# Digital Technologies and Big Data in CNS Diseases

**Vaibhav A. Narayan, PhD MBA**

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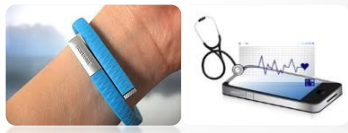
# Twin Revolutions in Neurobiology and Mobile Computing


**On-Demand Genomics**
*(GWAS, Deep Sequencing)*



**On-Body**
**Physiology, Behavior**
*(EEG, HRV, GSR, Sleep, Speech, Physical/Social Activity, Cognition)*

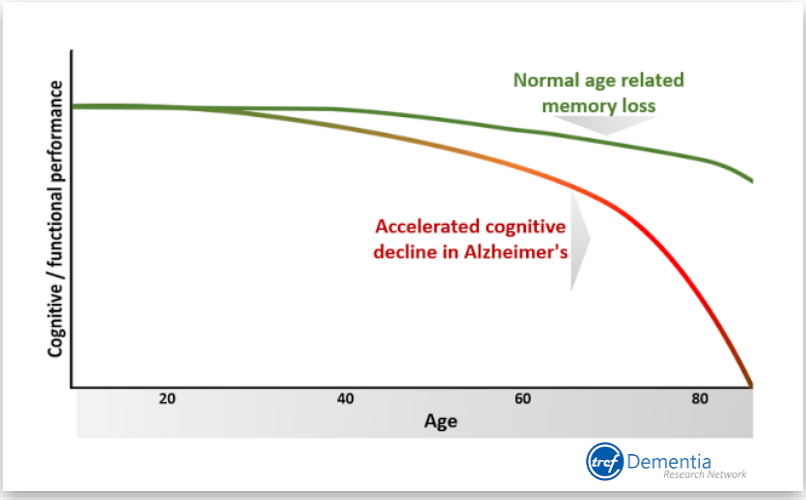

**Point of Need Biochemistry**
*(CRP, Cortisol, Cytokines)*

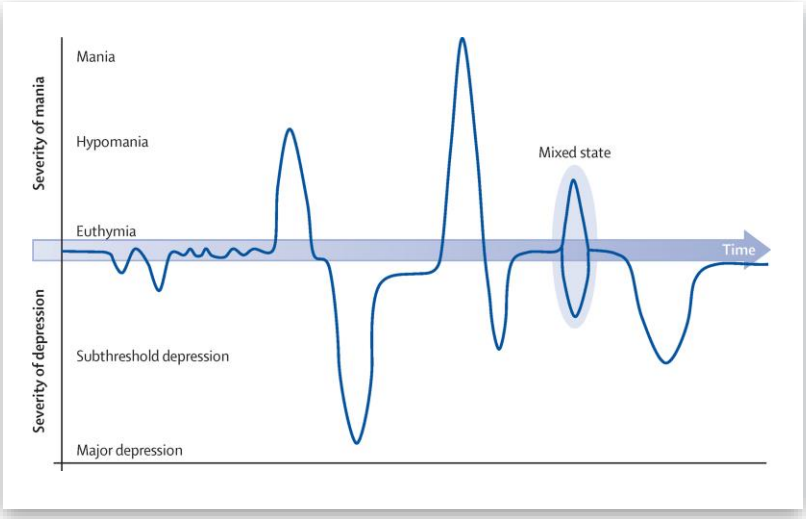
**Computer based cognitive and behavioral therapies**

Recent advances
referred to as
**"the biggest breakthroughs in Psychiatry in 40 yrs"**
*– NIMH Director*

**Beyond magic bullets: true innovation in health care** Vaibhav A. Narayan[1], Marco Mohwinckel[2], Gary Pisano[3], Michael Yang[4] & Husseini K. Manji[1] · *Nature Reviews Drug Discovery* **12**, 85-86 (February 2013)

