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Foreword

Alzheimer's Disease Neuroimaging Initiative: A decade of progress in Alzheimer's disease

Today, more than 5 million people are living with Alzheimer's disease in the United States [1]. Every year, approximately 500,000 of these individuals pass away who would not otherwise have been expected to die [2]. In addition to its terrible human toll, Alzheimer's disease exacts a dear price from the American economy. The average annual per-person payments for health care and long-term care are more than three times greater for Medicare beneficiaries >65 years with Alzheimer's or another dementia ($47,752) than for those without Alzheimer's or another dementia ($15,115). Total payments for individuals with Alzheimer's disease and other dementias will reach $226 billion in 2015, with Medicare and Medicaid accounting for $153 billion (68%) of that total [1]. Alzheimer's is already the costliest disease to society [3] and that is only expected to worsen over time unless disease-modifying treatments are found. By 2050, only 35 years from now, it is expected that nearly 14 million Americans will be living with Alzheimer's disease, with total payments for health care, long-term care, and hospice care estimated to top $1.1 trillion (in 2015 $) [4]. Worldwide, more than 44 million people are living with dementia, a figure that is projected to increase to 135 million by 2050 [5].

Although Alzheimer's disease was described more than a century ago [6,7], progress in therapy development has remained elusive. Current therapies only provide symptomatic relief and do not halt or even slow the progression of the underlying disease process. The search for disease-modifying therapies has been hampered by a lack of knowledge about the course of the disease process. This gap in knowledge, coupled with the years-long progression of Alzheimer's disease from diagnosis to death, and the lack of measures sensitive enough to detect small but important treatment effects, virtually guaranteed that a disease-modifying treatment would remain elusive.

It was in this context that a decade ago, in 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was born, with the critical goal of improving biomarkers in Alzheimer's disease clinical trials. The study was originally designed to provide longitudinal data on 800 participants from 56 study sites in the United States and Canada. Participants were recruited to three groups—those with normal cognitive aging, mild cognitive impairment (at that time a relatively new concept), or early Alzheimer's disease.

Beginning in the 1980s, the U.S. National Institute on Aging began establishing a network of Alzheimer's disease centers, teams composed of interdisciplinary researchers at major research institutions [8]. Together, the centers provided a framework for shared infrastructure and resources, a framework on which ADNI built. Several additional efforts by the Alzheimer's Association (notably the Workgroup on Neuroimaging), the NIA, and others were critical in establishing the conceptual framework for an ADNI-type study [9,10]. ADNI also incorporates private stakeholders, including pharmaceutical and biotechnology companies and non-profit organizations, in both funding and decision-making roles. This model has set the standard for public-private partnerships in the national and international research enterprise.

From the standpoint of generating new knowledge about Alzheimer's disease, ADNI has been an unmitigated success. During the past decade, well over 600 articles have been published by the initiative. These publications have influenced the field in dramatic ways. For example, ADNI data influenced the development of what is now the most widely accepted model of temporal dynamics of biomarkers in the development and progression of Alzheimer's disease [11–13]. This model helped to create a sea change in the Alzheimer's disease research landscape, supporting the deliberations that led to the revised Alzheimer's disease criteria recommended by the National Institute on Aging-Alzheimer's Association workgroups [14–16], as well as informing the design of large scale Alzheimer's studies that are currently testing methods that may delay or even completely prevent the onset of dementia symptoms in individuals whose biomarkers suggest they are in the presymptomatic phase of the disease [17]. The introduction and individual articles [18–30] in this special issue of *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* highlight many other seminal contributions of ADNI to the field's scientific and clinical understanding of Alzheimer's disease, including genetics, imaging of

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Alzheimer's pathology in the living brain, enhancing the reliability and validity of cognitive measures, and clarifying disease prognosis.

