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Clinical value of Alzheimers disease biomarker testing.

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Journal

Alzheimer's & Dementia: Translational Research & Clinical Interventions, 10(2)

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Publication Date

2024

DOI

10.1002/trc2.12464

Peer reviewed

RESEARCH ARTICLE

Clinical value of Alzheimer's disease biomarker testing

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Funding information

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Abstract

INTRODUCTION: In the Investigating the Impact of Alzheimer's Disease Diagnostics in British Columbia (IMPACT-AD BC) study, we aimed to understand how Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarker testing—used in medical care—impacted medical decision-making (medical utility), personal decision-making (personal utility), and health system economics.

METHODS: The study was designed as an observational, longitudinal cohort study. A total of 149 patients were enrolled between February 2019 and July 2021. Patients referred to memory clinics were approached to participate if their dementia specialist ordered AD CSF biomarker testing as part of their routine medical care, and the clinical scenario met the appropriate use criteria for lumbar puncture and AD CSF biomarker testing. For the medical utility pillar, detailed clinical management plans were collected via physician questionnaires pre- and post-biomarker disclosure.

RESULTS: Patients with completed management questionnaires ($n = 142$) had a median age of 64 (interquartile range: 59–69) years, 48% were female, and 60% had CSF biomarker profiles on the AD continuum. Clinical management changed in 89.4%

Khushbu J Patel and David Yang contributed equally to this work.

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of cases. AD biomarker testing was associated with decreased need for other diagnostic procedures, including brain imaging (–52.0%) and detailed neuropsychological assessments (–63.2%), increased referrals and counseling (57.0%), and guided AD-related drug prescriptions (+88.4% and –50.0% in biomarker-positive and -negative cases, respectively).

DISCUSSION: AD biomarker testing was associated with significant and positive changes in clinical management, including decreased health care resource use, therapy optimization, and increased patient and family member counseling. While certain changes in management were linked to the AD biomarker profile (e.g., referral to clinical trials), the majority of changes were independent of baseline clinical presentation and level of cognitive impairment, demonstrating a broad value for AD biomarker testing in individuals meeting the appropriate use criteria for testing.

KEYWORDS

Alzheimer's disease, biomarkers, cerebrospinal fluid, clinical decision making, counseling, dementia, diagnosis, drug prescriptions, patient care management, physicians, referral and consultation

1 | BACKGROUND

The diagnostic accuracy of the concentration of amyloid- β ($A\beta$) peptides and tau proteoforms in cerebrospinal fluid (CSF) for the detection of Alzheimer's disease (AD) pathology has been well established.¹ Additionally, the modest diagnostic performance of clinical diagnosis relative to both neuropathological findings (71%–87% sensitivity; 44%–71% specificity)² and amyloid positron emission tomography (PET; 63.8% concordance),³ underlines the need for wider implementation of AD biomarkers in clinical practice. While the diagnostic performance of CSF biomarkers and amyloid PET is comparable,^{4–8} within the Canadian health care system only CSF testing is a pragmatic solution given considerations such as cost effectiveness, resource availability, and equity.⁹ However, broad and optimal implementation, along with long-term sustainability, of this diagnostic service requires a comprehensive understanding of how AD CSF biomarker testing impacts clinical management.

Several studies in Europe have documented the change in diagnosis and physicians' diagnostic confidence related to the use of AD CSF biomarkers;^{10–14} however, none performed a comprehensive examination of the downstream changes in clinical management. Those that captured aspects of clinical management did so in a biased manner (captured after biomarker results were reported) and included limited aspects of management.^{12,13} In addition to lacking a comprehensive understanding of the medical utility of biomarker testing in usual medical care, we also lacked confirmation of applicability to the Canadian health care system—a publicly funded single-payer system that provides universal coverage for medically necessary services.

To address these knowledge gaps, we sought to investigate the impact of AD biomarker testing on patient management in the context of usual medical care provided by memory clinics. In the Investigating the Impact of Alzheimer's Disease Diagnostics in British Columbia (IMPACT-AD BC) study, we examined the impact of CSF testing for

core AD biomarkers on medical decision-making (medical utility), personal decision-making (personal utility),¹⁵ and health system economics. Herein, we report the results of the primary and secondary outcomes for the medical utility arm, which includes comprehensive assessments of the changes in clinical management (overall, by clinical presentation, and by clinical disease stage) and change in physicians' diagnosis and diagnostic confidence.

2 | METHODS

2.1 | Study design

The IMPACT-AD BC study was designed as an observational, longitudinal cohort study assessing the impact of AD CSF biomarker testing on clinical management, diagnosis, health system use, and patients and their care partners,¹⁵ with outcomes preregistered with ClinicalTrials.gov (NCT05002699) and following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹⁶ Patients for whom physicians deemed biomarker testing to be medically appropriate were eligible to participate. This study was approved by the University of British Columbia and Providence Health Care Research Institute ethics review board (H17-01339). Dementia specialists were asked to complete detailed questionnaires before and after learning the biomarker results (Figure 1).

