ISCTM
International Society for CNS Clinical Trials and Methodology

Behavioral and psychiatric symptoms in dementia (BPSD) apathy/agitation working group

February 18, 2026

Dr. Krista Lanctôt & Dr. David Miller

Dr. Paul Rosenberg

Disclosures

- Faculty: Krista L. Lanctôt
- Relationships with financial interests:
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Disclosures

- Faculty: David Miller
- Relationships with financial interests: VP of Signant Health

Agenda

Time	Topic
4:45-4:50pm	Welcome and introduction
4:50-5:30pm	Update on Apathy Discussion
5:30-6:15pm	Update on Agitation Discussion

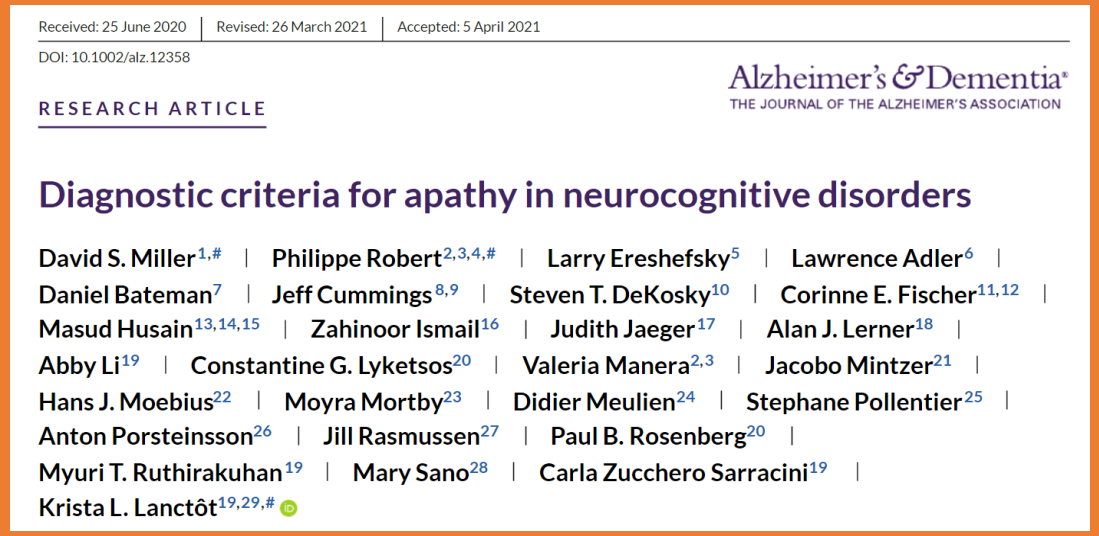
Apathy update

Dr. Krista Lanctôt & Dr. David Miller

Diagnostic criteria for Apathy in NCDs

Diagnostic criteria for apathy in NCD

expert consensus 2021



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Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Diagnostic criteria for apathy in neurocognitive disorders

David S. Miller[1,#] | Philippe Robert[2,3,4,#] | Larry Ereshefsky[5] | Lawrence Adler[6] | Daniel Bateman[7] | Jeff Cummings[8,9] | Steven T. DeKosky[10] | Corinne E. Fischer[11,12] | Masud Husain[13,14,15] | Zahinoor Ismail[16] | Judith Jaeger[17] | Alan J. Lerner[18] | Abby Li[19] | Constantine G. Lyketsos[20] | Valeria Manera[2,3] | Jacobo Mintzer[21] | Hans J. Moebius[22] | Moyra Mortby[23] | Didier Meulien[24] | Stephane Pollentier[25] | Anton Porsteinsson[26] | Jill Rasmussen[27] | Paul B. Rosenberg[20] | Myuri T. Ruthirakuhan[19] | Mary Sano[28] | Carla Zucchero Sarracini[19] | Krista L. Lanctôt[19,29,#]

- International Society for CNS Clinical Trials and Methodology (ISCTM), AAGP, NPS PIA, IPA
- Input from academia, clinicians, and regulatory stakeholders
- Applicable in neurocognitive disorders (NCD)
  - Focus on observable behaviours
- Compatible Robert et al 2019 transdiagnostic criteria
  - Social dimension separate

Miller, Robert, Cummings, Sano, Fisher, Baker, Mintzer … Lanctôt, (2021)

