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REVIEW ARTICLE

The Alzheimer's Biomarker Consortium-Down Syndrome: Rationale and methodology

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Funding information

National Institute on Aging; Eunice Kennedy Shriver National Institute for Child Health and Human Development, Grant/Award Numbers: U01 AG051406, U01 AG051412; The Alzheimer's Disease Research Centers Program, Grant/Award Numbers: P50 AG008702, P30 AG062421, P50

Abstract

Introduction: Adults with Down syndrome (DS) are at exceptionally high risk for Alzheimer's disease (AD), with virtually all individuals developing key neuropathological features by age 40. Identifying biomarkers of AD progression in DS can provide valuable insights into pathogenesis and suggest targets for disease modifying treatments.

Methods: We describe the development of a multi-center, longitudinal study of biomarkers of AD in DS. The protocol includes longitudinal examination of clinical, cognitive, blood and cerebrospinal fluid-based biomarkers, magnetic resonance imaging

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AG16537, P50 AG005133, P50 AG005681, P30 AG062715; Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers Program, Grant/Award Numbers: U54 HD090256, U54 HD087011; National Centers for Advancing Translational Sciences, Grant/Award Numbers: UL1TR001873, UL1 TR00237, UL1 TR001414, UL1 TR001857, UL1 TR002345; National Centralized Repository for Alzheimer Disease and Related Dementias, Grant/Award Number: U24 AG021886; Eunice Kennedy Shriver National Institute of Child Health and Human Development

and positron emission tomography measures (at 16-month intervals), as well as genetic modifiers of AD risk and progression.

Results: Approximately 400 individuals will be enrolled in the study (more than 370 to date). The methodological approach from the administrative, clinical, neuroimaging, omics, neuropathology, and statistical cores is provided.

Discussion: This represents the largest U.S.-based, multi-site, biomarker initiative of AD in DS. Findings can inform other multidisciplinary networks studying AD in the general population.

KEYWORDS

ABC-DS, Alzheimer's disease, dementia, Down syndrome

1 | INTRODUCTION

Adults with Down syndrome (DS) are at exceptionally high risk for Alzheimer's disease (AD), with virtually all individuals developing neuropathology by 40 years of age, consistent with a brain tissue AD diagnosis, including amyloid plaques, neurofibrillary tangles, and granulovacuolar degeneration.¹⁻⁴ The prevalence of dementia in DS increases with age, with the majority of individuals exhibiting indications of clinical decline by 60 years of age.^{5,6}

Within the general adult population, there is a need to understand critical pathophysiological mechanisms of AD to provide a window for therapeutic intervention.⁷ Individuals with DS share the same need. However, understanding the conversion to dementia in DS is often confounded by other factors, including varying degrees of baseline intellectual disability⁸ and associated medical comorbidities.⁹ In addition, there is considerable variability in the age of onset of dementia in DS, ranging from prior to age 40 to over age 70.¹⁰ Empirically supported methods for detecting AD-related clinical progression in DS, the biological characterization of the preclinical and early phases of this progression, and the identification of risk factors are critical for the development of effective interventions.¹¹ This report will focus on the methods used to address these areas in a multidisciplinary, longitudinal study of biomarkers of AD in adults with DS, examining clinical, cognitive, blood and cerebrospinal fluid (CSF)-based fluid biomarkers, magnetic resonance imaging (MRI) and positron emission tomography (PET) measures, as well as genetic polymorphisms associated with AD progression.

2 | RATIONALE FOR THE APPROACH

The etiology of AD in DS (trisomy 21) is linked to a lifelong overproduction of amyloid beta ($A\beta$). This overproduction is due to the presence of three copies of chromosome 21, each containing one copy of the amyloid precursor protein (APP) gene (ultimately leading to a 1.5-fold increase in the production of $A\beta$ protein).¹²⁻¹⁴ The rare instance of a partial trisomy 21, in which there is duplication but not triplication of

APP, is associated with the absence of clinical and pathological signs of AD, demonstrating the key role played by APP overexpression.^{14,15} The early striatal pattern of $A\beta$ deposition in DS is similar to that in autosomal dominant AD (ADAD) mutation carriers.^{16,17} Yet, it is clear that factors in addition to overexpression of APP contribute to the wide variation in age of onset of AD in the DS population.^{3,18,19} Gaining a full understanding of these modifiers of risk could provide important insights into pathways representing promising targets for disease-modifying treatments.

AD in DS provides an example of both amplified vulnerability and an opportunity to examine protective factors that may modify the relations among $A\beta$, neurodegeneration, and dementia. Thus, a range of genotypic and phenotypic variations in adults with DS may serve to increase relative risk (eg, hypercholesterolemia, neuroinflammation) or act as protective factors (eg, high estrogen bioavailability, lower peripheral vascular disease, higher baseline IQ).^{20,21} A large-scale biomarker initiative, similar to the Alzheimer's Disease Neuroimaging Initiative (ADNI) or the Dominantly Inherited Alzheimer Network (DIAN), targeting AD in DS is needed to identify these factors, to provide the field with empirically validated tests that can inform diagnosis and predict risk, and to support the development of therapeutic trials specifically designed for the prevention and treatment of AD in this population. ADNI was designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD in the general population through a public-private partnership, with a hallmark feature of providing data without embargo to scientists around world. The DIAN study focuses on both observational studies and clinical trials, using clinical, imaging, genetic, and biochemical biomarkers similar to ADNI, to identify solutions to treat or prevent autosomal dominant AD. In recognition of the importance of these issues facing adults with DS, the U.S. National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute on Child Health and Human Development (NICHD) provided the resources to support a similar large-scale biomarker initiative focusing on DS, establishing the program described herein.

Our current knowledge indicates that the earliest signs of AD development in the general population occur at least 20 years prior to

the appearance of clinical symptoms.²² This hypothesized “cascade” starts with the aggregation of soluble $A\beta_{42}$ in the brain into insoluble plaques, as evidenced by early reductions in concentrations of $A\beta_{42}$ in the cerebrospinal fluid (CSF), followed by amyloid deposition detectable by positron emission tomography (PET). Increases in CSF tau and phosphorylated tau, indicative of neuronal injury, and neurofibrillary tangle formation, respectively, ensue, followed by subsequent changes in brain structure (eg, decreased hippocampal volume), and glucose hypometabolism.²³ Finally, early clinical symptoms begin to be detected, most commonly in episodic memory.^{24,25} While it is hypothesized that the pathophysiological features of AD in adults with DS are similar to that of late-onset AD (LOAD), the course of the AD disease process is only partially understood. The mean age of diagnosis of AD in DS is 55.8 years and survival after a diagnosis of dementia appears to be shorter in comparison to LOAD.²⁶ Unlike the general population, there is ample evidence of deposition of insoluble amyloid in the brains of the vast majority of adults with DS by the early 40s (and soluble amyloid much earlier),^{27,28} along with documented changes in brain structure (eg, enlarged lateral ventricles, reduced hippocampal volume).²⁸⁻³⁰

Comparison of the risk, biomarker, and genetic profiles in DS with those with AD in the general population (as well as with other groups, such as individuals with ADAD) can help to define common pathways and mechanisms. It is an ultimate goal of all of these investigations to identify a window for therapeutic intervention before the inexorable decline associated with AD.

