

Alzheimer's Disease Severity Progression: Prevalent Population Estimates Over Time

Commissioned by Eli Lilly and Company

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An analysis using public and published research to estimate the number of people with Medicare coverage who have mild cognitive impairment or mild dementia due to Alzheimer's disease and track their progression to moderate or severe dementia due to Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a progressive brain disease that results in a gradual decline in memory, thinking, behavior, and social skills. It is characterized by changes in the brain, including the presence of amyloid plaque and neurofibrillary (tau) tangles that result in loss of neurons and their connections.¹ The first therapy directed against amyloid plaque was approved in June 2021.² However, in April 2022, the Centers for Medicare & Medicaid Services (CMS) instituted a National Coverage Determination (NCD) for monoclonal antibodies directed against amyloid for treatment of AD.³ The NCD restricts access by requiring Coverage for Evidence Development (CED) for these therapies, which authorizes coverage of the treatment only in the context of approved clinical studies. CMS may reconsider the NCD "when additional scientific evidence that was not considered during the most recent review" becomes available or when a requester presents "plausible arguments that [CMS' initial] conclusion materially misinterpreted the existing evidence at the time the NCD was decided."⁴

In December 2022, the Alzheimer's Association filed a formal request for reconsideration after a second therapy directed against amyloid plaque published new Phase III data demonstrating clinical benefit from the use of the treatment.⁵ CMS issued a response declining to reconsider the NCD because "there is not yet evidence meeting the criteria for reconsideration."^{6,7} CMS also noted they will "expeditiously review any new evidence that becomes available that could lead to a reconsideration and change in the NCD."⁶

Impact of the NCD on individuals with mild cognitive impairment (MCI) or dementia due to AD: Patients with MCI or mild dementia stages of AD with evidence of amyloid beta pathology are the anticipated indicated patient population for the approved and pipeline therapies that are subject to the NCD. Patients who cannot access treatments while they are in the MCI or mild

dementia stages of the disease may progress to a more severe form of dementia due to AD and miss the opportunity for treatment if they are not enrolled in an approved clinical study.

In the Alzheimer's Association's request for reconsideration of the NCD, it noted more than 2,000 individuals aged 65 or older with AD may progress per day from mild dementia to moderate dementia, and therefore progress beyond the indicated population for the currently approved and pipeline therapies.⁷

Given the impact of the NCD on access to treatment, Eli Lilly and Company engaged us to prepare this report. [The purpose of this report is to:](#)

1. Estimate the number of people (i.e., the prevalent population) with MCI due to AD and mild dementia due to AD progressing to moderate or severe dementia over 24 months, and
2. Provide transparency to the sources, assumptions, and process used to inform the estimates.

The prevalent population in this analysis was estimated based on published and public research. The published studies reflect population or disease characteristics from closely studying a sample of individuals over time. However, a notable characteristic of MCI and dementia due to AD is a high rate of underdiagnosis, late diagnosis, or misdiagnosis. Additionally, diagnostic tools used to evaluate the presence of amyloid are not widely used due to policy and reimbursement barriers.^{8,9} For these reasons, the U.S. prevalent population estimates represented in this study include individuals who have not yet been diagnosed with AD, as well as individuals who have not yet been confirmed to be amyloid positive. See the discussion section for further details.

Lastly, patients must have evidence of amyloid plaque in the brain to qualify for the approved therapies directed against amyloid. Hence, not all individuals with MCI or mild dementia due to AD are medically qualified or indicated for the approved and pipeline therapies subject to the NCD. This paper does not intend to size the number of individuals who qualify for or would choose to be treated by one of the approved or pipeline monoclonal antibodies directed against amyloid.

Note: "AD with dementia" and "dementia due to AD" are interchangeable terminology in this report. The use of the former is due to space constraints in the tables.

