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CASE STUDY

Transforming patient-centric early Alzheimer's disease care

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The approval of disease-modifying therapies for early, symptomatic Alzheimer's disease is raising new hope and expectations among Alzheimer's patients and their caregivers. Within the next five years we can expect the approval of additional drug therapies and of diagnostics that will not only expand options for treatment but create new capabilities for diagnosis. Capabilities are expanding to diagnosis both early, symptomatic Alzheimer's disease, and abnormal accumulation of amyloid proteins in the brains of asymptomatic patients, a condition that has been termed Pre-Clinical Alzheimer's disease. (See Appendix E)

The health care system is not prepared to serve all the patients who may be eligible for Alzheimer's disease modifying treatment. Even today, patients and caregivers experience limited access and long wait times to be seen by neurologists, geriatric psychiatrists and other specialists for confirmation of an Alzheimer's diagnosis. As these new diagnostics and treatments come to market and more patients become eligible for care, experts and stakeholder groups believe that it will be essential to expand the capabilities of primary care practitioners and non-specialists to diagnose and treat patients with Alzheimer's disease.

Currently, eighty percent or more of preliminary diagnoses of dementia, including Alzheimer's disease, are made by non-specialist physicians, typically primary care physicians.[i] A 2019 analysis of Medicare beneficiaries found that only slightly over a third (36 percent) of patients diagnosed preliminarily with dementia are seen by a specialist within five years.[ii] To accommodate increasing patient demand for active treatment of Alzheimer's disease, primary care physicians and their teams[1] would remain the first point of contact for patients and caregivers, and assume a greater role in assessing, confirming and treating Alzheimer's disease. The time and attention of neurologists, geriatric psychiatrists and other specialists would be reserved for those patients who are medically complex or whose test results may be positive but not entirely conclusive for AD (i.e. borderline cases) or for expert consultation, collaborating with primary care practitioners when needed.

At the same time, new therapies and diagnostics for Alzheimer's treatment are emerging at a time when primary care is under considerable stress, and fewer new physicians are entering the field. [iii] Older patients (i.e. the patients most likely to present with early Alzheimer's disease) frequently suffer from chronic conditions, mostly managed by primary care practitioners. Two thirds of Medicare beneficiaries are thought to suffer from two or more chronic conditions.) Patients with

1 Throughout this briefing, we recognize that primary care teams will likely play a role in AD care going forward. Primary care teams include a PCP, nurse, NPs, PAs, medical assistants and so on. Each member of the primary care team is important to the overall structure, and the success, of patient care for Alzheimer's Disease.

Alzheimer's disease are no exception. (See Appendix D.) Any effort to expand the capability of U.S. primary care to address Alzheimer's disease must come about in the context of stabilizing primary care overall.

To add more complexity, Alzheimer's disease carries a stigma with patients, caregivers, and clinicians alike, where there is little confidence that treatments will make a difference, and concerns that a diagnosis will evoke negative reactions that would impact the lives of patients and their families. In part as a reaction to these circumstances, PCP offices do not routinely conduct or document patient cognitive assessments. In many cases, patients are assessed for Alzheimer' disease and other dementias at a point when symptoms are manifest, and the likely effectiveness of disease modifying treatment for Alzheimer's is reduced or patients are no longer eligible for treatment.

To move beyond these challenges, we must address solutions at multiple levels across the U.S. healthcare systems. The goal of the elucidation phase of the NEWDIGS Alzheimer's Disease Case Study is to identify pathways that lead us from the status quo of today to a future in which patients in need, who are clinically eligible for Alzheimer's disease-modifying therapy, can make a fully informed decision and access therapy if they prefer.

To this end, the NEWDIGS case study is framed around a "future state" in which emerging innovations in therapeutics and diagnostics are fully available to primary care physicians within five years. In this future state:

- Multiple FDA-approved disease-modifying therapies are available, and in multiple forms of administration (by IV infusion and by subcutaneous injection).
- FDA approval of disease-modifying therapies is expanded to treatment of Stage One Alzheimer's disease, (a stage in which patients have detectable Alzheimer's pathology but no signs of symptoms).
- Risks of adverse events, as noted on FDA labels, are well understood and managed.
- Brief cognitive assessment tools, highly accurate for early detection of mild cognitive impairment and dementia, are validated and available for use by primary care practitioners.
- Blood biomarker tests, highly sensitive and specific for detection of Alzheimer's pathology, are FDA-approved or CLIA-regulated, and available for use in the primary care setting.

