

Perspective

Taking stock: A multistakeholder perspective on improving the delivery of care and the development of treatments for Alzheimer's disease

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Abstract

Health-care stakeholders increasingly recognize that the scientific and economic challenges associated with Alzheimer's disease (AD) are simply too great for individual stakeholder groups to address solely from within their own silos. In the necessary spirit of collaboration, we present in this perspective a set of multicountry multistakeholder recommendations to improve the organization of existing AD and dementia care and the development of new treatments. In brief, the five recommendations are (1) health-care systems must make choices regarding the patient populations to be diagnosed and treated, (2) health-care systems should use an evidence-based standard of care, (3) increased collaboration between public and private institutions is needed to enhance research, (4)

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reimbursement end points need to be agreed on and validated, and (5) innovative business models should be used to spur the introduction of new medicines.

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1. Introduction

Alzheimer's disease (AD), the most common form of dementia, creates a vast social and economic burden on society and takes a heavy emotional toll on patients, caregivers, and families [1]. With the prevalence of dementia expected to exceed 115 million worldwide by 2050, it is noteworthy that relatively little progress has been made in developing and introducing medicines that may slow or halt the progression of AD or in establishing integrated systems to manage patient care [2]. Additionally, before 2007, the diagnostic guidelines for AD dementia had remained unchanged for 23 years [3]. Recent scientific advances have driven the advancement of new clinical diagnostic criteria for AD dementia and mild cognitive impairment (MCI) due to AD, together with a research agenda for preclinical AD [4-8]. These diagnostic criteria should yield a more accurate assessment of AD prevalence and increase our understanding of its etiology, pathophysiology, and progression.

In 2012, the Alzheimer's Disease Working Group (ADWG) was assembled as a multicountry multistakeholder forum for public- and private-sector stakeholders to address the challenges of AD and identify potential solutions that could benefit European health systems [9]. Over the course of three in-person meetings and numerous group teleconferences, the ADWG integrated international perspectives across the varied elements of health and social care that touch AD patients and their carers. ADWG participants and guests included general practitioners, clinical specialists, patient/policy advocates, medicine and diagnostic developers, health economists, social care representatives, regulators, health technology assessors (HTAs), and payers. All participants acknowledged that the scientific and economic challenges associated with AD are simply too great for stakeholders to address solely from within their own silos.

The ADWG was assembled and independently led by Tapestry Networks and was financially underwritten by Bristol-Myers Squibb, GE Healthcare, and Johnson & Johnson. Tapestry Networks endeavored to include as many competing stakeholder viewpoints as possible in the ADWG while maintaining an intimate size (~20-25 participants) to foster engaged discussion and active development of new approaches. The ADWG had continuous engagement from the same participants throughout the yearlong multimeeting process. Stakeholder representation was balanced to ensure strong public-sector pres-

ence and cross-sector expertise including: 6 to 8 regulators, HTAs, and payers; 6 to 8 subject matter experts; 2 to 3 patient and policy advocates; and 5 to 6 industry representatives. Nonindustry participants or their institutions received an honorarium and/or were reimbursed by Tapestry Networks for travel expenses to the extent it was in accordance with the mandates of the participant's institution and not incompatible with national laws or professional bodies of which the participant was a member.

All ADWG participants co-shaped the agenda and had an equal voice in the discussion. The focus was generally on European countries' health-care challenges in AD with the acknowledgment that the science and challenges in AD were global. Given the size parameters, the ADWG did have limitations. For example, the ADWG did not have direct patient participation. Instead, to integrate the broad consortia of advocacy across AD and ensure strong technical knowledge, the ADWG had representation from Alzheimer's Disease International and the Alzheimer's Society in the United Kingdom. Guest speakers were brought in to challenge viewpoints or balance overrepresented viewpoints. ADWG meeting summaries with full lists of participants and guests are freely available via Tapestry Networks' Web site.