2.2 | Study population

A total of 149 patients were enrolled between February 2019 and July 2021. Patients referred to memory clinics were approached to participate if (1) their dementia specialist ordered AD CSF biomarker testing as part of their routine medical care, and (2) the clinical

scenario met the appropriate use criteria for lumbar puncture (LP) and AD CSF biomarker testing.¹⁷ A dementia specialist was defined as a self-identified physician in a specialty practice (e.g., neurology, psychiatry, geriatric medicine) who devotes a substantial proportion ($\geq 25\%$) of patient contact time to the evaluation and care of adults with acquired cognitive impairment or dementia.¹⁸ Complete inclusion/exclusion criteria can be found in the [Supporting Information](#).

2.3 | Study procedures

2.3.1 | Pre-biomarker management plan

Prior to CSF biomarker analysis, dementia specialists completed a pre-biomarker management plan questionnaire (see [Supporting Information](#)) that included demographic data, diagnostic considerations, physician-rated diagnostic confidence as percentages and likelihood of the presence of AD pathology on a 10-point scale (1 ["definitely not present"] to 10 ["definitely present"]), routine clinical exams completed prior to the LP, and the physician's intended management plan assuming CSF biomarker testing was not available.

2.3.2 | AD CSF biomarker analysis and disclosure

Collection and processing of CSF samples was performed as part of medical care and followed validated clinical procedures, including CSF collection into validated polypropylene tubes (Rose Scientific, Cat#17022).^{19,20} Biomarker analysis, which included A β 42, A β 40, and total tau (t-tau), was performed by St. Paul's Hospital in Vancouver, Canada. For the purpose of data analysis only, biomarker profiles were grouped into two categories, that is, "on the AD continuum" or "not on the AD continuum" (see [Supporting Information](#) for details).

2.3.3 | Post-biomarker management plan

After receiving the biomarker results, dementia specialists repeated the detailed management questionnaire with the addition of questions pertaining to their interpretation of the biomarker findings and the disclosure discussion with the patient/care partner (Figure 1, [Supporting Information](#)). Physicians were instructed to complete this questionnaire immediately after they disclosed the result to the patient and/or care partner, or if they deemed disclosure was not appropriate (e.g., for safety and/or comprehension reasons), near the point they decided not to disclose the result.

2.4 | Outcome measures

The primary outcome measure was the percentage change between intended patient management without biomarkers (pre-biomarker

RESEARCH IN CONTEXT

- 1. Systematic review:** The use of Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarker testing is known to increase diagnostic accuracy and physicians' diagnostic confidence; however, the downstream effects on clinical management, in particular when used as part of medical care, are not well understood.
- 2. Interpretation:** This first-of-its-kind study has provided a comprehensive understanding of the value of AD CSF biomarker testing in guiding medical decision-making. Biomarker testing was associated with significant and positive changes in clinical management, including decreased health care resource use, pharmacotherapy optimization, and increased patient and family member counseling.
- 3. Future directions:** These findings have important implications for optimizing positive impacts of biomarker testing amid the ongoing expansion of dementia-related biofluid diagnostics and increasing availability/access to disease-modifying therapeutics. They also demonstrate the potential for savings in health system costs with the addition of CSF biomarker testing.

results) and with biomarkers (post-biomarker results) in a composite measure of at least one of the following domains: (1) AD symptomatic medications, (2) other dementia-relevant medications, (3) diagnostic procedures, and (4) referrals and counseling (see [Supporting Information](#) for details).

The secondary outcome measures included: (1) Changes in clinical management by clinical presentation (typical clinical presentation of AD vs. atypical clinical presentation of AD vs. non-AD neurodegenerative disorders), (2) Changes in clinical management by clinical disease stage (mild cognitive impairment [MCI] vs. dementia), and (3) Percentage change in diagnosis and physician-rated diagnostic confidence.

2.5 | Statistical analyses

For analysis of the primary outcome measure, binomial estimates of the proportion of change in clinical management were calculated with Wilson 95% confidence intervals (CIs) for overall composite and each of the composite components.

Two exploratory analyses were undertaken. First, the concordance between pre-biomarker diagnosis and AD biomarker profile was reported as rate of agreement with 95% Wilson CI. Second, the association between the AD biomarker profile and change in clinical management was determined using mixed-effects logistic regression (see [Supporting Information](#) for details).

