Validity and utility of the NIH Toolbox in an Alzheimer’s prevention clinic

Katherine Hackett, B.A.
Agenda

**Setting**
The WCM/NYP Alzheimer’s Prevention Clinic (APC)

**The Present Study**
Validity of the NIHTB-CB in a neurology clinic

**Implications**
Utility & Feasibility
Drawbacks
Suggestions
General Alzheimer’s disease (AD) Statistics

• Approximately 5.8 million Americans carry a diagnosis of Alzheimer’s dementia in 2019, a number that is expected to grow to 13.8 million by 2050¹

• AD pathology begins in the brain 10-20 years before clinical symptoms manifest²

If at Age 85, 45% have Alzheimer’s...
• Disease first started at **Age 55-65**

If at Age 65, 10% have Alzheimer’s...
• Disease first started at **Age 35-45**

¹ Alzheimer’s Association, 2019; ² Elias et al., 2000; Reiman et al., 2012
Methodology at the Alzheimer’s Prevention Clinic

**Three key considerations:**

- Evidence-based and safe
- Not a “one-size-fits-all” approach
- Not an “algorithm”
Intervention paradigm

**BIOMETRICS**
- Waist/hip
- % Body fat
- % Lean dry mass

**BIOMARKERS (examples)**
- **METABOLISM**
  - Fasting Glucose
  - Fasting Insulin/HOMA-IR
  - HbA1C
- **LIPIDS**
  - Chol.
  - HDL
  - LDL
  - LDL-p
- **SERUM FATTY ACIDS**
  - EPA/DHA
  - Omega 6:3 ratio
- **OTHER**
  - HCY
  - Plasma Vit. D

**GENETICS**
- APOE
- MTHFR

**SUPPLEMENTS**
- Vit. B12
- EPA/DHA
- Vit. D
- Cocoa flavonoids
- Plant sterols
- Berries
- Low carb/high fiber
- Caloric restriction
- Omega-3 rich fish
- Overnight fasting
- High intensity

**DIET**
- Aerobic & resistance
- Referral to cardiologist
- Sleep
- Stress reduction
- Intellectual stimulation
- Dental hygiene

**NUTRITION**

**EXERCISE**

**MISC.**

**GENERAL HEALTH**

**INTERVENTIONS (examples)**
- Typical recommendation
- Optional recommendation
- Increased emphasis on intervention
- DNA-to-biomarker pathway
The clinical practice of risk reduction for Alzheimer’s disease: A precision medicine approach

Richard S. Isaacson, Christine A. Ganzler, Hollie Hristov, Katherine Hackett, Emily Caesar, Randy Cohen, Robert Kachko, Josefina Meléndez-Cabrero, Aneela Rahman, Olivia Scheyer, Mu Ji Hwang, Cara Berkowitz, Suzanne Hendrix, Monica Mureb, Matthew W. Schelke, Lisa Mosconi, Alon Seifan, Robert Krikorian

*Department of Neurology, Weill Cornell Medicine and NewYork-Presbyterian, New York, NY, USA
School of Nursing, Hunter College, City University of New York, New York, NY, USA
School of Medicine, Chicago, IL, USA
School of Medicine, Crystal Run Healthcare, Middletown, NY, USA
Inner Source Health, New York, NY, USA
Department of Neurology, Weill Cornell Medicine, San Juan, PR, USA
Weill Cornell Medicine-Qatar, Doha, Qatar
Weill Cornell Medicine, New York, NY, USA
Biosatistics, Pentara Corporation, Salt Lake City, UT, USA
Department of Neurology, Columbia University College of Physicians & Surgeons, New York, NY, USA
Compass Health Systems, Miami, FL, USA
Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA
ABC’s OF ALZHEIMER’S PREVENTION MANAGEMENT

**Anthropometrics**
Examples:
- % Body Fat • Phase Angle
- Lean Mass • Waist:Hip Ratio
- Body Fat Distribution

**Cognition**
Examples:
- NIH Toolbox • Odor Identification
- Paper-based Tests • Web-based Tests
- Mobile-based Tests

**Blood Biomarkers**
Examples:
- Lipids • Inflammation
- Metabolism • Nutrition • Genetics

Clinical History & Physical Exam
Precision Medicine
Management options in effort to reduce risk
The Present Study

Is the NIHTB-CB a valid, useful and feasible method to characterize cognition in a memory-disorders population?

