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Perspective: The Alzheimer's Disease Neuroimaging Initiative and the role and contributions of the Private Partner Scientific Board (PPSB)

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Abstract The Alzheimer's Disease Neuroimaging Initiative (ADNI) Private Partner Scientific Board (PPSB) is comprised of representatives of private, for-profit entities (including pharmaceutical, biotechnology, diagnostics, imaging companies, and imaging contract research organizations), and nonprofit organizations that provide financial and scientific support to ADNI through the Foundation for the National Institutes of Health. The PPSB serves as an independent, open, and precompetitive forum in which all private sector and not-for-profit partners in ADNI can collaborate, share information, and offer scientific and private-sector perspectives and expertise on issues relating to the ADNI project. In this article, we review and highlight the role, activities, and contributions of the PPSB within the ADNI project, and provide a perspective on remaining unmet needs and future directions.

Keywords: Alzheimer's Disease Neuroimaging Initiative; ADNI; Private Partner Scientific Board; PPSB; FNIH; Foundation for the National Institutes of Health; Pharmaceutical industry

1. Introduction

The Alzheimer's Disease Neuroimaging Initiative (ADNI) began as a 5-year research project launched in 2004 as a public-private partnership with public funding provided by the National Institute of Aging (NIA), and private funding, facilitated through the Foundation for the National Institutes of Health (FNIH), provided by pharmaceutical companies, and a nonprofit foundation (Alzheimer's Association). The overarching aim of ADNI has been to accelerate the understanding and validation of biomarkers and thereby improve the speed and success rate of clinical trials of novel Alzheimer's disease (AD) therapeutics. ADNI comprises cross-sectional and longitudinal biomarker and clinical data in a natural history setting across the full disease spectrum, including cognitively normal, mild cognitive impairment (MCI), and Alzheimer's dementia patients

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[1,2]. A core focus of the project has been the validation and standardization of biomarker acquisition and analysis methods for application to clinical trials; the discovery of novel biomarkers has been a secondary, longer-term objective. The ADNI project was successfully renewed in 2010 with the 2-year National Institutes of Health (NIH)-funded Grand Opportunity (ADNI-GO) grant, which enabled a new cohort of early MCI subjects to be enrolled, biomarker methods to be updated (http://www.adcs.org/studies/imagineadni.aspx), and provided a bridge to the ADNI-2 5-year grant renewal in 2011. ADNI is funded under a unique model with grant funds from the NIA being partially matched by contributions from private companies and nonprofit organizations.

From the outset, ADNI emphasized a collaborative arrangement between the academic investigators and private partners. Input from private and patient advocacy participating members was coordinated in a precompetitive arrangement via an Industry Scientific Advisory Board (ISAB). Although private funder membership was originally heavily weighted toward large pharmaceutical companies, participation broadened over the duration of the ADNI project, and to reflect this, the ISAB was renamed the Private Partner Scientific Board (PPSB) at the onset of ADNI-2. Throughout the ADNI project, the operating structure has remained stable and proved of enduring effectiveness. Over the decade since its inception, the degree and breadth of participation in the PPSB and the impact of ADNI data and methodology on the practice of AD clinical trials have continually increased. Although now more commonplace, at the outset the notion of a precompetitive consortium in which private companies, otherwise competitors in the same marketplace, could come together to address common methodological problems was rare and not guaranteed to succeed [3]. ADNI represented an early instance of this model, and the first in the field of AD. The concept has proven both successful and impactful. Other consortia have since closely mimicked the ADNI model (e.g., the Parkinson's Progression Markers Initiative) [4], and other models of public-private collaboration have been developed [5]. In this article, we review and highlight the role, activities, and contributions of the PPSB within the ADNI project, and provide a perspective on remaining unmet needs and future directions.

2. The ADNI PPSB

2.1. History, membership profile, and working relationship with the FNIH

The FNIH is an independent, not-for-profit organization authorized by the U.S. Congress in 1990 to support the mission of the NIH—improving health through scientific discovery—through the creation and facilitation of public-private partnerships. FNIH is responsible for soliciting, administering, and managing private sector donations in support of ADNI and its potential renewal. In addition, FNIH convenes the PPSB, manages the PPSB working group efforts, and provides logistical support for PPSB meetings (teleconference and face-to-face), as needed.

Initially, private funding of ADNI was achieved through the fundraising efforts of the FNIH. Each individual company's contribution was originally based on its market capitalization, but was later scaled to the company's worldwide sales. In total, these contributions have to date provided ~32% of the funding of the ADNI project. Representatives of participating companies comprised the ISAB (now PPSB), which served as a forum for member organizations to formulate input on aspects of study design, biomarker selection, clinical assessments, organization of data and relevant methodological issues, and trial management.

