Definitions of Dementia and Predementia states in Alzheimer Disease and Vascular Cognitive Impairment

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Abstract

The most recent set of consensus recommendations in Canada on Alzheimer disease (AD) diagnosis were published in 2006 following the 3rd Canadian Consensus Conference on Diagnosis and Treatment of Dementia meeting (CCCDTD). Since then, there have been several newly proposed sets of diagnostic criteria for AD, advanced by the National Institute of Aging/Alzheimer's Association (NIA-AA) working groups (2011) and the International Working Group (IWG, 2007 and 2010). They each aim to provide broader disease stage coverage with incorporation of disease biomarkers into the diagnostic process. They have focused particular attention on the earlier identification of disease with focus on the preclinical and predementia stages. This paper reviews these diagnostic criteria and provides 2012 CCCDTD consensus recommendations on their applications in both clinical and research settings.

Key words: Alzheimer's disease, preclinical, predementia, diagnostic criteria, prodromal AD

Introduction

This report constitutes a background paper for the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD), to be held in May 2012. The most recent set of consensus recommendations in Canada on dementia and Alzheimer disease (AD) diagnosis were published in 2006 following the 3rd CCCDTD(Chertkow 2007). Since 2006, there have been several newly proposed sets of diagnostic criteria for AD, advanced by the National Institute of Aging/Alzheimer's Association (NIA-AA) working groups (2011) and the International Working Group led by Bruno Dubois (IWG, 2007 and 2010). The recommendations of these groups were reported in a series of articles – the IWG (Dubois) committee proposals for Prodromal AD presented in (Dubois, Feldman et al. 2007) (Dubois, Feldman et al. 2010), and the three NIA committees whose work reported new guidelines for diagnosis of dementia and Alzheimer's Disease (McKhann, Knopman et al. 2011), Mild Cognitive Impairment (Albert, Dekosky et al. 2011), and defining the preclinical stages of Alzheimer's Disease (Sperling, Aisen et al. 2011), along with various commentaries about these five important papers(Jack, Albert et al. 2011).

The IWG criteria were clearly proposed as research criteria. The NIA-AA committees concentrated largely on research but defined new clinical guidelines as well for dementia states and MCI with variable applicability in the clinic. These working groups have aimed to make recommendations on the integration of in-vivo Alzheimer pathology biomarkers in the diagnostic process and provided expanded diagnostic coverage of the disease stages within their proposed criteria: preclinical, , mild cognitive impairment, and AD dementia.

The potential for earlier AD diagnosis has been supported by the advent of promising in-vivo cerebrospinal (CSF measures of A-beta 1-40, 1-42, total tau and phospho-tau), and neuroimaging biomarkers (structural MRI, amyloid PET, FDG PET) that reflect the presence of the neuropathological AD pathological process (AD-PP). While these biomarkers enable the identification of the pathology of AD in vivo, there is much to still learn about the significance of pathology in asymptomatic individuals and

the increased risk of AD dementia this portends. Additionally these biomarkers have not yet reached regulatory approval in Canada and are not yet funded for use in clinical settings, yet they form an important opportunity to improve the accuracy of diagnosis in research studies across the disease stages.

The major focus of this background paper is to review the diagnostic framework of each of these working groups and to provide consensus recommendations for their potential application in clinical and research settings of care, as well as outlining the potential translational steps to advance these biomarkers to clinical care in Canada in the next 5 years. In as much as there are no randomized controlled clinical-pathological studies comparing subjects diagnosed according to these different diagnostic criteria, our recommendations would all be rated as level 3 evidence only.

There are a number of important considerations to this background paper and in its review of the reports of the Working Groups. (Jack, Albert et al. 2011) (McKhann, Knopman et al. 2011), (Albert, Dekosky et al. 2011), (Dubois, Feldman et al. 2007; Dubois, Feldman et al. 2010; Sperling, Aisen et al. 2011). First, the focus is on AD primarily, with consideration of its preclinical , predementia and dementia stages. The issues of differential diagnosis, diagnostic criteria for other non-Alzheimer dementias, and mixed dementias, are neither the focus of the new AD criteria nor of this review. Second, there is a deliberate effort to distinguish between the clinical syndromes pertaining to AD (AD-C), and the biomarker evidence of its pathologic process (AD-PP). Other papers in this CCCDTD will further address the developmental issues pertaining to the biomarkers in question, while this paper focuses more centrally on AD-C. Third, preeminence is given to the presence of amyloid pathology, given its early presence as a molecular neuropathological marker of the disease with the hypothesis that therapeutic strategies to enhance its clearance could be preventive if administered early enough in the disease process. (Jack, Lowe et al. 2009; Jack, Knopman et al. 2010). Finally these models are evolving as conceptual frameworks, and still largely hypothetical at the present time. In this paper, we will discuss each of the clinical syndromes and proposed diagnostic criteria by disease stage with consensus recommendations for the CCCDTD4.

This background paper focuses on AD where there have been major efforts towards new definitions and paradigm shifts in thinking about the disease. It also includes a section on Vascular Cognitive Impairment, where a new proposed diagnostic framework is sufficiently comprehensive to warrant consideration for the CCCDTD4. It should be noted that there have indeed been developments in diagnosis of Lewy body dementia (LBD) and in Frontotemporal dementia (FTD). While we are cognizant that new diagnostic criteria have been proposed for specific syndromes (behavioral variant (Rascovsky, Hodges et al. 2011); language variant of FTD (Gorno-Tempini, Hillis et al. 2011), we have opted not to deal with these developing areas at the present time. Therefore, this paper does not address novel diagnostic issues pertaining to LBD and FTD at the CCCDTD4.

2. The syndrome of dementia

Dementia is typically defined as a clinical syndrome of cognitive (historically memory is here privileged) decline that is sufficiently severe to interfere with social or occupational functioning. It remains an anchor point of reference within the revised AD diagnostic criteria proposals. Routine clinical practice shows that the cognitive and functional changes of dementia are typically accompanied by changes in behaviour and in personality, but these have had variable prominence in diagnostic criteria and are felt to lack sufficient diagnostic specificity.

