D4.1 Catalogue of RWE relevant AD models and simplistic disease stage framework

116020 - ROADMAP

Real world Outcomes across the AD spectrum for better care: Multi-modal data Access Platform

WP4 – Disease Modelling and Simulation

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V1.2	28/04/2017	Integration of comments from consortium review (Chris Edgar, ROCHE) and final version

Definitions

- Partners of the ROADMAP Consortium are referred to herein according to the following codes:
  - **UOXF**. The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom) – **Coordinator**
  - **NICE**. National Institute for Health and Care Excellence (United Kingdom)
  - **EMC**. Erasmus University Rotterdam (Netherlands)
  - **UM**. Universiteit Maastricht (Netherlands)
  - **SYNAPSE**. Synapse Research Management Partners (Spain)
  - **IDIAP JORDI GOL**. Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (Spain)
  - **UCPH**. Københavns Universitet (Denmark)
  - **AE**. Alzheimer Europe (Luxembourg)
  - **UEDIN**. University of Edinburgh (United Kingdom)
  - **UGOT**. Goeteborgs Universitet (Sweden)
  - **AU**. Aarhus Universitet (Denmark)
  - **LSE**. London School of Economics and Political Science (United Kingdom)
  - **CBG/MEB**. Aagentschap College ter Beoordeling van Geneesmiddelen (Netherlands)
  - **IXICO**. IXICO Technologies Ltd (United Kingdom)
  - **RUG**. Rijksuniversiteit Groningen (Netherlands)
  - **Novartis**. Novartis Pharma AG (Switzerland)
  - **Eli Lilly**. Eli Lilly and Company Ltd (United Kingdom)
  - **BIOGEN**. Biogen Idec Limited (United Kingdom)
  - **ROCHE**. F. Hoffmann-La Roche Ltd (Switzerland)
  - **JPNV**. Janssen Pharmaceutica NV (Belgium)
  - **GE**. GE Healthcare Ltd (United Kingdom)
  - **AC Immune**. AC Immune SA (Switzerland)
- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ROADMAP project (116020).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ROADMAP Consortium, comprising the above-mentioned legal entities.
- **Consortium Agreement.** Agreement concluded amongst ROADMAP participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

Ab	Amyloid beta
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living
ADL	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AMCI	Amnestic Mild Cognitive Impairment
APCC	Alzheimer's Prevention Initiative Composite Cognitive test score
ApoE	Apolipoprotein E
BDRS	Blessed Dementia Rating Scale
BRaiNS	Biologically Resilient Adults in Neurological Studies
BRSD	Behavior Rating Scale for Dementia
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
ChEI	Cholinesterase Inhibitor
CSF	Cerebrospinal Fluid
DADE	Dependence in Alzheimer's Disease in England
EMCI	Early Mild Cognitive Impairment
EPS	Extrapyramidal Symptoms
FAQ	Functional Activities Questionnaire
FTC	Full-Time Care
IADL	Instrumental Activities of Daily Living
LASER	London and South-East Region
LMCI	Late Mild Cognitive Impairment
MCI	Mild Cognitive Impairment
mMMS	Modified Mini-Mental State Examination
MMSE	Mini-Mental State Examination
NACC-UDS	National Alzheimer Coordinating Center-Uniform Data Set
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory Questionnaire
PSMS	Physical Self-Maintenance Scale
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized Controlled Trial
SATS	Swedish Alzheimer Treatment Study
SIB	Severe Impairment Battery

Publishable Summary

This deliverable provides an inventory of existing disease progression models for mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia. Based on a systematic literature review, a total of 40 disease progression models were identified. For each model, contextual information (including data sources and size, disease stage, population characteristics, etc.), model outcome, and input variables required by the model were extracted. Additionally, three unpublished models developed by the EFPIA Consortium members were reviewed and described in a similar manner.

The models generate a variety of outcomes and cover various time horizons and disease stages. A large group of models predict changes in a clinical assessment scale, among which ADAS-cog and MMSE are the most frequent. Another group of models use transition probabilities to predict the probability of various disease stages or institutionalization. Several models provide an estimate of time-to-event, such as onset of AD or full-time care.

Four classes of input variables are distinguished: demographic, clinical, biomarker, and assessment scale. Many models incorporate demographic variables, in particular age and sex. Clinical variables, such as hypertension or psychotic symptoms, are infrequently used, with the exception of medication. Imaging biomarkers, such as hippocampal volume, are only used in a few studies, but presence of a mutation in the ApoE gene is considered more often. All models use one or more assessment scales as input variables. There is a wide variety of assessment scales across models, with ADAS-cog and MMSE being used most frequently. The number of variables per model varies between one and nine, with the great majority of models having five variables or less.

The results from this deliverable are a first step in achieving one of the main objectives of WP4, population of a "data cube" that offers an overview on data suitability and availability for modeling.

1. Introduction

In the past decades, various disease progression models for Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) dementia have been proposed in the literature. Disease progression models play a crucial role in both the assessment of any therapeutic intervention in the disease process and understanding the (economic) impact of these interventions, and may inform patient recruitment for randomized clinical trials (RCTs). In ROADMAP, we want to review and validate the available disease models, and to contribute to the further development of methods and data for disease modelling.

One of the primary objectives of WP4 is to build a "data cube" that offers a view on data suitability for modelling. In that data cube, the axes represent (a) the various disease stages, (b) the outcomes and variables in these stages, and (c) the availability of data in the various databases in ROADMAP. In this deliverable, we take a first step in building such a cube by making an inventory of the disease stages, input variables, and outcomes of existing disease progression models, and the context in which these models have been proposed.

A systematic literature review on MCI and AD dementia progression models performed by Biogen, one of the partners in ROADMAP, has been the starting point of this deliverable. As the literature search for this review was carried out in March 2016, an additional search was performed to include any relevant models that were published after that date.

In this deliverable, we focus on disease progression models. We explicitly excluded dementia risk prediction models. Health economics/decision-analytic models are included in the review, but we only considered the disease progression component of the model, ignoring the economic evaluation component.

This deliverable presents an inventory of the outcomes that are predicted by the models in combination with an inventory of the various input variables that the models require with their scope of applicability. We do not perform a detailed analysis or comparison of the strengths and weaknesses of the various models. We adopt a simple approach where we reduce the models to 'input' and 'output'. In addition, we provide a brief characterisation of the population for which the models shall be used. We do not express value judgements on the models, nor do we examine in detail whether the models were submitted to external validation.

2. Methods

The starting point for this deliverable was a systematic literature review, commissioned by Biogen, to identify published disease progression models for patients with MCI or AD dementia. The review included studies that reported disease progression models and economic evaluations with an underlying model, and covered literature up to March 2016. All studies characterized the progression of AD over time. A detailed description of the methods used to perform the literature review, can be found in the report of Biogen ("Systematic Literature Review on Disease Progression Models for Alzheimer's Disease and Mild Cognitive Impairment", contact person Michele Potashman, michele.potashman@biogen.com). Briefly, Pubmed and Embase searches were carried out using disease-specific, economic, epidemiological, and disease-progression model search terms (see Annex I for details). Studies were included if they focused on MCI or AD dementia and aimed at disease modelling or health-economic modelling. Non-English or animal studies were excluded, as were case studies, cross-sectional analyses, conference abstracts, and studies that did not provide full equations or only assessed the impact of risk factors on disease progression. A total of 37 models were identified, based on the full text of 101 articles that were reviewed by two researchers. Table 1 summarizes the list of such models with references, following the naming and chronological numbering from the Biogen report.

From this starting point, the model catalogue was updated by two means:

- First, a supplementary review was conducted to update the review with recently published models. Using the PubMed search terms as specified in the Biogen report, we identified and included another three models that were published after the search for the systematic review in March 2016 (Table 1).
- Second, three unpublished models developed by the EFPIA Consortium members were reviewed on a voluntary basis and integrated in the review (Table 2).

This deliverable therefore covers a total of 43 models.

Table 1. Disease progression models identified in the literature.

