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The impact of the Alzheimer's Disease Neuroimaging Initiative 2: What role do public-private partnerships have in pushing the boundaries of clinical and basic science research on Alzheimer's disease?

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Abstract In the growing landscape of biomedical public-private-partnerships, particularly for Alzheimer's disease, the question is posed as to their value. What impacts do public-private-partnerships have on clinical and basic science research in Alzheimer's disease? The authors answer the question using the Alzheimer's Disease Neuroimaging Initiative (ADNI) as a test case and example. ADNI is an exemplar of how public-private-partnerships can make an impact not only on clinical and basic science research and practice (including clinical trials), but also of how similar partnerships using ADNI as an example, can be designed to create a maximal impact within their fields.

Keywords: ADNI; Alzheimer's disease; Public private partnerships; Consortia; FNIH; NIA; Foundation for the National Institutes of Health; National Institute on Aging

1. Introduction

Recent studies and commentaries have examined the increase in the development of biomedical research consortia and other similar collaborative efforts, and the effect on research productivity and innovation derived through these collaborations [1–5]. In fact, "research by consortia" has increased at such a rapid rate, that *FasterCures*, a center of the Milken Institute, initiated a consortia-pedia project to analyze the landscape of research consortia [6]. The conclusions of these studies are that such collaborations yield higher research productivity, reduce research risk, and foster increased innovation by introducing a diversity of scientific perspectives. Moreover, they provide the path to an enabled broader scope of research through the development and sharing of knowledge, expertise, and resources [1–6]

Among common major diseases, the value of collaborative research approaches has been most keenly appreciated in the field of Alzheimer's disease (AD), a complex disorder that now affects some 5.2 million individuals in the United States, costs the American people $214 billion in 2014, and that is increasing in prevalence [7]. By combining National Institutes of Health (NIH) research expertise and funding resources with those of the private-sector, it is apparent that an impact can be made on complex diseases further and faster together than can be made alone.

Indeed, there are numerous consortia in the Alzheimer's research realm that aim to address different critical research needs and knowledge gaps through a collaborative framework [8,9]. How did we get to this remarkable point in the development of the field, where we are collaborating at breakneck speed to produce clinically meaningful outcomes for AD, with multisector partnerships an apparent preferred mode of operation? Many would agree that the current AD research landscape owes a great debt to one of the first and largest AD research collaborations among the government (NIH), pharmaceutical companies, and nonprofit organizations—the Alzheimer's Disease Neuroimaging Initiative (ADNI).

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An important question in AD clinical trials is whether a drug's positive effects are disease-modifying rather than purely of symptomatic benefit. This key question formed much of the rationale for ADNI. In the early 2000s, the clinical and neuropsychological outcome measures available for use in clinical trials were not able to discriminate between these two outcomes, making it difficult to determine the efficacy of a particular drug for modifying the course of the disease. It was thought that by directly interrogating the processes in the brain believed to be associated with AD, using various imaging modalities and fluid biomarkers, and using the standard clinical, neuropsychological, and neuropsychiatric tests for comparisons, the best biomarker or combination of biomarkers of disease progression could be identified.

To test this hypothesis, the National Institute on Aging (NIA) of the NIH launched ADNI, with cofunding from a number of other NIH Institutes and Centers, and private partner support from a number of pharmaceutical companies and nonprofit associations provided through the Foundation for the National Institutes of Health (FNIH). ADNI is a naturalistic, observational, multicenter study of AD progression that obtains clinical, neuropsychological, neuropsychiatric, and genetic data from a variety of subjects including cognitively normal older individuals and participants with subjective memory complaints, mild cognitive impairment, or AD. ADNI studies also include structural and functional neuroimaging, using magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography (PET), and beta-amyloid PET, and fluid biomarkers (cerebrospinal fluid [CSF] and blood). When launched in 2004, ADNI's scale and scope, and the tightness of collaboration between the public and private sectors it accomplished, were unprecedented.

A good deal of ADNI's success can be attributed to the strategic establishment of research standards among the partnership's stakeholders. Before the funding of ADNI, the NIA held a series of workgroup discussions that included both academic and industry scientists to evaluate and discuss the development of common protocols for the various measures (i.e. clinical, neuropsychological, neuropsychiatric, neuroimaging, and fluid biomarker) to determine the best methods to include in the data collection protocols and standard operating procedures for each domain of the study, at each ADNI site (57 sites in total in the United States and Canada at the beginning of ADNI; 63 sites in total in the United States and Canada currently).