The Patient with Apathy Syndrome

Diminished goal-directed behaviour as shown by:

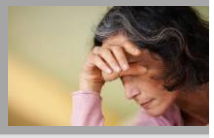
Initiative

- Less spontaneous and/or active than usual self
- Less likely to initiate usual activities
  - Hobbies
  - Chores
  - Self-care
  - Conversation
  - Work-related or social activities

Interest

- Less enthusiastic about usual activities
  - Less interested in, or less curious about events in their environment
  - Less interested in activities and plans made by others
  - Less interested in friends and family
  - Reduced participation in activities even when stimulated
  - Less persistence in maintaining or completing tasks or activities

Emotional Expression



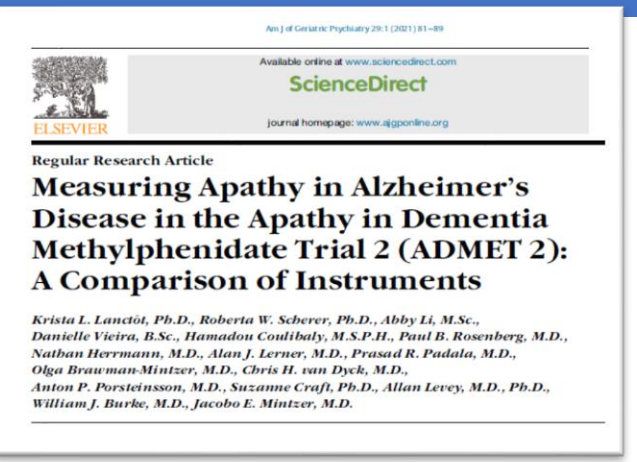
- Less spontaneous emotions
  - Less affectionate compared to their usual self
  - Expresses less emotion in response to positive or negative events
  - Less concerned about the impact of their actions on other people
  - Less empathy

Miller et al, J Alzheimer's & Dementia 2021

Measuring and defining apathy

NPI-A cut-off

- 180 participants with apathy
- ✓ scoring at least 4 on NPI-Apathy
- ✓ 93.9%(N=169) met diagnostic criteria for apathy


Am J of Geriatric Psychiatry 29:1 (2021) 81–89

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journal homepage: www.ajgponline.org

ELSEVIER

Regular Research Article

Measuring Apathy in Alzheimer's Disease in the Apathy in Dementia Methylphenidate Trial 2 (ADMET 2): A Comparison of Instruments

Krista L. Lanctôt, Ph.D., Roberta W. Scherer, Ph.D., Abby Li, M.Sc., Danielle Vieira, B.Sc., Hamadou Coulibaly, M.S.P.H., Paul B. Rosenberg, M.D., Nathan Herrmann, M.D., Alan J. Lerner, M.D., Prasad R. Padala, M.D., Olga Brawman-Mintzer, M.D., Chris H. van Dyck, M.D., Anton P. Porsteinsson, M.D., Suzanne Craft, Ph.D., Allan Levey, M.D., Ph.D., William J. Burke, M.D., Jacobo E. Mintzer, M.D.

Lanctôt et al 2021


Received: 22 August 2022 | Accepted: 17 January 2023

DOI: 10.1002/gps.5882

REVIEW ARTICLE

International Journal of Geriatric Psychiatry

Distinguishing apathy from depression: A review differentiating the behavioral, neuroanatomic, and treatment-related aspects of apathy from depression in neurocognitive disorders

Krista L. Lanctôt[1,2,3] | Zahinoor Ismail[4] | Kritleen K. Bawa[1,2] | Jeffrey L. Cummings[5] | Masud Husain[6,7] | Moyra E. Mortby[8,9] | Philippe Robe

Lanctôt et al 2024

Minimal Clinically Important Differences

- 260 ADMET and ADMET2 participants
- ✓ MCID for NPI-A = 4 points
- ✓ MCID for AES-I = 3 points
- ✓ Influenced by MMSE, apathy severity