1	Stern ADAS-Cog Model (1994)
	Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiat. 1994;151:390-396.
2	Stern Growth Model (1996)
	Stern Y, Liu X, Albert M, et al. Application of a growth curve approach to modeling the progression of Alzheimer's disease. J Gerontol A-Biol. 1996;51:M179-184.
3	Smith ADAS-Cog Model (1996)
	Smith F. Mixed-model analysis of incomplete longitudinal data from a high-dose trial of tacrine (Cognex) in Alzheimer's patients. J Biopharm Stat. 1996;6:59-67.
4	Stewart MMSE Model (1998)
	Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. Int J Geriatr Psych. 1998;13:445-453.
5	Fenn and Gray MMSE Model (1999)
	Fenn P, Gray A. Estimating long-term cost savings from treatment of Alzheimer's disease. A

	modelling approach. Pharmacoeconomics. 1999;16:165-174.
6	O'Brien MMSE Model (1999)
	O'Brien BJ, Goeree R, Hux M, et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. J Am Geriatr Soc. 1999;47:570-578.
7	Kungsholmen-MMSE Model 1 (Jonsson et al 1999)
	Jonsson L, Lindgren P, Wimo A, Jonsson B, Winblad B. Costs of Mini Mental State Examination-related cognitive impairment. Pharmacoeconomics. 1999;16:409-416.
8	CERAD-MMSE Model 1 (Mendiondo et al 2000)
	Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA. Modelling mini mental state examination changes in Alzheimer's disease. Stat Med. 2000;19:1607-1616.
9	CERAD-MMSE Model 2 (Ashford and Schmitt 2001)
	Ashford JW, Schmitt FA. Modeling the time-course of Alzheimer dementia. Curr Psychiat Rep. 2001;3:20-28.
10	AHEAD Model (Caro 2001)
	Caro JJ, Getsios D, Migliaccio-Walle K, Raggio G, Ward A. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. Neurology. 2001;57:964-971.
11	CERAD-CDR Model (Neumann 2001)
	Neumann PJ, Araki SS, Arcelus A, et al. Measuring Alzheimer's disease progression with transition probabilities: estimates from CERAD. Neurology. 2001;57:957-964.
12	Rotterdam MMSE Model (McDonnell 2001)
	McDonnell J, Redekop WK, van der Roer N, et al. The cost of treatment of Alzheimer's disease in The Netherlands: a regression-based simulation model. Pharmacoeconomics. 2001;19:379-390.
13	Fuh CDR Model (2004)
	Fuh JL, Pwu RF, Wang SJ, Chen YH. Measuring Alzheimer's disease progression with transition probabilities in the Taiwanese population. Int J Geriatr Psych. 2004;19:266-270.
14	Jones Memantine MMSE Model (2004)
	Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. Drug Aging. 2004;21:607-620.
15	Teipel MCI MMSE Model (2007)
	Teipel SJ, Mitchell AJ, Moller HJ, Hampel H. Improving linear modeling of cognitive decline in patients with mild cognitive impairment: comparison of two methods. J Neural Transm. 2007;Suppl 72:241-247.
16	Ito AChEI ADAS-cog Model (2010)
	Ito K, Ahadieh S, Corrigan B, French J, Fullerton T, Tensfeldt T. Disease progression meta-analysis model in Alzheimer's disease. Alzheimers Dement. 2010;6:39-53.
17	CERAD-SIB Model (Weycker et al 2007)
	Weycker D, Taneja C, Edelsberg J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Curr Med Res Opin. 2007;23:1187-1197.
18	Wattmo ADAS-Cog/MMSE Model (2008)
	Wattmo C, Hansson O, Wallin AK, Londos E, Minthon L. Predicting long-term cognitive outcome with new regression models in donepezil-treated Alzheimer patients in a naturalistic setting. Dement Geriatr Cogn. 2008;26:203-211.
19	CERAD-MMSE Model 3 (Getsios 2010)
	Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics. 2010;28:411-427.
20	Rive ADAS-cog Model (2010a and b)

	Rive B, Le Reun C, Grishchenko M, et al. Predicting time to full-time care in AD: a new model. J Med Econ. 2010;13:362-370.
21	Ito ADNI ADAS-cog Model (2011)
	Ito K, Corrigan B, Zhao Q, et al. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. Alzheimers Dement. 2011;7:151-160.
22	Kavanagh Galantamine MMSE Model (2011)
	Kavanagh S, Van Baelen B, Schauble B. Long-term effects of galantamine on cognitive function in Alzheimer's disease: a large-scale international retrospective study. J Alzheimers Dis. 2011;27:521-530.
23	Lachaine Institutionalization Model (2011)
	Lachaine J, Beauchemin C, Legault M, Bineau S. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. Can J Psychiat. 2011;56:596-604.
24	Abner MCI Model (2012)
	Abner EL, Kryscio RJ, Cooper GE, et al. Mild cognitive impairment: statistical models of transition using longitudinal clinical data. Int J Alzheimers Dis. 2012;2012:291920.
25	Djalalov aMCI Model (2012)
	Djalalov S, Yong J, Beca J, et al. Genetic testing in combination with preventive donepezil treatment for patients with amnestic mild cognitive impairment: an exploratory economic evaluation of personalized medicine. Mol Diagn Ther. 2012;16:389-399.
26	Gomeni AChEI ADAS Model (2012)
	Gomeni R, Simeoni M, Zvartau-Hind M, Irizarry MC, Austin D, Gold M. Modeling Alzheimer's disease progression using the disease system analysis approach. Alzheimers Dement. 2012;8:39-50.
27	NACC-UDS CDR Model (Spackman et al 2012)
	Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD. Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Curr Alzheimer Res. 2012;9:1050-1058.
28	Samtani MCI-AD ADNI ADAS-cog Model (2012)
	Samtani MN, Raghavan N, Shi Y, et al. Disease progression model in subjects with mild cognitive impairment from the Alzheimer's disease neuroimaging initiative: CSF biomarkers predict population subtypes. Brit J Clin Pharmaco. 2012;75:146-161.
29	Delor ADNI CDR-SOB Model (2013)
	Delor I, Charoin JE, Gieschke R, Retout S, Jacqmin P. Modeling Alzheimer's disease progression using disease onset time and disease trajectory concepts applied to CDR-SOB scores from ADNI. CPT Pharmacometrics Syst Pharmacol. 2013;2:e78.
30	Handels Kungsholmen MMSE Model (Handels 2013)
	Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365.
31	Liu CDR/MMSE Model (2013)
	Liu W, Zhang B, Zhang Z, Zhou XH. Joint modeling of transitional patterns of Alzheimer's disease. PLoS One. 2013;8:e75487.
32	William-Faltaos ADAS-cog Model (2013)
	William-Faltaos D, Chen Y, Wang Y, Gobburu J, Zhu H. Quantification of disease progression and dropout for Alzheimer's disease. Int J Clin Pharm Th. 2013;51:120-131.
33	Yu MCI Model (2013)
	Yu H, Yang S, Gao J, al. e. Multi-state Markov model in outcome of mild cognitive impairments among community elderly residents in Mainland China. Int Psychoger. 2013;25:797_804.
34	Qiu ADNI ADAS-Cog Model (2014)

	Qiu Y, Li L, Zhou TY, Lu W. Alzheimer's disease progression model based on integrated biomarkers and clinical measures. Acta Pharmacol Sin. 2014;35:1111-1120.
35	Samtani ADNI CDR-SB Model (2014)
	Samtani MN, Raghavan N, Novak G, Nandy P, Narayan VA. Disease progression model for Clinical Dementia Rating-Sum of Boxes in mild cognitive impairment and Alzheimer's subjects from the Alzheimer's Disease Neuroimaging Initiative. Neuropsychiatr Dis Treat. 2014;10:929-952.
36	Hu Severity-Dependency Model (2015)
	Hu S, Yu X, Chen S, Clay E, Toumi M, Milea D. Memantine for treatment of moderate or severe Alzheimer's disease patients in urban China: clinical and economic outcomes from a health economic model. Expert Rev Pharmacoecon Outcomes Res. 2015;15:565-578.
37	Samtani ADAS-cog Bapineuzumab Model (2015)
	Samtani MN, Xu SX, Russu A, et al. Alzheimer's disease assessment scale-cognitive 11-item progression model in mild-to-moderate Alzheimer's disease trials of bapineuzumab. Alzheimers Dement Transl Res Clin Interv. 2015;1:157-169.
38	Green Multidomain Model (2016)
	Green C, Zhang S. Predicting the progression of Alzheimer's disease dementia: a multidomain health policy model. Alzheimers Dement. 2016;12:776-785.
39	Wattmo ADAS-Cog/MMSE/IADL/PSMS Model (2016)
	Wattmo C, Minthon L, Wallin AK. Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. Alzheimers Res Ther. 2016;8:7.
40	Guerrero Personalized Time-to-Conversion Model (2016)
	Guerrero R, Schmidt-Richberg A, Ledig C, et al. Neuroimage. 2016;142:113-125.

