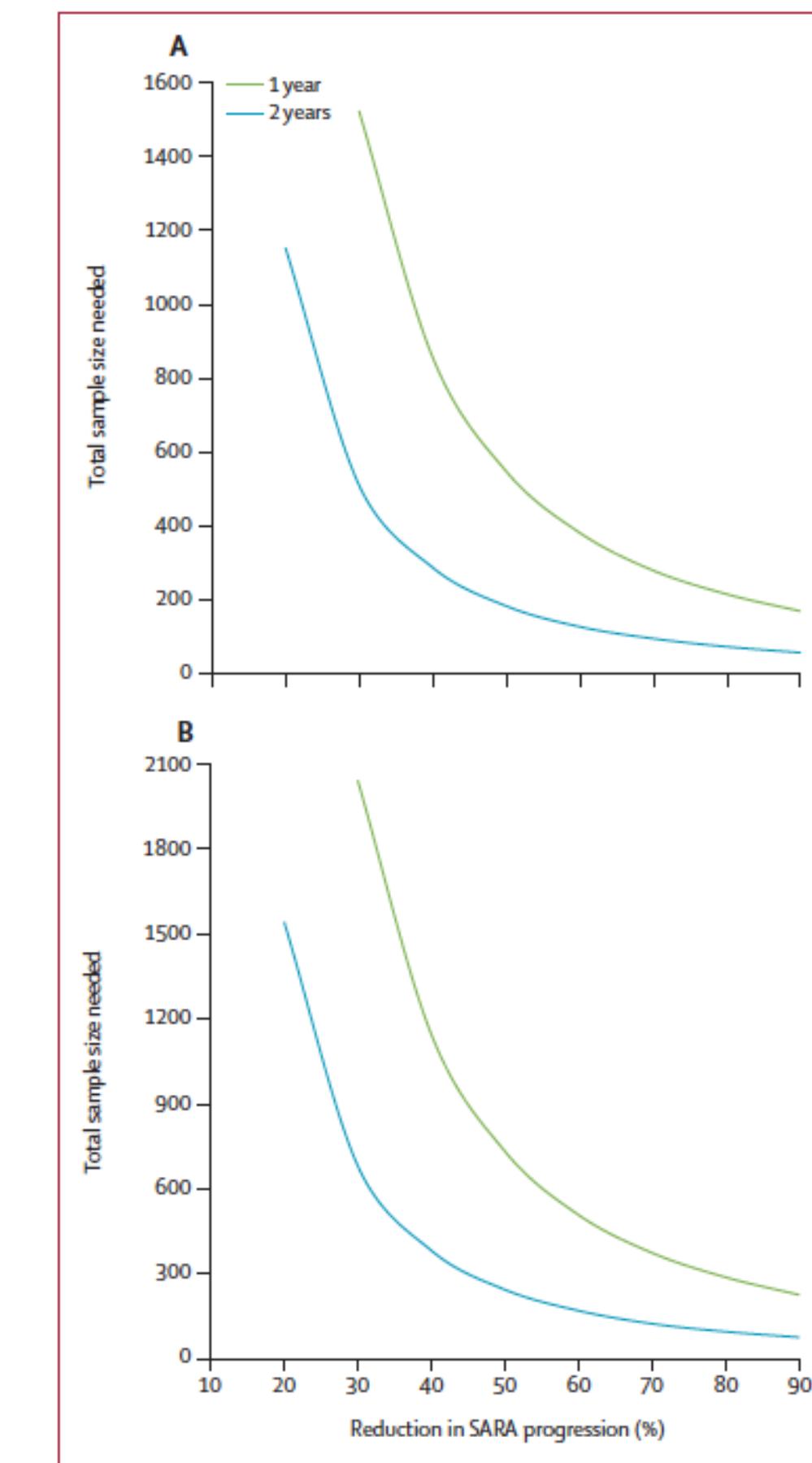
## Chronological overview - from natural history studies to clinical trials



# The EFAC TS Registry

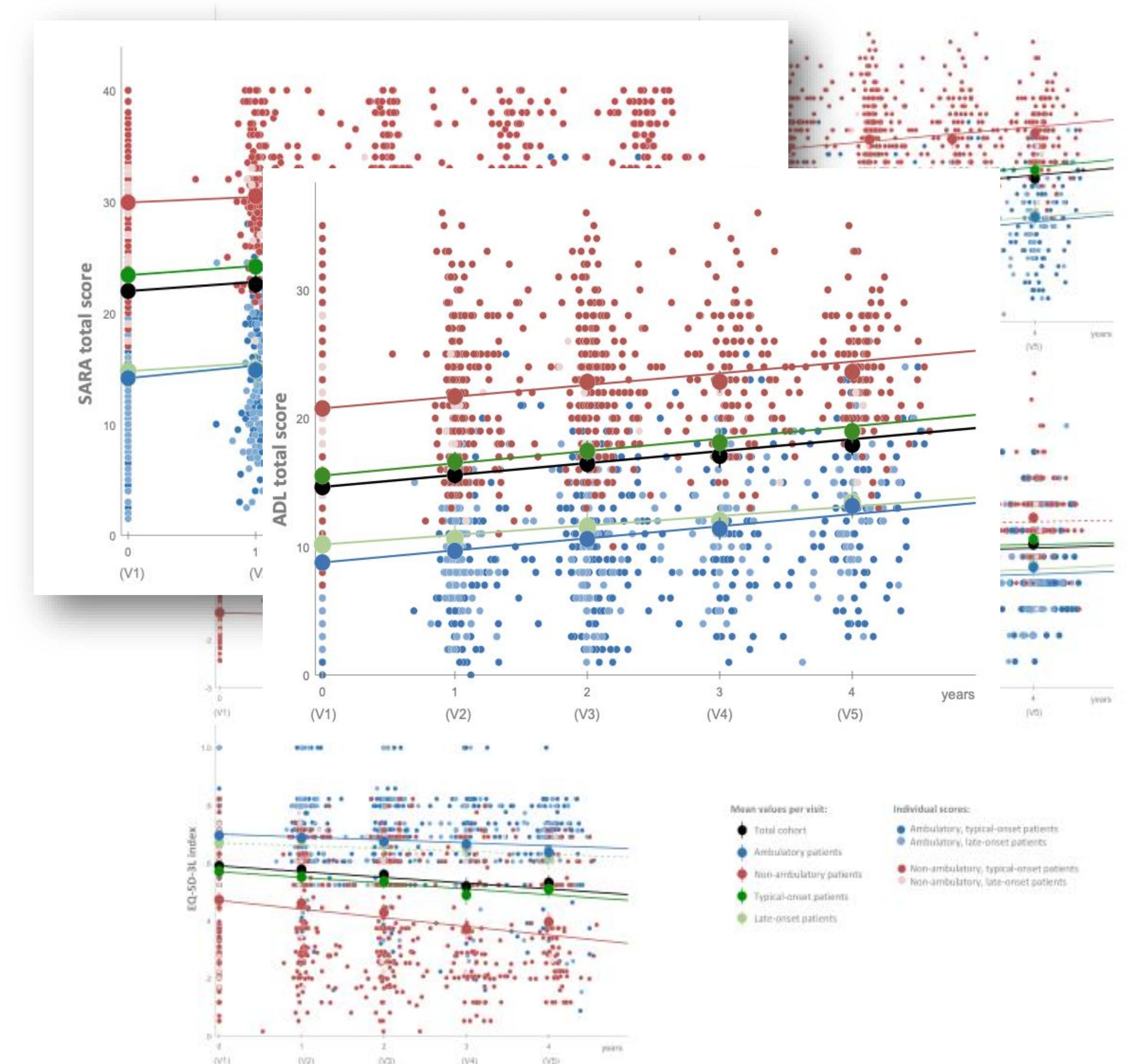
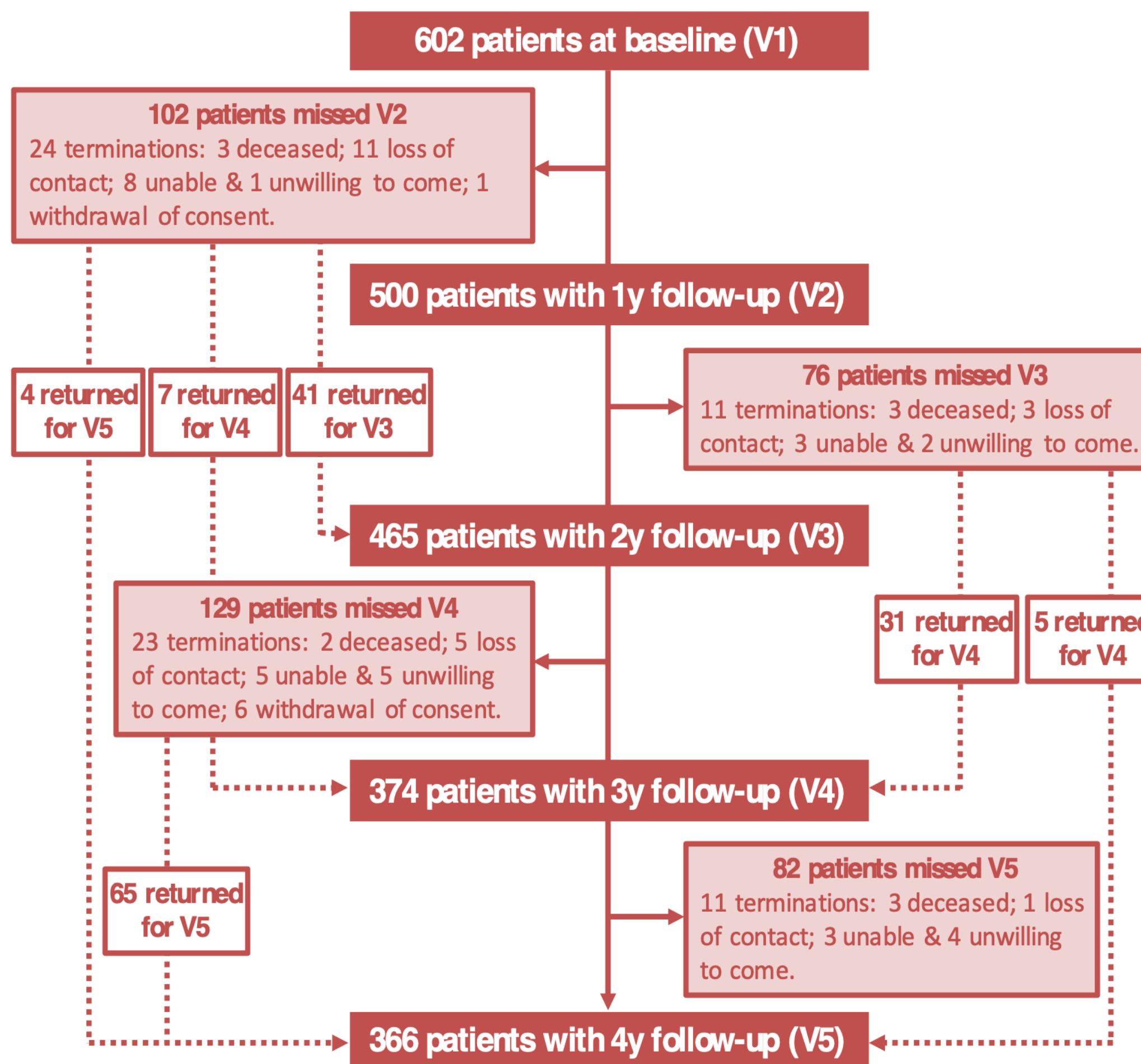


