

Turning the Light on Alzheimer's: PET•CT Solution Ushers in a Brighter Future for Patients and Caregivers

By Kathy F. Mahdoubi



My grandfather was a carpenter who painstakingly hand-built the kitchen cabinets, the carport and a carpenter's shed behind his home. He and my grandmother lived in a small town in Texas, USA. Collectively, they were known in their community as, simply, Honey and Speedy. Growing up, my grandfather would carve me rings from peach cores and little wooden trinkets that I cherished. I remember sitting around a campfire one summer, reminiscing when my grandfather, uncharacteristically unsure of himself, began telling a story. He was a master storyteller. As I listened, I became aware for the first time how he seemed to have lost track of where he was in the story. His memory was not very good anymore, but that did not seem too out of the ordinary for a man of his age. However, once he finished his story and my father spoke up, my grandfather suddenly interrupted him and proceeded to retell the story he had just told. Everyone got very quiet because they knew something was wrong. This forgetfulness was

impacting daily life, too. Within five years, the light that was my grandfather dimmed significantly, and within a decade, it went out. He became a shell of his former self, long since devoid of language and barely able to remember how to move or swallow. For the 35.6 million people affected by Alzheimers and other causes of cognitive decline worldwide, this is an all-too-familiar experience.¹

Daughter, Wife and Advocate

There are wives, husbands, sons, daughters and grandchildren who are losing their loved ones to this disease, one moment at a time. Like the author of this story, Meryl Comer has personal experience with Alzheimer's disease (AD). Comer's husband, Harvey R. Gralnick, MD, was diagnosed with Alzheimer's 18 years ago at the age of 57.

Gralnick was chief of hematology/oncology research at the National Institutes of Health for more than two decades and an expert in von Willebrand's disease. Forced to put her own career as a

journalist on hold to take care of her husband, Comer began writing about her personal experiences with Alzheimer's, as well as the politics of the disease. Her advocacy led to an appearance on "PBS NewsHour" to document the challenges real-time for caregivers and the physical, financial and emotional realities of Alzheimer's disease on families. Today, Comer is a zealous Alzheimer's advocate as president of the Geoffrey Beene Gives Back Alzheimer's Initiative.

"My physician/researcher husband and I have both been POAs—prisoners of Alzheimer's—ever since he was diagnosed with early onset at age 57," says Comer. "Eighteen years later, I still have him at home along with my 85-year-old mother who has dementia as well. I joke, painfully, that I run a spa."

When the Lights Go Out

Cognitive decline and the many forms of dementia affect almost every community across the globe, and according to the World Health Organization (WHO), of the

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Meryl Comer, President, Geoffrey Beene Gives Back Alzheimer's Initiative



The Path to Evaluating Alzheimer's disease in the Living Brain



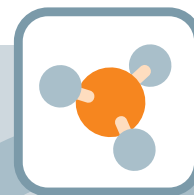
Signs

Alzheimer's begins with lapses in memory and other signs of cognitive decline. Loved ones notice something is wrong and eventually seek medical help.



Ordering Test

In conjunction with other diagnostic evaluations, the referring physician orders a PET imaging examination.



Manufacturing

Siemens PETNET Solutions has standardized its equipment and production processes, invested in redundant set-up and employed dedicated staff for the manufacturing of imaging biomarkers, providing a high level of delivery reliability.

35.6 million people currently diagnosed with dementia, the vast majority have Alzheimer's disease. Cases of the chronic neurodegenerative disease are expected to reach 115.4 million by 2050. That means the number of people living with the disease will be slightly less than the populations of France, Spain and the Netherlands combined. In the United States, someone is newly diagnosed with Alzheimer's every 68 seconds, and an estimated 5.4 million Americans are affected, making it the sixth leading cause of death.² Alzheimer's disease is being called an epidemic as deaths from AD continue to rise, while other major causes of death decline. For example, from 2000 to 2008, there has been a 66 percent spike in Alzheimer's cases in the United States alone.² The global financial impact of Alzheimer's disease in 2010 was more than USD \$604 billion and is rising year after year. Annual costs of care will rise correspondingly, to USD \$1.11 trillion in just 20 years.