Key definitions

- **Prevalent population:** The proportion or number of individuals who have a certain disease, condition, or risk factor. In epidemiological studies prevalence is often estimated by closely studying a sample of individuals over time.
- **Diagnosed population:** The proportion or number of individuals who visited a health care provider and received a diagnosis for a certain disease, condition, or risk factor. Diagnoses are identifiable in medical records or claims using ICD-10-CM (diagnosis) codes.
- **Indicated population:** The proportion or number of individuals who meet all qualifications, inclusion, or exclusion criteria to receive a particular drug, procedure, or treatment.
- **Treated population:** The proportion or number of individuals who receive a particular drug, procedure, or treatment.

Methodology

The assumptions used for this analysis were based solely on published and public research and data. This included peer reviewed journal articles and manuscripts, the Alzheimer's Association 2022 annual report, U.S. census data, and Medicare enrollment data. Citations and assumptions from each source are noted in the References and Appendix section of this paper.

Due to the variation in the published rates associated with prevalence, severity, etc., the results are presented as a decision tree, with each "node" of the tree representing possible population estimates, given the variation in assumptions. The decision tree is structured such that each subsequent node is a subset of the population in the previous node. The decision tree of population estimates is ordered as follows:

1. The number of people with MCI or symptoms of dementia clinically attributed to AD in the United States.
2. The subset of individuals who have Medicare coverage; under and over age 65.
3. The subset of individuals who are mild severity (*specific to dementia due to AD only*).
4. The portion of individuals with MCI and mild dementia clinically attributed to AD with evidence of amyloid pathology (amyloid positive)

† Calculated as dementia prevalence (source 6) times U.S. census by age band (source 7), adjusted to include age 90+ age segmentation (source 8), multiplied by

The resulting populations estimated in node (4) were used as the basis for applying annual transition probabilities, using a Markov Chain approach. The source used for severity transition probabilities (Potashman 2021)¹⁰ contained annual probabilities of transitioning between each symptomatic stage of amyloid-positive Alzheimer's disease and death. The source noted a small likelihood of transitions from more severe to less severe stages of AD, e.g., an individual with moderate dementia due to AD transitioning to mild dementia due to AD. To be consistent with the source's published rates, backward transitions were allowed.

The results were modeled as a closed cohort; new individuals were not added over time.

The top-line prevalent population estimates used three different methods, from which all other nodes branched:

1. A lower prevalent population estimate for dementia due to AD, calculated using U.S. dementia prevalence rates by age applied to U.S. census data times the proportion of dementia that is clinically attributed to AD^{†,11,12,13,16}
2. A higher prevalent population estimate for dementia clinically attributed to AD, with the age 65+ population informed from a published study of the prevalence of dementia due to AD in Chicago^{†,14} and
3. A prevalent MCI population estimate, with MCI prevalence rates by age informed from a published meta-analysis applied to U.S. census data.^{†,12,13,15}

The analysis utilized more than a dozen different sources to estimate a range of prevalent population estimates of individuals with mild dementia due to AD or MCI progressing to moderate or severe dementia due to AD over time. These sources were determined to be the most appropriate for the analysis because they (1) are related to the dementia, MCI, and/or amyloid positive populations, (2) they are widely cited and/or, (3) they presented results consistent with other independent publications.

Within the sources used in the analysis, often there was a range provided for a particular endpoint. For example, the rate of amyloid positivity for individuals with mild dementia clinically attributed to AD was noted to be between 70%¹⁶ to 87%.¹⁷ The low end and high end of the ranges were used to inform the minimum and maximum values for the nodes. The midpoint estimates ("mid estimates") were also noted in the decision tree. For the amyloid positivity example, the mid estimate reflected the midpoint, 79%, as the assumed rate. Additionally, the mid

the rate of AD among total dementia (source 11 noted 60-80% of dementia is due to AD; this analysis assumed the midpoint of 70%)

estimate reflects sources that were most specific to the modeled population and published in the last 10 years.

Results

Figure 1 displays a summary of the mid estimates and the overall range of results. Figure 2 displays the calculations and sources used for the mid estimate population estimates. A table of all modeled scenarios and their associated sources is available in the appendix.

The major difference between the lower and higher estimates is the size of the U.S. dementia due to AD population (age 65 and older). The lower prevalence estimate results in approximately 3.2 million age 65 and older individuals with dementia due to AD in the United States, while the higher prevalence estimate results in approximately 6.5 million individuals, seen in figure 2.