Reetz et al., Lancet Neurol 2015;

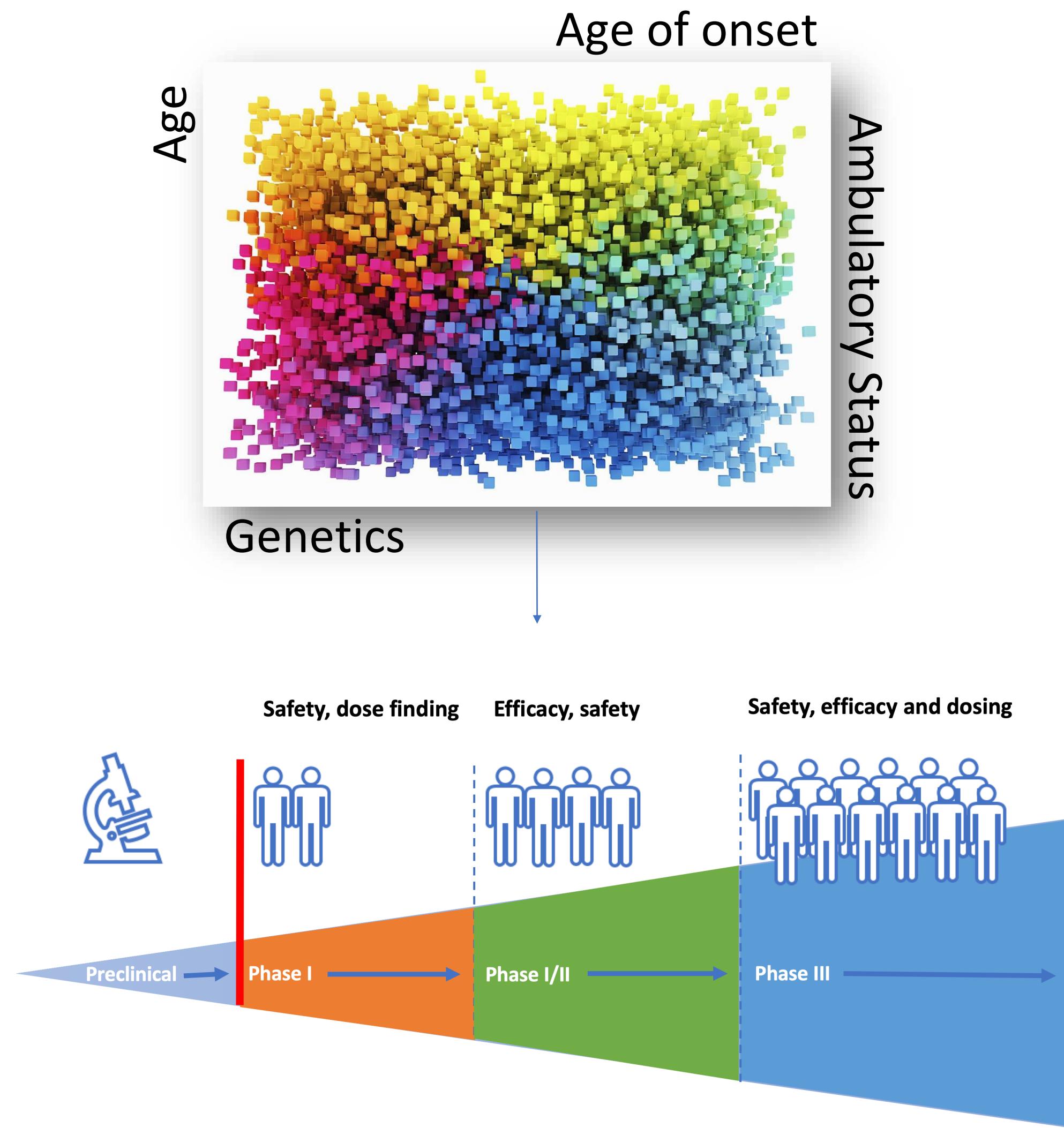


Reetz et al., Lancet Neurol 2016;

