

# Centenarians and oldest-olds in Liguria – COOL: a multidisciplinary approach to investigate the genetic determinants of cognitive well-being in the oldest population

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Background  
Rationale  
Aim

## Focus:

### cognitive health in the oldest-old

#### Key points:

- Cognitive health in the elderly is a global health issue
- A relevant proportion of dementia in the oldest-old is related to non-AD pathologies
- Risk factors for cognitive impairment in the oldest-old differ from younger elderly
- Individual cognitive status in the oldest-old is highly variable

#### Question:

may human genetics help...  
to explain differences in centenarians' cognitive profile?  
to identify genomic biomarkers of healthy cognitive ageing?

DESIGN  
PROTOCOL



#### Protocol Design:

- Observational cohort study
- Multicentric
- Not-for-profit, no sponsors
- Promoting Centre: Galliera Hospital, Genoa

[approved by the Regional Ethical Review Board, 2021 – amended July 2023]

#### Population:

- Centenarians living in Genova – N ≥100
- Individuals aged >99 are eligible for the study.

#### Observation:

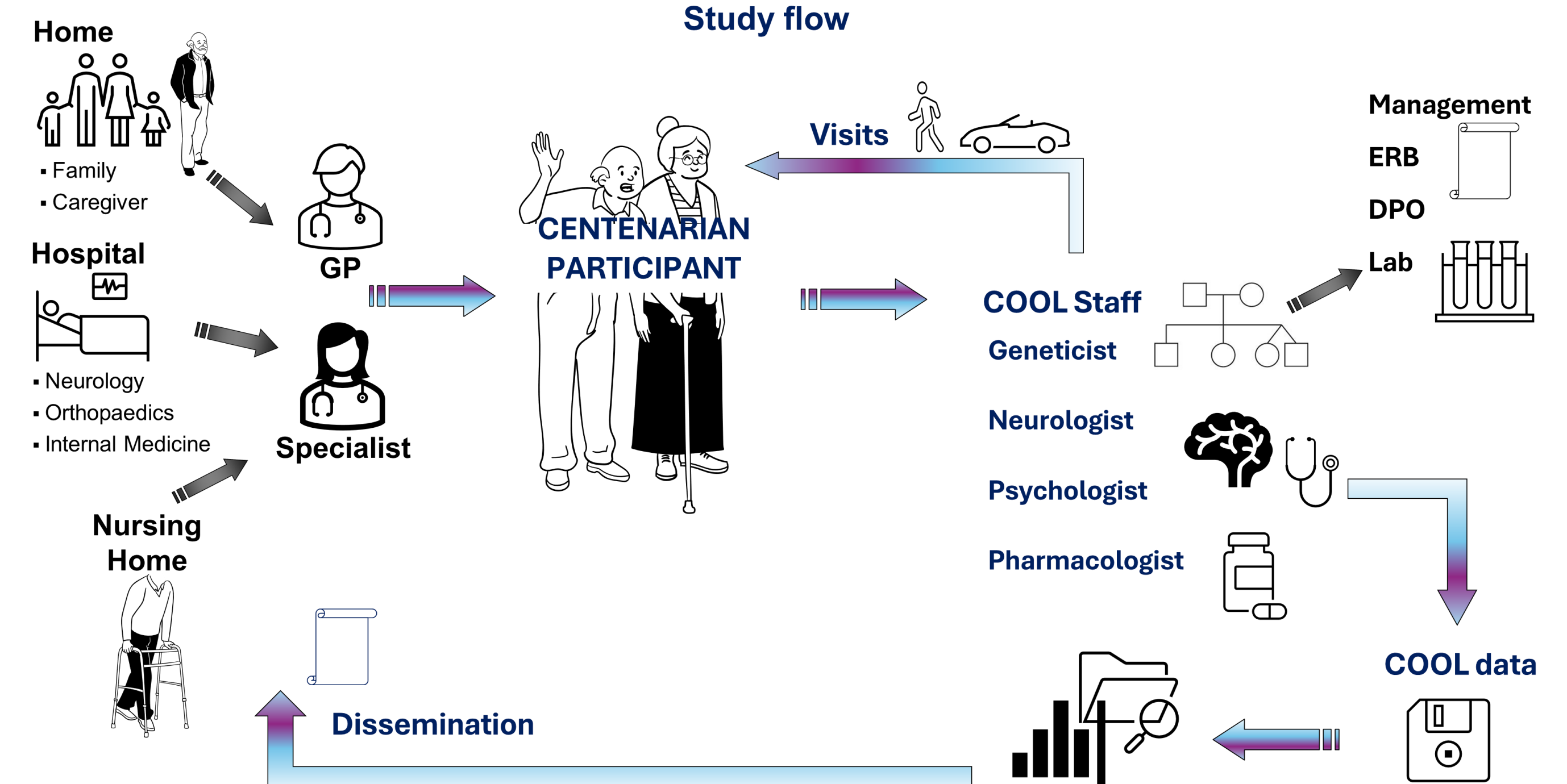
- Participants are examined by the means of standard clinical assessments and neuropsychological tests