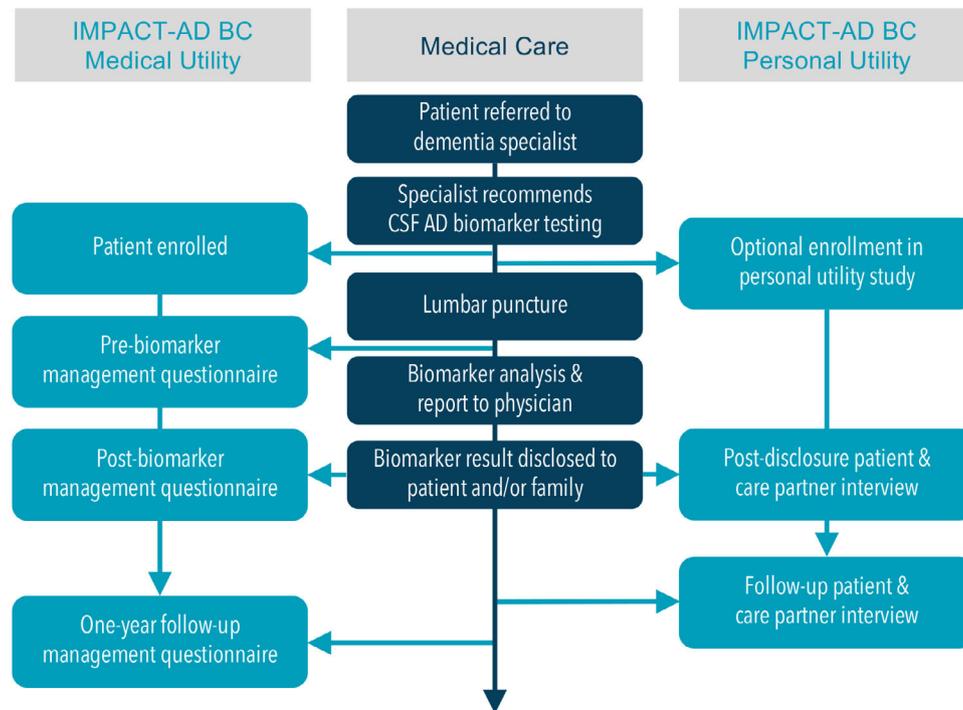


FIGURE 1 The observational Investigating the Impact of Alzheimer's Disease Diagnostics in British Columbia (IMPACT-AD BC) study in relation to medical care. AD, Alzheimer's disease; CSF, cerebrospinal fluid.

Additional post hoc analysis examined the change in overall use of each management domain stratified by the baseline level of cognitive impairment and AD biomarker profile, as well as the change in primary diagnosis and diagnostic confidence stratified by biomarker profile.

3 | RESULTS

3.1 | Patient and physician participants

Of the 149 patient participants enrolled, 142 cases had complete pre-/post-biomarker management plan questionnaire pairs and were included in the final analysis (Figure S1). Patients had a median age of 64 (interquartile range [IQR]: 59–69), 48% were female, and 67% had partially or fully completed post-secondary education (Table 1, Table S1). The patient cohort was 80% White, 16% Asian, 2% Indigenous, 1.4% Middle Eastern, and 0.7% Black. At baseline, more than half of the patients had MCI (55%), AD symptomatic medications were being prescribed in 28% of cases, and 97% had completed either a head computed tomography (CT) or magnetic resonance imaging (MRI) scan (Table S2). The biomarker profile was consistent with being on the AD continuum in 60% of cases. For physician participants (see Table S3 for additional details), the median time between the completion of the pre-biomarker questionnaire and result disclosure to the patient/study partner was 15 weeks (IQR 10.0, 28.1) and between the completion of the pre- and post-biomarker questionnaires, 27 weeks (IQR 14.9, 43.9).

3.2 | Primary outcome measure

3.2.1 | Change in clinical management

Overall changes in clinical management due to AD biomarker testing occurred in 89.4% (95% CI: 83.3%–93.5%) of patients (Table 2). Changes in individual components of the composite score included 64.8% (95% CI: 56.6%–72.2%) for diagnostic procedures (e.g., imaging, neuropsychological testing, etc.), 57.0% (48.8%–64.9%) for referrals and counseling, 39.4% (31.8%–47.7%) for use of AD symptomatic medications, and 19.0% (13.4%–26.3%) for use of other dementia-relevant medications. Detailed changes for each of these components can be found in Tables S4–6.

3.3 | Secondary outcome measures

3.3.1 | Change in diagnostic confidence

Without AD biomarker results, physicians rated the likelihood of AD pathology to be in the diagnostic gray zone (i.e., 4–7 Likert scale) in the majority of cases (64.1% [95% CI: 55.9%–71.5%]; Figure 2A). With biomarker results, the number of cases in this diagnostic gray zone was reduced to 10.2% (95% CI, 6.2%–16.4%; Figure 2B). With the use of biomarkers, physician-rated confidence in the primary diagnosis increased by 18.0% (95% CI, 15.5%–21.0%, $P < 0.001$ for paired Wilcoxon test; Figure S2).

TABLE 1 Demographic characteristics of the patient participants in IMPACT-AD BC.

Characteristics	Patients (n = 142)
Age, median (IQR), years	64 (59–69)
Sex, no. (%)	
Male	74 (52)
Female	68 (48)
Race ^a , no. (%)	
White	117 (80)
East Asian	12 (8.2)
Southeast Asian	7 (4.8)
South Asian	5 (3.4)
Indigenous (First Nations, Inuk/Inuit, Métis)	3 (2.0)
Middle Eastern	2 (1.4)
Black or African American	1 (0.7)
Highest level of education ^b , no. (%)	
Education that ended before high school	5 (3.5)
High school graduation or less	42 (30)
Some post-secondary education	24 (17)
Post-secondary degree/diploma	71 (50)
Cognitive impairment at baseline, no. (%)	
Subjective cognitive impairment	8 (5.6)
Mild cognitive impairment	78 (55)
Dementia	56 (39)
Taking AD symptomatic medications at enrolment, no. (%)	40 (28)
Head CT or MRI scan performed prior to enrolment, no. (%)	137 (97)
Biomarker profile, no. (%)	
AD continuum	85 (60)
Not on AD continuum	57 (40)

Abbreviations: AD, Alzheimer's disease; CT, computed tomography; IMPACT-AD BC, Investigating the Impact of Alzheimer's Disease Diagnostics in British Columbia; IQR, interquartile range; MRI, magnetic resonance imaging.

