Opportunities and Challenges in Using Digital Biomarkers as Trial Outcomes

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PRESENTATION OUTLINE

I. Advantages of using digital biomarkers as clinical trial outcomes

II. Selection bias within minority cohorts?

Lessons learned from the I-CONECT project

Advantages of Digital Biomarkers as Trial Outcomes

CHALLENGES IN DEMENTIA TRIALS

- **Large intra-individual variability & fluctuations**

  Fluctuations within a short time duration (i.e., morning vs. at night, or good day vs. bad day) can easily override the long-term changes which occur gradually in one year or even several years.

- **Large inter-individual variability**

  Pathological burden ≠ Symptoms (due to variability in inter-individual levels of cognitive reserve and resilience)

Comparing average changes in outcomes by trial groups does not work!!

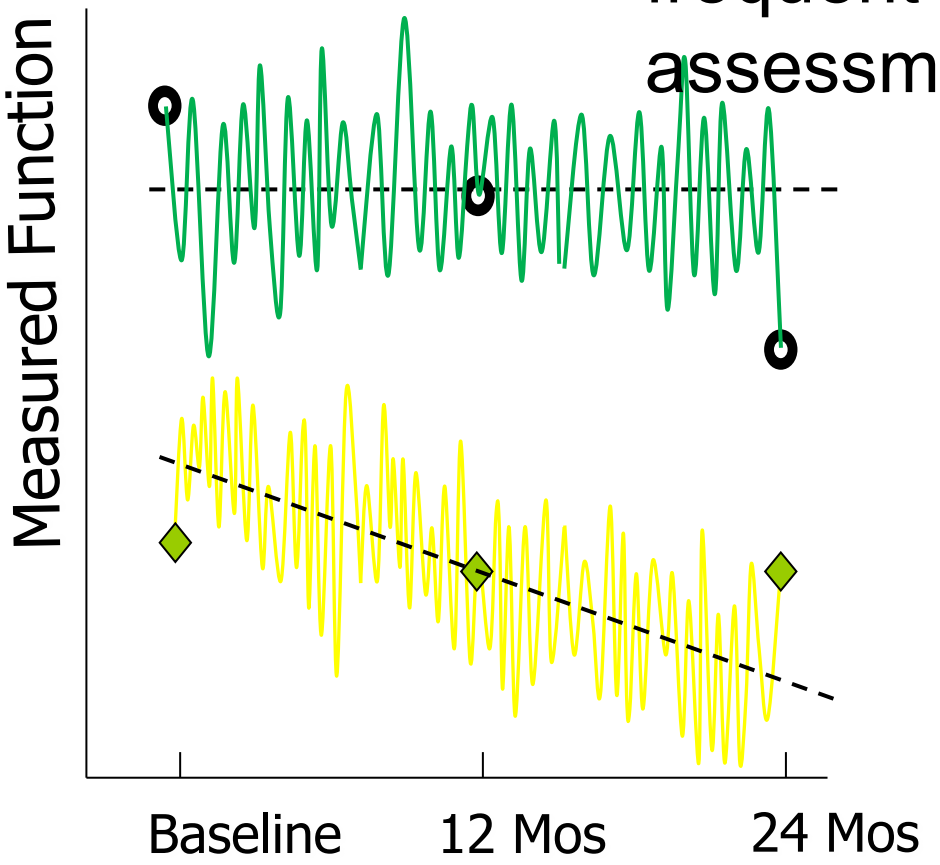
-- hard to obtain high signal-to-noise ratios

Advantage of Digital Biomarkers (1)

Top line: “annual assessment” indicates that the measured function is declining.

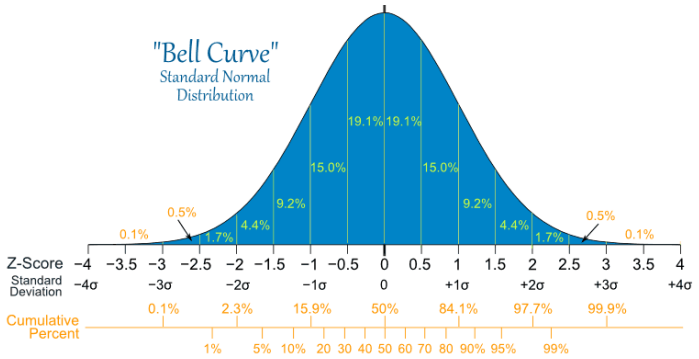
Bottom line: “annual assessment” indicates that the measured function is stable.

If we had more frequent assessments....



Precision improves by monitoring intra-individual variability

Advantage of Digital Biomarkers (2)

