Digital Signatures: The need and Overview on Mapping them with Cognitive domains

Meemansa Sood
PhD Student
Fraunhofer SCAI &
University of Bonn

Fraunhofer SCAI

Outline

- Digital signatures used as biomarkers
- Real time examples
- Measurables from digital devices
- Association of digital biomarkers with cognitive function
- Workflow for RADAR-AD
- Advantages of digital signatures
- Limitations of using digital signatures

Digital technologies used as biomarkers: The Need

- Conventional measures of neuropsychiatric disorders have several challenges
  - Obtrusive
  - not ecological
  - episodic

- High variability in existing cognitive tests scores at baseline (& over trial course): **produced false signals in phase 2 -> costly failures in phase 3 [1]**

- Problems with existing tools:
  - accuracy of self and clinician reported measures [2]
  - substantial variability among individual administering tests

Digital signatures used as biomarkers: The Need

- Digitized forms improve data quality
- Enhance guidance during test by proactively responding to errors
- Calculate results automatically
- Check for consistency in responses
- Immediate response to missing data
- Integrate audio and video data capture into assessments
- Lead to increase in both accuracy and precision

Real time examples

- **Daily activity assessments with accelerometers:** used as a **primary end point** to test the ability of nitrates to enhance activity tolerance in patients with heart failure [3]

- **Alzheimer's Disease (AD):** Ankle mounted wearable accelerometers used to measure changes in daily motion behavior even in the absence of major behavioral impairments [4]

- **Distinguish between Mild cognitive impairment (MCI) and Normal cognition:**

  High frequency in home monitoring data [5]

  - such data could reduce sample size needed for clinical trials
  - reduce exposure of participants to potentially harmful drugs

Measurables from digital devices (sensors)

- Measures the behavior of subjects:
  - Sleep, mood, physical activity, social activity, eating behaviors

