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## Health Outcomes Research of Novel Disease Modifying Medications in Alzheimer's Disease and Cost Burden of Early Onset Dementia

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HEALTH OUTCOMES RESEARCH OF NOVEL DISEASE  
MODIFYING MEDICATIONS IN ALZHEIMER'S DISEASE  
AND COST BURDEN OF EARLY ONSET DEMENTIA

BY

RAMI BEIRAM

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE  
REQUIREMENTS FOR THE DEGREE OF  
DOCTOR OF PHILOSOPHY  
IN  
PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2017

DOCTOR OF PHILOSOPHY DISSERTATION

OF

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2017

## **ABSTRACT**

The main etiologies of dementia, a neurodegenerative disease, consist of: Alzheimer's Disease (AD), Vascular Dementia (VD), Frontotemporal Lobar Dementia (FTD), and Lewy Body Dementia (LBD). AD the most common form of dementia is the sixth leading cause of death in the US, where currently 5.3 million Americans are diagnosed with Late-Onset and 95% of cases are 65 years and older. Early-Onset represents the remaining 5% of cases where ages at diagnosis is younger than 65 years. AD is characterized by a progressive loss of neurons with impact on patient cognition, function, and behavior.

The 2015 Alzheimer's Association Report estimated direct and indirect costs of AD and other dementias will reach \$226 billion with an expected five-fold increase to \$1.1 trillion by the year 2050. With no treatment available that stops, or slows down progression of the disease places the cost estimates of AD and dementia among the most expensive chronic diseases.

The next generation of AD medications being investigated will target progression of the disease. Disease-modifying medications (DMMs) are being developed with a mechanism of action directed towards the main hallmarks found in AD patients: the amyloid-beta ( $A\beta$ ) plaques, and the tau tangles. Tolfenamic acid, a non-steroidal anti-inflammatory (NSAID) drug, is being repurposed in the US as a DMM for AD treatment; human clinical trials still pending. Aducanumab, a monoclonal antibody, binds  $A\beta$  and increases its clearance; Phase III human clinical trials are in progress. DMMs are anticipated to improve cognition, function and behavior.

The objectives, hypotheses, methods and results of this dissertation follow the manuscript format, and are three fold:

Manuscript 1: The objective was to estimate cost-effectiveness of novel disease-modifying medication (DMM) compared to standard medication currently used in the treatment of Alzheimer's disease. The hypothesis was that the DMM option will show a favorable cost-effectiveness when compared to standard care. Using a Markov Model with a study population comprised of a hypothetical 1000 patients, 65 years and older, we evaluated quality life years (QALYs) gained by the new DMM and an appropriate price to develop a cost-effectiveness framework for the new product. In the Markov model we were able to determine an increase in QALYs when compared to standard of care with a cost value for DMM much higher than current standard care while still showing cost-effectiveness as a new treatment option.

Manuscript 2: The objective was to determine affordability to payer's budget i.e. insurance or hospital upon the introduction of the new cost-effective disease-modifying medication (DMM) class in treatment of Alzheimer's disease. The hypothesis was that the introduction of DMM will have minimal budgetary changes to direct costs incurred by payers. Using a 1-year budget impact analysis, a prospective short-term analysis was conducted using Optum Clinformatics™ Data Mart (January 2010-December 2012), a large national insurer database with administrative health claims information, with a study population of patients 65 years and older. Two scenarios are to be compared: current mix treatment costs of medications used in Alzheimer's versus a new mix treatment cost that included the addition of DMM to current mix treatment. The difference in total payer cost of the two scenarios

represents the budget impact of the new therapy implementation, allowing us to predicate future cost of new treatment mix. The study estimated a total per-member-per-month (PMPM) treatment cost pre- and post- introduction of DMM that would be affordable to payer's and recommended to be added to formulary.

Manuscript 3: The objective was to describe prevalence, incidence, and direct total cost predictors associated with Early-Onset Dementia (EOD) and its etiologies. The hypothesis was that Alzheimer's disease would be main predictor of overall EOD direct cost. We conducted a retrospective cohort study using Optum Clinformatics™ Data Mart (January 2010-December 2012), a large national insurer database with administrative health claims information, with a study population of patients 21-64 years and older. Total cost components include: physician visits, hospital visits, nursing home care, and prescription drugs associated with EOD treatment. Using a Generalized Linear Model (GLM) to assess the relationships between total cost and the covariates of interest, we identified age, geographical regions, EOD subtypes, and comorbidities as total cost predictors of EOD.

## ACKNOWLEDGMENTS

I would like to show gratitude to several people who have assisted and encouraged me while I was working towards my doctoral degree. First and foremost, I would like to thank my major advisor, Dr. Stephen Kogut for being an extraordinary mentor to me throughout this process. His guidance, advice, and expertise helped me tremendously as I navigated through my research and in writing my dissertation. Dr. Kogut gave me every opportunity to nurture my ideas, and developed as a competent researcher all while providing the necessary guidance and tools for my success.

In addition, I would like to extend my greatest appreciation and gratitude to the rest of my dissertation committee: Dean Paul Larrat, Dr. Natallia Katenka, and Dean Nasser Zawia for their insightful recommendations, comments, constructive criticism, and encouragement. I also want to give a special thank you to Dean Nasser Zawia who was the main influence in my decision to come to the University of Rhode Island and pursue my doctoral degree in the area of Alzheimer's disease.

My appreciation to Dr. Zahratul Mahmud my academic advisor at the UAE Embassy for her advice and help during my time at the University of Rhode Island. Lastly and most important I would like to thank the UAE government headed by His Highness Sheikh Khalifa Bin Zayed Al-Nahyan for being the greatest advocate for many of us Emirati students who pursue our higher education overseas, and providing us with all the necessary financial and emotional support to be successful in our endeavors.

## **PREFACE**

This dissertation is written in the manuscript format, and is comprised of three manuscripts, which evaluated (1) cost-effectiveness of new novel disease-modifying medications in Alzheimer's disease, (2) the affordability to payers of said new novel medications, (3) the direct cost predictors in Early-Onset Dementia.



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## **Manuscript 1**

**Title:** Cost-Effectiveness of Disease-Modifying Medication in Alzheimer's Disease

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**Funding:** Unfunded

**Keywords:** Alzheimer's, disease modifying, cost-effectiveness

**Target Journal:** Alzheimer's & Dementia: The Journal of the Alzheimer's Association

**Format:** Short-form paper

**Publication Status:** Being prepared for publication in Alzheimer's & Dementia: The Journal of the Alzheimer's Association

## **1.1 Abstract**

Our purpose was to estimate the cost-effectiveness of novel disease-modifying medication (DMM) in patients with Alzheimer's disease. A 20 year Markov decision-analysis model was developed using data from previous studies and databases to measure lifetime costs and quality-adjusted life years of DMM compared with current standard of care drug therapy. The modeled population was a hypothetical cohort of 55 year-old patients assigned to the initial Mild Cognitive Impairment (MCI) health state in our Alzheimer's disease model. Health states and progression were defined according to the Clinical Dementia Rating Scale (CDR). Patient movement between the health states was simulated using transition probabilities derived from published sources. The willingness-to-pay threshold was \$100,000/quality-adjusted life-year gained.

In the base case, costs for the proposed DMM were \$22,000 (SD=\$5,000) producing a quality-adjusted life years (QALY) estimate at 8.97 (SD=3.50), while the standard of care treatment yielded 7.24 QALYs (SD=3.38), having an incremental cost effectiveness ratio of \$89,222/QALY. In the Monte Carlo probabilistic sensitivity analysis the DMM option was cost-effective in 92% of the simulations versus 8% of the simulations for the standard of care option.

The cost-effectiveness of novel DMM in Alzheimer's patients will depend on medication pricing and prolonging time spent in the community against early entry to nursing home care.

## **1.2 Introduction**

Alzheimer's disease (AD) affects 5.3 million Americans with 95% of patients being 65 years or older, two-thirds being female, and with early symptoms showing 5 to 10 years prior to official diagnosis.<sup>1-3</sup> The prevalence of AD is projected to increase by 40% in the next 10 years reaching an estimated 14 million patients by the year 2050.<sup>1-3</sup> The incidence of AD increases with age and doubles every 5 years after the age of 65.<sup>1-4</sup> In 2015 a projected 700,000 people aged 65 or older will have AD as cause of death, and although deaths from other major chronic diseases (e.g. HIV) have experienced drastic declines it was reported that between 2000-2012 there was a 68% increase in cause of death attributed to AD.<sup>5,6</sup> The most common cause of death in patients with AD is pneumonia.<sup>5,6</sup>

The 2015 Alzheimer's Association report estimated direct and indirect costs of AD and other dementias will reach \$226 billion with an expected five-fold increase to \$1.1 trillion by the year 2050. These estimates place AD and dementia as one of the most expensive chronic diseases. Current AD medication cost to payers range between \$2500 and \$3500 annually.<sup>7,8</sup>

AD progression is characterized by the accumulation of amyloid-beta ( $A\beta$ ) plaques and tau tangles leading to neuronal death and loss.<sup>9-11</sup> The amyloid precursor protein (APP) is cleaved via enzymes into the  $A\beta$  peptides which then aggregate, deposit into plaques, and initiate the pathology of AD.<sup>9-11</sup> In addition to the  $A\beta$  plaques tau protein is hyperphosphorylated resulting in aggregation and tau tangle formations initiating AD pathology.<sup>12-14</sup> These processes are the leading causes of decline in cognitive function, behavior, and performance of daily activities in patients

with AD.<sup>12-14</sup> The mechanism of action of current AD medications do not target either of the previous mentioned triggers of AD development and progression.<sup>8,15,16</sup>

The next generation of AD medications being investigated will target progression of the disease.<sup>15-17</sup> Disease-modifying medications (DMMs) are being developed with a mechanism of action directed towards the main hallmarks found in AD patients: the amyloid-beta (A $\beta$ ) plaques, and the tau tangles.<sup>15,16</sup> Tolfenamic acid, a non-steroidal anti-inflammatory (NSAID) drug, is being repurposed in the US as a DMM for AD treatment; human clinical trials still pending.<sup>15,16</sup> Monoclonal antibody drug class, e.g. Aducanumab along with other anti-A $\beta$  trial drugs, target A $\beta$  and increases its clearance; Phase III human clinical trials are in progress for some of these new drug therapies.<sup>17-19</sup> Majority of these new therapies will be targeting the early mild stages of AD, anticipating improvement in cognition, function and behavior.<sup>17-19</sup> Early detection of AD and providing DMM therapy has potential of limiting AD progression, spending more time in the earlier less severe and costly stages of disease and increasing time in the community.<sup>20,21</sup>

Predicting the efficacy of novel DMM for AD will exceed current treatment options, certainly these medications will be priced at a premium. We assessed the value of DMM by conducting a cost-effectiveness analysis. We used Markov modeling to simulate the anticipated states of disease progression, and model patients with AD transitioning through the different health states predicting clinical outcome and cost of DMM therapy.

### **1.3 Methods**

This study design was a Markov model utilizing published clinical data and



registry databases as primary data source for: cost, utility values, transition probabilities, and medication efficacy converted to relative risk reduction.

The study population was comprised of a hypothetical cohort of patients, 55 years-old, assigned to the initial Mild Cognitive Impairment (MCI) health state of the Markov model. Patient movement between the health states was simulated using transition probabilities reflecting rates of clinical progression, assigning cost to each health state..<sup>20-23</sup> (Figure 2)

The study's model was built on a set of specific health states in which a patient transitioned through while occupying only one health state at any given time.<sup>24-26</sup> The model investigated the transitions through several time specified cycles where patients entered, stayed, or exited the health state; each health state cycle lasting for 1 year and over a 20 year life span of the entire model.<sup>24-26</sup> Transition probabilities determined the movement among the health states between the two arms of our model, DMM vs Standard of Care, as informed by observed rates of disease progression for patients treated with currently available medications, as determined in clinical and epidemiologic research.<sup>24-26</sup> Costs and utility values were assigned to each health state, calculated at each cycle, and then aggregated to estimate cost-effectiveness of each option. Incremental Cost-Effectiveness Ratios (ICERs) for both the DMM and Standard of Care were used for comparison. The DMM arm of the model represents any of the current novel proposed DMMs that are in clinical trials, while our Standard of Care arm represents the available Alzheimer's medication therapy available, currently marketed in the U.S.<sup>27,28</sup> e.g. Donepezil and Memantine.

As defined by the National Institute on Aging, of the US Department of Health

and Human Services, characterizations of AD progression; our model uses five distinctive health states: MCI, mild AD, moderate AD, severe AD, and death.<sup>20-22,29</sup> All five health states were defined using the Clinical Dementia Rating (CDR) Scale.<sup>20,21,29</sup> The CDR Scale is a universal measure for patient cognitive function determined by assigning scores to questions covering six fields: memory, orientation, judgement & problem solving, home & hobbies, community affairs, and personal care.<sup>30</sup> CDR scores range from a minimum of 0 to a maximum of 3, and are categorized in our study as follows: 0.5 (MCI) 1 (mild AD), 2 (moderate AD), and 3 (severe AD).<sup>22,30-32</sup> Scores were calculated from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) database, and used in prior studies.<sup>30,31</sup> The transition probabilities, utility values, and cost analysis studies, from which we extracted our input parameters, used CDR as their scale to define the AD health states.<sup>22,31-33</sup>

The model began with a hypothetical 1000 patient population distribution assigned to the initial MCI health state and simulates patient movement through the progressive states using transition probabilities.<sup>20-22,34</sup> The transition probabilities defined the rate of progression through the health states; for example a patient in moderate AD can remain in that same state, move to severe state, or enter the absorbing state of death which they do not exit.<sup>20-22,34</sup> No movement backwards to a less severe state was permitted.

The simulated patient cohort was assigned transition probabilities based on therapy received: DMM or Standard of Care. Completion of each individual cycle produced an estimated cost and quality-adjusted life years (QALY) gained, for treatment comparisons. The measure effect was in incremental cost/QALY gained,

assessing the influence of DMM treatment on AD progression as compared to Standard of Care.

Model parameter inputs included: costs (medications, outpatient visits, inpatient stays, and long-term facility e.g. nursing home); utility values used for quality-adjusted life years (QALY) gained calculation, transition probabilities, and relative risk (RR) representing DMM treatment effect. With most of the DMM under consideration still undergoing clinical trials we made a RR assumption value of 0.5, predicting that DMM will be at least as effective as Donepezil where the RR of transitioning from mild to moderate AD was 50% less in treatment group when compared to placebo group.<sup>35</sup> We assumed that DMM will in fact impact progression of the disease unlike current treatments available.<sup>17,36</sup> The RR value was applied to produce new transition probabilities, in the DMM arm of the model, to simulate the impact of new therapy. From the previous unsuccessful DMM monoclonal antibody clinical trials, and the current ongoing trials the population target is those in the early stages of Alzheimer's that will benefit most from DMM therapy i.e. MCI or mild Alzheimer's patients<sup>17-19,36</sup>. We applied the RR to transition probabilities, in DMM arm, to health states of MCI and Mild AD, reducing transition probabilities from the earlier states to the more severe states. Published literature was primary source for: cost, utility values, transition probabilities, and RR. Micromedex Redbook database was the source of price for Standard of Care medications, using Average Wholesale Price (AWP) as our benchmark. (Table 1)

To predict DMM future market cost we considered Multiple Sclerosis (MS)-a neurodegenerative illness which uses disease-modifying medication type therapies.

