Winter 12-1-2013

Tests, Tests, and More Tests: A New Era for Dementia Diagnosis

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A thesis presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the
degree of Master of Arts

December 2013

St. Louis, Missouri

St. Louis, Missouri

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Acknowledgements

First and foremost, I thank my advisor, Dr. Brian Carpenter, for his guidance throughout each stage of this project. I would also like to thank the other members of my committee, Drs. Denise Head and David Balota, for their feedback and guidance. This project would not have been possible without the many contributions of our collaborators at the Knight Alzheimer's Disease Research Center, including Drs. Joy Snider and John Morris, Mary Coats, and Natalie Selsor. In addition, I would like to thank the Clinical Geropsychology Lab at Washington University for their support. Finally, I would like to acknowledge the support I have received from the Washington University Aging & Development training grant (NIH grant # T32 AG 00030-37).

ABSTRACT OF THE THESIS

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Master of Arts in Psychology

Washington University in St. Louis, 2013

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Cerebrospinal fluid (CSF) proteins correlate with pathological changes that are hallmarks of Alzheimer's disease (AD). CSF biomarkers have been used in research settings to predict AD diagnosis and rate of cognitive decline, however their use in clinical settings is limited. Given their potential utility in identifying preclinical AD and in increasing diagnostic confidence in clinical settings, we sought to understand how clinicians use CSF biomarkers in conjunction with other clinical details to diagnose AD. Participants (N = 193) were physicians and other medical professionals who routinely evaluate older adults for neurodegenerative disease. In a within-subjects factorial design, participants were randomized and viewed normal, borderline, AD-consistent, or no CSF information along with two clinical vignettes portraying patients with borderline and mild AD symptoms. In addition, clinicians reported on their use and the utility of CSF lab results in clinical practice. Clinicians reported infrequent use and limited utility of CSF biomarkers in clinical practice, yet CSF biomarkers affected clinical decisions on two vignettes. AD-consistent CSF values made clinicians 6-12 times more likely to make an AD-related diagnosis, increased diagnostic confidence, and led clinicians to initiate treatment more often than other CSF values. Furthermore, clinicians relied on CSF evidence more heavily when AD-consistent CSF values were presented in the context of a borderline case of memory impairment.

In sum, CSF biomarkers have a significant impact on clinical decisions, and show different effects depending on contextual factors. Therefore, as CSF biomarkers become more widespread in clinical practice, clinicians should consider the potentially significant effect of biomarkers on their clinical decisions.

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the United States, and if left untreated is expected to affect nearly 14 million people by the year 2050 (Hebert, Weuve, Scherr, & Evans, 2013). AD is widely conceptualized as a clinical and pathological process, encompassing memory impairment and functional decline as well as brain changes such as neurofibrillary tangles and amyloid plaques (Dubois et al., 2010). Clinical tools commonly used to assess patients with memory complaints who may have AD range from neuropsychological testing and functional assessments to laboratory blood analysis and neuroimaging. Increasingly, cerebrospinal fluid (CSF) biomarkers shown to correlate with AD pathological changes have been used in research settings to evaluate cases of suspected incipient AD, discriminate among different etiologies, predict rate of disease progression, and track pathological changes in clinical trials (Blennow, 2005; Snider et al., 2009; Toledo et al., 2012). However, recent practice guidelines have not endorsed the use of CSF biomarkers in clinical settings, citing the need for further research on laboratory standardization of biomarker measurements and interpretation of indeterminate biomarker results (McKhann et al., 2011). Furthermore, it is unclear how clinicians would interpret CSF information in conjunction with other clinical details in clinical practice (Zetterberg, Lunn, & Herukka, 2012). As CSF biomarkers become more widespread in clinical practice, we sought to evaluate their influence on clinical dementia evaluations and to understand how clinicians interpret CSF information in various clinical contexts. In this study, we employed a vignette-based survey with clinicians who evaluate older adults to examine the impact of CSF biomarker information on diagnostic decisions, diagnostic confidence, and treatment choices for two hypothetical patients with memory complaints.

The role of CSF information in clinical dementia assessment is evolving. While CSF biomarkers are widely used in research settings and have shown good predictive ability for AD diagnosis, their use in clinical settings is limited (Blennow & Zetterberg, 2009). Concerns about laboratory standardization and potential for conflicting or ambiguous CSF values have kept biomarker tests from widespread clinical use (McKhann et al., 2011). Furthermore, the possibility of identifying pathological processes in clinically normal individuals raises ethical issues given a lack of meaningful treatment options for dementia. Yet, CSF biomarkers could play an important role in clarifying ambiguous cases, discriminating among the dementias, and predicting progression of cognitive impairment and dementia (Snider et al., 2009; Tabaraud et al., 2012; Zetterberg et al., 2012). A recent study addressing concerns about unreliable cross-laboratory measurements concluded that locally standardized procedures could increase the reliability and usefulness CSF measures (Mattson et al., 2012). Importantly, early reliable diagnosis of AD could be necessary for preventative treatment, and could give comfort to patients and families who are eager to understand possible causes of cognitive decline.

It remains unknown, however, how clinicians might use CSF biomarker information in clinical practice. Previous studies have examined the utility of CSF information in research settings, finding good diagnostic sensitivity and correlation with pathological markers of AD progression such as structural brain changes (Blennow, 2005; Fagan et al., 2009). Other studies have supported the utility of CSF biomarkers in identifying AD pathology in preclinical and MCI populations, and in older adults with suspected AD (Mattson et al., 2012; Parnetti, Lanari, Silvestrelli, Saggese, & Reboldi, 2006; Stomrud, Hansson, Blennow, Minthon, & Londos, 2007). No research to our knowledge, however, has surveyed clinicians to examine how CSF information might be used in conjunction with other clinical details to diagnose dementia.

Furthermore, no previous studies to our knowledge have evaluated the utility of CSF biomarkers in combination with other clinical details in evaluating patients with memory complaints.

