UDSv4 – Update

Allan Levey, MD, PhD

June 3, 2022

Agenda

Time (Pacific)	Topic	Speaker
8:00	Overview of UDSv4	Allan Levey, MD, PhD
8:05	Neuropsychiatric Symptoms	Kostas Lyketsos, MD
8:15	NPS/MBI Discussion	
8:25	AD Specific Treatment Form	Suzanne Schindler, MD, PhD
8:35	AD Treatment Form Discussion	
8:45	Subjective Cognitive Decline	Andy Saykin, PhD
8:55	SCD Discussion	
9:05	Social Determinants of Health	Lisa Barnes, PhD / Megan Zuelsdorff, PhD
9:15	SDOH Discussion	
9:25	COVID F2/F3 Forms	Carlos Cruchaga, PhD
9:35	COVID Discussion	
9:45	UDSv4 - Next steps	Sarah Biber, PhD / Laura McLeod
9:55	Open Question Time	

UDS Data – Impact

45,000+ Participants with data at NACC

166,000+ Clinical assessments
(1-17 visits per participant; median =3)

6,980+ Neuropathology datasets
(From 58% of deceased participants)

900+ Published studies using NACC data

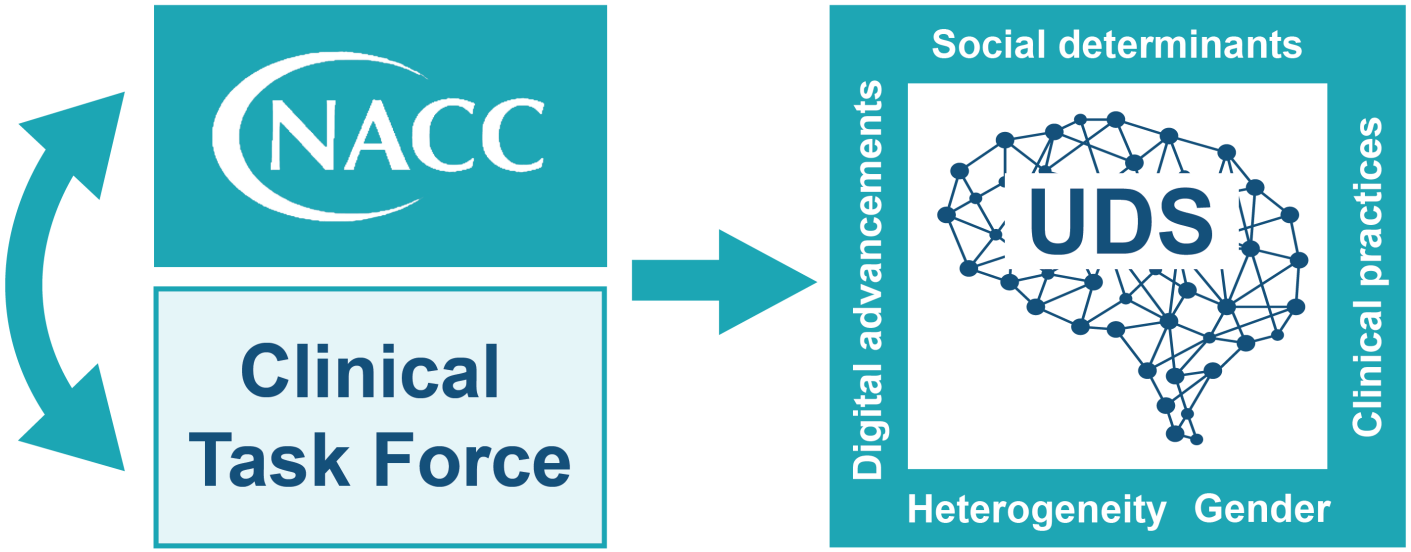
37 ADRCs are contributing data
(Across 26 states)

State with NIA-Designated Center(s)

State with Exploratory Center

UDSv4 – Content Update

- **Expand UDS participation** (Currently > 45,000 participants)
- **Streamline and reduce participant burden**
- **Reflect advances in science, technology, clinical practice, and our understanding of social determinants**



UDSv4 – CTF Collaboration with NACC

Collaboration with the Clinical Task Force (CTF)	Lead: Allan Levey, MD, PhD
Technology Workgroup	Lead: Rhoda Au, PhD
Clinical Measures and Diagnosis Workgroup	Co-leads: Cindy Carlsson, MD, MS and Greg Jicha, MD, PhD
Behavioral Workgroup	Co-leads: Howie Rosen, MD and Kostas Lyketsos, MD
Cognitive Workgroup	Co-leads: Andy Saykin, PsyD and Lisa Barnes, PhD
Social Determinants of Health Workgroup	Co-lead: Lisa Barnes, PhD and Megan Zuelsdorff, PhD

Collaborate on meeting agendas, setting strategic goals, and tracking deliverables

The ADRC Nucleus: The Uniform Data Set (UDS)

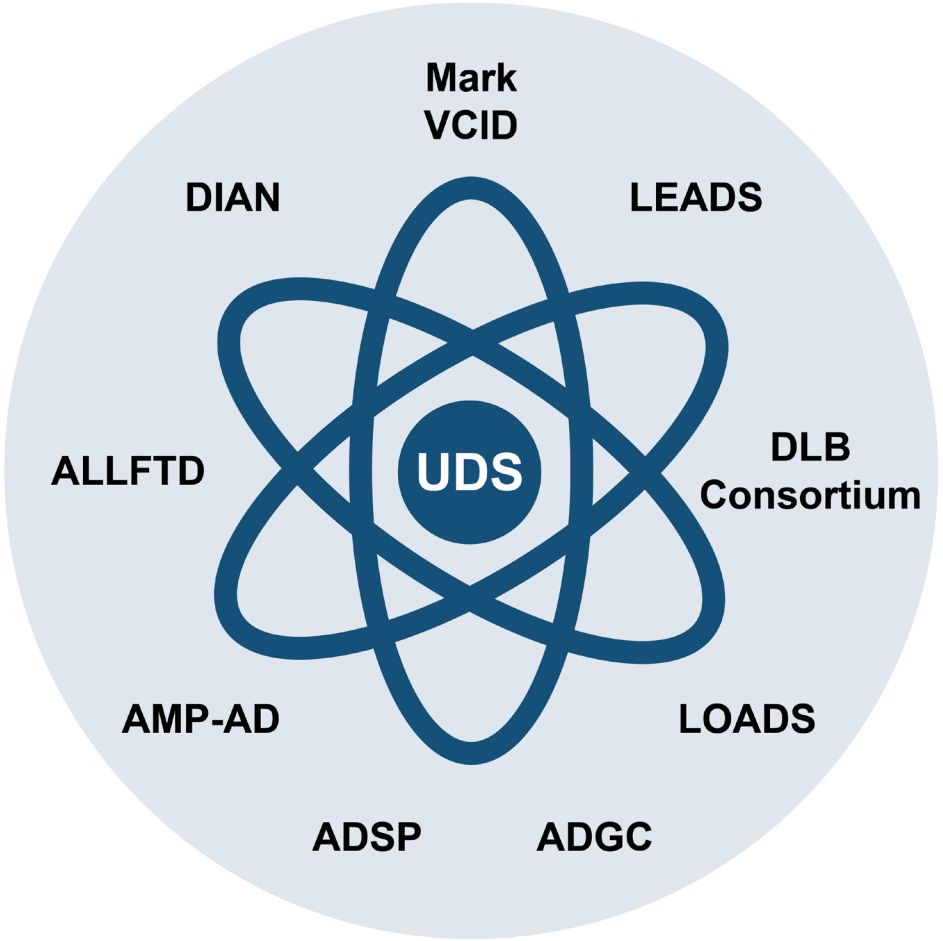
Supporting Numerous Consortia Advancing the Field

Who
Demographics (A1)
Co-participants (A2)
Family History (A3)

Risks & Comorbidities
Medications (A4)
Medical History (A5; D2)
Physical exam (B1)
Neurological exam (B8)

Cognition
Neuropsychological Battery (C2)

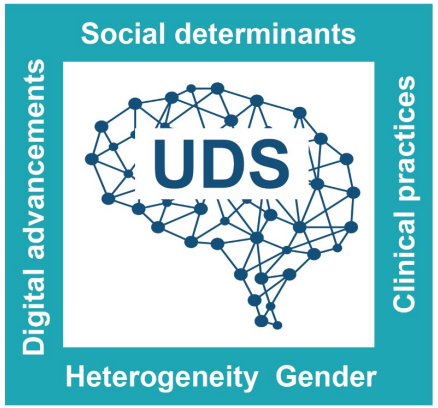
Research Diagnosis
Clinician Impression (B9)
Diagnosis (D1)



Benefits
- Enabling Harmonization
- Efficiencies in Recruitment
- Understanding Disease Overlap and Heterogeneity
- Supporting Genetics and Biomarker Studies

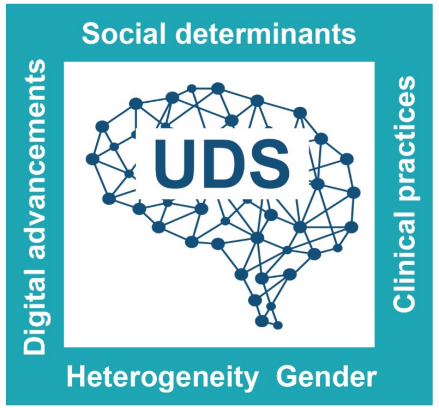
UDS4 – Highlights of Modifications Previously Presented

- Consolidate Subject Health History into a single form **A5/D2**
- Split **D1 Clinical Diagnosis** into two forms:
  - **D1a Clinical Diagnosis**
    - Expand primary dementia syndrome: include PSP, CBD, VCI/VaD
  - **D1b Biomarker Diagnosis**
    - Section 1: Biomarkers, imaging, and genetics
    - Section 2: Etiologic diagnosis
- Revive Form **B3 UPDRS- Parkinson's Form** from UDSv2
- Shorten **A2 Co-participant Demographics** and **A3 Subject Family History** reduced to first degree relatives



Update UDS Content

UDS4 – Today's Update



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CTF-NACC
UDSv4 Forms Update: Neuropsychiatric Symptoms

Presented by: Kostas Lyketsos

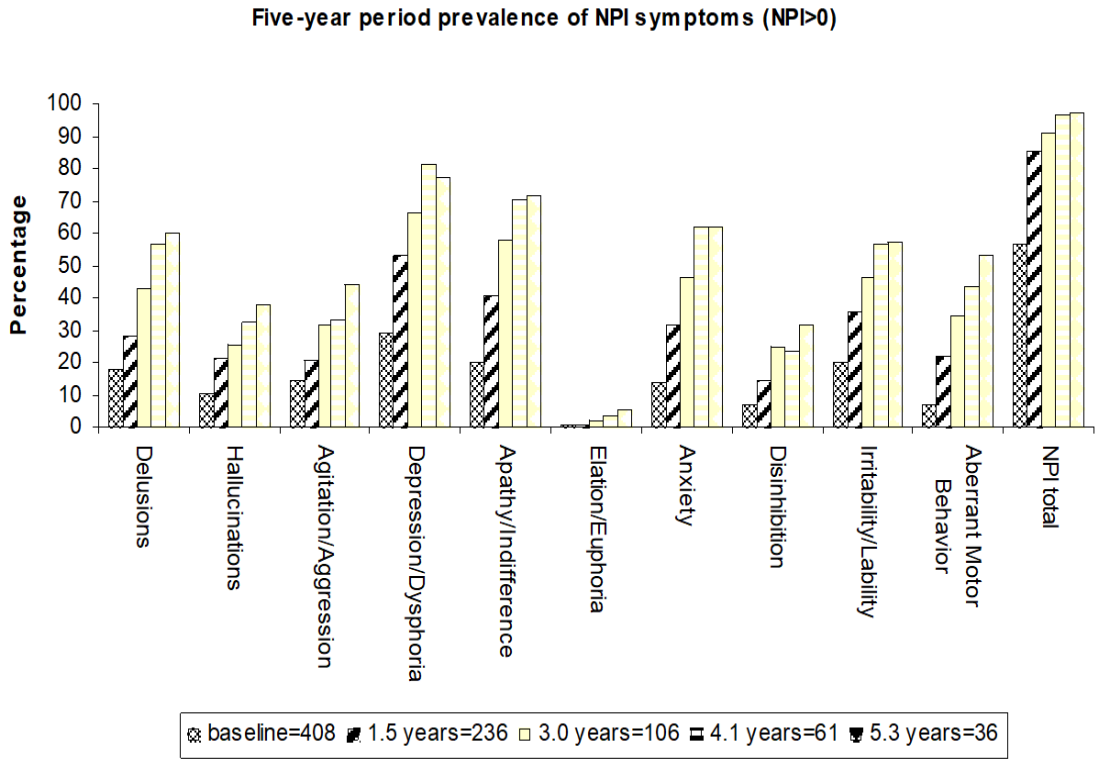
CTF Behavioral Workgroup

Why is the topic important?

- Growing importance of NPS in early phases of cognitive disorders
- Strengthen existing UDS elements around NPS
  - Better capture in participants without dementia
    - Differentiate age of onset
  - Standardize diagnosis of DSM-5-TM disorders
    - Symptoms v. syndrome v. disorder
  - Incorporate diagnosis of Mild Behavioral Impairment (MBI)

NPS are UNIVERSAL in Dementia

Cache County Dementia Progression Study



NPS affect at least half with MCI

Cardiovascular Health Study

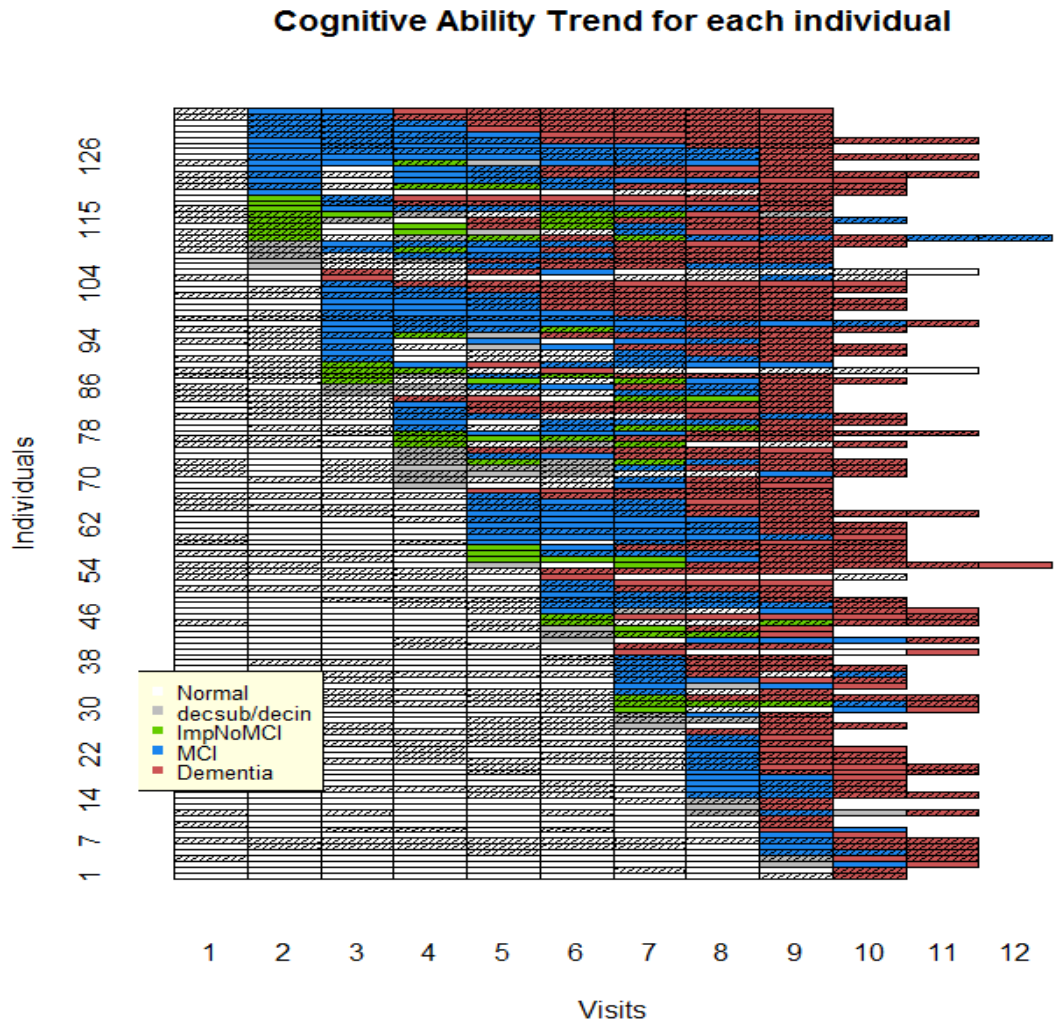
Table 3. Cumulative Prevalence of Individual NPI Symptoms From the Onset of the Cognitive Symptoms in the 2 Groups*

Symptoms	No. (%) MCI (n = 320)	No. (%) Dementia (n = 362)	χ^2 Test†
Delusions	15 (4.7)	109 (30.1)	75.6
Hallucinations	8 (2.5)	59 (16.3)	37.1
Agitation/aggression	47 (14.7)	145 (40.1)	54.4
Depression	84 (26.3)	158 (43.6)	23.0
Anxiety	33 (10.3)	92 (25.4)	27.9
Euphoria	4 (1.3)	11 (3.0)	
Apathy	58 (18.1)	164 (45.3)	61.2
Disinhibition	13 (4.1)	66 (18.2)	33.7
Irritability	53 (16.6)	123 (34.0)	28.3
Aberrant motor behavior	13 (4.1)	62 (17.1)	31.2
Sleep	57 (17.8)	109 (30.1)	16.9
Eating	56 (17.5)	112 (30.9)	16.8
Any 1 NPI disturbance	139 (49.6)	233 (80.1)	88.8

*NPI indicates Neuropsychiatric Inventory; MCI, mild cognitive impairment. For any 1 NPI disturbance, the total number of symptoms for MCI was 280 and for dementia was 291.
†$P<.001$ for all symptoms except for euphoria ($P = .09$, exact test).