# Neurodegenerative and Neuropsychiatric Changes: Different Time Scales

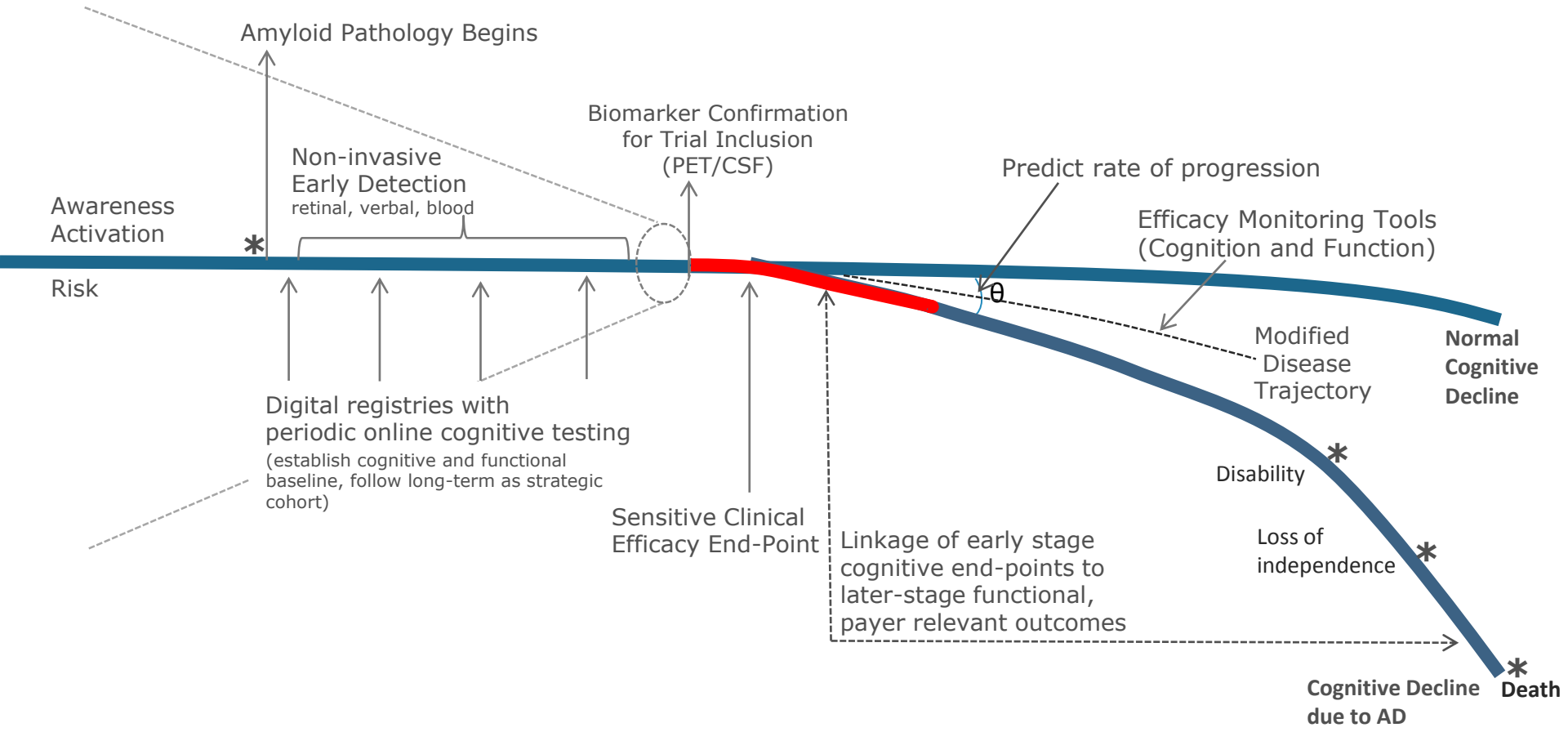




Grande, Iria et al. The Lancet , 2016 Volume 387 , Issue 10027 , 1561 - 1572

# ALZHEIMER'S DISEASE: COGNITION AND FUNCTION




**Regulators:** will only provide conditional approval, without function

**Payers:** want to see impact on function which drives cost and care-giver burden

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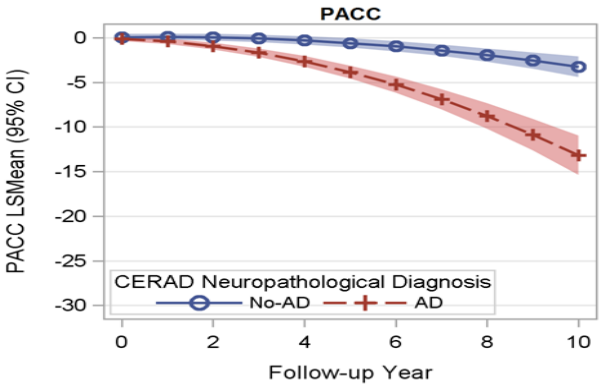
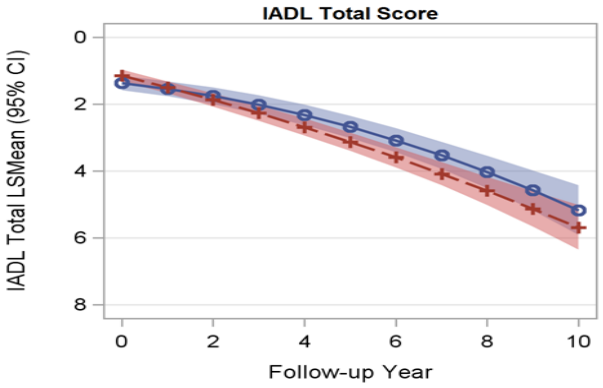
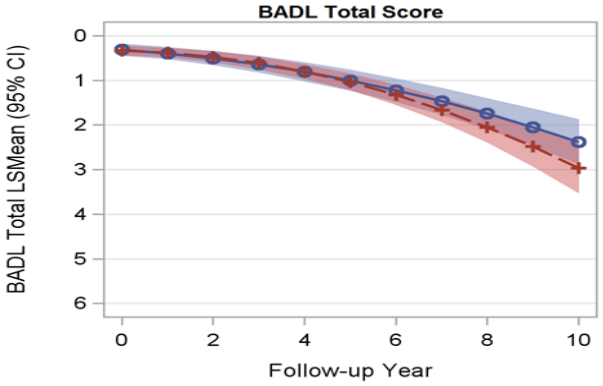
# Longitudinal Changes in Function