Furthermore, ADNI is governed by a Steering Committee which is comprised of the ADNI principal investigator (PI), the core leaders from the eight ADNI cores (clinical, MRI, PET, neuropathology, biomarker, genetics, biostatistics, and informatics), all the site PIs, representatives from the NIH and the US Food & Drug Administration (FDA), and representatives of the entities contributing funding (as nonvoting observers). The NIH serves as an "honest broker" between the pharmaceutical industry and academia. An important stakeholder in the project is the FNIH, which both coordinates fund-raising efforts from private partners for the project and acts as a neutral convener and manager of the ADNI Private Partner Scientific Board (PPSB). The PPSB is currently composed of 27 industry partners, 2 nonprofit partner organizations, and 1 government organization (Canadian Institutes for Health Research). A 501(c) (3) not-for-profit organization established in 1990 by the U.S. Congress, FNIH supports NIH in its mission through raising private funds and facilitating public-private partnerships that advance scientific research to "extend healthy life, and to reduce the burdens of illness and disability." The FNIH convenes the PPSB on a monthly basis and provides the ADNI leadership with valuable private partner viewpoints and feedback. There is also an ADNI Executive Committee consisting of the ADNI PI, the leaders of the cores, and the NIH program officer and an External Advisory Board consisting of non-ADNI affiliated scientists. Together, all these groups contribute to scientific perspectives from academia, industry, and the nonprofit sector regarding the progress, development, and evolution of ADNI.

2. The impact of ADNI

The impact of ADNI in the field of AD research—both at the basic and clinical level—is undeniable. A groundbreaking approach to AD research, ADNI is providing the global scientific community with high quality data to address critical questions about the development and progression of the disease. Over the past 10 years, ADNI data have transformed how the research community views AD. Preclinical changes in biomarkers measured by ADNI have demonstrated earlier and earlier pathological changes in the brain before the onset of symptoms, affirming the recognition by the research community that AD onset occurs decades before symptoms. This change in viewpoint has had several resultant effects, including a shift in focus to prevention vs. treatment trials, and is also reflected in the National Institute on Aging (NIA)/Alzheimer's Association Workgroup's diagnostic guidelines for AD [10–13]. And, in addition to the data it has contributed, the partnership itself has proved to be a valuable example of how public-private partnerships can work effectively.

2.1. Open-access data and sample sharing

Before the funding of ADNI, the NIA realized that the amount of data that ADNI could generate would be enormous. It was evident that the ADNI investigators would not be able to do all the analyses that such a rich data set would support, so the NIA held discussions about how the data would be shared. It was established that data would be housed in a database hosted by the Laboratory of Neuroimaging (LONI) (originally housed at

University of California Los Angeles; currently housed at the University of Southern California), the LONI Data Archive, and that the data would be available nearly immediately after acquisition, after quality control analysis. It was decided that there would be no embargo on the availability of the resources generated by ADNI—no special access or period of exclusive use with respect to either the data or the biofluid and DNA samples from the participants—for either the ADNI investigators or the private partners. Additionally, the decision was made that there would be no preemptive intellectual property rights associated with the data in the database. The data and the samples would be open to the entire scientific research community public, establishing a precedent for current discussions and policies that facilitate the transparency of federally funded research. All data generated from the use of ADNI samples would also be made openly and immediately available on the ADNI LONI website.

As a result, ADNI data have been queried millions of times by investigators around the world, from government, academic, and company research sites. As of February 2015, there have been over 7 million downloads of ADNI data worldwide [14], and over 924 publications using ADNI data. Most applications for ADNI data have been from university researchers, followed by pharmaceutical/biotechnology companies, scanner manufacturers, government scientists, and other members of the public, including high school teachers. Described as "a radical experiment in open data access" by the head of the ADNI Data and Publications Committee, ADNI has set a laudable precedent for how data sharing works to push forward the frontiers of a field.