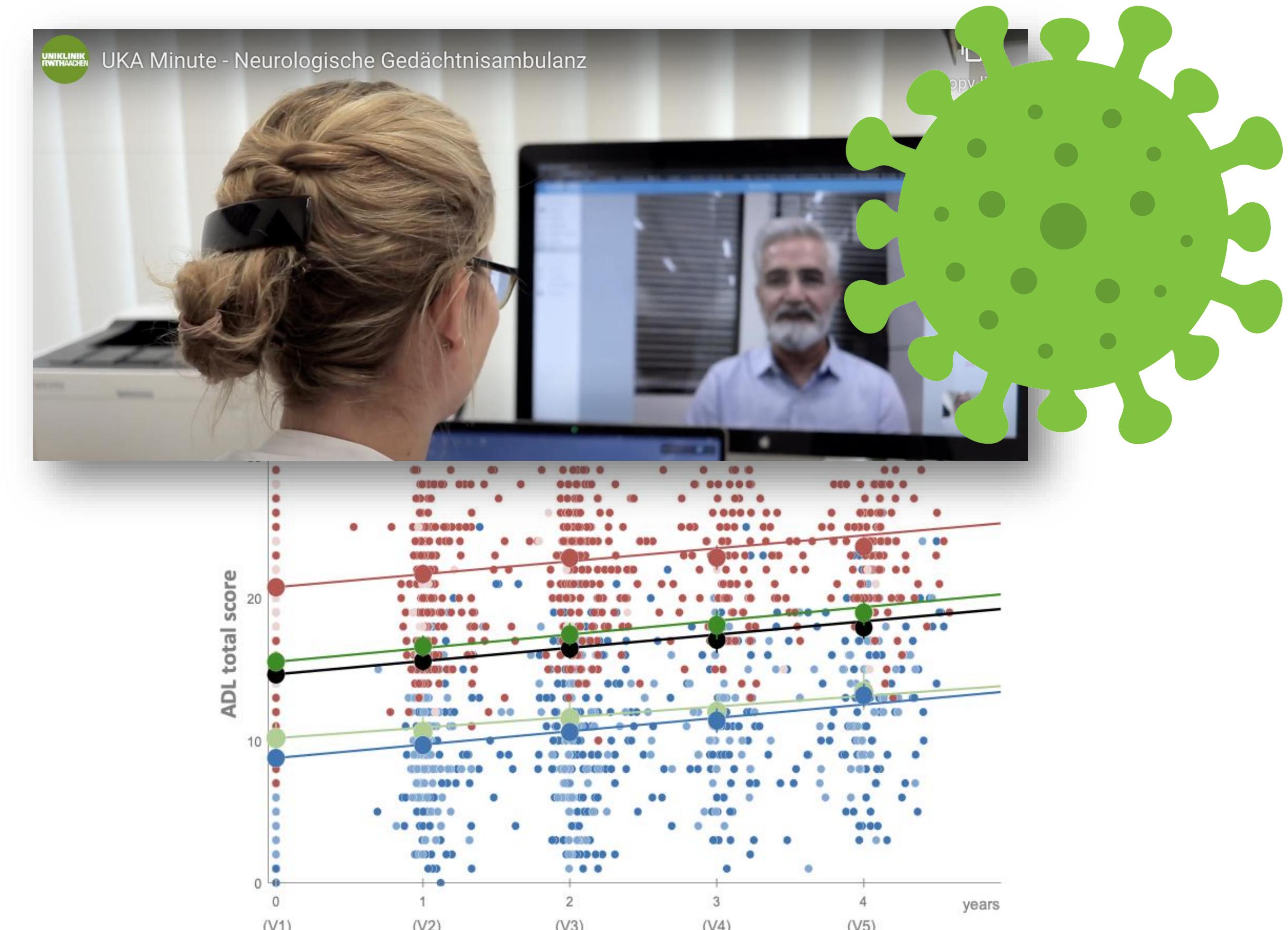
# 4y Natural History Data



# Stratification

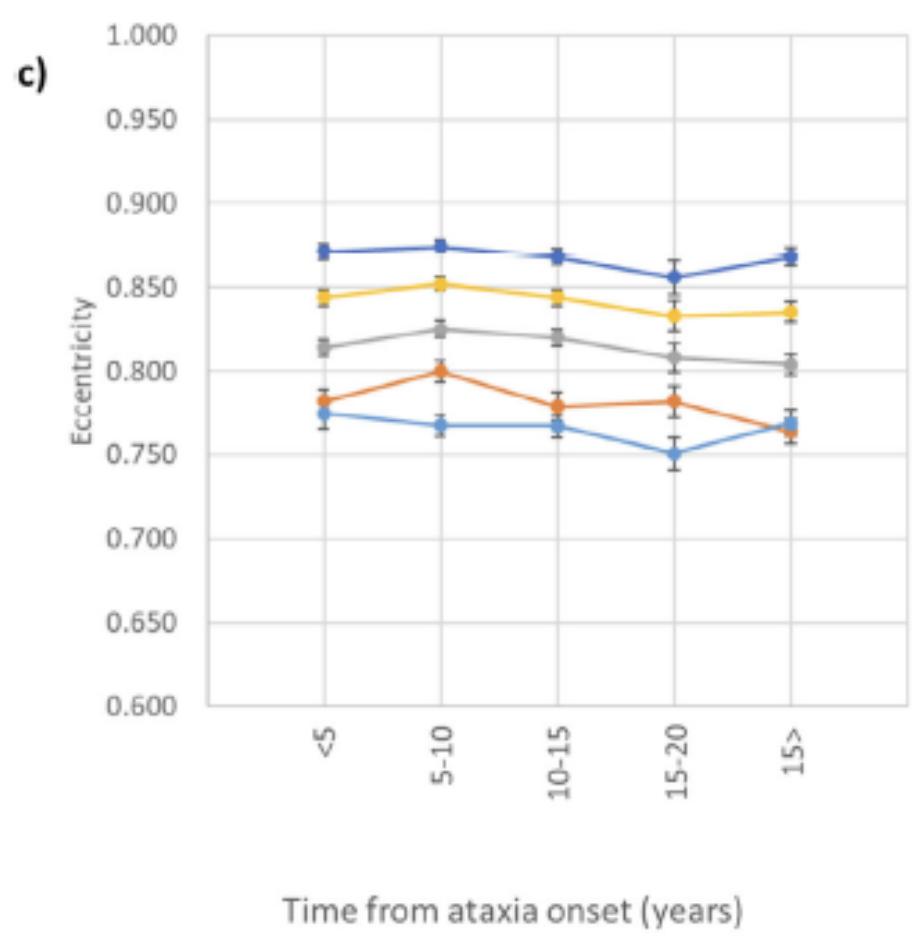
