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AAIC 17

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CONTACT: Alzheimer's Association International Conf. Press Office, +44 (0) 20-7069-6000, media@alz.org
Niles Frantz, Alzheimer's Association, +1 312-365-8782, nfrantz@alz.org

FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2017

UNDERUTILIZATION OF BRAIN AMYLOID SCANS DRIVES COST AND HURTS ALZHEIMER'S DISEASE CARE

- Clinical trials show brain PET imaging improves dementia diagnosis –
- More than 80 percent of Alzheimer's patients and caregivers receptive to PET scanning –

Disclosure: The IDEAS Study is following more than 18,000 Medicare beneficiaries to determine the clinical value of a brain amyloid PET scan in diagnosing and managing treatment of patients 65 and older with MCI or dementia of uncertain cause. The IDEAS Study is funded, in part, by the Alzheimer's Association, who also provide study leadership, and managed by the American College of Radiology/American College of Radiology Imaging Network.

LONDON, July 16, 2017 – Research reported at the Alzheimer's Association International Conference (AAIC) 2017 in London highlighted the clinical value of amyloid-β PET scans, which detect the presence of amyloid-beta plaques in the brain - one of the hallmarks of Alzheimer's disease. Studies also revealed an underutilization of amyloid-β PET imaging in clinical care, contributing to misdiagnosis of dementia.

Two studies at AAIC 2017 reported that brain PET imaging allows for more accurate detection or exclusion of Alzheimer's in a larger proportion of individuals than standard clinical assessment supported by structural and metabolic imaging, and cerebrospinal fluid (CSF), and that use of amyloid PET scans may lead to a change in diagnosis in up to two-thirds of cases. A meta-analysis of data in a large population of participants found that brain amyloid PET scans led to a change in diagnosis in approximately 20 percent of these individuals.

Other PET-related research reported at AAIC 2017 included the following findings:

- A survey of individuals with cognitive impairment and their caregivers found that more than 80 percent were receptive to undergoing a PET imaging study if it was recommended by their doctor, and clinicians would base decisions about future patient care on brain PET scan findings. Many study participants were frustrated by the lack of availability of brain amyloid PET scans in clinical practice.
- An analysis of Medicare claims data found that approximately 60 percent of dementia cases are missed in clinical practice, particularly cases of early dementia.

"A negative brain PET scan indicating sparse to no amyloid plaques rules out Alzheimer's disease as the cause of dementia symptoms. This makes it a valuable tool to clarify an uncertain or difficult diagnosis," said James A. Hendrix, PhD, Alzheimer's Association Director of Global Science Initiatives. "Misdiagnosis is costly to health systems, and expensive and distressing to persons with dementia and their families."

"Beyond the data reported at AAIC 2017, the IDEAS Study will provide further evidence to demonstrate the utility of amyloid PET imaging in a clinical setting," said Hendrix. "A swift and accurate diagnosis has a huge impact on access to Alzheimer's treatments, eligibility for research trials, plus much-needed support and information services." The IDEAS Study is led by the Alzheimer's Association and managed by the American College of Radiology and American College of Radiology Imaging Network.

Utilization of PET Scanning Greatly Enhanced Diagnosis of Alzheimer's Disease

Identification of amyloid-β in clinical practice has relied largely on CSF testing and the administration of cognitive and psychiatric tests that are not specific to Alzheimer's disease. The emergence of PET imaging has been instrumental in advancing Alzheimer's research, but despite the high rate of misdiagnosis in this disease, the prevailing wisdom has been that PET imaging does not provide sufficient additional diagnostic accuracy to justify its cost. Two small studies and a meta-analysis presented at AAIC are challenging that view.

In an ongoing study of individuals with cognitive complaints performed at Oslo University Hospital by Nenad Bogdanovic, MD, PhD, of the University of Oslo in Norway, amyloid PET imaging was found to be a key contributor to either diagnosing or excluding a diagnosis of Alzheimer's disease in all 50 (100 percent) of participants. In contrast, CSF amyloid testing allowed for diagnosis or exclusion in 44 of 50 individuals (88 percent) using a higher detection cutoff and in only 21 individuals (42 percent) using traditional cutoffs.