In this study, we presented clinicians with two clinical vignettes to illustrate a typical ambiguous and mild-AD presentation in a clinic or hospital. Clinical vignettes are a valuable, cost-effective research method for understanding professional judgment of multiple clinical factors while mirroring plausible real-world scenarios (Veloski, Tai, Evans, & Nash, 2005). Clinicians, including physicians, nurse practitioners, physician assistants, and advanced practice nurses, were randomized into one of four groups according to the type of CSF biomarker information they viewed. Three of the groups viewed CSF values consistent with normal, borderline, or AD patient presentations, while the fourth group did not view any CSF information embedded in the vignettes. Given previous studies about the utility of CSF information in research settings, we hypothesized that biomarker values would influence diagnosis, diagnostic confidence, and treatment planning. In addition, we assessed demographic factors, clinician use of and confidence in clinical tools for assessing patients with memory impairment, and clinician evaluation of clinical details in the vignettes.

Method

Participants

Recruitment. Physicians (MD and DO), nurse practitioners and advanced practice nurses (NP and APRN), and physician assistants (PA) were eligible for the study if they routinely evaluate patients over age 65. We targeted academic and nonacademic clinicians and recruited from primary care, internal medicine, neurology, geriatrics, and geriatric psychiatry. Potential participants were contacted using publicly available e-mail addresses on university and medical

center websites and professional organization e-mail lists and public contact information. Between January and July, 2013, we distributed recruitment e-mails describing the scope of the study and including a link to the questionnaire, which was hosted by Qualtrics, a secure online survey platform. Informed consent was obtained from all participants in the study, which was approved by the Washington University Human Research Protection Office.

Sample size. Based on a desired power of .8, alpha set at .05, and a conventional medium effect size, G*Power suggested a required sample size of 192 to perform chi-square analyses (Cohen, 1988; Faul, Erdfelder, Lang, & Buchner, 2009). Out of 291 individuals who began the questionnaire, 248 respondents were eligible to participate and were randomized into conditions in the study. A total of 193 participants completed the entire questionnaire, while 55 partially completed the questionnaire. Completers and partial completers were statistically similar in terms of age, years in clinical practice, approximate percentage of patients seen over the age of 65, practice specialty, and practice setting.

Materials

The study design and materials (details below) were developed by a team of investigators representing neurology, nursing, clinical psychology, and social work. We pilot tested the questionnaire with 10 clinicians at the Knight Alzheimer's Disease Research Center and revised it for clarity based on their feedback. The questionnaire included demographic and clinical practice questions, one page of education materials about CSF biomarkers for diagnosing AD, and two clinical vignettes with follow-up diagnostic questions.

Demographic and practice questions and randomization. At the start of the questionnaire, participants completed a series of demographic and professional background questions. If they met inclusion criteria, participants were randomized into one of four

experimental groups according to the type of CSF information they viewed with each of two clinical vignettes, consistent with a 2 x 4 within-subjects factorial design. Participants in groups 1, 2, and 3 were shown normal, borderline, or AD-consistent CSF values, respectively, with each vignette, while participants in group 4 were not shown any CSF information. After randomization, participants responded to clinical practice questions (i.e., how often they collect, and how useful they find, various diagnostic tests for cognitive impairment). Figure 1 outlines randomization and procedural flow.

CSF education. We developed a one-page education sheet outlining the clinical use of CSF biomarkers in identifying AD pathology (see Appendix A). This information was presented directly before the two clinical vignettes and contained sensitivity and specificity information for $A\beta_{42}$, ttau, ptau, and the ratio between $A\beta_{42}$ and ttau, which usually provides the best classification information for people with and without AD pathology (Fagan et al., 2007). The education sheet noted the limitations of these data due to overlap between diagnostic groups and the fact that CSF values indicate pathological, and not necessarily symptomatic, changes (Price et al., 2009; Price & Morris, 1999).

Clinical vignettes. The two vignettes included information about age, gender, memory, functional status, mood, subjective complaints, and an informant report (see Appendix B). One vignette described a borderline or unclear case with ambiguous presenting symptoms, and the second described a patient with symptoms consistent with mild AD. Embedded in the vignettes were $A\beta_{42}$, ttau, ptau, and ratio values consistent with each CSF condition (normal, borderline, or AD consistent), for participants randomized to receive CSF information. The order of the vignettes was counterbalanced across participants.

After each vignette, participants chose a diagnosis from a list of six options (normal/no diagnosis, mild cognitive impairment (MCI) due to unknown causes, MCI due to AD, AD dementia, memory loss due to uncertain causes, or depression); rated their diagnostic confidence on a scale from 1 (*not at all confident*), 3 (*moderately confident*), to 5 (*very confident*); and indicated their recommendation for treatment, if any, in an open-ended response. Next, participants were asked whether each clinical detail in the vignette (i.e., age, gender, memory, functional status, mood, informant report, CSF values) made them less or more confident in their diagnosis on a 5-point Likert-type scale: 1 (*less confident*), 3 (*neither less nor more confident*), 5 (*more confident*). Finally, participants were asked in an open-ended question what additional clinical details they would have liked in order to evaluate each vignette. While answering these questions, participants were able to view the relevant vignette and the CSF education page.

Data analysis

Statistical analyses were conducted in three phases using SPSS (version 21). First, descriptive statistics of demographic and practice information were calculated in order to examine sample characteristics. Second, chi-squares, t-tests, and analyses of variance were conducted in order to evaluate whether CSF information was related to diagnostic choices, diagnostic confidence, and treatment plan. Finally, a series of logistic regressions were conducted to model multivariate associations between clinician diagnosis and CSF group assignment, demographic and practice variables, and clinical detail ratings.

Results

Demographic and practice information

Table 1 summarizes demographic information for the sample. Respondents were mostly physicians (90%), although the non-MD clinicians did not differ from the physicians on any demographic or practice characteristics and were therefore included in the final sample to represent the diversity of clinicians evaluating and treating patients with neurodegenerative disease in the United States. Overall, participants reported a variety of practice specialties and were experienced in caring for older adults.

