## Executive Summary

Table below provides a summary of the key events and a pipeline assessment of the biomarkers in the Alzheimer’s disease (AD) market.

### Biomarkers in the AD Market: Key Events and Pipeline Assessment

<table>
<thead>
<tr>
<th>Key Events</th>
<th>Level of Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012: Amyvid (Eli Lilly) approval – first US Food and Drug Administration (FDA) approval of diagnostic assay for AD</td>
<td>↑↑</td>
</tr>
<tr>
<td>2013: US FDA draft guidance issued for industry development of treatments for early-stage AD; final guidance anticipated in Q4 2013</td>
<td>↑↑</td>
</tr>
<tr>
<td>2013: Centers for Medicare &amp; Medicaid Services (CMS) to issue ruling on Amyvid reimbursement in July</td>
<td>↑↑</td>
</tr>
<tr>
<td>2013: [18F] Flutemetamol (GE Healthcare) submitted for FDA and European Medicines Agency (EMA) review</td>
<td>↑</td>
</tr>
<tr>
<td>2013: [18F] Florbetaben (Piramal) submitted for FDA and EMA review</td>
<td>↑</td>
</tr>
</tbody>
</table>

### Pipeline Assessment – Total Products Profiled

<table>
<thead>
<tr>
<th>Profiled Products</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Biomarkers</td>
<td>8</td>
</tr>
<tr>
<td>Amyloid positron emission tomography (PET) imaging</td>
<td>3</td>
</tr>
<tr>
<td>Cerebrospinal fluid (CSF) amyloid assays</td>
<td>3</td>
</tr>
<tr>
<td>Other amyloid assays</td>
<td>2</td>
</tr>
<tr>
<td>Tau Biomarkers</td>
<td>3</td>
</tr>
<tr>
<td>CSF tau assays</td>
<td>2</td>
</tr>
<tr>
<td>Other tau assays</td>
<td>1</td>
</tr>
<tr>
<td>Other Molecular AD Biomarkers</td>
<td>7</td>
</tr>
<tr>
<td>CSF assays</td>
<td>1</td>
</tr>
<tr>
<td>Blood-based assays</td>
<td>6</td>
</tr>
</tbody>
</table>

Source: GlobalData

### Nascent AD Biomarker Market Provides Opportunities for Companies with Innovative Products to Establish their Presence

From a commercial standpoint, the AD biomarkers market is still relatively young. Biomarkers for AD can be classified in terms of pathological mechanism and also in terms of the assay technology used to detect and assess the biomarker. Magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET) are valuable biomarker tools for assessing brain structure and function. However, these imaging tests can be administered in AD patients, at least at the basic level, without the need for AD-specific products or modifications. These tools don’t provide as many opportunities for further development in AD compared with other biomarkers and thus there aren’t many companies that have been involved in the development and commercialization of structural and functional imaging biomarker products for AD.

Molecular biomarkers of AD, on the other hand, present more viable opportunities for the development of novel assays with commercial potential. At the time of this writing, Amyvid ([18F] Florbetapir), an amyloid positron emission tomography (PET) imaging ligand marketed by Eli Lilly, is the only diagnostic assay approved by the Food and Drug Administration (FDA) for AD.
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Despite Lilly’s market monopoly at present, there are several similar amyloid PET imaging ligands in the pipeline, with GE Healthcare’s [18F] Flutemetamol and Piramal’s [18F] Florbetaben currently undergoing regulatory review in the US and the European Union (EU), and these are likely to provide active competition.

There are also several companies actively developing fluid-based biomarker panel assays for AD, including Innogenetics, which has produced assay kits for amyloid and tau proteins that are widely used in academic research and in clinical drug development. Some of these Innogenetics AD biomarker kits have received CE (Conformité Européenne) marking in the EU, but to date, none are FDA approved for clinical diagnostic use in the US.

Blood-based assays for AD biomarkers hold great promise as screening tests that can be widely applied in a cost-effective manner and are a major unmet need for AD. Several companies, such as Exonhit, Ctyox, Proteome Biosciences, DiaGenic, and Amarantus, have products in development that, if validated, may satisfy this need.

**Novel Biomarker Products would be Welcomed to Meet the Numerous Unmet Needs in the AD Biomarker Market**

The AD biomarker field is rife with unmet needs, both environmental and clinical. Environmental unmet needs include limited physician knowledge of the appropriate application of existing biomarker tools, as well as limited public awareness of the disease, which prevents people from seeking a clinical diagnosis. Often, Alzheimer’s symptoms are ascribed to normal aging. Cost and accessibility are currently limiting the widespread use of the available biomarker tools, since most of these are imaging-based technologies (MRI, PET) that can be quite expensive and require access to specialized imaging facilities.

There are also several unmet needs intrinsic to the biomarkers themselves. There is a lack of biomarkers that adequately assess the multiple pathological processes that are thought to contribute to AD; although tools to assess amyloid as a biomarker for AD have been actively developed, molecular measures of neurodegeneration, inflammation, and oxidative stress remain limited. Consequently, there remains plenty of room in the market for products that can satisfy these needs, provided that their accuracy and validity can be demonstrated. However, there have been challenges in producing widely reproducible assays, as described below.
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Existing AD Biomarker Assays Face Challenges in Validation and Standardization that may be Addressed through Public-Private Collaborations

The biomarker assays that have been developed suffer from a lack of standardization and validation, which has limited their clinical utility. However, the challenge of financing the large studies needed for assay validation has limited smaller companies from advancing their products to the clinical stage, and although several assays and kits are now commercially available, many are restricted to research or investigational use only.

