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RESEARCH ARTICLE

Validity of one-time assessments for identifying prodromal Alzheimer's disease in adults with Down syndrome

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Abstract

Introduction: New Alzheimer's disease (AD) treatments have created an urgent need for accurate early diagnosis of high-risk adults with Down syndrome (DS), distinguishing prodromal DS-AD symptoms from lifelong cognitive impairments. Often, clinicians will need to evaluate dementia status during a single assessment, and here we describe empirically supported methods effective under such circumstances.

Methods: Archived data collected between 1987 and 2017 included longitudinal findings for 144 individuals maintaining cognitive stability and 126 developing prodromal DS-AD. Response operating characteristic analyses compared groups, defined by the presence/absence of prodromal DS-AD, for a single assessment.

Results: Groups differed on all measures without adjusting for developmental history, $0.717 <$ areas under the curve < 0.859, $Ps < 0.0001$. The balance between sensitivity and specificity improved slightly when developmental histories were considered.

Discussion: The present study demonstrated that one-time assessments can inform clinical judgments when diagnosing adults at risk for DS-AD. Knowledge of developmental history is valuable but non-essential.

KEYWORDS
Alzheimer's disease, Down syndrome, mild cognitive impairment, prodromal Alzheimer's disease

Highlights

- Non-overlapping distributions were observed for preclinical and prodromal Alzheimer's disease (AD) groups.
- Receiver operating characteristic area under the curve analyses were in the acceptable to excellent range for all measures.
- Performance was sensitive to both the severity of intellectual disability and the stage of Down syndrome-AD progression.

Sharon J. Krinsky-McHale and Wayne Silverman have contributed equally to this manuscript.

- Episodic memory tests were sensitive to the transition from preclinical to prodromal AD.
- Performance results at a single time point can inform dementia status decisions.

1 | INTRODUCTION

The increased risk for Alzheimer's disease (AD) in adults with Down syndrome (DS; DS-AD) has attracted considerable interest, due to two distinct but interrelated reasons. First, DS-AD has become a public health concern, with an affected population in the United States at ≈ 300,000 based on estimates of birth incidence and life expectancy.[1] This constitutes the largest population of high-risk individuals due to an identifiable genetic cause.[2] Second, having a large number of adults sharing a primary genetic driver of risk, in this case triplication of the gene coding for amyloid precursor protein (*APP*) and its consequent overexpression, provides unique opportunities for expanding our understanding of AD pathogenesis,[2] both specific to *APP* overexpression and more broadly. That knowledge can suggest promising directions for the discovery of disease-modifying treatments and diagnostic biomarkers capable of tracking progression and predicting risk with greater precision.

Valid diagnosis is an obvious key concern, especially during early stages. The subtle declines that characterize prodromal AD can be difficult enough to recognize in adults with neurotypical developmental histories,[3] but they become even more difficult to diagnose when they occur against a background of pre-existing cognitive impairments characteristic of the "Down syndrome cognitive phenotype".[4]

The development of promising disease-modifying treatments, some already approved for use by authorized prescribers and some in late-stage clinical trials, makes clinical classification of DS-AD–related status a pressing task. These agents typically target individuals at early stages (individuals with a positive amyloid positron emission tomography [PET] scan, along with a diagnosis of prodromal AD), and therefore, validated methods and suitable outcome measures are needed for adults with DS who might benefit from these treatments.

Fortunately, empirically supported methods able to distinguish between preclinical and prodromal DS-AD (mild cognitive impairment [MCI]-DS), have recently been described. [2,5–8] These include both informant questionnaires[9–11] and direct tests of cognition.[12,13] Krinsky-McHale et al.[12] demonstrated that multiple measures within a longitudinal assessment battery showed stability for adults with DS maintaining their preclinical DS-AD status while showing declines with the onset of prodromal DS-AD (see Aschenbrenner et al.)[5]

1.1 | Objectives

Krinsky-McHale et al.[12] identified the magnitude of change in performance occurring with the onset of prodromal DS-AD rather than in the determination of differences between the performance of affected and unaffected individuals at any single point in time, similar to the focus of other groups.[5,7,8] Recognizing that clinicians providing direct care to adults with DS will invariably be asked to make diagnoses with limited or no concrete information regarding either developmental history or recent aging-related profiles of cognitive stability or decline, our first objective was to reexamine those measures found to change significantly with the onset of prodromal DS-AD to determine whether these same methods can inform staging of DS-AD based on a single evaluation.

A second objective was to understand the extent to which having objective knowledge about histories of lifelong impairments contributes to diagnostic confidence or the extent to which the absence of such information increases diagnostic uncertainty.

2 | METHODS

2.1 | Participants

The present analyses capitalized on the rich set of archived data described by Krinsky-McHale et al.,[12] collected from 1987 to 2017. While the database included information on > 600 adults with DS ranging in age from 30 to 82 years at the time of their enrollment, the present analyses only included individuals who have either maintained an overall profile of cognitive stability (CS/preclinical DS-AD) or developed prodromal DS-AD (incident MCI-DS) at some time after a preclinical baseline. Further inclusion criteria for these analyses were: (1) phenotype or genetic diagnosis consistent with DS; (2) ≥ 30 years of age at baseline; (3) vision and hearing sufficient for compliance with testing procedures; (4) documentation of a historical Stanford–Binet IQ (or equivalent) ≥ 25; (5) a determination at baseline of preclinical DS-AD status; (6) longitudinal follow-up for at least 18 months; (7) absence of "complicating" or co-occurring conditions that could mimic prodromal DS-AD (e.g., severe illness or traumatic life events); (8) provision of consent by the participant, if they were determined to have sufficient capacity and/or consent from a legally authorized representative; and (9) communication ability sufficient to assent (note: an individual could be determined to lack capacity to consent but still have capacity to assent).