Estimating the scale of patient need

Unlike many other disease areas, the Alzheimer's disease patient population potentially eligible for treatment is difficult to estimate. Recent estimates suggest that the number of Americans with mild cognitive impairment will climb to over 16 million by 2030 (a 13 percent increase from 2025), and the number of persons with clinical Alzheimer's disease will reach 8.5 million people, (a 19 percent increase).[iv] However, this increase does not translate into direct estimates of patients who will seek care or receive disease-modifying therapy because patients must be found clinically eligible for treatment. Physicians face challenges to determine clinical eligibility, especially at the earliest (most treatable) stage in the disease. Clinical eligibility for treatment must be addressed if we are to understand what healthcare system changes are needed to

equitably treat these populations. Appendix A presents several recent estimates of eligible patient populations.

To improve patient health and embrace new opportunities in AD care, these challenges must be addressed. Specifically:

- *Early engagement about cognitive health*: Currently, patients, caregivers and physicians are not proactive in addressing cognitive health or decline.[v]
    - With stigmas around the disease, few people seek a diagnosis
    - With limited time per appointments and limited reimbursement for cognitive testing, PCPs are unable to engage with potential patients meaningfully.
- *New time and step-saving diagnostic tools are not yet well understood or commonly utilized in the primary care setting.*
    - While new diagnostic tools such as brief digital cognitive assessments and blood biomarker tests may facilitate earlier diagnoses, these are still tasks that must be integrated (i.e. squeezed into) PCP workflows. PCP teams must also reach a new level of comfort in initiating cognitive assessment and biomarker testing, and in interpreting results for patients.
- *USFDA has identified Stage One Alzheimer's disease, a pre-clinical stage, where the progression of Alzheimer's pathology is present, but patients do not manifest symptoms.*

Patients with no cognitive decline, but detectable levels of abnormal amyloid are at significantly elevated risk for the onset of Alzheimer's disease in comparison to persons with normal levels of amyloid, and that risk increases with age.[vi] Near and mid-term risks of progression to early Alzheimer's disease have become clearer, suggesting that it is now possible technologically to identify patients who might prove eligible for disease-modifying therapy. (See Appendix E)

As these diagnostic challenges are addressed, early Alzheimer's disease will be detected more easily and increase the number of patients who might prove eligible for disease-modifying therapy. Yet confirmation of amyloid positivity alone may not render patients eligible for anti-amyloid therapy. Other patient characteristics and co-occurring conditions may influence eligibility. These conditions may include a history of stroke, significant cardiovascular disease, seizure and immunological disorders, and a susceptibility to brain bleeds as indicated by magnetic resonance imaging (MRI) that reveals amyloid-related imaging abnormalities (ARIA) indicative of brain bleeding risks.

As diagnostic and therapeutic innovations make earlier identification and treatment of Alzheimer's disease feasible, clinical guidelines and care practices will need to evolve to expedite these determinations of eligibility for disease-modifying therapy, particularly if eligibility is to be determined within primary care, or with coordination between primary care and specialists.

Early symptomatic Alzheimer's disease is also largely undetected and undiagnosed today, typically not recognized until symptoms are clearly evident and at a stage in which disease-modifying therapy is likely to be less effective or non-effective. However, the large underlying prevalence of mild cognitive impairment and mild dementia confirmed for Alzheimer's pathology is such that upwards of several hundred thousand patients could be eligible for therapy in a given year, even after a significant number are deemed ineligible for treatment. The US health care systems is mostly unprepared to meet this level of patient demand safely, equitably and effectively.[vii] We

expect that the primary care setting will be the first (and main) point of contact to meet this scale of new patient demand. To prepare for these new opportunities, primary care sites will require substantial support to expand their capacities, to build capabilities and to collaborate with specialists in neurology, geriatric psychology and related specialties.

