Received: 30 March 2023 | Revised: 26 May 2023 | Accepted: 10 July 2023

DOI: 10.1002/alz.13419

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Advancing specificity in delirium: The delirium subtyping initiative

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Funding information
Departmental funding from the Critical Care and Respiratory Research group, Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast

Abstract

BACKGROUND: Delirium, a common syndrome with heterogeneous etiologies and clinical presentations, is associated with poor long-term outcomes. Recording and analyzing all delirium equally could be hindering the field's understanding of pathophysiology and identification of targeted treatments. Current delirium subtyping methods reflect clinically evident features but likely do not account for underlying biology.

METHODS: The Delirium Subtyping Initiative (DSI) held three sessions with an international panel of 25 experts.

RESULTS: Meeting participants suggest further characterization of delirium features to complement the existing Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision diagnostic criteria. These should span the range of delirium-spectrum syndromes and be measured consistently across studies. Clinical features should be recorded in conjunction with biospecimen collection, where feasible, in a standardized way, to determine temporal associations of biology coincident with clinical fluctuations.

DISCUSSION: The DSI made recommendations spanning the breadth of delirium research including clinical features, study planning, data collection, and data analysis for characterization of candidate delirium subtypes.

KEYWORDS
acute encephalopathy, biomarkers, clinical features, cognitive change, delirium, endotype, subphenotype, subtype

Highlights

- Delirium features must be clearly defined, standardized, and operationalized.
- Large datasets incorporating both clinical and biomarker variables should be analyzed together.
- Delirium screening should incorporate communication and reasoning.

1 | INTRODUCTION

Characterized by an acute change in attention, global cognition, and arousal/level of consciousness, delirium is thought to result from pathophysiological disruption of key brain networks.[1] It presents as a spectrum of clinical features in heterogeneous populations.[1] In addition to the distress delirium may cause to patients, caregivers, and relatives, and the health-care costs incurred, delirium is associated with poor outcomes including incident or accelerated dementia, institutionalization, and death.[2–4] The multifactorial pathophysiological mechanisms underlying the delirium syndrome remain largely hypothetical. Detailed characterization of these pathways and their clinical manifestations is needed to guide the development of effective prevention and treatment strategies.[5,6]

Delirium is commonly categorized by psychomotor symptoms: hypoactive, hyperactive, and mixed delirium, as first described by Lipowski in 1980.[7–9] Additionally, patients who experience intermediate features between "no delirium" and "clinical delirium" groups are categorized as having subsyndromal delirium.

The acute pathophysiological brain process clinically expressed as subsyndromal delirium, delirium, or coma is described as acute encephalopathy.[5,6] A consensus on nomenclature is important to integrate the literature of acute encephalopathy with that of delirium.[6] The term "delirium disorder" has been proposed to integrate neurophysiological changes and the clinical phenotype.[5] Consensus is also required for subtyping terminology. Potential terms are shown in Table 1.[10,11]

Potential novel subtypes of delirium have been suggested with classification systems considering both symptoms and underlying pathophysiological disturbances.[11–15] To date, only a few studies have examined delirium subtypes, either based on etiology or on the pattern of clinical features.[12,16–18] Girard et al. investigated delirium phenotypes based on potential underlying causes (e.g., hypoxia, sepsis, sedative exposure, renal or hepatic dysfunction), and found substantial overlap in these candidate phenotypes.[12] The prevalence of each phenotype during critical illness and their association with cognition 3 and 12 months after hospital discharge were assessed. Only 32% of participant-delirium days involved one phenotype, whereas 68% involved two or more phenotypes.[12] Sedative-associated delirium was most common, and prediction of poor outcomes varied between the phenotypes.[12]

Tieges et al. and Todd et al. assessed outcomes in relation to individual domains of delirium features, suggesting that attention deficits,[16] and altered level of arousal,[16,17] are independently associated with increased mortality. These findings indicate that recording and investigating specific delirium features may aid prognosis.

Thorough guidelines, statements, and core outcome sets for delirium have previously been produced using consensus methods.[13 19–30] For example, the Network for Investigation of Delirium: Unifying Scientists (NIDUS) 2020 Scientific Think Tank listed identifying etiologic subtypes of delirium as a priority.[31] The think tank suggested that future studies should use standardized approaches to identify contributors to delirium, to incorporate biomarkers, and to use subtyping to guide targeted treatments.