"The number of Alzheimer's cases in the United States and indeed, worldwide, is growing very rapidly on the basis of extended life expectancies and the known age associated with incidence and prevalence of Alzheimer's," says Kirk Frey, MD, PhD, Professor in the Department of Radiology, Division of Nuclear Medicine, and the Department of Neurology, Chief of the Division of Nuclear Medicine and Director of the PET Center at The University of Michigan

Hospitals in Ann Arbor, Michigan.

"Twenty years ago, this was a problem that very few patients might encounter in their lifetime," Frey continues. "And now it is something that perhaps as many as half of the current population may suffer from during their lifespan. Also, much of our research on potential effective therapeutics for Alzheimer's disease is limited by our inability to correctly identify patients who don't have the illness. The pharmaceutical industry would like to find medications that are effective earlier in the course of the disease, and hopefully slow, or even arrest, its progression.

But to do that effectively, one needs to know at the earliest onset of symptoms who is likely to develop Alzheimer's disease versus who has an alternative explanation for their memory or other cognitive complaints."

Assessment Is Lacking

Existing clinical tests to assess for Alzheimer's disease are prolonged and cumbersome. Many people with suspected Alzheimer's disease start with an in-office screening that includes family history, reflexes, memory, attention, medications and MMSE (Mini-Mental



Biograph™ mCT scanner



Delivery

With the world's largest network of PET radiopharmaceutical manufacturing facilities, Siemens PETNET Solutions is able to reliably deliver amyloid imaging biomarkers in the U.S.



Molecular Scanner

With the industry's finest volumetric resolution¹² of 87 mm³, Siemens' Biograph mCT PET•CT attains the highest image quality¹³ for results that are quantifiable and accurate, enabling physicians to visualize different brain matter.



Quantitative Software

syngo®.PET Amyloid Plaque software¹⁰ is intended to automatically enable physicians to quantify amyloid uptake ratios. Combined with visual assessment, these capabilities may give physicians added information about the presence of amyloid plaques.



The Value of Knowing

Siemens integrated amyloid imaging solution¹⁰ seeks to enable the detection of amyloid plaque buildup in the living brain and assist physicians in assessing patients who are being evaluated for Alzheimer's disease.

State Exam) score, which measures cognitive decline. While providing some insight into the situation, these screening techniques can be unreliable and are limited in their ability to identify early-stage disease. Further lab tests, such as B12 and TSH, may help in the evaluation by ruling out other causes of memory issues. A far more invasive test, the lumbar puncture, can measure amyloid proteins, one of the indicators of Alzheimer's disease, in spinal fluid. However, this test is considered painful and inconvenient and has high inter-patient variability.

Imaging exams such as computed tomography (CT) and magnetic resonance imaging (MRI) also offer some insight into Alzheimer's, but again lack accuracy and the ability to evaluate early stage disease. A CT study can be used to rule out other conditions, such as tumors and multi-infarct dementia, while an MRI scan can show atrophy in the brain later in disease progression.^{3,4,5,6,7,8} Yet, like other tests, these studies lack a true ability to assess Alzheimer's disease early, and are most often used in late-stage disease, once significant symptoms have appeared and atrophy has already permanently damaged the brain. Historically, only a post-mortem histological exam of the brain provided the definitive step in diagnosing Alzheimer's disease.⁹