Figure 1 presents a flowchart of participants who were considered for inclusion in these analyses. Table 1 provides an overall description of this sample, stratified by AD clinical status and premorbid IQ group. (It is important to note that IQ data were taken from medical records that extended back over many years, and various forms of these tests were used. We generated a "consensus Full Scale IQ (FSIQ)" for each participant, using either the results actually obtained or, in

RESEARCH IN CONTEXT

1. **Systematic Review**: Literature on methods for detecting preclinical and prodromal Alzheimer's disease (AD) in adults with Down syndrome (DS) was reviewed using traditional sources (e.g., PubMed and related citations). We describe empirically supported methods that address this issue, which are crucially important now that promising treatments are close at hand. The relevant citations are appropriately referenced.
2. **Interpretation**: One-time performance comparing individuals showing cognitive stability or declines, characteristic of prodromal DS-AD, showed that our measures can inform diagnostic decision making about dementia status with good sensitivity and specificity. Consistent with our previous findings, episodic memory tests were highly sensitive to dementia progression.
3. **Future Directions**: Future studies must validate whether these methods are (a) useful as tools in discovery studies for biomarkers, (b) able to track the transition of clinical status from preclinical to prodromal AD longitudinally, and (c) have potential as an outcome measure in clinical trials.

cases in which data were only available from the Wechsler Adult Intelligence Scale,[14] an estimated "Stanford–Binet equivalent" calculated to address the compelling evidence that the various editions of the Wechsler Adult Intelligence Scale generate substantially higher IQs for this population compared to other assessments.[15])

2.2 | Available data

Specific components of the assessment battery were: (1) review of medical charts for determination of basic demographic information, developmental history (including past IQ testing), and medical diagnoses and medication histories with particular emphasis on the presence of conditions that would complicate interpretation of changes in functional abilities and cognitive performance (e.g., acute illness) or suggest the presence of age-related neuropathology in addition to AD (e.g., stroke, Parkinson's disease); (2) interviews with knowledgeable informants using questionnaires for determination of functional abilities, neuropsychiatric concerns, the presence of any recent stressful life events that might account for, but are unrelated, to declines otherwise indicative of AD-related clinical progression, and (3) direct one-on-one assessment focused on cognitive domains likely to be sensitive to DS-AD–related clinical progression, including onset of its prodromal stage. Full details and descriptions of the specific components of this battery have been provided in previous publications (e.g., Krinsky-McHale et al.,[12] Silverman et al.,[16] and Zigman et al.[17]). For the present study, we did not analyze the full assessment battery; rather, we selected the measures that have shown the most promise for use as outcome measures (see Appendix S1 in supporting information). These assessments were completed at baseline and at ≈ 18-month intervals, with a maximum of eight follow-up evaluations.

Analyses were conducted for performance during a single follow-up evaluation. For individuals maintaining cognitive stability, we selected their second evaluation, given their status was confirmed at that time point. For individuals who transitioned from preclinical to prodromal DS-AD, we selected the first time performance profiles that showed changes consistent with MCI-DS. Of critical importance, ratings of clinical status at these follow-ups were based on profiles of stability for the first group and declines for the second, rather than on any one-time measure of performance. Although the assessment methods were the same, the metrics used for group assignment and quantification of performance were distinct, negating concerns associated with possible circularity.

2.3 | Consensus determination of clinical status

After completion of a test cycle, the clinical status of participants was rated during consensus conferences, based upon consideration of all information available. Clinical status was classified as: (1) preclinical DS-AD (also referred to as cognitively stable), indicating with reasonable certainty that significant impairment was absent; (2) prodromal DS-AD (also referred to as MCI-DS), indicating that there was some indication of mild cognitive and/or functional decline but importantly, the observed change(s) did not meet dementia criteria; (3) DS-AD, indicating with reasonable confidence that dementia was present based upon substantial decline over time; (4) status uncertain due to complications, indicating that the criteria for dementia had been met, but symptoms might be caused by some other concern, usually a medical condition unrelated to a dementing disorder. A classification rating was made based upon the majority opinion of investigators. The present analyses only included cases that were preclinical at baseline and either maintained their preclinical status or developed prodromal DS-AD at follow-up.

2.4 | Statistical analyses

Analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS, version 26.0). Participant characteristics and test scores were analyzed using descriptive statistics, with overall differences between clinically defined groups assessed using a series of univariate analyses of covariance (ANCOVA). Mean, standard deviation, and minimum and maximum values and number of cases were calculated for continuous variables. A Student *t* test was used to examine between-group differences.

Receiver operating characteristic (ROC) analyses were used to examine the degree to which distributions of scores overlapped for groups defined by their clinical status. The "area under the curve (AUC)" effectively summarized the overall diagnostic accuracy of the tests.