In terms of their practice behaviors, clinicians reported frequent use of cognitive screening tests and neuroimaging, moderate use of comprehensive cognitive testing, and infrequent use of metabolic and CSF tests (see Table 2). In terms of perceived utility, cognitive screening and comprehensive examinations were rated as very useful by most clinicians, whereas fewer respondents agreed on the utility of neuroimaging, and few clinicians rated metabolic or CSF testing as useful for diagnosing dementia. Significant differences were notable across practice specialties. Neurologists reported greater use of cognitive testing, neuroimaging, and lumbar puncture as compared to geriatricians and nonspecialists such as primary care and internal medicine clinicians. Neurologists also reported finding neuroimaging and lumbar puncture more useful than did nonspecialists and geriatricians.

Does the presence of any type of CSF information influence clinical decisions?

In order to examine the effect of CSF information on diagnostic decisions, we consolidated diagnostic categories from the questionnaire to eliminate small cell sizes and to reflect our interest in clinician choice of underlying etiology (AD-consistent or unknown etiology) rather than in diagnostic labels that may vary across practice specialty or setting. The

presence of CSF information was significantly related to diagnostic choices for the borderline vignette, $\chi^2(1, N = 165) = 9.09$, $p = .003$, but not for the AD vignette, $\chi^2(1, N = 187) = 0.19$, $p = .67$. Clinicians who received CSF information of any type were more likely to make an AD-related diagnosis than clinicians who did not receive CSF information (47% compared to 22%; $z = 3.0$, $p < .01$).

Diagnostic confidence ratings are detailed in Table 3. Clinicians who had CSF information with the AD vignette, but not the borderline vignette, rated their diagnostic confidence significantly higher than clinicians who did not have CSF information, $t(191) = 2.83$, $p = .005$. Furthermore, clinicians who chose an AD-related diagnosis on the AD vignette and had CSF information reported higher diagnostic confidence than clinicians who made the same diagnosis but did not have CSF information, $t(96) = 2.03$, $p = .045$. In other words, even when making a similar diagnosis with otherwise identical clinical information, clinicians reported higher diagnostic confidence when they had CSF information.

Regarding treatment decisions, clinicians who had CSF information were more likely to suggest initiating treatment on the borderline vignette, $\chi^2(1, N = 161) = 9.31$, $p = .002$, but not on the AD vignette, $\chi^2(1, N = 161) = 1.07$, $p = .30$. While most clinicians (70.8%) chose not to treat, those who had CSF information were more likely to initiate treatment (35.9%) in the borderline vignette compared to those who did not have CSF information (11.4% $z = 3.1$, $p < .01$).

Do particular CSF protein values influence clinical decisions?

Type of CSF information (normal, borderline, AD-consistent, or no CSF protein values) was related to clinician diagnosis for both the borderline and the AD vignette, as detailed in Figure 2. For both vignettes, the diagnosis chosen by clinicians depended, in part, on the CSF

values presented. When given normal CSF values, few clinicians made an AD-related diagnosis (19.4% for the borderline vignette, 27.3% for the AD vignette). The proportion of clinicians assigning a diagnosis related to AD was higher when they received borderline CSF values (41% for the borderline vignette, 47.7% for the AD vignette), and higher still when they received AD-consistent CSF values (77.5% for the borderline vignette, 86% for the AD vignette). Clinicians who did not receive CSF information assigned diagnoses in equal numbers for the AD vignette, while most clinicians (78%) diagnosed unknown etiology for the borderline vignette.

Regarding diagnostic confidence, there was a significant effect of CSF group on confidence ratings for both vignettes (for the borderline vignette, $F(3,188) = 4.05$, $p = .008$; for the AD vignette, $F(3,189) = 5.66$, $p = .001$). On the borderline vignette, clinicians who received AD-consistent CSF values were significantly more confident in their diagnosis compared to clinicians who did not view CSF information (see Table 3). On the AD vignette, clinicians who received AD-consistent CSF values were more confident in their diagnosis than clinicians who viewed borderline CSF values or no CSF information. In addition, clinicians who made an AD-related diagnosis on the AD vignette and had AD-consistent information reported the highest diagnostic confidence compared to clinicians with borderline or no CSF information, $F(3,94) = 3.96$, $p = .01$.

There was a significant effect of CSF values on the decision to treat for the borderline vignette, $\chi^2(3, N = 161) = 13.44$, $p = .004$, but not for the AD vignette, $\chi^2(3, N = 161) = 6.61$, $p = .086$. Although most clinicians (70.8%) chose not to start treatment in the borderline vignette, clinicians who had AD-consistent CSF were significantly more likely to treat than those who had borderline or normal CSF values (48.5% versus 35% and 27.3%, respectively; $z = 2.7$, $p < .01$). On the AD vignette, adjusted residual scores indicated that clinicians receiving AD-consistent

CSF were more likely to initiate treatment than clinicians who received borderline or normal CSF values (58.8% versus 35.9% and 34.9%, respectively; $z = 2.6$, $p < .01$), although the omnibus chi-square test was not significant and this result should be interpreted with caution.

Finally, a series of binary logistic regression models were evaluated to determine whether clinician demographic variables, CSF group assignment, and post-vignette responses predicted diagnostic choices (AD etiology versus unknown etiology; see Table 4). The most parsimonious models included CSF group as the only significant predictor variable for the borderline vignette, and CSF group and post-vignette confidence rating of the informant report as significant predictors of diagnosis on the AD vignette (see Table 4). For both vignettes, receiving AD-consistent CSF values led to increased odds of choosing an AD-related diagnosis, while clinicians who rated the informant report as valuable in forming a diagnosis were more likely to choose an AD diagnosis on the AD vignette (but not the borderline vignette). Variables that were not significant predictors of diagnostic choices included demographic factors (years in practice, percentage of patients over age 65, and practice specialty), practice questions related to lumbar puncture use, and post-vignette clinical measure ratings (aside from informant report).

