Patient self-report for evaluating mild cognitive impairment and prodromal Alzheimer’s disease

Lori Frank1*, William R Lenderking2, Kellee Howard2 and Marc Cantillon3

Abstract

Patient-reported outcome (PRO) measures are used to evaluate disease and treatments in many therapeutic areas, capturing relevant aspects of the disorder not obtainable through clinician or informant report, including those for which patients may have a greater level of awareness than those around them. Using PRO measures in mild cognitive impairment (MCI) and prodromal Alzheimer’s disease (AD) presents challenges given the presence of cognitive impairment and loss of insight. This overview presents issues relevant to the value of patient report with emphasis on the role of insight. Complex activities of daily living functioning and executive functioning emerge as areas of particular promise for obtaining patient self-report. The full promise of patient self-report has yet to be realized in MCI and prodromal AD, however, in part because of lack of PRO measures developed specifically for mild disease, limited use of best practices in new measure development, and limited attention to psychometric evaluation. Resolving different diagnostic definitions and improving clinical understanding of MCI and prodromal AD will also be critical to the development and use of PRO measures.

Introduction

Patient-reported outcome (PRO) measures are used to evaluate the impact of disease and treatment in many therapeutic areas. Among the advantages of patient report is the potential to capture aspects of the disease and treatment experience uniquely accessible to patients and, relatedly, to improve the measurement of therapeutic intervention effects [1]. The clinician’s specialized framework of knowledge makes the clinician the most accurate reporter for some aspects of the disease experience. For which is the patient the more accurate reporter?

The most recent recommendations for core clinical criteria for the diagnosis of mild cognitive impairment (MCI) due to Alzheimer’s disease (AD) [2] note that despite 'preservation of independence in functional abilities’ some impairment in complex functional tasks may be evident, such as higher error rate, taking longer, and/or being less efficient. The companion statement on research criteria for preclinical stages of AD [3] raises the possibility that biomarkers in combination with ‘subjective assessment of subtle change will prove to be useful.’ Subtle but potentially important features of the disease experience may be inaccessible to those other than the patient, raising the interesting possibility that the patient may have the most comprehensive and accurate knowledge of performance [4].

Although impairment in social or occupational functioning is part of AD diagnostic criteria [5], the place of functioning in diagnostic definitions of MCI is still evolving [2,6-8]. Initial definitions of MCI were based on cognitive impairment and intact activities of daily living [9], but empirical data support the presence of functional deficits encompassing skills and activities beyond instrumental activities of daily living (ADLs), many of them subtle [10-15]. Functioning therefore emerges as an area of potential value for patient self-report. Two other areas with substantial prior research on patient self-report in AD and MCI are neuropsychiatric symptoms and health-related quality of life.

There are of course several important obstacles to use of patient self-report in cognitive impairment. Disease-related disruptions to memory and cognition may interfere with the ability to complete a questionnaire accurately, as might loss of insight with progressive disease [16], leading to reliance on informant and clinician report [15]. However, accuracy of informants, especially family caregivers, can also be suboptimal for multiple reasons, including the distortions introduced by caregiver depression and lack of caregiver awareness of some symptoms (for example, [17]).

The focus of this overview is on the value of patient report for evaluating disease course and treatments in
MCI and in prodromal, or ‘early’ AD [18]. The emphasis is on early disease, corresponding to newer terminology referencing prodromal AD, as well as to the less specific ‘mild cognitive impairment’ referenced by Petersen and colleagues [9].

Methods and findings
Domains important for patient report in cognition were identified based on literature reviews completed for the Cognition Initiative, now the Cognition Working Group of the Critical Path Institute, between August 2009 and January 2011. Initial searches were limited to the period from January 2004 to June 2009 with subsequent updates through March 2011. Functioning, variously defined, emerged as an important area for self-report in early disease. There has been recent PRO measure development and empirical studies in the areas of complex ADL functioning and neuropsychological aspects of functioning (for example, executive functioning); additional work in self-reported neuropsychiatric symptoms and health-related quality of life was also identified. Each of these areas is considered briefly below, followed by a discussion of the role of insight in patient self-report. Details of the search and literature review are available below. A summary of selected measures is presented in Table 1.