Recently, Siemens announced an integrated amyloid imaging solution to

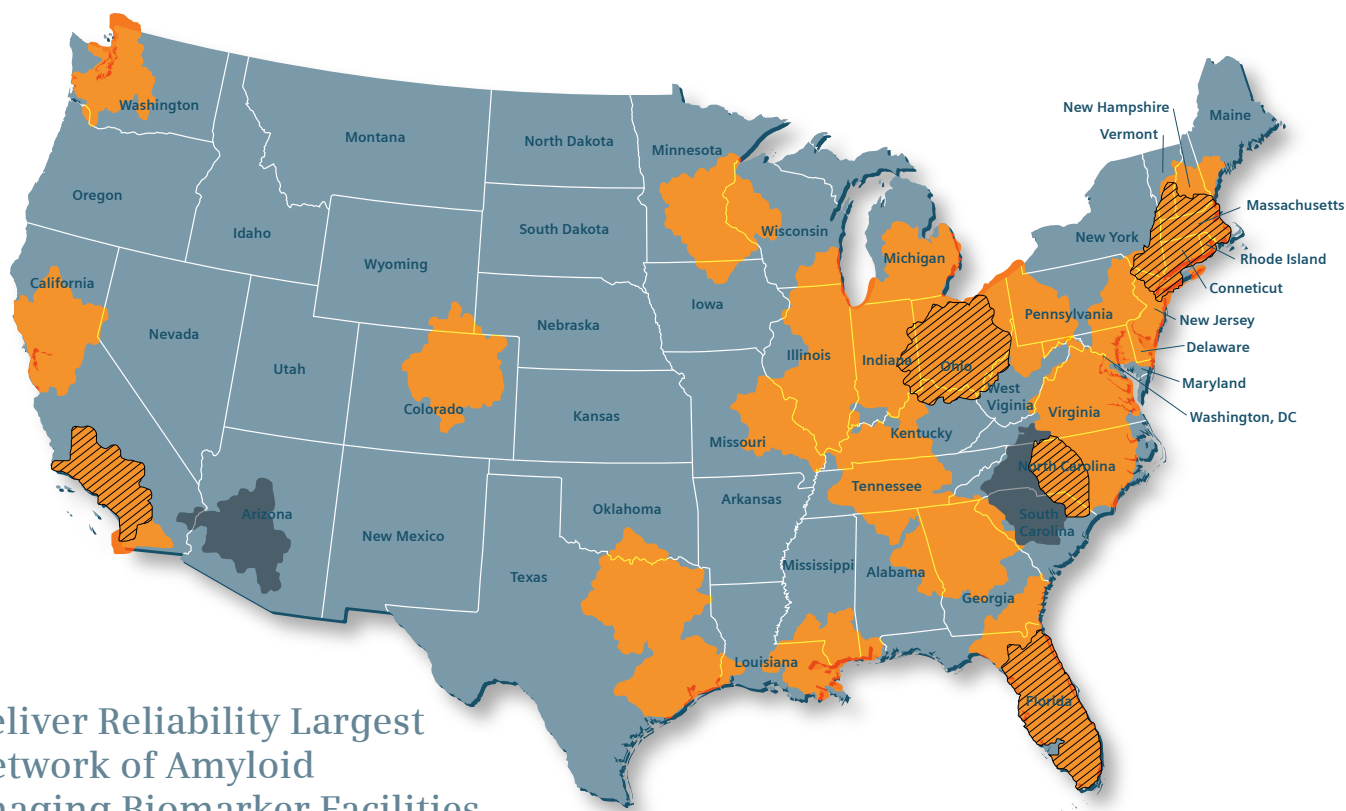
assist in the evaluation of Alzheimer's in the living brain, which includes Siemens PETNET Solutions imaging biomarker production expertise along with the new Siemens Biograph™ mCT scanner. In addition, Siemens pending U.S. Food and Drug Administration 510(k) application for *syngo*®.PET Amyloid Plaque proprietary quantification software¹⁰ is intended to enable physicians to calculate uptake ratios.