Debate persists regarding the relative merits of approaching delirium based solely on its core features as a manifestation of its common final pathway—that is, regarding all delirium as "all-cause delirium." We suggest that delirium research needs to evaluate the relationship between distinct clinical phenotypes and the discrete pathophysiological pathways underlying them. The primary goal of the Delirium Subtyping Initiative (DSI) is to identify the primary infrastructure required to propose and investigate novel approaches to delirium subtyping. The DSI also aimed, in these sessions, to assess the field's readiness for identification of delirium subtypes using novel data-informed methods, while considering the importance of clinical viability of new subtypes, to generate "knowledge-based" subtypes. We consider clinical features of delirium, including those described in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision (DSM-5-TR),[32] and nomenclature in conjunction with lessons that can be learned from previous subtyping works in other medical conditions such as asthma and acute respiratory distress syndrome (ARDS).[33–36] Herein, we provide recommendations for all delirium researchers, clinicians, health data managers, and research funders. We propose shared future goals to enable collaborative progress toward identification of delirium subtypes.

2 | METHODS

A multidisciplinary group of clinicians and researchers who had published on delirium subtyping, from a range of institutions and spanning the breadth of relevant disciplines, were engaged via e-mail by E.B., E.L.C., and M.O. Early conversations and discussion on the topic of delirium subtypes were held via Zoom and e-mail between September 2021 and March 2022 to gather support, generate ideas, and establish

RESEARCH IN CONTEXT

1. **Systematic review**: Delirium is a common public health problem characterized by an acute change in attention, global cognition, and arousal/level of consciousness in patients. Delirium is most often categorized as either present, absent, or by psychomotor agitation. This study proposes that existing delirium subtyping methods fail to provide an account of the full pathophysiological picture of this syndrome. The primary goal of the Delirium Subtyping Initiative is to identify the primary infrastructure required to propose and investigate novel approaches to delirium subtyping.
2. **Interpretation**: Our findings suggest that clinical features of delirium must be better characterized and operationalized across studies. Patients spanning the whole spectrum of delirium symptoms must be accounted for, and biospecimens collected in conjunction with clinical data.
3. **Future directions**: Better defined clinical and biomarker data will increase understanding of the biological mechanisms of delirium. Large-scale data analyses combining this data may allow characterization of novel subtypes, for further investigation in clinical trials for validation by differential treatment response.

clear aims for the initiative. The DSI included the presidents and members of the three international delirium societies: American Delirium Society (ADS), Australasian Delirium Association (ADA), and European Delirium Association (EDA). After initial discussions and ahead of the planned in-person meeting, a list of key questions was distributed to the committee (Table 2).

TABLE 1 Suggested terms for application to novel delirium subtypes, as defined by Lötvall et al.[10]

Term	Definition
Phenotype	A set of clinical features in a group of patients who share a common syndrome or condition.
Subphenotype	A set of features in a group of patients who share a phenotype that distinguishes the group from other groups of patients within the same phenotype—for example, a shared risk factor, clinical characteristic, diagnostic feature, biomarker, mortality risk, or outcome in response to treatment.
Endotype	A distinct biological mechanism of disease, often associated with an anticipated response to treatment, shared by a subgroup of patients and that might be indicated by shared mortality risk, clinical course, or treatment responsiveness. (As the pathophysiological mechanisms of delirium are unclear, true endotypes cannot yet exist.)

TABLE 2 Initial questions distributed to the Delirium Subtyping Initiative Steering Committee.

1.	a) What are the most important clinical features of delirium?
	b) How can these be measured?
2.	a) How should biomarkers of delirium in general be classified? For example: fluid, electrophysiological, imaging; before, during, and after delirium; inflammatory, neuronal damage, melatonin levels, neurotransmitter presence, network connectivity extent, presence of oxidative stress, etc.
	b) Are there any classification systems or designations that you would oppose?
3.	What baseline information about patient populations is relevant to the purposes of subtyping?
4.	What information regarding precipitants should be considered?
5.	What information regarding patient response deserve consideration with regard to subtyping?
6.	What confounders are relevant?

A program for a DSI meeting was constructed based on the e-mail responses (Table 3). The program consisted of three sessions:

1. Clinical features
2. Validation and refinement
3. Methods for data handling and statistics

Session 1 focused on clinical features, including primary diagnostic signs and symptoms, especially in relation to DSM-5-TR criteria, the delirium construct, and variables to be included in delirium subtyping. We use the term "features" throughout to encompass both objective signs and subjective symptoms. Session 2 centered on the clinical and biomarker variables to be considered, consensus terminology, and defining success of subtype identification. Prior subtyping projects in other medical conditions, such as asthma and ARDS, were reviewed as the foundation of this session. The third session covered methods for handling data and statistics, including various cluster analysis options, factors to consider when combining datasets, and logistical considerations.

