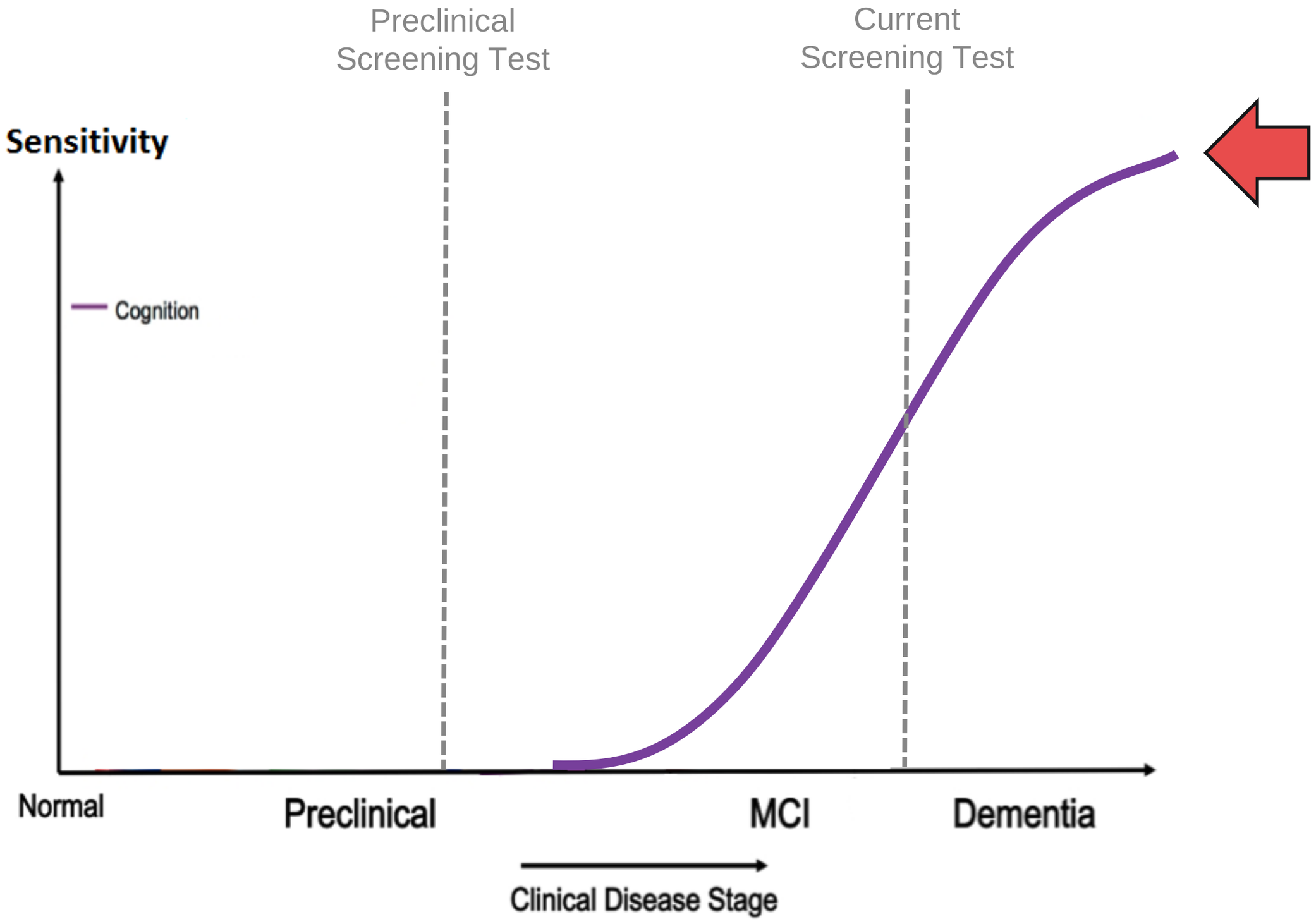
Technology Enablement of Digital Biomarkers for the Futurization of AD Research

Rhoda Au, Ph.D.

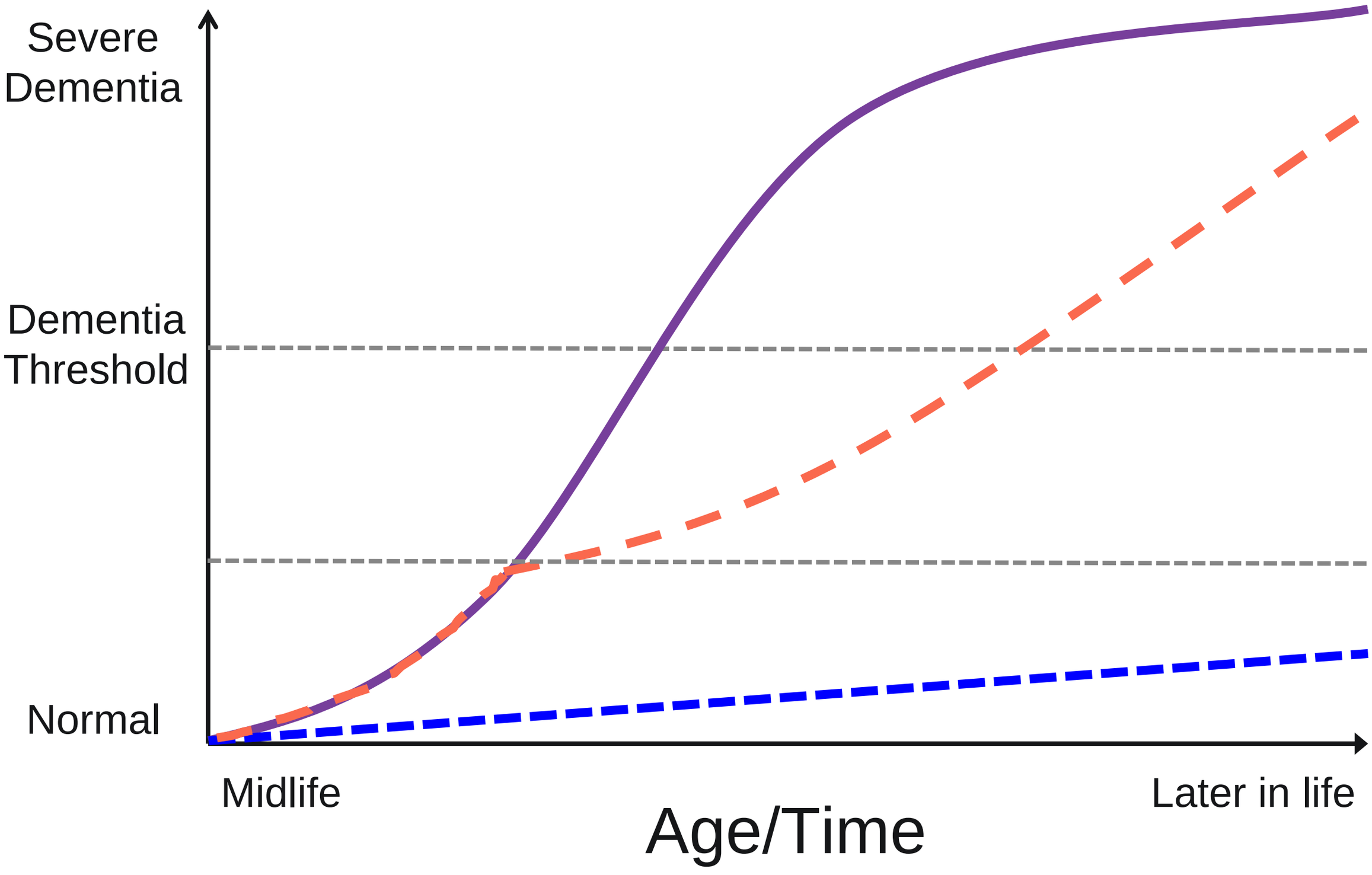
4-20-18

Our New Strategy



Adapted by Drs. Dana Penney and Randall Davis from Fig 3 of *Criteria For Preclinical Alzheimer's Disease,* Alzheimer's Association report (2010), which in turn cites Jack C R, et al., Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, *The Lancet*, **9**:1, Jan 2010, pp 119-128.

The Impact



Alzheimer's Association. "Changing the Trajectory of Alzheimer's Disease." *Washington DC* (2010).