2.2. Private partner collaboration

In the growing landscape of public-private partnerships, successful and impactful efforts, such as ADNI, require significant investment, both financially and intellectually. There are more AD public-private partnerships than ever before, investing limited public and private funds into important clinical questions about the biomarkers, progression, and ultimately, treatment of this disease that takes such a toll on the worldwide populace. To date, ADNI has been supported not only by nearly $105M in public funds from the NIH, but also nearly $49M in funding from its private partners, an investment that has been imperative to achieve the impact and success of this model effort.

In fact, one of the key ways that ADNI distinguishes itself is in the strength of its private partners. Involved not solely in a financial, but also in a guidance capacity from before the inception of the study, the industry partners joined together to form the ADNI Industry Scientific Advisory Board (ISAB). The name of this group later changed to the Private Partner Scientific Board (PPSB), to more appropriately reflect the broad group of private stakeholders supporting the project. Managed by FNIH, the PPSB is an independent, precompetitive forum for all ADNI private sector partners (pharmaceutical companies, biotechnology companies, and nonprofits). The role of the PPSB is to collaborate and share information, and to provide private-sector views and expertise regarding ADNI. Over the course of ADNI (1, GO, and 2), this group of stakeholders has not only contributed industry expertise and knowledge to the project, but has also undertaken and funded add-on projects that were not originally included in the parent grant, through the development of PPSB project-specific working groups. For example, a PPSB-led PET endpoints working group was developed to examine the usage of PET (FDG and amyloid PET) for use in clinical trials as treatment endpoints. This working group undertook a project examining Pittsburgh Compound B, the first PET imaging ligand for beta-amyloid, and additionally released a separate technical guidance statement intended to reduce variability in the quantitative analysis of amyloid PET [11]. Another example can be found in the PPSB AD Assessment Scale-Cognitive Subscale (ADAS-Cog) Working Group, that completed a project to improve the sensitivity of the ADAS-Cog to measure cognitive performance in mild cognitive impairment/AD clinical trials [15,16]. In addition, several industry-led projects, including one on blood and CSF proteomics, have also found their way to the Biomarkers Consortium, another FNIH-managed consortium established to discover, develop, and qualify biomarkers to support drug development, preventive medicine, and medical diagnostics—and just one example of ADNI's impact on other consortia in the field [17].

2.3. External impacts: Setting a precedent

Since its inception, the success of ADNI has not only fostered a large number of research projects interrogating the ADNI data set to ask important research questions about AD progression, but has also inspired a host of public-private partnerships, both domestic and international, that seek to emulate and complement the project. Most notable is the extension of ADNI (also referred to as North American ADNI) to multiple areas around the world. As of February 2015, eight linked ADNI initiatives are ongoing around the globe: North American ADNI (NA-ADNI), European ADNI, Japan ADNI, Australian ADNI (AIBL), Taiwan ADNI, Korea ADNI, China ADNI, and Argentina ADNI. This global effort, known as Worldwide ADNI (WW-ADNI) [18], is managed by one of the founding nonprofit partners of NA ADNI, the Alzheimer's Association. It seeks to harmonize projects, protocols, and results across different geographic sites around the world, and to provide insight as to the global picture of AD, as a whole, and in the context of particular countries. To facilitate global collaboration among WW-ADNI sites, the Alzheimer's Association convenes the WW-ADNI partners each year at their annual meeting. An additional goal of the WW-ADNI efforts is to

continue the data sharing precedent set by NA-ADNI. Although many of the WW-ADNI efforts have yet to make their data openly available to the world, some AIBL data are available along with NA-ADNI in the ADNI LONI database; it is hoped that the other worldwide efforts will follow suit.

A second notable impact of ADNI on other partnerships in neurodegenerative disease is noted in the development of the Parkinson Progression Marker Initiative (PPMI) [19], an effort that was strongly influenced by the success of the open access model and public-private partnership structure of ADNI. Founded and managed by the Michael J. Fox Foundation, the PPMI is very similar to ADNI, in that it is an observational multicenter study designed to identify Parkinson's disease (PD) progression biomarkers to both improve the understanding of the disease etiology, and to facilitate clinical trials in PD. Similar to ADNI, PPMI data are housed in an openly accessible database in the LONI website, and similar to the ADNI PPSB, PPMI has its own ISAB that provides similar industry perspectives and guidance to the PPMI effort. Most recently, the Michael J. Fox Foundation, in collaboration with the Alzheimer's Association and the Garfield Weston Foundation, developed *Biomarkers Across Neurodegenerative Disease*, a research grant program that funds research that uses the existing ADNI and PPMI data sets and biological samples to explore similarities and differences between the two neurodegenerative diseases. Other similar "ADNI-like" naturalistic observational studies for neurological disease include Transforming Research and Clinical Knowledge in Huntington's Disease (TRACK-HD), a 3-year multisite international study, aimed to determine the best clinical outcome measures for trials in Huntington's disease [20], and Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI), a multicenter prospective observational study of traumatic brain injury (TBI), aimed to improve the clinical and basic science infrastructure for TBI research [21].

