Alzheimer's Disease and Cost-effectiveness Analyses: Ensuring Good Value for Money?

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Abstract: Cost-effectiveness analyses (CEA) employ rigorous methods to help payers and governments allocate scarce health care resources in an efficient manner. A potential problem arises, however, when this resource-rationing mechanism, and the explicit (or implicit) valuation it places on health benefits, deviates from socially-optimal levels; for example, when the true economic value of a health benefit exceeds the amount that a payer or government is willing to pay for the benefit. In the United Kingdom, the National Institute for Clinical Excellence (NICE) uses a $50,000 per quality-adjusted life year (QALY) threshold for access under its National Health System (NHS). This is substantially lower than recent estimates in the United States of the value of a life year, which are close to $175,000. When a QALY is valued at $175,000, new drugs that would produce a 5-year delay in Alzheimer's disease (AD) onset for all new cases between 2010 and 2050 would be worth almost $4 trillion ($2006).
Policymakers proposing to use CEA in the United States must be careful in setting threshold acceptability criteria for new pharmaceutical innovations, especially in the area of Alzheimer's treatments.

I. Introduction: Cost-effectiveness Analysis and The Value of Medicine

Increasingly, analyses that seek (by assigning a dollar amount to projected or measured benefits) to determine the relative value of health care services are being used by health insurers and government health systems in justifying reimbursement, coverage and clinical guidelines decisions. In particular, policymakers and insurers claim that cost-effectiveness analysis can be used to obtain a specific measure that in turn can be applied as a benchmark for establishing the comparative value of different technologies and services designed to address a particular illness or condition. The application of cost-effectiveness analysis to assess the comparative effectiveness of new medical technologies against old ones in particular is at the heart of what is commonly called "evidence-based medicine."

Cost-effectiveness analysis is therefore a tool for arriving at a "cut-off" point for what is valuable, and society should pay for, and what should not be covered. It is envisioned a means for achieving a socially efficient resource allocation in health care (Reinhardt, 2004, Wilensky, 2007). The cut-off point used by cost-effectiveness experts to determine whether or not to pay for a new drug or service is approximately $50,000 to a single year of life in perfect health[1] or a quality-adjusted life year (QALY). Anything that costs more is not valuable and anything that costs less is therefore "worth it."

In practice, the process of a panel of "experts" deciding what care is valuable and who should get what new treatments has been decidedly less than efficient (Ubell, Chernew, 2000). Studies have shown, for example, that many services and technologies – particularly preventive health screenings for women and *in vitro* fertilization – were not

[1] This is not an absolute threshold. NICE evaluates new technology within the context of the technology's specific circumstances as they relate to numerous factors, both clinical and economic. As such, NICE has approved the use of some new technologies with incremental cost-effectiveness rations in excess of $50,000 per QALY and restricted use of some technologies with rations less than $50,000 per QALY. However, on average, the evidence, both empirical and anecdotal, demonstrates that $50,000 is approximately the threshold NICE employs. See, for example, Vernon, Hughen, and Johnson (2005).

valuable using established cut-off points while Viagra was extremely valuable (Ubel, 2000).

Moreover, the attempt to use a single QALY standard on all patients has not been without controversy. The recent decision by the National Institute for Clinical Excellence (NICE), the cost-effectiveness watchdog organization for the United Kingdom's National Health Service (NHS), to restrict use of Alzheimer's disease (AD) drugs in all but the most seriously ill patients, those with advanced stages of the disease, was met with a maelstrom of criticism by patient advocacy groups, physicians, and industry organizations. The controversial NICE decision was based on the judgment that the four available AD drugs (donepezil, rivastigmine, galantamine, and memantine) were not "cost-effective." To illustrate the consternation felt by many in the medical community over this decision, the following quote from David Anderson of the Royal College of Psychiatrists is provided:

> *"This is a terrible decision based on a deeply flawed process ... Implementation of this guidance will set the treatment of Alzheimer's disease back 10 years."*
>
> --- David Anderson, M.D.,
> Royal College of Psychiatrists

NICE was not silent in the face of the criticism its decision evoked, and it anticipated the public's response when it upheld an appeal of its decision. Addressing these concerns, NICE Chief Executive, Andrew Dillon, acknowledged the public disappointment and frustration, but defended the organization's decision to restrict patient access:

> "*We realize that today's announcement will be disappointing to people with Alzheimer's and those who treat and care for them, but we have to be honest and say that based on all the evidence, including data presented by the drug companies themselves, our experts have concluded that these drugs do not*

make enough of a difference for us to recommend their use for treating all stages of Alzheimer's disease."