- IRB-approved Comparative Effectiveness Dementia & Alzheimer’s Registry (CEDAR)
- N = 247 patients (mAge = 61 ± 15 years) with subjective cognitive decline (SCD; n=46), amnestic mild cognitive impairment (MCI; n=27), non-amnestic MCI (n=19), mild dementia due to AD (n=26) and normal cognition (CN; n=129)
- Clinical interview (with informant), medical and neurological examinations, anthropometric and laboratory measures, neuropsychological testing, and structural brain MRI when indicated
- Consensus diagnoses by neurologist, family nurse practitioner, multi-disciplinary healthcare team members
- Examine performance on the baseline NIHTB measures vs. traditional neuropsychological measures commonly used in dementia evaluations

Hackett et al., 2018
## Neuropsychological measures

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>NIHTB-CB tests</th>
<th>Traditional tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning/Memory</td>
<td>RAVLT 1, 2, 3*</td>
<td>MMSE-DR*</td>
</tr>
<tr>
<td></td>
<td>RAVLT-DR*</td>
<td>Logical Memory immediate recall*</td>
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<tr>
<td></td>
<td></td>
<td>Logical Memory delayed recall*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FNAME*</td>
</tr>
<tr>
<td>Executive Function/</td>
<td>DCCS†</td>
<td>FAS*</td>
</tr>
<tr>
<td>Attention/</td>
<td>Flanker†</td>
<td>ANT*</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>Pattern Comparison*</td>
<td>MMSE-attention*</td>
</tr>
<tr>
<td></td>
<td>ODS*</td>
<td>Trail-Making Test Part B*</td>
</tr>
<tr>
<td>Crystallized Intelligence</td>
<td>Picture Vocabulary†</td>
<td>Education</td>
</tr>
<tr>
<td></td>
<td>Oral Reading Recognition†</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NIHTB-CB, NIH Toolbox Cognition Battery; RAVLT, Rey Auditory Verbal Learning Task immediate recall trials 1-3; RAVLT-DR, Rey Auditory Verbal Learning Task delayed recall; DCCS, Dimensional Change Card Sort; Flanker, Flanker Inhibitory Control/Attention; Pattern Comparison, Pattern Comparison Processing Speed; ODS, Oral Digit Symbol; MMSE-DR, Mini Mental State Examination delayed recall subscore; FNAME, Face Name Associative Memory-cued first letter; FAS, verbal fluency under phonemic constraint to letters F-A-S; ANT, verbal fluency under categorical constraint (animals); MMSE-attention, Mini Mental State Examination attention subscore.

NOTE. Trail-Making Test Part B score represents time to completion (seconds).

NOTE. Raw and computed scores are unadjusted for demographics.

*raw score.
†computed score (provided by the NIH toolbox, used for computer adaptive tests and tests whose score requires combination of accuracy and reaction time vectors).
Statistical analyses

- **Principal Component Analysis (PCA) of NIHTB** (with/without RAVLT-DR) and traditional tests; factor-based scores computed using averaged z-scores of strongly loading tests
- **Spearman’s partial correlations** to assess relations between NIHTB and traditional factor scores*
- **Univariate General Linear Model (GLM)** tests with pairwise comparisons to test diagnostic group differences in NIHTB and traditional factor scores*
- **Discriminant function analysis** of cognitive factor scores as predictors of diagnostic group reclassification (CN, aMCI, naMCI, AD)*

* covarying for age, sex and education
### Participant demographics

#### Demographic characteristics of participants by diagnostic group

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Total (N = 247)</th>
<th>CN (n = 129)</th>
<th>SCD (n = 46)</th>
<th>naMCI (n = 19)</th>
<th>aMCI (n = 27)</th>
<th>AD (n = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>61.0 (14.7)</td>
<td>52.5 (12.0)</td>
<td>62.9 (11.2)</td>
<td>71.8 (8.1)</td>
<td>74.3 (7.2)</td>
<td>78.4 (8.5)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Age range</td>
<td>27-94</td>
<td>27-82</td>
<td>34-80</td>
<td>56-88</td>
<td>58-86</td>
<td>66-94</td>
<td></td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>52%</td>
<td>55%</td>
<td>63%</td>
<td>32%</td>
<td>48%</td>
<td>38%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education (mean, SD)</td>
<td>15.6 (1.2)</td>
<td>15.9 (1.0)</td>
<td>15.6 (1.0)</td>
<td>15.4 (1.3)</td>
<td>15.4 (1.7)</td>
<td>14.7 (1.7)</td>
<td>.001†</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>65%</td>
<td>62%</td>
<td>72%</td>
<td>63%</td>
<td>67%</td>
<td>69%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total MMSE</td>
<td>28.2 (3.3)</td>
<td>29.5 (.8)</td>
<td>29.4 (1.4)</td>
<td>28.7 (1.4)</td>
<td>26.3 (2.2)</td>
<td>19.8 (4.4)</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

Abbreviations: CN, cognitively normal; SCD, subjective cognitive decline; naMCI, non-amnestic MCI; aMCI, amnestic MCI; AD, Alzheimer's disease; MMSE, Mini Mental State Examination; n.s., nonsignificant.