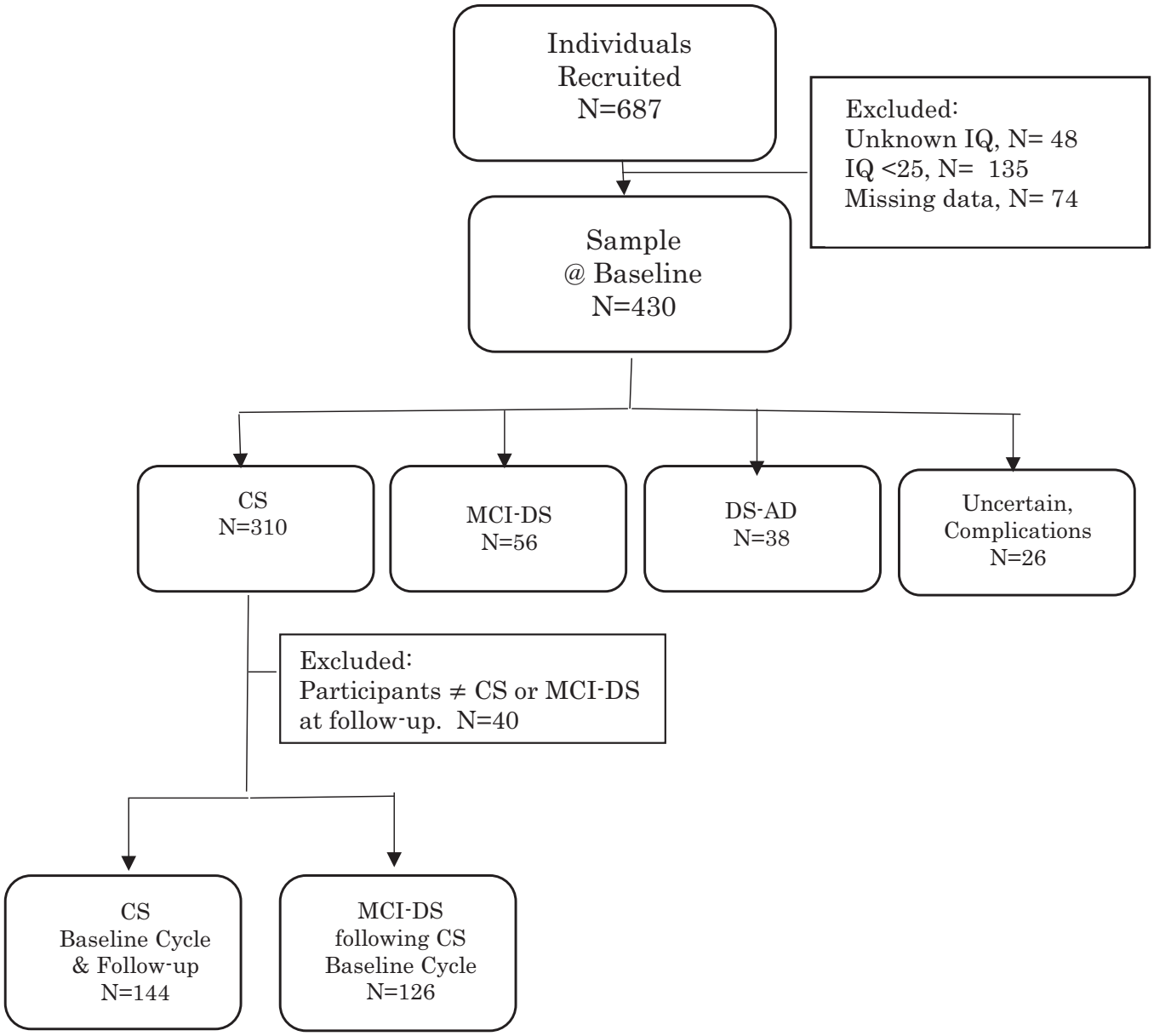

FIGURE 1 Flowchart of study participants focusing on the determination of the final sample. AD, Alzheimer's disease; CS, cognitively stable; DS, Down syndrome; MCI, mild cognitive impairment

3 | RESULTS

3.1 | Study population

Table 1 presents participant characteristics for groups stratified by diagnostic status and IQ group. Premorbid IQ was comparable for the two groups, with a majority in the moderate ID range. At baseline, participants who subsequently progressed to prodromal DS-AD were older compared to those that maintained their preclinical status ($t[268] = 9.2$, $P < 0.001$, Cohen $d' = 1.1$).

An initial set of analyses used a series of ANCOVAs to examine overall group differences. Each measure of performance served as a dependent variable; sex and diagnostic status were between-subjects variables, and FSIQ and age were covariates. Table 2 presents summary statistics stratified by diagnostic status and IQ group. As expected, performance on all the measures between the males and females was comparable; all measures were strongly associated with premorbid FSIQ, and performance differed systematically across diagnostic status groups.

3.2 | ROC analyses

ROC analyses provide quantitative measures of the degree of overlap in score distributions between groups (Table 3). When the probability of a true positive (sensitivity), in this case the correct identification of an individual with prodromal DS-AD, and the probability of a false positive (or 1 – specificity), in this case the diagnosis of a

TABLE 1 Participant characteristics for subsample stratified by AD clinical status classification and premorbid IQ group.

	Preclinical DS-AD ($N = 144$)	Prodromal DS-AD ($N = 126$)	$X^2(270)$ *or* $t(268)$, p, effect size
Sex			
Total sample *N* (%)			9.6, $P = 0.002$, Φ0.19
Male	35 (25%)	54 (42.9%)	
Female	108 (75%)	72 (57.1%)	
Stratified by IQ group *N* (%)			
25 ≤ IQ ≤ 34			
Males	11 (26%)	16 (38.1)	
Females	32 (74%)	26 ()61.9	
35 ≤ IQ ≤ 44			
Males	21 (26.6)	34 (47.2)	
Females	58 (73.4)	38 (52.8)	
45 ≤ IQ ≤ 68			
Males	4 (18.2)	4 (33.3)	
Females	18 (81.8)	8 (66.7)	
Premorbid IQ			
Total sample mean,(SD), [range]	38.1 (6.5) [25–59]	36.6 (6.5) [25–68]	1.9, ns
Stratified by IQ group *N*, mean (SD) [range]			
25 ≤ IQ ≤ 34	43, 31.1 (2.8) [25–34]	42, 30.1 (3.1) [25–34]	
35 ≤ IQ ≤ 44	79, 38.8 (2.8) [35–44]	72, 38.3 (2.9) [35–44]	
45 ≤ IQ ≤ 68	22, 49.0 (3.9) [45–59]	11, 48.9 (6.4) [45–68]	
Age (years) at baseline cycle			
Total sample mean (SD) [range]	47.9 (7.0) [30.5–66.3]	49.4 (7.1) [31.9–68.1]	9.2, $P \leq 0.001$, Cohen's $d' = 1.1$
Stratified by IQ group *N*, mean (SD) [range]			
25 ≤ IQ ≤ 34	43,49.2 (6.6) [32.3–62.8]	42, 55.7 (5.2) [44.4–68.9]	
35 ≤ IQ ≤ 44	79, 47.9 (7.1) [30.5–66.3]	72, 54.1 (5.1) [46.4–72.6]	
45 ≤ IQ ≤ 68	22, 45.7 (7.1) [31.5–57.9]	11, 45.7 (7.1) [31.5–57.9]	
Age (years) at follow-up cycle[1]			
Total sample *N*, mean (SD) [range]	49.5 (7.1) [31.9–68.1]	56.8 (5.3) [46.1–74.6]	9.4, $P \leq 0.001$, Cohen $d' = 1.1$
Stratified by IQ group			
25 ≤ IQ ≤ 34	43, 50.7 (6.7) [33.9–64.6]	42, 57.6 (5.3) [46.1–70.2]	
35 ≤ IQ ≤ 44	79, 49.5 (49.5) [30.5–66.3]	72, 55.9 (5.2) [47.9–74.6]	
45 ≤ IQ ≤ 68	22, 47.4 (7.3) [33.1–59.4]	11, 47.4 (7.3) [33.1-59.4]	
Mean time (years) to follow-up (interval between baseline cycle and follow up cycle)			2.0, $p = 0.050$, Cohen $d' = 0.24$
Total sample *N*, mean (SD) [range]	1.6 (0.61) [.9–5.3] 50.7	1.8 (1.02) [1.1–5.9]	
Stratified by IQ group			
25 ≤ IQ ≤ 34	43, 1.6 (0.36) [1.1–3.4]	42, 1.8 (1.0) [1.1–5.8]	
35 ≤ IQ ≤ 44	79, 1.6 (0.6) [.9–5.3]	72, 1.8 (1.0) [1.1–5.9]	
45 ≤ IQ ≤ 68	22, 1.7 (0.8) [1.2–5.2]	11, 1.7 (1.0) [1.1–5.0]	
Mean number of cycles completed			
Total sample *N*, mean (SD) [range]	4 (1.9) [2–9]	6 (2.0) [2–9]	6.7, $p \leq 0.001$, Cohen $d' = 0.82$
Stratified by IQ group			
25 ≤ IQ ≤ 34	43, 4.1 (1.7) [2–8]	42, 5.7 (2.4) [2–9]	
35 ≤ IQ ≤ 44	79, 4.1 (2.1) [2–9]	72, 5.5 (1.8) [2–9]	
45 ≤ IQ ≤ 68	22,3.9 (1.8) [2–9]	11, 6.5 (1.7) [3–9]	

