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REVIEW ARTICLE

CCCDTD5: Clinical role of neuroimaging and liquid biomarkers in patients with cognitive impairment

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Abstract

Since 1989, four Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTDs) have provided evidence-based dementia diagnostic and treatment guidelines for Canadian clinicians and researchers. We present the results from the Neuroimaging and Fluid Biomarkers Group of the 5th CCCDTD (CCCDTD5), which addressed topics chosen by the steering committee to reflect advances in the field and build on our previous guidelines.

Recommendations on Imaging and Fluid Biomarker Use from this Conference cover a series of different fields. Prior structural imaging recommendations for both computerized tomography (CT) and magnetic resonance imaging (MRI) remain largely unchanged, but MRI is now more central to the evaluation than before, with suggested sequences described here. The use of visual rating scales for both atrophy and white matter anomalies is now included in our recommendations. Molecular imaging with [^{18}F]-fluorodeoxyglucose ([18F]-FDG) Positron Emisson Tomography (PET) or [^{99m}Tc]-hexamethylpropyleneamine oxime/ethylene cysteinate dimer ([^{99m}Tc]-HMPAO/ECD) Single Photon Emission Tomography (SPECT), should now decidedly favor PET. The value of [^{18}F]-FDG PET in the assessment of neurodegenerative conditions has been established with greater certainty since the previous conference, and it has now been recognized as a useful biomarker to establish the presence of neurodegeneration by a number of professional organizations around the world. Furthermore, the role of amyloid PET has been clarified and our recommendations follow those from other groups in multiple countries. SPECT with [^{123}I]-ioflupane (DaTscan^{TM}) is now included as a useful study in differentiating Alzheimer's disease (AD) from Lewy body disease. Finally, liquid biomarkers are in a rapid phase of development and, could lead to a revolution in the assessment AD and other neurodegenerative conditions at a reasonable cost.

We hope these guidelines will be useful for clinicians, researchers, policy makers, and the lay public, to inform a current and evidence-based approach to the use of neuroimaging and liquid biomarkers in clinical dementia evaluation and management.

1 | INTRODUCTION

Since 1989, four Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTDs) have led to evidence-based recommendations on the diagnosis and treatment of Alzheimer's disease (AD) and related dementias.[1–4] The 5th CCCDTD (CCCDTD5) convened in October 2019 in Quebec City, in conjunction with the Canadian Conference on Dementia in order to re-assess the previous guidelines based on updated information relevant to the field. Topics included: (1) the utility of the National Institute on Aging (NIA) research framework for diagnosing AD; (2) updating diagnostic criteria for vascular cognitive impairment (VCI) and its management; (3) detection of neurodegenerative disease using cognitive, behavioral, and functional rating scales; (4) use of neuroimaging and fluid biomarkers in diagnosis; (5) use of non-cognitive markers of dementia for better dementia detection; (6) risk reduction/prevention; (7) psychosocial and non-pharmacological interventions; and (8) de-prescription of medications used to treat dementia. The general report from the conference is already available.[5]

This paper presents the results of our work in the field of clinical neuroimaging.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors did a systematic review of the English medical literature since the last Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) (CCCDTD4, 2012) on the use of neuroimaging and liquid biomarkers in diagnosing Alzheimer's disease (AD).
2. **Interpretation**: Significant advances have been made since that previous set of recommendations in all fields of imaging and in measurements of biomarkers from body fluids, leading to a necessary reassessment of the roles of different modalities, including some, which were not discussed in 2012. The current version offers guidance to clinicians, allowing for better patient management of subject and available resources.
3. **Future research**: The role of new imaging approaches (tau imaging for instance; the search for imaging ligands binding other abnormal protein aggregates is actively conducted) remains to be evaluated clinically in large populations. The best combinations of liquid biomarker measurements, imaging studies, and other clinical parameters (neuropsychological tests, genetic markers, and so on) have not yet been defined. Given the speed of developments, regular re-assessment of recommendations in this field will be critical.

2 | METHODS

The methodology was based on the approach suggested by the Appraisal of Guidelines for REsearch & Evaluation II (AGREE II) collaboration,[6] of which 20 of the 23 criteria were met. The steering committee chose the topics for the CCCDTD5 based on a needs assessment and advances in the field. Working groups included representation from neurology, psychiatry, medical imaging, geriatric medicine, and primary care, and scientists with expertise in the field. Literature searches were tailored to working group needs and varied depending on whether the recommendations were an update of existing recommendations or were based on de novo topics. Where possible, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was followed in keeping with current recommendations for the conduct of consensus conferences.[7] A semi-structured consensus building methodology was used, based on the Delphi process.[4,8] Recommendations were posted to a password-protected site, along with all documentation, and were voted on by a panel of more than 50 Canadian experts across the spectrum of background education/expertise. Recommendations were endorsed or rejected, with comment boxes for participant feedback. Consistent with previous conferences, the a priori threshold for acceptance of a recommendation was set at 80% endorsement. Any recommendation that obtained 60% to 80% endorsement was reviewed and revised with re-voting at an in-person meeting. Recommendations that obtained less than 60% endorsement were dropped. Stakeholders in the care of patients with dementia including non-voting representatives from industry, government, the international community, and other organizations involved in dementia guidelines were invited as observers to the CCCDTD5. Online voting closed 3 days before the conference, which was held in Quebec City on October 3rd, 2019. At the conference, each topic was summarized along with the results of the online voting. Recommendations requiring revision were discussed in detail followed by an anonymous vote. The same ≥80% threshold was required to pass the revised recommendations. All endorsed recommendations are listed in the tables of this article, followed by the GRADE of evidence and percentage endorsement attained.

