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Version 3 of the National Alzheimer's Coordinating Center's Uniform Data Set

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Introduction: In 2015, the US Alzheimer's Disease Centers (ADC) implemented Version 3 of the Uniform Data Set (UDS). This paper describes the history of Version 3 development and the UDS data that are freely available to researchers.

Methods: UDS Version 3 was developed after years of coordination between the National Institute on Aging-appointed Clinical Task Force (CTF), clinicians from ~30 ADCs, and the National Alzheimer's Coordinating Center (NACC). The CTF recognized the need for updates to align with the state of the science in dementia research, while being flexible to the diverse needs and diseases studied at the ADCs. Version 3 also developed a non-proprietary neuropsychological battery.

Results: This paper focuses on the substantial Version 3 changes to the UDS forms related to clinical diagnosis and characterization of clinical symptoms to match updated consensus-based diagnostic criteria. Between March 2015 and March 2018, 4820 participants were enrolled using UDS Version 3. Longitudinal data were

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available for 25,337 of the 37,568 total participants using all UDS versions.

Discussion: The results from utilization of the UDS highlight the possibility for numerous research institutions to successfully collaborate, produce, and use standardized data collection instruments for over a decade.

Key Words: Alzheimer disease center, National Alzheimer's Coordinating Center, Alzheimer disease, Lewy body disease, frontotemporal degeneration, MCI

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In 1984, the US National Institute on Aging (NIA) of the National Institutes of Health inaugurated the Alzheimer's Disease Centers (ADC) program, aimed at providing a comprehensive approach to research on Alzheimer disease (AD) and related disorders. Through their research, ADCs are expected to aid in early detection, diagnosis, treatment, and prevention of neurodegenerative disease. As part of the ADC program, Centers' data must be collected in a standardized manner, but also in a way that allows individual Centers to maintain their unique research foci and strategies. To date, the NIA has funded 39 past and present ADCs that are located at medical institutions across the United States, and the ADC program has continually evolved to adapt to the state of the science.

At the start, ADCs collected data primarily retrospectively (eg, chart review) as part of the Minimum Data Set (MDS), with data collection coordinated by the National Alzheimer's Coordinating Center (NACC) starting in 1999. The MDS was a cross-sectional data set consisting of limited data on demographics, clinical diagnoses, and neuropathologic findings (when available). It largely served as a library/cataloging service.

In 2005, ADCs began collecting longitudinal demographic, clinical, neuropsychological, and diagnostic data on participants using Version 1 of the Uniform Data Set (UDS). Details on the data collected and the process of developing UDS Version 1 can be found elsewhere.[1] UDS Version 2 was implemented in 2008, resulting in a mostly minor update to the original data collection instruments such as adding a few new questions to the forms, restructuring of form logic (eg, skip patterns), and adding a few neuropsychological test elements [eg, Mini Mental State Exam (MMSE)[2] pentagon item score].

In contrast, numerous important changes were made with the implementation of UDS Version 3, including the addition of the Form C2 neuropsychological test battery.[3] The aims of this paper are to describe the history of development and implementation of UDS Version 3, the UDS data that are currently available, and the types of studies that can be conducted using this important resource. Previous published papers focus on the UDS Version 3 neuropsychological test battery only.[3,4] This paper describes the overall development of the UDS Version 3, which consists of a number of instruments beyond the neuropsychological test battery; the particular clinical data it collects; and the supplementary data that are available.

METHODS

The original impetus for the development and adoption of UDS Version 3 was the desire for an updated neuropsychological test battery, details of which have been thoroughly described elsewhere.[3] Some of the benefits of the updated test battery are that it is nonproprietary and that it includes a new episodic memory test to reduce practice effects observed in repeatedly using the prior version. A primary goal in the development of the UDS Version 3 neuropsychological battery was a set of nonproprietary tests that would allow sharing and comparison across various studies. Thus, some of the chosen tests were initially missing norms with which to reference until sufficient sample size allowed UDS Version 3 norms to be posted on the NACC website and to be published in 2018.[3] In addition, the new test battery now captures visuospatial and nonverbal memory function, domains not previously tested in UDS Versions 1 and 2. The careful review, evaluation, and implementation of the new battery took a number of years and was overseen by the Neuropsychology Work Group, a subcommittee of the ADCs' Clinical Task Force (CTF). Before implementation, the ADCs pilot tested the new battery (ie, the Crosswalk Study[4]), which allowed the Neuropsychology Work Group to assess if new and old tests capturing the same domains could be equated and used in longitudinal analyses. Results from the crosswalk study indicated that Version 3 neuropsychological tests were well correlated with Version 2 tests ($\rho = 0.68$ to 0.78).[4] The crosswalk study also suggested methods to convert scores on the Version 3 tests to comparable scores from the Version 2 battery. These conversion factors allow for comparison of all available initial visit test scores among individuals, whether they received UDS Version 2 or 3 at baseline, and for longitudinal comparison of test scores for participants who received both Version 2 and subsequently Version 3 tests during follow-up.