In this perspective, we present a set of recommendations that highlight key consensus areas and gaps that need to be bridged across stakeholder groups to make progress in the fight against AD. The recommendations are an attempt to faithfully capture and summarize the ADWG's discussions, and the vast majority of ADWG participants have contributed to the authorship of this article. All participants, regardless of authorship, had an opportunity to comment, and all views were integrated. However, because a small number of participants chose not to author or were precluded by their organizational mandates, we note that the recommendations are those of the individual coauthors and not the entire ADWG. Most importantly, the authorship group accurately reflects the broad range of stakeholder views expressed within the ADWG meetings.

The following recommendations together encompass the view that stakeholders must work together to improve the organization and delivery of existing treatments and simultaneously create a more receptive environment for the development and use of future medicines [Table 1](#).

Table 1

Key recommendations

Key recommendations for improving the organization and delivery of AD care

- In the face of limited resources, health-care systems must make specific choices regarding the patient populations to be diagnosed and treated. Although routine screening of the general population is not warranted, there is a lack of consensus between the patient and payer perspectives on the value of an early AD diagnosis in the absence of a disease-modifying treatment.
- Health systems should use an evidence-based integrated care standard for AD. Although regional differences exist, all care standards should share the following core principles: (1) patients and their families should be at the center of the care standard, (2) the care standard must accept patients at all stages of AD, (3) the success of any care standard needs to be tied to its ability to deliver better AD health outcomes, (4) the care standard should be designed to engage symptomatic patients as early as possible, and (5) the care standard should be defined in terms of functions to be delivered rather than elucidating the role of a particular practitioner.

Key recommendations for improving the development of new AD treatments

- Increased collaboration between and across public and private institutions is necessary to enhance research on the etiology and progression of AD.
- Reimbursement end points need to be agreed on and validated. All stakeholders have a role in collecting this evidence.
- Innovative business models or agreements should be used to spur the development of new AD medicines.

Abbreviation: AD, Alzheimer' disease.

2. Key recommendations for improving the organization and delivery of AD care

2.1. In the face of limited resources, health-care systems must make specific choices regarding the patient populations to be diagnosed and treated. Although routine screening of the general population is not warranted, there is a lack of consensus between the patient and payer perspectives on the value of an early AD diagnosis in the absence of a disease-modifying treatment

Researchers, clinical specialists, and diagnostic developers have made significant progress in the identification and measurement of early biological markers of AD [10]. Potentially useful tools for making an early diagnosis include positron emission tomography (PET) scans to measure brain amyloid and assays to measure AD biomarker proteins in the blood and spinal fluid [11,12]. These advanced diagnostic technologies are making important contributions to the research and development of new AD medicines. Additionally, appropriate use criteria for amyloid-detecting PET radiopharmaceuticals have been proposed jointly by the Society of Nuclear Medicine and the Alzheimer's Association [13]. If upcoming trials and analyses of public databases confirm the validity of one or more of these technologies as an early diagnostic tool with a satisfactory level of sensitivity and specificity, payers should consider coverage in the research setting. However,

at this time, given the limited resources of European Union health-care systems and the unknown magnitude of the risk of false-positive cases, we do not endorse the use of advanced diagnostic tools to screen the general population for AD. Instead, health systems must decide which specific at-risk populations to diagnose, set clear diagnostic guidelines, and provide education and training to frontline professionals. As described in the following, we recognize that these explicit choices are especially challenging in a context of disagreement over what treatments to provide.

