# A Paradigm in Evolution

Molecular imaging is helping to pave the way for early detection and treatment of debilitating diseases, such as Alzheimer's, prior to the appearance of symptoms. This approach does, however, pose a number of scientific, ethical and legal challenges that will have to ultimately be addressed

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Although the utilisation of imaging in clinical research is well documented, there are ongoing discussions between the academic community, industry and regulatory agencies regarding the specific role of imaging in clinical drug trials. In many oncology studies, computed tomography (CT) and magnetic resonance imaging (MRI) are used to reliably monitor target lesion size, as well as provide follow-up objective clinical data supporting disease response and/or progression according to well-established criteria. Investigators are also identifying additional avenues for drug discovery and therapeutic development through the use of molecular imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT).

The unique abilities of PET and SPECT imaging, in combination with an ever-expanding library of radiotracer-labelled molecular imaging probes, provides a myriad of opportunities for developing new strategies to investigate disease. However, in some situations, PET and SPECT alone do not supply a complete understanding of the disease state, and in other instances, anatomic imaging is insufficient by itself for assessing and monitoring the disease state. The ability to combine anatomic and physiologic imaging techniques together into a single platform using hybrid imaging devices such as PET/CT, SPECT/CT and PET/MR can result in a more complete understanding of the process being investigated.

## Hybrid Imaging Approach

Advancements in molecular imaging techniques over the past decade have made it easier to probe the inner workings of the human body at the cellular level and potentially provide researchers with tools that can identify the evolution of disease. Thus, clinical research has the opportunity to evolve from a reactionary process that seeks to treat disease after symptoms are already present, to a preventative paradigm, where therapeutic approaches are developed to treat disease before it progresses to a clinically more advanced phase of the illness. As a result, there is a growing interest in the use of customised biomarkers and cutting-edge imaging techniques as methods to further the investigation of many areas of clinical research, such as in oncology, cardiology and neurology.

Assessment of neurodegenerative disease is one area in which this hybrid imaging approach appears particularly promising. Unlike oncology, diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and other forms of dementia do not necessarily present discreet lesions that can be easily identified, measured and monitored visually on routine anatomic imaging during the course of a clinical trial. Magnetic resonance assessment of early changes in AD and PD requires more advanced volumetric techniques, combined with sophisticated computer algorithms that allow for improved three-dimensional assessments of brain structures. This approach has already been shown to be of value in the assessment of AD, and current investigations are focused on the relevance of these measurements to early disease recognition and the integration with other imaging methods. Combining relevant anatomic imaging data with molecular imaging techniques that monitor the metabolic activity and the expression of certain biomarkers in specific regions of the brain can help to identify key signature patterns – essential in the understanding of the pathogenesis and pathophysiology of the disease – and the efficacy assessments of investigational new therapies.

The availability of new imaging devices, acquisition techniques and data regarding the role of imaging biomarkers in AD comes at an opportune time. The increasing aging population around the world, including the 'baby boomer' generation in the US, is creating a significant impetus to move forward with new clinical trials that investigate existing as well as new biomarkers, hone the reliability of early detection, and develop new effective preventative and disease-modifying treatments. According to current demographic models, the percentage of all Americans who are aged 65 and older will balloon from just over 13 per cent today to almost 20 per cent by the year 2030 (1). Assuming the current AD rate of 13 per cent for those 65 and older continues, by 2030 almost 2.5 per cent, or 7.8 million people and by 2050, 13.5 million – over four per cent – of the entire US population will be at risk of developing AD. In the absence of significant progress towards treating or delaying the onset of AD, the worldwide costs over the next few decades will be trillions of dollars, coupled with the additional emotional, physical and financial impact on the care giver, families or individuals with AD.

## Treatment Trial Challenges

Investigations are being conducted by clinician-researchers around the world who understand that AD poses a greater threat to society as other medical advancements extend human life expectancy. There are, however, a number of challenges that still need to be addressed as new treatment trial strategies are being implemented. The evolution and use of imaging in combination with established trial methodologies may help tackle some of the challenges specific to AD – in particular, the AD latency period and establishing causality between the changes observed in available biomarker expression and the actual pathophysiology that is occurring in the human brain. Investigators are currently grappling with these issues as clinical investigations continue to progress.

The first of these challenges relates to the significant latency period between pathophysiological processes occurring in the brain at the cellular level and the subsequent expression of clinical symptoms. This latency period has been thought to range from 10 to 20 years; however, the actual cellular process likely begins at an earlier point in time (2).

Consequently, clinical trials using a recruitment model of subjects with early AD or even mild cognitive impairment are treating the disease after early symptoms are present, and are not likely – as has been observed in a number of completed trials – to have the desired outcomes (3). This is most probably due to the disease progressing to a point where irreversible neuronal damage occurs, which prevents the therapeutic agent from achieving a desired clinical benefit. Unlike many other cells in the body, neurons have limited ability to replicate themselves and replace cells that are damaged beyond repair; therefore, it is critical to treat or prevent neurodegenerative pathophysiology at the earliest stage possible.