Along with the neuropsychological test changes, a number of other substantive edits were made to the forms in Version 3. These changes were instituted by the CTF in order to streamline the forms and adapt to the latest diagnostic criteria, including biomarker measures. Moreover, new questions were added to assess clinical characteristics of related neurodegenerative disorders [eg, frontotemporal lobar degeneration (FTLD) mutations, repeated traumatic brain injuries (TBIs)], reflecting the ADC program's expanding and diversifying research priorities. Decisions were made by the entire CTF, wherein consensus if not unanimity almost always was achieved whenever possible. The CTF Chair was tasked with resolving any impasses that arose.

With the goal of streamlining the UDS, the CTF worked with the NACC to review UDS Version 2, form by form, identifying questions that were redundant across forms and opportunities to increase the clarity of the questions and/or instructions. The decision to eliminate entire forms or large numbers of items was made by the CTF if items were both infrequently used by researchers and deemed no longer necessary to the basic clinical work-up.

After a comprehensive review of the forms, few data elements from Version 2 were eliminated due to redundancy, and a few wording and coding changes were suggested to clarify data elements. In the end, the major changes (Table 1) included modifications to the clinical diagnosis form (Form D1), the removal of the Hachinski Ischemic Score (Form B2) [given the increased use of magnetic resonance imaging (MRI) to document ischemic burden] and the Unified Parkinson's Disease Rating Scale (UPDRS; Form B3), and the addition of summary neurological examination findings (Form B8) and clinician-assessed

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TABLE 1. Major Changes Implemented With Version 3 of the Uniform Data Set Initial Visit Packet

Form	Major Changes From Version 2 to Version 3
A1: Subject Demographics	No major changes to form
A2: Co-participant Demographics	No major changes to form
A3: Subject Family History	Added questions on: (1) family history of AD and FTLD mutations; (2) diagnosis and age of onset for family members reported as having cognitive impairment
A4: Subject Medications	No major changes to form
A5: Subject Health History*	Added questions on: (1) TBI without loss of consciousness and repeated TBI; (2) sleep disorders (eg, sleep apnea); (3) psychiatric conditions (eg, PTSD, anxiety); (4) alcohol use/frequency; and (5) medical conditions (eg, diabetes type, arthritis.) Form is no longer completed at follow-up in lieu of Form D2
B1: Evaluation Form—Physical	No major changes to form
B2: Hachinski Ischemic Score	Removed altogether (ie, to streamline the UDS)
B3: Unified Parkinson's Disease Rating Scale	Removed altogether (ie, to streamline the UDS)
B4: Clinical Dementia Rating	No major changes to form
B5: Neuropsychiatric Inventory Questionnaire	No major changes to form
B6: Geriatric Depression Scale	No major changes to form
B7: Functional Assessment Scale	No major changes to form
B8: Neurological Examination Findings	Newly added form assessing neurological findings supportive of clinical diagnoses (eg, eye movements consistent with PSP)
B9: Clinician Judgment of Symptoms	Added questions on: (1) ages of onset of behavioral and motor symptoms; (2) changes in motor function consisting with ALS
C2: Neuropsychological Battery Scores†	Replaced proprietary tests (MMSE, Logical Memory Immediate and Delayed, BNT, Digit Symbol) with nonproprietary tests: MoCA, Craft Story Immediate and Delayed, Number Span Forward and Backward, MINT
D1: Clinician Diagnosis	Added questions and/or updated diagnostic criteria related to: (1) all-cause dementia; (2) dementia syndromes (eg, PPA, bvFTD, DLB); (3) etiologic diagnoses (eg, AD, FTLD, VBI, TBI); (4) biomarker and imaging findings; (5) presence of AD and FTLD mutations
D2: Clinician-assessed Medical Conditions	Newly added form assessing clinician-confirmed medical conditions (eg, diabetes)

*Self-participant and co-participant reported.