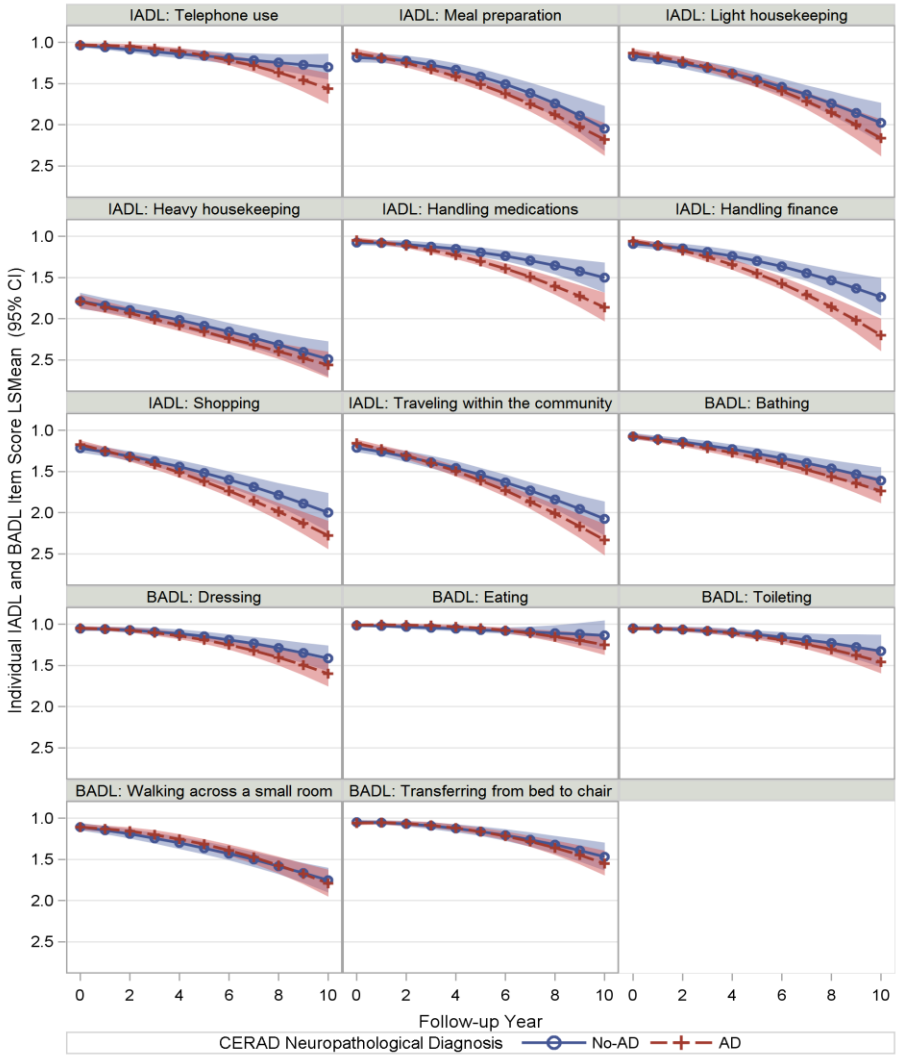




## IADL

- Managing finances
- Handling transportation (driving or navigating public transit)
- Shopping
- Preparing meals
- Using the telephone and other communication devices
- Managing medications
- Housework and basic home maintenance