Search methods
The initial literature search strategy targeted publications on AD and MCI (specifically ‘AD, moderate to severe’ and ‘MCI or very early AD’), crossing this literature with specific domain terms (functioning, functional status, executive functioning, HRQL, affect/mood/behavior). The search was limited to English language publications from 2004 to 2009 in MedLine and Embase. To ensure that relevant measures used in clinical trials for currently marketed AD drugs were included, separate searches were conducted for MCI and AD in each domain of interest, limited to 1999 to 2009, with the main focus on ‘Alzheimer’s disease’ OR ‘mild cognitive impairment’ OR ‘cognitive impairment no dementia.’ Since treatment efficacy was not the focus of this review, but rather measures used to assess efficacy and effectiveness from the perspective of patients and caregivers, this part of the search was limited to review articles. Searches were conducted in PubMed initially, followed by Medline, Cochrane Library of Systematic Reviews, PsychINFO, and Embase.

Full articles were retrieved if information on measure development, psychometric evaluation, and/or use were mentioned in the abstract. Information from retrieved articles was abstracted into tables addressing each of these elements. All relevant titles and abstracts were screened (level 1). Full papers were obtained for any studies considered potentially eligible or where uncertainty existed as to whether a paper should be included in the review. Full papers were formally assessed for relevance (level 2). Level 1 and 2 reviews for the literature review conformed to pre-determined inclusion and exclusion criteria, including focus on early AD/MCI patients, and caregiver- and patient-reported outcomes were included. Electronic data extraction forms were completed by reviewers trained in the critical assessment of evidence. A third reviewer independently examined any inconsistencies in extracted data elements between extractors and missing data fields. Any discrepancies in extracted data were resolved by consensus and any disagreements were resolved by consulting with a third investigator, as necessary. The consensus version of the extracted data was subsequently exported to the evidence tables. The extracted data elements from each accepted study included study design and measures, instruments, and domains and items of interest.

Patient-reported outcome measurement by domain

Everyday functioning: complex activities of daily living
Definitions of ‘functioning’ vary but generally include both basic activities of daily living (for example, bathing, dressing) and instrumental activities of daily living (for example, handling finances, cooking, phone use) [19-21], with the latter set widely used to assess MCI and prodromal AD [22-32]. The term ‘everyday functioning’ is used to indicate basic, instrumental, and complex or ‘higher order’ ADLs (for example, planning social functions; see, for example, [33]).

Consensus on the specific functional deficits that characterize MCI or prodromal AD has not been reached, especially since early definitions of MCI required the absence of functional deficits. The presence of MCI, as well as subtlety of functional deficits relative to AD, is now recognized [34].

Many AD functioning measures exist given the centrality of functioning to the expression of disease, but most are informant reported, including in: the Physical Self-Maintenance Scale [35-37]; the Blessed Dementia Scale [36-38]; the Dependence Scale in Alzheimer’s Disease [39]; the Disability Assessment for Dementia Scale [40,41]; the Interview for Deterioration in Daily Living Dementia [42,43]; and the Progressive Deterioration Scale [44].