3 | PROTOCOL OVERVIEW

The Alzheimer’s Biomarker Consortium-Down Syndrome (ABC-DS) was formed in 2015, combining two programs developed independently in response to an initiative of the U.S. National Institutes of Health (NIH-RO1-RFA-AG-15-011). Harmonization of these two separately funded programs was intended to produce standardization of diverse and complex procedures. This effort was largely successful with some exceptions, as described in the Challenges section below. This unification process helped to address many of the general obstacles in conducting longitudinal research focused on DS, including methods for surrogate consent, appropriate recruitment materials, participant retention, data security, and safety oversight.

While the ABC-DS developed into a unified study, the original program designations prior to harmonization were preserved in recognition of components unique to these two separate but closely collaborating programs. The first, titled Alzheimer’s Disease Down Syndrome (ADDS), includes enrolling sites in New York, NY (Columbia University/New York State Institute for Basic Research in Developmental Disabilities); Boston, MA (Massachusetts General Hospital, Harvard University); and Irvine, CA (the University of California, Irvine) supported by collaborators at the Johns Hopkins University Schools of Medicine and Public Health and the University of North Texas Health Science Center. The second program, titled Neurodegeneration in Aging Down Syndrome (NiAD), includes an additional four enrolling sites located

RESEARCH IN CONTEXT

1. Systematic review: We describe the development of a multi-center, longitudinal study of biomarkers of Alzheimer’s disease (AD) in Down syndrome (DS) involving seven performance sites. The protocol includes examination of clinical, cognitive, blood and cerebrospinal fluid-based biomarkers, magnetic resonance imaging (MRI) and positron emission tomography (PET) measures (at 16-month intervals), and genetic modifiers of AD risk and progression.
2. Interpretation: More than 400 individuals are being enrolled. This represents the largest U.S.-based, multi-site, biomarker initiative to target AD in the DS population. It has similarities to other efforts such as the Alzheimer Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer Network (DIAN).
3. Future directions: The Alzheimer’s Biomarker Consortium-Down Syndrome (ABC-DS) is poised to have a substantial impact on our ability to characterize AD in DS, both by identifying those biomarkers that clarify risk for transition from cognitive stability to early clinical progression to AD and in the identification of biomarkers of preclinical AD progression.

in Pittsburgh, PA (University of Pittsburgh); Madison, WI (University of Wisconsin); St. Louis, MO (Washington University); and Cambridge, England (University of Cambridge). Each enrolling site has been conducting ongoing recruitment with a participation target of between 50 and 100 adults with DS ages 25 years and older (for NiAD) and 40 or older (for ADDS). The ABC-DS protocol comprises research visits at baseline, 16 months, and 32 months. These time intervals were chosen based upon the extensive knowledge of the research team members regarding the time course of AD progression, as well as considerations related to safety and participation burden for a population with intellectual disability. A 3-month appointment window around these follow-up intervals is allowed to provide sufficient flexibility for scheduling, due to participants’ and informants’ other demands on their time.

The protocol components are listed in Table 1. Study visits have typically occurred across 2 separate days. The cognitive assessment battery, physical/ neurological exam, and caregiver questionnaires tend to be scheduled on the first day. The MRI and PET scans, blood draws and optional lumbar puncture (LP) for the collection of CSF are typically scheduled on the second day (the actual order of assessments may differ slightly across sites). Sometimes a third day is needed to complete the assessments. Table 1 lists the time points and procedures of the study. (Note that some procedures that do not require on-site facilities may be conducted during staff visits to participants’ homes or program sites when logistically necessary.)

A few important differences in the ADDS and NiAD protocols were deliberately retained after harmonization. ADDS enrollment focuses

TABLE 1 Alzheimer's Biomarkers Consortium–Down Syndrome assessments

Procedure	Month 0	Month 16	Month 32
Cognitive battery	X	X	X
Physical/neurological exam	X	X	X
Informant interviews/questionnaires	X	X	X
Blood draw	X	X	X
MRI	X	X ^a	X
Amyloid PET	X	X ^a	X
Tau PET	X ^b	X ^b	X ^b
FDG PET		X ^c	
Optional LP/CSF	X ^d	X ^d	X ^d
Consensus classification	X	X	X

^aMonth 16 magnetic resonance imaging (MRI) and amyloid PET for ADDS group only.

^bNiAD conducts Tau PET month 0 and 32; ADDS conducts Tau PET month 16 and 32.

^cNiAD only.

^dADDS collects CSF at month 0, 16, and 32; NiAD collects cerebrospinal fluid (CSF) at month 16.

Abbreviations: ADDS, Alzheimer's Disease Down Syndrome; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; LP, lumbar puncture; MRI, magnetic resonance imaging; NiAD, Neurodegeneration in Aging Down Syndrome; PET, positron emission tomography.

on individuals 40 years of age and older with the aim of identifying transitions from cognitive stability to early clinical progression of AD and from mild cognitive impairment (MCI-DS) to frank dementia. A major goal is to determine those biomarkers that clarify risk for these transitions and that can inform differential diagnosis. NiAD shares these broad goals, but permits enrollment of adults as young as 25 to discover biomarkers of preclinical AD progression (ie, prior to the MCI-DS stage), understanding that these earliest stages of disease can occur decades prior to symptom onset.

As described in Table 1, there were also differences between the two protocols for when PET scans and LPs are conducted. In addition, only the NiAD group has conducted FDG PET scans (at the month 16 visit). Finally, the NiAD protocol has included enrollment of a biomarker reference group composed of a smaller number of age-matched siblings without DS. Siblings have to be free of symptoms of dementia (assessed via the Montreal Cognitive Assessment [MOCA]³¹ and the Eight-Item Interview to Differentiate Aging and Dementia [AD8]^{32,33}) or other neurological disorders. They undergo the same scanning, and LP and blood draws, but are not administered additional cognitive testing, physical/neurological examinations, or informant interviews.