^aIncludes five individuals identified as Indigenous-White ($n = 2$), East Asian-White ($n = 2$), and East Asian-Southeast Asian ($n = 1$).

^bPost-secondary education includes trade/apprenticeship/community college, bachelor's programs, post-graduate programs, and professional degrees.

3.3.2 | Change in diagnosis

Among patients with a pre-biomarker non-AD diagnosis, 35 of 91 (38.5%, 95% CI: 29.1%–48.7%) were changed to AD with the use of biomarkers, and for those with a pre-biomarker AD diagnosis, 7 of 46 (15.2%, 95% CI: 7.6%–28.2%) were changed to non-AD with the use of biomarkers. A majority of the non-AD to AD changes occurred in patients for whom no pathological designation was initially specified for the cognitive impairment (Figure 2C). Stratification by level of cognitive impairment at baseline (subjective cognitive impairment [SCI] to

TABLE 2 Changes in the composite clinical management plan due to use of AD CSF biomarkers.

	Patients (n = 142)	
	No.	% Change (95% CI)
Primary outcome		
Overall change	127	89.4 (83.3–93.5)
Changes by component		
AD symptomatic medications	56	39.4 (31.8–47.7)
Other dementia-relevant medications	27	19.0 (13.4–26.3)
Diagnostic procedures	92	64.8 (56.6–72.2)
Referrals and counseling	81	57.0 (48.8–64.9)

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; CSF, cerebrospinal fluid.

dementia) revealed that AD biomarker testing assisted physicians in ruling in or out AD pathology and making a subsequent change in diagnosis, regardless of the patients' baseline level of cognitive impairment (Figure S3).

3.3.3 | Change in clinical management by presentation and level of impairment

Typical AD versus atypical AD versus other neurodegenerative disorders versus non-neurodegenerative disorders

AD biomarker testing resulted in substantial changes in management for all clinical presentation groupings in the following rank order: typical AD (94.4%), other neurodegenerative diseases (90.8%), atypical AD (90.0%), and non-neurodegenerative disorders (76.2%; Table S7). For all presentation groupings, the use of additional diagnostic procedures was the most commonly changed management domain, followed by referrals and counseling.

SCI versus MCI versus dementia

The overall change in post-biomarker clinical management was greatest in patients with dementia at baseline (94.6%), followed by MCI (88.5%) and SCI (62.5%; Table S8). Change in the use of additional diagnostic procedures, closely followed by changes in referrals and counseling, were the most common management domain changes in MCI (65.4% and 56.4%, respectively) and dementia (67.9% and 57.1%, respectively). Despite the small sample of patients with SCI, a similar pattern was observed, albeit with referrals and counseling being the most common change, followed by diagnostic procedures (62.5% and 37.5%, respectively).

3.4 | Exploratory analyses

3.4.1 | Concordance between pre-biomarker diagnosis and biomarker profile

The biomarker profile, that is, on or not on the AD continuum, was concordant in 36 of 47 patients (76.6%, 95% CI: 62.8%–86.4%)