Like most measures of functioning used in AD, the Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) was developed as an interview-based informant-reported measure of level of independence in specific tasks [45]. Subsequently, a version for use with MCI, the ADCS ADL-MCI, was developed with both informant- and patient-completed versions; item content includes complex and instrumental ADLs, such
Table 1. Summary of select measures relevant to patient-reported outcomes in mild cognitive impairment

| Measure | Reporter | Patient population | Description | Psychometric performance | Comments |
|---------|----------|--------------------|-------------|--------------------------|----------|
| Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) and ADCS ADL-MCI [47,123] | Patient, informant | Mild through severe AD | 23-item inventory of ADL, rated based on extent of assistance the patient requires (independently, with supervision, with physical help). 0 (total independence in performing an activity) to 4 (total inability to act independently). Each question varies in the number of options to choose. Total score range: 0 to 78; higher scores indicate less functional impairment. ADCS ADL-MCI: 18 item and 24 item versions | Validity: Item content developed by a subcommittee of the ADCS Initial item pool included ADL items from existing scales and novel items based on clinical experience. Items refined following pre-testing. ADCS ADL-MCI: 24 item version demonstrated superior sensitivity and specificity for aMCI discrimination from controls. | Widely used, including as endpoint in clinical trials. Developed based on substantial clinical experience; comprehensive item capture. |
| Alzheimer’s Disease Cooperative Study Prevention Study (ADL-PI) [51-53,56] | Patient, informant | Used in mild through severe AD | 20-item measure of ADLs and physical functioning. Five difficulty-based response options from ‘as well as usual/no difficulty’ to ‘a lot of difficulty’; with ‘not at all’ option. Total score ranges from 0 to 45; higher scores indicate less functional impairment. | Validity: Items selected based on discrimination between MCI and normal subjects. Discriminated between CDR 0 and 0.5. Scores related to cognitive performance. Moderate correlation of ADL-MCI patient rating with informant rating, although most scores near ceiling. Reliability: Test-retest reliability acceptable to good (3-month interval). | Good psychometric performance; item content from established measures. |
| Perceived Deficits Questionnaire (PDQ) [124] | Patient | Developed for multiple sclerosis; used in AD and MCI | The PDQ is a part of the Multiple Sclerosis Quality of Life Inventory that assesses self-perceived cognitive difficulties. It consists of 20 items that address cognitive difficulties in four dimensions (attention/concentration, planning/organization, retrospective memory and prospective memory). Items are rated on a five-point scale ranging from 1 (never) to 5 (almost always). | No psychometric data available for MCI/AD | Developed for multiple sclerosis population but content relevant to MCI/AD. |
| Multidimensional Assessment of Neurodegenerative Symptoms questionnaire (MANS) [125] | Patient, informant | Neurodegenerative disorders generally, early detection through more severe levels | Developed as a multidimensional measure permitting early detection and patient and informant comparison and applicable from mild severity onward. Developed to measure cognitive personality, functional, and motor symptoms. Items are rated on a five-point frequency scale from 0 (never) to 4 (routinely) with once/occasionally/more than monthly as intermediate anchors. | Validity: Four subscales supported by exploratory factor analysis. Construct validity supported through moderate to high correlation with clinical measures. Reliability: High internal consistency (alpha = 0.98) for both versions. | Multiple domains targeted to aid with differential diagnosis. Seeks to be gender-neutral, overcoming gender/activity confounds of other measures. Frequency scale may limit sensitivity. |