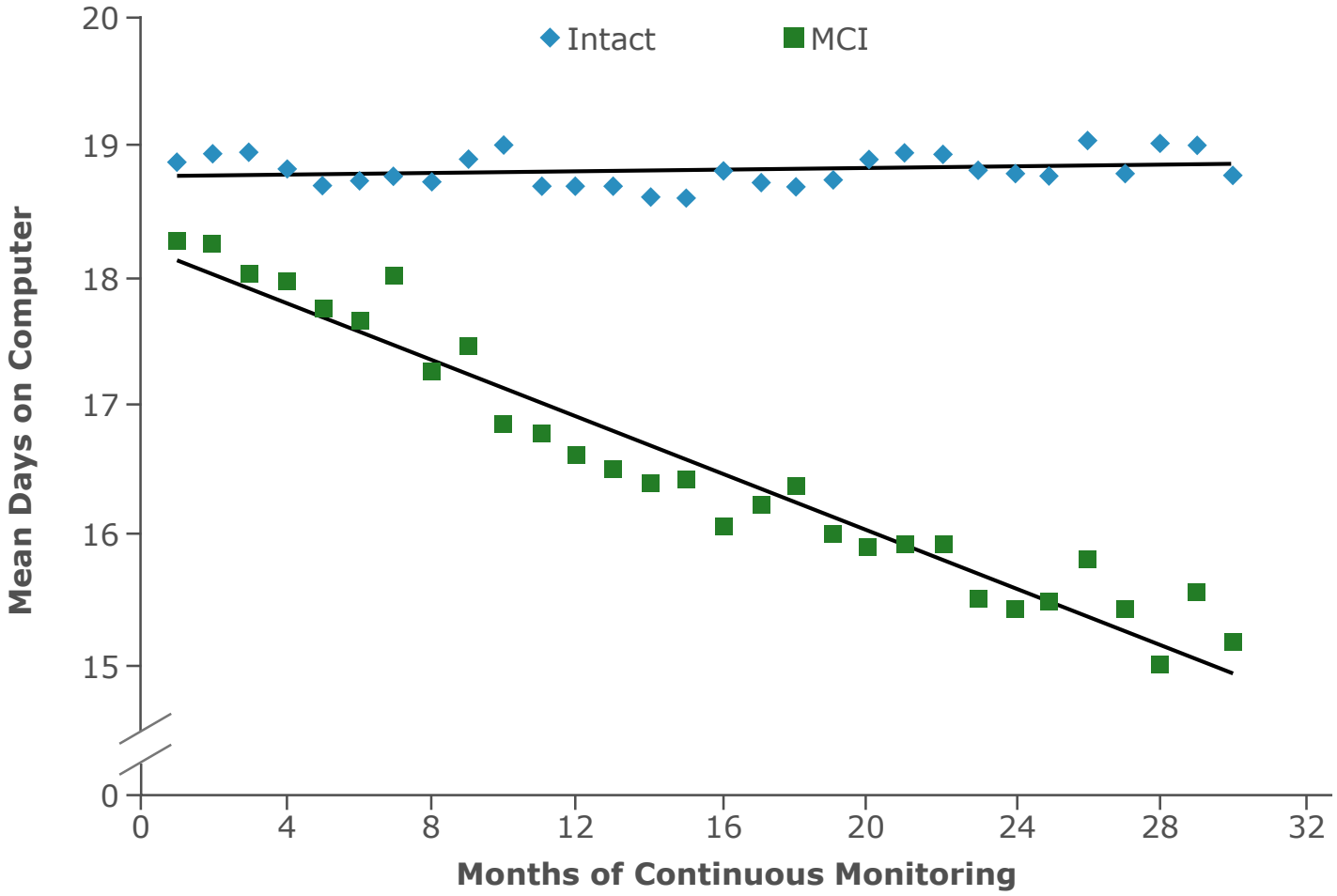
## BADL

typically restricted to activities involving functional mobility (ambulation, wheelchair mobility, bed mobility and transfers) and personal care (feeding, hygiene, toileting, bathing and dressing)




Data from The Religious Orders Study (ROS) (D. a Bennett, Schneider, Arvanitakis, & Wilson, 2012) and the Rush Memory and Aging Project (MAP) (D. a Bennett, Schneider, Buchman, et al., 2012)

# Unobtrusive Measurement of Daily Computer Use to Detect Mild Cognitive Impairment




Kaye J., Mattek N., Dodge H. H., Campbell I., Hayes T., Austin D., et al. (2014). Unobtrusive measurement of daily computer use to detect mild cognitive impairment. Alzheimers Dement. 10, 10–17.10.1016/j.jalz.2013

# The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study

Manuel Montero-Odasso,[1,2,3] Afua Oteng-Amoako,[1] Mark Speechley,[1,2,3] Karen Gopaul,[1] Olivier Beauchet,[4] Cedric Annweiler,[4] and Susan W. Muir-Hunter[1,2]

[1]Gait and Brain Lab, Parkwood Hospital, Lawson Health Research Institute, [2]Schulich School of Medicine and Dentistry, Department of Medicine and Division of Geriatric Medicine and [3]Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada. [4]Department of Neuroscience, Division of Geriatric Medicine, Angers University Hospital, Angers, France.