†All newly enrolled participants must use Form C2 at their Initial Visit; however, participants originally enrolled using earlier UDS versions can continue using Form C1 neuropsychological battery during follow-up.

AD indicates Alzheimer disease; ALS, amyotrophic lateral sclerosis; BNT, Boston Naming Test; bvFTD, behavioral variant frontotemporal dementia; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; MINT, Multilingual Naming Test; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; PPA, Primary Progressive Aphasia; PSP, progressive supranuclear palsy; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury; VBI, vascular brain injury.

medical conditions (Form D2) forms. Of note, the UPDRS was incorporated into a module that assesses Lewy body disorders (LBD module), which ADCs implemented in August, 2017.

The Clinical Diagnosis Form D1 was updated to not only adapt to the 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for AD that incorporated biomarkers [preclinical AD,[5] mild cognitive impairment due to AD (MCI-AD),[6] and AD dementia[7]], but also to the latest diagnostic criteria for conditions such as frontotemporal degeneration (eg, behavioral variant frontotemporal degeneration[8] and primary progressive aphasia[9]) and vascular brain injury. In addition, Version 3 of Form D1 incorporated new specific questions on AD and FTLD mutations and on conditions including posterior cortical atrophy (PCA), multiple system atrophy, human immunodeficiency virus–associated neurocognitive disorder (HAND), and psychiatric conditions including bipolar disorder and posttraumatic stress disorder. The Neurological Exam Findings Form B8 was a new addition for Version 3, aimed at capturing signs from the neurological exam consistent with specific neurodegenerative conditions such as Parkinson disease (PD), progressive supranuclear palsy, amyotrophic lateral sclerosis, and cerebrovascular disease. Finally, Form D2 was added to gather data on medical conditions that may confer risk for AD or dementia, such as cardiovascular disease and diabetes, with the goal of improving reliability and validity compared with the participant/co-participant self-reported medical conditions collected on Subject Health History Form A5.

In the months preceding implementation of UDS Version 3, NACC staff developed the documentation necessary for ADCs to begin using the forms. This included developing data element dictionaries[10] (coding guides for all variables), guidebooks[11] (to guide clinicians on form completion), neuropsychological battery instructions[12] for clinicians, and data quality checks (to stop or flag potentially erroneous data entry), among other documentation. The data element dictionaries and accompanying documentation were provided to ADCs in advance so that they could program their databases to submit the data to NACC on the implementation date. In addition, NACC created electronic forms for ease of data entry and modified the UDS Oracle database and UDS data submission system to allow for entry and storage of the Version 3 data. Before implementation, ADC clinical leaders participated in a webinar to learn about Version 3 changes and how to complete the forms. UDS Version 3 was implemented by all ADCs on March 15, 2015.

In October 2017, the Spanish translation of UDS Version 3 became available (Initial and Follow-up Visit Packet; Neuropsychological Battery). Spanish translation involved preliminary translation and content review by expert clinicians, and pilot testing at 3 US and 4 Latin American sites (see the Acknowledgments section). Pilot testing revealed minimal issues with the initial translation for the Montreal Cognitive

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Assessment (MoCA) (original Spanish version), Benson Complex Figure (Copy and Delayed Recall), Number Span Forward and Backward, Category Fluency (Animals and Vegetables List Generation), and Trail Making Test Parts A & B. However, adaption was required for the Craft Story (Immediate and Delayed Recall), Verbal Fluency: Phonemic Test (English: words beginning with F and L; Spanish: words beginning with P and M), and the Multilingual Naming Test (MINT). Once the Spanish translation became available to ADCs, the Centers were asked to submit a Linguistic History form to ascertain levels of acculturation for all UDS participants who identify as Hispanic or Latino. In addition to the Spanish translation, UDS Version 3 has been translated into Chinese, with plans for use in Alzheimer's research centers in China.