Note: For participants with prodromal DS-AD at the follow-up test cycle, this variable is the average age at diagnosis.
Abbreviations: DS-AD, Down syndrome-Alzheimer's disease; SD, standard deviation.

TABLE 2 Sample size, mean, standard deviation, minimum/maximum score [in brackets] comparing performance of cases in the preclinical stage of DS-AD (maintaining cognitive stability) and those developing incident prodromal DS-AD (MCI-DS).

Measure (maximum score)	Preclinical DS-AD	Prodromal DS-AD	Diagnostic status ANCOVA
ABSI-T (maximum score = 280)			
Total sample *N*, mean (SD) [range]	134, 214.6 (32.3) [130–273]	126, 185.4 (31.8) [82–256]	$F(1,256) = 17.3^1, \eta_p^2 = 0.06$
Stratified by IQ group			
25 ≤ IQ ≤ 34	40, 200.6 (28.8) [138–264]	42, 167.0 (31.5) [82–218]	
35 ≤ IQ ≤ 44	72, 214.0 (31.4) [130–273]	72, 191.6 (26.8) [113–252]	
45 ≤ IQ ≤ 68	22, 242.2 (23.1) [194–273]	12, 212 (28.5) [169–256]	
DLD-SCS (maximum score = 50)			
Total sample *N*, mean (SD) [range]	143, 6.3 (6.7) [0–33]	122, 11.4 (6.78) [0–35]	$F(1,261) = 13.0^1, \eta_p^2 = 0.11$
Stratified by IQ group			
25 ≤ IQ ≤ 34	43, 9.5 (6.3) [0–29]	40, 3.6 (7.3) [0–29]	
35 ≤ IQ ≤ 44	78, 5.7 (6.6) [0–33]	70, 10.4 (6.1) [0–27]	
45 ≤ IQ ≤ 68	22, 2.4 (4.9) [0–20]	12, 9.6 (7.4) [1–21]	
DSMSEM-T (maximum score = 24)			
Total sample *N*, mean (SD) [range]	142, 14.6 (4.88) [1–23]	123, 7.58 (34.16) [0–18]	$F(1,261) = 75.3^1, \eta_p^2 = 0.22$
Stratified by IQ group			
25 ≤ IQ ≤ 34	42,13.4 (5.9) [1–23]	41, 6.3 (3.9) [0–15]	
35 ≤ IQ ≤ 44	78,14.8 (4.6) [1–23]	70,8.2 (4.1) [1–17]	
45 ≤ IQ ≤ 68	22, 16.4 (2.7) [11–21]	12, 8.4 (6.4) [2–18]	
DSMSE-T (maximum score = 79)			
Total sample *N*, mean (SD) [range]	142, 55.3 (13.3) [0–77]	123, 41.8 (12.0) [9–71.5]	$F(1262) = 36.1^1, \eta_p^2 = 0.12$
Stratified by IQ group			
25 ≤ IQ ≤ 34	43, 47.5 (16.4) [0–74.5]	41, 35.2 (10.9) [9–58]	
35 ≤ IQ ≤ 44	78, 56.6 (10.1) [22–77]	70, 44.8 (10.0) [20–71.5]	
45 ≤ IQ ≤ 68	22, 65.4 (7.4) [44–75]	12, 46.6 (17.3) [16–66]	
BLOCK-T (maximum score = 74)			$F(1258) = 33.2^1, \eta_p^2 = 0.11$
Total sample *N*, Mean (SD) [range]	141, 17	121, 7.9 (6.8) [0-32]	
Stratified by IQ group			
25 ≤ IQ ≤ 34	50, 11.6 (8.1) [0–31]	50, 5.0 (4.4) [0–21]	
35 ≤ IQ ≤ 44	82, 19.1 (10.8) [0–59]	699.4 (7.2) [0–32]	
45 ≤ IQ ≤ 68	9, 31.7 (5.6) [24–40]	2, 14.5 (20.5) [0–29]	
CF-T (maximum score = 74)	143, 7.6 (4.0) [0–18]	1224.5 (3.2) [0–13]	$F(1,261) = 27.0^1, \eta_p^2 = 0.10$
Total sample *N*, mean (SD) [range]	143, 7.6 (4.0) [0-18]	122, 4.5 (3.2) [0-13]	
Stratified by IQ group			
25 ≤ IQ ≤ 34	50, 6.3 (3.5) [0–14]	49, 3.8 (2.9) [0–10]	
35 ≤ IQ ≤ 44	84, 8.1 (4.1) [0–18]	71, 4.8 (3.3) [0–12]	
45 ≤ IQ ≤ 68	9, 11.0 (4.0) [5–18]	2, 10.0 (4.2) [7–13]	
MMMSE-DS-T (maximum score = 74)			
Total sample *N*, mean (SD) [range]	14,258.3 (15.18) [0–74]	11,448.5 (14.85) [0–73]	$F(1, 252) = 9.8^2, \eta_p^2 = 0.04$
Stratified by IQ group			
25 ≤ IQ ≤ 34	4249.2 (16.3) [0–74]	3638.6 (15.0) [0–63]	
35 ≤ IQ ≤ 44	7860.3 (13.3) [0–74]	6653.1 (10.2) [23–69]	
45 ≤ IQ ≤ 68	2268.7 (9.2) [43–74]	1253.3 (21.5) [0–73]	