Each session was introduced with a short presentation to provide context (given by A.M., P.S., and E.B., respectively). After this, the ensuing discussion was moderated by the chair (E.L.C.). Full details of each session were recorded by A.S. and E.B. The outputs from each session were synthesized into key sections: challenges, recommendations, and aspirational goals. To ensure the whole-group opinion was represented, each committee member was given the opportunity to edit and comment on the statements.

TABLE 3 Program of the Delirium Subtyping Initiative 2022 meeting.

Session	Aims and discussion points:
Session 1: Clinical features	• Discuss how primary features should be selected for delirium diagnosis.
Introductory presentation by Alasdair Maclullich	• Current DSM-5-TR features for delirium • The delirium construct: delirium disorder, acute encephalopathy, integration • How should we select and validate variables to consider for delirium subtyping? (with consideration for clinical features and biomarkers)
Session 2: Refinement and validation	• Discuss definitive terminology
Introductory presentation by Pratik Sinha	• Decide categories for clinical features and biomarkers deemed most important in delirium subtyping and clinical application • Discuss how we define "success" in finding new subtypes: How do we validate our work? • Definitions of phenotype, subphenotype, endotype, treatable trait • What can we learn from previous subphenotyping successes? (e.g., ARDS, AKI, sepsis) • Features and signs thinking of subphenotyping delirium and biomarkers with consideration of underlying encephalopathy • Biomarkers of presumed etiologies and/or biomarkers of specific pathophysiological processes/damage • For example, signs/symptoms, biomarkers, long-term outcomes, populations, restricted populations, risk profiles, precipitants, measurement, domain measurement
Session 3: Methods for handling data and statistics	• Discuss ideas on statistical methods for finding subtypes (e.g., cluster analysis, latent class analysis etc.)
Introductory presentation by Emily Bowman	• Discuss factors to consider when combining datasets, and ways of making data sharing more accessible • Discuss suggestions for study planning, participant consent, data recording (e.g., features and not delirium yes/no). • Logistical factors: How data sets can be combined in the search for subtypes, statistical methods, study planning
Next steps	Planned meeting outputs and information dissemination plan

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision.

TABLE 4 A list of the core disciplines of the 25 experts involved in the Delirium Subtyping Initiative at the time of the November 2022 meeting.

Specialty	N
Critical care medicine	7
Geriatric medicine	5
Science—neurochemistry, molecular biology, neuroscience, physiology, anatomy, public health, data science, and epidemiology	4
Neurology	3
Psychiatry	3
Anesthesiology	2
Nursing—critical care	2
Psychology	1
Subspecialties—gerontology, internal medicine, pulmonary disease, sleep medicine, emergency medicine	4

3 | RESULTS

Twenty-five experts were involved in this initiative, with core disciplines spanning 18 areas, summarized in Table 4. The challenges, recommendations, and future goals identified from each meeting session are summarized in Figure 1. The recommendations are aimed at all delirium researchers and clinicians involved in delirium identification and management, as well as managers of electronic health record systems and research funders.

3.1 | Session 1: clinical features

3.1.1 | Challenges

The diagnostic criteria of delirium in the DSM-5-TR (Table 5) [32] offer only a partial picture of the delirium syndrome. The DSM takes an indexical approach to diagnosis in that its diagnostic criteria include a subset of features that reliably index a given condition, as opposed to a constitutive approach, which would provide a comprehensive list of features.[37] As a result, there may be features not included in the DSM that are important for subtyping purposes. For instance, many of delirium's most distressing neuropsychiatric disturbances, such as hallucinations or dissociative experiences, are not included. Relying on the core diagnostic features of delirium alone is likely inadequate for advancing delirium science and for clinical care. Moreover, it remains unclear how best to define and operationalize these core features, for example, attention deficits. Experienced clinicians may be confident they "know delirium when they see it," but identifying certain features in a reproducible, operationalized fashion remains challenging.