Confidence ratings of clinical measures and preference for additional tests

Following each vignette, participants rated whether clinical details that appeared in the vignette made them less or more confident in their diagnosis. Clinicians reported high diagnostic confidence ratings for collateral information from a family member and patient functional status, while patient age and CSF information were rated as least useful in formulating a diagnosis (see Table 5). In addition, post-vignette CSF ratings differed significantly from initial clinical practice questions. Clinicians rated CSF information included in the vignettes as significantly more useful compared to ratings of CSF biomarker utility in their clinical practice (for the borderline

vignette, $M = 3.22$ vs. 2.19, $t(130) = 1.03$, $p < .001$; for the AD vignette, $M = 3.36$ vs. 2.20, $t(128) = 1.16$, $p < .001$).

Furthermore, post-vignette ratings of CSF utility depended in part on CSF group (for the borderline vignette, $F(2, 132) = 5.99$, $p = .003$; for the AD vignette, $F(2, 130) = 8.37$, $p < .001$). Tukey post-hoc tests showed that clinicians receiving AD-consistent CSF values on the borderline vignette rated CSF information as more useful than did clinicians who received borderline CSF values ($M = 3.58$ vs. $M = 2.93$). Clinicians who received AD-consistent CSF values on the AD vignette rated CSF information as more useful than did clinicians who received normal or borderline CSF values ($M = 3.84$ vs. normal CSF, $M = 3.15$ and vs. borderline CSF, $M = 3.11$). Taken together, these results indicate that while clinicians rated collateral reports and functional status as the most helpful clinical tools in formulating a diagnosis, viewing AD-consistent CSF values provided a similar level of diagnostic confidence and they were rated as more helpful than borderline or normal CSF values.

Finally, clinicians indicated which additional diagnostic tests they would have found useful in formulating a diagnosis in an open-ended response. For both vignettes, 25-30% of clinicians requested neuroimaging, neuropsychological testing, and laboratory information such as blood analysis. Fewer clinicians (approximately 15%) indicated that brief neuropsychological screening or a depression evaluation would have been useful. Clinicians also described a wide variety of additional information they would have collected. Some clinicians indicated that additional testing was required to arrive at a diagnosis (e.g., “Really must have cognitive testing as well.”). Others wrote that they would like longitudinal follow-up information as well as medical history. About 20% of participants requested one additional test, and another 20% each

requested two or three additional tests. Others (14% for the borderline vignette, 18% for the AD vignette) did not request any additional information.

Discussion

This study is one of the first to examine how clinicians use CSF biomarkers in combination with other clinical information to diagnose cognitive impairment. Participants responded to practice questions and evaluated two vignettes describing patients with ambiguous borderline symptoms and with mild memory complaints. While clinicians reported infrequent use and limited utility of CSF biomarkers in their current clinical practice, the inclusion CSF information influenced diagnosis, diagnostic confidence, and the decision to treat. Taken together, these results highlight the influence of CSF biomarkers on clinical decisions, even when that information is weighed alongside other clinical details routinely reported as more useful in clinical practice. Examining these findings more closely, a number of trends are apparent.

First, results from this study suggest that holding CSF information makes clinicians more likely to assign an AD-related diagnosis, increases diagnostic confidence, and influences the decision to treat. Overall, clinicians who had CSF information of any type were more than twice as likely to make an AD-related diagnosis and were more likely to initiate treatment on a borderline case. In addition, clinicians who had CSF information reported significantly higher diagnostic confidence on a mild AD vignette. In sum, these results suggest that merely viewing CSF information of any type affects clinical decisions regardless of the particular protein values. It is notable that these effects were driven by clinicians who had borderline and AD-consistent CSF values, which could suggest that evaluating the impact of all three CSF groups together may not be meaningful. However, protein values are continuous measures, and therefore these effects

may apply to the virtually infinite combinations of CSF protein values clinicians are likely to encounter in clinical practice.

Second, as CSF values increasingly reflected AD pathology, clinicians made AD-related diagnoses with increasing frequency and with greater confidence (see Figure 2). Clinicians who viewed normal CSF values disproportionately made diagnoses with unknown etiology, while most clinicians who viewed AD-consistent CSF values made AD-related diagnoses. Furthermore, the proportion of clinicians choosing to initiate treatment on the borderline vignette rose as CSF values increasingly pointed to AD pathology (27.3%, 35%, and 48.5% for normal, borderline, and AD CSF values, respectively). Finally, clinicians with AD-consistent CSF values reported the highest diagnostic confidence compared to clinicians with other types of CSF data. As such, AD-consistent CSF biomarkers may exert a confirmatory effect relative to more familiar, established clinical details with which clinicians currently have more experience.

Third, ambiguous CSF values had little effect on clinical decisions. Clinicians who viewed borderline CSF information made unknown etiology and AD-related diagnoses in relatively equal frequency, suggesting that CSF information had no effect on diagnosis for these participants. Moreover, the decision to initiate treatment was not significantly different between clinicians who viewed normal or borderline CSF values on the AD vignette, suggesting that values showing relatively increased risk for AD pathology (i.e., borderline CSF values) did not affect treatment planning. Current practice guidelines and diagnostic criteria for AD do not endorse use of CSF biomarkers in part because of the potential for indeterminate biomarker values (McKhann et al., 2011). Furthermore, Zetterberg and colleagues (2012) caution that clinicians may misinterpret CSF biomarker results as definitive, without considering the entire clinical picture. The results of this study suggest that when presented with ambiguous or

indeterminate CSF values, clinicians rely on other clinical details to make diagnostic and treatment decisions.

Fourth, inconsistent pathological and clinical information affects clinical decisions. Clinicians who viewed normal CSF values in a vignette that included other clinical details consistent with AD most often chose a diagnosis with unknown etiology. In contrast, clinicians who viewed AD-consistent CSF values in a vignette that included other ambiguous clinical details were swayed by those CSF values and made an AD-related diagnosis. In sum, clinicians appear to give less weight to CSF biomarkers when they are in the normal range, and greater weight when they are consistent with AD pathology, even when paired with ambiguous clinical details. Furthermore, on the borderline vignette, clinicians who had AD-consistent CSF information were 12 times more likely to make an AD-related diagnosis than clinicians who did not have CSF information. In contrast, the same comparison was relatively muted for the AD vignette, in part because clinicians who did not have CSF information made unknown etiology and AD-related diagnoses in equal numbers. In terms of treatment, CSF values affected the decision to initiate treatment in the borderline vignette, whereas this effect was questionable for the AD vignette. Taken together, in the setting of borderline clinical details, AD-consistent CSF values are likely to be more impactful on diagnosis and treatment planning, whereas the same values had less effect on clinical decisions in a mild AD case.