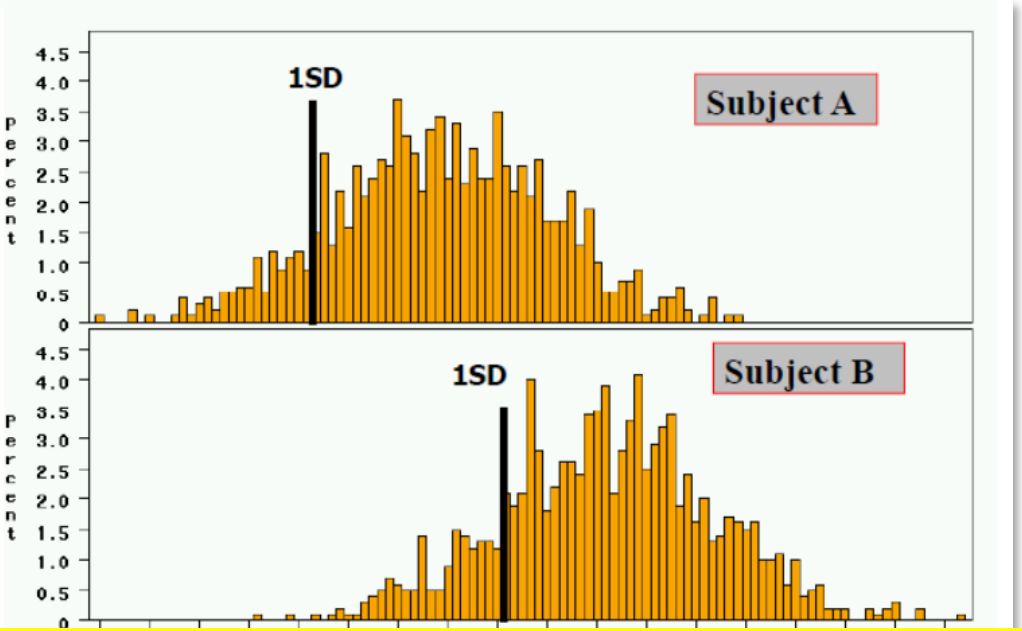


Distribution can be generated for EACH individual within short duration of data accrual periods

Your walking speed ≠ my walking speed

Your computer use ≠ my computer use

Using continuously monitored data:



In-Home Walking Speed Observed During the 90 days for 2 subjects

Transforming Clinical Trials with High Frequency, Objective, Continuous Data: "Big Data" for Each Subject

MCI Prevention Trial – Sample Size Estimates

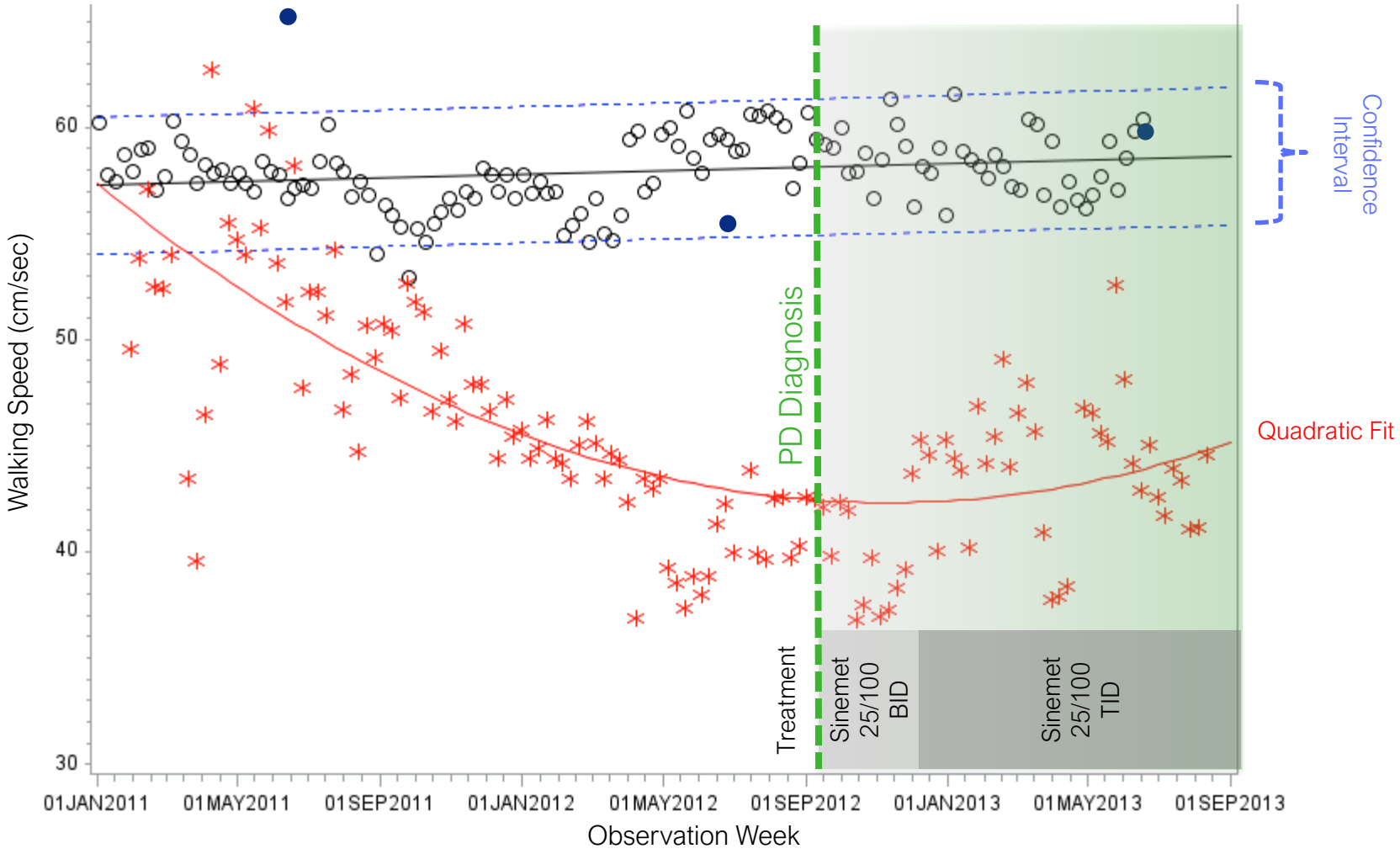
	Current Method	Using Subject-Specific Cutpoint as outcomes	
	LM Delayed Recall*	Computer Use**	Walking Speed ***
SAMPLE SIZE TO SHOW 50% EFFECT	688	10	94
SAMPLE SIZE TO SHOW 40% EFFECT	1076	16	148
SAMPLE SIZE TO SHOW 30% EFFECT	1912	26	262
SAMPLE SIZE TO SHOW 20% EFFECT	4300	58	588

: 40th% low, *: 10th%tile low

- Reduces required sample size
- Reduces exposure to harm (fewer needed/ fewer exposed)
- More precise estimates of the trajectory of change; allows for *intra-individual* predictions.
- Provides the opportunity to substantially improve efficiency and inform go/no-go decisions of trials.