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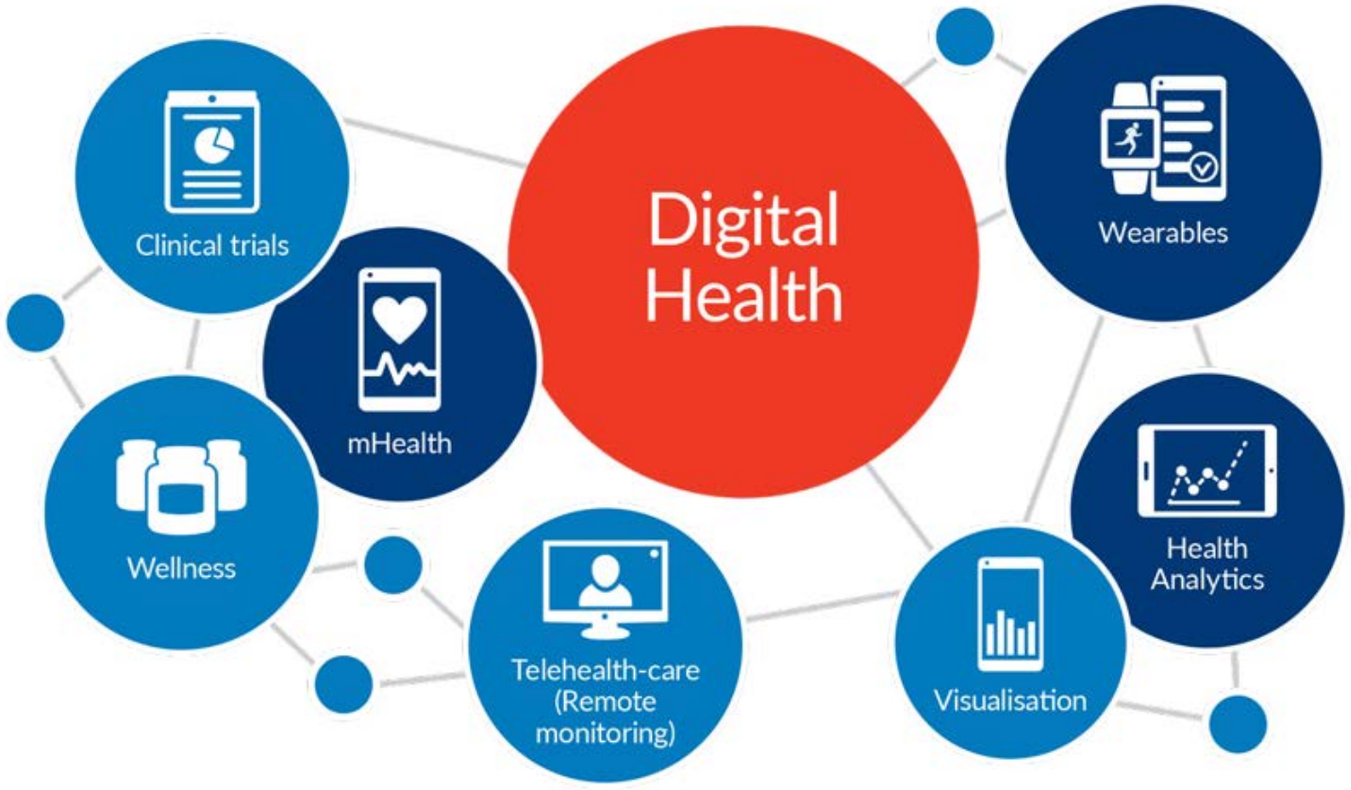
Aging Well Institute

Converting Ideas into Reality

FDA Digital Health Initiative

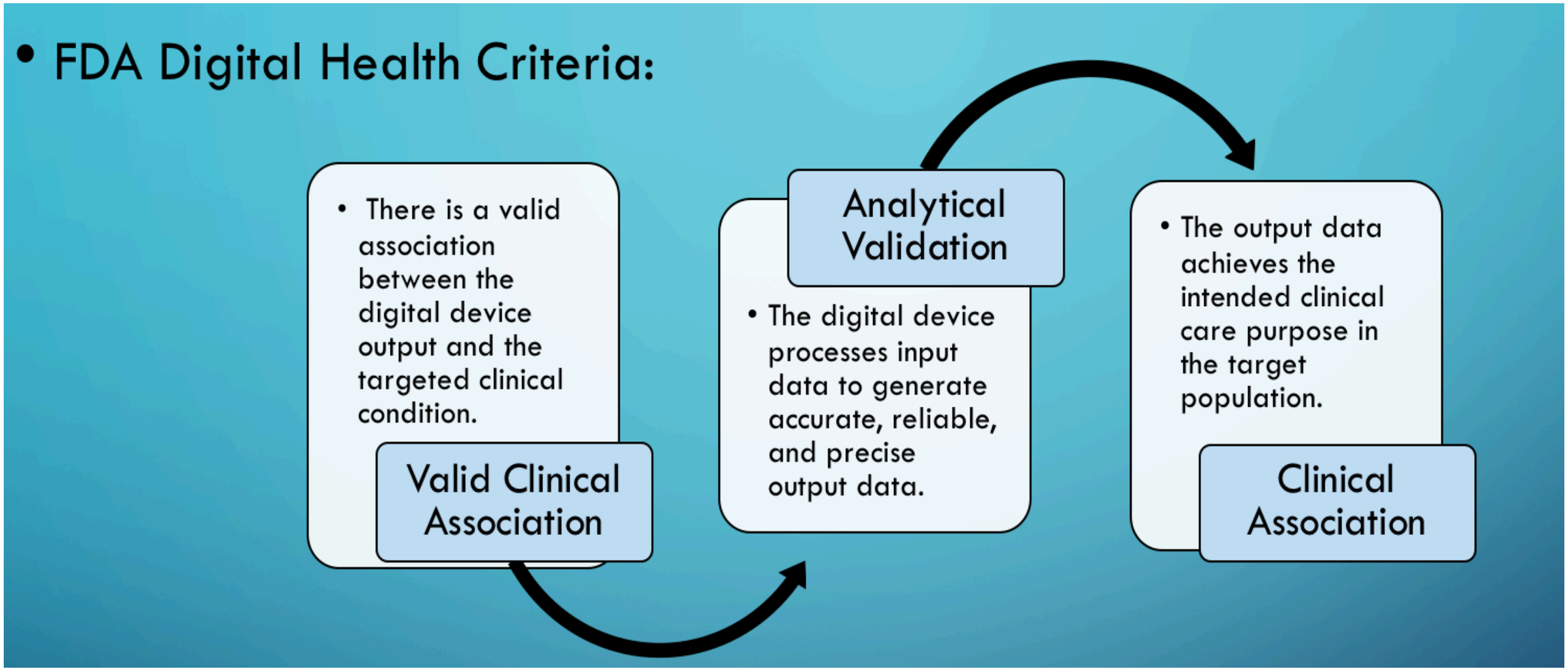


The FDA has implemented the *Digital Health Innovation Action Plan*

Promote the development and use of digital health technologies

Source: https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm

Digital Health Initiative



Digital health technologies may act as susceptibility/**risk biomarkers**

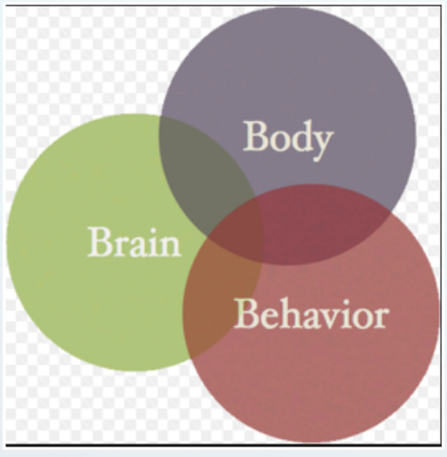
Sources: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM524904.pdf
https://www.ncbi.nlm.nih.gov/books/NBK326791/pdf/Bookshelf_NBK326791.pdf

Digital Biomarkers

DIGITAL BIOMARKERS

Background

- Behavioral activity markers offer an alternative tool for detecting normal cognitive aging to MCI transitions.



Methods

- Average talk time/day collected through small wearable digital recording devices.
- Data examined by speech detection algorithms.

Results

- MCI subjects used more words during conversations and exhibited longer daily talking time than normal subjects.
- MCI subjects exhibit subtle language processing deficits that are sensitive to transitions to MCI.

Source: Kaye, J., Gregor, M., Matteck, N., Asgari, M., Bowman, M., Ybarra, O., & Dodge, H. (2014). SOCIAL BIOMARKERS FOR EARLY SIGNS OF DEMENTIA: INCREASED SPOKEN WORD COUNTS AMONG OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT (MCI). *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *10*(4), P915-P916.

Digital Assessment & Cognitive Training

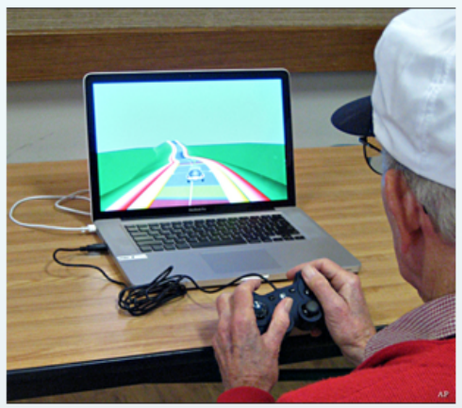
DIGITAL BIOMARKERS

Background

- The aging population exhibits multitasking difficulties and cognitive control deficits.

Methods

- Multitasking performance assessed with a custom-designed 3-D video game (NeuroRacer).



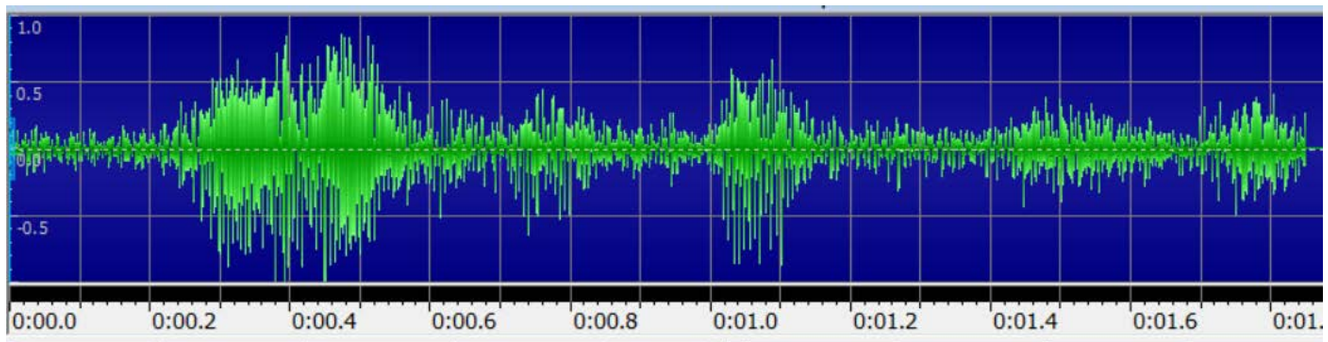
Results

- Highlighted plasticity of the prefrontal cognitive control system.
- Showed digital technology can be used to assess cognitive abilities across lifespan, evaluate neural mechanisms and serve as a tool for cognitive enhancement.