Two contrasting viewpoints, reflecting the differing stakeholder priorities, have emerged regarding the value of an early AD diagnosis in the absence of a disease-modifying treatment (DMT). Specialists and patient advocates tend to support a prompt and accurate AD diagnosis, particularly if requested by a concerned patient with credible risk—that is, a person seeking medical advice for symptoms indicating the potential for a serious brain disease. These stakeholders maintain that a timely diagnosis is critical for proper patient management and has psychological benefits arising from relief from the burden of uncertainty. In addition, they believe that existing treatments, including nonpharmacological treatments, can be beneficial. However, payers, HTAs, and some primary care physicians remain skeptical. Payers in particular would promote diagnostic testing for AD only if it was known that this information would change patient treatment and improve clinical outcomes. According to this viewpoint, a predementia diagnosis of AD should not be reimbursed in the absence of a specific DMT. To bridge this divide, we encourage development of a more robust evidence base illustrating the effectiveness of existing interventions, including nonpharmacological treatments, to support the case for early diagnosis in the absence of a DMT.

Regardless of which patients receive it, diagnostic testing for AD will require clear guidelines and a set of simple tests for frontline providers in community/primary care clinics. For example, health systems should promote AD diagnostics that show clear evidence of accuracy and precision. Additionally, even if DMTs became available, access to diagnostic testing would still depend on patient risk factors, including family history, age, and lifestyle. Other considerations include symptoms, the stage of the disease, comorbidities, and the clinical and cost-effectiveness of contemplated therapies. In the event that advanced diagnostic technologies receive coverage, referral networks may be necessary to guide patients to those clinics with the appropriate infrastructure.

Finally, to facilitate a coordinated approach, we believe that the AD community needs a shared set of definitions of the different stages of AD. For example, the International Working Group for New Research Criteria for the Diagnosis of AD proposed a “clinicobiological” lexicon that could serve as a common conceptual framework in the future [5]. Education for frontline health-care providers on the consensus definitions will be necessary before effective implementation of diagnostic and treatment criteria. In

addition, consistently applied definitions should help in the referral, enrollment, and interpretation of clinical studies. Additional education for general providers on advanced diagnostic tools will be necessary if those technologies move from the research setting into the clinic.

2.2. Health systems should use an evidence-based integrated care standard for AD. Although regional differences exist, all care standards should share certain core principles

As explained in the United Kingdom's National Dementia Strategy, AD and dementia require us "to transcend existing boundaries between health and social care and the third sector, between service providers and people with dementia and their carers" [14]. In that spirit, the ADWG agreed on a vision for an idealized care pathway for AD:

Empowered patients and caregivers going through a patient-centred, de-stigmatised journey of diagnosis and treatment; who move through a co-ordinated and integrated primary, specialty and social care system; a system that is supported by appropriate infrastructure, education, budgets and incentives for efficient and cost-effective care [15].

To realize this vision, all health systems should use an evidence-based integrated care standard. The United Kingdom, for example, developed its national clinical guideline according to the best available evidence, which included qualitative evidence [16]. Although we acknowledge the diversity of systems and regional and cultural biases in the delivery of care, we believe that all care standards should share the following core principles:

First, patients and their families should be at the center of the care standard. Assigning a "navigator" to coordinate a patient's care would help centralize treatments, recognize comorbidities, minimize the burden and expenses of care handoffs, and assist in identification of community resources. This navigator, or care coordinator, could be housed in a physical location such as a memory clinic, primary care office, or municipal center or could be accessed through an Internet portal. Additionally, the care standard should include clinical and social services assessments and a referral to support groups.

Second, the care standard must accept patients at all stages of AD. Although the hope is that all patients will enter these pathways at the early stage, the reality is that stigma and misconceptions will prevent many from receiving a timely diagnosis. The types and amount of required coordinated services will vary by the disease stage.

Third, the success of any care standard is tied to its ability to deliver better AD health outcomes. Therefore, it is critical to define those outcomes and begin to measure them rigorously. Launching an integrated standard of care in a time of strained health budgets is not possible unless the care standard contains an explicit promise to evaluate its own benefits. Outcome measurement needs to be built directly

into the care standard. Although health system designers should emphasize objective measures such as activities of daily living, cognitive performance, delayed time to institutionalization, or costs, they should also consider less tangible patient-reported outcomes such as quality of life and caregiver satisfaction. Wherever possible, the selected outcomes should be standardized across health systems. Finally, because the costs and benefits of an integrated care standard are distributed throughout society, policy makers will need to apply a societal viewpoint that extends beyond departmental budgetary concerns.