These findings suggest that clinicians do not view CSF values in a vacuum, but consider their utility in combination with other clinical details to make decisions. Clinician reports on the use and the utility of clinical tools shed light on how evaluations are currently conducted, and how they might evolve as CSF testing becomes more widespread in clinical settings. Overall, reported use of neuropsychological screening and testing, neuroimaging, and lumbar puncture

were consistent with current practice guidelines for evaluating patients with memory complaints (McKhann et al., 2011). However, there were variations in ratings of use and utility of each tool and significant differences between practice specialties, suggesting the lack of standardization in dementia assessment. Neurologists report the greatest use and utility of cognitive assessments and neuroimaging. In contrast, nonspecialists in solo private practice or smaller clinics may rely more heavily on clinical history due to limited resources or specialized training. Heterogeneity in assessment techniques was also apparent in response to the vignettes. While a quarter of the sample agreed that neuropsychological testing, neuroimaging, and laboratory values would have been useful as part of the vignettes in forming a diagnosis, there were many infrequent responses. Only 16% of clinicians requested medical history or follow-up visit information, and only 6% mentioned the importance of exploring potentially reversible causes of dementia, all of which are recommended according to current practice guidelines (McKhann et al., 2011). Future studies might examine how clinicians assess CSF information in combination with additional common clinical measures or as part of potential future clinical practice criteria.

This study was the first, to our knowledge, to examine how clinicians use CSF information to diagnose dementia. A number of limitations, however, should be acknowledged. First, the vignettes were brief in order to encourage participation among busy clinicians and lacked the more extensive detail that some clinicians might have access to in practice. Future studies could include additional test results, such as neuropsychological test scores, MRI reports, and functional assessments, and examine how various combinations of results influence clinical decision-making. More extensive vignettes comprised of formal diagnostic criteria could allow for a more complete understanding of the function of CSF information within current practice guidelines. Furthermore, future studies could incorporate factors likely to be present in deciding

to order CSF testing, such as cost and patient willingness. Second, our sample disproportionately included physicians employed in academic medical centers, whose familiarity with CSF values may differ from clinicians in private practice. Therefore, although we obtained some heterogeneity in our sample, which also included non-physicians, the generalizability of our results may be limited. Third, we were not able to examine the effect of CSF values on specific diagnoses due to small cell sizes, nor did this study assess the utility of biomarkers in differential diagnosis across the dementias. Given that CSF biomarkers have been useful for differential diagnosis of dementia in research settings, it is important to understand how CSF information would influence decision-making for varied patient presentations.

Despite these limitations, this study suggests that CSF values impact clinical decisions, even while clinicians do not view them as especially useful. CSF information is likely to become more widely used in clinical practice in the years ahead, particularly as clinicians attempt to identify preclinical cases for early intervention. This study represents a first step in exploring the potential role of CSF biomarkers in clinical evaluations, and in understanding how clinicians integrate clinical and pathological information to make clinical decisions.

References

Blennow, K. (2005). CSF biomarkers for Alzheimer's disease: Use in early diagnosis and evaluation of drug treatment. *Expert Review of Molecular Diagnostics, 5*, 661-672. doi:10.1586/14737159.5.5.661

Blennow, K., & Zetterberg, H. (2009). Cerebrospinal fluid biomarkers for Alzheimer's disease. *Journal of Alzheimer's Disease, 18*, 413-417. doi:10.3233/JAD-2009-1177

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (second ed.). NY: Lawrence Erlbaum Associates.

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., DeKosky, S. T., Barberger-Gateau, P., . . . Scheltens, P. (2010). Revising the definition of Alzheimer's disease: A new lexicon. *Lancet Neurology, 9*, 1118-1127. doi:10.1016/S1474-4422(10)70223-4

Fagan, A. M., Head, D., Shah, A. R., Marcus, D., Mintun, M., Morris, J. C., & Holtzman, D. M. (2009). Decreased cerebrospinal fluid $A\beta_{42}$ correlates with brain atrophy in cognitive normal elderly. *Annals of Neurology, 65*, 176-183. doi:10.1002/ana.21559

Fagan, A. M., Roe, C. M., Xiong, C., Mintun, M. A., Morris, J. C., & Holtzman, D. M. (2007). Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Archives of Neurology, 64*, 343-349. doi:10.1001/archneur.64.3.noc60123.

Faul, F., Erdfelder, E., Lang, A., & Buchner, A. (2009). G*Power (Version 3.1.5). [Computer software]. Available from http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*, *80,* 1778-1783. doi:10.1212/WNL.0b013e31828726f5

Mattson, N., Rosen, E., Hansson, O., Andreason, N., Parnetti, L., Jonsson, M., . . . Zetterberg, H. (2012). Age and diagnostic performance of Alzheimer's disease biomarkers. *Neurology, 78*, 468-476. doi:10.1212/WNL.0b013e3182477eed

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7,* 263-269. doi:10.1016/j.jalz.2011.03.005

Parnetti, L., Lanari, A., Silvestrelli, G., Saggese, E., & Reboldi, P. (2006). Diagnosing prodromal Alzheimer's disease: Role of CSF biochemical markers. *Mechanisms of Ageing and Development, 127,* 129-132. doi:10.1016/j.mad.2005.09.022

Price, J. L., & Morris, J. C. (1999). Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Annals of Neurology, 45*, 358-368.