As ADNI has evolved, so too has the participation profile of the industry and nonprofit partners. The PPSB has seen some members leave, with some re-joining and recent expansion to include many smaller companies (especially diagnostics and biotechnology). This wider group of stakeholders has broadened the perspectives, insight, and expertise the PPSB is able to provide to ADNI. A complete list of private partners that have participated in the ADNI project is provided in Table 1 and the breakdown of private partner funding by sector is shown in Fig. 1.

Table 1
Comprehensive list of Alzheimer's Disease Neuroimaging Initiative (ADNI) Industry Scientific Advisory Board (ISAB)†/Private Partner Scientific Board (PPSB) Members (as of February 2015)

AbbVie (Abbott Laboratories)*	***Genentech, Inc.****
Alzheimer's Association*	GlaxoSmithKline
Alzheimer's Drug Discovery Foundation (Institute for the Study of Aging)*	***Institut De Recherches Internationales Servier***
Amorfix	***IXICO Ltd.***
Araclon (Grifols)	Janssen Alzheimer's Immunotherapy
AstraZeneca*	***Janssen Research and Development****
Bayer HealthCare Pharmaceuticals Inc.	***Lundbeck***
BioClinica (Synarc)*	Medpace, Inc.*
Biogen	***Merck***†
Bristol Myers Squibb*	***Meso Scale Diagnostics, LLC.***
CereSpir	***NeuroRx***
Eisai†	***Neurotrack Technologies***
Elan†	***Novartis Pharmaceuticals Corporation****
Eli Lilly and Company*	***Pfizer Inc.****
EUROIMMUN	***Piramal Imaging, SA***
F. Hoffman-La Roche Ltd.*	***Takeda Pharmaceuticals International, Inc.***
Fujirebio (Innogenetics)*	TransTech Pharma Inc.
GE Healthcare	

*Asterisk denotes support of ADNI-1 and ADNI-2 phases; bold italics denote current members as of February 2015.

†The Industry Scientific Advisory Board (ISAB) was renamed the Private Partner Scientific Board (PPSB) to reflect the broader range of funding partners.

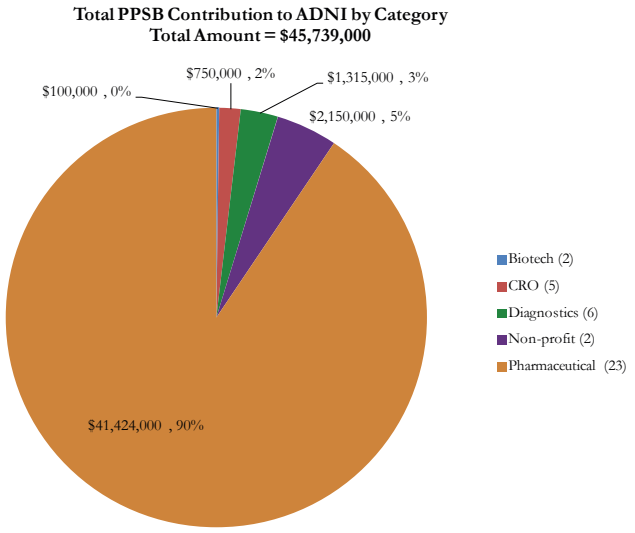

Fig. 1. Financial contributions from the Private Partner Scientific Board (PPSB) to Alzheimer's Disease Neuroimaging Initiative (ADNI), split by industry sector.

2.2. PPSB organization and participation in ADNI project management

The PPSB is led by a Chair and a Chair-Elect. Both must be employees of PPSB member organizations. The Chair serves as an ex-officio, nonvoting, observer to the ADNI Executive and Steering Committees. The Chair and Chair-Elect positions rotate on an annual basis and are determined through an open nomination (member organizations only) and election process (one vote per member organization). The ADNI Principal Investigator (PI) also serves on the PPSB as an ex-officio member. The PPSB Chair works closely with the FNIH project/program managers to coordinate monthly PPSB teleconferences, biannual face-to-face meetings, and other activities.

Two representatives from each member organization of the PPSB participate as ex-officio, nonvoting, observers who may attend the ADNI Steering Committee meeting, providing an important opportunity to critically review and provide input on the progress and most recent data from each of the ADNI cores. To further maintain dialog and line-of-sight to ongoing ADNI activities, the PPSB has assigned liaisons, with relevant expertise and experience, to each of the ADNI cores (although participation is not restricted). Thus, PPSB members are active participants in the ADNI cores and provide pertinent perspectives regarding the current and future needs of industry partners. As was done in developing the first renewal of ADNI, the PPSB has been in active discussions with the ADNI-PI and cores to incorporate the perspective of the private partners in the ADNI-3 renewal application. An overview of the PPSB structure is provided in Fig. 2.

