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ORIGINAL ARTICLE

Evaluation of the National Task Group-Early Detection Screen for Dementia: Sensitivity to 'mild cognitive impairment' in adults with Down syndrome

Wayne Silverman[1] | Sharon J. Krinsky-McHale[2,3] | Florence Lai[4] | H. Diana Rosas[4] | Christy Hom[2] | Eric Doran[1] | Margaret Pulsifer[5] | Ira Lott[1] | Nicole Schupf[6,7,8] | The Alzheimer's Disease in Down Syndrome (ADDS) Consortium

[1]Department of Pediatrics, University of California, Irvine, Irvine, CA, USA

[2]New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA

[3]Department of Psychiatry, University of California, Irvine, Irvine, CA, USA

[4]Department of Neurology, Massachusetts General Hospital, Harvard University, Boston, MA, USA

[5]Department of Psychiatry, Massachusetts General Hospital, Harvard University, Boston, MA, USA

[6]Sergievsky Center, Taub Institute, New York, CA, USA

[7]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, CA, USA

[8]Department of Epidemiology, School of Public Health, Columbia University, New York, CA, USA

Correspondence
Sharon J. Krinsky-McHale, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314, USA.
Email: Sharon.Krinsky-McHale@opwdd.ny.gov

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Abstract

Background: The accuracy of the National Task Group-Early Detection Screen for Dementia (NTG-EDSD) was evaluated in a sample of 185 adults with Down syndrome (DS), emphasizing 'mild cognitive impairment (MCI-DS)'.

Method: Knowledgeable informants were interviewed with the NTG-EDSD, and findings were compared to an independent dementia status rating based on consensus review of detailed assessments of cognition, functional abilities and health status (including physician examination).

Results: Results indicated that sections of the NTG-EDSD were sensitive to MCI-DS, with one or more concerns within the 'Memory' or 'Language and Communication' domains being most informative.

Conclusions: The NTG-EDSD is a useful tool for evaluating dementia status, including MCI-DS. However, estimates of sensitivity and specificity, even for detecting frank dementia, indicated that NTG-EDSD findings need to be supplemented by additional sources of relevant information to achieve an acceptable level of diagnostic/screening accuracy.

KEYWORDS
Alzheimer's disease, dementia, down syndrome, mild cognitive impairment, NTG-EDSD

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1 | INTRODUCTION

A dramatically increased risk for early-onset Alzheimer's disease (AD) is now an established phenotypic feature of Down syndrome (DS, defined cytogenetically by Trisomy 21), with cumulative risk for dementia reaching 0.5 prior to age 60 years (McCarron et al., 2017; Sinai et al., 2018). This population-wide high risk has been attributed, at least in large measure, to triplication of the gene coding for amyloid precursor protein located on chromosome 21 (Robakis et al., 1987; Sinai et al., 2018), although other genes are likely to play roles in modifying this risk (Gomez et al., 2020).

The association between DS and AD has attracted considerable interest in recent decades, and for several compelling reasons. First, the life expectancy for people with DS, estimated at 9 years of age just after World War II (Penrose, 1949), has increased to almost 60 years (Torr et al., 2010), with many adults living considerably longer (Yang et al., 2002). Combined with a stable birth incidence that is estimated to be approximately one in 700 (Parker et al., 2010), this creates a large subpopulation of patients developing AD and needing intensive levels of supports and services associated with its progressive dementia and physical frailty (see Silverman et al., 1998). In fact, this is the largest population we know of with high AD risk driven by a specific genotype, constituting a substantial public health concern in its own right.

A second reason for increased attention to this association is related to the first. The knowledge about AD risk has increased concerns among individuals with DS and their families, especially when adults with DS reach middle age or older. Additionally, increased needs for supports have strained some service systems, which often have mandated requirements for meeting the needs of individuals with developmental disorders that are over and above those of Medicare and Medicaid. Thus, there have been community-wide calls to action to address these concerns.

Third, the substantial population of adults with DS at risk and developing AD provides unique opportunities to further our understanding of AD progression, both specific to this population and for pathogenesis more broadly. Research targeting AD in adults with DS could provide key insights into mechanisms initiating the neuropathological cascade, influencing its progression, identifying factors modifying that risk and progression, and determining targets for effective prevention and treatment. The translational impacts of advancing our understanding of AD specifically in the population with DS could be enormous.

Effective methods for recognizing early clinical progression of AD in adults with DS are key to all these interests. Clinically, early diagnosis is of critical importance for current planning of supports and will be of even more value as future treatments affecting disease progression are developed. Scientifically, early diagnosis is needed to evaluate promising treatments in clinical trials, in the discovery of biomarkers with high sensitivity and specificity, especially during preclinical stages of AD when effective intervention might prevent irreversible brain damage, and in tracking that progression as it does occur. Unfortunately, effective methods for detecting early AD clinical progression in adults who developed neurotypically are uninformative for adults with DS, who invariably have pre-existing cognitive and functional impairments associated with their developmental disability, and these impairments are far more significant than the relatively subtle impairments that characterize mild cognitive impairment (MCI), the earliest stage of AD clinical progression (Albert et al., 2011).