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Table 1. Continued

| Measure                                                                 | Reporter          | Patient population | Description                                                                                                                                                                                                                                                                                                                                 | Psychometric performance                                                                 | Comments                                                                                     |
|------------------------------------------------------------------------|-------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Patient-Reported Outcomes in Cognitive Impairment (PROCOG) [14]        | Patient, informant| MCI through moderate AD | 55-item measure of cognitive impairment symptoms and their impact in patients with MCI and mild to moderate AD. There are seven subscales: affect, skill loss, semantic memory, short-term memory, cognitive functioning, social impact, and long-term memory. Items are rated on a five-point Likert scale. Total scores range from 0 to 220. Higher scores indicate greater impact of cognitive impairment. | Validity                                                                                   | Developed based on clinician input and focus groups with patients and informants. Subscale and total scores were lowest for controls and highest for AD patients, with MCI patients intermediate. Highest correlations with the PROCOG were observed for the QOL-AD (r = -0.53) and CES-D (r = 0.60). PROCOG Aff ect subscale was most highly correlated to the CES-D. Correlations with the neuropsychological measures were low to moderate. MCI and DAT scores differed significantly (P ≤ 0.05 for total and subscale scores with the exception of 'social impact'). 'Long-term memory' item did not distinguish among the three groups. 'Skill loss' and 'memory for recent events' subscales showed the most separation between MCI and DAT patients. |
| Mail-In Cognitive Function Screening Instrument [56]                    | Patient           |                    | 14-item brief screening instrument assessing cognitive and functional decline; prior year recall period. Response options are 'yes' (1), 'no' (0), or 'maybe' (0.5). Total scores range from 0 to 14; higher score indicate worse status.                                                                                                                                                                                   | Validity                                                                                   | Patient scores associated with clinical measures. Patient/informant core difference associated with mMMSE, NYU Paragraph immediate and delayed recall, free and cued reminder test. Trend toward relationship to APOE genotype group (none, at least one) for patient but not informant score. Brief screening measure demonstrating sensitivity to subjective memory complaints. Brevity limits comprehensiveness but for intended purpose content is appropriate. |
| Executive functioning                                                  |                   |                    |                                                                                               | No psychometric data reported                                                                                                                                  | Item content targets accepted executive functioning skills.                                                                                         |

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### Table 1. Continued

| Measure                                      | Reporter        | Patient population | Description                                                                                                                                                                                                 | Psychometric performance                                                                                                                                                                                                 | Comments                                                                 |
|----------------------------------------------|-----------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Cognitive Difficulties Scale (CDS) [126-128] | Patient, informant |                   | Multiple versions (original was 39-item self-report, 26-item version and 38-item version; family report version available). The 38-item self report version includes items related to difficulties in attention, concentration, orientation, memory, praxis, domestic activities and errands, facial recognition, task efficiency, and name finding. Items are rated on a five-point Likert scale on frequency of difficulty over prior month, from 0 (not at all) to 4 (very often) | Validity: Derived and adapted from existing measures Profile of Mood States, Inventory of Psychic and Somatic Complaints, and Minnesota Multiphasic Personality Inventory. Item content also based on expert clinical opinion. 38-item self-report version: moderate to high correlation with performance on neuropsychological measures of memory and attention. | Developed from established measures. Provides measure of anosognosia. |
| Everyday Cognition (ECog) [64]               | Patient, informant |                   | 39-item measure of neuropsychological functioning related to cognitive impairment. Items are rated on a four-point scale: 1, better or no change compared to 10 years earlier; 2, questionable/occasionally worse; 3, consistently a little worse; 4, consistently much worse. Higher scores represent worse daily function. | Validity: Developed through clinical input with reference to literature; designed to address key memory and cognition symptoms that can be linked to specific neuropsychological deficits. Data support six domain factors and one global factor: everyday memory, everyday language (which includes everyday semantic knowledge), everyday visuospatial abilities, and the executive domains of everyday planning, organization, and divided attention. Psychometric performance acceptable, with discrimination by clinical severity level and discrimination by different MCI subtypes. Low correlation with age and educational level (r = 0.19 and -0.16, respectively), suggestive of minimal education level bias. Convergent validity supported based on magnitude of correlation to the clinical measures and relationship to diagnostic category. | Developed to minimize confound with educational level. |
| Frontal Systems Behavior Scale (FrSBe) [71,129] | Patient, informant | Multiple therapeutic areas | 46-item behavior scale rates the frontal impairments of apathy, disinhibition, and executive dysfunction, on a five-point Likert scale ranging from almost never (1) to almost always (5) for a maximum score of 240. Higher scores indicate more abnormal behavior. | Validity: High intrascale reliability (0.95) in normal and pathological populations, subscale reliabilities of 0.78 or higher, Adequate internal consistency reliability (Cronbach’s alpha: 0.92), and construct and criterion-related validity in multiple studies. | Widely used across medical/psychiatric diseases. Captures cognitive-behavioral aspects of frontal symptoms. |