Additionally, the PPSB has provided a number of important contributions to other consortia, including the FNIH-managed Biomarkers Consortium. A number of projects started in the ADNI and PPSB working groups have transitioned to the Biomarkers Consortium (http://www.biomarkersconsortium.org/), resulting in a number of important private-partner led contributions to the field [6–8].

3. PPSB initiatives

Over the course of the ADNI project, the PPSB has developed progressively greater collaborative relationships between its member organizations and with the ADNI academic cores. Recognizing common issues or gaps in knowledge, the PPSB also initiates its own working groups, to address specific issues that may not be covered through the ADNI/ADNI Core activities. These working groups create possibilities to within the precompetitive space establish longer term collaborations directly between industry partners, and also create an opportunity to include invited participation from academia and others outside the PPSB to provide additional expertise. The number of working groups initiated has increased considerably during the time frame of ADNI-2, whereas others have achieved their objectives and have been closed out. In many instances, the working groups publish their findings.

3.1. PPSB efforts on biofluids biomarkers

3.1.1. Proteomic efforts in cerebrospinal fluid and plasma

Although ADNI-1 collected cerebrospinal fluid (CSF) and blood for future exploratory work, funding to conduct the work had not originally been provided in the ADNI-1 budget. In 2009, funding was provided by a subset of the PPSB member companies to complete proteomic analysis in both serum and plasma using targeted multiplex panels from Myriad/Rules Based Medicine and more widespread profiling (Caprion). The activities of this working group were constituted under the Neuroscience Steering Committee of the FNIH Biomarkers Consortium to enable funding as a subproject to ADNI and to enable participation by parties beyond the PPSB membership. In 2011 also, a similar activity on multiplex based analysis of CSF was initiated, which was supported and coordinated in the same manner. Additionally, there was interest in examining CSF levels of Beta-site APP-cleaving enzyme (BACE) enzyme and enzyme activity and this was also included as part of the subteam's objectives. The efforts on plasma and CSF multiplex analysis of ADNI samples, and the BACE enzyme activity analysis of CSF have been successfully completed. The data have been posted to the ADNI data repository hosted by the University of Southern California's Laboratory of Neuro Imaging (LONI; http://adni.loni.usc.edu/) and several meeting reports and papers have resulted from this particular effort [6–11]. Some of the top candidate biomarkers associated with AD and AD progression have been replicated in independent cohorts [12].