Krinsky-McHale and Silverman (2013) provided an in-depth discussion of the complications introduced by highly variable lifelong impairments among adults with DS when interpreting assessments of clinical dementia status, (see Silverman, 2007). Briefly, prior to any risk for AD (or any other cause of dementia), adults with DS would be expected to perform well below diagnostic criteria indicative of concern, either for MCI or dementia, based on current standard/best practice in dementia clinics and research centres. These procedures were developed to identify cognitive impairments relative to mean performance levels of the overall population and were never intended for the purpose of discriminating between impairments arising during early development and those arising in old age. Further, because many adults with DS will perform at or near floor prior to any impacts of advanced age or progressive neuropathology, the ability of these procedures to measure decline is limited. Nevertheless, with AD neuropathology being slowly progressive and unfolding over a period of many years, MCI and dementia should reflect comparable stages of clinical impairment, at least conceptually, in adults with and without DS (Krinsky-McHale & Silverman, 2013).

The main feature of MCI for all adults is decline in cognitive abilities greater than expected with ageing, per se, but of insufficient severity to merit a dementia diagnosis. For neurotypical adults, this can usually be inferred when performance is judged against a population-referenced standard. However, for adults with DS, performance must be judged in relation to expectations that accept the presence of lifelong impairments, and therefore, no fixed level of subpar achievement is meaningful. Rather, decline for each individual must be quantified directly through serial assessments or must be inferred based upon expectations anchored to his or her lifelong abilities. This has become 'best practice' within the field, although no consensus has emerged regarding 'gold standard' methods. Recognizing that MCI for adults with DS needs to be operationalized in a distinct way, we have adopted the practice of referring to this diagnostic category as MCI-DS.

Lack of a consensus with respect to best practices for diagnosing MCI-DS, regarding either assessment methods or diagnostic criteria, represents an urgent unfilled need. Best practice methods must address several priorities, including (a) testability, defined by the ability of individuals at risk (but unaffected) to perform at levels that allow quantification of clinically significant decline, (b) validity, defined by high sensitivity (rate of detection of disease among affected individuals) and specificity (rate of detection of disease absence among unaffected individuals), and (c) utility, defined by administration ease, cost and feasibility for translation into broad clinical practice.

The National Task Group (NTG) on Intellectual Disabilities and Dementia Practices developed an informant-based questionnaire format that clearly meets the first and third of these criteria (Esralew et al., 2013, 2018). Titled the 'NTG-Early Detection Screen

for Dementia' (NTG-EDSD), it is widely available online (http://www.the-ntg.org/ntg-edsd) for no cost, respondents can be either laypersons or professionals, it requires only a modest investment of time to complete, and it has been translated into multiple languages (18 at the time of this writing). Most important, its contents are designed to be appropriate for individuals with varying ID severity. It can be completed autonomously online by informants or as a face-to-face interview (the procedure for the present study). It includes several sections focused on (a) basic demographics and categorical diagnostic information, (b) health status and history, including physician diagnoses of MCI or dementia, and (c) dementia-related areas of concerns adapted from the Dementia Screen for Individuals with Intellectual Disabilities (DSQIID; Deb et al., 2007).

While the NTG-EDSD manual clearly states that the instrument is not intended for diagnosis, its structure is clearly suggestive of that application. In fact, anecdotal reports indicate that it is being used in this way. Inclusion within the NTG-EDSD of an adaptation of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID; Deb et al., 2007) adds to its other appealing features and increases the likelihood that it can inform diagnostic decisions in clinical settings. However, empirical support for the DSQIID as a screen specifically for MCI-DS, and by extension the NTG-EDSD, has been limited (e.g. Kuske et al., 2017), most validation studies to date focus on the presence/absence of frank dementia (e.g. Deb et al., 2007; Li et al., 2015; Lin et al., 2014). Given the explicit focus of the NTG-EDSD on detection of early/prodromal AD, there is a clear need to examine the validity of this instrument with a more explicit focus on early stages of clinical decline. That is, the goal of the analyses presented herein.

For sporadic, or late onset AD, the early stage of AD-related clinical progression is currently diagnosed as MCI (Albert et al., 2011). Diagnostic criteria include evidence of decline from previous abilities defined as performance levels of approximately 1.5 standard deviations below the mean for standardized neuropsychological assessments. Because the vast majority of adults with DS perform below this level prior to any impacts of either ageing or AD, MCI for this subpopulation needs to be operationalized differently. There would need to be evidence of decline in abilities from a baseline level, either based on direct observations of decline over time or inferred from performance below expectations with reference to the subpopulation of individuals with comparable severity of ID. Quantitatively, decline associated with MCI would have to be greater than what would be expected with ageing, per se, but would not be severe enough to suggest a diagnosis of dementia. This stage of AD progression will therefore be labelled MCI-DS herein to acknowledge that, while it is conceptually identical to MCI as currently defined, its operationally defining features are necessarily somewhat distinct.

2 | METHOD

All procedures were reviewed and approved by Institutional Review Boards at participating institutions (New York State Institute for Basic Research in Developmental Disabilities, Columbia University Irving Medical Center, Massachusetts General Hospital, the University of California, Irvine, The Johns Hopkins University Schools of Medicine and Public Health, and the University of North Texas Health Science Center). In every case, informed consent was obtained either from participants or their legally authorized representatives, along with participant assent.