(Continues)

TABLE 2 (Continued)

Measure (maximum score)	Preclinical DS-AD	Prodromal DS-AD	Diagnostic status ANCOVA
MSRT-TR (maximum score = 48)			
Total sample *N*, mean (SD) [range]	142, 29.7 (12.4) [0–48]	119, 15.3 (9.4) [0–14]	$F(1,257) = 52.4^1, \eta_p^2 = 0.17$
Stratified by IQ group			
25 ≤ IQ ≤ 34	43, 23.2 (13.6) [0–47]	40, 13.1 (8.6) [0–40]	
35 ≤ IQ ≤ 44	77, 31.6 (11.5) [1–48]	69, 16.4 (9.1) [0–41]	
45 ≤ IQ ≤ 68	22, 36.7 (8.0) [23–47]	10, 16.7 (13.3) [0–41]	

Abbreviations: ABSI-T, American Association on Mental Deficiency Adaptive Behavior Scale, Part I-Total Score; AD, Alzheimer's disease; ANCOVA, analyses of covariance; BLOCK-T, Block Design subtest-Total Score; CF-T, Category Fluency Test-Total Score; DLD-SCS, Dementia Questionnaire for People with Learning Disabilities, Sum of Cognitive Scores; DS, Down syndrome; DSMSE-T, Down Syndrome Mental Status Examination-Total Memory Score; DSMSEM-T, Down Syndrome Mental Status Examination-Total Score; MCI, mild cognitive impairment; MMMSE-DS-T, Modified Mini-Mental State Examination-Down Syndrome-Total Score; MSRT-TR, Modified Selective Reminding Test-Total Recall Score; SD, standard deviation.

TABLE 3 Summary of response operating characteristic analyses from the follow-up test cycle comparing performance of cases in the preclinical stage of DS-AD (maintaining cognitive stability) and those with prodromal DS-AD (incident MCI-DS).

Measure	AUC (SE)	*P*	95% confidence interval
ABSI-T	**0**.745 (0.030)	<0.00001	0.685–0.805
DLD-SCS	0.726 (0.031)	<0.00001	0.665–0.786
DSMSEM-T	0.859 (0.023)	<0.00001	0.814–0.904
DSMSE-T	0.793 (0.028)	<0.00001	0.736–0.847
BLOCK-T	0.774 (0.029)	<0.00001	0.717–0.831
CF-T	0.728 (0.031)	<0.00001	0.667–0.788
MMMSE-DS-T	0.717 (0.032)	<0.00001	0.654–0.779
MSRT-TR	0.833 (0.026)	<0.000001	0.782–0.885

Abbreviations: ABSI-T, American Association on Mental Deficiency Adaptive Behavior Scale, Part I-Total Score; AD, AUC, area under the curve; BLOCK-T, Block Design subtest-Total Score; CF-T, Category Fluency Test-Total Score; DLD-SCS, Dementia Questionnaire for People with Learning Disabilities, Sum of Cognitive Scores; DS, Down syndrome; DSMSE-M, Down Syndrome Mental Status Examination-Memory Score; DSMSE-T, Down Syndrome Mental Status Examination-Total Score; MCI, mild cognitive impairment; MMMSE-DS-T, Modified Mini-Mental State Examination-Down Syndrome-Total Score; MSRT-TR, Modified Selective Reminding Test-Total Recall Score; SE, standard error.

preclinical individual with prodromal DS-AD, are plotted across the entire range of possible scores, an AUC of 0 would indicate a perfectly inaccurate test and an AUC of 1.0 would indicate a completely accurate test. AUCs ranged from 0.717 for the Modified Mini-Mental State Examination-Total Score (MMMSE-T) to 0.859 for the memory summary score from the Down Syndrome Mental Status Examination-Total Score (DSMSEM-T). As expected, the total recall score from the Modified Selective Reminding Test-Total Recall Score (MSRT-TR) also had an AUC > 0.8, confirming that tests of episodic memory were most sensitive to the transition from preclinical to prodromal DS-AD.

Routine practice for ROC analyses typically identifies a single classification criterion that strikes the best balance between sensitivity and specificity, with AUCs ≥ 0.7; the expectation would be that a single score is associated with sensitivity and specificity values ≥ 0.7. However, consideration of a broader range of scores can be more informative in clinical practice than any single score. Raising the classification criterion will decrease specificity but rule out prodromal DS-AD with increased confidence. Likewise, lowering the scoring criterion will present problems for the interpretation of scores above that criterion but will increase confidence in interpretation for cases failing to meet that criterion

Table 4 provides an expanded description of the trade-offs between sensitivity and specificity for the analyzed measures. The summary findings for the DSMSEM-T are illustrative of how the trade-off between sensitivity and specificity operated. A score of 19 had a sensitivity of 1.0, indicating that no individual with prodromal DS-AD achieved that score (or better) in contrast to 23% of individuals with preclinical DS-AD. At the other extreme, 20% of individuals with prodromal DS-AD scored < 4, while that was the case for only 2% of the group with preclinical DS-AD. Intermediate scores provided intermediate trade-offs between sensitivity and specificity, with a criterion of 12 providing values of 0.80 and 0.79, respectively. Stated another way, an estimated four out of five adults with prodromal DS-AD will score < 12 compared to only one in five that are preclinical DS-AD.