As part of a 135-person study, doctoral student Antoine Leuzy,MSc, of Karolinska Institute in Stockholm and colleagues presented PET imaging results for 61 individuals diagnosed with mild cognitive impairment (n=38), Alzheimer's disease (n=13), other types of dementia (n=8) or severe cognitive impairment (n=2). PET imaging studies led to a change in diagnosis in 68 percent of these participants. Agreement between CSF testing and PET imaging was only 53–57 percent, depending on the approach used to read the PET scan. Where results disagreed, 75–77 percent of individuals were amyloid-β positive on PET scanning. Results from these small studies highlight not only the diagnostic value of PET but also the potential for misdiagnosis using traditional assessments.

Enrico Fantoni, PhD, of GE Healthcare in Amersham, UK, is performing an ongoing meta-analysis of four clinical trials conducted between 2000 and 2017 to evaluate the value of amyloid PET (aPET) in a large population of individuals with cognitive impairment. A preliminary evaluation of four studies with more than 1,100 clinical cases revealed that the use of aPET led to a change in diagnosis in over 20 percent of people independent of PET scan outcome.

- In those individuals with a prescan Alzheimer's diagnosis and a positive aPET scan, the diagnosis was subsequently confirmed in 99 percent. Conversely, an Alzheimer's diagnosis was ruled out in the majority of cases with a negative aPET scan (similarly, 99% of cases).
- If the prescan diagnosis was non-Alzheimer's, however, a positive aPET scan led to reassessment as Alzheimer's in 60 percent of cases.
- If the prescan diagnosis was Alzheimer's, a negative aPET scan led to exclusion of Alzheimer's in 54 percent of cases.

Thus, aPET was valuable for excluding and confirming diagnoses of Alzheimer's disease.

Limited Access Leads to Underutilization of PET Scanning

While research supports the value of PET scans for clarifying a diagnosis of Alzheimer's disease, Liana Apostolova, MD, of Indiana University School of Medicine in Indianapolis and colleagues presented a study at AAIC 2017 that indicates that limited access to PET imaging is proving frustrating to individuals and their caregivers, and it leads to continued frequent misdiagnoses of people who would benefit from early intervention.

The team surveyed 510 participants and caregivers (predominantly in the U.S.) to gauge their attitudes about PET imaging as a part of patient care. Between 85 percent and 91 percent of respondents indicated they were dissatisfied with the availability of PET scans, supported additional research on PET imaging and were willing to undergo PET scans if they were recommended by their physician.

Medicare Claims Frequently Misidentify Dementia

Carolyn Zhu, PhD, of Icahn School of Medicine at Mount Sinai in New York and colleagues analyzed data from 2,144 participants in the Washington Heights-Inwood Columbia Aging Project and found that Medicare claims frequently misidentified dementia cases. The sample included 1,689 individuals not diagnosed with dementia and 455 with a clinical diagnosis of dementia based on a rigorous clinical assessment performed at study enrollment. Medicare claims prior to study enrollment allowed for successful identification of 1808 subjects (85 percent), suggesting moderate agreement between claims data and subsequent clinical diagnoses. However, 281 subjects (62 percent) diagnosed with dementia at study enrollment were not identified as such based on prior treatment reported in Medicare claims. These people were younger and had better general health and cognitive function than those identified as having dementia based on Medicare claims.

While the U.S. Congress has recently provided additional funding for Alzheimer's research at the National Institutes of Health (NIH), the commitment falls far short of the need. In 2017, for every $100 the NIH spends on Alzheimer's research, Medicare and Medicaid will spend $12,500 caring for those with the disease. Congress must continue its commitment to the fight against Alzheimer's and other dementias by increasing funding for Alzheimer's research by at least an additional $414 million in fiscal year 2018.

About Alzheimer's Association International Conference

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2017 home page: www.alz.org/aaic/
AAIC 2017 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer's Association

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call +1 800.272.3900.

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- Nenad Bogdanovic, MD, PhD, et al. Measurement of Pathological Amyloid in Routine Clinical Assessment: The Clinical Impact of Visual [18f]Flutemetamol PET and CSF Analysis. (Funder(s): GE Healthcare)
- Antoine Leuzy, MSc, et al. Investigating the Clinical Impact of [18F]flutemetamol PET in a Tertiary Memory Clinic Setting in Patients with Uncertain Diagnosis. (Funder: Vinnova, Swedish Research Council; Swedish Foundation for Strategic Research (SSF); Regional Agreement on Medical Training and Clinical Research (ALF) for Stockholm County Council; Swedish Brain Foundation; Swedish Alzheimer's Foundation; Gun and Bertil Stohne's Foundation; Demensfonden)
- Enrico Fantoni, PhD, et al. Amyloid PET Utility in Clinical Practice: A Systematic Review and MetaAnalysis. (Funder(s): GE Healthcare)
- Liana Apostolova, MD, MS, et al. Patient and Caregiver Assessment of the Benefits from the Clinical Use of Amyloid PET Imaging (Weds). (Funder(s): U.S. National Institute on Aging)
- Carolyn Zhu, PhD, et al. The Accuracy of Dementia Diagnosis in Medicare Claim.