#### Exposure:

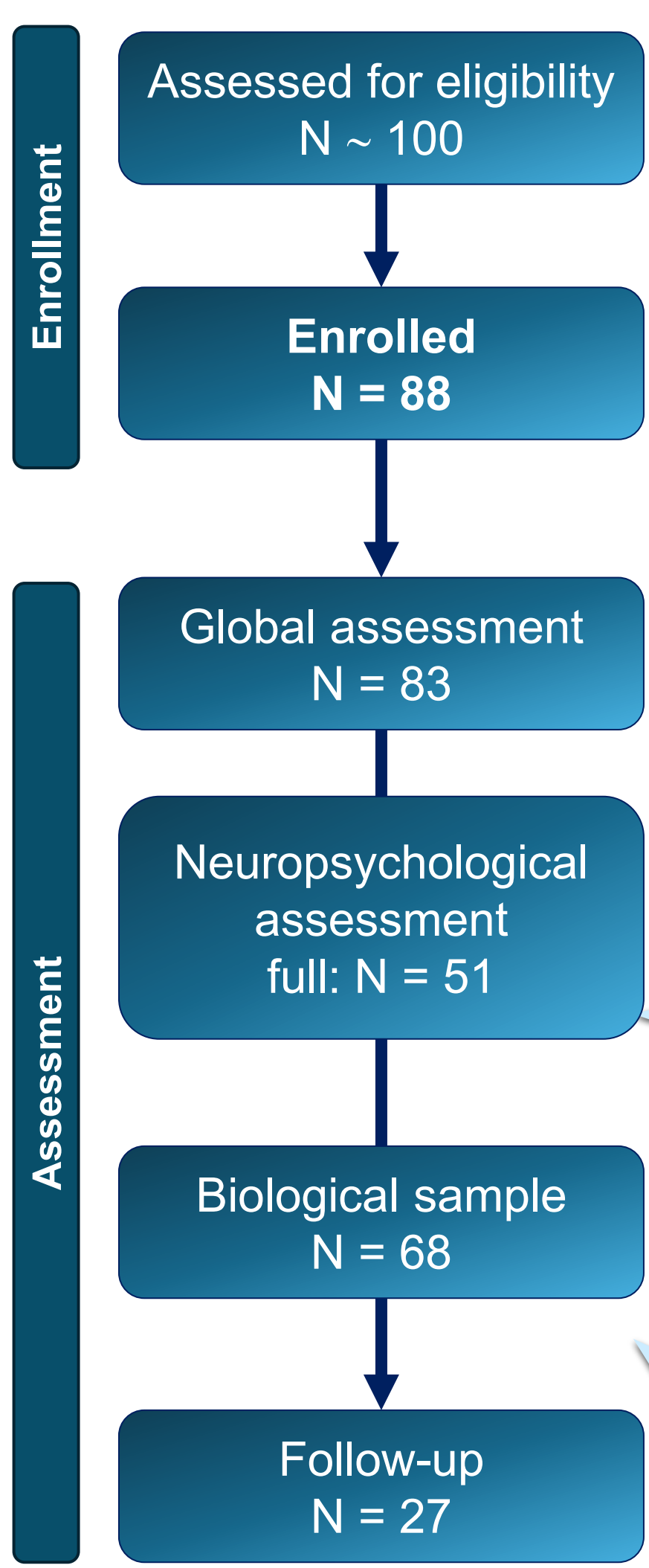
- Genomic markers and peripheral biomarkers associated with the cognitive profile

#### Outcomes:

- Cognitive status
- General health profile; cognitive decline



COHORT – preliminary descriptive analysis



As of June 2025:

- 88 centenarians
- living in the Genoa metropolitan area
- age range 99-108; 81% women
- Italian ancestry
- 55% lived in a nursing home, 31% in their household, 13% alone
- education: 8 years (median); 75% worked at least 10 years

Centenarians with and without cognitive impairment showed a wide distribution of cognitive status

- MMSE range 3-30, avg 22.7±5.6, mdn 24 [n=51]
- CDRS range 5-0 [n=64]
- Comorbidity index (CIRS): 3±2.37; functional level (Barthel Index) 52.5±33 – not shown
- Cognitive Reserve Index 97-170, avg 104±19, mdn 102