FIGURE 1: AD WITH MILD DEMENTIA AND MCI POPULATION PROGRESSION ESTIMATES: MID ESTIMATES AND RANGE

Population Estimates	MID ESTIMATES		OVERALL RANGE	
	Lower	Higher	Lowest	Highest
Dementia clinically attributed to AD, U.S. population	3,325,934	6,670,000	3,325,934	6,670,000
MCI, U.S. population	10,682,074	10,682,074	10,682,074	10,682,074
AD with mild dementia (amyloid positive)	1,259,021	2,578,473	636,372	2,839,584
AD with MCI (amyloid positive)	4,748,594	4,748,594	4,283,046	5,214,143
AD with MCI or mild dementia, Medicare covered	6,007,615	7,327,067	4,919,418	8,053,726
Population Progressing to AD with Moderate or Severe Dementia Over Time (# and % of Amyloid Positive Medicare Population)				
Avg. per day (year 1): Began as AD with mild dementia	1,307	2,677	661	2,948
Avg. per day (year 1): Began as MCI	559	559	505	614
Total avg. per day during year 1	1,867	3,237	1,165	3,563
By month 12	681,359 (11.3%)	1,181,431 (16.1%)	425,356 (8.6%)	1,300,410 (16.1%)
By month 24	1,417,926 (23.6%)	2,040,389 (27.8%)	1,043,404 (21.2%)	2,244,352 (27.9%)

Footnote: See appendix for sources and calculations associated with each column. The "Overall Range Lowest" is the aggregation of scenario 1 (AD) and scenario 13 (MCI), the "Overall Range Highest" is the aggregation of scenario 12 (AD) and scenario 15 (MCI), the "Lower Mid Estimate" is the aggregation of scenario 5 (AD) and scenario 14 (MCI), and the "Higher Mid Estimate" is the aggregation of scenario 11 (AD) and scenario 14 (MCI).

Numbers may not sum due to rounding.

FIGURE 2: AD WITH MILD DEMENTIA AND MCI POPULATION PROGRESSION ESTIMATES: DETAILED MID ESTIMATES

U.S. Population	(Lower) Dementia due to AD Population Estimate	(Higher) Dementia due to AD Population Estimate	MCI Population Estimate	Calculation
Age 65+	3,157,057 ^{11,12,13,16}	6,470,000 ¹⁴	9,268,776 ^{12,16}	A
Age <65	168,877 ^{11,12,13,16}	200,000 ¹⁶	1,413,298 ^{12,15}	B
Total U.S. population	3,325,934	6,670,000	10,682,074	C = A+B
AD with MCI or Mild Dementia Population with Medicare Coverage - Original Medicare & Medicare Advantage				
Age 65+	3,157,057	6,470,000	9,268,776	D = A*100% ^{18,19}
Age <65	5,042	5,971	42,193	E = B*3% ^{18,19}
Total Clinical MCI / AD with dementia population with Medicare	3,162,099	6,475,971	9,310,969	F = D+E
AD with mild dementia (% of AD)	50% ²⁰	50% ²⁰	NA	G
Total mild	1,593,698	3,263,889	9,310,969	H = F*G
Rate of amyloid positivity	79% ^{16,17}	79% ^{16,17}	51% ¹⁷	I
Total AD with MCI / mild dementia (amyloid positive)	1,259,021	2,578,473	4,748,594	J = H*I
Population Progressing to Moderate or Severe Dementia due to AD Over Time (# and % of Amyloid Positive Medicare Population)				
Avg. per day during year 1	1,307	2,677	559	J* [Transition probabilities]¹⁰
By month 6	238,585 (19.0%)	488,621 (19.0%)	102,095 (2.2%)	
By month 12	477,169 (37.9%)	977,241 (37.9%)	204,190 (4.3%)	
By month 18	535,562 (42.5%)	1,096,829 (42.5%)	514,080 (10.8%)	
By month 24	593,955 (47.2%)	1,216,418 (47.2%)	823,971 (17.4%)	

Footnote: The (lower) Dementia due to AD population column is scenario 5 in Appendix A, the (higher) dementia due to AD population column is scenario 11 in Appendix B, and the MCI population column is scenario 14 in Appendix C.

