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

Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Clinical/Medical

Revision 1

New FDA Guidance 2018 – Clinical Trial Challenges

Earlier in disease spectrum	Trial duration	Clinical Meaningfulness
• 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?

0.13% 2.14% 13.59% 34.13% 34.13% 13.59% 2.14% 0.13%

SD   −3   −2   −1   0   1   2   3

Percentile   1   5   20   50   80   95   99

1 SD below the norm, cut-off for MCI
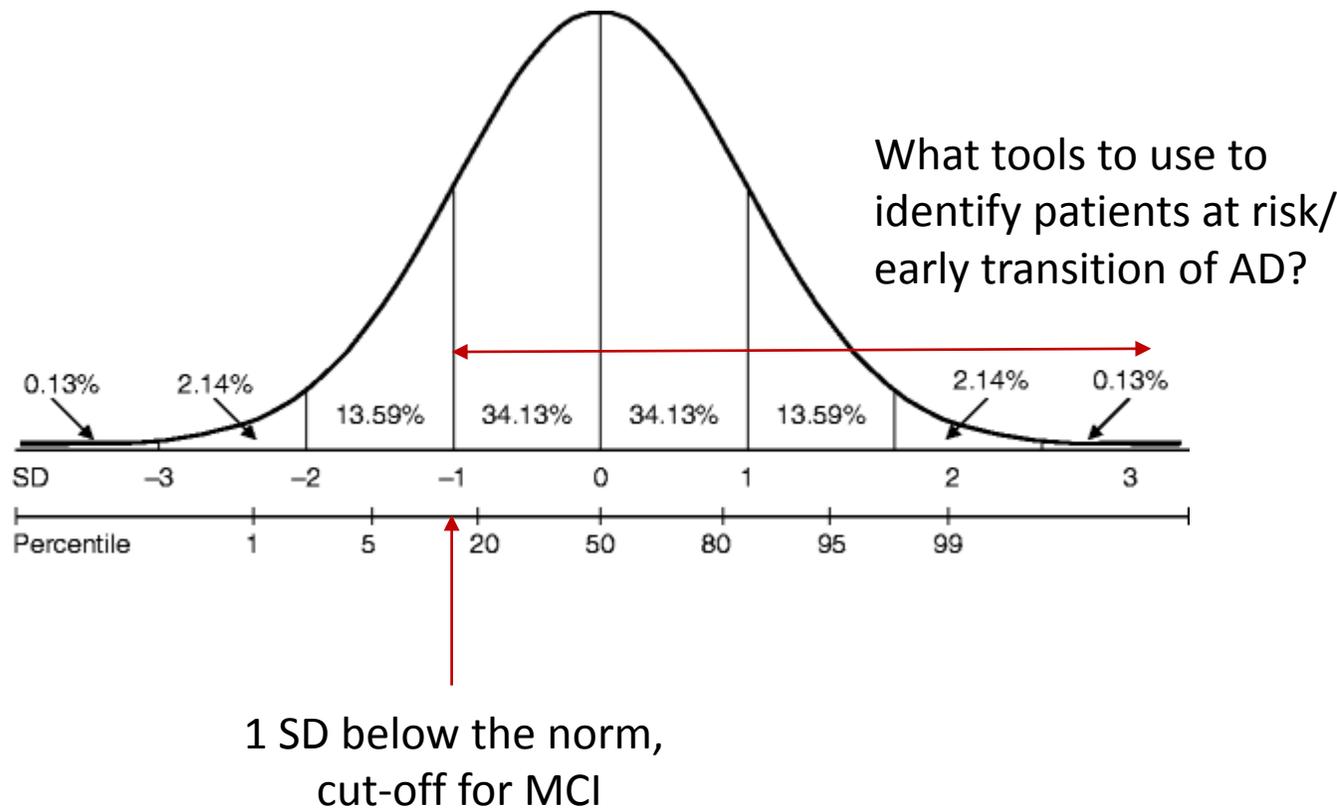
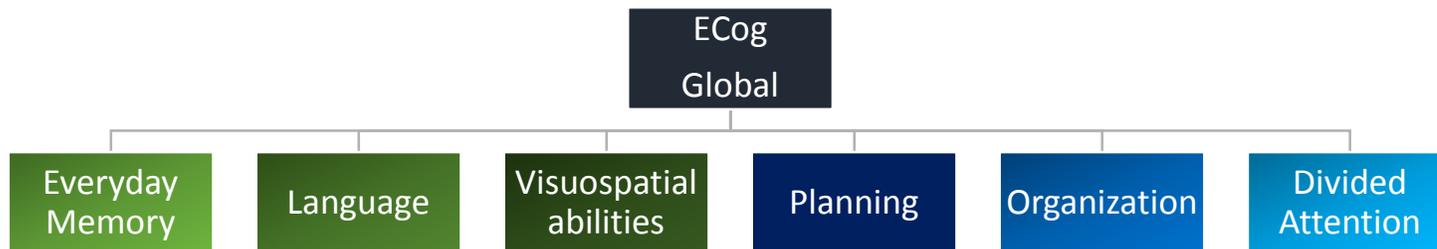- Suggested alternative - Ask individuals/informants