Amyloid and Alzheimer's

Understanding of the pathology of Alzheimer's disease has advanced dramatically in recent years with research focusing on amyloid deposition. Amyloid is a naturally occurring protein throughout the body and is implicated in a range of diseases. In the case of Alzheimer's, when amyloid plaques building up between neurons are combined with the development of neurofibrillary tangles within the neurons, they induce neurodegeneration, loss of connection between neurons, and eventually, cell death. PET now offers a unique way to view amyloid protein in the living brain. "These advancements are the most exciting advance in clinical dementia care in my 30 years of practice," says Norman L. Foster, MD, Director of the Center for Alzheimer's Care, Imaging and Research; Professor of Department of Neurology; and Senior Investigator of The Brain Institute at the University of Utah in Salt Lake City.

An Integrated Solution Starts with Imaging Biomarker Production

A PET amyloid imaging examination starts with access to an imaging biomarker. However, reliably manufacturing and widely delivering amyloid imaging biomarkers to hospitals and imaging facilities is no easy task. The radiopharmaceutical manufacturing process can have an impact on the ability to produce products in a reliable manner. At Siemens PETNET Solutions, there are eight standard steps in traditional PET radiopharmaceutical production. Reliability on this process for manufacturing traditional PET imaging biomarkers is greater than 99 percent. On the other hand, the combination of more complex and highly sensitive production and purification process of next-generation PET imaging biomarkers demands the need for new production and purification techniques, as well as new manual and automated manufacturing steps. With amyloid imaging, there are six additional and highly manual steps, including advanced preparation and quality control, sterile filtering and more cleaning. "You have to start with the radioisotope, and the one we use is F18," says John Beyer, a radiopharmacist and pharmacy manager for Siemens PETNET Solutions in St. Louis, MO, USA. "We run a cyclotron for up to 100 minutes, and this produces the F18 isotope. From there, we transfer it to an



Deliver Reliability Largest Network of Amyloid Imaging Biomarker Facilities

■ PETNET Solutions ■ Other distributors ■ PETNET Solutions and other suppliers

Phase 1	Phase 2	Phase 3
Atlanta	Hackensack	Cleveland
Chicago	Minneapolis	Denver
Dallas	Boston	Raleigh
Houston	Pittsburgh	Fort Lauderdale
Jacksonville	Detroit	Nashville
Palo Alto		Charlottesville
Philadelphia		Indianapolis
Seattle		New Orleans
Saint Louis		Los Angeles
		San Diego
		Sacramento

Based on 2.5 hours normal drive time. Actual time may vary.

Explora™ synthesis box to produce the drug in an unpure form.” Next, it moves through high-performance liquid chromatography in a semi-preparative HPLC system. “The material goes through a column, the impurities come off, and you get the purified imaging biomarker. Once it is collected, we sterile filter it into a product vial, run quality control testing on it, and then it’s ready for release and distribution.” Addressing these manufacturing challenges, Siemens PETNET Solutions has

standardized its equipment and training processes across its entire network to reduce the level of complexity in production. The company also has invested in redundant equipment for key processes, thus reducing the likelihood of failure at each of the risk points. In addition, Siemens PETNET Solutions employs dedicated staff and a fully-integrated operational support infrastructure for the production of amyloid imaging biomarkers. As a result, Siemens PETNET Solutions is able to offer imaging centers and hospitals a high level of delivery reliability of 96 percent, adding to their confidence in being able to scan patients as scheduled.

Largest Network for Broad Access

Once purification and quality testing is complete, the amyloid imaging biomarker is shipped from the closest Siemens PETNET Solutions center to the

imaging facility. The integration of manufacturing and radiopharmacy distribution is just another way that the Siemens PETNET Solutions network provides a dependable supply chain of radiopharmaceuticals. “PET as an industry is very time-sensitive,” says Beyer. “Everything we do that is F18-based has a two-hour half-life.” Due to time-constraints that come with the short half-lives of PET imaging biomarkers, Siemens PETNET Solutions has developed a distribution network to ensure its ability to meet currently projected demand and easily expand to meet increased demand. Siemens PETNET Solutions has set up nine amyloid imaging manufacturing facilities in cities across America, including Chicago, Seattle, Philadelphia, Houston, St. Louis, Palo Alto, CA, and Jacksonville, FL. Offering reliable delivery and coverage in high Alzheimer’s disease-prevalent areas across the

country, Siemens PETNET Solutions is in the process of preparing an additional 16 manufacturing centers, with potential for international expansion. Broad and reliable access to an amyloid imaging biomarker is the first element of Siemens proposed integrated Alzheimer's imaging solution.