RESULTS

Table 1 outlines the major changes to the UDS with Version 3 implementation. As of March 1, 2018, the UDS (all versions) contains data on 37,568 participants followed at 39 past and present ADCs. Longitudinal data (≥ 2 visits) are available for 25,337 of the participants, with some participants having up to 13 UDS visits to date. Version 3 initial visit packets have been submitted on 4820 individuals. Results reported below are based on data collected from September 2005 through March 2018 using all 3 UDS versions.

Approximately 4000 participants were younger than 60 years of age and ~1000 were 90 years or older at their initial visit (Table 2). Reflecting the shift in AD research toward earlier detection, the age demographic shifted to younger ages when comparing those enrolled using UDS Version 3 to those enrolled using UDS Version 1 to 2 forms. In addition, the number of individuals who were asymptomatic (global Clinical Dementia Rating = 0) increased from 37% among those enrolled using UDS Version 1 to 2 to 46% among those enrolled using Version 3. Forty-one percent had at least one apolipoprotein E (APOE) ε4 allele. Although the large majority of the participants are white (80%) and non-Hispanic (92%), 4726 participants are African American, 896 are Asian, and 3079 are Hispanic.

MCI and dementia were clinically diagnosed in 7949 and 13,532 individuals at their initial visit, respectively (Table 3). ADC clinicians are required to indicate the primary and contributing etiologic diagnosis for MCI or dementia. AD was the primary etiologic diagnosis for 40% of those with MCI and 73% of those with dementia. Among the MCI participants, primary etiologic diagnoses other than AD were not as common (eg, 5% LBD, 5% vascular brain injury/dementia, 4% depression), and in the remainder of dementia participants, most had a diagnosis of LBD including PD (6%) or FTLD with behavioral variant frontotemporal degeneration or primary progressive aphasia syndromes (12%). Table 3 additionally provides the number of participants who have at least 2 UDS visits (ie, longitudinal data) by their primary etiologic diagnosis at their initial visit. For example, among MCI participants with a primary etiologic diagnosis of LBD at their initial visit, 126 completed 2 or 3 UDS visits and 97 completed at least 4 UDS visits.

A number of major additions and edits were made to Clinician Diagnosis Form D1, including newly collected information whether the subject had an AD (n = 14) or FTLD (n = 27) mutation. Table 4 highlights the new data elements collected with the implementation of UDS

TABLE 2. Demographics and Clinical Characteristics of Uniform Data Set Participants

Characteristic	Version 1-2 Initial Visit Packet	Version 3 Initial Visit Packet	All Participants Combined
Sample size (n)	32,748	4820	37,568
Age at initial visit [n (%)]			
< 60 y	3607 (11.0)	651 (13.5)	4258 (11.3)
60-69 y	8577 (26.2)	1588 (33.0)	10,165 (27.1)
70-79 y	12,028 (36.7)	1897 (39.4)	13,925 (37.1)
80-89 y	7459 (22.8)	638 (13.2)	8097 (21.6)
≥ 90 y	1077 (3.3)	46 (1.0)	1123 (3.0)
Male [n (%)]	14,113 (43.1)	2061 (42.8)	16,174 (43.1)
Education [n (%)]			
< 12 y	2924 (9.0)	165 (3.5)	3089 (8.3)
High school degree	6493 (20.0)	679 (14.3)	7172 (19.3)
Some/completed college	23,099 (71.0)	3905 (82.2)	27,004 (72.5)
Unknown			
Race [n (%)]			
White	26,090 (79.7)	3807 (79.0)	29,897 (79.6)
Black/African American	4096 (12.5)	630 (13.1)	4726 (12.6)
American Indian/Alaska Native	182 (0.6)	51 (1.1)	233 (0.6)
Native Hawaiian/ Pacific Islander	25 (0.1)	2 (0.0)	27 (0.1)
Asian	757 (2.3)	139 (2.9)	896 (2.4)
Multiracial	1065 (3.3)	106 (2.2)	1171 (3.1)
Unknown	533 (1.6)	85 (1.8)	618 (1.7)
Hispanic ethnicity [n (%)]			
Not Hispanic	30,112 (92.0)	4377 (90.8)	34,489 (91.8)
Mexican/ Chicano/ Mexican-American	834 (2.6)	86 (1.8)	920 (2.5)
Puerto Rican	550 (1.7)	77 (1.6)	627 (1.7)
Cuban	241 (0.7)	95 (2.0)	336 (0.9)
Dominican	256 (0.8)	29 (0.6)	285 (0.8)
Central American	148 (0.5)	34 (0.7)	182 (0.5)
South American	321 (1.0)	79 (1.6)	400 (1.1)
Other/unknown Hispanic origin	150 (0.5)	24 (0.5)	174 (0.5)
Ethnicity unknown	136 (0.4)	19 (0.4)	155 (0.4)
No. UDS visits [n (%)]			
1	8902 (27.2)	3329 (69.1)	12,231 (32.6)
2-3	9779 (29.9)	1489 (30.9)	11,268 (30.0)
4-5	6508 (19.9)	2 (0.0)	6510 (17.3)
6-7	3757 (11.5)	0	3757 (10.0)
8+	3802 (11.6)	0	3802 (10.1)
≥ 1 APOE ε4 allele [n (%)]	10,417 (40.6)	613 (39.4)	11,030 (40.6)
Global CDR at initial visit [n (%)]			
0	12,253 (37.4)	2203 (45.7)	14,456 (38.5)
0.5	11,839 (36.2)	1732 (35.9)	13,571 (36.1)
1	5482 (16.7)	617 (12.8)	6099 (16.2)
2	2046 (6.3)	165 (3.4)	2211 (5.9)
3	1128 (3.4)	103 (2.1)	1231 (3.3)