TABLE 1 Participant characteristics

	CS	MCI-DS	Dementia
N	111	36	38
% Male	58.6	66.3	50.0
Age, Years			
Mean	49.2	54.2	55.6
(SD)	(6.69)	(7.29)	(6.30)
ID Severity (% Participants)			
Mild	54.1	41.7	39.5
Moderate	42.3	50.0	47.4
Severe	3.6	8.3	13.2

2.1 | Participants

The current sample included 185 adults with DS ranging from 40 to 82 years of age. Demographic characteristics of the sample are summarized in Table 1. All participants were enrolled in a larger, multidisciplinary programme of research focused on biomarkers of AD in adults with DS. All participants were based in New York, NY (N = 55, enrolled at the New York State Institute for Basic Research in Developmental Disabilities and Columbia University Irving Medical Center), Boston, MA (N = 70, enrolled at the Massachusetts General Hospital), or Orange County, CA (N = 60, enrolled at the University of California, Irvine). Additional inclusion criteria included the following: (a) ability to participate, at least in part, with direct-testing assessment procedures, (b) absence of significant sensory or motor impairments, and (c) willingness to provide a routine blood sample for studies of fluid-based biomarkers of AD.

2.2 | Procedures

The procedures relevant to the present analyses were embedded within a broader ongoing study examining biomarkers of AD in adults with DS (see, Handen et al., 2020). That broader programme included neuroimaging studies (brain MRI, amyloid and tau PET) as well as targeted and untargeted genomics, proteomics, and metabolomics. Enrolment is continuing at the time of this writing, as is longitudinal tracking of programme participants, but the present analyses only focused on clinical assessments conducted between September of 2016 and February of 2020. These included review of

clinical records, physical and neurological examinations, interviews with informants (who had to have interacted with the participant regularly for no less than the prior 6 months) focused on cognitive and functional abilities (including severity of intellectual disability), health-related conditions and medical history, and neuropsychiatric concerns. Participants were also tested one-on-one with a core battery developed explicitly for assessing dementia status in adults with ID and covering the spectrum of cognitive domains (such as, memory and language) that are expected to be affected by early as well as later clinical progression (Silverman et al., 2004; Krinsky-McHale et al., 2020).

The clinical dementia status of each participant was determined consensus case reviews with consideration of profiles of performance on a wide range of 'core' participant and informant assessments. Informant measures included two summary scores from the *Dementia Questionnaire for People with Learning Disabilities* (DLD—formerly the DMR; Evenhuis, 1990, 1995), one reflecting cognitive abilities (DLD-SCS) and one reflecting social skills (DLD-SOS). *The Vineland Adaptive Behavior Scales, 3rd edition* (VABS-3; Sparrow et al., 2016) and the *American Association on Mental Deficiency Adaptive Behavior Scale, Part I* (ABSI; Nihira et al., 1974—only for New York-based participants) provided indications of functional abilities across a broad range of domains. Finally, the *Reiss Screen for Maladaptive Behavior* (Reiss, 1994; Urv et al., 2003), an interview developed specifically as a screen for neuropsychiatric concerns and maladaptive behaviours in individuals with ID, provided overviews of neuropsychiatric status.

The core battery of direct one-on-one tests required approximately 1.5 to 2 hours to complete and included the following: (a) a modified version of the *Selective Reminding Test* (mSRT), now requiring free recall of 8 items over 3 trials (see, Buschke, 1973; Krinsky-McHale et al., 2002), (b) an enhanced version of the *Down Syndrome Mental Status Examination* (DSMSE, Haxby, 1989), expanding the number of items included in tests of working memory (from 3 to 9 objects), (c) a simplified version of the *Mini Mental Status Evaluation (MMSE*; Folstein et al., 1975) developed specifically for use with adults with ID (Wisniewski & Hill, 1985), (d) *The Test for Severe Impairment* (TSI; Albert & Cohen, 1992), developed to track progression of dementia in neurotypical adults no longer able to perform above floor on the MMSE, (e) an adaptation of the McCarthy (1972) *Category Fluency Test* (with slightly liberalized scoring), (f) the *Block Design* subtest from the *Wechsler Intelligence Scale for Children* (WISC-Revised, Wechsler, 1974) supplemented and always beginning with less complex items from the original DSMSE (Haxby, 1989), and (g) the *Beery–Buktenica Developmental Test of Visual-Motor Integration* (long form, Beery, & Buktenica, 1989).

Consensus Case Conference members (see, Silverman et al., 2004) included programme investigators at each site, senior staff and research assistants who had direct contact with the participant under consideration (never fewer than three people with extensive experience evaluating dementia status in adults with DS). Dementia status was classified into the following categories, generally consistent with recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability (Aylward et al., 1997; Burt &Aylward, 2000): (a) *Cognitively Stable (CS)*, indicating with reasonable certainty that clinically significant impairment was absent (although allowing for declines expected with ageing, per se), (b) *MCI-DS*, indicating that there was some indication of cognitive and/or functional decline beyond what would be expected with ageing, per se, but of insufficient severity to suggest frank dementia, (c) *Possible Dementia*, indicating that some signs and symptoms of dementia were present but were not judged to be totally convincing, (d) *Definite Dementia*, indicating with high confidence that dementia was present, and (e) *Uncertain* (due to complications), indicating that evidence of clinically significant declines was present but might be caused by some other substantial concern, usually a medical condition unrelated to a dementing disorder or a significant life event (e.g. severe sensory loss, poorly resolved hip fracture, death of a loved one). A classification rating was made based upon the majority opinion of the group.