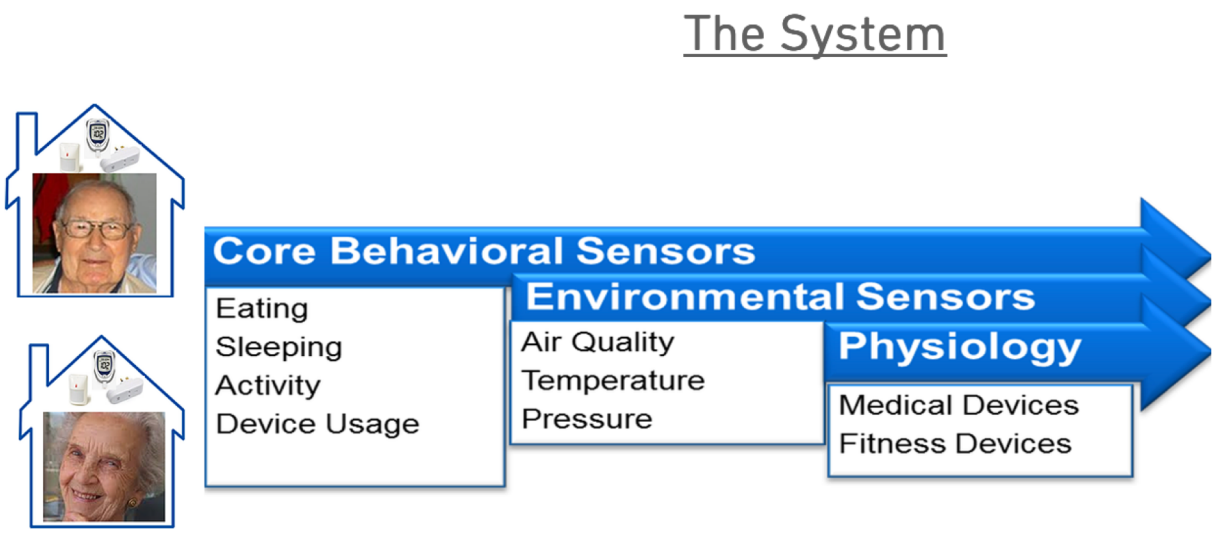
- Infer cognitive and functional status

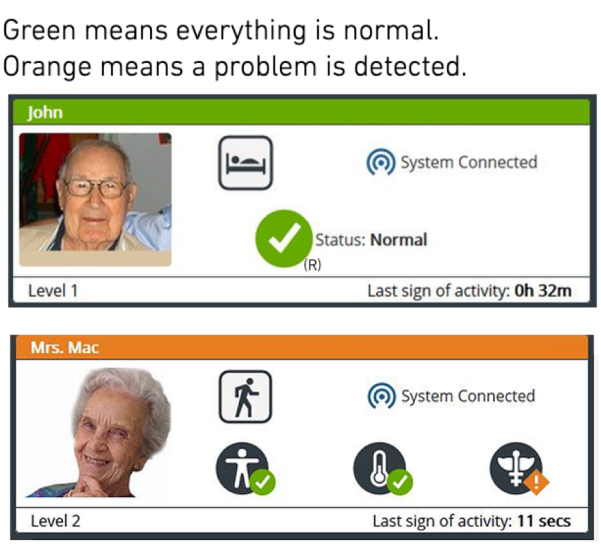
Platforms:

- **Oregon center for aging and technology:** time and location of sleep, patterns of movement around home, taking of medications, use of a phone or computer, driving, opening and closing of doors and refrigerators [6]

Measurables from digital devices (sensors)

- **EmPowerYu:** sensors to detect motion within a fixed space, appliances being turned on and off, doors opening closing
  - time/sequence tracking with **machine learning approaches** to assess gait, pacing, night wandering, repetitive activities, medication compliance





Fraunhofer SCAI

Measurables from digital devices (sensors)