Fourth, care standards should be designed to engage symptomatic patients as early as possible. We believe that care standards can further improve AD and dementia awareness by framing the benefits of earlier identification as providing options rather than confirming a dreaded suspicion. Evidence-based nonpharmacological interventions and services that benefit patients but do not require a formal AD diagnosis should be applied. We recognize that many health systems under economic pressures will not have budgets to accommodate a broad adoption of validated advanced diagnostics. Nevertheless, policy makers should consider using these tools as part of the differential diagnosis for specific sets of early stage patients and should provide access to clinical trials when medically appropriate.

Fifth, the care standard should be defined in terms of functions to be delivered rather than elucidating the role of a particular practitioner. Given current economic pressures, health-care systems should focus on providing cost-effective integrated AD services that satisfy their quality standards, whether delivered by specialist nurses, general practitioners, social carers, or specialists. On a related note, health authorities also need to consider whether existing management structures are sufficient for implementing and operating an integrated care standard for AD.

3. Key recommendations for improving the development of new AD treatments

3.1. Increased collaboration between and across public and private institutions is necessary to enhance research on the etiology and progression of AD

With so many open questions regarding the underlying causes and mechanisms of AD, the need for increased collaboration between and across public and private institutions is enormous. Although the AD field has many active consortia, we believe that a more expansive cooperation across public and private stakeholders will yield the most timely and deep understanding of AD etiology and progression. ADWG discussions suggested that greater payer involvement in these collaborations could speed the pace of AD understanding. In particular, capitalizing on payers' ability to track outcomes could assist in AD biomarker validation, patient stratification, and the development of longitudinal studies.

Identifying and validating an expanded repertoire of AD biomarkers is critical to address the biological complexity of AD. Collaborating to test the validity and reliability of AD biomarkers in representative clinical populations will yield two major benefits. First, validated diagnostic biomarkers will enable earlier diagnosis of AD and allow for more streamlined clinical development of potential therapies. For example, clinical trials could be designed around patients with a less advanced disease phenotype, and diagnostic biomarkers may allow stratification of the clinical trial patient population. The result would be an enriched and more cost-effective clinical trial process. Second, validated biomarkers of AD progression will help to establish baseline comparators for clinical and cost outcomes.

To accelerate progress in diagnostic AD biomarkers, industry should build on recent efforts to expand the precompetitive space through sharing of raw data from clinical trials. For example, GlaxoSmithKline has announced a plan to allow qualified researchers open access to the anonymized patient-level clinical trial data for both its approved medicines and its nonapproved investigational medicines [17]. Regulators, too, are embracing the benefits of science as an open enterprise. The European Medicines Agency (EMA) announced that it does not consider submitted clinical trial data to be commercially confidential and plans to proactively publish these data as of January 1, 2014 [18,19]. A collaborative strengthening of the AD evidence base will allow stakeholders to independently confirm published findings, more efficiently perform meta-analyses and genome-wide association studies, validate trial end points and biomarkers, and ultimately stratify the patient population into treatable subgroups. As noted previously, patient stratification should, in turn, spur more efficient and effective clinical trials with the promise of a more rapid delivery of safe and innovative medicines to the public.

Regarding biomarkers of AD progression, stakeholders must continue to work together to explore the natural course of the disease. Although public-private partnerships such as the Alzheimer's Disease Neuroimaging Initiative [20] and the Coalition Against Major Diseases [21] successfully gather, standardize, and disseminate AD-related data to qualified researchers free of charge, we believe that stakeholders could accelerate the understanding of AD through greater engagement of payers and existing outcome data.