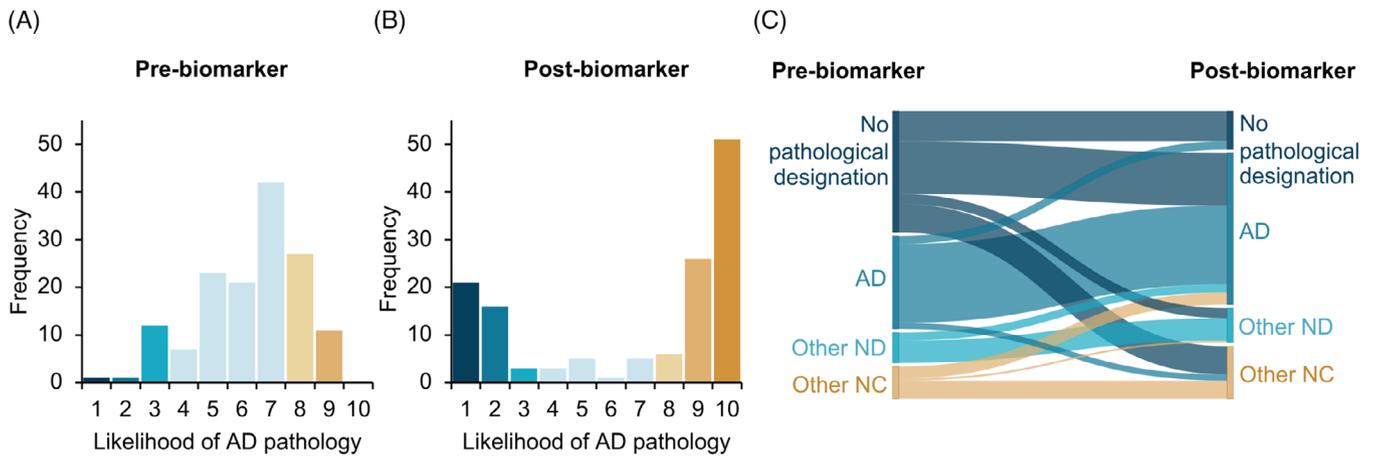


FIGURE 2 Changes in physicians' rating of the likelihood of the absence/presence of AD pathology and primary diagnosis as a result of the use of AD cerebrospinal fluid biomarkers. A and B, Likelihood of the absence/presence of AD pathology was rated on a scale of 1 ("definitely not present") to 10 ("definitely present"). C, Connection map of the primary working diagnosis by case for the entire cohort. No pathological designation refers to cases in which the physician did not specify a diagnosis beyond subjective cognitive impairment, mild cognitive impairment, or dementia; Other ND refers to cases in which a suspected primary neurodegenerative disorder, other than AD, was specified (e.g., frontotemporal dementia, dementia with Lewy bodies, etc.); Other NC refers to cases in which a neurological condition, not including neurodegenerative disorders, was the suspected primary pathology (e.g., psychiatric disorder, traumatic brain injury, etc.). AD, Alzheimer's disease pathology; Other ND, other neurodegenerative disorders; Other NC, other neurological conditions.

with a pre-biomarker AD diagnosis, and 46 of 95 patients (48.4%, 95% CI: 38.6%–58.3%) with a pre-biomarker non-AD diagnosis, respectively.

3.4.2 | Interactions

Logistic regression analyses adjusted for age and sex revealed an interaction between pre-biomarker diagnosis and AD CSF biomarkers on change in the use of AD symptomatic medications (Figure S4A; χ^2 for interaction = 8.59, $P = 0.003$). Among patients with a pre-biomarker non-AD diagnosis, a biomarker profile on the AD continuum was associated with increased probability of a change in AD medication use (62%, standard error [SE] = 7%) compared to a biomarker result not on the AD continuum (11%, SE = 5%; $P < 0.001$ for comparison). This change in probability was not observed for patients with a pre-biomarker AD diagnosis ($P = 0.94$ for comparison). Similarly, an interaction between pre-biomarker diagnosis and the AD biomarker profile was not observed for other domains of clinical management (Figure S4B–E).

3.5 | Post hoc analysis

3.5.1 | Changes in clinical management by AD biomarker profile

The use of AD symptomatic medications (i.e., cholinesterase inhibitors and memantine) was substantially increased for individuals with biomarker profiles on the AD continuum and decreased for those not on the AD continuum (+88.4% and –50.0%, respectively; Figure 3A).

Cholinesterase inhibitors were the most commonly prescribed symptomatic medication, and their use was increased by 54.5% based on the use of AD biomarker testing (Table S4, Figure S5A). Only modest increases were noted for other dementia-relevant medications (Figure S5B), and these increases were independent of the biomarker profile (Figure 3B). These findings were found to be consistent across all clinical disease stages (Figure S6A and S6B).

The reliance on diagnostic procedures was substantially reduced, irrespective of the AD biomarker profile (Figure 3C). The greatest reductions were observed for detailed neuropsychological assessments (–63.2%) and imaging procedures (–52.0%; Figure 4). Among the imaging modalities, decreased use of MRI (–44.4%), CT (–100.0%), single-photon emission computerized tomography (SPECT; –76.9%), and ^{18}F -fluorodeoxyglucose-PET (FDG-PET; –75.7%) were noted after the use of AD biomarker testing (Figure 4). Detailed changes in the use of diagnostic procedures, including biofluid testing, are provided in Table S5.

The use of AD biomarker testing resulted in increased referrals to clinical trials (+166.7% and +42.9% for AD and non-AD trials, respectively), and increased physician-initiated counseling regarding caregiver and family support services (+54.9%) and long-term care counseling (+58.3%) (Figure 3D, Figure 4, Table S6).

3.5.2 | Changes in diagnosis and diagnostic confidence by AD biomarker profile

For individuals with biomarker profiles on the AD continuum there was an increase in a diagnosis of AD with the use of biomarkers (42.4% [95% CI: 32.4%–53.0%] to 80.0% [95% CI: 70.3%–87.1%]), and a decrease for those not on the continuum (19.2% [95% CI:

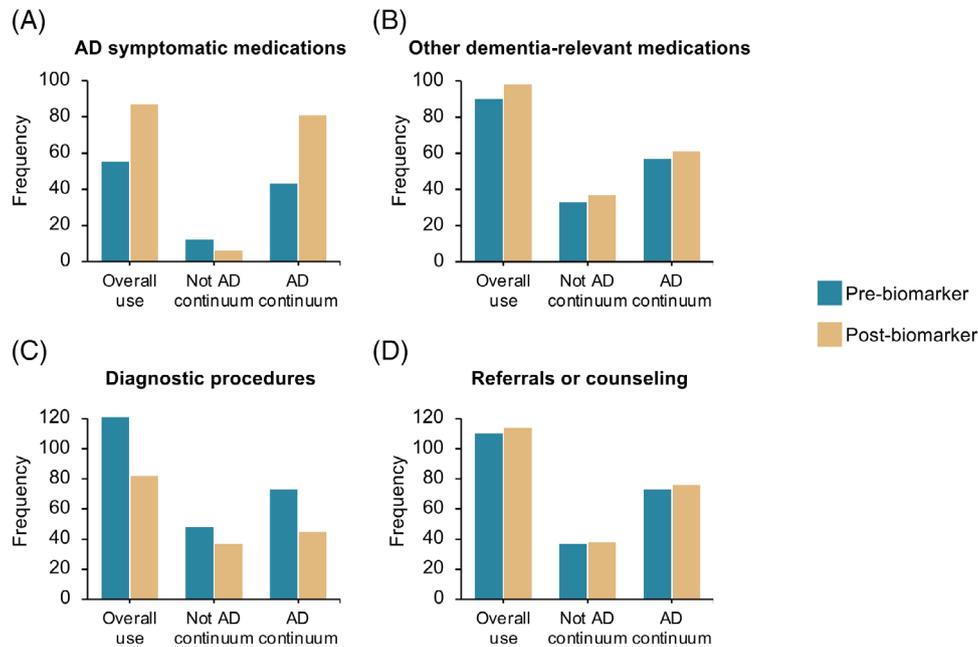


FIGURE 3 Changes in the individual clinical management domains by AD cerebrospinal biomarker profile for (A) AD symptomatic medications, (B) other dementia-relevant medications, (C) additional diagnostic procedures, and (D) referrals or counseling. AD, Alzheimer's disease

10.8%–31.9%] to 11.5% (95% CI, 5.4%–23.0%]; Figure S7A). Correspondingly, a significant increase was noted in confidence in the primary diagnosis, irrespective of the biomarker profile ($P < 0.001$ paired Wilcoxon test, Figure S7B).

4 | DISCUSSION

In this observational, longitudinal study of the impact of AD CSF biomarkers used in medical care, biomarker testing significantly altered clinical management, increased certainty in the presence/absence of AD pathology, and increased diagnostic confidence. AD biomarker testing substantially reduced physicians' need for additional costly diagnostic procedures, guided the prescription of AD symptomatic medications and referral to clinical trials, and increased counseling, in particular regarding long-term care and community support services. While certain changes in management were linked to the AD biomarker profile (e.g., use in AD symptomatic medications and referral to clinical trials), most changes were independent of baseline clinical presentation and level of cognitive impairment, demonstrating a broad value for AD biomarker testing in individuals meeting the appropriate use criteria for testing.

Of the four domains examined, the greatest change was in the diagnostic procedure domain in which an overall decrease in use was observed. With increased confidence in the diagnosis, there was decreased need to perform additional/follow-up testing, such as a repeat head CT/MRI to identify/monitor progression of neurodegeneration, reflecting a change in perceived utility of the information arising from imaging in the context of the availability of AD biomarker

information. The decrease was independent of the patients' baseline clinical presentation or level of cognitive impairment. From the health system perspective, the decreased reliance on imaging is anticipated to be highly impactful due to procedure costs and, in many countries, resource scarcity.²¹ In Canada, for example, medical imaging is a system stress point where timely access is a well-documented and ongoing challenge.^{22,23} This study investigated clinical management decisions up to 1 year post-biomarker testing, thus these findings may have compounding effects over the patients' ongoing medical care.

The reduction in the need for detailed neuropsychological assessment was highlighted by study physicians as being of high value to patients. Patients often experience significant stress and anxiety about having to undergo a detailed neuropsychological assessment, which in addition to the negative emotional impact, can negatively impact performance on cognitive testing.²⁴ As with imaging, detailed neuropsychological assessments are time-consuming, costly, and have long wait times,^{22,25,26} and thus the health system, in addition to the patient, may benefit from a reduction in reliance on testing.

The domain with the second greatest change in management was referrals and counseling. For counseling, there was an increase in counseling across all categories examined, irrespective of biomarker profile. This was likely a result of increased diagnostic confidence, which enabled the communication of more specific recommendations to patients and their care partners (e.g., connecting with community programs and support groups). For referrals, the overall increase was largely driven by referrals to clinical trials for those with an AD biomarker signature; however, biomarker testing increased appropriate clinical trial referrals for both AD and non-AD trials. While there