--- Reuters News Wire, October 16, 2006

While Mr. Dillon's remarks did not explicitly acknowledge that the NICE decision to restrict access was based on a cost-effectiveness criterion, the official NICE report supporting this decision certainly does[2]. The use of cost-effectiveness analyses (CEA) by NICE to make rationing decisions is based upon the assumption that market forces are unable to produce efficient allocations of resources in health care technology markets, an outcome attributed to the uncertainties associated with new technology and information asymmetry between those using the technology and those payers and patients who, respectively, pay for and receive it (Enthoven, 1993). But many health system participants and observers maintain that the NICE criterion used to define "good value for money," referred to as the cost-effectiveness threshold, is too low, as evidenced by the recent adverse public reaction to the NICE decision to restrict access to the four AD drugs. Based on past NICE decisions, and recent research, this "good value for money" criterion, or cost-effectiveness threshold, assigns a value of approximately $50,000 to a single year of life in perfect health[3].

If this valuation of a QALY is too low, efficient resource allocations will not be achieved and the economic incentives for medical and pharmaceutical research and development (R&D) will, as a result, fall below socially-optimal levels. This position, within the context of the NICE decision on Alzheimer's drugs, is reflected in the remarks made by Nigel Brooksby, President of the Association of the British Pharmaceutical Industry (ABPI):

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[2] This report is available at http://www.nice.org.uk/page.aspx?o=245910 (accessed November 15, 2006).

[3] This is not an absolute threshold. NICE evaluates new technology within the context of the technology's specific circumstances as they related to numerous factors, both clinical and economic. As such, NICE has approved the use of some new technologies with incremental cost-effectiveness rations in excess of $50,000 per QALY and restricted use of some technologies with ratio's less than $50,000 per QALY. However, on average, the evidence, both empirical and anecdotal, demonstrate that $50,000 is approximately the threshold NICE employs. See, for example, Vernon, Hughen, and Johnson (2005).

"This decision makes it harder for companies to justify devoting the enormous sums of money and resource necessary to research and develop new medicine"

---Nigel Brooksby, President, Association of the British Pharmaceutical Industry

The controversy stems from the fact that NICE revisited the Alzheimer's disease guidelines it had issued in 2001 and made new recommendations that the drugs donepezil, rivastigmine, and galantamine should no longer be made available under the NHS to treat Alzheimer's disease (Kmietowicz, 2005; Page 2005). The group said that while there was evidence to suggest that these drugs have positive effects that are significantly different from the effects of a placebo, they may not significantly influence important outcomes such as quality of life, time to hospitalization, etc. Furthermore, they believed that the results of cost-effectiveness studies showed that these drugs did not represent good value for money. These directives created a controversy because these are the only drugs that have been approved for the treatment of Alzheimer's disease. There is considerable concern that this decision, to deny access to available pharmacological treatments, will substantially reduce incentives to seek early diagnosis and treatment (Kmietowicz, 2005; Page 2005).

This controversy comes at a critical time in our nation's effort to address the problem of Alzheimer's for three reasons.

1. The science of genomics and the identification of new proteome-based plasma biomarkers appear to be on the verge of making it possible, in combination with a new generation of medicines, to identify, earlier than ever before, patients in the beginning stages of this disease, and also individuals at high risk for AD in the future (Hye, et al, 2006). Any diagnostic tool that allows for earlier diagnosis of Alzheimer's disease means that treatment, closer monitoring, and follow-up offers considerable hope for persons with Alzheimer's disease and their caregivers. One of the problems of Alzheimer's

disease is that symptoms of disease appear to develop only after substantial cell loss has occurred in the brain. Effective biomarker tests could help prevent and/or delay such devastating damage from occurring. This will be particularly important once a cure or more effective medications become available. Medications at present for Alzheimer's disease can only provide some short-term improvements in cognitive function.

Currently there exist several biomarkers for Alzheimer's disease. These include Beta-amyloid measured in cerebrospinal fluid; Tau protein measured in cerebrospinal fluid; and Neural thread protein/AD7C-NTP measured in cerebrospinal fluid and urine. Alzheimer's disease-specific biomarkers clearly are needed for the differential diagnosis of cognitive impairment in the elderly. What sets age-related disorders like hypertension, hypercholesterolemia and diabetes mellitus apart from Alzheimer's disease is that each has biomarkers that can be followed easily and repeatedly, not simply to diagnose, but also to monitor response and optimize treatment. In contrast, the current role of clinical laboratory evaluation for dementia is exclusionary. The development of such biomarkers is critical to translating efficiently the new therapeutic approaches for AD under development by many research groups into treatments for the millions who suffer from AD.