APOE indicates apolipoprotein E; CDR, Clinical Dementia Rating; UDS, Uniform Data Set.

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TABLE 3. Primary Etiologic Diagnoses for Mild Cognitive Impairment or Dementia at Initial Visit, by Number of Visits

	MCI (N = 7949)				Dementia (N = 13,532)			
Primary Etiologic Diagnosis*	**1 Visit (n)**	**2-3 Visits (n)**	**≥4 Visits (n)**	**Total [n (%)]**	**1 Visit (n)**	**2-3 Visits (n)**	**≥4 Visits (n)**	**Total [n (%)]**
AD	990	1023	1134	3147 (39.6)	3960	3313	2650	9923 (73.3)
LBD including PD	140	126	97	363 (4.6)	345	316	163	824 (6.1)
FTLD								
PSP	10	16	4	30 (0.4)	77	49	12	138 (1.0)
CBD	15	15	5	35 (0.4)	88	70	23	181 (1.3)
MND	1	0	0	1 (0.0)	9	1	0	10 (0.1)
Other (eg, bvFTD)	65	93	67	225 (2.8)	600	597	408	1605 (11.9)
VBI/vascular dementia	151	138	107	396 (5.0)	126	75	54	255 (1.9)
Depression	142	78	87	307 (3.9)	14	2	5	21 (0.2)
Total including other etiologies	2541	2518	2890	7949 (100.0)	5538	4581	3413	13,532 (100.0)

*Including participants administered any version of the UDS (ie, Version 1, 2, or 3).

AD indicates Alzheimer disease; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; col, column; FTLD, frontotemporal lobar degeneration; LBD, Lewy body disease; MCI, mild cognitive impairment; MND, motor neuron disease; PD, Parkinson disease; PSP, progressive supranuclear palsy.

TABLE 4. Highlights of Data Added to Assessment for Version 3, By Form

Data From Initial Visit for n = 4820 Participants	**Presence [n (%)]**
Form A3 (Subject Family History)	
Family member(s) with known AD mutation	27 (0.6)
Family member(s) with known FTLD mutation	51 (1.1)
Form A5 (Subject Health History)	
TBI without loss of consciousness	320 (6.6)
Repeated TBI	222 (4.6)
Form B8 (Neurological Exam Findings)	
Parkinsonian signs	471 (9.8)
Neurological signs consistent with cerebrovascular disease	143 (3.0)
Higher cortical visual problem suggesting PCA	57 (1.2)
Findings suggestive of PSP, CBS, or related disorder	134 (2.8)
Findings suggestive of ALS	27 (0.6)
Normal-pressure hydrocephalus: gait apraxia	8 (0.2)
Form D1 (Clinician Diagnosis)	
Participant has AD mutation	14 (0.3)
Participant has FTLD mutation	27 (0.6)
PCA syndrome	42 (0.9)
FTLD with motor neuron disease	16 (0.3)
Presumed FTLD subtype	
Tauopathy	81 (1.7)
TDP-43 proteinopathy	75 (1.6)
Other/unknown subtype	160 (3.3)
Significant vascular brain injury	305 (6.3)
Essential tremor	70 (1.5)
Symptoms consistent with chronic traumatic encephalopathy	17 (0.4)
Posttraumatic stress disorder	32 (0.7)
Form D2 (Clinician-assessed Medical Conditions)	
Cancer	689 (14.3)
Arthritis	2250 (46.7)
Sleep apnea	745 (15.5)
Antibody-mediated encephalopathy	7 (0.2)

