AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 04: Dementia (Including Alzheimer's Disease)

December 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. HHSA290201000006C). 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 close to diffusion into practice in the United States. 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 interventions that experts deemed, 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 6 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 horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

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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 emerging technologies and innovations in health care and to create an inventory of interventions 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 identifying and monitoring 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 analyzing 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 use 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 email to: effectivehealthcare@ahrq.hhs.gov.

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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 identifying 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, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

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 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) 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 information on topics and issuing topic 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 the 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

(COIs). 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 designation of potentially high impact. 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 table below lists the three topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before September 21, 2012, in this priority area; *and* (3) we received six to nine sets of comments from experts between January 19, 2011, and October 26, 2012. (Twenty-two topics in this priority area were being tracked in the system as of October 26, 2012.) For the Potential High-Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). Topics in this Executive Summary and report are organized alphabetically by class of therapy and then by individual topic within each class. We present two summaries on three topics (indicated by an asterisk) that emerged as higher impact potential on the basis of expert comments and assessment of potential impact.

Priority Area 04: Dementia (Including Alzheimer's Disease)

Topic	High-Impact Potential
1. * Florbetapir F18 (Amyvid)-enhanced positron emission tomography (PET) for detection of beta-amyloid plaques	Lower end of the potential high-impact range
2. * Flutemetamol-enhanced PET for detection of beta-amyloid plaques	Lower end of the potential high-impact range
3. * Off-label intranasal insulin for treatment of Alzheimer's disease	Moderately high

Discussion

Most of the research activity in the dementia priority area focuses on Alzheimer's disease (AD)—its diagnosis 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, interrupting memory storage and recall. Over time, damage spreads from the 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 United States 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. AD's cause 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 AD's causes has focused on two hallmark structures found in the brains of patients with AD: 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. Earlier diagnosis could enable earlier intervention, although available treatments do not make much of an impact on patient outcomes 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 in development are being tracked in the system, and the constellation of potential effects is likely to change as more data emerge and as more experts' perspectives accumulate about these drugs. Currently, the beta-amyloid antibody drug class is being investigated for treating AD. In trials to date, minimal yet statistically significant data have emerged in patients with early stages of AD, warranting the need for further studies of beta-amyloid antibodies.

Positron Emission Tomography (PET) Imaging Agents for Detection of Beta-Amyloid Plaques

- **Key Facts**: Two imaging agents intended for use with PET emerged as interventions with potential for high impact. Flutemetamol F18 (GE Healthcare division of General Electric Co., Fairfield, CT) and florbetapir F18 (Amyvid™, Avid Radiopharmaceuticals 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 when injected into the patient intravenously during a PET imaging procedure. The developers believe that flutemetamol will be able to differentiate patients in early AD stages 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 and serve 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.

U.S.-based phase III trials are ongoing for flutemetamol, and the manufacturer anticipates a premarket application submission to the U.S. Food and Drug administration (FDA) for the agent in late 2012. Florbetapir was approved for marketing by FDA in 2012. The Centers for Medicare & Medicaid Services (CMS) does not currently cover PET beta-amyloid imaging and will convene a meeting on January 30, 2013, to review available evidence and hear public testimony on its use and clinical impact on health outcomes of patients.

- **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 patient safety and care.

- **Potential for High Impact**: Lower end of the potential high-impact range

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

- **Key Facts**: Insulin delivered intranasally is being investigated for treating AD and might have potential to modify the disease's rate of progression. This approach is based on research findings that suggest that insulin plays a role in cognitive deficits observed in AD. This theory is being explored by several research institutions, rather than by insulin manufacturers. In completed and ongoing clinical trials, several methods have been used for ensuring intranasal delivery, including needle-less nostril syringes, a nasal drug electronic atomizer device, and nasal spray bottles. Because insulin is not approved for treating AD, its use for AD is considered off label.

- **Key Expert Comments**: Experts agreed that, in theory, an affordable, widely accessible, noninvasive, and easily administered therapy such as this might realize dramatic long-term health care cost savings and might improve patient health. Experts stated that their enthusiasm is predicated on an assumption of efficacy in modifying AD progression rate and that the preliminary data must be confirmed by larger trials. Based on this input, our overall assessment is that this intervention is in the moderate potential high-impact range.