Contents lists available at ScienceDirect

International Psychogeriatrics

journal homepage: www.sciencedirect.com/journal/inpsyc

ELSEVIER

Original Research Article

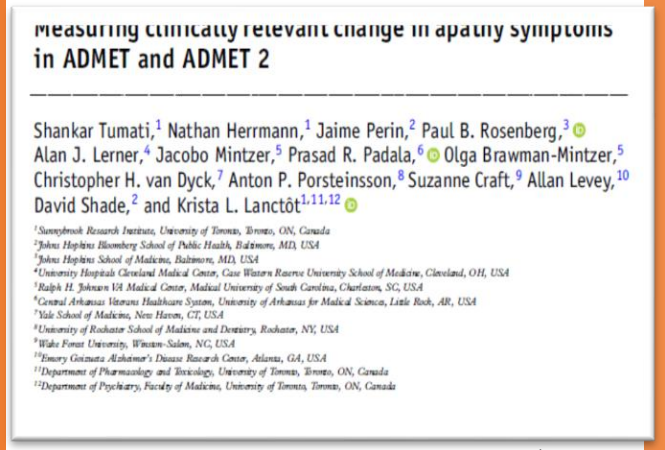
Mapping of validated apathy scales onto the apathy diagnostic criteria for neurocognitive disorders☆

K. Sankhe[a,b,c,1], K.K. Bawa[a,b,1], D.S. Miller[d], D. Bateman[e], J.L. Cummings[f], L. Ereshefsky[g,h], M. Husain[i], Z. Ismail[j], V. Manera[k,l], J. Mintzer[m,n], H.J. Moebius[o], M. Mortby[p,q,r], A. Porsteinsson[s], P. Robert[l,t], K.L. Lanctôt[a,b,c,u,2,*]

Sankhe et al 2025

Distinguishing apathy from depression

- ✓ Behavioural differences
- ✓ Neuroanatomic differences
- ✓ Differences in impact
- ✓ Different treatments


Measuring clinically relevant change in apathy symptoms in ADMET and ADMET 2

Shankar Tumati,[1] Nathan Herrmann,[1] Jaime Perin,[2] Paul B. Rosenberg,[3] Alan J. Lerner,[4] Jacobo Mintzer,[5] Prasad R. Padala,[6] Olga Brawman-Mintzer,[5] Christopher H. van Dyck,[7] Anton P. Porsteinsson,[8] Suzanne Craft,[9] Allan Levey,[10] David Shade,[2] and Krista L. Lanctôt[1,11,12]

Tumati et al 2024

Scale items and diagnostic criteria for apathy in NCD

- ✓ 82% of NPI-C items mapped onto DCA
- ✓ 33% of AES items mapped onto DCA
- ✓ NPI-C > AES

Literature update

Apathy and biomarkers

Apathy and affective NPS associated with neurodegeneration

Alzheimers Dement (Amst). 2025 Jul 29;17(3):e70151. doi: 10.1002/dad2.70151

Apathy and affective symptoms associated with elevated plasma neurofilament light but not p-tau181 in Alzheimer's disease

Matthew J Y Kang [1,2,✉], Dhamidhu Eratne [1,2], Samantha M Loi [1,2], Christa Dang [3,4], Alexander F Santillo [5], Henrik Zetterberg [6,7,8,9,10,11], Kaj Blennow [6,7,12,13], Philip B Mitchell [14], Malcolm Hopwood [2,15], Charles B Malpas [16,17], Dennis Velakoulis [1,2]

- N=781 participants with MCI and AD dementia enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI)

- Elevated plasma NfL associated with NPI presence of apathy, anxiety and depression
  - apathy linked to significantly faster increase in NfL over time

- Apathy and affective NPS not associated with plasma p-tau181

- Apathy and affective NPS associated with greater neurodegeneration
  - Apathy specifically linked to steeper rise in plasma NfL, indicating rapid neurodegeneration

MBI apathy associated with core AD biomarkers

cross-sectionally and longitudinally

BRAIN

Brain. 2025 Jun 2;148(12):4345–4358. doi: 10.1093/brain/awaf194

Mild behavioural impairment-apathy and core Alzheimer's disease cerebrospinal fluid biomarkers

Daniella Vellone [1,2], Rebeca Leon [3], Zahra Goodarzi [4,5,6,7,8], Nils D Forkert [9,10,11,12], Eric E Smith [13,14,15], Zahinoor Ismail [16,17,18,19,20,21,22,23]