2. Alzheimer’s disease, absent new treatments, threatens to become a pandemic. According to a 2007 study, Alzheimer’s Disease Facts and Figures (Alzheimer’s Association, 2007), there are now more than 5 million people in the United States living with Alzheimer’s disease. This number includes 4.9 million people over the age of 65 and between 200,000 and 500,000 people under age 65 with early onset Alzheimer’s disease and other dementias. This is a 10 percent increase from the previous nationwide prevalence estimate of 4.5 million. The new study notes:

- Without a cure or effective treatments to delay the onset or progression of Alzheimer’s disease, the prevalence could soar to 7.7 million people with the disease by 2030, which is more than the population of 140 of the 236 United Nations countries.

- By mid-century, the number of people with Alzheimer's disease is expected to grow to as many as 16 million, more than the current total population of New York City, Los Angeles, Chicago and Houston combined.

- As the prevalence impact of Alzheimer's grows, so does the cost to the nation. The direct and indirect costs of Alzheimer's and other dementias amount to more than $148 billion annually, which is more than the annual sales of any retailer in the world excluding Wal-Mart.

3. Policymakers and healthcare experts are proposing that the Medicare system use cost-effectiveness analysis to make coverage and reimbursement decisions in the same manner as the NICE in the United Kingdom. Recently the trade group, America's Health Insurance Plans (AHIP) recommended that Centers for Medicare and Medicaid Services (CMS) be "given explicit authority by Congress to use available data on comparative effectiveness and cost-effectiveness in determining coverage policies. Similarly CMS should be empowered to set its reimbursement rates for new technologies more in alignment with added (for marginal) value of a new technology over established alternatives" (AHIP, 2007). Health systems in other countries that are used a reference point for Medicare reimbursement decisions and as a model for conducting comparative effectiveness evaluations have tended to rely upon a measure of $50,000 for each quality-adjusted life year, which as mentioned previously, is an additional year of life measured not just in terms of actual survival but in terms of gains in physical mobility, ability to self care, ability to carry out activities of daily living, absence of pain and discomfort, and absence of anxiety and depression.

The amount of $50,000 for each additional QALY goes back nearly 30 years when the cost-effectiveness for kidney dialysis in the Medicare program was calculated. Since that time, the $50,000 threshold has been the "rule of thumb," never adjusted for advances in technology, increased valuations about life, or for the cost of care. That is, the "rule of

thumb" is a form of price controls or rationing designed to control both the use of technological innovation as well as its rate of introduction.

This rule of thumb has been integrated into decisions about the pricing and adoption of Alzheimer's drugs in the health systems of such countries as Canada, Australia and the United Kingdom. Most of Western Europe, Canada, Australia, and New Zealand use explicit or implicit forms of CEA. (Jommi, 2001; Gosling, 2000) The United Kingdom has the most stringent and formal CEA review embodied in their NICE, which was introduced in 1999 to ensure that healthcare funding is used efficiently, that policies on treatment choice are consistent across the country, and to evaluate the cost-effectiveness of pharmaceutical products deemed to significantly increase health system expenditures (Atkinson, 2002).

This proposal was based on an evaluation of how cost-effectiveness analysis was used in health systems in other countries. Each country uses a different agency to evaluate the cost-effectiveness claims of products and to determine prescribing guidelines under which a drug could be considered comparatively more effective than other medicines. In the United Kingdom, the authority to determine comparative effectiveness belongs to NICE. Such guidelines include requirements that patients fit a certain diagnostic category or that an illness meet a certain severity level before coverage is provided. Coverage can also be limited to a specific period of time.

Similarly, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia is stressing the ability of drugs to save money within a therapeutic class. The PBAC provides information used in setting pricing for new drug products, which in turn is used by Australia's Pharmaceutical Benefits program in determining what drugs to pay for, and for how much. In the case of Alzheimer's disease, Australian prescribing guidelines for Aricept, Exelon and Razadyne are highly restrictive compared to U.S. guidelines. Namenda is not available in Australia because it is not considered cost-effective. A recent study found that nearly 25 percent of all Alzheimer's patients in the U.S. would be

denied their current drugs for AD if the Australian "comparative effectiveness" guidelines were imposed here (IMS, 2006).

No one would dispute that controlling the cost of Alzheimer's care is a laudable goal or that using resources efficiently is a good idea. The question remains as to whether the underlying assumptions of the value of life or – to use the words of AHIP – "added marginal or incremental value of new technology" capture the full gains of innovations in the diagnosis and treatment of Alzheimer's disease.

