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Meeting Report

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 subsequent reimbursement approval decisions. As a result, persons with Alzheimer's disease may have difficulty accessing the benefit 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 and the evaluation of this evidence differ and are 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. Although 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 in patients, developing evidence to support reimbursement will become as important as obtaining regulatory approval.

Keywords: Alzheimer's disease; Health policy; Health insurance reimbursement; Health services research; Drug approval; Cost-benefit analysis; Radiopharmaceuticals; Health care value; Cost-effectiveness; Disease prevention; Care management; Evidence-based medicine

1. 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 AD 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 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, third-party payers, government health plans, and private insurance companies

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must decide whether or not to reimburse the use of drugs and diagnostics. Although without third-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, third-party payers increasingly have been unwilling to automatically reimburse drugs and diagnostics based on 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 that the benefits justify the 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].

Although 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 pathology 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, DC, on April 15 and 16, 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.

2. Cost-effectiveness, value, and payer perceptions

The concept of value has moved to the forefront of health-care 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 comorbid illnesses are generally excluded, and it is uncertain whether results can be replicated outside the rigorous research setting. Payers also want data that address 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, whereas 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 on 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. Payers may have divergent views about value depending upon their various responsibilities for payment of services. The fragmented nature of care for Alzheimer's disease means that there often are different payers for acute care, outpatient services and long-term care.

A recent example emerged from the recent regulatory approvals of Amyvid (Lilly USA, Indianapolis, IN, USA), Vizamyl (GE Healthcare, Medi-Physics, Inc., Arlington Heights, IL, USA), and Neuraceq (Piramal Imaging SA, IBA Molecular North America, Dulles, VA, USA) 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 composed of experts from academia, health-care providers, nonprofit 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 current literature. This analysis found that of 15 PET amyloid imaging studies, 14 assessed diagnostic accuracy to establish clinical validity and only 1 assessed diagnostic impression. Importantly, none established analytical validity by capturing action based on 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 Food and Drug Administration (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 do not 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.