Given that performance was expected to be sensitive to the severity of ID as well as prodromal DS-AD, such large AUCs obtained for unadjusted scores were unexpected. To verify that performance for these methods was indeed sensitive to variation in severity of ID, findings for individuals within the preclinical group at the follow-up test cycle were correlated with IQ. Results verified that expected relationships were indeed significant, $0.23 \leq rs \leq 0.58$ (see Appendix S2 in supporting information for the correlation between IQ and each measure). These correlations suggest that trade-offs between sensitivity and specificity for specific scores should vary somewhat depending on ID severity, with false positive findings increasingly more likely with lower IQs, and false negative findings increasingly more likely with higher IQs. These possibilities were confirmed descriptively by relating sensitivity to specificity across the range of possible scores for subgroups within three ranges of IQ: (1) 25 to 34, (2) 35 to 44, and (3) 45 to 68. Table 5 presents these findings.

TABLE 4 Sensitivities of specific scores on selected measures of performance along with corresponding specificities.

	Sensitivity							
Measure	**1**	**0.95**	**0.9**	**0.8**	**0.7**	**0.6**	**0.2**	**0.1**
ABSI-T								
Score	259	233	220	211	205	196	165	144
Specificity	0.12	0.32	0.48	0.61	0.64	0.72	0.93	0.98
DLD-SCS								
Score	–	2	4	6	7	9	18	21
Specificity	–	0.29	0.45	0.56	0.61	0.76	0.9	0.97
DSMSEM-T								
Score	19	16	15	12	10	9	4	3
Specificity	0.23	0.51	0.57	0.79	0.89	0.9	0.98	0.98
DSMSE-T								
Score	–	60	56	52	48	46	30	26
Specificity	–	0.45	0.58	0.69	0.74	0.77	0.94	0.97
BLOCK-T								
Score	–	21	17	13	10	8	2	–
Specificity	–	0.34	0.5	0.65	0.74	0.82	0.93	–
CF-T								
Score	–	10	9	8	7	6	2	–
Specificity	–	0.34	0.43	0.52	0.61	0.69	0.92	–
MMMSE-DS-T								
Score	74	68	65	61	58	55	39	29
Specificity	0.09	0.34	0.46	0.58	0.64	0.68	0.89	0.95
MSRT-TR								
Score	42	32	28	24	20	17	7	4
Specificity	0.19	0.46	0.63	0.72	0.82	0.85	0.92	0.94

Abbreviations: ABSI-T, American Association on Mental Deficiency Adaptive Behavior Scale, Part I-Total Score; BLOCK-T, Block Design subtest-Total Score; CF-T, Category Fluency Test-Total Score; DLD-SCS, Dementia Questionnaire for People with Learning Disabilities, Sum of Cognitive Scores; DS, Down syndrome; DSMSE-M, Down Syndrome Mental Status Examination-Memory Score; DSMSE-T, Down Syndrome Mental Status Examination-Total Score; MMMSE-DS-T, Modified Mini-Mental State Examination-Down Syndrome-Total Score; MSRT-TR, Modified Selective Reminding Test-Total Recall Score.

For the lower IQ group ($25 \leq IQ \leq 34$), a reduction in specificity for the same approximate score would result in misclassification of a greater proportion of preclinical individuals (false positives). On the other hand, achieving comparable sensitivity for the higher IQ group ($45 \leq IQ \leq 68$) required higher scores. (Note that the smaller number of cases within these six subsamples (DS-AD stage × IQ group) reduced estimate precision, and the values for sensitivity and specificity in Table 5 may have been rounded to the nearest one decimal point.)

To verify that the scores used for the present analyses were representative of baseline performance, a final set of analyses compared performance at baseline and at the first 18-month follow-up for only the preclinical group. A series of *t* tests for repeated measures failed to show any differences in performance that approached significance, *t*s < 1.0, *P*s > 0.3 (see Appendix S3 in supporting information).

4 | DISCUSSION

Individuals with DS are living longer, representing the largest population genetically predisposed to developing AD at atypically early ages, with cumulative risk reaching 50% by their late 50s.[18–20] While the high risk is recognized, no consensus has developed regarding best practice methods for diagnosing prodromal DS-AD or, for that matter, distinguishing prodromal DS-AD from more advanced dementia. These facts necessitate developing strategies for recognizing the earliest indicators of AD-related declines, especially now that disease-modifying treatments are becoming available.[21] This task is complicated by the absence of defined "gold standard" assessment methods and consensus criteria for the clinical staging of DS-AD. In past papers, we described validated methods for distinguishing preclinical DS-AD from its prodromal stage and more advanced clinically defined stages based on objectively quantified longitudinal changes in performance on a

TABLE 5 Sensitivities and associated specificities for specific scores for three groups varying in historical full scale IQ.

