

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

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

**Prepared for:**

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## **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. HHSA290-2010-00006-C). 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**

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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## 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](mailto: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 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 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 a year. Topics eligible for inclusion are those interventions expected to be within 0–3 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 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 150 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 five to 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 high-impact-potential 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 having potentially 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 two topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Sixteen topics in this priority area were being tracked in the system as of November 4, 2014.) A single topic emerged as having some potential for higher impact on the basis of expert comments. Readers are encouraged to read the detailed information that follows the Executive Summary.

### Priority Area 04: Dementia (Including Alzheimer’s Disease)

Topic	High-Impact Potential
1. Off-label citalopram for treatment of agitation associated with Alzheimer’s disease	No high-impact potential; archived on basis of expert comments
2. * Off-label intranasal insulin for treatment of Alzheimer’s disease	Lower end of the high-impact-potential range

## Discussion

Although the bulk of research in this AHRQ priority area focuses on Alzheimer’s disease (AD), clinically regarded as the leading cause of dementia, this priority area actually incorporates several brain disorders that cause incapacitating declines in cognitive and social functioning. Most available dementia and AD interventions are approved to manage symptoms; however, promising research focuses on developing disease-modifying medications and early detection diagnostic tools for at-risk patients.

The Healthcare Horizon Scanning system has identified relatively few interventions over the past few years of searching in this area. With a limited number of viable neurobiological targets and neuropsychological markers for AD, new noninvasive diagnostic and therapeutic tools have had little room to innovate; most recently identified interventions in these categories are incremental improvements on existing technologies and methodologies. For pharmacotherapies, this stagnation is in part due to the difficulties associated with specifically quantifying improvements in disease state and symptoms for patients in whom AD has been diagnosed. Although FDA has recently approved multiple radiological contrast imaging agents useful in diagnosis of probable AD, no pharmaceutical

interventions have gained FDA approval during this period, primarily due to failure to meet stated endpoints or demonstrate treatment efficacy in phase III trials.

The National Institute on Aging defines AD as a progressive, irreversible disorder, marked by degraded memory and cognitive abilities that eventually impede a patient's daily functioning; the institute and other clinical experts acknowledge that AD's underlying etiology is unknown. Research has primarily focused on neuronal inflammation and two potential AD biomarkers: amyloid plaques and neurofibrillary tangles, both identified in the brains of many patients in whom AD has been diagnosed. Amyloid plaques purportedly damage neurons in the brain and interrupt typical neuronal processes. Similarly, researchers hypothesize that neurofibrillary tangles adversely affect neuron function, leading to cell death.

Often, preclinical AD cases are not associated with these biomarkers, and characteristic AD-related behavioral symptoms can be dismissed or misdiagnosed; however, with disease progression, beta-amyloid proteins accumulate abnormally, leading to plaques and reduced neuronal efficiency. In later-stage AD, neural atrophy and damage profoundly degrade patients' executive and memory functioning, particularly affecting brain regions including the hippocampus, parietal lobe, and temporal lobe.

Recent National Center for Health Statistics data rank AD as the sixth leading cause of death among Americans. The nonprofit Alzheimer's Association estimates that more than 5 million Americans were living with AD in 2013. Nationwide, an estimated 11% of Americans older than age 65 years and 32% of elderly Americans older than 85 years have AD. Although common convention, also used in this report, refers to patients as having a diagnosis of AD, available diagnostics can only identify individuals as "probable" AD patients. Definitive AD diagnosis can be made only through postmortem neuroanatomical examination.

The unresolved etiology of AD and related progressive cognitive impairment disorders are key factors limiting recent clinical developments in this priority area, with most progress restricted to basic academic research. This lack of scientific clarity, in turn, limits the number of interventions we identify and track, because the horizon scanning protocol places an emphasis on late-phase interventions that could have high-impact potential. However, new evidence has provided strong support for a cohesive neurobiological origin of AD. Of particular note is a late-breaking publication in the November 13, 2014, issue of *Nature*, from a team led by Dr. Rudolph Tanzi and colleagues at Massachusetts General Hospital. These investigators developed a three-dimensional cell culture system in which they grew human neural stem cells with two genetic variants underlying early-onset familial AD. Their cell culture system holds promise as method for screening candidate drugs for AD more efficiently than by using existing animal models. Using this system, they demonstrated that deposition of beta-amyloid precedes formation of neurofibrillary tangles—comprising aggregated hyperphosphorylated tau protein. The investigators found that by blocking amyloid-beta production using beta or gamma secretase inhibitors, they were able to diminish formation of tangles, and that glycogen synthase kinase 3 (GSK3) regulates the phosphorylation of tau mediated by beta-amyloid. These and other findings suggest that beta- or gamma-secretase inhibitors or related precursor inhibitors could underlie the most promising candidate AD pharmacotherapies. We have identified and are currently monitoring multiple potential therapies with these properties, including an investigational receptor for advanced glycation-endproducts (RAGE) inhibitor and two beta-amyloid precursor protein site-cleaving enzyme (BACE) inhibitors, currently in late-phase clinical trials.