4 | INSTITUTIONAL REVIEW BOARDS AND CONSENT

Institutional Review Board (IRB) approval and informed consent (and assent when appropriate) have been obtained from all study participants or their proxy/legally authorized representative (LAR). DS

is more common than all other forms of autosomal dominant dementia combined. However, the field has not yet answered a number of ethical imperatives for determining the ability of individuals with DS to participate in longitudinal studies such as ABC-DS as well as in clinical trials.³⁴ Regulations for surrogate consent in biomedical research differ across states. For example, some states require that a LAR sign the consent for an adult with a developmental disability to participate in research (while the adult with DS signs an assent). Other states assume that all adults with developmental disabilities are capable of consenting for themselves unless proven otherwise. In addition, permission for procedures considered "more than minimal risk" (eg, LP, PET) is restricted for residents of some states because of regulations originally developed to protect people with developmental disorders from exploitation. Such restrictions tend to be in response to a history of controversial research in individuals with intellectual disability,³⁵ leading to the adoption of rigorous protections for research participation. While every ABC-DS performance site has obtained regulatory approval to conduct the entire project protocol, a small minority of prospective study enrollees are restricted to participating in only those procedures deemed to be minimal risk. The ethics of clinical research for individuals with intellectual disability remains a complex issue^{36,37} and ABC-DS is contributing to that discussion.

5 | PARTICIPANT RECRUITMENT

Participants have been recruited both locally and regionally. Some sites have outpatient clinics that specifically serve adults with DS that provide an excellent referral source. All participating sites have legacy studies involving adults with DS, many of whose participants have enrolled in the ABC-DS effort. Sites have also included study information on websites and in newsletters published by local DS advocacy groups and have also used university-supported efforts to enroll participants in research. Finally, ABC-DS investigators and staff have focused on community engagement, including developing educational videos and presenting at local, regional, and national conferences. Of particular importance has been the availability of a link describing this research effort through DS Connect,³⁸ which is a research registry supported by NICHD.

6 | ADMINISTRATIVE CORE

NiAD and ADDS have separate administrative sites located at the University of Pittsburgh and Columbia University, respectively. Together, the administrative units manage all components of ABC-DS including budget, frequent teleconferences, and monthly communication with NIA/NICHD officials. In addition, an annual in-person investigators meeting is held. The Consortium's Data Safety Monitoring Board, comprising members unaffiliated with the ABC-DS, meets every 6 months to review progress and to address any risk-related concerns associated with participation. This independent oversight ensures that the program is continuing to be conducted consistent with the highest

ethical standards. Website communications are maintained for families with links to participating institutions as well as to NIA/NICHD. Participant blood samples are shipped, processed, and stored at the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD). NCRAD subsequently provides blood samples to ABC-DS investigators to conduct protocol-related genetics, proteomics, and metabolomics analyses. In addition, outside investigators can request access to samples for additional studies of their own. An ABC-DS biospecimens committee has been established to review such requests to ensure that these valuable samples are utilized effectively (eg, to avoid redundancy with studies already in progress). Once approved, NCRAD makes samples available to these qualified, outside researchers. CSF samples are shipped to the Fagan Biomarker Lab at Washington University for processing and analyses. This lab similarly stores CSF samples to be made available to outside investigators. All ABC-DS data, including unprocessed MRI and PET scans, are stored and made available to external researchers through the Laboratory of Neuro Imaging (LONI) data repository at the University of Southern California (USC).³⁹ A Publication Committee coordinates dissemination of findings generated by ABC-DS investigators and minimizes duplication of effort within the ABC-DS team. This committee also facilitates access to ABC-DS data when requested by outside qualified investigators.

Finally, cross-site training has been an important part of the harmonization process. Subcommittees were formed to harmonize the neuropsychological assessments, clinical evaluations, neuroimaging sequences, and blood and CSF processing. As a result, ABC-DS has created discipline-specific protocols, case report forms, and data dictionaries. The harmonization process was facilitated further through several NIA supplements to expand biomarker availability, investigate sleep parameters, and to add additional ligands to the PET procedures.

7 | CLINICAL AND NEUROPSYCHOLOGICAL EVALUATIONS

The potential impact of medical and psychiatric comorbidities on cognitive performance profiles of adults with DS has been well documented.⁸ Some of these comorbidities can be signs of AD clinical progression or can indicate the presence of some unrelated condition with a clinical presentation that can mimic AD (or a different aging-related dementing disorder). To address these potential complications, a standardized medical history, chart review, and neurological examination are conducted to provide key information needed for differential diagnosis as well as clinical dementia status. Conditions of particular interest in this population include thyroid dysfunction, sleep apnea, seizures, neuropsychiatric conditions, medication use, and other systemic illnesses.

The ABC-DS group has selected a set of neuropsychological measures that have the strongest evidence base for defining different stages of dementia. Most of these tools were developed specifically for adults with DS, as the available tools used to assess aging-related dementia in "neurotypical" adults would show performance profiles

well below criteria for a diagnosis of frank dementia, due to developmental impairments unrelated to AD. In DS samples, declines in cognition are associated with early AD-related neuropathological changes²⁷ as well as with the onset of MCI-DS and dementia.⁴⁰ These include declines in measures of episodic memory, attention, executive functioning, visuospatial ability, and motor planning and coordination.⁴¹⁻⁴⁵ For the ABC-DS effort, the choice of specific procedures was based upon extensive past experience and the published literature indicating that: (1) almost all adults with DS can understand instructions and the task demands, (2) most individuals can perform significantly above floor (>2 standard error of the mean [SEMs]) prior to developing AD-related decline, (3) measures have good psychometric properties, and (4) measures are sensitive to early indications of AD clinical progression and subsequent decline. Many of the selected measures were used in our own related legacy studies of dementia in DS, and these data have proven to be a rich resource for participant recruitment and for tracking status over time. Informant and direct-testing measures in the ABC-DS protocol are listed in Table 2, along with the primary cognitive/functional domains the tests are intended to assess. It should be noted that in addition to the harmonized core of measures used by both the ADDS and NiAD sites, a number of supplemental assessment tools were included at various sites to evaluate their utility/validity.

7.1 | Diagnostic determination

Clinical dementia status has been determined individually for each participant following each assessment cycle during a Consensus Case Conference. These discussions include at least three study staff who have clinical training (eg, licensed clinical psychologist or physician) or longstanding expertise in evaluating dementia in the DS population. The following information is considered: (1) review of the medical and psychiatric history as well as findings from the neurological exam, (2) "core" informant interviews, and (3) the participant's overall profile of performance on a "core" battery of direct tests. For participants who have participated in the study at multiple time points, all time points of information are considered. Overall pattern of change in performance is considered rather than focusing on specific cutoff scores or any one measure. Performance is considered in relation to the participants' baseline IQ, medical and psychiatric conditions, and any major life events. During consensus determinations, study staff has been blind to the status of all other ABC-DS biomarker findings, including apolipoprotein E (APOE) genotype, MRI and PET findings, fluid biomarkers, and supplemental measures of cognitive or functional status.