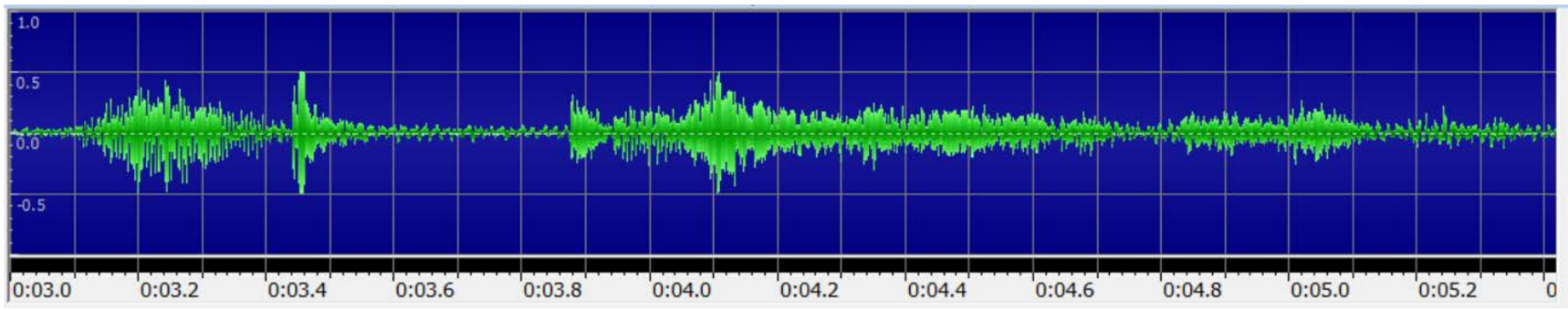
Source: Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., … Gazzaley, A. (2013). Video game training enhances cognitive control in older adults. *Nature*, *501*(7465), 97–101. http://doi.org/10.1038/nature12486

FHS Digital Voice

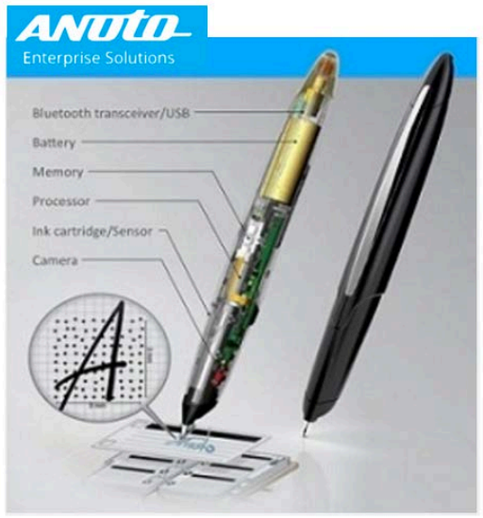
Not Demented: 2009

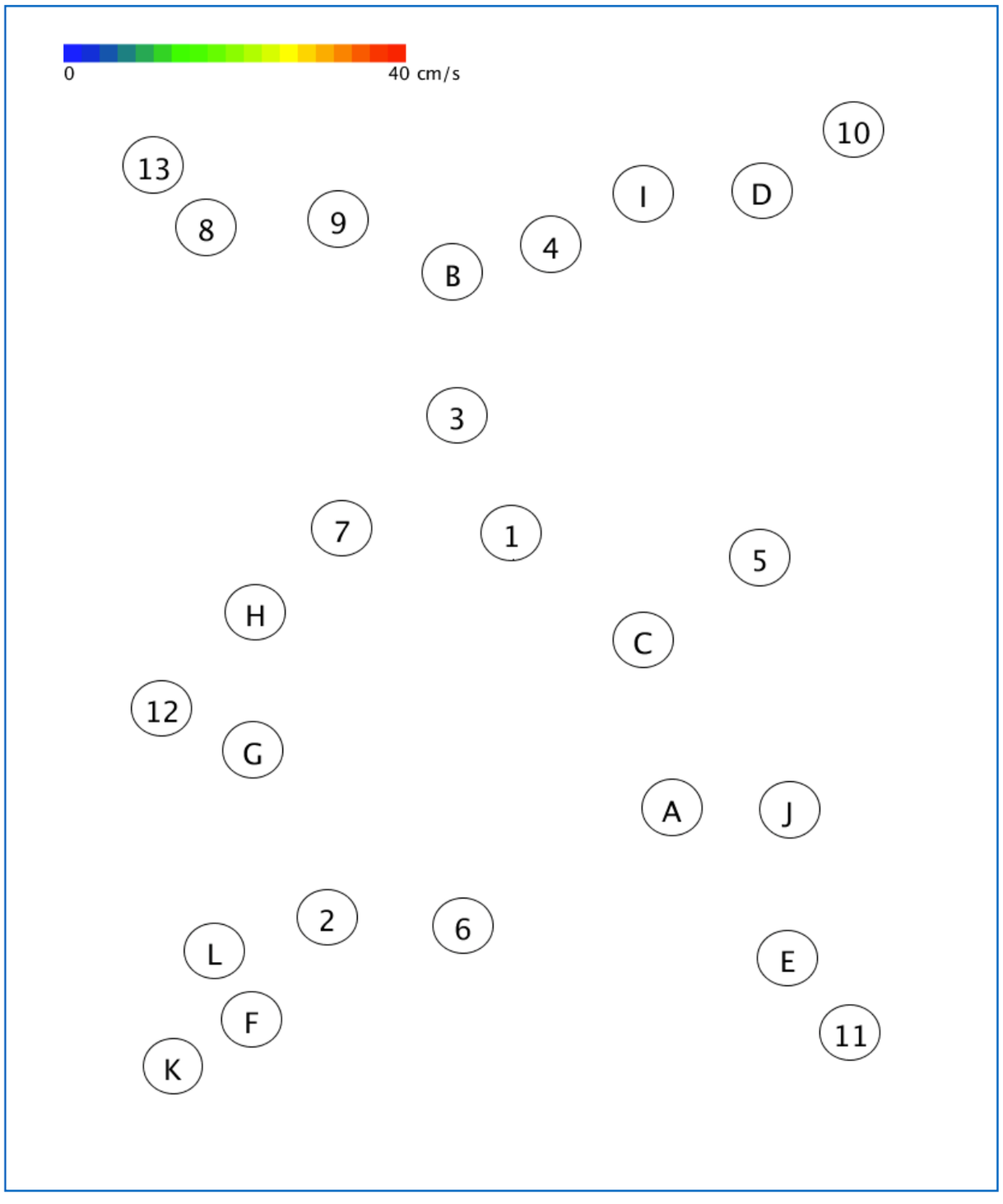


Mild Cognitive Impairment:2015



FHS Digital Drawing





Digital Pen
Supportive Research

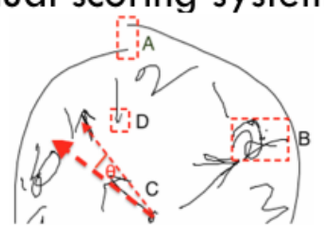
LEARNING CLASSIFICATION MODELS OF COGNITIVE CONDITION FROM SUBTLE BEHAVIORS IN THE DIGITAL CLOCK DRAWING TEST SOUILLARD-MANDAR ET AL. (2015)

Background

- Clock Drawing Test
  - screening tool for cognitive impairment
  - commonly used to help diagnose cognitive dysfunction (AD, PD)
- Researchers at MIT/Lahey developed software to analyze data acquired using a digitized ballpoint pen
  - >900 variables

Methods

- 2169 digital clock tests organized into 4 categories
  - memory impairment disorders (AD/MCI)
  - vascular cognitive disorders
  - PD
  - cognitively normal
- Compared screening and diagnosis accuracy of machine learning (ML) compared to 8 manual scoring systems (MSS)



Significance

- Screening:
  - ML: 0.89-0.93 AUC
  - MSS: 0.70-0.73
- Diagnosis:
  - ML: 0.79-0,83 AUC
  - MSS: 0.65-0.69
- Conclusion:
  - Detect cognitive impairment earlier
  - Detect treatment efficacy

Digital Pen
Supportive Research

AGE AND GRAPHOMOTOR DECISION MAKING ASSESSED WITH THE DIGITAL CLOCK DRAWING TEST: THE FRAMINGHAM HEART STUDY PIERS ET AL. (2017)

Background

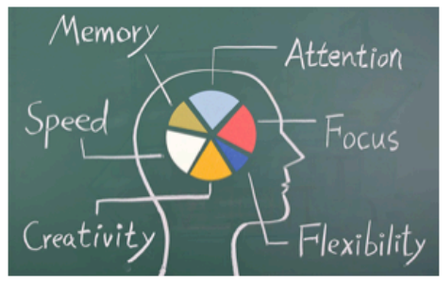
- Challenge in differentiating performance in cognitively normal individuals
- Age remains the biggest predictor of dementia/AD
- dCDT provides means for detecting change in a higher risk non-demented population

Methods

- FHS participants (n=1791)
  - stroke & dementia free
  - dCDT to command and copy with hands set for "10 after 11."
- Six age groups were constructed (28-98).