In most cases, there was clear consensus, but on occasion, opinions were mixed following what could be extensive discussions, and in these cases, the classification supported by the most people was marked as 'provisional'. (Note that provisional cases retaining that status over time were not included in this sample (N = 6), nor were Uncertain cases (N = 5).) For any participant that was rated as having MCI-DS or Dementia (DEM), additional findings were reviewed to establish an aetiological diagnosis. These could be AD, a mix of AD with evidence of significant other ageing-related neuropathology (symptoms or imaging findings), vascular dementia or uncertain.

The Core assessment battery described above was supplemented with a number of additional assessments that were not considered in any way during consensus discussions. These additional assessment procedures included the NTG-EDSD, which were added specifically for the purpose of evaluating their validity against the independently determined 'standard' provided by consensus classifications.

The present analyses focused on the relationship between NTG-EDSD dementia-related concerns and three consensus categories of dementia status (CS, MCI-DS or DEM). The NTG-EDSD includes 51 items distributed among 6 cognitive/functional domains: (a) Activities of Daily Living (7 items), (b) Language and Communication (referred to herein as simply 'Language'—6 items), (c) Sleep–Wake Change Patterns (8 items), (d) Ambulation (4 items), (e) Memory (but includes other aspects of cognition—9 items), and (f) Behavior and Affect (17 items). Two additional indications of concerns focus on (a) Adult's Self-reported Problems (6 items) and (b) Notable Significant Changes Observed by Others (6 items).

Each of these NTG-EDSD items is rated on a 4-point scale: (a) Always been the case, (b) Always but worse, (c) New symptom in the past year and (d) Does not apply. In this way, dementia-related concerns could be evaluated against variable backgrounds of ID-related impairment. Following the original DSQIID scoring, ratings of (a) and (d) above indicated the absence of dementia-related concern, while

(b) and (c) indicated presence, resulting in a binary scale of 'presence' = 1 and 'absence' = 0.

Given the stated purpose of the NTG-EDSD is to provide screening for early AD clinical onset, an a priori priority focused on differences between CS and MCI-DS groups. However, indications of dementia were also examined. Multi-level analyses examined group differences for individual items, domain totals and total number of concerns across all domains.

3 | RESULTS

3.1 | Screening for early dementia-related decline

An initial analysis examined the correspondence between consensus classifications of dementia status and NTG-EDSD items 16–18 which focused on a diagnostic history of MCI-DS or dementia. Results indicated that this section of the NTG-EDSD was largely uninformative. While 99% and 97% of individuals with a CS rating had no reported history of MCI or dementia, respectively, only 8.3% and 7.9% of cases in the MCI-DS and DEM consensus groups, respectively, had a reported history of MCI and only 76.3% of the group with DEM had a reported history of dementia. Further, 16.7% of the group with a consensus classification of MCI-DS had a reported history of dementia, indicating that the distinction between MCI-DS and dementia among clinicians in the community was not clearly demarcated.

Deb et al. (2007) found extremely impressive sensitivity (0.92) and specificity (0.97) for a DSQIID total score criterion of 20 indications of concern when comparing their original 'unaffected' and 'demented' groups of adults with DS. Therefore, a total score for NTG-EDSD concerns was calculated, as were sums for the sub-domains of (a) Activities of Daily Living, (b) Language, (c) Sleep–Wake Change Patterns, (d) Ambulation, (e) Memory, and (f) Behavior and Affect. These results are summarized in Table 2, along with those from sections reflecting self-reported problems and changes of observed by others.

Total scores (omitting self-reported concerns and those of others) for the three consensus groups were compared employing a Kruskal–Wallis nonparametric analysis of variance followed by Mann–Whitney *U* tests examining pairwise group differences. No adjustments were made for multiple comparisons, given a desire to minimize type-2 errors. As expected and shown in Table 2, the total number of concerns increased monotonically with clinical progression, with the CS group showing significantly fewer concerns than the other two groups and the MCI-DS group showing fewer concerns than the DEM group, $H(2, N = 185) = 82.4$, $p < 0.0001$. Additional examination focused on the Deb et al. (2007) criterion of 20 concerns, and here our finding showed considerable divergence from expectations. Only 16 of the 38 cases with DEM had 20 or more concerns (sensitivity = 0.421). Likewise, only 2 of the 36 cases with MCI-DS met this criterion (sensitivity = 0.056).

Next, differences between groups were examined, again employing Kruskal–Wallis analyses of variance, followed by Mann–Whitney pairwise contrasts, for each of the six NTG-EDSD domains (see Table 2) as well as the sum of the 'Memory' and 'Language and Communication' domains. Not surprisingly, results were mixed. While overall differences were highly significant in all cases, $H(2, N = 185)$ ranged from 23.2 for the 'Sleep–Wake Pattern' domain to 91.4 for the combined 'Memory' and 'Language' domains, $ps < .0001$. However, as indicated in Table 2, differences between the CS and MCI-DS groups fell short of significance for Activities of Daily Living, Sleep–Wake Patterns and Ambulation (the only instance where the CS group had a greater number of concerns than did the MCI-DS group). The largest effect sizes were observed for the Memory and Language domains, $ps < 0.0001$, while a smaller but still significant difference was found for the Behavior and Affect domain, $p < 0.01$(Note that an overall low prevalence of ambulation-related concerns may have reflected the fact that screening procedures for the present study excluded individuals with significant gross motor impairments and therefore the Ambulation domain may be more sensitive to emergent concerns for the broader population of affected adults.)