Table 2. Disease progression models as developed by EFPIA Consortium members.

41	Roche Guo Model Extension (2017)
	Based on Guo et al. (Pharmacoeconomics. 2014;32:1129-39) and extended to multiple order Markov chain structure.
42	Novartis Longitudinal Model (2017)
	Unpublished prevention longitudinal model describing time-to-MCI and time-to-dementia in correlation with biomarkers time course.
43	Eli Lilly PenTAG/GERAS Institutionalisation Model (2017)
	Unpublished time-to-institutionalisation model based on Green's PenTAG model updated with recent data from the GERAS study.

We then gathered the following information by screening the original publications of all models in Table 1 and by asking the developers of the models in Table 2:

- Contextual. This included information about data source(s) (e.g., RCT, cohort, or a specific well-known cohort such as ADNI (www.adni-info.org)), size (number of cases used in developing the model), sex, age, disease stages of the patient population that was used to develop the model (MCI, moderate-severe AD dementia, etc.), and follow-up period.
- Outcome. The outcome of the disease progression models included outcomes related to assessment scales of disease progression (e.g., ADAS-cog or MMSE), transition probabilities (such as transition from MCI to AD dementia), and time-to-event (e.g., time to full-time care).

Note that a model could provide several outcomes, e.g., if multiple clinical assessment scales were modelled.

- Variables. These were the input variables required by each model to generate the outcome. We subdivided the input variables in four categories: demographic (age, sex, race, etc.), clinical (hypertension, diabetes, medication, etc.), biomarker (ApoE, etc.), and clinical assessment scale (ADAS-cog, MMSE, etc.).

3. Results

Information about context, outcome, and input variables was extracted for all models in Tables 1 and 2. The detailed results for each individual model are given in Annex II. Here we focus on the disease stages of the study population that was used to develop the model, the outcome of the model, and on input variables.

The results for disease stages are presented in Table 3. The model numbers following each outcome refer to the model numbers in Tables 1 and 2. The far majority of the models are based on AD dementia patients, mostly covering all AD dementia stages from mild to severe, but also focussing on subgroups of mild to moderate or moderate to severe AD dementia patients. A minority of models included patients with MCI, sometimes distinguishing between different stages of MCI. Only a few studies cover the whole spectrum from normal to AD dementia. The definitions of the different disease stages vary across studies. Some use a cognition scale (such as MMSE), but others use more elaborate scoring systems, in particular for (staging of) MCI. These definitions will have to be carefully considered when externally validating the models to make certain that a model is applied to a similar population that was used to derive the model.

Table 3. Disease stages of the study population that was used to develop disease progression models.

Stage	Model number
AD	1, 2, 8, 9, 11, 12, 13, 18, 19, 20, 22, 23, 27, 28, 30, 31, 38, 41, 43
mild-moderate AD	3, 4, 6, 10, 16, 26, 32, 37, 39
moderate-severe AD	14, 17, 36
AMCI	15, 25
LMCI/AD	35
MCI	28, 30, 33
MCI/AD	5, 7, 29, 40
normal/EMCI/LMCI/AD	34
normal/MCI stages/dementia	24
normal/MCI/AD	21, 42

The various model outcomes are presented in Table 4. Many models predict (rate of) change in a clinical assessment scale. A variety of scales have been studied, but most models focus on ADAS-cog or MMSE. Other models use transition probabilities to estimate the probability of a particular disease stage or institutionalization with progressing disease, often as part of a health economics model. A number of studies focus on predictors of transitions between different stages. Finally, several models provide time-to-event estimates, where the event can be, e.g., full-time care or onset of AD dementia.

Table 4. Outcomes of disease progression models.

Outcome	Model number
ADAS-cog	1, 3, 16, 18, 21, 26, 28, 32, 34, 37, 39
ADAS-cog rate	1
Katz ADL	30
ADL rate	19
APCC	42
CDR-SB	29, 35
IADL	39
IADL rate	2, 19
mMMS rate	2
MMSE	18, 30, 39, 41
MMSE rate	9, 12, 15, 19, 22
NPI	41
NPI rate	19
PSMS	39
SIB rate	17
Predictors of transition AD stages/death	27
Predictors of transition MCI/global impairment/AD	33
Predictors of transition normal/MCI stages/dementia/death	24
Predictors of transition stage-to-stage/death	13
Predictors of transition stage-to-stage/nursing home/death	11
Probability AD stage	31, 38
Probability AD stage/death	4, 6, 7
Probability AD stage/dependent/aggressive/death	36
Probability AD stage/dependent/institutionalized/death	14
Probability AD stage/institutionalized/death	27
Probability AMCI/AD/death	25
Probability institutionalized/death	12, 23
Time to AD	30
Time to FTC	10, 20
Time to MCI/AD	40, 42
Time to MMSE	5, 8, 9
Time to death	10, 43
Time to institutionalisation	43

Table 5 shows the input variables of the different progression models. Models use a variety of demographic variables. Age and sex are the most frequently used.

Clinical variables are hardly incorporated, except for medication. It should be noted that we chose to only mark if a medication variable was used in the model, without indicating the specific medication (e.g., which cholinesterase inhibitor was studied). The specific definition of this variable may therefore vary from model to model.

A mutation in the ApoE gene is included as a biomarker in 11 models, but other (imaging) biomarkers are only used in five studies.

Clinical assessment scales are used as input variables in most models. MMSE and ADAS-cog are the most frequently used clinical scales, followed at some distance by CDR and NPI. Different rating scales for ADL are employed (ACDS-ADL, Katz index of ADL, IADL scale). Some studies do not specify the ADL scales that were used (models 19 and 36). Most of the other scales are only used by one or two models.

Table 5. Variables in disease progression models.

Variable	**Model number**
Demographic	
Age	5, 10, 11, 12, 13, 19, 21, 22, 24, 26, 27, 28, 29, 30, 31, 33, 34, 37, 39, 40, 41, 42, 43
Age onset AD	28, 30, 37, 43
Education	12, 24, 26, 27, 33, 39, 40
Ethnicity	27
Institutionalization	11, 12, 14, 23, 27, 39
Married	27
Race	19, 27, 30
Reading	33
Sex	10, 11, 12, 13, 19, 21, 24, 27, 30, 33, 37, 40, 41, 42, 43
Time since baseline	1, 3, 12, 16, 18, 19, 22, 26, 39
Time since last visit	27
Clinical	
Diabetes	33
EPS	10
Family history of dementia	24
Hypertension	24, 33
Medication	4, 5, 6, 7, 13, 14, 19, 22, 23, 25, 35, 36, 37, 39
Psychotic symptoms	10, 13
Biomarker	
ApoE	12, 21, 24, 25, 26, 28, 31, 34, 37, 40, 42
CSF tau/Ab ratio	28, 34, 35, 42
Hippocampal volume	28, 29, 34, 35
Intracranial volume	29
Serum cholesterol	28
Ventricular volume	28
Assessment scale	
ADAS-cog	1, 3, 16, 18, 20, 26, 28, 29, 32, 34, 39, 40
ADCS-ADL	14, 20, 43
ADL	19, 36
APCC	42

BDRS	2
BRSD	11
CDR global	11, 13, 27, 31
CDR-SB	29, 35, 40
Delayed logical memory	35
FAQ	29, 31, 38, 40
IADL	19, 39
mMMS	2, 10
MMSE	4, 5, 6, 7, 8, 9, 12, 14, 15, 18, 19, 21, 22, 25, 26, 29, 30, 31, 32, 36, 38, 39, 40, 41, 43
NPI	19, 20, 36, 41, 43
NPI-Q	38
PSMS	39
Previous stage	27, 34
RBANS	42
SIB	17
slope ADAS-cog	20
slope ADL	20
Trail A test	35
Trail B test	28

The number of input variables per model varies, from one to nine variables. Figure 1 shows the distribution according to the number of variables per model. (Note that a single study in Table 1 can have more than one outcome, and thus multiple models.) The majority of models contains five variables or less (48/62), while a third (21/62) has only one or two variables.