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Table 3. Dual-Task Gait Cost (%) Differences in a-MCI and na-MCI

| Walking Test Condition [Mean (±*SD*)] | Full MCI Sample (*n* = 64) | na-MCI (*n* = 22) | a-MCI (*n* = 42) | *p* Value* |
|---|---|---|---|---|
| Velocity dual-task cost (%) | | | | |
| Counting gait | 7.60 (±11.63) | 3.44 (±9.28) | 9.79 (±12.24) | **.04** |
| Naming animals gait | 18.34 (15.43) | 12.32 (±13.39) | 21.50 (±15.63) | **.03** |
| Serial sevens gait | 20.10 (±16.52) | 14.15 (±15.59) | 23.21 (±16.31) | **.03** |
| Stride time variability dual-task cost (%) | | | | |
| Counting gait | 59.91 (±92.03) | 47.36 (±77.98) | 66.49 (±98.84) | .43 |
| Naming animals gait | 61.09 (±82.60) | 72.11 (±74.89) | 54.88 (±86.98) | .63 |
| Serial sevens gait | 63.46 (±88.08) | 59.03 (±73.22) | 65.74 (±95.68) | .89 |

*Notes:* CI = confidence intervals; MCI = mild cognitive impairment; *SD* = standard deviation.
*Linear regression modeling adjusted for age, sex, Trail Making Test B, physical activity level, and comorbidities; significant values are in bold.

Table 4. Association Between Dual-Task Gait Cost (%) and Episodic Memory and Learning Performance (RAVLT) in the MCI Group

| Dual-Task Cost (%) (Predictor) | Change in RAVLT (Unadjusted β Coefficient) | *t* Statistic | *p* Value* | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Velocity | | | | | |
| Counting gait | .079 | 2.556 | **.013** | .017 | .140 |
| Naming animals gait | .058 | 2.437 | **.018** | .010 | .105 |
| Serial sevens gait | .053 | 2.422 | **.019** | .009 | .096 |
| Stride time variability | | | | | |
| Counting gait | .003 | .779 | .439 | −.005 | .012 |
| Naming animals gait | .001 | .795 | .430 | −.002 | .005 |
| Serial sevens gait | −.005 | −1.014 | .316 | −.015 | .005 |

*Notes*: MCI = mild cognitive impairment; RAVLT = Rey Auditory Verbal Learning Test; changes shown above represent 1% increase in dual-task cost.
*Linear regression adjusted for age, sex, Trail Making Test B, physical activity level, and comorbidities; significant values are in bold.

# Detecting Declining Financial Skills in Preclinical Alzheimer's Disease: The Financial Capacity Instrument--Short Form

Daniel C. Marson, PhD, JD [1,2], Kristen L. Triebel, PsyD[1,2], Adam Gerstenecker, PhD[1], Roy C. Martin, PhD[1,2], Kelly Edwards, MA[3], Vernon S. Pankratz, PhD[3], Dana Swenson-Drawis, MA[4,5], and Ronald C. Petersen, MD, PhD [4,5]

[1] Department of Neurology, University of Alabama at Birmingham (UAB), Birmingham, AL; [2] Alzheimer's Disease Center, UAB, Birmingham, AL; [3] Division of Biomedical Statistics and Informatics, Mayo Clinic and Foundation, Rochester, MN; [4] Department of Neurology, Mayo Clinic and Foundation, Rochester, MN; [5] Mayo Clinic Alzheimer's Disease Research Center, Mayo Clinic and Foundation, Rochester, MN