Building Alzheimer's care and treatment within primary care

A brief overview of the context

The biological understanding of Alzheimer's disease is evolving rapidly, and as new diagnostics and treatments become available for patients, U.S. healthcare systems must adapt to ensure that patients have efficient and equitable access to care. Given the expected increase in patients seeking care, it is especially pertinent to think about the future role of primary care providers (PCPs) in treating the disease. PCPs also serve at the frontline of care for conditions that influence pre-onset risks for Alzheimer's disease and other dementias. (Hypertension, for example; see Appendix B for a list of modifiable risk factors for Alzheimer's disease.) Modeling conducted by RAND in 2024 suggests care provided in the primary care setting could substantially reduce waiting times for patients seeking Alzheimer's disease diagnosis and care.[viii]

PCPs must now be prepared to assess, diagnose and treat Alzheimer's disease at the two stages of disease amenable to treatment (as per FDA-approved treatment indications). (See Appendix C for definitions of Alzheimer's disease staging.) However, this must be done in the context of diagnosing and treating other medical complexities found among Alzheimer's disease patients, including co-occurring neurological conditions (resulting in 'mixed etiologies' of the patient's dementia), and treating chronic conditions that frequently co-occur with Alzheimer's disease (such as cardiovascular diseases). (See Appendix D for background on dementia, mixed etiologies, and co-occurring chronic conditions). Finally, the primary care practitioner must have access to specialists for prompt referrals when patients present with severe or especially complex cases.

Anti-amyloid therapy is likely to be the primary focus of Alzheimer's treatment over the next five years. Drugs recently approved by the FDA for active treatment of Alzheimer's disease are bioengineered, monoclonal antibody drugs that bind to amyloid-beta proteins in the brain and trigger an immune response that clears amyloid plaques and prevents further accumulation in the brain. Clinical trials have shown that these drugs slow patients' cognitive decline, and thus are disease-modifying, (DMTs). Three anti-amyloid therapies (Leqembi/Eisai-Biogen, Kisunla/Eli Lilly, and Aduhelm/Biogen-Eisai) have been approved by the FDA.[ix] Approximately 23 other anti-amyloid drugs are in active development, with 7 now in Phase III trials.[x] Currently approved anti-amyloid drugs are indicated for treatment of early symptomatic Alzheimer's disease (mild cognitive impairment and mild dementia due to Alzheimer's disease). Late-stage trials are underway to investigate the administration of these therapies to patients with pre-clinical Alzheimer's disease.[xi]

While the currently approved, anti-amyloid drugs are administered intravenously, the first subcutaneous formulation administered by injectable pens may receive FDA approval by year-end

2025,[xii] and other subcutaneous anti-amyloid formulations are in active development. Injectable anti-amyloid therapy that eliminates the necessity of infusion is expected to greatly enable PCP administration or supervision of anti-amyloid therapy.

Other disease-modifying therapies now in development include drugs targeting abnormal tau protein accumulation in the brain, ('anti-tau therapy'), and therapeutic vaccines to trigger immune system clearance of amyloid and tau.

In addition to new treatments, blood biomarker testing for amyloid plaque will make diagnosis of Alzheimer's disease within the primary care setting a realistic option, as physicians will be able to order testing through standard lab testing procedures. Recent studies indicate that Negative Predictive Values and Positive Predictive Values have both reached levels around 90 percent.[xiii] To date, the standard diagnostics for detection of amyloid-related Alzheimer's disease are accurate but challenging to administer. PET imaging sites are unevenly distributed throughout the U.S. and long waiting times for appointments are common.[xiv] In CSF analysis, circulating particles of beta-amyloid proteins are detected in cerebrospinal fluid collected by lumbar puncture, an intrusive procedure that can be painful to some patients, and which not all primary care teams are trained to administer (although innovative CSF-based biomarkers of AD have created a capability for AD detection in primary care).

Emerging blood-based biomarker assays, marketed as Clinical Laboratory Improvement Act (CLIA)-regulated products, are now available as minimally invasive options for detection of AD pathology. These less intrusive products can be administered through routine phlebotomy, enabling primary care physicians to make preliminary determination of AD, triage patients for further evaluation, and potentially to make a confirmatory diagnosis of Alzheimer's disease. It also creates the potential capability to detect asymptomatic, pre-clinical Alzheimer's disease in patients who might be deemed at high risk, such as patients with a family history or genetic predisposition to the disease. As diagnostic tools progress, and treatments are more available, it will be possible for providers to become more proactive in engagement with patients who may be eligible for disease-modifying therapy.

Core challenges, barriers, and potential solutions

Multiple barriers and challenges will confront stakeholders if primary care is to take a leading role in Alzheimer's disease treatment. Overcoming these barriers and challenges will require collaborative solutions from patients, caregivers, healthcare practitioners, payers, manufacturers and other groups. While the Alzheimer's patient journey can be complex, the challenges facing each stakeholder group fall into several fundamental steps, from the point in time when patients, caregivers and clinicians first decide to take action, to the initiation of assessment of suspected Alzheimer's disease or other dementias, to diagnosis and identification of patients eligible for treatment, and to the administration of treatment itself.