II. Estimating the Gains from AD Treatment Innovations

There is a rich body of research demonstrating that drugs delaying progression of AD are cost effective. Our study goes beyond that issue to deal with a larger concern. We develop a framework for evaluating the gains from improved health and longevity from new medicines that would delay the progression of Alzheimer's disease. It is important to note at the outset that this is not a measure of how much the use of a new drug can save in the use of other health care services. Rather, it is a measure of the value – in economic terms – of a longer and healthier life.

In their study "The Value of Health and Longevity," University of Chicago Graduate School of Business professors Kevin M. Murphy and Robert H. Topel assess the "social value" of improved health and longevity. Social value refers to the estimated amount that additional life years, or other health improvements, are worth to individuals. For economists, the classic way to measure the value of any good is calculating "willingness to pay" for a given product, in this case, health and longevity. While there are no direct measures of what people are willing to pay for another year of life, there are many indirect measures based on actual behavior and life choices (i.e., revealed preference), such as risk factors on the job, where people live, or whether they smoke. From these life choices, it is possible to infer people's willingness to pay for improvements in health.

Murphy and Topel's economic framework for valuing improvements to health and life expectancy is based on data about individuals' willingness to pay. It is an error to value improvements in health based simply in gains in an individual's productivity or earnings. This is especially true today, since most health improvements apply to older individuals who may have retired. Traditional measures of economic growth and welfare do not account for this source of rising living standards, and therefore underestimate improvements in well being. In addition, public expenditure accounts for a large portion of both medical research and the provision of medical care. Efficient decisions for health spending require a way to measure the value of treatment and research-based medical progress. Murphy and Topel find that over the twentieth century, cumulative gains in life expectancy were worth over $1.2 million per person to members of the current population.

To put this figure into perspective, Topel offers the following example: "Suppose you were offered $1.2 million to trade your health for that of an average American in 1900, when life expectancy was 30 years shorter. If you would refuse that offer and demand more in order to sacrifice that much life expectancy, then you may think our estimate is actually conservative." From 1970 to 2000, increased longevity added approximately $3.2 trillion per year to national wealth, the equivalent of half of the average annual gross domestic product (GDP) over the period. Half of these gains were due to progress against heart disease alone. Reduced mortality from heart disease has increased the value of life by about $1.5 trillion per year since 1970. The values of improvements in health care over the twentieth century are equal to or possibly greater than gains in material well-being.

Murphy and Topel's Long-Term Evidence of Improvements in Health

From 1900 to 1950, improvements in longevity came at birth and during youth, due to large declines in infant mortality and deaths from childhood diseases. After 1970, improvements in health shifted toward older individuals, reflecting progress against heart disease, stroke, and other older-age ailments. From 1970 to 2000, gains in longevity

were greatest for people between the ages of 40 and 60, and greater for men than for women, mostly because of advances in the treatment of heart disease.

Advances in health-related knowledge and its application can take many forms, ranging from the development of new medicines and techniques for treating disease to improvements in public health infrastructure. These advances affect the quality of life and the risks of mortality at various stages of the life cycle. The authors find that the value of remaining life is age dependent – first rising and then falling – as a person ages. The more life you have left, the greater the value of improvements in health. The cumulative post-1970 gains for men total $61 trillion and $34 trillion for women. Combining gains for both genders, reductions in mortality between 1970 and 2000 yielded additional life-years with an end of century value of $95 trillion, or about $3.2 trillion per year. Of this amount, separate calculations show that two-thirds ($64 trillion) accrued to people alive in 2000, and one-third will be enjoyed by future generations.

Applications to Alzheimer's Disease

The current social value of a medical advance in predicting AD and delaying AD is proportional to the size of the current and future population to which it applies, and rises with wealth. Thus, economic growth is a boon to health related investments. Richer societies invest proportionately more in health because life itself is more valuable economically.

The value of progress against AD is greatest when the current age is close to, but before, the typical age of onset of the disease. For example, progress against heart disease is concentrated at ages 50 and above. Therefore, the expected present value of progress against AD will be greater at age 45 than at ages 25 or 90. Improvements in health and longevity are partially determined by society's stock of medical knowledge. The United States invests more than $50 billion annually in medical research, 30 percent of which is federally funded. It is necessary to weigh the costs of implementing new technologies for predicting onset of AD through biomarkers and delaying onset earlier against the

potential benefits of improving health. Overall we find that the value of increased longevity through such potential innovations will greatly exceed the rising costs of health care.

Furthermore, mortality-reducing improvements in the battle against AD are complementary. Progress against one disease raises the value of progress against other life-threatening ailments and diseases related to AD such as depression or schizophrenia, because individuals are more likely to be alive to enjoy the benefits. Improvements in the types of health problems that increase with age also are complementary; progress against Alzheimer's raises the value of progress against arthritis.