Dodge et al., Plos One (2015). "Use of High-Frequency In-Home Monitoring Data May Reduce Sample Sizes Needed in Clinical Trials."

Walking Speed Declines Prior to PD Diagnosis



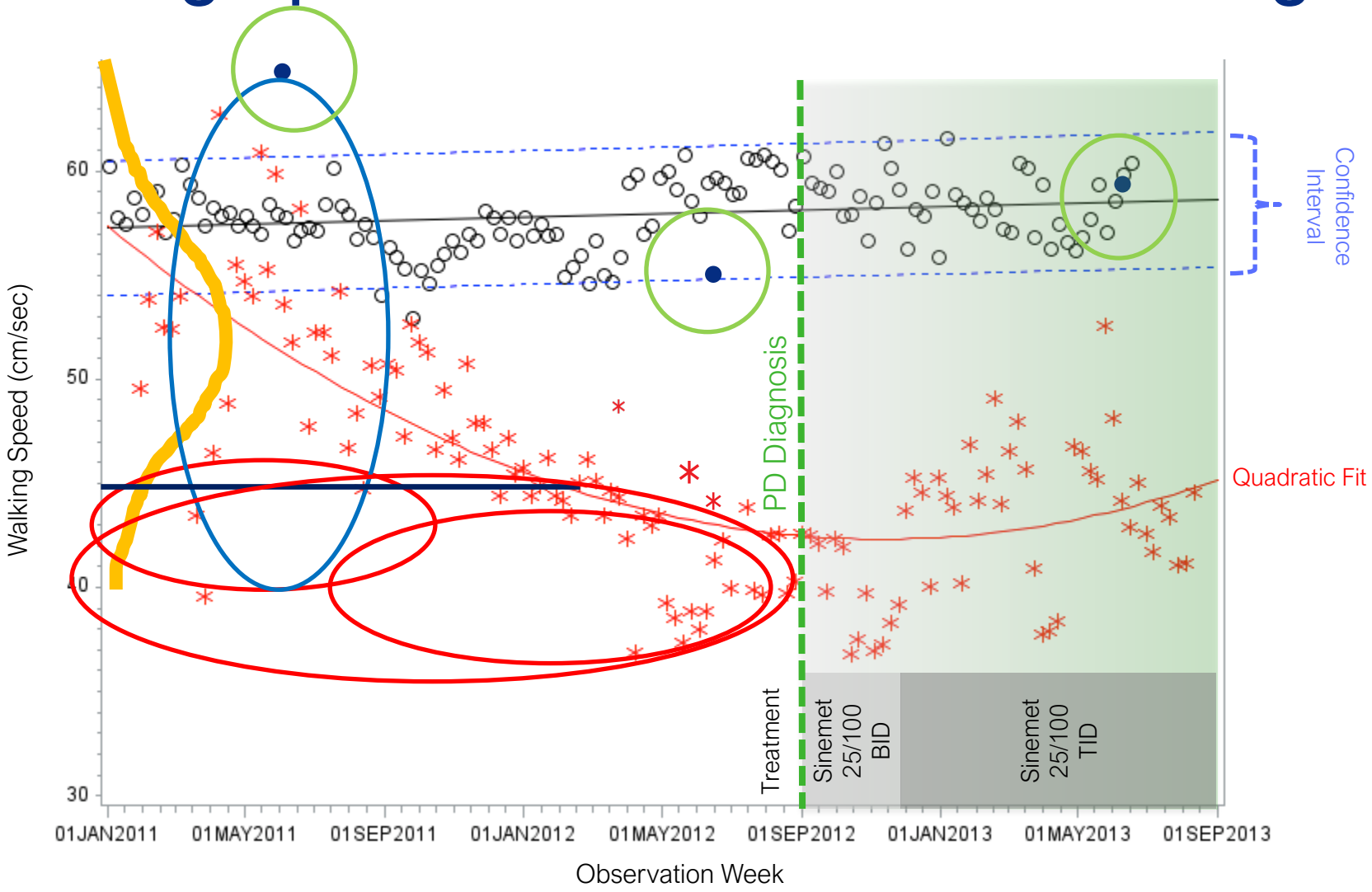
Subject P, stopwatch speed at in-person visit

Peer group, normal mean in-home speed (n=100)

Subject P, mean in-home walking speed

Data from Oregon Center for Aging and Technology (ORCATECH), PI: Kaye

Walking Speed Declines Prior to PD Diagnosis



Subject P, stopwatch speed at in-person visit

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Subject P, mean in-home walking speed