Steinberg 2008; Lyketsos 2002

Over half with dementia develop NPS BEFORE cognitive diagnosis



Sequencing of NPS Presence with Cognitive Diagnosis in NACC
(overall N=1,980)

Normal→ MCI
NPS Before MCI: 55%

Normal→ Dementia
NPS Before MCI 55%

Normal→ Dementia (no MCI)
NPS Before Dementia 64%

Wise 2019

NPS in CIND/MCI

faster conversion to dementia

Neuropsychiatric Symptoms as Risk Factors for Progression From CIND to Dementia: The Cache County Study

M. E. Peters, M.D., P. B. Rosenberg, M.D., M. Steinberg, M.D., M. C. Norton, Ph.D., K. A. Welsh-Bohmer, Ph.D., K. M. Hayden, Ph.D., J. Breitner, M.D., M.P.H., J. T. Tschanz, Ph.D., C. G. Lyketsos, M.D., M.H.S., and the Cache County Investigato

Objectives: *To examine the association of neuropsychiatric symptom (NPS) severity with risk of transition to all-cause dementia, Alzheimer disease (AD), and vascular dementia (VaD).* **Design:** *Survival analysis of time to dementia, AD, or VaD onset.* **Setting:** *Population-based study.* **Participants:** *230 participants diagnosed with cognitive impairment, no dementia (CIND) from the Cache County Study of Memory Health and Aging were followed for a mean of 3.3 years.* **Measurements:** *The Neuropsychiatric Inventory (NPI) was used to quantify the presence, frequency, and severity of NPS. Chi-squared statistics, t-tests, and Cox proportional hazard ratios were used to assess associations.* **Results:** *The conversion rate from CIND to all-cause dementia was 12% per year, with risk factors including an APOE ε4 allele, lower Mini-Mental State Examination, lower 3MS, and higher CDR sum-of-boxes. The presence of at least one NPS was a risk factor for all-cause dementia, as was the presence of NPS with mild severity. Nighttime behaviors were a risk factor for all-cause dementia and of AD, whereas hallucinations were a risk factor for VaD.* **Conclusions:** *These data confirm that NPS are risk factors for conversion from CIND to dementia. Of special interest is that even NPS of mild severity are a risk for all-cause dementia or AD.* (Am J Geriatr Psychiatry 2012; 00:1–9)

Key Words: agitation, anxiety, Cache County, CIND, dementia, depression, MCI, NPS, NPI

The Association of Neuropsychiatric Symptoms in MCI with Incident Dementia and Alzheimer Disease

Paul B. Rosenberg, M.D., Michelle M. Mielke, Ph.D., Brian S. Appleby, M.D., Esther S. Oh, M.D., Yonas E. Geda, M.D., Constantine G. Lyketsos, M.D. M.H.S.

Objectives: *Individuals with mild cognitive impairment (MCI) are at high risk of developing dementia and/or Alzheimer disease (AD). Among persons with MCI, depression and anxiety have been associated with an increased risk of incident dementia. We examined whether neuropsychiatric symptoms in MCI increased the risk of incident dementia (all-cause) and incident AD.* **Design:** *Longitudinal cohort study followed annually (median: 1.58 years).* **Setting:** *National Alzheimer's Coordinating Center database combining clinical data from 29 Alzheimer's Disease Centers.* **Participants:** *A total of 1,821 participants with MCI.* **Measurements:** *1) Progression to dementia (all-cause) or AD, 2) Neuropsychiatric Inventory Questionnaire (NPI-Q), 3) Geriatric Depression Scale (GDS), 4) Clinical Dementia Rating Global Score and Sum of Boxes, and 5) Mini-Mental State Examination (MMSE). The association of covariates with risk of incident dementia or AD was evaluated with hazard ratios (HR) determined by Cox proportional-hazards models adjusted for age, ethnicity, Clinical Dementia Rating Global Score and Sum of Boxes, and MMSE.* **Results:** *A total of 527 participants (28.9%) progressed to dementia and 454 (24.9%) to AD. Baseline GDS > 0 was associated with an increased risk of incident dementia (HR: 1.47, 95% CI: 1.17–1.84) and AD (HR: 1.45, 95% CI: 1.14–1.83). Baseline NPI > 0 was associated with an increased risk of incident dementia (HR: 1.37, 95% CI: 1.12–1.66) and AD (HR: 1.35, 95% CI: 1.09–1.66).* **Conclusions:** *Neuropsychiatric symptoms in MCI are associated with significantly an increased risk of incident dementia and AD. Neuropsychiatric symptoms may be among the earliest symptoms of preclinical stages of AD and targeting them therapeutically might delay transition to dementia.* (Am J Geriatr Psychiatry 2013; 21:685–695)

Key Words: Alzheimer disease, dementia, depression, longitudinal study, mild cognitive impairment, neuropsychiatric symptoms

NPS in unimpaired

faster conversion to MCI

Article

Baseline Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Population-Based Study

Geda, M.D., M.Sc.
O. Roberts, M.B., Ch.B.
M. Mielke, Ph.D.
Knopman, M.D.
H. Christianson, B.Sc.
S. Pankratz, Ph.D.
F. Boeve, M.D.
ochor, M.D.
angalos, M.D.
. Petersen, M.D., Ph.D.
. Rocca, M.D., M.P.H.

Objective: The authors conducted a prospective cohort study to estimate the risk of incident mild cognitive impairment in cognitively normal elderly (aged ≥70 years) individuals with or without neuropsychiatric symptoms at baseline. The research was conducted in the setting of the population-based Mayo Clinic Study of Aging.

Method: A classification of normal cognitive aging, mild cognitive impairment, and dementia was adjudicated by an expert consensus panel based on published criteria. Hazard ratios and 95% confidence intervals were computed using Cox proportional hazards model, with age as a time scale. Baseline Neuropsychiatric Inventory Questionnaire data were available for 1,587 cognitively normal persons who underwent at least one follow-up visit.

Results: The cohort was followed to incident mild cognitive impairment (N=365) or censoring variables (N=179) for a median of 5 years. Agitation (hazard ratio=3.06, 95% CI=1.89–4.93), apathy (hazard ratio=2.26, 95% CI=1.49–3.41), anxiety (hazard ratio=1.87, 95% CI=1.28–2.73), irritability (haza 95% CI=1.31–2.58), and depr ratio=1.63, 95% CI=1.23–2.16), tially, increased risk for later impairment. Delusion and hal not. A secondary analysis, lim cance by the small number c ipants, showed that euphoria and nighttime behaviors we predictors of nonamnestic n impairment but not amnestic impairment. By contrast, de dicted amnestic mild cognitiv (hazard ratio=1.74, 95% CI=1 not nonamnestic mild cognitiv

Conclusions: An increased mild cognitive impairment v in community-dwelling elder had nonpsychotic psychiatric baseline. These baseline psy toms were of similar or great as biomarkers (genetic and s in increasing the risk of incid nitive impairment.

(Am J Psychiatry 2014; 1

ELSEVIER

Alzheimer's & Dementia ■ (2015) 1-8

Alzheimer's & Dementia

Perspective

Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment

Zahinoor Ismail[a,b,c,d,*], Eric E. Smith[b,d], Yonas Geda[e,f], David Sultzer[g,h], Henry Brodaty[i], Gwenn Smith[j], Luis Agüera-Ortiz[k], Rob Sweet[l,m], David Miller[n], Constantine G. Lyketsos[o], for the ISTAART Neuropsychiatric Symptoms Professional Interest Area

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[b]Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada
[c]Mathison Centre for Mental Health Research & Education, University of Calgary, Calgary, Alberta, Canada
[d]Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
[e]Department of Psychiatry, Mayo Clinic, Scottsdale, AZ, USA
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[g]Psychiatry Department, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA
[h]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

ISTAART research diagnostic criteria for MBI

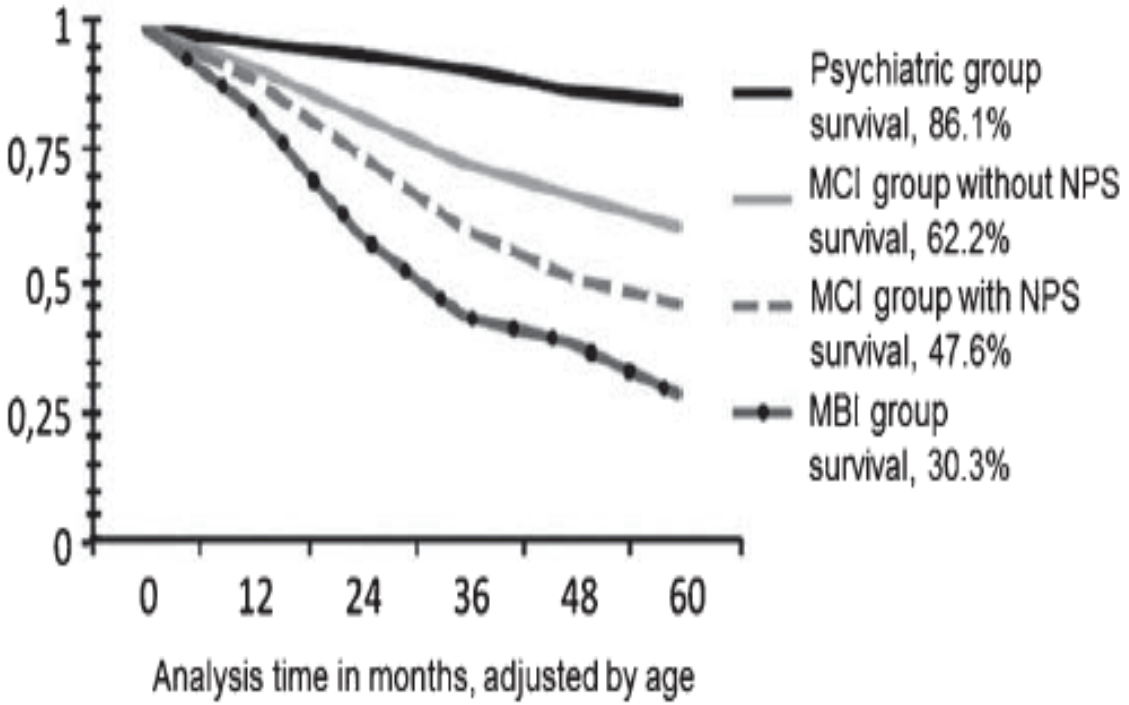
1. Changes in behavior or personality observed by patient, informant, or clinician, starting later in life (age ≥50 years) and persisting at least intermittently for ≥6 months. These represent clear change from the person's usual behavior or personality as evidenced by at least one of the following:
   a. Decreased motivation (e.g., apathy, aspontaneity, indifference)
   b. Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
   c. Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind)
   d. Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits)
   e. Abnormal perception or thought content (e.g., delusions, hallucinations)
2. Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:
   a. Interpersonal relationships
   b. Other aspects of social functioning
   c. Ability to perform in the workplace

   The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.
3. Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.
4. The patient does not meet criteria for a dementia syndrome (e.g., Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

Abbreviations: ISTAART, International Society to Advance Alzheimer's Research and Treatment; MBI, mild behavioral impairment; MCI, mild cognitive impairment.

Mild Behavioral Impairment (MBI)

faster conversion to dementia than MCI alone



REPLICATIONS IN LARGE MCI COHORTS

- MBI v. no MBI/psych: ORs 2.13 to 8.07
  - USA, NACC
  - French
  - Japanese

REPLICATION IN A LARGE SCD COHORT

- MBI v. no MBI: OR 8.15
  - Canadian

NACC

Taragano 2018

McGirr 2022; Chen 2021; Matsuoka 2019; Ismail 2021

Current approach in UDS

- Symptom capture on NPI-Q and GDS
- Psychiatric disorder capture on B9
- Contribution to cognitive disorder on D1

Proposed ap

- Continue a
  - ADD item
  - ADD MBI

use disorders

nventory

Mild Behavioral Impairment Checklist (MBI-C)

Date: _____

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3

Proposed approach-2

- NEW questions to D1 to capture NPS better
  - Are clinically significant NPS present?
  - If yes, are they recurrent or persistent from earlier life onset?
    - Specify age of onset
  - If no, do they meet syndromic DSM-5-TR criteria?
  - If no, do they meet criteria for MBI?

Thank you!

The CTF Behavioral Subgroup:

Rosen (lead), Lyketsos, Sano, Burns, Boeve, Raskovsky

Any Questions? (10 minutes)

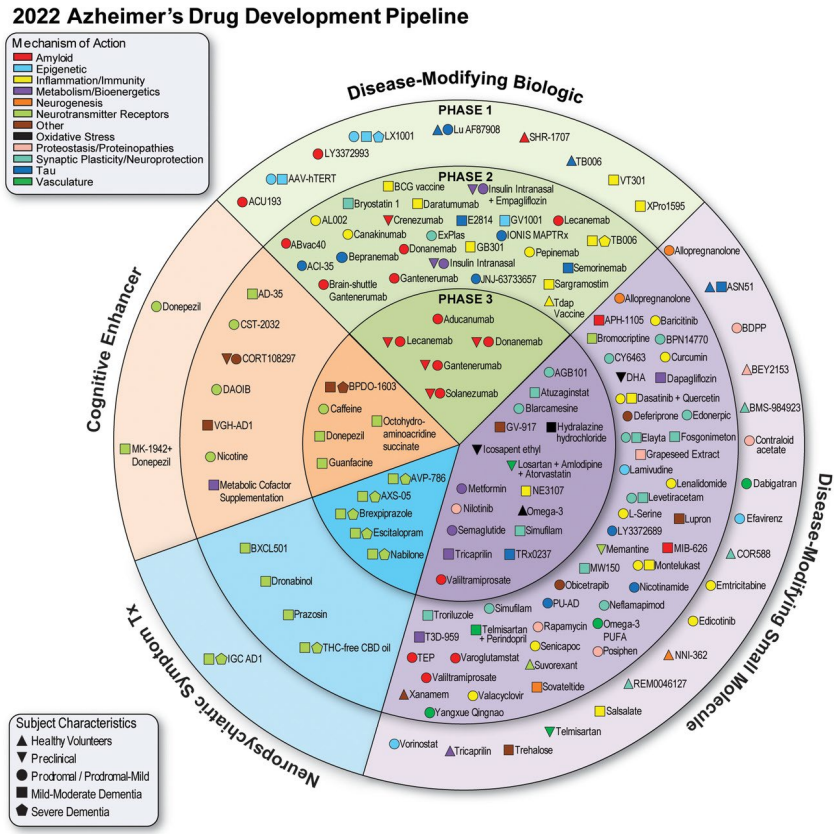
AD-specific treatments form

Presented by: Suzanne E. Schindler, MD, PhD

CTF Clinical Measures and Diagnosis Workgroup

Proliferation of AD-specific treatments

- Aducanumab was FDA approved in 2021—it currently has very limited clinical use
- In 2022 there are 143 agents in 172 AD clinical trials*
- Currently recruiting trials require 50,575 participants
- Some agents have major effects on ADRD biomarkers
- Some of our research participants are receiving these treatments



* Cummings et al., *Alzheimer's and Dementia* 2022

Why do we need a new form?

