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ABSTRACT

Alzheimer's Disease (AD) affects one in ten people aged 65 or older and is the most expensive disease in the United States. We describe the central economic questions raised by AD. While there is overlap with the economics of aging, the defining features of the 'economics of Alzheimer's Disease' is an emphasis on cognitive decline, choice by cognitively impaired patients, and a host of issues where dynamic contracts between patients and caregivers are hard to enforce. There is enormous scope for economists to contribute to our understanding of AD-related issues, including drug development, efficient care delivery, dynamic contracting within the family and with care providers, long-term care risk, financial decision-making, and public programs for AD. These topics overlap with many areas of economics – labor economics, health economics, public finance, behavioral economics, experimental economics, family economics, mechanism design, and the economics of innovation – suggesting the presence of a rich research program that should attract many economists.

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Why Alzheimer's Disease?

Economist readers of this article may be puzzled about an article on the economics of Alzheimer's Disease: do we, the authors, believe that a new economics of consumer or firm behavior needs to be developed for a particular disease? How is the economics of Alzheimer's different from the economics of cancer, or arthritis, or aging? What can a social science discipline like economics have to say about a particular medical condition?

While there is overlap between the economics of Alzheimer's Disease (AD) and of aging, the defining feature of the 'economics of AD' is an emphasis on cognitive decline, decision-making by cognitively impaired patients that may be different from 'behavioral bias', and a host of issues where dynamic contracts between patients and insurers and caregivers are hard to enforce. Although some of these features could apply to other health conditions that affect the elderly, the role of cognitive decline is central to the clinical definition of AD (which we detail in the next section), and how firms, families and patients respond to--or exploit--this decline. In addition, the issue of innovation--in prevention, delivery and medicines--is a central topic in economics but its importance is amplified in the economics of AD, where there may be insufficient investments in basic science and where a fragmented insurance system (at least in the United States) discourages private investments in these innovations. Finally, the disease is colossally expensive--more costly than cancer--and mostly paid for by the government, which means that any discipline that can think systematically about how to finance this spending will improve the quality of resource allocation. The 'economics of Alzheimer's Disease' therefore overlaps with a number of areas of economics: health economics, public finance, behavioral economics, experimental economics, family economics, mechanism design, and the economics of innovation, suggesting that the topic should attract almost all economists.

We share five key facts about Alzheimer's Disease to make this point:

Prevalence: AD is the most common cause of dementia, accounting for 60-80% of dementia cases and affecting an estimated five million Americans aged 65 or older (Alzheimer's Association, 2020a). By 2050, this number is expected to almost triple to 14 million (Centers for Disease Control and Prevention, 2019 and Kelley and Petersen, 2007). As of 2020, AD is the sixth leading cause of death in America, though some estimates rank it just behind heart disease and cancer as the third leading cause of death for elderly people (National Institute on Aging, 2014). While death rates for heart disease and cancer have been falling, death rates due to AD have been rising. Research has also indicated that AD (among other dementias) may be under-reported on death certificates (National Institute on Aging, 2014). Although AD primarily affects people over age 65, a form of AD known as early-onset AD affects patients younger than 65 and represents approximately 6% of all AD cases (Mayo Clinic, 2020). Race and gender disparities are first order issues in the prevalence of AD, with disproportionately higher rates among women, blacks and Hispanics.

Cost: According to the Center for Disease Control, it cost an estimated $159-$215 billion to treat AD in 2010, with annual costs predicted to rise to between $379 and $500 billion by 2040 (Hurd et al, 2013). In comparison, treatment costs for heart disease and cancer were $102 billion and $77 billion, respectively (Hurd et al., 2013). While the Medicare program covers

most medical costs, much of the cost of AD care is driven by long-term care expenses, covered predominantly by the Medicaid program or paid out of pocket. On aggregate, roughly 41% of total costs for AD care are paid by Medicare, 34% by Medicaid, 26% out of pocket, and a smaller percent by private insurance (Zissimopoulos, Crimmins, and St. Clair, 2015). However, direct health care expenditures are only part of the total cost: an estimated 3.6 million to 18 million unpaid caregivers spent a total of 3.6 to 18.5 billion hours providing care in 2018, time valued at another $233 billion (Alzheimer's Association, 2020a, Friedman et al., 2015). In total, therefore, the US spends close to half a trillion dollars annually on AD-related care. AD is a critical public policy priority due to the immense resources devoted to AD care as well as the vast human cost of the disease in terms of the suffering of patients and the toll on caregivers.

Long-term care delivery: For individuals living with AD, management of the disease can involve substantial amounts of health care and long-term care, care that often requires substantial amounts of co-production and cognitive decision-making. Individuals survive an average of four to eight years post-diagnosis, which typically occurs after the onset of symptoms such as memory loss and the inability to perform daily activities (Tom et al., 2015). Around 30-40% of individuals with AD reside in nursing homes at any given time, while 70% will die in a nursing home (Joyce et al., 2018) compared to 20% of those with cancer (Mitchell et al., 2005). Half of the long-term nursing home population in the US has a dementia diagnosis, and AD is the third most common primary diagnosis for Medicare beneficiaries in hospice after heart disease and other circulatory conditions. Given the decreased cognitive capacity among individuals suffering from AD, there is large scope for inefficiencies in care delivery that may translate to poor health outcomes and high costs. There is also a large role for insuring these risks which brings up a set of challenges around the design of insurance contracts.

Cognitive decline: AD has two definitions: a clinical one, which focuses on cognitive decline (beyond normal cognitive aging), and a scientific one, which focuses on the precise biology behind this decline that can occur long before the onset of clinical symptoms. We believe that economists have a larger comparative advantage in engaging with the first definition. AD is the largest source of age-related dementia, and while not all age-related dementia is a consequence of AD, much progress can be made by focusing on the sequela of cognitive decline. Age-related changes in cognition affect memory, decision-making, judgement, processing speed, and learning (Institute of Medicine, 2015), and may explain changes in risk preferences and choice consistency at older ages that would affect economic decision-making (Tymula et al., 2015). The rate of cognitive decline differs substantially across individuals, due in part to differences in socioeconomic status, health, lifestyle, genetics, and other factors. AD patients are at one end of a spectrum of cognitive decline and thus of particular interest for study, but there are many opportunities for economists to engage with the broader issue of cognitive decline and decision-making. At the same time the presence of severely cognitively-challenged patients raises a number of issues for economists who study family bargaining, care delivery, prevention, and dynamic contracting.

Innovation: The scientific definition of AD requires a precise diagnosis, and will challenge economists who want to work on cohorts of patients who have the precise medical diagnosis of AD. Economics can also provide insights into this definition of the disease. Better and faster

diagnosis would spur medical innovation through the expansion of market size. Push and pull incentives are also key for the development of transformational drugs for AD: firms will be drawn to AD because of its large market size and unmet medical need, but discouraged by the relatively poor understanding of the disease's basic science and the fact that treatments may have to be given to prodromal patients who are relatively young, with the benefits being captured many decades later, potentially by a different payer. The presence of different targets and a complicated disease suggests that it is unlikely that a single medicine will be the panacea for this disease and that there may be a role for alternative pricing structures. Economists are well-versed in understanding and quantifying the tradeoffs between various incentive and pricing structures (Budish, Roin, Williams, 2015; Chandra and Garthwaite, 2017), and we believe there is opportunity to apply these insights to developing policies around therapeutics for AD.

As a consequence of these 5 facts--some of which are shared by other diseases but no disease offers the singular combination--there is enormous scope for economists to engage with AD-related issues, be it around inducing new medical innovations in treatment, incentivizing efficient care delivery, dynamic contracting within the family and with long-term care facilities, insuring long-term care risk, saving, decision-making by cognitively impaired individuals, or designing public programs for AD. Greater attention by economists to this disease has the potential to lead to important policy insights. The goal of this essay is to encourage economists to engage in the emerging public policy debate surrounding AD by providing them with a basic understanding of the underlying science of this unique disease and by laying out the central economic questions raised by AD where broader lessons from economic theory, labor economics, public economics, and the economics of aging, health, innovation, regulation, and the family can be applied to develop new insights.

We begin this essay in Section 1 with a short primer on the basic science and epidemiology of AD highlighting basic facts that are relevant to economics research. The next sections dive into particular areas of research where economists are well suited to contribute to our understanding of AD. In Section 2, we turn to the role of incentive structures in health care and long-term care markets, valuing informal care, and the market design of insurance for AD. Section 3 discusses the relevance of AD for labor supply, savings, and financial decision-making. In Section 4 we describe the scientific understanding for the causes of the disease (as of the time of writing), and note current methods for diagnosis and therapeutics. We discuss the role of market frictions and 'missing medicines' in drug innovation and highlight how frameworks and toolkits of economists can help in our understanding of the determinants and effects of AD on health. Our goal is to describe what questions have been studied by economists and how the answers might be refined to apply to Alzheimer's, and what questions have not been studied, i.e., 'open research questions', particularly those for which economists have a unique comparative advantage in offering answers. For this reason, our discussion of the literature is not exhaustive; rather, we point the reader to papers that contain longer summaries, facts, and models. We conclude every section with a discussion of topic areas ripe for economists to study and conclude the paper with a call for investment in data resources and collaborations to accelerate research on this important disease.

1 What is Alzheimer's Disease?

Alzheimer's Disease (AD) is a progressive neurocognitive disease of the brain that eventually causes dementia. Dementia is not a disease but rather a general term for a loss of cognitive functioning that interferes with daily activities. While AD is the most common cause of dementia, other causes include Parkinson's Disease, Lewy body dementia, vascular disease, and other conditions. Symptoms of dementia could also be caused by issues such as sleep disturbances, medication side effects, infections or other temporal non-AD dementias. Although commonality exists between different forms of dementia, they can differ in progression, neuropathology, treatment plans, populations affected, and risk factors. Relative to other causes of dementia, AD is characterized by the presence of specific biochemicals – amyloid plaques and neurofibrillary, tau-based tangles – in the brain.[1]

The progression of AD can be divided into three phases: preclinical disease, mild cognitive impairment (MCI), and Alzheimer's dementia. The final phase may be further subdivided into periods of mild, moderate, and severe dementia due to AD. During the preclinical phase, biological signs of the disease are present in the brain, but the individual maintains normal cognitive function. This phase can last 15 to 20 years (Scharre, 2019). During the MCI phase, the individual has memory lapses, decreased planning and problem-solving skills, and other deficits, but maintains independence in instrumental activities of daily living (IADLs) like driving, cooking, and managing finances.

Each year, individuals with MCI have a 10-15% chance of developing Alzheimer's dementia (Michaud et al., 2017). In this phase, cognitive impairment is severe and the individual loses the ability to perform IADLs and basic activities of daily living (ADLs) like dressing and feeding. Patients may retain the ability to read (possibly without understanding), dance, sing, tell stories, and reminisce, as these abilities are controlled by parts of the brain that are affected later in the disease's progression. Other symptoms may include weight loss, seizures, frequent groaning or moaning, restlessness, tremors, and slow, stiff or repetitive movements. Mood and behavior changes may occur, including depression, anger, delusions, and wandering. About 20% of AD patients also experience sun-downing—a phenomena beginning at sunset in which patients exhibit a worsening of symptoms that lasts throughout the night (Alzheimer's Association, 2020b). Patients in this phase become completely reliant on caregivers and are susceptible to malnourishment, dehydration, and infection due to diminished swallowing and bowel control function. Median time from the onset of Alzheimer's dementia to death is 7 years, 4 years less than survival time for comparable persons without AD (Fitzpatrick et al., 2005).

It is useful to distinguish AD from the normal cognitive aging process. Cognitive abilities are often measured in terms of fluid intelligence (reasoning with novel information) and crystallized intelligence (reasoning that relies on previous knowledge). Studies regularly show that fluid

[1] AD was first characterized by Dr. Aloysius "Alois" Alzheimer in 1906 after he discovered abnormal brain tissue in a former patient named Auguste Deter. After Deter's death, Dr. Alzheimer found that several odd clumps of protein and tangled bundles of fibers were present throughout her brain (Maurer et al., 1997). These clumps were later named and identified as beta-amyloid plaques while the tangles were called neurofibrillary tangles (NFT).

intelligence declines with age (Salthouse, 2005). As crystallized intelligence rises with age and many real-world tasks rely on a combination of both skills, performance often exhibits a hump-shaped pattern with respect to age, peaking in mid-life. At older ages, the decline in fluid intelligence dominates, leading to declining cognitive performance with age (Agarwal et al., 2009). A clinical diagnosis of AD requires cognitive impairment beyond what would be expected due to age. However, individuals without AD may experience normal age-related cognitive decline that eventually impedes their decision-making ability.