The AHRQ Healthcare Horizon Scanning System continues to track several other interventions and diagnostics for treating dementia, AD, and associated symptoms. Among the tracked topics are experimental biologics hypothesized to treat underlying causes of cognitive decline; neuroprotective pharmacotherapies targeting amyloid plaque accumulation; off-label uses of implantable neurostimulators; and multiple noninvasive diagnostics intended to accurately identify

presymptomatic and prodromal disease. This report discusses one potential high-impact topic, off-label intranasal insulin for treating cognitive symptoms of AD.

## Eligible Topic Not Deemed to Have High Impact Potential

- **Off-label citalopram for treatment of agitation associated with Alzheimer's disease:** Citalopram is a selective serotonin reuptake inhibitor known to increase extracellular serotonin levels; it is approved by the U.S. Food and Drug Administration (FDA) for antidepressant use. Researchers hypothesize that reduced serotonin levels are a primary cause of agitation symptoms in patients with Alzheimer's disease (AD), leading investigators to study serotonin-boosting drugs, such as citalopram, for this indication. In early 2014, results from a large phase III clinical trial indicated that citalopram was more effective than placebo in improving patients' agitation symptoms. However, experts concluded this intervention has no high-impact potential, citing the available clinical trial data and citalopram's noted adverse effects when administered to this patient population. Multiple experts wanted to see additional efficacy data, including evidence of citalopram's superiority over other standard medications. Our searches of American and international registries found no significant ongoing clinical trials for this indication; consequently, we have archived this topic.

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

- **Key Facts:** Converging neurobiological studies suggest that dysfunctional cerebral insulin signaling may contribute to AD etiology. Complimentary research has also identified insulin receptors and insulin-sensitive glucose transporters co-localized in brain regions implicated in AD progression. Researchers hypothesize that an intervention that enhances insulin signaling or provides supplemental insulin in these regions may improve AD-related cognitive symptoms and modify typical disease progression.

Based on these hypotheses, American and European clinical trials are investigating intranasal insulin's efficacy for treating cognitive AD symptoms. Investigators propose that intranasal delivery could offer all of insulin's hypothesized neuroprotective benefits, while bypassing its known adverse effects on blood glucose levels. To date, only small clinical trials have published results (e.g., Craft et al., 2012; Craft et al., 2013; Rosenbloom et al., 2014). These limited findings suggest that intranasal insulin treatment may slightly improve cognitive function in patients with probable AD or amnesic mild cognitive impairment. Additionally, preliminary data from two trials indicate a possible genetic basis for treatment efficacy, with patients carrying the apolipoprotein e4 (*ApoE-ε4*) allele responding more favorably to intranasal insulin administration than patients lacking this allele.

Larger American- and European-based clinical trials are ongoing; results from these studies may clarify ideal insulin administration frequencies, dosages, and formulations for treating AD. The largest clinical trial to date is scheduled to conclude in 2015. Without additional clinical data, off-label use may be limited for this indication. Insulin's limited retail availability will also limit this intervention's diffusion. Presently, American retailers do not sell prefabricated intranasal insulin products; liquid insulin is available, though, with retail prices between \$25 and \$260 per 10 mL.

- **Key Expert Comments:** Experts acknowledged a significant unmet need for effective, disease-modifying treatments for AD; some consulted experts agreed that intranasal insulin has potential to address this need. However, a lack of clinical trial data and clear treatment



protocols reduced experts' support for this intervention. Several experts' concerns may be resolved by larger, ongoing clinical trials.

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

## **Dementia (Including Alzheimer's Disease) Interventions**

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

**Unmet need:** In 2010, 4.7 million Americans had a diagnosis of Alzheimer's disease (AD); experts anticipate that the patient population will grow to 16 million by 2050.<sup>1</sup> Medications approved by the U.S. Food and Drug Administration (FDA) treat only AD symptoms; they are not disease-modifying. Additionally, these medications are not effective for all patients and have side effects that may deter patient adherence.<sup>2</sup> An unmet need exists for effective, disease-modifying pharmacotherapies for patients with AD. Intranasal insulin is under investigation for treating AD, although no manufacturer is sponsoring the trials, so use is off-label. If effective, it may address this unmet need, as a well-tolerated, potentially disease-modifying treatment for this indication.