3 | RECOMMENDATIONS FOR THE IMAGING APPROACH TO THE DIAGNOSIS OF DEMENTIA

3.1 | Structural imaging

The previous iteration of the CCCDTD conference, held in Montreal in 2012, made the following recommendations regarding structural imaging for the diagnosis of dementia[4,9]:

The new recommendations are presented and discussed below.

Indications for structural neuroimaging in subjects presenting with cognitive impairment remain controversial, with certain authors suggesting neuroimaging in all subjects while others promote a selective approach.[10–12] We propose the above recommendations for routine

initial evaluation of subjects with cognitive decline. These are substantively the same as previously with the caveat that the reference to age 60[4] has been removed (this was considered arbitrary as no satisfactory justification was found in the literature).

Similar to the prior recommendation, uncertainty remains pertaining to the use of computerized tomography (CT) versus magnetic resonance imaging (MRI) as the first neuroimaging test to obtain. CT can detect large cortical ischemic lesions, space-occupying lesions, hydrocephalus, and subdural hematomas. However, the sensitivity of CT for subcortical ischemic lesions, in particular white matter disease, as well as for other rarer conditions such as prion diseases and auto-immune encephalitides, is inferior to MRI. Again, authors are divided regarding the best first-line modality, but MRI is generally favored over CT.[10,13–17] One cost-effectiveness study found CT to be a superior first-line approach compared to MRI.[18] Local practices and imaging modality availability is another factor to consider when ordering studies.

Dementia imaging protocols vary across centers. Proposed baseline imaging sequences endorsed by the European Society of Neuroradiology (ESNR) and the European Academy of Neurology (EAN) have been described elsewhere.[16] This includes the following sequences: three-dimensional (3D) T1-weighted, fluid-attenuated inversion recovery (FLAIR), T2*-weighted or susceptibility weighted imaging (SWI), T2-weighted, and diffusion-weighted imaging. Typically, studies are performed without intravenous gadolinium contrast injection, unless there is a specific indication such as the possibility of underlying neoplastic, infectious, or inflammatory disorder. If available and if there is no contraindication, 3T imaging is favored over 1.5 T MRI.[19] The proton density (PD) sequence, although rarely included in routine clinical practice, may be helpful for research. More advanced sequences, such as resting-state functional MRI, arterial spin labeling, MR spectroscopy, and diffusion tensor imaging, remain research tools that are not validated for routine clinical use.[20]

Space-occupying lesions are generally easy to detect, and interpretation of CT and MRI studies should go beyond excluding such processes.[21,22] Atrophy severity and patterns as well as ischemic lesion burden including white matter changes are important features to describe. The use of a systematic approach to the interpretation of such studies is recommended to maximize its yield.[16,21,23] Although most radiology reports remain in the traditional narrative style, there is interest in moving toward structured reporting, incorporating a systematic approach.[24] The use of quantitative scales to report patterns of atrophy is also encouraged. These include the Scheltens (Medial Temporal Atrophy [MTA])[25,26] and Pasquier (Global Cortical Atrophy [GCA]) scales.[27–29] In addition, lobar patterns and asymmetry should be noted.[21] Despite the fact that these scales are typically aimed at MRI scan interpretation, they are transferable to CT scan interpretation.[21,22,30] To better assess the MTA scale on CT, coronal (or oblique coronal) reformation should be performed.[22,30] Training has an effect on the reliability of how these scales are applied and the use of reference images is recommended, especially for readers who are less experienced with these grading schemes.[28] For white matter disease, the Fazekas scale[31] is the most widely used grading system. The terminology to describe small vessel disease has also been reported.[32]

Despite the widespread use of quantification software in research, the adoption of one or more of many quantification software packages in clinical practice is rare. This is likely due to limited availability and the time needed for use of those packages as well as the questionable external validity of research results.[16,33] Moreover, the additional diagnostic information provided compared to subjective interpretation needs to be assessed in routine clinical practice. One recent study did not find a significant difference in medial temporal lobe atrophy grading accuracy when comparing visual ratings and the use of a commercially available software.[34]

Overall, there remains a lack of evidence for the use of quantification software either for the initial diagnosis of AD or for the purpose of differential diagnosis.[35,36] Artificial intelligence and the rapidly evolving area of deep learning-assisted quantification is likely to augment imaging analysis in the future but the need for validation of these tools in clinical practice remains.[37]

3.2 | Functional and ligand-based imaging

The previous iteration of the CCCDTD conference, held in Montreal in 2012, made the following recommendations about the use of functional and ligand-based imaging for the diagnosis of dementia[8,9]:

This statement is more direct than the previous statement regarding the performance of [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) Positron Emisson Tomography (PET), as evidence has accumulated since 2012 about the usefulness of this procedure. That additional evidence is presented here.

The references reviewed are from 2012 or later, except for a few important papers not included in the 4th CCCDTD discussion.

First, it should be mentioned that the risk associated with [^{18}F]-FDG is essentially non-existent. Only one clear case of a reaction to [^{18}F]-FDG has been documented since 2015; specifically, a skin rash was found (a subsequent injection after administration of steroids was uneventful).[38] To put this in perspective, the number of [^{18}F]-FDG PET scans performed in the United States in 2018 is estimated to have been above 2,000,000.[39]

The Alzheimer's Society of Canada refers to recommendations from the 4th CCCDTD in the section of its website about the diagnosis of AD,[40] endorsing their validity. Somewhat unexpectedly, several other groups including the American Academy of Neurology, American Geriatrics Society, American Neurological Association, American Psychiatric Association, Canadian Academy of Geriatric Psychiatry, Canadian Association on Gerontology, Canadian Geriatrics Society, Gerontological Society of America, and International Psychogeriatric Association do not comment on the role of molecular imaging in the diagnosis of subjects presenting with cognitive impairment.

