Justifying reimbursement for Alzheimer's diagnostics and treatments: seeking alignment on evidence

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Abstract

The increasing cost of health care combined with expensive new drugs and diagnostics is leading to more frequent gaps between regulatory and reimbursement approval decisions. As a result, persons with Alzheimer's disease may have difficulty accessing the benefits of medical advances. In contrast to the long history and established structure for drug approval, payer decision-making is dispersed, not standardized and perspectives on necessary evidence differ and often poorly defined. Particularly challenging is how to demonstrate the value of drugs and diagnostics for patients who do not yet have significant functional decline. While discussions to develop consensus continue, clinical trials should begin to incorporate health system and patient-oriented outcomes. In some situations additional studies designed to demonstrate value and comparative effectiveness will be needed. Such studies should examine outcomes of representative populations in community settings. To assure scientific advances in diagnosis and treatment benefit patients, developing evidence to support reimbursement will become as important as obtaining regulatory approval.

Introduction

The health care system is in transition, exemplified by implementation of the Patient Protection and Affordable Care Act (ACA) in the United States [1]. A worldwide financial crisis has resulted in dwindling resources for medical services. The pressure to provide better care and treatment for people with Alzheimer's disease (AD) and their families is particularly acute, as the number of people with dementing disease worldwide is expected to exceed 100 million by 2050 [2]. In the United States the cost of Alzheimer care is higher than many other nations, yet the quality of dementia care is still poor, fragmented, and inadequately reimbursed [3].

Randomized controlled trials (RCTs) have long been considered the "gold standard" for clinical research in humans [4] and the path that pharmaceutical companies follow in order to gain approval for new drugs from regulatory agencies. These trials are traditionally randomized, placebo-controlled and use highly selected patient populations to most convincingly demonstrate an effect on disease. Diagnostics are evaluated on their basis to reliably and selectively detect disease. Once approved, 3rd party payers, government health plans and private insurance companies, must decide whether or not to reimburse the use of drugs and diagnostics. Although without 3rd party reimbursement individuals can have access by paying the full cost out-of-pocket, drugs and diagnostics may be out of financial reach for many and availability may be severely restricted if pharmacies and providers decide to not offer them because of low demand. In recent years, 3rd party payers increasingly have been unwilling to automatically reimburse drugs and diagnostics based upon regulatory approval. Cognizant of both the escalating costs of new drugs and the desire to limit health care expenditures, they have decided to deny coverage despite evidence of significant benefits demonstrated in randomized clinical trials. The issue, according to payers, is that RCTs do not necessarily aim to or incorporate measures that demonstrate "real world benefits" to patients and families, to demonstrate the benefits justify the

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costs. Responding to those concerns, agencies have been established in the United Kingdom, Canada, and Australia to consider both comparative effectiveness and cost effectiveness in determining which treatments will be covered [5].

While no disease-modifying drugs for AD or other dementias have reached clinical practice, three diagnostics for amyloid imaging have received regulatory approval [6-8] and there are nearly 100 medicines and diagnostics currently in development [9]. In anticipation of a new disease modifying and possibly expensive treatments for AD becoming available, the Alzheimer's Association's Research Roundtable, a consortium of scientists from the pharmaceutical, biotechnology, imaging, and cognitive testing industries, met in Washington, D.C. on April 15th and 16th, 2013, with insurers, health economists, regulatory and academic scientists, and policy experts to develop strategies that best address the concerns of payers while ensuring continued progress in drug development.

1. Cost effectiveness, value, and payer perceptions

The concept of value has moved to the forefront of healthcare decision making as per capita spending on health care is reaching unsustainable levels in the United States and many other countries without a corresponding improvement in health outcomes [10, 11]. Indeed, the ACA mentions value 214 times. Payers looking for evidence of clinical effectiveness and value in real world settings often are not satisfied with the results from RCTs. RCTs developed for regulatory approval typically demonstrate effectiveness only using relatively small, homogeneous and unrepresentative clinic populations. Patients with co-morbid illnesses are generally excluded and it is uncertain results can be replicated outside the rigorous research setting. Payers also want data that addresses whether the benefits of treatment are worth the cost,

although these data are typically not available from clinical trials [12]. For example, payers think of benefits in terms of functional outcomes, while RCTs involving dementing disease typically emphasize and report on cognitive measures. Observational studies are useful for collecting real world data, although outcomes collected often differ across studies and fail to have adequate controls [13].