The contributions of ADNI have expanded past the research arena and into clinical practice. In 2004, the new technology of amyloid imaging using positron emission tomography (PET) was being explored, allowing researchers to see for the first time amyloid buildup in the living human brain [31]. Recognizing the potential for this technology, the *Alzheimer's Association* provided funding to include amyloid PET imaging in ADNI. The results of the amyloid PET imaging add-on study prompted the requirement of amyloid imaging for all participants in subsequent ADNI renewals. Furthermore, the success of amyloid imaging in ADNI provided support for the 2012 approval by the U.S. Food and Drug Administration (FDA) of the first amyloid PET imaging agent. Three amyloid PET imaging agents are now approved for clinical use by both the FDA and the European Medicines Agency. Data from ADNI and related studies have also been used to develop ethical guidelines for the disclosure of amyloid status and dementia risk [32]. In the clinic, ADNI has contributed invaluable knowledge regarding the development and progression of cognitive and neuropsychiatric signs and symptoms in Alzheimer's disease, which in turn has informed diagnosis, prognosis, and clinical decision making.

A major reason for the success of ADNI is its commitment, from the very beginning, to open data sharing. This model allows for the valuable data collected to be accessed and analyzed by researchers all over the world. In addition to the original North American ADNI, this commitment to data sharing has now carried over to the *Alzheimer's Association*-led Worldwide ADNI (WW-ADNI). WW-ADNI includes initiatives in North America, Europe, Japan, Australia, Taiwan, Korea, China, and Argentina [26]. The groundwork for data standardization and harmonization laid by ADNI is supporting the work being done today by WW-ADNI members. ADNI required the development of new computer architecture for storing and sharing clinical and biomarker data, which later spurred the development of a federated network for storing, sharing, and analyzing data from multiple large Alzheimer's data sets—the Global Alzheimer's Association Interactive Network (GAAIN; www.gaain.org).

Much of what we now know about Alzheimer's disease simply would not yet be known without ADNI. Looking to the future, ADNI data and the ADNI model will continue to be used to inform strategies for clinical trial design, and we will soon begin to see results from prevention studies built around the framework of knowledge that ADNI has provided [15]. WW-ADNI will continue to expand, collecting clinical and biomarker data from around the globe and making it freely available to researchers. In addition to amyloid imaging, tau imaging is now becoming a reality and may be included in the next iteration of ADNI. Given evidence suggesting that tau-based neurofibrillary tangles closely approximate the cognitive decline seen in Alzheimer's disease, the addition of tau imaging to ADNI may provide crucial information on its potential value as a surrogate biomarker in clinical trials, perhaps bringing effective treatments to the clinic faster than ever.

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References

[1] Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015;11:332–84.
[2] James BD, Leurgans SE, Hebert LE, Scherr PA, Yaffe K, Bennett DA. Contribution of Alzheimer disease to mortality in the United States. Neurology 2014;82:1045–50.
[3] Hurd MD, Martorell P, Langa KM. Monetary costs of dementia in the United States. N Engl J Med 2013;368:1326–34.
[4] Alzheimer's Association. Changing the trajectory of Alzheimer's disease: How a treatment by 2025 saves lives and dollars. Available at: http://www.alz.org/documents_custom/trajectory.pdf. Accessed June 11, 2015.
[5] Alzheimer's Disease International. Policy brief for heads of government: The global impact of dementia 2013-2050. Available at: https://www.alz.co.uk/research/GlobalImpactDementia2013.pdf. Accessed June 11, 2015.
[6] Alzheimer A. Uber eine eigenartige erkrangkung der hirnrinde. Allg Z Psychiat 1907;64:146–8.
[7] Alzheimer A. Uber eigenartige krankheitsfalle des spateren Alters. Z Gesamte Neurol Psychiat 1911;4:356–85.
[8] Khachaturian ZS. A chapter in the development of Alzheimer's disease research: A case study of public policies on the development and funding of research programs. Alzheimers Dement 2007; 3:243–58.
[9] Khachaturian ZS. Diagnosis of Alzheimer's disease: Two-decades of progress. J Alzheimers Dis 2006;9:409–15.
[10] Khachaturian ZS. Perspective on the Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans. Alzheimers Dement 2010;6:199–201.
[11] Jack CR Jr, Kknopman DS, Jagust WJ, petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16.
[12] Jack CR Jr, Kknopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9: 119–28.
[13] Jack CR Jr, Vemuri P, Wiste HJ, Weigand SD, Aisen PS, Trojanowski JQ, et al. Evidence for ordering of Alzheimer disease biomarkers. Arch Neurol 2011;68:1526–35.
[14] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9.

