AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 04: Dementia (Including Alzheimer's Disease)
Potential High Impact Interventions Report

Prepared for:
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Contract No. HHSA290201000006C

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January 2012

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA29020100006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual Topic Profiles are developed for technologies and programs that appear to be closer to diffusion into practice in the United States. Drafts of those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify those interventions that experts deem, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually, and topics included may change depending on expert comments received on interventions issued for comment during the preceding six months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High Impact Interventions: Priority Area 04: Dementia (Including Alzheimer's Disease). (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. January 2012. http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor target technologies and innovations in health care and to create an inventory of target technologies that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is the identification and monitoring of new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is the analysis of the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future utilization and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling a profile on topics and issuing topic profile drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses

the structured form to also disclose any potential intellectual or financial conflicts of interest (COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The material on interventions in this Executive Summary and report is organized according alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary. The table below lists the three topics for which (1) preliminary phase III data were available; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February and November 1, 2011. (A total of 25 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present one summary on two topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts' comments and their assessment of potential impact.

Priority Area 04: Dementia (including Alzheimer's disease)
1. Camera device (Vicon Revue) for episodic memory impairment in patients with Alzheimer's disease
2. *Florbetapir F18 (Amyvid)-enhanced positron emission tomography (PET) for detection of beta-amyloid plaques
3. *Flutemetamol-enhanced PET for detection of beta-amyloid plaques

Discussion

Most of the research activity in the dementia priority area focuses on Alzheimer's disease (AD), how to diagnose it, and new disease-modifying (rather than symptom management) treatments in development.

AD is characterized by cognitive impairment and memory loss and is the most common cause of dementia among individuals 65 years of age and older. Brain cells located in the hippocampus (the brain's memory center) begin to die, thereby interrupting the process of memory storage and recall. Over time, damage spreads from the brain's memory center to areas that control thinking and judgment, behavior, and communication. Patients may become bed-bound and completely dependent

on caregivers. Although AD is potentially fatal, patients can live as long as 20 years after diagnosis and often have coexisting age-related diseases that contribute to their deaths. According to the National Institute on Aging, about 12.5% of people 65 years of age and older (or about 5 million cases) currently have the disease. Women are more likely to develop AD, in part because, on average, women live longer than men do. The anticipated doubling of the number of people aged 65 years and older by 2040 portends an increase in AD cases by 200% or more. According to the U.S. National Center for Health Statistics, in the U.S. in 2005, AD was the seventh-leading cause of death overall and the fifth-leading cause of death in people 65 years of age and older. The cause of AD is currently unknown, but researchers suspect that factors involved in disease development include age, genetics, oxidative damage to neurons, serious head injury, brain inflammation, and environmental factors.

Much research into the causes of AD has focused on two hallmark structures found in the brains of AD patients: amyloid plaques and neurofibrillary tangles. Amyloid plaques are thought to disrupt and/or damage neurons in the brain. Neurofibrillary tangles may cause cell dysfunction and eventually cell death. Other researchers point to inflammation as a possible cause of the progressive cell death seen in the brains of patients with AD.

Currently, a definitive diagnosis can be made only by postmortem examination of the brain because many other conditions can mimic AD. In this report, two new imaging agents are discussed from a class of six or seven similar positron emission tomography (PET) radiopharmaceuticals in development that are intended to aid in detecting the beta amyloid plaques that many think are associated with AD. There is the hope that earlier diagnosis would enable earlier intervention, though available treatments do not make much of an impact on patient outcomes yet in terms of slowing or halting disease progression. In the absence of effective treatments, many programs intended to aid communities and caregivers in understanding how to best support loved ones affected with AD are being piloted.

The search is on for ways to definitively diagnose AD and for drugs, biologics, and alternative or complementary interventions that modify the disease or better manage symptoms to keep patients as independent as possible for as long as possible. Many drugs are in development and being tracked in the system currently, and the constellation of potential impacts is likely to change as more data emerge on them and as more experts' perspectives accumulate about these drugs.

Diagnostic Imaging Agents

- **Key facts**: Two imaging agents intended for use with PET emerged as potential high impact interventions. Flutemetamol F18 (Amersham Health, a unit of General Electric Co., Fairfield, CT) and florbetapir F18 (Amyvid, Avid Radiopharmaceuticals, a subsidiary of Eli Lilly and Co., Indianapolis, IN) are intended to aid detection of beta amyloid plaques and possible diagnosis of AD. Flutemetamol binds specifically to beta-amyloid protein, which is a major component of the amyloid plaques that are considered a hallmark of AD pathology. Both are labeled with an isotope of fluorine (F18), which allows detection by PET scanning. The developers hypothesize that flutemetamol will be able to differentiate patients in the early stages of AD from patients without AD based on the increased uptake of the compound by nascent amyloid plaques in patients developing AD. Florbetapir is said to be highly specific in binding to beta-amyloid plaque aggregates and does not bind to tau, synuclein, or other targets. These agents are intended to be used in similar capacities. When performing a PET scan, a small amount of the agent is injected intravenously, and a scanner is used to generate images that highlight areas of high tracer uptake. After image reconstruction, the physician interpreting the images makes a binary assessment (positive or

negative) of whether beta-amyloid plaque is present. One U.S.-based phase III trial is ongoing for flutemetamol. Phase III clinical trials for florbetapir have been completed and a new drug application was submitted to the U.S. Food and Drug Administration (FDA) in January 2011 that FDA considered and led to ongoing controversy about whether the imaging agent should be approved because of issues over interpretation of data in the trial and a perceived potential for substantial inter-reader variability among independent, extensively trained readers of florbetapir-PET scans.