The prevalence of both dementia and cognitive impairment without dementia rise sharply with age. One estimate indicates a dementia prevalence rate of 1.7% at ages 65 to 69, 6.5% at ages 75 to 79, and 30.1% at ages 85 and above. Rates of cognitive impairment without dementia are higher still, suggesting that about half of people in their 80s and over 70 percent of people in their 90s experience one or the other of these conditions (Agarwal et al., 2009).

Women account for around two-thirds of AD cases. However, it is not known whether this is due primarily to women's longevity advantage over men or whether other factors play a role. There is thus far no consensus in the literature as to whether women have higher age-specific AD prevalence rates, nor whether any differences in AD rates reflect the effect of biology or social factors (Beam et al., 2018).

Racial disparities in AD prevalence are substantial: Blacks are twice as likely to develop AD or other dementias as whites, while Hispanics are one and a half times as likely ("AAIC 2018", 2017). It has been hypothesized that the higher rates of AD in these groups may be partly due to a higher prevalence of comorbidities such as stroke, heart attack and diabetes, although the exact biological mechanisms have not yet been determined (Anderson 2004). Other possible explanations for racial differences include genetic and social factors as well as bias in measurement of cognitive function (Manly and Mayeux, 2004).

Finally, educational attainment is strongly associated with reduced dementia risk (Meng and D'arcy, 2012). One theory is that education leads to changes in brain structure that provide a "cognitive reserve" against age- and disease-related pathology, although other pathways may also play a role (Langa, 2018).

1.1 What causes Alzheimer's Disease?

The most prominent theories of how and why AD occurs involve the biochemicals associated with AD, amyloid and tau. To understand these theories, one must delve into biology.

Amyloid Precursor Protein (APP) is a naturally occurring protein that exists in our brains and other organs, though its exact function is unknown. APP is broken down by several enzymes, most notably BACE1 enzyme and gamma-secretase complex, into a small molecule called Ab peptide. Pieces of Ab peptide aggregate in the brain to form amyloid plaques.

According to the Amyloid Cascade Hypothesis, the buildup of amyloid plaques in the brain is the root cause of AD. It ultimately leads to the accumulation of other harmful debris in the brain,

causes damage to neurons, and leads to cognitive decline. Evidence for this hypothesis includes abnormal APP creation in people with very early onset AD and the presence of amyloid plaques in the brains of AD patients at autopsy. However, there is little correlation between amyloid deposits and cognitive symptoms, and therapeutics that aim to lower amyloid levels in the brain have thus far failed to slow cognitive decline. This lack of success has caused some to suggest that amyloid is a response to AD, not its cause (Makin, 2018).

An alternate hypothesis is that tau, a protein that exists within the neurons of the brain, may be the driver of disease. Tau protein can be altered in specific ways that causes it to clump together and form neurofibrillary tangles. Unlike amyloid, tau accumulation in specific parts of the brain correlates with cognitive impairment. Moreover, tangles can self-propagate, possibly accounting for disease progression over time.

Most scientists believe that neither theory is sufficient to explain AD on its own, and instead subscribe to a combined theory of amyloid and tau cascade. Amyloid is thought to develop first and put the brain at risk for tau accumulation. An analogy can be made to a trigger and a bullet--while amyloid is the trigger that sets the brain up to be vulnerable to damage, it is not until tau, the bullet, develops that the damage occurs and individuals begin experiencing cognitive decline.

While this combined theory remains the leader in AD research, a number of other contributors to AD have been considered in parallel. First, immune system activation appears to play a role in AD development. Some population studies suggest that individuals who take NSAIDs (i.e., ibuprofen) and immunosuppressants over long periods of time have reduced incidence of AD. In addition, individuals with AD have been noted to have higher levels of immune cells in their nervous system, although it is unclear whether immune cells are protective against worsening disease or increase the speed of disease progression. Second, infections may increase risk for AD. Ab peptide can kill some bacteria, which has led to a hypothesis that the initial formation of amyloid may be a defense mechanism against illness, with unfortunate downstream consequences. This hypothesis has been supported by an increased level of herpes virus found in the brains of AD patients.

Genetics are a known contributor to AD. APOE4 is the most important genetic risk factor for AD -- inheriting one copy of the gene from a parent increases risk 2- to 3-fold and inheriting two copies increases risk 12-fold (Michaelson, 2014). Researchers continue to explore why APOE4 raises AD risk and to identify other genes associated with AD. Genes play a particularly important role in early onset AD, the roughly 5 percent of AD cases in which symptoms develop before age 65. Inheriting a copy of any one of three mutated genes (APP, PSEN1, PSEN2) makes it probable that a person will develop early onset AD (Mayo Clinic, 2020b). Those with Down syndrome are also at a higher risk for developing AD, as they have three copies of chromosome 21; it houses the APP gene, which plays a role in the creation of beta-amyloid plaques (Mayo Clinic, 2020). Although not everyone with Down syndrome will develop AD, researchers have estimated that about 75% of those with Down syndrome over the age of 65 have AD (Alzheimer's Association, 2017). People with Down syndrome tend to develop symptoms of AD one to two decades earlier than those without it (Head et al., 2012).

Finally, AD has also been linked to several behavioral risk factors including poor sleeping patterns, smoking, and a lack of exercise (Mayo Clinic, 2018). Research has indicated that AD shares many of the same risk factors as heart disease and other vascular or metabolic conditions, particularly hypertension (Launer, 2019) and that later-life depression is associated with an increased risk for AD (Diniz et al., 2013). Recent research also suggests a scientific link between air pollution and dementia (Block et al., 2012; Underwood, 2017).

1.2 Diagnosing Alzheimer's Disease

It is useful to differentiate between a biological and a clinical diagnosis of AD. A biological diagnosis relies on biomarkers – something that can be reliably measured to indicate the presence of disease. Until recently, a diagnosis of AD was possible only via autopsy after death. Currently there are two tests that allow for the detection of biochemicals associated with AD. A positron emission tomography (PET) scan can look for amyloid deposits in the brain. A spinal tap, which extracts a sample of cerebrospinal fluid, can detect changes in amyloid components and tau levels. Using these biomarkers, AD can be diagnosed in the pre-clinical phase.

A clinical diagnosis is based on physicians applying clinical guidelines created by the American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, or DSM-V) or the National Institute on Aging and the Alzheimer's Association (NIA-AA) to assess patients with AD symptoms. While the two sets of guidelines differ in some respects, neither requires memory loss and both require cognitive impairment for AD diagnosis.[2] Physicians may perform an office-based multi-domain cognitive assessment if AD is suspected. As patients may view early AD symptoms – which often begin with short-term memory loss (Lakhan, 2019) – as normal signs of aging, they wait an average of 3 to 4 years after onset to raise the issue with their physician (Scharre, 2019). Clinical diagnosis occurs during the MCI or dementia phase.

Biomarkers can be used to improve the accuracy of a clinical diagnosis, as even experienced clinicians render an inaccurate diagnosis in 10 to 15 percent of cases (Thai et al., 2006). Further, biomarkers can be used for three other purposes: to detect AD during the pre-clinical phase, track disease progression in AD patients, and evaluate AD interventions in clinical trials.

With respect to the first of these, PET imaging has yet to be implemented as a routine screening test in clinical practice. Insurance companies argue that using PET scans for early diagnosis is expensive and unnecessary because there are currently no treatments to alter disease progression (Apostolova, 2016). Routine screening may also lead to unnecessary psychological

[2] The DSM-V currently recognizes two cognitive syndromes: major cognitive impairment and mild cognitive impairment. To be diagnosed with major cognitive impairment, individuals must show a measured decline in cognition that is extreme enough to impede activities of daily living. It must also not be caused by any other medical, neurological or psychiatric disorder. Individuals with mild cognitive impairment must show some decline in cognition but can otherwise live independently while still being able to perform relatively complex tasks like driving. The NIA-AA guidelines recognize the three general stages of AD discussed above. To be diagnosed with dementia, individuals must show diminishment in two cognitive domains or one cognitive domain and one behavioral domain, as well as drastic declines in everyday functioning.

strain, as many individuals who never develop clinical AD during their lifetimes have been found to have abnormal amyloid deposits upon post-mortem examination (Mormino et al., 2018). Appropriate Use Criteria for amyloid PET imaging recommend its use in three instances: for patients who have already developed symptoms of MCI with memory loss, patients already in the dementia stage or with atypical AD presentations, and patients with early onset AD (Apostolova, 2016). Scans are not recommended for cognitively normal individuals based on family history alone or for the purpose of determining dementia severity. The second and third goals of AD diagnostics are closely related. Biomarkers can allow doctors to understand whether and how quickly their patients are getting worse. They may also allow drug developers to assess the efficacy of an intervention more quickly than when clinical outcomes are used, leading to more efficient and less costly clinical trials (Thal et al, 2006).

Further development of AD diagnostics focuses on two goals. The first is to find tools that allow for earlier and less invasive detection of disease, such as a blood or saliva test that could be administered at an annual checkup.[3] The second is to better characterize disease trajectory to aid in AD treatment and research. Further validation of specific biomarkers is necessary before they can be used as a surrogate endpoint – a marker that is known or very likely to produce clinical benefit and can be used to support drug approval (Brioch et al, 2011).[4] Better and earlier diagnosis may also induce innovation by revealing market size and heterogeneity in the disease.

1.3 Further reading and future research on AD diagnosis and prevalence and disparities

There are several promising avenues for economic research in this area. First, economists could validate whether epigenetic and epidemiological risk factors for AD are causal or not. Such an effort would reveal potential preventive measures and interventions to reduce the burden of disease. This research program would resemble the work that economists have done to assess the causal effect of education on mortality, or birthweight on the well-being of infants, or in-utero exposures on later health, where the associations noted by epidemiologists were validated by economists as being causal while others were not. Second, understanding forces that reduce disparities in quality of health care, particularly for women and minority patients, is an area in which economists have a comparative advantage. This could build on the approaches used by Alsan et al. (2019) to study the effect of racial congruity between patients and their physicians on health, Baicker and Staiger (2005) on the conditions for which public assistance can improve patient outcomes, and Skinner et al. (2005) on the role of geography in racial disparities in health care.

[3] Other easy-to-administer tests might serve a dual diagnosis and prevention role. One such example, Neurotrack, provides users with a Cognitive Health Program, which works to improve users' brain function now in an attempt to delay decline later. Taking the form of a mobile application that can be used on tablets and smartphones, the program includes measures such as eye tracking, processing speed, and recognition memory to determine areas in which users might be at most risk of cognitive decline or at risk for dementia.

[4] One biomarker that has garnered enthusiasm in recent years is the neurofilament light chain, a marker of general damage to brain cells. It is not specific to AD and has been seen in increased amounts in many conditions, including other dementias and traumatic brain injuries. While it would not be useful in distinguishing AD from other conditions, serial measurements of such a marker may help predict if the disease is worsening or improving.

2 Health care and long-term care for Alzheimer's Disease

Treatment for AD typically involves a combination of drug therapies to slow cognitive decline and health care and long-term care to manage the disease. Current pharmaceutical treatments, however, have only small effects on the progression and symptoms of the disease, so many of the pressing questions for individuals currently suffering from AD fall within the realm of care delivery within the health and long-term care spheres. We now turn to the economics of this care, and we return to drug therapeutics in Section 4.