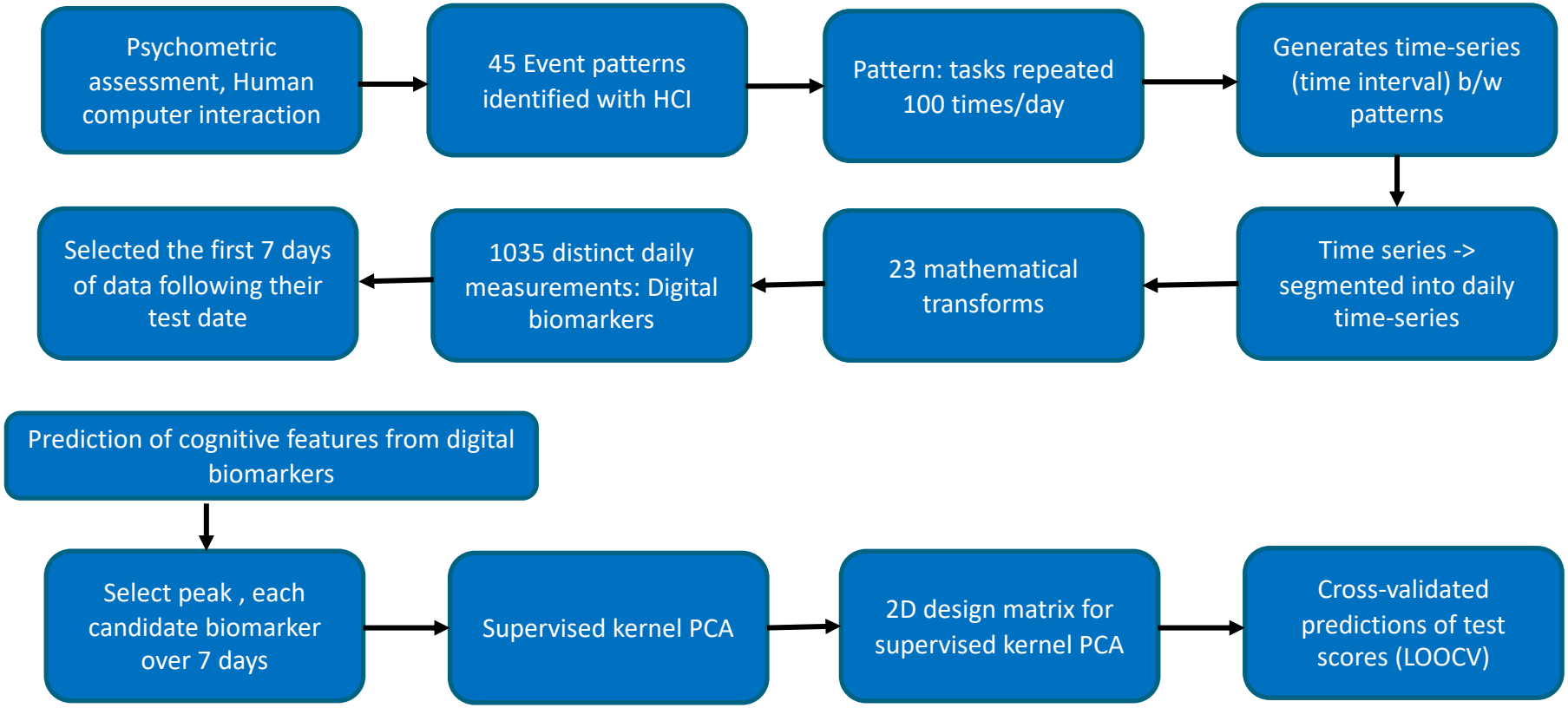
- **EmPowerYu:** sensors to detect motion within a fixed space, appliances being turned on and off, doors opening closing
  - time/sequence tracking with **machine learning approaches** to assess gait, pacing, night wandering, repetitive activities, medication compliance
- Assessing **cognition from behavioral and functional changes**, many devices capture metadata that may even capture subtle cognitive changes
- **Digital pen** as an **alternative in Trails B test or Clock Drawing Test**: also tracks when pen is lifted from paper, which may indicate altered cognitive processes [7]
- **Speech patterns**: might be **early markers** of cognitive decline in AD [8]