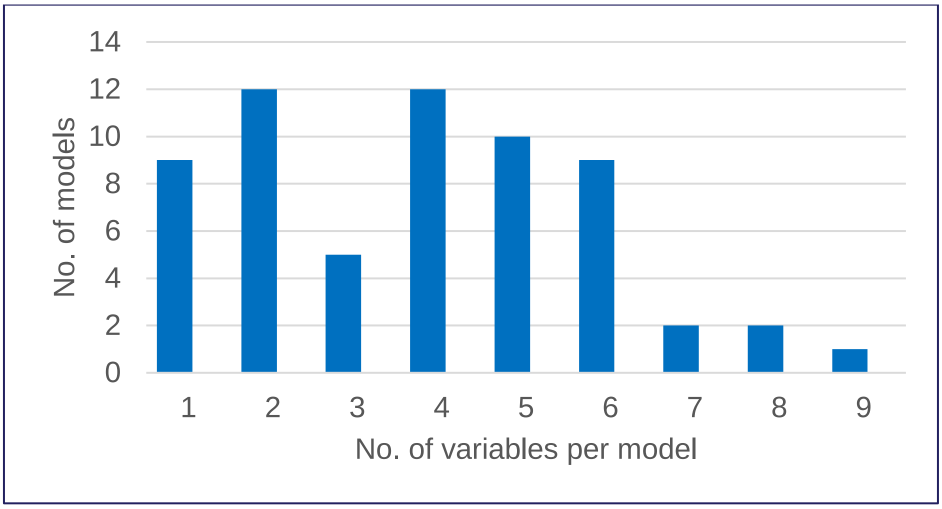

Figure 1. Distribution of models according to the number of variables per model.

4. Discussion

We have made an inventory of the data requirements of existing disease progression models for MCI and AD dementia, focusing on the input variables and outcome of the models. The data requirements and model outputs of the various models vary considerably and typically depend on the modelling objectives and disease stages covered by the model.

The “rate of change” models typically show the average rate of decline and often use the assessment score, either alone (e.g., models 1, 2, 9 in Table 1) or in combination with other predictors among which demographics (e.g., models 12 or 19) to adjust for the non-linearity (often caused by floor and ceiling levels at which progression rate is slow). Models describing an assessment score over time often have time as the main predictor and use demographic and other variables to adjust for individual differences and non-linearity. The number of covariates typically is small. In most cases, such covariates are not time-dependent, hence may not disentangle population variability from differences in disease stage.

Age and sex are most frequently incorporated. Other covariates are often only used in a few models. In some of the more recent models, multiple assessment scales are used as input variables (e.g., models 31, 37, 38, 40).

Some of the MCI to AD dementia models are based on survival analysis (e.g., model 30), and predict time-to-event rather than using time as an independent variable in models that describe changes in symptoms over time, such as many of the models in dementia stages. This is probably due to a lack of sensitive scales for MCI to model changes over time.

A large number of models are based on transition probabilities between disease stages, e.g., mild, moderate, and severe AD dementia. Given an initial stage, these models can estimate the probability of disease progression in a certain time period. To determine the stage of the disease, some studies use a cognition scale (such as MMSE), but other studies use a more elaborate scoring system.

Very few models were externally validated. Essential in the external validation of disease progression models will be the accurate staging of the patients in the data source that provides the data for the validation. One also will need to ensure that the population for which the model is applied is in line with the population that was used to derive the model.

In models based on transition probabilities (Markov models), covariates that affect the probabilities are presented in two ways. In some models (e.g., 12, 14, 36), transition probabilities are provided for each combination of stage and covariate(s). In essence, one needs to know the value of the variable in order to select the appropriate probabilities. In other studies (11, 13, 24, 27, 33), hazard ratios are estimated to determine which covariates are significant predictors of transitions between two stages – but the transition probabilities themselves are not adapted or modified based on the covariate. In limited cases, covariates are considered time-dependent (inhomogeneous Markov models). In very few cases, a second- or third-order Markovian structure is considered in order to capture patient history for the prediction of future states (model 41).

Note that especially for time-to-event models, time-to-death would need to be considered as a default outcome in order to account for competing risk, which is not negligible given the aging population of interest.

One of the objectives of WP4 is to perform external validation of existing disease progression models. Based on the results of this deliverable, we will query the data sources participating in ROADMAP in order to get an understanding whether they can provide the required data (outcome and variables). This will allow us to start filling the data cube and to determine which data sources would be able to perform an external validation of a given model. Note that the collection of additional data is not foreseen in this stage (the first two years of ROADMAP).

It should be pointed out that once model validation is started, a detailed analysis will have to be performed to harmonize or align data from the data sources and model requirements. We expect that such an analysis will reveal significant challenges that must be addressed in the validation protocol. We also anticipate that, in order to focus validation efforts, we will have to select a limited number of disease progression models.

5. Conclusion and next steps

A variety of models have been proposed to describe disease progression to MCI and AD dementia. From a data requirement perspective, the total list of variables is large but individual models generally include a limited number of variables, typically five or less. Demographic variables and assessment scales are the most frequently used variables.

Almost all of the disease progression models that were identified in this deliverable have been published in the literature. Unpublished models from three EFPIA partners in ROADMAP have also been included. EFPIA partners are invited to consider sharing further information about their internally used models for inclusion in the model inventory presented in this deliverable.

Next steps include querying the available data sources in ROADMAP for the variables and outcomes identified in this deliverable. This will allow us to further fill the data cube, and indicate which models, in principle, could be validated. We anticipate significant challenges related to data alignment between data sources and model requirements. In order to limit the workload, we need to identify the most promising models that will be the subject of a validation study.

The current inventory focused on disease progression models. At a later stage in WP4 we will also do a similar exercise for dementia risk prediction models.

ANNEXES

ANNEX I. Literature-review methodology

The methodology to perform the systematic literature review that has been the starting point of this deliverable, has been described in the Biogen report "Systematic Literature Review on Disease Progression Models for Alzheimer's Disease and Mild Cognitive Impairment" (contact person Michele Potashman, michele.potashman@biogen.com). The following description has been taken from the Biogen report:

> Separate searches within Pubmed/MEDLINE and Embase/Proquest search were carried out on March 29, 2016 using disease-specific search terms, economics search terms, and disease progression models search terms (see below for full search term details). Once each search was executed within Pubmed and Embase, hits were combined and deduplicated to obtain a total of 2643 hits. Titles and abstracts were searched by a total of four researchers; each article was individually screened by two individuals. Discrepancies in the screening process between the individual screeners were then resolved by each screener at each stage.
>
> Studies were included if they focused on Alzheimer disease or mild cognitive impairment and belonged to any one of the following broad study types:
>
> a) Health economic modeling / decision analytic studies
>
> b) Disease modeling study where objective is to model progression through time
>
> c) Systematic reviews and/or meta-analysis evaluating disease progression through time or economic models for citation review.
>
> Studies were excluded based on the following:
>
> a) Non-English articles
>
> b) Non-human animal studies
>
> c) Basic science/molecular studies
>
> d) Case studies and case series
>
> e) Cross-sectional analyses
>
> f) Studies that evaluate disease progression but do not provide full equations or solely evaluate the impact of risk factors on disease progression
>
> g) Conference abstracts, editorials, letters, commentaries, non-systematic review articles

Search Terms for Pubmed

Disease Search Terms

1. "Alzheimer Diseases"[MeSH]
2. "Mild Cognitive Impairment"[MeSH]
3. "mild cognitive impairment"[tiab] OR "MCI"[tiab]
4. Alzheimer*[tiab]
5. 1 or 2 or 3 or 4

Subtotal = 126,943

Economics Search Terms

6. “Cost-Benefit Analysis”[MeSH]
7. “Cost-Effectiveness”[tiab]
8. “Cost-Utility”[tiab]
9. “Economic”[tiab] AND model*[tiab]
10. “Decision Theory”[MeSH]
11. Markov*[tiab] AND model*[tiab]
12. “Markov Chains”[MeSH]
13. “Discrete Event Simulation”[tiab]
14. “DES”[tiab] AND model*
15. “Decision analytic”[tiab] AND model*[tiab]
16. Decision tree*[tiab]
17. “Monte Carlo”[tiab]
18. “Monte Carlo Method”[MeSH]
19. “Models, Economic”[MeSH]
20. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

Subtotal = 177,305

Disease Progression Models Search Terms

21. "Disease Progression"[MeSH]
22. “disease progression"[tiab] OR “progression of disease”[tiab]
23. "Natural History"[MeSH]
24. "natural history"[tiab]
25. 21 OR 22 OR 23 OR 24
26. "Models, Statistical"[MeSH]
27. "Models, Biological"[MeSH]
28. Model*[tiab]
29. "Disease Models, Animal"[MeSH]
30. 25 AND (26 OR 27 OR 28) NOT 29