## Table 2: FCI-SF Performance Scores by PiB Status

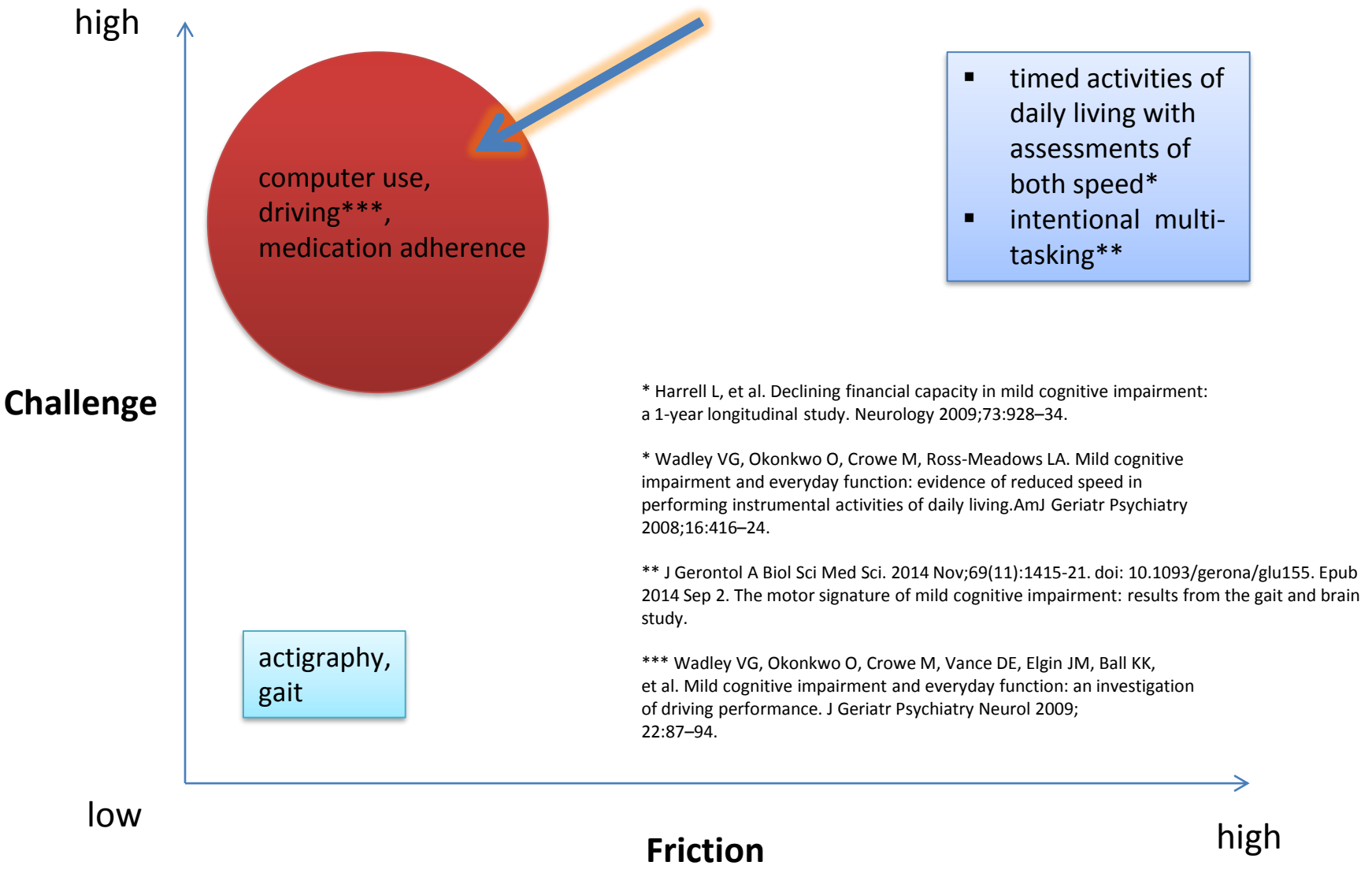
| | Max Score | Amyloid Negative N = 120 | Amyloid Positive N = 66 | *p* |
|---|---|---|---|---|
| **Total Score** | | | | |
| FCI-SF Total Score | 0-74 | 64.2 (8.3, 33-74) | 62.1 (7.9, 44-74) | .094 |
| **Component Performance Scores** | | | | |
| Bank Statement Management | 0-14 | 11.0 (2.2, 2-13) | 10.4 (2.5, 3-13) | .080 |
| Mental calculation problems | 0-4 | 3.6 (0.9, 0-4) | 3.4 (0.9, 2-4) | .125 |
| Check/Register/Deposit Transactions | 0-28 | 23.1 (4.9, 4-28) | 22.2 (5.3, 8-28) | .230 |
| Financial Conceptual Knowledge | 0-8 | 7.0 (1.3, 1-8) | 6.8 (1.4, 4-8) | .319 |
| Single Check Transactions/Register | 0-20 | 18.8 (1.9, 10-20) | 18.8 (1.7, 14-20) | .987 |
| **Select FCI-SF Test Items** | | | | |
| How many quarters in $ | 0 or 2 | 1.9 (0.4) | 1.7 (0.7) | .011 |
| Correct amount of deposit | 0 or 2 | 1.6 (0.8) | 1.3 (1.0) | .022 |
| Checks cleared in bank statement | 0 or 2 | 1.3 (1.0) | 1.0 (1.0) | .028 |