3.2. Reimbursement end points need to be agreed on and validated. All stakeholders have a role in collecting this evidence

During the ADWG meetings, discussion repeatedly turned to the critical role of reimbursement in supporting innovative AD treatments. In general, demonstrating cost-effectiveness for approved AD drugs has been difficult, and we anticipate DMTs to be especially difficult to value because heterogeneous progression and the long natural course of AD make a quick demonstration of functional

improvement unlikely. For example, contrast these medicines to oncology drugs, for which outcomes are generally more readily assessed. These difficulties have resulted in a great deal of confusion regarding which outcomes best demonstrate real-world effectiveness in AD treatments to HTAs and payers. The challenge is to model long-term outcomes for these new treatments on the basis of short-term data. Although some uncertainty will surely remain, stakeholders should agree on end points that, taken together, could provide a composite picture of long-term effectiveness. These end points must be clinically and economically relevant to HTAs and payers, realistic to developers, and important to patients and carers. After selecting a set of standardized end points, stakeholders should then use innovative tools and statistical models to validate them.

Although currently preferred reimbursement end points vary by stakeholder group, we believe that agreement on a suite of measures to serve as primary and secondary end points is achievable. The measures should capture both the clinical and cost-effectiveness of the treatment at issue. In general, HTAs and payers demonstrated a clear preference for objective end points such as functional measures or resource consumption measures, whereas patient advocates placed greater emphasis on quality-of-life metrics. Developers emphasized that the measures must be ascertainable within an economically viable time frame; that is, they should not unduly erode the treatment's period of exclusivity. Integrating these views, the ADWG identified end points that could demonstrate effectiveness within 2 years after the launch of a DMT and from 2 to 5 years after the launch. This list of end points provides one perspective on a starting point for gauging the real-world effectiveness of AD treatments [Table 2](#).

The validation of selected reimbursement end points is another rich opportunity for multistakeholder collaboration. In particular, public and private stakeholders should work together to conduct and finance the long-term follow-up necessary for end point validation. Although acknowledging that no tool is perfect, we believe that innovative technologies and statistical/economic models should be used to track the connection between reimbursement end points and long-term outcomes. In particular, we support the use of broad-scale registries, electronic medical records, and other databases to monitor downstream outcomes. Investing in the collection of these data ultimately will assist all stakeholders. For example, these data could serve as baseline comparators for a novel DMT to demonstrate cost savings attributable to a shortening of the severe stage of AD. Alternatively, they could be used to anticipate expenditures associated with the slowing of progression and lengthening of stages of the disease.

3.3. Innovative business models or agreements should be used to spur the development of new AD medicines

Despite the immense unmet medical need, many pharmaceutical companies have scaled down their search for new

Table 2
Clinical effectiveness end points*

Clinical effectiveness end points, <2 years after a launch
<ul style="list-style-type: none"> • Prevention/lowering of cognitive decline • Better ADL functioning scores • Patient autonomy/maintenance of independence • Patient and caregiver consumption of resources (e.g., effect on referral patterns, decreased use of psychotropics) • Quality of life or satisfaction (patient-reported outcomes or caregiver as a proxy) • Biomarkers that are linked to slowing disease progression • Safety and reduction of adverse events
Clinical effectiveness end points, 2–5 years after a launch
Same outcomes as above with the addition of the following:
<ul style="list-style-type: none"> • Duration of response • Time to the next stage of disease progression such as “progression of prodromal to dementia or from dementia to severe dementia defined by MMSE of 10” • Delay to nursing home/reduced rate of institutionalization, nursing home readiness score • Mortality/longer life • Compliance with treatment

Abbreviations: ADL, activity of daily living; MMSE, Mini-Mental State Examination.

*Selected reimbursement end points should be validated against desired long-term outcomes.