The concept of "value" in health care can have many different meanings depending upon the perspective of those involved. Patients, physicians, health care systems, companies, researchers, regulators, and both public and private payers apply different metrics of "value". For example, the "innovativeness" of a diagnostic test may be of high commercial value, but of little value to patients, doctors, or payers. Likewise, the benefit of an accurate and confident diagnosis may be of high value to patients and physicians, but difficult to measure and demonstrate to payers.

A recent example emerged from the recent regulatory approvals of Amyvid, Vizamyl and Neuraceq positron emission tomography (PET) ligands that allow the in vivo imaging of amyloid in the human brain. The effort to get payers to reimburse the clinical use of these imaging agents sparked the need to evaluate the utility of diagnostics for dementing diseases. The Institute for Clinical and Economic Review (ICER) at the Massachusetts General Hospital's Institute for Technology Assessment convened a Policy Development Group (PDG) composed of experts from academia, health care providers, non-profit organizations, and the insurance and pharmaceutical industries to evaluate the available evidence to help guide decision making about insurance coverage for these tests [14]. They applied an evidence hierarchy developed in the early 1990s [15] to analyze the current literature. This analysis found that of 15 PET amyloid imaging studies, 14 assessed diagnostic accuracy to establish clinical validity and only one

assessed diagnostic impression. Importantly, none established analytic validity by capturing action based upon diagnosis, patient outcomes (e.g., cognitive/function decline), societal outcomes (e.g., cost-effectiveness), or technical efficacy. Thus, ICER concluded that these studies, although in compliance with FDA guidelines, failed to provide persuasive evidence that insurers could use to demonstrate improved outcomes. Improved patient outcomes become a critical part of the discussion for payers, particularly when current treatments have limited benefits, physicians don't apply consistent diagnostic and treatment algorithms, and interventions may expose patients to unnecessary risks and costs. Without dramatic short-term treatment benefits, improved patient outcomes from use of diagnostic tests will be difficult to demonstrate, particularly improvement in daily function.

Roundtable discussion found that payers currently use the same methods for judging the value of diagnostics and drug treatments, despite their different purpose. For payers in the United States, there is no dominant structured process for rating benefits and costs in a formal decision-making process as exists in other countries. Instead, each individual health plan and public payer has its own system for review. In terms of diagnostics, payers are more likely to find testing compelling when it influences the use of expensive or high risk treatments or when testing is limited to a narrow population shown conclusively to benefit. Accountable care organizations will play an increasingly important role in decision making about the value of tests and treatments as they are embedded in a system of care.

3.0 Improving value: prevention and care management

In the United States, implementation of the ACA and the National Plan to Address Alzheimer's Disease [16] is likely to focus more attention on prevention as a means of increasing

the value. Secondary prevention (i.e. preventing symptoms after Alzheimer pathology is present) and tertiary prevention (i.e. preventing dementia when symptoms are already present) currently are being pursued and are considered potentially attainable goals of treatment [17-23]. Thus, payers are particularly interested in evidence regarding clinical effectiveness and value in treating mild cognitive impairment and better understanding the outcomes of those with biomarker evidence of amyloid pathology.

Simulation models of different patient scenarios enable payers, researchers, and policy makers to estimate the costs and benefits of both diagnostic and treatment strategies for AD [24] For example, Cohen et al. modeled a hypothetical disease modifying treatment using a modestly priced biologic agent, with treatment effectiveness assumptions based on early trial results [25]. Assuming that the treatment had no impact on life expectancy, and omitting diagnostic costs, the model demonstrated greater cost effectiveness in younger patients and in patients with MCI compared to AD. When a diagnostic test that selected patients likely to benefit from the treatment was added to the model, costs increased as did the benefits, especially in younger patients at earlier stages of disease.

Targeted early intervention is not only more cost effective but has other benefits in terms of better outcomes from secondary prevention measures. Preventing complications of the disease and managing co-morbidities, accomplished through better care management of individuals with multiple chronic conditions, also holds promise for improving the value of care [26]. Indeed, several successful care management programs proved successful in delivering high-quality dementia care to patients and caregivers through the use of well-defined protocols and tools and frequent encounters with a team of health professionals [27-29].