AD, Alzheimer’s disease; ADCS, Alzheimer’s Disease Cooperative Study; ADL, Activities of Daily Living; ADL-PI, Activities of Daily Living Prevention Instrument; aMCI, amnestic MCI; APOE, apolipoprotein E; BRI, Behavioral Rating Index; BRIEF-A, Behavior Rating Inventory of Executive Function - Adult version; CDR, Clinical Dementia Rating scale; CDS, Cognitive Difficulties Scale; CES-D, Center for Epidemiologic Studies Depression Scale; DAT, dementia of Alzheimer’s type; ICC, intra-class correlation coefficient; MCI, mild cognitive impairment; MI, Metacognitive Index; mMMSE, Modified Mini-Mental State Examination; PDQ, Perceived Deficits Questionnaire; PROCOG, Patient-Reported Outcomes in Cognitive Impairment; QOL, quality of life.
as handling finances, shopping, travel, and remembering appointments [46]. To meet the need for a brief in-home rated ADL measure, the Activities of Daily Living Prevention Instrument was developed by the Alzheimer’s Disease Cooperative Study Prevention Instrument Project, and is based in part on items from the ACDS ADL-MCI, the Functional Activities Questionnaire [47], and the Disability Assessment for Dementia Scale [46,48-52]. There are both patient- and informant-rated versions; item content overlaps substantially with the ADCS ADL-MCI.

The ADCS Prevention Instrument Project also developed the Mail-In Cognitive Function Screening Instrument, with patient- and informant-completed versions. Although intended as a screening tool, item content includes a range of everyday functioning, including social activities and work performance [41,42,51-54].

The Patient-Reported Outcomes in Cognitive Impairment (PROCOG) [14] measures the impact of MCI and early AD-associated cognitive impairment on multiple domains, including specific everyday functioning skills and social functioning. Similarly, the Perceived Deficits Questionnaire addresses a range of symptoms and functional impacts of memory loss based on patient self-report and has proven useful for signal detection in a treatment trial for MCI, although it was originally developed for use in multiple sclerosis [4]. The Perceived Deficits Questionnaire is an example of a measure of ‘subjective memory complaints,’ most of which include cognition symptom report along with functioning (for example, Questionnaire d’auto-évaluation de la mémoire (QAM)/Self-Evaluation Complaint Questionnaire [55]; Self-Rating Scale of Memory Functions [56]).

A summary of some relevant measures is provided in Table 1. As noted by others, few published reports on functioning measures include psychometric performance [32], although for the measures with patient-reported versions, available test-retest reliability data and concurrent or predictive validity data generally indicate good psychometric performance, providing some evidence of accurate measurement. Of note is that despite content overlap in existing measures, some domains are relatively under-represented, such as social functioning or functioning related to language skills - both areas for which patient report may be particularly well-suited.

The domain of functional status in cognitive disorders is one with a long history of scale development and use, and AD research is currently well-served by existing informant-reported scales for assessing moderate to severe disease. However, most item content fails to capture subtle deficits, and few patient-reported measures have been developed to date.

Some performance-based assessments address areas that could be promising for adaptation as self-rated measures, including financial capacity [57,58], facial emotion processing [59], and route navigation [60]. Linking functioning to specific cognitive skills through these and other areas may expand clinical characterization of prodromal AD [61].

Because of limited use of qualitative data collection from patients in the measure development process, a step key to best practice in measure development [1], further refinement of ‘functioning’ measures may be warranted, including through identifying and measuring aspects of functioning most relevant to early disease, and establishing consensus on the definition of everyday functioning and complex ADL functioning.

Executive functioning

Executive functioning represents the cognitive skills required for the planning, initiation, sequencing, and monitoring of complex goal-directed behavior, such as household chores [5,62,63]. Executive functioning impairment is a criterion for dementia diagnosis [6].