Recognition of the importance of imaging biomarkers to establish a diagnosis of AD originated in 2011 with the publication of four articles jointly written by the National Institute on Aging (NIA) and the Alzheimer's Association. The first article describes their introduction

in the diagnostic evaluation of AD.[41] Two [42,43] of the remaining three articles discuss their usefulness in the assessment of patients with major cognitive impairment (MaCI) and minor cognitive impairment (MiCI) suspected to be AD related. The fourth article suggests a way to identify preclinical AD in a research context.[44] In the first three, [^{18}F]-FDG PET is presented as a marker of neuronal injury (alongside cerebrospinal fluid [CSF] tau measurements and structural MRI) capable of modulating the probability of AD in the context of a large array of clinical and laboratory results.

Several organizations subsequently confirmed that [^{18}F]-FDG PET plays a valuable role in evaluating subjects with cognitive impairment. In 2012, the European Federation of Neurological Societies recommended the use of [^{18}F]-FDG PET in the evaluation of subjects with cognitive impairment for whom a diagnosis remained ill-defined, both to decide if a neurodegenerative condition was present and to differentiate specific conditions.[45] In 2014, the International Working Group on AD concurred that the addition of biomarkers (citing [^{18}F]-FDG among others) was likely to improve diagnosis.[46] The same group reinforced this notion, particularly in the preclinical phase and in cases of atypical AD or mixed disease.[47] A Cochrane Review[48] from the same period concluded that a recommendation on the routine use of [^{18}F]-FDG PET in patients with MiCI was difficult to make, one of their reasons being that [^{18}F]-FDG PET was expensive, which has changed as the price of [^{18}F]-FDG has decreased. In addition, the review noted only a few articles with small patient numbers (14 studies with a total of 421 subjects) evaluating MiCI conversion to MaCI with suspected AD were available.

Recommendations from the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers[49] established five indicators of [^{18}F]-FDG PET "clinical maturity" based on a literature review following criteria already used for oncology. The biological validity of [^{18}F]-FDG PET to study neurodegeneration (Phase 1 clinical maturity) was considered to have been established. Demonstrating that [^{18}F]-FDG PET was capable of distinguishing subjects with AD from normal subjects or subjects with other neurodegenerative conditions was deemed as essentially completed (Phase 2 clinical maturity). That [^{18}F]-FDG PET was capable of detecting early clinical phases of the disease (Phase 3 clinical maturity), was considered partially confirmed, whereas the defining value of [^{18}F]-FDG PET in prodromal cases (Phase 4 clinical maturity) was declared to be a work in progress. Proof of a favorable cost/benefit ratio (Phase 5 clinical maturity), was unmet due to an absence of studies on actual cost per Quality-Adjusted Life Year (QALY) added, death prevented, or comparison to other diagnostic approaches. This does not mean that there has been no attempt at evaluating the economic impact of [^{18}F]-FDG PET early in the course of the disease (vide infra). Furthermore, it would be difficult to assess the usefulness of [^{18}F]-FDG PET given no disease course-modifying therapy is available.

In 2018, the Alzheimer's Association released an online set of guidelines for primary and specialty care physicians[50] including that diagnostic accuracy is increased by [^{18}F]-FDG PET in subjects where no clear diagnosis has been established after clinical evaluation and structural imaging (preferably MRI). The recommendation states that molecular imaging should be ordered by a dementia specialist, a prescription we have adopted in our own recommendations.

The same year, The National Institute for Health and Care Excellence (NICE) in the UK, which advises the National Health System on a variety of topics, also published recommendations on molecular imaging[51] suggesting molecular imaging be requested by a dementia specialist if the diagnosis remains in doubt after clinical assessment, laboratory evaluation and structural imaging, and a diagnosis would change patient management.

Again in 2018, the European Association of Nuclear Medicine and Molecular Imaging and the European Academy of Neurology jointly published recommendations on the use of [^{18}F]-FDG PET in the evaluation of subjects with cognitive decline and neurodegenerative conditions.[52] Using a Delphi process, the authors reviewed 58 articles (of an initial potential pool of 1435) deemed to contain enough quantitative information for passing a judgment on the effectiveness of the technique. Underscoring the limited quality of the evidence, the two associations agreed that [^{18}F]-FDG PET was useful for the early detection of AD, as well as for the differential diagnosis of neurodegenerative disorders leading to cognitive decline. They also suggested the use of pattern recognition software packages could improve performance.

Finally, the NIA (United States) and Alzheimer's Association published a framework for the diagnosis of AD based on biological (non-clinical) criteria only.[53] Initially this was proposed for research purposes, but the potential for generalization to clinical practice is under review. This framework is based on showing the presence or absence of amyloid and tau pathology as well as neurodegeneration using a variety of tests of which [^{18}F]-FDG PET is a validated marker, again confirming its usefulness in establishing a diagnosis of AD.

It is important to assess the cost of the technique (in itself and as compared to alternatives) in terms of the information provided and the impact on patient management and outcome. Such studies are challenging to complete due, at least in part, to non-uniformity in cost, access, local expertise, and so on.[54] Over the years, several attempts in different countries[55–57] have been made to define a useful index representative of a typical cost/benefit ratio. The results of those admittedly imperfect efforts all point at potential savings and improvements in the quality of life of subjects, using a technique with an established safety record. Several additional studies,[58–60] although not focussed on PET, have suggested that knowing the diagnosis of AD early in the course of the disease leads to improved patient management in terms of the medications prescribed and the use of specialized care, in addition to higher quality of life. Finally, the risk of harming patients and their caregivers by revealing a diagnosis carrying a poor prognosis has been largely discussed and dismissed: Generally, both groups appreciate being given a clear diagnosis, which allows them to chart a life course better adapted to the situation.[61]