- 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

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

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                    ECog
                   Global
   ┌──────┬──────┬──────┼──────┬──────┬──────┐
Everyday  Language  Visuospatial  Planning  Organization  Divided
Memory              abilities                              Attention
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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

Reference: Farias et al. The measurement of everyday cognition (ECog): Scale development and psychometric properties. *Neuropsychology*. 2008;22(4):531-544.

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.

Table 3
Associations between SP-ECog and participant Cogstate scores

Cogstate subtest	Estimate	Standard Error	P value	Residual error	Effect size	R^2	Other significant variables	Significant interactions with SP-ECog
Whole cohort, $n = 2693$								
DET (time)	0.04	0.01	**.003**	0.09	0.44	0.292		Spouse, YK
IDN (time)	0.01	0.01	.562	0.07	0.08	0.255		Spouse, YK
ONB (accuracy)	−0.04	0.04	.235	0.25	0.17	0.245		Spouse, YK
OCL (accuracy)	−0.05	0.02	**.010**	0.14	0.37	0.249	Edu	Spouse
CU only, $n = 2354$								
DET (time)	0.00	0.01	.900	0.09	−0.02	0.047	Gender*	YK
IDN (time)	0.00	0.01	.690	0.06	0.06	0.042		
ONB (accuracy)	−0.04	0.03	.207	0.20	0.20	0.034		
OCL (accuracy)	−0.04	0.02	.092	0.15	0.27	0.065	Edu	Spouse
MCI only, $n = 250$								
DET (time)	0.23	0.03	**<.001**	0.09	2.46	0.340	Gender,† Edu	Spouse, YK
IDN (time)	0.05	0.03	**.01**	0.08	0.70	0.254	Gender,† Edu	Spouse, YK
ONB (accuracy)	0.12	0.09	.186	0.28	0.44	0.340	Gender,* Edu	Spouse
OCL (accuracy)	−0.02	0.05	.658	0.14	0.15	0.259	Gender,* Edu	
AD only, $n = 65$								
DET (time)	0.11	0.02	**<.001**	0.07	1.62	0.519	Age, gender,* Edu, GDS	YK
IDN (time)	0.13	0.01	**<.001**	0.05	2.48	0.442	Age, gender,* Edu	
ONB (accuracy)	−0.22	0.06	**<.001**	0.22	1.00	0.194		
OCL (accuracy)	−0.09	0.02	**<.001**	0.08	1.14	0.397	Gender,* Edu	Spouse, YK
CU with subjective memory concern, $n = 1582$								
DET (time)	0.01	0.02	.538	0.08	0.14	0.098		
IDN (time)	0.01	0.01	.218	0.05	0.28	0.139	Gender*	Spouse
ONB (accuracy)	−0.11	0.05	**.020**	0.20	0.53	0.076		
OCL (accuracy)	−0.08	0.03	**.005**	0.13	0.64	0.224	Edu	YK

Abbreviations: AD, Alzheimer's disease; CU, cognitively unimpaired; DET, detection task to measure processing speed; Edu, education level; GDS, Geriatric Depression Scale; IDN, identification task to measure attention; MCI, mild cognitive impairment; OCL, One Card Learning; ONB, One-Back Test; SP-ECog, Study partner-reported Everyday Cognition scale score; Spouse, spouse partners; YK, number of years that the dyad has known each other.

NOTE. The "Other significant variables" column includes all variables with $P < .05$ and effect size >0.2 in the multivariable models. Significant dyad relationship variables includes those dyad relationship variables with a significant interaction with SP-ECog, $P < .05$, and effect size >0.20.

Bold values indicate statistical significance of $P < .001$.

*Females score worse than males.

†Males score worse than females.