The price of new therapies in MS, which are mainly of the monoclonal drug class, are usually 5 times higher than current medication treatments.<sup>37</sup> Average cost of monoclonal antibodies currently on the market, in other disease states, were also considered to aid in the assumption as to the cost of these proposed new therapies in AD. Using this rationale the study assumed a cost of \$22,000 per year, included in which was cost of physician visit where administration of medication would occur. Descriptive statistics were presented for AD costs, while the simulation following patient movements between the health states calculates expected costs and quality-adjusted life years (QALY) gained. This was carried out for each specific health state at each cycle the model goes through producing an incremental cost per QALY for each state, weighted by the proportion of patients in the health state before totaling across all cycles.<sup>38-40</sup> The process described uses a Monte Carlo Simulation. The Monte Carlo simulation allows the above mentioned process to be repeated 1000 times through the time horizon of the entire model.<sup>38-40</sup> The incremental cost/QALY produced was compared to the Willingness-to-Pay/QALY (\$100,000 per QALY) to determine cost-effectiveness of DMM treatment.<sup>38-41</sup>

Probabilistic sensitivity analysis (PSA) was used to reflect input parameters' uncertainty.<sup>38,42,43</sup> Input parameters' distributions were assigned as follows: beta distribution for utilities, gamma distribution for DMM cost, and log-normal applied to the Relative Risk and transition probabilities.<sup>40,42</sup>

PSA in the Monte Carlo simulation chose a random value from each of the input parameters from the specified distribution assigned for each model iteration.<sup>40,42</sup> Each single model run generated a single incremental cost-effectiveness ratio (ICER)

value, and with repeating the process 1000 times produced a distribution of ICERs. The resulting ICERs with confidence intervals was plotted on a cost-effectiveness plane graph. Given the time value of costs and QALYs, a dollar and QALY is worth more today than it would be tomorrow, a standard discount rate of 3% to present value of future costs and QALYs was incorporated.<sup>40,42</sup> Model building and all statistical analysis were performed using TreeAge Software, Inc. version Pro 2016 (Williamston, MA).

#### **1.4 Results**

Diagram representation of the Markov model (Figure 2) illustrates that all patients start at 55 years-old with Mild Cognitive Impairment (MCI). Patients' cycle between health states until death occurs or the 20-year model time horizon was reached. The length of each cycle was 1 year. Illustrated in the diagram was the decision node (square), chance nodes (circles) directed by transition probabilities, Markov nodes (circle with 'M'), and terminal nodes (triangles). Markov branch for the standard of care (SC) therapy was identical to the disease-modifying medication (DMM) branch shown.

In the base case (Table 2), quality-adjusted life expectancy (QALY) for our disease-modifying medication (DMM) was 8.98 (SD=3.32) versus the standard of care (SC) 7.41 (SD=3.28). When compared to SC, DMM produced an additional 1.57 QALY at a cost of \$154,852, estimating an incremental cost-effectiveness ratio (ICER) of \$89,222 per QALY, and below our established willingness-to-pay (WTP) threshold of \$100,000 per QALY.

One-way sensitivity analyses were conducted for our model parameters to

determine the variables with most impact on our results. Key input parameters were varied one input at a time while holding other constant at their base-estimates.

Sensitivity analyses was conducted on costs, probabilities, and utilities.

A tornado diagram (Figure 6) illustrating the cost variables in descending order of influence was developed. The horizontal bars in the diagram represent net monetary benefit values expected from the range of values evaluated for each of our influential model parameters. The vertical black line on the bars represents a change in the DMM arm when the variable starts producing net monetary benefit. Parameters with most impact on the model were costs: price of the DMM therapy; probabilities: transition probability from Mild Cognitive Impairment (MCI) to Mild AD; utilities: utility value for MCI, and the relative risk reduction (RR) parameter.

The Monte Carlo Probabilistic Sensitivity Analysis (PSA) incorporated both intra-individual and parameter uncertainty respectively produced results presented in Table 2. Using the WTP of \$100,000 our DMM produced an ICER of \$89,812/QALY with 92% of the iterations showing cost-effectiveness when compared to 8% in SC. (Figure 4). The cost-effectiveness acceptability (CEA) curve also illustrates the probability that DMM therapy will be cost-effective at varying WTP thresholds for a patient (Figure 5).

Table 3 presents the sensitivity analyses for the ICERs associated when varying parameter assumptions. When DMM cost was considered we estimated an ICER of \$53,627/QALY and \$128,549/QALY for 10% decrease and 10% increase in the price of the drug therapy, respectively. The results shown in other parameters were sensitive to varying the assumptions of their values. Varying the probability of disease

progression (MCI to Mild AD) estimated ICERs of \$76,695/QALY and \$106,645/QALY for 10% decrease and 10% increase, respectively. Utility weight for MCI had ICERs of \$105,651/QALY and \$81,284/QALY for 10% decrease and 10% increase, respectively.

### **1.5 Discussion**

Our study demonstrated that a disease-modifying medication (DMM) delaying the cognitive decline, increasing time spent in the less severe and costly health states of Alzheimer's disease (AD) can possibly be cost-effective when compared to current medication therapies. This study can provide a framework or working design that estimates the assumed and possible effect of these newly proposed novel DMM that are currently in clinical trial pipelines. The study used published data to build the decision, but with deficiencies in direct evidence on DMM effects or possible costs associated with the new therapy. Currently there are several anti-amyloid beta monoclonal antibodies in the pipeline of companies, with some of the more recent trials reaching Phase III but unfortunately not being able to show progress.<sup>17-19,36,44</sup> Aducanumab, a monoclonal antibody, is currently the most promising of the pipeline products showing credible progress in Phase III trials in the early less severe AD health states<sup>18,19</sup> i.e. MCI and Mild AD. Given that no such DMM is on the market yet we had to make an assumption of expected price, using sensitivity analysis to determine with all our input parameters and WTP level that a price as high as \$23,189 per year will maintain cost-effectiveness favorability of new therapy. In similar manner, we estimated that a relative risk reduction of 0.546 would maintain cost-effectiveness for new therapy. Despite these uncertainties our model framework can

still provide hypothetical information on what to expect from DMM, and the model inputs can be updated once more of the clinical trial results become available and published. Additional uncertainty highlighted in our model were the direct cost inputs of the various health states of AD i.e. mild or moderate, community or nursing home. Rice et al. 1994 was one of the very few studies available that broke down the costs of AD by level of severity in a population in North California. Similarly, two review studies by Mauskopf et al. (2010 and 2011), estimating the cost of AD in the U.S. as well as the association of cost with disease severity provided a source of cost information for our model to make up for the lack of current cost studies in AD.<sup>45,46</sup> The use of a claims database of a U.S. population might provide a solution and useful information in AD cost studies, but patients are not diagnosed based on disease severity and are usually recorded as AD and not as mild AD or moderate AD. The severity of disease states might be recorded in the medical record as notes but not captured in a database. Hence, a study similar to the Rice et al. 1994 study that categorizes patients by disease severity in a healthcare setting and follows them as they progress to capture their costs would be ideal way to capture more definite and specific costs.

An aspect of our study to consider is that using DMM patients are expected to spend more time in the less severe states spending more time in the community setting, and if considering a societal perspective then we would predict a delay in nursing home placement and its cost but at the expense of increased unpaid family caregivers to aid with the patients.<sup>22</sup> Our model focuses primarily of direct cost of care, when the biggest factor contributing to the rising cost of AD are the indirect costs; costs



associated with unpaid family caregivers, loss of productivity associated with both patients and caregivers.<sup>22,45</sup> When considering our study using a payer e.g. Insurance perspective we should be cautious when trying to generalize it to an insurer or a managed care plan. Given the uncertainty in relative risk reduction proposed for these DMM still in clinical trials, the utility values based on current AD status which we would expect to change with the slowing down of cognitive decline, and the cost information based on several older studies we are restrained when interpreting our results.

### **1.6 Limitations**

This study provides a look into complexity of trying to model a chronic condition such as AD. All the assumptions, inputs, and sensitivity analysis are to be considered carefully given the lack of current DMM efficacy, cost, or impact on utility values. Our basic assumption was that DMM will work particularly well in the early less severe stages of AD, despite the several setbacks in clinical trials during the past years but with still compounds being developed in the pipeline. The direct costs our study used are dependent on the U.S. health system and might not be generalizable to other countries given the wide range of different health insurance systems available. The utility values (QALYs) were not validated in any trial using DMM so we have no information on how the DMM will affect utility values or how they will change as disease progresses. Side effects and their costs are usually part of cost-effectiveness calculations, however with DMM still in clinical trial phases we yet to have access to such information and being a simulation no such information was added to our model.

## **1.7 Conclusion**

Our model results, using available data, showed that future disease-modifying medications in Alzheimer's disease may be cost-effective when adopting a willingness-to-pay of \$100,000, and adding additional quality-of life year gained to patients. We conclude that at cost of \$23,000 or less and relative risk reduction of 0.546 or more disease-modifying medications would be cost-effective. Considering current evidence and developments of these medications and other interventions, we can update and re-evaluate the cost-effectiveness studies for Alzheimer's disease in the future.

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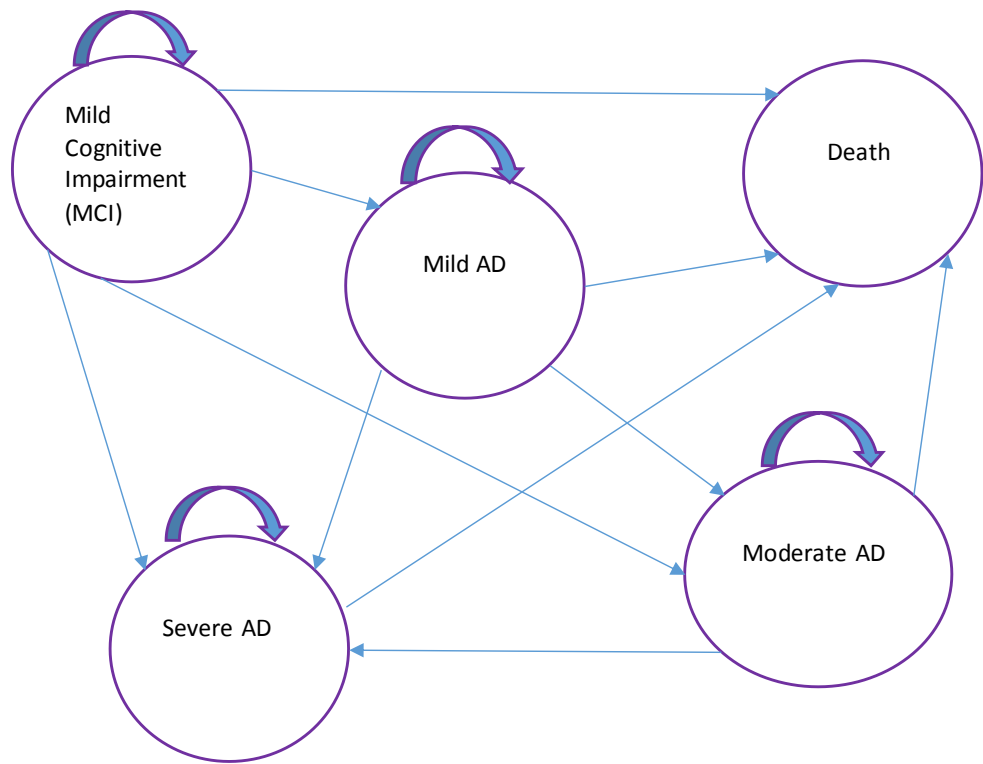
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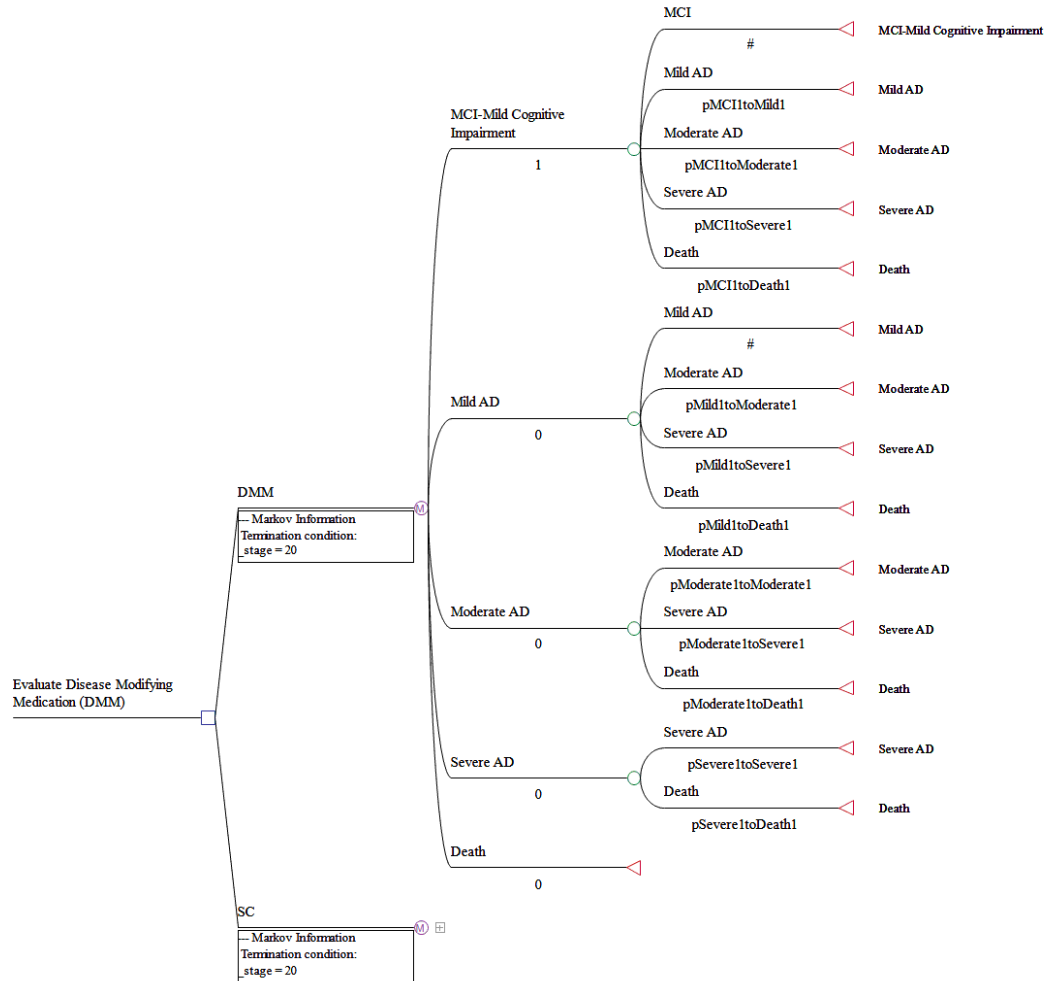
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**Figure 1. Model Framework**



**Figure 2. Schematic representation of the Markov model framework of Disease-Modifying Medication (DMM). Patients cycle between health states until death occurs or 20-year model-time horizon is achieved. Decision node (square), chance nodes (circles) directed by transition probabilities, Markov nodes (circle with “M”), and terminal nodes. Standard of Care (SC) branch is identical to DMM branch**



**Table 1. Projected Costs, Quality Adjusted Life Years (QALYs), and Incremental Cost Effectiveness Ratios (ICERs) comparing Disease-Modifying Medication (DMM) Therapy with current Standard of Care (SC) Therapy**