Care for individuals with AD draws upon decisions by a host of agents, including the patients, their families, health care and long-term care providers, and regulators. While many important questions related to the optimal care delivery for AD have parallels with broader literature in health economics and public finance, a distinction that makes AD care relatively unique is the role that cognitive constraints play in the delivery of care. As cognition – and decision-making ability more generally – declines over the course of the disease, demand-side forces may not operate as standard economic models would suggest. Instead, individuals with cognitive constraints may have to rely on altruistic agents (such as their family), regulatory checks, or self-enforcing dynamic contracts to ensure optimal care provision. Thus not only is AD care an area in which health economists can make progress, but economists studying family bargaining, regulation, and dynamic contracting problems can also add value to the study of AD. This section discusses the issues surrounding health care and long-term care for AD, with an eye toward the more unique features of AD for which efforts by economists may be particularly fruitful. We begin with an overview of how care decisions are made for individuals with limited cognitive capacity, and then discuss health care, long-term care (including the role of informal care), and insuring care for AD.

2.1 An overview of care delivery under cognitive constraints

The ability to advocate for oneself and act according to one's preferences -- regardless of whether they are deemed "rational" or "behavioral" -- is the launching pad of the study of consumer choice. In studying market outcomes, economists generally evaluate the functioning of a market relative to a frictionless, first-best world, and study particular deviations from first-best, such as asymmetric information or market power. But what happens when one side of the market -- the consumer -- does not have the cognitive capacity to act according to their preferences, and they become dependent on other forces to enforce their preferences? More generally, how should we conceptualize economic decision-making under cognitive constraints, when individuals may not remember past experiences, or where they are, or how to think? Theory and identification of market outcomes are difficult without a more precise understanding of how cognitive capacity manifests into choice, but insights from behavioral economics and psychology may lead us to a better understanding of whether cognitive constraints can be understood as rational inattention, or time inconsistent preferences, or something else entirely. How do market structures for health care delivery function under cognitive frictions? What mechanisms could mitigate these frictions? These are inherently

questions about market design, an area where economists are well-tooled to contribute to AD research.

One mechanism that mitigates cognitive frictions is the presence of altruistic agents that can act on a cognitively-constrained individual's behalf. A long tradition in family economics explores the role of adult children as caretakers and guardians for elderly parents. The literature that tests for altruistic motives versus exchange motives of children could be applied to families with AD as a relatively extreme test case: for example, do altruistic motives appear in children of parents with AD (who may not even recognize their children), even without the prospect of bequests? Economists could also contribute to the literature on family bargaining models to understand, for example, whether parental cognitive decline leads to changes in bargaining power, health care decisions, and ultimately health outcomes.

Another altruistic agent is the state, which uses regulation to discipline health care and long-term care practices. For example, the government sets minimum quality standards, such as staffing ratios in nursing homes, that aim to safeguard against low quality care, and monitors trends by collecting data on outcomes and quality measures of health care providers. These regulatory checks may be particularly valuable for the AD population, some of whom may not have others to act in their interest.[5]

An alternative path to mitigate cognitive frictions is to appeal to mechanism design. While cognitive frictions may prevent first-best allocations in a simple one-shot model of health care delivery, insights from contract theory may suggest that more complex--and likely dynamic--contracts could come closer to the frictionless allocation. For example, some providers (e.g., "continuing care facilities") offer long-term, dynamic contracts to individuals prior to cognitive decline that define care arrangements for all future care need contingencies. Whether this type of contract sustains agreed upon levels of quality care, particularly in cognitively constrained states of the world, could still depend on other safeguards like family advocates or regulatory constraints. Reputation effects could also generate better allocations for consumers, especially among long-standing providers. Government data collection and monitoring could have the added benefit of providing measurements of provider reputation.

In sum, the economics of health care delivery may be quite complex for individuals with AD, and could greatly benefit from insights of economists working in areas ranging from contract theory to family economics to regulation. We next discuss more specific areas related to health care and long-term care delivery for individuals with AD.

2.2 Health care for individuals with AD

Individuals with AD often receive many kinds of health care over the course of their disease. Initial diagnosis often occurs in a primary care setting, and patients receive care in a multitude of settings as the disease progresses, including hospitals, nursing homes, and the home. Thus all of the usual providers in the U.S. health care system are involved in AD-related care. Similarly,

[5] As fertility rates continue to decrease, the availability of children to act as advocates for their parents with AD will inevitably decline, suggesting further value in these safeguards.

the usual payers -- private insurance, Medicare, Medicaid, and patients -- all bear a share of the expenditures.

Given this complex network of payers and providers, an important area for economic research is how the incentive structures of all of these players interact to generate AD care. Within health care more broadly, a growing literature suggests that there is a substantial amount of "waste", with much of it attributable to the fact that private incentives of consumers, payers, and providers do not always align with the socially optimal levels of care (Fisher et al., 2009). Studying these incentive structures in the context of AD care -- i.e., care for cognitively constrained individuals whose care involves many players over many years -- could offer additional insights into the black box of this waste.

One example where the study of AD care can provide insight is the role of cognitive constraints in the demand-side incentives for health care. Classic demand theory suggests that health insurance leads to overuse of low-value care, and cost-sharing generates more efficient levels of care (at the cost of lower risk protection). However, there is increasing evidence that cost-sharing additionally leads to cuts in *high*-value care, a finding that is difficult to reconcile with standard theory. For example, Chandra et al. (2010) found that increases in patient-cost sharing for physician office visits and prescription drugs led to decreased spending on those services, but these savings were fully offset--and in fact exceeded--by spending increases on hospitalizations.[6] Similarly, Brot-Goldberg et al. (2017) found that patients introduced to a high-deductible health insurance plan decreased overall health spending, but did so seemingly indiscriminately, cutting back on both wasteful *and* valuable care. These findings are suggestive of "behavioral hazard" in which patients mistakenly cut back on high value care in response to cost-sharing (Baicker et al., 2015). These hazards may be particularly interesting to study in the context of AD patients, who--because of decreased cognitive capacity or awareness--may be more prone to such mistakes. This exploration could challenge the prevalent view that the price-elasticity of demand is a sufficient statistic for welfare.

The context of AD care may also be fruitful for studying the role of intertemporal incentives in health care. Specifically, fiscal externalities or free-riding can arise when the costs of (earlier) care accrue to different agents than the (later) benefits. Underinvestment in preventive measures is a prime example of this (Ellis and Manning 2007). Some research suggests that a healthy diet and exercise can improve later AD outcomes and lower AD costs (Pope et al., 2003), yet these investments can be costly or unpleasant to individuals. Because the downstream savings of these investments largely accrue to insurers, individuals may not find the preventive measures to be worth the immediate costs, leading to underinvestment in preventive care.

Similar intertemporal incentive problems may arise when different insurers provide coverage at different ages (Fang and Gavazza, 2007). Given that health care for AD can span decades, this

[6] Furthermore, Chandra et al. (2010) also showed evidence of fiscal externalities arising from multiple insurers: the savings accrued to a supplemental insurer that covered physician visits and drugs, while the offsetting hospital costs accrued to Medicare. Given the multitude of insurers and payers involved in Alzheimer's care, this could be a relevant concern for AD payer design.

issue may be particularly acute for AD care: for instance, a private insurer may not want to cover an expensive but effective early-stage intervention (e.g., diagnostic testing) because the later stage savings accrue to Medicare or Medicaid. Whether or not these incentives are empirically relevant, however, is an open question, as there is currently little consensus on the appropriateness of early stage interventions. For example, while the World Health Organization promotes "early diagnosis in order to promote early and optimal management", other research suggests that many of these strategies are poorly targeted and that there is insufficient evidence of their merits ("Dementia", 2018 and U.S. Preventive Services Task Force, 2020). Economic frameworks and causal methods could provide a useful lens to understand not only incentives for early stage AD interventions, but also to identify whether and when to recommend different diagnostic tests in the first place (e.g., Einav et al., 2019).

Provider-side incentives are also a growing area of research, and studying this topic in the context of AD could lead to insights given the many transitions between providers that AD patients experience. Because health care providers are often paid for the care rendered (e.g., fee-for-service) and not for outcomes (e.g., pay-for-performance), they face financial incentives to maximize payments rather than incentives to lower costs. The payment structure for end-of-life care for AD patients illuminates this issue. Nursing homes provide care to many AD patients near the end of life, many of whom are dually eligible for Medicare and Medicaid. Medicaid typically pays a relatively low per-diem rate for each nursing home resident regardless of their intensity of care needs, while Medicare reimburses at a higher rate but only covers 100 days of post-acute nursing home care. Because end-of-life AD patients are typically more costly than other patients, nursing homes face incentives to transfer patients near death--who need more intensive care--to hospitals, to temporarily shift their reimbursement to Medicare, which pays higher reimbursement rates (Goldfeld et al., 2013).[7] This not only increases costs of care, but is associated with increased use of "questionable medications" (Tjia et al., 2014) and is generally inconsistent with the goals of patients for comfort (Gozalo et al., 2015).

Studies suggest that Medicare payment structures that have pay-for-performance features (e.g., Medicare Advantage plans) result in lower-cost AD care as well as fewer burdensome hospital transfers (Goldfeld et al., 2013).[8] There is also growing evidence that coordinated care plans for individuals with AD, which--among other things--assign a care manager to coordinate the wide range of provider services, can result in positive health outcomes (see Hughes et al. (2017) for a review). These plans have not been widely implemented, however, in part because typical reimbursement systems once again do not incentivize coordinated care (Boustani et al, 2019). Nonetheless, a recent trend towards alternative payment models in Medicare more broadly, such as Accountable Care Organizations (ACOs) and bundled payments (e.g., McWilliams et al., 2015, and Finkelstein et al., 2018) suggest an appetite for payment redesign for AD care in the near future.

[7] This not only relieves the nursing home from high-intensity care during the hospitalization, but also shifts the reimbursement to Medicare for 100 days after the patient returns to the nursing home.

[8] Others have cautioned an interpretation of "hopeless" spending by showing that it is virtually impossible to predict death from health spending and suggesting that it is not clear that care for those who ex-post died was futile (Einav et al., 2018).

Some AD care is being funded via prospective payment under the Program of All-Inclusive Care for the Elderly (PACE). PACE providers receive capitated payments from Medicare and Medicaid to provide a full spectrum of health care services to frail elderly individuals with a need for long-term care, over half of whom have dementia (Mukamel et al., 2007). One long-standing concern about capitated payment systems is that providers may provide fewer services, potentially resulting in lower quality care (Rogers et al., 1990). This concern may be heightened in a context where the patient is not an effective self-advocate due to cognitive compromise. Additional research analyzing the cost savings and quality impacts of capitated payments for AD care would shed light on the value of this payment model in this context.

While many of the economic incentives discussed in this section are not unique to AD care, they may be particularly relevant for AD in the coming years for at least two reasons. First, the long-term nature of AD progression and the reliance on a wide range of providers and services makes relying on demand-side forces for navigating the care and treatment of the disease particularly challenging and susceptible to errors, especially for those with cognitive constraints. In other words, demand curves may not be well-defined for AD patients. Second, new developments in screening technologies and drug therapies for the disease as well as the rise of alternative payment models for AD care warrants study of how supply-side incentives evolve.

2.3 Long-term care and caregiving

Long-term care consists of care for activities of daily living (ADLs), such as bathing, dressing, eating, and walking and instrumental activities of daily living (IADLs), such as taking medications, managing money, and shopping for groceries. This care is most commonly provided either in a nursing home setting or at home, but also in assisted living facilities, adult day care centers, and other settings along the care continuum.[9] For individuals diagnosed with AD, one third live in a residential care setting (18% in nursing homes), though by the time of death, two thirds die in nursing homes (Kasper et al., 2015; Mitchell et al., 2005).[10] In 2019, nursing home care averaged $90,000-$100,000 per year, while formal home care cost around $23 per hour, or roughly $53,000 annually for 44 hours per week. In all, these long-term care costs rival the medical care costs of the disease. Medicare does not cover most long-term care costs, so the majority of these costs fall on the Medicaid program, individual savings, families, and, to a lesser extent, private insurance (Kelley et al., 2020).

These formal costs, however, paint an incomplete picture of the economic burden of long-term care for individuals with AD because they do not factor in the substantial amount of informal care. An estimated 7.4 billion hours of informal care was given to 3.6 million individuals with AD in 2010 (Friedman et al., 2015), and of the AD population receiving care in the community, 78% of care hours were informal (Kasper et al., 2015). Most AD caregivers are female spouses or children, and many live with the individual with AD. 30% of these caregivers provide over 20 hours of care per week, and the majority of them help with ADLs and IADLs (Alzheimer's

[9] There has also been a rise in dementia special care units (SCUs) within nursing homes over the past decade, which make up the largest type of specialized long-term care (Cadigan et al., 2012).
[10] In contrast, most deaths from cancer occur at home or in a hospital (Mitchell et al., 2005).