Confronting suspected MCI or dementia before initial testing in primary care

Current estimates suggest that mild cognitive impairment among U.S. adults is radically under-diagnosed. Upwards of 92 percent of adults with MCI may not have a formal diagnosis.[xv] A recent systematic review indicates that only 39 percent of all Americans with dementia are diagnosed.[xvi]

With such low levels of identified patients, the NEWDIGS, AD team endeavors to investigate the barriers and core challenges that impact patient engagement and diagnosis.

Typically, patients and their caregivers do not engage with physicians, or vice versa, until there is a suspicion of lapses in patient memory, cognition or function. As a result, patients may not be assessed for mild cognitive impairment or dementia until these conditions have progressed. This delayed engagement can be traced to the patient's and caregiver's reticence to seek treatment due to a lack of awareness of the disease (attributing problems to 'healthy aging,' for example), to fear of the stigma and discrimination attached to dementia, the patient's inability to self-advocate or their lack of a concerned caregiver, or all of these reasons.

At the same time, primary care practices may have limited time or incentive to pro-actively conduct a cognitive assessment, may not have the capabilities on site or within reach to diagnose Alzheimer's, and may be unfamiliar with the standard of dementia diagnosis or the risks and benefits of relatively new treatment options. As medical science across Alzheimer's care continues to advance, patients, caregivers and healthcare providers must shift their perceptions of Alzheimer's disease before they can change behaviors related to early diagnosis and treatment. Systemic and health systems-wide solutions will be necessary to support more robust (and timely) AD care across the United States. Some solutions might include:

- Enactment of legal protections against discrimination for patients with MCI and mild dementia, (akin to the protections afforded under the federal Genetic Information Non-Discrimination Act)
- Promote public health messaging and provider-patient communications that provide evidence-based information on the significance of brain health, and the risks of MCI, dementia, and Alzheimer's disease
- Educate patients about the correlations between chronic conditions and health behaviors known to impact brain health, (examples include cardiovascular disease, diabetes, a lifetime history of smoking, etc.)
- Adapt the Medicare Annual Wellness visit, and/or create new incentives to promote uptake of cognitive assessment within the Annual Wellness Visit and increase uptake of the Annual Wellness Visit itself

Integrating Alzheimer's disease detection and diagnosis within the primary care setting

As noted, patients with confirmable cases of Alzheimer's disease are severely under-diagnosed. Under-diagnosis not only reduces the identification of patients who may be eligible for disease-modifying treatment but reduces the ability of health care practitioners to recommend other interventions and follow-up care that may benefit patients and caregivers. Even today, with severely under-diagnosed patient populations, neurologists and other specialists are unable to handle the volume of current patients. With medical treatments expanding and diagnostic tools advancing, the key question becomes how steps in the Alzheimer's disease diagnosis process can be shifted to primary care, safely and effectively.

The diagnosis of Alzheimer's disease will remain complicated, as patients that present with an apparent memory or cognition problem do not necessarily have early Alzheimer's disease. The first step in the diagnostic process is a cognitive assessment to determine whether the patient has diagnosable mild cognitive impairment or mild dementia. Confirmed cases can then be further

assessed for confirmation of Alzheimer's disease, or for another neurological disorder, or both. Laboratory testing options available to the primary care practitioner include detection of Alzheimer's biomarkers in cerebrospinal fluid (CSF, collected through lumbar puncture) and blood biomarker testing (now available as CLIA-regulated testing.)

For discussion purposes we break down basic steps in the diagnostic process and potential solutions that might overcome barriers to shifting these steps into the primary care setting.

Scaling up first encounters between patient/caregivers and primary care practitioners regarding cognitive concerns:

The starting point for clinical attention to a patient who may have Alzheimer's disease is a first encounter with a clinician, most likely a primary care physician or primary care team, regarding a suspicion of a problem with memory, cognition or function. In current practice this first encounter does not happen routinely and often occurs at a point when symptoms of a problem are already evident, as noted earlier. Scaling up first encounters to identify early Alzheimer's disease at a level commensurate with the prevalence of the disease is a major challenge. Hypothetically, this first encounter can be triggered in several ways: pro-actively by the patient or patient's caregiver,[xvii] pro-actively by the PCP or PCP team, or pro-actively triggered as a routine care practice by clinical quality measure reporting and by quality and performance incentives.

