A Call to Action: 
Alzheimer’s Disease on the Threshold of Change

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Introduction: The Facts

Currently, an estimated 5.5 million Americans are living with dementia due to Alzheimer’s disease (AD). In 2017, the disease will cost the U.S. an estimated $259B, of which drug costs are only ~$2B. By comparison, there were roughly 1.7 million new cancer patients in the U.S. in 2016, and drug costs associated with all cancers cost the U.S. a combined ~$50B. As the population ages, the prevalence of AD is expected to grow substantially, roughly tripling to nearly 14 million U.S. patients by 2050. Falling age-specific risks of dementia (as seen in some high-income countries over the last 25 years) may relieve some of this future burden, but the overall growth of the elderly population will still lead to a large patient pool. In addition, AD is becoming a more common cause of death. Death records indicate that mortality attributed to AD has increased 89% between 2000 and 2014, while other leading causes of death like heart disease and stroke have consistently declined. Meanwhile, current treatments for AD target only symptoms and fail to slow the progression of disease.

Figure 1: AD prevalence projections through 2020 and estimated mortality of AD compared to other high-cost diseases including prostate cancer, heart disease, stroke and HIV

Source(s): 2017 Alzheimer’s Disease Facts and Figures (alz.org); 2016 SEER Cancer Statistics (NCI)
However, change may be on the horizon. Despite the recent failure of solanezumab, verubecestat and others, investment in clinical trials in AD is at an all-time high. Promising results of other agents, such as aducanumab, suggest that we may be closer than ever to the approval of a Disease Modifying Therapy (DMT) in AD.*

Given this potential for transformative change, it is more important than ever to consider whether the current healthcare system is developed enough to deliver the full benefit of such a treatment. We believe the answer is no, and we have identified five key challenges that stakeholders across the system – policy makers, providers, pharma, caregivers, patients and patient associations – will need to solve together in order to successfully realize the full benefit of a DMT.

Figure 2: Key challenges in provision of treatment in AD

* DMTs are treatments or interventions that affect the underlying pathophysiology of disease rather than treating symptoms, and contribute to beneficial outcomes by altering the course of disease.
Challenge 1: Identifying patients

Alzheimer’s disease is characterized by the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tangles (tau protein), synapse loss and metabolic dysfunction in the brain. As these changes advance, damage and destruction of neurons occur, resulting in memory loss and other symptoms of AD. The disease develops slowly, gradually worsening over time as the pathophysiology intensifies. Initial symptoms are essentially undetectable and are often mistaken for normal aging. In fact, changes in the brain may appear 20 years or more before symptoms. Unfortunately, early diagnosis or treatment is currently limited by screening capabilities, costs, and a lack of effective treatments to prevent progression of the pathological changes.

Figure 3: Disease progression in AD

Currently, patients approach physicians with clinically observable symptoms – primarily forgetfulness. A diagnosis is then made through standard neuropsychiatric tests such as the Mini-Mental Status Exam (MMSE) and/or a variety of other cognitive tests such as MoCA, ADAS-Cog, CDR-SB, RBANS and ADCS-ADL. Indeed, outside of clinical trials, more complex and time-consuming tests are typically not included in the standard workup for AD. However, as will be discussed later, evolving research indicates that treatment may be most effective before patients have shown the type of cognitive decline that currently precipitates a visit to a physician. Getting patients into the physician’s office sooner will be a critical challenge for AD treatments seeking to prevent or slow cognitive decline.

Even when presenting with clinically significant symptoms, patients may not be informed of their diagnosis: in the U.S., fewer than half of patients (or their caregivers) with a diagnosis of Alzheimer’s or other dementia in their medical records report being told of the diagnosis.
Furthermore, even when presenting with clinically significant symptoms, patients may not be informed of their diagnosis: in the U.S., fewer than half of patients (or their caregivers) with a diagnosis of Alzheimer’s or other dementia in their medical records report being told of the diagnosis, compared to 93% in oncology or 72% in cases of Parkinson’s disease. The availability of an effective DMT will likely increase diagnosis rates of AD, but will not be enough to ensure that eligible patients are consistently and reliably identified, informed of their diagnosis and treated. As will be discussed further with Challenge 3, system-wide education and funding, in addition to broadly accessible, cost-effective screening and/or diagnosis will be required.