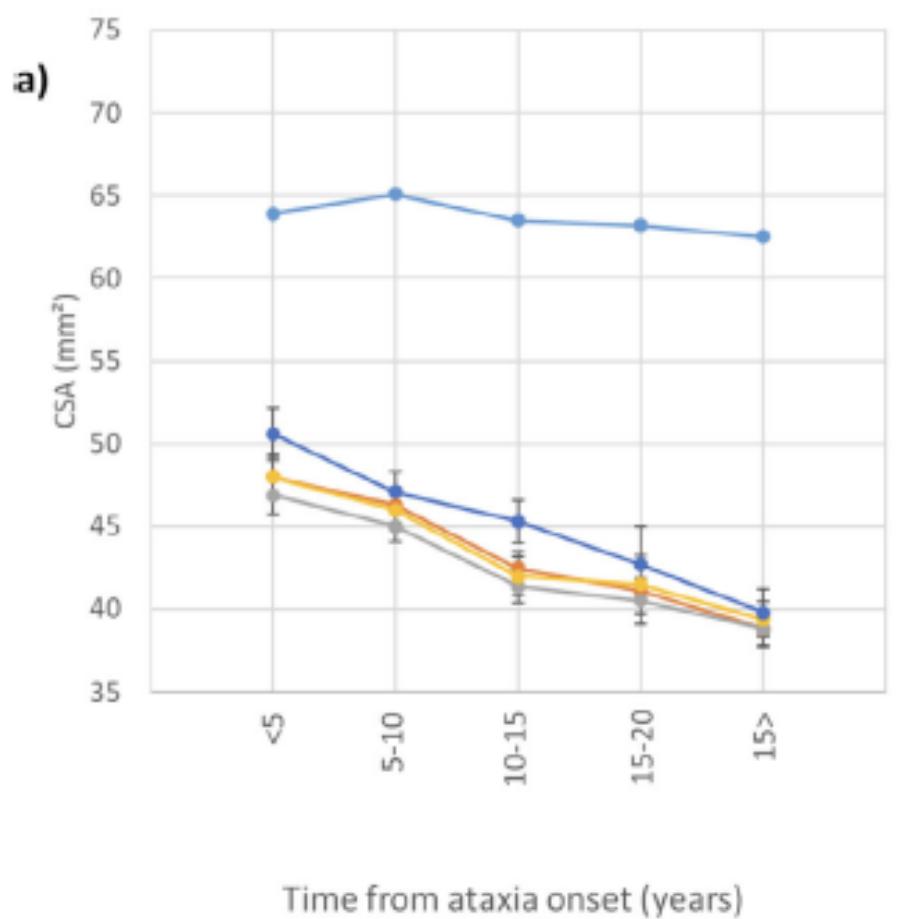
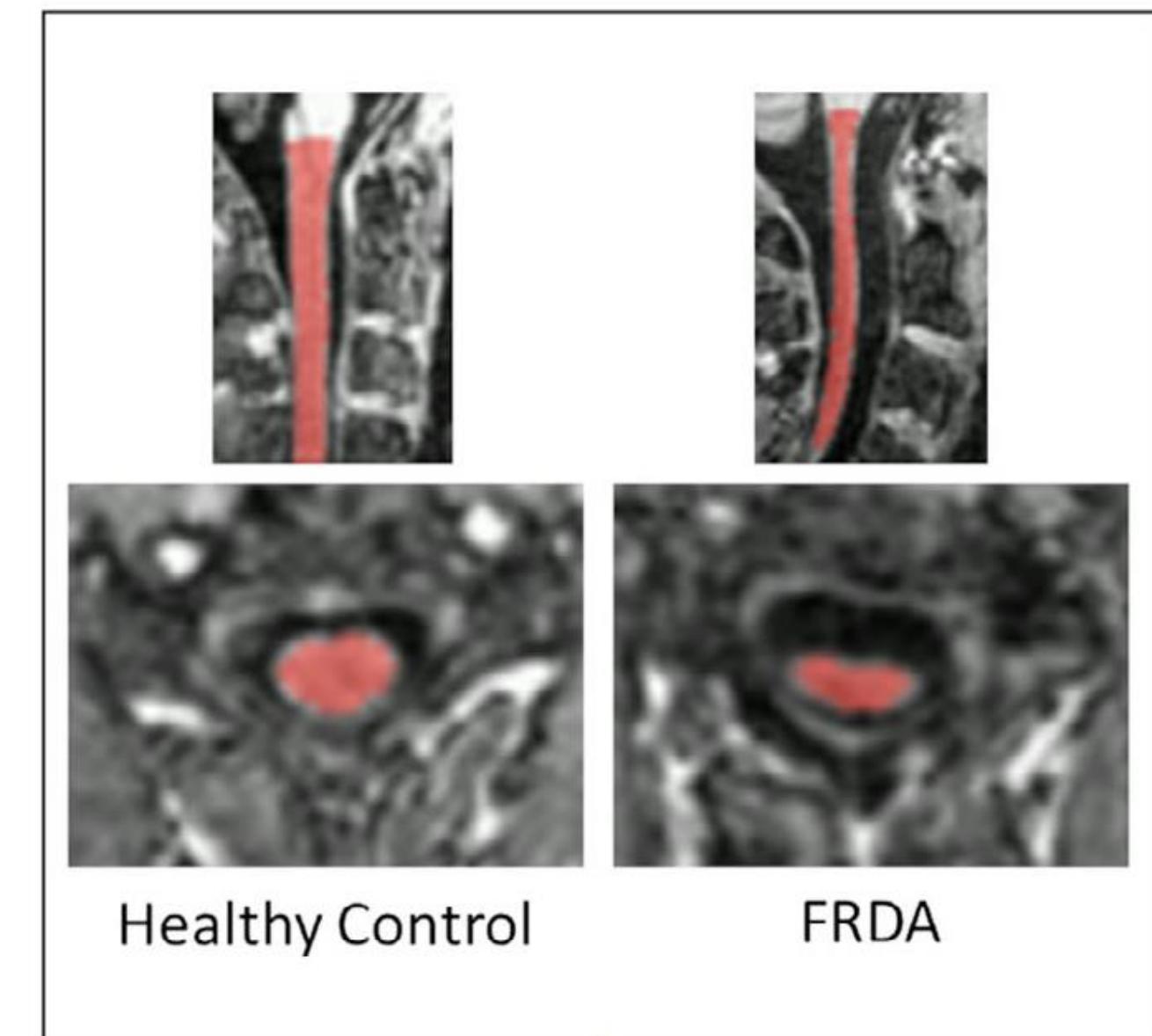
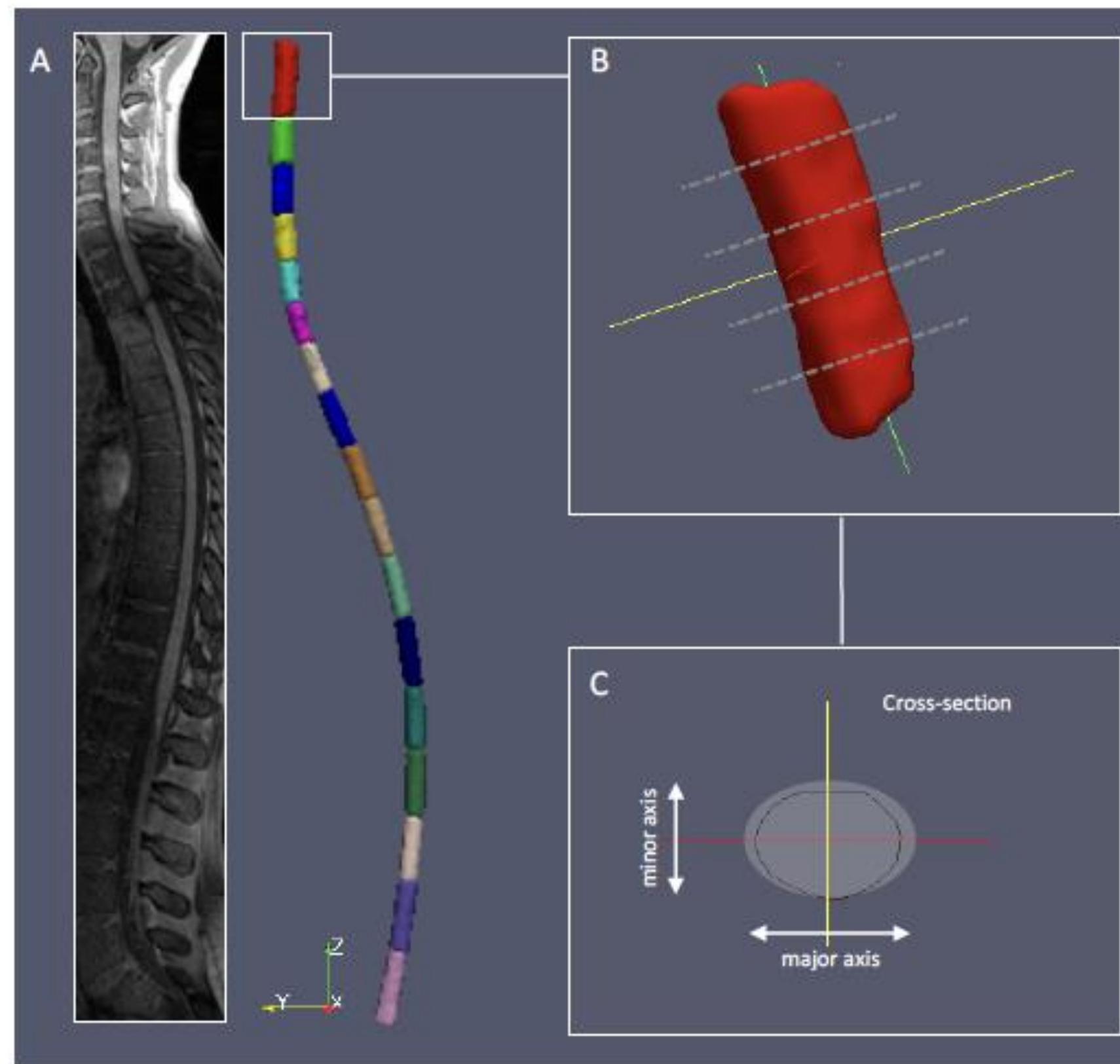