TABLE 2 Means and standard deviations (in parentheses) for the number of NTG-EDSD concerns within specific domains for the three dementia status groups and the overall significance of group differences.

	Group			Kruskal–Wallis *H* (2, N = 185)	
Domain (# Items)	**CS**	**MCI-DS**	**Dementia**	***H***	***P* Value**
Activities of Daily Living (7)	0.22 (.68)	0.53 (1.08)	3.32 2.26)	82.1	<.0001
Language and Communication (6)	0.16 (.48)	0.68 (1.06)	2.21 (1.85)	69.1	<.0001
Sleep–Wake Patterns (8)	0.36 (1.00)	0.64 (1.25)	2.03 (2.38)	23.2	<.0001
Ambulation (4)	0.32 (.84)	0.22 (0.64)	1.76 (1.28)	61.8	<.0001
Memory (9)	0.31 (.77)	1.94 (1.96)	4.11 (2.80)	87.7	<.0001
Behavior & Affect (17)	0.89 (2.00)	2.31 (3.49)	6.32 (4.31)	54.1	<.0001
TOTAL CONCERNS (51)	2.26 (3.94)	6.33 (6.82)	18.66 (10.77)	82.4	<.0001
Self-reported Problems (6)	0.34 (0.98)	0.97 (1.33)	1.66 (1.66)	35.9	<.0001
Changes Observed by Others (6)	0.71 (1.03)	1.28 (1.26)	2.29 (1.59)	36.1	<.0001

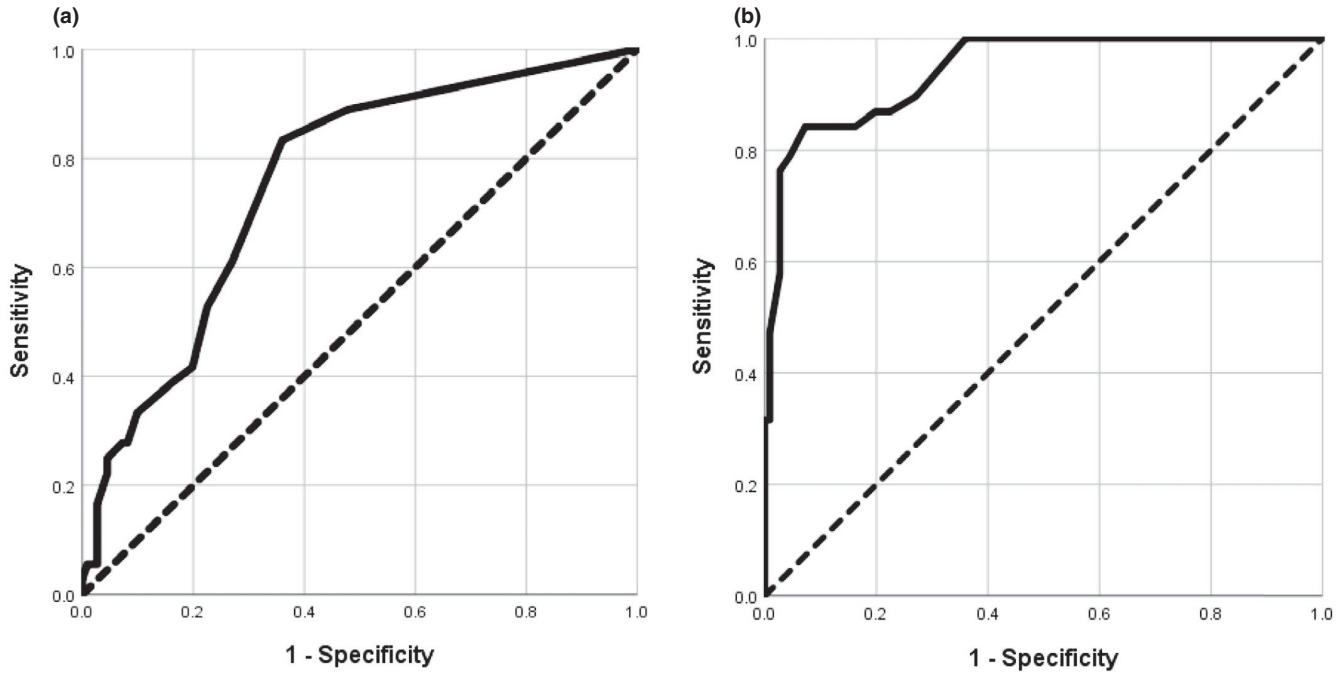

FIGURE 1 ROC curves for total number of concerns: (a) comparing CS adults with Down syndrome to their peers with MCI-DS, and (b) comparing CS adults to peers with dementia

TABLE 3 Summary of receiver operating characteristic (ROC) analyses of NTG-EDSD concerns (total[a] and within each domain), with estimated sensitivity (Sen) and specificity (Spe) based on the presence of one or more concerns for each person