Association, 2019). They also have other demands for their time: 60% also work part or full time, and a quarter are also caregivers to young children (National Alliance for Caregiving in Partnership with the Alzheimer's Association, 2017).

2.3.1 Measuring the cost of informal care

Measuring the cost of informal care can be difficult because these hours do not have an explicit market or monetary value. One simple method, which attempts to quantify the *savings* from an hour of informal care, is to price it at its replacement cost, such as the market rate for purchased home care (roughly $20 per hour). A second simple method, which attempts to quantify the *cost* of an hour of informal care, is to price it at the cost of foregone wages if the caregiver had worked in the labor market instead of providing care. Hurd et al. (2013) estimate that the cost of informal care for individuals with dementia using the 'replacement cost' method is around $28,000 annually while using the 'foregone wages' method generates around $13,000 annually. Using the former method, the 7.4 billion hours of informal care for AD is "worth" $148 billion on aggregate, or roughly as much as the total formal payments for health care.

In reality, the true value of informal care is somewhere in between. An alternative method is an economic model that incorporates replacement costs, potential foregone wages, and other opportunity costs, in a unified framework of caregiver well-being. At a basic level, it specifies caregiver utility over monetary consumption and leisure and a budget constraint over labor income, consumption, and care costs. Caregivers make decisions over how to spend their time, which considers the value of each hour spent doing something else instead of caring, including potentially working (i.e., lost productivity) but also enjoying leisure, and evaluates it against the cost of doing so (i.e., purchasing the care on the formal market).[11] This type of model, which has been developed for informal care more broadly but not tailored to the particularities of AD, can then be used to calculate a more comprehensive measure of the welfare costs and benefits of informal AD care.[12]

2.3.2 Prices, costs, and selection among long-term care options

The existence of informal care and other long-term care options for individuals with AD raises important economic and policy questions about selection into various long-term care options. How do individuals decide whether to enter a nursing home versus receive informal care versus receive paid in-home care? To what extent do they care about price versus preferences versus health outcomes? These questions have implications not only for individual welfare but also social policy, given that social programs pay for many of these costs and there are substantial cost differences between modes of care. One question that economists have made progress answering is whether individuals are price-elastic in their long-term care decisions. The answer

[11] It can also include other possible costs of caregiving, such as mental and physical health costs (Coe and Van Houtven, 2009).

[12] The model can also be expanded to account for the welfare of the AD individual as well as their preferences over informal care, either with the addition of "warm glow" utility or a more complex model of family interactions (e.g., Barczyk and Kredler, 2018; Mommaerts, 2016).

appears to be yes: studies have shown that consumers are generally responsive to relative out-of-pocket costs for long-term care. For example, Coe, Goda, and Van Houtven (2015) and Mommaerts (2018) find evidence of substitution towards nursing home care and away from informal care when the out-of-pocket cost of nursing home care decreases. These studies, however, focus on the general long-term care population and an open question is whether individuals with AD--who are likely cognitively constrained--make similar choices. Additionally, more work is needed to understand the role of preferences (which are potentially less well defined under cognitive constraints) and perceived health benefits in these decisions.

A related question is whether these choices between long-term care options generate selection, and the ramification of this selection for providers. For example, the rise of assisted living facilities over the past few decades may pull healthier, cheaper patients out of nursing homes and leave nursing homes with a much sicker pool of patients. With fixed reimbursement rates that are independent of health, this suggests increased financial strain for these facilities. As new care arrangements arise, such as specialty care units, integrated care models, etc., and diseases requiring long-term care such as AD evolve, an important followup question is how demand and selection into various options interacts with the cost structures of care providers.

Another open question is whether different long-term care options lead to differences in overall health care costs. For example, while home-based care is generally less costly than nursing home care, it is not clear whether it leads to long-run savings on total health care costs. This is particularly relevant for state Medicaid policies, which have expanded home care in recent decades.[13] Evidence from community care demonstrations in the 1980's suggests that costs increased when home care was provided in lieu of nursing home care, but this was in large part because recipients were otherwise forgoing nursing home care (Kemper et al., 1987). Another example is the decision to use hospice at the end of life: Gozalo et al. (2015) found that individuals with AD who entered hospice had higher overall Medicare costs than those who did not enter hospice, despite efforts to design the Medicare hospice benefit to lower total health costs. Much more evidence on the effects of various care settings on costs is needed, particularly among the population suffering from AD whose health and long-term care needs may differ from those suffering from other ailments.

2.3.3 Quality of long-term care

Another important aspect of long-term care for AD that economists are well positioned to study is the market for quality long-term care, particularly in formal care settings. A persistent concern among policymakers is that many long-term care facilities provide low-quality care, and patients are not well informed about the wide variation in quality when making long-term

[13] The primary setting for Medicaid-covered long-term care was historically nursing homes, but in the past 40 years states have gradually shifted Medicaid funds toward long-term care benefits and services in the home. This shift is partly in recognition of a strong preference to remain in the community (and the Supreme Court's Olmstead decision in 1999 that reinforced this), but a second justification is economic: many policymakers believe that nursing home care is excessive for many with less-intensive long-term care needs, and thus allowing them to remain in the community may result in lower long-term care costs.

care decisions.[14] In general, if consumers can easily evaluate the quality of facilities, basic economic theory suggests that facilities have an incentive to compete with higher quality care; if consumers cannot evaluate their quality, facilities may underinvest in quality care. Empirical evidence confirms this for the broader long-term care population: for example, nursing home "report cards" lead to increased demand for higher quality facilities (at least when these report cards are easily interpretable), and competition among providers have meaningful effects on quality, but only when consumers have good information about the quality of nursing homes from which they are choosing (Grabowski and Town, 2011; Werner et al., 2016; Zhao, 2016).

Complicating this basic theory, however, is the fact that not all consumers of long-term care are the same: some are higher cost than others and providers may have an incentive to use quality as a screening device for patients. For example, lower Medicaid reimbursement rates lead to lower quality care for Medicaid patients (Hackmann, 2019) and even rationing of Medicaid patients by nursing homes (He and Konetzka, 2014). Moreover, the quality effects discussed above mainly arise in short-stay nursing home populations whose stays are typically covered by Medicare and thus have higher profit margins than long-stay residents who are typically covered by Medicaid (Grabowski and Town, 2011). It is not obvious how these incentive structures for quality care apply to the AD population. In hospital settings, for example, AD patients typically generate low to negative profits, and Colla et al. (2016) show that competition is associated with *lower* quality AD care, perhaps as a way to discourage these unprofitable patients. On the other hand, special care units for AD patients in nursing homes have been shown to provide higher quality care, at a higher price point (Joyce et al., 2018).

A related and understudied issue is the role of cognitive constraints in the demand for quality care. This is particularly relevant for the AD population, as individuals with AD may be less aware and/or less able to advocate for quality care.[15] Some have loved ones advocating for them. Others depend on the state as their advocate. As discussed at the beginning of this section, economists can bring insights from market design and contract theory to study the provision of quality care when consumers are cognitively constrained. For example, a possible contract structure is one in which individuals make care arrangement contingencies well in advance of cognitive decline (like an Arrow-Debreu security) to avoid making decisions under cognitive constraints. Continuing care communities, in which individuals enter the community at a relatively early age and move from independent living to assisted living to nursing home care as needed, are an example of this type of contract. Of course, there is no guarantee of high quality of care when it is needed years later, nor is it necessarily enforceable once the individual suffers from dementia. Future work could examine the possibility of alternative contract

[14] For example, while around 5% of nursing homes had zero out of around 175 types of "deficiencies" in 2016, over 20% of facilities received scores for the most egregious deficiencies of "actual harm or jeopardy" (Harrington et al., 2018).

[15] Exacerbating this is the high use of psychotropic drugs on AD patients. Not only do these drugs decrease awareness among AD patients, but studies have found increases in mortality among AD patients directly related to these drugs (Briesacher et al., 2013).

structures, as well as the role of regulation[16], for quality care for those unable to advocate for themselves.

2.3.4 The long-term care workforce

The production of quality long-term care is very labor-intensive, predominantly made up of direct care workers including nursing, home health, and personal aides that are typically low skilled, low paid, and often immigrant workers, and the US is currently facing a major shortfall of these workers (Zallman et al., 2019). Studies have shown that low pay is linked both to this shortage as well as lower quality care (Ruffini, 2020) and that tight labor markets lead to lower staffing levels in long-term care facilities and higher mortality rates (Stevens et al., 2015). At the same time, however, a significant fraction of long-term care provider financing is dictated by low Medicaid reimbursement rates that do not allow much room for pay adjustments, either to increase quality or respond to cost shocks. For example, Cawley and Grabowski (2006) found that exogenous increases in labor costs (through minimum wage law increases) led to substitution away from labor towards "capital", i.e., psychoactive drugs, for nursing home patient care.

The shortage of long-term care workers is projected to worsen as the older population in the US and their demand for long-term care grows. A ripe area for study is understanding the effectiveness of various policy levers to improve the supply of this workforce. For example, changes to immigration policy, labor market policies (e.g., minimum wage policy), and regulatory conditions could all play a major role in the future supply of long-term care workers, as could more ambitious changes to the organization of the occupation, such as the formation of career ladders. Moreover, the prospect of technological advancements that can act as substitutes for labor--such as GPS signals to safeguard AD patients' whereabouts--could also be a fruitful area of study.

Overall, there are many unanswered questions about the economics of long-term care for individuals with AD. Important directions for future research include a better understanding of care decision-making processes for individuals who cannot advocate for themselves, the design of payment structures that incentivize providers to provide high quality care to AD patients, the relative merits of various long-term care settings, and how informal care fits into this landscape.

2.4 Insuring care for AD

In the United States, insurance against medical expenditures operates in a largely distinct market from insurance against long-term care expenditures. While medical expenditures for AD care are relatively well insured, long-term care expenditures pose one of the largest uninsured financial risks to the elderly (Brown and Finkelstein, 2011). Crucially, Medicare does not cover most long-term care expenses.[17] Of the $310 billion in aggregate formal long-term care

[16] For example, regulations such as minimum staffing regulations and nursing home inspections have had modest success in increasing quality care in nursing homes (Werner and Konetzka, 2010).

[17] Medicare covers 100 days of post-acute care, but only after a hospitalization lasting at least three days.

expenditures in 2013, 8% was paid by private long-term care insurance, 72% was paid by public insurance (mostly Medicaid, the means-tested program for the impoverished), and 19% was paid out-of-pocket (Reaves et al., 2015).[18] These expenditures are not spread evenly across elderly individuals: while fewer than 50% of individuals will ever enter a nursing home, there is a long right tail in the duration of nursing home stays among those that do, with 15% of stays lasting over 5 years (Brown and Finkelstein, 2009). These tail events are the events for which insurance is most valuable, and AD patients are the population who often need this very long-term care.[19]

2.4.1 Private long-term care insurance

Despite the potential value of insurance in this setting, the private market for long-term care insurance is small (and continuing to shrink), and the contracts offered are very incomplete. In this market, the average applicant is in their mid-sixties, and payouts typically do not begin until years later. The average annual premium for an individual policy was $2,700 in 2015, and covered roughly $150 per day of nursing home or home care for up to four years (LifePlans, Inc., 2017). Overall, only around 10% of individuals 65 and over in 2015 owned a private long-term care insurance plan, and even with insurance they still pay for a substantial fraction of care out of pocket.