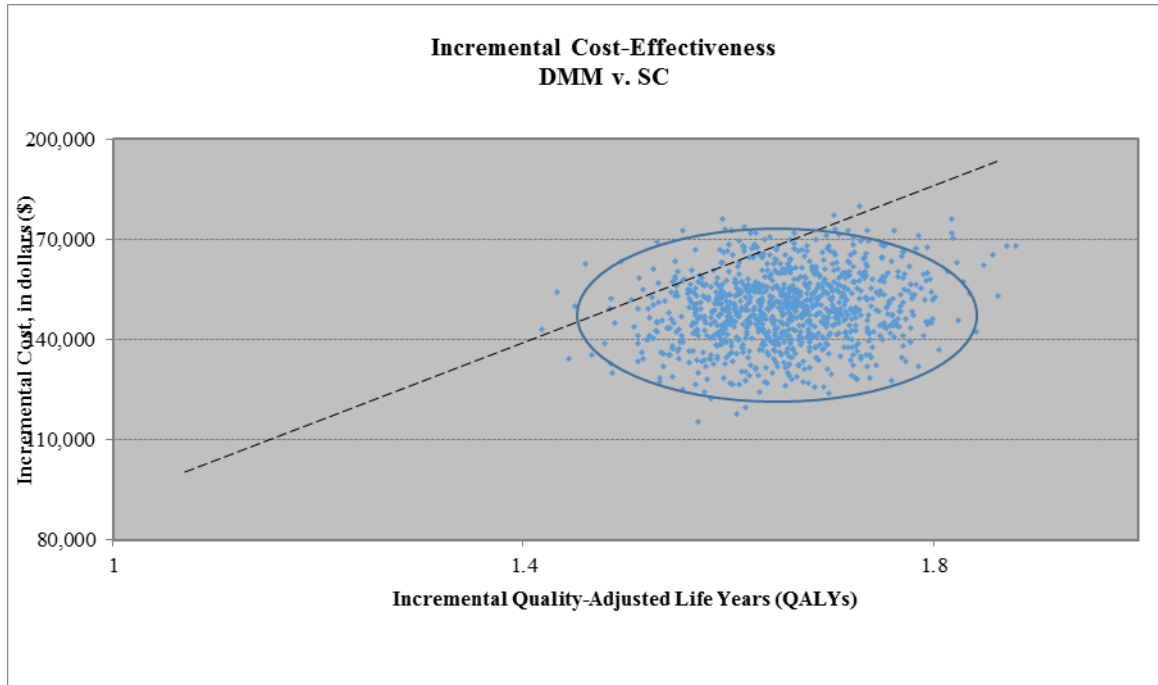
	<b>Base Case</b>		
	<b>Total Cost (SD)</b>	<b>QALY (SD)</b>	<b>ICER</b>
Standard of Care (SC)	\$446,918 (\$317,108)	7.24 (3.38)	...*
Disease-Modifying Medication (DMM)	\$601,770 (\$446,917)	8.97 (3.5)	\$89,222/QALY
	<b>Probabilistic Sensitivity Analysis (PSA)</b>		
	<b>Total Cost (SD)</b>	<b>QALY (SD)</b>	<b>ICER</b>
Standard of Care (SC)	\$447,817 (\$9,792)	7.46 (0.68)	...*
Disease-Modifying Medication (DMM)	\$596,616 (\$10,902)	9.11 (0.98)	\$89,812/QALY

ICER indicates incremental cost-effectiveness ratio;  
 QALY, quality-adjusted life year; SD, standard deviation  
 \*SC is the reference therapy for ICER calculation

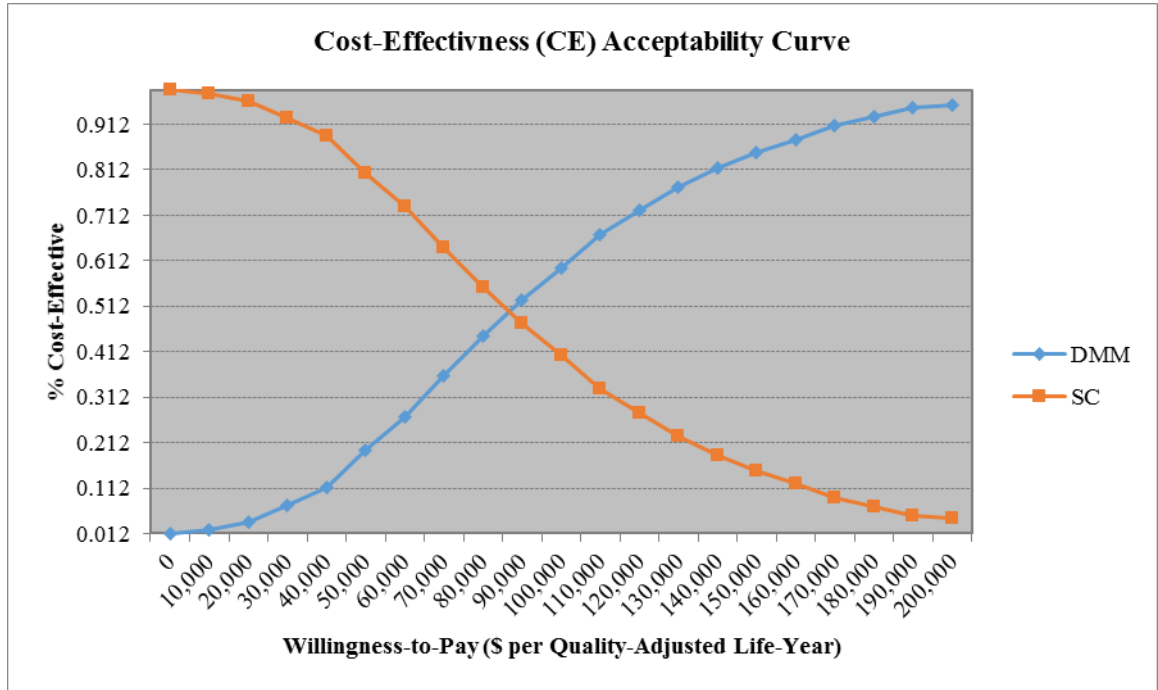
**Figure 3. Scatterplot of Disease-Modifying Medication (DMM) and the Standard of Care (SC). Illustrates the Total Cost (y-axis) and Total Quality-Adjusted Life Year (QALY) gained (x-axis) during the time-horizon of the model. DMM (purple) shows higher QALYs gained at higher Total Cost when compared to SC (green)**



**Figure 4. Scatterplot of Disease-Modifying Medication (DMM) versus Standard of Care (SC). Showing that with a Willingness-to-Pay (WTP) of \$100,000 (represented by dash line ---) per Quality-Adjusted Life Year (QALY), 92% of model iterations are below the WTP threshold and favoring the DMM Therapy arm of the Markov model and estimating an additional 1.5 to 1.82 QALY through the time-horizon of the model**



**Figure 5. Cost-Effectiveness (CE) Acceptability Curve Represents Probability that a Treatment will be CE (percentage iterations (y-axis) for which treatment was CE) at varying Willingness-to-Pay Thresholds (x-axis). The amount, in dollars, payer willing to pay to pay to achieve an additional quality-adjusted life year**



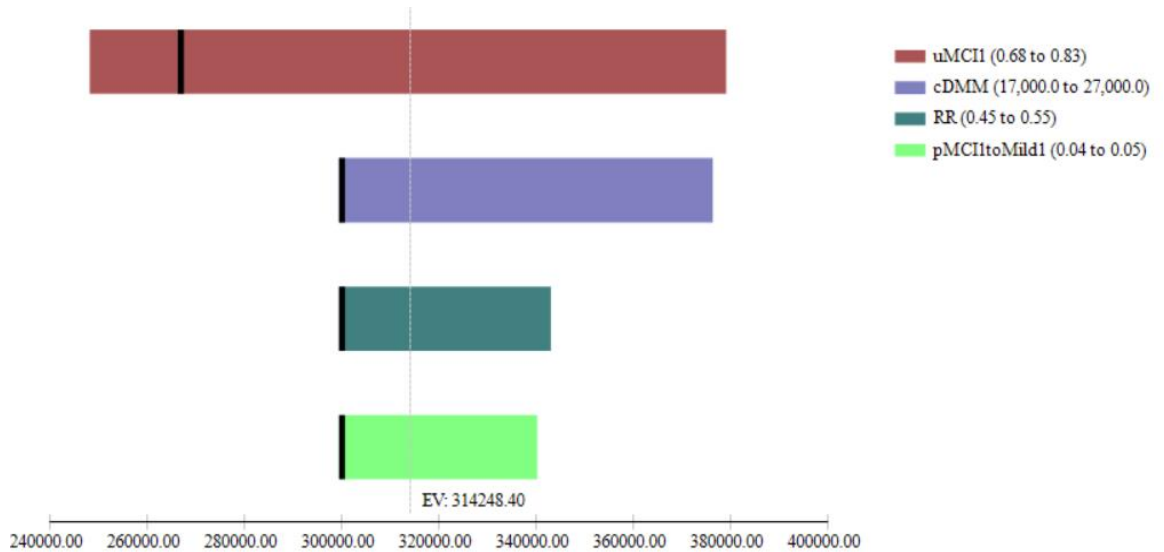
DMM – Disease-Modifying Medication (blue)  
 SC – Standard of Care (orange)



**Table 2. Sensitivity Analyses**

	Incremental Cost Effectiveness Ratio (ICER, \$)
Parameters	
Base Case	\$89,222
Relative Risk Reduction (Drug Effect)	
10 % Higher	\$87,977
10 % Lower	\$107,455
DMM cost (Drug Cost)	
10% Higher	\$53,627
10% Lower	\$128,549
Utility Weight (QALY for MCI)	
10% Higher	\$81,284
10% Lower	\$105,651
Probability of Disease Progression (MCI to Mild AD)	
10% Higher	\$106,645
10% Lower	\$76,695

**Figure 6. Tornado Diagram Represents Net Monetary Benefit (NMB) Values Expected from a Range of Values Evaluated for each Variable with Impact on the model. The Vertical black line represents the NMB Value that occurs where change to our preferred treatment i.e. Disease-Modifying Medication happens for the given variable**



uMCI – Utility Value Mild Cognitive Impairment (MCI)  
 cDMM – Cost of Disease-Modifying Medication (DMM)  
 RR – Relative Risk (RR) for DMM  
 pMCI1toMild1 – Transition Probability of Disease from Mild Cognitive Impairment (MCI) to Mild Alzheimer’s

**APPENDIX A. Decision Model Inputs: probabilities, costs, and utilities for both Arms of the Markov Model; Standard of Care (SC) and Disease-Modifying Medication (DMM)**

Standard of Care (SC)		
Item	Estimate	Data Source
Annual Transition Probabilities		
Stage to Stage		
MCI to MCI	0.88	33, 50
MCI to Mild	0.088	33, 50
MCI to Moderate	0.01	33, 50
MCI to Severe	0.008	33, 50
MCI to Death	0.014	33, 50
Mild to Mild	0.79	33, 50
Mild to Moderate	0.141	33, 50
Mild to Severe	0.023	33, 50
Mild to Death	0.046	33, 50
Moderate to Moderate	0.777	33, 50
Moderate to Severe	0.083	33, 50
Moderate to Death	0.14	33, 50
Severe to Severe	0.782	33, 50
Severe to Death	0.218	33, 50
*Costs, \$		
By Stage and Setting		
MCI:		
Community	\$8,000	22, 45, 49
Nursing Home	Not Reported	
Mild:		
Community	\$11,000	22, 45, 49
Nursing Home	\$67,000	22, 45, 49
Moderate:		
Community	\$14,000	22, 45, 49
Nursing Home	\$73,000	22, 45, 49
Severe:		
Community	\$23,000	22, 45, 49
Nursing Home	\$78,000	22, 45, 49
Other Costs		
Medications:		
Donepezil	\$3,000	AWP
Memantine	\$2,000	AWP
Quality-of-Life Weights (Utility)		
By Stage		
MCI	0.76	47, 48

Mild	0.69	47, 48
Moderate	0.53	47, 48
Severe	0.38	47, 48
Disease-Modifying Medication (DMM)		
Item	Estimate	Data Source
Annual Transition Probabilities		
Stage to Stage		
MCI to MCI	0.933	Author Calculations†
MCI to Mild	0.044	Author Calculations†
MCI to Moderate	0.005	Author Calculations†
MCI to Severe	0.004	Author Calculations†
MCI to Death	0.014	
Mild to Mild	0.872	Author Calculations†
Mild to Moderate	0.0705	Author Calculations†
Mild to Severe	0.0115	Author Calculations†
Mild to Death	0.046	33, 50
Moderate to Moderate	0.777	33, 50
Moderate to Severe	0.083	33, 50
Moderate to Death	0.14	33, 50
Severe to Severe	0.782	33, 50
Severe to Death	0.218	33, 50
*Costs		
By Stage and Setting		
MCI:		
Community	\$8,000	22, 45, 49
Nursing Home	Not Reported	
Mild:		
Community	\$11,000	22, 45, 49
Nursing Home	\$67,000	22, 45, 49
Moderate:		
Community	\$73,000	22, 45, 49
Nursing Home		
Severe:		
Community	\$23,000	22, 45, 49
Nursing Home	\$78,000	22, 45, 49
Other Costs		

Medications:		
Donepezil	\$3,000	AWP
Memantine	\$2,000	AWP
Disease-Modifying Medication (DMM)	\$22,000	Author Assumptions‡
Quality-of-Life Weights (Utility)		
By Stage		
MCI	0.76	47, 48
Mild	0.69	47, 48
Moderate	0.53	47, 48
Severe	0.38	47, 48
Effect of Disease-Modifying Medication		
MCI-to-Mild Transition	0.5	Author Assumptions‡
MCI-to-Moderate Transition	0.5	Author Assumptions‡
MCI-to-Severe Transition	0.5	Author Assumptions‡
Mild-to-Moderate Transition	0.5	Author Assumptions‡
Mild-to-Severe Transition	0.5	Author Assumptions‡

\* Costs were inflated and rounded up to estimate 2016 dollar values  
 AWP- Average Whole Sale Price. Using Micromedex Red Book  
 † Author Calculations using an assumed relative risk reduction of 0.5  
 ‡ Author Assumption using current treatment effectiveness, costs, and proposed medications undergoing clinical trials

## **Manuscript 2**

**Title:** Alzheimer's Disease: Budget Impact Analysis for Novel Disease-Modifying Medication

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**Funding:** Unfunded

**Keywords:** Alzheimer's, disease modifying, budget impact

**Target Journal:** Value In Health: The Journal of the International Society of Pharmacoeconomics & Outcomes Research

**Format:** Short-form paper

**Publication Status:** Being prepared for publication for Value In Health: The Journal of the International Society of Pharmacoeconomics & Outcomes Research

## **2.1 Abstract**

A new therapeutic class of disease-modifying medications (DMM) are now being developed for the management of Alzheimer's disease (AD). The objective of our study was to estimate the future financial consequences on a U.S. health care plan, having a population size of 2.6 million, after the introduction of proposed novel DMM. A 1- year budget impact model, estimating percentage of patients on current AD medications and quantities filled were measured using the 2010-2012 Optum Clinformatics™ Data Mart; a large national insurer database with administrative health claims information from a private health plan in the U.S. We identified 436 patients with an AD diagnosis, and having filled specific AD medications during the 2012 study period. Total budget costs of before and after the introduction of the proposed DMM were estimated in addition to the incremental changes in the per-member-per-month (PMPM) cost. Sensitivity analyses were performed to evaluate the impact of varying percentage of patients receiving AD medications, the price of new proposed medication, percentage of patients switching from current therapy to new medications, percentage of patients adding the new medication to their current therapy, and percentage of new cases utilizing the new medication therapy. The expected annual medication budgetary cost for AD medication utilization including the DMM was \$5,040,748 compared to \$1,004,954 cost prior to the including DMM, representing a 5-fold increase. The total incremental medication cost was \$0.1616 PMPM, an increase from the \$0.0322 PMPM cost before the DMM was introduced. Using administrative claims database to estimate AD medication cost and utilization, the introduction of novel DMM therapy will have a substantial effect on both the total

and PMPM cost for AD medication budget. Given the importance of affordability of new treatments to decision and policy-makers greater attention and planning needs to be afforded to the expected sizable change predicted to occur with introduction of new novel DMM therapy.