Results

- Age groups differences (copy & command):
  - total time to completion
  - total pen stroke count
  - higher-order decision making latencies
- Digital metrics can detect differences in those at risk but still asymptomatic for AD

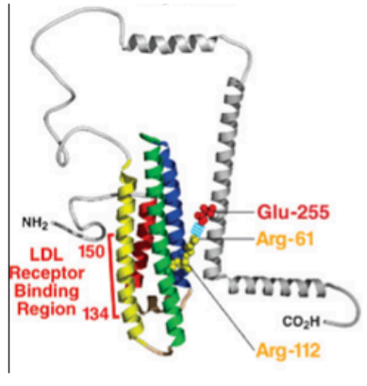


Digital Pen
Preliminary Findings

DETECTING SUBTLE COGNITIVE IMPAIRMENT ASSOCIATED WITH GENETIC APOE ALZHEIMER'S DISEASE RISK: A PRELIMINARY STUDY PENNEY, SOUILLARD-MANDAR, AU AND DAVIS

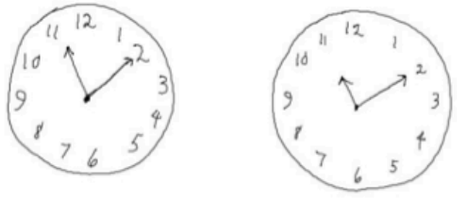
Background

- Apolipoprotein E4 allele (ApoE4) is a well- known genetic risk factor for AD
- Can dCDT detects subtle cognitive differences in those with and without AD genetic risk?



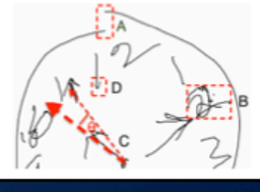
Methods

- 1243 dementia- free FHS participants (n=1243)
  - Dementia free
  - ApoE and divided into:
    - high AD risk (ApoE4+)
    - low AD risk (ApoE4-)
- Administered dCDT (copy & command)
- Applied Machine learning (ML)



Results

- Compared to ApoE4-, ApoE4+:
  - Command
    - lower drawing efficiency
    - longer average latency
  - Copy
    - worse information processing
    - highest longest latencies
    - higher long latency count
- ML algorithms can identify dCDT metrics that indicate poorer cognitive efficiency in people at higher AD genetic risk but asymptomatic for disease

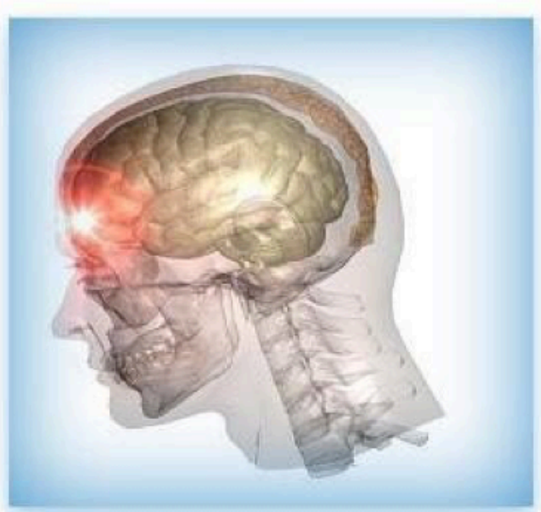


Digital Pen
Preliminary Findings

COGNITIVE EFFECTS OF TRAUMATIC BRAIN INJURY ASSESSED WITH THE DIGITAL CLOCK DRAWING TEST: A PRELIMINARY STUDY MCCLINTOCK ET AL.

Background

- Investigate cognitive changes associated with a history of traumatic brain injury (TBI) using the digital Clock Drawing Test (dCDT).



Methods

- FHS Generation 3 participants (n=713)
  - Retrospective medical record review for TBI and no TBI
  - administered dCDT (copy & command)
  - MRI measures:
    - hippocampal volume
    - white matter hyper intensity volume (WMH)

Results

- TBI participants had:
  - smaller hippocampal volume
  - greater WMH
- TBI participants on dCDT had:
  - longer total times to completion
  - Longer pre-2nd hand latencies (command condition only)
- History of TBI has chronic effects on behavioral and neuroimaging indices associated with preclinical AD
  - dCDT is able to detect subtle cognitive changes.

New Technology Development

dNP Platform

清華大學 Tsinghua University

北京協和醫院 PEKING UNION MEDICAL COLLEGE HOSPITAL

New Technology Development

dNP Platform

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Logical Memory: Recognition (WMS)

Circle the participant's response. "No Guess" = 6; however, strongly encourage participant to make a guess.

I'm going to ask you some questions about that story. one, of the three choices in each question, is correct.

	Response1	Response2	Resp
Was the story about:	a woman	a man	
Was her name:	Annie Thomas	Anna Thompson	
Was she from the:	Southwest	South Boston	
Was she:	a secretary	a housekeeper	or a
Did she work in:	a private home	a railroad station	an
Was she held up on:	Main Street	Beacon Street	o
Did it happen:	that morning	the night before	or t
Was she robbed:	of $5.00	$ 15.00	
Did she have:	no children	two children	or
Did the police:	arrest her	arrest the robber	or g
Had they not eaten for:	2 hours	2 days	

SCORE:

Score

Next

FINISH

BA

Verbal Fluency

Check here if test NOT completed ☐

F

I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say "B," you might give me bad, bottle, bed. However, I do not want you to use words that are proper names such as Boston or Brian. Also, I do not want you to use the same word again with a different ending, such as bake, baking, baked. Any questions?The first letter is F. Give me as many words as you can that begin with F.Begin.

IF THE PARTICIPANT MAKES TWO OF THE SAME ERRORS CONSECUTIVELY, CUE HIM/HER:
Remember we want words that start with the letter "F"
or Remember, no proper names
or Remember, don't use the same word with different endings.

F			Voice to text
0-15(sec)	Write all words produced by participant in order		
	WrongLetter		Correct Number
	BrokenRule		
	Perseveration		
	OtherError		
	SelfCorrection		
16-30(sec)	Write all words produced by participant in order		
	WrongLetter		Correct Number
	BrokenRule		
	Perseveration		
	OtherError		
	SelfCorrection		
31-45(sec)	Write all words produced by participant in order		
	WrongLetter		Correct Number
	BrokenRule		

Boston Naming Test

Record all participant responses verbatim in the appropriate column (e.g., if the phonemic cue is given, subsequent verbalizations should be written in the Phonemic Cue column for that item). Circle the appropriate score for each item. Circle all errors that were present for a particular item in the lower (shaded) portion of that item's row. Record in seconds the time of FINAL response. See Scoring Manual for complete scoring instructions.

I'm going to show you some pictures, and I'd like you to tell me the one word that best names the object in eac

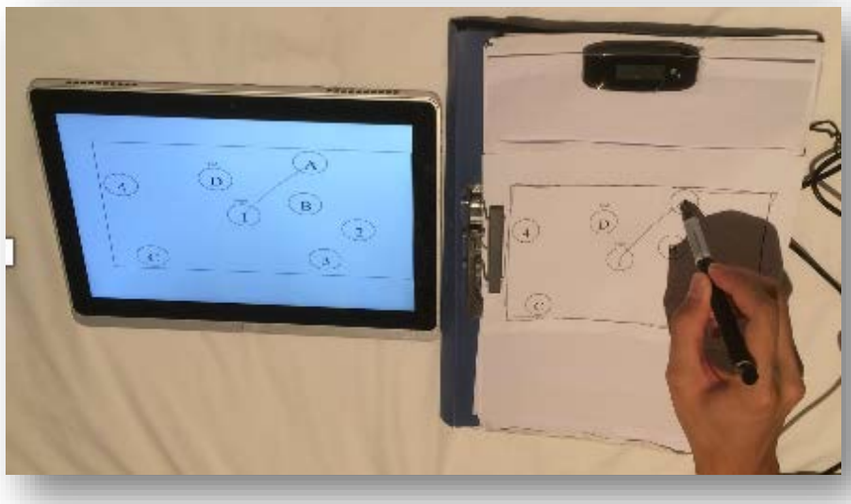
IF PERSON GIVES AN ANSWER THAT IS CLOSE, BUT NOT CORRECT (E.G., "HARNESS" FOR "YOKE"), SAY,
Can you tell me another word for that?
Can you be more specific? (E.G., "BOAT" FOR "CANOE")

