APPENDIX 1

Excess Costs Associated with Misdiagnosis of Alzheimer's Disease among U.S. Medicare Beneficiaries with Vascular Dementia or Parkinson's Disease

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Background: Recent developments in diagnostic technology have improved the ability to rule out Alzheimer's disease (AD) in patients with cognitive impairment. This study examined potential economic benefits of ruling out AD among patients eventually diagnosed with vascular dementia (VD) or Parkinson's disease (PD), by estimating excess medical costs for those previously misdiagnosed with AD. **Methods:** Retrospective analysis of de-identified administrative claims data for Medicare beneficiaries (5% random sample) identified two mutually exclusive patient cohorts with >2 claims for VD (ICD-9 CM: 290.4) or PD (332.x), without claims for other dementia types between or after their most recent VD/PD diagnoses. Within each cohort, patients were stratified based on prior diagnosis of AD in the three years preceding their first confirmed VD/PD diagnosis (defined as >2 claims with ICD-9-CM 331.0, or psychiatrist-diagnosed 290.0, 290.2, 290.3; patients with a single such claim were excluded). The index date was the first AD diagnosis for patients with prior AD, and first confirmed VD/PD diagnosis for patients with no prior AD. Patients were required to have continuous Medicare coverage for ≥ 6 months pre-index (baseline) and >12 months following the first confirmed VD/PD diagnosis, and were followed for up to 4 years post-index. Within each disease cohort, patients with prior AD were matched to similar patients with no prior AD using propensity score methods. Annual medical costs were compared between matched pairs in one year intervals, stratified by time to correct diagnosis. **Results:** Approximately 17% of VD patients and 8% of PD patients had prior AD diagnoses.2,088 matched pairs with VD and 2,058 with PD were analyzed. Post-matching, baseline characteristics were well-balanced for both cohorts. Patients previously diagnosed with AD incurred substantially higher medical costs in periods leading up to and including their confirmed VD/PD diagnoses, compared with their matched counterparts during the same timeframe. Excess costs declined - and eventually dissipated - following the confirmed VD/PD diagnoses (Figures 1 and 2). **Conclusions:** This administrative claims data-based analysis suggests that misdiagnosis of AD among Medicare beneficiaries with VD or PD results in substantial excess costs. The change in excess costs trend following correct diagnosis suggests potential benefits from earlier rule-out of AD.

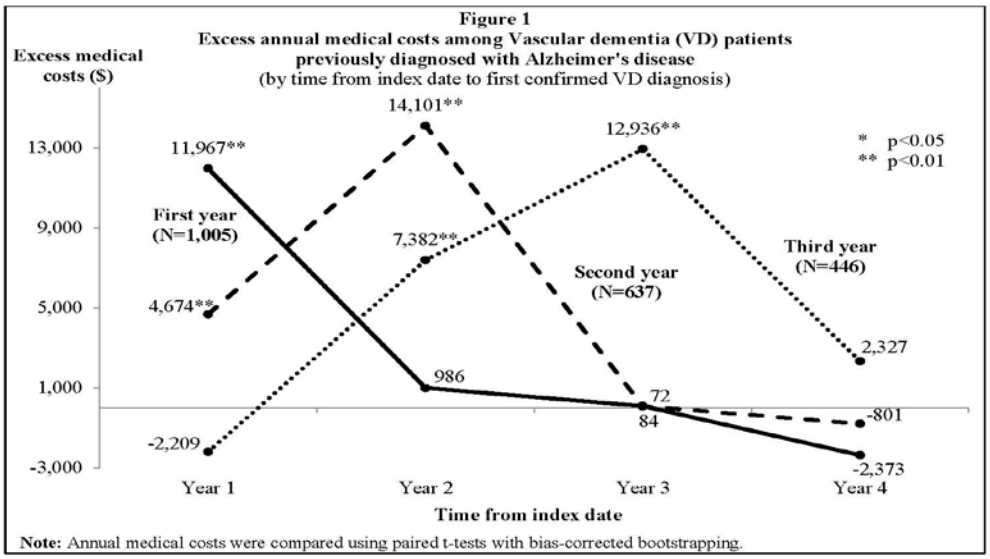
Figure 1
Excess annual medical costs among Vascular dementia (VD) patients previously diagnosed with Alzheimer's disease
(by time from index date to first confirmed VD diagnosis)
Excess medical costs ($)
13,000
9,000
5,000
1,000
-3,000
11,967**
14,101**
12,936**
7,382**
4,674**
-2,209
986
72
84
2,327
-801
-2,373
First year (N=1,005)
Second year (N=637)
Third year (N=446)
* p<0.05
** p<0.01
Year 1
Year 2
Year 3
Year 4
Time from index date
Note: Annual medical costs were compared using paired t-tests with bias-corrected bootstrapping.