Reference: Nosheny et al. Online study partner-reported cognitive decline in the Brain Health Registry. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2018;4:565-574.

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)[2] - 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%

ECog total scores for informant-report and self-report across diagnostic groups

Diagnostic group	Informant-ratings			Self-report			
	n	M	SD	n	M	SD	p-value[1]
Normal	300	1.17[2]	0.26	307	1.34[3]	0.31	<.0001
EMCI	305	1.64[2]	0.54	310	1.79	0.53	<.0001
LMCI	249	1.88[2]	0.64	251	1.81	0.54	.28
AD	211	2.82[2]	0.66	212	1.90	0.65	<.0001
Total	1,065	1.79	0.78	1,080	1.68	0.54	.08

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

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

Diagnostic group comparisons	Informant report			Self-report		
	n	AUC	Specificity at sensitivity = 80%	n	AUC	Specificity at sensitivity = 80%
1 AD vs Normal	511	.99 (CI = .98–.99)	99%	519	.79 (CI = .74–.83)	60%
2 LMCI vs Normal	549	.88 (CI = .85–.91)	82%	558	.80 (CI = .77–.84)	64%
3 EMCI vs Normal	605	.83 (CI = .80–.86)	71%	617	.79 (CI = .75–.82)	62%
4 "Impaired" vs Normal	1065	.89 (CI = .87–.91)	82%	1080	.79 (CI = .76–.82)	62%
5 AD vs EMCI	516	.90 (CI = .88–.93)	89%	522	.53 (CI = .48–.58)	16%
6 LMCI vs EMCI	554	.62 (CI = .57–.66)	33%	561	.51 (CI = .46–.56)	23%
7 AD vs LMCI	460	.84 (CI = .80–.88)	76%	463	.52 (CI = .46–.57)	16%

Note: Impaired = AD + EMCI + LMCI groups; AUC=area under the curve; CI=95% confidence interval; ECog=Everyday Cognition score

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

Table 3. Correlation between ECog, cognition, MRI, CSF and PET biomarkers

| Diagnostic groups | n | Neuropsychological markers | | | n | Structural neuroimaging | | n | CSF biomarkers(6) | | n | [18F]AV45 PET |
		RAVLT Learning	RAVLT Recall	TMT-B		VV	HV		Aβ 1–42	p-tau		summary SUVR
Informant-report												
Normals	297	−.05	−.12*	.09	189	.004	−.02	79	−.10	.13	251	.03
EMCI	301	−.05	−.17**	.06	299	.06	−.13*	104	−.14	.10	285	.09
LMCI	246	−.20**	−.27***	.27***	166	.07	−.21**	110	−.11	.23*	207	.26***
AD	206	−.21**	−.15*	.28***	126	.05	.01	102	−.02	−.05	141	−.06
Total Group	1,050	−.52***	−.53***	.43***	780	.19***	−.37***	395	−.34***	.25***	884	.29***
Self-report												
Normals	303	−.08	−.11	.04	193	.03	.07	79	−.004	−.13	254	−.04
EMCI	303	−.03	−.06	.07	301	.04	.12*	106	−.07	−.01	287	.02

- 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

Read the questions below and circle YES or NO		
a) Do you perceive he/she has cognitive or memory difficulties?	YES	NO
b) Would you advice him/her to ask a doctor about the cognitive difficulties?	YES	NO
c) In the last two years, has he/she experienced cognitive or memory decline?	YES	NO

Below is a list of activities. Please answer YES if you believe he/she performs them WORSE than roughly		
1. Finds it harder to learn new telephone numbers	YES	NO
2. Finds it harder to find personal possessions (keys, telephone, utensils, etc.).	YES	NO
3. Finds it harder to describe the plots of films	YES	NO
4. Finds it harder to remember doctor's appointments.	YES	NO
5. Finds it harder to follow the plot of a book.	YES	NO
6. Worse at recalling the details of a recent family event.	YES	NO
7. Finds it harder to remember the result of a recent sporting event.	YES	NO
8. Finds it harder to remember sums of money (payments or debts).	YES	NO
9....24	YES	NO
Total "YES"	**Total**	

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)

SCD	Cognitively Healthy	Cognitively Impaired	
	CTR N=59	Non-Aβ-CI N=12	Aβ-CI N=21
Total TheirCog	3.8 (4.9)*	15.3 (7.3)	13.4 (6.2)
TheirCog memory	1.8 (2.6) *	7.3 (3.5)	7.1 (3.1)
TheirCog language	0.9 (1.5)*	3.3 (2.4)	3.0 (1.7)
TheirCog executive	0.9 (1.5)*	4.8 (1.9)	3.6 (2.5)