Delirium is most commonly reported as a binary diagnosis—that is, present or absent. Reporting of the severity, or intensity, of delirium is increasing; however, the variability in assessments make combining

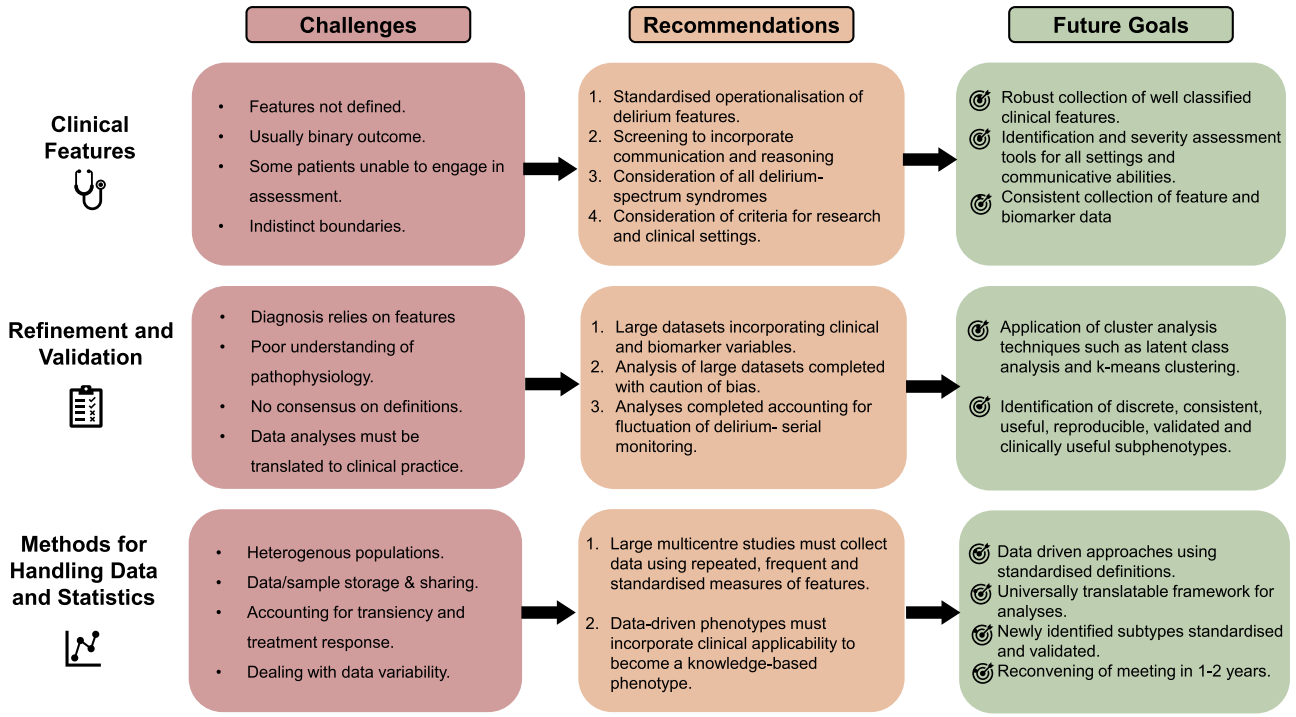

FIGURE 1 A summary of the challenges, recommendations, and future goals established from each session of the Delirium Subtyping Initiative meeting.

TABLE 5 Abbreviated paraphrase of DSM-5-TR diagnostic criteria.

Delirium*	
1	Disturbance in attention and awareness
2	Acute change from baseline that tends to fluctuate during the day
3	At least one additional cognitive disturbance (e.g., memory deficit or disorientation)
4	The disturbance is not better explained by another neurocognitive disorder or coma
5	The disturbance is directly attributable to another medical condition, the effects of a substance (either withdrawal or intoxication), or multiple causes

*Abbreviated paraphrase of DSM-5-TR diagnostic criteria.
Abbreviation: DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision.

studies difficult, even across similar populations. The Better Assessment of Illness Study (BASIL) group, alongside NIDUS, has undertaken efforts to harmonize and crosswalk existing delirium severity tools.[38–40] Nonetheless, their utility is limited in clinical practice due to time constraints, expertise, and the fluctuating course of the syndrome.[38–40]

It remains unclear how best to describe and treat people who are unable to engage with delirium assessment. Research has shown that people who are rated as "unable to assess" for delirium have even worse outcomes than those positive for delirium.[41] However, it is important to remember that the clinician is still able to, and should, assess basic elements of brain function (e.g., level of arousal, breathing pattern, cranial nerves, pupil light, reflexes after testing vital signs) when unable to assess the mental content of consciousness.