Association of digital biomarkers with cognitive function

- **Aim: to identify digital biomarkers correlated with neuropsychological performance**
- Analyzed human–computer interaction (HCI) from 7 days of smartphone use in 27 subjects (ages 18–34) who received a gold standard neuropsychological assessment
- Neuropsychological tests for:
  - working memory
  - memory
  - executive function
  - language
  - intelligence

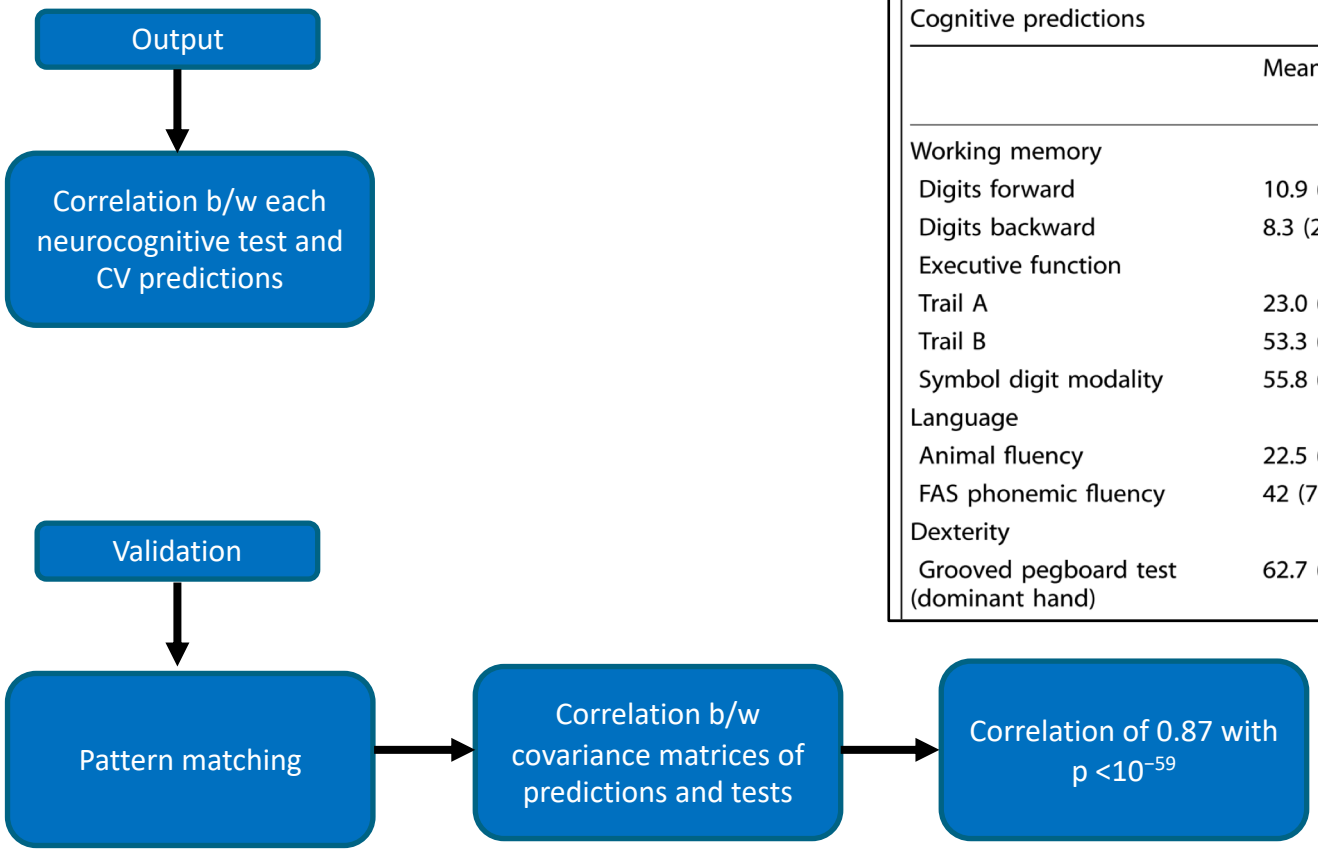
http://dx.doi.org/10.1038/s41746-018-0018-4

Association of digital biomarkers with cognitive function



Fraunhofer SCAI

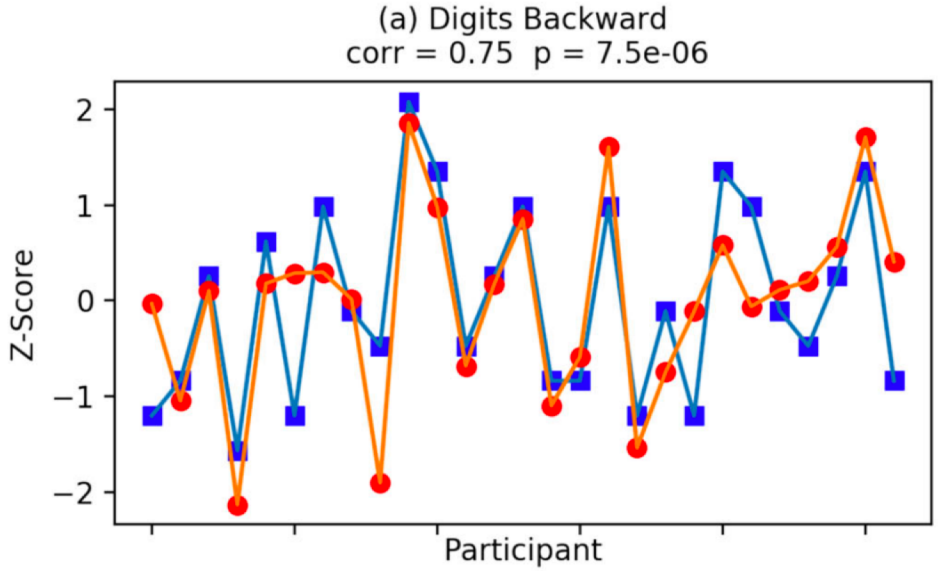
Association of digital biomarkers with cognitive function