Numbers may not sum due to rounding.

Among those starting the year as AD with mild dementia or MCI (amyloid positive), the mid estimates range from an average of 1,867 to 3,237 individuals with Medicare coverage progressing per day to moderate or severe dementia due to AD in the first 12 months, as seen in figure 1. The overall range was estimated to be as low as 1,165 per day to as high as 3,563 progressing per day to moderate or severe dementia due to AD, on average.

By month 12, approximately 9% to 16% of individuals who started as AD with mild dementia or MCI will have progressed to moderate or severe dementia due to AD. By month 24, approximately 21% to 28% of individuals will have progressed to moderate or severe dementia due to AD. Furthermore, approximately 81% to 89% of individuals remained as AD with mild dementia or MCI, and 2% to 3% of individuals died by month 12. By month 24, approximately 62% to 71% of individuals remained as AD with mild dementia or MCI, and 8% to 11% of individuals died.

Figure 3 presents the rate of severity progression over time for individuals who began the year as AD with mild dementia and figure 4 presents the rate of severity progression for individuals who began the year as MCI. Note that the estimates presented in figure 1 and in the previous paragraphs represent aggregated results for the combined AD with mild dementia and MCI populations, while figure 3 and figure 4 present the AD with mild dementia and MCI (amyloid positive) populations' severity progression separately.

Individuals who started the year with mild dementia due to AD are more likely to progress to moderate or severe dementia due to AD compared to individuals starting the year with MCI due to AD. By month 12, 37.9% of individuals with mild dementia due to AD progress to moderate (33.6%) or severe (4.3%) dementia due to AD, while only 4.3% of MCI individuals progress to moderate (3.7%) or severe (0.6%) dementia due to AD. By month 24, 47.2% of individuals with mild dementia due to AD progressed to moderate (32.2%) or severe (15.0%) dementia due to AD, while 17.4% of MCI individuals progressed to moderate (14.2%) or severe (3.2%) dementia due to AD.

FIGURE 3: SEVERITY PROGRESSION OVER TIME – MILD DEMENTIA DUE TO AD

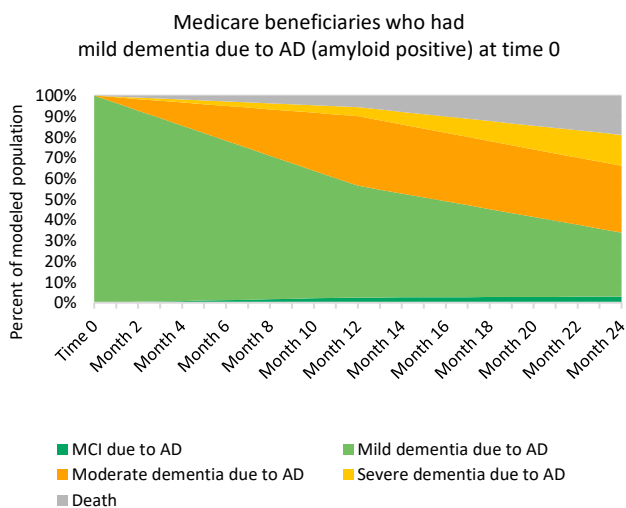
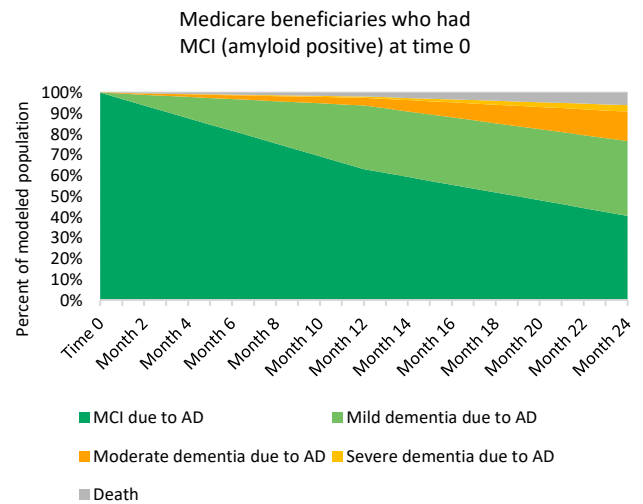