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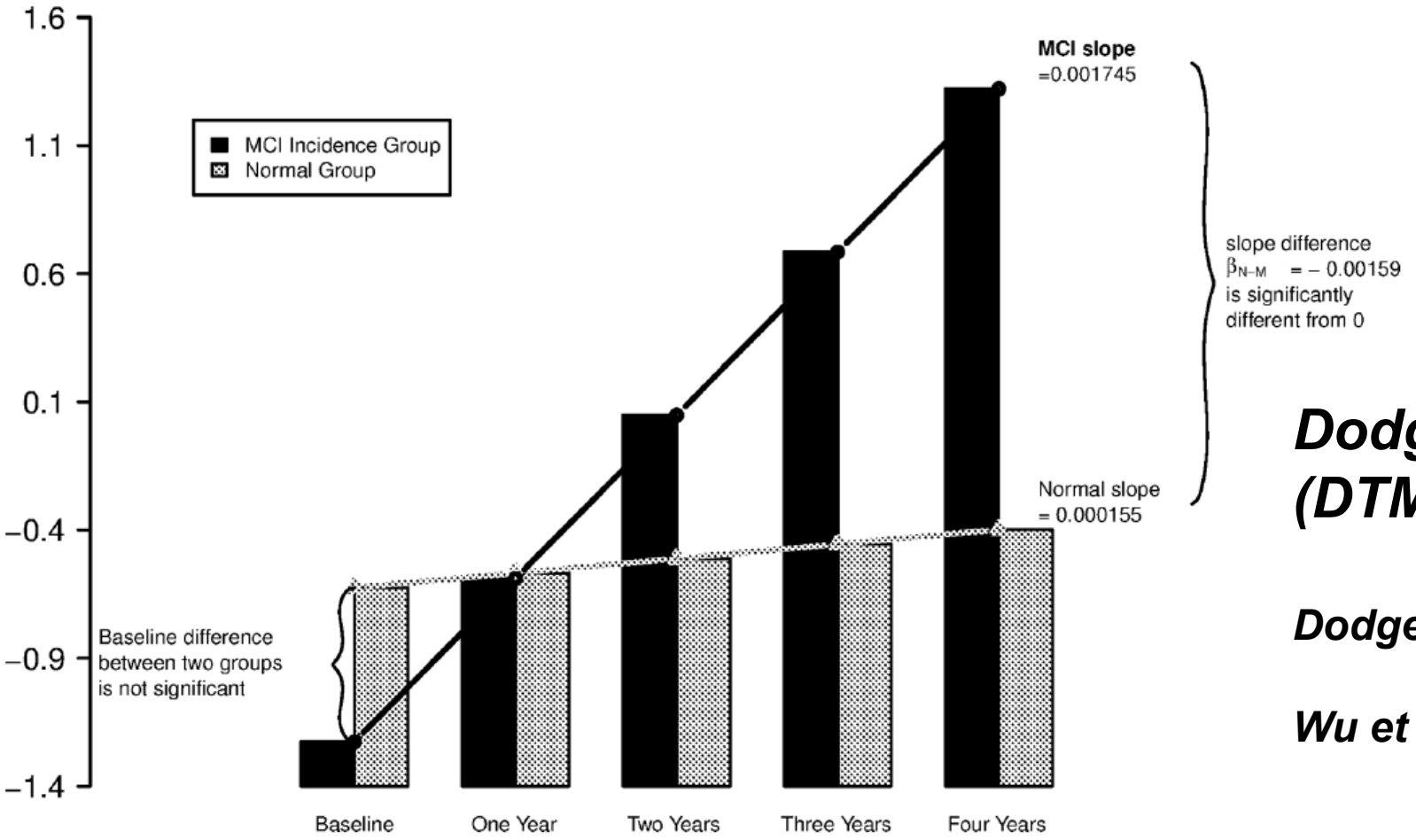
Continuous activity monitoring approach

		A. Empirically Derived Slope Differences			B. Clinical Trial Sample Size Estimation (estimates based on 4 years of follow-up, 80% Power)			
					Treatment Effect Size			
Model	Outcome	group effect on slope (Normal vs Incidence)*	(SE)	p-value	20% **	30%	40%	50%
Linear Mixed Effects Model*	walking speed	0.0038	0.0115	0.74	92600	41156	23150	14816
	computer usage**	0.0007	0.0003	0.01	1100	490	276	176
	walking speed variability	0.0021	0.0022	0.34	7550	3356	1888	1208
Generalized Mixed Model (with Random Intercept)	walking speed (likelihood of hitting 10th%tile low)	-0.0008	0.0005	0.1	588	262	148	94
	computer usage (likelihood of hitting 40th%tile low)	-0.0016	0.0002	<.0001	58	26	16	10
	walking speed variability (70th%tile high)	-0.0009	0.0003	0.0009	184	82	46	30

Dodge et al., Plos One 2015

Use person-specific thresholds



Dodge Threshold Model (DTM)

Dodge et al., Plos One (2015).

Wu et al., A & D: TRCI (2021)

Fig 2. Likelihood (log odds) of days with low threshold computer usage over time. Example: Computer use. For each participant, we calculated the 40th percentile of the first available 90 days of daily records of computer usage level (in minutes) and defined his/her individual-specific 40th percentile low threshold. Weekly average data based on these 90 days of daily records were then excluded from analysis, and the first week after these 90 days was defined as the baseline week of computer usage for this participant in our analysis. Model description detail is provided in Supplemental Material.

Advantage of Digital Biomarkers (2)

- ***Use each subject as their own universe*** in order to ***identify subtle changes*** or ***deviations*** from their own pre-morbid stage (i.e., use subject-specifically defined normative stage).

- "***Big Data" for Each Subject***

  Eliminate inter-individual variability → Increase signal-to-noise ratio > reduced sample size

Advantage of Digital Biomarkers (3)

Digital biomarkers are relevant for patients' daily function and well-being, i.e.,
clinically relevant and meaningful

Which one matters more for participant and his/her family and "clinical" diagnosis?

- My CSF Ab42 went up by 0.02 SD
- My MMSE score improved by 0.5 point
- My medication adherence improved: I do not often forget taking medications
- I sleep better at night and therefore am more active during daytime

Advantage of Digital Biomarkers (4)

Digital biomarkers are relevant for patients' daily function and well-being, i.e.,

clinically more relevant and meaningful

Which one matters more for participant and his/her family and "clinical" diagnosis?