Imaging Amyloid

The second piece of Siemens integrated amyloid imaging solution is the Biograph

mCT PET•CT scanner. PET offers a high negative predictive value and high accuracy in predicting progression to dementia.¹¹ "It's very important for us to have in hand a diagnostic test to seek the presence of Alzheimer's disease," says Frey, whose department is the first in the world to utilize the new Biograph mCT with integrated amyloid imaging. Traditional PET scanning technology in use today often lacks the fine volumetric resolution and high-contrast ratio

required to precisely differentiate between gray and white matter in the brain. The specific patterns of amyloid deposition and distribution in the white and gray matter of brain anatomy need to be taken into account during acquisition, processing and interpretation of image data. A PET signal from the biomarker in the white matter is not associated with the development of Alzheimer's disease, whereas a build up of amyloid in the grey matter signals potential neurodegeneration. Due to the interwoven nature of the white and grey matter in the brain, differentiating imaging biomarker deposition benefits from the finest volumetric scanner resolution available.¹²

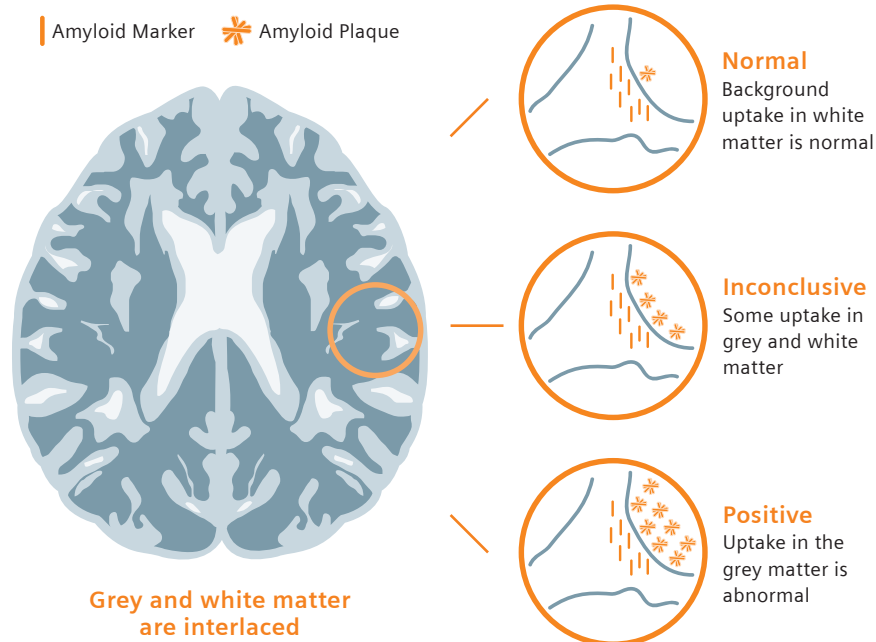
"The importance of scan resolution, particularly in looking for amyloid radio-tracer deposition, is the recognition that the target being imaged is cerebral cortical grey matter, which in normal individuals, is 3 to 5 millimeters at most in thickness," says Frey. "The signal can be readily detected and resolved even in scanners with lower resolution, but the higher the intrinsic anatomic resolution of the scanner, the more confident one can be that the signal actually emanates from cerebral cortical grey matter rather than other structures, and importantly, sub-cortical white matter as a potential confounder."