First it should be noted that subjects and families often have no personal preference for PET versus single-photon emission computerized tomography (SPECT).[62]

Only recently has supportive data for the above recommendation become available. For instance, Davison and O'Brien[63] reviewed 24 studies published between 1997 and 2011, 13 with PET, including 2382 subjects classified as either normal or cognitively impaired (AD, Lewy body dementia [LBD], or frontal temporal dementia [FTD]). None were head-to-head comparisons. Despite the large number of studies and cases, in that article published <10 years ago, the authors stated that the data were insufficient to choose one technique over the other. A review[64] of studies from 1989 to 2012 (35 studies with PET including 3199 subjects, and 38 studies with SPECT including 2178 subjects), suggested that PET had higher diagnostic accuracy than SPECT. However, the results from each study, when assessed with positive and negative likelihood ratios, depended on the technique used for classification and showed large variations in performance. This may be an indicator that better trained readers provide interpretations that are more helpful. Another review[65] of papers published between 1990 and 2010 (27 studies with PET and 19 with SPECT), suggested that PET had higher performance than SPECT for distinguishing AD cases from non-demented controls (area under the receiver operating characteristic (AUROC) curve—FDG: 0.96, confidence interval [CI] 0.93-0.97; SPECT: 0.90, CI 0.87-0.92) and from demented controls when MCI cases were included (0.91, CI 0.88-0.93 vs 0.86, CI 0.83-0.89), but not if MCI cases were excluded.

Results of head-to-head comparisons for SPECT and PET in the same subjects are rare. A study from Japan[66] compared PET to SPECT in 28 subjects with MaCI due to AD and 12 with MiCI linked to AD versus 15 without AD (10 LBD and 5 frontotemporal lobar degeneration (FTLD)). All subjects had [^{18}F]-FDG PET, [^{11}C]-Pittsburg compound B ([11C]-PiB) PET, [^{99m}Tc]- ethylene cysteinate dimer ([^{99m}Tc]-ECD), and MRI, and were clinically evaluated using the 2011 NIA-AA (Alzheimer's Association) criteria for AD, and the 1998 Neary and 2005 McKeith criteria for LBD and FTLD. All imaging interpretation was done visually (three physicians). The authors concluded that SPECT and PET had similar performance for the diagnosis of AD. The three readers had a diagnostic accuracy, with both techniques, ranging from 60% to 70%, that is at the lower limit of results from other studies for both. Distribution of the two agents was found to correlate poorly in the precuneus, posterior cingulate cortex, and occipital lobe, regions that are critical to the diagnosis of AD and LBD. However, the results are not presented for each subject, which makes their comparison difficult. A larger study from the same time[67] included 38 subjects with AD, 30 with LBD, and 10 controls. Diagnosis was established based on clinical evaluation only. Average time between scans was 11 days. SPECT was performed with [^{99m}Tc]-ECD. Interpretation (three physicians) was done both visually and using a Statistical Parametric Mapping (SPM)-based comparison to a normal database. The metric extracted was the AUROC curve. PET was superior to SPECT for both neurodegenerative versus normal (AUC: 0.93 PET, O.72 SPECT, $P < .001$) and AD versus LBD (0.80, 0.58, $P = .005$). The authors concluded that PET was preferred over SPECT when molecular imaging was necessary for diagnosing neurodegenerative conditions. Another study focused on early diagnosis.[68] Nine subjects with AD MaCI, 9 with LBD MaCI, 8 with AD MiCI, and 9 with LBD MiCI were assessed with PET and SPECT ([^{123}I]-IMP). Classification was made using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MaCI versus MiCI and the 2011 MIA-AA criteria and 2005 McKeith criteria for AD and LBD, respectively. Analysis was done by comparing subjects to normal databanks, limiting measurements to the occipital area. Significance was assessed using an AUROC curve approach. With [^{18}F]-FDG PET, the AUROC curve for AD versus LBD in the MaCI stage was 0.80 and 0.84, respectively, on the left and right hemispheres, as compared to 0.78 and 0.85 with SPECT, confirming that both techniques were capable of differentiating the two diseases at the MaCI stage. For MiCI subjects, FDG had AUROC curves of 0.85 and 0.89 for the left and right hemispheres, whereas SPECT did not reach significance. The authors recommended PET over SPECT for establishing a differential diagnosis of AD versus LBD at the MiCI stage. More recently, a report of a study of 20 subjects with mild MaCI, that is, Cinical Dementia Rating (CDR) score 0.5 or 1 of the Alzheimer's type, as defined by McKhann's 1984 criteria, and 18 controls who were studied with PET, SPECT, and MRI (T_1) has been published.[69] Studies were processed using a support vector machine–based image classification, with measurements of accuracy and AUROC curve, on images generated using different types of reconstruction and normalization schemes for both SPECT and PET. Functional imaging outperformed MRI. Accuracy and AUROC curve were 68% to 71% and 0.77 to 0.81 (depending on the normalization approach) for PET, 68% to 74% and 0.75 to 0.79 for SPECT (depending on the normalization approach and use of partial volume correction), and 58% and 0.67 for MRI. The authors concluded that SPECT and PET were comparable, and the reconstruction of SPECT benefited from partial volume correction, whereas PET did not.

Finally, we include a paper that was published after the CCCDTD5 meeting but before this article was written[70] because it is, to date, the largest head-to-head comparison of PET and SPECT in AD. One hundred twenty-six patients with AD (54% MiCI and 44% MaCI) confirmed to be amyloid positive by PET had both [^{18}F]-FDG PET and a SPECT ([^{99m}Tc]-ECD or [^{99m}Tc]-HMPAO), with a median time of 3 months between the two (median time between amyloid and FDG-PET and SPECT: 185 days). Readers felt more confident reading PET than SPECT (83% vs 67%, $P = .001$). PET results were superior to SPECT: AUROC curve for PET was 0.71 versus 0.61 for SPECT ($P = 0.02$). Sensitivity was 76% versus 43% ($P < .001$), whereas specificity was 74% versus 83% ($P = .45$), respectively for PET and SPECT.