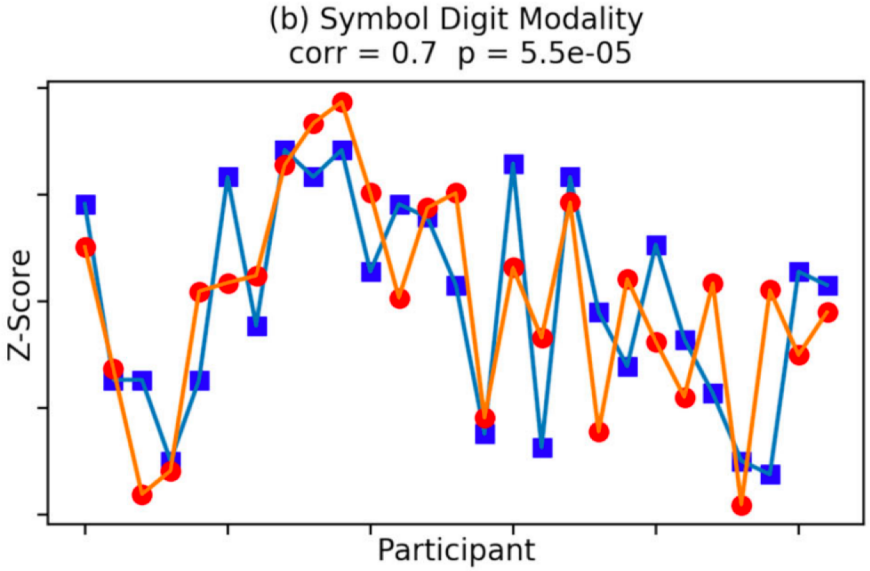


Cognitive predictions	Mean (SD)	Range	*R* (predicted), *p*-value
Working memory			
Digits forward	10.9 (2.7)	7–15	$0.71 \pm 0.10, 10^{-4}$
Digits backward	8.3 (2.7)	4–14	$0.75 \pm 0.08, 10^{-5}$
Executive function			
Trail A	23.0 (7.6)	12–39	$0.70 \pm 0.10, 10^{-4}$
Trail B	53.3 (13.1)	37–88	$0.82 \pm 0.06, 10^{-6}$
Symbol digit modality	55.8 (7.7)	43–67	$0.70 \pm 0.10, 10^{-4}$
Language			
Animal fluency	22.5 (3.8)	15–30	$0.67 \pm 0.11, 10^{-4}$
FAS phonemic fluency	42 (7.1)	27–52	$0.63 \pm 0.12, 10^{-3}$
Dexterity			
Grooved pegboard test (dominant hand)	62.7 (6.7)	51–75	$0.73 \pm 0.09, 10^{-4}$

Fraunhofer SCAI

Association of digital biomarkers with cognitive function





These preliminary results suggest that passive measures from smartphone use could be a continuous ecological surrogate for laboratory-based neuropsychological assessment.

Fraunhofer SCAI

Workflow for RADAR-AD

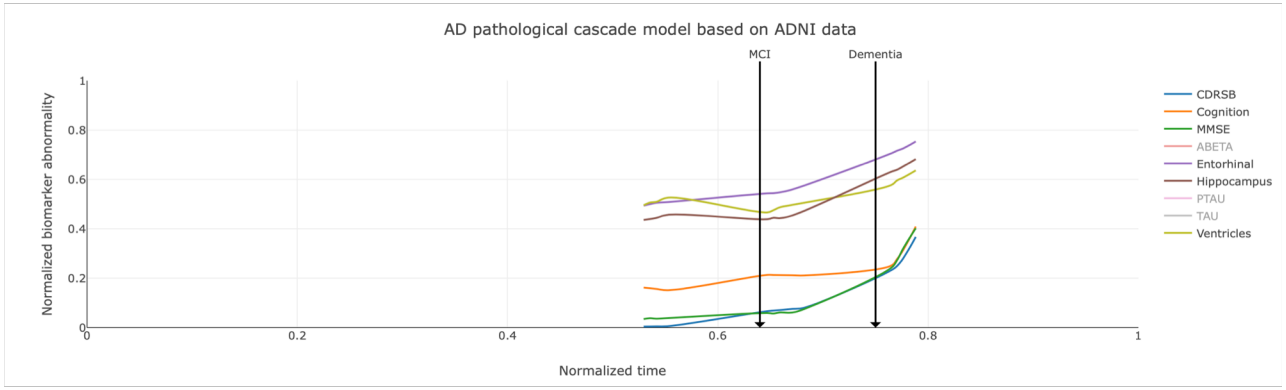
Identification of appropriate longitudinal cohorts (functional and cognitive domains