Siemens' Biograph mCT offers the highest image quality¹² and quantifiable results with proven accuracy; simply put, the resolution can help physicians distinguish white from gray matter. With its OptisoHD Detection System, UltraHD•PET and acquisition matrix of 400 x 400, Biograph mCT enables physicians to visualize different brain matter with the industry's finest volumetric resolution¹² of 87mm³ and four times improvement in contrast (signal to noise). With its unique combination of daily calibration and precise anatomical and functional co-registration, Biograph

Challenges of Interpreting Amyloid Clinical Cases Based on Visual Assessment Alone

Fleisher Concludes:

- **Accurate Localization:** Because grey and white matter are interlaced in such a compact way, distinguishing the two can be challenging¹
- **Quantification:** Cases where intensity of amyloid uptake is low, it may be challenging to accurately interpret based on visual assessment alone¹



1 Adam S. Fleisher et al: "Using Positron Emission Tomography and Florbetapir F 18 to Image Cortical Amyloid in Patients With Mild Cognitive Impairment or Dementia Due to Alzheimer Disease", Archives of Neurology, July 12, 2011

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Kirk Frey, MD, PhD, Professor in the Department of Radiology, Division of Nuclear Medicine, and the Department of Neurology, Chief of the Division of Nuclear Medicine and Director of the PET Center at The University of Michigan Hospitals in Ann Arbor, MI, USA



mCT can quantifiably improve diagnostic confidence in dementia diagnosis.

Quantitative Software

Due to the specific uptake pattern of PET amyloid imaging biomarkers, differentiating amyloid uptake through visual assessment alone can be challenging. Conventional interpretation software does not offer automatic quantification, leaving the reader to make a subjective visual interpretation. Quantification software, although it does not replace visual assessment by a physician, is intended to assist in making an interpretation of the PET image. Amyloid plaque localization with advanced PET and software technologies could provide clinicians greater insight.

Siemens 510(k)-pending proprietary quantification software, *syngo*.PET Amyloid Plaque,¹⁰ is intended to take a patient's PET amyloid exam and automatically register it against a reference model of a PET amyloid brain. *syngo*.PET Amyloid Plaque¹⁰ may enable physicians to automatically quantify uptake ratios. Combined with visual assessment, these capabilities may give physicians added information about amyloid-PET images. The integrated amyloid imaging

solution* thus encompasses three unique aspects: Siemens PETNET Solutions' imaging biomarker production expertise, the new Biograph mCT and FDA 510(k)-pending *syngo*.PET Amyloid Plaque quantification software.¹⁰ This new solution seeks to enable the detection of amyloid plaque buildup in the living brain and assist physicians in evaluating patients with cognitive impairment who are being evaluated for Alzheimer's disease.

The Value of Knowing

New hope in amyloid imaging could encourage physicians, patients and families to be more proactive when Alzheimer's is suspected, says Foster. "[With PET imaging,] it opens a whole new vista of opportunities for physicians to communicate with patients and families." Comer says she encountered terrible care when seeking help from physicians for her husband. "I am not unsympathetic to the dilemma for the doctors who fear that handing someone a diagnosis of Alzheimer's will ruin their lives," she says. "Yet, not to tell the patient and his or her family the truth is to deny them the most important option of all—the option to choose how the patient will live out what

good days he or she has left, leave a window of time to get their affairs in order rather than leave a mess, quit work, live the moment, see the world or tell your spouse and family you love them before you forget their name."

The University of Michigan's Frey agrees. "The knowledge of one's diagnosis, particularly early in the disease course, could lead to appropriate and important life decisions about what individual patients and their families would like to do," he says. "Often, our medical diagnostic system, at least in North America, discounts the standalone value of diagnosis. There are important family and financial decisions that would be much better informed by the ability to prognosticate about a patient's condition and what's likely to happen in the near future."

Some call this the value of knowing. A diagnosis of Alzheimer's disease to some is devastating, but to other individuals and their caregivers, it is an opportunity to build a support team and network, enroll in clinical trials and, for those early in disease progression, launch into mental activities to fortify brain activity and actively participate in planning and create directives regarding their care and finances.