Dementia has been and remains a clinical diagnosis, in which laboratory or imaging tests as yet provide only supportive roles. As such, the diagnosis is based on a careful history. In specialist practice, this is often done using a semi-structured interview with an informant (e.g. the Clinical Dementia Rating (CDR) although a wide variety of assessment approaches exist. It also involves a detailed medical and neurological examination, and a formal mental status exam including bedside cognitive testing. Brief assessment tools are often used for this (e.g., the Montreal Cognitive Assessment (Nasreddine, Phillips et al. 2005)) and in some referral centres extensive neuropsychological testing is used as an ancillary diagnostic aid. Functional assessment

- either structured or informal - is used to establish the presence and severity of functional disability.

Dementia diagnoses are most commonly based on the DSM IV-TR criteria (APA, 1994; Winblad, Palmer et al. 2004; APA, 2000). DSM-IV-TR requires impairment of memory and at least one of the following domains: language, praxis, gnosis, or executive functioning. These impairments need to be sufficiently severe to impair social or professional life, and must not occur as a consequence of a delirium, or be caused by another medical, neurological or psychiatric condition. It should be noted that memory impairment, though present in most people with dementia, is not an essential requirement; rather at least two cognitive domains must be impaired, and of course the other criteria must be met. The presence of dementia without a dominant memory complaint has been demonstrated in large cohorts of patients with dementia (Lopez, Becker et al. 2000; Feldman, Levy et al. 2003). The 2006 CCCDTD3 therefore proposed the following recommendations for changes in dementia diagnosis (Rockwood, Bouchard et al. 2007):

1. Although memory impairment is an important part of most dementias, there are some dementias (subcortical ischemic dementia, primary progressive aphasia, some other types of frontotemporal dementia) in which the requirement for memory impairment limits the sensitivity of a dementia diagnosis. The requirement for memory impairment should be dropped from the criteria for dementia, in favour of impairment in at least two domains of cognitive function.

2. The new onset of a mood disorder or behavioural disturbances, in the face of changes in cognition, should be seen as supportive of a diagnosis of dementia.

The 2011 NIA-AA revised core clinical criteria for dementia (McKhann, Knopman et al. 2011) have evolved to reflect some of these 2006 CCCDTD features. They indicate that dementia can be diagnosed when cognitive or behavioral symptoms meet the following criteria:

1. They interfere with the ability to function independently at work or at usual activities;

2. They represent a decline from prior levels of functioning and performing;

3. They are not explained by delirium nor major psychiatric disorder;

4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

5. The cognitive or behavioral impairment involves at least two of the following domains:

a) Impaired ability to acquire and remember new information – symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route

b) Impaired reasoning and handling of complex tasks, poor judgment – symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

c) Impaired visuospatial abilities – symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements or orient clothing to the body.

d) Impaired language functions (speaking, reading, writing) – symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling and writing errors.

e) Changes in personality, behavior or comportment – Symptoms: impaired motivation, initiative, increasing apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

These NIA-AA clinical criteria were designed to be flexible enough to be used by both general health care providers without access to neuropsychological testing, advanced imaging and CSF measures, as well as researchers and those at specialty clinics

Recommendations for clinicians on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD): Dementia diagnosis

indicates the presence of a significant functional disability that interferes with everyday social function. The pattern of cognitive impairment for this diagnosis can usually be determined at the bedside by clinical bedside assessment without recourse to biomarkers and ancillary diagnostic tools.

Recommendations for research and translational development to clinical care on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD):

In research settings, studies involving biomarkers should address the natural history of cognitive decline extending from predementia to dementia states, and the efficacy of treatments in delaying dementia.

Proposals to be brought forward for voting at the Fourth CCCD:

1. We propose that the Fourth CCCD adopt the recommendations around criteria for dementia proposed by the 2011 NIA-AA working group.

3. Alzheimer Disease Dementia (AD)

The clinical diagnosis of AD dementia has traditionally rested on a two step process; identifying the presence of dementia and then a clinical pattern of AD conforming to the 1984 NINCDS-ADRDA criteria(McKhann, Drachman et al. 1984). Indeed, the NINCDS criteria have been the diagnostic standard for more than 25 years with many validation studies against neuropathological gold standards having been performed. At the 3rd CCCDTD, there were a number of important diagnostic amendments to these NINCDS-ADRDA criteria discussed. There was consensus that diagnosis should not require an insidious onset and that plateaus in the course of AD could be consistent with the diagnosis. Several groups have observed that a significant minority of people with AD (about 15%) (Bowler, Munoz et al. 1998) show comparatively little disease progression. In reference to biomarkers it was noted that in the NINCDS ADRDA criteria AD was conceptualized as a disease of exclusion and that EEG and CSF studies could be “supportive” of AD. In that era, there were no

biomarkers reflecting in vivo AD-PP and positive disease identification through biomarkers was not included. Similarly, the 3rd CCCDTD considered that there was no reason a priori to exclude patients younger than 40 or older than 90. Additionally, these NINCDS ADRDA criteria did not adequately recognize atypical focal presentations. It was appreciated by the CCCDTD that atypical AD presentations occur and can be recognized in expert hands.

The current NIA-AA criteria propose some revisions to the NINCDS framework. In addition to the clinically determined Probable and Possible AD diagnosis that have been used up till now, a third grouping of "Probable or Possible AD with biomarker evidence of AD-PP" has been added (McKhann, Knopman et al. 2011). The use of biomarkers to enhance certainty of AD, was stated to be useful in three circumstances presently; investigational studies, clinical trials, and as optional clinical tools for use where the biomarkers are available and when deemed appropriate by the clinician. We will discuss this important third category at length below and in the other papers of the consensus conference.