- My CSF Ab42 went up
- My MMSE score improved by one point

Translational effects are measurable using digital devices

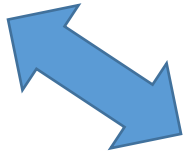
- My medication adherence improved: I do not often forget taking medications
- I sleep better at night and therefore am more active during daytime

Advantage of Digital Biomarkers (3)

Current Regulatory Perspective

Gold Standard Outcomes:

CDR, CDRSoB, Incidence, Traditional NP tests



Biomarkers

Targeted by a specific compound: Clear mechanistic hypothesis

Digital Biomarkers

Indicators of <u>daily functions , clinically meaningful</u>

Sensitive secondary endpoints (or even primary endpoints in the future)

Digital Biomarkers as Trial Outcomes: ADVANTAGES

- ❑ Non invasive (cost effective, low participants' burden)
- ❑ Clinically meaningful (closely tied with daily functions and well-being, clinical diagnosis)
- ❑ High-frequency data
  - ✓ Improve precision, increase signal-to-noise ratio
  - ✓ ***Use each subject as their own universe*** so that we can ***identify subtle changes*** or ***deviations*** from their own pre-morbid stage (e.g., *DTM)*
- ❑ Potentially reduce trial duration (e.g., changes in CDR or incidence of MCI take a long time, digital biomarker changes can be observed sooner)

Current Limitations

- Not many trials are using digital biomarkers as outcomes
- A big effort is needed to implement digital biomarkers as trial outcomes to establish more evidence (e.g., show higher efficacy than traditional outcomes)

More trials need to include digital biomarkers as secondary or exploratory outcomes

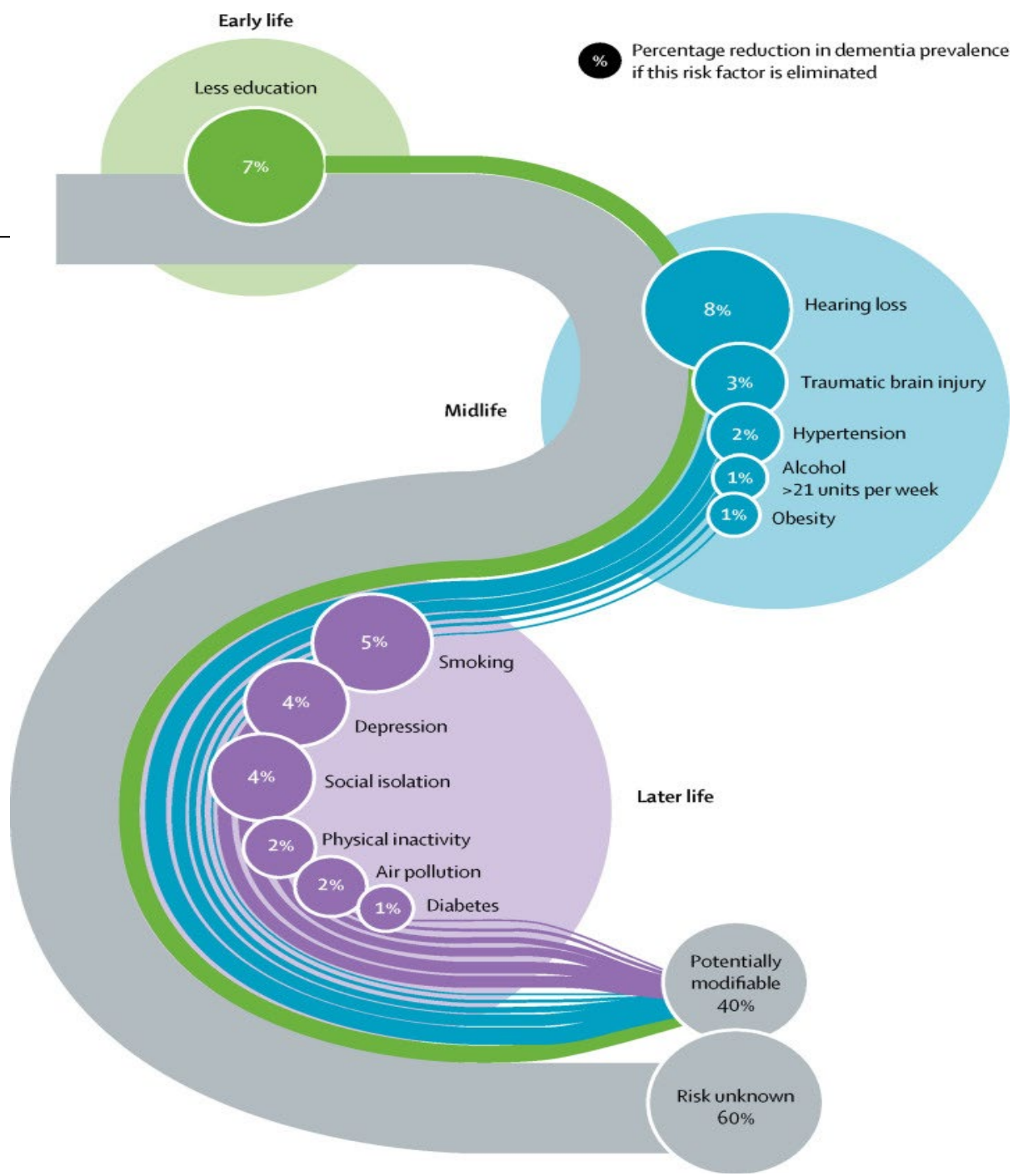
The theme of the ADC meeting: Diversity/Equity/Inclusion

SELECTION BIAS WITHIN MINORITY GROUPS ??