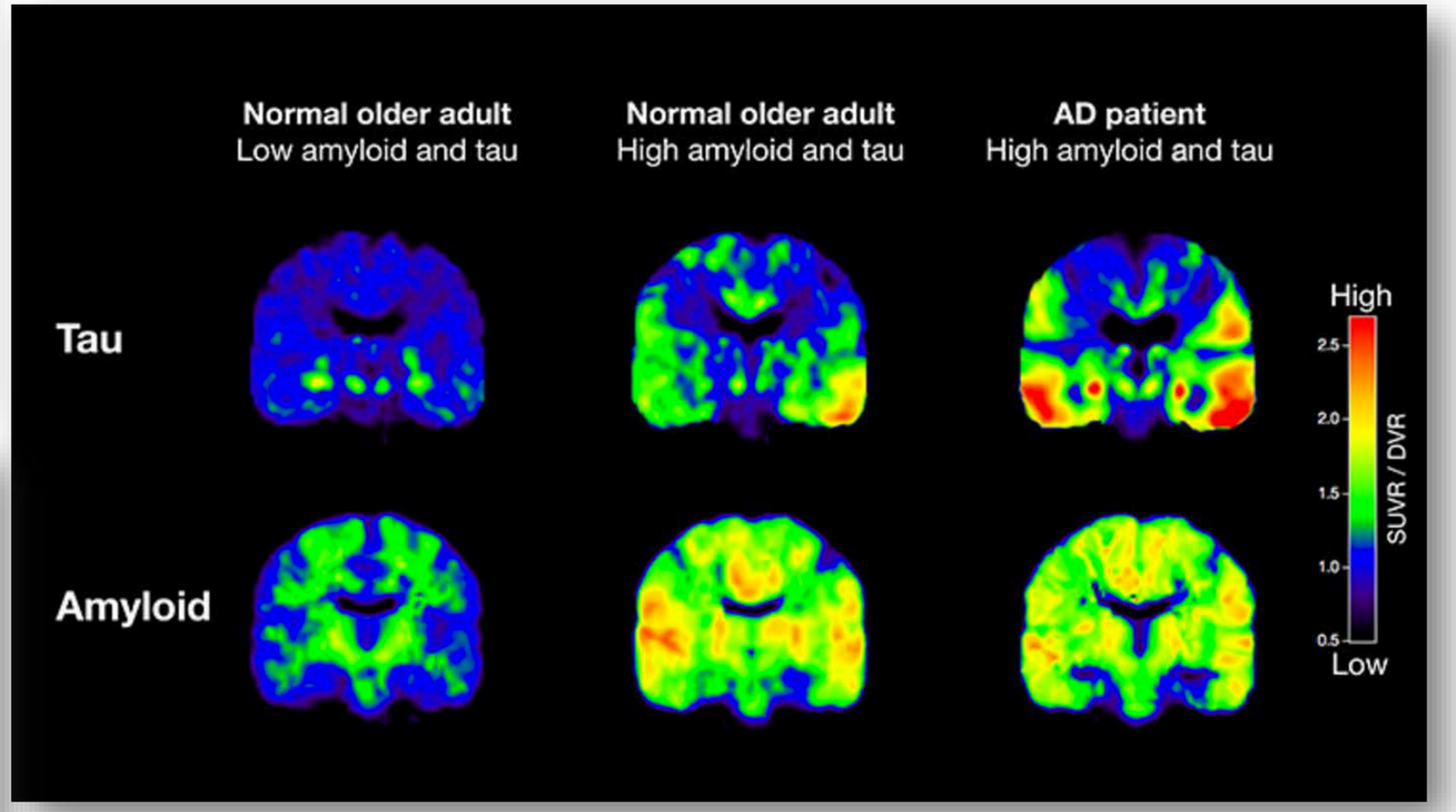
The following words are acceptable; however, if the phonemic cue is given, it should be for the word that is wr
"spyglass" in place of "telescope"
"settee" in place of "bench"
"toadstool" in place of "mushroom"
"spigot" for "faucet"

Semantic cue is given at 10 seconds.
Phonemic cue is given at 20 seconds.
TIME LIMIT for response is 40 seconds

	No Cue Circle 0 if incorrect Circle 1 if correct with no cues Circle 2 if correct immediately upon presentation; leave Time blank.			Semantic Cue Circle 0 if incorrect Circle 1 if correct with Semantic cue Leave blank if Semantic cue not given				
1. Tree	0	1	2	Something that grows	0	1	Tr	0
Errors: Circle all that apply	No error	Circumloc	Perseveration	Semantic Par.	Phonemic Par.	Perceptual		
2. House	0	1	2	A kind of building	0	1	Hou	0
Errors: Circle all that apply	No error	Circumloc	Perseveration	Semantic Par.	Phonemic Par.	Perceptual		
3. Scissors	0	1	2	Used for cutting	0	1	Sci	0
Errors: Circle all that apply	No error	Circumloc	Perseveration	Semantic Par.	Phonemic Par.	Perceptual		
4. Comb	0	1	2	Used for fixing hair	0	1	Co	0

Digital Cognitive Biomarkers





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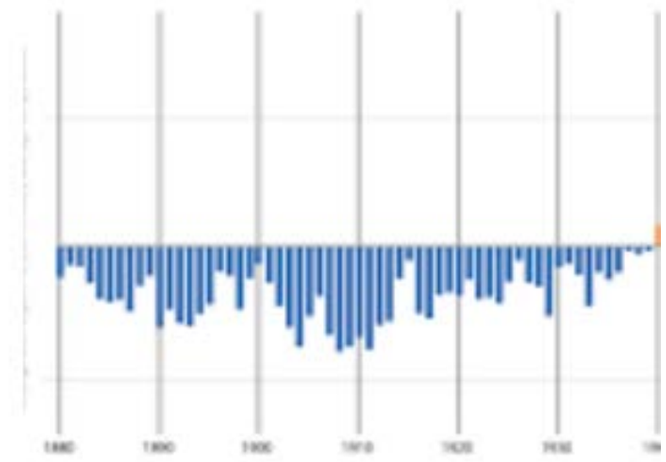
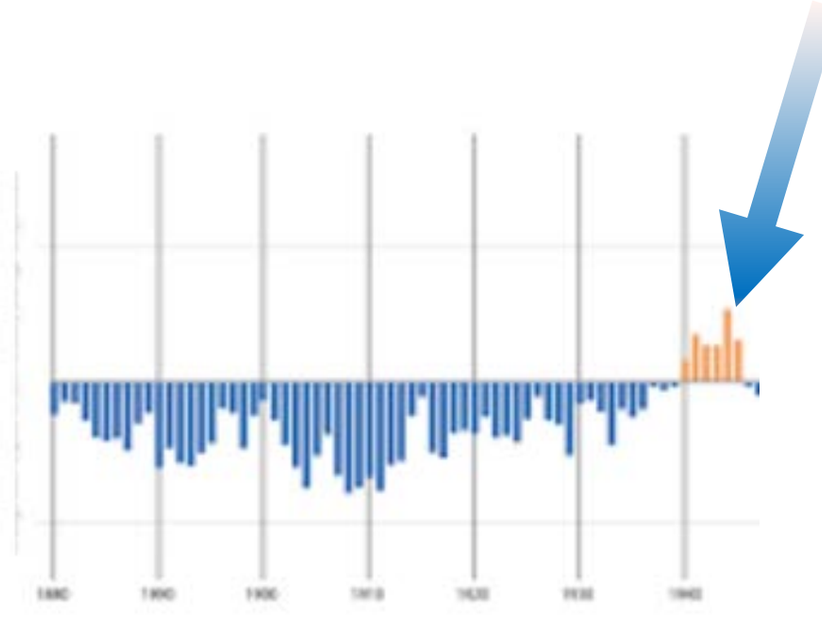
What Next?

Alzheimer’s Disease Onset is Insidious

Pre-symptomatic Monitoring





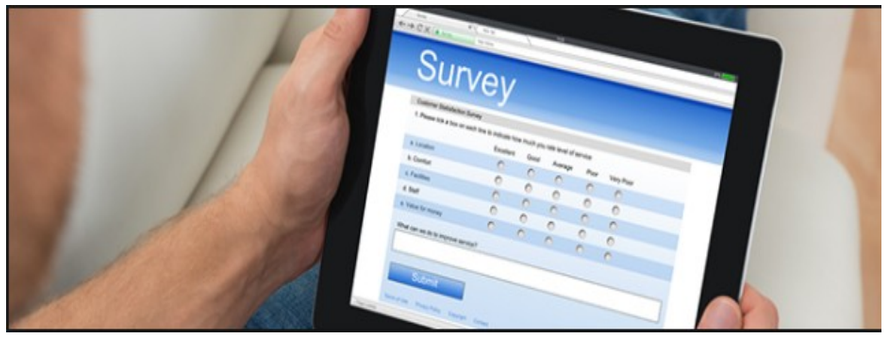
Brain Health Monitoring Platform

Traditional Data Collection: Clinic

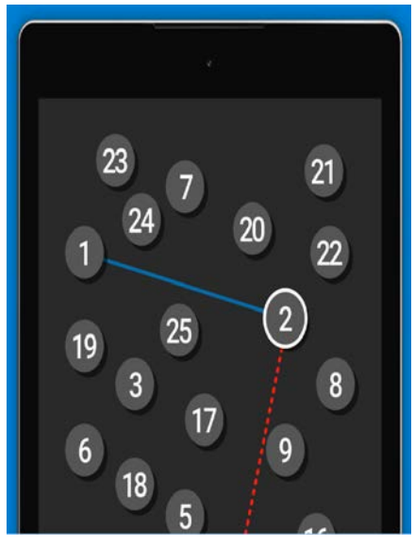
Maximize Digital Capture of Health Metrics