Challenge 2: Understanding the full patient population

Over the past 10 years, clinical understanding of the stages of AD has been evolving, including a recent distinction between clinical and pathological AD. Clinical AD, previously the only recognized form of AD, is characterized by three broad stages: mild, moderate and severe dementia. By contrast, pathological AD also includes prodromal and preclinical AD. Prodromal patients may present with Mild Cognitive Impairment (MCI), showing impairment of thinking but without impairment of activities of daily living, which may progress to Alzheimer’s dementia. Preclinical patients include both pre-symptomatic and patients at risk for AD. Pre-symptomatic patients show no cognitive symptoms but Aβ plaque formation or other hallmarks indicate the pathophysiological changes of AD are underway. By contrast, patients with a known mutation for AD are considered at risk, regardless of symptoms or pathophysiological evidence of disease. However, there is no definitive evidence to date that all subjects at the preclinical stage will go on to develop full clinical AD, and thus the question of how best to treat these patients remains unanswered. As the understanding of AD pathophysiology and segmentation evolves, it is becoming clear that prodromal and preclinical patient subpopulations will be critical targets for drug treatment if a DMT were to become available.
This evolution in understanding AD pathophysiology has been reflected in ongoing clinical trials, with nearly 90% of Phase III trials testing DMTs in early-stage prodromal patients/aMCI patients. Unfortunately, only ~10% of prodromal patients are currently diagnosed and treated because of the lack of guidelines to detect prodromal AD, and coupled with the lack of effective treatments. KOLs and physicians are most optimistic about treating patients in earlier stages, such as those with prodromal AD, due to the higher likelihood that patients will retain cognitive and functional capabilities and the hope that disease progression can be halted before significant damage has been done.

### Implications & considerations for understanding the full patient population

- Universally adopted segmentation will be key to a clear understanding of the utility of DMTs at various stages of disease evolution
- Preclinical and prodromal patients are currently untreated and largely undiagnosed but may be the most promising segments for effective treatment to stop and/or reverse the progression of disease
- In addition to segmenting patients by disease severity, biomarker segmentation may be critical to effective deployment of a DMT, offering the possibility to accurately identify the right treatment for the right patient

As not all preclinical patients go on to develop clinical AD, the figures represent the full potential patient population, including all prevalent patients at each stage.
Challenge 3: Expanding diagnostic infrastructure

The current diagnostic infrastructure presents a challenge for large-scale diagnosis of AD and access to a DMT.

A dizzying array of neuropsychiatric tests are available, albeit with no clear and universally adopted guidelines on the appropriate tests by stage of disease and no reliable, low-cost method to identify clear biomarkers of disease. As previously mentioned, current clinical diagnosis uses neuropsychiatric tests which can be inaccurate, unreliable and, particularly at early stages of the disease, may not be correlated with disease pathophysiology such as Aβ or tau levels.12 Rudimentary neuropsychiatric batteries like the Mini Mental Status Exam (MMSE) are still commonly first-line in AD diagnosis but are relatively insensitive to mild cognitive impairment.11,12 Sensitive cognitive end-points such as the ADAS-Cog, CDR-SB, RBANS and ADCS-ADL are being used rigorously in clinical trials as screening criteria, but are not commonly used in clinical practice.

Diagnostic methods to identify biomarkers of AD such as Aβ or tau have been developed, and are relatively reliable, but are expensive and invasive compared to the widely used but less reliable neuropsychiatric tests. Measurement of Aβ levels is currently possible through PET scans and both tau and Aβ can be detected with cerebrospinal fluid (CSF) tests. Biomarker diagnosis may be especially critical for DMTs targeting specific biomarkers of AD, namely Aβ and tau. Historical pipeline failures of agents targeting Aβ (e.g. bapineuzumab) showed that many patients in trials were diagnosed by neuropsychiatric tests but did not have detectable Aβ in the brain. Consequently, most current trials require Aβ positivity as an inclusion criterion.