- Currently, there is no uniform mechanism to identify participants who have received treatments that modify ADRD biomarkers
- Treatments that have major effects on ADRD biomarkers could confound analyses
- Limitations of the medication form:
  - Records medications at the time of administration, but does not include transient treatment (e.g., 6 months of treatment with aducanumab in-between study visits)
  - Not designed to capture participation in clinical trials, in which the treatment may or may not be known (e.g., placebo or active treatment)
  - Does not capture any drug effects related to treatments (e.g., ARIA) that can affect ADRD biomarkers (e.g., brain MRI)
- AD-specific treatments and trials are rapidly evolving, and a separate form would provide increased flexibility for frequent changes

Process for creating form

- Key considerations:
  - Burden on participants and centers
  - Respecting contracts with pharmaceutical companies
  - Alignment with other constructs (e.g., CADRO classification)
  - Flexibility
- Sub-group of CTF Clinical Measures and Diagnosis Workgroup met and generated a first draft
- The CTF Clinical Measures and Diagnosis Workgroup discussed the draft form and made revisions
- Feedback was elicited from all the centers (April 22, 2022) and incorporated into a revised draft
- The form will primarily be used to identify individuals with data that may be confounded by AD-specific treatments, not to provide detailed information for analysis of AD-specific treatments

Question #1

Has the participant ever been enrolled in a clinical trial of a treatment expected to modify ADRD biomarkers or been prescribed a clinical treatment expected to modify ADRD biomarkers?

Yes/No/Unknown

If no, end of form.

Question #2

Please provide information about the clinical treatment(s) and/or trial(s):

Type of treatment	Specific treatment and/or trial (if known and can be shared)	Start date (month/year)	End date (month/year)	Was the treatment provided as part of clinical care, a clinical trial, or both?	If the treatment was provided as part of a clinical trial, in which arm was the participant?
Drop down box				Drop down box	Drop down box

Drop down options:

- Treatment affecting amyloid beta
- Treatment affecting tau
- Treatment affecting inflammation
- Treatment affecting synaptic plasticity/neuroprotection
- Other treatment (free entry box)

Drop down options:

- Clinical care
- Clinical trial
- Clinical care and clinical trial

Drop down options:

- Active treatment
- Placebo
- Unknown

Question #3

Has the participant ever experienced amyloid related imaging abnormalities-edema (ARIA-E), amyloid related imaging abnormalities-hemorrhage (ARIA-H), or other major adverse events associated with treatments expected to modify ADRD biomarkers?

Yes/No/Unsure

If yes or unsure,
Drop down options (allow multiple options to be highlighted):

- Amyloid related imaging abnormalities-edema (ARIA-E)
- Amyloid related imaging abnormalities-hemorrhage (ARIA-H)
- Other issues (free entry box)

Future of the form

- Form will initially be optional, and the major use will be to identify individuals who have received treatments that confound biomarker analyses
- It is likely that the form will be revised often, especially if new drugs are approved
- If a larger proportion of participants start taking AD-specific treatments, a greater level of detail (e.g., doses, more details about adverse effects) may be appropriate to add

Thank you!

The CTF Clinical Measures and Diagnosis Workgroup

Special thanks to:
Greg Jicha, Jeff Burns, Teresa Gomez-Isla, Nina Silverberg

Any Questions? (10 minutes)

CTF-NACC UDSv4 Update
Subjective Cognitive Decline:
Assessment of Cognitive Concerns & SCD Classification

Presented by: Andrew Saykin, PsyD (Indiana ADRC)

CTF Cognitive Working Group

June 3, 2022

Why are cognitive concerns and SCD important?

- Subjective or “self-perceived” cognitive concerns are a well-established early risk factor for cognitive decline and dementia
- Cognitive concerns are a key element of the clinical syndrome in early prodromal stages of AD dementia and one of the defining features of MCI
- Informant (collateral or co-participant) concerns are widely recognized as important elements of clinical and research assessments for dementia
- There has been growing interest in subjective cognitive decline (SCD) as an early clinical presentation (International SCD Consortium, now an Alzheimer’s Association PIA) and in use of quantitative assessment approaches to characterize self- and informant- perceptions of cognitive functioning
- For precision medicine in the biomarker & genomic era, it is important to have a well-defined phenotypic characterization
- Cognitive concerns have a role in early detection, enrichment for clinical trials, patient reported outcomes of interventions, among other uses

What scales were assessed in deciding on these questions?

- Issues addressed by the CTF Cognitive Work Group:
  1. How should cognitive concerns be assessed in UDS4?
     - One or more screening questions?
     - Quantitative scale(s)?
  2. Should we classify individuals as meeting research criteria for SCD? If so, what criteria should be employed?
- Overview of CTF WG process
  - Reviewed literature, available ADRC survey data, and approach used in UDS2/3
  - Invited presenters including Laura Rabin (Brooklyn College & ESA) & Shannon Risacher (IU ADRC) who presented analyses of scales, items, biomarkers & outcome data; Discussed with ADNI WG examining parallel issues
  - Considered widely used scales and approaches in the context of the 2018 A/T/N research framework; Considered available data from diverse settings
  - Considered cost/benefit factors for various approaches, including time required and participant and staff burden; issue of standardization vs post-hoc harmonization

Jessen/Geerlings SCD Question

ORIGINAL ARTICLE

Prediction of Dementia by Subjective Memory Impairment

Effects of Severity and Temporal Association With Cognitive Impairment

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Context: Subjective memory impairment (SMI) is receiving increasing attention as a pre-mild cognitive impairment (MCI) condition in the course of the clinical manifestation of Alzheimer disease (AD).

Objectives: To determine the risk for conversion to any dementia, dementia in AD, or vascular dementia by SMI, graded by the level of SMI-related worry and by the temporal association of SMI and subsequent MCI.

Design: Longitudinal cohort study with follow-up examinations at 1½ and 3 years after baseline.

Setting: Primary care medical record registry sample.

Participants: A total of 2415 subjects without cognitive impairment 75 years or older in the German Study on Aging, Cognition and Dementia in Primary Care Patients.

Main Outcome Measures: Conversion to any dementia, dementia in AD, or vascular dementia at follow-up 1 or follow-up 2 predicted by SMI with or without worry at baseline and at follow-up 2 predicted by different courses of SMI at baseline and MCI at follow-up 1.

Results: In the first analysis, SMI with worry at baseline was associated with greatest risk for conversion to any dementia (hazard ratio [HR], 3.53; 95% confidence interval [CI], 2.07-6.03) or dementia in AD (6.54; 2.82-15.20) at follow-up 1 or follow-up 2. The sensitivity was 69.0% and the specificity was 74.3% conversion to dementia in AD. In the second analysis, SMI at baseline and MCI at follow-up 1 were associated with greatest risk for conversion to any dementia (odds ratio [OR], 8.92; 95% CI, 3.69-21.60) or dementia in AD (19.33; 5.29-70.81) at follow-up 2. Furthermore, SMI at baseline and amnestic MCI at follow-up 1 increased the risk for conversion to any dementia (OR, 29.24; 95% CI, 8.75-97.78) or dementia in AD (60.28; 12.23-297.10), with a sensitivity of 66.7% and a specificity of 98.3% for conversion to dementia in AD.

Conclusion: The prediction of dementia in AD by SMI with subsequent amnestic MCI supports the model of a consecutive 3-stage clinical manifestation of AD from SMI via MCI to dementia.

Arch Gen Psychiatry. 2010;67(4):414-422

Table 1. Baseline Characteristics of the Study Subjects

Characteristic	No SMI (n=1027)	SMI Without Worry (n=1006)	SMI With Worry (n=382)	Statistic	*P* Value
Sex, No. (%)				χ^2=24.56	<.001
Female	685 (66.7)	591 (58.7)	273 (71.5)		
Male	342 (33.3)	415 (41.3)	109 (28.5)		
Age, mean (SD), y	79.4 (3.4)	79.8 (3.6)	79.8 (3.5)	*F*=2.87	.06
Education status, No. (%)[a]				χ^2=18.44	.001
Low	697 (67.9)	641 (63.7)	271 (70.9)		
Middle	252 (24.5)	247 (24.6)	68 (17.8)		
High	78 (7.6)	118 (11.7)	43 (11.3)		
ApoE4 genotype, No. (%)/total subpopulation	195/990 (19.7)	200/962 (20.8)	78/369 (21.1)	χ^2=0.51	.77
SISCO score, mean (SD)[b]	49.4 (3.2)	49.7 (3.2)	49.4 (3.3)	*F*=2.42	.09
Geriatric Depression Scale score, mean (SD)[c]	1.8 (2.0)	2.1 (2.1)	3.2 (2.7)	*F*=63.22	<.001

Table 2. Baseline Characteristics of 2075 Subjects in 4 Temporal Sequences

Characteristic	No SMI at Baseline and no MCI at Follow-up 1 (n=766)	SMI at Baseline and no MCI at Follow-up 1 (n=1025)	No SMI at Baseline and MCI at Follow-up 1 (n=108)	SMI at Baseline and MCI at Follow-up 1[a]: Amnestic (n=21)	SMI at Baseline and MCI at Follow-up 1[a]: Nonamnestic (n=155)	Statistic	*P* Value
Sex, No (%)						χ^2=4.91	.29
Female	514 (67.1)	642 (62.6)	71 (65.7)	14 (66.7)	94 (60.6)		
Male	252 (32.9)	383 (37.4)	37 (34.3)	7 (33.3)	61 (39.4)		
Age, mean (SD), y	79.3 (3.3)	79.5 (3.7)	79.8 (3.1)	79.8 (4.1)	80.4 (3.7)	*F*=3.84	.004
Education status, No. (%)[b,c]						χ^2=131.00	.001
Low	545 (71.1)	709 (69.2)	43 (39.8)	13 (61.9)	57 (36.8)		
Middle	169 (22.1)	189 (18.4)	48 (44.4)	5 (23.8)	77 (49.7)		
High	52 (6.8)	127 (12.4)	17 (15.7)	3 (14.3)	21 (13.5)		
ApoE4 genotype, No. (%)	139 (18.8)	201 (20.4)	20 (19.2)	10 (47.6)	34 (22.7)	χ^2=11.33	.02
SISCO score, mean (SD)[d]	49.7 (3.0)	50.1 (3.0)	48.9 (3.6)	46.3 (3.4)	49.3 (3.3)	*F*=12.28	<.001
Geriatric Depression Scale score, mean (SD)[d]	1.7 (1.9)	2.3 (2.3)	1.8 (1.9)	2.6 (1.8)	2.3 (1.2)	*F*=10.23	<.001

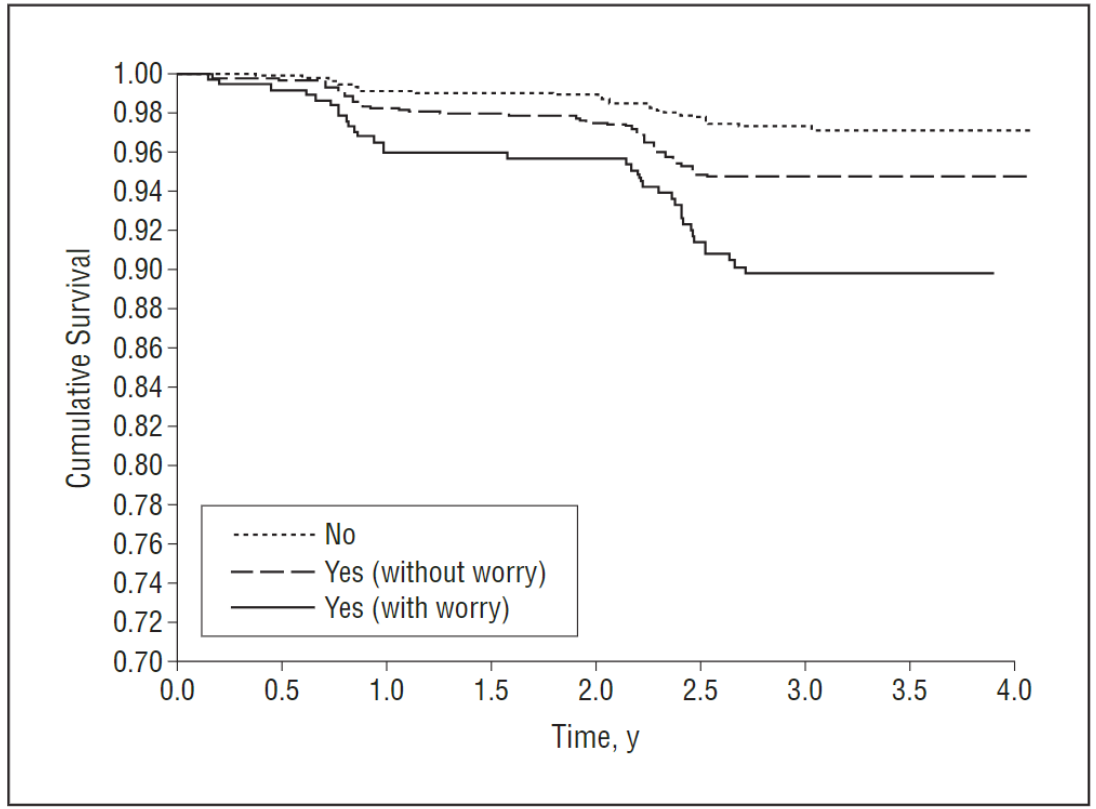


Figure. Kaplan-Meier survival curves showing the conversion to dementia in Alzheimer disease relative to the presence of subjective memory impairment with or without worry at baseline.

Questions (Geerlings et al 1999): "Do you feel like your memory is becoming worse?" Possible answers were "no," "yes, but this does not worry me," or "yes, this worries me."

Jessen et al Prediction of Dementia by Subjective Memory Impairment. *Arch Gen Psychiatry.* 2010;67(4):414-422.

Geerlings et al Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am J Psychiatry. 1999;156(4):531-537

Subjective Cognitive Decline: Outcome Datasets

ELSEVIER

Check for updates

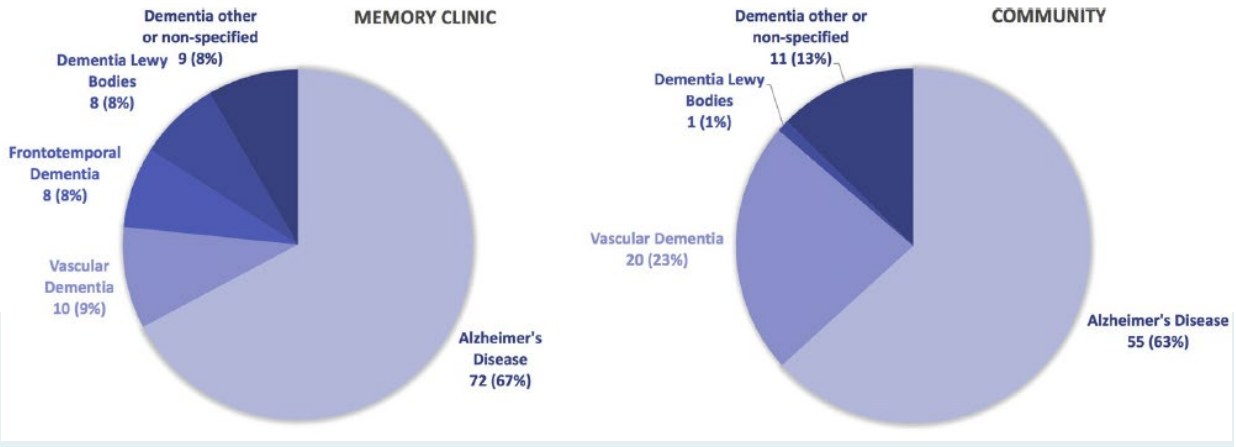
Alzheimer's & Dementia 15 (2019) 465-476