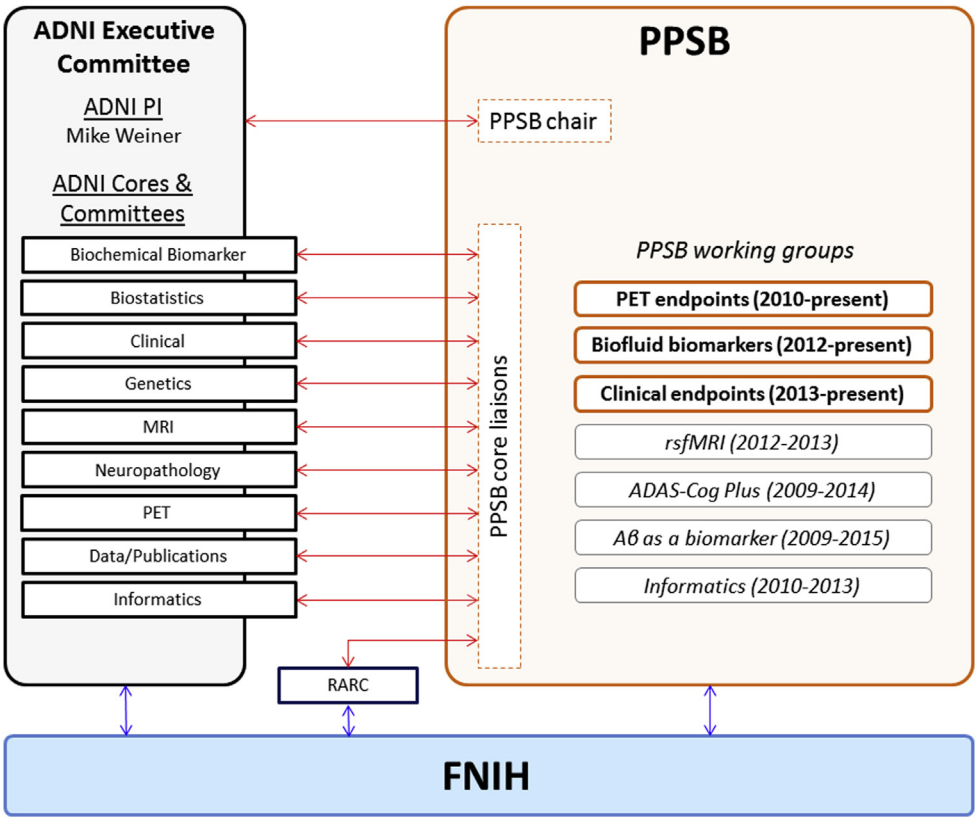

Fig. 2. Overview of the Private Partner Scientific Board (PPSB) and its relationship to the Alzheimer's Disease Neuroimaging Initiative (ADNI) executive committee, its constituent cores and to the Foundation for the National Institutes of Health. Ongoing PPSB working groups are shown in bold text, while working groups which have concluded the work are show in italics. *Note: Biospecimens collected from ADNI participants are available through ADNI and managed by the Resource Allocation Review Committee (RARC).

3.1.2. Biofluids biomarkers working group

To coordinate the various biochemical biomarker activities within ADNI, including the Biomarkers Consortium industry funded projects on Plasma and CSF Proteomics, joint meetings were held with the ADNI Biomarker Core academic group and PPSB member organizations. Those meetings, which were organized by the Biomarkers Consortium, provided a platform for PPSB members to collaborate with the Biomarkers Core, covering many aspects on ADNI fluid collections and analyses, such as standardization efforts involving the immunoassay of CSF amyloid beta (Aβ)1–42, t-tau, and p-tau181, ADNI plasma Aβ42/40 analyses. However, at the time the Plasma and CSF Proteomics projects were in the process of completing the work in late 2011, a new mechanism was needed to maintain the critical interaction between the PPSB group and the ADNI Biomarker Core. Moreover, the PPSB pharmaceutical industry partners felt a need for a more close interaction with diagnostics companies that were involved in progressing biofluids biomarker assays via regulatory pathways, for the eventual marketing of In Vitro Diagnostics assays (IVD). A key driver for this interest was the increasing use of CSF biomarker-based enrichment of patients in clinical trials in early AD, a use which could be classified as a companion diagnostics application with the need to adhere to IVD technical and regulatory requirements.

Thus, in early 2012, the Biofluids Biomarker Working Group was formed to serve as a forum to discuss ADNI biomarker sample collection, new analyses, and sample management with the Biomarker Core Leaders, and to evolve projects as needed in precompetitive space to address gaps for biofluid biomarker assay validation and clinical qualification with internal and external partners. The emphasis continued to be on the "most mature" CSF biomarkers, which were gaining further momentum via two other precompetitive efforts, the External Quality Control Program, which evaluates the intra- and interlaboratory variability of specified CSF Aβ and tau research use only assays [13,14] and the Global Consortium for the Standardization of CSF Biomarkers which develops CSF biomarkers reference methods, and via the Institute for Reference Materials and Measurements develop certified Aβ42, total tau, and P-tau reference materials. Both these efforts are coordinated by Alzheimer's Association, USA, and have active participation of PPSB member companies and the ADNI Biomarkers Core.

In the progression of CSF assays for diagnostic use or trial enrichment purposes, access to appropriate clinical samples

to be able to establish assay-specific cut points remain a challenge. In an attempt to facilitate cut-point determinations for three candidate CSF IVD assays, the Biofluids Working Group made a request for the release of a set of ADNI CSF samples in late 2012. However, the activity was at that time point hampered by the competitive nature of the goals and the fact that the Research allocation committee, which would grant such an access from the ADNI sample collection, viewed the work as repetitive to already completed CSF analyses and requesting a too large number of precious samples. Nevertheless, the ADNI samples remain a highly valuable sample set for paving the way for the development of a new generation CSF assays, the Biofluids Working Group is therefore currently reconsidering the possibility.

The Biofluids Working Group has also recognized recent advances in the development of blood-based biomarkers for AD. For example, at the ADNI PPSB meeting in Silver Spring, Maryland, in November 2012, a major session was organized with presentations from invited diagnostic companies engaged in AD CSF and blood-based biomarker assay development.

The work done through the PPSB member companies and the Biofluids Working Group and in related activities in the precompetitive space has generated a number of conference presentation and publications, including position papers on assay validation and the clinical qualification of CSF and blood biomarkers.