If an Aβ-targeting DMT is approved, it is likely that clinicians will need – and payers may require – proof of Aβ positivity before prescribing or approving use. Likewise, if a tau-targeting DMT is approved, reliable evidence of tau protein will likely be required for use. This requirement is expected to be driven by several factors: the anticipated cost of a DMT, the limited utility of current neuropsychiatric tests at early stages and the requirement for proof of biomarker positivity in ongoing trials. Therefore, the most pressing question is how testing for Aβ/tau positivity or other biomarkers will be adopted in clinical practice, and how the full population of patients who should be screened can be reached.

Irrespective of cost, relying on existing PET scanning infrastructure in the U.S. and Europe will only screen a fraction of the total population, especially when considering the potential size of the early-stage population. There are currently “2,000 PET scanners in the U.S. (mostly used for cancer diagnosis), six of which are currently used for AD diagnosis.” In addition, not all of these 2,000 PET scanners will be suitable for amyloid PET assessment, given that PET ligands must be used within a defined geographical area to their labelling and distribution centers. Furthermore, for preclinical patients in particular, there are obvious ethical challenges to be considered when exposing a subject – who may never go on to develop full symptomatic AD – to radioactivity.
The cost associated with PET scanning is driven primarily by the expense of PET tracers themselves, and stakeholders are beginning to look into how existing PET scanning capacity can be more efficiently utilized and funded. The Centers for Medicare & Medicaid Services (CMS) recently initiated the $100M IDEAS Study (Imaging Dementia – Evidence for Amyloid Scanning) to evaluate the cost-benefit of amyloid PET scans by studying ~19k patients.\textsuperscript{14} If proven cost-effective, CMS will remove restrictions on amyloid-PET imaging. Even so, remaining questions on capacity and infrastructure highlight the urgency behind existing efforts to:

- expand PET capacity
- create effective pre-screening tools
- develop less expensive PET tracers and/or CSF tests with greater sensitivity
- identify sensitive and specific blood-based biomarkers

When a DMT is approved, we will be faced with questions of who should be screened and how it will be paid for as patients and providers push for early diagnosis. Before this happens, payers and policy makers will need to guarantee appropriate funding, physicians will need to ensure implementation and the general population will need to be made aware of the importance of early screening.

**Challenge 4: Transforming the treatment paradigm**

When a DMT does come to market, key stakeholders will be faced with the challenge of determining how products best fit into the treatment paradigm and how to use various agents together. Current trials and academic literature focus primarily upon three MoAs: (1) anti-A\textsubscript{\beta} therapies such as monoclonal antibodies to A\textsubscript{\beta}, active A\textsubscript{\beta} vaccines and secretase inhibitors (i.e. BACE inhibitors), (2) anti tau strategies such as tau inhibitors, passive and active vaccines and (3) other approaches such as metabolic strategies.

It is unclear at this stage whether any particular class is more suited for use in certain stages of the disease or in certain patient populations, and further research is required to identify the right drug for the right patients. Furthermore, many KOLs hypothesize that the use of combination regimens to successfully target the complex underlying disease...
Pathology is on the horizon in AD, especially if/when DMTs become the standard of care. But while combination therapy could be an effective solution to treating AD, it is unlikely that the healthcare system would pay for 2 NCEs at current market prices, and therefore innovative solutions must be developed to afford the cost of care. However, for both mono- and combination therapy approaches, the success of a new DMT will depend on early disease detection. Biomarker identification will be critical to correctly identifying at-risk patients eligible for treatment in the preclinical and prodromal stages, before symptoms begin to appear.

**Figure 5: Pipeline disease-modifying products by targeted clinical segment(s) currently in Phase II or III company-sponsored trials**

<table>
<thead>
<tr>
<th>Molecule Name</th>
<th>MoA</th>
<th>Preclinical</th>
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<th>Mild</th>
<th>Moderate</th>
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<tr>
<td>BAN-2401 (Biogen + Elsai)</td>
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<td>✠</td>
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<tr>
<td>AZD-3293 (AZN + Lilly)</td>
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<tr>
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<td>E-2609 (Biogen + Elsai)</td>
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- Target Population Enrolled In Trial(s)
- Not Currently Enrolled In Trial(s)

Source(s): ClinicalTrials.gov and company websites

Implications & considerations for transforming the treatment paradigm

- No currently available treatment can effectively stop or reverse progression of AD, and the approval of a DMT will completely displace old, low-cost, ineffective treatments
- Stakeholders will need to work towards a clear treatment paradigm that defines the right drug for the right patient at the right time
Challenge 5: Affording the cost of care

Even if we can successfully address the key challenges in delivering treatment to patients seeking care, perhaps the largest hurdle facing DMTs in AD is the commercial risk surrounding reimbursement and funding. Currently, payer spending associated with AD is modest given availability of generic treatments, but total costs such as hospitalizations are nearly $260B.\(^1\) However, an innovative (and likely expensive) DMT will add to the short-term costs of AD, borne primarily by commercial and government payers. In the longer term, an effective DMT is expected to decrease hospitalizations and overall caregiver burden, lowering the total cost of AD.