AD indicates Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CBS, corticobasal syndrome; FTLD, frontotemporal lobar degeneration; PCA, Posterior Cortical Atrophy; PSP, primary supranuclear palsy; TBI, traumatic brain injury.

Version 3. Twenty-seven individuals reported having family members with a known AD mutation (*PS1*, *PS2*, *or APP*), and 51 reported family with an FTLD mutation (*MAPT*, *PGRN*, *C9ORF72*, *FUS*).

With Version 3, additional details are collected on TBI, including individuals with TBI without loss of consciousness (n = 320) and repeated TBI (n = 222) (Table 4). Detailed neurological examination findings on the new Form B8 included parkinsonian signs (n = 471 participants) and higher cortical visual problem suggesting PCA (n = 143). A number of diagnoses not previously collected were also added to Form D1, including PCA syndrome (n = 42 participants), FTLD with motor neuron disease (n = 16), essential tremor (n = 70), symptoms consistent with chronic traumatic encephalopathy (n = 17), and posttraumatic stress disorder (n = 32). Finally, the new Clinician-assessed Medical Conditions Form D2 records data on a variety of clinician-endorsed conditions, including cancer (n = 689 participants), arthritis (n = 2250), and sleep apnea (n = 745).

A substantial number of UDS participants have additional data sets that are also available at NACC. Neuropathology (NP) data[13] are available for 5135 UDS participants who have died and consented to autopsy (Table 5). Data from the FTLD module (symptoms, diagnoses, imaging evidence, and neuropsychological test findings specific to FTLD) are available for 1324 UDS participants. MRI are available to download for 4616 participants. Among individuals with MRI, 1317 have measures of regional brain volumes (eg, hippocampal volume). Amyloid positron emission tomography (PET) is available for download for 370 participants and cerebrospinal fluid (CSF) biomarker data for 1100 participants. In addition, genetic data are available for 13,180 UDS participants by request from the Alzheimer's Disease Genetics Consortium (ADGC), and deoxyribonucleic acid (DNA) samples are available for 23,381 by request from the National Cell Repository for Alzheimer's Disease (NCRAD).

Table 5 provides finer grained details on the number of participants who have these additional data by their primary etiologic diagnosis. For instance, the large majority of individuals (81%) with amyloid PETs available for

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TABLE 5. Additional Data Available on Uniform Data Set Participants by Primary Etiologic Diagnosis at Most Recent Visit

	Additional Data Available (n)							
	Neuropathology	FTLD Module	MRI	MRI Calculated Volumes	Amyloid PET	CSF Biomarker	Genetic Data at ADGC	DNA Sample at NCRAD
Normal cognition	553	347	1978	689	275	394	6209	8941
Impaired, not MCI	73	33	129	22	25	38	248	981
MCI, etiologic dx								
AD	210	37	467	109	24	76	698	2157
LBD including PD	33	10	35	8	1	19	35	179
FTLD								
PSP	4	5	0	0	0	0	0	14
CBD	7	12	2	1	0	1	0	19
MND	0	2	0	0	0	0	0	2
Other (eg, bvFTD)	10	58	13	2	0	5	6	81
VBI/vascular dementia	43	4	95	40	3	4	93	287
Total MCI	427	159	806	209	50	160	1083	3780
Dementia, etiologic dx								
AD	2721	150	1353	347	17	381	5172	7249
LBD including PD	353	8	114	11	0	34	167	551
FTLD								
PSP	86	56	13	1	0	4	7	115
CBD	91	44	10	0	0	7	30	151
MND	5	14	1	0	0	1	1	16
Other (eg, bvFTD)	550	479	98	6	0	29	98	1074
VBI/vascular dementia	93	3	42	16	0	8	116	225
Total dementia	4082	785	1703	397	20	508	5640	9679
Total participants	5135	1324	4616	1317	370	1100	13180	23381