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Care management is an issue not only for health care providers but for insurers as well. Insurers may not identify AD as a singular condition, but as a complex, progressive chronic illness that is best managed through a carefully constructed progressive specialized program. For example, diabetes is typically managed in this way, with interventions identified at each stage that can prevent progression to the next stage. Whether a similar map can be created for AD is speculative at present, requiring markers at various levels of disease severity that can demonstrate the effectiveness of treatment.

Payers in different countries and settings view AD through different lenses. For example, recognition and awareness about the importance of AD is high in the United Kingdom and elsewhere in Europe (but less so in Asia), with national policies placing a high priority on determining the cause of dementia and providing treatment and comprehensive care. As a result of those policies, the willingness to pay varies across countries. In China, for example, AD drugs are not included in the National Reimbursement Drug List (NRDL) or the Essential Drug List (EDL), which outline reimbursement rates in different settings. Reimbursement for diagnostics also varies across countries.

Awareness is increasing in the United States, where the Medicare annual wellness visit now includes a cognitive assessment. Yet while this suggests that Medicare recognizes the importance of early identification of cognitive decline, reimbursement for amyloid PET imaging, a newer technology that might also aid in early identification, is not covered by most private insurers or by Medicare, except under Coverage with Evidence Development or CED [30]. Medicare has a prescription drug benefit, but lacks a comprehensive plan to ensure better AD care, with coverage benefits varying according to the care setting. Demonstration projects funded by the Center for Medicare and Medicaid Services (CMS) Innovation Center are testing various

models for improving care delivery for patient. One of these, the Aging Brain Care (ABC) model at Indiana University [31], which was developed to provide improved and cost-effective care to people with dementia and their families, has been implemented in Indiana's Wishard Health Services system, with anticipated cost savings estimated at 30%.

4.0 Filling the evidence gaps

Despite the fact that there are some 19,000 RCTs published every year, along with tens of thousands of other clinical studies, systematic reviews routinely conclude that the quality of evidence is poor. For example, The American College of Physicians (ACP and American Academy of Family Physicians (AAFP) reviewed available evidence on drug treatments for dementia in 2008, concluding that there was weak evidence to support existing clinical recommendations, including no convincing comparative studies, the use of outcome measures not routinely used in clinical practice, and trials with insufficient follow-up [32]. At the regulatory level, a few agencies provide forums for dialogue, advice, and guidance regarding the data needed for trials, but at the payer level, public and private payers make varying independent decisions. Moreover, payers have limited capacity within their organizations to provide advice or guidance to regulators or researchers, nor do they have the expertise or mechanism to coordinate communication about evidence.

Researchers and 3rd party payers have developed strategies to address gaps between the evidence obtained in typical RCTs and evidence needed to establish real world effectiveness. Comparative effectiveness research, a central feature of the ACA, is designed to assess outcomes, quality of life, and survival. Importantly, it also provides better evidence to inform decisions and enables physician-patient dialogue about risks, benefits, and personal preferences

in choosing treatment alternatives. Yet comparative effectiveness trials also have disadvantages, making studies larger, more complicated, and more expensive.

The Center for Medical Technology Policy (CMTP), an independent non-profit aimed at making health care more effective and affordable, established the Green Park Collaborative to develop condition-specific recommendations regarding evidence needed to support decision-making on coverage and payment issues. In April, 2013, the Collaborative released an evidence guidance document on the design of clinical studies of AD therapies [33]. Their recommendations addressed the representativeness of enrolled subjects, including inclusion and exclusion criteria; interventions and comparators; primary and secondary outcome assessments; the need for standardization; and the need to include a measure of effects on care partners.

The scientific evidence payers need to make reimbursement decisions may be similar to that needed by academics and regulators developing guidelines, but how that evidence is evaluated and the importance of various aspects of the evidence varies significantly. For example, in developing guidelines for market approval, the strength of the evidence and magnitude of benefit may be of primary importance, while payers want to determine if the treatment or diagnostic is medically necessary and whether it improves health outcomes.

The desire by payers for better evidence of functional improvement is complicated in the early disease by the lack of functional deficits in preclinical AD. The FDA suggested in its recent draft guidance [34] that for clinical trials, cognitive tests linked to biomarker outcomes may support a claim of disease modification. How the payer community will deal with preclinical AD has yet to be determined, and is complicated by data showing that a substantial number of individuals diagnosed with MCI revert back to normal [35, 36]. One factor contributing to these "conversions" is the variability in cognitive and functional assessments used to diagnose MCI,

including both informant- and patient-reported measures [37]. How the diagnosis is reached will also play a role, with the specificity of subjective memory complaint diminishing as the diagnostic setting moves from specialty to primary to community care.