[15] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.

[16] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280–92.

[17] Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, et al. The A4 study: stopping AD before symptoms begin? Sci Transl Med 2014;6:228fs13.

[18] Weiner MW, Veitch DP. Introduction to special issue: Overview of Alzheimer's Disease Neuroimaging Initiative. Alzheimers Dement 2015;11:730–3.

[19] Aisen PS, Petersen RC, Donohue M, Weiner MW, for the Alzheimer's Disease Neuroimaging Initiative. ADNI 2 clinical core: Progress and plans. Alzheimers Dement 2015;11:734–9.

[20] Jack CR Jr, Barnes J, Bernstein MA, Borowski BJ, Brewer J, Clegg S, et al. Magnetic resonance imaging in ADNI. Alzheimers Dement 2015;11:740–56.

[21] Jagust WJ, Landau SM, Koeppe RA, Reiman EM, Chen K, Mathis CA, et al. The ADNI PET core: 2015. Alzheimers Dement 2015;11:757–71.

[22] Kang JH, Korecka M, Figurski MJ, Toledo JB, Blennow K, Zetterberg H, et al., the Alzheimer's Disease Neuroimaging Initiative. The ADNI biomarker core: A review of progress and plans. Alzheimers Dement 2015;11:772–91.

[23] Saykin AJ, Shen L, Yao X, Kim S, Nho K, Risacher SL, et al., and for the Alzheimer's Disease Neuroimaging Initiative. Genetic studies of quantitative MCI and AD phenotypes in ADNI: Progress, opportunities, and plans. Alzheimers Dement 2015;11:792–814.

[24] Franklin EE, Perrin RJ, Vincent B, Baxter M, Morris JC, Cairns NJ, the Alzheimer's Disease Neuroimaging Initiative. Brain collection, standardized neuropathologic assessment, and comorbidity in Alzheimer's Disease Neuroimaging Initiative participants. Alzheimers Dement 2015;11:815–22.

[25] Beckett LA, Donohue MC, Wang C, Aisen P, Harvey DJ, Saito N, Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's Disease Neuroimaging Initiative phase 2: Increasing the length, breadth, and depth of our understanding. Alzheimers Dement 2015;11:823–31.

[26] Toga AW, Crawford KL. The Alzheimer's Disease Neuroimaging Initiative informatics core: A decade in review. Alzheimers Dement 2015;11:832–9.

[27] Liu E, Luthman J, Cedarbaum JM, Schmidt ME, Cole PE, Hendrix J, et al. Perspective: The Alzheimer's Disease Neuroimaging Initiative and the role and contributions of the Private Partner Scientific Advisory Board (PPSB). Alzheimers Dement 2015;11:840–9.

[28] Hendrix JA, Finger B, Weiner MW, Frisoni GB, Iwatsubo T, Rowe CC, et al. The worldwide Alzheimer's Disease Neuroimaging Initiative: An update. Alzheimers Dement 2015;11:850–9.

[29] Jones-Davis DM, Buckholtz N. The impact of ADNI: What role do public-private partnerships have in pushing the boundaries of clinical and basic science research on Alzheimer's disease? Alzheimers Dement 2015;11:860–4.

[30] Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Cedarbaum J, et al., Alzheimer's Disease Neuroimaging Initiative. Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014. Alzheimers Dement 2015;11:865–84.

[31] Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306–19.

[32] Harkins K, Sankar P, Sperling R, Grill JD, Green RC, Johnson KA, et al. Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. Alzheimers Res Ther 2015;7:26.