Potential solutions to scaling-up these three types of encounters include:

- To increase first encounters triggered by patients and caregivers:
    - Raise awareness of mild cognitive impairment and dementia (through patient education, public health messaging).
    - Build knowledge of brain health risks coinciding with common chronic conditions such as hypertension, high LDL cholesterol, and diabetes; raise awareness of preventive measures to reduce modifiable risk factors, (also through patient education, public health messaging, etc.)
    - Ensure patient access to cognitive assessment at low or no costs to patients and caregivers through insurance coverage
- To increase first encounters triggered by primary care practitioners:
    - Incorporate cognitive assessment within standards of care for routine primary care visits, (through clinical practice guidelines, quality and performance metrics, etc.).
    - Establish criteria for selective cognitive assessment of patients seen in primary care, (i.e. criteria for pro-actively offering cognitive assessment to patients based on their family history of dementia, or on prior analysis of the patient's risk factors or on the basis of a validated dementia risk score.)
    - Increase incentives for uptake of thorough cognitive assessments administered during the Medicare Annual Wellness Visit and improve incentives for increasing uptake of the wellness visit itself.
- To increase first encounters triggered as a routine care practice:
    - Validate and adopt performance and quality measures for cognitive assessment within provider accreditation and payment programs, (e.g. patient centered primary care accreditation, MIPS, ACO metrics, HEDIS measures, etc.)
    - Organize collaborative action to expedite updated evidence on the clinical costs and benefits of cognitive assessment and seek new U.S. Preventive Services Task Force evaluation

of cognitive assessment and consideration of an A or B grade, (grades of A and B triggering coverage of cognitive assessment under ACA-regulated health plans and within Medicare.)
- Create incentives for completion of rigorous cognitive assessment within the Medicare Annual Wellness Visit, or as a complement to the Annual Wellness Visit, (for example, as follow-up or reflex testing for patients triaged on the basis of findings from the Wellness Visit.)
- Create and validate risk scoring to identify patient sub-populations at higher risk of AD; triage for patient referral to rigorous cognitive assessment

Deploying brief cognitive assessments

Cognitive assessment of the patient is the first step in the patient-PCP encounters described above. Cognitive assessments are likely to remain the first step or an early and automatic step in the future, even if blood biomarker testing for AD pathology becomes a routine part of adult preventive health care.

The initial cognitive assessment needs to be necessarily brief to fit within the limits of a routine clinical visit and to ensure integration with the clinician's workflow.[xviii] Standard cognitive assessment tools (such as the Mini Mental State Examination and the Montreal Cognitive Assessment) typically require 5-10 minutes for administration, and enhanced versions of these and competing tools are now designed for administration in even less time. Brief cognitive assessment is an essential first step towards defining whether a patient's perception of memory loss or cognition ('subjective cognitive decline') can be objectively measured. A negative finding (i.e. a patient perceives a problem but tests normal on a cognitive assessment) can be essential for follow-up examination and testing by the PCP to determine if non-Alzheimer's factors may be contributing to the patient's complaint and whether there are reversible causes of the complaint, (for background see Appendix B- Modifiable Risk Factors of Alzheimer's Disease & Primary Care.) Similar follow-up is necessary ordinarily when the patient 's cognitive assessment indicates that the patient is, in fact, suffering from loss of memory or cognition.

Potential solutions to promote greater uptake of cognitive assessment at scale include—

- Disseminate lessons learned from ongoing pilot projects on integration of comprehensive dementia prevention, detection and care within primary care practice, including lessons on streamlining inclusion of brief cognitive assessments within patient visits. (For example: lessons learned from uptake of brief cognitive assessment by the flagship sites of the Davos Alzheimer's Collaborative on healthcare system preparedness.)[xix]
- Disseminate lessons learned from cognitive assessment practices in evidence-based models of collaborative care for dementia.[xx]
- Disseminate care protocols on administration of brief cognitive assessments outside of scheduled patient visits, (i.e. in clinician waiting rooms, at home or in community settings.[xxi]
- Adapt and adopt standard cognitive assessment tests for rapid and clinically comprehensive brief cognitive assessments, (for example: through validation and uptake of AI-enabled digital cognitive assessment tests, now often developed for rapid administration via tablet or smartphone.) Validation of advanced, clinically comprehensive cognitive assessment tools will be particularly important for early detection of what the USFDA now defines as Stage 2 Alzheimer's Disease.[xxii]