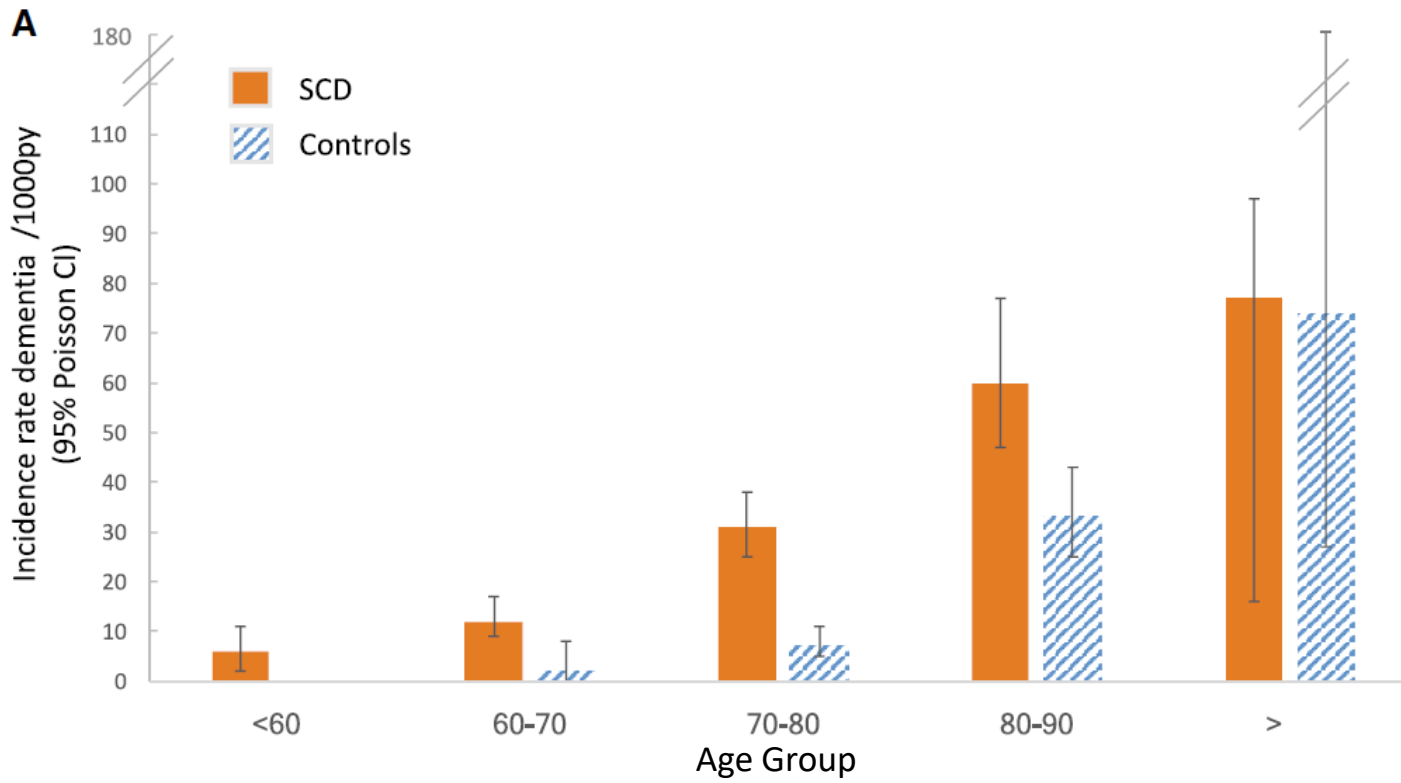
Alzheimer's & Dementia

Featured Article

Subjective cognitive decline and rates of incident Alzheimer's disease and non–Alzheimer's disease dementia

Rosalinde E. R. Slot[a], Sietske A. M. Sikkes[a,b], Johannes Berkhof[b], Henry Brodaty[c], Rachel Buckley[d,e,f], Enrica Cavedo[g,h,i,j], Efthimios Dardiotis[k], Francoise Guillo-Benarous[l], Harald Hampel[g,h,i,j], Nicole A. Kochan[c,m], Simone Lista[g,h,i,j], Tobias Luck[n,o], Paul Maruff[e,p], José Luis Molinuevo[q], Johannes Kornhuber[r], Barry Reisberg[l], Steffi G. Riedel-Heller[n], Shannon L. Risacher[s,t], Susanne Roehr[n,u], Perminder S. Sachdev[c,m], Nikolaos Scarmeas[v,w], Philip Scheltens[a], Melanie B. Shulman[l], Andrew J. Saykin[s,t], Sander C. J. Verfaillie[a], Pieter Jelle Visser[a,x], Stephanie J. B. Vos[x], Michael Wagner[y,z], Steffen Wolfsgruber[y,z], Frank Jessen[y,aa], the Alzheimer's Disease Neuroimaging Initiative, the DESCRIPA working group, the INSIGHT-preAD study group, on behalf of the SCD-I working group, Wiesje M. van der Flier[a,b,*]





Collaborative multicenter study:

- included 2978 participants with SCD
- SCD is a prodrome of both AD and non-AD dementia

Risk factors for progression from SCD to dementia:

- higher age, lower MMSE, APOE4, memory clinic setting

Slot RER et al, Alzheimers Dement 2019;15:465-476.

SCD in the NIA-AA Framework Context

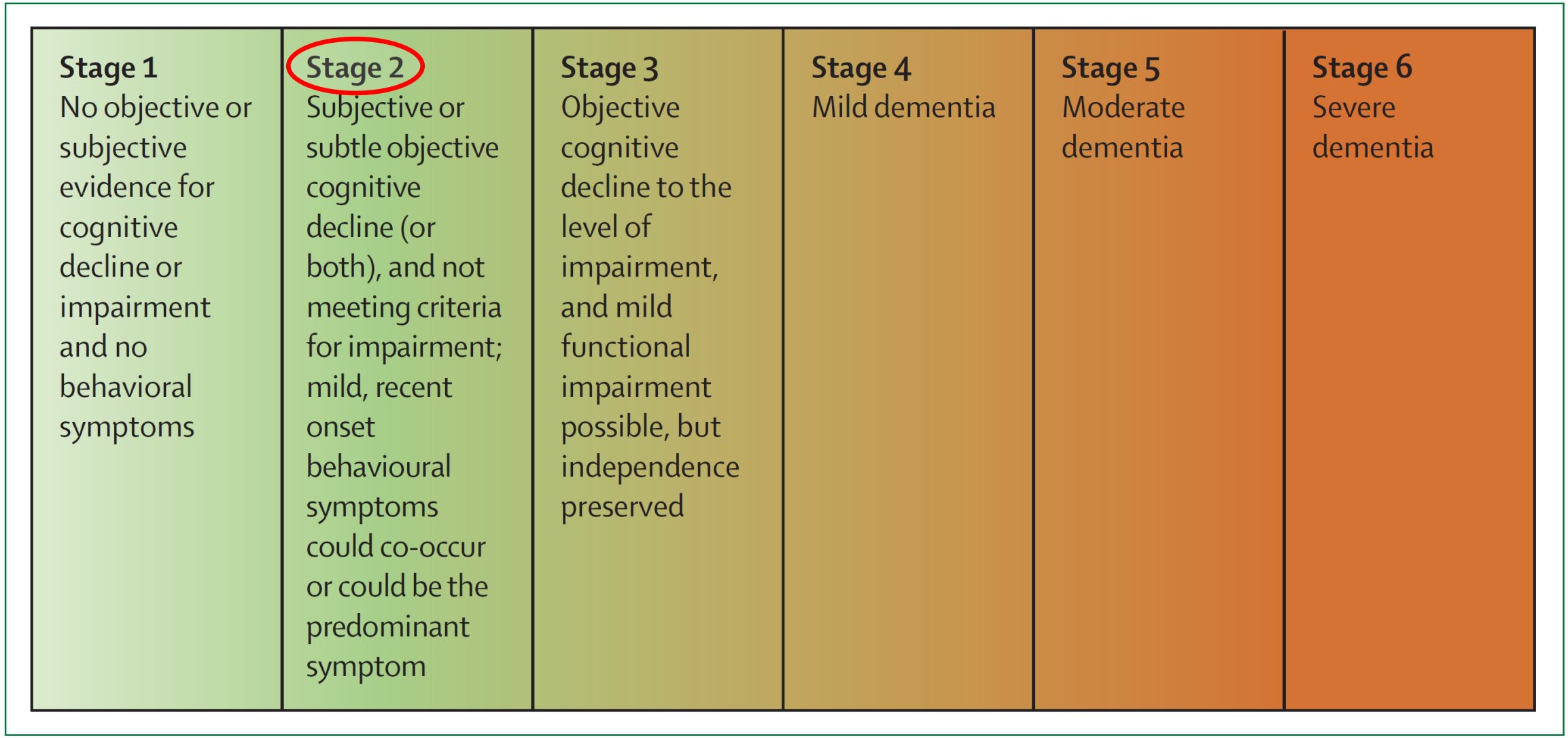


Figure 2: **Symptomatic stages of Alzheimer's disease according the NIA-AA research framework**

www.thelancet.com/neurology **Published online January 17, 2020 https://doi.org/10.1016/S1474-4422(19)30368-0**

Questions to be added to UDSv4 (Form TBD)

(1) Do you feel like your memory is becoming worse?

Response choices: "no," "yes, but this does not worry me," or "yes, this worries me"

Sources for item 1: Geerlings et al 1999; Jessen et al 2010

(2) How often do you have trouble remembering things?

Coded as 1=never, 2=rarely, 3=sometimes, 4=often, 5=very often

(3) Compared to 10 years ago, how would you rate your memory?

Coded as 1=much better, 2=little better, 3=same, 4=little worse, 5=much worse

Sources for items 2-3: Barnes et al 2006; Arvanitakis et al 2018

- The sum of the two scores is a memory score, classified as memory complaints if 8 to 10
- Sample for items 2-3 included Black and White participants, with and without dementia

Sources:

Geerlings et al: Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am J Psychiatry. 1999;156(4):531-537.

Jessen et al: Prediction of Dementia by Subjective Memory Impairment. *Arch Gen Psychiatry.* 2010;67(4):414-422.

Barnes et al 2006: Memory complaints are related to Alzheimer disease pathology in older persons. Neurology. 2006 Nov 14;67(9):1581-5.

Arvanitakis et al: Memory complaints, dementia, and neuropathology in older blacks and whites. Ann Neurol. 2018 Apr;83(4):718-729.

Optional Recommended Cognitive Concern Scales

For ADRCs interested in cognitive concerns, the CTF recommends administering the self and informant versions of either:

(1) Everyday Cognition (ECog) – 39 items (~8-10 minutes)

(2) Cognitive Change Index (CCI) – 20 items (~4-5 minutes)

- **Item level data capture to NACC**
- **Rationale: Two of the most frequently employed cognitive rating scales across ADRCs**
- **ECog and CCI scores can be harmonized with crosswalk table available (Wells et al 2022)**
- **Both have short and revised/expanded versions available but listing original version here and there may be further guidance on specific forms**

References:

Farias S Tomaszewski, Mungas D, Reed B, Cahn-Weiner, D, Jagust W, Baynes K, et al. (2008) The measurement of everyday cognition (ECog): Scale development and psychometric properties. *Neuropsychology* 22, 531–544.

Rattanabannakit C, Risacher SL, Gao S, Lane KA, Brown SA, McDonald BC, Unverzagt FW, Apostolova LG, Saykin AJ, Farlow MR (2016) The Cognitive Change Index as a measure of self and informant perception of cognitive decline: Relation to neuropsychological tests. *J Alzheimers Dis* 51, 1145-1155.

Wells LF, Risacher SL, McDonald BC, Farlow MR, Brosch J, Gao S, Apostolova LG, Saykin AJ; Alzheimer's Disease Neuroimaging Initiative. Measuring Subjective Cognitive Decline in Older Adults: Harmonization Between the Cognitive Change Index and the Measurement of Everyday Cognition Instruments. *J Alzheimers Dis*. 2022;87(2):761-769. doi: 10.3233/JAD-215388.

Everyday Cognition (Ecog) – 39 items

Compared to 10 years ago, has there been any change in…

Response options: Better or no change, Questionable or occasional problems, Consistently a little worse, Consistently much Worse, Don't know

Memory

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 I have placed objects.
5. Repeating stories and/or questions.
6. Remembering the current date or day of the week.
7. Remembering I have already told someone something.
8. Remembering appointments, meetings, or engagements.

Language

1. Forgetting the names of objects.
2. Verbally giving instructions to others.
3. Finding the right words to use in a conversation.
4. Communicating thoughts in a conversation.
5. Following a story in a book or on TV.
6. Understanding the point of what other people are trying to say.
7. Remembering the meaning of common words.
8. Describing a program I have watched on TV.
9. Understanding spoken directions or instructions.

Everyday Cognition (Ecog) – 39 items

Visual-spatial and Perceptual Abilities

1. Following a map to find a new location.
2. Reading a map and helping with directions when someone else is driving.
3. Finding my car in a parking lot.
4. Finding the way back to a meeting spot in the mall or other location.
5. Finding my way around a familiar neighborhood.
6. Finding my way around a familiar store.
7. Finding my way around a house visited many times.

Executive Functioning: Planning

1. Planning the sequence of stops on a shopping trip.
2. The ability to anticipate weather changes and plan accordingly (i.e. bring a coat or umbrella).
3. Developing a schedule in advance of anticipated events.
4. Thinking things through before acting.
5. Thinking ahead.

Executive Functioning: Organization

1. Keeping living and work space organized.
2. Balancing the checkbook without error.
3. Keeping financial records organized.
4. Prioritizing tasks by importance.
5. Keeping mail and papers organized.
6. Using an organized strategy to manage a medication schedule involving multiple medications.

Executive Functioning: Divided Attention

1. The ability to do two things at once.
2. Returning to a task after being interrupted.
3. The ability to concentrate on a task without being distracted by external things in the environment.
4. Cooking or working and talking at the same time.

Cognitive Change Index (CCI) – 20 items

Circle the number that best fits your current ability level compared to 5 years ago, using the scale from 1 to 5 below. Select the best choice for each item and *please do not skip any questions*:

Normal Ability	Slight/Occasional Problem	Mild Problem	Moderate Problem	Severe Problem
No Change *(compared to 5 years ago)*	Minimal Change *(compared to 5 years ago)*	Some Change *(compared to 5 years ago)*	Clearly Noticeable Change *(compared to 5 years ago)*	Much Worse *(compared to 5 years ago)*
1	2	3	4	5

- Recalling information when I really try
- Remembering names and faces of new people I meet
- Remembering things that have happened recently
- Recalling conversations a few days later
- Remembering where things are usually kept
- Remembering new information told to me
- Remembering where I placed familiar objects
- Remembering what I intended to do
- Remembering names of family members and friends
- Remembering without notes and reminders
- People who know me would find that my memory is
- Remembering things compared to my age group

- Making decisions about everyday matters
- Reasoning through a complicated problem
- Focusing on goals and carrying out a plan
- Shifting easily from one activity to the next
- Organizing my daily activities

- Understanding conversations
- Expressing myself when speaking
- Following a story in a book, movie or TV

SCD Consortium / PIA Criteria to be captured

The characterisation of subjective cognitive decline

Frank Jessen, Rebecca E Amariglio, Rachel F Buckley, Wiesje M van der Flier, Ying Han, José Luis Molinuevo, Laura Rabin, Dorene M Rentz, Octavio Rodriguez-Gomez, Andrew J Saykin, Sietske A M Sikkes, Colette M Smart, Steffen Wolfsgruber, Michael Wagner

A growing awareness about brain health and Alzheimer's disease in the general population is leading to an increasing number of cognitively unimpaired individuals, who are concerned that they have reduced cognitive function, to approach the medical system for help. The term subjective cognitive decline (SCD) was conceived in 2014 to describe this condition. Epidemiological data provide evidence that the risk for mild cognitive impairment and dementia is increased in individuals with SCD. However, the majority of individuals with SCD will not show progressive cognitive decline. An individually tailored diagnostic process might be reasonable to identify or exclude underlying medical conditions in an individual with SCD who actively seeks medical help. An increasing number of studies are investigating the link between SCD and the very early stages of Alzheimer's disease and other neurodegenerative diseases.

Lancet Neurol 2020

Published Online
January 17, 2020
https://doi.org/10.1016/S1474-4422(19)30368-0

See Online/Comment
https://doi.org/10.1016/S1474-4422(20)30002-8

Department of Psychiatry,

Search strategy and selection criteria

References for this Personal View were identified by searching PubMed for articles published in English up to July 2019 (without a starting date) and from the references of selected articles. The following search terms were used: "subjective cognitive decline", "SCD", "subjective cognitive impairment", "subjective memory impairment", "cognitive complaint", "cognitive concerns", "memory complaint", and "memory concerns". Full documentation of all search results has not been included in this Personal View. The reference list was generated based on relevance to the topic of this Personal View.

Panel: Features that increase the risk of cognitive decline (SCD plus)

- Subjective decline in memory irrespective of function in other cognitive domains[5,14]
- Onset of SCD within the past 5 years[24,25]
- Onset of SCD at 60 years and older[4]
- Concern (worry) associated with SCD[14,26]
- Persistence of SCD over time[23,27,28]*
- Seeking of medical help[6,29]*
- Confirmation of cognitive decline by an observer[30,31,32]

*Not part of the original SCD plus features.[4] SCD=subjective cognitive decline.

Some open questions and options under consideration:

1) **Include recommended cutoff scores to consistently define SCD?**
2) **Leave presence of SCD as a clinical determination?**
3) **If cutoffs are provided, should they be for just the 3 screening questions? For ECog & CCI?**
4) **Include co-participant cutoffs?**
5) **Leave this issue open for future research to address?**

Thank you!