Many explanations for this poorly functioning market have been offered, and developments in AD prevalence, treatment, and information could exacerbate these issues. One explanation is the aggregate risk inherent in insuring against contingencies that can occur far into the future. Long-term care insurance contracts are written and signed years, often decades, before AD risks are realized, and there is a great deal of uncertainty over what the long-term care landscape will look like in the coming decades (Cutler, 1996). For example, unexpected advances in technologies and treatments for AD and unexpected increases in AD prevalence rates can result in (unexpectedly) higher future costs to insurers. To safeguard against this risk, insurers can impose higher premiums or "quantity rationing" such as payout caps, which ultimately results in less attractive, incomplete insurance to policyholders (Brown and Finkelstein, 2007).[20]

Another explanation is the role of private information about one's risk for developing AD. When insurees have more knowledge about their underlying risk than insurers, adverse selection can result, whereby higher risk (i.e., higher cost) individuals purchase insurance. This drives up prices and results in lower risk individuals being priced out of the market; at its worst, it can lead to unraveling of the market. A first-order question is the degree to which advancements in genetic and diagnostic technologies for AD will exacerbate adverse selection in the long-term care insurance market. If individuals are able to privately obtain this information or insurers are not allowed to price on it, this could exacerbate adverse selection. On the other hand, if insurers are able to screen applicants with these tools, this could lead to more price discrimination and ultimately a pool of uninsurable higher risk individuals. For example,

[18] These numbers correspond to long-term care expenditures for all underlying ailments, not only AD.
[19] For example, among a sample of AD patients, mean nursing home use was three years (Welch et al., 1992).
[20] Reinsurance, which insurers can purchase to insure this aggregate risk, is also small in this market.

Hendren (2011) shows that insurers use health conditions (including AD diagnoses) to screen and reject high risk individuals in the long-term care insurance market, while Zick et al. (2005) and Taylor et al. (2010) show that individuals who learn that they have a variant of ApoE that increases the risk of developing AD are significantly more likely to purchase long-term care insurance.[21] The Genetic Information Nondisclosure Act currently bans the use of genetic tests in health insurance pricing, but does not regulate the use of genetic testing (nor biomarkers) in long-term care insurance pricing (Arias et al., 2018). Thus the full effects of current and future AD testing advancements on the functioning of the long-term care insurance market is an open and pressing question.

Private information may also lead to moral hazard. In particular, because some care is valuable even to those who don't need it (e.g., housekeeping and errands), there are incentives for insured individuals to over-use these services, which in equilibrium leads to higher-cost, lower-value insurance.[22] One solution to this type of problem is to create a targeting mechanism so that only those who truly need care will use it (Nichols and Zeckhauser, 1982; Lieber and Lockwood, 2019). The downside to this type of screening mechanism is that the resulting insurance provides inferior coverage. For example, given that most individuals would prefer to remain at home as long as possible, a policy that only covers nursing home care will only attract use from those who need care, but at the cost of less preferred care. Indemnity insurance, on the other hand, would allow individuals to receive the care they prefer, but would not provide the screening benefits and would likely be subject to over-use. Complicating the concern of moral hazard in the context of AD is the underlying assumption of rationality behind the behaviors of those suffering from AD: what does moral hazard and "over-use" mean for someone who does not have normal cognitive functioning, who may not know where they are or that they even have insurance? An open question is how to formulate the behavior of individuals with AD into an economic model of decision-making in order to further understand, in this case, how moral hazard interacts with AD care.

2.4.2 Substitute sources of long-term care insurance

Without formal insurance, most individuals rely on alternative sources of insurance against AD risk, including precautionary savings, Medicaid, and informal insurance from the family. Precautionary savings, however, can come with high opportunity costs, though Lockwood (2018) shows that bequest motives lower this opportunity cost by providing value to unused savings.[23] The Medicaid program provides long-term care insurance to individuals with very low income and assets. Nevertheless, it crowds out demand for private insurance even for wealthy individuals: Brown and Finkelstein (2008) and De Nardi, French, and Jones (2016) show that

[21] Similarly, Oster et al. (2010) shows that genetic testing for Huntington's disease (another degenerative disease) results in selective purchase of long-term care insurance.

[22] Moral hazard problems of this sort also occur in health insurance (e.g., additional screenings, unnecessary procedures) when it is not obvious to insurers whether the patient needs the screening but patients derive value (e.g., peace of mind) from the extra services, as well as in disability insurance when it is difficult for disability examiners to ascertain whether an applicant is truly disabled.

[23] In addition to liquid savings, Davidoff (2010) shows that individuals also use housing assets as a hedge: if individuals need care, they can sell their house and use the equity to pay for nursing home care; if they do not need care, they can continue to live in their house.

Medicaid acts as "catastrophic" insurance, and, coupled with precautionary savings, is more valuable than private insurance contracts in their current form for much of the wealth distribution.

Perhaps the largest substitute for formal long-term care insurance is the family. A series of papers show that expectations of informal care from family members acts as implicit insurance and suppresses demand for formal insurance (Mommaerts, 2016; Coe, Goda, and Van Houtven, 2015; Mellor 2001). This is not a perfect substitute for insurance, however, as informal care comes with its own costs and can lead to further selection problems in the formal insurance market (Ko, 2016). As rates of AD grow and the availability of informal caregivers decreases (e.g., due to lower fertility rates), more research will be needed to assess the evolving role of the family in insuring care for AD.

Going forward, more comprehensive social insurance for long-term care--which exist in many European countries--could provide a solution to the challenges of offering private insurance for AD care.[24] A classic benefit of social insurance is its ability to mitigate adverse selection issues by imposing mandatory participation. Moreover, social insurance may also be better equipped to weather aggregate risk associated with AD and its associated expenditures because it can more easily spread the risk across generations. However, a classic downside of social insurance is that it could exacerbate moral hazard concerns, particularly if it comes with the generous benefits that are typical in other countries. For example, the Netherlands recently scaled back its long-term care program due to ballooning costs often attributed to excessive use (Maarse and Jeurissen, 2016). These European programs will be useful case studies for the US as it grapples with how to insure an aging population in the coming decades amidst an evolving AD landscape.

A final point to consider in insuring AD care—both privately and publicly—is the role of preferences and beliefs in shaping demand for insurance. Behavioral constraints, such as limited financial literacy, incorrect beliefs of the risks and costs associated with AD, procrastination, and the perceived risk of insurer bankruptcy limit the demand for private insurance (Brown, Goda, and McGarry, 2012, 2016). These are features that policy may seek to ameliorate, for example by information campaigns, tight regulations on insurers, changing defaults, or providing social insurance. On the other hand, it is also important to consider whether preferences support (fully) insuring the state of the world in which one needs long-term care for AD. If marginal utility of consumption is much lower when one is suffering from AD, then it may not be welfare improving to have insurance coverage for these states of the world. This notion of state-dependent utility has been studied in a variety of contexts, with mixed results (Ameriks et al., 2020; Finkelstein, Luttmer, and Notowidigdo, 2013). The extent to which state-dependent utility is relevant for AD is an open and important question for further research.

In sum, while our understanding of the insurance market for long-term care has grown substantially over the past decades, there are still many unanswered questions, particularly as

[24] The CLASS Act was an attempt in 2010 to create a voluntary social long-term care insurance program as part of the Affordable Care Act, but was ultimately struck from the final bill over concerns about adverse selection.

the market relates to care for AD. Will it be possible to privately insure the risk of AD in the coming decades, or will the aggregate risk associated with changes in AD prevalence and treatment render it infeasible? How should the use of diagnostic testing be regulated in this market? How should we model the concept of moral hazard, and decision-making more generally, for cognitively impaired individuals? The following section expands on the economics of financial decision-making for individuals with AD.

2.5 Further reading and avenues for future research in care for AD

This section has suggested several areas for future research on the economics of AD care, including a deeper understanding of care choices under cognitive constraints, how supply side incentives react to these constraints, the role of regulation, payment models, and alternative contract structures in this environment, the impact of future enhanced diagnostic testing on the functioning of the long-term care insurance market, and the role of informal care in care and insurance decisions.

Beyond the studies discussed above, broader literatures on care delivery and long-term care challenges may serve as useful resources for readers interested in further research on these topics. For understanding health care choices under cognitive constraints, Keane and Thorp (2016) review the literature on health care decisions under complex choice environments, and Ericson and Sydnor (2017) review theory and evidence on how consumer constraints such as confusion (which may be a relevant friction for individuals suffering from AD) impact health insurance choice and interact with market forces such as adverse selection. On the supply side, Gaynor, Ho, and Town (2015) provide an overview of the industrial organization of health care markets and provider incentives that serves as a useful building block for the study of supply side responses to consumer constraints. For further reading on long-term care issues more generally, Norton (2016) reviews theory and evidence on the market for long-term care, and Brown and Finkelstein (2011) outline the broader challenges presented in the long-term care insurance market.

3 Labor supply and Financial Decision-Making

The risk of developing AD can affect many life-cycle decisions beyond the health care and insurance decisions discussed above, including labor supply choices, savings, and investment decisions. This section discusses these topics and the role of financial literacy and financial mistakes for cognitively compromised individuals.

3.1 Labor supply

An individual who develops AD prior to his or her planned age of retirement may need to exit the labor force, reduce hours, or switch to a different job to accommodate the AD-related decline in cognitive, behavioral, and social skills. Thus, AD poses a risk to labor earnings.

The risk of developing AD or MCI at an age when many people are still working appears to be low, although obtaining precise age-specific prevalence rates is difficult due to the limited number of studies focusing on younger age groups. Using an expert elicitation approach, Ferri et al. (2005) report a mean AD prevalence rate of 0.9 percent at ages 60-64 and 1.5 percent at ages 65-69 for Western European countries. Meta-analyses suggest that MCI prevalence rates in developed countries may be on the order of 3 percent at ages 60 to 64 and 6 percent at ages 65 to 69 (Ward et al., 2012; Roberts et al., 2013). The magnitude of the (maximum) earnings loss experienced by an affected individual will be determined by the length of time between AD or MCI onset and the intended retirement age.

Economists could estimate how AD onset affects work and retirement trajectories and estimate lost earnings (Moschetti et al., 2015), which are part of the societal cost of AD. Economists are also well-positioned to explore how the Americans with Disabilities Act (ADA), workplace policies, and access to Social Security Disability Insurance benefits help workers cope with the shock of an AD diagnosis, building on general research on these topics in the past (Acemoglu and Angrist, 2001; Hill et al., 2016). Recent work estimating work capacity by comparing individuals' self-reported functional abilities to the functional requirements of occupations (Garcia et al., 2019) could be adapted to assess the work capacity of those with AD or MCI.

As discussed in section 2.3, the onset of AD can also affect the labor supply of informal caregivers, who are typically spouses or adult children of the affected individual. Caregiving can affect labor supply at both the intensive and extensive margins: caregivers experience not only a reduction in work hours due to the time spent caregiving (the intensive margin), but they may leave the workforce entirely or choose a worse paying (or otherwise less satisfying) job to achieve more flexibility or proximity to caregiving obligations (the extensive margin). Van Houtven, Coe, and Skira (2013) finds some evidence of both margins of labor supply adjustment in response to caregiving demands, while Loken, Lundberg, and Riise (2017) only find intensive margin responses. There may also be dynamic effects of caregiving on downstream labor outcomes if there is human capital depreciation or labor market frictions in finding a new job. Using a model with these features, Skira (2015) estimates welfare costs of caregiving that are seven times the size of foregone wages. Furthermore, labor market protections for caregiving, such as paid family leave or the Family Medical Leave Act, reduce the use of nursing homes and provide savings on government expenditures for long-term care (Skira, 2015; Barczyk and Kredler, 2018; Aurora and Wolf, 2018). These studies of caregiver labor supply, however, are not specific to AD care and more research is needed to understand how AD in particular--which may involve more inflexible, around the clock care--affects the labor supply of informal caregivers.

Future work in this area could make use of variation in the timing of AD onset to estimate a causal effect of AD on own or caregiver labor supply, following the example of Fadlon and Nielson (2015). To explore whether government policies mitigate labor supply responses to AD, a valid source of variation in benefits would need to be identified, which likely presents a more difficult challenge.

3.2 Financial Decision-Making

3.2.1 Saving and Dissaving

How much should households save for retirement, and how should they spend down their assets during retirement? The risk of AD may affect these decisions. We briefly review the relevant economic theory before turning to the implications of AD.

In the standard life-cycle model of consumption and saving, forward-looking individuals who seek to maximize lifetime utility accumulate wealth during their working years and decumulate assets during retirement in order to equate the marginal utility of consumption over time. However, a large literature has identified numerous empirical phenomena that are not easily explained in the context of the simple model. These include low levels of retirement wealth for the typical household, heterogeneity in retirement wealth among similar households, an observed drop in consumption at retirement, and low rates of wealth decumulation in retirement (Browning and Crossley, 2001). These revelations have spurred the development of more complex life-cycle models that incorporate elements such as uncertainty in longevity, earnings, and medical expenses, capital and insurance market imperfections, bequest motives, and access to social insurance programs (Hubbard et al., 1994, 1995; Dynan et al., 2002) in order to help explain these phenomena.