Subtotal = 27,857

Combination of Search Terms

31. 5 AND 20 (n=807)
32. 5 AND 30 (n=1300)
33. 31 OR 32

Total in Pubmed = 2,031

Search Terms for Embase/Proquest

Disease Search Terms

1. emb.explode(“alzheimer disease”)
2. emb.explode(“mild cognitive impairment”)
3. ti(Alzheimer) OR ab(Alzheimer)

4. mesh.EXACT.explode(“alzheimer disease”)
5. mesh.EXACT.explode(“mild cognitive impairment”)
6. emb.exact.explode(“mild cognitive impairment”)
7. ti(mild cognitive impairment) OR ab(mild cognitive impairment OR ti(MCI) OR ab(MCI)
8. la.exact(“English”)
9. rtype.exact(“Conference Abstract”)
10. (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7) AND 8 NOT 9

Subtotal = 153,182

Economics Search Terms

11. emb.exact.explode(“cost benefit analysis”)
12. emb.exact.explode(“decision theory”)
13. mesh.exact.explode(“Markov Chains”)
14. mesh.exact.explode(“Discrete Event Simulation”)
15. ti(DES) OR ab(DES)
16. ti(decision analytic) OR ab(decision analytic)
17. ti(decision tree) OR ab(decision tree)
18. ti(monte carlo) OR ab(monte carlo)
19. emb.exact.explode(“Monte Carlo Method”)
20. ti(cost effectiveness) OR ab(cost effectiveness) OR ti(cost-effectiveness) OR ab(cost-effectiveness)
21. ti(cost utility) OR ab(cost utility) OR ti(cost-utility) OR ab(cost-utility)
22. emb.exact.explode(“Models, Economic”)
23. emb..exact.explode(“Cost-Benefit Analysis”)
24. la.exact(“English”)
25. rtype.exact(“Conference Abstract”)
26. (11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23) AND 24 NOT 25

Subtotal = 160,162

Disease Progression Models Search Terms

27. emb.exact.explode(“disease progression”)
28. ti(“disease progression” OR “progression of disease” OR ab(“disease progression” OR “progression of disease”
29. emb.exact.explode(“natural history”) OR ti(“natural history” OR ab(“natural history”)
30. 27 OR 28 OR 29
31. emb.exact.explode(“models, statistical”)
32. emb.exact.explode(“models, biological”)
33. ti(model) OR ab(model)
34. 31 OR 32 OR 33
35. la.exact(“English”)
36. rtype.exact(“Conference Abstract”)
37. 30 AND 34 AND 35 NOT 36

Subtotal = 13,925

Combination of Search Terms

38. 10 and 26 (n=864)
39. 10 AND 37 (n=665)
40. 38 OR 39

Total in Embase = 1,494

Total in PubMed and Embase = 2,643

ANNEX II. Characteristics of disease progression models

The contextual, outcome, and variable information for each of the 43 disease progression models identified in the literature and developed by EFPIA Consortium members is presented in the list below, in chronological order. If a study had multiple outcomes, a separate entry is provided for each outcome. Study number and name in the list for the first 37 models are the same as those in the Biogen report.

An Excel file with all extracted information is also available.

Study: 1. Stern ADAS-Cog Model (1994)
Reference: Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiat. 1994;151:390-396.
Data source: Cohort
Size, n: 111
Female, %:
Age, yr: 68
Disease stage: AD
Follow-up, yr:
Outcome: ADAS-cog rate
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: ADAS-cog

Study: 1. Stern ADAS-Cog Model (1994)
Reference: Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiat. 1994;151:390-396.
Data source: Cohort
Size, n: 72
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: ADAS-cog
Variables:
Demographic: Time since baseline
Clinical:
Biomarker:
Assessment scale: ADAS-cog

Study: 2. Stern Growth Model (1996)
Reference: Stern Y, Liu X, Albert M, et al. Application of a growth curve approach to modeling the progression of Alzheimer's disease. J Gerontol A-Biol. 1996;51:M179-184.
Data source: Cohort
Size, n: 236
Female, %: 59

Age, yr: 73
Disease stage: AD
Follow-up, yr:
Outcome: mMMS rate
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: mMMS

Study: 2. Stern Growth Model (1996)
Reference: Stern Y, Liu X, Albert M, et al. Application of a growth curve approach to modeling the progression of Alzheimer's disease. J Gerontol A-Biol. 1996;51:M179-184.
Data source: Cohort
Size, n: 236
Female, %: 59
Age, yr: 73
Disease stage: AD
Follow-up, yr:
Outcome: IADL rate
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: BDRS

Study: 3. Smith ADAS-Cog Model (1996)
Reference: Smith F. Mixed-model analysis of incomplete longitudinal data from a high-dose trial of tacrine (Cognex) in Alzheimer's patients. J Biopharm Stat. 1996;6:59-67.
Data source: RCT
Size, n: 663
Female, %:
Age, yr:
Disease stage: mild-moderate AD
Follow-up, yr: 0.6
Outcome: ADAS-cog
Variables:
Demographic: Time since baseline
Clinical:
Biomarker:
Assessment scale: ADAS-cog

Study: 4. Stewart MMSE Model (1998)
Reference: Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. Int J Geriatr Psych. 1998;13:445-453.
Data source: Cohort, RCT
Size, n:
Female, %:
Age, yr:

Disease stage: mild-moderate AD
Follow-up, yr:
Outcome: Probability AD stage/death
Variables:
Demographic:
Clinical: Medication
Biomarker:
Assessment scale: MMSE

Study: 5. Fenn and Gray MMSE Model (1999)
Reference: Fenn P, Gray A. Estimating long-term cost savings from treatment of Alzheimer's disease. A modelling approach. Pharmacoeconomics. 1999;16:165-174.
Data source: RCT
Size, n: 1333
Female, %:
Age, yr:
Disease stage: MCI/AD
Follow-up, yr:
Outcome: Time to MMSE
Variables:
Demographic: Age
Clinical: Medication
Biomarker:
Assessment scale: MMSE

Study: 6. O'Brien MMSE Model (1999)
Reference: O'Brien BJ, Goeree R, Hux M, et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. J Am Geriatr Soc. 1999;47:570-578.
Data source: RCT
Size, n: 473
Female, %: 62
Age, yr: 73
Disease stage: mild-moderate AD
Follow-up, yr: 0.5
Outcome: Probability AD stage/death
Variables:
Demographic:
Clinical: Medication
Biomarker:
Assessment scale: MMSE

Study: 7. Kungsholmen-MMSE Model 1 (Jonsson et al 1999)
Reference: Jonsson L, Lindgren P, Wimo A, Jonsson B, Winblad B. Costs of Mini Mental State Examination-related cognitive impairment. Pharmacoeconomics. 1999;16:409-416.
Data source: Cohort, RCT
Size, n: 1522, 473
Female, %: 76,
Age, yr: 82,
Disease stage: MCI/AD

Follow-up, yr: 3.3, 0.6
Outcome: Probability AD stage/death
Variables:
  Demographic:
  Clinical: Medication
  Biomarker:
  Assessment scale: MMSE

Study: 8. CERAD-MMSE Model 1 (Mendiondo et al 2000)
Reference: Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA. Modelling mini mental state examination changes in Alzheimer's disease. Stat Med. 2000;19:1607-1616.
Data source: CERAD
Size, n: 719
Female, %: 58
Age, yr: 72
Disease stage: AD
Follow-up, yr: 2.3
Outcome: Time to MMSE
Variables:
  Demographic:
  Clinical:
  Biomarker:
  Assessment scale: MMSE

Study: 9. CERAD-MMSE Model 2 (Ashford and Schmitt 2001)
Reference: Ashford JW, Schmitt FA. Modeling the time-course of Alzheimer dementia. Curr Psychiat Rep. 2001;3:20-28.
Data source: CERAD
Size, n: 981
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: MMSE rate
Variables:
  Demographic:
  Clinical:
  Biomarker:
  Assessment scale: MMSE

Study: 9. CERAD-MMSE Model 2 (Ashford and Schmitt 2001)
Reference: Ashford JW, Schmitt FA. Modeling the time-course of Alzheimer dementia. Curr Psychiat Rep. 2001;3:20-28.
Data source: CERAD
Size, n: 981
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: Time to MMSE
Variables:

Demographic:
Clinical:
Biomarker:
Assessment scale: MMSE

Study: 10. AHEAD Model (Caro 2001)
Reference: Caro JJ, Getsios D, Migliaccio-Walle K, Raggio G, Ward A. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. Neurology. 2001;57:964-971.
Data source: Cohort
Size, n: 236
Female, %:
Age, yr:
Disease stage: mild-moderate AD
Follow-up, yr:
Outcome: Time to FTC
Variables:
Demographic: Age
Clinical: Psychotic symptoms, EPS
Biomarker:
Assessment scale: mMMS

Study: 10. AHEAD Model (Caro 2001)
Reference: Caro JJ, Getsios D, Migliaccio-Walle K, Raggio G, Ward A. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. Neurology. 2001;57:964-971.
Data source: Cohort
Size, n: 236
Female, %:
Age, yr:
Disease stage: mild-moderate AD
Follow-up, yr:
Outcome: Time to death
Variables:
Demographic: Sex
Clinical: EPS
Biomarker:
Assessment scale: mMMS

Study: 11. CERAD-CDR Model (Neumann 2001)
Reference: Neumann PJ, Araki SS, Arcelus A, et al. Measuring Alzheimer's disease progression with transition probabilities: estimates from CERAD. Neurology. 2001;57:957-964.
Data source: CERAD
Size, n: 1145
Female, %: 60
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: Predictors of transition stage-to-stage/nursing home/death
Variables:
Demographic: Age, Sex, Institutionalization

Clinical:
Biomarker:
Assessment scale: BRSD, CDR global

Study: 12. Rotterdam MMSE Model (McDonnell 2001)
Reference: McDonnell J, Redekop WK, van der Roer N, et al. The cost of treatment of Alzheimer's disease in The Netherlands: a regression-based simulation model. Pharmacoeconomics. 2001;19:379-390.
Data source: Cohort pop
Size, n: 306/95
Female, %: 77/80
Age, yr: 85/84
Disease stage: AD
Follow-up, yr: 2.1
Outcome: MMSE rate
Variables:
Demographic: Age, Time since baseline, Sex, Education
Clinical:
Biomarker: ApoE
Assessment scale:

Study: 12. Rotterdam MMSE Model (McDonnell 2001)
Reference: McDonnell J, Redekop WK, van der Roer N, et al. The cost of treatment of Alzheimer's disease in The Netherlands: a regression-based simulation model. Pharmacoeconomics. 2001;19:379-390.
Data source: Cohort pop
Size, n: 306/95
Female, %: 77/80
Age, yr: 85/84
Disease stage: AD
Follow-up, yr: 2.1
Outcome: Probability institutionalized/death
Variables:
Demographic: Age, Time since baseline, Sex, Institutionalization
Clinical:
Biomarker:
Assessment scale: MMSE

Study: 13. Fuh CDR Model (2004)
Reference: Fuh JL, Pwu RF, Wang SJ, Chen YH. Measuring Alzheimer's disease progression with transition probabilities in the Taiwanese population. Int J Geriatr Psych. 2004;19:266-270.
Data source: Observational
Size, n: 365
Female, %: 54
Age, yr: 73
Disease stage: AD
Follow-up, yr: 2.5
Outcome: Predictors of transition stage-to-stage/death
Variables:
Demographic: Age, Sex
Clinical: Psychotic symptoms, Medication

Biomarker:
Assessment scale: CDR global

Study: 14. Jones Memantine MMSE Model (2004)
Reference: Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. Drug Aging. 2004;21:607-620.
Data source: RCT, LASER
Size, n: 252,
Female, %:
Age, yr:
Disease stage: moderate-severe AD
Follow-up, yr:
Outcome: Probability AD stage/dependent/institutionalized/death
Variables:
Demographic: Institutionalization
Clinical: Medication
Biomarker:
Assessment scale: MMSE, ADCS-ADL

Study: 15. Teipel MCI MMSE Model (2007)
Reference: Teipel SJ, Mitchell AJ, Moller HJ, Hampel H. Improving linear modeling of cognitive decline in patients with mild cognitive impairment: comparison of two methods. J Neural Transm. 2007;Suppl 72:241-247.
Data source: Cohort
Size, n: 78
Female, %: 49
Age, yr: 72
Disease stage: AMCI
Follow-up, yr: 1
Outcome: MMSE rate
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: MMSE

Study: 16. Ito AChEI ADAS-cog Model (2010)
Reference: Ito K, Ahadieh S, Corrigan B, French J, Fullerton T, Tensfeldt T. Disease progression meta-analysis model in Alzheimer's disease. Alzheimers Dement. 2010;6:39-53.
Data source: RCT meta-analysis
Size, n:
Female, %:
Age, yr: 74
Disease stage: mild-moderate AD
Follow-up, yr:
Outcome: ADAS-cog
Variables:
Demographic: Time since baseline
Clinical:
Biomarker:

Assessment scale: ADAS-cog

Study: 17. CERAD-SIB Model (Weycker et al 2007)
Reference: Weycker D, Taneja C, Edelsberg J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Curr Med Res Opin. 2007;23:1187-1197.
Data source: Cohort
Size, n: 180
Female, %:
Age, yr:
Disease stage: moderate-severe AD
Follow-up, yr:
Outcome: SIB rate
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: SIB

Study: 18. Wattmo ADAS-Cog/MMSE Model (2008)
Reference: Wattmo C, Hansson O, Wallin AK, Londos E, Minthon L. Predicting long-term cognitive outcome with new regression models in donepezil-treated Alzheimer patients in a naturalistic setting. Dement Geriatr Cogn. 2008;26:203-211.
Data source: SATS
Size, n: 435
Female, %: 65
Age, yr: 75
Disease stage: AD
Follow-up, yr: 3
Outcome: ADAS-cog
Variables:
Demographic: Time since baseline
Clinical:
Biomarker:
Assessment scale: MMSE, ADAS-cog

Study: 18. Wattmo ADAS-Cog/MMSE Model (2008)
Reference: Wattmo C, Hansson O, Wallin AK, Londos E, Minthon L. Predicting long-term cognitive outcome with new regression models in donepezil-treated Alzheimer patients in a naturalistic setting. Dement Geriatr Cogn. 2008;26:203-211.
Data source: SATS
Size, n: 435
Female, %: 65
Age, yr: 75
Disease stage: AD
Follow-up, yr: 3
Outcome: MMSE
Variables:
Demographic: Time since baseline
Clinical:

Biomarker:
Assessment scale: MMSE

Study: 19. CERAD-MMSE Model 3 (Getsios 2010)
Reference: Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics. 2010;28:411-427.
Data source: CERAD
Size, n:
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: MMSE rate
Variables:
Demographic: Age
Clinical:
Biomarker:
Assessment scale: MMSE

Study: 19. CERAD-MMSE Model 3 (Getsios 2010)
Reference: Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics. 2010;28:411-427.
Data source: CERAD
Size, n:
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: NPI rate
Variables:
Demographic: Time since baseline, Race
Clinical: Medication
Biomarker:
Assessment scale: MMSE, NPI

Study: 19. CERAD-MMSE Model 3 (Getsios 2010)
Reference: Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics. 2010;28:411-427.
Data source: CERAD
Size, n:
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: ADL rate
Variables:
Demographic: Time since baseline, Race
Clinical: Medication
Biomarker:

Assessment scale: MMSE, ADL

Study: 19. CERAD-MMSE Model 3 (Getsios 2010)
Reference: Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics. 2010;28:411-427.
Data source: CERAD
Size, n:
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: IADL rate
Variables:
Demographic: Time since baseline, Sex
Clinical: Medication
Biomarker:
Assessment scale: MMSE, ADL, IADL

Study: 20. Rive ADAS-cog Model (2010a and b)
Reference: Rive B, Le Reun C, Grishchenko M, et al. Predicting time to full-time care in AD: a new model. J Med Econ. 2010;13:362-370.
Data source: Cohort
Size, n: 117
Female, %: 81
Age, yr: 80
Disease stage: AD
Follow-up, yr: 5
Outcome: Time to FTC
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: ADAS-cog, ADCS-ADL, NPI, slope ADAS-cog, slope ADL

Study: 21. Ito ADNI ADAS-cog Model (2011)
Reference: Ito K, Corrigan B, Zhao Q, et al. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. Alzheimers Dement. 2011;7:151-160.
Data source: ADNI
Size, n: 229/402/186
Female, %: 48/36/47
Age, yr: 76/75/75
Disease stage: normal/MCI/AD
Follow-up, yr: 3
Outcome: ADAS-cog
Variables:
Demographic: Age, Sex
Clinical:
Biomarker: ApoE
Assessment scale: MMSE