The CTF Cognitive Workgroup

Lisa Barnes & Andy Saykin (co-chairs), Rhoda Au, Suzanne Craft, Mary Sano, Sandra Weintraub

Thanks to Laura Rabin, Shannon Risacher, Greg Jicha, Cindy Carlsson, Gary Chan, Hiroko Dodge, NACC Team and NIA Program

Any Questions? (10 minutes)

CTF-NACC
UDSv4 Forms Update:
Social Determinants of Health

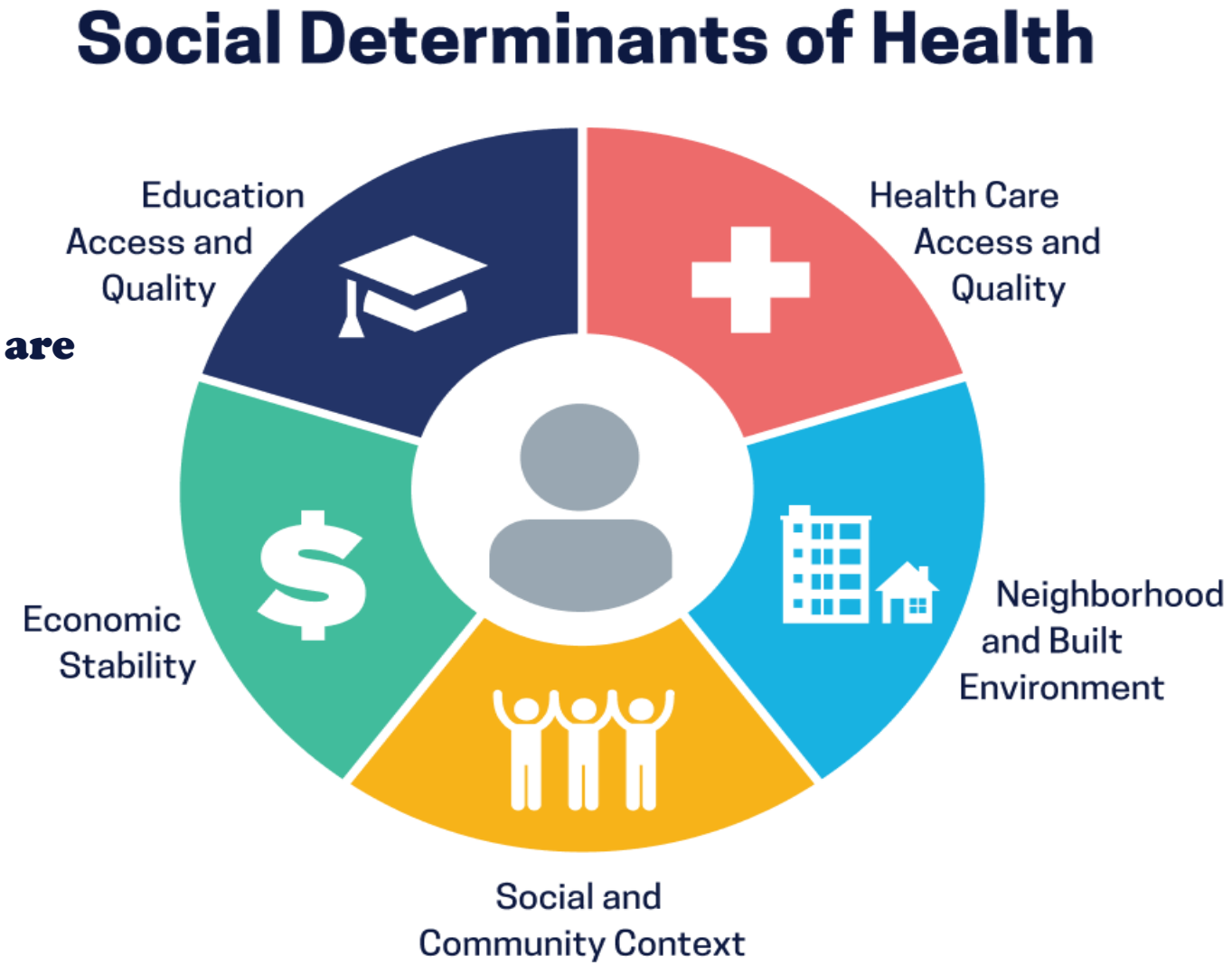
Presented by: Lisa L. Barnes, PhD & Megan Zuelsdorff, PhD

CTF SDOH Subgroup

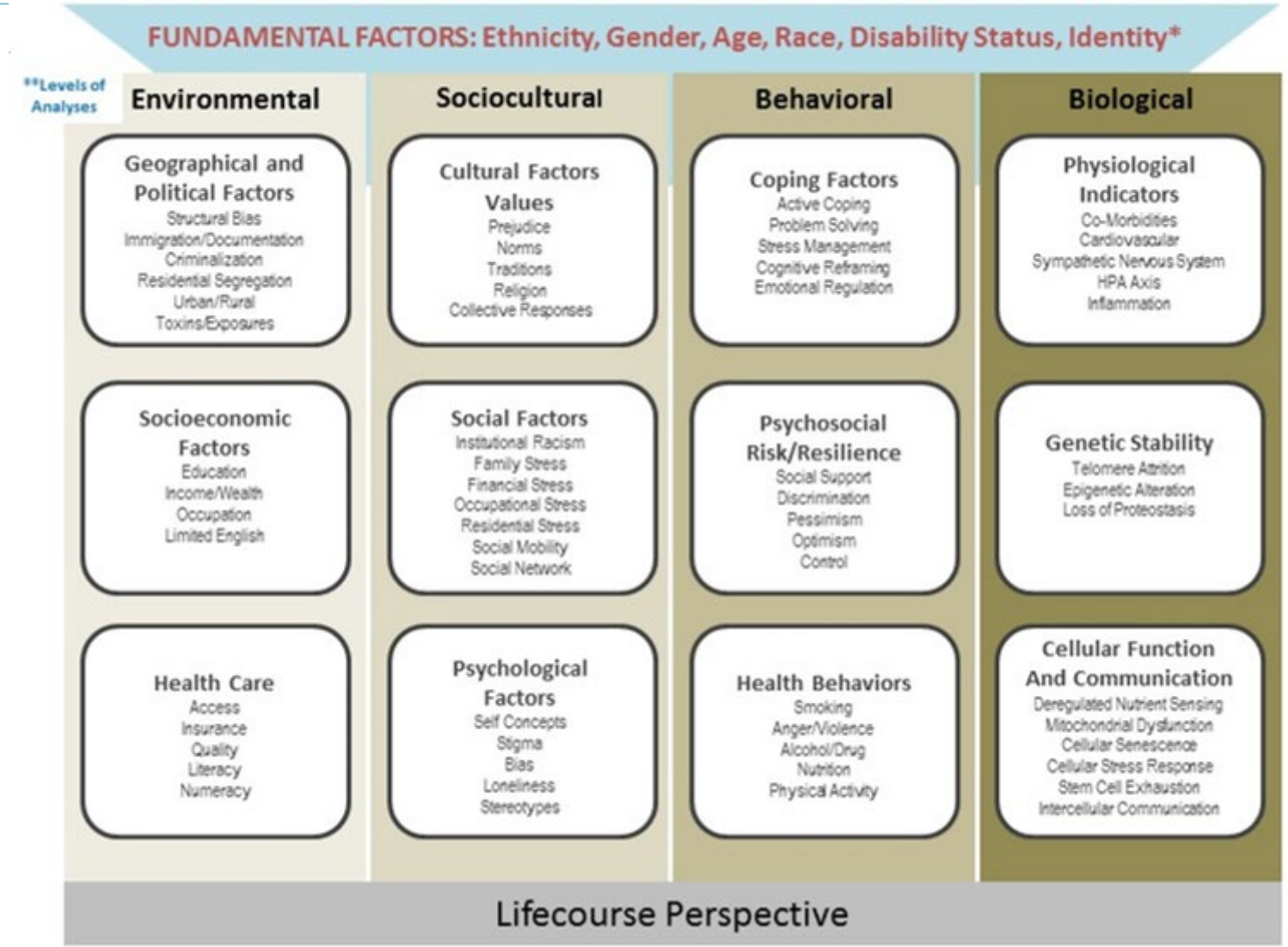
Why is the topic important?

conditions in the environments where people are born, live, learn, work, play, and age

Non-medical factors that influence health outcomes



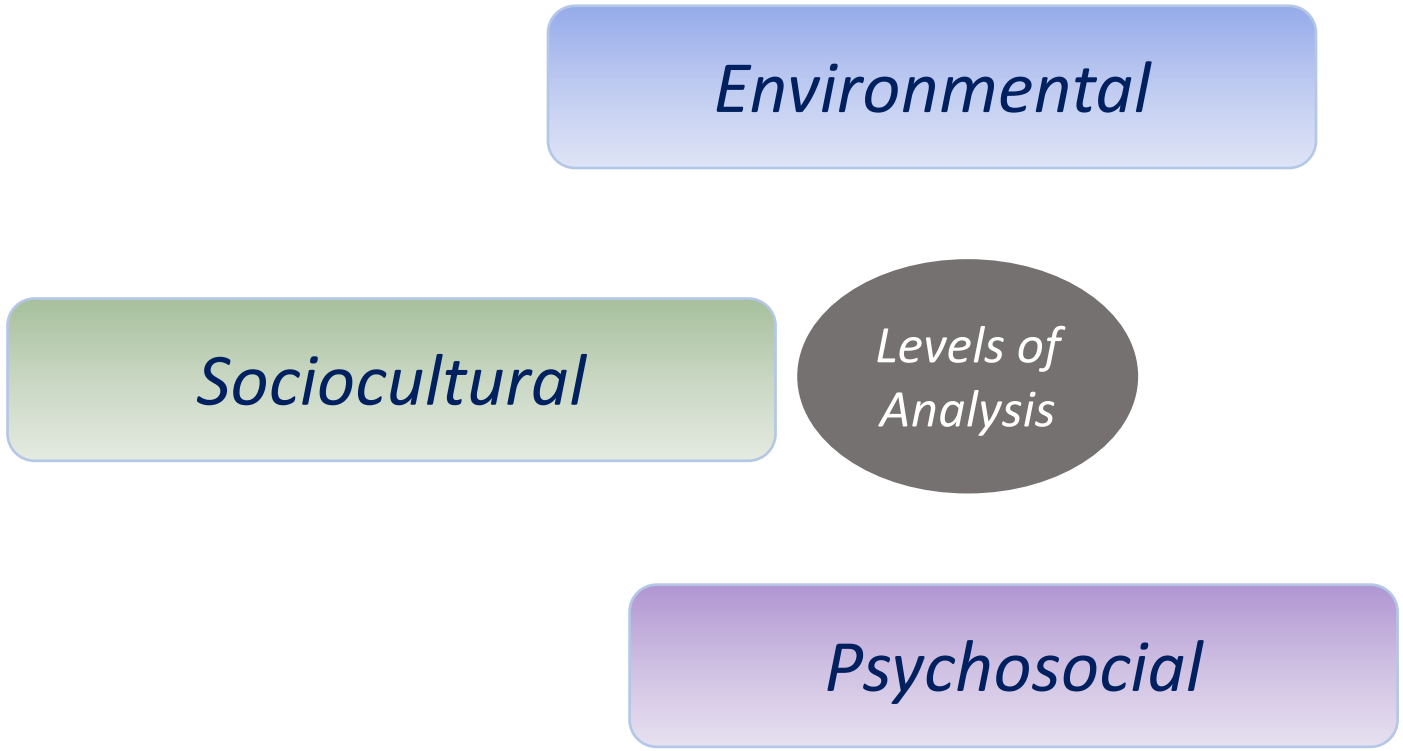
NIA Health Disparities Framework



Hill et al., 2015

Diagnosis, disease progression and access/response to treatment may each be affected by:

Age
Socioeconomic Position
Gender Identity
Stress
Race/Ethnicity
Disability Status and Geography



Source: Hill CV, Perez-Stable EJ, Anderson NA & Bernard MA, *Ethnicity & Disease*, 25 (3), 2015

Current social determinants captured in core UDSv4

- Income sufficiency
- Household income amount
- Access to health insurance, healthcare services, medications
- Experiences of unfair treatment
- Social network (# relatives/friends keep in touch with)
- Occupation (code look-up)
- State of residence for ADI

Decision Process

- Committee Input: Monthly meetings, Nov 2021 – May 2022

Lisa Barnes, PhD
Erin Abner, PhD, MPH
Joyce Balls-Berry, PhD, MPE
Gregory Jicha, MD, PhD
Patricia Jones, DrPH, MPH
Serggio Lanata, MD, MS
Gladys Maestre, MD, PhD

Megan Zuelsdorff, PhD
Monica Rosselli, PhD
Nina Silverberg, PhD
Shana Stites, PsyD, MS
Rachel Whitmer, PhD
Consuelo Wilkins, MD, MSCI

- Establishing criteria for construct selection
  - Representation of risk and protective factors from multiple “levels”
  - Empirical associations with brain health and dementia risk and/or with dementia risk factors, diagnosis, and care
  - Variability among ADRC cohorts and in NACC dataset (e.g., sensitive to diversity)
  - Availability of validated instrumentation
  - Data not available through geocoding or linkage with public datasets

Questions to be added to UDSv4 SDoH Module

Environmental

Transportation Security

1. Do you have consistent access to transportation? (often, sometimes, never)

2. How often were you **not** able to leave the house when you wanted to because of a problem with transportation?

3. How often did you worry about whether or not you would be able to get somewhere because of a problem with transportation?

4. In the past 30 days, how often did it take you longer to get somewhere than it would have taken you if you had different transportation?

Murphy, Alexandra K., Alix Gould-Werth, and Jamie Griffin. 2021

Questions to be added to UDSv4 SDoH Module

Sociocultural

Financial Security/Stress

How satisfied are you with your/your immediate family's (e.g., people in your household) financial situation? (1 = completely, 5 = not at all)

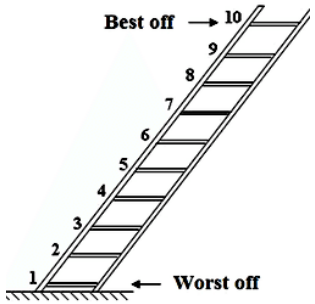
If you ever had current or ongoing financial problems that have lasted twelve months or longer, how upsetting has it been to you?
(no, didn't happen = 1, yes, but not upsetting = 2, yes, somewhat upsetting = 3, yes, very upsetting = 4)

At any time, have you ended up taking less medication than was prescribed for you because of the cost? (no = 0; yes = 1) → *Follow up: Past 12 months*

How difficult is it for you to meet monthly payments on your bills? (not at all difficult = 1, not very difficult = 2, somewhat difficult = 3, very difficult = 4, completely difficult = 5).

Social Status "Ladder":

- Where would you place yourself today on this ladder relative to others in your community?
- Relative to others in the U.S.?
- Where do you think you and your family stood in your community during your childhood?



What was your parent or guardian's (e.g., person who raised you) highest level of education?

- What was this person's relationship to you? _____
- *Follow up: Second parent or guardian*

Health and Retirement Study (HRS)
Americans' Changing Lives Study (ACL)
MacArthur studies

Questions to be added to UDSv4 SDoH Module

Sociocultural

Social Isolation & Connectedness

- I experience a general sense of emptiness (1= strongly agree to 5=strongly disagrees)
- I miss having people around (1= strongly agree to 5=strongly disagrees)
- I feel like I don't have enough friends (1= strongly agree to 5=strongly disagrees)
- I often feel abandoned (1= strongly agree to 5=strongly disagrees)
- I miss having a really good friend (1= strongly agree to 5=strongly disagrees)

- How often do you have contact with your parents (including mother, father, mother-in-law, and father-in-law) either in person or by phone or mail? [1= once a year or less; 2= several time a year; 3=several times a month; 4=several times a week; 5=everyday or almost everyday]
- *Follow up: Contact with (a) children, (b) close friends, (c) participation in religious, educational, health-related, or charitable activities*

RADC; de Jong-Gierveld Loneliness Scale

Questions to be added to UDSv4 SDoH Module

Psychosocial

Differential treatment: Medical discrimination and healthcare seeking

The next 5 questions ask about how the healthcare system is meeting your needs. Please answer the questions in reference to your regular medical doctors (not your research study doctors).

- In the past year, did you delay seeking attention about a medical problem that was bothering you? (1=often, 2=sometimes, 3=rarely, 4=never)
- In the past year, did you fill a prescription from a physician when it was prescribed?
- In the past year, did you miss a follow-up medical appointment that was scheduled?
- In the past year, did you follow a doctor's advice or treatment plan when it was given?
- How frequently in your day to day life do you receive poorer service or treatment than other people from doctors or hospitals?