Whether it is appropriate to categorize stupor as delirium remains contested. In 2014, the EDA and ADS jointly authored a statement advocating for an expansive definition of delirium that includes stupor,[42] followed by successful efforts to modify the text of the forthcoming DSM-5.[43] This allowed patients with "minimal responses to verbal stimulation" to be scored as inattentive, consistent with delirium. Patients with minimal responses only to physical stimulation were excluded from delirium by Criterion D. A debate on the subject was held in 2016 at the annual meeting of the ADS and subsequently published.[44] In 2022 the DSM-5-TR modified its position, explaining that "minimal responses to verbal or physical stimulation" should be classified as coma or stupor and "not as delirium."[32] Coma is a state of unarousable unconsciousness, characterized by a severe disturbance in arousal and the alerting system of the brain, in which eyes remain closed as response to any type of stimulation.[45] "Stupor" is ill defined but regarded to be present in patients who open their eyes in response to verbal stimuli, with no eye contact.[46]

The broader range of features of acute brain dysfunction alongside the core diagnostic criteria of delirium and relevant underlying pathophysiology were discussed within the session. It is unclear whether "possible/probable delirium" is a useful construct or indeed whether research and clinical criteria should differ.[47] Boundaries between clinical syndromes, for example, delirium and dementia, can be indistinct and are likely to remain so. The existence of this continuum is a topic of debate among the DSI.

Delirium, as with all psychiatric conditions, is defined by its clinical features, and it remains uncertain whether novel biomarkers (e.g., blood or cerebrospinal fluid [CSF] markers, neuroimaging, or electroencephalography [EEG]) might aid clinical practice. However, patient experience remains the centerpiece of delirium, both as a potential indicator of underlying pathophysiology and as an unmet need for effective intervention. It is possible that the diagnostic threshold for delirium or the pattern of core features may differ between populations of varying age or illness severity. Detailed mental status evaluations are important and involve more than evaluating attention, cognition, and arousal. All potentially distressing disturbances are important to note, including emotional lability, fear, hallucinations, paranoia, apathy, or dissociation. We recognize the time restraints that may arise in suggesting all clinicians complete detailed mental status examinations, and that evidence-based treatments for distressing symptoms are still needed.

Delirium severity may be relevant to subtyping as increasing levels of severity are associated with clinically relevant outcomes.[48] However, it is not yet clear how to best measure and quantify delirium severity. The domains assessed by existing delirium severity tools vary.[49] Delirium severity is associated with biomarkers of systemic inflammation,[50] neurofilament light,[51] plasma tau,[52] short- and long-term mortality,[48,53] length of stay,[54,55] and cognitive decline.[56] Similarly, consensus is required on the necessary clinical, biological, and patient-experience variables to measure when assessing severity.

Development and use of distinct research and clinical criteria for delirium subtyping was discussed during the DSI meeting. Research criteria have been published by Trzepacz et al. based on detailed phenomenological analysis;[47] however, consensus was not reached during our DSI sessions. Future candidate subtypes may incorporate and define what constitutes delirium in unique medical populations. Separate diagnostic criteria for delirium may, in the future, be explored for use in clinical and specific research settings.

Delirium already shares interfaces, for example, with dementia, and it is expected that subtyping will introduce additional boundaries that must be approached with caution. Further research may also differentiate multiple sets of core delirium syndromes (e.g., different core features in hepatic encephalopathy vs. septic encephalopathy), but such expressions of delirium should nevertheless be understood as subtypes of a unified model of delirium.

3.1.2 | Recommendations

- -Attempts to operationalize the features of delirium need to be standardized across studies to facilitate combination and comparison of results.
- -Use of the term "delirium" without a specified etiology, pathophysiology, or subtype should be understood as "all-cause delirium," similar to "all-cause dementia."

Clearly defining and operationalizing the identification of key features will advance understanding of the lived delirium experience. Approaching delirium research independently of iterative changes across DSM editions may help identify delirium subtypes by facilitating consideration of the lesser-discussed features. To represent the entire spectrum of delirium presentations, a comprehensive description of delirium should be constitutive—that is, incorporating the full spectrum of delirium features, rather than merely its indexical criteria.

For subtyping purposes, the same features must be assessed consistently using comparable tools. Features not captured by DSM-5-TR criteria should be systematically assessed, recorded, and standardized along with core features. Such efforts will require close collaboration as the range of potential features are broad and, to date, incompletely characterized and understood.

- -In addition to measuring specific features, delirium screening should involve a patient's level of verbal communication and reasoning.