**Intervention:** Insulin receptors and insulin-sensitive transporters are located together in the brain, and research suggests that brain insulin levels mediate some cognitive deficits associated with AD.<sup>3,4</sup> Patients with AD also exhibit subnormal cerebrospinal fluid insulin levels.<sup>3</sup> Additionally, clinical and epidemiologic studies have associated type 2 diabetes and insulin resistance with increased risk of developing AD.<sup>5</sup> This evidence led researchers to hypothesize that modulating insulin levels with exogenous insulin may offer a novel, effective option for treating AD.

In preliminary trials, use of intravenous or intranasal insulin was associated with dose-dependent cognitive performance improvements in patients with AD.<sup>6-9</sup> Intranasal insulin is 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. Limited exposure purportedly prevents adverse blood glucose level changes observed during intravenous administration.<sup>4,10</sup> Consequently, most clinical trials for this indication use intranasal delivery mechanisms.

Clinical trials have not established optimal intranasal insulin dosage levels and frequencies for treating AD; commonly tested protocols include 20 and 40 IU insulin, delivered intranasally once or twice daily.<sup>11,12</sup>

**Clinical trials:** Clinical trials have tested intranasal insulin delivery using methods including needleless syringes, nasal spray bottles, and a proprietary nasal drug electronic atomizer (ViaNase, Kurve Technology, Inc., Lynnwood, WA).<sup>3,4,11,13,14</sup> Trials have also studied various insulin formulations including human insulin, insulin detemir, and insulin glulisine.<sup>11,15-17</sup>

In the largest completed trial (n=104), Craft and colleagues investigated intranasal insulin efficacy in patients with mild to moderate AD or amnesic mild cognitive impairment (MCI), a condition considered to be a prodromal AD stage.<sup>11,18</sup> Patients were randomly assigned to groups receiving 20 IU or 40 IU intranasal insulin or placebo, twice daily for 16 weeks. Intranasal insulin treatment improved patients' cognitive performance (p<0.05; measured by delayed story recall scores), and general functioning (measured by caregiver ratings and Alzheimer's Disease Assessment Scale - cognitive subscale).<sup>11</sup> All patients showed cognitive improvements when administered 20 IU intranasal insulin, but only male patients' cognition improved when given 40 IU intranasal insulin.<sup>11</sup>

Linkage research identified apolipoprotein e4 (*ApoE-ε4*) allele as a genetic risk factor for developing AD. Subsequent clinical trials screened patients with AD, showing that patients' response to intranasal insulin treatment differed based on whether patients were *ApoE-ε4* carriers.<sup>3,18,19</sup> Craft et al. conducted a secondary analysis of patients administered 40 IU intranasal insulin, finding that although *ApoE-ε4*-positive patients remained cognitively stable, *ApoE-ε4*-negative men showed cognitive improvements, but *ApoE-ε4*-negative women's cognition performance declined.<sup>18</sup> In a separate clinical trial (n=58), the same research group reported that patients with AD or MCI who carried the *ApoE-ε4* allele had improved cognitive scores when

administered daily 40 IU insulin detemir.<sup>20</sup> Noncarriers' cognitive scores declined with the same treatment; however, all patients' working memory performance improved, irrespective of *ApoE-ε4* carrier status.

In 2013, the Alzheimer's Disease Cooperative Study registered the largest randomized, controlled trial to date (n=240) for this intervention. This trial, testing the effects of twice-daily 20 IU intranasal insulin administrations on cognition and neuroanatomy, is scheduled to conclude in February 2015.<sup>12</sup> A large German clinical trial (n=90) testing insulin aspart treatment efficacy is also ongoing.<sup>21</sup>

**Manufacturer and regulatory status:** In U.S.-based clinical trials, investigators largely study various branded, FDA-approved insulin formulations, including Humulin<sup>®</sup> and Humulin R<sup>®</sup> (Eli Lilly and Co., Indianapolis, IN), and Novolin R<sup>®</sup> and NovoLog<sup>®</sup> (Novo Nordisk a/s, Bagsvaerd, Denmark).<sup>22,23</sup> FDA has approved these medications for treating diabetes. Because relevant manufacturers are not leading clinical trials or formally pursuing expanded AD-related indications for their products, using intranasal insulin to treat AD constitutes an off-label use.

