Informant report to detect amyloid related cognitive decline in the absence of dementia

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Early Alzheimer’s Disease: Developing Drugs for Treatment – FDA Guidance of Industry 2018

Stage 1
- Characteristic pathophysiologic changes (biomarkers) of AD but no evidence of clinical impact
- Truly asymptomatic with no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures

Stage 2
- Characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures but no functional impairment
- Emergence of subtle functional impairment

Stage 3
- Characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment
- Functional impairment not severe enough to warrant a diagnosis of AD
## New FDA Guidance 2018 – Clinical Trial Challenges

<table>
<thead>
<tr>
<th>Earlier in disease spectrum</th>
<th>Trial duration</th>
<th>Clinical Meaningfulness</th>
</tr>
</thead>
</table>
| • Identify the target AD population  
  • Presence of amyloid with or without neurodegeneration in asymptomatic or minimally symptomatic older individuals | • Pace of progression vs. trial duration  
  • How long should clinical trials be to detect treatment signal?  
  • Time to clinical meaningfulness on clinical endpoints | • Neuropsychological test uncertain independent clinical meaningfulness  
  • Functional impairment scales may not be suitable for AD stage 1-3  
  • Clinical endpoints sensitive to change (floor and ceiling effects)  
  • Sample heterogeneity (signs and symptoms) → selected COA not relevant to all |
Traditional Way to Identify Early AD

What tools to use to identify patients at risk/early transition of AD?

- Suggested alternative - Ask individuals/informants
- Subjective reported cognitive decline (SCD) may represent valid data for measuring disease progression – Segway to detect change from previous level of function
- SCD meaningful to individuals/informants
- Evidence to support SCD (everyday cognition/function) and the risk of future decline and AD diagnosis

1 SD below the norm, cut-off for MCI
ECog Scale

- ECog - a 39 item scale to assess cognitive function/IADL in everyday life related to six domains
- Response options: no change, occasionally, little worse, much worse

Items from the Memory Domain:
Compared to 10 years ago, has there been any change in...
1. Remembering a few shopping items without a list
2. Remembering things that happened recently (such as recent outings, events in the news)
3. Recalling conversations a few days later
4. Remembering where she/he has placed objects
5. Repeating stories and/or questions
6. Remembering the current date or day of the week
7. Remembering he/she has already told someone something
8. Remembering appointments, meetings, or engagements

ECog Correlation with Neuropsychological Tests: Brain Health Registry Online assessments

1. In all cognitively unimpaired (CU) individuals combined, there was no significant correlation between objective cognitive tests and subjective complaints.

2. If you restrict CU cases to those with study partner report of memory decline, the study partner ratings are correlated to objective tests of memory but not to tests of attention or processing speed.

3. If you restrict to MCI, study partner ECog ratings are correlated with attention/processing speed but not memory.

4. In AD, ECog ratings are highly correlated with objective cognitive test performance in all domains tested.

Informant ECog Scores in comparison to objective markers of AD

- ECog diagnostic group comparisons - All groups were significant different from one another (Normal, EMCI, LMCI, AD) - Greater functional impairment was reported with increased disease severity

- ROC curve analysis - Informant-reports consistently provided better group discrimination than self-report across diagnostic groups. LMCI vs. Normal reached the pre-set level specificity at sensitivity of 80%

Receiver operating characteristic curve using ECog total score by informant-report and self-report

<table>
<thead>
<tr>
<th>Diagnostic group comparisons</th>
<th>n</th>
<th>AUC</th>
<th>Specificity at sensitivity = 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 AD vs Normal</td>
<td>511</td>
<td>.99</td>
<td>(CI = .98 - .99)</td>
</tr>
<tr>
<td>2 LMCI vs Normal</td>
<td>549</td>
<td>.88</td>
<td>(CI = .85 - .91)</td>
</tr>
<tr>
<td>3 EMCI vs Normal</td>
<td>617</td>
<td>.87</td>
<td>(CI = .80 - .96)</td>
</tr>
<tr>
<td>4 &quot;Impaired&quot; vs Normal</td>
<td>106</td>
<td>.80</td>
<td>(CI = .77 - .84)</td>
</tr>
<tr>
<td>5 AD vs EMCI</td>
<td>516</td>
<td>.89</td>
<td>(CI = .88 - .91)</td>
</tr>
<tr>
<td>6 LMCI vs EMCI</td>
<td>551</td>
<td>.62</td>
<td>(CI = .57 - .66)</td>
</tr>
<tr>
<td>7 AD vs LMCI</td>
<td>463</td>
<td>.84</td>
<td>(CI = .80 - .88)</td>
</tr>
</tbody>
</table>

Note: ECog=Everyday Cognition score; M=mean; SD=standard deviation

Reference: Rueda et al. Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer’s Disease. Alzheimer’s and Dementias. 2015; September 11(9):1080-1089.
Informant ECog Scores in comparison to objective markers of AD (cont.)

