Supplementary Online Content

Cosentino S, Schupf N, Christensen K, Andersen SL, Newman A, Mayeux R. Reduced prevalence of cognitive impairment in families with exceptional longevity. *JAMA Neurol*. Published online May 6, 2013. doi:10.1001/jamaneurol.2013.1959.

eAppendix. Algorithm Development and Validation Against Autopsy Data

eTable. NACC Validation Sample Selection Process

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix: Algorithm Development and Validation Against Autopsy Data

Algorithm Development: The diagnostic algorithm used to assign case status in LLFS was validated in the NACC dataset against individuals with clinically diagnosed Probable AD. NACC data was obtained on individuals >=65 years of age, all of whom underwent a neurological evaluation as well as cognitive testing with a battery that contains the tests used in LLFS. The Clinical Dementia Rating (CDR) scale was completed for all NACC participants, and imaging and bloodwork were considered for diagnoses when available. A clinical diagnosis was determined for each individual in NACC during a consensus conference attended by neurologists and neuropsychologists. Diagnoses of AD were made according to the National Institute of Neurologic Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria. Autopsy data were available for a subset of individuals.

The final sample of NACC participants (n=4,087) used to develop criteria for cognitive impairment in LLFS was determined using the selection methods detailed in eTable 1. The sample included 2,861 cognitively healthy individuals whose maximum CDR score was 0 over at least two visits, and 1,226 individuals diagnosed with AD (674 prevalent and 552 incident cases). The diagnostic cognitive algorithm was developed using data from the first visit at which dementia cases obtained a CDR score of 1.

A series of logistic regression models was used to determine the optimal algorithm for discriminating between participants clinically diagnosed with AD and healthy control participants in the NACC sample, using cognitive test scores and demographic variables. The variables included in the regression analyses were selected based on a priori hypotheses regarding the nature of AD, the demographic factors that have been associated with this disease, and the cognitive abilities that are known to be affected in this disease. The first model included age, education, sex, and Logical Memory II (delayed) as predictors of case status (AD versus healthy control) in the NACC data set. An iterative process was then applied, such that non-significant predictors were removed from the model, and additional cognitive variables were added one at a time. Receiver Operating Curves (ROC) were used to examine the sensitivity and specificity of each model. Variables which did not improve the area under the curve (AUC) in ROC analyses were not included in the model.

Validation Against Autopsy Data: Autopsy data was available for 133 individuals in our NACC sample. Average time from last clinical evaluation to autopsy was 19.11 (14.13) months. Time to autopsy differed as a function of algorithm case status, with non-cases having a shorter duration 9.39 (8.00) than cases 27.52 (12.87), $F(1, 131) = 91.89$, $p < .01$.

Of the 133 individuals in our NACC sample with neuropathological data, 71 individuals were classified as cases by the cognitive algorithm. AD was the primary pathological diagnosis in 47 (66%) of these cases, and was a contributing pathological diagnosis in 4 (6%) of cases. Of the 24 individuals who did not have AD as the primary diagnosis, primary classifications included: a low level of AD pathology that was insufficient for diagnosis (n = 6; 25%), 7 Lewy Body disease (LBD; 29.2%), 3 hippocampal sclerosis (12.5%), 3 vascular dementia (VaD; 12.5%), 3 pathologically normal (12.5%), and 2 other (8.3%).

2861 individuals in the NACC sample were labeled as non-cases by the cognitive algorithm. Of these, neuropathological data was available for 62 individuals. 16 of these individuals (26%) were labeled as pathologically normal. Of the remaining 46 individuals, primary classifications included: a low level of AD pathology that was insufficient for diagnosis in 31 individuals (67%), Alzheimer's disease in 7 (15%), vascular dementia in 4 (9%), and other in 4 (9%).

We examined the sensitivity and specificity of the algorithm for detecting pathology under three increasingly liberal conditions: 1) AD pathology only; 2) all cases that met any pathological criteria for all causes of dementia; and 3) the presence of any level of pathology, including the presence of AD pathology insufficient for a diagnosis of AD. Under the strictest condition, the sensitivity and specificity of the algorithm were .87 and .70, respectively. With an expanded definition of dementia pathology, sensitivity was comparable at .81 and specificity improved to .84. Finally, under the most liberal criteria for the presence of pathology, sensitivity dropped to .60, as the cognitive algorithm fails to identify people with a low level of pathology, while specificity remained at .84.

eTable. NACC Validation Sample Selection Process

	Controls	Cases
Dementia Status	7,991 Never Demented	4,037 Demented
CDR Status	4,073 Max CDR = 0	3,067 Max CDR = 1
Probable AD	NA	2,174
Algorithm data available	3,819	1,516
>=65	3,508	1,422
White	2,861	1,226

Note. Based on individuals who had more than one NACC visit.