Patients' understanding of why, who, what, and where should be evaluated: Is their thinking clear, and can they use language in a coherent, goal-directed, productive way? Where appropriate, their ability to use reason and appropriate syntax to communicate effectively or to interpret syntax correctly, should be evaluated. Open-ended questions can better assess the extent to which patients can engage productively and coherently. We also see a need to pursue additional ways of evaluating the mental content of consciousness in patients who are currently considered "unable to engage." In a review of 88,206 Confusion Assessment Method (CAM) records, people who were "unable to assess" had worse outcomes.[41] In critically ill patients, it may be the case that they are unable to speak due to an endotracheal tube rather than because of delirium. The definition of "inability to engage" deserves careful operationalization, and creative approaches to modifying assessments for people incapable of performing certain tasks should be explored and validated.

This recommendation applies to patients who are being screened due to risk of, or suspected, delirium. However, we acknowledge that often delirium screening is carried out for less specific purposes, for example, during overall monitoring for infection, and so this level of careful observation may not be necessary.

- -Delirium subtyping methods should consider including a broader range of "delirium-spectrum syndromes."

Identification of new methods for delirium subtyping should consider all "delirium-spectrum syndromes," ranging from mild subsyndromal delirium to stupor and coma, while maintaining the fidelity of delirium as a categorical entity. Starting with a broader clinical impression without restriction to delirium diagnosis could also provide a broader understanding of the spectrum of mental states ranging from subsyndromal delirium to delirium and perhaps reduce the risk of maintaining clinically unhelpful or arbitrary boundaries. This approach deserves consideration across clinical settings as there may be unique setting-specific applications.

TABLE 6 Display of the diagnostic process of acute myocardial infarction, and illustrative examples of how this framework might apply to delirium.

	Acute myocardial infarction	Example: septic encephalopathy
Symptom	Chest pain	Delirium: acute disturbance in attention and cognition
Clinical biomarker	ST segment elevation of electrocardiogram	Example: disturbance in brain activity recorded by EEG
Blood biomarker	Troponin	Example: elevated peripheral inflammatory biomarkers such as IL-6, IL-8, TNF-α, and/or more specific brain injury markers such as NfL and S100β
Diagnostic test	Left heart catheterization	Example: DSM criteria alongside biomarker threshold tests in blood/CSF/EEG
Intervention	Coronary artery stent	Example: non-pharmacological measures or future recommended pharmacological treatments

Abbreviations: CSF, cerebrospinal fluid; DSM, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; IL, interleukin; TNF, tumor necrosis factor; NfL, neurofilament light; S100β, calcium-binding protein B.

3.1.3 | Future goals

-Robust collection of individual, routine, and well-classified clinical features.

Detailed clinical features should be recorded both within research studies and, where possible, in routinely collected electronic care data. Recording of individual features would facilitate both identification and validation of subtypes within clinical research studies and testing of these subtypes in real-world data.

-Delirium identification and severity assessment tools for all medical settings and communicative abilities.

Delirium assessment and severity tools should be applicable in the settings of both verbal and non-verbal communication. Arousal, attention, orientation, and successful completion of tasks should be the starting point for assessing ability. Assessment of non-verbal patients needs to incorporate cues for attention, such as eye tracking. Delirium should also be assessable in patients with reduced levels of arousal. Delirium severity should be domain specific, for which severity of each feature should be measured. It may be appropriate to extend both the mild and severe ends of the delirium spectrum. Assessment tools should be common across, and modified for, different patient populations. Delirium-related distress should also be considered in assessments.

-Consistent collection of clinical feature data and biomarker data in both clinical and research settings.

Biomarkers characterize the encephalopathy presenting as delirium. Diagnosis is ideally based on reliable, empirical features, supported by biomarkers, as in other medical conditions. An example of applicability to delirium is shown in Table 6. Where a site can collect biomarker data reliably, this should be planned and completed in accordance with global standards regarding sampling, storage, and analysis. Biological samples must be collected alongside clinical data. Large-scale biological data are essential to consider association, causation, and ultimately pathophysiology of delirium. Datasets should be harmonized across institutions to facilitate large, comprehensive datasets capable of testing subtyping-based hypotheses.