A Lesson learned from the *I-CONECT Project Recruitment*

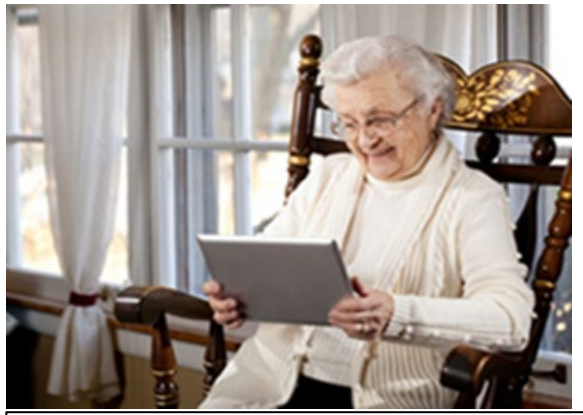
Social Isolation and Cognition

- The most recent report by the Lancet Commissions (Livingstone, et al., 2020) estimates that 4% of dementia cases can be prevented by eliminating social isolation (larger than 2% estimated for physical inactivity and 1% for diabetes.



I-CONECT Internet-based Conversational Engagement Clinical Trial

RCT Aimed to Enhance Cognitive Functions through Stimulations from Social Interactions Using Video Chats among the Older Old



- ✓ *Can start without much motivation*
- ✓ *Can be done at home (be delivered to those with chronic illness/homebound)*
- ✓ *Can assess translational effects*
- ✓ *Can be sustainable for the long long term*

PI: Dodge

I. NIA R01 AG0033581 (2010-2014) Completed (ClinicalTrials.gov: NCT01571427)

II. NIA R01 AG051628 (2016- 2021) Ongoing (Normal)

III. NIA R01 AG056102 (2017- 2022) Ongoing (MCI)

www.i-conect.org (ClinicalTrials.gov: NCT02871921)

Aka, I-CONECT

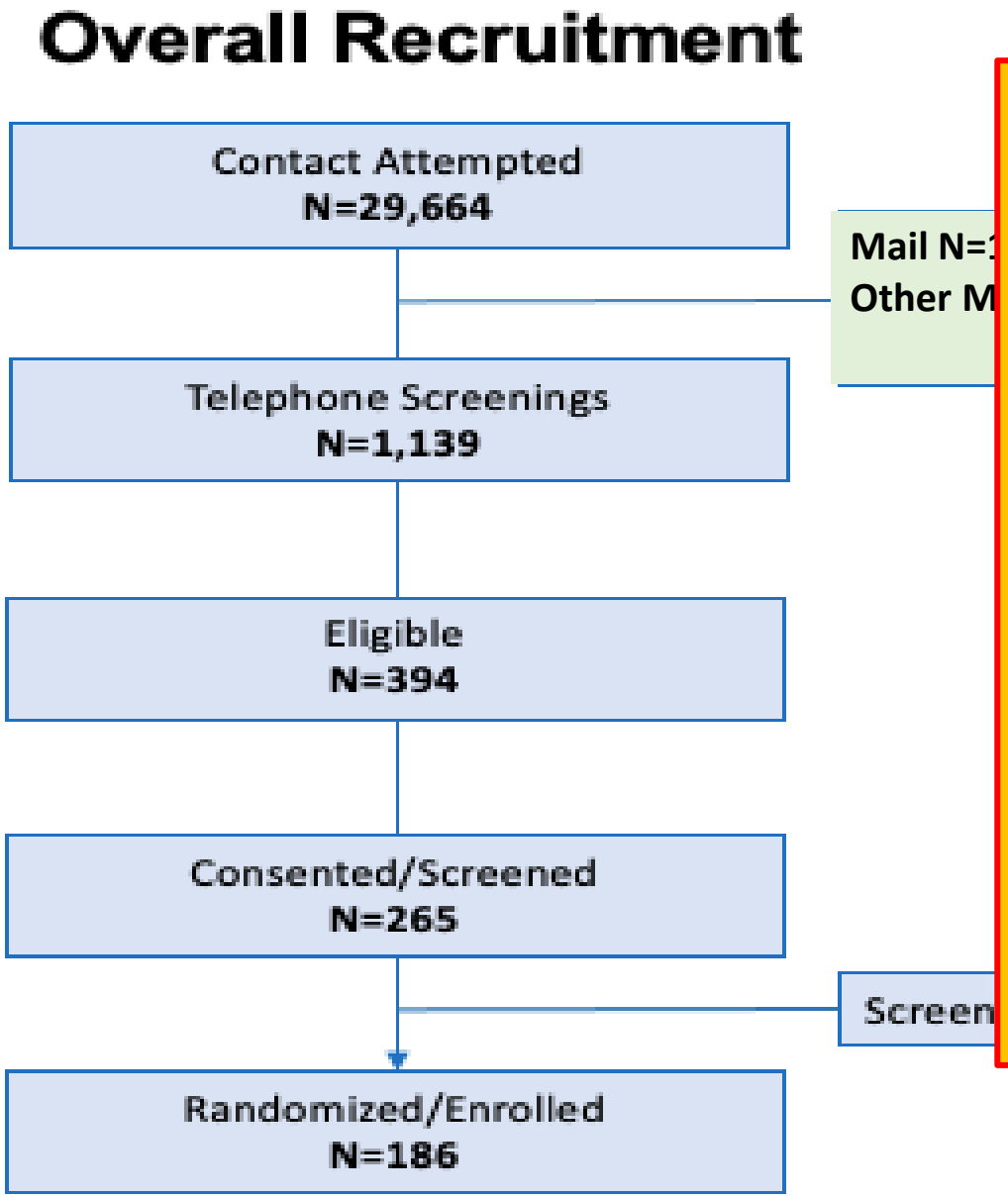
I-CONECT Internet-based Conversational Engagement Clinical Trial