3.1.3. CSF Aβ as a pharmacodynamic biomarker

The development of treatments that inhibit the generation and increased clearance of amyloidogenic peptides has been a significant focus among several PPSB member companies. The primary biomarkers used to reflect pharmacodynamic activity of such treatments are CSF Aβ peptides, including Aβ42. Although data from the ADNI cohort shed insight on the long-term changes in CSF Aβ42 in controls, MCI, and AD patients, the use of CSF Aβ peptides as a pharmacodynamic biomarker is commonly performed as short-term studies, after single or multiple dosing of drugs, followed by a 12- to 36-h, period of repeated sampling of CSF, using either lumbar puncture or more often indwelling catheters inserted into the subarachnoid space, allowing for frequent sampling. As different member companies within the PPSB group were conducting their own separate programs measuring CSF Aβ as a pharmacodynamic biomarker, they observed substantial temporal variability in the data that was sometimes larger than pharmacologically induced changes. For example, irrespective of therapy, variability due to short-term lumbar cannulation and collection tube type used were observed. As a result, a PPSB working group was formed in early 2010 in which PPSB participants partnered with leaders in academia to compile their collective data and experience with the goal of generating an understanding of factors that contribute to CSF Aβ42 peptide variability in healthy volunteers and AD under continuous cannulation collection or single lumbar puncture parameters. The analysis also included data from similar studies performed in primates or monkeys. The pooled data analysis revealed that Aβ levels fluctuate minimally in CSF collected via lumbar puncture; in contrast, levels are highly variable for serial collection via in-dwelling catheter. There was a strong correlation of change in CSF Aβ40 and Aβ42. A number of factors identified that led to CSF Aβ42 variability include the types of polypropylene or sterilizing filters used in collection, sampling procedures and frequency, the volume of collection, and diurnal contributions, but also age and gender of the study subjects. The Aβ as a Pharmacodynamic Biomarker WG has concluded its active work in 2012, and the results have been presented in a scientific meeting [15].

3.2. PPSB efforts on imaging biomarkers

3.2.1. PET endpoints working group

Shortly after ADNI-1 began enrollment, [^{11}C]-PiB PET {N-methyl-[11C]2-(4-methylaminophenyl)-6-hydroxybenzothiazole [Pittsburgh Compound B or PiB] Positron Emission Tomography [PET]}, a novel imaging method for the in vivo detection of fibrillar amyloid in the brain [16], emerged as a candidate marker of AD and disease progression. The ADNI-1 PET core took on the challenge of establishing "fit-for-purpose" site qualification and acquisition protocols for [^{11}C]-PiB PET [17]. Around the same time, pharmaceutical companies began including [^{11}C]-PiB as an exploratory measure for detecting effects of monoclonal antibodies targeting Aβ [18,19]. The challenge of detecting subtle differences in the change of signal in a subject who already has a significant fibrillar amyloid burden during a clinical trial readily became apparent. However, the use of "amyloid PET" as a quantitative measure demands far more than diagnostic use, not unlike the difference between determining the change in tumor size over time during the treatment of cancers compared with quantifying changes in physiological parameters.

To this end, a PET working group was formed by the PPSB early in ADNI-2 composed of representatives from private partners and the ADNI PET Core focusing on the "technical" validation of PET (FDG and amyloid PET) for use in clinical trials as treatment endpoints. Over the course of ADNI-2, the PET PPSB Working group has generated proposals for evaluating between site and within subject variability over time in FDG and [^{11}C]-PiB PET, and has completed a technical guidance statement on quantitative amyloid PET, intended to reduce measurement error in quantitative studies [20]. Although the analysis elements can be PET tracer/target specific, the acquisition guidance in this report is independent of the PET tracer that is used in AD studies. The recommendations should be equally applicable to tau PET imaging, a keystone in the next generation of ADNI and other clinical research for neurodegenerative disorders.

3.2.2. Modification of MRI imaging protocols in ADNI-2

PPSB members have actively participated in the MRI Core throughout the ADNI project, providing an industry perspective on the findings emerging and issues arising, and in particular providing input as the MRI protocol has evolved from ADNI-1 through ADNI-GO and ADNI-2 (and currently in the preparations for ADNI-3).