Kaiser Family Foundaation; Van Houtven et al., 2005

UDSv4 SDoH Module Administration

- Self-administered
- Intended for participant response; not intended for a proxy
  - *Participants determined capable of completing other survey data would complete the SDoH module*
- Should be filled out by all participants at least once
  - *Ideally at baseline for prospective prediction of outcomes*
- Anticipated time-to-completion: 5-10 minutes

Thank you!

The CTF SDOH Subgroup:

Any Questions? (10 minutes)

CTF-NACC
UDSv4 Forms Update:
COVID-19 Form

Presented by: Carlos Cruchaga PhD

COVID Subgroup

Why are COVID-19 forms important?

- COVID is unmatched in our lifetimes for its impact
  - 83M reported cases in US to date
    - Estimated more than half of the US population has been infected
  - 1M deaths in US to date
    - A leading cause of death
    - Strongly associated with aging and dementia

- NACC COVID-19 Impact forms launched June 2020
  - At a time before post-COVID syndrome/long-COVID/PASC had been described
  - Before period of major sociopolitical unrest in the country
    - Possible impact/influence on cognitive and behavioral symptoms
  - Prior to availability of vaccines or treatments for COVID-19
  - Prior to recognition of recurring infections.
  - Reflect current/recent experience, and not summative
    - Likely reflected thinking at the time that pandemic would resolve within the year
  - Unclear if they were to be completed more than once

Why COVID-19 is important for AD research?

- Dementia patients have twice the risk of COVID19
  - Mortality risk for people with dementia and COVID19 (20.99%) is higher than it was for people with COVID-19 but not dementia (4.81%, $P<0.001$). Wang et al., 2021

- COVID19 may result in brain damage and increase the risk of dementia and other neuropsychiatric symptoms

- African-American patients were nearly three times as likely to be infected with COVID19. Wang et al., 2021

- Current studies indicate that some of the genes important for COVID19 infection are also associated with AD and other related disorders

Is there any relation between COVID and AD?

APOE e4 Genotype Predicts Severe COVID-19 in the UK Biobank Community Cohort

Chia-Ling Kuo, PhD,[1,2,*] Luke C. Pilling, PhD,[2,3,*] Janice L. Atkins, PhD,[3,*] Jane A. H. Masoli, MBChB,[3,4,*] João Delgado, PhD,[3,*] George A. Kuchel, MD,[2] and David Melzer, MBBCh, PhD[2,3,*]

- *APOE* e4e4 homozygotes were more likely to be COVID-19 test positives (OR = 2.31, 95% CI: 1.65 to 3.24, $p = 1.19 \times 10^{-6}$) compared to e3e3 homozygotes.
- *APOE* e4e4 allele increases risks of severe COVID-19 infection, independent of preexisting dementia, cardiovascular disease, and type-2 diabetes.

ApoE-Isoform-Dependent SARS-CoV-2 Neurotropism and Cellular Response

Cheng Wang,[1,6] Mingzi Zhang,[1,6] Gustavo Garcia, Jr.,[2,7] E. Tian,[1,7] Qi Cui,[1] Xianwei Chen,[1] Guihua Sun,[3] Jinhui Wang,[4] Vaithilingaraja Arumugaswami,[2,5,*] and Yanhong Shi[1,8,*]

- Coronavirus infected more ApoE4 neurons and astrocytes than their ApoE3 counterparts in cell culture.

BIN1 rs744373 SNP and COVID-19 mortality

STEVEN LEHRER[1], PETER H. RHEINSTEIN[2]

[1]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY 10029;

[2]Severn Health Solutions, Severna Park, MD 21146, USA

- *SNP rs744373 on COVID-19-relaetd survival using UKB-derived data*
- The results revealed that the BIN variant was associated with the lowest mortality rate (11.7%),
- BIN allele may interfere with the replication of the SARs-Cov2 virus

Is there any relation between COVID and AD?

Article

Genetic Screens Identify Host Factors for SARS-CoV-2 and Common Cold Coronaviruses

Ruofan Wang,[1,13] Camille R. Simoneau,[2,3,4,5,13] Jessie Kulsuptrakul,[1] Mehdi Bouhaddou,[2,4,6,7] Katherine A. Travisano,[1] Jennifer M. Hayashi,[2,3,4] Jared Carlson-Stevermer,[8] James R. Zengel,[9] Christopher M. Richards,[9] Parinaz Fozouni,[2,3,4,5,10] Jennifer Oki,[8] Lauren Rodriguez,[11] Bastian Joehnk,[12] Keith Walcott,[12] Kevin Holden,[8] Anita Sil,[12] Jan E. Carette,[9] Nevan J. Krogan,[2,4,6,7] Melanie Ott,[2,3,4,*] and Andreas S. Puschnik[1,14,*]

nature genetics ARTICLES
https://doi.org/10.1038/s41588-021-00805-2
Check for updates

- genome-wide CRISPR screens for COVID 19 infection identified the distinct viral entry factors ACE2
- The lysosomal protein TMEM106B appeared unique to SARS-CoV-2 infection

Genome-wide CRISPR screening identifies TMEM106B as a proviral host factor for SARS-CoV-2

Jim Baggen[1✉], Leentje Persoons[1,8], Els Vanstreels[1,8], Sander Jansen[1,8], Dominique Van Looveren[1,2], Bram Boeckx[3,4], Vincent Geudens[5], Julie De Man[1], Dirk Jochmans[1], Joost Wauters[6], Els Wauters[5], Bart M. Vanaudenaerde[5], Diether Lambrechts[3,4], Johan Neyts[1], Kai Dallmeier[1], Hendrik Jan Thibaut[1,2], Maarten Jacquemyn[1], Piet Maes[7] and Dirk Daelemans[1✉],

CellPress Cell

- lysosomal protein TMEM106B is an important host factor for COVID 19
- TMEM106B is required for replication in multiple human cell lines
- new coronavirus host factors that may potentially serve as drug targets

Article

Genome-Scale Identification of SARS-CoV-2 and Pan-coronavirus Host Factor Networks

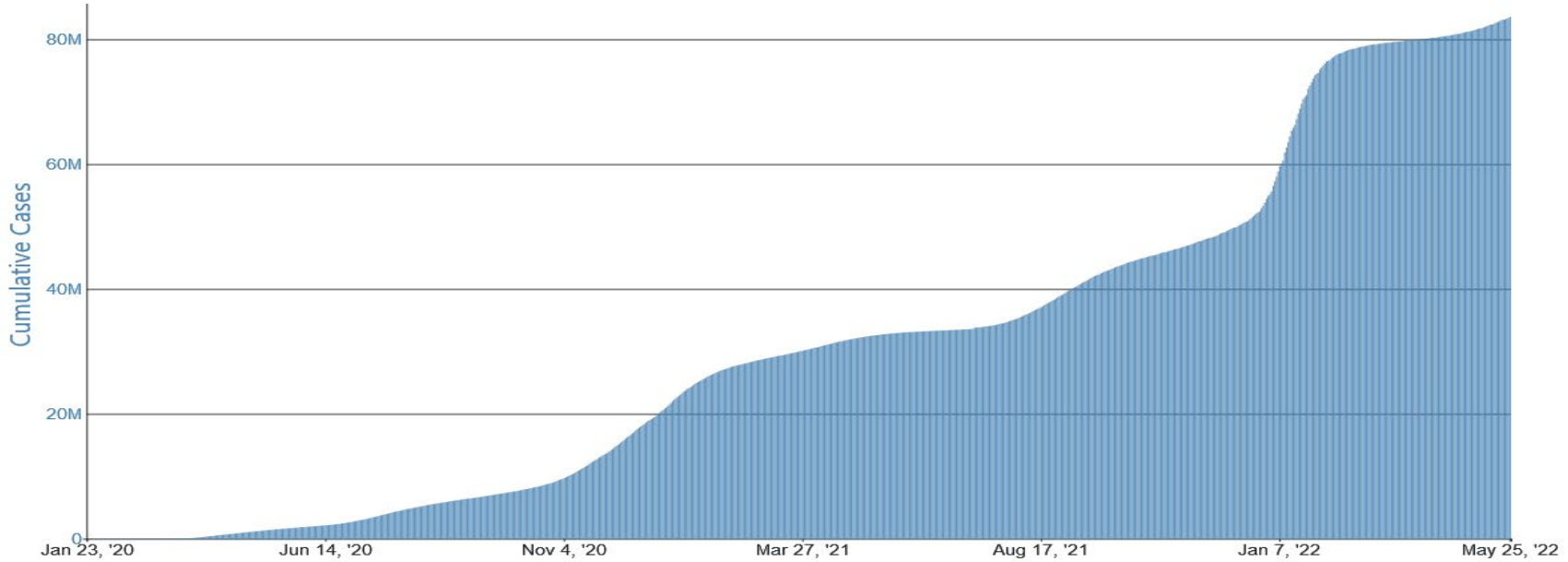
William M. Schneider,[1,5] Joseph M. Luna,[1,5] H.-Heinrich Hoffmann,[1,5] Francisco J. Sánchez-Rivera,[2,5] Andrew A. Leal,[3,6] Alison W. Ashbrook,[1,6] Jérémie Le Pen,[1,6] Inna Ricardo-Lax,[1] Eleftherios Michailidis,[1] Avery Peace,[1] Ansgar F. Stenzel,[1,4] Scott W. Lowe,[2] Margaret R. MacDonald,[1] Charles M. Rice,[1,*] and John T. Poirier[3,7,*]

- Host factors identified: TMEM106B, VAC14, and ACE2.

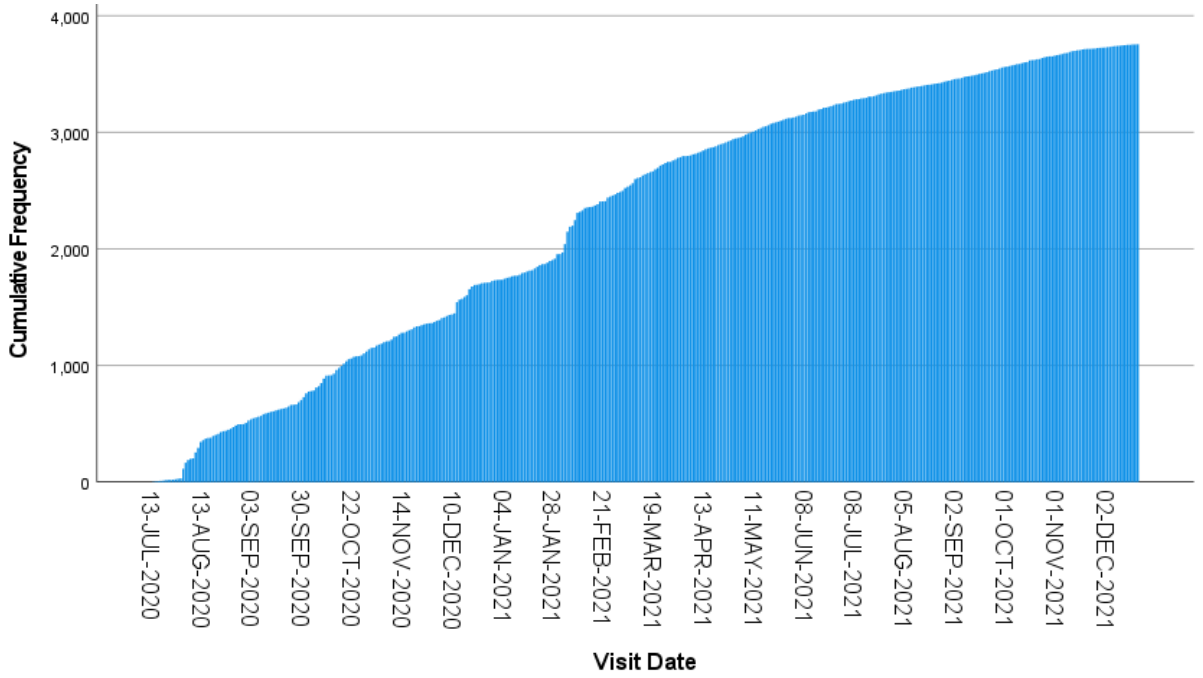
COVID-19 impact forms to date

- June 2020 launch through March 2022 data freeze
  - 3,756 unique F2 forms submitted
    - 17 centers submitted forms
    - Mean=221 (range 40 to 608)
  - 3,576 unique persons (180 with repeat forms)

  - For comparison, 15,513 NACC active/minimal contact
    - 23% of possible cohort

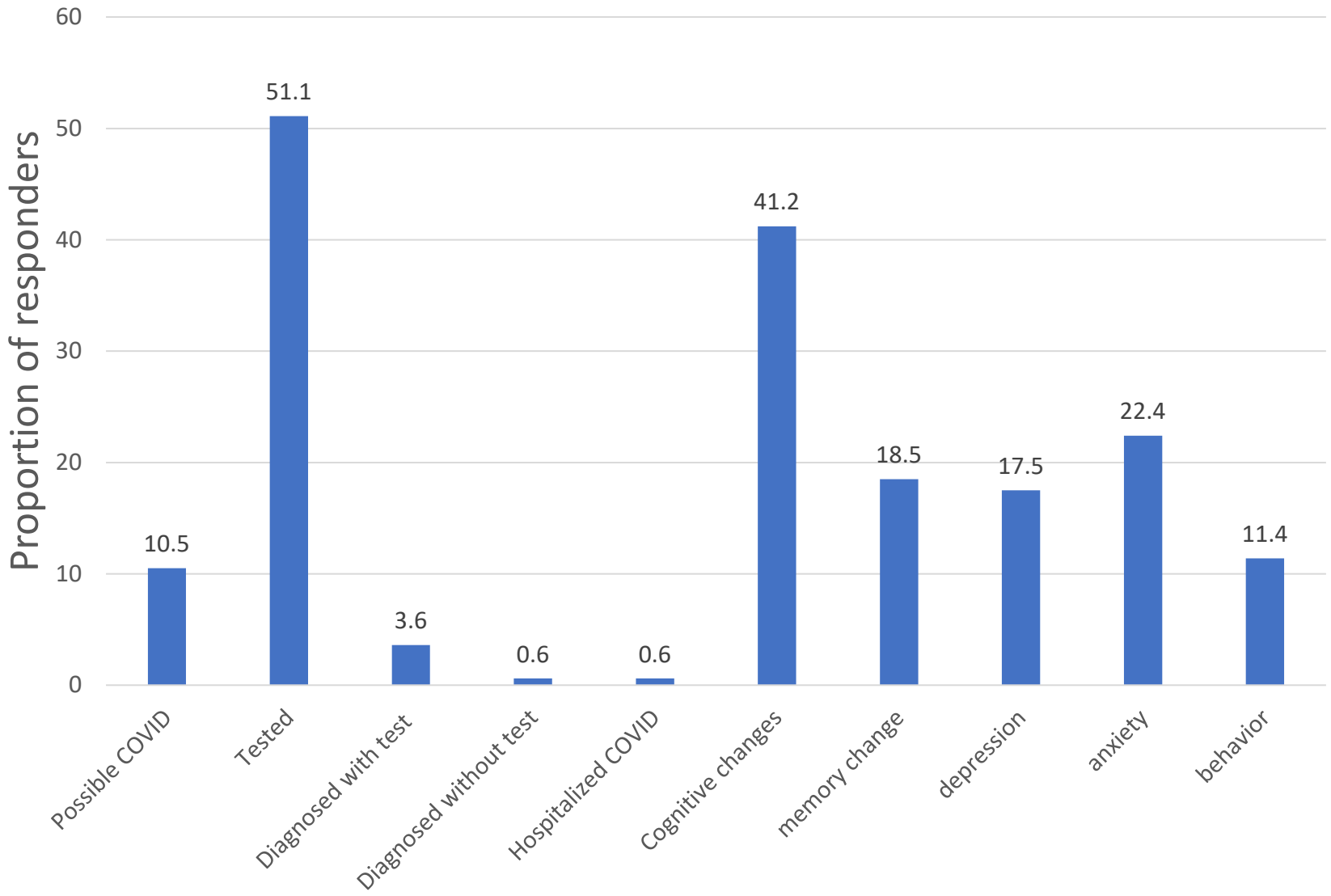


Total 83.9M COVID-19 cases as reported to CDC as of 5/27/2022



- 80% of COVID impact forms reflected visits completed by early May 2021, a time reflecting 39% of all US cases to date.
- 5 forms submitted Jan-March 2022, a period corresponding with Omicron/variants & 36% of all US cases to date