Executive functioning skills underlie the everyday functioning skills discussed above, but are considered separately here because measures of executive functioning focus on a specifically defined set of cognitive skills rather than on the tasks those skills enable. Data from Farias and colleagues [64,65] support distinguishing between measurement of daily living skills and measurement of neuropsychological functioning, based on data showing a moderate correlation between measures of each in a sample with AD (see also [66]). More recently, data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Cognitive Intervention Trial also support this distinction, as well as the relationship between cognitive skills and everyday functioning [67].

Executive functioning measures that have been used in MCI include the Behavior Rating Inventory of Executive Function - Adult version [68] (BRIEF-A [69]) and the Frontal Systems Behavior Scale [70,71], with patient- and informant-reported versions for each. The BRIEF is a measure of everyday behavioral manifestations of executive control and is sensitive to subtle changes in MCI patients and those with cognitive complaints [68,72]. Similar to findings from Farias and colleagues [65], BRIEF-A scores were only modestly correlated to neuropsychological measures of executive functioning, suggesting that self- and informant report provides unique information about executive functioning relative to performance-based measures. The Frontal Systems Behavior Scale is a rating scale of apathy, disinhibition, and executive function and has demonstrated sensitivity to impairment in an MCI sample [70].

Measures of executive functioning show promise for detection of subtle deficits in MCI [70,71]. As noted
above for everyday functioning measures, obtaining structured input from patients in accordance with best practice for measure development may usefully expand the set of relevant impacts to measure and/or aid with identifying differential importance of content from the patient perspective and by stage of disease.

**Neuropsychiatric symptoms**

Although neuropsychiatric symptoms are frequently an important part of the disease course of AD, their presence earlier in the disease is not as well-established. In recognition of the unique presentation and possible prognostic significance of major depressive disorder within AD, the National Institute of Mental Health developed a modified provisional set of criteria for depression in AD, distinct from the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria for major depressive disorder [73,74]. Work with these criteria has indicated that the prevalence of major depressive disorder is significantly underestimated in this population relative to DSM-IV-based prevalence estimates [74,75]. Behavioral and psychological symptoms are evident among some MCI and mild AD patients [11], and at elevated rates relative to the normal aging population [76]. Increased apathy and executive dysfunction have been documented in MCI [70,77]. There is preliminary evidence for higher rates of neuropsychiatric symptoms such as depression, anxiety, agitation, disinhibition, irritability, and sleep problems among those with executive dysfunction type MCI relative to both amnestic and non-amnestic MCI [76] and presence of depression (based on caregiver report) has been found to be predictive of progression from amnestic MCI to AD [75]. Few measures of neuropsychiatric symptoms have self-report versions and few are validated for use in early disease. Further research is required to develop evidence for the validity of patient self-report for these symptoms.

**Health-related quality of life**

Health-related quality of life (HRQL) is the subjective assessment of an individual's psychological, physical and social functioning or well-being [78,79] and is traditionally measured via self-report, although for AD, measures have both patient- and informant reported versions [80,81]. No MCI-specific HRQL scale exists; instead, existing AD measures have been used in MCI (for example, the Alzheimer’s Disease Related Quality of Life instrument [82]) as have generic measures (defined as measures intended for use with any population or therapeutic area; examples are the World Health Organization Quality of Life questionnaire, short version [83] and Short-Form (SF)-12 [84]). A systematic review of clinical trials in AD found very low use of HRQL measures (in <5% for trials conducted through part of 2006) [85]. Data from a small sample suggest that reliability and validity of HRQL self-report in MCI and AD is correlated with insight level [86]. While HRQL measures have been central to the rise of PRO assessment over the past two decades, the value of disease-specific HRQL assessment to treatment evaluation in MCI and prodromal AD is limited by lack of consensus on domains to include and lack of clarity about how to weight domains for scoring. The HRQL impact of MCI, distinct from that of later disease, remains to be defined. Further work exploring the relationship of HRQL to functioning, neuropsychological disease effects, and neuropsychiatric symptoms would enhance the quality of HRQL measurement and improve its usefulness for research applications.