Within the revised probable AD grouping there is recognition that there are both amnestic and non-amnestic presentations that can be clinically identified. The amnestic presentation which is most common, has both impairment in memory function as well as in a second cognitive domain, while the less common non-amnestic presentations can include progressive visuospatial impairment, syndromes of predominant frontal/executive dysfunction, or language impairments with prominent naming difficulties. Individuals diagnosed as probable AD by the previous criteria, remain probable AD by the current revised criteria.

The diagnostic designation of possible AD continues to include individuals with atypical course or clinical features including the presence of concomitant cerebrovascular disease , manifestations of dementia with Lewy bodies (including visual hallucinations, fluctuations or parkinsonian features) or the presence of another neurological or psychiatric disease comorbidity, or medication use that could be contributing to the dementia.

The third category of "probable or possible AD with biomarker evidence" includes either evidence of brain amyloidosis with low CSF Aβ42 or positive PET amyloid imaging, or alternatively downstream evidence of neuronal degeneration or injury with evidence of either elevated CSF tau, both total tau (t-tau) and phosphorylated tau (p-tau); decreased FDG uptake on PET in temporo-parietal cortex; or disproportionate atrophy on structural MR (sMRI) in medial, basal and lateral temporal lobe, and medial parietal cortex. This biomarker evidence is proposed to increase the certainty that the basis of the clinical dementia syndrome is the AD-PP. Given that these biomarkers have not yet been approved for diagnostic use by most regulatory or paying authorities in Canada, their use will be restricted in the near term to research studies. At the same time, it must be acknowledged that in a few centres and provinces (Quebec for one) the biomarkers are already available in certain circumstances for specialist physicians.

We have gone into considerable detail on the new criteria for AD, because they are extremely important. However, they are not terribly controversial in our opinion and they reflect the clinical and pathophysiological progress made in our understanding of AD. Indeed, the commentary on the papers by the Canadian group (most of whom are involved in this consensus conference), termed them as "offering no controversy" (Gauthier, Patterson et al. 2011). We propose the adoption of these criteria by the Canadian community.

While the McKhann paper proposes designating etiologically mixed presentations of AD as a form of "possible AD dementia", Dubois and his committee preferred the term "Mixed AD" for such individuals (Dubois, Feldman et al. 2007) (Dubois, Feldman et al. 2010). This underscores the deeper philosophical difference between the two criteria, with the IWG committed to definitely capturing AD-PP through biomarker support even when there is mixed pathology suspected.

Recommendations for clinicians on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD): The diagnosis of AD dementia is clinically based, with identification of different presentations of AD based on clinical

assessment. The NIA-AA criteria offer some useful adjustments to the clinical NINCDS-ADRDA criteria and should be adopted. The use of biomarkers in Canada is not yet available in most locales to offer pathophysiological support for the clinical diagnosis. Future adjustments in the clinical approach are likely in relation to biomarker availability and uptake in clinical settings.

Recommendations for research and translational development to clinical care on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD):

In research settings where there is availability of biomarkers, investigators should be encouraged to advance studies that include biomarkers to allow their further experience, validation and readiness for translation to care in the future. There should also be recognition of the prevalence of mixed AD and investigation into the biomarker signatures of its entities.

Proposals to be brought forward for voting at the Fourth CCCD:

We propose that the CCCD adopt the recommendations concerning Alzheimer's Disease dementia diagnostic criteria proposed by the 2011 NIA-AA working group.

4. Mild Cognitive Impairment and Prodromal Alzheimer's Disease

Since the proposal in Canada for Benign Senescent Forgetfulness (Kral 1962) the possibility of a diagnosis that falls short of dementia, but outside of normal cognition, has been considered with numerous terms utilized. In the Canadian context, over the last dozen years this has included diagnostic terms such as "Cognitive Impairment, No Dementia" (CIND) (Graham, Rockwood et al. 1997; Tuokko, Frerichs et al. 2003) and Mild Cognitive Impairment (MCI) and its subtypes (Petersen, Smith et al. 1999; Petersen 2004; Chertkow 2002; Winblad, Palmer et al. 2004)] and "questionable" Alzheimer's Disease (Morris, Storandt et al. 2001).

There has been an enormous increase in data indicating that MCI is an at risk condition to progress over time to develop AD dementia. The development of biological markers indicating the presence of AD-PP, has additionally supported a more refined clinico-biological definition of this at-risk state. Both the working groups of the NIA-AA and the IWG have undertaken to integrate biomarkers into the diagnostic formulation of this condition. The NIA-AA has conceptualized their approach around "MCI of the Alzheimer type" with the presence of AD-PP biomarkers increasing the probability of progression to AD dementia. The IWG has taken a different view that a characteristic clinical presentation of AD in the predementia stage (prodromal AD), supported by the presence of one or more AD-PP biomarkers, is sufficient to diagnose AD. While there are currently no proven therapies to influence the longer term outcomes of these conditions, both definitions support the research of predementia AD interventions, both pharmacological and non-pharmacological. We will review each proposal in detail below.

The IWG definition of Prodromal AD.

The IWG has taken the view that "the term 'Alzheimer's Disease' should …encompass the whole spectrum of its clinical course, from earliest specific clinical symptoms, to dementia." ((Dubois, Feldman et al. 2010), page 1120). Importantly, this allows a diagnosis of AD independent of a diagnosis of dementia. Prodromal AD would be the "predementia stage of AD", in which there is a typical AD-type clinical amnestic phenotype, along with positive AD biomarker(s) . The clinical amnestic phenotype includes the presence of definite impairment on specified memory tests that control for encoding and where there is a failure to normalize recall with cuing (e.g., impaired performance on the Free and Cued Selective Reminding Test). There is supporting evidence of at least one abnormal AD biomarker for a patient to be reclassified from MCI (a risk state) to "prodromal AD" (a phase of AD). Alternatively, atypical AD can be diagnosed in its prodromal stages when a known phenotype AD (posterior cortical degeneration, logogenic aphasia, or frontal behavioral variant) is supported by one or more abnormal AD biomarker. "AD dementia" transition occurs when cognitive symptoms become sufficiently severe to interfere with social functioning and instrumental activities of daily living (Dubois, Feldman et al. 2007) (Dubois, Feldman et

al. 2010). This highlights the IWG's view that a disease or conditional definition with distinctions around the extent functional impairment are fundamentally challenging to apply uniformly, lack a clear biological basis, and will be subject to endless unresolvable debate on the extent necessary to meet the criteria. In turn, the IWG has shaped its definition of AD with core clinical features being either typical (with the amnestic presentation) or atypical (with recognized non amnestic features) and with support by the presence of one or more AD biomarker(s) reflecting disease pathology. It has removed functional disability and the extent of cognitive impairment from the disease definition. Rather, it proposes that these parameters be used to describe the stage and severity of the disease which is biologically and clinically defined. The prodromal phase of the disease describes the predementia stage and AD dementia the later stages.