## Neurofibrillary Tangles

Investigators have already spent decades attempting to determine the pathogenesis and pathophysiology of neuritic plaques and neurofibrillary tangles – two unequivocal post-mortem pathological characteristics of AD. Over the past 20 years, AD research has largely focused on the protein fragment beta-amyloid, found in neuritic plaques, as a biomarker for detection and a potential target for treating AD. As the role of amyloid continues to be investigated, scientists are simultaneously expanding their search for additional biomarkers. One of the most promising areas of interest relates to neurofibrillary tangles. Neurofibrillary tangles contain aggregates of hyperphosphorylated tau protein, which result in the dysfunction of normal intracellular processes and are thought to contribute to neuronal cell death. As a result of investigations into the role of tau in AD pathophysiology, there is emerging evidence that using tau for AD detection and a measurement of disease progression may prove to be a reliable diagnostic biomarker and also a viable target for future therapeutic approaches.

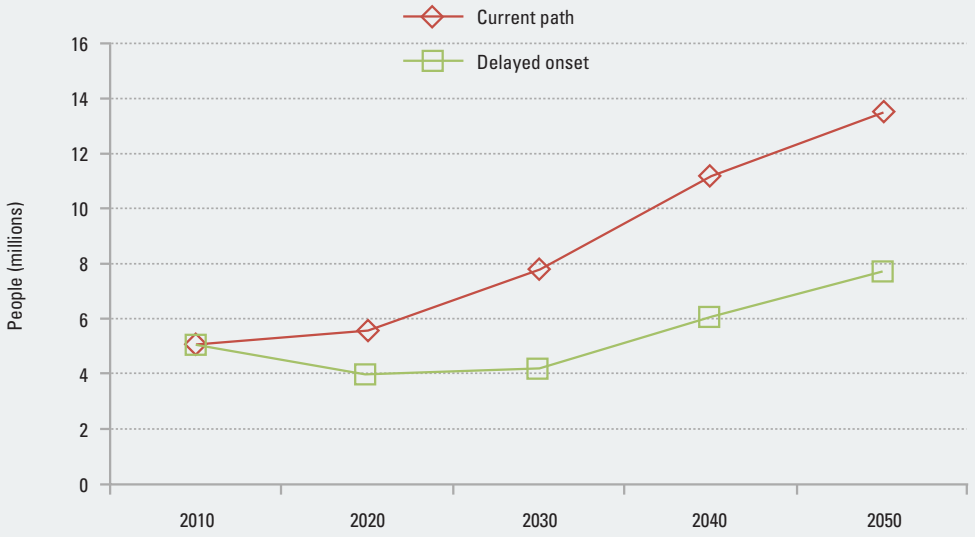
In 2011, as a result of extensive research into amyloid and tau proteins as biomarkers for AD, the Alzheimer's Association and the National Institute on Aging proposed changes to the 1984 criteria and guidelines for diagnosing AD. These changes update the criteria to incorporate the advances in biomarker research, which include measuring levels of amyloid and tau in blood and cerebrospinal fluid as potential early signals of AD pathophysiology (4). The revised criteria reflect the evolving clinical paradigm that the earliest possible identification of the at-risk population (up to 30 years before the onset of clinical symptoms) may be the best hope for achieving consistent and effective preventative or therapeutic results (5).

## Causality Concerns

In addition to the latency issue, another challenge for AD research is the causality dilemma. While the presence of

**Figure 1:** Americans aged 65+ with Alzheimer's disease 2010-2050

*Source: Modified from changing the trajectory of Alzheimer's disease (8)*



amyloid and tau malformations within brain tissue has been established as an unequivocal post-mortem diagnostic marker for AD, some important questions remain. What causes these plaques and tangles to form in the first place, and are these protein aggregates triggering the progressive dementia, or are they simply by-products of another pathophysiologic process?

Recently published data indicates a possible link between chronic neuroinflammation in the brain and increased expression of hyperphosphorylated tau – the precursor to neurofibrillary tangles – and diffuse amyloid plaques in children and young adults (6). Furthermore, data presented at a recent meeting of cell biologists appears to suggest some interdependence between amyloid and tau in the biochemical pathophysiology of AD (7). However, as with many human central nervous system trials, the aforementioned data was extracted from a mix of autopsy results, *in vitro* cell cultures and animal models without the benefit of investigating the potential for further downstream pathophysiologic effects of chronic neuroinflammation or amyloid-tau interactions in the living human brain. While the use of this type of data has been the standard since the inception of AD research, as techniques and tools for molecular imaging advance, the exciting prospect of collecting *in vivo* biomarker data in humans over periods extending through decades is beginning to usher in an entirely new phase of AD research. Over the past several years, molecular and functional imaging techniques have allowed investigators to acquire a clearer picture of AD pathophysiology.