Price, J. L., McKeel, D. W., Buckles, V. D., Roe, C. M., Xiong, C., Grundman, M., . . . Morris, J. C. (2009). Neuropathology of nondemented aging: Presumptive evidence for preclinical Alzheimer disease. *Neurobiology of Aging, 30*, 1026-1036. doi:10.1016/j.neurobiolaging.2009.04.002

Snider, B. J., Fagan, A. M., Roe, C., Shah, A. R., Grant, E. A., Xiong, C., . . . Holtzman, D. M. (2009). Cerebrospinal fluid biomarkers and rate of cognitive decline in very mild dementia of the Alzheimer type. *Archives of Neurology, 66,* 638-645. doi:10.1001/archneurol.2009.55

Stomrud, E., Hansson, O., Blennow, K., Minthon, L., & Londos, E. (2007). Cerebrospinal fluid

biomarkers predict decline in subjective cognitive function over 3 years in healthy elderly. *Dementia and Geriatric Cognitive Disorders, 24*, 118-124. doi:10.1159/000105017

Tabaraud, F., Leman, J. P., Milor, A. M., Roussie, J. M., Barriere, G., Tartary, M., . . . Rigaud, M. (2012). Alzheimer CSF biomarkers in routine clinical practice. *Acta Neurologica Scandinavica, 125*, 416-423. doi:10.1111/j.1600-0404-2011.01592.x

Toledo, J. B., Brettschneider, J., Grossman, M., Arnold, S. E., Hu, W. T., Xie, S. X., . . . Trojanowski, J. Q. (2012). CSF biomarker cutoffs: The importance of coincident neuropathological diseases. *Acta Neuropathologica*, *124*, 23-35. doi:10.1007/s00401-012-0983-7

Veloski, J., Tai, S., Evans, A. S., & Nash, D. B. (2005). Clinical vignette-based surveys: A tool for assessing physician practice variation. *American Journal of Medical Quality, 20*, 151-157. doi:10.1177/1062860605274520

Zetterberg, H., Lunn, M. P., & Herukka, S. (2012). Clinical use of cerebrospinal fluid biomarkers in Alzheimer's disease. *Biomarkers in Medicine, 6*, 371-376. doi:10.2217/bmm.12.47

Table 1

Participant Characteristics (N =193)

Characteristic	*M*/*n*	*SD*/%
Sex		
Male	102	53
Female	84	44
Unspecified	7	4
Age	50.98	10.80
Race/Ethnicity		
White	153	79
Asian	22	11
Hispanic, Latino, Spanish	6	3
Black or African American	4	2
Other	8	6
Degree		
MD	175	90
DO	7	4
NP	7	4
APRN	2	1
PA	2	1
Practice specialty		
Neurology	93	48
Geriatrics	59	31
Internal medicine	15	8
Primary care	14	7
Psychiatry	10	5
Unspecified	2	1
Practice setting		
University/Academic medical center	147	76
Veterans Administration Hospital	19	10
Clinic	13	7
Solo private practice	6	3
Hospital	3	2
Nursing home/Long term care	3	2
Unspecified	2	1
Percentage of patients >65 years (%)	73.13	23.02
Years in clinical practice	19.42	11.56

Note. DO = Doctor of Osteopathic Medicine, NP = Nurse Practioner, APRN = Advanced Practice Registered Nurse, PA = Physician Assistant.

Table 2

Frequency of Use and Utility of Diagnostic Tests (N = 193)

Test	How often used *M (SD)*	How useful *M (SD)*
Cognitive screening	4.59 (0.81)	4.10 (0.94)
Comprehensive cognitive testing	3.17 (1.29)	4.00 (1.17)
Structural neuroimaging	3.87 (1.23)	3.24 (1.16)
Metabolic neuroimaging	1.64 (0.73)	2.45 (1.30)
CSF analysis	1.56 (0.76)	2.16 (1.25)

Note. All values are on a 1-5 Likert-type scale, 1 (*Not at all*), 3 (*Moderately*), 5 (*Very*).

Table 3

Diagnostic Confidence Ratings (N = 193)

	Vignette	
CSF Condition	Borderline *M (SD)*	AD *M (SD)*
CSF present	3.40 (0.81)	3.59[b] (0.79)
CSF absent	3.16 (0.72)	3.24[b] (0.80)
Normal CSF	3.28 (0.83)	3.55 (0.78)
Borderline CSF	3.25 (0.81)	3.38[c] (0.72)
AD CSF	3.67[a] (0.75)	3.86[d] (0.80)
No CSF	3.16 [a] (0.72)	3.24[cd] (0.80)

Note. "CSF present" encapsulates the three CSF conditions. All values are on a 1-5 Likert-type scale of diagnostic confidence, 1 (*Not at all*), 3 (*Moderately*), 5 (*Very*).
Values that share subscripts are significantly different at the $p < .05$ level.

Table 4

Logistic Regression of Significant Predictors of Diagnostic Choice (AD Etiology versus Unknown Etiology)

Predictor	*B*	SE *B*	*Exp(B)*	95% C.I. *Exp(B)*
Borderline vignette				
Normal CSF group	-0.16	0.54	0.86	0.30 - 2.48
Borderline CSF group	0.90	0.47	2.47	0.98 - 6.22
AD CSF group	2.50	0.51	12.21***	4.50 - 33.17
AD vignette				
Normal CSF group	-1.16	0.46	0.31*	0.13 - 0.78
Borderline CSF group	-0.10	0.43	0.91	0.39 - 2.12
AD CSF group	1.53	0.54	4.60**	1.61 - 13.14
Post-vignette informant measure	1.16	0.29	3.17***	1.81 - 5.56

Note. Nonsignificant predictors removed from logistic regression: Years in clinical practice, percentage of patients over the age of 65, practice specialty, vignette diagnostic confidence.
*$p < .05$, ** $p < .01$, *** $p < .001$

Table 5

Post-Vignette Ratings of Whether Clinical Information Increased or Decreased Diagnostic Confidence, Full Sample and by CSF Condition (N = 193)