III. Approximating the Value of Delaying the Onset of AD

Using the data on the rates of progression through AD states and their respective qualities of life, survival, and other data on disease prevalence and growth to guide us, we pose the following hypothetical scenarios: what would be the social value of AD drugs that could delay the onset of disease by 1, 3, and 5 years? We adopt a conservative approach and assume that the new treatments only delay onset and do not delay progression. As such, our estimates should be viewed as lower bound measures of benefits. This exercise will shed light on the potential value of discovering and developing new AD drugs sooner. It will also provide a measure of the potential hazards of imposing prospective indirect price controls (via incorporating CEA guidelines to manage the new MMA Drug Benefit budget for example) on manufacturers who are currently researching AD cures or who are considering R&D projects for AD drugs, as we discuss in detail in the next section of our paper.

Using a real discount rate of 3 percent and assuming (conservatively) that AD has no effect on mortality rates, we calculate that the present value QALY gains from delaying onset of AD by 1, 3, and 5 years are 0.52, 1.32, and 1.73, respectively. According to the National Institutes of Health (NIH) and the Alzheimer's Association, the projected number of new AD cases in the year 2010 will be 454,000 and this number is expected to

climb to 959,000. For our analyses we will approximate the benefit of disease delay for all new AD cases from 2010 to 2050 (extrapolating beyond the NIH estimates would have only a marginal impact due to discounting). Table 1 presents the present value QALY gains associated with a new drug that by 2010 could delay disease onset by 1, 3, and 5 years.

Table 1: Present Value Benefits Gained From Delaying Onset of Alzheimer's Disease

AD Drug Effectiveness	Delay AD Onset by 1 Year	Delay AD Onset by 3 Years	Delay AD Onset by 5 Years
QALY Gains	6.86 million	17.29 million	22.66 million
Dollar Value ($100,000 per QALY)	$0.69 trillion	$1.73 trillion	$2.27 trillion
Dollar Value ($150,000 per QALY)	$1.03 trillion	$2.59 trillion	$3.40 trillion
Dollar Value ($175,000 per QALY)	$1.20 trillion	$3.03 trillion	$3.97 trillion

The dollar value estimates in Table 1 range from approximately $0.7 trillion ($2006), for a 1 year delay in AD onset for all new cases from 2010 to 2050, when a QALY is valued at $100,000, to almost $4 trillion ($2006), for a 5-year delay in AD onset for all new cases between 2010 and 2050, when a QALY is valued at $175,000. As was discussed in the last section, recent estimates of the value of a life year in the U.S. are approximately $175,000.

However, lower estimates are also used because AD patients are typically much older than the average citizen. It should be emphasized, however, that these benefits certainly represent a lower bound because we are not modeling a delay in disease progression of AD. We are only measuring the benefits of a delay in onset of disease. A new drug that

both delayed onset in patients prior to manifestation and slowed progression post-disease onset would likely confer significant social benefits in excess of those depicted in Table 1.

The primary objective of this exercise was only to demonstrate the magnitude of the benefits involved: they are in the trillions of dollars. These estimates are of comparable magnitude to the recent work by Murphy and Topel (2003) in which it was estimated that the value to Americans of a 10 percent reduction in mortality from cancer and heart disease would be approximately $10 trillion.

IV. Conclusion

In this paper we have shown how development of diagnostics and drugs based on recent insights into the molecular and biological pathways of Alzheimer's disease could have a profound global impact on this devastating illness. We have calculated in this paper that the benefits associated with delaying AD are quite substantial and in the trillions of dollars in most cases. Moreover, these first-order approximations are certain to be conservative lower bound estimates.

Previous researchers have concluded that, over the past half century, the value of the health gains in the U.S. have been at least as great as the combined gains coming from all other forms of economic growth, as measured by the Gross Domestic Product; and that in all likelihood, the United States is currently under-investing in medical and pharmaceutical research (Nordhaus, 2003; Murphy and Topel, 2003, Lichtenberg, 2003). Policies that would affect access to new Alzheimer's treatment would be quite troubling in this regard.

More the point, this paper examined the impact of applying comparative effectiveness analysis, including the QALY analysis and the $50,000 benchmark to new Alzheimer's treatments. Specifically, using comparative effectiveness of treatments and technologies in order to make coverage and reimbursement decisions based on additional or

incremental value that duplicate the analytical approach of NICE and similar systems would deny Americans significant social and economic gains from medical innovations associated with such innovations. A new comparative effectiveness agency that carried out such studies in support of Medicare coverage and reimbursement decisions, for example, might duplicate such outcomes in the United States.

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