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

Dementia (Including Alzheimer's Disease) Interventions

Positron Emission Tomography (PET) Imaging Agents for Detection of Beta-Amyloid Plaques

Currently, a definitive diagnosis of Alzheimer's disease (AD) can be made only by postmortem examination of the brain. Premortem clinical diagnosis of AD, particularly during the disease's early stages, is not straightforward, especially because many other conditions can cause symptoms that mimic AD. 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 patients and their families for monitoring patient welfare. One previously developed PET tracer, 11C-labeled beta-amyloid ligand Pittsburgh Compound B (PIB), has been investigated for this purpose, because it binds specifically to beta-amyloid protein, a major component of the amyloid plaques that are characteristic of AD pathology. However, this agent has limited practicality in clinical use because it has a short half-life and cannot be transported to centers unable to generate it onsite.[1,2] Two novel agents that may not have this limitation have been developed to help clinicians diagnose AD and are discussed here. Similar agents are in earlier phases of development.

Flutemetamol (GE Healthcare division of General Electric Co., Fairfield, CT) is an investigational radiopharmaceutical contrast agent under study for use in PET imaging to diagnose AD.[2] Flutemetamol is a thioflavin-D derivative of PIB that has been labeled with a fluorine isotope, which allows detection by PET scanning.[3-5] Its developers hypothesize that flutemetamol will be able to differentiate patients in the early AD stages from patients without AD based on the increased uptake of the compound by nascent amyloid plaques in patients developing AD.[6] In performing a PET scan, clinicians inject a small amount of flutemetamol into the patient's bloodstream and use a gamma camera or whole-body scanner to generate images that highlight areas of high tracer uptake.[7,8] Its manufacturer is also developing a software program intended to categorize flutemetamol PET scans into those exhibiting raised and normal beta-amyloid levels.[9]

Flutemetamol is being investigated in two phase III trials, which were expected to be completed in 2012 and 2013.[10,11] According to a recent manufacturer press release, a pooled analysis from 4 studies of 49 patients receiving flutemetamol before or after brain biopsy during shunt placement or intracranial pressure measurement and 68 subjects autopsied to determine the presence of brain amyloid pathology demonstrated that "[f]or patients with biopsy tissue samples, the study found that [18F]flutemetamol detected beta-amyloid with a pooled sensitivity of 93 percent and pooled specificity of 100 percent. In autopsied subjects, [18F]flutemetamol showed the ability to detect beta-amyloid with a sensitivity of 86 percent and specificity of 92 percent."[5]

Florbetapir (Amyvid™, Avid Radiopharmaceuticals subsidiary of Eli Lilly and Co., Indianapolis, IN) is another diagnostic radiopharmaceutical intended to detect the presence of beta-amyloid plaque deposits in the brain during PET imaging scans. Like flutemetamol, florbetapir is labeled with a fluorine isotope, allowing detection by PET scanning. Preclinical studies demonstrated that florbetapir was highly specific in binding to beta-amyloid aggregates and did not bind to tau, synuclein, or other targets.[12,13]

Phase III trials were completed and FDA approved it for marketing in the United States in April 2012.[14] According to the agent's prescribing information, florbetapir is indicated for use with PET imaging as follows:[15]

> [T]o estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathologic diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's

cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathologic examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.
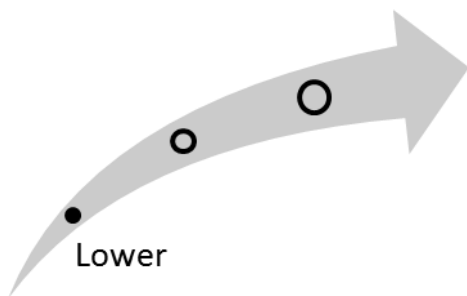
The prescribing information also notes florbetapir's limitations: a positive florbetapir scan does not establish a diagnosis of AD or other cognitive disorder, and florbetapir's safety and effectiveness have not been established for predicting development of dementia or other neurologic condition or monitoring responses to therapies.[15]

The Centers for Medicare & Medicaid Services (CMS) does not currently cover PET beta-amyloid imaging and will convene a Coverage Advisory Committee meeting on January 30, 2013, to review available evidence and hear public testimony on its use and clinical impact on health outcomes of patients.