## **2.2 Introduction**

Currently there is no cure for Alzheimer's disease (AD), guidelines by both the American College of Physicians and the American Academy of Family Physicians divide treatment for AD into 2 medication categories<sup>1,2</sup>: Acetylcholinesterase Inhibitors (AChEIs) e.g. Donepezil and N-methyl-D-aspartate (NMDA) e.g. Memantine. The AChEIs prevent the breakdown of acetylcholine, a neurotransmitter required for neuronal function, and help increase levels of the declining neurotransmitter due to neuronal loss.<sup>1-3</sup> The NMDAs reduce levels of glutamate receptor activation and decrease neuronal dysfunction.<sup>1-3</sup> The use of these therapeutic agents as monotherapies or in combination during various stages of AD improve cognition and daily functioning scale score slightly, but do not slow down progression, decline in cognition, or cure AD.<sup>3-5</sup>

AD progression is characterized by the accumulation of amyloid-beta ( $A\beta$ ) plaques and tau tangles leading to neuronal death and loss.<sup>6,7</sup> These hallmarks,  $A\beta$  and tau tangles, are the targets of new investigational disease-modifying medication (DMM), currently undergoing clinical trials, trying to slow AD progression and reduce cognitive decline.<sup>4,5,8,9</sup> Monoclonal antibody drug class, e.g. Aducanumab along with other anti- $A\beta$  trial drugs, target  $A\beta$  and increases its clearance; Phase III human clinical trials are in progress for several of these new drug therapies.<sup>5,9,10</sup> Majority of



these new therapies will be targeting the early mild stages of AD, anticipating improvement in cognition, function and behavior.<sup>5,9,10</sup> With the efficacy of proposed DMM monoclonal anti-body therapy expected to target the underlining causes of AD, these DMM are expected to be priced at a premium. Current AD medications, AChEIs and NMDAs, cost to payers range between \$2500 and above \$3500 annually. With limited resources, decision makers have to determine the future budgetary impact with the addition of new therapies, and judge competing treatments on both clinical and cost effectiveness.

### **2.3 Methods**

This study design was a 1-year retrospective before and after budget impact analysis used to estimate the medication treatment cost of Alzheimer's disease (AD) before and after the introduction of a proposed disease-modifying medication (DMM). Pharmacy claims data from Optum Clinformatics™ Data Mart served as the primary data source for estimates of cost and utilization for current AD medications. Optum Clinformatics Datamart™, a large national insurer database with administrative health claims information for approximately 19 million patients, collected from January 2010 to December 2012.

The study population was comprised of continuously enrolled patients, from 2010 to 2012, who were 55 years and older with AD diagnosis and had an AD specific medication prescription e.g. AChEIs or NMDAs filled during the 2012 year.

Population selection was as follows: all continuously enrolled patients who were at risk (55 years and older<sup>4,5</sup>), with a diagnosis of AD in accordance with the International Classification of Disease 9<sup>th</sup> Edition Clinical Modification [ICD-9-CM]

medical codes (AD ICD-9-CM code 331.0). Relevant codes were reviewed and selected from the Agency for Healthcare Research and Quality (AHRQ), using the Clinical Classification Software (CCS) from the Healthcare Cost and Utilization Project (HCUP). The Clinical Classification Software (CCS) for ICD-9-CM is a tool on the HCUP website, sponsored by AHRQ, which provides over 14,000 diagnosis codes and 3,900 procedure codes. AD patients who were enrolled during 2012 and met the age criterion of 55 years and older, and had AD specific medications filled during the 2012 year made up our cohort used for analysis.

AD specific medications considered were AChEIs: Aricept (donepezil), Exelon (galantamine), Razadyne (rivastigmine), and NMDAs: Memantine. During 2012 Namenda was only available as brand with the generic (memantine) not entering the market until 2014, and the new Namzaric (donepezil/memantine) not available until 2016. Namenda XR also did not become available till 2014. We expect the price of Namenda XR and Namzaric to be comparable to Namenda. The medications collected from our database captured all formulations and dosage strengths that were prescribed. The current or before addition of DMM mix (2012) of medications were categorized as; AChEIs monotherapy, NMDA monotherapy, or AChEIs plus NMDA dual therapy and the same categorization was completed for the new or after addition of DMM mix.<sup>1,3</sup>

Two scenarios were compared: current mix treatment costs consisted of medication costs before DMM available on market, and the new mix treatment after following DMM introduction to the market. (Figure 1)

Current treatment mix costs was based on the 2014 prices of our Optum

Clinformatics™ Data Mart databases as our baseline. The costs for each of our medication categories (AChEIs, NMDA, and AChEI+NMDA) represented amount charged to the insurer, minus patient coinsurance, copay or patient out of pocket payments towards their deductible. Current mix included: total number of prescriptions for each medication category, the number of patients utilizing the prescriptions, and an estimate mean cost of per prescription along with per patient prescription utilization mean for each of our medication category was determined.

New treatment mix was developed using 3 assumptions: 2% of newly diagnosed AD patients measured as coming into the health plan at the start of the year, 20% of patients on current treatment category (AChEIs, NMDA, and AChEI+NMDA) will switch to the new DMM therapy, and 10% of patients on current treatment category (AChEIs, NMDA, AChEI+NMDA) will add the new DMM therapy to their current mix. Patients with Cardiac arrhythmias were contraindicated to start, switch, or add new DMM monoclonal antibody therapy per the clinical trial results conducted on these newer medications.<sup>4,10</sup> Patients who switched have their prescriptions and its costs subtracted from the new mix total cost and prescription count, replaced with the DMM cost and prescription count. Data from current and previous clinical trials on proposed monoclonal anti-body DMM therapy proposed a one-time infusion of the medication every 4 weeks.<sup>4,5,10</sup> Current AD medications, AChEIs and NMDAs, cost to payers range between \$2500 and above \$3500 annually.<sup>3,11</sup> To predict DMM future market cost we considered Multiple Sclerosis (MS)-a neurodegenerative illness which uses disease-modifying medication type therapies. The price of new therapies in MS, which are mainly of the monoclonal drug class, are usually 5 times higher than current

medication treatments.<sup>12</sup> Average cost of monoclonal antibodies currently on the market, in other disease states, were also considered to aid in the assumption as to the cost of these proposed new therapies in AD. Using this rationale the study assumed a cost of \$24,000/year or \$2,000 for a monthly prescription. We can assume a single prescription a month for 12-months of the new DMM therapy to determine the annual total cost with a per prescription cost of \$2,000 that was previously assumed.

New treatment mix costs, after DMM introduction include: the cost of the newly diagnosed patients entering the health plan with no current therapy starting DMM, cost of current mix that was not lost to patients switching, and cost of patients that added the new therapy to their current medications. (Figure 1) The difference in total payer cost of the two scenarios (current mix minus new mix) represents the budget impact of DMM therapy implementation.<sup>13,14</sup> (Figure 1) In addition the study estimated the total per-member-per-month (PMPM) AD treatment cost before and after introduction of DMM therapy, determined by dividing the total cost by the population at risk eligible to receive DMM and dividing result by 12 months<sup>13,14</sup>.

One-way sensitivity analyses were used to evaluate the impact of varying parameters on total cost and the PMPM value. In our model the following parameters were varied: percentage of AD patients on AD specific medications, price of DMM therapy, percentage of new cases utilizing DMM, percentage of patients switching from current therapy to DMM, and percentage of patients adding DMM to their current therapy. Each parameter was varied from the default value by  $\pm 50\%$  for each of our parameters to estimate the lowest total cost and PMPM, and the highest total cost and PMPM compared to the base-case assumptions. The model was built, and

calculations estimated using Microsoft Excel.

## **2.4 Results**

The total population at risk for Alzheimer's disease (AD), in the Optum Clinformatics™ Data Mart database, was approximately 2.6 million individuals (55 years and older). Among them we found 2,203 that had an AD diagnosis and enrolled between the 2010-2012 years. Among those individuals a total of 436 patients (20%) had AD specific medications filled e.g. Donepezil or Memantine filled during 2012. Measuring utilization of AD medications (Table 1) and categorizing them by drug class Acetylcholinesterase Inhibitors (AChEIs): Donepezil (Aricept), Galantamine (Exelon), Rivastigmine (Razadyne),, and N-Methyl-D-Aspartate (NMDA): Memantine (Namenda); patients received a total 5,088 prescriptions (Rx) of AD medications. Among those prescriptions 1,526 (30%) Rx in 144 patients were for AChEIs monotherapy with an average of 10.6 Rx filled per patient, 585 (11.5%) in 44 patients were for NMDA monotherapy with an average of 13.3 Rx filled per patient, 2,976 (58.5%) in 248 patients were for dual therapy of AChEIs plus NMDA with an average of 12 Rx filled per patient. Mean costs per Rx for each of the drug class categories are presented in Table 1: \$147 per Rx filled in AChEIs monotherapy, \$271 per Rx filled in NMDA monotherapy, and \$209 per Rx filled in dual therapy of AChEIs plus NMDA. Total cost of prescriptions among the various drug classes was as follows: AChEIs monotherapy \$224,380, NMDA monotherapy \$158,589, and dual therapy AChEIs plus NMDA \$621,984 (Table 2)

After introduction of DMM (Table 1), 44 (2%) of our AD cohort (2,203) were

considered newly diagnosed in health plan annually during the 2010-2012 years. The study assumed switching of patients from current medication treatment to DMM as well as adding DMM to current treatment; yielding an additional 88 (20%) patients who switched and 45 (10%) that added DMM and bringing total amount of patients receiving DMM therapy to 177. With each DMM patient receiving 1 Rx per month the number of prescriptions added to the new treatment mix were 2,122 prescriptions, and increasing total number of prescriptions to 6,159 ( 21% increase) after the addition of DMM and subtracting the cost and number of prescriptions that switched therapy (Table 2). We estimated new treatment mix total prescriptions 6,159: DMM 2,122 (34%), AChEIs monotherapy 1,208 (20%), NMDA monotherapy 461 (7.5%), and dual therapy AChEIs plus NMDA 2,368 (38.5%). Total cost of prescriptions among the new treatment mix was as follows: DMM \$4,243,200, AChEIs monotherapy \$177,534 NMDA monotherapy \$125,052, and dual therapy AChEIs plus NMDA \$494,961 (Table 2). Represented in Table 2 are costs of prescriptions before and after addition of DMM, included are: total cost, per-member-per-month [PMPM], incremental cost with total change. Total cost and PMPM before DMM was \$1,004,954 [\$0.0322] compared to \$5,040,748 [\$0.1616] after DMM addition, with an incremental cost change of \$4,035,794 [\$0.1294] an increase of 400%. The breakdown of cost by the drug categories was as follows: DMM \$0 before compared to \$4,243,200 after, AChEIs monotherapy \$224,380 compared to \$177,534 after DMM addition with an incremental cost decrease of \$46,846 (20.8%), NMDA monotherapy \$158,589 compared to \$125,052 after DMM addition with an incremental cost decrease of \$33,537 (21.1%), and dual therapy AChEIs plus NMDA \$621,984 compared to

\$494,961 after DMM addition with an incremental cost decrease of \$127,023 (20.4%).

Table 3 summarizes the findings from one-way sensitivity analyses in our new treatment mix with a total cost of \$5,040,748 and a PMPM \$0.1616 as our base-case assumptions. In our model the following parameters were varied: percentage of AD patients on AD specific medications, price of DMM therapy, percentage of new cases utilizing DMM, percentage of patients switching from current therapy to DMM, and percentage of patients adding DMM to their current therapy. Each parameter was varied from the default value by  $\pm 50\%$  to estimate the lowest total cost and PMPM, and the highest total cost and PMPM. Results were as follows; percentage of patients with AD prescriptions: low value with 50% decrease was \$3,050,774 [\$0.0978] and high value \$7,030,723 [\$0.2253], cost of DMM therapy: low value \$2,919,148 [\$0.0936] and high value \$7,162,348 [\$0.2296], percentage of new cases utilizing DMM: low value \$4,483,828 [\$0.1437] and high value \$6,101,548 [\$0.1956] percentage of patients switching current therapy to DMM: low value \$4,090,401 [\$0.1311] and high value \$5,991,095 [\$0.192], percentage of patients adding DMM to current therapy: low value \$4,510,348 [\$0.1446] and high value \$5,571,148 [\$0.1786].

Figure 2 summarizes the PMPM findings of our one-way analyses using a tornado diagram, ranking the parameters from most to least influence on our model and overall outcome of total cost and PMPM. When the price of DMM was increased by 50% the total cost increased by 42% (or by \$0.068 PMPM). When percentage of patients using AD medications was increased by 50% total cost increased by 39% (or by \$0.0637 PMPM). When new cases utilizing DMM was increased by 50% the total cost increased by 21% (or by \$0.034 PMPM). When percentage of patients switching

to DMM was increased by 50% the total cost increased by 19% (or by \$0.0304 PMPM). When percentage of patients adding DMM was increased by 50% the total cost increased by 10.5% (or by \$0.017 PMPM).

## **2.5 Discussion**

Alzheimer's disease (AD) has become one of the most financially taxing chronic diseases on individuals, the health care system, and society.<sup>15-18</sup> There is no cure or treatment for AD with current available medications not impacting progression of disease or slowing down cognitive decline.<sup>3,4</sup> Future disease-modifying medications (DMM) currently in clinical trials are the focus of the future treatment paradigm of AD.<sup>4,5,19</sup> In this study, with the perspective of a payer as our focus, we were able to suggest that the future introduction of a DMM into a health care plan, or a formulary list given that the new therapy is cost-effective will have a substantial increase on the budgetary strategy of the health care systems. The overall budget model in our 2.6 million eligible population, using medication utilization and cost data from the Optum Clinformatics™ Data Mart, revealed a budget impact of almost 4-fold, a 1 year budget difference of before and after DMM introduction of approximately \$4,035,796. Our study estimated that prior to DMM introduction the per-member-per month (PMPM) for AD prescription medications was \$0.032, and increased by \$0.129 after the introduction of DMM for our health plan eligible population of 2.6 million patients. For we are expecting these new DMM drugs to be priced at a premium, and despite using a conservative estimate of the cost of DMM therapy the model's sensitivity analyses identified cost of DMM as the most influential parameter in the model. With the introduction of DMM the total cost ranged from \$2,919,148 to \$7,162,348 when



priced at \$1,000 and \$3,000 per prescription, respectively and a PMPM from \$0.0936 to \$0.2296. Considering that based on the various health plans and the amount allocated in terms of PMPM for prescription medications, these PMPM values might have an increased, decreased, or no effect on budgets once DMM is introduced.<sup>20-22</sup> Most health plans medication benefits range between \$25 to \$35 PMPM.<sup>20</sup> But, an acceptable increase in PMPM for the implementation of a new therapy or drug to be considered affordable for health plans is between 0.5%-1%, per the Institute for Clinical and Economic Review (ICER) framework. In our study the increase in overall cost was significant but when considering the PMPM impact on medication benefits, will be within the acceptable 0.5%-1% range when using a \$35 PMPM bench mark. In terms of the substantial increase in overall cost, given the disease-modifying and slowing down of disease progression properties associated with these new medications can lead us to assume or expect; that an increase in the drug expenditure associated with a DMM therapy may be offset by some of the savings resulting from effect of drug in delaying institutionalized high costs. i.e. nursing homes.