→

Mixed models for NL, MCI, Dementia

→

Sub population trajectories (Mean trajectories)



Fraunhofer SCAI

Workflow for RADAR-AD

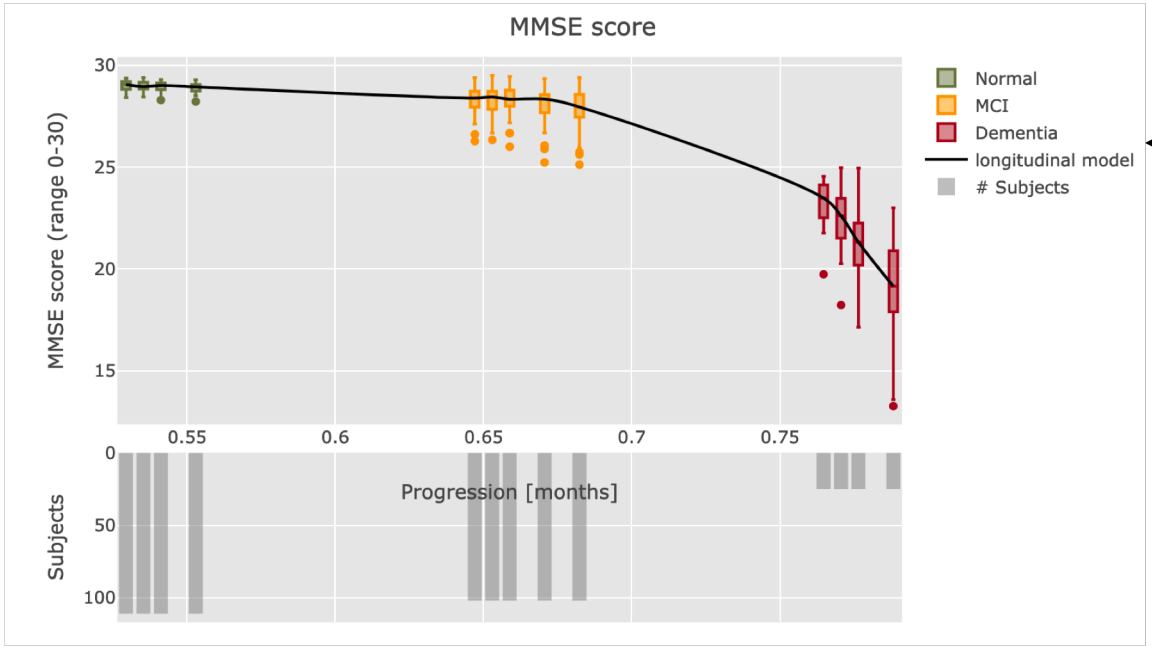
Identification of appropriate longitudinal cohorts (functional and cognitive domains

Mixed models for NL, MCI, Dementia

Sub population trajectories (Mean trajectories)