Thus the literature supports our recommendation that [^{18}F]-FDG PET is preferable to SPECT regional cerebral blood flow for the investigation of cognitive impairment.

Guidelines suggest that amyloid PET may be helpful in patients with objective, clinically confirmed cognitive impairment of uncertain etiology and in whom knowledge of amyloid deposition may alter management.[71,72] Appropriate use criteria of amyloid PET suggest the need to be cognizant of the clinical implications of a negative[73,74] or a positive test,[75,76] and to be capable of defining what constitutes an atypical presentation of cognitive impairment (early onset, slowly progressive MiCI); that is, the ability to recognize patients who will benefit from amyloid PET is important. This has led to the

recommendation[71,77] that ordering amyloid PET be limited to physicians who dedicate a significant proportion of their practice to subjects with cognitive impairment.

[^{18}F]-FDG-PET provides valuable information in the evaluation of subjects with cognitive impairment. The cost associated with [^{18}F]-FDG-PET is lower and the access is easier than for amyloid PET. As such, it is preferable to obtain [^{18}F]-FDG-PET prior to obtaining amyloid PET. From a scientific perspective, there is little ground for proposing a systematic approach as to the sequence of [^{18}F]-FDG-PET or amyloid PET[78]: The two techniques are complementary.[79] Furthermore, [^{18}F]-FDG-PET can suggest typical or variant-type AD, while amyloid PET cannot.[80]

In 2004, the first study of 16 humans with AD imaged with [^{11}C]-PIB was published[81]; the 20-minute half-life of ^{11}C limited availability of ^{11}C-PIB to centers with access to an on-site cyclotron. Today, several PET radiopharmaceuticals are available to detect amyloid deposition in the brain including [^{18}F]-florbetapir (Amyvid),[82] [^{18}F]-flutemetamol (Vizamyl),[83] [^{18}F]-florbetaben (NeuraCeq),[84,85] as well as [^{18}F]-NAV-4694 (formerly known as AZD4694; not approved for clinical use).[86] Of those, only [^{18}F]-florbetaben has been approved for human use in Canada. The half-life of ^{18}F is ≈110 minutes, allowing shipping of imaging agents across large distances. These radiopharmaceuticals bind to amyloid plaque and, non-specifically, to white matter. Typically, amyloid PET is interpreted visually in a binary manner, using manufacturer-recommended specific image color scales, as positive (loss of gray-white matter differentiation) or negative. A positive scan implies moderate to frequent amyloid plaques (which is not equivalent to a diagnosis of AD) and a negative scan suggests no or sparse amyloid plaque and essentially eliminates the possibility of AD.[53] Quantitation of total amyloid burden and loco-regional accumulation may be insightful.[87,88]

Arguably the most commonly encountered PET radiopharmaceutical for amyloid imaging is ^{18}F-florbetapir. ^{18}F-florbetapir PET has sensitivity (87%) and specificity (95%) for distinguishing none to sparse from moderate to frequent amyloid plaque as confirmed at autopsy.[74] The performance of [^{18}F]-florbetaben, again when validated by autopsy results (in 74 subjects), is at least as good, with a sensitivity of 98% (95%CI 94%-100%) and specificity of 90% (95% CI 77%-100%).[73]

In 2013, the Amyloid Imaging Task Force, a collaborative group of the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), recommended that amyloid PET be considered if the results of imaging could change management.[89] To derive supportive data, the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study was launched in 2016. This study was designed to assess if amyloid PET could help clinicians diagnose the cause of cognitive impairment, provide treatment recommendations, and ultimately improve long-term health outcomes.[90] Of 11,409 subjects 65-years of age or older (with MCI or dementia of uncertain etiology) who met the appropriate use criteria (AUC) for amyloid PET and completed the study, a change in management between pre- and post-PET visits was recorded in 60% of subjects with MCI and 63% of subjects with dementia.[91]

[^{123}I]-Ioflupane SPECT became available in Canada in December 2017,[92] later than in other jurisdictions because of issues related to the classification of the molecule as a controlled drug, which could not be imported into Canada. The Health Canada approval was specifically for [^{123}I]-ioflupane as a diagnostic agent (showing the level of dopaminergic innervation of the striatum) to be used in the differential diagnosis between essential tremors and neurodegenerative parkinsonian syndromes (idiopathic Parkinson disease, multisystem atrophy, progressive supranuclear palsy, and cortical basal ganglia degeneration). Approval was not granted for use in the evaluation of neurocognitive disorders, although it can be helpful for that purpose (ie, used off-label). The safety profile of [^{123}I]-ioflupane is well established and its use can be considered to represent essentially no risk to patients.[93]

Although most reports on [^{123}I]-ioflupane concern the evaluation of patients with movement disorders, three review articles on the evaluation of LBD (written in English) were published since the CCCDTD in 2012. A Cochrane Review[94] included a single study[95] of 22 autopsy-confirmed subjects with clinical criteria compatible with AD, LBD, or a mixture of both. Differentiation of LBD cases from non-LBD with [^{123}I]-ioflupane using a quantitative analysis, had a sensitivity of 1.00 (CI 0.66-1.00) and a specificity of 0.92 (0.64-1.00), whereas using a visual evaluation in 19 of the 22 subjects yielded a sensitivity of 0.86 (0.42-1.00) and a specificity of 0.83 (0.52-0.78). The authors concluded that the performance of [^{123}I]-ioflupane SPECT was likely better than clinical assessment alone, and a negative result in the setting of moderately severe MaCI with a strong pre-test probability of LBD, likely eliminated the diagnosis of LBD.