## Table 3: FCI-SF Task Completion Times by PiB Status

| | Max score/time | Amyloid Negative N = 120 | Amyloid Positive N = 66 | *p* |
|---|---|---|---|---|
| **Time Variables** | | | | |
| Medical deductible problem (sec) | 90 sec | 17.2 (23.4) | 18.9 (24.4) | .637 |
| Income tax problem (sec) | 90 sec | 7.1 (10.1) | 10.2 (11.0) | .062 |
| Check/register task (sec) | 240 sec | 112.4 (34.6) | 125.4 (36.2) | .017 |
| Check/register/deposit task (sec) | 300 sec | 225.1 (62.8) | 250.1 (54.9) | .007 |
| 2 check tasks composite time (sec) | 540 sec | 337.7 (87.1) | 375.5 (77.4) | .004 |
| Overall composite time (sec) | 720 sec | 359.6 (95.6) | 404.6 (87.2) | .002 |

- Functional change in the form of subtle financial skill decline occurs in preclinical AD and is detectable using a brief performance measure of financial skills. Both slower financial task completion times, and diminished performance of complex financial tasks, characterized the A+ group and represent measurable very early functional changes in preclinical AD.
- Performance measures of complex everyday function may outperform cognition variables as predictors of preclinical AD. In a logistic model of participant amyloid status, only FCI-SF predictors (composite time and two complex performance items) entered the model. Age and cognitive variables were not retained in the model.
- Brief performance based measures of complex everyday function like the FCI-SF represent a promising new addition to AD clinical trial outcomes. Such measures appear to be sensitive to early functional changes across preclinical, prodromal, and clinical dementia stages of AD, and have face and ecological validity for consumers, families, and clinicians and researchers. Future studies will be needed to confirm our present findings.
- Measures like the FCI-SF should be considered for AD prevention and clinical trials.

# Digital Technologies, Big Data and AD Function




* Harrell L, et al. Declining financial capacity in mild cognitive impairment: a 1-year longitudinal study. Neurology 2009;73:928–34.

* Wadley VG, Okonkwo O, Crowe M, Ross-Meadows LA. Mild cognitive impairment and everyday function: evidence of reduced speed in performing instrumental activities of daily living.AmJ Geriatr Psychiatry 2008;16:416–24.

** J Gerontol A Biol Sci Med Sci. 2014 Nov;69(11):1415-21. doi: 10.1093/gerona/glu155. Epub 2014 Sep 2. The motor signature of mild cognitive impairment: results from the gait and brain study.

*** Wadley VG, Okonkwo O, Crowe M, Vance DE, Elgin JM, Ball KK, et al. Mild cognitive impairment and everyday function: an investigation of driving performance. J Geriatr Psychiatry Neurol 2009; 22:87–94.