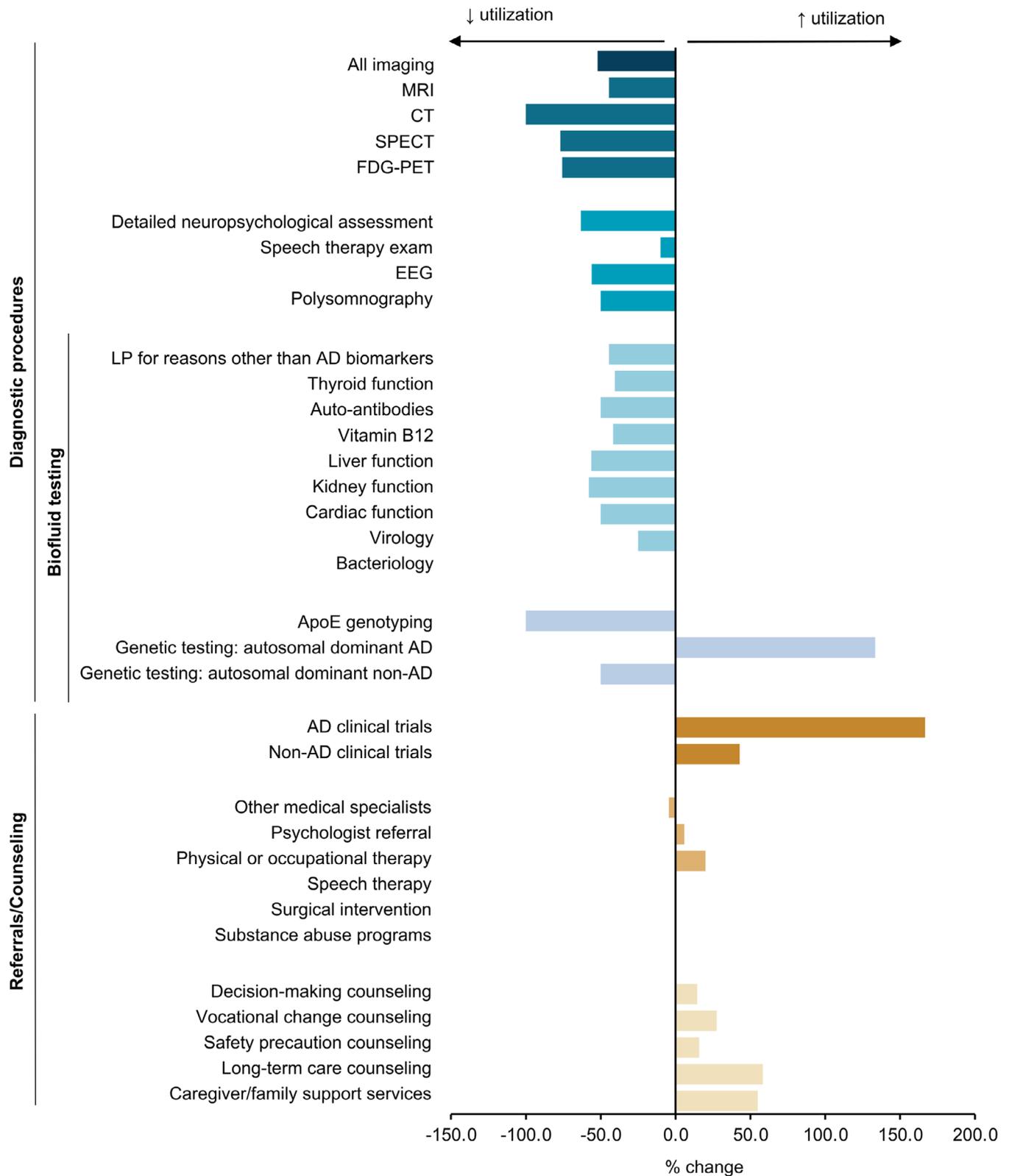


FIGURE 4 Change in resource use for diagnostic procedures, referrals, and counseling after the use of AD cerebrospinal fluid biomarker testing. AD, Alzheimer’s disease; APOE, apolipoprotein E; CT, computer tomography; EEG, electroencephalogram; FDG-PET, ¹⁸F-fluodeoxyglucose-positron emission tomography; LP, lumbar puncture; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography

is regulatory approval in some countries for the use of AD disease-modifying therapies (DMTs), many countries either do not yet have approval (as is the case in Canada) or do not have a facile reimbursement program for patients to access therapies.²⁷⁻³⁰ For many, current access to DMTs remains tied to research (e.g., clinical trial or registry), for which timely diagnosis is critical given the focus on intervention early in the symptomatic phase of disease.³¹ Delayed diagnosis could result in loss of opportunity to access a DMT (e.g., trial exclusion based on disease severity), or the potential for decreased efficacy if not started at the optimal time.³¹ Compared to symptomatic therapies that have potential benefits in non-AD dementias,^{32,33} an even tighter relationship between AD biomarker profile and DMT prescriptions is expected. Taken together, the pharmacotherapy findings herein demonstrate the value in AD biomarker testing in both optimizing AD symptomatic therapies and guiding timely access to DMTs.

To our knowledge, this is the first observational study to examine the impact of AD CSF biomarker testing used in medical care. Another strength was the collection of detailed, comprehensive, and longitudinal clinical management plans, which enabled detailed reporting of the downstream effects of biomarker use. As an observational study meant to capture the intended population for testing in Canada during the time frame of this study, we purposefully did not set enrollment targets by any characteristics such as age, race, baseline diagnosis, or disease severity. Notably, the patient cohort closely reflected both the racial composition of the Canadian population (which is 74% White, 17% Asian, 5% Indigenous, and 4% other³⁴) and the educational level of Canadians over the age of 55 (of whom 53% have completed post-secondary education³⁵). A downside of this enrollment approach was the small number of participants with SCI, which limited our ability to interrogate differences in management for this group relative to the MCI group.

Another limitation of this study included the time elapsed between the pre-biomarker management plan and both the disclosure visit and completion of the post-biomarker management plan. The observed intervals were well within the usual follow-up visit time of 26 to 52 weeks for these specialty clinics, but this is a noted limitation of the observational study design in which there is the potential confounder of disease progression. Physicians would have documented their management plans in the clinical record in a timely manner after the result disclosure visit, and used this resource to complete the post-biomarker questionnaire when they had available time.