- N=477 dementia-free participants with MCI or normal cognition from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were stratified by NPS status
  - Apathy: MBI apathy based on Neuropsychiatric Inventory (NPI) or NPI-Questionnaire (NPI-Q)

- <u>Cross sectional:</u>
  - MBI-apathy associated with higher CSF p-tau181/Aβ42 and t-tau/Aβ42 ratios compared with no-NPS group
  - MBI-apathy associated with higher CSF p-tau181

- <u>Longitudinal:</u>
  - MBI-apathy associated with CSF p-tau_{181}/$Aβ_{42}$ and t-tau_{181}/$Aβ_{42}$ over 2 years.
  - MBI-apathy associated with higher CSF p-tau_{181} and t-tau over 2 years.

- MBI-apathy associated with core Alzheimer's disease biomarkers both cross-sectionally and longitudinally

Predictors of treatment response

Potential biomarkers

Int Psychogeriatr. 2026 Jan 10:100181. doi: 10.1016/j.inpsyc.2025.100181. Online ahead of print.

Peripheral biomarkers associated with apathy and predicting response to methylphenidate: Secondary analysis of the Apathy in Dementia Methylphenidate Trial 2 (ADMET2) study

Krushnaa Sankhe [1], Myuri Ruthirakuhan [2], Ana C Andreazza [3], Olga Brawman-Mintzer [4], Suzanne Craft [5], Nathan Herrmann [6], Zahinoor Ismail [7], Alan J Lerner [8], Allan I Levey [9], Jacobo Mintzer [4], Prasad R Padala [10], Jamie Perin [11], Anton P Porsteinsson [12], Paul B Rosenberg [13], David Shade [11], Shankar Tumati [14], Christopher H van Dyck [15], Krista L Lanctôt [16]

56% of AD patients showed no benefit from methylphenidate

Variability in treatment response may have a biological basis

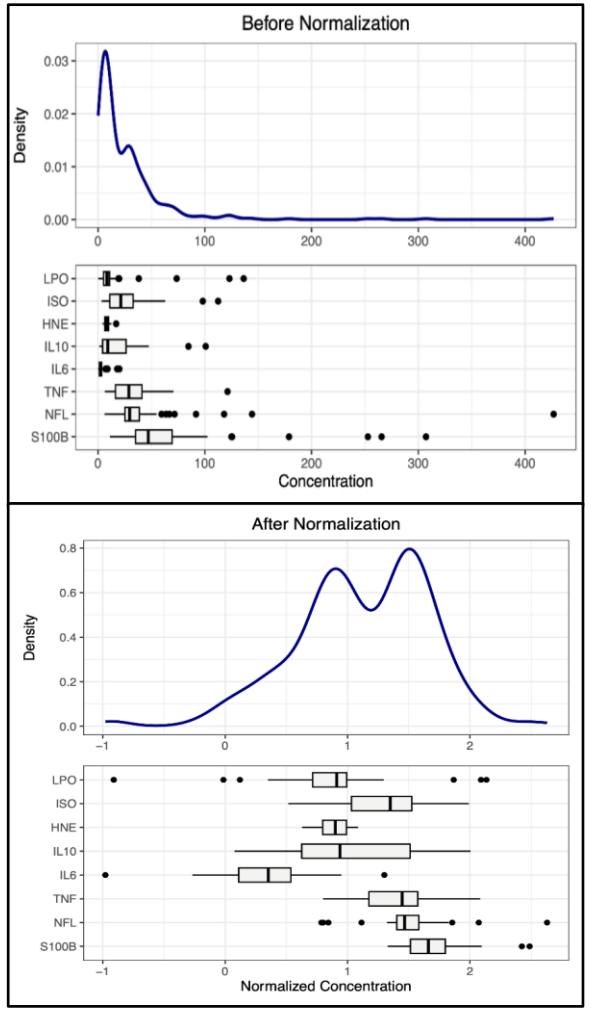
Personalized interventions based on biomarkers or genetics are key in neuropsychiatric drug development

Determine biomarkers that will help distinguish responders from non-responders

Supported by the National Institute for Aging (R01 AG046543)