# Patient-reported outcome measures



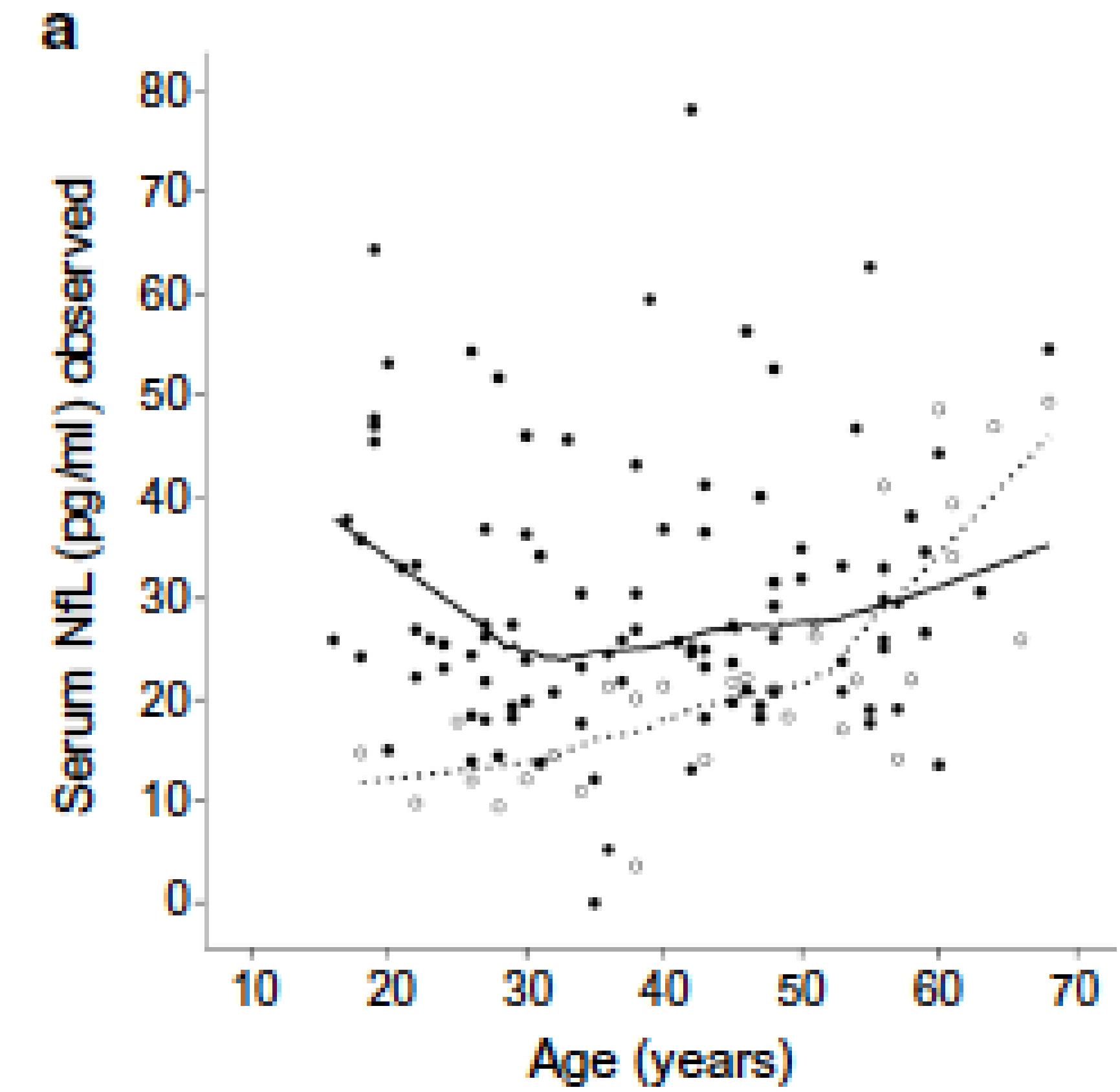
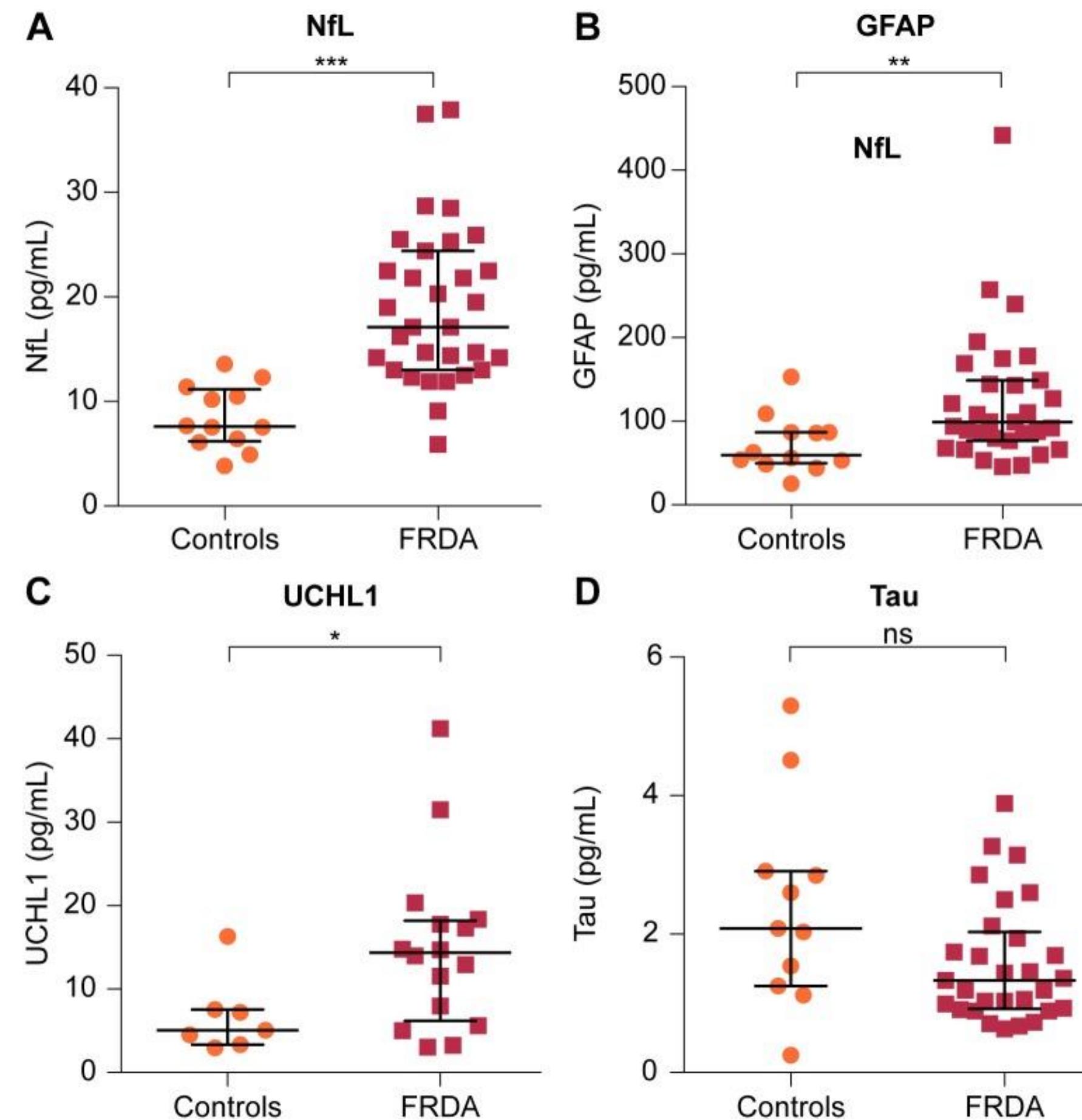
# The EFAC TS Registry