- Develop and adopt protocols for shared decision making among patient, caregivers and clinicians so that clinicians convey assessment results clearly to patients and caregivers, and patients and caregivers are empowered to make well-informed and consensual decisions on the patient's course of care.
- Raise awareness among PCPs and health care delivery systems regarding new payment codes for evaluation of cognitive impairment.[xxiii]

Streamlining the pathway to confirmatory diagnosis

When a brief cognitive assessment indicates a patient may be suffering from a form of early Alzheimer's disease, further testing must be done to determine a specific diagnosis that might ultimately result in a confirmation of pathology that results in a diagnosis of Alzheimer's disease. The pathway to confirmation of pathology may include physical examinations, blood testing (or non-AD biomarkers), detailed patient and family medical histories, cerebrospinal fluid analysis and/or PET imaging. This is a multi-step process that in current practice is often subject to significant time delays, potentially jeopardizing patient eligibility for disease-modifying therapy due to continued progression of disease. More recently, the advent of blood biomarker testing offers a new tool that could expedite this process by providing an objective measurement of amyloid and tau concentrations that can be ordered within the primary care setting.

However, whether wider use of blood biomarkers expedites AD diagnosis in reality depends crucially on greater uptake of brief cognitive assessments in primary care, as described above,[xxiv] and on how use of blood biomarker tests (BBMs) will be sequenced within the process of patient diagnosis. For example, blood biomarker tests might be used to rule out referral to PET imaging (a use of BBMs to triage patients), to confirm AD pathology after PET imaging and potential eligibility for disease-modifying therapy (a use of BBMs as a confirmatory test), or ultimately, use of BBMs as standalone confirmatory tests. Recommendations recently published by the Blood-based Biomarker Working Group of USAgainstAlzheimer's outline a sequence in which BBMs are used for triage and a sequence in which BBMs serve as confirmatory tests that follow PET imaging.[xxv]

Potential solutions would address either or both of two challenges:

- Expediting the diagnostic process by improving efficient coordination between PCPs and PCP teams and specialists:
- Improving or creating expedited patient referral by PCPs to geriatric primary care practices[xxvi] or other primary care practices that enjoy prompt access to in-network imaging centers; and parallel development of payer utilization management policy that enables efficient referrals.
- Improved Medicare and other payer support for development and expansion of geriatric primary care or primary care sub-specialties with a focus on Alzheimer's disease care, (for example: further elaboration of the current Medicare GUIDE Model.)
- Develop criteria in clinical practice guidelines on the referral or handoff of complex and high-risk patients by PCPs to specialty care for PET imaging and specialized diagnostic work-ups.
- Expediting validation of BBMs as triaging (AD ruled-out) and confirmatory (AD rule-in) tests as used within primary care practices. Potential solutions include (a) FDA approval of BBM tests (otherwise available as CLIA-regulated tests), (b) increased PCP and PCP team education on the use of BBMs and interpretation of BBM results.

Integrating Alzheimer's disease–modifying therapy within the primary care setting

Extending the role of primary care teams beyond patient cognitive assessment into diagnosis and treatment will represent a significant expansion in primary care scope of practice. Diagnosis of Alzheimer's disease today is largely centered around specialty services, including confirmation of pathology through PET imaging. Currently approved DMTs are administered by infusion, typically at infusion centers. Neurologists and other specialists provide active oversight of patients to ensure safe administration and avoid adverse events. Oncoming innovations such as the launch of injectable DMTs (now fast tracked by the FDA, with approvals possible in 2025[xxvii]) will facilitate administration of therapy in the primary care setting, but active patient oversight will still be necessary.

Primary care's role in the management of other, non-Alzheimer's conditions may provide some inspiration, if not translatable models for expansion of Alzheimer's care within the primary care setting.

For example, therapies for anti-coagulation (use of 'blood thinners') and for control of type 2 diabetes are examples of therapies administered for highly prevalent conditions in which primary care teams play a leading role. In both cases consultation with specialists may be necessary for some patients, but in both cases there is a widely held assumption that there are far too many patients to be served by specialists alone, and that primary care practitioners are well equipped to provide evidence-based care given proper training.[xxviii] In both cases evidence-based practice requires careful and recurring monitoring of patients and their use of medications. Administration of disease-modifying therapy for Alzheimer's disease also seems likely to require close monitoring of patients. (See "Primary Care and Use of Closely Monitored Drugs".)