<u>The NIA-AA definition of "MCI due to AD".</u>

The NIA group has taken a different approach, applying a four step process to establish the framework for a diagnosis of "MCI due to AD" (Albert, Dekosky et al. 2011). They characterized the first step as establishing the presence of MCI, building on the published literature of the past 15 years. The second step involved the characterization of the cognitive and functional measures for assessment to establish the diagnosis. The third step considers establishing an "etiological diagnosis" of MCI of the AD type based on ruling out vascular, traumatic, and other medical causes of MCI, looking for evidence of progressive decline, and looking at AD genetic factors where available. The final step addresses the presence of positive biomarkers for AD, classifying these as biomarkers of brain amyloid-beta (Aβ) protein deposition or biomarkers of downstream neuronal degeneration or injury.

Regarding the first step, there were subtle but important innovations suggested for the clinical core criteria for a diagnosis of MCI due to AD. In considering the presentation, there is a stipulation that there should be concern from either the individual or their informant regarding a change in cognition, in comparison with the person's previous level, with objective evidence of lower than expected performance in one or more cognitive domains. The cognitive changes would "typically" be 1 to 1.5 standard deviations below the mean for the age and education of the individual with

reference to appropriate normative data. It was emphasized that these ranges were guidelines and not cut-off scores.

In the second step there was consideration of the cognitive assessment domains that should be evaluated to establish a diagnosis of MCI of the AD type. These were recommended to include memory, executive functions, language, visuo-spatial skills, and attentional control. Many clinical neuropsychogical measures are referred to, without any one being named as the "gold standard". Certainly, no one test is given priority, and in fact, bedside testing with simple informal techniques is acceptable if formal cognitive testing is not feasible. These informal techniques, however, will likely be insensitive to subtle cognitive dysfunction.

In addressing the important issue of functional disability within MCI due to AD, the description within the proposed criteria indicates "generally mild functional impairment for complex tasks, but basic ADLs should be preserved" (pg 4) (Albert, Dekosky et al. 2011). Individuals should not be diagnosed with dementia in that "there is no evidence of a significant impairment in social or occupational functioning" (page 3) and that there should be preservation of independence in functional abilities. This important acknowledgement that persons with MCI due to AD commonly have mild problems performing complex functional tasks they used to perform previously, represents a further elaboration of a difficult area in the diagnosis. "They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance." (pg. 3). The critical factor separating MCI and dementia (presumably AD) in the NIA-AA framework consists of the a) severity and extent (at least into two cognitive domains) of the cognitive/behavioural deficit, and b) the presence or not of a significant degree of functional impairment. Unfortunately, assessing functional decline is difficult, depends largely on how carefully performance of daily activities is assessed, the quality of the caregiver/families' responses, and what activities there actually exist to interrogate.

The final step of analysis in the NIA-AA approach to MCI addresses biomarkers within research criteria of MCI due to AD. They proposed a nomenclature designating the use of biomarkers to increase the likelihood of "MCI due to AD" in any

individual. Thus, if both the Aβ and neuronal injury (tau, FDG, or structural MRI) biomarkers are "positive", that is, indicating AD-PP, then the "Highest biomarker probability" of AD etiology exists. If one of the two categories of biomarker is untested and the other is positive, then the level of probability is only intermediate. In cases where the two results were conflicting (i.e., Aβ markers suggest AD, but neuronal injury biomarkers do not), or results were not clear, or the tests were not carried out, then the biomarker probability is termed "uninformative" and only MCI core clinical criteria would be met.

An important caveat was provided by the NIA-AA Working Group around the intended application of the MCI due to AD criteria. The Core Clinical Criteria for MCI were designed to be applicable in all clinical settings, but the research criteria with biomarkers were currently restricted to research because of lack of standardization of biomarkers, limited experience with cut-points for diagnosis, and limitations in access. The research criteria were designed to be "a work-in-progress that will be updated regularly as new information becomes available". (pg. 2).

<u>The question of functional impairment</u>

Given the new criteria that recognize non-memory domains such as language as the predominant feature in atypical AD, functional impairment is now the key dividing line between pre-dementia and dementia states. Unfortunately, assessing functional decline is difficult, depends largely on how carefully performance of daily activities is assessed, the quality of the caregiver/families' responses, and what activities there actually exist to interrogate. Some prominent researchers such as David Bennet have suggested abandoning function questions completely, and developing algorithms based on cut-off scores on normed cognitive measures in order to designate AD, and this appears actually to correlate as accurately with post-mortem pathology! (Bennett, Schneider et al. 2006).

If function is preserved completely, then the individual is clearly MCI. But how much functional impairment is necessary to be "significantly impaired"? Recently, Morris complained that with the new criteria, there was somehow more leeway for

functionally impaired individuals to be labelled as MCI rather than dementia(Morris 2012). Morris complains that if a liberal interpretation is applied, individuals who are only mildly impaired on a range of functions might still be considered to be "functionally independent", and therefore MCI. He reviewed data suggesting that indeed most mild AD subjects could be reclassified as MCI in this manner. However, his interpretation of the data seems strained. For instance, most clinicians would consider scores over 6 (out of a possible 30) on the Functional Assessment Questionaire to be incompatable with independence (Marshall, Olson et al. 2011). In the paper by Marshall and colleagues, normal controls scored 0.1 mean on the FAQ, and MCI subjects scored 3.8 mean. Morris suggests that a score as high as 15 might be compatable with a diagnosis of MCI. This seems unlikely to most clinicians. In summary, while the area of functional impairment continues to be challenging and dissatisfying, the current suggestions seem appropriate and feasible. The authors of the NIA-AA papers stress that "the clinical syndrome (of MCI) is almost identical to the one previously described by Petersen et al" (pg. 4). While functional impairment will continue to be a difficult and vague criterion, we doubt that the new description will change in the least the clinical approach to MCI and dementia diagnosis.