Clinical Pathway at Point of This Intervention

After a patient initially presents with mild cognitive impairment, a physician performs a clinical examination to differentiate mild cognitive impairment caused by incipient AD from mild cognitive impairment caused by any number of other conditions.[16] PET imaging performed with these imaging radiopharmaceuticals would be used to rule out the presence of pathologically significant levels of beta amyloid in the brain and aid in differentiating AD from other forms of dementia.

Figure 1. Overall high-impact potential: positron emission tomography (PET) imaging agents for detection of beta-amyloid plaques

Lower

Overall, the experts commenting on this intervention agreed that these 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 planning for patient safety and care. Experts noted that because PET is a well-established technology, these agents would not cause dramatic changes to health system operations. Based on this input, our overall assessment is that this intervention is in the low range of high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on flutemetamol, and 8 different experts, also with clinical, research, and health systems backgrounds, offered perspectives on florbetapir, for a total of 14 sets of experts' comments on these two imaging agents.[17-30] Despite the fact that each agent received comments from different groups of individuals, all experts described each agent as having a similar potential impact on the health care system.

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 these isotopes in PET scans to meet this unmet need is credible. 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 although administration of these agents would not require a steep learning curve for clinicians (because their administration is similar to that of other imaging agents), learning to read the images produced by the scan would require some training. Image-interpretation issues (i.e., how the images are interpreted) raised after expert comments were received for this report 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 reduce costs associated with AD treatment in the long term. Experts commented that the potential long-term savings might be realized through a variety of mechanisms, including improved health outcomes (through earlier treatment of either AD or other conditions, if this test is able to rule out AD), reduced need for long-term care, and avoided use of ineffective therapies for incorrect diagnoses.

One major theme the emerged through the expert comments is that no disease-modifying therapy for AD currently exists. This point is underscored 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, help patients and families plan for the patient's care and safety. Indeed, most experts commenting on these interventions agreed that the greatest potential impact of these 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 pathway for AD.

Overall, experts commenting on these interventions agreed that these 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.

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

According to the U.S. National Institute on Aging, currently available pharmacotherapies indicated for use in patients with AD treat only the disease symptoms; these medications do not change the underlying disease process, are effective for some but not all people, and may help for only a limited time.[31] Therefore, an unmet need exists for novel, effective, potentially disease-modifying agents for treating this condition. Intranasal insulin, if proven effective, might be positioned as the first disease-modifying agent for AD.

Research has suggested that insulin may play a role in cognitive deficits in AD.[32] Insulin receptors and insulin-sensitive glucose transporters, which regulate energy metabolism in the central nervous system by mediating glucose uptake in cells, are colocated in brain structures that are involved in memory and have been shown to be compromised in patients with AD.[32,33] Additionally, "peripheral insulin abnormalities" (e.g., insulin resistance) have been associated with increased risk for AD, and patients with AD have shown reduced insulin levels in their cerebrospinal fluid.[32] Finally, research has shown that administering insulin intravenously to patients with AD (while maintaining normal blood glucose levels) improves memory in a dose-dependent manner.

In light of these findings, several research organizations have been begun investigating the use of intranasally delivered insulin for treating AD.[32-34] The rationale for using intranasal delivery is based on concerns that delivering insulin via other routes (e.g., intravenously) could adversely alter blood glucose levels.[33] Drugs administered intranasally, however, are delivered directly to the central nervous system via the olfactory and trigeminal neural pathways, bypassing the blood-brain barrier and reducing systemic exposure to the drug.[33] Response to intranasal insulin in patients with AD may differ depending on whether patients have the apolipoprotein e4 allele, which is known to be a genetic risk factor for AD; research has suggested that patients with the allele show cognitive response to lower doses of insulin than do patients without it.[32]