3.2 | Session 2: refinement and validation

3.2.1 | Challenges

Delirium diagnosis currently relies on observing and identifying clinical features. Previous subtyping works in ARDS, sepsis, and asthma relied on the study of biomarkers combined with clinical data in cluster-style analyses.[10,33,34,57,58] Previously identified ARDS subphenotypes included plasma levels of interleukins 6 and 8 (IL-6 and IL-8), tumor necrosis factor (TNF) receptor-1, and plasminogen activator inhibitor (PAI)-1.[33] Asthma endotyping uses biomarkers such as blood eosinophilia, fractional exhaled nitric oxide, and immunoglobin E.[10] Subtypes of sepsis were identified based on more commonly collected clinical variables such as albumin, bicarbonate, bilirubin, blood urea nitrogen, chloride, C-reactive protein, sodium, and troponin.[58]

Previous subphenotyping works have adopted unsupervised statistical methods including latent class analysis (LCA),[33,35] and K-means clustering.[59] LCA is a probabilistic, finite mixture modeling approach allowing data clustering with statistical inference.[60,61] K-means is an iterative algorithm that partitions datasets into predefined distinct clusters, in which each data point belongs in one group.[62] These methods are unsupervised discovery methods that separate data into meaningful subgroups. The translatability of these methods into clinical practice may be limited due to bias introduced by missing data. This is not an exhaustive list of methods for performing cluster analyses; however, these methods do allow large-scale analyses that have previously yielded reliable results in other medical conditions. The data required for these analyses will, in many cases, be already available from existing delirium research cohorts.

Large, combined, replicable patient cohorts are required to facilitate big-data–driven analyses. At present, the categories of delirium features and biomarkers deemed most important are not consistently reported or, in most instances, even measured in studies.

Heterogeneity also remains in populations, restrictions within populations, risk profiles, precipitants, and assessment of long-term outcomes.

3.2.2 | Recommendations

-Use of large datasets incorporating clinical and biomarker variables.

Prior work using cluster analyses of patients with varying neuropsychiatric profiles has yielded proposals for a core-feature model of delirium.[47,63,64] Future analyses should include both clinical and biomarker data in an unbiased approach.[63,65] Included biomarkers should be selected based on hypothesized underlying mechanisms, availability of biomarker measurement, and access to samples. For example, inflammation might be investigated using analytes such as IL-6 or IL-8 from blood plasma or CSF.

-Analysis of large datasets deserves circumspection.

We must be cautious about underestimating the interrelationship between variables in a model and in dealing with datasets that underrepresent patients with low arousal or limited ability to communicate verbally. Identified latent classes must clearly display subgroups of patients with delirium rather than simply highlighting patterns among variables included in statistical models. The transient nature of delirium must be addressed using longitudinal assessment, in which subgroups are identified and tracked over time using serial monitoring.

3.2.3 | Future goals

-Application of cluster analysis techniques (e.g., latent class analysis) in delirium cohorts.

Data complexity and feature quality should dictate clinical phenotypes. Methods used must be explainable and understood by researchers and clinicians.

-Identification of strong delirium subtypes.

Strong phenotypes should be discrete, consistent, reproducible, validated, and clinically useful. Endotypes should be identified by linking clinical features to a biological phenotype, derived from biomarker data. Multivariable phenotyping and prognostic enrichment will allow for the ultimate goal of predictive enrichment: the ability to identify groups of patients with specific treatment responses or treatable traits. Analyses should be replicated across phenotypes and populations. We should also define success in subtyping, by establishing methods for subtype validation and how to update subtypes when new developments arise.

3.3 | Session 3: methods for handling data and statistics

3.3.1 | Challenges

Adequately recording the heterogeneity of delirium presentations (across features, duration, and response to treatment), populations (across medical settings, demographics, precipitants, physiological insults, levels of pre-existing cognition), and subsequent outcomes in ways that facilitate sharing and consolidation is challenging. In addition, differences are anticipated between hypotheses and data- or sample-driven studies. Even where the same tests are used in different studies, often the exact methods and thresholds used vary.

3.3.2 | Recommendations

-Large multicenter studies should collect data using repeated, frequent, and standardized measures of clinical features.

Biomarker analyses, where feasible, should be completed alongside robust recording of features, tracked feature fluctuation, and relevant clinical variables. Subphenotype stability should be tracked throughout the delirium fluctuations in course. Standardization of features to be recorded, methods of tests, and thresholds will allow researchers to be selective in formation of analyses. Analyses should be completed in both similar and different populations.

-Data-driven phenotypes must incorporate clinical applicability to become a knowledge-based phenotype.

Groups identified using data-driven models should be compared to a "knowledge-based phenotype," written according to existing knowledge of the clinical signs and symptoms of delirium.

3.3.3 | Future goals

-Data collection (in the written and sample form) should be robust, consistent, and with the ability to share statistical protocols across investigators.
-Operationalization and standardization of all recommendations is essential for data-driven approaches to be adopted alongside clinical features to identify new delirium subtypes.
-A universally translatable language within which we are collecting data based on a framework is required.
-Newly identified subtypes should not be defined as correct before being standardized and validated.
-The DSI plans to reconvene in 1 to 2 years for progress updates and review of goals.