<u>Adjudicating and assessing the new terminology.</u>

How should the Canadian research community respond to the distinctions between the NIA-AA and the IWG proposals? Both the Dubois and the Albert terminology have their pros and cons. The IWG Dubois approach (Dubois, Feldman et al. 2010) would render a subset of individuals currently classified as MCI (a high risk state), as having AD in a prodromal form. "A clinical phenotype combined with biomarker evidence will now no longer be predictive of AD, but diagnostic, in accordance with the new criteria" (pg 1123). These individuals would be studied and treated as AD. Pragmatically, though, do the clinical benefits (one benefit is bypassing the whole issue of defining functional impairment) outweigh risks inherent in the new terminology? Given that the criteria have not been longitudinally validated, and given the likelihood that any lexicon designated "for research" will quite soon be applied in clinical situations, the fallout is not negligeable. Can we really be certain at this point that all "prodromal AD" subjects will definitely go on to AD dementia over a concrete

period of time? What if some individuals with prodromal AD never get worse? Perhaps the criteria need modification, and only those with two positive biomarkers will have 100% progression! Will any subjects revert from prodromal AD to MCI over longitudinal follow-up? These are challenging and important empirical questions that may be answered within the next five years.

The Albert et al NIA-AA approach, far more conservative, makes far fewer assumptions. If biomarker tests are not available, the core clinical criteria for MCI are considered and will continue to be considered adequate. Indeed, there is no suggestion that more than this should be done clinically at the present time. Even were the MCI criteria to become used in clinical settings, the only change would be adding "Highest biomarker probability" of AD etiology in view of added biomarker information. The NIA-AA approach leaves open the door to more clinical use of the biomarker diagnosis as further longitudinal data becomes available, without committing itself to a specific memory test or group of biomarkers for clinical use.

A further advantage of the NIA-AA approach is that it is, despite all the emphasis on biomarkers for research, more compatable with clinical care which does not have access to those very biomarkers. Both for AD and MCI, the core clinical criteria are separated out and given primacy. One can continue to do adequate medicine without recourse to FDG PET, amyloid imaging, sMRI, or CSF testing. The NIA-AA criteria thus allow seamless transition from routine care into novel models that may become available in the future. The concept of "prodromal AD" in the Dubois criteria, in contrast, can only be established with use of the ancillary biomarkers. It raises the spectre of patients demanding these tests in order to get the optimal diagnosis. The advantage of being reclassified from vague MCI to a more accurate designation as prodromal AD, may be very small indeed. Nevertheless, it could force family doctors to refer all their patients to specialty clinics in order to get access to this cutting edge sophisticated neuroimaging. In a sense, the concept of MCI, along with easy means of establishing it with tools such as the MoCA, has empowered family physicians in Canada to diagnose mildly impaired individuals. The institution of "prodromal AD" would again encourage family physicians to rely on specialists who have better access to brain imaging technology.

Recommendations for clinicians on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD): Given the absence of approved AD biomarkers for use in clinical settings of care, the current recommendation is to adopt the Core clinical criteria of the NIA-AA for "MCI due to AD". Because the term "prodromal AD" has considerable potential merit for clinical use, a commitment should be made to revisit the NIA-AA terminology when biomarkers have advanced to regulatory approval and payer acceptance. It is foreseeable that this clinical use will occur in specialist settings, and that family practitioners will need to have guidelines on when to make such specialist referrals.

Recommendations for research and translational development to clinical care on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD):

In research settings where there is availability of biomarkers, investigators should be encouraged to advance studies that include biomarkers to allow their further experience, validation and readiness for translation to care in the future. Both the IWG and NIA-AA research criteria referencing AD biomarkers require further validation studies. Such studies should in particular assess the predictive utility of biomarkers of amyloid deposition compared with biomarkers of neuronal injury, with regard to prediction of further cognitive or functional decline, and rates of progression to AD dementia.

Proposals to be brought forward for voting at the Fourth CCCD:

The CCCD at present endorses the Core clinical criteria for MCI proposed by the 2011 NIA-AA working group(Albert, Dekosky et al. 2011). We will entertain the possibility of transitioning to the concept of prodromal AD in the future when AD-PP biomarkers are available, validated, and ready for use in Canada.

5. Preclinical stages of Alzheimer's Disease and normal elderly subjects

An important contribution of the NIA-AA working groups was to open the discussion on how to approach research studies of cognitively normal subjects with abnormal AD biomarkers. These subjects would be in what is hypothesized as the long preclinical phase of AD preceding MCI, where there is evolving AD-PP, particularly Aβ peptide accumulation and initial neuronal injury. The NIA-AA working group on preclinical AD (Sperling, Aisen et al. 2011) addressed this thorny but important issue, with the proposal of a draft operational research framework for detecting and staging preclinical AD . They liken their proposal to preclinical disease conditions in other medical specialties, for example carcinoma in situ, or Type II diabetes, where it is accepted that symptoms are not necessary to diagnose disease. The operational framework is based on the growing ability to detect abnormal biomarkers in individuals who might otherwise be classified as "elderly normals". Considerable evidence indicates that there are between 20% and 40% of clinically normal older individuals who demonstrate evidence of amyloidopathy (Morris, Storandt et al. 1996) and there is reason to think that positive amyloid biomarkers on imaging precede dementia by 10-15 years (Mintun, Larossa et al. 2006). There are also a set of elderly individuals who show evidence of neuronal degeneration, with changes on MRI or FDG PET. There are even individuals who show both of these, along with very subtle cognitive changes but no real complaints of memory loss. These individuals do not meet criteria for MCI.