RCT Aimed to Enhance Cognitive Functions through Stimulations from Social Interactions Using Video Chats among the Older Old

In this series of RCTs

- Participants in the experimental group engaged in 30 minutes of conversation with trained interviewers (conversational staff) using internet/webcam (control: only 10 mts weekly phone calls)
- Conversations: semi-structured in order to standardize interactions, yet require participants to understand interviewers, organize and convey their own thoughts in a natural conversational setting like talking with their friends.
- Expose participants to different conversational staff each week (if possible) to enhance novelty of the experience

Challenge: Recruiting Socially Isolated Older Old



Socially Isolated 75+ yrs, Normal or MCI

Caucasians:

96% of the targeted (149/160)

African Americans (AA):

23% of the targeted (37/160)

TOTAL: 186 randomized (20% AA)

Data collection completion/un-blinded: 8/2021

Methods

- **Emotion characteristics were compared between the AA and Caucasians** using **NIH toolbox emotion battery** (NIHTB-EB), including 3 domains and 17 subscales.
- **Baseline data** from the Internet-Based Conversational Engagement Clinical Trial (I-CONECT)
- **Linear regression models** comparing the NIHTB-EB outcomes between Caucasian and AA participants

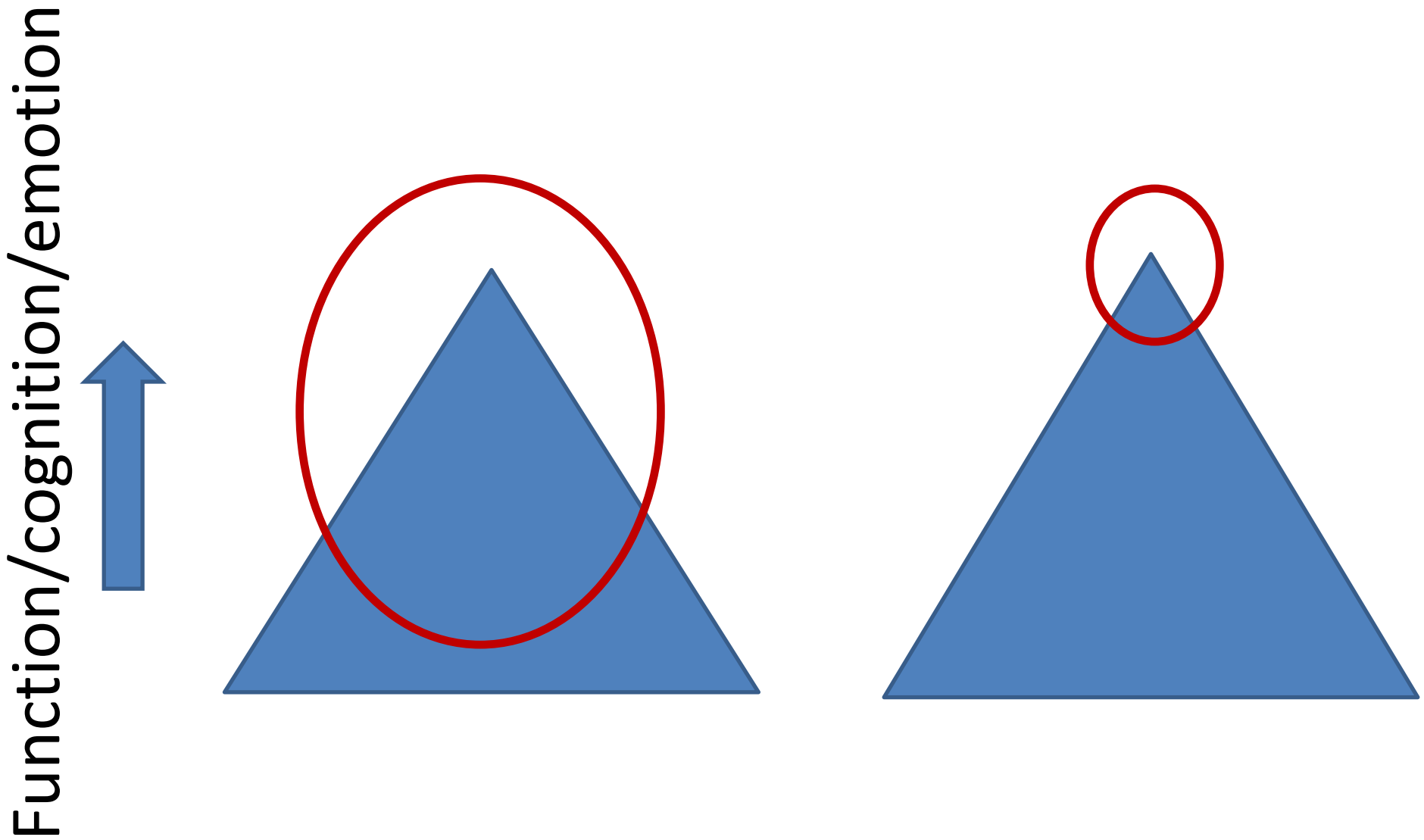
Kexin Yu, Post Doctoral Fellow

Table 1. Linear regressions compare NIH toolbox emotion battery domain scores of AA and Caucasian participants **(N=163, Reference group – Caucasian participants)**