The success of ADNI also has inspired the development of a number of other partnerships that are working to develop, validate, and ultimately, qualify biomarkers of progression for usage in clinical trials. ADNI synergizes with, yet does not duplicate these efforts. In addition to the previously mentioned FNIH Biomarkers Consortium, these include the AD component of the Accelerating Medicines Partnership (AMP-AD, also managed by FNIH), and the Critical Path Institute's (C-Path) Coalition Against Major Diseases (CAMD) Initiative. While AMP-AD is designed to identify and validate novel biological targets for AD, CAMD works with regulatory agencies such as the FDA and European Medicines Agency (EMA) to develop a regulatory path for AD imaging and fluid biomarker qualification for use in clinical trials. All of CAMD's regulatory decisions to date were enabled by partnership with ADNI, a crowning example of ADNI's partnership and influence on other consortia. Additionally, the methodological procedures used in ADNI are currently being implemented in current FDA- and EMA-qualified Phase II and Phase III AD clinical trials.

Finally, the longitudinal nature, diversity, and openness of the ADNI data have made it useful as the basis for a number of "open innovation" competitive data mining and analysis challenges related to AD. In 2013, the Geoffrey Beene Foundation issued their Global Neurodiscovery Challenge to the general scientific community, funding prizes for analyzing gender-based differences in AD using publicly available data sets, including the ADNI data set [22]. Additionally, the Global CEO Initiative on Alzheimer's disease (a partnership among Fortune 500 CEOs to accelerate AD prevention research), partnered with Sage Bionetworks, the Dialogue on Reverse Engineering Assessment and Methods (DREAM) project, the Broad Institute, MD Anderson Cancer Center and Rice University, to develop a DREAM challenge to find novel predictive AD biomarkers, using the ADNI data set as the "test" data set [23]. And CAMD used ADNI data to develop an AD clinical trial modeling and simulation tool, endorsed by the EMA and the FDA, which aims to optimize clinical trial design [24,25]. This tool is now publically available to all requesters.

3. Looking forward

As ADNI nears the end of its second phase (ADNI 2) and prepares to enter ADNI 3, the AD research community finds itself in a vastly different landscape than that in the early 2000s. The advent of new research tools and technologies, such as Tau PET imaging and computerized cognitive testing, are pushing the boundaries of what markers can be measured, how we define disease progression, and, in the case of computerized testing, the conditions under which we can obtain clinically meaningful patient data. But equal to the growth noted in new tools and technologies is a renewed sense of urgency in addressing the threat to global health of the increased prevalence of Alzheimer's, as reflected in grand challenges such as the National Alzheimer's Project Act/National Plan to Address Alzheimer's Disease's goal to prevent or treat AD by 2025 [26], and an acceleration of the cultural shift in the neuroscience community inspired by the original ADNI so that industry, academia, and nonprofits can work ever more closely together to share resources, knowledge, and data to address these challenges. In other words, both the imperative and the tools to meet that Imperative, have never been greater. The Director of NIH, Dr. Francis Collins, said in his introductory remarks to the NIA's Alzheimer's Disease Summit 2015, when quoting a Carrie Newcomer song, "If not now, tell me when?" Truly, the time is now to come together to make a truly meaningful progress toward therapeutics and a cure for AD.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g. PubMed) sources, as well as a general internet search of existing research consortia.
2. Interpretation: Research consortia and public-private-partnerships such as ADNI can have far-reaching impacts not only on clinical and basic science research and practice (including clinical trials and regulatory guidance), but also on how similar partnerships can be designed to create a maximal impact within their fields.
3. Future directions: Despite limited public and private funds for supporting new research consortia, ADNI makes the case for the clear impact of, and rationale for, continued investment in these endeavors.

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