*P<0.05

- 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

SCD	CSFAβ^{42}	CSFtau	CSFptau
Total TheirCog	-0.21*	0.28*	0.28*
TheirCog memory	-0.25*	0.37*	0.36*
TheirCog language	-0.18	0.17	0.17
TheirCog executive	-0.12*	0.23*	0.26*

*Correlation coefficient significant at p<0.05

- Provides further evidence of SCD/TheirCog and the correlation of objective markers of AD pathology (Aβ and tau)

Reference: Valech et al. Informant's perception of subjective cognitive decline helps to discriminate preclinical Alzheimer's Disease from normal aging. *Journal of Alzheimer's Disease*. 2015;48:S87-S98.

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

ROC Curve for Model
Area Under the Curve = 0.8695
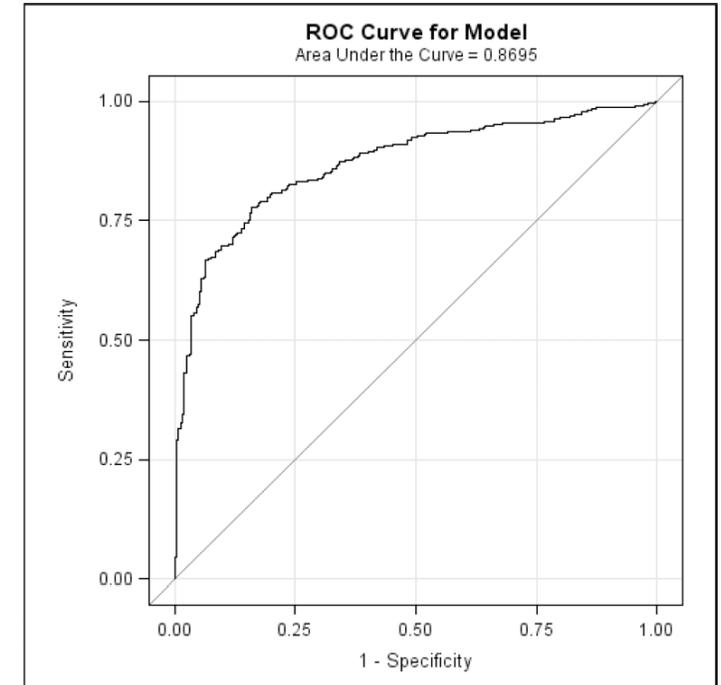
Figure 4.
The ROC curve corresponding to the logistic regression model indicates the specificity and sensitivity of the optimal linear combination of 3 informant-based ECog items (and the covariates of age and AMNART IQ) retained in the final model discriminating MCI from CN. AMNART IQ (American National Adult Reading Test intelligence quotient), CN (clinically normal), ECog (Everyday Cognition), MCI (mild cognitive impairment), ROC (receiver operating characteristic).

- 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

Reference: Marshall et al. Everyday Cognition scale items that best discriminate between and predict progression from clinically normal to mild cognitive impairment. *Current Alzheimer Research*. 2014:11(9):853-861.

Cognitive Function Instrument (CFI): Informant Report

Answer all questions with reference to one year ago.

1.	Do you feel the subject has had a significant decline in memory compared to one year ago?	☐ Yes	☐ No	☐ Maybe
2.	Does the subject tend to ask the same question over and over?	☐ Yes	☐ No	☐ Maybe
3.	Has the subject been misplacing things more often?	☐ Yes	☐ No	☐ Maybe
4.	Does it seem to you that lately the subject is relying more on written reminders (e.g., shopping lists, calendars)?	☐ Yes	☐ No	☐ Maybe
5.	Does the subject need more help from others to remember appointments, family occasions or holidays?	☐ Yes	☐ No	☐ Maybe
6.	Does the subject have more trouble recalling names, finding the right word, or completing sentences?	☐ Yes	☐ No	☐ Maybe
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)?	☐ Yes	☐ No	☐ Maybe
8.	Compared to one year ago, is the subject having more difficulty managing money (e.g., paying bills, calculating change, completing tax forms)?	☐ Yes	☐ No	☐ Maybe
9.	Is the subject less interested in social activities?	☐ Yes	☐ No	☐ Maybe
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?	☐ Yes	☐ No	☐ Maybe
11.	Does the subject have more trouble following the news, or the plots of books, movies or TV shows, compared to one year ago?	☐ Yes	☐ No	☐ Maybe
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?	☐ Yes	☐ No	☐ Maybe
13.	Is the subject more likely to become disoriented, or get lost, for example when traveling to another city?	☐ Yes	☐ No	☐ Maybe
14.	Does the subject have more difficulty using household appliances (such as the washing machine, VCR or computer)?	☐ Yes	☐ No	☐ Maybe