We classify participants into four groups, generally following the recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability.^{76,77} Participants have been classified as cognitively stable (CS) if they are without cognitive or functional decline beyond what would be expected with adult aging, per se. Mild cognitive impairment (MCI-DS) is assigned for participants who have shown some cognitive and/or functional decline that is greater than would be expected with "healthy aging" but not of sufficient magnitude to

TABLE 2 Harmonized core and supplemental measures

Domain	Task	ADDS	NiAD
Mental status	Down Syndrome Mental Status Examination ⁴⁶	X	X
	Dementia Questionnaire for People with Learning Disabilities (DLD) ⁴⁷	X	X
	NTG-Early Detection Screen for Dementia (NTG-EDSD) ⁴⁸	X	X
	Modified Mini-Mental Status Examination ⁴⁹	X	
	Test for Severe Impairment ⁵⁰	X	
	Severe Impairment Battery (SIB) ⁵¹		X
	Rapid Assessment for Developmental Disabilities (RADD) ⁵²	X	
Functional abilities	Vineland Adaptive Behavior Scale ⁵³	X	X
	AAMR Adaptive Behavior Scale ⁵⁴	X	
Language/cognitive	Categorical/Verbal Fluency ^{55,56}	X	X
	Boston Naming Test ⁵⁷	X	
	Expressive-One Word Picture Vocabulary Test ⁵⁸		X
	Peabody Picture Vocabulary Test ⁵⁹		X
	Stanford-Binet (5th ed.) Abbreviated Battery ⁶⁰		X
Visuospatial construction	Block Design and Extended Block Design ^{46,61}	X	X
	Beery Buktenica Developmental Test of Visual Motor Integration (VMI) ⁶²	X	X
Memory	Cued Recall Task ⁶³	X	X
	Rivermead Behavioral Memory Test for Children—Face & Picture Recognition ⁶⁴	X	X
	Selective Reminding Test ⁶⁵	XX	
	Selective Reminding Test Post 10 minute delay		
	WISC-IV Digit Span Forward ⁶¹		X
	Forward Corsi Span ⁶²		X
	WMS-IV Logical Memory I & II ⁶⁶		X
Neuropsychiatric symptoms/ behavior problems	Neuropsychiatric Inventory (NPI) ⁶⁷	X	X
	Reiss Screen for Maladaptive Behavior ⁶⁸	X	X
	The Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD) ⁶⁹	X	
	Psychiatric status and history		X
Executive processing and speed	Stroop Dog and Cat ⁷⁰	X	X
	The Purdue Pegboard ⁷¹	X	X
	Dimensional Change Card Sort ⁷²	X	
	Flanker Inhibitory Control and Attention Task ⁷²	X	
	NEPSY Visual Attention Subtest ⁷³		X
	Pattern Comparison Processing Speed ⁷²	X	
	Cancellation Task ⁷⁴	X	
	WISC-IV Digit Span Backward ⁶¹		X
	Backward Corsi Span ⁶²		X
	Tinetti Assessment Tool: Gait ⁷⁵	X	X
Health status and life events	Demographic Health Questionnaire	X	X
	Comprehensive chart review	X	
	Life stressors index [Seltzer, G, Personal Communication, 2002]	X	

Note: Harmonized Core is indicated in bold.

Abbreviations: ADDS, Alzheimer's Disease Down Syndrome; NiAD, Neurodegeneration in Aging Down Syndrome.

TABLE 3 Alzheimer's Biomarker Consortium–Down Syndrome (ABC-DS) cohort characteristics as of September 2019 (*N* = 370 participants)

Characteristics	<i>n</i> (%)
Sex	
Males	199 (54%)
Females	171 (46%)
Age	
25 to 34	53 (14%)
35 to 44	110 (30%)
45 to 54	131 (35%)
55 to 64	69 (19%)
65+	7 (2%)
Race	
White	354 (96%)
Nonwhite	16 (4%)
Status ^a	
Cognitively stable	241 (68%)
MCI-DS	52 (15%)
Dementia	42 (12%)
Undetermined	18 (5%)
Co-occurring	
Stroke	7 (2%)
Diabetes	19 (5%)
Hyperlipidemia	113 (31%)
Hypothyroidism	221 (60%)
Seizures	34 (9%)
Obesity	179 (48%)
APOE	
Any $\epsilon 4$ allele	64 (17%)

Abbreviation: MCI-DS, mild cognitive impairment.

^a353 with consensus diagnosis.

meet dementia criteria. Participants have been classified as demented if there is a history of progressive memory loss, disorientation, and functional decline over a period of at least 1 year, and if no other medical or psychiatric conditions that might result in or mimic dementia are present (eg, traumatic life event, recent surgery). The ADDS sites include an additional category, "possible dementia," which has been collapsed with the "dementia" category for purposes of analysis. Fidelity has been ensured by close supervision of training and conducting an independent second consensus diagnosis on a random subset of participants at each site.

As the ABC-DS continues to actively recruit study participants, we are only able to provide information on those enrolled in the cohort to date. Table 3 summarizes the demographic characteristics of the first 370 participants with DS as of September 2019. More than two thirds of participants have been determined (via consensus conference) to be cognitively stable. Seventeen percent have at least one

APOE $\epsilon 4$ allele. The most commonly occurring medical comorbidities are hypothyroidism, obesity, and hyperlipidemia. Over the past 3 years, 21 study participants have died ($\approx 5\%$ of the cohort). Finally, 96% of the cohort is white, demonstrating the challenges of recruiting and enrolling participants from under-represented minorities.

8 | NEUROIMAGING STUDIES

The MRI- and PET-derived outcome measures have been harmonized as much as possible between the seven clinical sites in the study. The MRI acquisition plan (whose sequences are shown in Table 4) has followed the guidance of the ADNI 3 and Human Connectome Project (HCP) protocols. All MRI scans are read by a neuro-radiologist following institution-specific guidelines and any clinically significant findings are reported to the participant's primary care provider, designated representative, and/or family. The scans are analyzed for key outcome measures by laboratories within the ABC-DS network with expertise in the respective modality, following internal quality control (QC) and analytic procedures. They are additionally uploaded to the image repository and placed in quarantine pending the approval of the QC procedures. The T1-weighted scans are used as the reference images to indicate the quality of all of the imaging sequences. If the QC inspection is deemed acceptable, then all of the imaging sequences for each study participant are removed from quarantine and made accessible for image processing to outside researchers. Acceptable tolerance of image quality is determined by researchers for each individual image sequence (eg, motion tolerance in resting state functional MRI [rs-fMRI]) to determine their inclusion for analyses and hypothesis testing.