	CS vs. MCI-DS				CS vs. DEM			
NTG-EDSD Domain	AUC	*P*	95% CI	Sen/Spe	AUC [SE]	*p*	95% CI	Sen/Spe
Activities of Daily Living	0.5620.	>0.25	0.449-0.675	0.250/0.864	0.894	<0.0001	0.820-0.967	0.842/0.864
Language and Communication	0.650	<0.01	0.538-0.763	0.417/0.874	0.861	<0.0001	0.778-0.943	0.789/0.874
Sleep–Wake Patterns	0.573	>0.15	0.462-0.685	0.306/0.847	0.695	<0.0001	0.586-0.803	0.500/0.847
Ambulation	0.489	>0.80	0.382-0.597	0.139/0.847	0.822	<0.0001	0.737-0.906	0.789/0.847
Memory	0.793	<0.0001	0.699-0.887	0.722/0.838	0.902	<0.0001	0.833-0.972	0.868/0.838
Behavior & Affect	0.654	<0.05	0.547-0.762	0.583/0.703	0.857	<0.0001	0.781-0.934	0.868/0.703
Memory +Language	0.813	<0.0001	0.727-0.899	0.806/0.802	0.915	<0.0001	0.851-0.980	0.895/0.802
Total Concerns[a]	0.755	<0.0001	0.668-0.842	0.889/0.522	0.943	<0.0001	0.905-0.981	10.00/0.522
Self-reported Problems	0.692	<0.001	0.585-0.798	0.556/0.828	0.735	<0.0001	0.632-0.838	0.605/0.828
Changes Observed by Others	0.637	<0.01	0.530-0.744	0.667/0.559	0.800	<0.0001	0.715-0.885	0.816/0.559

[a]Total excluded Self-reported Problems and Changes Observed by Others.

Further analyses were conducted to examine differences in score distributions between CS and the two other consensus groups for the total number of concerns, concerns within each domain, and for the Memory and Language domains combined. Receiver operating characteristic (ROC) analyses were employed. These analytic methods provide direct pairwise comparisons of groups by plotting true-positive rates (sensitivity) against false-positive rate (1-specificity) over the entire distribution of possible scores. The area under the curve (AUC) reflects the magnitude and statistical significance of the difference between the two groups, with an AUC = 1 indicating complete distribution separation while an AUC = 0.5 indicates complete overlap. (Note that the only circumstance under which an AUC can be less than 0.5 is when the group expected to have higher scores actually has lower scores, as was the present case when Ambulation concerns were compared between the CS and MCI-DS groups.)

ROC curves were first examined for the total number of concerns between participants who were CS and the two other groups, as illustrated in Figure 1. Summary statistics are provided in Table 3, with sensitivity estimates maximized based on a criterion of even a single reported concern. For the comparison between the CS and MCI-DS groups (Figure 1a), the AUC was .755, standard error (SE) = 0.045, $p < 0.0001$, 95% CI = 0.668-.842 with a maximum sensitivity was 0.889. However, a sensitivity of 0.522 for this criterion indicated that just under half of all unaffected individuals would screen as positive. A cut-off score of ≥2 gave a sensitivity of .833 but specificity of .640. remained a concern. However, increasing the criterion to ≥3 caused sensitivity to drop to .611.

An ROC curve for the total number of concerns between participants who were CS and DEM was also constructed (Figure 1b), now with AUC = 0.943, SE = 0.020, $p < 0.0001$, 95% CI = 0.905–0.981, and improved differentiation of groups. Now sensitivity was a perfect 1.0 but again specificity was poor (0.522). A criterion of ≥3 still retained a high sensitivity of 0.895 while increasing specificity to .730. A further increase in the criterion to ≥5 had only a minor impact on sensitivity (0.868), now with specificity of 0.802.

Table 3 presents summary statistics for an ROC analyses of individual NTG-EDSD domains, as well as the combination of Memory and Language and Communication domains. Sensitivity and specificity were again based on the presence of at least one concern within the respective domain(s). For the CS versus MCI-DS groups, sensitivity ranged from 0.806 (Memory & Language combined) to 0.139 (Ambulation). Specificity ranged from 0.874 (Language & Communication) to 0.703 (Behavior & Affect). As expected, comparisons between the CS and DEM groups showed greater sensitivity, with estimates ranging from 0.895 (Memory & Language) to 0.500 (Sleep/Wake). Of course, specificity estimates remained unchanged.

Finally, the presence/absence of each individual concern was compared to consensus classification (see Table 4). Out of the 63 individual concerns (including the domains of Self-reported Problems and Changes Observed by Others), 56 (88.9%) showed a significant difference between the CS and DEM groups, but only 22 (34.9%) showed an association with MCI-DS presence/absence.

4 | DISCUSSION

As indicated by its name, the NTG-EDSD was developed to serve as a screen for early indications of dementia in adults with ID. In the case of adults with DS, old age-associated dementia, when present, is associated with clinical progression of AD in the vast majority of cases. (This assumes exclusion of 'pseudo-dementias' associated with conditions unrelated to brain pathology developing in adulthood.) The NTG-EDSD has many attractive features, including a user-friendly format, content validity and wide availability at no cost. The findings presented here provide solid empirical support for many sections of this instrument by validating NTG-EDSD information against an independent standard based on extensive assessments of cognition, function and health status. Therefore, this instrument has considerable potential value for informing diagnostic decisions. However, the evidence supporting the utility of the NTG-EDSD for informing clinical diagnosis of ageing-related dementing disorders has to be qualified by recognition of its imperfect sensitivity and specificity, especially with respect to the insensitivity of much of its content for MCI-DS.