A review from the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers[96] included six studies (over 974 subjects: data not available for all studies) where the use of [^{123}I]-ioflupane was evaluated in a variety of conditions (normal subjects, Parkinson disease, LBD, AD, LBD and AD, Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), and "others"). The authors concluded: (1) [^{123}I]-ioflupane shows a difference between AD and LBD and (2) it is a valid approach to the differential diagnosis of AD versus LBD. However, none of the studies that were included investigated the prodromal stages of LBD (phase 3), the progression of this biomarker over time in subjects with LBD (phase 4) or the impact on disease outcome (phase 5). Therefore, the authors suggested that [^{123}I]-ioflupane SPECT needed to be further characterized before it could be a "confirmed" approach for differentiating DLB from AD.

Finally, the Fourth consensus report of the DLB Consortium[97] included [^{123}I]-ioflupane SPECT in its diagnostic algorithm as an "Indicative Biomarker" of disease. Their recommendation was to the effect that "If one or more of these (Indicative Biomarker) is found, associated with one or more core clinical features, probable LBD should be diagnosed." Thus experts from that that Consortium endorsed this test as part of the diagnostic algorithm for the disease under specific circumstances.

Of note, there is evidence[98] that ≈8% of patients with LBD have only cortical disease and that this may result in a negative [^{123}I]-ioflupane SPECT study.

TABLE 1 Structural imaging: Recommendations from the CCCDTD4 Conference (2012)

1. We recommend a head MRI when a radiologist/neuroradiologist and/or a cognitive specialist (neurologist, geriatrician, or geriatric psychiatrist) can interpret patterns of atrophy and other features that may provide added diagnostic and predictive value as deemed appropriate by the specialist (Grade 2B).
2. Standardization of clinical acquisition of core MRI dementia sequences is recommended in Canadian Centers that have radiologists and cognitive specialists with expertise in assessing cognitive disorders, particularly when repeat MRI images can provide additional diagnostic, prognostic, and safety information (Grade 2B).
3. In addition to previously listed indications for structural imaging, a CT or MRI should be undertaken in the assessment of a person with cognitive impairment if the presence of unsuspected cerebrovascular disease would change the clinical management.
4. When available in the clinic, we recommend that cognition specialists use the computer images of the brain to educate persons with cognitive impairment about changes in the brain. This knowledge may reinforce adherence to vascular risk factors management and to lifestyle modifications to improve brain health (Grade 3C).

TABLE 2 Structural imaging: First recommendation from the CCCDTD5 Conference (2019)

1. Even in older subjects, anatomical neuroimaging is recommended in most situations, using the following list of indications: onset of cognitive signs/symptoms within the past 2 years, regardless of the rate of progression; unexpected and unexplained decline in cognition and/or functional status in a patient already known to have dementia; recent and significant head trauma; unexplained neurological manifestations (new-onset severe headache, seizures, Babinski sign, etc.), at onset or during evolution (this also includes gait disturbances); history of cancer, in particular if "at risk" for brain metastases; subject at risk for intracranial bleeding; symptoms compatible with normal pressure hydrocephalus; significant vascular risk factors. 1C.

The price of the [^{123}I]-ioflupane and [^{18}F]-FDG-PET tracers vary widely across Canada. Generally, however, the price of [^{123}I]-ioflupane is significantly higher than that of [^{18}F]-FDG-PET. Numerous papers, including most recently[99] have indicated that the performance of [^{18}F]-FDG-PET in diagnosing LBD is high. A further study[100] confirmed increased [^{18}F]-FDG in the striatum as a useful marker of dopamine loss in the striatum, which is a major differential diagnostic element between AD and LBD.[100]

4 | RECOMMENDATIONS FOR THE USE OF LIQUID BIOMARKERS IN THE DIAGNOSIS OF DEMENTIA

The previous iteration of the CCCDTD conference, held in Montreal in 2012, made the following recommendations regarding structural imaging for the diagnosis of dementia[4]:

The lack of standardization for CSF test result interpretation, the absence of a national accredited infrastructure for the analysis of CSF in Canada, and the absence of a disease-modifying intervention supported this recommendation.[4] However, liquid biomarkers, CSF amyloid beta (Aβ)1-42, and tau were considered useful in the context of research protocols for observational and therapeutic studies.[101]

The CCCDTD5 recommendations are supported by significant progress in the field. First, our systematic review of the literature shows that a large number of individuals have had a lumbar puncture as part of their assessment for neurodegenerative disease, and that the safety of a lumbar puncture is well-established.[102] Next, standards for handling and analysis of CSF, lacking at the time of the previous CCCDTD, are now established.[103] Although comparison of results across platforms remains a work in progress, a number of certified commercial platforms and, in Canada, two academic laboratories, are available to conduct these tests and routinely perform these analyses for clinical purposes.

The CCCDTD5 members felt the complexity of obtaining, handling, interpreting, and integrating CSF studies into the patient's clinical data (age and apolipoprotein E [*APOE*] genotype) should limit the use of liquid biomarkers to centers specialized in cognitive disorders.[103–110] In addition, because multiple brain pathologies are commonly present concomitantly in the aging brain, interpreting a positive CSF amyloid biomarker as diagnostic for AD requires careful expert assessment[111] and is likely more helpful to exclude AD pathophysiology than for including it in the diagnosis.[112]

Three CSF biomarkers are considered clinically relevant at this time, and their usefulness is supported by multiple reports: Aβ 1-42 (Aβ1-42) and tau protein phosphorylated at position 181 (p-tau-181) are core AD biomarkers. Total tau (t-tau) is a validated, non-specific indicator of neurodegeneration.[113–127]

Six key references led to the adoption of the first recommendation,[128–133] although 11 more formed the basis of the second recommendation.[134–144] It was recognized that the level of evidence for these recommendations is good (1C), but may be subject to change depending on the evidence obtained in future large scale, randomized clinical trials.