FIGURE 4: SEVERITY PROGRESSION OVER TIME – MCI DUE TO AD



Discussion

The assumptions used to inform the national population estimates of dementia due to AD and MCI are based on published prevalence and population studies. Using these varying sources resulted in a wide range in the estimated total number of individuals with dementia due to AD in the U.S., as seen in the top-line numbers of Figure 1. Variations in prevalence between the sources are likely due to the study population's characteristics and instruments or metrics used to measure and define MCI or dementia due to AD.

Additionally, prevalence studies are typically performed by closely studying a sample of individuals over time. For this reason, a prevalence estimate can include individuals who are diagnosed, as well as individuals who have the condition but are not yet diagnosed. A notable characteristic of MCI and dementia due to AD is a high rate of underdiagnosis, late diagnosis, or misdiagnosis. Among older adults with probable dementia, 58.7% were either undiagnosed (39.5%) or unaware of the diagnosis (19.2%).²¹ Another report noted that up to 30% of people with AD are misdiagnosed.²² Therefore, the U.S. prevalent population estimates represented in this study are likely to include individuals who have not yet been diagnosed.

There are many reasons why individuals with dementia due to AD, or MCI are underdiagnosed or misdiagnosed. According to one study:

- Undiagnosed individuals are more likely to be non-White and have lower educational attainment and less functional impairment.²¹
- There is a greater likelihood of being undiagnosed or unaware of a dementia diagnosis if an individual goes to doctor visits alone.²¹

In addition to social or demographic factors, there are other key contributors to misdiagnosis or underdiagnosis, including:

- The inherent uncertainty in clinical diagnosis.²³
- Lack of access to providers specialized in testing and diagnosing MCI or dementia due to AD.²²
- Policy barriers. As part of an NCD implemented in 2013, Medicare only covers amyloid PET scans for patients enrolled in a CED study, and furthermore, only covers one scan per patient per lifetime.⁸
- Reimbursement barriers. Diagnostic radiopharmaceuticals used to evaluate the presence of biomarkers, such as amyloid in a PET scan, are subject to a Hospital Outpatient Prospective Payment System (HOPPS) rate for Medicare patients. In a 2021 U.S. Government Accountability Office (GAO) study, hospitals noted that the HOPPS case rate does not adequately reimburse the entire cost of these types of tracers, making it financially infeasible for outpatient providers to use it regularly due to incurring a financial loss for each procedure performed.⁹
- Clinical stigma from the patient's perspective. A lack of public awareness and understanding of the disease can prevent people from seeking medical treatment when symptoms are present and receiving an early diagnosis or any diagnosis at all.²²
- Clinical stigma from the provider's perspective. Historical lack of effective and accessible treatment options may be a barrier to diagnosis, with one in three providers believing nothing can be done to treat the condition (as of a 2021 report).²²

In summary, the results presented in this report represent a prevalent population that assumes all individuals with AD or MCI have been diagnosed, their severity has been properly classified, and they have been tested to be amyloid positive. In the real world, there is a gap between the prevalent population and the diagnosed population, and furthermore, even fewer who have been tested for AD biomarkers, such as amyloid plaque. If patterns in diagnosing MCI and dementia due to AD improve, this could help “close the gap” between the currently diagnosed population and the prevalent population estimated in this analysis.

Conclusion

Among those starting the year with mild dementia or MCI clinically attributed to AD who are amyloid positive, it is estimated that an average of 1,867 to 3,237 individuals with Medicare coverage progress per day to moderate or severe AD in the first 12 months. The overall range was estimated to be as low as 1,165 per day to as high as 3,563 progressing per day to moderate or severe AD, on average. By month 12, approximately

9% to 16% of individuals who started as AD with mild dementia or MCI will have progressed to AD with moderate or severe dementia. By month 24, approximately 21% to 28% of individuals will have progressed to AD with moderate or severe dementia.