**Insight and patient self-report**

Insight into illness is a critical issue for patient self-report in MCI and AD given that insight into disease effects declines as the disease progresses [87-91]. Lack of insight is defined as lack of the ability to elaborate on the experience of a disease, label the symptoms of the disease as pathological, or have knowledge of the deeper effects that the symptoms or disease will have on one’s environment [92]. Anosognosia is defined as unawareness of deficits, specific cognitive dysfunction, and lack of insight [16,93-96]. The terms 'lack of insight' and 'anosognosia' are used largely interchangeably in the cognitive impairment literature.

The relationship of insight to progression in MCI is less clear than it is for AD. For a review of insight in MCI see [95]. There is currently no consensus on the best method to measure insight. Most methods rely on informant report as a ‘gold standard’ with patient/informant concordance taken as an indirect measure of patient insight. When the informant is the caregiver, accuracy of report bears critical examination. Caregiver burden, level of depression and anxiety, and caregiver health, including cognitive health, may influence accuracy of caregiver report (for example, [97,98]).

Within the AD literature, there has been examination of concordance along with caregiver factors in reporting [17,86,99,100]. Data on patient/informant concordance and informant accuracy are limited for the milder levels of cognitive impairment. In general, data support an inverse correlation between insight and severity of cognitive impairment and an inverse correlation between patient and caregiver report and severity of cognitive impairment [88,101,102]. Dementia patients likely underestimate their deficits in comparison to caregiver informants [103], with concordance further reduced as disease progresses (for example, [104]).

Some empirical reports conclude MCI patients have preserved insight. For example, Farias and colleagues [15]
found that MCI patient self-report was concordant with reports of others, suggesting that MCI patients do not under-report actual deficits in cognition and functioning. Other studies suggest lack of MCI patient insight (see [95] for a review). Conflicting findings about insight and ability of patients to self-report may be due to different definitions of insight, different definitions of MCI, and/or different methods of measuring insight. Most studies of insight focus on insight for memory functioning; few studies address insight for other cognitive skills, everyday functional abilities, behavior, or affect [95]. The current literature on insight in MCI is limited by lack of specificity about domains affected, a critical point given evidence of differential insight by domain for MCI patients [91,105-107]. Insight may be well-preserved in some domains across a range of disease severity, but may diminish more rapidly in others [95]. For example, Clement and colleagues [91] found that some but not all domains assessed corresponded to performance deficits in global cognitive score and executive functioning for MCI patients, suggesting MCI patients may be aware of general cognitive deficits but not specific memory deficits. To date, the literature on MCI supports the conclusion that insight in MCI is not a single construct and that insight might be spared for some but impaired for other domains (see Roberts and colleagues [95] for a review).

Evidence suggests that MCI patients may have knowledge of deficits in advance of when deficits are clinically discernible [108-110]. Kalbe and colleagues [93] found that MCI patients overestimate cognitive deficits relative to informants on a 13-domain complaint interview; mild AD patients underestimate their deficits relative to an informant. The validity of the conclusion of ‘overestimation’ is worth challenging, however, as early cognitive loss may be apparent to the patient but no one else, in part because of the nature of the deficits and in part because MCI patients may actively hide symptoms from others.

To optimize patient self-report, further research is warranted to determine the relationship of insight to level of disease severity, attending to potential differences in insight by domain rather than treating insight as a single global construct. It will be particularly interesting to identify those domains for which patients, especially MCI patients, may have the most accurate view of performance relative to other informants, including clinicians.

Some patient-reported insight scales are presented in Table 1.

**Conclusion**

The increasing interest in MCI due to AD [2], preclinical AD [111], and prodromal AD [18] presents an opportunity to advance outcomes measurement in cognitive disorders by addressing ceiling effects of existing measures and by expanding the range of measurement targets beyond neuropsychological assessments into the realm of patient-reported outcomes. Patient self-report also offers a means of expressing, and perhaps quantifying, the clinical significance of specific clinical changes.