4 | DISCUSSION

At the meeting for the DSI, attendees reviewed the field's readiness for identification of novel delirium subtypes. The areas covered included

clinical features, refinement and validation, and data handling and statistics. The committee agreed that the core clinical features of delirium should be operationalized and standardized to allow for comparison and combination of results across datasets. Drawing together large data facilitates cluster analyses that will indicate meaningful clusters of patients with delirium. Description and measurement of features must be completed consistently in studies using validated methods and include modifications to suit patient populations or needs. A suite of tests for each clinical domain being assessed, clearly defining user instructions and thresholds, is needed to enhance reliability. Studies should include the range of "delirium-spectrum syndromes."

Such recommendations for meticulous measurement and documentation will be met with many challenges. While thorough record of all relevant clinical and biological features would optimize big-data–driven analyses, comprehensiveness of assessment and recording will be limited by acceptability to both patients/participants and staff.

The discussions of delirium's clinical presentations highlight ongoing questions regarding the boundaries of delirium; they also suggest that we should revisit basic theories of delirium en route to delirium subtypes. Ground-breaking work requires, at the very least, that some ground be broken, and advances in delirium subtyping naturally invite skepticism when such work challenges traditional models. "Lumping" of information has advanced our knowledge of the delirium syndrome and has brought us to this point where some splitting is required.

Refinement and validation require reproducibility of analyses across multiple large cohorts. We should learn from previous subphenotyping projects, while ensuring all generated models are clinically applicable to delirium. This task includes determining how delirium subtypes should be defined—as subphenotypes, endotypes, or by an alternative nomenclature. Analyses should include an array of clinical features and biomarker measurements taken from blood, CSF, EEG, and magnetic resonance imaging. These measurements and analyses should be as uniform as feasible across cohorts to identify strong endotypes, and eventually, treatable traits and preventive strategies. These endotypes should be knowledge based as well as data driven, to ensure they are clinically useful. Updates of identified and validated subtypes must be completed as knowledge on delirium expands. A stepwise approach may lead to the success of expanding information on delirium, alongside identification of meaningful clusters.

5 | CONCLUSION

Delirium remains an umbrella term for a syndrome of heterogenous populations with varied physiological parameters, cognitive health, environmental factors, vulnerabilities, underlying mechanisms, etiologies, and clinical manifestations. Treating all episodes of delirium as equal, a type of "all-cause delirium," can hinder identification of underlying physiological mechanisms and, thus, effective, or preventive, treatments.

The broad range of clinical features across delirium-spectrum syndromes should be measured consistently across studies, to allow for finer characterization, subtype identification, and comparisons across sites. Detailed instruments should also be able to screen patients unable to communicate verbally. Individual features should be evaluated regularly to monitor for fluctuation, with concurrent bio-samples collection. Clustering analyses of large, multicenter datasets should incorporate both clinical and biomarker data for identification of reproducible potential subphenotypes and endotypes. Stratification by identified endotypes in delirium trials will facilitate validation and manipulation of treatable traits.

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ACKNOWLEDGMENTS

The DSI meeting was hosted using departmental funding in the Critical Care and Respiratory Research Group (Principal Investigator Professor Danny McAuley), at the Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast.[2]

CONFLICT OF INTEREST STATEMENT

T.D.G. receives research funding from Ceribell and served previously on an advisory board for Lungpacer Medical Inc. S.C.L. receives funding from the National Institute on Aging (R03AG074035), Larry L. Hillblom Foundation (A137420), UCSF Claude D. Pepper Older Americans Independence Center funded by National Institute on Aging (P30 AG044281), and the Bakar Aging Research Institute. She also receives royalties from Oxford University Press. H.L.L. receives funding from the National Institute on Aging (K23AG076662). E.S.O. receives funding from the National Institute on Aging and National Institutes of Health (R01AG076525, R01AG057725). K.M.P. receives funding from the National Heart, Lung, and Blood Institute (T32HL007820). H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). All other authors have no disclosures. Author disclosures are available in the supporting information.

CONSENT STATEMENT

No consent was required for the completion of this work.

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SUPPORTING INFORMATION

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

How to cite this article: Bowman EML, Brummel NE, Caplan GA, et al. Advancing specificity in delirium: The delirium subtyping initiative. *Alzheimer's Dement*. 2024;20:183–194. https://doi.org/10.1002/alz.13419