The NCD instituted by CMS for monoclonal antibodies directed against amyloid for treatment of Alzheimer's disease authorizes coverage of anti-amyloid treatments in the context of approved clinical studies only due to the CED requirement. Currently, patients who cannot access treatments while they are in the MCI or mild dementia stages of the disease may progress to a more severe form of dementia due to AD and miss the opportunity for treatment if they are not enrolled in an approved clinical study.

The results described in this analysis represent the amyloid positive AD with mild dementia and MCI prevalent population with Medicare coverage who progress to AD with moderate or severe dementia. Given the high rate of underdiagnosis or misdiagnosis of AD with MCI or dementia, there is a gap between the prevalent population and the currently diagnosed population. Key contributors to under- or misdiagnosis include social factors, reimbursement barriers, lack of specialty providers, and clinical stigma related to these conditions.

Limitations

Some sources used in this analysis are dated, e.g., Graham 1997²⁴, or are based on study populations in a small geographic location, e.g., Rajan 2021¹⁴ (Chicago, IL neighborhoods) and Yuan 2021²⁰ (Framingham, MA). Therefore, while these studies are published and frequently cited, there may be reasons why their findings are not nationally representative of AD and MCI in the United States.

The estimated number of people who are amyloid positive with MCI or mild dementia due to AD is not expected to be the number of people who will be treated with an amyloid-targeting therapy. Not all individuals with MCI or dementia due to AD may be considered appropriate for the approved and pipeline therapies by their healthcare provider.

Differences between the estimates and the actual number of individuals living with MCI or mild dementia due to AD depend on the extent to which future experience conforms to the assumptions made for this analysis. It is certain that actual experience will not conform exactly to the assumptions used in this analysis. The actual number of individuals will differ from estimated to the extent that actual experience deviates from expected experience.

Guidelines issued by the American Academy of Actuaries require actuaries to include their professional qualifications in all actuarial communications. Jessica Naber is a member of the American Academy of Actuaries and meets the qualification standards for performing the analyses in this report.

Appendix

APPENDIX A: LOWER TOP-LINE U.S. DEMENTIA DUE TO AD POPULATION ESTIMATES

Dementia due to AD (Lower)	Calculation	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5*	Scenario 6
Age 65+ ^{11,12,13,16 **}	A	3,157,057	3,157,057	3,157,057	3,157,057	3,157,057	3,157,057
Age <65 ^{11,12,13,16 **}	B	168,877	168,877	168,877	168,877	168,877	168,877
Total U.S. population	C = A+B	3,325,934	3,325,934	3,325,934	3,325,934	3,325,934	3,325,934
Dementia due to AD: Population with Medicare Coverage							
Dementia due to AD: Population with Medicare Coverage	Calculation						
Age 65+ ^{18,19 ±}	D = A*100%	3,157,057	3,157,057	3,157,057	3,157,057	3,157,057	3,157,057
Age <65 ^{18,19 ±}	E = B*3%	5,042	5,042	5,042	5,042	5,042	5,042
Total AD with dementia, Medicare cvg.	F = D+E	3,162,099	3,162,099	3,162,099	3,162,099	3,162,099	3,162,099
AD with mild dementia (% of AD)	G	28.8% ²⁴	28.8% ²⁴	28.8% ²⁴	50.4% ²⁰	50.4% ²⁰	50.4% ²⁰
Total AD with mild dementia	H = F*G	909,103	909,103	909,103	1,593,698	1,593,698	1,593,698
Amyloid positive (% of AD Mild Dem)	I	70.0% ^{16,17}	79.0% ^{16,17}	87.0% ¹⁷	70.0% ^{16,17}	79.0% ^{16,17}	87.0% ¹⁷
Total AD with mild dementia (amyloid positive) population	J = H*I	636,372	718,192	790,920	1,115,588	1,259,021	1,386,517
Progression to AD with Moderate or Severe Dementia	Percent of Total AD with Mild Dementia Pop.	Calculation: J*[Annual Transition probabilities] ¹⁰					
Avg. per day during year 1	NA	661	746	821	1,158	1,307	1,440
By month 6	19.0%	120,593	136,097	149,879	211,404	238,585	262,745
By month 12	37.9%	241,185	272,195	299,759	422,808	477,169	525,490
By month 18	42.5%	270,700	305,504	336,441	474,548	535,562	589,796
By month 24	47.2%	300,214	338,813	373,124	526,289	593,955	654,102
Remain AD with Mild Dementia or MCI							
By month 6	78.3%	497,961	561,985	618,895	872,948	985,184	1,084,950
By month 12	56.5%	359,550	405,778	446,870	630,307	711,347	783,382
By month 18	45.2%	287,523	324,490	357,349	504,040	568,845	626,449
By month 24	33.9%	215,495	243,201	267,829	377,772	426,342	469,516
Death							
By month 6	2.8%	17,818	20,109	22,146	31,236	35,253	38,822
By month 12	5.6%	35,637	40,219	44,292	62,473	70,505	77,645
By month 18	12.3%	78,150	88,198	97,129	137,000	154,615	170,272
By month 24	19.0%	120,663	136,177	149,967	211,528	238,724	262,899