PET scans have been acquired from the majority of participants to quantitate the A β and tau burden (along with a subset of participants to measure glucose metabolism) for cross-sectional and longitudinal analyses. The acquisition of the PET data closely adheres to the ADNI specifications for uptake period and scanning duration for the A β ([C-11]PiB—four sites and florbetapir/[F-18]AV-45—three sites), tau (flortaucipir/[F-18]AV1451—all sites), and glucose metabolism (FDG—three sites). The details for acquisition are listed in Table 5.

The initial harmonization process for the PET procedures across all sites required consideration of initial protocol variations in the order of scans at participant visits, the use of different PET radiotracers for measuring A β deposition, and local regulatory requirements for radiation use and exposure. The NiAD sites have been acquiring A β (PiB) and tau scans at the baseline and 32-month visits. The ADDS sites have been acquiring A β (florbetapir) at the baseline and 32-month visits, and tau scans at the 16-month visit. Three of the four NiAD sites have been acquiring FDG scans at the 16-month visit. For harmonization across sites, reconstruction parameters of the PET images have followed the specifications defined by the ADNI trials for specific PET and PET/CT scanner models. The Centiloid Scale was developed to permit comparisons between different A β radiotracers (eg, Pittsburgh compound B [PiB] and florbetapir) in cross-sectional and longitudinal studies.^{78,79} It has not been previously studied in a cohort of adults with DS and is a focus for our Neuroimaging Unit. The same tau (flortaucipir) and

TABLE 4 Magnetic resonance imaging (MRI) studies

MRI scan sequence	Purpose	Outcome measures
T1-weighted MPRAGE	Structural morphometry	Cortical thickness, regional volumetry
T2-weighted	Pathology detection/morphology	Intracranial volume
T2-FLAIR	Detection of ischemic disease	White matter hyperintensities—volume
T2 Star	Detection of hemorrhagic lesions	Presence/location of cerebral microbleeds
DTI	Integrity of white matter tissue	Fractional anisotropy
pASL ^a	Index of cerebral perfusion	Cerebral blood flow
Rs-fMRI	Functional connectivity	Network connectivity

^aThe ASL sequence has been acquired only at four NiAD sites.

Abbreviations: DTI, diffusion tensor imaging; FLAIR, x; NiAD, Neurodegeneration in Aging Down Syndrome; pASL, pulsed arterial spin labeling; Rs-fMRI, resting state functional magnetic resonance imaging.

TABLE 5 Positron emission tomography (PET) procedures

PET procedure	Targeted injected dose (10% tolerance)	Uptake period	PET acquisition period
[C-11]PIB	15 mCi ^a (555 MBq)	0 to 40 min	50 to 70 min
Florbetapir ([F-18]AV45)	10 mCi ^a (370 MBq)	0 to 40 min	50 to 70 min
Flortaucipir ([F-18]AV1451)	10 mCi ^a (370 MBq)	0 to 65 min	75 to 105 min
[F-18]FDG	5 mCi ^a (185 MBq)	0 to 20 min	30 to 60 min

^aMaximum injected dose is specific to each participating site as required by local restrictions.

glucose metabolism (fluorodeoxyglucose [FDG]) radiotracers have been used across sites to enable harmonization of these measures. Table 1 provides the time points for the administration of the MRI and PET scans and any differences across sites.

9 | OMICS STUDIES

The ABC-DS omic approaches have been designed to identify and quantitate potential biomarkers of AD progression and risk modifiers associated with genes (genomics), proteins (proteomics), and low molecular weight molecules (metabolomics) obtained from blood and CSF. The omics data are being used for two parallel lines of analyses. First, we are testing specific hypotheses using targeted analyses, wherein markers that have already been identified in previous research are being examined to validate those earlier findings, further distinguishing true associations from false discoveries. In addition, novel biomarkers may emerge in the future and warrant rapid evaluation in the ABC-DS cohort. Thus, in a parallel line of work, we are also employing untargeted approaches, wherein a far broader range of biomarkers is captured for discovery analysis. This combination of targeted and untargeted omics approaches allows us to investigate specific a priori identified targets in addition to providing broad, unbiased omics datasets to explore new hypotheses.

1. *Targeted Approaches*: Planned targeted omics studies have been driven by current knowledge in the field as well as previous findings

from members of our investigative team. We are targeting genes, proteins, and metabolites involved in relevant biological pathways including inflammation, oxidative stress, mitochondrial activation, and lipid and cellular energy metabolism.⁸⁰⁻⁸³

- a. *Targeted Genomics Analysis*: While collecting genome-wide association data (GWAS) using Illumina Infinium Global Screen Array version 2.0, a priori determined canonical pathways of inflammation, oxidative stress response, lipid and energy metabolism are being examined to identify candidate genes or regions related to AD risk and progression. We are using candidate gene analysis to evaluate single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) to assess genetic contribution from genes likely (or known) to be involved in AD risk in adults with DS, those with ADAD, as well as in the general population. In this rapidly evolving field, the candidate genes we are investigating include *APP*, *APOE*, *SOD1*, *S100β*, *SORL1*, as well as other genes that have been shown to be significantly associated with AD risk.⁸⁴
- b. *Targeted Proteomic Assays*: Given recent literature on the potential utility of novel ultra-sensitive measures of plasma neurofilament light chain (NfL), amyloid, and tau, the ABC-DS team is using an automated ultra-sensitive single molecule array (Simoa) technology (Quanterix Corp.) to measure plasma amyloid ($A\beta_{40}$, $A\beta_{42}$), total tau and NfL. Additional targeted ultra-sensitive assays will be added for future analyses. In addition to the Simoa assays, we are quantifying a 21-protein panel as described in the AD Blood Screen previously published by some of our team