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Abstract 17642 / Proposal ID P1-381
Diagnosis and Prognosis: Neuroimaging
Posters Sunday, July 16, 2017: 9:30 AM

Measurement of Pathological Amyloid in Routine Clinical Assessment: The Clinical Impact of Visual [^{18}f]Flutemetamol PET and CSF Analysis

Nenad Bogdanovic[1]**(nenad.bogdanovic@medisin.uio.no)**, Gill Farrar, PhD[2] and Enrico R Fantoni, PhD[2],
[(1)]Oslo University, Oslo, Norway, [(2)]GE Healthcare, Amersham, United Kingdom

Background: Amyloid beta can be detected with similar accuracy by both CSF testing and amyloid PET scanning (Palmqvist, 2015). However, the CSF Aβ42 threshold required to establish a "positive" diagnosis of Aβ plaque accumulation varies between sites. This study analyses the concordance between [^{18}F]flutemetamol PET and CSF measures in clinical practice and the impact of amyloid CSF and amyloid PET on the diagnostic decision- making for cognitively impaired subjects.

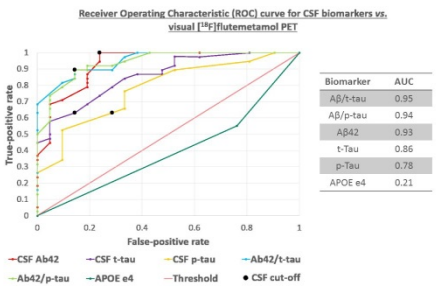
Methods: 50 patients with cognitive complaints (mean age 69) referred to the Oslo University Memory Clinic, Norway (a tertiary medical clinic, patient consent register no. 2009/1953-S-08143a) underwent a battery of tests including routine neuropsychological tests, lumbar CSF sampling analysed with INNOTEST ELISA, visual [^{18}F]flutemetamol amyloid PET, [^{18}F]FDG-PET, MRI, [^{123}I]ioflupane SPECT imaging (9/50 subjects at risk of a parkinsonian disease). Additionally, the clinician provided pre- and post-tests diagnoses and his diagnostic confidence (on a scale from 1 to 3) for each subject.

Results: For an amyloid detection comparable to histopathologically validated [^{18}F]flutemetamol PET (Ikonomovic, 2016), CSF cut-offs need adjustment to 770 pg/mL for Aβ42, 500 pg/mL for t-tau, 70 pg/mL for p- tau, 2.3 for Aβ42/t-tau ratios and 15 for Aβ42/p-tau ratios (Figure 1). [^{18}F]Flutemetamol PET was a key contributor in identifying a specific diagnosis or excluding AD in 50/50 of cases. This figure was somewhat lower for the "new" CSF cut-offs (44/50, 88%), whereas the traditional cut-offs were unable to drive a diagnostic decision in a consistent number of cases (21/50, 42%).

Conclusions: Knowledge of amyloid status during clinical work-up can be fundamental as a tool to assign accurate diagnoses. Previous CSF cut-offs (Mudler, 2010) were lower than identified in this cohort, which compromised their ability to identify early pathological amyloid and tau. The suggested cut-off alterations result in similar utility of amyloid CSF and amyloid PET data to the diagnosis decision-marking, although the biological significance of the form of amyloid detected differs.

References: Ikonomovic MD et al., *Acta Neuropathologica Communications* (2016) 4:130; Mudler C et al., *Clinical Chemistry* (2010) 56:248-253; Palmqvist S et al., *Neurology* (2015) 85:1-10.