The behavioral economics literature offers an alternative explanation for these outcomes, stressing the potential for "bounded rationality" and "bounded willpower" to affect decisions (Mullainathan and Thaler, 2001). Factors such as overconfidence, loss aversion, and mental accounting can lead individuals to make choices that are inconsistent with the standard model, while self-control problems can limit individuals' ability to achieve their desired outcome. Consistent with this, numerous studies find that individuals are strongly influenced by defaults when making decisions about their employer-provided pension plan (Beshears et al., 2009). This literature also encompasses new savings models that incorporate features like time-inconsistent preferences (e.g., Laibson, 1997).

The role of health care expenditure risk in saving and dissaving decisions is of particular relevance in the context of AD. Medical expenditures of the elderly are substantial and rise with age. DeNardi et al. (2016) report that average annual medical expenditures rise from about $7,000 at age 65 to over $25,000 at age 90 and above. Expenditures are highly skewed, with the top 5 percent of spenders responsible for over one-third of total spending and average annual spending of nearly $100,000 within that group. Long-term care, which features prominently in the treatment of those with AD, accounts for one-fifth of total health care spending among those ages 65 and above, as well as most of the growth in spending with age. Long-term care costs are financed primarily by Medicaid (30%), Medicare (24%), and out-of-pocket spending (28%). Medicare covers short stays (up to 100 days of skilled nursing care per illness), while Medicaid coverage is limited to those with low income and assets.

Research using augmented life-cycle models confirms the importance of medical expenditure risk in saving decisions. Hubbard, Skinner, and Zeldes (1994, 1995) find that incorporating uncertainty in medical expenditures, longevity, and earnings helps to explain the saving

behavior of individuals who accumulate significant assets during their lifetime as well as aggregate asset accumulation. They also show that means-testing within social insurance programs helps to explain the low asset accumulation of a significant fraction of the population. Based on simulations of a 55-period life-cycle model, Kotlikoff (1989) estimates that adding uncertain medical expenses raises aggregate savings by one-third, while incorporating a means-tested Medicaid program reduces savings by three-quarters.

Medical expenditure risk may also affect the rate of decumulation of assets during retirement. Poterba, Venti, and Wise (2011) report that in 2008, most households with a head between ages 65 and 69 had financial assets (87%), home equity (80%), and personal retirement accounts (52%), with median non-annuitized wealth of $222,000 and median financial assets (including retirement accounts) of $52,000. They find that households in the top half of the wealth distribution largely do not spend down their financial assets in the early decades of retirement. Venti and Wise (2004) report that households tend to preserve home equity during retirement until they experience a shock such as the death of a spouse or the entry of either spouse into a nursing home. These patterns of behavior are consistent with households holding wealth during retirement to insure against medical expenditure risk, though alternative hypotheses – that wealth-holding primarily reflects concerns about longevity risk, bequest motives, or bounded rationality – are also possible.

Studies based on life-cycle models offer support for the former hypothesis. DeNardi et al. (2010) estimate that assets would decline much more rapidly with age in the absence of out-of-pocket medical expenditure risk. The effect is primarily due to the risk of living longer and incurring average age-specific medical expenditures, rather than to the risk arising from variation in age-specific expenditures, and is largest for high-income individuals, for whom the consumption floor provided by means-tested programs is less relevant. Palumbo (1999) also finds that uncertain medical expenditures help to explain slow draw down of asset wealth. Ameriks et al. (2011) introduce a “Medicaid aversion” parameter in a model of post-retirement saving and find that this phenomenon helps to explain low rates of decumulation among middle-class retirees. Ameriks et al. (2020) add health state-dependent utility to the model and conclude that this feature contributes to greater asset accumulation pre-retirement and can also motivate continued asset accumulation during retirement.

In the future, researchers who estimate life-cycle models of saving could incorporate AD into their models by distinguishing between dementia-related and non-dementia-related medical expenditure risks and allowing Medicaid aversion or utility to vary across these states of the world, potentially leading to a better understanding of saving decisions. Analysts could also explore the empirical effect of cognitive decline or AD risk on wealth decumulation, as distinct from portfolio allocation in retirement, the subject we turn to next.

3.2.2 Portfolio Allocation

Older households face a number of risks that may influence portfolio allocation decisions, including longevity risk, investment risk, inflation risk, and expenditure risk.

Annuities are a potentially attractive investment because they allow insured individuals to convert a lump sum of wealth into a guaranteed stream of income that lasts as long as they live, providing protection against longevity risk. Annuities also offer a higher rate of return than traditional investments because payments go only to surviving annuitants and the initial investment is not returned upon the buyer's death (the "mortality credit"; Brown, 2009). Given these advantages, the small size of the private annuity market has been seen as a puzzle (Benartzi et al., 2011); indeed, Davidoff et al. (2005) show that individuals should annuitize all wealth in the absence of a bequest motive. Among the reasons advanced for this puzzle are bequest motives, the degree of annuitization provided by Social Security and defined benefit pensions (Dushi and Webb, 2004), adverse selection (Finkelstein and Poterba, 2004), and behavioral biases (Brown et al, 2008, 2011).

Medical expenditure risk – such as the risk posed by AD – may also help to explain low annuity demand. Sinclair and Smetters (2004) model annuity demand using a dynamic programming model and find that full annuitization is not optimal given uninsured medical expenditure risk. Laitner et al. (2018) explore how the availability of Medicaid changes the demand for annuities using a tractable model of post-retirement saving. They find heterogeneous effects by wealth – for median-wealth households, Medicaid reduces optimal annuitization because households are unsatisfied with the care provided by Medicaid and need to hold liquid assets to insure against out-of-pocket medical spending, while optimal annuitization is high among low-wealth households (who are satisfied with Medicaid) and high-wealth households (who are unlikely to use Medicaid even at high levels of annuitization). An annuity product that provides protection both against longevity risk and the risk of long-term care expenditures may reduce the cost of these products and make them available to more buyers (Murtaugh et al., 2001).

Portfolio choice involves deciding not only what fraction of retirement wealth to annuitize but also how to allocate non-annuitized assets across asset classes that vary in risk, return, and liquidity. A long line of research beginning with Merton (1969) and Samuelson (1969) examines optimal portfolio composition. Although a classic result from this literature (see Kaschützke and Mauer, 2016, for a review) is that individuals should invest a constant fraction of their wealth in the risky asset regardless of age, empirical evidence suggests that retired individuals shift their portfolio towards less risky assets as they age (Ameriks and Zeldes, 2004; Guiso et al., 2002).

Health status and health risk may help to explain risk-taking behavior in the post-retirement portfolio. Rosen and Wu (2004) find that households in poor health hold less of their wealth in risky assets and Edwards (2008) reports that older individuals decrease financial risk as they age as a hedge against rising health risk, although Fan and Zhao (2009) and Smith and Love (2010) argue that these findings may be driven by unobserved heterogeneity. Coile and Milligan (2009) potentially surmount this concern by focusing on health shocks and find that shocks are associated with a shift out of housing wealth and into low-risk assets such as bank accounts and CDs. Yogo (2016) estimates a life-cycle model with stochastic health depreciation and establishes that it can explain why the share of the portfolio held in stocks is low and positively related to health while the share held in housing is negatively related to health and falling with age. Goldman and Maestas (2013) report that households who face reduced medical

expenditure risk because they hold a Medigap or other supplemental health insurance policy are more likely to hold risky assets.

A number of studies have established a strong relationship between cognition and portfolio choice, although whether this represents a causal effect is not yet well understood. McArdle et al. (2009) provide a descriptive analysis of the association between cognition and wealth holdings in the HRS and Kezdi and Willis (2003) report higher levels of stockholding among HRS respondents who provide more precise answers to subjective probability questions (e.g., fewer focal points). Christelis et al. (2010) find that higher cognitive abilities are more strongly associated with stock than bond ownership in European SHARE data. Grinblatt et al. (2011) show that higher IQ individuals in Finland are more likely to hold stocks, conditional on income and wealth and controlling for family fixed effects. However, Pak and Babiarz (2018) conclude that there is no causal effect of cognition on portfolio choice based on an analysis that exploits variation in cognition driven by seasonal affective disorder. In a rare example of AD-specific research on this topic, Shin et al. (2019) find that AD risk is associated with increased holding of "hands off" assets like CDs.

A useful next step for this literature would be to examine how portfolio allocation is affected by cognitive decline. By exploiting plausibly exogenous variation in the onset or timing of MCI or AD, researchers could potentially gain a better understanding of the causal relationship between cognition and asset holdings. Analysts who focus on changes in cognition over time should be alert to the possibility of measurement error resulting from taking the difference of two survey observations (Bound et al. 2001).

3.2.3 Financial literacy and financial mistakes

Financial literacy may enhance individuals' ability to make better financial decisions (Lusardi and Mitchell, 2014). Financial literacy peaks in midlife and declines at older ages (Finke et al., 2017), an effect that may primarily reflect the effect of declining cognitive abilities (Lusardi et al., 2014). While financial education can improve financial literacy and affect financial behaviors (Kaiser et al., 2020), this treatment may be more effective for younger individuals who lack crystallized intelligence than for older individuals experiencing declining fluid intelligence.

A nascent literature explores age patterns in financial decision-making and the effects of AD on these decisions. Consistent with the age patterns in financial literacy, financial mistakes like excess interest rate and fee payments rise with age (Agarwal et al., 2009). Financial capacity such as checkbook management declines as AD progresses (Triebal et al., 2009; Sudo and Laks, 2017). Medicare beneficiaries with AD are more likely to select a suboptimal prescription drug plan (Keane et al., 2019), an effect that arises even before AD diagnosis (Bishop et al., 2018).

Becoming a victim of financial fraud may be a particularly costly financial mistake. Over one-third of older individuals report attempted or successful fraud over the past five years, with attempted or actual unauthorized use of an account accounting for most of the incidents (DeLiema et al., 2018). In 2017, U.S. financial institutions reported 63,500 cases of elder financial exploitation to the government, representing $1.7 billion in suspicious activity but only

a “tiny fraction of actual incidents of elder exploitation” (CFPB, 2019). Several studies suggest that weak cognitive skills put older individuals at greater risk of financial fraud (Judges et al., 2017; Gamble et al., 2014; Spreng et al. 2016).

Future research on the effect of AD on financial decision-making could have important policy implications. If individuals begin to make financial mistakes during the asymptomatic period prior to an AD diagnosis, routine financial monitoring could be used to help detect AD at an early stage (Nicholas et al., in progress). If financial mistakes in the early stages of AD are sufficiently common and costly, this could suggest a need for more early screening for AD (e.g., via imaging) even in the absence of an effective medical treatment for AD.

Economists could be helpful in designing and assessing the impact of policies to protect older individuals with diminished cognitive capacity from financial mistakes or exploitation. Advances in technology could allow for earlier detection of fraud. Potential regulatory remedies include financial “driver’s licenses,” greater regulation of financial products, and stronger fiduciary requirements (Agarwal et al., 2009). A variety of contractual or legal models could be used, including long-term wealth management contracts, financial advanced directives, and Social Security’s Representative Payee Program, which is currently used by 9% of beneficiaries with AD and 2% with MCI (Belbase and Sanzenbacher, 2016). Finally, economists could develop new models of financial decision-making that reflect the reality that many older people receive assistance from adult children with these tasks.

3.3 Further reading and future research on labor supply and financial decision-making

This section has discussed how AD poses a risk to the labor supply of those afflicted by AD and their caregivers, how the medical expenditure risk associated with AD may affect saving and portfolio allocation decisions, and how cognitive impairment may impact financial decision-making. Promising avenues for future empirical research include estimating the effect of AD on own or caregiver labor supply and estimating the effect of cognitive decline on asset decumulation, portfolio allocation, and financial mistakes. Another direction for future work is the expansion of life-cycle models of saving or models of annuity demand to allow for multiple types of expenditure risk (AD- and non-AD-related), which may have different effects on utility.