The following clinical presentations are specific examples of circumstances where CSF biomarkers may have impact on the management of subjects with cognitive impairment.

1. Subjects with rapidly progressive dementia. There is evidence to the effect that CSF biomarkers can be of benefit in identifying the underlying pathology.[145–148]
2. Young subjects with dementia (early onset disease), specifically those younger than 65 years of age. The relative prevalence of AD dementia in young individuals is lower than in older individulas.

TABLE 3 Structural imaging: Second recommendation from the CCCDTD5 Conference (2019)

2. Magnetic resonance imaging (MRI) is recommended over computerized tomography (CT), especially given its higher sensitivity to vascular lesions as well as for some subtypes of dementia and rarer conditions. (2C). If available, and in the absence of contraindications, 3 Tesla MRI should be favored over 1.5 Tesla. (2C). If MRI is performed, we recommend the use of the following sequences: 3D T1 volumetric sequence (including coronal reformations for the purpose of hippocampal volume assessment), fluid-attenuated inversion recovery (FLAIR), T2* (or if available susceptibility-weighted imaging [SWI]), T2-weighted and diffusion-weighted imaging (DWI). 1C. We recommend against the routine clinical use of advanced MR sequences such as resting-state fMRI, MR spectroscopy, diffusion tensor imaging, and arterial spin labeling. However, these sequences are promising research tools that can be incorporated into a research setting or if access to advanced expertise is present. 2C.

TABLE 4 Structural imaging: Third recommendation from the CCCDTD5 Conference (2019)

3. If CT is performed, we recommend a non-contrast CT and the use of coronal reformations are encouraged to better assess hippocampal atrophy. 1C.

TABLE 5 Structural imaging: Fourth recommendation from the CCCDTD5 Conference (2019)

4. We recommend the use of semi-quantitative scales for routine interpretation of both MRI and CT scans including the medial temporal lobe atrophy (MTA) scale for medial temporal involvement, Fazekas scale for white matter changes, and global cortical atrophy (GCA) to qualify global atrophy. 1C.

TABLE 6 Structural imaging: Fifth recommendation from the CCCDTD5 Conference (2019)

5. We recommend against the routine clinical use of quantification software pending larger studies demonstrating the added diagnostic value of these tools. Of note, this is a rapidly evolving field and this recommendation could change in the future. 2C.

TABLE 7 Functional and ligand-based imaging: Recommendations from the CCCDTD4 Conference (2012)

1. For a patient with a diagnosis of dementia who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose underlying pathological process is still unclear, preventing adequate clinical management, we recommend that the specialist obtain a [^{18}F]-FDG PET scan for differential diagnosis purposes (Grade 1B).
2. If such a patient cannot be practically referred for a [^{18}F]-FDG PET scan, we recommend that a SPECT rCBF study be performed for differential diagnosis purposes (Grade 2C).

TABLE 8 Functional and ligand-based imaging: First recommendation from the CCCDTD5 Conference (2019) - a

1a. For a patient with a diagnosis of a cognitive impairment who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a cognitive disorders specialist but whose underlying pathological process is still unclear, preventing adequate clinical management, a [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) PET scan is an effective and accurate tool for differential diagnosis purposes. 1A.

TABLE 9 Functional and ligand-based imaging: First recommendation from the CCCDTD5 Conference (2019) - b

1b. If such a patient cannot be practically referred for an [^{18}F]-FDG-PET scan, we recommend that a SPECT regional cerebral blo flow (rCBF) study be performed for differential diagnosis purposes. 1B.

TABLE 10 Functional and Ligand-Based Imaging: Second Recommendation from the CCCDTD5 Conference (2019) - a

2a. As recommended by The Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging as well as by The Canadian Consensus Conference on the Use of Amyloid Imaging, ordering amyloid PET should be limited to dementia experts. 1A.

TABLE 11 Functional and ligand-based imaging: Second recommendation from the CCCDTD5 Conference (2019) - b

2b. Because of cost issues, it is preferable to obtain an [^{18}F]-FDG-PET (fluorodeoxyglucose positron emission tomography) scan before proceeding to amyloid PET. 1A.

TABLE 12 Functional and ligand-based imaging: Second recommendation from the CCCDTD5 Conference (2019) - c

2c. Use should follow The Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging as well as The Canadian Consensus Conference on the Use of Amyloid Imaging appropriate use criteria. This will result in improved diagnostic classification and management. 1B.

TABLE 13 Functional and ligand-based imaging: Third recommendation from the CCCDTD5 Conference (2019) - a

3a. [^{123}I]-Ioflupane (DaTscan) and single-photon emission computed tomography (SPECT) can be useful to establish a diagnosis of cognitive impairment linked to Lewy body disease (DLB) in cases where such a diagnosis is suspected but remains unconfirmed after evaluation by a specialist with experience in the evaluation of neurodegenerative disease, thereby preventing adequate clinical management. 2B.

TABLE 14 Functional and ligand-based imaging: Third recommendation from the CCCDTD5 Conference (2019) - b

3b. Because of cost issues, it is preferable to obtain an [^{18}F]-FDG-PET scan before proceeding to [^{123}I]-Ioflupane SPECT, as this has a high probability of establishing the diagnosis. 1A.