Major factors in adapting primary care practice to enable administration of disease-modifying therapy for Alzheimer's includes the following:

- Final confirmation of amyloid pathology and its status in the patient's brain: any definitive confirmation of pathology not already achieved in primary care (through blood biomarker testing, for example) might require further confirmation through standard diagnostics, including PET imaging and cerebrospinal fluid analysis, thus requiring referral from the primary care physician.
- The physician's qualifications to administer therapy: the primary care physician will need full training in the administration of anti-amyloid therapy, including an understanding of therapy risks and limitations.
- Shared decision making and other patient/caregiver counseling: the primary care physician and team will need tools and capability to counsel patients and caregivers on the risks and limitations of treatment and enable patients and caregivers to make a fully informed decision on treatment in conformance with the patient's preferences.
- Capabilities for the primary care physician and primary care team to coordinate the patient's care over the duration of treatment and to monitor the patient's treatment outcomes and overall health.
- Clear guidance on criteria for care handoffs to specialists for complex cases, or for more intensive care of patients who face adverse events or other health problems during the course of treatment.

Primary care and the use of closely monitored drugs, suggestive examples

Over the years primary care physicians and primary care teams have assumed roles in management of some chronic conditions that previously were performed mostly by medical specialists. In some cases, these changes were prompted by shortages in specialists available to serve patients, or by the introduction of innovations in care that facilitated primary care delivery, (introduction of new oral medications, for example.) Experience from these examples might offer lessons for the primary care role in Alzheimer's disease diagnosis and treatment, especially lessons regarding use of drugs that require close patient monitoring.

The use of anti-coagulant medications (blood thinners) in primary care is one example. In the 1970s, the use of warfarin increased in the treatment of atrial fibrillation, deep vein thrombosis, pulmonary embolisms and related conditions. By the 2010s, newer drugs (direct oral anti-coagulants, or 'DOACs') began to supplant use of warfarin. Both drug classes carry FDA black box warnings of bleeding side effects and require regular patient blood testing and medication management. A 2021 analysis of 2013-2018 Medicare prescribing data found that nearly 80 percent of anti-coagulant prescribers were non-specialists, (internists, family physicians, physician assistants and nurse practitioners.)[i] Both primary care physicians and specialists have made use of referrals to anti-coagulation clinics (now often termed 'anti-coagulation management services,' or AMS) for complex cases. However, evidence on improvements in patient outcomes and in efficiency of care delivery using AMS services appears to be mixed.[ii]

A second example is found in primary care administration of medications for treatment of type 2 diabetes. While only some diabetes drugs carry black box warnings, evidence-based practice requires that patients on these drugs monitor themselves for adverse themselves (hypo- and hyper-glycemia) and receive ongoing medication management from providers. A 2024 analysis of prescribing patterns indicated that 80 percent or more of diabetes medications are prescribed by primary care practitioners, (PCPs, nurse practitioners and physician assistants.)[iii] An oral, generic medication (metformin) is typically the first line treatment for type 2 diabetes and is generally prescribed by primary care practitioners. Moreover, a 2018 survey of PCPs suggested that upwards of 85 percent of insulin initiation also originates with primary care practitioners.[iv]

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Potential solutions might include—

- Development and dissemination of best practices or standards of accreditation for geriatric primary care practice in administration of anti-amyloid disease modifying treatment for Alzheimer's disease, including the process of determining patient eligibility for treatment.
- Creation or enactment of incentives for increasing the number of geriatricians and geriatric

primary care practice. (Currently only one percent of U.S. physicians are board-certified in geriatrics.)
- Adaptation of current best practice models of elder medical care (such as PACE) to encompass assessment of patients for Alzheimer's disease modifying treatment, and for administration of therapy.
- Dissemination of best practices of care coordination between primary care physicians and virtual (telehealth) geriatric medicine, neurology, and geriatric psychiatry. Virtual specialty services can augment the capabilities of primary care physicians and fill gaps in care for patients who live in remote and underserved areas, (so-called 'neurology deserts,' for example).
- Development of provider payment models for value-based delivery of therapy and ancillary or wraparound services such as patient monitoring. (For example: adaptation of the current Medicare GUIDE model.)

Outcomes tracking and evidence development infrastructure

Data collection on the real-world utilization and patient outcomes is a requirement of the anti-amyloid drug therapies approved thus far by the Food and Drug Administration. Physicians who prescribe Leqembi and Kisunla must enter a core set of data points into a registry created under terms of Medicare's Coverage with Evidence Development (CED) coverage policy. Real world evidence on the effectiveness of therapies (previously approved or yet to come) could emanate from the Medicare CED registry, or from other sources such as the collaborative Alzheimer's Disease Data Initiative.