Clinical information	Borderline vignette *M (SD)*	AD vignette *M (SD)*
Collateral report	4.16 (0.73)	4.28 (0.67)
Normal CSF	4.23 (0.70)	4.22 (0.73)
Borderline CSF	4.18 (0.72)	4.20 (0.70)
AD CSF	4.26 (0.88)	4.56 [c] (0.55)
No CSF	4.02 (0.64)	4.17 [c] (0.63)
Functional status	4.02 (0.75)	4.10 (0.72)
Normal CSF	4.11 (0.67)	4.11 (0.74)
Borderline CSF	4.07 (0.84)	4.14 (0.73)
AD CSF	4.14 (0.74)	4.16 (0.75)
No CSF	3.83 (0.73)	4.02 (0.69)
Patient age	3.54 (0.73)	3.52 (0.72)
Normal CSF	3.36 [b] (0.79)	3.35 [d] (0.67)
Borderline CSF	3.53 (0.69)	3.41[e] (0.72)
AD CSF	3.84 [b] (0.72)	3.93 [d,e,f] (0.70)
No CSF	3.48 (0.66)	3.43[f] (0.68)
CSF information[a]	3.21 (0.93)	3.36 (0.98)
Normal CSF	3.15 (0.91)	3.15[h] (1.01)
Borderline CSF	2.93[g] (0.72)	3.11[i] (0.78)
AD CSF	3.58[g] (1.03)	3.84[hi] (0.97)

Note. Headings reflect values for entire sample; subheadings reflect values by CSF condition. All values are on a 1-5 Likert-type scale, 1 (*Less confident*), 3 (*Neither less nor more confident*), 5 (*More confident*).
[a]Those who did not receive CSF information were not asked a follow-up question about it.
Values that share subscripts are significantly different at the $p < .05$ level.

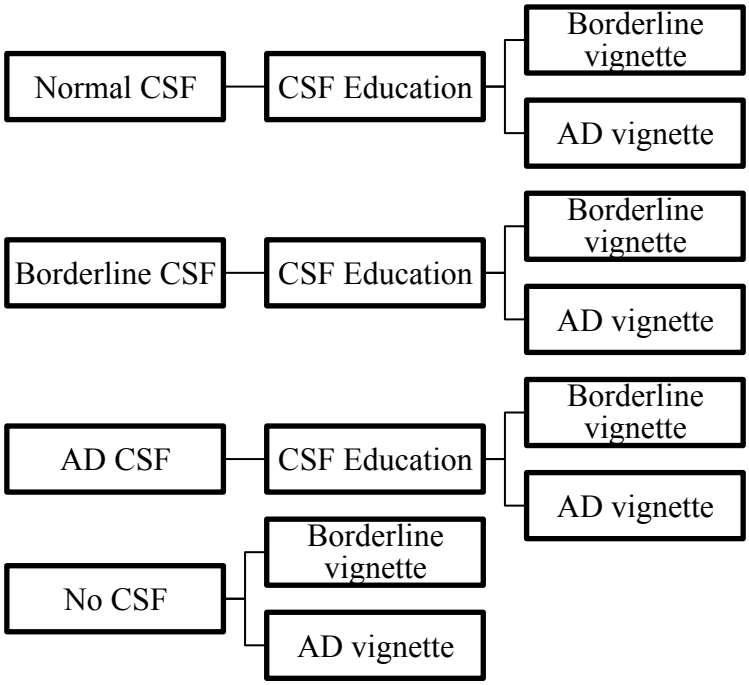

*Figure 1***.** Randomization and procedural flow.

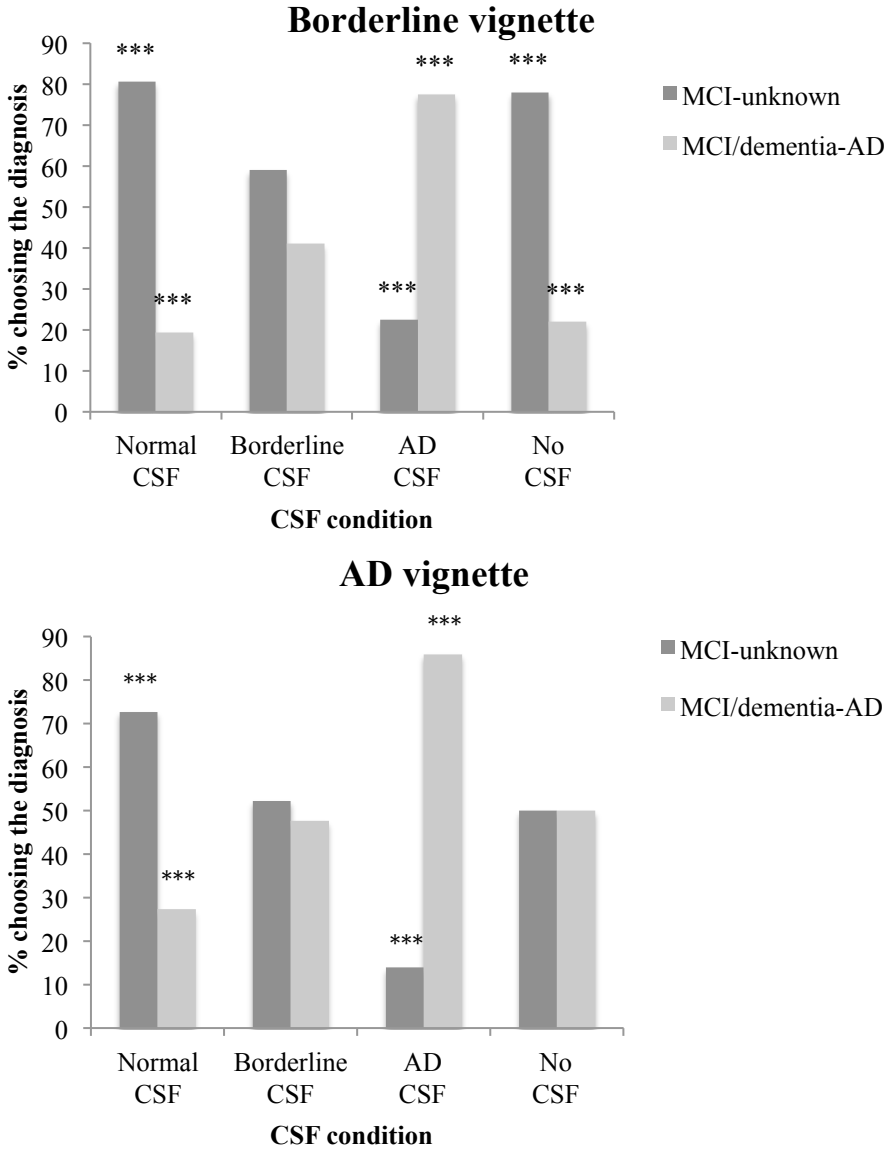

Figure 2. Percentage of clinicians choosing diagnostic categories by CSF condition for the borderline and AD vignettes. Adjusted standardized residuals, signifying difference from expected chi-square distribution, are significant at the ***$p < .001$ level.