- EMCI Informant ECog ratings demonstrated correlation with memory (delayed recall) and hippocampal volume.

- LMCI Informant ECog ratings demonstrated correlations with both memory (immediate and delayed recall) and executive function, as well as hippocampal volume, higher CSF p-tau, and lower Aβ1-42.

- Informant ECog reports useful to distinguish diagnostic groups (Normal, EMCI, LMCI, AD).
- Data suggesting ECog conceptually consistent with the progression of AD pathology on objective disease markers.

Reference: Rueda et al. Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer’s Disease. Alzheimer’s and Dementias. 2015; September 11(9):1080-1089.
Subjective Cognitive Decline Questionnaire (SCD-Q)

**SCD-Q:**
- Part 1 – subject report (MyCog)
- Part 2 – informant report (TheirCog)
- 3 domains – memory (11 items), language (6 items), executive function (7 items)
- Recall period: changes in the last 2 years

**Below is a list of activities. Please answer YES if you believe he/she performs them WORSE than roughly two years ago.**

<table>
<thead>
<tr>
<th>Activity</th>
<th>YES</th>
<th>NO</th>
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<tbody>
<tr>
<td>1. Finds it harder to learn new telephone numbers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Finds it harder to find personal possessions (keys, telephone, utensils, etc.)</td>
<td></td>
<td></td>
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<tr>
<td>3. Finds it harder to describe the plots of films</td>
<td></td>
<td></td>
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<tr>
<td>4. Finds it harder to remember doctor’s appointments.</td>
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<td></td>
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<tr>
<td>5. Finds it harder to follow the plot of a book.</td>
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<tr>
<td>6. Worse at recalling the details of a recent family event.</td>
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<td></td>
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<tr>
<td>7. Finds it harder to remember the result of a recent sporting event.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Finds it harder to remember sums of money (payments or debts).</td>
<td></td>
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</tbody>
</table>

**Total “YES”**

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**Read the questions below and circle YES or NO**

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
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<tbody>
<tr>
<td>a) Do you perceive he/she has cognitive or memory difficulties?</td>
<td></td>
<td></td>
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<tr>
<td>b) Would you advice him/her to ask a doctor about the cognitive difficulties?</td>
<td></td>
<td></td>
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<tr>
<td>c) In the last two years, has he/she experienced cognitive or memory decline?</td>
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</table>

*Recall period: changes in the last 2 years*
Informants’ SCD to Discriminate Preclinical AD from Normal Aging (Aβ± and CSF tau)

- Cognitively impaired scored worse on SCD TheirCog total score and across individual domains respectively (memory, language, and executive function)
- TheirCog Total (whole sample) correlated significantly with biomarkers (Aβ_{42}, tau, and p-tau)
- CSF Aβ42 levels were inversely correlated with the memory and executive items ratings
- CSF tau/p-tau levels were directly correlated with memory and executive items ratings

Discrimination Between Diagnostic Groups – Predictive Value of ECog

- Longitudinal analysis to assess time to change in diagnosis, from baseline diagnosis of Clinically Normal to endpoint diagnosis of MCI or AD
- Memory domain: discrimination of healthy normal vs. MCI
- Predictive value of individual items normal vs MCI:
  - Remembering a few shopping items - memory domain
  - Remembering appointments – memory domain
  - Keeping emails and papers organized – executive function domain
  - ROC AUC: 0.8695
- Everyday Language domain: discrimination of MCI vs. dementia

- Demonstrate predictive value of ECog – subjective complaints (classification of diagnostic groups: CN → MCI → AD)
- ECog conceptually consistent with the progression of pathology and neuropsychological impairment that occurs with AD