TABLE 6 Targeted proteomic and metabolomic species

Targeted proteomics		Targeted metabolomics	
ECL platform	Simoa platform	Lipidizer	Polar metabolites
A2M	A β 1-40	Triacylglycerols (TAG) (502 lipids)	Amino acid synthesis, metabolism and degradation (50 metabolites)
B2M	A β 1-42	Diacylglycerols (DAG) (67 lipids)	Purine metabolism (25 metabolites)
CRP	T-tau	Free fatty acids (FFA) (28 lipids)	Pyrimidine biosynthesis (20 metabolites)
Eotaxin-3	NfL	Cholesterol esters (CE) (34 lipids)	Single carbon metabolism and folate metabolism (17 metabolites)
FABP3		Phosphatidylcholines (PC) (161 lipids)	Glycolysis, Gluconeogenesis and Pyruvate metabolism (12 metabolites)
Factor 7		Phosphatidylethanolamines (PE) (233 lipids)	Citric acid cycle (11 metabolites)
I-309		Lysophosphatidylcholines (LPC) (28 lipids)	Urea cycle (10 metabolites)
IL-10		Lysophosphatidylethanolamines (PE) (28 lipids)	Oxidative phosphorylation (7 metabolites)
IL-18		Sphingomyelins (16 lipids)	Sugar and amino sugar metabolism (7 metabolites)
IL-5		Ceramides (56 lipids)	Fatty acid metabolism (6 metabolites)
IL-6			Tryptophan metabolism (6 metabolites)
IL-7			Pentose phosphate pathway (5 metabolites)
PPY			Phenylalanine metabolism (5 metabolites)
SAA			Vitamin metabolism and biosynthesis (4 metabolites)
sICAM-1			Lipoic acid metabolism (2 metabolites)
sVCAM-1			Nicotinate and nicotinamide metabolism (2 metabolites)
TARC			Others (81 metabolites)
Tenacin-C			
TNF- α			
TPO			

Note: The 24-metabolite panel is derived from 24 lipids and metabolites collected in the Lipidizer and Polar Metabolite panels.

Abbreviations: A β , amyloid beta; A2M, alpha 2 macroglobulin; B2M, beta 2 microglobulin; CRP, c-reactive protein; ECL, electrochemiluminescence; FABP3, fatty acid binding protein; Factor 7, eotaxin3; factor VII; IL, I309; interleukin; NfL, neurofilament light chain; PPY, pancreatic polypeptide; SAA, serum amyloid A; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM1, circulating vascular cell adhesion molecule-1; TARC, thymus and activation regulated chemokine; TNF- α , tumor necrosis factor-alpha; TPO, thrombopoietin; T-tau, total tau.

members⁸⁵ using an automated (Hamilton Robotics) system and the multi-plex MSD platform (Meso Scale Diagnostics, LLC; see Table 6).

- c. *Targeted Metabolomics Assays:* We are using stable Isotope dilution, multiple reaction monitoring, mass spectrometry (SID-MRM-MS) for targeted quantitation of low molecular weight metabolites involved in lipid and cellular energy metabolism. Specifically, we are using the Lipidizer platform (SCIEX, Ltd) to quantitate \approx 1100 lipids and a bespoke 270 metabolite panel covering cellular energy and related metabolic pathways. These methods allow for the extraction of our published 24-metabolite panel⁸⁶ (see Table 6).
- d. *Targeted CSF Assays:* In CSF we are employing the state-of-the-art automated LUMIPULSE platform for immunoassay measurement of A β 40, A β 42, total tau, and phosphory-

lated tau181. We are using a microparticle-based immunoassay with Single Molecule Counting (SMC)TM utilizing antibodies developed in the laboratory of Dr. Jack Ladenson at Washington University to measure these emerging markers of neuronal injury and synaptic dysfunction; visinin-like protein 1 (VILIP1), neurogranin (Ng), and synaptosomal-associated alpha-synuclein (SNAP-25).⁸⁷ We are using standard commercial enzyme-linked immunosorbent assay (ELISA) to measure chitinase-3-like protein (YKL-40) (a marker of astrogliosis/neuroinflammation), NfL (a marker of axonal injury), and alpha-synuclein (aSN). The team plans to assay all CSF-based markers in blood using electrochemiluminescence (ECL) and single molecule array (SIMOA). Many of these assays in blood and CSF will also be measured in post-mortem brain tissue (see the Neuropathology Approaches section).

2. **Untargeted Approaches:** Untargeted omics analyses provide extensive, unbiased datasets that allow us and other investigators the chance to explore emerging or as-yet-unknown hypotheses for AD biomarkers in DS. We are not limiting the specific markers that are being quantified, but acknowledge that the technologies employed for each untargeted omic modality have limitations for the quality of the data, the scope of coverage, or the certainty of analyte identity. Untargeted approaches that we are currently using include the following:
 - a. **GWAS:** Untargeted genomic analysis is being conducted and considers the entire genome beyond AD candidate genes that have been previously identified in adults with DS, individuals with ADAD, and in the general population.
 - b. **Untargeted Proteomics Assays:** Untargeted (shotgun) proteomics are using dedicated MS equipment using standard protocols. Proteins are being analyzed using the highly sensitive Orbitrap Fusion Tribrid mass spectrometer in-line with a Dionex 3000 ultimate UHPLC using SPS-MS3-based tandem mass tag (TMT) method. Data are annotated using Proteome Discoverer 2.2 for database search and TMT reporter ions quantification.
 - c. **Untargeted Metabolomics Assays:** Untargeted metabolomics are being performed using ultra-performance liquid chromatography electro-spray ionization-quadrupole-time of flight-mass spectrometry (UPLC-ESI-QTOF-MS) based data acquisition following standard protocols. Data are acquired in centroid MS mode from 50 to 1200 m/z mass range for TOF-MS scanning as single injection per sample. Approximately 1900 features are identified by mass to charge ratio (m/z) in the positive ion mode and ≈ 2800 features in the negative ion mode for a total of ≈ 4700 features. Putative features identified by m/z and column retention time are expressed in relative abundance units.

10 | NEUROPATHOLOGY APPROACHES

A neuropathological diagnosis is essential for a final diagnosis for participants enrolled in ABC-DS and fulfills several important functions including (1) providing reports to families, (2) providing a final diagnosis to clinicians and researchers in ABC-DS, (3) obtaining *post-mortem* neuroimaging outcomes to relate to *ante-mortem* imaging and neuropathology, and (4) providing clinically characterized rapid autopsy brain tissue for neurobiological studies dedicated to DS that can be shared nationally and internationally. In ABC-DS, protocols for the procurement of brain tissue and dissection use well established methods used by Alzheimer's Disease Centers.

This protocol involves the fixation of half of the brain in either 10% formalin or 4% paraformaldehyde and obtaining frozen coronal sections of the left hemisphere. Prior to processing for a neuropathological diagnosis, the ABC-DS study will now include *post-mortem* neuroimaging of the fixed hemisphere to obtain T1 MPRAGE, SWI and T2 FLAIR sequences, if the participant had neuroimaging data prior to death. Neuropathologic examination is performed blinded to clinical information in accordance with current National Institute on Aging-

Alzheimer's Association (NIA-AA) guidelines.^{88,89} Final NP and data will be collected using the National Alzheimer Coordinating Center NP forms (NACC forms).⁹⁰ When the neuropathology diagnosis is completed, neuropathology slides will be scanned (Aperio Versa system) to acquire digital pathology images that can be shared and quantified using either or both positive pixel and the nuclear algorithms.^{91,92} Thus, neuropathology data that will be available include systematic neuropathology data, digital images, quantitative measures of AD pathology, *post-mortem* imaging, and rapid autopsy high quality tissue for research.