Appendix A

CSF education document

Amyloid plaques and neurofibrillary tangles are the pathological hallmarks of Alzheimer's disease (AD). Amyloid beta peptide, most commonly the 42 amino acid form ($A\beta_{42}$) is the major component of amyloid plaques; neurofibrillary tangles are made primarily of aggregated tau proteins, including tau phosphorylated at residue 181 ($ptau_{181}$). $A\beta_{42}$, total tau protein and $ptau_{181}$ can be detected in cerebrospinal fluid (CSF). Many studies have shown that AD patients as a group have CSF with lower levels of $A\beta_{42}$ and higher levels of tau and $ptau_{181}$ than cognitively normal people. A ratio of tau/$A\beta_{42}$ or $ptau_{181}/A\beta_{42}$ usually provides the best sensitivity and specificity to discriminate Alzheimer's disease from cognitively normal, but there is overlap of values between groups. This may be in large part because about 30% of cognitively normal people over the age of 65 have pathological and CSF changes typical of AD (Fagan et al., 2007; Price and Morris, 1999; Price et al., 2009). Several studies have shown that cognitively normal people whose CSF shows these changes are five-fold more likely than those without the changes to develop AD in the next 3-4 years (Fagan et al., 2007). Thus, changes in CSF (reduced levels of $A\beta_{42}$ and increased levels of tau and $ptau_{181}$) may be very specific for the brain *pathology* of AD but can be seen in people who do not have the *symptoms* of AD; these people are at higher risk of having AD in the future and may have "preclinical" or "presymptomatic" AD.

Clinical testing for AD CSF biomarkers is available commercially from Athena Diagnostics. Athena provides values of $A\beta_{42}$, tau and $ptau_{181}$ without reference ranges and provides a normalized ratio of $A\beta_{42}$ to total tau (called the AT index) and level of ptau to discriminate patients with Alzheimer's disease from those with etiologies for cognitive change.

An AT index of less than 1.0 and P-tau concentration of > 61 pg/ml are suggestive of AD. They note that there is some overlap between normal individuals and those with AD (e.g. AT index 0.8-2.0 and ptau 54-68 pg/ml are in a "borderline" range). Athena cites a sensitivity of 85-94% and a specificity of 83-90% for this ratio, citing two studies (Hulstaert et al., 1999; Andreasen et al., 2001).

For reference, we also provide CSF biomarker values observed in research participants who had a clinical assessment at Washington University (Table 1) and values observed observed in a subset of these research participants who had autopsy proven AD.

Table 1. *CSF Biomarker Values in Research Participants at the Knight ADRC Comparing Cognitively Normal Individuals (Clinical Dementia Rating (CDR) of 0) to Those Who Have Very Mild or Mild AD (CDR 0.5 or 1).*

	No AD (n=90)		Mild AD (n=33)	
	Mean	Standard deviation	Mean	Standard deviation
$A\beta_{42}$	567	207	434	211
tau	342	175	565	302
$ptau_{181}$	62	26	86	45

Note: All values shown are in pg/ml. The data were aggregated and did not allow calculation of ATI.

Table 2. *CSF Biomarker Values in 29 Individuals with Autopsy Proven AD (unpublished data from the Knight ADRC)*

	Mean (Standard Deviation)	MIN	MAX	MEDIAN
$A\beta_{42}$	425 (171)	183	786	360
tau	574 (287)	156	1200	544
$ptau_{181}$	84 (38)	25	192	78
ATI	0.54 (0.3)	0.12	1.58	0.52

Note: All values shown are in pg/ml.

Appendix B

Borderline vignette

A 73-year-old retired pilot comes to your office for routine follow-up with his son who lives nearby and sees him several times per week. His son reports he is concerned about his father's memory. The son reports that his father has always been a little repetitious but now might tell the same story within a day. He is more dependent on his calendar to keep track of appointments, checking it several times per day. He might forget the details of some recent events, but recalls events well "if it interests him." He still drives but has been reluctant to drive to his son's new home. He still goes to church and plays golf with friends. He still does minor home repairs but they take him longer. He is independent in activities of daily living. The patient is not overly concerned about his memory, stating some things just aren't important to him anymore. The patient and his son both report his mood is low sometimes, but he denies having low mood most days for two weeks or more.

AD vignette

A 71-year-old retired real estate agent comes to your office. His wife is also your patient and while you are seeing her she mentions she has some concerns about her husband's memory. She reports he has forgotten several appointments in the past year and often forgets things she has told him. He recalls recent events but is less likely to recall the details. He is still driving, but struggles to find less familiar places. He attends church but stopped serving as a deacon last year because he was having difficulty making decisions; he still meets with retired friends often. She noted that he takes longer to do home repairs and has taken several months to put up shelves in the garage and they are not up to his usual standard. He is independent in his

activities of daily living. The patient reports his wife is worried about his memory but that he has not noticed any changes. They both denied low mood.

CSF values accompanying vignettes

Normal CSF: $A\beta_{42}$ = 750 pg/ml

Total tau = 330 pg/ml

$ptau_{181}$ = 40 pg/ml

ATI (Athena) =1.2

Borderline CSF: $A\beta_{42}$ = 502 pg/ml

Total tau = 216 pg/ml

$ptau_{181}$ = 60 pg/ml

ATI (Athena) = 1.0

AD CSF: $A\beta_{42}$ = 300 pg/ml

Total tau = 619 pg/ml

$ptau_{181}$ = 86 pg/ml

ATI (Athena) = 0.31