ADMET 2 Biomarkers

- Pilot study of blood-based biomarkers from the ADMET 2 randomized clinical trial (n=44)
- Inflammation and oxidative stress induced by activated microglia can directly damage dopaminergic neurons [She et al 2024]
  - **Inflammation**: Interleukin (IL)-6, IL-10, tumor necrosis factor-alpha (TNFα)
  - **Oxidative stress**: lipid hydroperoxide (LPH), 4-hydroxynonenal (4-HNE), 8-isoprostane (8-ISO), and 8-ISO to LPH ratio [Bawa et al 2022]
  - **Neuronal loss**: Neurofilament light (NFL), S100B
- Log transformed
- Least Absolute Shrinkage and Selection Operator (LASSO) regression performed for feature selection of baseline markers predicting apathy at Month 6 (M6)



Sankhe et al 2026

Blood-based biomarkers associated with apathy symptoms

- Higher TNF and lower S100B at baseline associated with higher (worse) apathy at month 6
  - Multivariable regression with BL biomarkers as independent predictors and baseline apathy (NPI-A) as a covariate
- Higher baseline TNF associated with worsening apathy over time
  - Responders had lower baseline TNF [B(SE)=−0.21(0.09), 95% boot CI (−0.39,−0.05), p=.02], adjusting for baseline apathy
  - Remitters had lower baseline TNF [B(SE)=−0.20(0.09), 95% boot CI (−0.39,−0.01), p=.03], adjusting for baseline apathy

➢ Consistent with inflammation and possibly lower disease severity being associated with apathy, and inflammation with sustained apathy

Baseline biomarker N=44	B (SE), bootstrapped 95% CI, p-value
TNF	**8.28 (1.61), [5.35, 11.34], p<.0001**
S100B	**−6.41 (1.95), [−9.78, −1.91], p=.002**
4-HNE	6.02 (3.88), [−0.67, 13.65], p=.13
NfL	−2.68 (1.56), [−6.54, 0.28], p=.09
Covariate baseline apathy	−0.04 (0.22), [−0.43, 0.26], p=.86