We attempted to reduce, where possible, the two key considerations for bias in an observational cohort study, that is, selection bias from either subject recruitment or rates of participation. For patient participants, we aimed to reduce these potential biases through non-targeted enrolment as described earlier and facile study participation, requiring no study-specific visits or activities. This study design led to a cohort whose sociodemographics were similar to the Canadian older adult population. For physician participants, we enrolled from three diverse geographical catchments (Northern British Columbia, Vancouver Island, and the Lower Mainland), which serve a wide range of patients from rural/remote to metropolitan areas. Physician participation was affected by the limited number of memory clinics in the

province and from the substantial time requirements for questionnaire completion. In interpreting and applying the findings herein, characteristics of the physicians and patients who participated in this study should be carefully considered. The physicians were experts in dementia care, worked in specialized memory clinics (i.e., high prevalence AD setting, with likely higher proportion of young-onset dementia and atypical presentations compared to non-specialized practice), and were familiar with the use and interpretation of AD CSF biomarkers prior to this study (primarily through interventional trials and continuing education activities). The patients for their part had navigated the health care system to the point of being referred for specialist care, and had the benefit of being counseled by an expert in AD biomarkers. Even at this relatively late stage in the patients' medical journey, we observed substantial changes in clinical management, including optimization of care and health care resource use. Thus, biomarker implementation at an earlier stage of care (e.g., CSF testing by specialists in more general practice) has the potential to amplify the benefits observed herein and is an opportunity for further examination. In the related reporting of the personal utility outcomes of this study, the characteristics of the patient-physician dyad, translatability to other dyads and contexts, are further discussed.¹⁵

In summary, this study has revealed via empirical evidence that AD biomarker testing changes patient management and optimizes use of health system resources. This is accomplished by biomarker testing increasing appropriate use of resources (e.g., increased prescription of AD medications for persons with AD pathology and increased targeted counseling) and by decreasing the need for other diagnostic testing modalities (e.g., decreased need for repeat head imaging). These findings have important implications for optimizing positive impacts of biomarker testing amid the ongoing expansion of dementia-related biofluid diagnostics and increasing availability/access to DMTs.

ACKNOWLEDGMENTS

The authors thank all IMPACT-AD BC study participants including physicians, patients, and their care partners as without their contributions this work would not be possible. MLD is the recipient of the Michael Smith Health Research (MSHR) Scholar Award and acknowledges grant funding from Brain Canada through the Canada Brain Research Fund with the financial support of Health Canada, MSRH, University of British Columbia's Faculty of Medicine and the Djavad Mowafaghian Centre for Brain Health, Women's Brain Health Initiative, and the St Paul's Foundation.

CONFLICT OF INTEREST STATEMENT

DY, JRB, CC, and CRF declare no conflicts of interest. Outside of the submitted work, the authors report the following disclosures. KJP reports speaker fees from Roche. PEL reports payment from Eli Lilly for presentation at an advisory board, and participation on an advisory board for Eisai. AHB reports grant funding from Green Valley (Shanghai), Intelgenx, ANAVEX, Cerevel, CABHI, and Victoria Hospitals Foundation; grant funding and personal fees from NovoNordisk and Roche; personal fees from Boehringer Ingelheim, Cowan Conference, and WestCoast Conference on Aging. DJF serves on the board of

directors of the Canadians for Leading Edge Alzheimer Research (CLEAR) foundation. JAP reports an honorarium from Eisai for participation in a scientific advisory board meeting. HHF reports grant funding from Annovis, Vivoryon, AC Immune, Biohaven Pharmaceuticals, and LuMind; consulting with all payments made to the University of California San Diego (UCSD) with LuMind, Axon Neuroscience, Genentech, Roche/Banner, Tau Consortium, Biosplice Therapeutics, Novo Nordisk, Janssen Research & Development, and Arrowhead Pharmaceuticals; an issued patent with royalties paid (Detecting and Treating Dementia, PCT/US2007/07008); and a philanthropic donation to UCSD from the Epstein Family Alzheimer's Disease Collaboration. HBN reports consulting for Roche. GRH reports grant funding from Biogen, Roche, Cassava Sciences, and Eisai; consulting for Biogen, Roche, Novo Nordisk, Eisai, and Eli Lilly; GRH serves as President of the Consortium of Canadian Centres for Clinical Cognitive Research. MLD reports consulting for Siemens and Eisai, and consulting and lecturing fees from Roche. Author disclosures are available in the [Supporting Information](#).

CONSENT STATEMENT

Patient and physician participants in the IMPACT-AD BC study provided informed written consent to participate in the study. In instances where the patients' cognitive symptoms had advanced to a stage that affected their decision-making capacity, their substitute decision-maker provided informed written consent. The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data are not available. The analysis code is available upon request.

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SUPPORTING INFORMATION

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

How to cite this article: Patel KJ, Yang D, Best JR, et al. Clinical value of Alzheimer's disease biomarker testing. *Alzheimer's Dement*. 2024;10:e12464. <https://doi.org/10.1002/trc2.12464>