Figure 6: Financial burden of AD

An innovative (and likely expensive) DMT will add to the short-term costs of AD, borne primarily by commercial and government payers. In the longer term, an effective DMT is expected to decrease hospitalizations and overall caregiver burden, lowering the total cost of AD.

Source(s): 2017 Alzheimer’s Disease Facts and Figures (alz.org); IMS SMART; QuintilesIMS Analysis
A high-level estimate of potential drug costs puts the magnitude of this problem into perspective. A mAb priced at $18,500 per patient per year would result in ~$30B in drug costs per year if used in clinical AD patients in the U.S. alone. This would mean a drastic increase in overall spending on clinical AD from just ~$2B in 2016. If prodromal patients also seek disease modifying treatments, overall spending on AD could grow to be as high as $55B. The budget impact of drug costs in other high-cost TAs would be dwarfed in comparison: drug spending across all of oncology is estimated to have reached $50B in 2016, while RA costs payers only (by contrast) an estimated $32B.

Apart from the direct costs of DMTs, many mAbs in development will also require continuous diagnostic monitoring using MRI/CT scans to monitor adverse events such as amyloid-related imaging abnormalities (ARIA). MRIs cost ~$300/scan and on average, mAb DMTs require ~6 scans per year, costing the system ~$2000/patient. Such monitoring requirements could increase the cost burden by an additional ~$3B.

Depending on the type of product, different types of payers will be directly affected by the enormous budget impact of a new DMT launch. In the case of mAbs (HCP administered), the majority of patients will be covered by Medicare Part B and Medicare Advantage. Under the current workings of this system, the federal government would...
bear the cost burden and would be unable to restrict access, raising the critical question of how government funds can and should be used to support AD treatment. On the other hand, potentially self-administered products such as BACE inhibitors would be covered by Part D and payers in this case can be expected to impose restrictions to reduce budget impact if a DMT is approved. In a restricted environment, favorable reimbursement and access will depend on a clearly defined sub-set of patients who benefit most from DMT treatment, as well as convincing evidence of cost savings, accounting for not only the cost of treatment but also costs associated with diagnosis, monitoring and patient care.

**Summary**

These five challenges span stakeholders and health systems, and addressing them will require innovative solutions. To succeed in AD, it will be critical for pharma and biotech to adopt an “act now” mentality and bring disruptive business models to the forefront of the AD market. These challenges present a unique opportunity for the industry to lead the charge to shape the AD market in a way that is feasible, sustainable and truly transformative.

Stakeholders in AD, including pharma, patient groups, policy makers and payers, have a combined responsibility to address these challenges, as medical innovation alone won’t be enough to address the complexity and uncertainty posed by AD. In upcoming papers in this series, we propose a framework to map out potential future scenarios in AD based on stakeholder actions, and subsequently, how these stakeholders can work together to effectively reach the largest segment of this patient population: patients with preclinical AD. The scale and impact of these five challenges are unprecedented, but by taking steps to nurture collaboration across different stakeholders, we believe that they can be overcome and the healthcare landscape surrounding AD will be transformed for the better.

**Implications & considerations for affording the cost of care**

- AD will have a significant and unprecedented budget impact on payers and healthcare systems once a DMT is approved
- Therefore, AD should be prioritized over other disease areas to ensure widespread funding and access
- Pharma must proactively invest in developing innovative payment systems to balance the future costs that will be associated with a DMT

2. IMS MIDAS (accessed August 24, 2016)


5. Lilly Announces Top-Line Results of Solanezumab Phase 3 Clinical Trial https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871


10. ClinicalTrials.gov


15. QuintilesIMS analysis of IMS MIDAS (accessed November 17, 2016)
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