Sankhe et al 2026

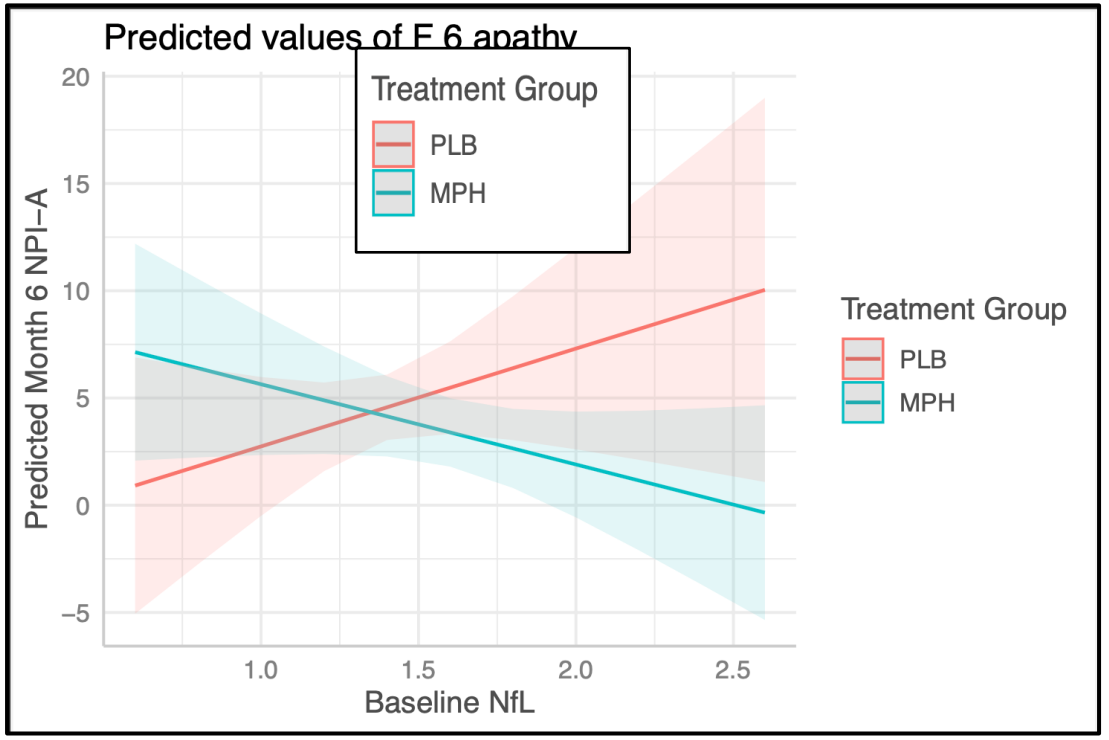
MPH treatment response

- In MPH group, lower baseline TNF associated with lower apathy at M6
  - adjusting for baseline apathy (8.61 (2.45), [4.63, 14.31], p = .002)
- MPH remitters (n=9) displayed
  - lower baseline TNF than non-remitters (n=12) [B(SE)=−0.28(0.11), 95% boot CI (−0.49,−0.07), p=.02]
  - higher baseline NfL compared to non-remitters adjusting for baseline apathy [B(SE)= 0.34(0.14), 95% boot CI (0.08,0.67), p=.02]
- Interaction effect between baseline NfL and treatment group in predicting apathy at M6 (Figure)
  - Adjusted for baseline apathy (-8.30 (4.26), [-25.65, -1.00], p=.06)

➢ lower inflammation at baseline may predict better apathy outcomes and better MPH treatment response

➢ MPH supplementation provides more benefit when neuronal injury more severe

Individuals with greater neuronal injury **more** likely to respond to MPH



Sankhe et al 2026

Apathy and function

Apathy is a key indicator of functional deterioration

J Neuropsychiatry Clin Neurosci. 2025 Jun 26:appineuropsych20250015.
doi: 10.1176/appi.neuropsych.20250015. Online ahead of print.

Understanding the Role of Neuropsychiatric Symptoms in Functional Decline in Alzheimer's Disease

Carolyn W Zhu [1], Lon S Schneider [1], Laili Soleimani [1], Judith Neugroschl [1], Hillel T Grossman [1], Corbett Schimming [1], Mary Sano [1]

- N=9,797 MCI or AD participants at baseline in the National Alzheimer's Coordinating Center Uniform Data Set
  - Function: Measured with the Functional Assessment Questionnaire
  - NPS: Assessed by using clinician judgment

- Latent class analysis revealed four NPS classes ranging from mild symptoms to a group with high levels of all symptoms
  - NPS classes not associated with rate of functional decline

- After controlling for NPS classes, persistent apathy remained strongly associated with a faster rate of functional decline

- **Conclusions:** Apathy, rather than overall NPS pattern, is a key indicator of functional deterioration in AD

Summary of the last meeting

- Since our last meeting, Drs. Lanctot, Miller and the Workgroup published *“Mapping of validated apathy scales onto the diagnostic criteria for apathy in neurocognitive disorders”*, led by PhD candidate Krushnaa Sankhe in the International Psychogeriatrics Journal.

- We discussed the Diagnostic Criteria for Apathy (DCA) checklist, which was developed by our apathy expert panel based on the NPI-C apathy domain and is currently being validated in our ongoing study, *“Validation of a brief assessment tool for apathy in neurocognitive disorders.”*

Current status

- Recruitment and data collection are progressing across multiple international sites.
  - Sunnybrook Research Institute (Canada) has completed recruitment (n = 60): *PhD Candidate Krushnaa Sankhe*
  - New York site (n=60) has completed retrospective data collection: *PI Dr Laili Soleimani*
  - France site is nearing completion: *PI Dr Valeria Manera*
- Our next steps for this project include initiating data analysis, and we hope to present preliminary findings at the next meeting.

Agitation update

Dr Paul Rosenberg

Disclosures
Paul B. Rosenberg M.D.

- Research support
  - Lilly, Vaccinex, National Institute on Aging, Alzheimer's Association, Functional Neuromodulation (FNMI), Lilly, Alzheimer's Disease Cooperative Study (ADCS), Alzheimer's Disease Trials Research Institute (ATRI), Alzheimer's Clinical Trials Consortium (ACTC), Richman Family Precision Medicine Center of Excellence on Alzheimer's Disease
- Consulting/advisory boards
  - GLG, Leerink, Cerevel, Cerevance, Bioxcel, Sunovion, Acadia, Food and Drug Administration, Medalink, Novo Nordisk, Noble Insights, TwoLabs
- DSMBs
  - Synaptogen
- No royalties, patents, stock