The use of fluorodeoxyglucose PET imaging and functional MRI has led to a better understanding of cellular metabolism in the brain. In addition, radiotracers such as the Pittsburg Compound B (PiB), the recently FDA-approved imaging agent for visualising amyloid plaque deposits in the brain, $^{18}$F-florbetapir (Amyvid), as well as other $^{18}$F-labelled compounds in development, such as florbetaben and flutemetamol, are shedding more light on the latency and causality challenges. As the resolution of molecular imaging tools improves, the reliability of detecting early metabolic changes, especially in small critically important structures, such as the hippocampus, improves as well. The combination of improved metabolic data, together with reliable biomarker data and accurate volumetric assessments, should prove to be invaluable for analysing the pathophysiological picture of AD from its pre-clinical origins through severe dementia. With this information, researchers will hopefully be able to better design trials that optimise the timing and delivery of investigational compounds so as to have the best chance at achieving the desired clinical outcomes.

## Supporting Research

Designing future clinical trials investigating AD will require significant planning. The start of disease processes in late onset AD, which affects those aged 65 and older, may actually start as early as the third decade of life. This creates several significant logistical challenges, which include determining the at-risk subject population, managing long-term clinical trials and ensuring the resultant data withstands statistical scrutiny. Potential informed consent difficulties regarding the enrollment of outwardly healthy subjects into a long-term, late phase, clinical trial will also have to be addressed. While the nature of these logistical and ethical challenges are not new to clinical research, the use of advanced imaging techniques in AD trials may help navigate them.

> “The use of fluorodeoxyglucose PET imaging and functional MRI has led to a better understanding of cellular metabolism in the brain”

The longitudinal, multi-centre Alzheimer's Disease Neuroimaging Initiative (ADNI), founded in 2004, is already addressing many of these challenges by collecting data using various imaging tools, and investigating the predictive value of certain biomarkers as they correlate with disease diagnosis and progression. Data compiled from the ADNI is assisting researchers in determining the appropriate use of imaging techniques and correlating specific blood and cerebrospinal fluid biomarker results. This approach should help to achieve a reliable paradigm for identifying the at-risk population and quantitatively measuring the efficacy of investigational therapies. Through the combined use of various imaging agents and hybrid imaging devices, as seen in the ADNI, scientists may soon be able to establish optimal windows for therapeutic intervention, closely monitor the pathology of the disease, and reliably evaluate treatment efficacy over extended periods of time. Recent AD forums clearly indicate that the focus of AD research has moved into the preclinical detection phase, with prevention of clinical symptoms as the ultimate goal.

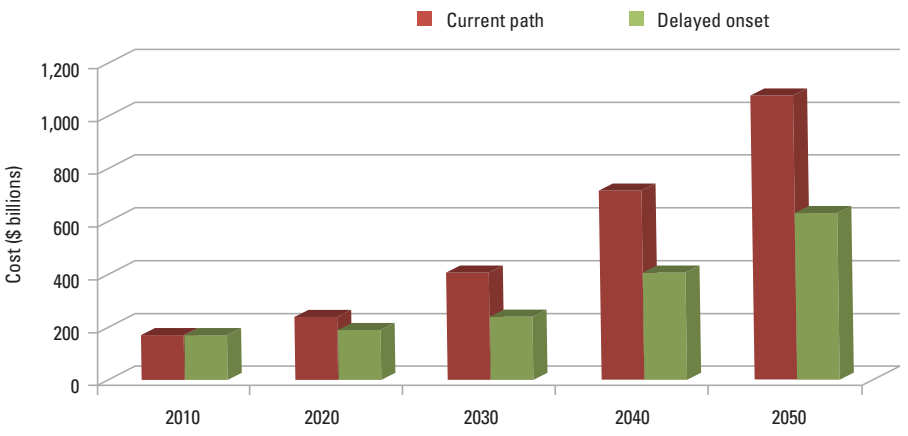
## Conclusion

The reward for the preventative approach for dealing with AD is considerable. The Alzheimer's Association has calculated that a therapeutic breakthrough that delays the onset of AD by five years, starting in 2015, would result in a significant decrease in the incidence of AD in the US over the next several decades compared to the current trajectory (see Figure 1) as well as significant cost savings (see Figure 2 on page 28) (8). Any additional delay in disease onset would result in an even greater decrease in the number of afflicted individuals and the overall cost of caring for AD patients. The success of such a strategy has wide-ranging societal implications – from millions of individuals and their families having a much better quality of life in their later years, to savings of many trillions of dollars over the next 30-40 years.

Although the pathway to treatment is clearly circuitous, it is encouraging that there continues to be a pipeline of clinical

investigations scheduled to begin or expand in 2013 (3,9). A number of these studies will employ 'cutting-edge' technologies, including molecular imaging, that should help in the continuing evolution of a paradigm to treat AD.

**Figure 2:** Impact of a five-year delay in onset on costs. Americans aged 65+ with Alzheimer's disease 2010-2050




*Source: Modified from changing the trajectory of Alzheimer's disease (8)*

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