- **Key Expert Comments**: Overall, the experts commenting on these agents agreed that F18 imaging agents have potential to fulfill the unmet need associated with AD diagnosis, but because no disease-modifying treatments for AD are available, some experts were uncertain about the degree to which this would actually improve patient health outcomes. On the other hand, some thought that knowing that a patient has AD could aid planning in terms of safety and care of the patient.

- **Potential for High Impact**: Moderately high

Dementia (Including Alzheimer's Disease) Interventions

Intervention

Positron emission tomography (PET) imaging agents for detection of beta-amyloid plaques

Currently, a definitive diagnosis of AD can be made only by postmortem examination of the brain. Premortem clinical diagnosis of AD, particularly during the early stages of the disease, is not straightforward, especially because many other conditions can cause symptoms that mimic AD. Therefore, an unmet need exists for ways to aid clinicians in diagnosing AD because even in the absence of effective treatments, a diagnosis could provide useful information to a patient and family for monitoring patient welfare, security, and planning. Two agents in late-phase development for this purpose are discussed here. Similar agents are in earlier phases of development.

Flutemetamol F18 (Amersham Health, a unit of General Electric Co., Fairfield, CT) is a radiopharmaceutical contrast agent used during PET that is undergoing study for the diagnosis of AD.[1] Flutemetamol is a thioflavin-D derivative of 11C-labeled beta amyloid ligand Pittsburgh Compound B (an agent created by the University of Pittsburgh that has limited practicality in clinical use because it cannot be transported) that binds specifically to beta-amyloid protein, a major component of the amyloid plaques that are a hallmark of AD pathology.[1,2] Flutemetamol has been labeled with an isotope of fluorine (F18), which allows detection by PET scanning.[1] The developers hypothesize that flutemetamol will be able to differentiate patients in the early stages of AD from patients without AD based on the increased uptake of the compound by nascent amyloid plaques in patients developing AD.[3]

Florbetapir F18 (Amyvid™, Avid Radiopharmaceuticals, a subsidiary of Eli Lilly and Co., Indianapolis, IN) is also a diagnostic radiopharmaceutical intended to detect the presence of beta-amyloid plaque deposits in the brain during positron emission tomography (PET) imaging scans. Similarly to flutemetamol, florbetapir has been labeled with F18, which allows detection by PET scanning. According to a U.S. Food and Drug Administration (FDA) advisory committee briefing, florbetapir is highly specific in binding to beta-amyloid plaque aggregates and does not bind to tau, synuclein, or other targets.[4]

These agents are intended to be used in similar capacities. When performing a PET scan, a small amount of the agent is injected intravenously, and a scanner is used to generate images that highlight areas of high tracer uptake.[5,6] After image reconstruction, the physician interpreting the images makes a binary assessment (positive or negative) of whether beta-amyloid plaque is present.

One U.S.-based phase III trial is ongoing for flutemetamol. Results from a phase II trial were released in 2009 and were updated in 2010. The study examined flutemetamol imaging data from clinically diagnosed AD in patients, healthy volunteers, and patients with mild cognitive impairment.[1] The study established a flutemetamol standard update value ratio cut-off in lateral frontal, lateral parietal, and lateral temporal cortex that was able to discriminate between people with AD and healthy volunteers.[1] By this cut-off criteria, 25 of 27 patients with AD exhibited elevated flutemetamol uptake while only one of 15 healthy volunteers older than the age of 55 years exhibited elevated uptake.[1] This represents a sensitivity of 93.1% and a specificity of 93.3% in this group of patients with probable AD diagnoses.[1]

Florbetapir has completed phase III clinical trials, and FDA reviewed a new drug application (NDA) for florbetapir and assigned it a priority review classification. In January 2011, FDA's peripheral and central nervous system drugs advisory committee voted 13-3 to recommend against FDA approval of florbetapir based on the available data. However, an FDA advisory panel voted unanimously to recommend that FDA approve the NDA for florbetapir with a condition requiring a

reader training program that demonstrates reader accuracy and consistency through a reread of previously acquired scans.[6] In March 2011, according to the Wall Street Journal, FDA rejected the NDA, stating that it would be more willing to approve the agent once the training program was created.[7] According to a company press release, the manufacturer is "working to address the FDA's questions."[8] As of November 2011, the agent is still listed on the manufacturer's Web site as a product under active development.[9]