Study: 22. Kavanagh Galantamine MMSE Model (2011)
Reference: Kavanagh S, Van Baelen B, Schauble B. Long-term effects of galantamine on cognitive function in Alzheimer's disease: a large-scale international retrospective study. J Alzheimers Dis. 2011;27:521-530.
Data source: RCT, open label
Size, n: 258
Female, %: 59
Age, yr: 72
Disease stage: AD
Follow-up, yr: 4
Outcome: MMSE rate
Variables:
Demographic: Age, Time since baseline
Clinical: Medication
Biomarker:
Assessment scale: MMSE

Study: 23. Lachaine Institutionalization Model (2011)
Reference: Lachaine J, Beauchemin C, Legault M, Bineau S. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. Can J Psychiat. 2011;56:596-604.
Data source: Cohort
Size, n: 943
Female, %: 67
Age, yr: 73
Disease stage: AD
Follow-up, yr: 5
Outcome: Probability institutionalized/death
Variables:
Demographic: Institutionalization
Clinical: Medication
Biomarker:
Assessment scale:

Study: 24. Abner MCI Model (2012)
Reference: Abner EL, Kryscio RJ, Cooper GE, et al. Mild cognitive impairment: statistical models of transition using longitudinal clinical data. Int J Alzheimers Dis. 2012;2012:291920.
Data source: BRaiNS
Size, n: 554
Female, %: 64
Age, yr: 73
Disease stage: normal/MCI stages/dementia
Follow-up, yr:
Outcome: Predictors of transition normal/MCI stages/dementia/death
Variables:
Demographic: Age, Sex, Education
Clinical: Family history of dementia, Hypertension
Biomarker: ApoE
Assessment scale:

Study: 25. Djalalov aMCI Model (2012)

Reference: Djalalov S, Yong J, Beca J, et al. Genetic testing in combination with preventive donepezil treatment for patients with amnestic mild cognitive impairment: an exploratory economic evaluation of personalized medicine. Mol Diagn Ther. 2012;16:389-399.
Data source: RCT, meta-analysis
Size, n:
Female, %:
Age, yr:
Disease stage: AMCI
Follow-up, yr: 3
Outcome: Probability AMCI/AD/death
Variables:
 Demographic:
 Clinical: Medication
 Biomarker: ApoE
 Assessment scale: MMSE

Study: 26. Gomeni AChEI ADAS Model (2012)
Reference: Gomeni R, Simeoni M, Zvartau-Hind M, Irizarry MC, Austin D, Gold M. Modeling Alzheimer's disease progression using the disease system analysis approach. Alzheimers Dement. 2012;8:39-50.
Data source: RCT
Size, n: 926
Female, %: 59
Age, yr: 73
Disease stage: mild-moderate AD
Follow-up, yr: 1
Outcome: ADAS-cog
Variables:
 Demographic: Age, Time since baseline, Education
 Clinical:
 Biomarker: ApoE
 Assessment scale: MMSE, ADAS-cog

Study: 27. NACC-UDS CDR Model (Spackman et al 2012)
Reference: Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD. Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Curr Alzheimer Res. 2012;9:1050-1058.
Data source: NACC-UDS
Size, n: 3852
Female, %:
Age, yr: 77
Disease stage: AD
Follow-up, yr:
Outcome: Probability AD stage/institutionalized/death
Variables:
 Demographic: Institutionalization
 Clinical:
 Biomarker:
 Assessment scale: CDR global

Study: 27. NACC-UDS CDR Model (Spackman et al 2012)

Reference: Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD. Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Curr Alzheimer Res. 2012;9:1050-1058.
Data source: NACC-UDS
Size, n: 3852
Female, %:
Age, yr: 77
Disease stage: AD
Follow-up, yr:
Outcome: Predictors of transition AD stages/death
Variables:
Demographic: Age, Time since last visit, Sex, Race, Ethnicity, Married, Education
Clinical:
Biomarker:
Assessment scale: CDR global, Previous stage

Study: 28. Samtani MCI-AD ADNI ADAS-cog Model (2012)
Reference: Samtani MN, Raghavan N, Shi Y, et al. Disease progression model in subjects with mild cognitive impairment from the Alzheimer's disease neuroimaging initiative: CSF biomarkers predict population subtypes. Brit J Clin Pharmaco. 2012;75:146-161.
Data source: ADNI
Size, n: 198
Female, %: 33
Age, yr: 75
Disease stage: MCI
Follow-up, yr: 3
Outcome: ADAS-cog
Variables:
Demographic:
Clinical:
Biomarker: Hippocampal volume, CSF tau/Ab ratio
Assessment scale: ADAS-cog, Trail B test

Study: 28. Samtani MCI-AD ADNI ADAS-cog Model (2012)
Reference: Samtani MN, Raghavan N, Shi Y, et al. Disease progression model in subjects with mild cognitive impairment from the Alzheimer's disease neuroimaging initiative: CSF biomarkers predict population subtypes. Brit J Clin Pharmaco. 2012;75:146-161.
Data source: ADNI
Size, n: 191
Female, %: 47
Age, yr: 76
Disease stage: AD
Follow-up, yr: 2
Outcome: ADAS-cog
Variables:
Demographic: Age, Age onset AD
Clinical:
Biomarker: Serum cholesterol, ApoE, Ventricular volume, Hippocampal volume

Assessment scale: ADAS-cog, Trail B test

Study: 29. Delor ADNI CDR-SOB Model (2013)
Reference: Delor I, Charoin JE, Gieschke R, Retout S, Jacqmin P. Modeling Alzheimer's disease progression using disease onset time and disease trajectory concepts applied to CDR-SOB scores from ADNI. CPT Pharmacometrics Syst Pharmacol. 2013;2:e78.
Data source: ADNI
Size, n: 380/180
Female, %:
Age, yr:
Disease stage: MCI/AD
Follow-up, yr: 3
Outcome: CDR-SB
Variables:
Demographic: Age
Clinical:
Biomarker: Hippocampal volume, Intracranial volume
Assessment scale: MMSE, ADAS-cog, CDR-SB, FAQ

Study: 30. Handels Kungsholmen MMSE Model (Handels 2013)
Reference: Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365.
Data source: Cohort pop
Size, n: 153
Female, %: 75
Age, yr: 83
Disease stage: MCI
Follow-up, yr:
Outcome: Time to AD
Variables:
Demographic: Sex
Clinical:
Biomarker:
Assessment scale:

Study: 30. Handels Kungsholmen MMSE Model (Handels 2013)
Reference: Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365.
Data source: Cohort pop
Size, n: 323
Female, %: 83
Age, yr: 87
Disease stage: AD
Follow-up, yr:
Outcome: MMSE
Variables:
Demographic: Age, Age onset AD
Clinical:
Biomarker:

Assessment scale:

Study: 30. Handels Kungsholmen MMSE Model (Handels 2013)
Reference: Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365.
Data source: Cohort pop
Size, n: 323
Female, %: 83
Age, yr: 87
Disease stage: AD
Follow-up, yr:
Outcome: Katz ADL
Variables:
Demographic: Age, Age onset AD, Race
Clinical:
Biomarker:
Assessment scale: MMSE

Study: 31. Liu CDR/MMSE Model (2013)
Reference: Liu W, Zhang B, Zhang Z, Zhou XH. Joint modeling of transitional patterns of Alzheimer's disease. PLoS One. 2013;8:e75487.
Data source: NACC-UDS
Size, n: 746
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: Probability AD stage
Variables:
Demographic: Age
Clinical:
Biomarker: ApoE
Assessment scale: MMSE, CDR global, FAQ

Study: 32. William-Faltaos ADAS-cog Model (2013)
Reference: William-Faltaos D, Chen Y, Wang Y, Gobburu J, Zhu H. Quantification of disease progression and dropout for Alzheimer's disease. Int J Clin Pharm Th. 2013;51:120-131.
Data source: RCT
Size, n: 2479
Female, %: 41
Age, yr: 76
Disease stage: mild-moderate AD
Follow-up, yr: 0.5-1.5
Outcome: ADAS-cog
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: MMSE, ADAS-cog

Study: 33. Yu MCI Model (2013)
Reference: Yu H, Yang S, Gao J, al. e. Multi-state Markov model in outcome of mild cognitive impairments among community elderly residents in Mainland China. Int Psychoger. 2013;25:797_804.
Data source: Cohort pop
Size, n: 600
Female, %: 71
Age, yr: 70
Disease stage: MCI
Follow-up, yr:
Outcome: Predictors of transition MCI/global impairment/AD
Variables:
Demographic: Age, Sex, Education, Reading
Clinical: Diabetes, Hypertension
Biomarker:
Assessment scale:

Study: 34. Qiu ADNI ADAS-Cog Model (2014)
Reference: Qiu Y, Li L, Zhou TY, Lu W. Alzheimer's disease progression model based on integrated biomarkers and clinical measures. Acta Pharmacol Sin. 2014;35:1111-1120.
Data source: ADNI
Size, n: 395
Female, %: 48/45/48/33
Age, yr: 73/70/72/75
Disease stage: normal/EMCI/LMCI/AD
Follow-up, yr:
Outcome: ADAS-cog
Variables:
Demographic: Age
Clinical:
Biomarker: ApoE, Hippocampal volume, CSF tau/Ab ratio
Assessment scale: ADAS-cog, Previous stage

Study: 35. Samtani ADNI CDR-SB Model (2014)
Reference: Samtani MN, Raghavan N, Novak G, Nandy P, Narayan VA. Disease progression model for Clinical Dementia Rating-Sum of Boxes in mild cognitive impairment and Alzheimer's subjects from the Alzheimer's Disease Neuroimaging Initiative. Neuropsychiatr Dis Treat. 2014;10:929-952.
Data source: ADNI
Size, n: 301
Female, %:
Age, yr: 74/75
Disease stage: LMCI/AD
Follow-up, yr:
Outcome: CDR-SB
Variables:
Demographic:
Clinical: Medication
Biomarker: Hippocampal volume, CSF tau/Ab ratio
Assessment scale: CDR-SB, Delayed logical memory, Trail A test

Study: 36. Hu Severity-Dependency Model (2015)
Reference: Hu S, Yu X, Chen S, Clay E, Toumi M, Milea D. Memantine for treatment of moderate or severe Alzheimer's disease patients in urban China: clinical and economic outcomes from a health economic model. Expert Rev Pharmacoecon Outcomes Res. 2015;15:565-578.
Data source: RCT
Size, n:
Female, %:
Age, yr:
Disease stage: moderate-severe AD
Follow-up, yr:
Outcome: Probability AD stage/dependent/aggressive/death
Variables:
Demographic:
Clinical: Medication
Biomarker:
Assessment scale: MMSE, ADL, NPI

Study: 37. Samtani ADAS-cog Bapineuzumab Model (2015)
Reference: Samtani MN, Xu SX, Russu A, et al. Alzheimer's disease assessment scale-cognitive 11-item progression model in mild-to-moderate Alzheimer's disease trials of bapineuzumab. Alzheimers Dement Transl Res Clin Interv. 2015;1:157-169.
Data source: RCT
Size, n: 2451
Female, %:
Age, yr:
Disease stage: mild-moderate AD
Follow-up, yr:
Outcome: ADAS-cog
Variables:
Demographic: Age, Age onset AD, Sex
Clinical: Medication
Biomarker: ApoE
Assessment scale:

Study: 38. Green Multidomain Model (2016)
Reference: Green C, Zhang S. Predicting the progression of Alzheimer's disease dementia: a multidomain health policy model. Alzheimers Dement. 2016;12:776-785.
Data source: NACC-UDS
Size, n: 3009
Female, %: 56
Age, yr: 76
Disease stage: AD
Follow-up, yr:
Outcome: Probability AD stage
Variables:
Demographic:
Clinical:
Biomarker:
Assessment scale: MMSE, FAQ, NPI-Q

Study: 39. Wattmo ADAS-Cog/MMSE/IADL/PSMS Model (2016)
Reference: Wattmo C, Minthon L, Wallin AK. Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. Alzheimers Res Ther. 2016;8:7.
Data source: SATS
Size, n: 1021
Female, %: 64
Age, yr: 75
Disease stage: mild-moderate AD
Follow-up, yr: 3
Outcome: MMSE
Variables:
Demographic: Age, Time since baseline
Clinical: Medication
Biomarker:
Assessment scale: MMSE, IADL

Study: 39. Wattmo ADAS-Cog/MMSE/IADL/PSMS Model (2016)
Reference: Wattmo C, Minthon L, Wallin AK. Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. Alzheimers Res Ther. 2016;8:7.
Data source: SATS
Size, n: 1021
Female, %: 64
Age, yr: 75
Disease stage: mild-moderate AD
Follow-up, yr: 3
Outcome: ADAS-cog
Variables:
Demographic: Age, Time since baseline, Education, Institutionalization
Clinical: Medication
Biomarker:
Assessment scale: ADAS-cog, IADL

Study: 39. Wattmo ADAS-Cog/MMSE/IADL/PSMS Model (2016)
Reference: Wattmo C, Minthon L, Wallin AK. Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. Alzheimers Res Ther. 2016;8:7.
Data source: SATS
Size, n: 1021
Female, %: 64
Age, yr: 75
Disease stage: mild-moderate AD
Follow-up, yr: 3
Outcome: IADL
Variables:
Demographic: Time since baseline
Clinical: Medication
Biomarker:
Assessment scale: MMSE, IADL

Study: 39. Wattmo ADAS-Cog/MMSE/IADL/PSMS Model (2016)
Reference: Wattmo C, Minthon L, Wallin AK. Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. Alzheimers Res Ther. 2016;8:7.
Data source: SATS
Size, n: 1021
Female, %: 64
Age, yr: 75
Disease stage: mild-moderate AD
Follow-up, yr: 3
Outcome: PSMS
Variables:
Demographic: Time since baseline
Clinical: Medication
Biomarker:
Assessment scale: MMSE, PSMS

Study: 40. Guerrero Personalized Time-to-Conversion Models (2016)
Reference: Guerrero R, Schmidt-Richberg A, Ledig C, et al. Neuroimage. 2016;142:113-125.
Data source: ADNI
Size, n:
Female, %:
Age, yr:
Disease stage: MCI/AD
Follow-up, yr:
Outcome: Time to MCI/AD
Variables:
Demographic: Age, Sex, Education
Clinical:
Biomarker: ApoE
Assessment scale: MMSE, ADAS-cog, CDR-SB, FAQ

Study: 41. Roche Guo Model Extension (2017)
Reference: Unpublished
Data source: CERAD, DADE,RCT
Size, n:
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: MMSE
Variables:
Demographic: Age, Sex
Clinical:
Biomarker:
Assessment scale: MMSE, NPI

Study: 41. Roche Guo Model Extension (2017)
Reference: Unpublished
Data source: CERAD, DADE,RCT
Size, n:

Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr:
Outcome: NPI
Variables:
 Demographic: Age, Sex
 Clinical:
 Biomarker:
 Assessment scale: MMSE, NPI

Study: 42. Novartis Longitudinal Model (2017)
Reference: Unpublished
Data source: ADNI, NACC-UDS, Rush
Size, n:
Female, %:
Age, yr:
Disease stage: normal/MCI/AD
Follow-up, yr: 10
Outcome: Time to MCI/AD
Variables:
 Demographic: Age, Sex
 Clinical:
 Biomarker: ApoE, CSF tau/Ab ratio
 Assessment scale: APCC, RBANS

Study: 42. Novartis Longitudinal Model (2017)
Reference: Unpublished
Data source: ADNI, NACC-UDS, Rush
Size, n:
Female, %:
Age, yr:
Disease stage: normal/MCI/AD
Follow-up, yr: 10
Outcome: APCC
Variables:
 Demographic: Age, Sex
 Clinical:
 Biomarker: ApoE, CSF tau/Ab ratio
 Assessment scale: APCC, RBANS

Study: 43. Eli Lilly PenTAG/GERAS Institutionalisation Model (2017)
Reference: Unpublished
Data source: GERAS
Size, n: 1495
Female, %:
Age, yr:
Disease stage: AD
Follow-up, yr: 3
Outcome: Time to institutionalisation
Variables:
 Demographic: Age

Clinical:
Biomarker:
Assessment scale: MMSE, ADCS-ADL, NPI

Study:	43. Eli Lilly PenTAG/GERAS Institutionalisation Model (2017)
Reference:	Unpublished
Data source:	GERAS
Size, n:	1495
Female, %:	
Age, yr:	
Disease stage:	AD
Follow-up, yr:	3
Outcome:	Time to death
Variables:	
Demographic:	Age, Age onset AD, Sex
Clinical:	
Biomarker:	
Assessment scale:	MMSE, ADCS-ADL, NPI