Active Engagement Technology

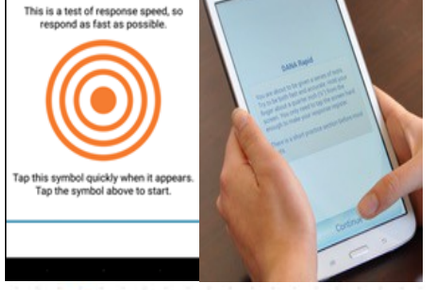
Remote Monitoring



shimmer
DISCOVERY IN MOTION



SAVONIX



DANA™

mymeds

Paradigm Shifting Approach for AD Prevention

BOSTON UNIVERSITY

Alzheimer's Disease Center

FRAMINGHAM HEART STUDY

Three Generations of Dedication

1948 1971 2002

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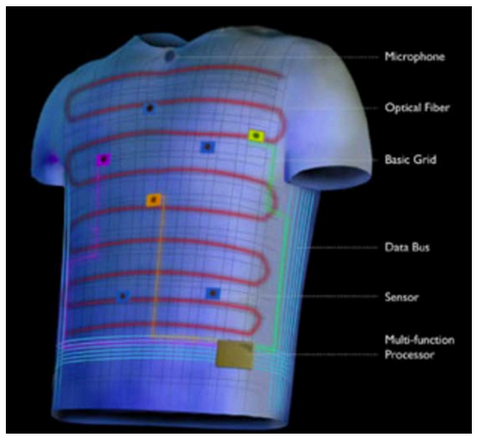
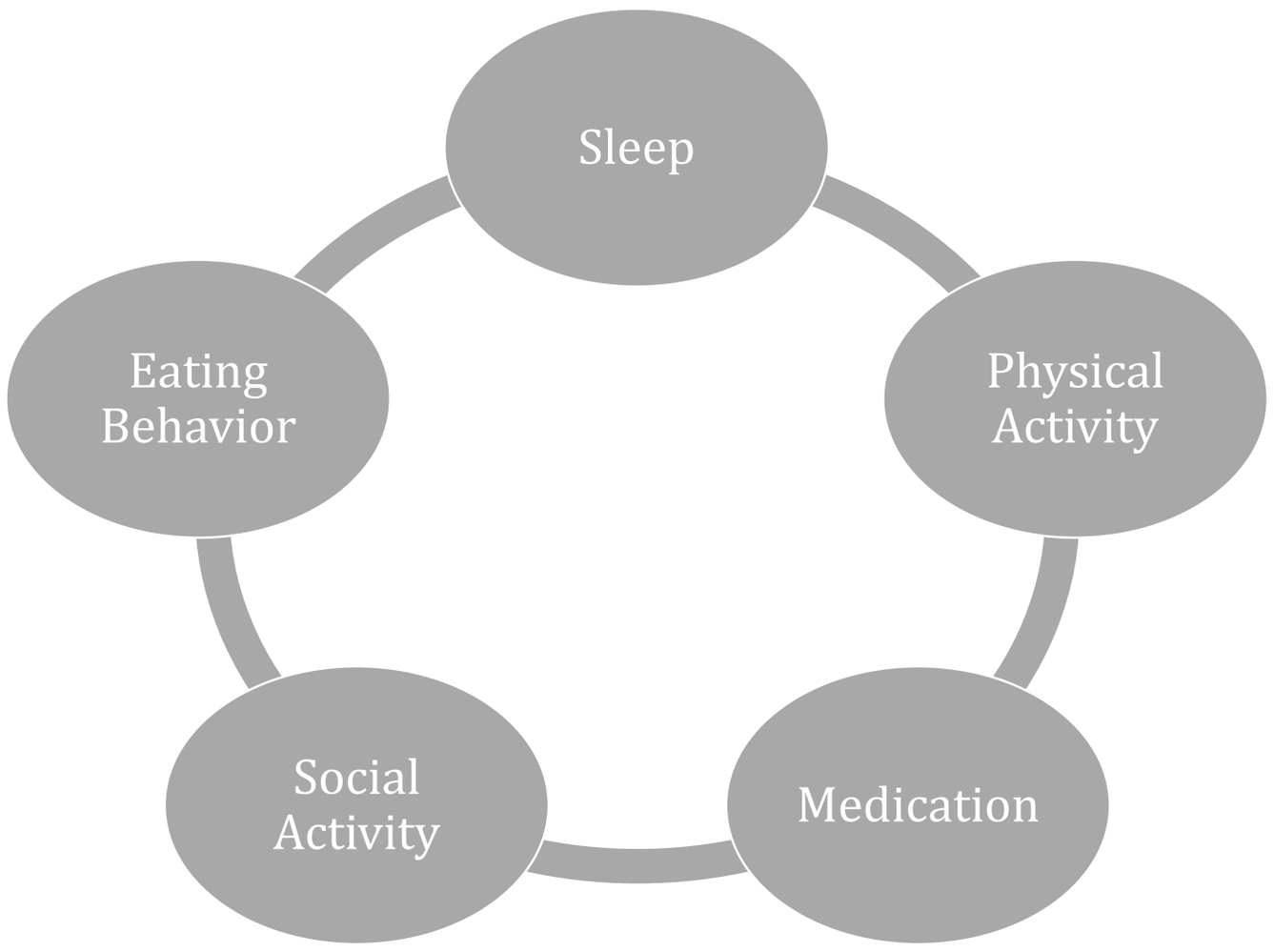
Where Next?