In determining our model we decided to focus on AD prescription medication cost and assumptions on the switching, and adding of DMM to future AD population. The study's focus was not to determine or estimate any off-setting costs or measure the impact of other cost sources such as physician visits, hospital visits, or long-term facility care. DMM therapy is expected to improve patients' cognition, function, and behavior but as to the implications that might have on utilization cost of other medical services remains to be determined once the new therapy reaches the market.<sup>4,5,19,23,24</sup>

Budget impact models are essential methods used by health plans, and

hospitals in determining effect and affordability of implementing a new therapy, allowing decision- makers to evaluate both the clinical and economic implications on medical and pharmacy budgets.<sup>13,20-23</sup>

## **2.6 Limitations**

Potential limitation of the study was the percentage of patients switching from current therapy or adding to their current therapy the new DMM medication. The assumptions concerning the new treatment mix may or may not be representative of what we might see in terms of utilization of a new DMM therapy. The model assumptions concerning that there will be patients switching or adding or first time users of DMM was reasonable, and that hospitals or other payers perform using similar method when conducting their own budget impacts. Another potential limitation was not including any costs other than medication cost, and not showing any offsetting costs to other medical services, or side effect costs that introduction of DMM might result in, but those would have been difficult to make educated assumptions on and would have more reliable data once medication is on the market. Further, we know that DMM specifically target patients in the early less severe stages of AD and an assessment of disease severity could not be obtained from this database. This might be essential in determining a more accurate representation on who would be more eligible to use the new therapy. Being a commercial based health care plan our results might not be generalized to government or other non-private health care plans.

## **2.7 Conclusion**

This study, to the best of our knowledge, is first to predict and quantify a

budget impact for a proposed disease-modifying medication for the treatment of Alzheimer's disease. Our model demonstrated a substantial increase in the overall total cost after the introduction of the new therapy. The study highlighted that the cost of the new therapy will be the main cost factor to the impact seen in budget analyses conducted in other health plans, and hospitals.

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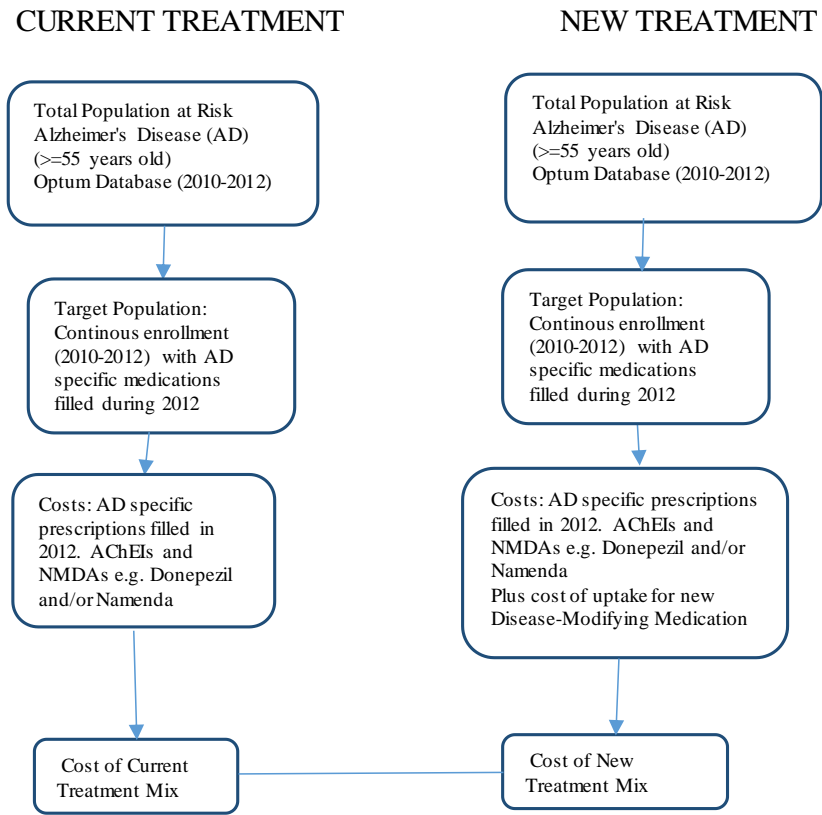
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**Figure 1. Budget Impact Flowchart**



*Difference=Budget Impact*



**Table 1. Unit Costs Applied to Base-Case Analysis and Prescription Utilizations Among the Drug Classes Before and After Introduction of Disease-Modifying Medication (DMM)**

BEFOR DMM <sup>1</sup>						
Resource	Rx <sup>2</sup>	Patients	Cost (\$) / Rx	Rx / Patient	Reference	
Alzheimer's Medications						
AChEIs <sup>3</sup>	1526	144	147	10.6	Optum Datamart™ (2014 \$)	
NMDA <sup>4</sup>	585	44	271	13.3	Optum Datamart™ (2014 \$)	
AChEI+NMDA	2976	248	209	12	Optum Datamart™ (2014 \$)	
Total	5088	436				
AFTER DMM						
Resource	Rx	Patients	Cost (\$) / Rx	Rx / Patient	Reference	
Alzheimer's Medications						
DMM	2122	177	2,000	12	Author*	
AChEIs	1208	117	147	10.6	Optum Datamart™ (2014 \$)	
NMDA	461	35	271	13.3	Optum Datamart™ (2014 \$)	
AChEI+NMDA	2368	202	209	12	Optum Datamart™ (2014 \$)	
Total	6159	530				

1- Disease-Modifying Medication  
2- Prescriptions (Rx)  
3- Acetylcholinesterase Inhibitors e.g. Donepezil  
4- N-Methyl-D-Aspartate e.g. Namenda  
\* Calculation using assumptions of expected cost and utilization of new drug

**Table 2. Total Budget Impact: Health Plan of 2.6 Million Members Before and After Introduction of Disease-Modifying Medication (DMM)**

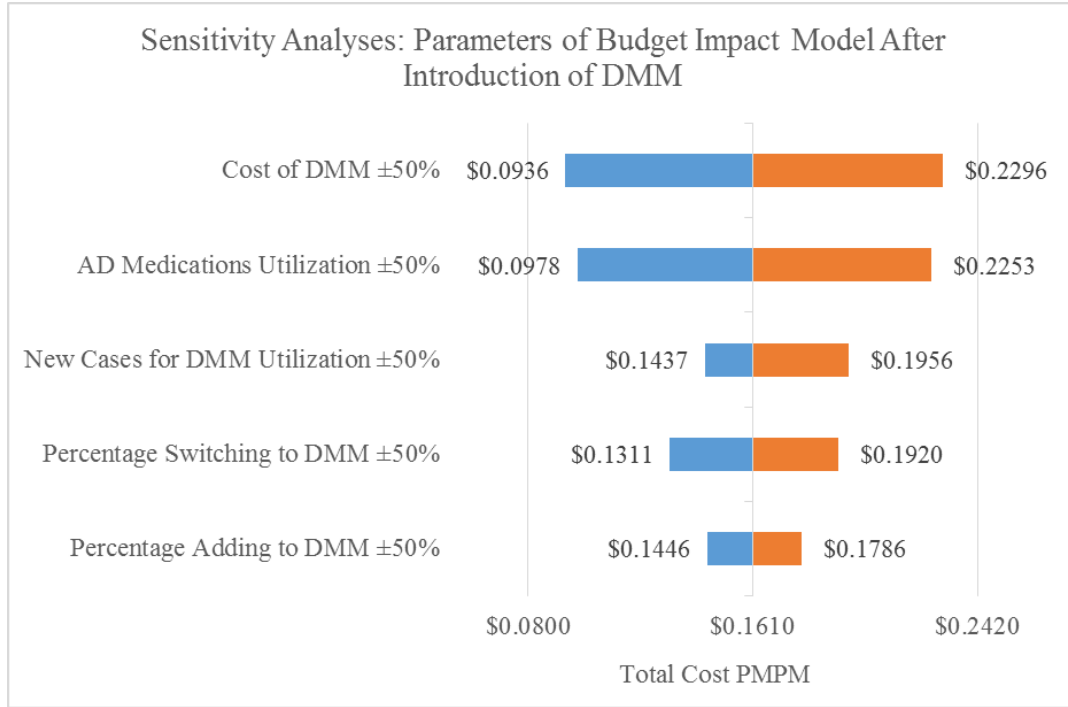
		Before DMM Total (\$) [PMPM]	After DMM Total (\$) [PMPM]	Incremental Cost (\$) Total (% Change) [PMPM]
Alzheimer's Medications				
DMM <sup>1</sup>		\$0	\$4,243,200	\$4,243,200
AChEI <sup>2</sup>		\$224,380	\$177,534	\$-46,846 (-20.8)
NMDA <sup>3</sup>		\$158,589	\$125,052	\$-33,537 (-21.1)
AChEI+NMDA		\$621,984	\$494,961	\$-127,023 (-20.4)
Total Costs		\$1,004,954 [\$0.0322]	\$5,040,748 [\$0.1616]	\$4,035,794 (400) [\$0.1294]

PMPM=per member per month [(Total Cost /# of members in health plan) / 12 months]

**Table 3. Sensitivity Analyses: Total Costs and Per-Member-Per-Month (PMPM) Costs After Introduction of Disease-Modifying Medication (DMM)**

Total Cost		
Base Case	\$5,040,748.69	
	LOW	HIGH
Percentage Adding to DMM ±50%	\$4,510,348.69	\$5,571,148.69
Percentage Switching to DMM ±50%	\$4,090,401.66	\$5,991,095.72
New Cases for DMM Utilization ±50%	\$4,483,828.69	\$6,101,548.69
AD Medications Utilization ±50%	\$3,050,774.34	\$7,030,723.03
Cost of DMM ±50%	\$2,919,148.69	\$7,162,348.69
Total PMPM		
Base Case	\$0.1616	
	LOW	HIGH
Percentage Adding to DMM ±50%	\$0.1446	\$0.1786
Percentage Switching to DMM ±50%	\$0.1311	\$0.1920
New Cases for DMM Utilization ±50%	\$0.1437	\$0.1956
AD Medications Utilization ±50%	\$0.0978	\$0.2253
Cost of DMM ±50%	\$0.0936	\$0.2296

**Figure 2. Tornado Diagram: Sensitivity Analyses Per-Member-Per-Month (PMPM) Cost For Model Parameters After Introduction of Disease-Modifying Medication (DMM)**



### **Manuscript 3**

**Title:** Effects of patient characteristics on direct medical costs among patients newly diagnosed with Early-Onset Dementia

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**Funding:** Unfunded

**Keywords:** Alzheimer's, Lewy Body Disease, Cost, Generalized Linear Model

**Target Journal:** Alzheimer's & Dementia: The Journal of the Alzheimer's Association

**Format:** Short-form paper

**Publication Status:** Being prepared for publication in Alzheimer's & Dementia: The Journal of the Alzheimer's Association

### **3.1 Abstract**

Our purpose was to estimate direct cost of care for patients newly diagnosed with Early-Onset Dementia (EOD), age 21-64 years old, and evaluating predictors on total cost using a Generalized Linear Model (GLM). The sample was drawn from Optum Clinformatics™ Data Mart, a large national insurer database with administrative health claims information collected for up to 3 years from a private health plan. Direct cost included cost for dementia-related services associated with settings in: outpatient, inpatient, and long-term care, as well as prescription medications for dementia. Patient characteristics, considered and analyzed by the model, included age, gender, EOD subtypes, geography, and comorbidities. Total direct cost per patient was \$10,932 (SD \$27,612) with a 66.7% increase in total cost seen among patients in the Midwest, a 43.9% and 38.7% increase in patients age 32-42 years old and 43-53 years old, respectively. Total direct cost of EOD patients increased considerably in various clinical and demographic variables. Age; 32-42 years-old, 43-53 years old, Geography; Midwest region, Comorbidity; hypertension, depression, and rheumatoid arthritis, were all associated with the highest direct cost..

### **3.2 Introduction**

Dementia has become a public health concern given the U.S. aging population, and although often associated with old age few studies estimate 220,000 to 640,000 of Americans suffer from Early-Onset Dementia (EOD)<sup>1-3</sup> comprising 1-5% of all dementia cases. EOD is defined, arbitrarily, as individuals suffering from dementia symptoms under the age of 65, while still having the same symptoms and subtypes as seen in the older population in that Alzheimer's Disease, Vascular Dementia, Lewy

Body Dementia, and Frontotemporal Dementia are all identified in EOD.<sup>1-3</sup> EOD has an impact affecting people in their productive years of life holding both professional and personal responsibilities when the disease strikes them.<sup>3-5</sup> The burden of disease is both personal and economic, impacting the patients, their families, communities, and the health care system. The literature is scarce regarding the prevalence and incidence of EOD, and despite the high financial implication of dementia most of the analysis of cost burden have paid little attention to EOD compared to dementia with age of onset 65 or older.<sup>3-6</sup> This study aimed to provide information describing the direct cost of care associated with EOD and how patient clinical and demographic characteristics impact that total cost.

### **3.3 Methods**

The primary data source was the Optum Clinformatics™ Data Mart, a large national insurer database with administrative health claims information for approximately 19 million patients, collected from January 2010 to December 2012. Available information about these patients with private insurance included: member demographics, medical claims, pharmacy claims, lab results, and inpatient claims.

The study population was comprised of patients with only a single subtype EOD categorized by following etiologies: Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), Vascular Dementia (VD), Frontotemporal Lobar Dementia (FTD), Lewy Body Dementia (LBD), and Dementia Non-Specific (DNOS) that does not fit in the previous mentioned diagnoses.<sup>1,2</sup> Age, gender, dementia subtypes, geographic locations by states, and comorbidities were the patient characteristics considered and analyzed.

Population selection was as follows: diagnosis associated with EOD etiologies in accordance with the International Classification of Disease 9<sup>th</sup> Edition Clinical Modification [ICD-9-CM] medical codes. Relevant codes were reviewed and selected from the Agency for Healthcare Research and Quality (AHRQ), using the Clinical Classification Software (CCS) from the Healthcare Cost and Utilization Project (HCUP). The Clinical Classification Software (CCS) for ICD-9-CM is a tool developed for HCUP sponsored by AHRQ, which provides over 14,000 diagnosis codes and 3,900 procedure codes. Continuous enrollment was required for a minimum of 18 months to allow for a look back of 365 days to capture the newly diagnosed cases, and then only consider the new cases that had a minimum of 12 month follow up to estimate cost of care. Early-Onset newly diagnosed dementia patient ages' 21 to 64 years old inclusive, and excluding any patients with a cancer diagnosis. Cancer diagnosis is associated with high cost of care and would introduce bias in our cost estimates for newly diagnosed EOD patients. To meet the newly diagnosed criteria we concentrated on incident cases or first time diagnosis, which was determined by our 365 days look back period among patients with 18 months continuous enrollment. Patients that recorded a diagnosis of dementia that was less than 365 days were captured. This helped us make the assumption that the patients did not come into the cohort with the diagnosis previously.

Two analytic samples were created comprising patients with EOD as primary, secondary or any other diagnosis, and patients having EOD as their primary diagnosis only. EOD as primary diagnosis only was used for cost analysis (i.e. expenses for services associated with EOD care) and descriptive characteristics, while the group



identified with EOD codes as primary or non-primary diagnoses was also analyzed to describe characteristics of the overall EOD population. (Figure 1). Study outcome (dependent variable) was total annual per-patient cost for all health care service use associated with care for EOD, with independent variables represented by: age, gender, EOD subtypes, geography, and comorbidities.

Age was grouped into separate categories: 21-31 years old (Category1), 32-42 (Category2), 43-53 (Category3), and 54-64 (Category4). Gender separated into male and female. EOD subtypes were represented by: MCI, AD, LBD, VD, FTD, and DNOS. Geography was categorized as U.S. regions: Northeast, South, Midwest, and West. Comorbidities were defined and searched using the Elixhauser Comorbidities Index having the following comorbidity items included:<sup>7</sup> congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension, paralysis, chronic pulmonary disease, diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer disease, AIDS/HIV, rheumatoid arthritis, coagulopathy, obesity, weight loss, fluids and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, depression, other mental disorders. Patients were categorized as: no comorbidity or any comorbidity, with any comorbidity representing patients with 0,1, 2 or more of the above searched comorbidities.