NOTE. MMSE P values reflect General Linear Model test of between subjects effect after covarying for age, sex and education.

*P<.001.

†P<.01.
### Results: Principal component analyses

#### Principal component analyses of NIHTB-CB tests

<table>
<thead>
<tr>
<th></th>
<th>PCA 1a (including RAVLT-DR, N = 197)</th>
<th>PCA 2a (excluding RAVLT-DR, N = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Component 1</td>
<td>Component 2</td>
</tr>
<tr>
<td></td>
<td>Memory (MEM\textsubscript{NIH})</td>
<td>Executive Function (EF\textsubscript{NIH})</td>
</tr>
<tr>
<td>RAVLT Trial 2</td>
<td>0.886</td>
<td></td>
</tr>
<tr>
<td>RAVLT-DR</td>
<td>0.853</td>
<td></td>
</tr>
<tr>
<td>RAVLT Trial 3</td>
<td>0.852</td>
<td></td>
</tr>
<tr>
<td>RAVLT Trial 1</td>
<td>0.818</td>
<td></td>
</tr>
<tr>
<td>Flanker</td>
<td>0.897</td>
<td></td>
</tr>
<tr>
<td>DCCS</td>
<td>0.874</td>
<td></td>
</tr>
<tr>
<td>Pattern Comparison</td>
<td>0.833</td>
<td></td>
</tr>
<tr>
<td>ODS</td>
<td>0.741</td>
<td></td>
</tr>
<tr>
<td>Oral Reading Recognition</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Picture Vocabulary</td>
<td>0.702</td>
<td></td>
</tr>
<tr>
<td>% Explained Variance</td>
<td>35%</td>
<td>33%</td>
</tr>
<tr>
<td>Total % Explained Variance</td>
<td>83%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NIHTB-CB, NIH Toolbox Cognition Battery; PCA, Principal Component Analysis; RAVLT, Rey Auditory Verbal Learning Test immediate recall; RAVLT-DR, Rey Auditory Verbal Learning Task delayed recall; Flanker, Flanker Inhibitory Control/Attention; DCCS, Dimensional Change Card Sort; Pattern Comparison, Pattern Comparison Processing Speed; ODS, Oral Digit Symbol

NOTE. PCA was conducted using Varimax with Kaiser Normalization. Factors with eigenvalues greater than 1, with a maximum iteration of 25, were extracted. Factor loadings shown after orthogonal rotation.

NOTE. PCA 1a rotation converged in 5 iterations. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy = .90.

NOTE. PCA 2a rotation converged in 3 iterations. KMO = .89.
Results: Principal component analyses

**Principal component analysis of traditional tests**

<table>
<thead>
<tr>
<th>Component</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory: (MEM₁)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical Memory immediate recall</td>
<td>0.875</td>
<td></td>
</tr>
<tr>
<td>Logical Memory delayed recall</td>
<td>0.807</td>
<td></td>
</tr>
<tr>
<td>FNAME</td>
<td>0.727</td>
<td></td>
</tr>
<tr>
<td>MMSE-DR</td>
<td>0.626</td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>ANT</td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>MMSE-attention</td>
<td>0.718</td>
<td></td>
</tr>
<tr>
<td>Trails B</td>
<td>-0.648</td>
<td></td>
</tr>
<tr>
<td>% Explained Variance</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Total % Explained Variance</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PCA, Principal Component Analysis; FNAME, Face Name Associative Memory- cued first letter; MMSE-DR, Mini Mental State Examination delayed recall subscore; FAS, verbal fluency under phonemic constraint to letters F-A-S; ANT, verbal fluency under categorical constraint (animals); MMSE-attention, Mini Mental State Examination attention subscore.