COVID-19 impact forms through March 2022



COVID-19 impact forms (vJune 2020) key points

- NACC COVID impact forms thus far have not really captured the pandemic
  - Due to lack of completion relative to the pandemic
  - 23% of all possible NACC participants
    - May be biased to healthy persons overall and within cohort
  - Seldom used in period corresponding to 61% of the 83M US cases
- With these caveats, COVID-19 cases are rare in COVID-19
  - 127 diagnosed, 20 presumed, 21 hospitalized, 8 went to ICU.
- Possible COVID symptoms outnumbered diagnosed infections
  - 3 to 1
- New cognitive/behavioral symptoms were common and may be independent of COVID infection
- Challenging to capture brief illness out of sync with ADRC visits
- Rapidly evolving problem, even now
- Temporary experiences are very different from summative ones

COVID-19 today

- Now recognized: Impact on clinical and biological aging
  - Clinical decline
  - MRI, plasma biomarkers associated with ADRD

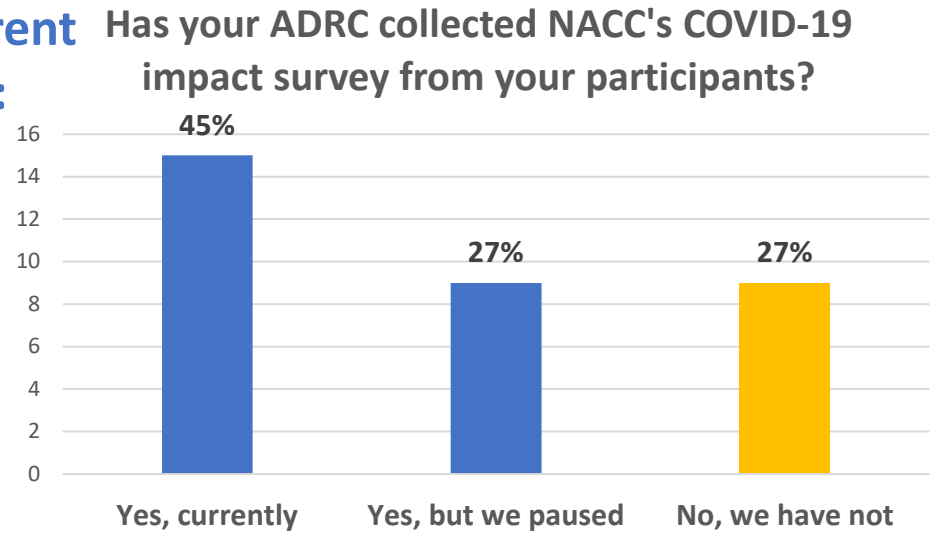
- Primary goals of updated form:
  - Capture information to inform key scientific questions about biological impact of COVID-19
  - Validated instruments
  - Focus on cases of COVID-19 (not tests done or possible cases)
  - Minimize burden
    - No difference in length for those who have not been infected or had vaccine complications
    - Per NACC forms, 95% had not been infected as of March 2022

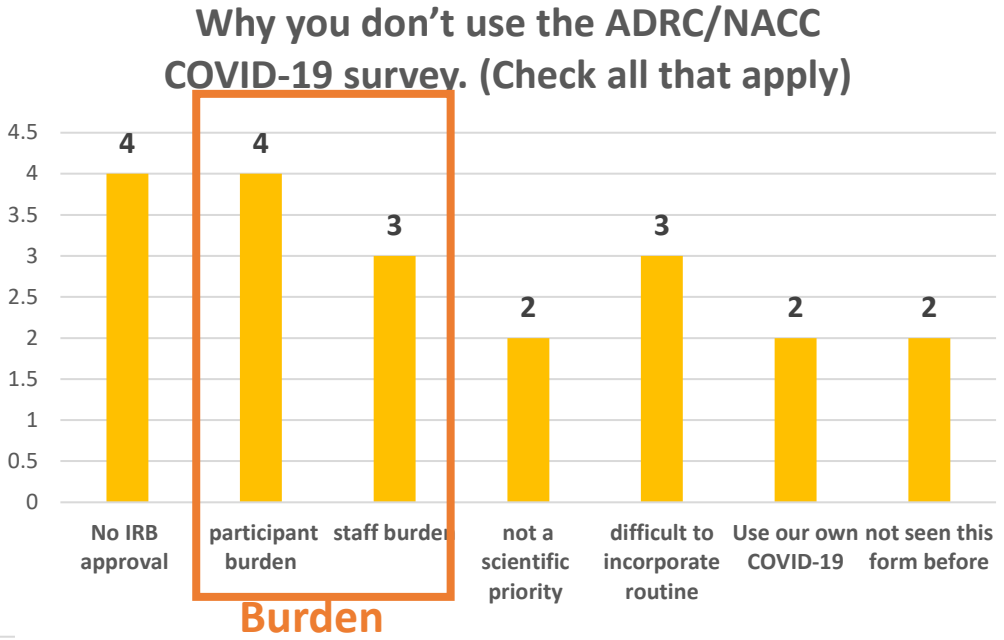
Updated F2 form (v2)

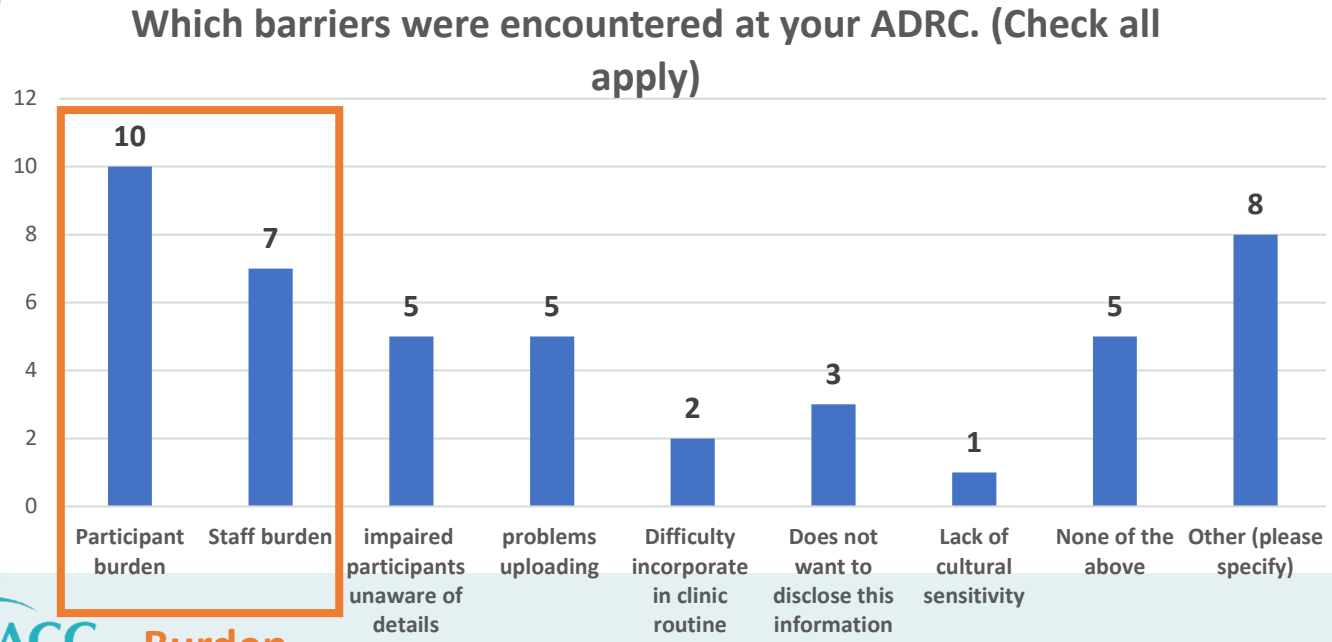
- Important information to be collected
  - History of infection (including multiple infections)
    - Lasting symptoms
    - First and most recent experiences
  - History of vaccination & treatment
  - Validated questions of cumulative stress in last year and coping
- F3 form largely unchanged
- Eliminated:
  - Questions about testing
  - Cognitive/behavioral symptoms (captured in other NACC forms)

COVID Survey Results: Highlights Current Use

Current Use:







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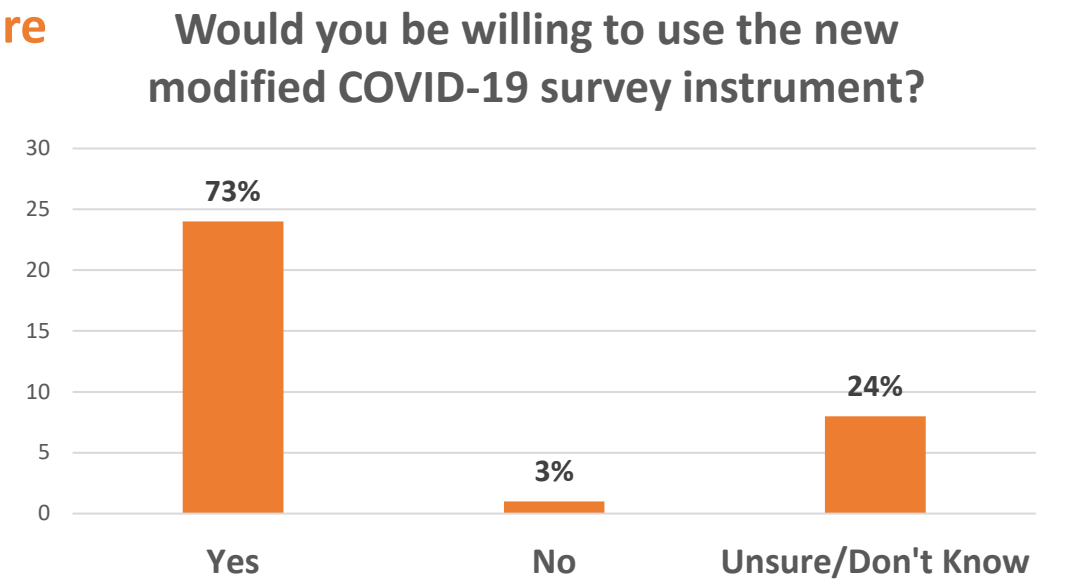
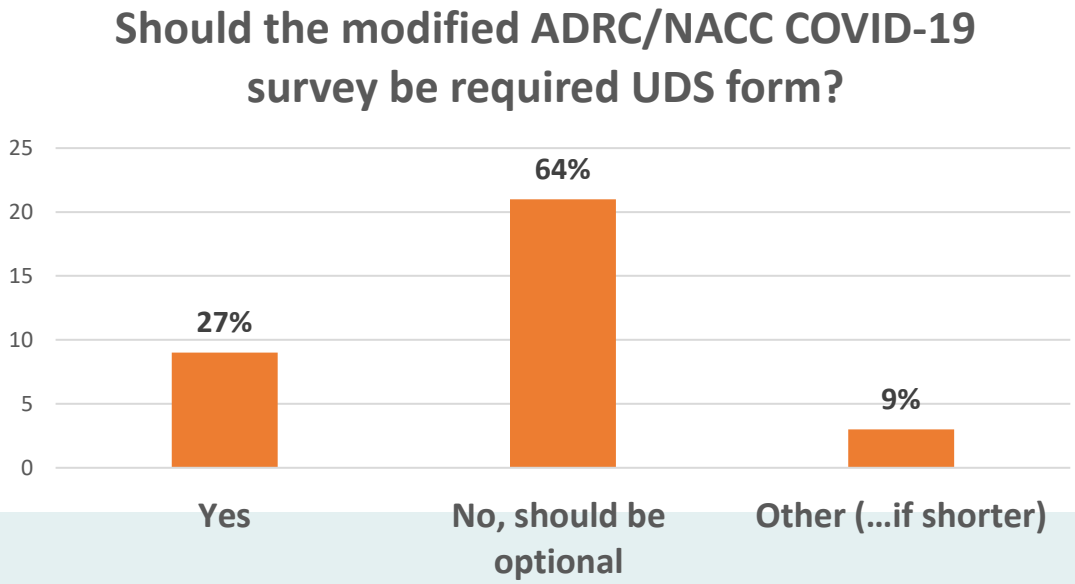
COVID Survey Results: Future Use Modified Forms

Future Use:





- The ADRCs are willing to use the modified form
- There is still a time burden to consider

Modifications to the COVID Forms to streamline process

- Questions about some vaccination side effects (sore arm) without losing essential research value of these forms, can be removed

- *New REDCap Forms were developed that can be deployed on an iPad in the waiting room*.
  - These forms could be distributed electronically for participants/co-participants to fill at home

Thank you!

The COVID Subgroup:

James Noble (Columbia University)
Melissa Lerch, Kari A. Stephens (NACC)
Carlos Cruchaga (Washington University)

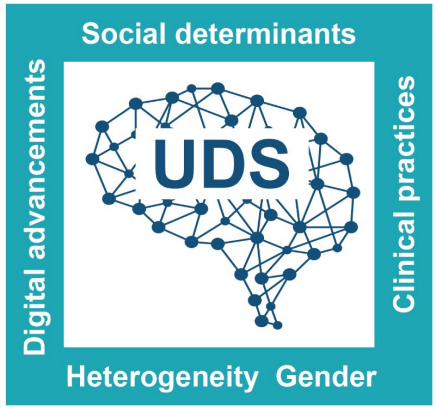
Any Questions? (10 minutes)

UDSv4 – Next Steps

Sarah Biber, PhD and Laura McLeod

June 3, 2022 – CTF Forms Update

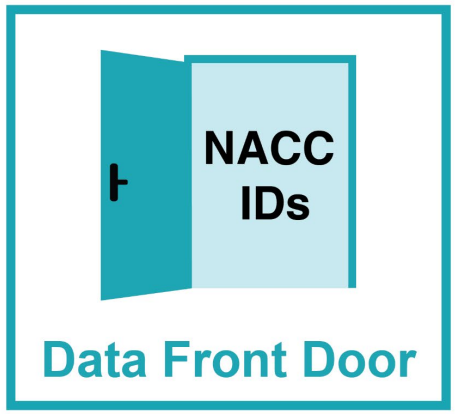
UDS4 – The Full Picture



Updated UDS Content

Streamlined Submission System

Integrated Pipeline and Database



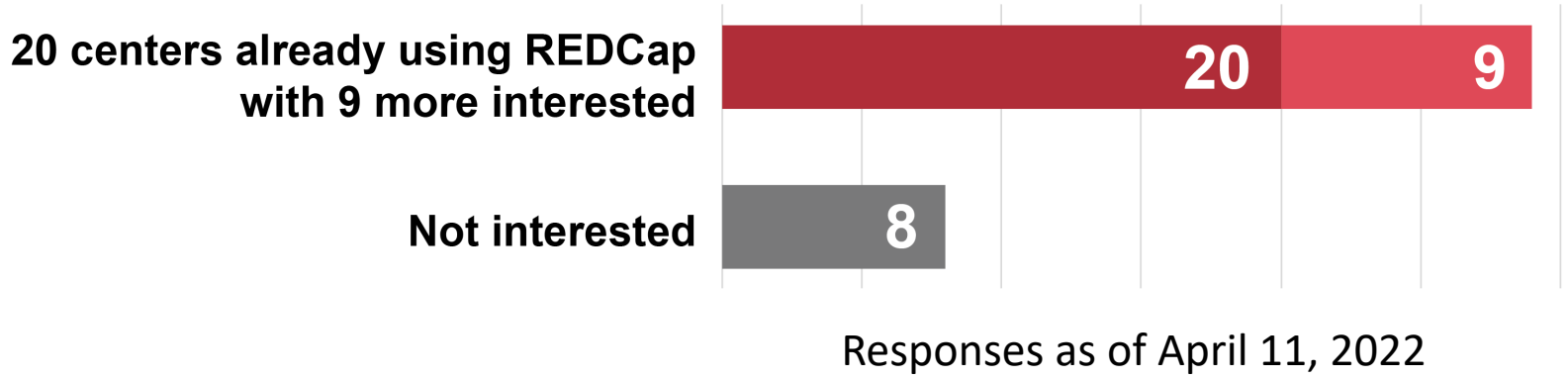
Expanded Search and Access Portal

UDSv4 – New Submission System

- **Existing system is 20 years old and needs to be updated to be more cloud friendly and virtualized**

- **Goals:**
  - Streamline UDS data collection for the ADRC program
  - NACC will continue to host a range of options

- **Why are we starting with REDCap?**
  - Canonical tool for forms data capture



Responses as of April 11, 2022

UDSv4 – Electronic Data Capture (EDC) Workgroup

- **Electronic Data Capture Working Group:**
  - **Launched January 24th, 2022 in collaboration with the Data Core Steering Committee**
- **60 people across 20 ADRCs that are collaborating with us to:**

UDSv4 – New Submission System

All data will go through REDCap at NACC in the future via one of these options:

Direct data entry into NACC REDCap

Synchronize local ADRC REDCap instances through REDCap APIs

Bulk upload of .csv files into NACC REDCap

UDSv4 – Electronic Data Capture (EDC) Workgroup

- **Thank you, EDC Workgroup members!**
  - **Co-Leads:** Sudeshna Das and Sarah Biber
  - **Development Co-Leads:** Jon Reader and Ben Keller
  - **Requirements Co-Leads:** Meredith Zozus and Kari Stephens
  - **Documentation and Training Co-Leads:** Alice Spalitta, Leah Reuter, and Laura McLeod

Scan QR code and fill out the form to join!