Total annual per-patient cost, as the dependent variable, included Outpatient care, Inpatient stay, Long-Term Facility stay, and Prescription drugs were dementia specific medications: Anticholinesterase Inhibitors (AChEIs) e.g. Donepezil, and NMDAs e.g. Memantine, . Outpatient care included: office visits, home care, urgent

care facility, outpatient hospital, and ambulatory surgical center. Inpatient stays included sites: inpatient hospital, emergency room visits, inpatient psychiatric facility, and partial hospitalization-psychiatric facility. Long-Term Facilities included: skilled nursing home facility, nursing facility, custodial care facility. Outpatient, inpatient, and long-term facilities were defined using the American Medical Association (AMA) Current Procedural Terminology (CPT) Manual. Costs represented amount charged to the insurer, minus patient coinsurance, copay or patient out of pocket payments towards their deductible.

Differences in mean total costs between the variable categories were assessed using an ANOVA test. While evaluating the relationship between total cost and covariates of interest, and because of the skewed nature of cost, we utilized a Generalized Linear Model (GLM).<sup>8-10</sup> Predictors of cost were determined using the GLM using a forward predictive approach, and implementing Modified Park test to determine dependent variable distribution.<sup>8-10</sup> GLM was best method for the model using a “link” and “family” function due to skewed nature of the cost variable, and since log transformation could not achieve normality using Ordinary Least-Squares (OLS).<sup>8-11</sup> We used the link function to specify the relationship between the mean of our outcome variable, total cost, and predictors.<sup>8-11</sup> While family function which corresponds to the distribution of data which in this case was a Gamma distribution informed by the Modified Park Test.<sup>8-11</sup>

For all analyses, statistical significance was considered a 2-sided P-value <0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). This study was reviewed and approved as exempt by the University of

Rhode Island's Institutional Review Board.

### **3.4 Results**

The cohort sample was created after applying inclusion and exclusion criteria (Figure 1): patients with primary diagnosis of any subtype of dementia (n=2,150) were used for the descriptive statistics presented in Tables 1 and 2, health service utilization (Table 3), and used for the development of the GLM used for our cost analysis.

We initially identified 42,226 patients, from total number of 19 million patients with approximately 2 in 1,000 prevalence, having at least one primary or non-primary diagnosis for dementia (Figure 1); from which 13,185 patients were excluded for not being continuously enrolled for a minimum of 18 months. A further 21,120 patients were excluded for being older than 64 years of age or younger than 21 years of age. An additional 96 patients were excluded for having a cancer diagnosis.

In the sample frequency demographic (n=2150) of newly diagnosed EOD patients in our Table 1, females comprised 1183 (55.03%) of the population while males account for 967 (44.97%). The age variable was divided into four categories with patients aged 54-64 years old comprising 1198 (55.7%) of the population followed by those age 43-53 years old accounting for 516 (24%); while those age 32-42 years old were 250 (11.62%), and accounting for the remaining cases were the 21-31 years old with 186 (8.65%). As for the various dementia subtypes the frequencies were as follows: MCI 1001 (46.55%), Dementia-NOS 762 (33.4%), AD 243 (11.3), VD 101 (4.69%), FTD 30 (1.39%), and LBD 13 (0.61%). Dementia Non-Specific (NOS) represents dementia that had a diagnosis code of dementia that did not fit any of the other more specific subtypes. The majority of our population was found in the

South 994 (46.23%), followed by the Midwest 444 (20.65%), and with the West and Northeast at similar frequencies of 358 (16.65%) and 354 (16.64%), respectively. Final variable of interest was comorbidity and whether patients had any of the Elixhauser comorbidities, patients were divided into having; 0, 1, 2 or more comorbidity. Patients with only 1 comorbidity accounted for 956 (44.4%), while patients with 2 or more comorbidity recorded 661 (30.9%). The remaining group of 533 (24.7%) recorded no or 0 comorbidity. In our Table 2 (n=2,150) we provide descriptive statistics of sample frequencies in patients categorized by dementia subtypes.

Among patients with EOD documented as Mild Cognitive Impairment (MCI, n=1001) we found a statistically significant difference by Geographical regions (P-value<0.0001) with majority of our cohort residing in the South (n=467; 46.65%). Most patients with MCI recorded at least 1 or more diagnosis for a relevant diagnosis, showing statistically significant difference in Comorbidity variable (P-value=0.017). MCI patients 240 (23.98%) documented no comorbidity, 477 (47.65%) accounted for having 1 comorbidity only, and remaining 284 (23.67%) MCI patients recorded 2 or more comorbidity. Differences in MCI prevalence by age or gender were not statistically significant. (P-values=0.073 and 0.58, respectively).

Among patients having an EOD documented as Alzheimer's Disease (AD, n=243), there was no statistically significant difference in frequencies among the various Age Categories (P-value=0.22), no difference in gender (P-value=0.05), no difference among Geographical regions (P-value=0.58), and no statistically significant difference between the Comorbidity Categories (P-value=0.27).

Among patients with a diagnosis of Lewy Body Dementia (LBD, n=19), Frontotemporal Dementia (FTD, n=49), and Vascular Dementia (VD, n=212) no statistically significant difference (P-values >0.05) was found in the relationship of having a diagnosis of one of those subtypes and in any of our variable of interests of; Age, Gender, Geography, or Comorbidity.

Finally, among patients with Dementia-NOS (n=762) statistically significant differences was found in Age, Geography, and Comorbidity. Age 54-64 years old was the majority of Dementia-NOS patients at 405 (53.15%) and the least cases at 71 (9.32%) in the 21-31 years old category (P-value=0.04). Most of the Dementia-NOS patients were located in the South 329 (43.18%) followed by the Midwest 189 (24.8%), the remaining split between Northeast 136 (17.85%) and West 108 (14.17%) (P-value=0.0004). Dementia-NOS patients with 0 or no comorbidity were 184 (24.15%) followed by 312 (40.94%) with 1 comorbidity, and remaining 266 (16.79%) with 2 or more comorbidity (P-value=0.013). Gender showed no statistically significant difference in Dementia-NOS patients (P-value=0.16).

In Table 3 we present the frequency and percentage of patients utilizing outpatient and inpatient services, long-term care and prescription medication for dementia, for events associated with a primary diagnosis of dementia (n=2,150 patients). All patients had at least 1 outpatient visit for dementia, as this was a study inclusion criterion, and thus we did not apply a test for statistical significance. Among these 2,150 patients, 205 (9.5%) had at least 1 inpatient stay. A majority of these patients (n=1001, 46.5%) were diagnosed with MCI, 30.7% had a diagnosis of Dementia-NOS, while 11.3% had a diagnosis of AD. Statistically significant

differences were observed among the frequency of inpatient stays by Geography (P-value=0.0008) with largest inpatient stays occurring in the South (n=94, 45.5%) followed by the Midwest (n=61, 29.7%). Inpatient stay statistically significant difference was seen in comorbidity categories (P-value <0.0001) with patients (n=105, 51.22%) having 2 or more comorbidity had an inpatient stay compared to patients (n=89, 43.41%) with 1 comorbidity, and patients (n=11, 5.37%) having no or 0 comorbidity having an inpatient stay.

For Long-Term Facility (LTC) stay we have patients (n=43, 2%) that entered LTC. Statistically significant differences, for LTC stay, in frequencies among the variables was found in the Geography variable (P-value <0.0001) and Comorbidity variable (P-value=0.0003). Patients (n=19, 44.1%) with LTC stay were found mostly in the Midwest. Patients (n=23, 53.49%) with 2 or more comorbidity had LTC stay compared to patients (n=19, 44.19%) that had 1 comorbidity having LTC stay.

Finally, patients (n=79, 3.6%) recorded prescription dementia drugs being filled. Statistically significant differences in frequencies among the variables was found in the Comorbidity categories (P-value=0.005). Patients (n=43, 54.43%) with 1 comorbidity recorded filling prescriptions for dementia medications compared to patients (n=27, 34.18%) with no or 0 comorbidity, and patients (n=9, 11.39%) with 2 or more comorbidity when filling prescriptions for dementia medications. Some notable counts captured showed that of the 79 prescriptions filled; 20 MCI patients, 25 AD patients, and 30 Dementia-NOS patients had dementia specific drugs filled.

Following the care setting frequencies we estimated the mean and total cost, in dollars, of each care setting during a 12-month time frame for our new cases of

primary EOD diagnosis (n=2,150), as presented in Table 4.

Total cost for each setting was as follows: outpatient (n=2,150, 100%) was approximately \$16.1million, inpatient (n=205, 9.5%) was approximately \$6.6million, LTC (n=43, 2%) was \$560,755 and Rx (n=79, 3.6%) was \$ 146,597 yielding a total cost of care at approximately \$23.5million for these 2,150 newly diagnosed patients with primary EOD diagnosis. Mean cost per care setting when utilized by this cohort (n=2,150) results in: outpatient cost approximately \$7,524 (SD=\$19,123), inpatient cost approximately \$3,079 (SD=\$16,275), LTC cost approximately \$260 (SD=\$2,441), and total mean cost of all services approximately \$10,932 (SD=\$27,612).

These costs differ from the mean cost per patient in each care setting utilized, yielding the following results: outpatient (n=2,150, 100%) cost approximately \$7,524 (SD=\$19,123), inpatient (n=205, 9.5%) cost approximately \$32,300 (SD=\$42,918), LTC (n=43, 2%) cost approximately \$13,040 (SD=\$11,587), and Rx (n=79, 3.6%) cost approximately \$1,855 (SD=\$2,427).

In Table 5 we provide descriptive statistics of the total cost given the specific care settings in each of our variables, and determining statistical significance among the variable categories' cost using an ANOVA test.

Outpatient visits showing statistically significant differences were found in patients with comorbidities (P-value <0.0001), where patients with no or 0 comorbidity averaged a direct cost of \$2,469 (SD=\$3,652) compared to patients with 1 comorbidity \$8,819 (SD=\$24,938), and \$9,726 (SD=\$20,327) in patients with 2 or more comorbidity. No statistically significant difference was shown in outpatient visit

cost among the various Age categories (P-value=0.11), or in Gender (P-value=0.96), or among the various dementia Subtypes (P-value=0.82), or Geographical regions (P-value=0.18).

Inpatient stay showing statistically significant differences were found among the Age categories (P-Value=0.008) with 21-31 years old having a mean cost of \$66,159 (SD=\$95,155), followed 54-64 years old with \$31,614 (SD=\$37,008), 43-53 years old at \$28,685 (SD=\$33,217), and the lowest mean cost of \$17,892 (SD=\$20,417) among 32-42 years old. Statistically significant differences were shown in Geographical regions (P-value=0.01) with the West averaging \$48,335 (SD=\$74,695), followed by the Northeast at \$39,293 (SD=\$49,094), the Midwest at \$38,811 (SD=\$44,959), and the South at \$22,526 (SD=\$26,526). In addition, statistically significant difference was shown in Comorbidity categories with \$17,426 (SD=\$2,791) in patients with 0 comorbidity compared to \$24,803 (SD=\$26,449) in patients with 1 comorbidity, and \$42,982 (SD=\$56,427) in 2 or more comorbidity. Gender (P-value=0.72), and dementia Subtype (P-value=0.06) all showed no statistically significant differences in mean cost in each of the specific variable categories for inpatient stay.

Long-Term Facility (LTC) stay, showed no statistically significant differences in mean cost LTC stay among our variables of interest: Age (P-value=0.85), Gender (P-value=0.94), dementia Subtypes (P-value=0.91), Geography (P-value=0.51), and Comorbidity (P-value=0.43).

Prescription drugs (Rx), dementia specific medications, mean cost showed no statistically significant differences among the variables of interest: Age (P-



value=0.49), Gender (P-value=0.55), dementia Subtypes (P-value=0.94), and Geography (P-value=0.68). Comorbidity (P-Value=0.01) showed statistically significant differences in the mean cost, with \$1,371 (SD=1,995) in patients with 0 comorbidity compared to \$1,942 (SD=2,154) in patients with 1 comorbidity, and \$2,893 (SD=\$4,254) with 2 or more comorbidity. All 79 patients with dementia prescription drugs filled recorded No comorbidity.

Using GLM we identified several statistically significant (P-values <0.05) predictors of cost as seen in Table 6: Age 43-53 years old, Midwest region, and Comorbidity. Comorbidities with most impact included: Chronic Heart Failure (CHF), Hypertension (HTN), Cardiac Arrhythmias (CARDARR), Psychoses (PSYCH), Chronic Pulmonary Disease (CHRLUNG), Rheumatoid Arthritis (ARTH), Deficiency Anemia (ANEMDEFF), Coagulopathy (COAG), Pulmonary Circulations (PULMICRC), Peripheral Vascular Disorders (PERIVASC), Valvular Disease (VALVE), Fluid and Electrolyte (LYTES).

The model developed estimated that mean direct total cost of care in newly diagnosed patients with Early-Onset Dementia (EOD) was \$10,932 (SD=\$27,612); an increase of up to 66.7% in patients living in the Midwest compared to the South as the reference, increase of 38.7% in 43-53 years old when compared to the reference 21-31 years old. Increases in mean total cost of care having specific comorbidities, when compared to the absence of the comorbidity, were as follows: 664.1% (or 6.6 times) in patients diagnosed with CHF as a comorbidity, 62.4 % (or 1.6 times) with HTN, 263.5% (or 2.63 times) with CARDARR, 62.2% (or 1.6 times) with PSYCH, 82.2% (or 1.8 times) with CHRNUNG, 87.8 % (or 1.8 times) with ARTH, 101.4% (or 2

times) with ANEMDEFF, 148.5% (or 2.5 times) with COAG, 318% (or 3.1 times) with PULMCIRC, 125.6% (or 2.2 times) with PERIVASC, 155.7 % (or 2.5 times) with VALVE, and 324.1% (or 3.2 times) with LYLES.

Our Table 7 compares the mean cost of all the significant predictors, from our GLM, versus the mean cost of the reference compared with. In Age category (reference 21-31 years old vs predictor 43-53 years old); \$10,474 (SD=\$37,106) vs \$12,078 (SD=\$27,448), Region Category (reference South vs predictor Midwest); \$9,812 (SD=\$20,771) vs \$15,081 (SD=\$40,509), CHF comorbidity (reference CHF absent vs CHF present); \$10,061 (SD=\$25,730) vs \$53,609 (SD=\$62,528), HTN; \$10,062 (SD=\$28,724) vs \$13,154 (SD=\$24,426), CARDARR; \$9,410 (SD=\$25,927) vs \$24,284 (SD=\$36,891), PSYCH; \$10,823 (SD=\$27,514) vs \$17,929 (SD=\$33,012), CHRNLUNG; \$10,788 (SD=28,177) vs \$13,177 (SD=17,309), ARTH; \$10,924 (SD=\$27,754) vs \$11,570 (SD=\$13,418), ANEMDEFF; \$10,710 (SD=\$27,079) vs \$16,620 (SD=\$38,622), COAG; \$10,894 (SD=\$27,624) vs \$16,429 (SD=\$26,042), PULMCIRC; \$10,646 (SD=\$27,112) vs \$31,146 (SD=\$39,171), PERIVASC; \$10,771.39 (SD=\$27,440) vs \$25,238 (SD=38,117), VALVE; \$10,596 (SD=\$27,546) vs \$21,078 (SD=\$28,749), LYLES; \$10,523 (SD=\$26,204) vs \$32,511 (SD=\$66,268). Dementia patients with 1 or more comorbidities can expect an increased overall cost of care, with cardiac comorbidities being the greatest contributors to cost.