**PCA 3:** traditional tests, 2 factor solution explaining 67% variance.
Results: Correlation analyses

- NIHTB factor scores significantly correlated with corresponding traditional factor scores ($P’s<0.01$), demonstrating **convergent validity**

- Evidence of **discriminant validity** included lower correlations with traditional factor scores of different cognitive domains

<table>
<thead>
<tr>
<th></th>
<th>MEM$_{NIH}$</th>
<th>EF$_{NIH}$</th>
<th>Cl$_{NIH}$</th>
<th>EF/WM$_{NIH}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCA 1 (NIHTB-CB with RAVLT-DR)</td>
<td>.471*</td>
<td>.320*</td>
<td>0.196</td>
<td>.500†</td>
</tr>
<tr>
<td>MEM$_T$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF$_T$</td>
<td>.423†</td>
<td></td>
<td></td>
<td>.519†</td>
</tr>
<tr>
<td>education</td>
<td>.312†</td>
<td>.171*</td>
<td></td>
<td>.468†</td>
</tr>
<tr>
<td>PCA 2a (NIHTB-CB without RAVLT-DR)</td>
<td></td>
<td></td>
<td></td>
<td>.547†</td>
</tr>
</tbody>
</table>

Nonparametric Spearman’s partial correlations NIHTB-CB and traditional factor-based scores

**Abbreviations**: NIHTB-CB, NIH Toolbox Cognition Battery; PCA, Principal Component Analysis; MEM$_{NIH}$, NIHTB-CB memory factor; EF$_{NIH}$, NIHTB-CB executive function factor; Cl$_{NIH}$, NIHTB-CB crystallized intelligence factor; EF/WM$_{NIH}$, NIHTB-CB executive function/working memory factor; MEM$_T$, traditional memory factor; MEM$_T$, traditional memory factor with most available data; EF$_T$, traditional executive function factor.

**NOTE**: Partial correlations controlled for age, sex and education.

* $P<.05$
† $P<.001$
Results: Univariate GLM analyses

- Estimated marginal means of factor scores (accounting for age, sex, education) compared across diagnostic groups
- Significant effect of group for each factor score
- Pairwise comparisons demonstrated expected relative performance trends according to type and level of cognitive impairment (CN/SCD<MCI<AD)
Results: Discriminant function analyses

- Three discriminant function analyses show relative rates of accurate group reclassification comparing NIHTB-CB with/without RAVLT to traditional protocol.
- Overall Chi-square tests were significant (p’s < .001).
- Overall, NIHTB with RAVLT-DR as good as traditional tests.
- NIHTB with RAVLT-DR (1a) better than without (2a).
- Relative weakness in distinguishing MCI common to all.

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>naMCI</th>
<th>aMCI</th>
<th>AD</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHTB with DR</td>
<td>98%</td>
<td>40%</td>
<td>47%</td>
<td>82%</td>
<td>84%</td>
</tr>
<tr>
<td>NIHTB without DR</td>
<td>96%</td>
<td>33%</td>
<td>58%</td>
<td>89%</td>
<td>84%</td>
</tr>
<tr>
<td>Traditional</td>
<td>95%</td>
<td>39%</td>
<td>64%</td>
<td>70%</td>
<td>85%</td>
</tr>
</tbody>
</table>
Conclusions

• NIHTB-CB augmented with a delayed recall subtest is a valid & useful method of cognitive assessment in a memory clinic setting
  ▪ Factor structure supported the domains the NIHTB-CB was designed to measure
  ▪ Performance on the NIHTB-CB varied in a manner consistent with performance on traditional neuropsychological tests
  ▪ NIHTB-CB explained more variance in cognitive performance and demonstrated a higher agreement rate with consensus diagnoses when RAVLT-DR was included
  ▪ NIHTB-CB with RAVLT-DR demonstrated classification agreement similar to that of the traditional tests.
Utility and Feasibility

• Administered by RA’s/technicians, scored by the program, interpreted by licensed neuropsychologist/neurologist in context of other clinical info – efficiency in a clinic setting

• Majority of adult participants had little trouble acclimating to computer-based protocol & completed in 35-40 minutes

• Use of fully-adjusted scores to account for influence of demographics on cognitive test performance

• Crystallized composite to determine relative impairments/ decrements from estimated premorbid functioning (increased sensitivity to subtle changes seen in preclinical AD)
Limitations & future directions

• NIHTB Picture Sequence Memory and List Sorting Working Memory subtests too challenging for participants with cognitive impairment - not included due to low completion rates.
  ▪ Delayed list learning task more appropriate
• Accurate diagnosis of MCI is challenging
• iPad normative data was not yet complete – validate in this format
• Additional validation studies within diverse populations (including low education, low computer proficiency/self-efficacy)
• Development of cut scores for more efficient diagnostic classification/flagging for comprehensive evaluation
• At-home self-administered version?
THANK YOU!

WCM/NYP Alzheimer’s Prevention Clinic leadership
• Richard Isaacson, M.D.
• Lisa Mosconi, Ph.D.
• Robert Krikorian, Ph.D.

Temple Cognitive Neuropsychology Lab
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• Rachel Mis, M.A.
• Ross Divers, M.A.