The NIA-AA group proposed an operational research framework for staging preclinical AD. Stage 1 preclinical AD was defined as asymptomatic amyloidosis, Stage 2 as asymptomatic amyloidosis accompanied by evidence of neurodegeneration (evidence of either elevated CSF tau, both total tau (t-tau) and phosphorylated tau (p-tau); decreased FDG uptake on PET in temporo-parietal cortex; or disproportionate atrophy on structural MR (sMRI)), and Stage 3 included individuals showing the same biomarker features as stages 1 and 2, accompanied by subtle cognitive decline. Sperling et al. underscored that the framework is not intended for clinical diagnostic

purposes, and that many individuals meeting criteria of the three stages may never actually develop the clinical features of AD in their lifetime. They acknowledged that "the definitive studies to determine whether the majority of asymptomatic individuals with evidence of AD-PP are indeed destined to develop AD dementia….will likely take more than a decade to fully accomplish" (Sperling et al, pg. 11). The group took great pains to point out limitations and confounding factors in the current findings of abnormalities in "normal" elderly subjects. They noted that there is a cohort bias, and these positive biomarkers might not be present to the same degree in community samples. Thus, researchers must be highly restricted in how they present such biomarker data to participants, or whether to present them at all. "Inappropriate use of this information in this context could be associated with unwarranted concern…" (pg. 8). Nevertheless, they presented their operational research framework for staging preclinical AD as a means to enable work on therapy and natural history to proceed in a coherent fashion with a shared language for classification.

The IWG applied the more cautious definition of 'Asymptomatic at-risk for AD' to cognitively normal individuals with positive pathophysiological markers including brain amyloidosis, and reserved "presymptomatic AD" to individuals identified as affected by autosomal dominant AD mutations and therefore certain to develop AD symptoms in the future (Dubois, Feldman et al. 2010). This approach acknowledged explicitly that AD-PP in the absence of clinical symptoms should not be seen as a disease state, and should not be diagnosed. Consistent with the philosophy of AD as a clinic-biological entity, the IWG would consider shifting the border between normal and disease only if there were validated very early cognitive or behavioral changes that predate the features of prodromal AD, and co-occur with AD-PP abnormalities.

The two approaches highlight the enormous challenges in defining the asymptomatic stage between the earliest AD-PP events and the onset of specific cognitive changes. While there is no doubt that this stage exists, at present it is not known whether in-vivo biomarkers of AD-PP can unambiguously identify individuals without cognitive symptoms as being in this stage. In particular, there is concern about amyloidopathy being present in a substantial portion of normal individuals, whether by

amyloid tracer PET or on autopsy. The proportion of amyloid positive individuals among normal elderly samples is far higher the estimated prevalence of AD in the population, cautioning against equating these two states. There is mixed evidence as to whether brain amyloidosis is associated with very mild episodic memory or other cognitive deficits (Jack, Lowe et al. 2008) (Pike, Savage et al. 2007). There is currently no longitudinal evidence yet on the rates of progression to symptomatic states in individuals with brain amyloidosis though they are already recognized as being at higher risk (Morris, Roe et al. 2009). The possibility of clinically silent AD associated with AD-PP has been suggested (Iacono, Markesbery et al. 2009). On this basis we suggest that it is premature to consider brain amyloidosis as an asymptomatic disease state. We suggest instead that asymptomatic at risk/preclinical AD should be conceptualized like MCI was presented a decade ago: as a heterogeneous grouping that potentially includes both individuals who indeed will develop AD, and those who will not.

Recommendations for clinicians on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD): At present, there is no support for an assessment of preclinical or asymptomatic at-risk states of AD in the clinical care of non-demented, non-MCI individuals. AD-PP biomarkers should not be used for clinical purposes in these individuals. The pathological significance of AD-PP positive biomarkers remains unclear.

Recommendations for research and translational development to clinical care on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD):

The most pressing research questions for investigators in settings where normal elderly are evaluated, are longitudinal outcomes of individuals with AD-PP positive markers, and potentially, the identification of very subtle memory and cognitive deficits associated with these states, leading to the possible distillation of a true preclinical AD phenotype, associated with progression to prodromal AD and eventually AD dementia. In turn, this phenotype would in the future provide new and

important opportunities for primary prevention trials and for risk assessment for AD offered in clinical settings.

Proposals to be brought forward for voting at the Fourth CCCD:

The CCCD endorses the IWG definition of "asymptomatic at-risk for AD" states (Dubois, Feldman et al. 2010), with the associated caveat of not equating brain amyloidosis with future development of AD. The medical community should be clear in its discussions with patients, the media and the general population that presence of brain amyloid in normal people is of unclear significance at the present time.

6. Vascular dementia (VaD) and Vascular Cognitive Impairment (VCI)

Vascular dementia occuring with Alzheimer's Disease is common, but 'pure' vascular dementia appears to be uncommon (Roman, Tatemichi et al. 1993; O'Brien, Erkinjuntti et al. 2003). A full review of the management of dementia with a cerebrovascular component was developed in Canada in the CCCDTD3 and was presented by Bocti, Black, and Lysy (Bocti, Black et al. 2007). There are both conceptual and pragmatic difficulties in trying to portray vascular dementia as a distinct entity. Of the criteria now in use (the NINDS-AIREN (Roman, Tatemichi et al. 1993) and ADTCC criteria (Chui, Victoroff et al. 1992) have been especially influential) no set is perfect. In practice, most are insensitive (Rockwood, Davis et al. 2003) and different sets of criteria give differing estimates of who has VaD (Rockwood, Davis et al. 2003; Gold, Bouras et al. 2002). Vascular lesions are found in many dementia patients, including those with otherwise classical AD, where they are often detected only by routine neuroimaging. On the other hand, patients with only vascular pathology as the cause of their dementia have been uncommon in many series (Holmes, Cairns et al. 1999; Knopman, DeKosky et al. 2001). Most patients have mixed pathology, so that patients with vascular lesions commonly have evidence of other neurodegenerative disorders(Tomlinson, Blessed et al. 1970). It is also important to note that many patients with positive imaging do not have a stroke history, implying a high occurrence of "silent strokes".