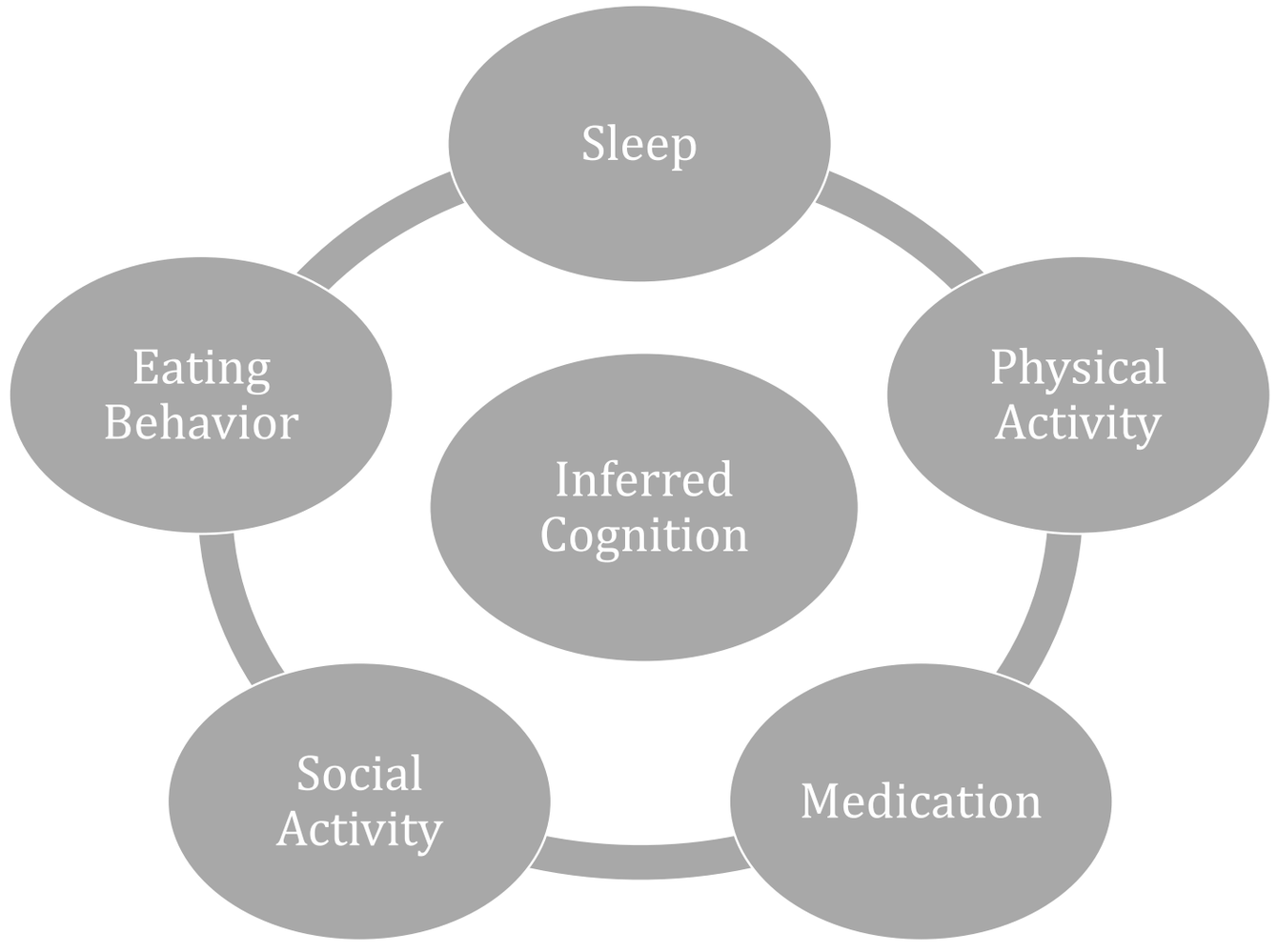
Ambient Technology

Sustainable Remote Monitoring



iCarbonX 碳云智能


Sleep
Eating Behavior
Physical Activity
Social Activity
Medication


Sleep
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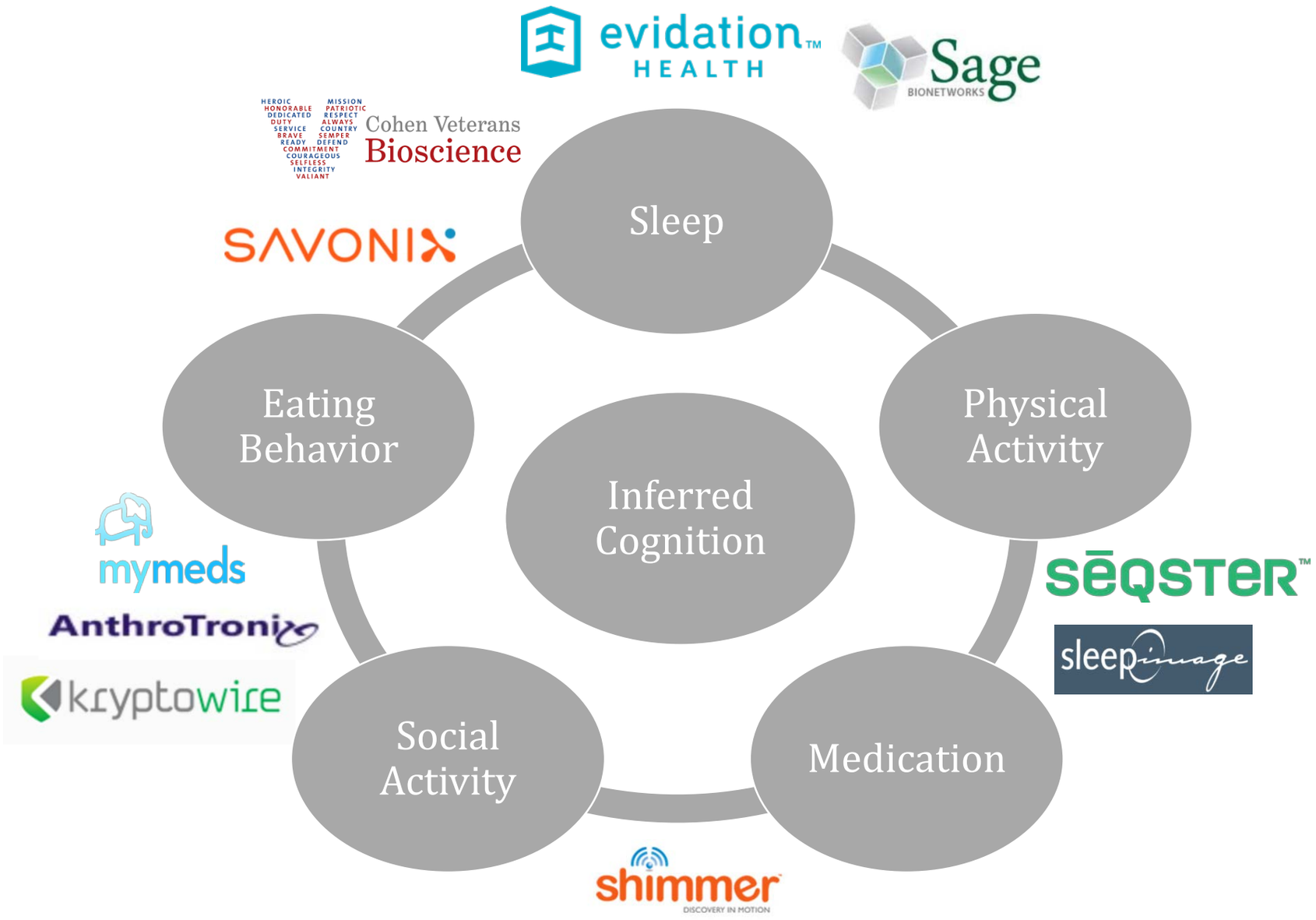
Physical Activity
Inferred Cognition
Social Activity
Medication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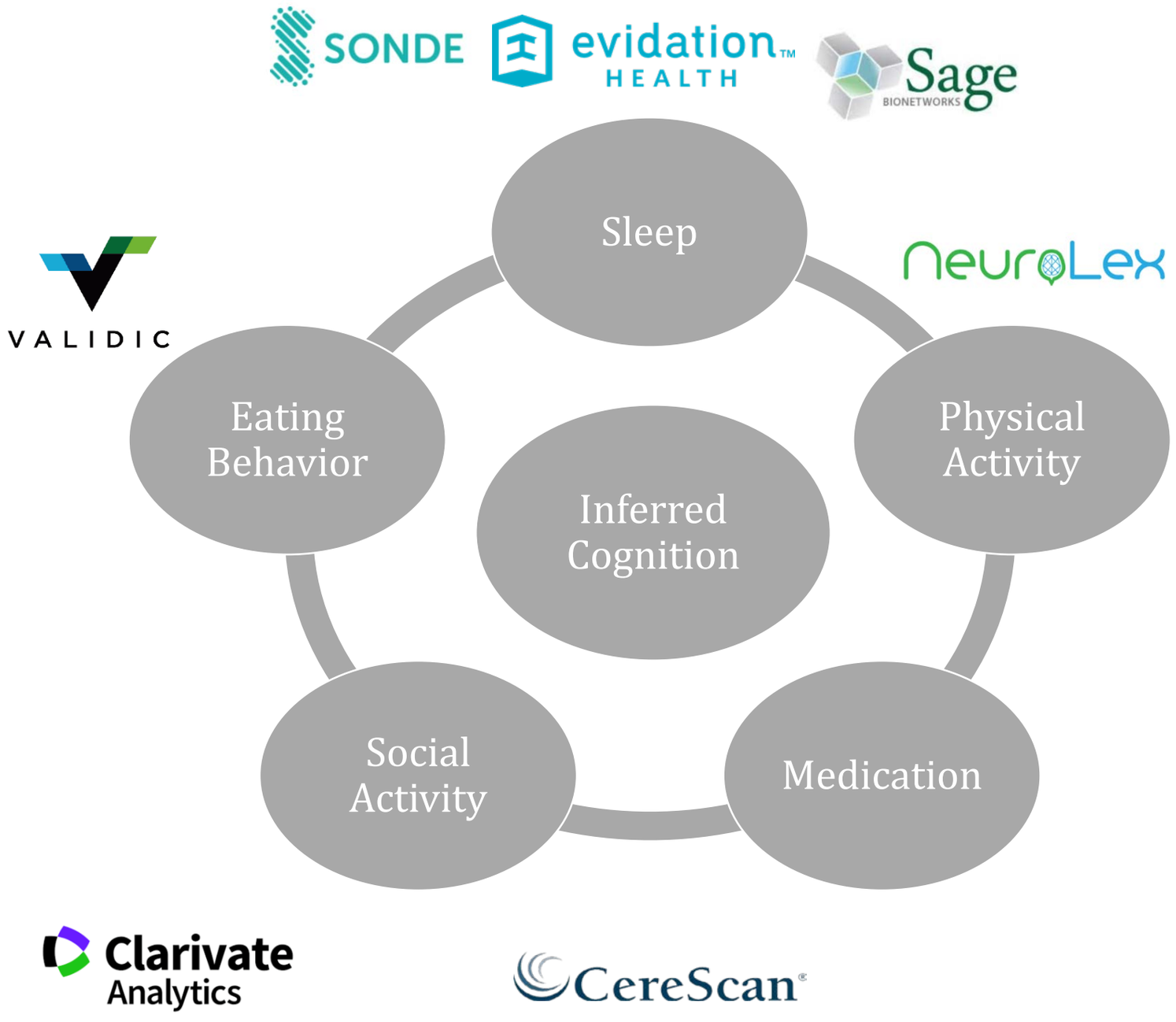
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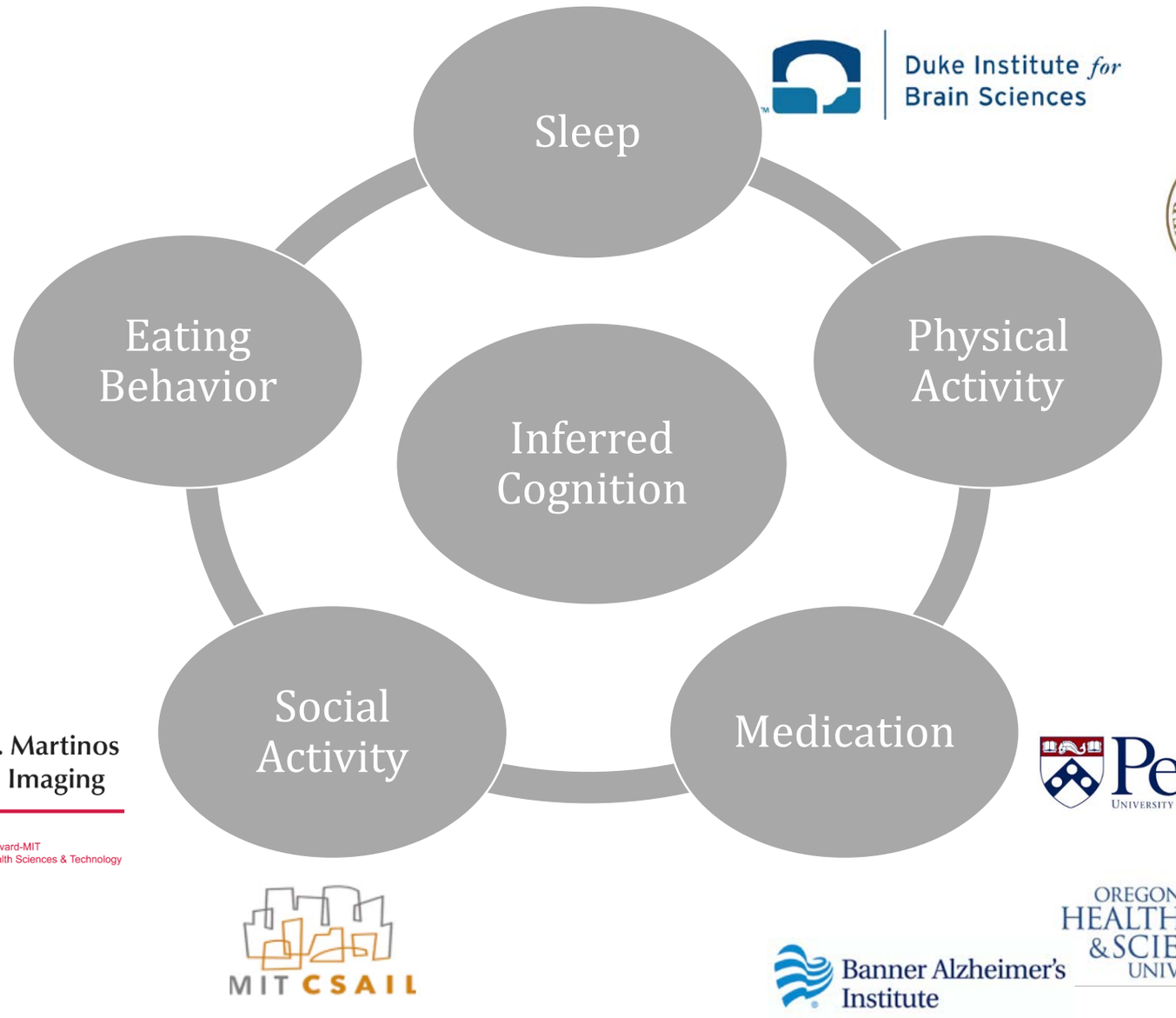


Duke Institute for Brain Sciences

Arizona State University

MGH/HST Athinoula A. Martinos Center for Biomedical Imaging

MASSACHUSETTS GENERAL HOSPITAL

Harvard-MIT Health Sciences & Technology

MIT CSAIL

UNIVERSITY OF WASHINGTON 1861

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING

HNRCA

Tufts UNIVERSITY

UF UNIVERSITY of FLORIDA

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Penn UNIVERSITY of PENNSYLVANIA