Tables and Figures:



Biomarker	AUC
Aβ/t-tau	0.95
Aβ/p-tau	0.94
Aβ42	0.93
t-Tau	0.86
p-Tau	0.78
APOE e4	0.21

Abstract 19062 / Proposal ID P1-357
Diagnosis and Prognosis: Neuroimaging
Posters Sunday, July 16, 2017: 9:30 AM

Investigating the Clinical Impact of [^{18}F]flutemetamol PET in a Tertiary Memory Clinic Setting in Patients with Uncertain Diagnosis

Antoine Leuzy[1]**(antoine.leuzy@ki.se)**, Konstantinos Chiotis, MD[1], Vesna Jelic[2], Pia Andersen[2], Jennifer Friman[3], Johan Lilja[3,4], Irina Savitcheva[2] and Agneta Nordberg, MD, PhD[1,5],
[(1)]Karolinska Institutet, Stockholm, Sweden, [(2)]Karolinska University Hospital, Huddinge, Sweden, [(3)]Uppsala University, Uppsala, Sweden, [(4)]Hermes Medical Solutions, Stockholm, Sweden, [(5)]Karolinska University Hospital Huddinge, Stockholm, Sweden

Background: Since the first application of carbon-11 Pittsburgh Compound-B ([^{11}C]PIB) PET more than a decade ago, amyloid PET has been instrumental in advancing the research agenda for Alzheimer's disease (AD). By detecting a core feature of AD pathology, amyloid PET holds potential in clinical settings, particularly given the high rate of misdiagnosis.

Clinical studies using recently approved amyloid PET tracers, however, have far been few, with these mainly in highly selected research cohorts. The aim of the present study was thus to investigate the added clinical value of [^{18}F]flutemetamol PET in memory clinic patients whose diagnosis remained uncertain following routine clinical work up.

Methods: 135 patients were included from the Department of Geriatric Medicine, Karolinska University Hospital, Huddinge, Sweden, following referral from primary care physicians. Following standard diagnostic workup, including medical and neurological examination, clinical chemistry (including CSF A$\beta_{1\text{-}42}$), rating batteries for depression and neuropsychiatric symptoms, neuropsychological assessment, and structural imaging, the clinical picture remained unclear. [^{18}F]flutemetamol PET was thus performed, using a Biograph mCT PET/CT (Siemens/CTI, Knoxville, TN), with the acquisition protocol consisting of a static 20-min scan, 90-min post-injection of 185 MBq. In addition to visual assessment by an experienced nuclear medicine physician, [^{18}F]flutemetamol uptake was quantified on a region of interest basis using a fully automated software (Hermes Hybrid BRASS).

Diagnoses before and after [^{18}F]flutemetamol investigations were reached using a multidisciplinary consensus based approach.

Results: Based on preliminary results from 61 subjects (38 MCI, 13 AD, 6 dementia NOS, 2 SCI, one FTD, and one DLB), [^{18}F]flutemetamol investigations led to a change in diagnosis in 68% of patients. Agreement between visual and quantitative assessment of [^{18}F]flutemetamol images was high (89%). Concordance between CSF A$\beta_{1\text{-}42}$ (<550 pg/mL) and [^{18}F]flutemetamol was 57% and 53%, using visual and quantitative approaches, respectively. Among discordant cases, most showed isolated [^{18}F]flutemetamol positivity (75% using visual, 77% using quantification).

Conclusions: While further analyses are ongoing for the remaining 74 patients, preliminary findings highlight the added value of [^{18}F]flutemetamol over standard diagnostic work-up. Discordance between CSF A$\beta_{1\text{-}42}$ and [^{18}F]flutemetamol PET highlights the issue of biomarker interchangeability in clinical settings.

Abstract# 17413 / Proposal ID P1-363
Diagnosis and Prognosis: Neuroimaging
Posters Sunday, July 16, 2017: 9:30 AM

Amyloid PET Utility in Clinical Practice: A Systematic Review and Meta-Analysis

Enrico R Fantoni, PhD (enrico.fantoni@ge.com) and Gill Farrar, PhD, GE Healthcare, Amersham, United Kingdom

Background: Diagnosing cognitively impaired subjects with a specific disease is still problematic, partially because of their complex aetiology. Amyloid PET (aPET) imaging is now available as a diagnostic tool for clinical practice. Its use has high potential to substantially support clinicians in the differential diagnosis of dementias, and several studies have endeavoured to quantify such impact. However, most studies included a limited number of participants and there is no consensus over the extent of impact that aPET can have in clinical practice.

Methods: This is a systematic review of all studies published in English language between 2000 and 2017 and pertaining the individual impact of visual aPET imaging in the differential diagnosis of cognitively impaired subjects in both clinical and research practice. Only pre-scan and post-scan diagnoses within <12 months of each other have been considered. The review also comprises a meta-analysis of the diagnostic value added by aPET in each study.