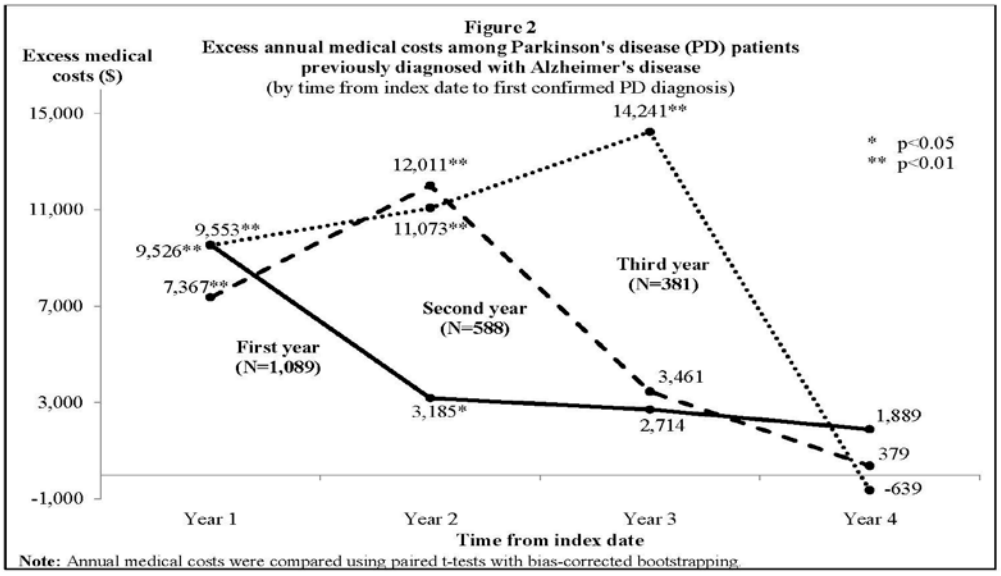
Figure 2
Excess annual medical costs among Parkinson's disease (PD) patients previously diagnosed with Alzheimer's disease
(by time from index date to first confirmed PD diagnosis)
Excess medical costs ($)
15,000
11,000
7,000
3,000
-1,000
14,241**
12,011**
9,553**
9,526**
11,073**
7,367**
3,185*
3,461
2,714
1,889
379
-639
First year (N=1,089)
Second year (N=588)
Third year (N=381)
* p<0.05
** p<0.01
Year 1
Year 2
Year 3
Year 4
Time from index date
Note: Annual medical costs were compared using paired t-tests with bias-corrected bootstrapping.

Figure:

APPENDIX 2

Incidence and Clinical Progression of Placebo-Treated Amyloid-Negative Subjects with Mild-Moderate Alzheimer's Disease (AD): Results from the Phase 3 PET Sub-studies of bapineuzumab and solanezumab

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Background: Bapineuzumab and solanezumab are anti-amyloid-beta monoclonal antibodies evaluated in Phase 3 trials in mild-moderate AD. A subset of subjects was classified as "amyloid-negative" based on amyloid PET imaging at baseline. To compare the clinical course of amyloid-negative (Aβ-) and -positive subjects (Aβ+) randomized to placebo. **Methods:** Baseline amyloid scans were obtained in PET sub-studies of bapineuzumab (11 C-PiB; 45 APOE ε 4 carriers, 22 non-carriers)and solanezumab (18 F-florbetapir;73 APOE ε 4 carriers, 60 non-carriers) trials. Cortical average standard uptake value ratios (SUVr) were calculated in regions known to accumulate substantial fibrillar amyloid in AD.Subjects were classified as Aβ- or Aβ+ based on predefined study-specific SUVr cutpoints. Subjects were evaluated on cognitive measures at ~3 month intervals for 78 weeks. We compared the change from baseline to 78 weeks between Aβ- and Aβ+ subjects on the ADAS-Cog/11, MMSE, and CDR-SB, co-varying for age and baseline values, in placebo-treated completers, (subjects with a baseline amyloid PET scan who completed at least one of these outcome measures at week 78), in each program. **Results:** In placebo completers,22.4% bapineuzumab subjects and 23.3% solanezumab subjects were Aβ-. The proportion of Aβ- subjects was lower in APOE ε4 carriers than non-carriers (11.1% vs 45.5% for the bapineuzumab studies and 8.2% vs 41.7% for solanezumab) and higher in mild vs moderate dementia subjects (33.3% vs 4.0% for bapineuzumab and 27.5% vs 14.3% for solanezumab). Baseline scores on the ADAS and MMSE tended to be worse for Aβ+ subjects. The LS mean decline over 18 months in Aβ- vs Aβ+ subjects were: ADAS - bapineuzumab 5.7 (2.12) vs 7.4 (1.09) and solanezumab 0.9 (1.48) vs 6.1 (0.80), MMSE - bapineuzumab 0.9 (1.40) vs 3.1 (0.71) and solanezumab -0.1 (0.81) vs 3.9 (0.44), and CDR-SB- bapineuzumab 0.5 (0.79) vs 2.5 (0.41) and solanezumab 0.6 (0.45) vs 2.3 (0.24). **Conclusions:** More than 20% of patients diagnosed with AD based on clinical criteria were amyloid negative in the PET sub-studies of bapineuzumab and solanezumab, with higher proportions of Aβ- among APOE ε4 non-carriers and mild dementia. Aβ- subjects did not demonstrate the same rate of cognitive decline typically observed in AD dementia