The NINDS-AIREN criteria for VaD are problematic, as they adhere to a multiple infarction model, and also privilege memory impairment amongst cognitive deficits, when in fact executive dysfunction often predominates(O'Brien, Erkinjuntti et al. 2003). Although the requirement for a temporal relationship between dementia and stroke makes sense for cases of post-stroke dementia, it does not apply to the cases (which in memory clinics typically will be the majority (Rockwood, Davis et al. 2003)) where cognitive deterioration may be slowly progressive rather than stepwise. Moreover, it does not acknowledge the common incidence of silent infarctions (Chui, Victoroff et al. 1992; Vermeer, Prins et al. 2003).

Against this background, the proposal to expand the concept from vascular dementia to one of Vascular Cognitive Impairment (VCI) makes sense (Hachinski 1992; Pike, Savage et al. 2007). This has led the American Heart Association and the American Stroke Association (AHA/ASA) to form a working group which has issued a consensus position paper entitled "Vascular Contributions to Cognitive Impairment and Dementia" in 2011 (Gorelick et al, Stroke, 2011) . This consensus position paper proposes an update of diagnostic criteria for VCI as well as several recommendations regarding neuroimaging, non-pharmacolgical and pharmacological management at different stages of the clinical spectrum. According to the AHA/ASA paper, VCI should include all stages of cognitive disorders associated with cerebrovascular disease, from mild symptoms to overt dementia. "Simply put, VCI is a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least 1 cognitive domain" (page 4). The practical diagnostic approach presented has the merit of being independent from the specific underlying cerebrovascular process (cardioembolic, atherosclerotic, ischemic, etc.). Diagnostic criteria are proposed for vascular dementia (VaD) (probable and possible), and vascular mild cognitive impairment (VaMCI) (probable, possible, and unstable).

Based on cognitive testing of a minimum of 4 cognitive domains (executive function, memory, language, and visusopatial functions), the diagnosis of dementia requires a decline on at least two domains, sufficient to interfere with functioning. Probable VaD requires the presence of a clear temporal relationship between a cerebrovascular event and cognitive impairment or a clear relationship between the

severity and pattern of cognitive impairment and neuroimaging evidence of subcortical cerebrovascular disease. The diagnostic criteria for Possible VaD are fulfilled if there is no clear relationship between cognitive impairment and cerbrovascular disease, if the information available is insufficient or clinical symptoms preclude assessment, or if there is evidence of a concomitant neurodegenerative process that may contribute to the cognitive impairment. These criteria represent clear progress as they do not require the traditional stepwise progression of cognitive impairment associated with multi-infarct dementia, and they are not conditional on memory impairment being present. The diagnostic criteria for probable and possible VaMCI parallel those of probable and possible Va D with the important exception that instrumental activities of daily living should be normal or only mildly impaired. Interestingly, the ASA/AHA introduce the concept of unstable VaMCI to account for individuals whose impairment may revert to normal during follow-up.

Recommendations for clinicians on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD): The concept of VCI has merit, as it moves away from the models of post-stroke dementia and multi-infarct dementia, and it emphasizes opportunities for prevention of modifiable cerebrovascular disease. It should be adopted for clinical diagnosis.

Recommendations for research and translational development to clinical care on behalf of the the 4th Fourth Canadian Consensus Conference on Diagnosis (CCCD): Neuroimaging research should be pursued to better characterize the vascular contribution do dementia syndrome in general and AD in particular. Long-term trials should be encouraged to define the role of non-pharmacological and pharmacological interventions in primary prevention in midlife.

Proposals to be brought forward for voting at the Fourth CCCD:

The CCCD endorses the 2011 ASA/AHA recommendations for the diagnosis of VCI (Gorelick et al, Stroke, 2011).

7. What's missing? What's needed in the future?

This paper has focussed on the new diagnostic formulations of Alzheimer's disease that support the earlier identification of disease based on biomarker integration. There is currently an emerging belief in the field that the failure to make progress in therapeutics of the disease is arising from interventions that are too late in the processed pathophysiological process. The emergence of biomarkers that identify the pathology of AD ahead of its symptomatic expression may in the future allow the potential for studies directed at earlier intervention including those directed at prevention of AD/dementia.

In relationship to the new diagnostic criteria there are a number of key areas that will hopefully be informed with additional research attention in the coming years. In the area of AD dementia, it will be possible to perform biomarker tests that confirm the presence of Alzheimer pathology. Recent studies suggest that there is room for such improvement where it has been estimated that 15-20% of patients diagnosed with AD in the Alzheimer Disease Neuroimaging Initiative do not have amyloid pathology on biomarker studies suggesting that they do not have the correct pathology for the clinical diagnosis. In the area of MCI due to AD and prodromal AD there is residual uncertainty around whether this condition progresses invariably to AD dementia and if so with what supporting biomarkers and at what levels of abnormality. In the area of asymptomatic or minimally symptomatic states with positive Alzheimer biomarker's there is an opportunity to define the risk of progression to AD dementia and in turn to understand the need and balancing of risk/benefit for potential interventions while still in the asymptomatic state.

It may be time to reconceptualize the functional impairment criteria for AD diagnosis given some of the significant decade long challenges of defining the 'right amount of impairment '.Defining functional impairment cut-off points is very difficult, and even assessing function in many cases is unworkable, given its significant social and gender context.

Outside of AD are the considerations of the status of mixed dementia vs. pure AD and VaD. In the clinic, we have all confronted the fact that the majority of patients have some evidence of vascular as well as neurofibrillary pathology, and if we had (or will have in the future) better imaging techniques, this fraction will likely rise.