### **3.5 Discussion**

In this study, we estimated the total direct mean cost for disease specific patients with Early-Onset Dementia (EOD), and determined patients' clinical and demographic predictors of the overall care cost. The purpose of our study was to

provide a source of cost information for an underrepresented population in studies conducted in both cost, and epidemiology fields.<sup>1,3,12,13</sup> We estimated an annual per-patient direct cost for medical care among newly diagnosed cases of EOD of \$10,932 (SD=\$27,612). In addition we have the cost breakdown for each of the medical care settings, providing context and cost information to guide allocation of resources when planning healthcare services for patients with EOD. With cost analyses for Early-Onset Dementia difficult to find we relied on cost information studies for Dementia and Alzheimer's in Late-Onset (>65years) patients to compare with our findings. Given that there currently no treatment is available for dementia the type of care setting and services for both Early-Onset and Late-Onset are expected to be similar.<sup>13,14</sup> Zhu et al., in a 2006 Alzheimer's study consisting of a cohort across 3 US medical facilities found a total direct mean cost per-patient equal to \$12,587 (SD=\$20,849) over a 4 year period. This study categorized care settings as: outpatient treatment, hospitalization, and medications with no Long-term Facility cost recorded.<sup>15,16</sup> In a 2011 systemic literature review study, by Mauskopf and Mucha, on direct and indirect medical and non-medical cost across the different level of severity in Alzheimer's disease; found that the mean direct cost in mild Alzheimer's in 19 studies from 1993-2009 ranged approximately between \$4,000 to as high as \$19,000 per patient. Most of the studies collected by Mauskopf categorized the direct cost under outpatient, inpatient, medications and with a few including cost of Long-Term Facility care.<sup>17</sup> Murman et al. 2007 in evaluating the direct cost of care in degenerative dementia patients found an approximate mean of \$17,000. In the Murman study Nursing Home care costs were included in addition to the outpatient, inpatient, and

medication costs.<sup>18,19</sup>

Our study focused on the total cost increases of the medical care settings that occurred in patients with specific clinical and demographic characteristics. In this 12 month period higher costs were associated with ages 43-53 years old, the Midwest region, and specific comorbidities. Dementia subtype patients were diagnosed with were not a predictor of cost, and neither was gender.

The majority, approximately 75%, of new cases with EOD as a primary diagnosis in our patient population, were diagnosed as either Mild Cognitive Impairment (MCI) or DNOS and 10% having an Alzheimer's disease (AD) diagnosis. In this study the variable of Gender showed no statistically significant difference in terms of frequency of medical care setting utilization or their cost, or in frequencies among the various dementia subtypes except in AD were more females (60%) than males (40%) where diagnosed (P-value=0.05).

In this study we showed a direct relationship between increased cost of care in EOD patients per number comorbidities. We included each of the captured comorbidities into our model to estimate the ones associated with higher costs. Results showed that:

congestive heart failure (CHF), hypertension (HTN), Cardiac Arrhythmias (CARDARR), Psychoses (PSYCH), Chronic Pulmonary Disease (CHRLUNG), Rheumatoid Arthritis (ARTH), Deficiency Anemia (ANEMDEFF), Coagulopathy (COAG), Pulmonary Circulations (PULMCIRC), Peripheral Vascular Disorders (PERIVASC), Valvular Disease (VALVE), and Fluid and Electrolyte Disorders (LYTES) were associated with increased cost of care. In Figure 2 all the predictor

costs were plotted against our total mean cost \$10,932 (SD=\$27,612), and having Congestive Heart Failure (CHF), Cardiac Arrhythmias (CARDARR), and three other comorbidities as the predictors showing statistically significant difference from our total mean cost \$10,932 (SD=\$27,612). Patients with cardiac comorbidities can expect an increased utilization of care settings and producing the higher costs.

We found cost differences across Geographical regions, attributed to differences seen in terms of care setting utilizations and cost among dementia patients across the US.<sup>20-23</sup> Patients in the Midwest showed the highest cost when compared to the other three regions of the country. These variations in cost across regions may be due to regional pricing differences, availability of services, socioeconomic differences, ethnic and racial differences which would need further examination<sup>16,20-23</sup>.

We found the most frequent EOD was either MCI or DNOS, but with none of the types being a predictor of cost in our overall model. Expectations was that AD would account for majority of the diagnosis given that the few estimations found in the literature show that AD would account for about 30% of all EOD.<sup>3,5,6,23</sup> In addition most of the cost analyses done specifically target dementia and AD in ages 65 and older making it difficult to have comparable values in EOD patients, and relying on the assumption and the expectation that costs seen in EOD, and specifically AD, mirror what is produced in the older patient groups.

### **3.6 Limitations**

There are several limitations in our study. The database did not provide information on race, education level, income or marital status, and these factors may have been associated with cost differences. The cost information collected was total

direct cost for dementia care, and not incremental costs associated with development of the disease. In order to produce the incremental cost we would have to develop a non-EOD patient group with similar characteristics of those of our EOD to show the increasing or decreasing cost between developing EOD and not having EOD.

However, this was not the main concern of the study as we were trying to provide a descriptive informative review on direct costs associated with services for EOD and its subtypes. Being a commercial based health care plan our results might not be generalized to government or other non-private health care plans.

### **3.7 Conclusion**

Results of our study provided needed information for the direct cost in Early-Onset Dementia patients. The study highlighted the significant variation of cost estimates for the different care settings of interest, and producing a total mean direct cost of care \$10,932 (SD=\$27,612) per patient. The study in addition provided an understanding of predictors associated with higher cost in the Early-Onset Dementia population; where patients with specific comorbidities were associated with increased cost, patients 43-53 years old recorded higher mean cost, and patients living in the Midwest region of the U.S. seen with higher costs. In providing these type of cost-of-illness studies decision makers are more informed as to the implications, and distribution of these direct cost on the Early-Onset Dementia population.

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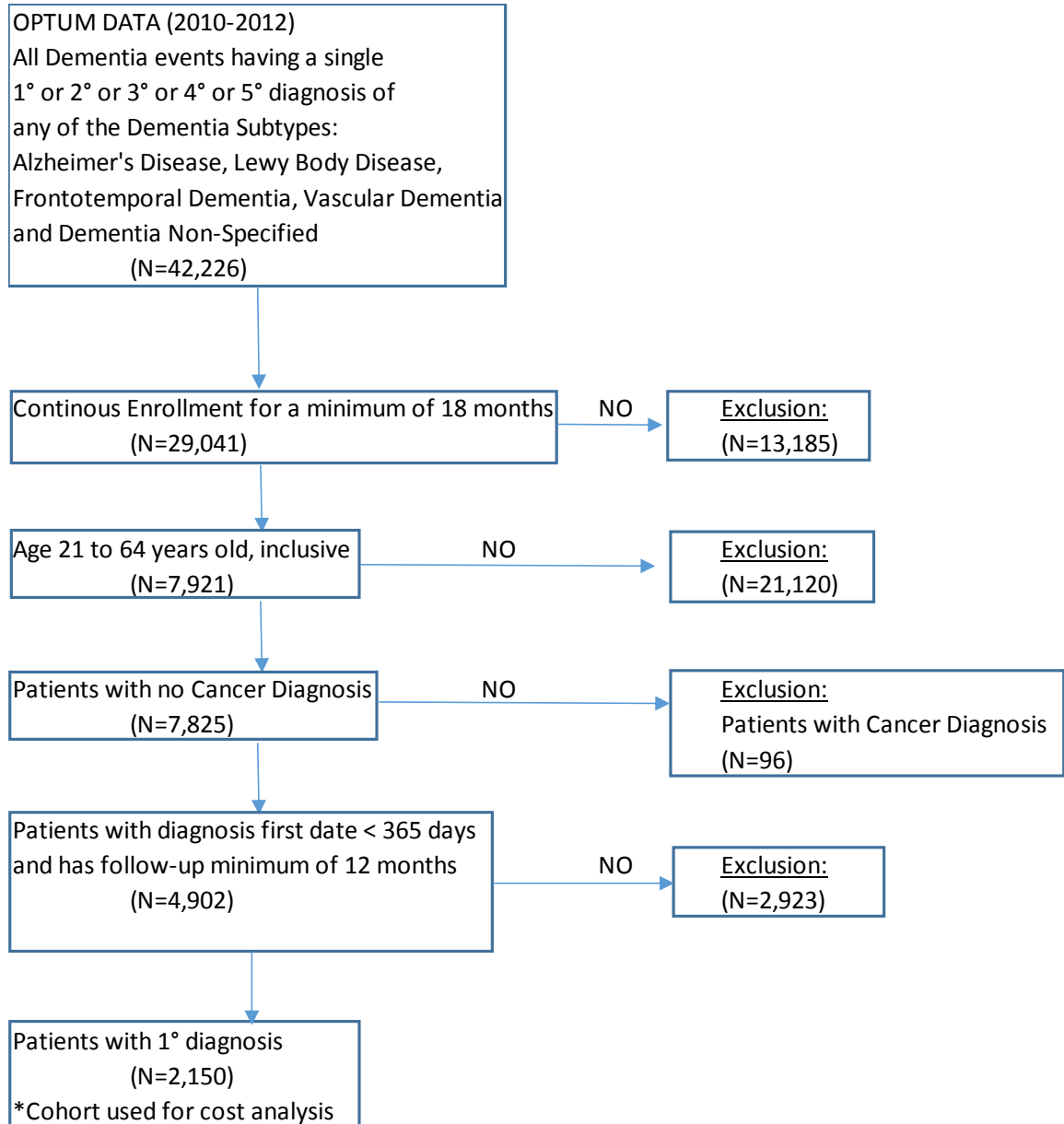
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**Figure 1. Population Flowchart**



**Table 1. Sample Frequency Demographic and Clinical Characteristics of Newly Diagnosed Early-Onset Dementia (EOD) patients**

Sample Size (N)	2150
Variables	
Age Category, Yrs, N (%)	
21-31	186 (8.65%)
32-42	250 (11.62%)
43-53	516 (24%)
54-64	1198 (55.7%)
Gender, N (%)	
Female	1183 (55.03%)
Male	967 (44.97%)
Subtypes, N (%)	
MCI <sup>1</sup>	1001 (46.55%)
AD <sup>2</sup>	243 (11.3%)
LBD <sup>3</sup>	13 (0.61%)
FTD <sup>4</sup>	30 (1.39%)
VD <sup>5</sup>	101 (4.69%)
Dementia NOS <sup>6</sup>	762 (35.44%)
Geography, N (%)	
Northeast	354 (16.46%)
South	994 (46.23%)
Midwest	444 (20.65%)
West	358 (16.65%)
Comorbidity, N (%)	
No Comorbidity	533 (24.7%)
1	956 (44.4%)
2 or more <sup>7</sup>	661 (30.9%)

1 - Mild Cognitive Impairment

2 - Alzheimer's Disease

3 - Lewy Body Disease

4 - Frontotemporal Dementia

5 - Vascular Dementia

6 - Dementia Non-Specific characteristic under senile or pre-senile dementia

7- Had at least 2 and up to 4 comorbidities

**Table 2. Descriptive Statistics of Sample Frequency Demographic and Clinical Characteristics in Newly Diagnosed Patients with specific Early-Onset Dementia Subtypes**

	MCI	AD	LBD	FTD	VD	Dementia NOS
Sample Size (N=2150)	1001(46.55%)	243 (11.3%)	13 (0.61%)	30 (1.39%)	101 (4.69%)	762 (33.4%)
Variables						
Age Category, Yrs, N (%)						
21-31	86 (8.59%)	22 (9.05%)	< 5**	< 5	< 5	71 (9.32%)
32-42	105 (10.49%)	24 (9.88%)	< 5	< 5	12 (11.88%)	107 (14.04%)
43-53	264 (26.37%)	48 (19.75%)	< 5	7 (23.33%)	17 (16.83%)	179 (23.49%)
54-64	546 (54.55%)	149 (61.32%)	11 (84.62%)	19 (63.33%)	68 (67.33%)	405 (53.15%)
P-Value	0.073	0.22	Not Reported	0.77	0.05	0.04*
Gender, N (%)						
Female	557 (55.64%)	148 (60.91%)	4 (30.77%)	14 (46.67%)	56 (55.45%)	404 (53.02%)
Male	444 (44.36%)	95 (39.09%)	9 (69.23%)	16 (53.33%)	45 (44.55%)	358 (46.98%)
P-Value	0.58	0.05	0.07	0.35	0.93	0.16
Geography, N (%)						
Northeast	158 (15.78%)	36 (14.81%)	< 5	6 (20%)	18 (17.82%)	136 (17.85%)
South	467 (46.65%)	120 (49.38%)	7 (53.85%)	15 (50%)	56 (55.45%)	329 (43.18%)
Midwest	175 (17.48%)	52 (21.41%)	< 5	8 (26.67%)	17 (16.83%)	189 (24.8%)
West	201 (20.08%)	35 (14.4%)	< 5	1 (3.33%)	10 (9.9%)	108 (14.17%)
P-Value	<0.0001*	0.58	Not Reported	0.25	0.12	0.0004*
Comorbidity, N (%)						
No Comorbidity	240 (23.98%)	73 (30.04%)	< 5	10 (33.33%)	22 (21.78%)	184 (24.15%)
1	477 (47.65%)	104 (42.8%)	5 (38.46%)	16 (53.33%)	42 (41.58%)	312 (40.94%)
2 or more	284 (23.67%)	66 (12.76%)	< 5	4 (13.34%)	37 (36.64%)	266 (16.79%)
P-value	0.017*	0.27	0.07	0.19	0.11	0.013*

\* p < 0.05  
 \*\* < 5 are cells that recorded under 5 counts

**Table 3. Descriptive Statistics of Utilization given the specific Care Setting in Early-Onset Dementia Patients**

	Outpatient <sup>1</sup>	Inpatient <sup>2</sup>	Long Term Care <sup>3</sup> (LTC)	Prescription Drugs <sup>4</sup> (Rx)
Sample Size (N=2150)	2150 (100%)	205 (9.53%)	43 (2%)	79 (3.67%)
Variables				
Age Category, Yrs, N (%)				
21-31	186 (8.65%)	15 (7.31%)	< 5**	< 5
32-42	250 (11.62%)	16 (7.8%)	< 5	< 5
43-53	516 (24%)	54 (26.34%)	9 (20.93%)	< 5
54-64	1198 (55.7%)	120 (58.53%)	30 (69.76%)	76 (96.21%)
P-Value		0.245	0.281	Not reported
Gender, N (%)				
Female	1183 (55.03%)	107 (52.19%)	19 (44.18%)	41 (51.9%)
Male	967 (44.97%)	98 (47.81%)	24 (55.82%)	38 (48.1%)
P-Value		0.391	0.149	0.569
Subtypes, N (%)				
MCI	1001 (46.55%)	63 (30.73%)	< 5	20 (25.31%)
AD	243 (11.3%)	21 (10.24%)	< 5	25 (31.64%)
LBD	13 (0.61%)	3 (1.46%)	< 5	< 5
FTD	30 (1.39%)	3 (1.46%)	< 5	< 5
VD	101 (4.69%)	17 (8.29%)	< 5	< 5
Dementia NOS	762 (35.44%)	98 (47.8%)	33 (76.74%)	30 (37.97%)
P-Value		<0.0001*	Not reported	Not reported
Geography, N (%)				
Northeast	354 (16.46%)	31 (15.12%)	12 (27.9%)	8 (10.12%)
South	994 (46.23%)	94 (45.58%)	10 (23.25%)	37 (46.83%)
Midwest	444 (20.65%)	61 (29.75%)	19 (44.18%)	18 (22.78%)
West	358 (16.65%)	19 (9.26%)	2 (4.65)	16 (20.25%)
P-Value		0.0008*	<0.0001*	0.419
Comorbidity, N (%)				
No Comorbidity	533 (24.7%)	11 (5.37%)	< 5	27 (34.18%)
1	956 (44.4%)	89 (43.41%)	19 (44.19%)	43 (54.43%)
2 or more	661 (30.9%)	105 (51.22%)	23 (53.49%)	9 (11.39%)
P-value		<0.0001*	<0.0001*	0.005*