Results: For 1106 cognitively impaired clinical cases (from 4 studies analysed to date) the use of aPET leads to a change in diagnosis in 20.1% subjects, independent of PET scan result. The diagnosis was reconfirmed as AD in 98.6% of pre-scan AD cases with positive aPET, whereas it was reassessed as AD in 59.8% of pre-scan non-AD diagnosis and positive aPET (Figure 1). Conversely, 54.1% of patients with a previous AD diagnosis and a negative aPET scan had AD ruled out.

Conclusions: This review is the first to quantify the impact of amyloid PET for a large cohort of patients with disparate symptoms and over multiple clinical centres globally. The results highlight the value of aPET as a tool to rule out AD as well as indicating that in combination with clinical information the scan is able to reinforce the diagnosis of AD. Further research is needed to identify the optimal position of aPET in the clinical pathway of each patient type.

References: Pontecorvo MJ et al., Alzheimer's and Dementia (2015) 11:P334, Grundman M et al., Alzheimer. Dis. Assoc. Disord. (2013) 27:4- 15, Zwan M et al., Alzheimer's Research & Therapy (2017) 9:2, Boccardi M et al., JAMA Neurology (2016) 73:1417-1424.

PET utility image2.jpg (103.1KB)

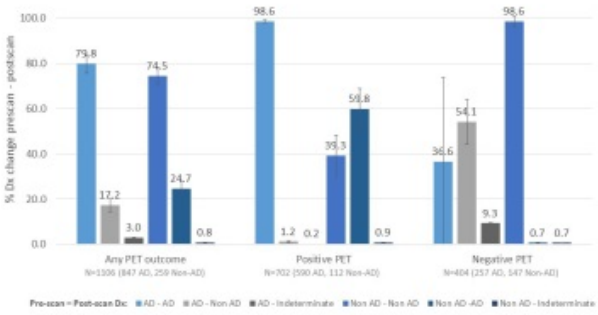


Figure 1 Pre- and post- scan diagnostic (Dx) trajectories grouped by PET scan outcome. Trajectories are expressed as percentages (with 95% CI) of cases with pre-scan diagnosis X and PET scan result Y retaining the same diagnosis or changing to a different one.

Abstract 16478 / Proposal ID P4-327
Public Health and Psychosocial: Dementia Care Research (nonpharmacological)
Posters Wednesday, July 19, 2017: 9:30 AM

Patient and Caregiver Assessment of the Benefits from the Clinical Use of Amyloid PET Imaging

Liana G. Apostolova, MD, MS[1,2,13]**(lapostol@iu.edu),** Rafid Mustafa, BS[1], Jared R. Brosch, MD[1,2], Gil D Rabinovici, MD[3,4,5], Bradford C. Dickerson, MD[6,7], Maria C. Carrillo, Ph.D.[8], Bradley S. Glazier[1,2], Sujuan Gao, PhD[9], Martha Tierney, LCSW[8], Keith Fargo, PhD[8], Mary Guerriero Austrom, PhD[1,2], Susan de Santi, PhD[10], and David G. Clark, MD[11,12].
[(1)]Indiana University School of Medicine, Indianapolis, IN, USA, [(2)]Indiana Alzheimer Disease Center, Indianapolis, IN, USA, [(3)]University of California San Francisco, San Francisco, CA, USA, [(4)]Lawrence Berkeley National Laboratory, Berkeley, CA, USA, [(5)]University of California Berkeley, Berkeley, CA, USA, [(6)]Massachusetts General Hospital, Charlestown, MA, USA, [(7)]Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA, [(8)]Alzheimer's Association, Chicago, IL, USA, [(9)]Indiana University, School of Medicine, Department of Biostatistics, Indianapolis, IN, USA, [(10)]Piramal Imaging Inc., Boston, MA, USA, [(11)]Medical University of South Carolina, Charleston, SC, USA, [(12)]Ralph H. Johnson VA Medical Center, Charleston, SC, USA, [(13)]University of California, Los Angeles, Los Angeles, CA, USA

Background: While many studies have evaluated the diagnostic or prognostic implications of amyloid PET imaging, few have explored patient and caregiver views on the clinical use of amyloid PET.

Methods: We designed a 7-item questionnaire to assess patient and caregiver views (510 total respondents) toward amyloid PET imaging and its inaccessibility in routine clinical practice. The questionnaire was advertised broadly through alz.org/trialmatch.