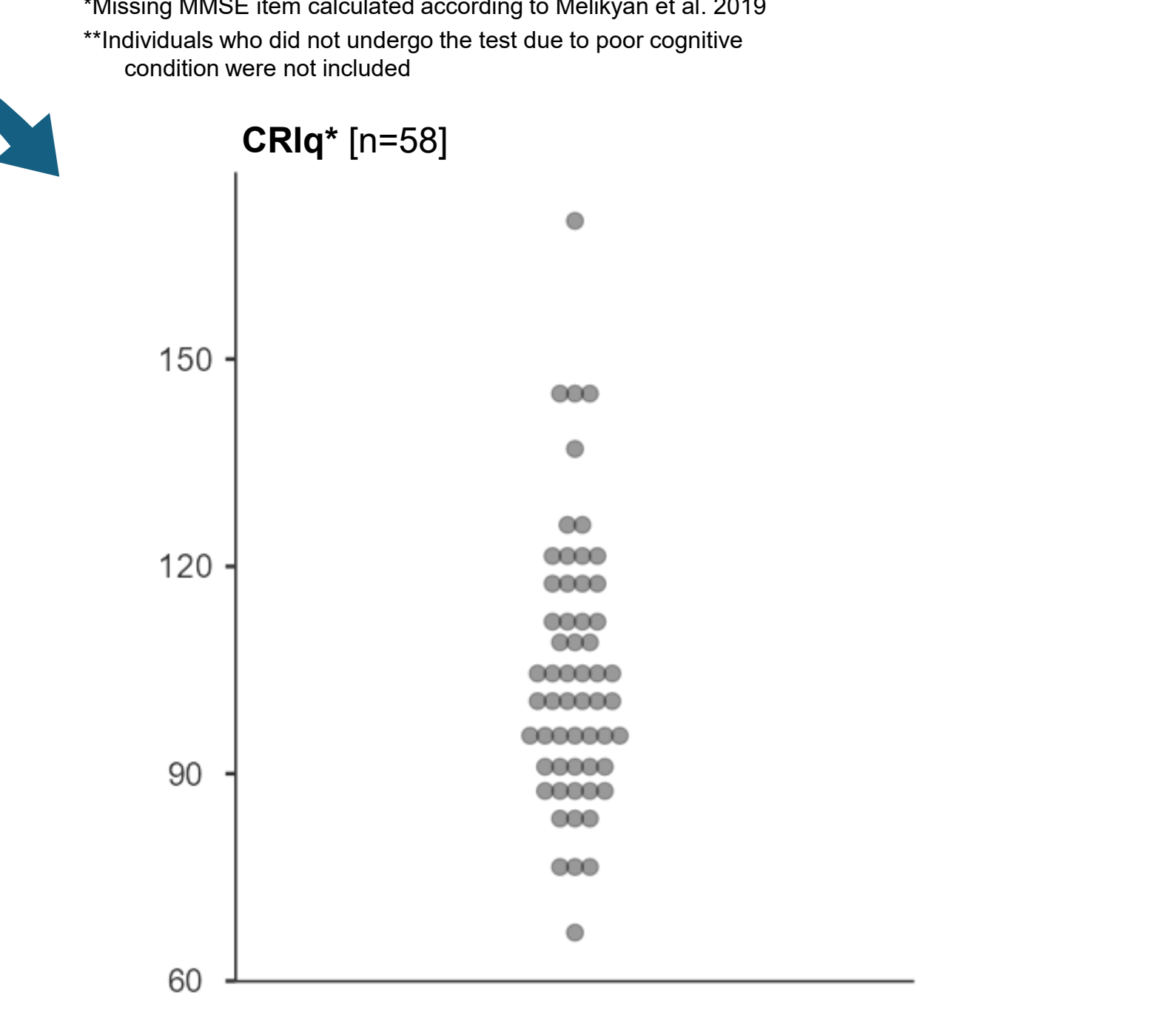
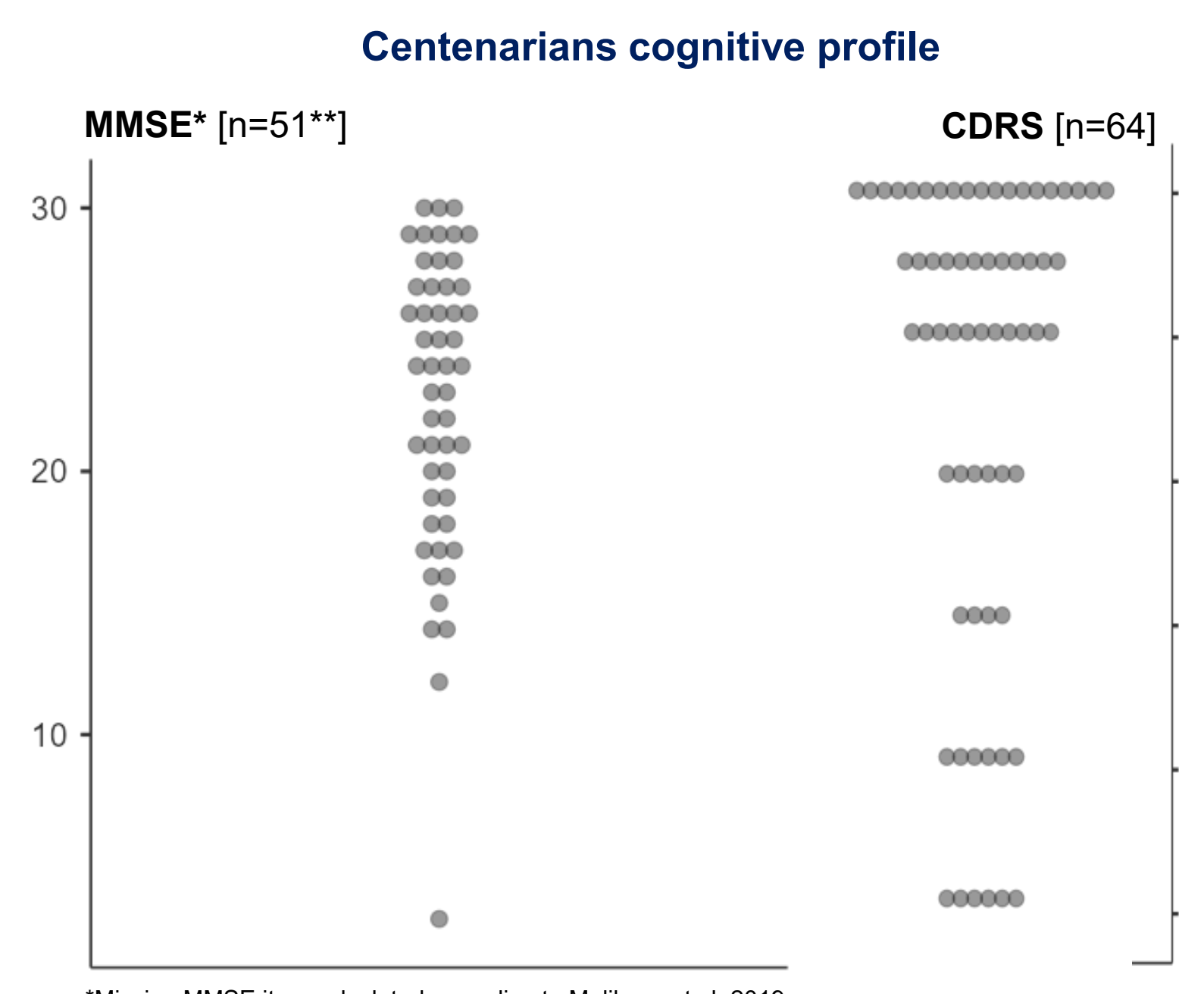
Genotyping:

- 68 blood samples and DNA
- APOE genotyping completed
- Pilot WGS to be planned
- Goal: long-read sequencing (Partner Lab)

APOE genotype	N	(%)
e2e2	1	1
e2e3	8	12
e3e3	55	81
e3e4	4	6
e4e4	0	0
e2e4	0	0
Tot	68	100

APOE allele	N	(%)
e2	10	7
e3	122	90
e4	4	3
Tot	136	100



Lessons learnt

#### Lesson 1:

- ✓ Enrolling and assessing Centenarians in the real-world setting is feasible

#### Strength:

- ✓ The protocol was demonstrated to be acceptable for participants and their families
- ✓ Genetic variability of cognitive ageing: participants with diverse origin shared the same environment
- ✓ Phenotype variability: wide range of cognitive status
- ✓ Different recruitment settings expanded the eligible population

#### Lesson 2:

- ✓ Multidisciplinary approach and multiprofessional engagement provided an added value

#### Limitations/risks:

- ☒ Enrolment/ascertainment bias
- ☒ Limited generalisability
- ☒ Confounders: healthy cognitive ageing correlates with longevity
- ☒ Highly demanding, time-consuming protocol
- ☒ High cost of WGS



The COOL study network

The COOL study Investigators include: Amaro A.A., Astuni P., Baiardi G., Boi R., Brasesco P., Bussi F., Del Sette P., El Rashed Z., Flego G., Fuliano P., Giusto R., Maioli E., Mazzocco M., Muscolino E., Parodi N., Pfeffer U., Piras F., Poeta M.G., Sacchi N., Salivetto M., Schirizzi E., Spatera P.

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Contributing Centres:



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