Cognitive Function Instrument (CFI): Informant Report

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Maybe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you feel the subject has had a significant decline in memory compared to one year ago?</td>
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<tr>
<td>2. Does the subject tend to ask the same question over and over?</td>
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<tr>
<td>3. Has the subject been misplacing things more often?</td>
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<td>4. Does it seem to you that lately the subject is relying more on written reminders (e.g., shopping lists, calendars)?</td>
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<td>5. Does the subject need more help from others to remember appointments, family occasions or holidays?</td>
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<tr>
<td>6. Does the subject have more trouble recalling names, finding the right word, or completing sentences?</td>
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<tr>
<td>7. Is the subject having more trouble driving (e.g., do you drive more slowly, have more trouble at night, tend to get lost, have accidents)?</td>
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<tr>
<td>8. Compared to one year ago, is the subject having more difficulty managing money (e.g., paying bills, calculating change, completing tax forms)?</td>
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<td>9. Is the subject less interested in social activities?</td>
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<tr>
<td>10. Do you believe, based on your own observations or comments from the subject’s co-workers, that the subject’s work performance (paid or volunteer) has declined significantly, compared to one year ago?</td>
<td></td>
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<tr>
<td>11. Does the subject have more trouble following the news, or the plots of books, movies or TV shows, compared to one year ago?</td>
<td></td>
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<tr>
<td>12. Are there any activities (e.g., hobbies, such as card games, crafts) that are substantially more difficult for the subject now compared to one year ago?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>13. Is the subject more likely to become disoriented, or get lost, for example when traveling to another city?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Does the subject have more difficulty using household appliances (such as the washing machine, VCR or computer)?</td>
<td></td>
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</tbody>
</table>
Tracking Early Cognitive Decline (CFI) in Individuals at Risk for AD

- APOE group differences significant for CFI Partner at months 36 and 48; and combined CFI Self+Partner at 24-48 months. (CFI Self n.s.)
- CDR-Global progression group differences are significant at every visit (CFI Self n.s. at month 3 and 12).
- Even stronger predictive value when CFI Self+Partner combined (greatest separation of groups)
- Predictive value of groups of items representing either cognitive or functional abilities did not reach statistical significance (data not shown).

- Replicate findings from Marshall et al study of predictive value of SCD to track future cognitive impairment
- Failed on predictive value of groups of items – suggest that the combination of all items together is important
Informant Reported SCD – Literature Review

Summary

• Informant reported decline is reliably associated with magnitude of cognitive impairment determined from neuropsychological assessment - SCD utility when neuropsychological test may not be available

• Informant reported impairment is mild-moderately associated with abnormal levels of AD biomarkers (hippocampal volume, Aβ, and tau) – early and late MCI

• SCD/Everyday cognition has predictive value for future decline - conversion from normal status to MCI

• Informants are a common component in many AD clinical studies/trials, and thus may help discriminate between diagnostic groups and predict progression from cognitively normal status to MCI

Findings suggesting that informant SCD/ECog ratings should provide sound basis for identification of subjects in very early AD
Conclusion – Utility of SCD (ECog)

1. Informant SCD reports can predict longitudinal change at a single point in time
   • May serve as a screening tool to identify individuals at risk and clinical trial inclusion

2. SCD is demonstrating a meaningful change from previous level of functioning (as noticed by the informant)
   • Has a potential as a clinical trial endpoint to track disease progression and demonstrate meaningful change to prove treatment effect

“An integrated scale that adequately and meaningfully assess both daily function and cognitive effects in early AD patients is acceptable as a single primary efficacy outcome measure.” (FDA, 2018)
Thank you!
Everyday Cognition (ECog) – Instrument Development

• Early functional changes predict rapid decline in early AD  
  • ECog Scale developed to detect early functional changes in the progression to AD (preclinical AD/MCI)

• Functional changes resulting from cognitive decline reflect obvious meaningful endpoints for trials and clinical management.
  • ECog designed to measure everyday function in multiple domains, each domain defined by the underlying cognitive abilities (i.e., correspond well with neuropsychological test domains)

• ECog is intended to have both research and clinical utility  
  • Research: Detecting group differences and longitudinal change 
  • Clinical: Multiple domains has potential for helping diagnostic differentiation and improved understanding of limitations, care needs, and interventions

• Subjective reports from individuals and/or informants who know the individual well

Subjective Cognitive Decline in Preclinical AD

Opportunities

- SCD (everyday cognition/IADL) closely reflects on how individuals is performing in the real world (ecologically valid – highly relevant to patients and caregivers)
- SCD can indicate decline before it become obvious on standardized neuropsychological tests
- Previous studies indicate subjective complaint to be a predictor of later AD (Normal → MCI → AD)

Challenges

- People differ greatly in the everyday tasks → a single scale may not be sensitive enough to detect signal of an intervention in very early disease in a heterogeneous sample
- Definition of concept studied (i.e., heterogeneity of concept, decline in memory vs. cognition, reference period matters)
- Finding the right scale – sensitive to change (yes/no vs. scale)
- Control confounding variables for over-reporting of SCD (mood, anxiety, etc.)
- In clinical trial use – SCD placebo effects unknown (compare neuropsychological tests)