*syngo.PET Amyloid Plaque** quantification software from Siemens is pending approval for the U.S. FDA.

Flipping the Switch on Potential Therapies

The hope of better diagnosis goes hand in hand with the creation of effective therapies to treat Alzheimer's disease. A few pharmaceutical companies are now testing anti-amyloid therapies. "Much of our research on effective therapeutics for Alzheimer's disease is limited by our inability to make a confident diagnosis early in the course of the illness," says Frey. And there is more positive momentum in the fight on Alzheimer's. The U.S. government in May launched an ambitious plan, a first of its kind among governments across the globe, to help prevent and treat the disease. The National Alzheimer's Plan will invest \$156 million to tackle Alzheimer's disease.¹⁴ U.S. Department of Health and Human Services Secretary Kathleen Sebelius, who announced the plan, says "A short time ago, the fight against Alzheimer's lacked a national focus and a consistent, coordinated partnership with the nation's Alzheimer's community. Today, we have made the first historic investment of funds and a 15-year commitment to prevention and treatment." "The field is energized," says Francis Collins, Director of the U.S. National

Institutes of Health. "And so it is the right time, both given the enormous public health significance and the significance to individuals and families." Through innovative software and scanner technologies, Siemens is helping progressive health care systems and

organizations to advance their lead in their fight against Alzheimer's.

Kathy F. Mahdoubi regularly writes on topics related to molecular imaging. She is based in Texas, USA.

* *syngo.PET Amyloid Plaque* is pending 510(k) clearance and is not yet commercially available in the US.

References:

- 1 World Health Organization data, 2010.
- 2 Alzheimer's Association. 2012 Alzheimer's Disease Facts and Figures, Volume 8, Issue 2.
- 3 Chatzidakis, EM. et al. Brain CT Scan Indexes in the Normal Pressure Hydrocephalus: Predictive Value in the Outcome of Patients and Correlation to the Clinical Symptoms. *Ann Ital Chir.* 2008 Sep-Oct;79(5):353-62.
- 4 Bowen, JD. et al. Interrater reliability and accuracy in identifying ischemic strokes using computed tomography scans in people with dementia. *J Am Geriatr Soc.* 2005 Oct;53(10):1743-7
- 5 Kim GN. et al. Topography of cortical thinning areas associated with hippocampal atrophy (HA) in patients with Alzheimer's disease (AD). *Arch. Gerontol Geriatr.* 2012 Mar-Apr;54(2):e122-9. Epub 2011 Nov 15
- 6 McEvoy, LK and Brewer JB. Quantitative structural MRI for early detection of Alzheimer's Disease. *Expert Rev Neurother.* 2010;10(11):1675-1688.
- 7 Lim A, Tsuang D, Kukull W, et al. Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. *J Am Geriatr Soc.* 1999;47(5):564-569.
- 8 Petrovitch H, White LR, Ross GW, et al. Accuracy of clinical criteria for AD in the Honolulu-Asia Aging Study, a population-based study. *Neurology.* 2001;57(2):226-234.
- 9 Herholz, K and Heiss WD. Positron Emission Tomography in Clinical Neurology. *Molecular Imaging and Biology.* 2004. Vol 6, No. 4, 239-269.
- 10 *syngo.PET Amyloid Plaque* is pending 510(k) clearance and is not yet commercially available in the US. For rest of world, *syngo.PET Amyloid Plaque* is intended for use only with approved amyloid radiopharmaceuticals in the country of use.
- 11 Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging—Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement.* 2012;8(1):1-13
- 12 Based on competitive information available at time of publication. Data on file.
- 13 2011 PET Image Quality Survey conducted in the U.S. and Europe as a custom study by IMV, a neutral, third-party market research company.
- 14 Full plan available at: <http://aspe.hhs.gov/daltcp/napa/NatPlan.shtml#intro>