In completed and ongoing clinical trials investigating intranasal insulin's efficacy in patients with AD, several delivery methods have been used, including needle-less syringes inserted into alternating nostrils, a nasal drug electronic atomizer device (ViaNase™, Kurve Technology, Inc., Lynnwood, WA), and nasal spray bottles.[32,34,35] Various insulin products already approved for use in patients with diabetes have been employed in conjunction with these administration devices, including Novolin R and NovoLog® (Novo Nordisk a/s, Bagsvaerd, Denmark).[32,34,35]
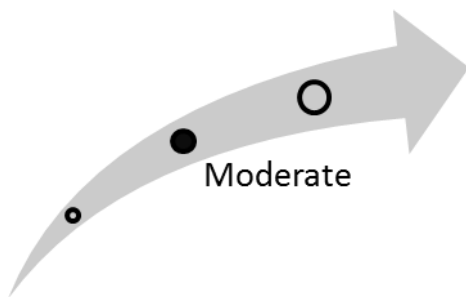
Insulin manufacturers do not appear to be pursuing development of their products for this indication at this time. Instead, ongoing trials are sponsored by several different research groups, including the University of Kansas (Lawrence), the HealthPartners Research Foundation (Minneapolis, MN), and the University of Washington (Seattle).[36-38] Because insulin is not approved for treating AD, use of the drug for AD is considered off label.

In results of a recently completed (2011) trial of 104 adults with mild amnestic cognitive impairment or mild to moderate AD who received placebo or intranasal insulin for 4 months, trial researchers stated that the insulin treatment "improved delayed memory ($P < .05$)," "preserved caregiver-rated functional ability ($P < .01$)," and "preserved general cognition as assessed by the [Alzheimer's Disease Assessment Scale - cognitive subscale] score for younger participants and functional abilities as assessed by the [Alzheimer's Disease Cooperative Study – activities of daily living] scale for adults with AD ($P < .05$)."[34]

Clinical Pathway at Point of This Intervention

Pharmacotherapy is the primary intervention for AD. Donepezil, rivastigmine, and galantamine are approved by FDA to treat the symptoms of mild to moderate AD, and memantine is approved to treat the symptoms of moderate to severe AD.[31] None of these drugs has been shown to be disease-modifying.[31] Intranasal insulin would likely be used in conjunction with background AD pharmacotherapy.

Figure 2. Overall high-impact potential: off-label intranasal insulin for treatment of Alzheimer's disease

Experts commenting on this intervention agreed that the need for disease-modifying treatments for AD is extremely important and that intranasal insulin is, in theory, an affordable, widely accessible, and easily administered therapy that could realize dramatic long-term health care cost savings and improvements in patient health. This enthusiasm, however, is predicated on the assumption that the agent is efficacious in modifying AD's rate of progression. Several experts stated that the available clinical trial data are not yet robust enough to assume efficacy, and they were skeptical about the agent's potential to improve health outcomes. 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 clinical, research, and health systems backgrounds, offered perspectives on this intervention.[39-44] Experts unanimously agreed that the need for disease-modifying treatments for AD is extremely important, citing both the debilitating nature of the disease and the expected increase in its prevalence as the population ages.

However, several experts expressed uncertainty about intranasal insulin's ability to meet this need. Although most experts agreed that preliminary trial data are somewhat promising, several experts noted that these results do not unequivocally demonstrate disease regression or slowing of disease progression. One expert with a research background noted that only one of two insulin doses used in the trial appeared to be effective, and another research-based expert commented that it is unclear whether the therapy will provide ongoing benefit or whether patients may develop insulin resistance. Another expert with research experience stated that although many researchers are investigating the use of intranasal proteins for brain-related conditions, these attempts have been generally ineffective because of the variability in the percentage of the drug that actually reaches the brain or because they do not provide benefit to patients.

Despite this skepticism about efficacy, most experts agreed that if the drug were proven to be effective in modifying AD's course, it could have a dramatic impact on the health care system, especially because it would be the first agent to treat the underlying cause of AD as opposed to simply alleviating symptoms for a limited period of time. Additionally, experts noted that because insulin is widely available and relatively inexpensive, it would likely be accessible to a sizable

proportion of the population. Furthermore, experts thought that the drug's well-known safety profile and long history of use (in diabetes) would increase physician acceptance and adoption of the intervention. Experts generally thought patient acceptance of the therapy would be widespread, citing its ease of use and lack of invasiveness. In terms of cost, most experts agreed that the minimal cost of adding insulin to a patient's treatment regimen in the short term would be outweighed by the potentially significant long-term cost savings that would be realized if this agent were to be proven to modify AD progression. If the agent can improve the functional capabilities of patients with AD, experts noted, the sizable costs of their care would also be alleviated, or at least postponed.

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