A potential strength of the NTG-EDSD rests on its inclusion of an adaptation of the DSQIID (Deb et al., 2007). Concerns in the domains of Memory and Language were found to be informative for distinguishing between cognitively stable adults and those with early clinical progression of AD, classified as MCI-DS, with acceptable sensitivity and specificity. Other domains were less informative at this stage of AD progression, although all domains distinguished between groups of adults with and without frank dementia. However, the present findings failed to replicate the near perfect sensitivity (0.92) and specificity (0.97) for distinguishing between cognitively stable and demented adults in the original Deb et al. report, and for the present cohort their diagnostic criterion of 20 total concerns for dementia presence yielded an unacceptably low sensitivity of only 0.42. The implication is that adults with dementia enrolled by Deb et al. may have been in a relatively advanced stage of disease compared to the present sample and that cases with MCI-DS were either excluded or merged with cognitively stable adults to form their 'non-demented' group. The present results did indicate that, with a specificity of 0.802, a criterion of 5 total concerns or more achieved a sensitivity of .868 for dementia, but only 0.417 for MCI-DS.

Of considerable interest, a narrowed focus on just the Language and Memory Domains (the latter actually encompassing a broader spectrum of cognition than just memory) provided a better balance between specificity and sensitivity than did the total number of concerns. A criterion of 1 or more concerns across these two domains provided specificity of 0.802 balanced against a sensitivity for dementia of 0.895 and for MCI-DS of 0.806.

TABLE 4 Prevalence of each individual concern for adults with consensus classifications of cognitively stable (CS), mild cognitive impairment (MCI-DS) or dementia (DEM)

	Group			Mean difference significance[b]	
Domain/Item[a]	CS	MCI-DS	DEM	CS/MCI-DS	CS/DEM
Activities of Daily Living					
Needs help washing/bathing	0.04	0.08	0.63	>0.3	<0.001
Needs help dressing	0.03	0.06	0.63	>0.3	<0.001
Dresses inappropriately	0.01	0.03	0.5	>0.4	<0.001
Undresses inappropriately	0.01	0	0.05	>0.9	>0.15
Needs help eating	0.02	0.06	0.47	>0.25	<0.001
Needs help using bathroom	0.01	0.08	0.47	>0.05	<0.001
Incontinent	0.1	0.22	0.55	>0.05	<0.001
Language and Communication					
Does not initiate conversation	0.02	0.08	0.16	>0.05	<0.01
Does not find words	0.05	0.17	0.45	<0.05	<0.001
Does not follow simple instructions	0.04	0.11	0.55	>0.1	<0.001
Gets lost in middle of conversation	0.04	0.17	0.53	<0.02	<0.001
Does not read	0.01	0.03	0.18	>0.4	<0.001
Does not write	0.01	0.14	0.34	<0.01	<0.001
Sleep–Wake Change Patterns					
Excessive sleep	0.05	0.11	0.21	>0.1	<0.01
Inadequate sleep	0.04	0.11	0.29	>0.1	<0.001
Wakes frequently at night	0.05	0.08	0.37	>0.3	<0.001
Confused at night	0.01	0.08	0.37	<0.05	<0.001
Sleeps excessively during day	0.1	0.08	0.29	>0.9	<0.01
Wanders at night	0.03	0.03	0.24	>0.6	<0.001
Wakes earlier than usual	0.04	0.03	0.18	>0.9	<0.01
Sleeps later than usual	0.05	0.11	0.08	>0.2	>0.4
Ambulation					
Not confident walking over cracks	0.12	0.08	0.55	>0.4	<0.001
Unsteady/loses balance	0.12	0.08	0.5	>0.9	<0.001
Falls	0.06	0.06	0.45	>0.6	<0.001
Requires aids to walk	0.03	0.06	0.26	>0.3	<0.001
Memory					
Does not recognize familiar persons	0.01	0.03	0.26	>0.4	<0.001
Does not remember familiar names	0.01	0.11	0.4	<0.02	<0.001
Does not remember recent events	0.01	0.19	0.55	<0.001	<0.001
Does not find way in familiar place	0.01	0.06	0.32	>0.1	<0.001
Loses track of time	0.04	0.31	0.47	<0.001	<0.001
Loses/misplaces objects	0.1	0.42	0.58	<0.001	<0.001
Puts things in wrong places	0.08	0.39	0.45	<0.001	<0.001
Problems with writing own name	0.03	0.22	0.5	<0.001	<0.001
Problems learning new tasks	0.03	0.22	0.58	<0.001	<0.001
Behavior and Affect					
Wanders	0.02	0.08	0.26	>0.09	<0.001
Withdraws from social activities	0.05	0.14	0.34	>0.09	<0.001
Withdraws from people	0.05	0.06	0.32	>0.5	<0.001

(Continues)

Table 4 (Continued)