AD treatments in recent years. According to the Pharmaceutical Research and Manufacturers of America, between 1998 and 2011, only three new medicines were approved to treat AD patients' symptoms. During that same period, 101 medicines in development “failed”—that is, they were either discontinued or rendered inactive [22]. Recent late-stage clinical trial failures have suggested the need to treat AD patients before they sustain irreversible damage and the need to consider combination therapies designed to halt disease progression by targeting multiple pathways. However, even if a developer could confidently turn its attention to asymptomatic patients, the necessary trials to demonstrate safety, efficacy, and functional benefit for approval and reimbursement would be prohibitively expensive because of the long natural course of AD. It appears that developing AD treatments has become too risky under conventional business models. To reinvigorate development programs, stakeholders should explore new business models and align earlier on pre- and postlaunch evidentiary requirements.

Interventions to improve nutrition and lifestyle are helpful, and investments are needed to study their potential to reduce overall risk to society. However, we do not believe that these risk-reducing strategies will prevent all persons from developing AD. Therefore, continued investment in drug discovery is also critical. Stakeholders should begin to pilot new development models and agreements that recognize the complexities of development and measuring AD outcomes. To lessen the massive cost and mitigate some of the risk of conducting AD trials, some form of public-private collaboration among industry, regulators, and payers is necessary. The ADWG discussed both regulatory and

reimbursement approaches as vehicles for managing the uncertainty of developing new medicines for AD, including conditional approval, adaptive licensing, managed entry, conditional reimbursement, and risk-sharing agreements. Alternatively, if the focus on AD treatments moves to prevention, AD innovation could be bolstered by a vaccine-like procurement model that is more in line with a low-margin high-volume market.

Days after the last ADWG meeting, on February 7, 2013, the US Food and Drug Administration issued new draft guidance on developing drugs for early stage AD, recognizing the need for new approaches to trial design and end point selection [23]. In a separate perspective, the authors of the US draft guidance described the extreme difficulty in assessing functional impairment in the earliest stages of AD (i.e., pre-clinical AD) and explained how the draft guidance provides a pathway for accelerated approval in this early stage population on the assessment of a cognitive outcome alone [24]. In such a scenario, a novel drug could be approved on a single cognitive end point, provided that the developer agrees to conduct postapproval studies to demonstrate a more complete picture of the clinical benefit. The European regulatory point of view, as shared by the Italian regulators, is slightly different in that a single primary cognitive end point would not be sufficient for conditional approval in the preclinical AD context. However, they voiced a similar strategy for demonstrating clinical efficacy in prodromal AD/MCI due to AD. Assuming that continuity exists between prodromal AD/MCI due to AD and overt AD dementia, efficacy for a drug that delays disease progression should be demonstrated in two trials. First, in a trial of prodromal AD/MCI patients with virtually no functional impairment at baseline, efficacy should be demonstrated on a composite end point such as the Clinical Dementia Rating scale Sum of Boxes. Second, in a mild AD dementia population, two coprimary end points addressing both cognition and function would be necessary. In this context, EMA would value a comprehensive assessment of efficacy including evidence from secondary end points and biomarkers in addition to clinical relevance from primary end points.

In addition to licensing collaboration, stakeholders need to align on postlaunch evidentiary requirements for AD medicines earlier in their development time frame. A greater emphasis on real-world effectiveness in postlaunch studies would help to bridge the gap between regulatory and reimbursement requirements. Such studies would allow all stakeholders to appreciate whether a new drug is a significant or merely incremental improvement.

For strategies such as conditional reimbursement to be most effective, stakeholders should agree before launch on the launch and postlaunch evidence needed to demonstrate efficacy and value. Additionally, any successful variation on this theme likely would require the coordinated involvement of HTAs across multiple countries to lower the costs of postlaunch data collection. Through conditional reimbursement, health authorities would be making an investment in

optimizing health care while simultaneously easing the burden on developers of generating the necessary effectiveness data. This approach facilitates the introduction of new medicines and provides health systems the ability to value and deploy those medicines more precisely. Although the validity and credibility of postlaunch pragmatic data may not be as robust as randomized controlled trial data, the power of large-scale real-world data may provide insight into the value of treatments despite current deficits in scientific understanding. We believe that industry, regulators, and HTAs should look for an opportunity to pilot this model with a novel medicine as soon as possible.