AD indicates Alzheimer disease; ADGC, Alzheimer's Disease Genetics Consortium; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CSF, cerebrospinal fluid; dx, diagnosis; FTLD, frontotemporal lobar degeneration; LBD, Lewy body disease; MCI, mild cognitive impairment; MND, motor neuron disease; MRI, magnetic resonance images; NCRAD, National Cell Repository for Alzheimer's Disease; PD, Parkinson disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; VBI, vascular brain injury.

download had a clinical diagnosis of normal cognition or impaired not MCI (some impairment that does not meet MCI criteria) at their most recent visit, and 166 MCI participants and 540 dementia participants with a diagnosis of LBD (including PD) have DNA samples stored at NCRAD.

DISCUSSION

After considerable deliberation, compromise, and collaboration, the CTF, the ADCs, and NACC implemented UDS Version 3 in March 2015. There was a relatively lengthy period of evaluation, discussion, and negotiation amongst the expert ADC clinicians who made up the regular CTF and those who were part of the associated ad hoc subcommittees as well as other ADC clinicians. The CTF considered how to incorporate new developments in the field, while preserving longitudinal continuity with the >10 years of data collected in the prior UDS versions. Deletions, updates, and additions to the UDS needed to balance the needs of ~30 Centers that each have their distinct research priorities and different participant characteristics (eg, age, primary diagnosis). Clinician opinion differs regarding the most important forms and questions to collect in the UDS within and across multiple ADCs. The CTF weighed the need to assess key clinical characteristics for the increasing number of neurodegenerative diseases studied within the ADC program against the need to keep the UDS as parsimonious as possible, being mindful of the clinicians', research staffs', and participants' time. The resulting UDS Version 3, as in the prior UDS versions, demonstrates the ability of researchers from numerous institutions to collaborate and implement a standardized data collection instrument for over a decade.

An important contribution of the UDS is that it provides standardized instruments that can be supplemented with additional modules such as the FTLD and LBD modules, which were implemented by ADCs in January 2012 and August 2017, respectively. ADCs voluntarily submit the modules for individuals suspected to have FTLD or LBD, but additionally for individuals with AD or controls, which aids in determining the discriminative capabilities of the module instruments. To date, 1324 participants have completed the FTLD module, 464 of which have longitudinal FTLD module visits. As of March 2018, the LBD module data have not accumulated in sufficient numbers to provide to researchers, but the initial visit forms and documentation for the LBD and FTLD modules are viewable on the NACC website (www.alz.washington.edu/WEB/dataforms_main.html). In addition, researchers outside of the ADCs may request permission to use the UDS or associated modules. In the future, additional modules can be added to the UDS to collect more detailed data on a specific subpopulation or neurodegenerative disease (eg, preclinical disease).

The UDS serves as a foundation to integrate not only standardized clinical assessments of participants with NACC's NP data set, but also to incorporate novel MRI, PET, and CSF biomarker data with these important clinical characteristics. The NACC database is adaptable and thus capable of receiving supplemental data such as the imaging and fluid biomarker data that complement the UDS and

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also reflect the trending research priorities of the ADCs. Along with the data that are either readily available at NACC or that can be linked to the UDS via the ADGC (eg, genome-wide association study) or NCRAD (eg, DNA samples), researchers can supplement the UDS data through a special request to one or more ADCs to obtain additional data not available at NACC (requests for UDS data, supplemental data and modules, and special requests for external data/specimens can be initiated at http://www.alz.washington.edu). This process of requesting external data from ADCs is initially coordinated by NACC. As an example, one such study gained approval from 15 ADCs to survey participants of 4 different racial/ethnic groups about their willingness to commit to post mortem brain donation.[14] Researchers also work with NACC to determine samples of brain tissue that may be available for sharing from one or more ADCs. An example is a published study that combined existing NP data at NACC with supplemental data on number of microinfarcts through abstraction of University of Washington and Oregon Health and Science University ADC records to examine the associations between mixed pathologies and domain-specific cognitive decline.[15]