				Sensitivity							
Measure (IQ group)	**AUC (SE)**	***P***	**95% CI**	**1**	**0.95**	**0.9**	**0.8**	**0.7**	**0.6**	**0.2**	**0.1**
ABSI-T (25 ≤ IQ ≤ 34)	0.796 (0.050)	<0.0001	0.698–0.893								
score				220	209	194	187	180	178	130	110
specificity				0.25	0.452	0.63	0.7	0.8	0.83	1	1
ABSI-T (35 ≤ IQ ≤ 44)	0.711 (0.043)	<0.0001	0.626–0.795								
score				255	230	222	213	208	203	172	160
specificity				0.1	0.33	0.47	0.6	0.61	0.64	0.89	0.96
ABSI-T (45 ≤ IQ ≤ 68)	0.786 (0.081)	=0.007	0.627–0.945								
score				257	–	249	243	240	–	190	173
specificity				0.38	–	41	0.59	0.59	–	1	1
DLD-SCS (25 ≤ IQ ≤ 34)	0.659 (0.060)	–0.013	0.542–0.775								
score				–	3	6	8	10	11	21	25
specificity				–	0.14	0.3	0.44	0.51	0.6	0.98	0.98
DLD-SCS (35 ≤ IQ ≤ 44)	0.744 (0.041)	<0.0001	0.664–0.824								
score				–	2	3	5	6	9	17	19
specificity				–	0.29	0.46	0.54	0.6	0.78	0.9	0.94
DLD-SCS 45 ≤ IQ ≤ 68)	0.867 (0.062)	<0.0001	0.745–0.824								
score				–	–	–	3	4	6	17	18
specificity				–	–	–	0.82	0.82	0.82	0.95	1
DSMSEM-T (25 ≤ IQ ≤ 34)	0.833 (0.045)	<0.0001	0.744–0.922								
score				16	14	12	10	9	7	3	2
specificity				0.45	0.55	0.64	0.79	79	0.83	0.95	0.95
DSMSEM-T (35 ≤ IQ ≤ 44)	0.850 (0.032)	<0.0001	0.787–0.912								
score				18	16	15	13	11	9	5	3
specificity				0.28	0.47	0.54	0.72	0.85	0.92	0.96	0.99
DSMSEM-T (45 ≤ IQ ≤ 68)	0.811 (0.091)	=0.003	0.631–0.990								
score				19	–	–	16	12	7	4	3
specificity				0.18	–	–	0.73	0.95	1	1	1
DSMSE-T (25 ≤ IQ ≤ 34)	0.750 (0.054)	<0.0001	0.643–0.856								
score				58	53	47	44	43	41	26	23
specificity				0.28	0.44	0.51	0.63	0.65	0.72	0.91	0.91
DSMSE-T (35 ≤ IQ ≤ 44)	0.813 (0.036)	<0.0001	0.743–0.883								
score				64	60	56	53	52	48	37	31
specificity				0.17	0.46	0.63	0.73	0.74	0.82	0.95	0.97
DSMSE-T (45 ≤ IQ ≤ 68)	0.879 (0.059)	<0.0001	0.764–0.994								
score				66	–	65	58	53	52	35	17
specificity				0.55	–	0.64	0.82	0.95	0.95	1	1
BLOCK-T (25 ≤ IQ ≤ 34)	0.753 (0.053)	<0.0001	0.649–0.857								
score				16	12	10	8	7	5	–	–
specificity				0.3	0.4	0.51	0.6	0.63	0.77	–	–
BLOCK-T (35 ≤ IQ ≤ 44)	0.780 (0.039)	<0.0001	0.704–0.856								
score				34	19	17	14	12	10	3	–
specificity				0.04	0.41	0.49	0.66	0.72	0.8	0.92	–

(Continues)

TABLE 5 (Continued)

				Sensitivity							
Measure (IQ group)	**AUC (SE)**	***P***	**95% CI**	**1**	**0.95**	**0.9**	**0.8**	**0.7**	**0.6**	**0.2**	**0.1**
BLOCK-T (45 ≤ IQ ≤ 68)	0.837 (0.072)	<0.0001	0.696–0.978								
score				30	–	29	27	25	23	3	–
specificity				0.55	–	0.55	0.64	0.64	0.73	1	–
CF-T (25 ≤ IQ ≤ 34)	0.719 (0.056)	<0.0001	0.609–0.829								
score				12	–	–	7	5	4	–	–
specificity				0.05	–	–	0.47	0.7	0.74	–	–
CF-T (35 ≤ IQ ≤ 44)	0.693 (0.043)	<0.0001	0.608–0.777								
score				13	–	10	–	8	6	3	2
specificity				0.09	–	0.32	–	0.54	0.71	0.9	0.92
CF-T (45 ≤ IQ ≤ 68)	0.883 (0.066)	<0.0001	0.754–1.00								
score				14	–	8	–	7	6	–	–
specificity				0.23	–	0.77	–	0.82	0.91	–	–
MMMSEM-T (25 ≤ IQ ≤ 34)	0.700 (0.059)	0.002	0.585–0.815								
Score				64	62	58	51	47	42	28	22
Specificity				0.21	0.26	0.38	0.5	0.57	0.71	0.93	0.95
MMMSEM-T (35 ≤ IQ ≤ 44)	0.744 (0.041)	<0.0001	0.663–8.25								
score				70	66	63	62	60	58	44	40
specificity				0.15	0.42	0.6	0.62	0.68	0.73	0.91	0.92
MMMSEM-T (45 ≤ IQ ≤ 68)	0.820 (0.074)	0.002	0.676–0.964								
score				74	73	72	69	68	65	37	18
specificity				0.32	0.5	0.55	0.82	0.82	0.83	1	1
MSRT-TR (25 ≤ IQ ≤ 34)	0.727 (0.058)	<0.0001	0.612–0.841								
score				41	28	25	20	16	14	6	3
specificity				0.12	0.4	0.44	0.63	0.74	0.77	0.84	0.86
MSRT-TR (35 ≤ IQ ≤ 44)	0.851 (0.033)	<0.0001	0.786–0.915								
score				42	32	29	25	22	19	9	7
specificity				0.21	0.55	0.66	0.77	0.84	0.9	0.94	0.94
MSRT-TR (45 ≤ IQ ≤ 68)	0.891 (0.074)	<0.0001	0.746–1.00								
score				42	–	33	24	22	19	2	–
specificity				0.32	–	0.55	0.95	1	1	1	–

Abbreviations: ABSI-T, American Association on Mental Deficiency Adaptive Behavior Scale, Part I-Total Score; AD, Alzheimer's disease; AUC, area under the curve; BLOCK-T, Block Design subtest-Total Score; CF-T, Category Fluency Test-Total Score; CI, confidence interval; DLD-SCS, Dementia Questionnaire for People with Learning Disabilities, Sum of Cognitive Scores; DS, Down syndrome; DSMSEM-T, Down Syndrome Mental Status Examination-Memory Score; DSMSE-T, Down Syndrome Mental Status Examination-Total Score; MCI, mild cognitive impairment; MMMSE-DS-T, Modified Mini-Mental State Examination-Down Syndrome-Total Score; MSRT-TR, Modified Selective Reminding Test-Total Recall Score; SE, standard error.

variety of measures. Here we were able to show that these same procedures have the added advantage of being able to support inferences regarding DS-AD–related clinical status based only on a single evaluation. This represents an important addition to the tools available to clinicians providing diagnostic services to this population. Together with other methods validated empirically,[9,12,22] the field now has in hand procedures that approximate a true gold standard.