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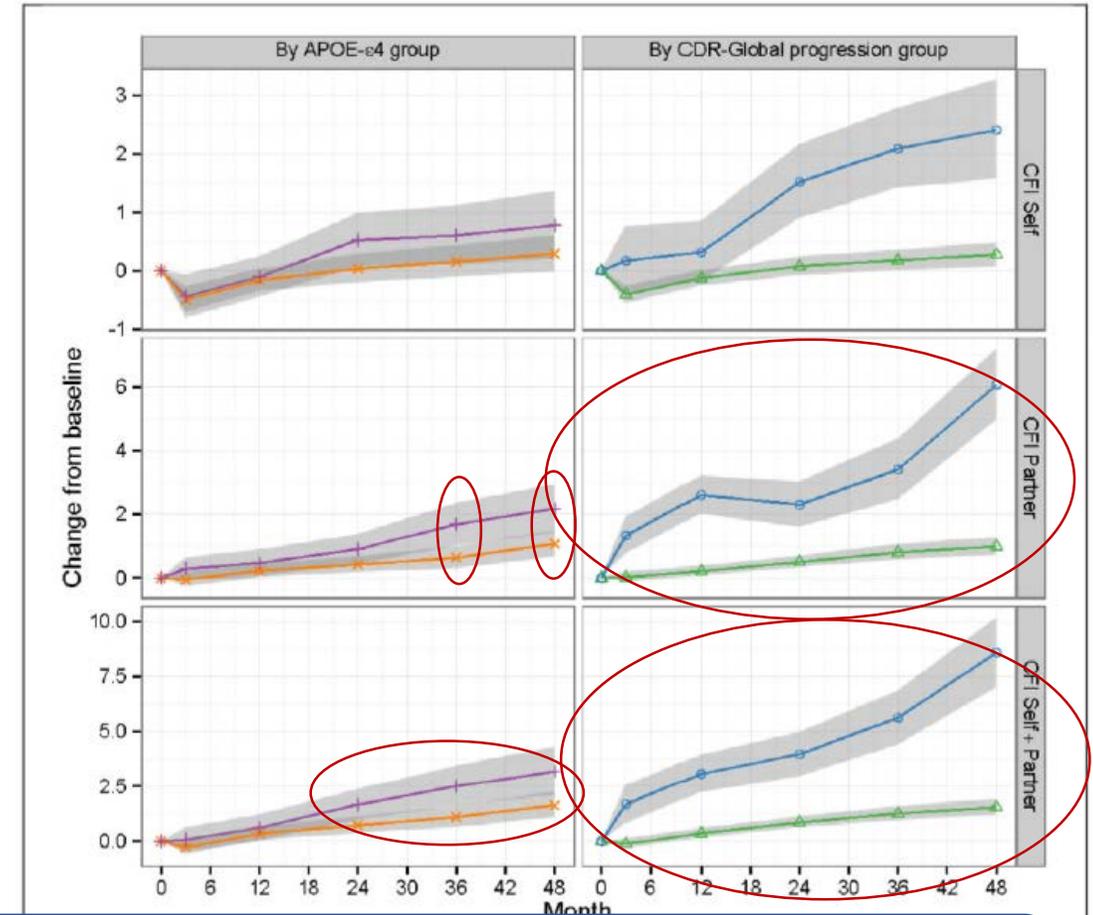
- Replicate findings from Marshall et al study of predictive value of SCD to track future cognitive impairment
- Failed on predictive value of groups of items – suggest that the combination of all items together is important

Cooperative Study Cognitive Function Instrument. *JAMA Neurl*. 2015;72(4):446-454.

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

Reference: Farias et al. The measurement of everyday cognition (ECog): Scale development and psychometric properties. *Neuropsychology*. 2008;22(4):531-544.

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)

Weintraub et al. Measuring cognition and function in the preclinical state of Alzheimer's Disease. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2018;4:64-75.