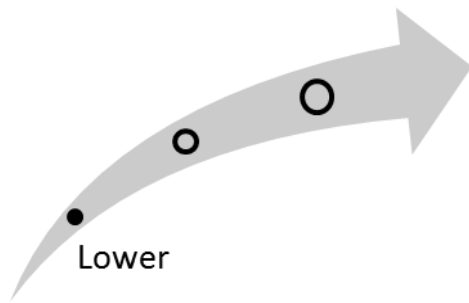
Investigators at the University of Kansas (Lawrence), University of Washington (Seattle), University of Texas at Austin, HealthPartners Institute for Education and Research (Bloomington, MN), and the Alzheimer's Disease Cooperative Study (La Jolla, CA) are among groups leading off-label clinical trials. The latter cooperative sponsors the largest ongoing trial, a phase II/III trial investigating intranasal administration of Humulin R for treating cognitive symptoms of AD.<sup>12</sup> An additional large trial is registered in Germany, sponsored by the University Hospital Essen (Duisberg/Essen, Germany).<sup>21</sup>

**Diffusion and cost:** This intervention's cost and diffusion are unclear because clinical trials have not established optimal dosage protocols or insulin formulations. Based on ongoing and completed clinical trials, any recommended off-label treatment protocol could involve one or more insulin formulations. For general comparison, a search of a U.S.-based online aggregator of prescription-drug prices found prices between \$25 and \$250 for a single 10 mL vial of various approved forms of insulin. Of these insulin products, human insulin (branded as Novolin R) was consistently less expensive than either insulin glulisine or insulin detemir.<sup>24-26</sup> However, American manufacturers do not market intranasal insulin, so exact unit-per-dollar conversions cannot be made.

## Clinical Pathway at Point of This Intervention

FDA has approved multiple cholinesterase inhibitors, including donepezil (Aricept<sup>®</sup>), galantamine (Razadyne<sup>®</sup>), and rivastigmine (Exelon<sup>®</sup>) for treating cognitive symptoms in patients with mild to severe AD.<sup>27</sup> Additionally memantine, an NMDA receptor antagonist, is approved to treat cognitive symptoms of moderate to severe AD.<sup>2</sup> None of these medications, however, has demonstrated disease-modifying properties.<sup>2</sup> Intranasal insulin could be used as an adjunct to these pharmacotherapies or with nonpharmacologic interventions. Depending on efficacy from ongoing trials and individual patients' disease progression, clinicians could also prescribe intranasal insulin as a preventive medication or monotherapy for AD and amnesic MCI.

**Figure 1. Overall high-impact potential: off-label intranasal insulin for treatment of Alzheimer's disease**



Experts evaluating this intervention agreed that a significant need exists for additional effective interventions for treating AD-related cognitive symptoms; they also concluded that intranasal insulin could possibly address this need. Some of the experts believe that as a potentially affordable, easily administered drug, intranasal insulin could improve patient health while providing cost savings over other AD medications. However, experts' support was curtailed by a lack of robust clinical trial data, and they thought administration protocols and an optimal patient population still need to be defined. Some experts were also concerned that intranasal insulin would not dramatically improve patient health outcomes when compared with alternative interventions, because it might treat only cognitive symptoms of AD without affecting overall disease progression. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

## Results and Discussion of Comments

Six experts, with clinical, health devices, and research backgrounds, provided perspectives on this intervention.<sup>28-33</sup> We have organized the following discussion of expert comments by the parameters on which they commented.

**Unmet need and health outcomes:** Although experts agreed that an unmet need exists for effective, disease-modifying treatments for AD, they were not overly optimistic that intranasal insulin has high potential to address this need. Three experts stated that available clinical trial data failed to demonstrate that intranasal insulin delayed or prevented AD progression; these experts also noted there was no evidence that this intervention was superior to approved AD medications.<sup>28,31,33</sup> Additionally, multiple experts thought that intranasal insulin may have limited potential to improve patient health outcomes, particularly if it is positioned as an adjunctive treatment, rather than a monotherapy.<sup>30,31,33</sup>

**Acceptance and adoption:** Given the paucity of disease-modifying treatments for AD, experts predicted that, if demonstrated to be effective, intranasal insulin would be widely accepted by both patients and clinicians. In this case, experts also agreed that patient adoption rates would be high, even with limited retail availability and no FDA approval.

**Health care delivery infrastructure and patient management:** Overall, most experts anticipated that this intervention would minimally disrupt current health care delivery infrastructure and patient management. Two experts with research backgrounds thought that if this intervention is effective and diffuses widely, health care infrastructure demands might be reduced because patients might remain independent for longer periods.<sup>30,32</sup>

**Health disparities:** This intervention would have little overall impact on health disparities, most experts thought. Multiple experts also noted that intranasal insulin treatments would likely be relatively inexpensive and would not increase health disparities. One expert, however, concluded that this intervention could have a large impact on health disparities, specifically citing preliminary gender-and *ApoE-ε4* carrier-based treatment response clinical trial data.<sup>32</sup>

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