Here we were able to take advantage of a large set of longitudinal findings that provided direct indications of whether DS-AD had progressed from its preclinical to prodromal stage, allowing us to show that declines associated with the transition can be inferred based on a single evaluation. Knowing the histories of developmental impairment was found to be helpful, but these methods proved extremely useful alone, even when information regarding that history is unavailable. The confidence of an inference will vary, being highest for scores falling in the distribution tails, but even intermediate scores can be useful in informing diagnostic decisions when findings are considered in the context of other measures and factors contributing to risk.

While these methods should be used to strengthen confidence in diagnostic decisions, especially when performance is at the extremes

of the scoring range, they should be one of several considerations. Age is the most obvious factor that should be considered when interpreting assessment findings given its key contribution to determining "predictive value," the likelihood that a given finding would result in a true or false diagnostic decision. With AD risk clearly associated with advancing age, a positive finding is far more likely to identify a true case of prodromal DS-AD for an individual older than 60, an age of high risk, compared to an individual in their 30s when risk is extremely low. While published estimates of age-specific prevalence of prodromal and more advanced DS-AD have varied,[13,19,23] all agree that risk prior to age 40 is very low and shows an accelerated increase after the mid-40s.

The utility of our methods for clinical practice can be seen if we take, for example, an individual who obtains a score of 10 on the DSMSEM-T. Only 20% of people with preclinical DS-AD scored < 12, compared to 80% of people with prodromal DS-AD. If the prevalence of prodromal DS-AD is ≈ 1% below the age of 40, then the probability that a person at that age truly has prodromal DS-AD is $0.8 \times 0.01 = 0.008$. On the other hand, the probability that this person is truly preclinical is $0.2 \times 0.99 = 0.198$ and it is far more likely that their assessment findings represent a false positive. Of course, the possibility of a true positive cannot be ruled out altogether, but a priority would focus on validating any evidence supporting a competing cause for the assessment results. Most importantly, a plan for retesting and/or longitudinal tracking would need to be considered to confirm the diagnostic decision based on the initial evaluation.

The same assessment findings for a person with DS > age 60 would most likely lead to a different strategy for follow-up. With a prodromal DS-AD prevalence possibly reaching 60%,[24] the probability of a true prodromal case becomes $0.8 \times 0.6 = 0.48$, while the probability of a false positive becomes $0.2 \times 0.4 = 0.08$, contributing to a high degree of confidence for an interpretation of true prodromal DS-AD. Nevertheless, the possibility that competing causes might be the source of poorer-than-expected performance still needs to be considered.

Other important factors to consider include developmental history, if available; apolipoprotein E genotype;[25–27] occurrence of stressful life events and illnesses unrelated to DS-AD that can present as a "pseudodementia"; and an individual's motivation and cooperation with testing. Clearly, informed clinical judgment will always play a central role.

The present analyses have several limitations. First, individuals with histories of the most severe ID, operationalized as having IQs < 25, were excluded. Experience has shown that adults with such severe ID most often perform at or near floor prior to developing prodromal DS-AD or are completely unable to cooperate with the test procedures. Other measures more suited to abilities characteristic of this subpopulation need to be developed and validated.

At the other extreme, the present sample included only a small number of individuals with histories of mild or even borderline ID. As shown in Table 5, the likelihood of a false negative score increases for these adults, even within the limited range sampled, and inferences based on evidence of decline associated with the transition from preclinical to prodromal DS-AD for these individuals need to be considered, especially when "mid-range" performance is found. Because our sample did not include those with a historical IQ > 68, the appropriateness of present methods for staging early DS-AD for older adults with higher IQs remains unknown.

It is important to emphasize that the present analyses focused only on the distinction between preclinical and prodromal DS-AD. The distinction between prodromal and more advanced DS-AD presents a different challenge. While functional declines in activities of daily living (ADLs) are typically a distinguishing feature of more advanced stages of late-onset AD,[28] Listwan et al.[29] recently demonstrated that longitudinal declines in ADLs can occur with the onset of prodromal DS-AD and the present finding of an AUC of 0.745 for the American Association on Mental Deficiency Adaptive Behavior Scale, Part I-Total Score (ABSI-T) supports interpretation of the longitudinal analyses. Thus, there does not seem to be a qualitative distinction between prodromal and more advanced stages of DS-AD; therefore, duration since progression beyond preclinical DS-AD and degree of decline must be a major consideration.

In summary, these analyses showed that assessments conducted at a single point in time can be used to inform inferences regarding the presence—or absence—of previously observed decline. Given current attitudes and policies limiting formal IQ testing, the data provided in Table 4 indicate that useful insights can be obtained in the absence of past IQ results, again acknowledging the limitations noted for extremes of the severity range (see Videla et al.[8]). However, valid information regarding developmental history should always be considered when available.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

CONSENT STATEMENT

Recruitment, informed consent, and study procedures were approved by the institutional review boards of the New York State Institute for Basic Research in Developmental Disabilities, New York State Psychiatric Institute, and Columbia University Irving Medical Center. Informed consent was obtained from those participants with capacity. Surrogate informed consent was obtained from legally authorized representatives for those participants lacking capacity. Assent was obtained from all participants just prior to assessment. The study was conducted in accord with the Declaration of Helsinki of 1975 and all its later amendments.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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