Link Here

NACC
WISCONSIN UNIVERSITY OF WISCONSIN-MADISON
COLUMBIA UNIVERSITY MEDICAL CENTER
Center of Excellence for Alzheimer's Disease
MASSACHUSETTS Alzheimer's Disease Research Center
University of Kentucky College of Medicine
UT Health San Antonio
UCI MIND
1Florida ADRC
Cleveland Clinic Lou Ruvo Center for Brain Health
UCDAVIS UNIVERSITY OF CALIFORNIA
UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Mesulam Center
OHSU BRAIN Institute
Michigan ADRC Alzheimer's Disease Research Center
Yale SCHOOL OF MEDICINE
SCHOOL OF MEDICINE INDIANA ALZHEIMER'S DISEASE RESEARCH CENTER
KnightADRC Alzheimer's Disease Research Center WASHINGTON UNIVERSITY ST. LOUIS
BU Alzheimer's Disease Research Center
NYU Langone Health
KU ALZHEIMER'S DISEASE CENTER The University of Kansas Medical Center
Duke UNIVERSITY
EMORY UNIVERSITY
Goizueta Alzheimer's Disease Research Center

Benefits of REDCap

- 2.1 million users worldwide
- 5971 institutions
- 145 countries
- Used for clinical research, operational workflows

REDCap Benefits for UDSv4

Data Collection Options	• Directly into EDC via computer or tablet • Directly entered by staff and/or participant - Optionally via survey link
Data Submission Options	Via API
QA/QC Options	Enforcement on question and form level; can also be applied across form
Export Options	Into R and Excel (amongst other options)
Staff Support	Training resources, including SOPs

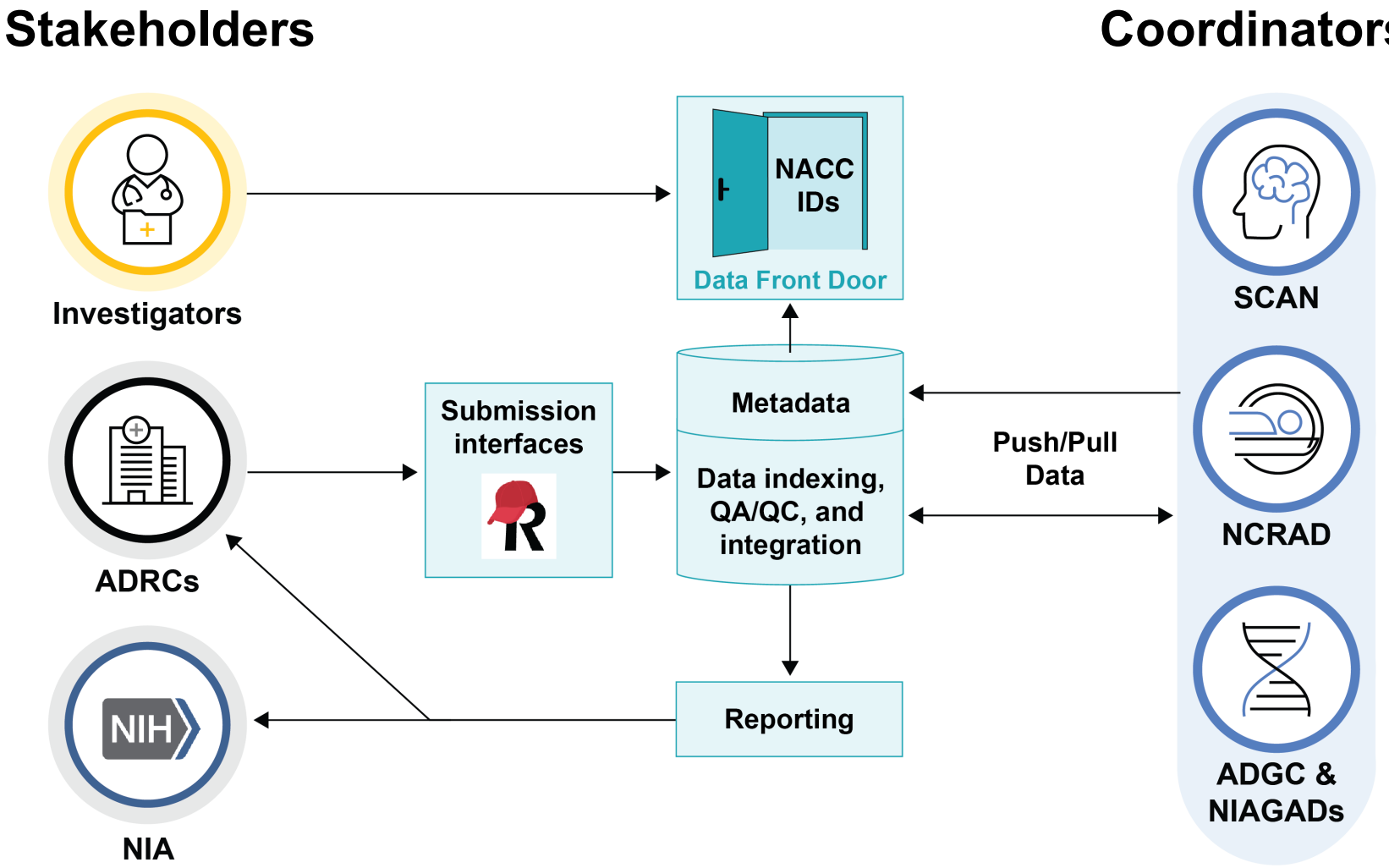
How this benefits you

Data Quality Improvement

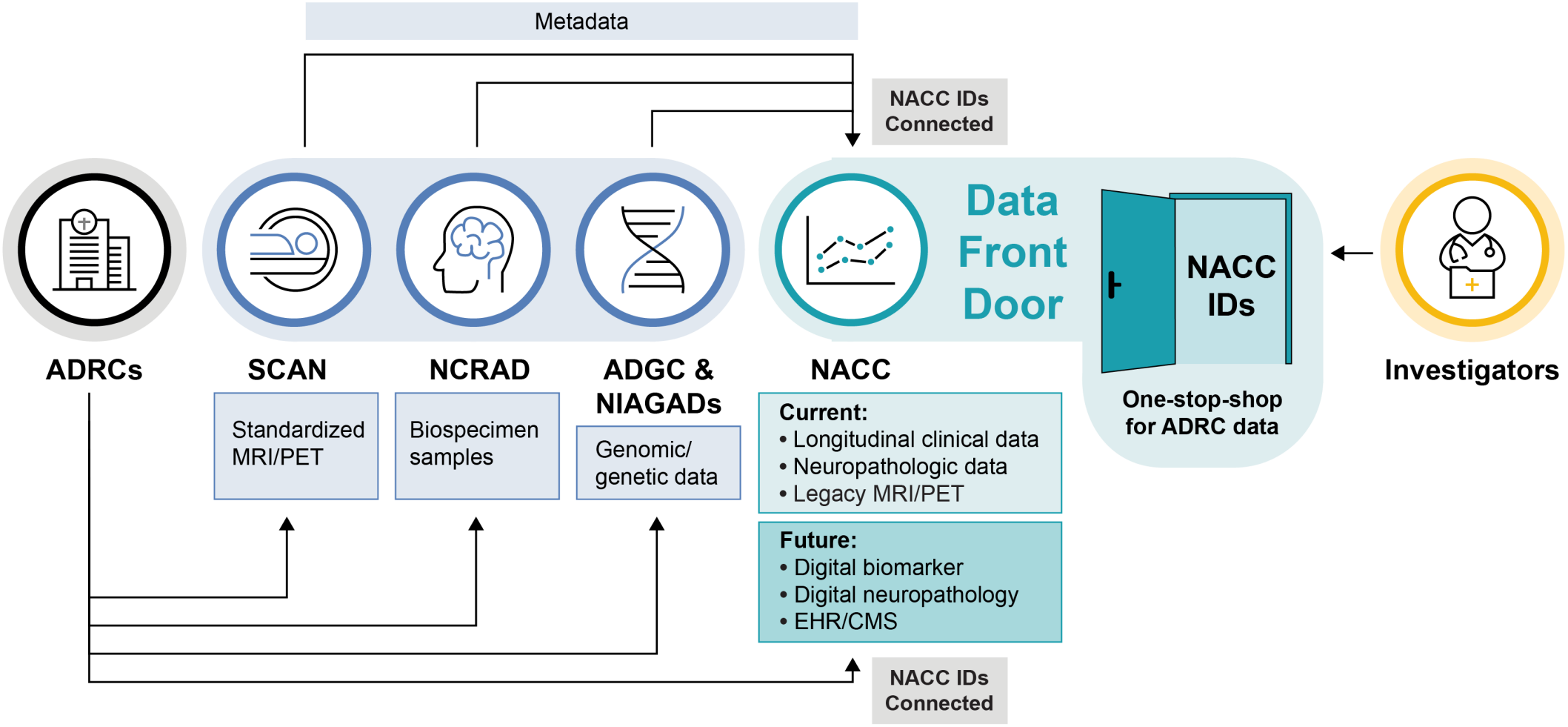
- More clarity on which questions are to be asked/which forms should be completed
- Time saved by having previously entered data carried over

- **Streamline Your Workflow**
  - Workflow to address errors
  - Fewer errors upon submitting to NACC
  - Time saved due to project being built for you and training resources already developed

UDSv4 – Pipeline and Database

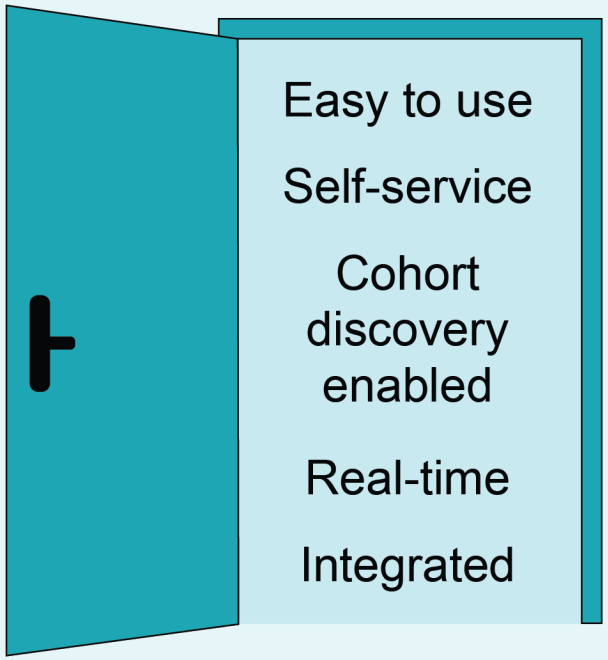


UDSv4 – Pipeline and Database



UDSv4 – Search and Access Portal

Data Front Door



One-stop-shop for ADRC data

Requirements Pilot Project

- **Collaboration between NACC, NCRAD, and NIAGADS**

Provide input!

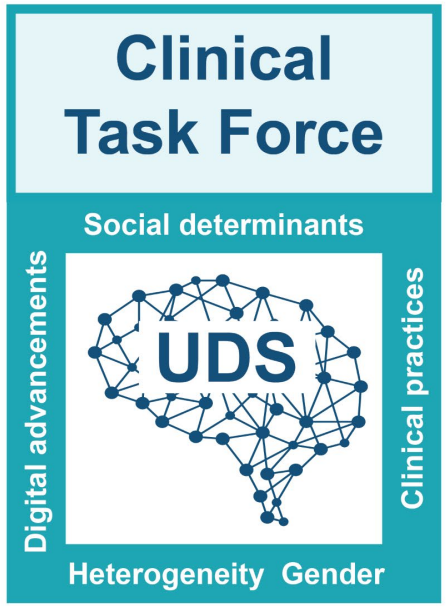
Join a thought leader focus group session

Link Here

Provide input via a survey

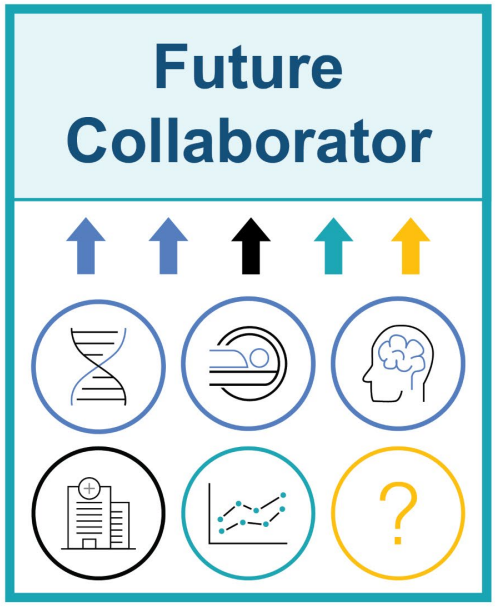
Link Here

UDS4 – The Full Picture

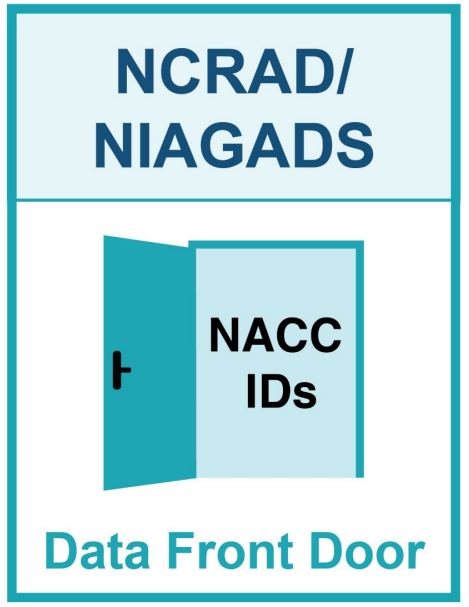


Updated UDS Content

Streamlined Submission System



Integrated Pipeline and Database

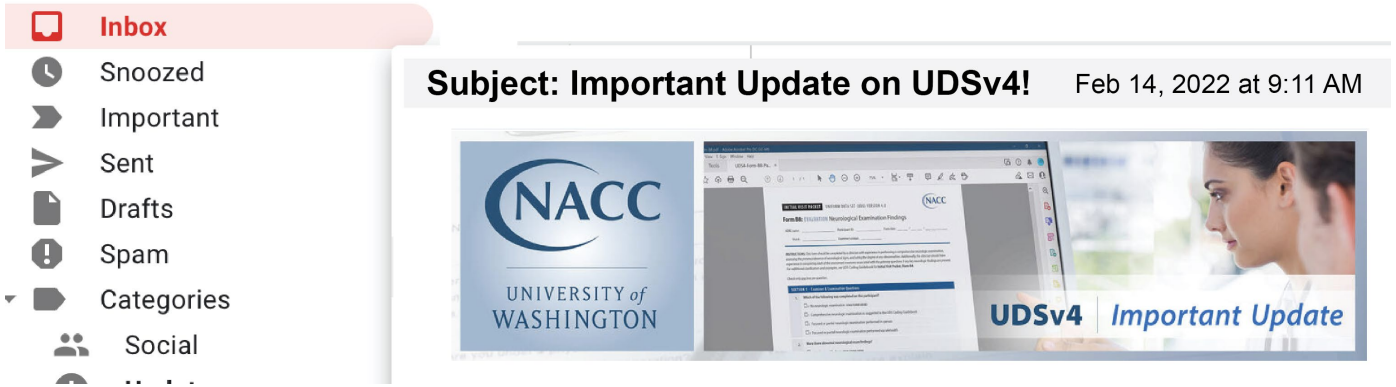


Expanded Search and Access Portal

So, when will all of this be available?

- **Timing constraints**
  - CTF content update
  - Architecture design and build

- **We're committed to keeping you in the loop!**
  - Regular progress updates to the ADRC community
    - Transparent tracking (shared CTF tracker and forms tracker)
    - Email, newsletters, website updates
  - Early forms access for testing with your systems



How do you want to receive updates?

Fill out the survey!

Link Here

Thank you!

NACC Update on UDSv4 Next Steps:
Dr. Sarah Biber and Laura McLeod

Any Questions? (10 minutes)

Thank you for attending!

This webinar will be posted to the NACC YouTube Channel.

https://www.youtube.com/c/NACCNationalAlzheimersCoordinatingCenter