Domain/Item[a]	Group			Mean difference significance[b]	
	CS	MCI-DS	DEM	CS/MCI-DS	CS/DEM
Loss of interest in hobbies/activities	0.05	0.11	0.42	>0.1	<0.001
Seems to go into own world	0.09	0.19	0.42	>0.08	<0.001
Obsessive/repetitive behaviours	0.07	0.22	0.34	<0.02	<0.001
Hides/hoards objects	0.04	0.22	0.18	<0.01	<0.01
Problem using familiar objects	0	0.03	0.24	>0.2	<0.001
Increased impulsivity	0.05	0.08	0.29	>0.3	<0.001
Uncertain/lacks confidence	0.03	0.14	0.42	<0.05	<0.001
Anxious/agitated/nervous	0.07	0.19	0.34	<0.05	<0.001
Depressed	0.06	0.11	0.16	>0.2	>0.07
Verbal aggression	0.07	0.14	0.34	>0.1	<0.001
Physical aggression	0.05	0.08	0.32	>0.3	<0.001
Tantrums/crying/shouting	0.05	0.22	0.32	<0.01	<0.001
Lethargy/listlessness	0.06	0.11	0.26	>0.2	<0.01
Talks to self	0.07	0.17	0.26	>0.09	00.01
Adult's Self-reported Problems					
Changes in abilities	0.06	0.28	0.53	<0.01	<0.001
Hearing things	0.04	0.06	0.05	>0.5	>0.5
Seeing Things	0.04	0.08	0.08	>0.3	>0.3
Changes in 'thinking'	0.09	0.11	0.24	>0.4	<0.05
Changes in interests	0.04	0.08	0.24	>0.2	<0.001
Changes in memory	0.06	0.36	0.53	<0.001	<0.001
Notable Changes Observed by Others					
In gait	0.18	0.17	0.74	>0.9	<0.001
In personality	0.06	0.28	0.45	<0.01	<0.001
In friendliness	0.06	0.19	0.13	<0.01	>0.1
In attentiveness	0.1	0.25	0.5	<0.03	<0.001
In weight	0.24	0.28	0.34	>0.4	>0.1
In abnormal voluntary movements	0.06	0.11	0.13	>>6	>0.1

[a]The names of some items have been altered to fit available space.

[b]Based on Fisher exact probabilities (one-tailed without adjustment for multiple tests).

The present NTG-EDSD data showed that informants were largely unaware of a history of MCI diagnoses, with no such history indicated for 92% of cases identified via consensus determinations. Given the broad awareness of AD risk specific to adults with DS, this suggests an especially pressing need for promoting greater awareness of MCI as a diagnostic entity, both for adults with DS and most likely with ID and related conditions across the board. NTG-EDSD data were more concordant with other sources of information regarding history of dementia, but a false-negative rate of 0.24 represents a level of insensitivity that is especially concerning for an instrument developed as an early screen.

The breadth of DSQIID items acknowledges that symptoms of dementia can be highly variable within this target population. However, analyses of individual items found that associations with dementia status varied considerably in strength. As indicated in Table 3, only 22 (out of 63) items showed a significant difference between cognitively stable adults and peers with MCI-DS. Six items even failed to show any differences associated with clinical status. Nevertheless, items with weaknesses in analyses of group effects may be informative for selected individuals, and items insensitive to the severity of dementia affecting the present sample of adults with DS might be informative in tracking progression of more advanced disease or in adults initially presenting with more severe developmental disability. Thus, the advantages of retaining the current NTG-EDSD format outweigh any pressing need for a revision that might provide a modest reduction in the effort needed for completion.

Several translational implications of the present results seem clear. First, the likelihood that an adult with DS without any emergent concerns reported in the Memory or Language and Communications domain is unaffected by AD clinical progression is quite high. Further, as no adult in the CS group had 5 or more concerns in these domains

combined, the likelihood is extremely high that an adult with 5 or more concerns in these domains affected by either MCI-DS or dementia. Similarly, while 68% of individuals with dementia have 15 or more total concerns (excluding self-reports and concerns expressed by others), that percentage fell to 11% for the MCI-DS group 3% for the CS group. Thus, relatively extreme scores, when present, can add to the strength of inferences regarding both screening and diagnostic decisions. As a screen for MCI-DS, though, it is important to accept the NTG-EDSD's limitations. Even with a maximally liberal criterion of one or more total concerns, estimated sensitivity was only 0.889 coupled with an estimated specificity of only 0.522. Thus, almost 50% of unaffected individuals would screen positive, while over 10% of true cases would be missed if clinical judgements were based solely on NTG-EDSD findings, pointing to a clear need for considering additional indicators of risk and concern in clinical practice (e.g. chronological age; *APOE* genotype; performance below expectation in other assessments; and changes in health status or living arrangements that could produce a pseudo-dementia).

This study has several limitations. First, the sample excluded people with more severe preclinical impairments, limiting generalizability of findings for that subpopulation. Second, only cross-sectional data were examined, and longitudinal findings would provide the strongest basis for determining the NTG-EDSD's sensitivity to MCI-DS onset. Third, the diagnosis of MCI is subject to error even for older adults without a history of developmental disability (see Machulda et al., 2019 for a discussion of high reversion rates) and the diagnosis of the condition is even more complicated in adults with DS because of their lifelong cognitive and functional impairments. Fourth, the standard provided by our consensus conference decisions is no doubt imperfect and some disagreements with the NTG-EDSD could reflect errors in this standard rather than in the NTG-EDSD itself. Finally, the NTG-EDSD includes other sections focused on developmental and health history, as well as current health-related concerns. While we were only able to perform a cursory examination of these sections, we found agreement with other sources to be the rule, although it was never perfect. A more targeted evaluation of these sections of the NTG-EDSD seems needed to provide users with a clearer picture of what information can be accepted at face value versus where there are needs for further investigation. Despite these limitations, this study provides strong empirical support for the overall validity of the NTG-EDSD and its potential utility for informing diagnostic and screening decisions focused on dementia status when its imperfections as well as its strengths are recognized.

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ORCID

Wayne Silverman https://orcid.org/0000-0002-7842-8600

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