The MRI sites in ADNI comprise a mixture of scanners across the three major MR vendors (Siemens, General Electric and Philips). In ADNI-1, a nonproduct sequence was used to ensure that three-dimensional (3D) T1 images were highly comparable across the different scanner types for quantitative structural brain analyses. However, these nonproduct sequences are not easily used in industry-sponsored trials. The PPSB encouraged the use of product sequences in ADNI-2 to better enable the translation of the ADNI standard 3D T1 sequence acquisition protocols to industry trials. Moreover, in the planning stages of ADNI-GO and ADNI-2, the PPSB strongly supported the incorporation of sequences to assess vasogenic edema and microhemorrhage (now known as Amyloid-Related Imaging Abnormalities) [21] to better understand the natural history of these processes.

Another innovation in the ADNI-GO/2 MRI protocol, strongly supported by the PPSB, was the inclusion of additional MRI sequences for arterial spin labeling (to measure resting brain perfusion), diffusion tensor imaging (to measure white matter integrity), and resting state functional magnetic resonance imaging (fMRI) (to measure functional connectivity). However, driven by the goals of maintaining a relatively short total scanning time and by the limited availability of some of these sequences across the different MRI vendors, a single scanner vendor was used for each technique. Although this did not provide explicit standardization of these methods across vendors, it did minimize scanner-driven variability and allowed the collection of a relatively large amount of publically available data spanning the disease spectrum.

3.2.3. The resting state fMRI working group

The resting state fMRI (rsfMRI) working group was established in 2012 to provide a forum for the ADNI MRI core and interested PPSB member companies to share analytical methodologies and compare results emerging from analyses of relevant data sets. This was prompted by the observation by both PPSB members and the MRI core that the cross-sectional and longitudinal changes in rsfMRI measures were not proving as sensitive to diagnostic category and temporal change as was hoped. The working group members discussed ongoing work and results emerging from in house studies and other consortia and ADNI data. Key aspects discussed included stability (test-retest performance) and longitudinal change as a function of disease stage. These discussions helped crystallize the need to include higher specification rsfMRI acquisition sequences in the ADNI-3 grant proposal.

3.3. Contributions to the genomics and genetics core

Financial contributions from the PPSB and other private donors have directly enabled genomics work not funded through the ADNI grants. The original genome-wide sequencing of ADNI samples was accomplished as a result of the general PPSB funding to the consortium. However, the subsequent whole genome sequencing (WGS) work of the ADNI-1 baseline samples was funded in mid-2012 by a generous private donation (the Brin-Wojcicki Foundation), in conjunction with the Alzheimer's Association. Some additional funding was thereafter provided via a special request to PPSB members, to further support the quality assessment and preparation of sequencing data. The WGS work has recently been completed and data are accessible for further analyses. Finally, one PPSB member supported the transcriptomic analysis on the baseline ADNI samples, which will soon be uploaded to the ADNI website at the University of Southern California's LONI. This provides genetic information at base pair resolution which, coupled with the dense phenotyping of the ADNI cohorts, will deepen our biological understanding of the links between genetics, pathology, biomarkers, and clinical presentation. In particular, the sequencing data provide a powerful opportunity for the identification of rare variants. The expression profiling data may provide opportunities to link genetic findings with changes in biomarker signals. ADNI genetic studies have confirmed known AD genetic risk factors, but also discovered novel susceptibility loci. Through the release of ADNI WGS data, and progressing work on gene expression, an impactful integration of next generation sequencing and multi-omics is made possible. Numerous ADNI genetics articles have been published, and the ADNI Genetics Core continues to have a critical engagement from scientists from the PPSB members companies [22].

3.4. Clinical outcome measures

A consensus has recently evolved that slowing disease progression may require the interception of the disease process at earlier stages, before substantial neurodegeneration has occurred [23]. Industry and academic interest has shifted toward the investigation of putative disease-modifying therapies in subjects in the predementia stages of the disease. Access to ADNI data on progressive changes in biomarkers and clinical readouts in these subjects has enabled the design of preclinical AD trials, but it remains a major challenge to derive clinical endpoints that would be sensitive enough to detect subtle impairments in cognition and function and to track change over time. Thus, the PPSB has recognized an urgent need to develop,

validate, and obtain regulatory endorsement for outcome measures useful in early stages of AD. Two PPSB working groups have been established to address these issues within the ADNI framework.

3.4.1. ADAS-Cog plus working group

The most widely used instrument for the assessment of cognition in clinical trials, the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) was developed and validated in subjects with significant cognitive impairment. However, it may be less sensitive in the early stages of the disease, as mildly affected subjects demonstrate substantial ceiling effects on many items [24]. The PPSB formed the ADAS-Cog Plus working group to evaluate whether a more granular analysis of item level data would increase sensitivity in the identification of mild impairment [25].