11 | BIOSTATISTICS AND DATA MANAGEMENT

Because the ABC-DS was originally developed as two separate programs, it was necessary to harmonize data across the program sites. This task took ≈ 8 months and has been largely successful. Because the two teams made significant investment in the original development of their databases, each has continued to use separate systems during the first few years of the project. However, variable definitions and values were established for all harmonized procedures so that the data could be compared across sites. The three ADDS sites have used the RED-cap system for data entry and the four NiAD sites have entered web-based data through the Alzheimer's Therapeutic Research Institute (ATRI). A transition is now underway in which all clinical, demographic, and project management functionality will be transferred to the ATRI system. Data (from the first assessment cycle) and research methodology is currently available to the scientific community through the LONI.

The Biostatistics and Data Management Core has had two major goals. The first was to develop a reliable and comprehensive database that could make ABC-DS findings readily available to both consortium investigators and to external researchers working in the field. This has included clinical and neuropsychological data, neuroimaging scans, and biological samples. In addition, the results from a range of analyses conducted by ABC-DS investigators (eg, proteomics, metabolomics, and genetic analyses; MRI findings) will also be shared with the greater research community. The second goal of the Core has been to provide direct support to ABC-DS investigators in the development of additional research questions and data analytics.

The biostatistical approach rests upon establishing a unified relational database across the key components of the project. As indicated above, ADDS/NiAD harmonization has now largely been achieved. The statistical approach involves an array of measures that can be combined in multivariate models for biomarker characterization to predict cognitive decline.

11.1 | Longitudinal data modeling

As a study examining the relationship between a range of potential biomarkers and functioning over time, longitudinal data modeling is an

TABLE 7 Comparison of biomarkers obtained for various Alzheimer's networks

Activity	ADNI	DIAN	ABC-DS
Amyloid PET tracer	Florbetapir (AV45) or florbetaben	Pittsburgh compound B (PiB)	Pittsburgh compound B (PiB) or florbetapir (AV45)
Tau PET tracer		[F-18]AV-1451 ^a	
FDG PET tracer		[F-18] FDG	
MRI sequences	T1-weighted MPRAGE, T2 FLAIR, T2 Star, DTI, pASL, Rs-fMRI		
CSF analysis	Univ. of Pennsylvania ADNI Biomarker Lab	Washington Univ. Fagan Biomarker Lab	Washington Univ. Fagan Biomarker Lab
Biofluid storage	NCRAD	Washington Univ. Fagan Biomarker Lab	NCRAD (plasma) Washington Univ. Fagan Biomarker Lab (CSF)
MRI QC		Univ. of Michigan Koeppel Lab (NiAD) or internally (ADDS)	
PET QC		Mayo Clinic Jack Lab (NiAD) or internally (ADDS)	
Data base	ATRI	Washington Univ.	ATRI
Data hosting	LONI	Washington Univ.	LONI

ADDS, Alzheimer's Disease Down Syndrome; ATR, Alzheimer Therapeutic Research Institute; CSF, cerebrospinal fluid; LONI, Laboratory of Neuro Imaging at USC; MRI, magnetic resonance imaging; NCRAD, The National Centralized Repository for Alzheimer's Disease and Related Dementias; PET, positron emission tomography; QC, quality control; Univ., university.

^aAlzheimer Disease Neuroimaging Initiative (ADNI) uses additional tau PET tracers as well.

important tool. By setting the outcome as one of the ATN biomarkers (A: amyloid, T: tau, N: neurodegeneration), linear mixed regression models⁹³⁻⁹⁵ have the feature to handle correlation in longitudinal data and will allow us to estimate not only covariate effects, but also biomarker changes/trajectories over time.

11.2 | Survival analysis

Some of the standard techniques such as the Kaplan-Meier estimator,⁹⁶ log-rank tests,⁹⁷ and Cox regression models,⁹⁸ will be employed to analyze survival data with right censoring when the outcome variable is time to MCI-DS or DS-AD. For those study participants with MCI-DS identified at baseline, only a proportion have the medical record of initial diagnosis date. To avoid sampling bias, the Cox model analysis will be extended and conducted based on those MCI-free participants at baseline, where the failure time data are known to be left-truncated and right-censored. Proper method approaches will be adopted to handle the additional sampling bias due to left truncation.^{99,100}

11.3 | ROC/AUC for biomarker evaluation

Conduct sensitivity and specificity analyses will be conducted for each of the ATN biomarkers using the following parameters: (1) the receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) for both binary outcome (MCI/no-MCI) defined at baseline and time-to-disease outcome (such as age at diagnosis of MCI), and

(2) time from MCI to dementia using well-established methods and software.¹⁰¹⁻¹⁰⁴ All resulting statistical models will include adjustment for site variability and procedures to ensure reproducibility of data as well as rigor of approach.

12 | ABC-DS PROTOCOL IN RELATION TO ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI) AND DOMINANTLY INHERITED ALZHEIMER NETWORK (DIAN)

The ABC-DS consortium is modeled, in part, after the ADNI and DIAN projects. Over the past 15 to 20 years, NIA has devoted considerable resources toward developing a wide range of common elements for NIA-funded AD research. Consistent with the ADNI/DIAN projects, the ABC-DS consortium has also included many of these elements in data acquisition and management pipelines (see Table 7). However, some differences exist across ADNI, DIAN, and ABC-DS, especially in terms of the frequency of visits. The DIAN protocol has visits at a 12-month interval for symptomatic participants and at a 24-month interval for asymptomatic participants. ADNI evaluates participants depending on their clinical status (cognitively normal [CN] participants are seen every other year, MCI-DS participants are evaluated yearly, and AD participants are followed annually for a total of three in-clinic visits and then followed by telephone interview). ABC-DS visits are conducted every 16 months, regardless of dementia status.