1 - Outpatient includes : Physician Office Visits, Urgent Care Facility, Ambulatory Center, and Outpatient Hospital

2 - Inpatient includes : Inpatient Hospital, Emergency Room Visits

3 - Long Term Care includes : Home Care, Skilled Nursing, Nursing facility

4 - Prescription Drugs : Dementia Specific Medications (AChEIs, and NMDAs)

\* p < 0.05

\*\* < 5 are cells that

recorded under 5 counts

**Table 4. Mean and Total Cost (\$) of Care Settings in Early-Onset Dementia Patients during a 12-Month Time Period**

	Outpatient	Inpatient	LTC	Rx	Total
Sample Size (N=2,150)	2150	205	43	79	
Total Cost of service, (\$)	\$16,176,849	\$6,621,504	\$560,755	\$146,597	\$23,505,699
Mean Cost per service, \$ (SD) denominator N=2150	\$7,524.11 (19,123.13)	\$3,079.77 (16,275.37)	\$260.8 (2,441.08)	\$68.18 (579.56)	\$10,932.88 (27,612.16)
Mean Cost per patient using the service, \$ (SD) denominator N=patient size utilizing service	\$7,524.11 (19,123.13)	\$32,300.02 (42,918.16)	\$13,040.82 (11,587.33)	\$1,855.66 (2,427.94)	
Median Cost per patient, \$	\$3,098.46	\$16,878.82	\$9,048.66	\$1,098.24	\$3,378.97

**Table 5 Descriptive Statistics of Total Mean Cost (\$) of Care Settings in Demographic and Clinical Characteristics of Early-Onset Dementia Patients, during a 12-month Time Period**

	Outpatient	Inpatient	LTC	Rx	Total
Sample Size (N=2150)	2150	205	43	79	
Age Category, Yrs	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)
21-31	\$4,974.12 (9,892.24)	\$66,159.67 (95,155.66)	\$15,317.13 (11,853.90)	Not Reported	\$10,474.28 (37,106.44)
32-42	\$7,864.38 (3,9064.30)	\$17,892.27 (20,417.68)	\$16,991.25 (21,832.58)	Not Reported	\$9,145.42 (40,010.68)
43-53	\$8,797.30 (19,197.17)	\$28,685.87 (33,217.94)	\$15,042.08 (12,966.71)	\$2,806.93 (2,026.10)	\$12,077.99 (27,448.39)
54-64	\$7,300.63 (12,791.84)	\$31,614.97 (37,008.05)	\$12,025.32 (11,092.65)	\$1,818.11 (2,446.13)	\$10,883.88 (22,306.49)
P-Value	0.11	0.008*	0.85	0.49	0.57
Gender	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)
Female	\$7,541.21 (14,163.91)	\$33,308.78 (42,980.62)	\$13,186.11 (11,975.55)	\$2,034.04 (2,416.60)	\$10,836.20 (24,293.10)
Male	\$7,503.20 (23,834.04)	\$31,198.63 (43,043.54)	\$12,925.79 (11,528.82)	\$1,663.2 (2,408.93)	\$11,051.17 (31,208.87)
P-Value	0.96	0.72	0.94	0.55	0.85
Subtypes	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)
MCI	\$7,850.47 (16,656.54)	\$22,600.05 (25,813.02)	\$10,531.03 (14,357.78)	\$2,089 (1,939.95)	\$9,356.67 (20,683.45)
AD	\$6,820.32 (12,519.70)	\$50,025.70 (61,189.08)	Not Reported	\$1,876.48 (2,512.71)	\$11,394.1 (28,682.89)
LBD	\$11,971.27 (17,851.8)	\$12,738.66 (15,101.26)	Not Reported	Not Reported	\$15,445.58 (20,000.46)
FTD	\$5,044.45 (6,491.23)	\$13,860.80 (9,184.72)	Not Reported	\$1,452.37 (1,045.95)	\$6,624.18 (8,116.48)
VD	\$8,319.39 (13,275.53)	\$23,353.46 (18,996.03)	\$17,413.63 (13,342.06)	Not Reported	\$12,939.82 (21,248.75)
Dementia NOS	\$7,236.08 (24,237.09)	\$34,452.6 (49,169.75)	\$12,973.29 (11,655.24)	\$1,736.52 (2,824.20)	\$12,683.02 (35,399.03)
P-Value	0.82	0.06	0.91	0.94	0.15
Geography	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)
Northeast	\$6285.54 (10,180.29)	\$39,293.52 (49,094.29)	\$18,880.99 (11,826.98)	\$1,209.55 (1,473.27)	\$10,292.17 (24,023.40)
South	\$7,495.41 (14,910.14)	\$22,526.86 (26,187.76)	\$10,804.56 (10,161.16)	\$2,101.79 (2,842.71)	\$9,812.65 (20,771.89)
Midwest	\$9,094.66 (31,278.94)	\$38,811.54 (44,959.15)	\$13,396.36 (12,527.94)	\$2,016.21 (2661.29)	\$15,081.88 (40,509.44)
West	\$6,880.73 (16,168.75)	\$48,335.62 (74,695.18)	\$3,803.4 (5,131.11)	\$1,428.98 (1,273.62)	\$9,531.14 (24,479.61)
P-value	0.18	0.01*	0.51	0.68	0.05
Comorbidity	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)	Cost (SD)
No Comorbidity	\$2,469.39 (3,652.19)	\$17,426.28 (2,0791.91)	Not Reported	\$1,371.4 (1995.98)	\$2,902.92 (5777.2)
1	\$8,819.62 (24,938.58)	\$24,803 (26,449.14)	\$11,076.75 (12,732.15)	\$1,942.41 (2,154.94)	\$13,128.66 (35,275.14)
2 or more	\$9,726.33 (20,327.32)	\$42,982.79 (56,427.07)	\$15,128.21 (10,517.08)	\$2,893.96 (4,254.73)	\$14,232.13 (24,189.9)
P-Value	<0.0001*	0.02*	0.43	0.01*	<0.0001*

\* p < 0.05



**Table 6. Generalized Linear Model Predictors of Total Direct Costs**

	Co-efficient	Standard Error (SE)	95% Confidence Interval	P-value	Marginal Effect <sup>1</sup>
GLM Parameters					
Age Category Yrs, (ref 21-31)					
32-42	0.0062	0.1367	(-0.2168, 0.2742)	0.9636	
43-53	0.3272	0.1141	(0.1036, 0.5507)	0.0041*	38.7
54-64	0.2063	0.1121	(-0.0134, 0.426)	0.0657	
Region (ref, South)					
Midwest	0.5116	0.0742	(0.3662, 0.657)	<0.0001*	66.7
Northeast	0.0478	0.0872	(-0.1232, 0.2188)	0.5838	
West	-0.0126	0.0869	(-0.1828, 0.1576)	0.8845	
Comorbidity (ref, Comorbidity Absent)					
Congestive Heart Failure (CHF)	2.036	0.1947	(1.6501, 2.4133)	<0.0001*	664.1
Hypertension (HTN)	0.4854	0.0648	(0.3585, 0.3124)	<0.0001*	62.4
Cardiac Arrhythmias (CARDARR)	1.2906	0.0927	(1.1088, 1.4724)	<0.0001*	263.5
Psychoses (PSYCH)	0.4839	0.2226	(0.0477, 0.9201)	0.029*	62.2
Chronic Pulmonary Disease (CHRNUNG)	0.6001	0.1115	(0.3816, 0.8185)	<0.0001*	82.2
Rheumatoid Arthritis (ARTH)	0.6312	0.2354	(0.1698, 1.0926)	0.007*	87.8
Deficiency Anemia (ANEMDEFF)	0.7002	0.1453	(0.4153, 0.985)	<0.0001*	101.4
Coagulopathy (COAG)	0.916	0.3266	(0.2758, 1.5563)	0.0005*	148.5
Pulmonary Circulations (PULMCIRC)	1.4306	0.231	(0.9779, 1.8833)	<0.0001*	318.1
Peripheral Vascular Disorders (PERIVASC)	0.8136	0.2578	(0.3083, 1.319)	0.0016*	125.6
Valvular Disease (VALVE)	0.9391	0.1544	(0.6364, 1.2418)	<0.0001*	155.7
Fluid and Electrolyte Disorders (LYTES)	1.445	0.2084	(1.0365, 1.8534)	<0.0001*	324.1

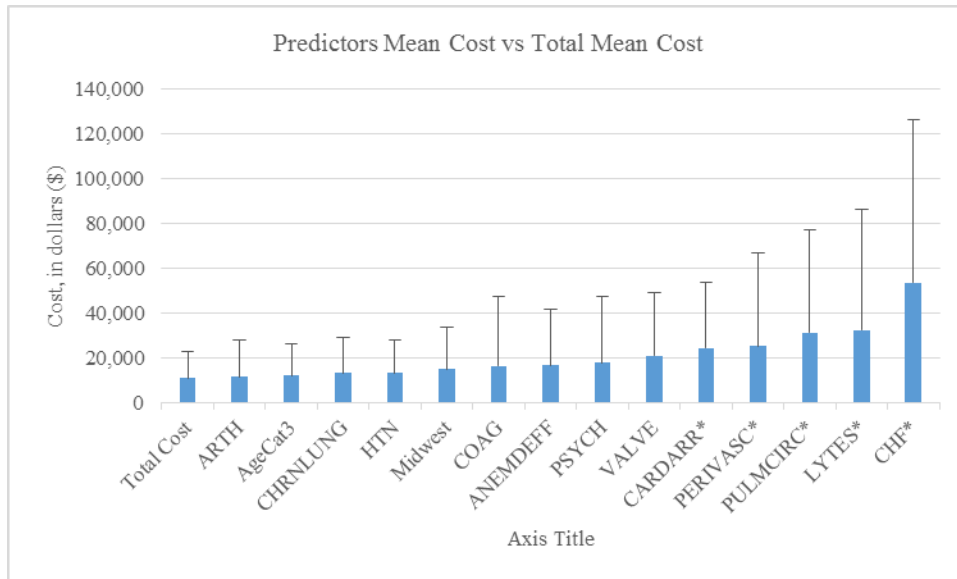
<sup>1</sup> - Marginal Effect represents the % increase in total cost when variable was present

\* p<0.05

**Table 7. Mean Cost, \$, Comparison between the Predictors of Total Mean Cost versus Mean Cost of Reference Variable, during a 12-month Time Period**

	Mean Cost, \$ (reference) vs Mean Cost, \$ (predictor)	95% Confidence Interval (predictor)	Sample Size (N=2,150)
Significant Predictors*			
Age Category, Yrs (ref 21-31)			
32-42*	\$9,145 (SD=\$28,014) vs \$9,338 (SD=40,010)	(\$8,446, \$12,945)	N=250
43-53	\$10,474 (SD=\$37,106) vs \$12,078 (SD=\$27,448)	(\$9,704, \$14,451)	N=516
54-64	\$10,883 (SD=\$35,225) vs 11,544 (SD=\$25,389)	(\$9,328, \$13,784)	N=1198
Region (ref, South)			
Midwest*	\$9,812 (SD=\$20,771) vs \$15,081 (SD=\$40,509)	(\$11,303, \$18,860)	N=444
Northeast	\$9,474 (SD=\$19,225) vs \$10,292 (SD=24,023)	(\$9,105, \$15,226)	N=358
West	\$8,755 (SD=\$23,555) vs \$9,531 (SD=\$15,331)	(\$8,066, \$15,116)	N=354
Comorbidity (ref, Comorbidity Absent)			
Congestive Heart Failure (CHF)*	\$10,061 (SD=\$25,730) vs \$53,609 (SD=\$62,528)	(\$34,365, \$72,825)	N=43
Hypertension (HTN)*	\$10,062 (SD=\$28,724) vs \$13,154 (SD=\$24,426)	(\$11,204, \$15,105)	N=605
Cardiac Arrhythmias (CARDARR)*	\$9,410 (SD=\$25,927) vs \$24,284 (SD=\$36,891)	(\$19,382, \$29,186)	N=220
Psychoses (PSYCH)*	\$10,823 (SD=\$27,514) vs \$17,929 (SD=\$33,012)	(\$6,224, \$29,635)	N=33
Chronic Pulmonary Disease (CHRNUNG)*	\$10,788 (SD=28,177) vs \$13,177 (SD=17,309)	(\$10,263, \$16,091)	N=138
Rheumatoid Arthritis (ARTH)*	\$10,924 (SD=\$27,754) vs \$11,570 (SD=\$13,418)	(\$6,446, \$16,674)	N=29
Deficiency Anemia (ANEMDEFF)*	\$10,710 (SD=\$27,079) vs \$16,620 (SD=\$38,622)	(\$8,080, \$25,160)	N=81
Coagulopathy (COAG)*	\$10,894 (SD=\$27,624) vs \$16,429 (SD=\$26,042)	(\$2,007, \$30,851)	N=15
Pulmonary Circulations (PULMCIRC)*	\$10,646 (SD=\$27,112) vs \$31,146 (SD=\$39,171)	(\$16,519, \$45,772)	N=30
Peripheral Vascular Disorders (PERIVASC)*	\$10,771.39 (SD=\$27,440) vs \$25,238 (SD=\$38,117)	(\$9,142, \$41,333)	N=24
Valvular Disease (VALVE)*	\$10,596 (SD=\$27,546) vs \$21,078 (SD=\$28,749)	(\$14,172, \$27,985)	N=69
Fluid and Electrolyte Disorders (LYTES)*	\$10,523 (SD=\$26,204) vs \$32,511 (SD=\$66,268)	(\$11,318, \$53,705)	N=40

**Figure 2. Cost of Predictors, in dollars, Compared to Overall Total Mean Cost, during a 12-month Time Period**



ARTH – Rheumatoid Arthritis

AgeCat3 – 43-53 years old

CHRNLUNG – Chronic Pulmonary Disease

HTN – Hypertension

Midwest – Region in U.S.

COAG – Coagulopathy

ANEMDEFF – Deficiency Anemia

PSYCH – Psychosis

VALVE – Valvular Disease

CARDARR\* – Cardiac Arrhythmias\*

PERIVASC – Peripheral Vascular Disorder\*

PULMCIRC – Pulmonary Circulations\*

LYTES – Fluid and Electrolytes Disorders\*

CHF – Congestive Heart Failure\*

\* Predictors that have a mean cost statistically significantly different than the total mean cost

**APPENDIX A. International Classification of Disease 9<sup>th</sup> [ICD-9] Edition medical codes - Agency for Healthcare Research and Quality (AHRQ), using the Clinical Classification Software (CCS) from the Healthcare Cost and Utilization Project (HCUP)**

Alzheimer's disease: 331.0
Frontotemporal Dementia: 331.19
Dementia with Lewy Body: 331.82
Mild Cognitive Impairment: 331.83
Vascular Dementia, Uncomplicated: 290.40
Vascular Dementia, with Delirium: 290.41
Vascular Dementia, with Delusion: 290.42
Vascular Dementia, with Depressed Mood: 290.43
Senile Dementia, Uncomplicated: 290.0
Senile Dementia, with Delusional Features: 290.20
Senile Dementia, with Depressive Features: 290.21
Senile Dementia, with Delirium: 290.3
Pre-Senile Dementia, Uncomplicated: 290.10
Pre-Senile Dementia, with Delirium: 290.11
Pre-Senile Dementia, with Delusional Features: 290.12
Pre-Senile Dementia, with Depressive Features: 290.13
Dementia in Conditions Classified Elsewhere, without Behavioral Disturbance: 294.10
Dementia in Conditions Classified Elsewhere, with Behavioral Disturbance: 294.11
Dementia, Unspecified, without Behavioral Disturbance: 294.20
Dementia, Unspecified, with Behavioral Disturbance: 294.21