To carry out this work, the team required access to item-level data from the various cognitive and functional instruments measured in ADNI. Unfortunately, the database as originally constructed contained only summary scores for each test. The extant ADNI-1 database thus had to be modified to contain item level scores from the ADAS-Cog and tests of verbal episodic memory, language, and executive function. A subset of PPSB member companies thus funded a project to modify the database and enter the item-level data into it.

Models built from Rasch analysis and Item Response Theory (IRT) methods were assessed for their psychometric characteristics, including the ability to predict worsening, impact on sample size required to detect change, and correlation with biomarker endpoints. A detailed summary of the results is available [26]. Of note, IRT analysis appeared to be more flexible than the Rasch approach in sampling across the range of cognitive tests in ADNI; the performance of the ADAS-Cog alone was only marginally improved by the addition of other cognitive test results; and the addition of tests of executive function to the ADAS-Cog might have the biggest impact on clinical trial efficiency, given the predominant weighting of memory in the latter.

3.4.2. Clinical Endpoints Working Group

PPSB efforts to find improved outcome assessments in the ADNI data continued beyond the ADAS-Cog Plus project. In a data mining session organized by the PPSB in April 2012, several pharmaceutical companies shared their internal efforts on developing better endpoints for predementia clinical trials. This led to the creation of a Clinical Endpoints Working Group (CEWG), consisting of four work-streams (WS). To promote a common understanding of the various proposed endpoints in prodromal AD/MCI, WS 1 conducted a detailed review of known efforts in developing novel, statistically derived composite measures in predementia stages of the disease. Those composites have been developed primarily using ADNI data, in some instances pooled with internal company data. To compare the performance of such composites, WS 1 developed a software package in the open-source statistical framework of R which was provided to individual PPSB member companies to allow for a uniformed analysis of proprietary data sets without the need for data sharing. Thus, the R-package represents a valuable tool as it can be modified for comparisons of any clinical outcome measure in a standardized manner. WS 2 focused on the characterization of target population sin clinical trials along the early AD spectrum with the ultimate goal to understand how such populations and instruments used in these populations can be compared. WS 3 aimed to create inventories of clinical trials and observational data sets in early AD or natural aging, including the cognitive instruments used in them. WS 4 performed a due diligence review of several computerized test batteries to identify the best one to be integrated into ADNI, according to preset criteria. From this exercise, the CogState battery was chosen and is currently being implemented with additional financial support from PPSB members in a pilot substudy attached to ADNI-2.

The work of the CEWG has been summarized in a series of presentations and publications, including a Featured Research Session at the Alzheimer's Association International Conference in 2014 that reviewed the efforts on defining target populations and the currently proposed composite outcome measures. The CEWG has also had an impact beyond the ADNI PPSB. An off-shoot of these efforts was the formation of the predementia clinical outcome assessment tool project in the Coalition Against Major Diseases (CAMD), a consortium within the nonprofit organization, Critical Path Institute (C-Path). CAMD has directly built on the work of the CEWG with the ultimate goal of achieving general qualification of a clinical outcome assessment tool for use in the MCI due to AD population. CAMD initiated regulatory engagement with EMA and FDA in 2013, and has since then advanced to the stage of obtaining feedback on a formal briefing document from the agencies.

3.5. Database working group

The Database/Informatics Working Group was established to collaborate with the Biostatistics and Informatics Cores from industry users' perspective to improve the description, standardization, and organization of the clinical and biomarker data available on the ADNI LONI database, to improve data access, facilitate data integration, and aid data analysis. Input from the working group resulted in the standardization of definitions in ADNI data dictionaries and the development/deployment of an ADNI LONI data interrogation system.

4. Value of ADNI and critical challenges for industry

The mission of ADNI from its inception was to collect longitudinal biomarker data, along with a battery of clinical measures, in a large cohort of subjects from cognitively

normal subjects and progressively through the different stages of the AD spectrum in an observational study. Those inclusion or exclusion criteria now closely match the design elements of therapeutic clinical trials currently being conducted, and this progress has without a doubt been invaluable to the AD research community.

ADNI and related activities in the field have resulted in a major shift in the design and implementation of clinical trials of agents aimed at modifying the course of the illness. Without ADNI, which provided a forum for industry, government and academia, and the regulatory representatives from the Federal Drug Administration (FDA, European Medicines Agency (EMA), and Pharmaceuticals and Medical Devices Agency (PMDA) to work together, the transformation would have taken much longer. Moreover, it would have involved competing "in-house" approaches that would make it much more difficult to learn from trials of different agents across sponsors because details of patient characterization and protocol design would vary greatly.