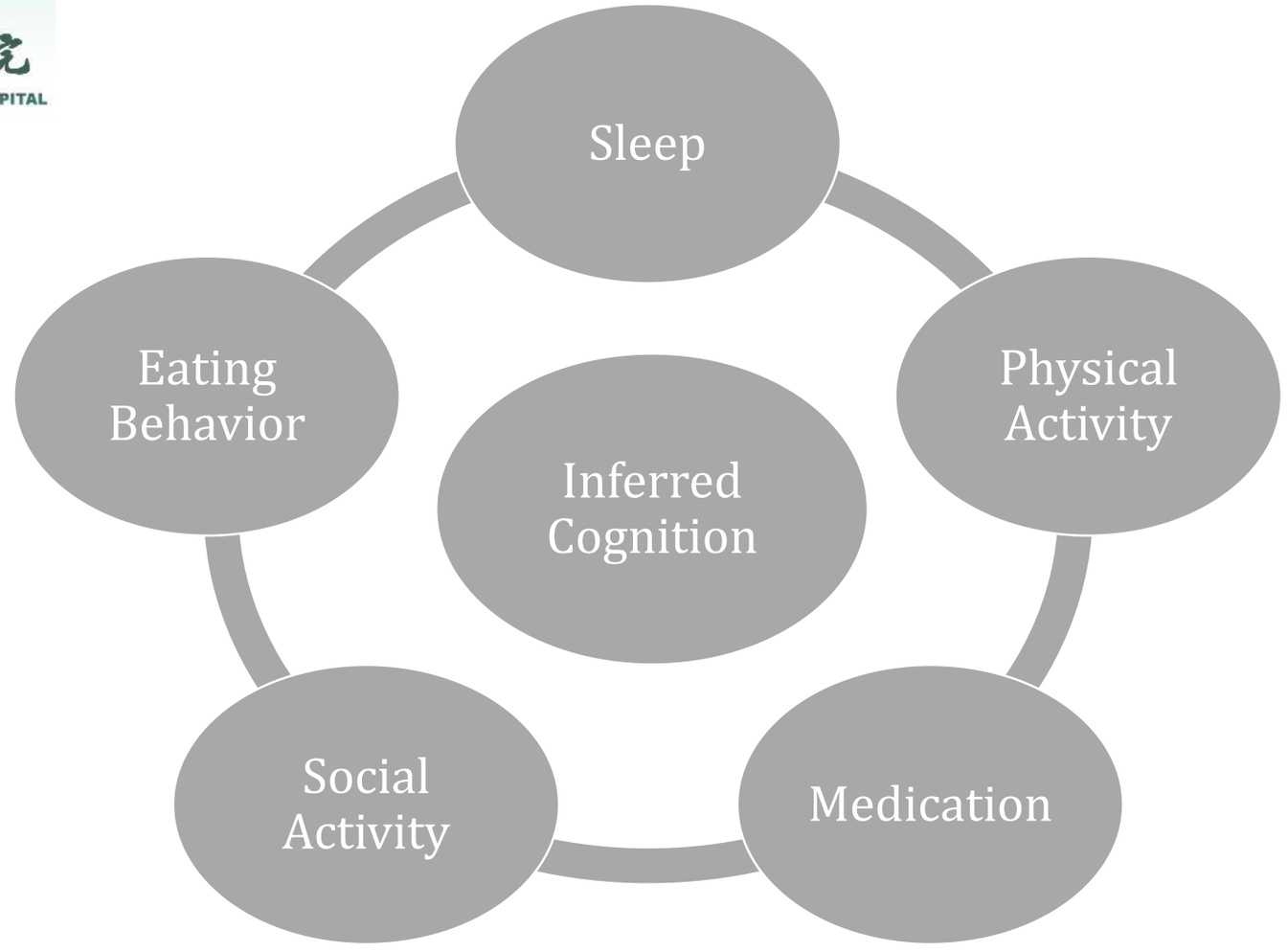
Banner Alzheimer's Institute

OREGON HEALTH & SCIENCE UNIVERSITY OHSU

Biogen

Pfizer

Lilly


Sleep
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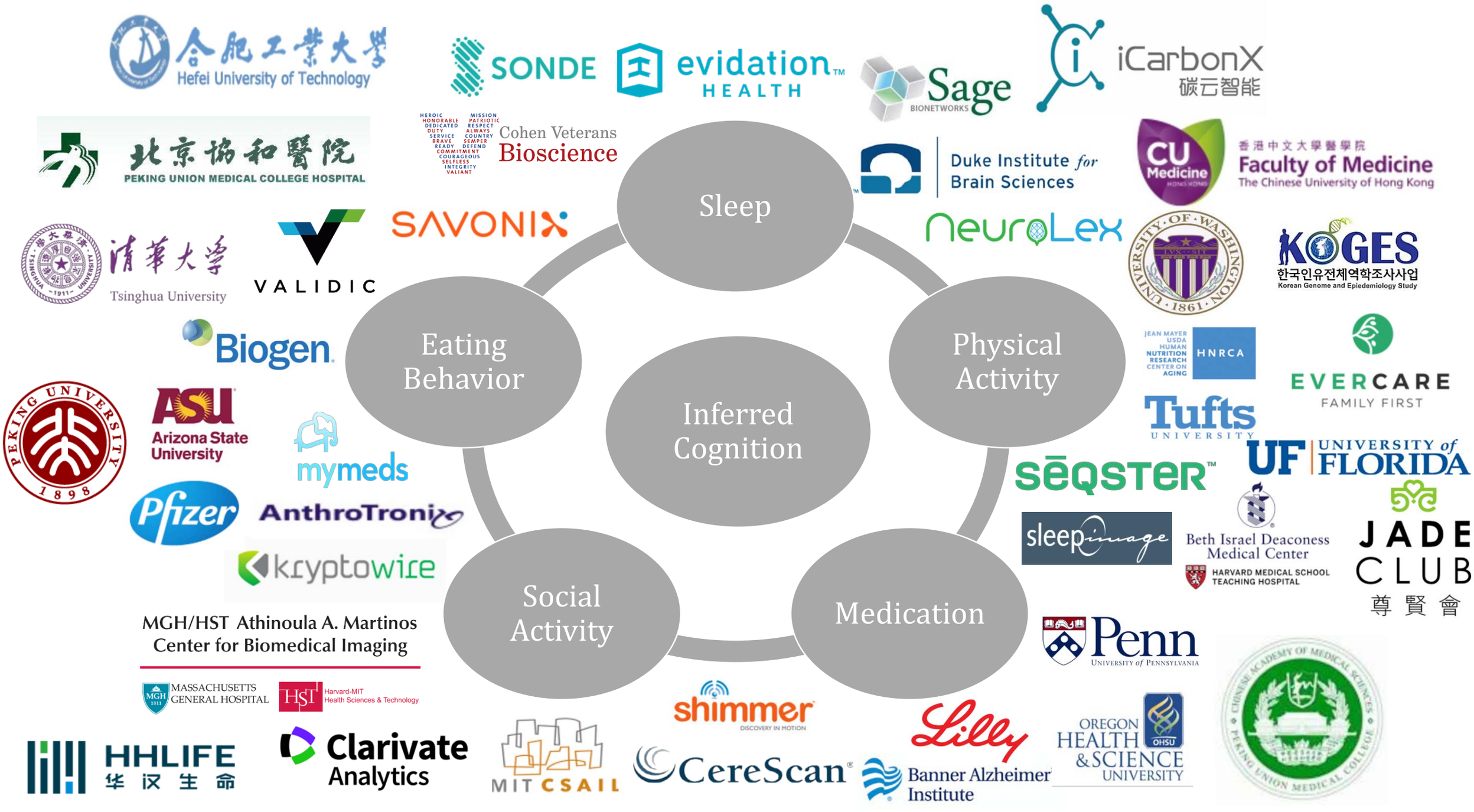
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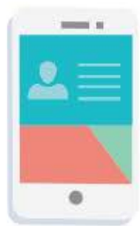
北京協和醫院
PEKING UNION MEDICAL COLLEGE HOSPITAL
Cohen Veterans Bioscience
Duke Institute for Brain Sciences
CU Medicine
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong
SAVONIX
NeuroLex
清華大學
Tsinghua University
VALIDIC
KOGES
한국인유전체역학조사사업
Korean Genome and Epiedemiology Study
Biogen
JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING
HNRCA
EVERCARE
FAMILY FIRST
PEKING UNIVERSITY 1898
ASU Arizona State University
mymeds
Tufts UNIVERSITY
UF UNIVERSITY of FLORIDA
Pfizer
AnthroTronix
SEQSTER
JADE CLUB
尊賢會
kryptowire
sleepimage
Beth Israel Deaconess Medical Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
MGH/HST Athinoula A. Martinos Center for Biomedical Imaging
MASSACHUSETTS GENERAL HOSPITAL
HST Harvard-MIT Health Sciences & Technology
Penn
University of Pennsylvania
shimmer
DISCOVERY IN MOTION
Lilly
OREGON HEALTH & SCIENCE UNIVERSITY
OHSU
HHLIFE 华汉生命
Clarivate Analytics
MIT CSAIL
CereScan
Banner Alzheimer Institute
CHINESE ACADEMY OF MEDICAL SCIENCES
PEKING UNION MEDICAL COLLEGE

Smart Brain Health Monitoring Ecosystem

Inferential Data Analysis

Smart Ecosystem



Passive Data Collection

Activities of Daily Living

Thanks.

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Three Generations of Dedication
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AWI Aging Well Institute