5.0 The regulatory perspective on payer concerns

The FDA issued a draft guidance in February 2013 about developing drugs for treatment of early stage AD [34, 38]. The draft guidance provides a framework for how drugs might be studied in early AD trials. While drugs for dementia are required to show benefits on both cognition and global function with separate outcome measures, the new draft guidance is specific to drugs for patients early in the disease process and symptom manifestation where few functional deficits may exist and sensitive functional scales are not available. The draft guidance thus outlines two possible ways that drugs might be approved: 1) for patients with early Alzheimer's disease dementia, a single primary outcome measure that combines cognition and function, such as the CDR Sum of Boxes (CDR-SB) [39] could be used; 2) for patients in the earliest stages of the disease with the most to gain from treatment but where clinical benefits are difficult to demonstrate, the guidance points to the accelerated approval mechanisms, which already exists in the Code of Federal Regulations (21 CFR 314.510).

The accelerated approval pathway allows drugs that address an unmet medical need to be approved based on a surrogate endpoint or an effect on an intermediate clinical endpoint such as a sensitive cognitive measure, with further post-marketing evaluation required to demonstrate a clinically meaningful effect. Utilization of this pathway requires both accurate identification of patients and identification of a biomarker or cognitive measure that captures early changes, two requirements that have yet to be met.

The FDA also regulates imaging devices used in connection with AD, and while similar principles guide the decision-making for drugs and diagnostics -- for example, risk-benefit considerations -- imaging products are not expected or required to demonstrate therapeutic benefits. For radiopharmaceuticals, approval is contingent on clarity of proposed use, pharmacologic activity, potential toxicity, estimated absorbed radiation dose, and demonstration that the product provides useful, accurate, and reliable clinical information.

While the FDA does not consider value as defined by payers in its decisions, and does not require elements to be incorporated into trials that would demonstrate value, FDA representatives have expressed willingness to engage in dialogue to address the concerns of payers. They pointed out, however, that requiring trials to enroll more heterogeneous populations with more co-morbidities and concomitant medications could have adverse consequences on the drug development process by introducing excessive variability in the target population and blurring evidence of possible treatment effects, making studies considerably more complicated and expensive. However, introducing endpoints, such as time to hospitalization, and trying to correlate those endpoints with changes on cognitive or functional measures might be possible to incorporate and speak to the question of value.

6.0 Conclusions

While the contrast between concerns of drug developers and payers is evident, the need for dialogue is clear. Pharmaceutical companies are beginning to shift their focus to consider not only whether a drug is going to work but also whether or not a reimbursement pathway is possible. Payers argue that reimbursement should be based on quality measures and improved

health outcomes (See Text Box). They are asking for more information, not just whether a drug affects cognitive decline, but what that means to the patient and caregivers.

Standards and evidentiary requirements for payer decision-making

- Better measures that capture information about real world functional impairments, including social functioning.
- Better means of targeted interventions with greater specificity.
- Evidence collected in real-world settings including primary care practices.
- Evidence that is sufficiently robust to compare to other interventions.
- Evidence that efficacy will translate into effectiveness.
- Evidence that clinical effectiveness will translate into tangible patient benefits.
- Evidence establishing the relationship between short-term measures of severity of AD and long-term outcomes.

There is an urgent need to change the way conventional clinical research is conducted, which focuses on FDA approval rather than developing and disseminating a drug that is accepted by the health care system. Developing a new research model will necessitate establishing large registries, longitudinal databases, and big data approaches to mine and analyze large amounts of data. An additional emerging need identified in the United States is to establish a peer-review process or oversight body for reimbursement decisions, similar to that which exists in the United Kingdom, Australia, and Canada. Such an agency might develop a standard for evidence requirements and reimbursement, which would enable trials designed to meet those standards.

Worldwide changes in the delivery of health care have shifted the emphasis toward improving patient outcomes and preventing disease, despite the fact that programs which provide

this kind of patient-centered care face barriers in terms of reimbursement. The challenge is multi-faceted and will require stakeholders from many perspectives to come together in the search for solutions.

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