Some controversy has arisen over the data, and in a May 2011 letter published in JAMA, members of Public Citizen stated that, "In their study on the use of florbetapir for positron emission tomographic (PET) imaging of brain β-amyloid, Dr. Clark and colleagues submitted to JAMA median values for PET scan reader scores but withheld critical individual reader score data that Avid Radiopharmaceuticals submitted to the Food and Drug Administration (FDA) on September 17, 2010. FDA analyses of these data show substantial inter-reader variability among independent, extensively trained readers of the florbetapir-PET scans for individuals in the autopsy cohort, emphasizing that florbetapir-PET imaging fails to provide an accurate and reliable assessment of amyloid burden."[10]

Clinical Pathway at Point of This Intervention

After a patient initially presents with mild cognitive impairment, a clinical examination is used to differentiate mild cognitive impairment caused by incipient AD from mild cognitive impairment caused by any number of other conditions. These F18 PET imaging agents are intended to be used in conjunction with this clinical examination to support the diagnosis of AD or rule it out. Following diagnosis, the patient is directed to treatments for AD or treatments for a number of other conditions that can mimic the initial cognitive symptoms of AD.

Figure 1. Overall High Impact Potential: Positron emission tomography (PET) imaging agents for detection of beta-amyloid plaques
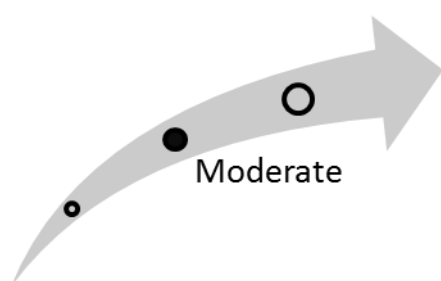
Overall, the experts agreed that the F18 imaging agents have the potential to fulfill the unmet need associated with AD diagnosis, but because no disease-modifying treatments for AD are available, some experts were uncertain about the degree to which this intervention would actually improve patient health outcomes. On the other hand, some experts thought that having the diagnosis would enable planing for safety and care of the patient. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Six experts, with research, clinical, and health systems backgrounds, offered perspectives on florbetapir, and six different experts, with clinical, research, and health systems backgrounds, offered perspectives on flutemetamol, for a total of 12 sets of experts' comments on these two imaging agents.[11-22] Despite the fact that each agent was commented on by different groups of individuals, all experts described each agent as having a similar potential impact on the health care system. It should be noted that at the time these comments were completed, FDA had not yet rejected florbetapir's NDA, nor had Public Citizen published its critique of florbetapir's trial results.

The experts strongly agreed that the lack of a diagnostic tool for AD is an important unmet need, and experts commenting on the information for both agents stated that the theory underlying the use of F18 isotopes in PET scans to meet this unmet need is credible. In support of this view, experts cited

both the established utility of PET and the viability of this particular isotope in binding to beta amyloid.

Experts generally believe that because PET scanning is an established procedure at many facilities, implementation of these imaging agents would not catalyze extensive changes to staffing, infrastructure, or health care processes. Some experts did note, however, that while administration of the F18 agent (a process similar to that of other imaging agents) would not require a steep learning curve on the part of clinicians, learning to read the images produced by the scan would require some training. The image interpretation issues raised since expert comments were received further emphasize this concern.

In terms of cost, most of the experts pointed out the obvious increase in short-term expenditures that PET requires, but some experts noted that early detection might lead to improved health outcomes, which could reduce the long-term costs associated with AD.

In terms of clinical and patient acceptance and potential controversy surrounding this technology, several themes consistently emerged. First, experts generally thought that both patients and clinicians would readily adopt this technology, whether to gain a definitive diagnosis of AD or to rule out AD as a cause of symptoms. However, several experts noted the potential controversy that may arise if these agents are approved, citing the current debate that has arisen over diagnostic tools for AD, a disease for which no disease modifying therapy currently exists. This point is highlighted by the fact that most experts thought that these agents, if approved, would have a very minor impact on clinical patient management, other than the potential for initiating patients on symptom-targeted therapy before symptoms are evident. A diagnosis could, however aid patients and families in planning for the care and safety of the patient.

Most experts commenting on these interventions agreed that the greatest potential impact of the F18 agents is in the realm of disease diagnosis, stating that because clinicians currently have no tools to provide a definitive diagnosis of AD, this technology has the potential to dramatically change diagnostic pathways for AD. One expert, speaking from a health systems perspective, also pointed out that this technology has the potential to change the diagnostic pathways for diseases other than AD, because of its purported ability to rule out AD in patients who have symptoms that are characteristic of several diseases. One clinical expert suggested that these diagnostic agents may also allow for more efficient monitoring of response to therapy, once treatment has begun.

Overall, experts commenting on these interventions agreed that the F18 imaging agents have the potential to fulfill the unmet need associated with AD diagnosis, but because no disease-modifying treatments for AD are available, the degree to which this intervention would actually improve patient health outcomes was noted as uncertain by some experts.

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