The ADNI and DIAN protocols are developed around cores. The ABC-DS team consists of cores focused on omics (genetic, CSF,

proteomics, and metabolomics), neuroimaging (tau, amyloid, and FDG PET; MRI), data, administrative, outreach, and clinical (neuropsychological assessment, caregiver questionnaires, medical and neurological evaluations) and include assessments that are similar to ADNI/DIAN protocols. Of necessity, the clinical measures represent the area of greatest difference between the ABC-DS and ADNI/DIAN, as adults with DS are unable to complete many of the standard AD neuropsychological assessment tools (or would score within the MCI/AD range on these tools). As detailed earlier, the same domains are assessed, but with tools that limit floor effects for the DS population. Similarly, DS-specific caregiver reporting tools are used to address similar domains covered in the ADNI/DIAN protocols (eg, adaptive functioning, AD symptoms, psychiatric symptoms). As a result, we anticipate that many of the ABC-DS findings will be able to be compared and contrasted with the ADNI and DIAN populations. Finally, both the ADNI and DIAN networks have been in existence for considerably longer than the ABC-DS (16 years and 12 years, respectively). Hence, both projects have been able to follow their participants for more extended periods of time and have been able to document early changes leading to AD in a far greater percentage of their cohorts.

We believe that results from ABC-DS will inform our understanding of the effects of known genetic mutations that lead to AD. Results from both ABC-DS and DIAN may be models for the development of LOAD, which is currently being evaluated by ADNI. Furthermore, comparisons between ABC-DS and DIAN will not only help elucidate the effects of gene dosage on development of AD, but also will serve as cohorts to assist in evaluating potential therapies for AD.

13 | CHALLENGES

Because ABC-DS was created from the integration of two separate programs, it was to be expected that some methodological differences would be present. These included some differences in selected neuropsychological assessment tools, different data coding systems, different acquisition sequences for MRI acquisition, and different ligands for amyloid PET imaging. Many of the differences were based on the rich trove of legacy data and experiences amassed by the many different ABC-DS investigators, some of whom have been working in this area for several decades. Thus, a major challenge has been data harmonization, exacerbated by the huge volume and diversity of data across participating institutions and longitudinal time epochs. The ensuing protocol harmonization effort has been quite successful but not perfect. Success can be claimed for harmonizing the medical evaluations, most of the neuropsychological testing, omics determinations, and many aspects of neuroimaging. As indicated above, differences remain in some aspects of site-specific neuroimaging due to local ligand availability and some other factors. The creation of a Centiloid scale for DS to harmonize data across different amyloid ligands is a bold step to address this challenge.

There have also been challenges that may be inherent to conducting research with adults with DS and that are common to longitudinal studies in general. Recruitment of participants, especially of minorities, has

been a continuing challenge to most ABC-DS sites. This could impact the representativeness of the study cohort to the overall population of adults with DS. Participant burden (including multiple scans and extensive neuropsychological assessment batteries) is always a concern and can challenge staff ability to consistently collect all planned measures and can adversely impact study retention. Many participants reside in community residential programs, resulting in frequent changes in staff across visits (with different “reporters” at each visit). The 5-year study span naturally limits the number of participants transitioning in status from CS to MCI-DS and to dementia within the limited duration of follow-up. Analysis issues arise, such as the proper handling of missing data (both within study visits and due to participant drop-out). There also remains a challenge in obtaining agreement for *post-mortem* follow-up and in making such arrangements, should the opportunity present itself. Finally, it is recognized that our consensus determinations are inherently imperfect, especially in the accurate classification of those individuals with possible MCI-DS.

14 | FUTURE PLANS

Future plans for ABC-DS are directed toward implementing a single core protocol for all sites with follow-up visits continuing at 16-month intervals. The number of enrolling sites is being expanded to add the University of Kentucky and a new enrollment target of 550 individuals with DS has been set. A highly coordinated effort will be put into place to enroll greater numbers of individuals from under-represented minority groups (primarily Hispanic and African American). The major programmatic aims will be to continue examination of the factors that modify risk for AD in DS, to determine the genetic and biomarker profile that modify risks within this high-risk population, to identify biomarkers of AD progression that can inform diagnostic decisions in clinical practice, and to generate a multi-tiered approach to indicate the most favorable indications for successful clinical trial intervention.

Future integration of ABC-DS data with those of other national and international initiatives, such as the Horizon 21 protocol in Europe, hold even greater promise for biomarker discovery and for supporting clinical trials to prevent or treat AD in DS. To this end, the Consortium has begun collaborating with two other programs: (1) the NACC to develop a DS module that will include a harmonized subset of the measures used in the ABC-DS protocol, and (2) the Alzheimer’s Clinical Trial Consortium for Down syndrome (ACTC-DS), which provides the infrastructure and support to bring researchers together to conduct clinical trials for AD in DS across 15 international sites.

The ABC-DS is poised to have a substantial impact on our ability to characterize AD in DS, both by identifying those biomarkers that clarify risk for transition from cognitive stability to early clinical progression to AD and in the identification of biomarkers of preclinical AD progression. Following the lead of outstanding established AD networks such as ADNI and DIAN, ABC-DS will also make a significant contribution to national efforts to improve the quality of life of our aging population through advancing progress toward effective prevention and treatment of AD. We expect to provide exciting new leads into

treatment targets for AD both for people with DS and, by translation, to all people with or who will develop AD.

ACKNOWLEDGMENTS

The Alzheimer's Biomarkers Consortium—Down Syndrome (ABC-DS) is funded by the [National Institute on Aging](#) and the Eunice Kennedy Shriver National Institute for Child Health and Human Development (U01 AG051406 and U01 AG051412). The work contained in this publication was also supported through the following National Institutes of Health Programs: The Alzheimer's Disease Research Centers Program (P50 AG008702, P30 AG062421, P50 AG16537, P50 AG005133, P50 AG005681, and P30 AG062715), the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers Program (U54 HD090256 and U54 HD087011), the National Centers for Advancing Translational Sciences (UL1TR001873, UL1 TR00237, UL1 TR001414, UL1 TR001857, UL1 TR002345), the National Centralized Repository for Alzheimer Disease and Related Dementias (U24 AG021886), and DS-Connect (The Down Syndrome Registry) supported by the [Eunice Kennedy Shriver National Institute of Child Health and Human Development](#).

The authors thank the ABC-DS study participants (adults with Down syndrome and their siblings), their families and care providers, and the ABC-DS research and support staff for their invaluable contributions to this study. Finally, the authors thank the staff contributing their many hours of support to this work, including Olga Del Rosario, Eric Doran, Leslie Dunn, Masha Glukovskaya, Monika Grigoroova, Courtney Jordan, Renee Makuch, Deborah Pang, Joni Vander Bilt, Liz Westerhaus, and Cathy Wolfe. The content is the sole responsibility of the authors and does not necessarily represent the official views of the NIH.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Handen BL, Lott IT, Christian BT, et al. The Alzheimer's Biomarker Consortium-Down Syndrome: Rationale and methodology. *Alzheimer's Dement.* 2020;12:e12065. <https://doi.org/10.1002/dad2.12065>