Results: We received 510 unique responses from 48 US states, two Canadian provinces, the Dominican Republic, and Greece. 42% of the participants identified with early onset cognitive decline (EOD, <65 years at disease onset). There were significantly more patients vs. caregivers among EOD than late onset cognitive decline (LOD) ($p < 0.0001$). 87% of respondents were from urban areas. By U.S. region, the responses were divided as 16% Northeast, 22% Midwest, 36% South, and 23% West (the remaining 3% of unclassifiable regions). Patients vs. caregivers and EOD vs. LOD did not differ in their rates of dissatisfaction with the clinical unavailability (range 85.2%-91.2% across categories), support for additional research on the clinical utility of amyloid imaging, and willingness to undergo amyloid imaging if recommended by their doctor. Patients vs. caregivers and EOD vs. LOD were as likely to pursue more information about the disease, to seek legal and financial planning, long term care and life insurance, and to communicate their diagnosis and prognosis with their families. EOD were more likely to explore options for disability insurance than those with late onset cognitive decline ($p = 0.03$). No differences in responses were seen between urban and rural dwellers. Responders from the Midwest were more likely to utilize information from amyloid imaging for legal planning ($p = 0.02$), disability insurance ($p = 0.02$), and life insurance ($p = 0.04$) than other US regions, particularly the South and the West.

Conclusions: Patients and caregivers supported the use of amyloid PET imaging in clinical practice and felt that the information would provide significant benefits particularly in terms of future planning.

Abstract 16393 / Proposal ID P2-556

Public Health and Psychosocial: Public Health and Psychosocial: Health Economics and Policy
Poster Monday, July 17, 2017: 9:30 AM-4:15 PM

The Accuracy of Dementia Diagnosis in Medicare Claim

Carolyn W Zhu, Ph.D.[1,2]**(carolyn.zhu@mssm.edu)**, Katherine Ornstein, PhD[2], Stephanie Cosentino, Ph.D.[3], Yian GU, Ph.D.[4], Howard Andrews, Ph.D.[4] and Yaakov Stern, PhD[4],
[(1)]James J. Peters VA Medical Center, Bronx, NY, USA, [(2)]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [(3)]Taub Institute at Columbia University, New York, NY, USA, [(4)]Columbia University, New York, NY, USA

Background: Medicare claims are commonly used to identify patients with dementia. But diagnoses recorded in claims may not capture mild dementia cases. Such mis-identification may result in biased estimates of disease prevalence and costs. This study estimates the sensitivity and specificity of Medicare claims to identify dementia in a cohort of older adults with clinically diagnosed dementia.

Methods: The sample was drawn from participants in the Washington Heights-Inwood Columbia Aging Project (WHICAP), a multiethnic, population-based, prospective study of cognitive aging in which dementia status was assessed using a rigorous clinical protocol. The current study included 455 subjects who were diagnosed with dementia at enrollment and 1,689 subjects who were never diagnosed with dementia any time during the study. ICD-9-CM diagnosis codes in all available Medicare claims were used to determine claims-based identification of dementia. Sensitivity and specificity of claims-identified dementia compared to clinically diagnosed dementia were computed, using clinical diagnosis as the gold standard. Logistic regression was used to estimate the relationship between patient clinical and demographic characteristics and predictive value in claims identification.

Results: Medicare claims correctly identified 1,808 cases (agreement rate with clinical diagnosis=84.7%), resulting in a kappa value of 0.43 (moderate agreement). The sensitivity and specificity of dementia identification in Medicare claims was 0.38 and 0.97, respectively. Among subjects clinically diagnosed with dementia, 281 (61.8%) were not identified in Medicare claims as demented. Individuals with a clinical diagnosis of dementia but not identified as having dementia in the claims data were younger, with lower education, eligible for Medicaid, had fewer comorbidities, and better function and cognition than those for whom there was agreement between claims data and clinical diagnosis. Among those who were clinically diagnosed as non-demented, 55 (3.2%) were identified in the claims as demented. Disagreement in this group was associated with older age, unmarried status, more comorbidities, worse function and cognition.

Conclusions: Mis-identification of dementia in Medicare claims is quite common, although there are both false positive and negative assessments of disease. Both clinical and sociodemographic characteristics affect predictive value of claims-based diagnoses. Mis-identification may be associated with biased estimation of disease prevalence and cost of AD.