* This is referred to as the lower AD mid estimate in the results section of the report. This scenario reflects sources that were most specific to the modeled population (e.g., AD with mild dementia, amyloid positive), was published in the last 10 years, and reflects the midpoint for the amyloid positive assumption.

**Calculated as dementia prevalence (source 11) times U.S. census by age band (source 12), adjusted to include age 90+ age segmentation (source 13), multiplied by the rate of AD among total dementia (source 16 noted 60-80% of dementia is AD dementia, this analysis assumed the midpoint of 70%).

± Calculated as U.S. Medicare enrollment (source 18) divided by U.S. census (source 19) by age band.

APPENDIX B: HIGHER TOP-LINE U.S. DEMENTIA DUE TO AD POPULATION ESTIMATES

Dementia due to AD (Higher)	Calculation	Scenario 7	Scenario 8	Scenario 9	Scenario 10	Scenario 11*	Scenario 12
Age 65+ ¹⁴	A	6,470,000	6,470,000	6,470,000	6,470,000	6,470,000	6,470,000
Age <65 ¹⁶	B	200,000	200,000	200,000	200,000	200,000	200,000
Total U.S. population	C = A+B	6,670,000	6,670,000	6,670,000	6,670,000	6,670,000	6,670,000
Dementia due to AD: Population with Medicare Coverage							
	Calculation						
Age 65+ ^{18,19 ±}	D = A*100%	6,470,000	6,470,000	6,470,000	6,470,000	6,470,000	6,470,000
Age <65 ^{18,19 ±}	E = B*3%	5,971	5,971	5,971	5,971	5,971	5,971
Total AD with dementia, Medicare cvg.	F = D+E	6,475,971	6,475,971	6,475,971	6,475,971	6,475,971	6,475,971
AD with mild dementia (% of AD)	G	28.8% ²⁴	28.8% ²⁴	28.8% ²⁴	50.4% ²⁰	50.4% ²⁰	50.4% ²⁰
Total AD with mild dementia	H = F*G	1,861,842	1,861,842	1,861,842	3,263,889	3,263,889	3,263,889
Amyloid positive (% of AD Mild Dem)	I	70.0% ^{16,17}	79.0% ^{16,17}	87.0% ¹⁷	70.0% ^{16,17}	79.0% ^{16,17}	87.0% ¹⁷
Total AD with mild dementia (amyloid positive) population	J = H*I	1,303,289	1,470,855	1,619,802	2,284,723	2,578,473	2,839,584
Progression to AD with Moderate or Severe Dementia	Percent of Total AD with Mild Dementia Pop.	Calculation: J*[Annual Transition probabilities] ¹⁰					
Avg. per day during year 1	NA	1,353	1,527	1,682	2,372	2,677	2,948
By month 6	19.0%	246,973	278,727	306,953	432,955	488,621	538,101
By month 12	37.9%	493,947	557,454	613,905	865,910	977,241	1,076,202
By month 18	42.5%	554,392	625,672	689,031	971,874	1,096,829	1,207,901
By month 24	47.2%	614,838	693,889	764,156	1,077,838	1,216,418	1,339,599
Remain AD with Mild Dementia or MCI							
By month 6	78.3%	1,019,824	1,150,944	1,267,495	1,787,795	2,017,655	2,221,974
By month 12	56.5%	736,358	831,033	915,188	1,290,868	1,456,837	1,604,365
By month 18	45.2%	588,846	664,554	731,851	1,032,272	1,164,993	1,282,967
By month 24	33.9%	441,333	498,076	548,514	773,676	873,148	961,568
Death							
By month 6	2.8%	36,492	41,184	45,354	63,972	72,197	79,508
By month 12	5.6%	72,984	82,368	90,709	127,944	144,394	159,017
By month 18	12.3%	160,051	180,629	198,921	280,576	316,651	348,716
By month 24	19.0%	247,118	278,890	307,132	433,209	488,907	538,416