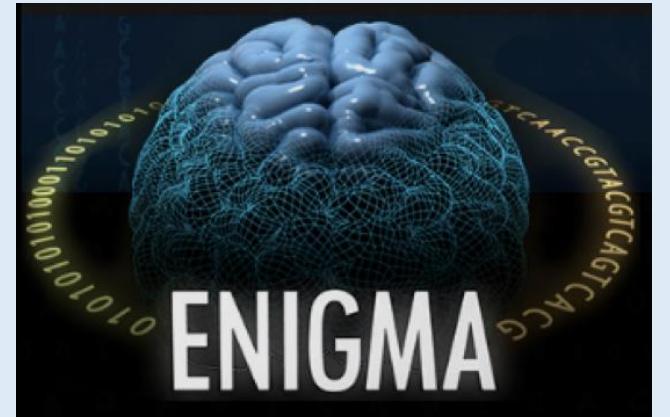
## Biomarkers



# The EFAC TS Registry

## Biomarkers





**ENIGMA ATAXIA**  
Dr. Ian Harding

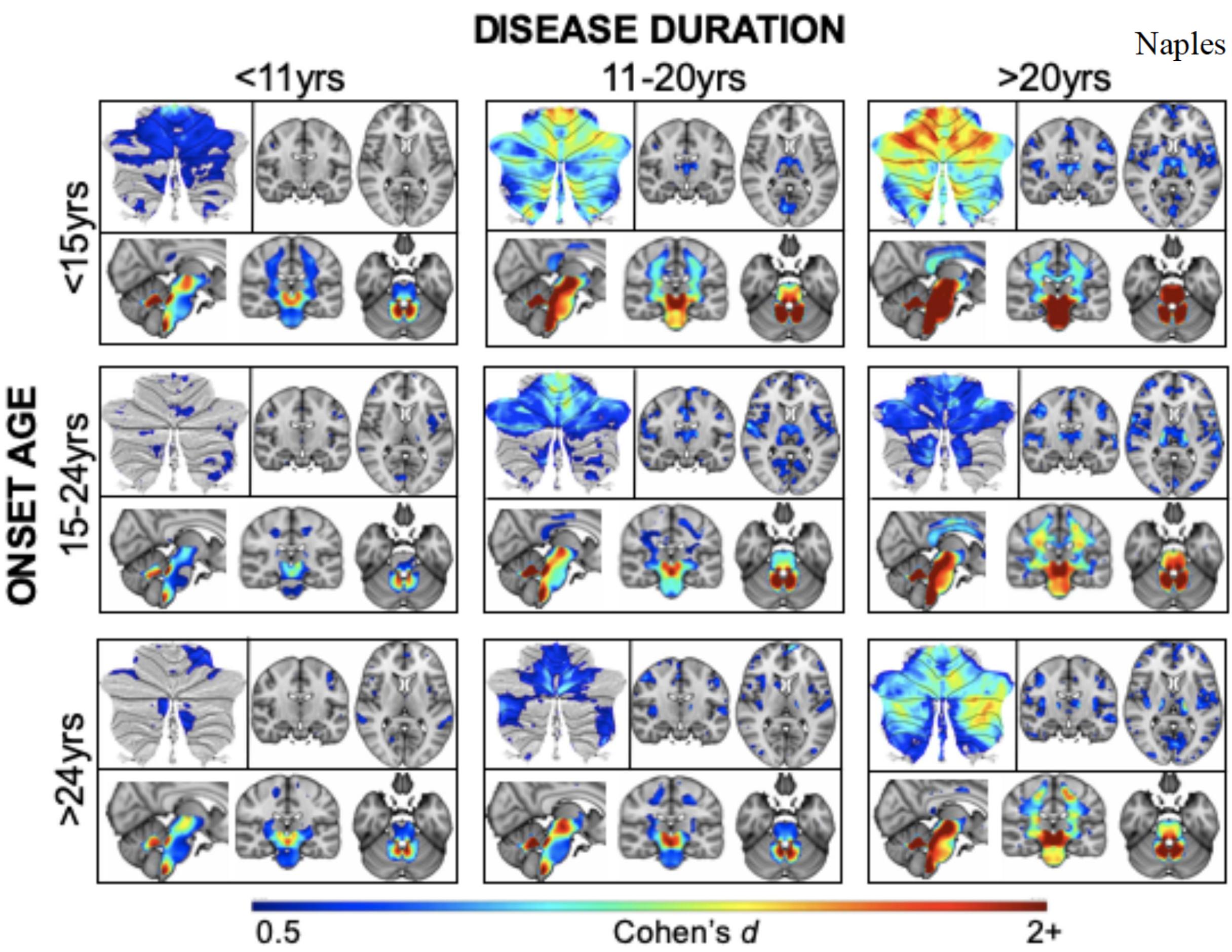
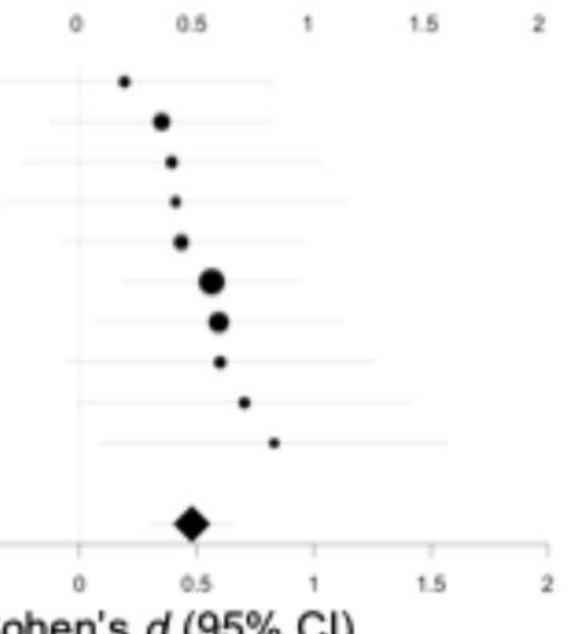