The great public need for improved AD detection and diagnosis, which is necessary to facilitate effective intervention, has led to the development of several public-private collaborations geared towards the large-scale validation of AD biomarkers. The largest of these efforts is the Alzheimer’s Disease Neuroimaging Initiative (ADNI), which represents a collaboration of researchers across multiple study centers who are participating in open-access and pre-competitive information sharing through the ADNI database. These efforts are sponsored though government or public funding sources, with contributions from private industry participants that have a vested interest in developing biomarker products or AD therapies.

Collaborative efforts such as ADNI have enabled faster and more efficient advancement of AD research, and are anticipated to resolve some of the validation barriers that have limited the widespread use of biomarkers in AD.

Regulatory Barriers and Reimbursement Hurdles Impede Growth of AD Biomarker Market

Once these biomarker assays have been developed and have gone through the clinical trial processes required for validation, they may be ready for clinical use, but still face regulatory barriers to market entry and market adoption. Most countries have rigorous regulatory standards for diagnostics, particularly the US, where the FDA requirements for the approval of diagnostic products are very stringent, and the process implicit in satisfying these requirements is a costly one. As such, only products with powerful stakeholders or financial backing may be able to successfully navigate this regulatory process. Once the products are approved for clinical marketing, they then face the ensuing challenge of obtaining health insurance coverage. Amyvid is a clear example of this challenge because although it has been FDA approved since April 2012, it is yet to be reimbursed by government or private payers, which has greatly limited its market penetration.
Physicians and Researchers Express Measured Optimism About the Future of the AD Biomarker Landscape

The key opinion leaders (KOLs) interviewed for this report shared their insights into the current state of the AD biomarker field: they shared the challenges impacting biomarkers development, the unmet needs, as well the opportunities and directions that are particularly promising for the future of this market. The KOLs were in agreement that concerns over the reproducibility, standardization, and ultimately the large-scale validation of biomarkers, were key challenges in advancing biomarkers into the clinical arena for AD. They also expressed a need for varied biomarkers to serve needs both in AD clinical diagnosis and prognosis, as well as to guide therapy development for AD.

“What is needed is] some kind of cholesterol [test] for Alzheimer’s disease, and that if we consistently reduce cholesterol levels, we know that we are going to consistently reduce morbidity and mortality from heart attacks. That’s what ADNI and all these related long-term biomarker studies are really going to enable us to do in the long run, and I think that is why they are worth the investment — that we are going to be able to link these biomarkers in the pre-symptomatic or mildly symptomatic stage to longer-term outcomes, and we are going to be able to say, let’s say that at least 90% of people who had this biomarker when they were asymptomatic were going on to get Alzheimer’s disease within 10 years.”

[US] KOL, March 2013

“None of the biomarkers has so far been validated as a surrogate outcome. This is what drug companies in all likelihood would like to have because that would allow them to save a lot of time and resources because they could do Phase II and Phase III trials of smaller size, of let’s say 30 to 40 patients instead of 250, as you must have now, or more, actually. So this is a big, big unmet need.”

[EU] KOL, May 2013
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The KOLs also reiterated that the market potential of these biomarker-based tools was largely tied to the successful development and approval of disease-modifying therapies for AD. However, they cautioned that the absence of such treatments should not be a deterrent for companies developing these biomarker assays because it will be important for these companies to establish themselves and their products in the market to ensure that they are strategically poised prior to these drug approvals.

“If somebody is a major player, has an interest in there, the market is still young, the opportunity and the potential is still there, the commercial value is there and the medical ethical value is there. You have to organize and coordinate that process with your product — I think that’s successful if sustained — and then not wait until a disease modifier becomes available because others will penetrate the market before you, and that will be a big disadvantage.”

[EU] KOL, April 2013

“These [biomarkers] will all penetrate the market within the next one to five years, and obviously, it would be a major boost in motivation as well as application, if there would be an approved disease modifier.”

[EU] KOL, April 2013
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Introduction

2 Introduction

2.1 Catalyst

The growing prevalence, devastating health outcomes, and social and economic impact of Alzheimer’s disease (AD) make it a disease of epidemic proportion, with severe implications for societies at large if not adequately addressed. Inherent to the process of tackling the AD scourge is the need for tools that will allow for the early and accurate diagnosis of AD, as well as the identification of populations at risk. However, well-validated and established biomarkers are required to satisfy these needs. Several recent regulatory and industry events have brought the AD biomarker field to the forefront:

- The recent unsuccessful late-stage clinical trials for AD drugs such as bapineuzumab have emphasized the need for a paradigm shift geared towards early intervention in the treatment of AD. However, biomarkers are required in order to identify patients with early AD pathology prior to the onset of overt clinical symptoms, and to assess the efficacy and target engagement of putative therapies in clinical trials.

- In early 2013, the FDA issued a draft guidance for industry providing its current thinking on the process of drug development for the early treatment of AD. The document highlighted the possible roles that could be satisfied by AD biomarkers once there was widespread evidence-based agreement regarding the clinical utility of these biomarkers.

- The AD market also saw the entry in 2012 of the only FDA-approved diagnostic assay for AD, Amyvid (Eli Lilly), which also recently received marketing approval in the EU. Amyvid is in many ways a pioneering biomarker product within the AD market that has illustrated some of the challenges that ensuing biomarker assays will face navigating the regulatory and reimbursement landscape.
Appendix

14.6 About GlobalData

GlobalData is a leading global provider of business intelligence in the healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

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