The growing depth and breadth of the UDS and of the additional data that can be linked to the UDS has resulted in an ever increasing number of published manuscripts using the NACC data (n = 481 as of March 16, 2018) (viewable under "Publications and Productivity" link at www.alz.washington.edu). Early papers using the UDS were limited in terms of sample size and tended to focus on descriptions of the UDS sample or various methodological issues. In contrast, papers published using the UDS data in the first quarter of 2018[16–32] investigated a wide range of topics, such as inappropriate medication use among those with incident dementia,[27] TBI history and early age of onset in autopsy-confirmed AD,[28] big data approaches to preclinical trial enrichment,[24] and predicting sex differences in MCI and AD using data on white matter hyperintensities and hippocampal volume.[17] Thus, the demonstrated increase in publications using UDS data suggests that the UDS revisions described in this article have tailored the standardized data collection to measures that are more useful for researchers.

The volume of the published articles and abstracts using the UDS and the continually increasing diversity of topics are evidence of the value of the data to junior and seasoned researchers alike. The strengths of the UDS include not only the types of data that can be linked to it, but its longitudinal nature and the availability of sufficient sample sizes to study rarer conditions or special populations not otherwise feasible. For instance, UDS data provide opportunities for finer grain analyses focused on Hispanics/Latinos of specific origins. In addition, the ability to merge clinical data with NP data is critical, as NP remains the gold standard for neurodegenerative diseases such as AD.

Although the UDS exhibits a number of strengths desirable to researchers, anyone using the data must acknowledge its weaknesses when conducting a study or interpreting findings. Recruitment methods for the UDS sample have varied between ADCs and within each ADC over time, and are often based on convenience samples such as recruitment through clinics or participant referrals. The benefit of this approach is that ADCs are able to enrich their samples with individuals who have or are more likely to develop neurodegenerative disease. In addition, as mentioned above, ADCs have distinct research priorities and sample characteristics. The differences in recruitment and sample characteristics across the ADCs provide a heterogenous and diverse group with which to study, but this also means that the sample is not population-based and thus may not truly reflect local ADC communities or the larger US population. Another limitation is that the UDS Version 3 neuropsychological battery is missing a verbal list learning task such as the Rey Auditory Verbal Learning Test. The Neuropsychology Work Group decided against adding a verbal list learning task because the options were mostly proprietary (a major goal in developing the UDS 3 battery was to be nonproprietary), and because of the wide range of verbal list instruments used across ADCs, which would have created burden on the ADCs that have long established cohorts using an instrument not chosen for UDS Version 3. Also, the UDS instruments have changed over time, which can present a challenge to investigators wishing to use the longitudinal data (ie, neuropsychological test battery changed from UDS Version 2 to 3) or wishing to use the largest possible samples sizes (definition of TBI history changed from UDS Version 2 to 3). NACC developed the researchers data dictionary (RDD-UDS[33]) to harmonize data across the UDS versions, whenever possible, to try to minimize this issue and ensure researchers are aware of important UDS version changes. In addition, NACC research staff are available to consult with researchers who have questions about version changes, or other details about the UDS data.

UDS Version 3 demonstrates a number of advantages and improvements over the prior versions, collecting new and pertinent data in line with the evolving research interests at the ADCs. UDS Version 3 was developed in a manner that allows it to be combined with the previous versions, so that the longitudinal nature of the UDS and the legacy data remain accessible to researchers. A distinct advantage of UDS Version 3 is that it is nonproprietary. With permission, Version 3 can be used in other studies, allowing for a common method of assessing cognition and clinical characteristics among those with normal cognition and various neurological diseases and also providing the ability to compare findings across various studies and cohorts. Examples of research studies that are using UDS forms include the Dominantly Inherited Alzheimer Network (DIAN), the Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium (ARTFL) and the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS). In addition, the UDS data can be combined with valuable data internal and external to NACC, including imaging, CSF biomarker, and genetic data. Since its inception in 2005, the UDS has highlighted the possibility for numerous research institutions with sometimes disparate priorities to collaborate with each other to produce and use standardized data collection instruments. Version 3 was no exception, and with its implementation, it provides researchers a unique, valuable resource to facilitate acceleration of novel AD and related disorders research.

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