For researchers interested in pursuing AD-related research in these areas, the following may be useful resources. Attanasio and Weber (2010) offers an introduction to the life cycle model of consumption and saving, while Kaschutzke and Maurer (2016) provides a useful discussion of asset decumulation and portfolio choice during retirement. Keane and Thorp (2016) highlight the many inconsistencies between the predictions of rational choice models and consumer behavior in the areas of retirement saving and health insurance purchase; their extensions to rational models to account for irrational behavior and “confusion” might be of use in modeling cognitive decline. Gomes et al. (2020) provides a very recent and wide-ranging review of household finance that includes a discussion of financial literacy and cognitive abilities.

4 Current and future therapeutics for AD

A transformational medicine for Alzheimer's Disease would be one way to get around many of these seemingly intractable challenges. Such a medicine might delay the onset of the disease, and ideally reverse its course. We are quite far from this goal and we review the opportunities to increase innovation here.

There are currently four FDA-approved treatments for AD. Each works to prevent the breakdown of neurotransmitters -- the signaling devices neurons release to communicate with each other-- which die as AD progresses, essentially correcting some of the damage done by the disease. Unfortunately, all have only a small effect on cognition. They also have no effect on the progression of the disease as they do not target the underlying causes of AD.

Pharmaceutical companies, biotechnology companies, and academic centers brought 413 AD drugs to trial between 2002 and 2012 (Cummings et al, 2014), with more introduced in recent years. Despite this investment, no new AD drug has been approved since 2003 and the failure rate for clinical trials exceeds 99%. Drug developers in Alzheimer's face several unique hurdles. The average cost of drug development is estimated to be $5.6 billion (an estimate that requires many assumptions), largely due to high preclinical and phase 3 trial costs (Cummings et al., 2018). This number greatly exceeds R&D costs for other drugs, where the median cost of development is estimated to be $2.5 billion (DiMasi et al., 2016). One reason for the high cost is the long trial time needed to see results – the average length of Alzheimer's drug development is 13 years. Patient recruitment into trials also poses an obstacle because gerontologists may not be close to trials in the same way that oncologists are.

Despite the challenges, many biotechnology and pharmaceutical companies persevere. Were a drug to gain FDA approval, potential sales would be large-- even for a treatment with a small effect size -- given the large market, lack of competitors, and relatively poor prognosis. In 2019, there were 132 potential therapeutics in the development pipeline (Cummings et al., 2019).

4.1 Future therapeutics

Drugs in development to treat AD fall broadly into two categories: symptomatic and disease-modifying. Symptomatic drugs aim to reduce suffering from AD. All existing treatments are in this category, as are one-quarter of the drugs in the pipeline in 2019. A majority of the drugs seek to enhance cognitive capacity, while the rest aim to alleviate psychiatric and behavioral symptoms (Cummings et al., 2019). Most of these drugs affect neurotransmitters, like existing treatments. These clinical trials receive less attention, as they often investigate off-patent drugs and are run by academic medical centers. Benefits to this approach include the known safety profiles, shorter clinical trial times, and low cost of many of these drugs.

Disease-modifying drugs aim to slow or stop the progression of disease. They generally target the underlying causes of disease, such as amyloid or tau. In 2019, there were 96 trials of disease-modifying medications across all stages of development (Cummings et al., 2019).

Amyloid was the first therapeutic approach to be explored, and remains the most common target of new therapeutics, with 38 trials targeting it in 2019 (Cummings et al., 2019). There are three drug development strategies based on the amyloid hypothesis.

Most amyloid-based therapeutics are immunotherapies, which aim to activate the immune system to clear amyloid from the brain. Immunotherapy medications may be delivered via vaccination or as an infusion of laboratory-formed immune components (i.e., antibodies). While multiple immunotherapies targeting amyloid have failed in clinical trials, more are under development.[25] BACE1 and Secretase inhibitors both aim to prevent the breakdown of APP and thus halt the formation of amyloid. Several BACE1 inhibitors have entered clinical trials but have not been successful.[26] Multiple recent trials have been suspended due to worsening cognitive function and weight loss, and there is concern that these side effects may exist across this entire class of drugs. While Secretase inhibitors have thus far failed due to lack of efficacy or side effects, there is hope that a drug that more specifically targets the secretase complex could be successful. The third amyloid-based strategy is based on the hypothesis that clinical trials have occurred too late in the disease progression. New trials have been focusing on individuals with preclinical AD and failed immunotherapies, including solanezumab and crenezumab, have been revived to try on individuals with high-risk genetics conditions before they develop any symptoms of the disease.

Another theory is that tau, not amyloid, is the proper target for drug developers. As with amyloid, most tau-directed therapeutics are immunotherapies, aimed at helping the immune system clear tau protein from the brain. While tau has not gained as much traction as amyloid in treatment of AD, it still accounted for 17 clinical trials in 2019 and several of these drugs have cleared safety-trials (Cummings et al., 2019).

Scientists are also exploring alternate therapeutic approaches. Inflammatory modulators up- or down-regulate the immune system more generally. As it is unknown whether the increased immune cells researchers see in AD are protective or harmful, both anti-inflammatory and pro-inflammatory strategies are being tested.[27] Gene therapy replaces genes implicated in AD. There appears to be some success in drugs targeting APOE4 in the lab, and early stage trials of high-risk individuals with two APOE4 genes are ongoing (Weill Medical College of Cornell

[25] Notable failures include Janssen and Pfizer's bapinezumab in 2012, Eli Lilly's solanezumab in 2012 and 2016, and Genentech's crenezumab in 2019. The most anticipated drug in development is Biogen's aducanimab. This drug originally began efficacy trials in 2015, which were terminated by Biogen in March 2019 when they failed to meet their goals. However, in October 2019, Biogen announced that patients who had received high doses of the drug appeared to have been responding. The company then re-initiated a follow up trial and claimed it would file for FDA approval in early 2020, only to push back its filing date for unknown reasons (George, 2019). This drug has in many ways re-energized the field and instilled ongoing hope in the potential of amyloid-directed immunotherapy.

[26] Eli Lilly worked to develop two of these drugs, but ultimately halted the pursuit when they were found to be toxic to the liver and worsened cognitive performance (Lahiri et al., 2014).

[27] Anti-inflammatory approaches have thus far failed to demonstrate efficacy. Trials of NSAIDs (i.e., ibuprofen), aspirin, and the immunosuppressant prednisone have all failed to reduce cognitive decline in mild Alzheimer's disease. Stakeholders have not lost hope in this approach: Intelgenx Corp. is running an Alzheimer's trial of anti-inflammatory Montelukast (trade name Singulair), that has been used to treat allergies and asthma since 1998 (Hajjar, 2019). Genzyme is taking a different approach by trialing sargramostim, an immune system stimulator that has been used to boost the immune system of patients with leukemia (Clinicaltrials.gov, 2017)

University, 2019). Editing of BACE-1 or other genes that relate to the formation of amyloid plaques have been suggested but not yet moved to human trials. Regenerative biology and stem cell approaches aim to increase the number of neurons in the brain, reversing some of the damage caused by AD. While success has been demonstrated in laboratory models, they have thus far gained less traction than the amyloid and tau strategies, especially in the US. Finally, there are approaches that evade the above categories. Blood from young donors has been prescribed off-label ever since studies found it improved age-related cognitive impairment in mice. While the FDA released a statement recommending against these blood transfusions, several trials investigating this solution are underway. In addition, regulators in China granted conditional approval of GV-971, a mixture of carbohydrates extracted from kelp, when a Chinese trial of 818 participants with mild to moderate Alzheimer's disease showed a trend toward increased cognitive functioning (Trial Site News, 2020).

Which of these therapeutic strategies will ultimately prevail--if any--is unknown. Multiple targets may be successful, or alternative ones may emerge. Alternatively, multiple therapeutic approaches may need to be combined. For example, it could be that tau and amyloid therapies only work when used in conjunction with one another.

4.2 Behavioral interventions

Behavioral interventions to prevent AD or slow disease progression could be very cost-effective, given the high costs of AD and potentially low cost of behavioral modifications. Unfortunately, the evidence base establishing the efficacy of interventions is still lacking, particularly evidence from randomized controlled trials. Two recent reports conclude that the current evidence does not justify large-scale public health investments aimed at preventing dementia, while noting that there is encouraging if inconclusive evidence that cognitive training, blood pressure management, and physical activity may be protective against disease (AHRQ, 2017; NAS, 2017).

4.3 Incentives for new therapeutics

There are three open questions in the economics of pharmaceutical innovation on whether there are sufficient economic incentives to bring drugs for AD to market. The first relates to the economics of "pull incentives". Pull incentives work by increasing the economic viability of R&D: expected profits ought to be higher than a project's cost-of-capital (the opportunity cost of capital), and expected profits depend on market size, potential prices, net manufacturing costs and the probability of failure. Policies that increase expected profits will increase innovative activity in an area-- for example, the Orphan Drug Act increased economic viability by lowering R&D costs (through R&D tax-credits) and increasing potential prices by protecting manufacturers from generic competition for a longer period of time (Bagley, Chandra, Garthwaite and Stern, 2018). Interestingly, there are very few pull incentives for discovering non-therapeutic ways to prevent AD (for example, better sleep) for it will be difficult to patent such ideas. This leads to an underinvestment in such discovery and a greater reliance on push-incentives for prevention.

Because the marginal costs of manufacturing drugs is relatively small compared to the large fixed costs of research and development, a variety of incentives, such as patents and exclusivity periods, are granted by governments to permit above-marginal cost pricing in order to help to induce innovation. Patents prevent competitors from using, making, or selling their intellectual property for a limited period of time (usually 20 years from the date the patent was filed). In exchange for these rights the patent holder discloses the existence of their innovation to the public. The key challenge here is whether the effective patent length is long enough to make the expected value of an R&D investment profitable. Ultimately, the difference in time between patent filing and bringing a product to market means that pharmaceutical companies receive much shorter periods of patent exclusivity than other industries; the longer the clinical trials take, the shorter the patent exclusivity life is. For example, evidence from Budish, Roain, and William (2015) shows that drug companies have more incentives to develop drugs to treat late stage cancers compared to early stage ones, because early stage cancers require longer clinical trials to confirm that they are effective in extending patient lives. It remains an open question whether transformative treatments for Alzheimer's require more generous protections to come to market as a result of the sometimes slow progression of the disease. Venture capitalists play a large role in this enterprise, but not much is known about the quality of their decision-making even though their decisions profoundly shape the medicines that come to market (Lerner and Nanda, 2020).

The second question relates to follow-on innovation in AD. Patents can lead to follow-on innovation by other firms because the invention is declared to the public and permits learning, but not copying. This generates incentives for follow-on innovation by competitors once the patent expires as well as inventions around the patent, both of which can increase social welfare. On the other hand, too expansive or too long of a patent could induce more innovation initially but discourage follow-on innovation and lead to decreased access to life saving treatments for patients. Too generous a patent could also reward infra-marginal medicines more than they require to be launched. Because AD treatment will likely involve multiple drugs for multiple targets, the tradeoffs surrounding inframarginal medicines and follow-on innovation may be particularly salient for R&D for AD. Frameworks used by economists, as summarized by Lakdawalla (2018), are central for making these determinations.

Finally, medicines build on "push incentives" such as public financing of basic science. Basic science research is an area ripe with market failure as it is hard to patent a basic science discovery and thus private firms will not pursue it. Discovering new and novel forms of non-therapeutic prevention (say through lifestyle changes), where it is hard to capture the value of the discovery will discourage innovation by firms that can be rectified by push-funding. There is evidence that public funding leads to more commercializable insights but is unclear what the optimal level of such funding is (Azoulay et al., 2017, 2019). A new area for research for economists is to measure the performance of the review process for basic science funding itself, for there is a tradeoff between expert reviewers and unbiased reviewers, with experts more likely to identify more successful applications but potentially less likely to bet on diverse (or high risk, high reward) ideas (Li, 2017; Begley, 2019).