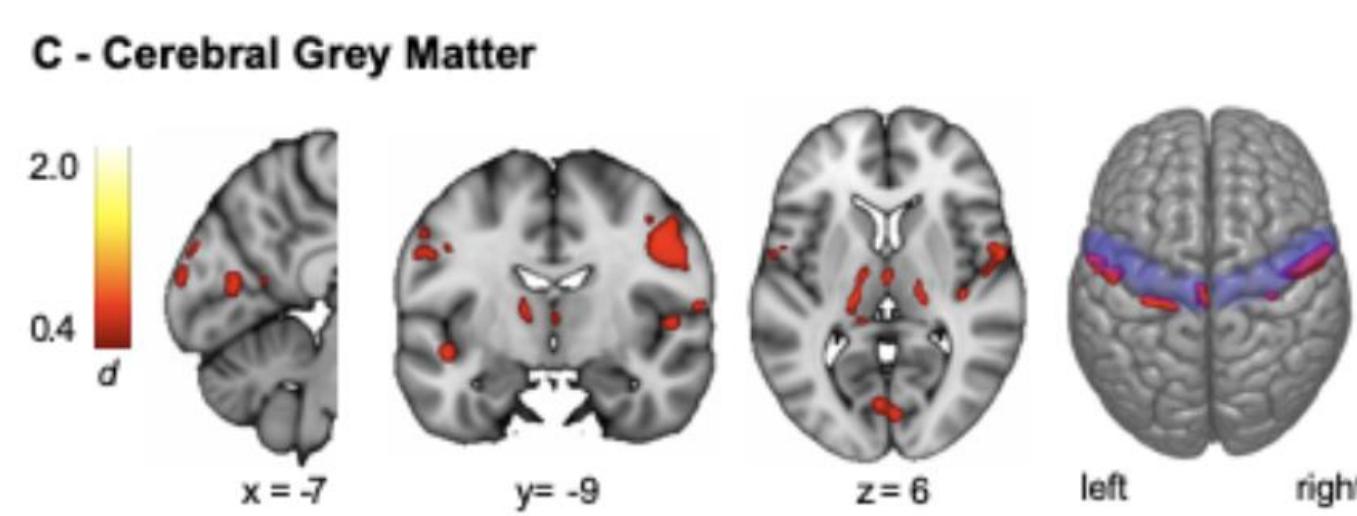
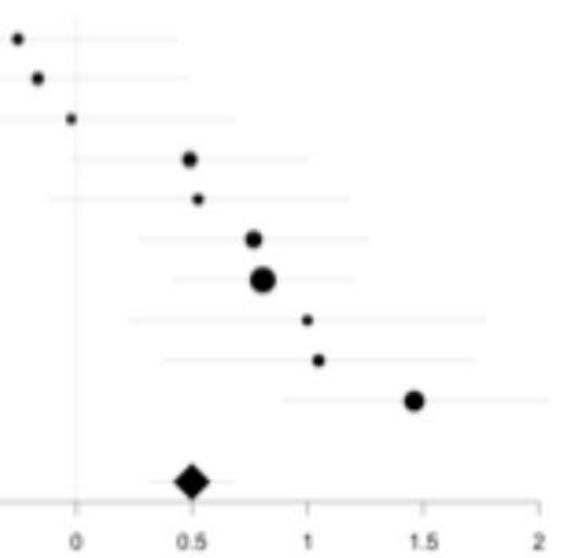
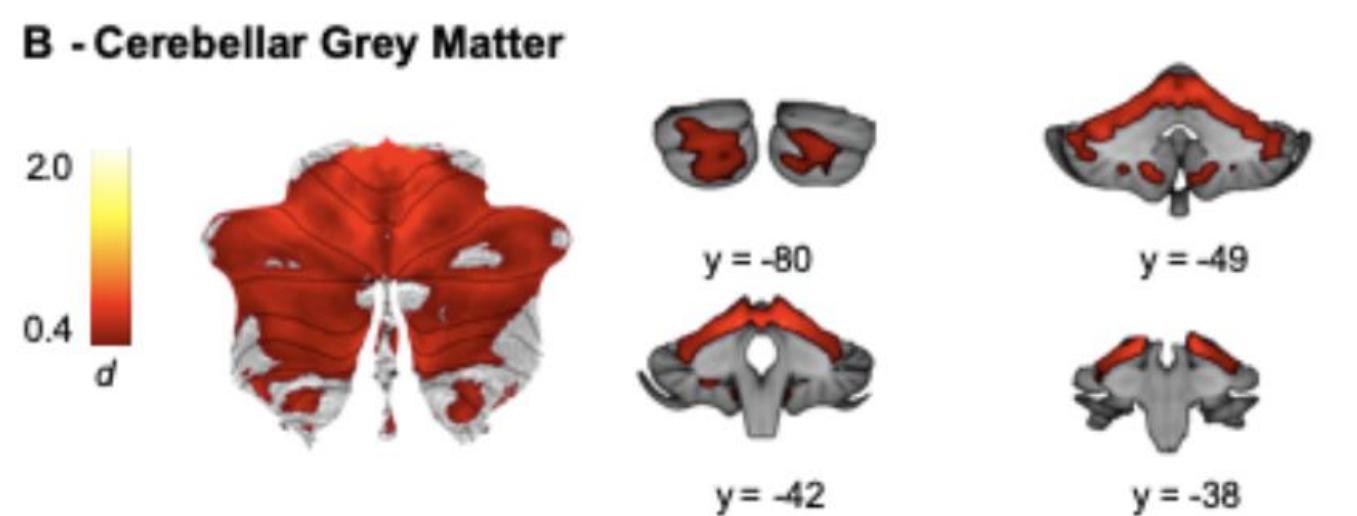
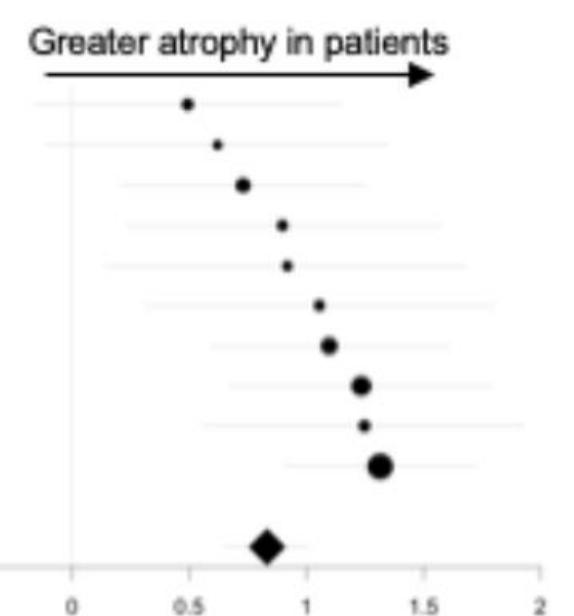
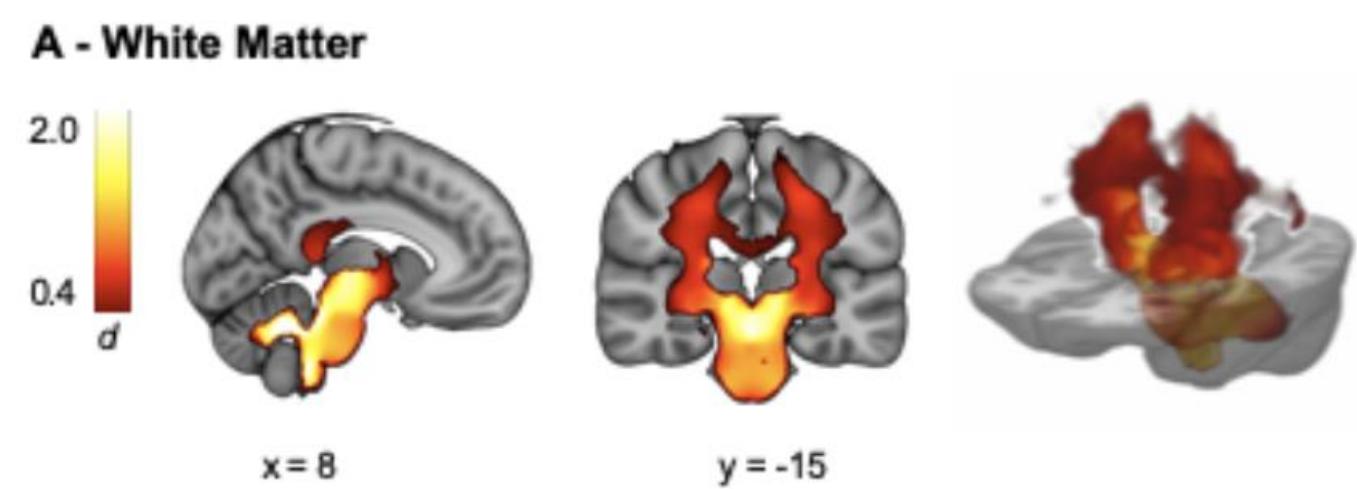
world-wide  
collaborations