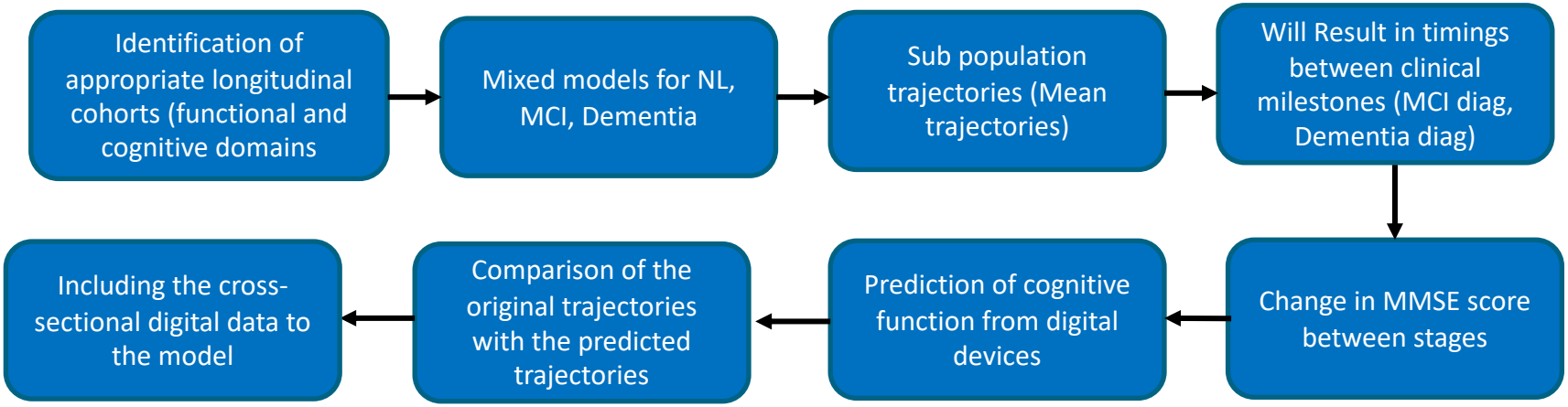
Will Result in timings between clinical milestones (MCI diag, Dementia diag)

Change in MMSE score between stages



Fraunhofer SCAI

Workflow for RADAR-AD



Fraunhofer SCAI

Advantages of digital technologies

- Unobtrusive, ecological and provide dense daily measurements
- Enhance the patient and caregiver experience
- Help patients learn about and manage their health
- Engage participants in drug development and other treatment protocols
- Tools facilitating early identification of cognitive impairment: might encourage people to enrol in trials earlier
- Identifying potential participants in early stages of cognitive impairment with digital tools:
    - reduce trial duration
    - costs
    - improve outcomes

Challenges of digital technologies

- Complex tools may require technology, motor or cognitive skills that some participants might not possess: use of different tools for different populations
- Ethical challenges when used in clinical trials: increase in time and cost of development
- Data privacy: biggest concern
    - participants usually less willing to share passive data
    - concerns like data sharing might impact their daily life
    - caregivers have concern: ability to turn off the device, info what is being recorded
- Small sample size relative to large number of potential biomarkers

References

1. Dorsey ER, Venuto C, Venkataraman V, Harris DA, Kieburtz K. Novel methods and technologies for 21st-century clinical trials: A review. JAMA Neurol 2015;72:582
2. Wild KV, Mattek N, Austin D, Kaye JA. “Are You Sure?”: lapses in self-reported activities among healthy older adults reporting online. J Appl Gerontol 2016;35:627–41
3. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med 2015;373:2314–24
4. Kirste T, Hoffmeyer A, Koldrack P, Bauer A, Schubert S, Schroder S, et al. Detecting the effect of Alzheimer’s disease on everyday motion behavior. J Alzheimers Dis 2014;38:121–32.
5. Dodge HH, Mattek NC, Austin D, Hayes TL, Kaye JA. In-home walking speeds and variability trajectories associated with mild cogni- tive impairment. Neurology 2012;78:1946–52

References

6. Kaye JA, Maxwell SA, Mattek N, Hayes TL, Dodge H, Pavel M, et al. Intelligent systems for assessing aging changes: home-based, unobtru- sive, and continuous assessment of aging. J Gerontol B Psychol Sci Soc Sci 2011;66:i180–90
7. Muller S, Preische O, Heymann P, Elbing U, Laske C. Increased diag- nostic accuracy of digital vs. conventional clock drawing test for discrimination of patients in the early course of Alzheimer's disease from cognitively healthy individuals. Front Aging Neurosci 2017; 9:101
8. Forbes KE, Venneri A, Shanks MF. Distinct patterns of spontaneous speech deterioration: an early predictor of Alzheimer's disease. Brain Cogn 2002;48:356–61