Progress in identification of treatments for cognitive impairment depends on accurate measurement. Among the concepts for which patient self-report could be valuable, and for which measurement appears feasible based on available psychometric data, are aspects of everyday functioning and complex activities of daily living and some aspects of executive functioning. Few measures currently address these concepts. Further, domains included in existing measures vary and no measure is comprehensive; consensus on specific functioning domains relevant to early disease would improve measurement. The extent to which under-studied areas, such as social functioning and language skills, are useful to assess is uncertain given lack of data.

Subtle changes in mood and affect specific to MCI may be usefully captured by self-report but to date there are limited data on validity of patient self-report of neuropsychiatric symptoms in early disease. Measurement of the health-related quality of life impact of MCI has proceeded largely on the basis of measures developed for AD; relevance to the MCI experience remains to be established. Understanding the MCI experience in greater depth can improve conceptualization of HRQL. Currently, HRQL assessments in MCI and mild AD are based largely on existing AD measures with little psychometric performance data on suitability for measurement of milder levels of impairment.

Other domains may prove useful to explore for self-report. For example, cognitive impairment is often associated with somatic changes, including changes in eating behavior, such as dysphagia, along with weight loss, changes in olfaction, sleep quality, balance, and increased fall risk [112-119].

The impact of fluctuating or declining insight in mild cognitive impairment on patient report is unclear. At what point does loss of insight make patient self-report no longer reliable and valid? Current research suggests that this point may vary by domain, with patients demonstrating sufficient insight to reliably and validly self-report about disease-related impairment in some areas well into mild to moderate AD.

Consideration of strategies for quantifying the impact of other variables on the accuracy of measurement should be part of measure validation. Cultural differences in symptom expression and interpretation are one example. Item response theory methods will likely be of
value to identifying differential item functioning and quantifying cultural confounds [120-122]. In addition to the possibilities of new measure development, such as being undertaken by the Cognition Working Group of the Critical Path Institute’s PRO Consortium, existing AD measures could be tested in the MCI population and converted to self-report if feasible.

The increasing emphasis of research on symptoms, correlates, and impact of cognitive impairment at mild levels suggests that the time is right for development of new patient-reported measures for MCI. Although measurement from the perspective of patients with MCI and prodromal AD is still at an early stage, the development of new measures and psychometric evaluation of existing AD measures for use in early disease should be pursued to increase the tools available and to expand our understanding of mild levels of cognitive impairment.

**Abbreviations**

AD, Alzheimer’s disease; ADCS-ADL, Alzheimer’s Disease Cooperative Study Activities of Daily Living; ADL, activities of daily living; BREF-A, Behavior Rating Inventory of Executive Function – Adult version; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HRQL, health-related quality of life; MCI, mild cognitive impairment; PRO, patient-reported outcome.

**Competing interests**

LF was a salaried employee of United BioSource Corporation (UBC) when some of the work included in this manuscript was completed. UBC held and still holds a contract with the Critical Path Institute for completion of work related to development of a new PRO measure and that work included literature reviews. Some content related to those literature reviews is included in this manuscript. During completion of this manuscript LF worked at MedImmune, LLC, owned by AstraZeneca, PLC, and served as an AstraZeneca industry sponsor representative to the Cognition Working Group of the Critical Path Institute. WRL holds stock in, and has a pension with, Pfizer. MC was an employee of Merck until 2010 and still holds stock, and has been a consultant with Critical Path Institute and the Cognition Working Group.

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**Author details**

1. Patient-Centered Outcomes Research Institute, Washington, DC 20006, USA
2. United BioSource Corporation, 7101 Wisconsin Avenue, Suite 600, Bethesda, MD 20814, USA
3. Wellness Managements LLC, 134 Walnut St, Livingston, NJ 07039, USA

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