Aachen  
Bologna  
Campinas  
Conegliano  
Florence  
Innsbruck  
Essen  
Melbourne  
Minnesota  
Naples

Courtesy of Ian Harding. Melbourne

## Brain atrophy in Friedreich ataxia preferentially manifests in cerebellar and cerebral motor areas: Results from the ENIGMA-Ataxia Consortium (248 FA & 262 controls)



# A Natural History Study to TRACK Brain and Spinal Cord Changes in Individuals With Friedreich Ataxia (TRACK-FA)



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## A Natural History Study to TRACK Brain and Spinal Cord Changes in Individuals With Friedreich Ataxia (TRACK-FA) ((TRACK-FA))

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT04349514

Recruitment Status [i](#) : Not yet recruiting  
First Posted [i](#) : April 16, 2020  
Last Update Posted [i](#) : July 20, 2020  
See [Contacts and Locations](#)

### Sponsor:

Monash University

### Collaborators:

University of Minnesota  
RWTH Aachen University  
University of Campinas, Brazil  
Children's Hospital of Philadelphia  
University of Florida  
Friedreich's Ataxia Research Alliance



**MONASH**  
University



murdoch  
children's  
research  
institute



RWTHAACHEN  
UNIVERSITY



UNIVERSITY OF MINNESOTA  
**Driven to Discover** SM

# Key facts about the project



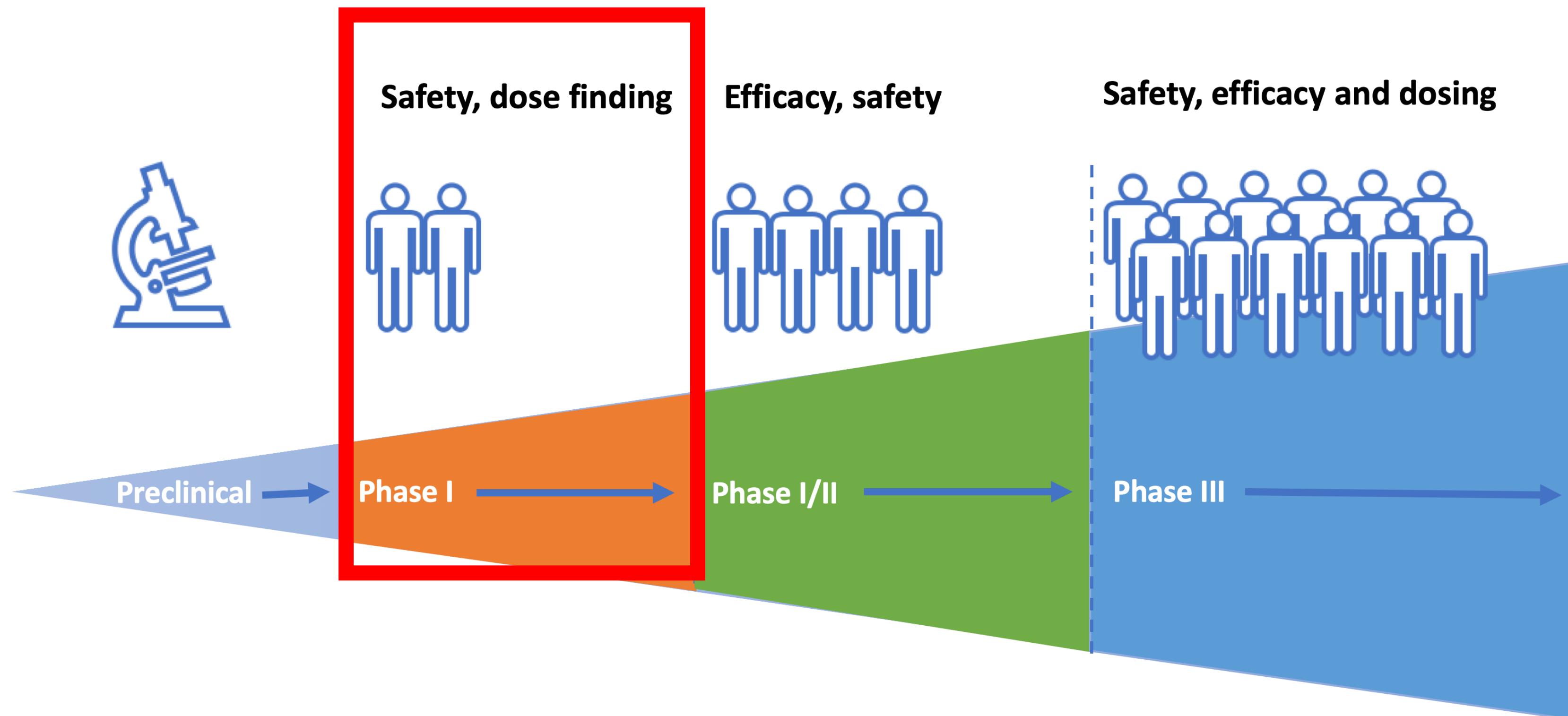
## ● Previous phase I study



Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study



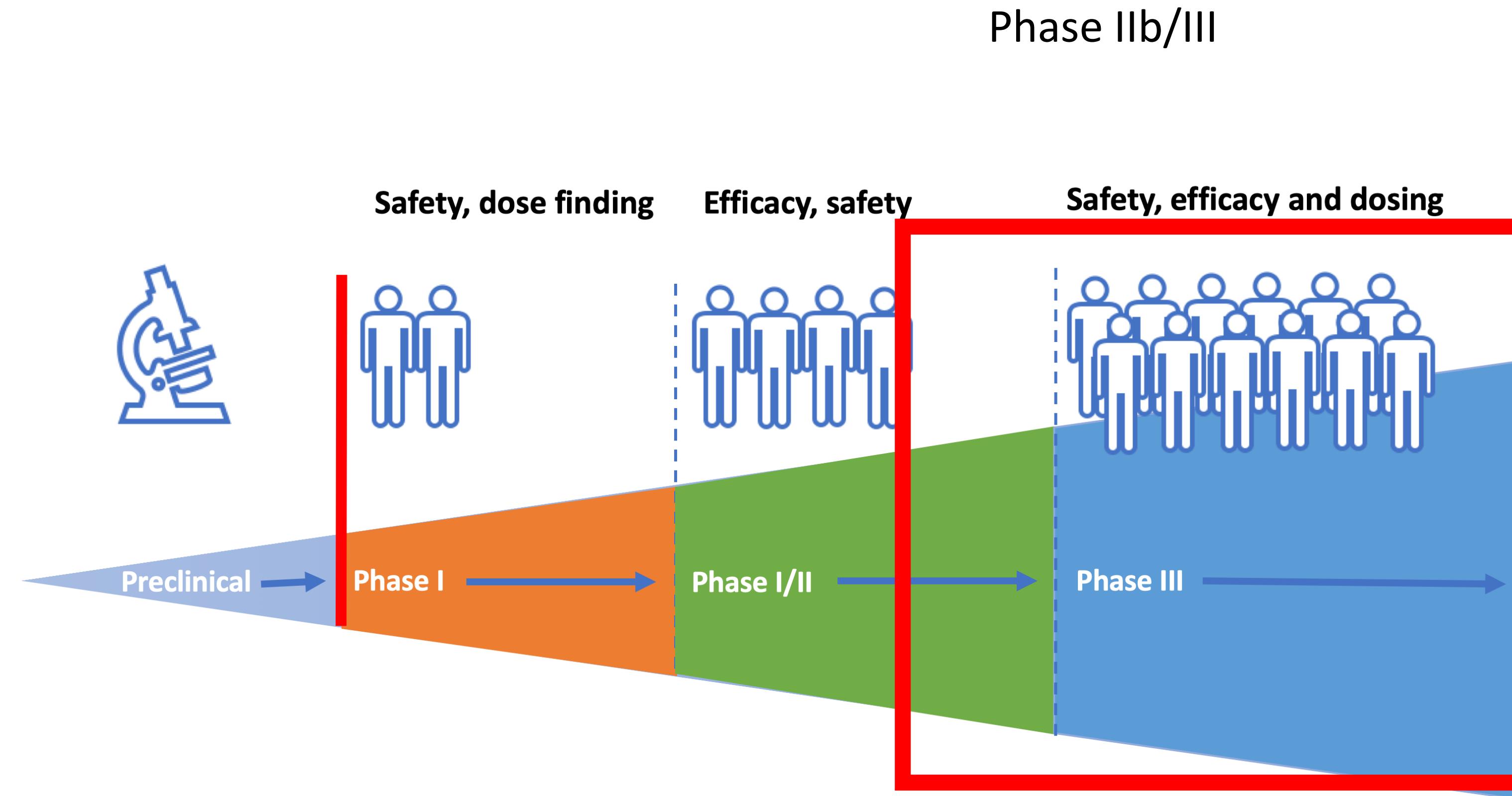
Vincenzo Libri\*, Cihangir Yandim\*, Stavros Athanasopoulos, Naomi Loyse, Theona Natisvili, Pui Pik Law, Ping Kei Chan, Tariq Mohammad, Marta Mauri, Kin Tung Tam, James Leiper, Sophie Piper, Aravind Ramesh, Michael H Parkinson, Les Huson, Paola Giunti, Richard Festenstein



# Key facts about the project



## ● Clinical phase



# PHASE A

Open-label dose adjustment  
wash-in period

weeks 0-3  
Titration:  
0.5g/d every 3d  
up to 4g/d

week 4

4g/d

# PHASE B

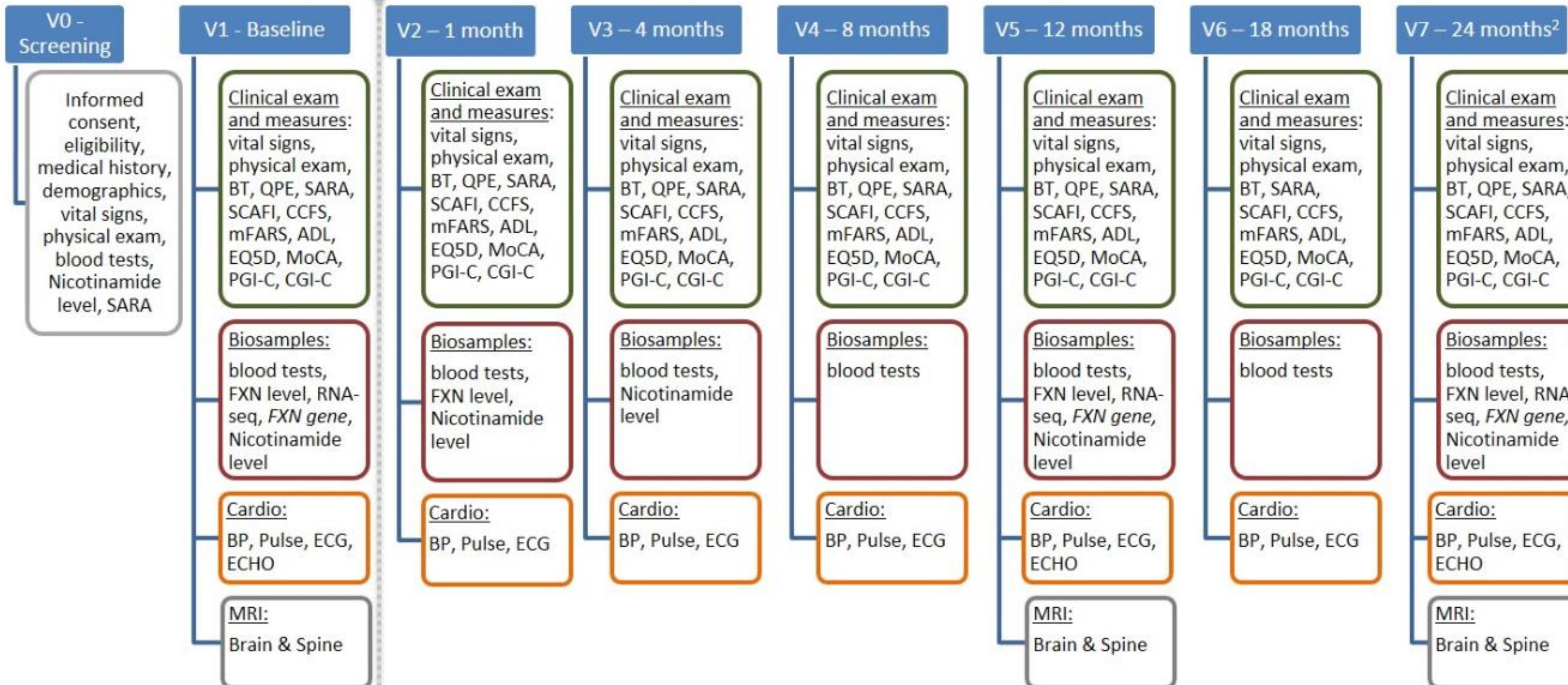
Randomized, double-blind, placebo-controlled and parallel group

## Randomization

2:1

Nicotinamide in  
capsules 4g/d p.o.  
(150 FRDA patients)

Placebo in capsules  
p.o. (75 FRDA patients)



# Results: clinical protocol development



Reetz et al. *Neurological Research and Practice* (2019) 1:33  
<https://doi.org/10.1186/s42466-019-0038-9>

Neurological Research  
and Practice

CLINICAL TRIAL PROTOCOL

Open Access

## Protocol of a randomized, double-blind, placebo-controlled, parallel-group, multicentre study of the efficacy and safety of nicotinamide in patients with Friedreich ataxia (NICOFa)



Kathrin Reetz<sup>1,2</sup> , Ralf-Dieter Hilgers<sup>3</sup>, Susanne Isfort<sup>4</sup>, Marc Dohmen<sup>4</sup>, Claire Didzun<sup>1,2</sup>, Kathrin Fedosov<sup>1,2</sup>, Jennifer Kistermann<sup>4</sup>, Caterina Mariotti<sup>5</sup>, Alexandra Durr<sup>6</sup>, Sylvia Boesch<sup>7</sup>, Thomas Klopstock<sup>8,9,10</sup>, Francisco Javier Rodríguez de Rivera Garrido<sup>11</sup>, Ludger Schöls<sup>12,13</sup>, Thomas Klockgether<sup>14,15</sup>, Massimo Pandolfo<sup>16</sup>, Rudolf Korinthenberg<sup>17</sup>, Philip Lavin<sup>18</sup>, Geert Molenberghs<sup>19</sup>, Vincenzo Libri<sup>20</sup>, Paola Giunti<sup>21†</sup>, Richard Festenstein<sup>22†</sup>, Jörg B. Schulz<sup>1,2,4\*</sup> and the EFANTS or NICOFa study group



## The EFAC TS Registry

- Thanks to all FA patients and their families participating in EFAC TS
- Thanks to all PIs
- Thanks to Myriam Rai, Claire Didszun, Jennifer Michels