The availability of ADNI data and ongoing open discussions on the implications of findings emerging from ADNI and other sources will continue to drive a degree of alignment as to the most effective ways to design and implement trials. Moreover, the repository of imaging and clinical data, and blood and CSF samples, which can be used for additional discovery efforts is unparalleled and as both genomic, proteomic, and metabolomic methods advance, major new insights will emerge. Longitudinal samples and data, over up to 10 years in some individuals, provide a special opportunity to uncover novel biomarkers of disease progression that could ultimately serve as readouts of therapeutic intervention.

5. Future perspectives

The PPSB membership is often asked by the ADNI leadership "What does 'Industry' want ADNI to provide?" As reviewed previously, the data that has emerged from ADNI in a public format has provided a wealth of information that has given pharmaceutical companies and academic collaborators the insights necessary to improve the designs of clinical trials in AD. These improvements have been especially important for informing research on the preclinical and prodromal stages of AD by providing detailed information on natural history, biomarker evolution, and correlation between biomarkers and clinical change. These understandings have led to more informed use of preexisting and evolving assessment instruments, and have revolutionized the way we think about the disease.

So what is needed in ADNI-3, and how can the PPSB partners most effectively interact with the ADNI academic leadership going forward? Expanding clinical experience with new clinical and biomarker tools to accelerate their application in clinical trials remains a key goal for ADNI-3. Examples of this type of collaboration include recent efforts to incorporate pilot studies on tau PET imaging and computerized cognitive batteries into ADNI-2.

Recently, Cummings [27] decried the high failure rate of clinical trials in AD. Not only is the cost of failed trials a great burden on our industry, but each failure increases the perceived risk of embarking on new ventures in AD therapeutics. One potential area of focus stems, paradoxically, from the success that ADNI has had in advancing potential biomarkers for clinical trials. Among the challenges that "Industry" faces in AD drug development are the cost, length, and complexity of clinical trials conducted under our current paradigm. The development and validation of tools and strategies that can be used early in the drug development process to stop the development of molecules with a high likelihood of failure could conserve and redirect finite resources into programs that would deliver therapies of real value to people. But new technologies are expensive and layering of multiple biomarkers and clinical tests onto clinical trial protocols add burden to patients and caregivers and multiplies costs. ADNI has led the way in the acquisition of the kind of real comparative data that are needed to identify the assessment protocols that deliver the greatest value with the greatest efficiency. These and other areas of collaboration will be carried forward and hopefully expanded in the upcoming grant renewal for ADNI-3.

Another challenge to ADNI and the PPSB going forward is how to keep up with the continuing evolution of tools and technologies and the ongoing progress in clinical and scientific progress in the AD field. An important role of the PPSB is to facilitate ADNI's ability to adapt to such developments. In 2015 and beyond, the availability of the first tau PET tracer will begin changing the AD biomarker landscape. This field will no doubt evolve further during the term of ADNI-3, with the appearance of additional tau imaging agents. Moreover, neuropathological evidence has highlighted the prevalence of mixed pathologies, including Lewy bodies, transactive response DNA binding protein 43 kDa; TAR DNA-binding protein (TDP-43), hippocampal sclerosis, and vascular disease in addition to Aβ and tau, in the ADNI population, with pure AD pathology seemingly a minority occurrence [28]. This biological heterogeneity impacts the clinical phenotype and may inform more specific populations that would be most suitable for a given treatment mechanism. To select patients for combination therapies will require a degree of biomarker subtyping that goes well beyond what current genetic state, imaging, and CSF findings provide. ADNI represents an ideal framework for the ongoing development and refinement of biomarkers to track these pathologies in vivo.

The environment of AD clinical trials continues to evolve and improve; ADNI has proven to be a critical effort leading to improvement in the use of imaging and biochemical biomarkers and of novel sensitive methods to assess clinical symptoms. Looking forward continued close collaboration

between the PPSB and ADNI academic leadership will lead to further improvements in the tools necessary to develop new treatments that will slow underlying disease progression. Working closely with the ADNI leadership as they craft the ADNI-3 renewal application is a major activity for PPSB in 2015. We look forward to the ongoing and continued success of the ADNI program.

RESEARCH IN CONTEXT

1. Systematic review: We searched *PubMed* to identify similar perspective articles on ADNI and found only one article (Schmidt 2010) that was similar.
2. Interpretation: ADNI is an observational study that has improved our understanding of biomarkers in AD and has fostered a collaborative model in pre-competitive space where researchers from industry, academia, non-profit organizations, and governmental agencies can work together to optimize use of pooled resources.
3. Future Directions: Future work in ADNI should reflect the needs of the field especially in next generation biomarkers to aid in development of novel AD therapies.

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