True, the McKhann paper proposes designating etiologically mixed presentations of AD as a form of "possible AD dementia", and Dubois and his committee refer to "Mixed AD" for such individuals (Dubois, Feldman et al. 2007; Dubois, Feldman et al. 2010). However, the clear emphasis remains on pure AD as the major diagnosis. Others (Richards and Deary 2005) consider that this approach should be turned on its head, and mixed pathology considered as the usual state, particularly in older individuals (Rockwood, Davis et al. 2003; Brayne, Richardson et al. 2009). As Richards and Brayne state in a recent BMJ editorial[Richards, 2010], "It is timely to interrogate the term Alzheimer's Disease. In older age groups, AD seems to be a diffuse clinical syndrome representing the gradual accumulation of multiple pathologies, arising from multiple interlocking risk factors over the life course. The term Alzheimer's syndrome seems more appropriate" (Richards and Brayne, 2010, pg. 865.).

Even at the research level, some important assumptions are inherent in the terminology proposed. Sperling and her group proposed an operational research framework for staging preclinical AD - in which Stage 1 was asymptomatic amyloidosis, Stage 2 was asymptomatic amyloidosis accompanied by evidence of neurodegeneration, and stage 3 was the same two features, now accompanied by subtle cognitive decline. Structuring things this way suggests strongly that individuals progress from stage 1 to 2 to 3 to MCI to dementia. There is little evidence to date that this is indeed the case, and the assumption requires serious longitudinal testing.

Lastly, one must be continually aware (as most of the authors of the recommendations are) of the rapid developments in the field, and the need to reconsider criteria every few years now. These NIA-AA recommendations have the strength of designating themselves as "works-in-progress". As such, we should feel no obligation to move the new terminology from the research lab to the clinical arena, until there is validation, harmonization of criteria, and proven advantages in terms of better prognostication and better treatment options. One criticism of the current papers might well be that there is no clear timeline for such reappraisals, and no clear mechanism to currently restrict the use of terms to the research setting. In Canada, Quebec has a plethora of public and private PET machines available for use. FDG PET is available, and recently the FDA has approved florbetapir, the first commercially

available amyloid PET imaging agent. Given the past experience in medicine, we can readily anticipate that patients will demand and will receive (at some considerable expense) the "Alzheimer's test" that might establish "MCI due to Alzheimer's Disease with highest biomarker probability of AD etiology" as their diagnosis. Patients will presumably start to request referral to centres where such biomarkers are available in order to get the best medical diagnosis. If we do not concur with this as the new medical care standard, what can and will be done to prevent it?

6. Proposals to be brought forward for voting at the Fourth CCCD:

Given the discussions above, we will bring the following proposals forward at the CCCD meeting for consensus approval:

1. We propose that the Fourth CCCD adopt the recommendations around criteria for dementia proposed by the 2011 NIA-AA working group.

2. We propose that the CCCD adopt the recommendations concerning Alzheimer's Disease dementia diagnostic criteria proposed by the 2011 NIA-AA working group(McKhann, Knopman et al. 2011).

3. The CCCD at present endorses the Core clinical criteria for MCI proposed by the 2011 NIA-AA working group(Albert, Dekosky et al. 2011). We will entertain the possibility of transitioning to the concept of prodromal AD in the future when AD-PP biomarkers are available, validated, and ready for use in Canada.

4. The CCCD endorses the IWG definition of "asymptomatic at-risk for AD" states (Dubois, Feldman et al. 2010), with the associated caveat of not equating brain amyloidosis with future development of AD. The medical community should be clear in its discussions with patients, the media and the general population that presence of brain amyloid in normal people is of unclear significance at the present time.

5. The CCCD endorses the 2011 ASA/AHA recommendations for the diagnosis of VCI (Gorelick et al, Stroke, 2011).

APPENDIX TO BE APPENDED TO ARTICLE:

Probable AD Dementia: Core NIA Clinical Criteria

In the new NIA-AA terminology, Probable AD Dementia was to be diagnosed when the patient met criteria for dementia already stated, and in addition: had an insidious onset of symptoms over months to years, and had clear-cut history of worsening of cognition by report or observation. Furthermore, it was now stated that the prominent cognitive deficits could occur in one of the following categories.

(1) Amnestic presentation: The most common syndromic presentation of AD dementia. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined above.

(2) Non-amnestic presentations:

For instance, Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. There could also be a non-amnestic presentation of predominantly visuospatial presentation with object agnosia, and syndromes of predominant frontal/executive dysfunction.

The group specified that The diagnosis of Probable AD Dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy Bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical co-morbidity or medication use that could have a substantial impact on cognition.

It was also specified that there were certain features that substantially increased the level of certainty, these being presence of a known FAD causative gene, and documented cognitive decline over time.

*

Possible AD Dementia: Core NIA Clinical Criteria

The diagnosis of possible rather than probable AD was to be made in either of the following circumstances.

a. Atypical Course: A patient who meets the Core Clinical Criteria for AD Dementia, but either had a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline,

OR

b. Etiologically Mixed Presentation: A patient who meets all Core Clinical Criteria for AD Dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy Bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical co-morbidity or medication use that could have a substantial impact on cognition

<u>Probable AD Dementia with evidence of AD-pathophysiology.</u>

This third category of AD, was determined to consist of those cases of probable or possible AD where there were available the results of relevant brain biomarkers. The major biomarkers of the AD pathophysiological process were divided into two classes based on the biology which they measure. Biomarkers of brain amyloid-beta (Aβ) protein deposition are low CSF Aβ42 and positive PET amyloid imaging. The second category is biomarkers of downstream neuronal degeneration or injury. The three major biomarkers in this category are elevated CSF tau, both total tau (t-tau) and phosphorylated tau (p-tau); decreased FDG uptake on PET in temporo-parietal cortex; and disproportionate atrophy on structural MR (sMRI) in medial, basal and lateral temporal lobe, and medial parietal cortex. According to the NIA committee, in persons who meet the Core Clinical criteria for Probable AD dementia, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. The use of biomarkers to enhance certainty of AD- were stated to be useful in three circumstances presently; investigational studies,

clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician.

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