# Biosensor Outcome Measures/Assessments of Clinical Signs: Uses in Clinical Trials

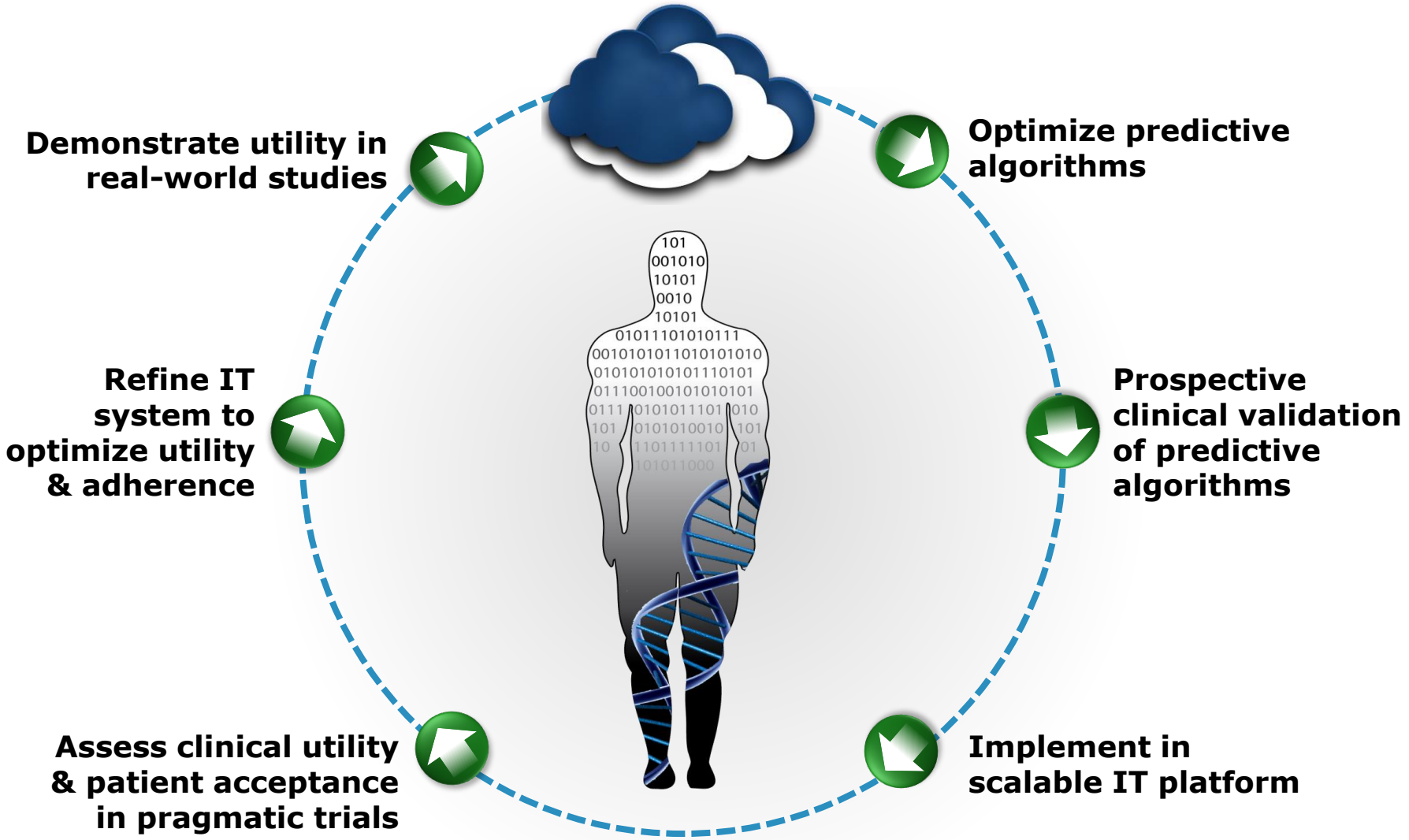
CAMD
CRITICAL PATH INSTITUTE

| Context-of-Use | Definition | CDISC Standards | Evidentiary Standards |
|---|---|---|---|
| Internal Decisions | Commercial devices that is not a medical device (e.g., Smartphones, Fitbits™, Home-sensor monitoring, etc.). | No | Arbitrary |
| Exploratory Measures | Commercial devices that is not a medical device for potential patient stratification (e.g., Smartphones, Home-sensor monitoring, etc.,) | No | |
| Prognostic Assessment | Medical devices for use in in trial enrichment to predict rate of disease progression | YES | |
| Predictive Assessment | Medical devices for trial enrichment to identify individuals who are more likely than similar patients without the outcome to experience a favorable or unfavorable effect from a specific intervention/ exposure. | YES | |
| Susceptibility/ Risk Assessment | Medical devices for use in in trial enrichment to indicate the potential for developing a disease or medical condition or sensitivity to an exposure in an individual without clinically apparent disease or medical condition. | YES | |
| Surrogate Endpoint | Medical devices in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. | YES | |
| Clinical Endpoint | Medical devices measuring precisely defined variable(s) intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined. | YES | |

Regulatory Endorsement

Robust; Multi-trial; Longitudinal

# The Data Driven **LEARNING** Engine




Manji, Husseini K., Thomas R. Insel, and Vaibhav A. Narayan. "**Harnessing the informatics revolution for neuroscience drug R&D.**" *Nature Reviews Drug Discovery* 13.8 (2014): 561-562.

Is his medication working?
Is he at a higher risk of relapse?
Is he taking his medication?

physician

Is my medication working?
Am I doing better?

patient

Is he doing well?
Does he need help?

care-giver

patient longitudinal
data (secure, private cloud)

physician

clinical assessments
point-of-care adherence test
(EHR)


patient

self-report symptoms
passive sleep, activity
(social, physical) data

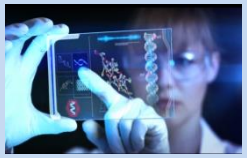
care-giver

independent
informer

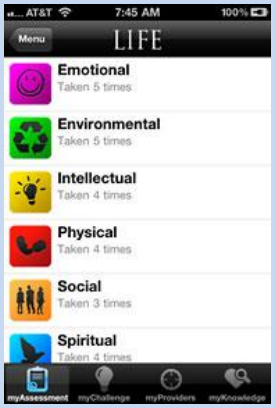
# From Diagnose and Treat to Predict and Preempt: A Look Ahead

## Pre-Diagnosis

awareness
education



risk




health & wellness
tracking

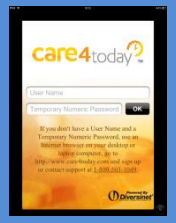
organ channels

## Early Disease

early diagnosis
disease progression monitoring

non-pharmacological
interventions

## Chronic Disease




adherence management, efficacy
monitoring, relapse prediction

low risk — high risk — early disease — managed disease

continuous, longitudinal engagement

*THANK YOU*

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