	Coefficient	SE	p	95% CI	
A. Three domains of NIHTB-EB					
Negative Affect	-2.573	1.597	0.109	-5.728	0.582
Psychological Wellbeing	5.670	1.589	0.000***	2.531	8.810
Social Satisfaction	7.915	1.804	0.000***	4.349	11.481
B. Subscales of the Negative Affect domain					
Anger Affect	-2.195	1.634	0.181	-5.424	1.033
Anger Hostility	-0.432	1.630	0.791	-3.651	2.788
Sadness	-5.394	1.969	0.007**	-9.283	-1.504
Fear Affect	-1.749	1.987	0.380	-5.674	2.176
Perceived Stress	-1.245	1.689	0.462	-4.582	2.092
C. Subscales of the Psychological Wellbeing domain					
Positive Affect	4.742	1.580	0.003**	1.620	7.863
Meaning and Purpose	7.698	1.553	0.000***	4.631	10.765
General Satisfaction	1.606	1.797	0.373	-1.943	5.156

Note: *p<.05, **p<.01, ***p<.001. All models controlled for age, sex, education, MCI status, marital status and depressive symptoms. **NIHTB-EB: population mean=50, SD=10.**

Selection Bias in Recruitment



Discussion

The findings comparing NIBTB-EB outcomes show that **AA participants were better off** than their Caucasian counterparts in psychological wellbeing and social satisfaction.

Selection bias among the minority groups since it's more difficult to recruit them??

Merely increasing the proportion of minority participants might introduce some unexpected bias in trial results.

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THANK YOU !!

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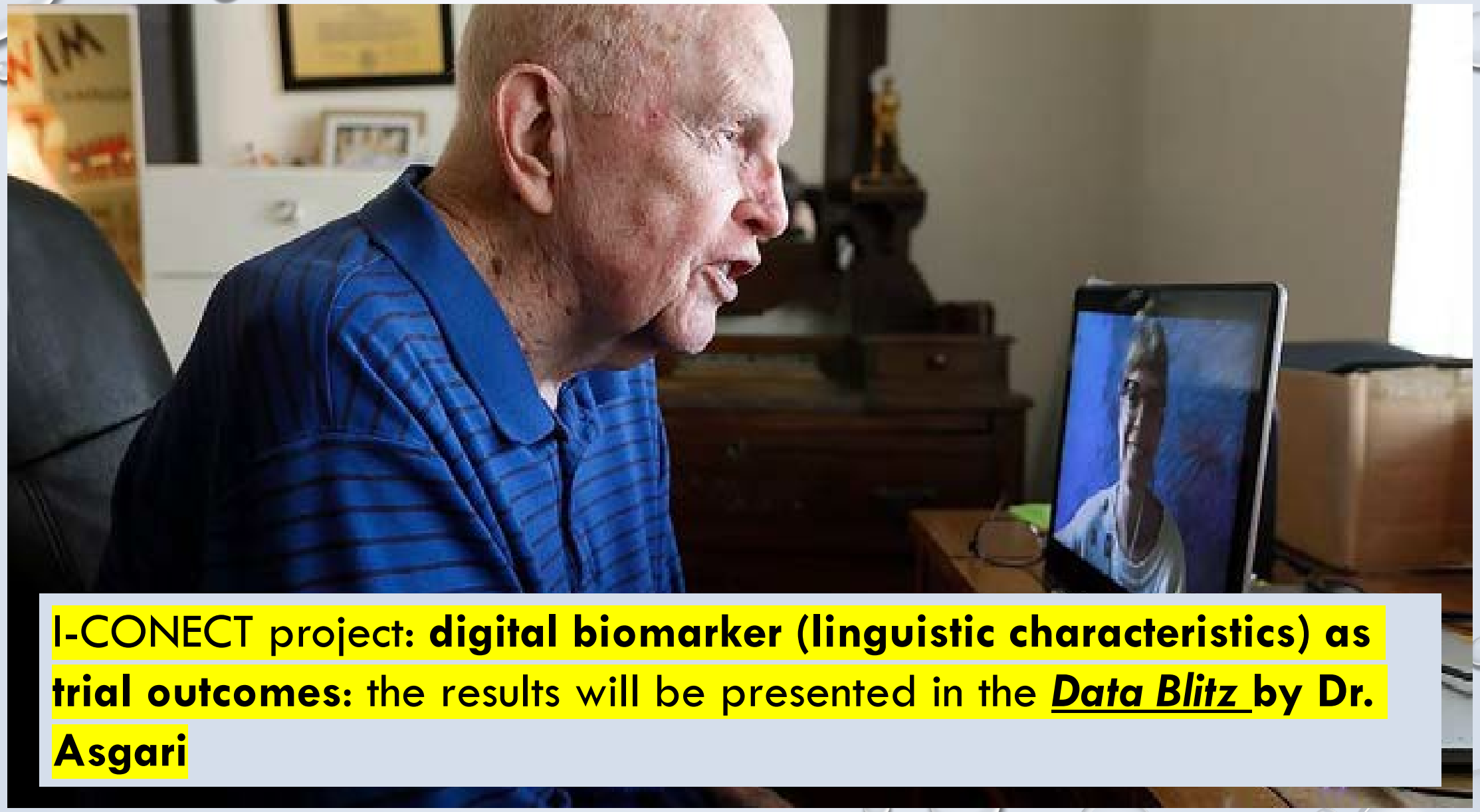

I-CONECT project: **digital biomarker (linguistic characteristics) as trial outcomes:** the results will be presented in the ***Data Blitz*** **by Dr. Asgari**

Operational Definition of Isolation in *I-CONECT*

- The participants were considered socially isolated if they met ***any one of the following three criteria***:
    1) Scoring <12 on the 6-item Lubben Social Network Scale (LSNS-6)
    2) Engaging in conversations lasting 30 minutes ≦ twice per week
    3) Answering "often" to at least one question of the three-item UCLA Loneliness Scale.