*This is referred to as the higher mid estimate in the results section of the report. This scenario reflects sources that were most specific to the modeled population (e.g., AD with mild dementia, amyloid positive), was published in the last 10 years, and reflects the midpoint for the amyloid positive assumption.

± Calculated as U.S. Medicare enrollment (source 18) divided by U.S. census (source 19) by age band.

APPENDIX C: U.S. MCI POPULATION ESTIMATES

U.S. MCI Population	Calculation	Scenario 13	Scenario 14*	Scenario 15
Age 65+ ^{12,16} **	A	9,268,776	9,268,776	9,268,776
Age <65 ^{12,15} **	B	1,413,298	1,413,298	1,413,298
Total U.S. MCI population	C = A+B	10,682,074	10,682,074	10,682,074
MCI Population with Medicare Coverage	Calculation			
Age 65+ ^{18,19} ±	D = A*100%	9,268,776	9,268,776	9,268,776
Age <65 ^{18,19} ±	E = B*3%	42,193	42,193	42,193
Total MCI population with Medicare	F = D+E	9,310,969	9,310,969	9,310,969
MCI, amyloid positive (% of AD)	G	46.0% ¹⁷	51.0% ¹⁷	56.0% ¹⁷
Total MCI due to AD population	H = F*G	4,283,046	4,748,594	5,214,143
Progression to AD with Moderate or Severe Dementia	Percent of Total MCI due to AD Pop.	Calculation: J*[Annual Transition probabilities] ¹⁰		
Avg. per day during year 1	NA	505	559	614
By month 6	2.2%	92,085	102,095	112,104
By month 12	4.3%	184,171	204,190	224,208
By month 18	10.8%	463,680	514,080	564,480
By month 24	17.4%	743,190	823,971	904,753
Remain AD with Mild Dementia or MCI				
By month 6	96.9%	4,150,271	4,601,388	5,052,504
By month 12	93.8%	4,017,497	4,454,181	4,890,866
By month 18	85.2%	3,650,104	4,046,854	4,443,605
By month 24	76.6%	3,282,710	3,639,527	3,996,343
Death				
By month 6	1.0%	40,689	45,112	49,534
By month 12	1.9%	81,378	90,223	99,069
By month 18	4.0%	169,262	187,660	206,058
By month 24	6.0%	257,146	285,096	313,047

* This is referred to as the MCI mid estimate in the results section of the report. This scenario reflects sources that were most specific to the modeled population (e.g., MCI, amyloid positive), was published in the last 10 years, and reflects the midpoint for the amyloid positive assumption.

**Age <65 prevalence calculated as <65 MCI prevalence (source 15) times U.S. census for <65 (source 12); age 65+ prevalence calculated as 65+ MCI prevalence (source 16) times U.S. census for 65+ (source 12).

± Calculated as U.S. Medicare enrollment (source 18) divided by U.S. census (source 19) by age band.

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