Non-AD dementia in young individuals might be linked to 3R or 4R tauopathies, synucleinopathies, TDP43, and other less-common dementia-inducing neurodegenerative conditions.[149] Furthermore, clinical presentation of AD is frequently atypical in these individuals and might resemble clinical syndromes associated with non-AD pathology. Indeed, a large body of literature, including clinical and autopsy series as well as meta-analyses, support the use of CSF biomarkers in distinguishing AD from frontotemporal lobar degeneration.[150–151] As such, CSF biomarkers may increase confidence in the diagnosis of AD in younger patients.[129–133]

3. Subjects with late onset of atypical clinical presentation (defined as those where the clinical presentation is dominated by language, visuospatial, behavioral, or executive deficits). For example, subjects with primary progressive aphasia, particularly its logopenic variant, or posterior cortical atrophy syndrome, often but not always show AD pathology and may benefit from CSF analysis.[118,135–139,151,152] Dysexecutive or "frontal" variant AD, with its prominent deficits in executive function relative to amnesia has also been shown to be correctly identified using fluid biomarkers.
4. Diagnosis of possible AD, applicable to individuals with atypical disease, questionable progressive decline, clinical findings of concomitant cerebrovascular disease or Lewy body dementia, as well as evidence for other neurologic, medical comorbidities, or receiving medication that could affect cognition. Although CSF biomarkers may help clinicians confirm or exclude AD pathophysiology in these individuals, the role of AD as a determinant of clinical dementia may remain uncertain even after a thorough clinical and biomarker investigation. Still, the presence of a CSF signature of AD may justify use of cholinesterase inhibitors or memantine in these cases. At this time, there is only evidence in the literature to support the use of CSF biomarkers in subjects younger than 65, or older than 65 years if presenting with atypical forms of dementia.
5. Neuropsychiatric symptoms, when these are the earliest and most prominent feature of a neurodegenerative condition.[153] Clinicians may consider neurodegenerative disease as a possible etiology for neuropsychiatric symptoms, especially in elderly subjects with new-onset neuropsychiatric symptoms in the absence of a history of psychiatric illness. Some individuals with atypical and mixed presentations of AD may have depression, hallucinations, compulsions, paranoid delusions, or more complex delusions such as Capgras syndrome early in the course of their disease.[154] Still, although elderly subjects whose dominant symptom is a change in behavior constitute an attractive target for ruling out AD pathology with biomarkers, there is no strong evidence in the literature supporting this indication.[155–158] Recently, CSF neurofilament light chain (NfL) has emerged as a promising biomarker to differentiate frontotemporal dementia from psychiatric conditions[155,159–161] and plasma NfL as a marker of mild behavioral impairment[162]; however, further studies are necessary to support the clinical utility of this biomarker.

4.1 | Additional considerations

1. There is no clear evidence in the literature to date that subjects with MiCI, even those who have persistent, progressive, and unexplained symptoms benefit from CSF biomarker measurements.[163,164] In fact, biomarker studies reveal that ≈50% of MiCI individuals have AD pathophysiology, reaching a 54% diagnostic rate in large autopsy studies.[112,165,166] Although the presence of an AD biomarker signature in MiCI may suggest that symptoms are caused by AD pathology,[167,168] it is important to consider the high prevalence of comorbidities in the aging brain. From a therapeutic perspective there are no interventions specifically designed for MiCI carriers of AD pathophysiology. Furthermore, there is no CSF biomarker signature for rapid progression to MaCI. Nevertheless,

TABLE 15 Use of liquid biomarkers: Recommendations from the CCCDTD4 Conference (2012)

Plasma Aβ1-42 levels are not recommended for clinical practice.

TABLE 16 Use of liquid biomarkers: First recommendation from the CCCDTD5 Conference (2019)

1. Cerebrospinal fluid analysis is not recommended routinely, but it can be considered in dementia patients with diagnostic uncertainly and onset at an early age (<65 years) to rule out AD pathophysiology. 1C.

TABLE 17 Use of liquid biomarkers: Second recommendation from the CCCDTD5 Conference (2019)

2. Cerebrospinal fluid analysis can also be considered in dementia patients with diagnostic uncertainly AND predominance of language, visuospatial, dysexecutive, or behavioral features to rule out AD pathophysiology. 1C.

the use of CSF biomarkers in MiCI may be reasonable in the context of clinical trials.

2. Subjects with typical late-onset dementia, amnestic presentation (typical cases), have pathological diagnosis discordant with clinical diagnosis in ≈10% to 30% of cases. Currently, the literature fails to indicate that CSF AD biomarkers have a clinical benefit in the management of these subjects.

5 | CONCLUSIONS

In this article we have strived to propose a series of evidence-based guidelines for imaging subjects with neurodegenerative conditions that maintain flexibility, allowing for adaptation to differences in services across Canada.

We recognize that the landscape in this area is rapidly evolving. For instance, [^{18}F]-flortaucipir, a PET radiopharmaceutical that binds tau protein aggregates, has recently been approved for clinical use by the US Food and Drug Administration (FDA), but is currently unavailable in Canada. Several studies suggest that this may have a profound impact on the diagnosis of AD and possibly other neurodegenerative conditions. The CCCDTD group might have to dedicate a specific review of tau imaging before its next general meeting, as has been the case for amyloid imaging in 2016. Radioligand binding to other abnormal protein aggregates is being developed (for instance, for detecting Lewy bodies in vivo). Further, liquid biomarkers are already used in the clinic for measuring molecules linked to neurodegeneration in the cerebrospinal fluid, although the need for a lumbar puncture is a limiting factor for wide dissemination. Additional biomarkers that are more "accessible" (in blood, urine, saliva) are already showing potential and may profoundly change how neurodegenerative conditions are diagnosed. Indeed, the pace of such developments is so rapid that predicting how AD and other degenerative proteinopathies will be diagnosed in 3 to 5 years from now is extremely difficult.

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CONFLICTS OF INTEREST

All authors have completed, or have confirmed having read, the ICMJE form on Conflicts of Interest. There is no conflict of interest to report.

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