Increasing amounts of public funding have been devoted to AD in recent years. In 2019, the National Institute of Health spent $2.2 billion on Alzheimer's research, considerably more than they spent on heart disease ($444 million) or stroke ($350 million); funding in 2020 is $2.8 billion. Part of these funds supports Alzheimer's Disease Research Centers at major medical institutions across the US. Despite this commitment to research, little progress has been made in developing therapeutics that extend life or slow cognitive decline. The cause is twofold: 1) ongoing ambiguity about the cause of AD, 2) lack of clear biological markers to inform physicians and researchers. Both of these hurdles are basic-science hurdles that are unlikely to be solved by private companies.

The key point for inducing new treatments for AD is that AD is a complicated disease so it is not likely there will be a single treatment that will change the course of this disease. As with oncology treatments, society will have to ensure that a variety of treatments come to market, with different treatments for different targets. These combination therapies also mean that medicines have complementary effects on each other whereby the value of one medicine may be increased by the presence of another. This feature may increase incentives for firms to partner to capture the value of their combination therapies, while also increasing the likelihood of static deadweight loss from less competition. Understanding the tradeoffs between long-run social welfare and short run deadweight loss is an area where economists have a unique comparative advantage (Kakani, Chernew and Chandra, 2020). Similarly, pricing schemes such as Ramsey pricing may be of particular interest in this area, pointing to the importance of economic insights from industrial organization, entrepreneurial finance, and the economics of innovation.

4.4 Health

Other factors beyond drug therapies may impact the development, progression, and health effects of AD, and economists have a useful toolkit to answer questions related to risk factors, genoeconomics, and the burden of disease.

Economists are well-positioned to contribute to the literature on the determinants of AD. An important set of contributions are likely to come from identifying plausibly exogenous sources of variation in order to generate causal estimates of the effect of AD risk factors on disease onset. Economists could use standard multiple regression analysis to examine the relationship between AD risk factors and disease onset. However, this type of an analysis would not be clearly distinct from the work of epidemiologists, who seek to understand patterns and causes of disease and other health-related states and events. It is also harder to establish causality in such analysis, due to the difficulty of controlling for all potentially confounding factors.

Despite these challenges, the economic literature on the long-run consequences of infant health provides an excellent model to understand whether epidemiological risk-factors are risk-factors or represent causal effects. If the latter, then one can think about policy levers to manipulate them. If the former, then they are only useful for predicting the future risk of AD. Researchers have used sibling differences (Black et al., 2007; Johnson and Schoeni, 2011) and events such as the 1918 influenza epidemic (Almond, 2006) or Chinese famine of 1959-1961

(Chen and Zhou, 2007) to generate exogenous variation in health at birth. Using quasi-experimental methods and longitudinal or large administrative data sets to exploit this variation, these studies have established that infant health has substantial long-run effects on adult health and economic outcomes (Currie, 2011). Bishop et al. (2018) illustrate how this approach could be used for AD-related work in their study of air pollution and dementia.

Relatedly, the emerging field of genoeconomics may offer some promise for AD-related research. As defined by Benjamin et al. (2007), genoeconomics is the field at the intersection of molecular genetics and economics. As discussed in Section 1, the scientific literature has identified several genes that are indicated in the development of AD, while concluding that AD is caused by a specific genetic mutation in fewer than one percent of cases. Polygenic scores (PGS) are used to predict an individual's probability of developing a complex disease in which multiple genes are indicated, such as AD. Scores are calculated by using genome-wide association studies to identify which genetic variations are found more frequently among those with a particular disease, then combining this with the individual's own genetic information to calculate an individual risk score.

The availability of datasets that provide PGS and economic data may facilitate genoeconomic research. The Health and Retirement Study (HRS) includes PGS data for 38 outcomes, including AD and other diseases, health outcomes, and economic outcomes. Benjamin et al. (2012) identify "four ways that the intersection of molecular genetics and economics promises ultimately to contribute to economics: (a) identifying and measuring latent traits, (b) identifying biological mechanisms that influence economic behavior, (c) providing exogenous proxies for preferences and abilities that may be used as control variables or—more problematically—as instrumental variables, and (d) predicting the differential effects of policies across individuals with different genetic constitutions."

The existing genoeconomic literature is fairly small, and it remains to be seen which areas hold the most promise for AD research. Replication is a key problem in these studies (Beauchamp et al., 2011). Shin et al. (2019) find a positive correlation between the PGS for AD and the share of wealth held in "hands off" assets like certificates of deposit, an example identifying biological mechanisms that influence economic behavior. Linnér and Koellinger (2020) find that the PGS for AD, parental lifespan, and smoking are associated with survival and may be better predictors than some conventional actuarial risk factors; they also find that greater genetic mortality risk is associated with a reduced probability of long-term care purchase. Future research could explore whether the genetic risk of AD is related to latent parameters such as time preference or risk aversion. The PGS for AD could be used as an instrument for cognition, though Benjamin et al. (2012) caution about the possible violation of the exclusion restriction, since genes often have multiple effects. Finally, it could be useful to explore whether policies (for example, to aid with financial decision-making) have differential effects by AD risk.

Economists can also help estimate the effect of AD on health to help quantify the burden of disease and the social value from reducing it. Health capital is the present discounted value of lifetime health, where health at each future age is the probability of being alive at that age multiplied by the average quality of life among those alive at that age (or quality weight,

ranging from 0 to 1) multiplied by the value of a year of life in perfect health (Grossman, 1972). Quality weights may be estimated from health survey data by regressing self-reported health status on a set of disease indicators to obtain the estimated effect of each condition on health, then multiplying these coefficients by disease prevalence rates by age to obtain an age-specific quality weight (Cutler and Richardson, 1999). Economists have estimated the value of a year of life by estimating the wage premium for risky jobs and or consumers' willingness to pay for safety improvements as well as by contingent valuation (Viscusi, 1993). This model can be used to quantify the total health cost of AD by calculating health capital using quality weights that include versus exclude these risks. The model can also illustrate the value of treatments or lifestyle changes that would delay disease onset or reduce its impact on quality of life.

Disability-free life expectancy is another health measure used by economists that could yield insights as to the impact of AD on health. It is calculated like standard life expectancy, except that the probability of being alive at future ages is multiplied by the age-specific probability of being non-disabled. Defining disability as having difficulty in performing activities of daily living or instrumental activities of daily living, Chernew et al. (2017) estimate that changes in AD and Parkinson's disease prevalence between the early 1990s and late 2000s led to a 0.13-year (0.10-year) decrease in life expectancy (disease-free life expectancy), mostly due to the change in AD. The societal willingness to pay (WTP) to avoid these declines may be large and may induce new innovations in therapeutics and care-delivery if there is a way for manufacturers and providers to capture some of this value; conversely, there may be market failure if WTP exists but these entities are not able to capture it because of insufficiently built markets for long term care. Economists likely have a comparative advantage in thinking through the limitations of these measures, even if their advantage in estimating them is less certain.

4.5 Further reading and future research on innovation for Alzheimer's Disease

For further reading on the topic of innovation, a starting point is Williams (2018), which provides an overview of the patent system through the lens of an economist and includes frameworks for thinking about the incentives underlying the patent system. Lakdawalla (2008) provides an overview of the pharmaceutical industry, the positive and normative implications for the R&D, pricing, and strategic decisions of pharmaceutical firms, including persistent gaps in this literature. In the context of AD--where there is some consensus among scientists that more basic science investments are needed--it is important to better understand the production function that converts basic science research into patents, and subsequently, into medicines. These push incentives are not well understood, with Azoulay et al (2019) pioneering the way to think about them. Moreover, there is a tendency to conflate 'basic science' (which is fundamental science that is detached from a particular disease or therapy) with disease-specific efforts such as the National Cancer Institute. Alzheimer's research received $350 million in funding from the US Congress in 2016 and that went up to almost $2.0 billion in 2020, which would serve to improve the scientific basis for new therapeutics. However, it is still not known whether this type of disease-specific funding unlocks better insights than investments in more fundamental biological processes of aging, or regenerative biology.

5 Accelerating research on economics of AD

Data resources will be key to accelerate the research agenda of the economics of Alzheimer's. When considering possible datasets for use in AD research, the researcher faces a familiar tradeoff (Coile and Maestas, 2018) between the richness of the data and sample size. The Health and Retirement Study (HRS), a longitudinal study of the US population age 50 and above that has spawned "sister studies" in many other countries, provides state of the art measures of memory and cognition (Ofstedal, 2005). In addition to the cognitive data collected at every wave, the Aging, Demographics, and Memory Study (ADAMS) and Harmonized Cognition Assessment Protocol (HCAP) provide data on dementia for a subset of participants. The HRS includes PGS and biomarker data and linkages to several administrative data sets. The richness of these data allows the researcher to examine a wide variety of AD-related questions. Yet the sample size of about 40,000 participants over the HRS' first 25 years may be limiting for the study of a disease that affects 1 in 15 individuals in their 70s. This concern is heightened if the researcher wishes to explore racial disparities.

Administrative datasets such as claims data from Medicare or private insurers provide large (or population) sample sizes and can be used to identify AD based on clinical data (Taylor et al., 2002) and to track health care utilization by AD patients. However, they lack biomarkers and genetic information and data on other outcomes of interest or potential confounding factors, and thus are suitable for a narrower set of questions.

There are several options for researchers seeking to expand their data options. Some researchers have worked to establish new linkages -- for example, between Medicare claims and consumer credit data (Nicholas et al., in progress) or Medicare and Medicaid claims (Hackmann and Pohl, 2019), to name just a couple of examples.[28] Investments by the NIA and other funders into more data linkages of this sort -- for example, linking credit data to the HRS or earlier life course data to data on older adults -- could greatly enhance the scope of AD-related questions economists can tackle. A second option is to use data from countries that provide access to linked administrative data covering numerous domains (e.g., health care, tax, and public benefit records) for the entire population. For many questions, the country of analysis seems unlikely to affect research outcomes, although these data would not be suitable for certain topics, such as an analysis of racial disparities in the US. Since many AD patients reside in nursing homes, data on these facilities may be an underutilized resource for AD research.[29] Finally, specialized surveys might need to be developed to explore hard-to-study aspects of AD, like the experience of caregivers or the role of adult children in financial decision-making. Online surveys like the RAND American Life Panel offer the potential to collect

[28] The link between Medicare and Medicaid records is particularly fruitful for AD research and long-term care more generally, given that Medicaid is a major payer of care for AD. Many studies thus far cannot observe the Medicaid side of the payer market, resulting in a major gap in our knowledge of the payer side of AD care.

[29] For example, the Minimum Data Set (MDS) Nursing Home Assessment, Transformed Medicaid Statistical Information System (T-MSIS), and Outcome and Assessment Information Set (OASIS) for home care clinicians all offer promise, and might be matched with Medicare Provider Analysis and Review (MEDPAR) or CASPER data.

custom data rapidly and inexpensively and link it to previously-collected data, but sample sizes may not be adequate for all projects.

In addition to seeking out new data, researchers should not overlook areas where new(er) theory or empirical methods may be useful. The insights of behavioral economics, which have been so important in understanding savings behavior, could fruitfully be applied to many AD-related topics. Indeed, it would be useful for researchers to grapple with the question of whether decision-making under cognitive constraints can be more fruitfully modeled within the rational consumer framework, a behavioral framework, or whether neither is fully adequate. Genoeconomic research may help to explain AD-related behavior, particular as the science of AD advances. Machine learning offers both promise and pitfalls for economic research (Mullainathan and Spiess, 2017; Athey and Imbens, 2019), including on health care topics (Mullainathan and Obermeyer, 2019).

This essay reviews existing economic research that is relevant for understanding the challenges posed by AD and highlights areas where future research by economists could generate valuable insights, many of which could inform public policy. There is important work to be done in understanding the causal forces behind Alzheimer's Disease -- an enterprise that could be particularly fruitful for economists if the disease turns out to have a strong epigenetic basis that requires rigorous identification and quantification of these forces. The high fraction of nursing home patients with dementia combined with the expected rise in AD cases and poor financial protection against this risk brings new urgency to questions around the adequacy of savings and long-term care insurance. The presence of cognitively challenged consumers also opens up new areas of study at the intersection of law and economics for it is not clear if firms will exploit these individuals or whether competitive forces will temper the behavior of firms. At the same time, there is great need for innovation in prevention and treatment which requires an understanding of the different policy levers that can be deployed to hasten such innovation. The prospects for economists working in many different fields to contribute to our understanding of AD appear to us to be very bright.

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