4. Conclusion

Scientists have proven AD to be incredibly complex, and so a “magic bullet” treatment remains elusive. Attention and resources must be properly allocated between improving the present quality of care and developing future treatments. Coming out of the focused engagement of the ADWG, we recognize that all stakeholders, including patients and their families, must increasingly work together to develop new paradigms that acknowledge the particular strengths and resource limitations of each stakeholder. Together, our five recommendations dictate that courageous leadership, collaboration, and creativity are needed to decipher the complex biological underpinnings of AD, sustainably manage the short- and long-term costs of patient care, and, most importantly, meet the needs of patients and their carers today and in the future.

References

- [1] Wimo A, Jönsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. *Alzheimers Dement* 2013;9:1–11.e3.
- [2] World Health Organization and Alzheimer's Disease International. *Dementia: a public health priority*. Geneva: World Health Organization; 2012.
- [3] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–44.
- [4] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007; 6:734–46.
- [5] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010;9:1118–27.
- [6] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, 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.
- [7] 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.
- [8] 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.
- [9] European Healthcare Innovation Leadership Network, “Alzheimer's Disease Working Group Launch Meeting: setting the agenda for change,” 14 June 2012. Available at <http://www.tapestrynetworks.com/initiatives/healthcare/Alzheimers-disease.cfm>. Accessed July 9, 2013.
- [10] Katsnelson A. Biomarkers on the brain. *Nature* 2011;479:139–40.
- [11] Nordberg A, Rinne JO, Kadir A, Långström B. The use of PET in Alzheimer disease. *Nat Rev Neurol* 2010;6:78–87.
- [12] Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer's disease. *Nat Rev Neurol* 2010;6:131–44.
- [13] Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *J Nucl Med* 2013;54:47–490.
- [14] Department of Health. *Living well with dementia: a National Dementia Strategy*. DH Publications Orderline; London: 2009, p.7.
- [15] European Healthcare Innovation Leadership Network. Alzheimer's Disease Working Group: advancing progress in the face of dynamic science and constrained resources, 2012. Available at <http://www.tapestrynetworks.com/initiatives/healthcare/Alzheimers-disease.cfm>. Accessed July 9, 2013.
- [16] National Institute for Health and Clinical Excellence (NICE) and Social Care Institute for Excellence (SCIE). *Dementia: supporting people with dementia and their carers in health and social care*. London, UK: The British Psychological Society & The Royal College of Psychiatrists; 2007.
- [17] Glaxo Smith Kline. GSK announces further initiatives to advance openness and collaboration to help tackle global health challenges. Available at: <http://www.gsk.com/media/press-releases/2012/GSK-announces-further-initiatives-to-tackle-global-health-challenges.html>. Accessed July 9, 2013.
- [18] Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G. Open clinical trial data for all? A view from regulators. *PLoS Med* 2012; 9:e1001202.
- [19] European Medicines Agency. Release of data from clinical trials. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa. Accessed July 9, 2013.
- [20] Alzheimer's Disease Neuroimaging Initiative. Welcome from the ADNI Principal Investigator. Available at: <http://www.adni-info.org/>. Accessed July 9, 2013.
- [21] Critical Path Institute. Coalition Against Major Diseases. Available at: <http://c-path.org/programs/camd/>. Accessed March 27, 2014.
- [22] PhRMA. *Researching Alzheimer's medicines: setbacks and stepping stones*. PhRMA; Washington, DC:2012, p. 13–14.
- [23] Food and Drug Administration's Center for Drug Evaluation and Research. *Alzheimer's disease: developing drugs for the treatment of early stage disease (draft guidance for industry)*. Office of Communications, Division of Drug Information, Center for Drug Evaluation and Research, FDA. Rockville, MD: 2013.
- [24] Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. *N Engl J Med* 2013;368:1169–71. <http://dx.doi.org/10.1056/NEJMp1302513>.