Rigorous real-world evidence (RWE) will be an important factor in supporting patients, caregivers and clinicians as they grapple with shared decision making on the use of these therapies. Key issues will include:

- The timeliness and accessibility of RWE for the education of patients, caregivers and clinicians
- The extent to which responsibility for data collection and analysis will fall on clinicians, and on primary care physicians for whom routine data collection for purposes of evidence generation will be an additional burden on routine practice

Estimating the value of Alzheimer's treatment and the implications for payers

Alzheimer's disease care and treatment create substantial costs today for patients, their families, and payers. The Alzheimer's Association estimates the total cost burden of Alzheimer's care and other dementias at $360 billion (2024 dollars), not including the costs of informal caregiving performed by family members and other caregivers. Medicare (45 percent) and Medicaid (19 per-

cent) combined shoulder nearly two thirds of this cost, while patient or family out-of-pocket costs represent about 25 percent (see table below).[xxix] Separate estimates made in 2024 suggest that the total cost of care of Alzheimer's and related dementias in the U.S. will grow by nearly 30 percent from 2025 to 2030.[xxx]

Medicare and Medicare Advantage shoulder the lion's share of medical benefit costs for Alzheimer's-related care today. Over ninety percent of the patient population with symptomatic Alzheimer's disease are 65 years or older.[xxxi] Medicare covers the currently approved anti-amyloid Alzheimer's therapies, although regional coverage may be conditioned on confirmation of the patient's amyloid pathology by PET imaging. All Medicare Advantage plans must cover anti-amyloid therapy, consistent with Medicare's national coverage determination on these therapies.[xxxii] Medicaid covers nursing home costs for about 60 percent of nursing home residents in the U.S.[xxxiii] Approximately 40 percent of nursing home residents have Alzheimer's disease or a related dementia, including patients with later stages of Alzheimer's disease that are unlikely to be indicated for disease-modifying therapy.[xxxiv]

The costs of Alzheimer's-related care represent a significant challenge for Medicare's future fiscal stability. Estimates made by the Alzheimer's Association suggest that Medicare spending will rise by as much as 177 percent by the year 2050, and account for one-third of all Medicare spending, ($453 billion in 2024 dollars.) Medicaid spending is projected to rise by as much as 173 percent, ($185 billion in 2024 dollars.)[xxxv]

In contrast, commercial self-insured and fully insured health insurance plans today incur a relatively minimal level of expense for coverage of Alzheimer's disease modifying treatment given the low rate of diagnosis of AD among the pre-65 patient population.[xxxvi] However, private insurers may see increased demand for coverage of disease-modifying therapy for Alzheimer's disease rise as clinician familiarity with highly sensitive and specific diagnostics improves and more pre-Medicare patients are identified as at risk for Alzheimer's disease. For example, costs to private insurers may rise if anti-amyloid therapies gain FDA approval for the treatment of Stage One (asymptomatic but pathological) Alzheimer's disease, a condition detectable among patients under the age of 65.

From a public health standpoint, greater uptake of disease modifying therapy for eligible patients could represent substantial savings. A recent analysis suggests that delaying the onset of Alzheimer's disease by one year at age 70 would avert approximately $500,000 in medical spending over the course of the patient's remaining life, savings that will compound given an expected significant increase in the number of Americans with Alzheimer's disease over the next 25 years.[xxxvii]

From the standpoint of payers, potential longer-term savings from the delay or arrest of Alzheimer's disease must be balanced against increased costs of earlier Alzheimer's diagnosis, conducted at greater scale than seen today, and subsequent costs of DMT treatment for patients who prove eligible.

Expansion of primary care's role in Alzheimer's care is seen by many as a strategy that will improve the value of Alzheimer's disease-modifying therapy by shifting care to settings that are less expensive than specialty care settings such as neurology, while improving patient access that is currently restricted because of a pervasive shortage in specialists available to serve patients. (Potential FDA approval of injectable forms of DMT treatment is one example, since injectable

therapies will reduce reliance on IV infusion of therapies and injectable therapies will facilitate PCP supervision of treatment.) To this end, primary care teams will need to develop the skills and capabilities to manage the multiple steps (brain health assessment, diagnosis, determinations of treatment eligibility and treatment itself) required by evidence-based care.

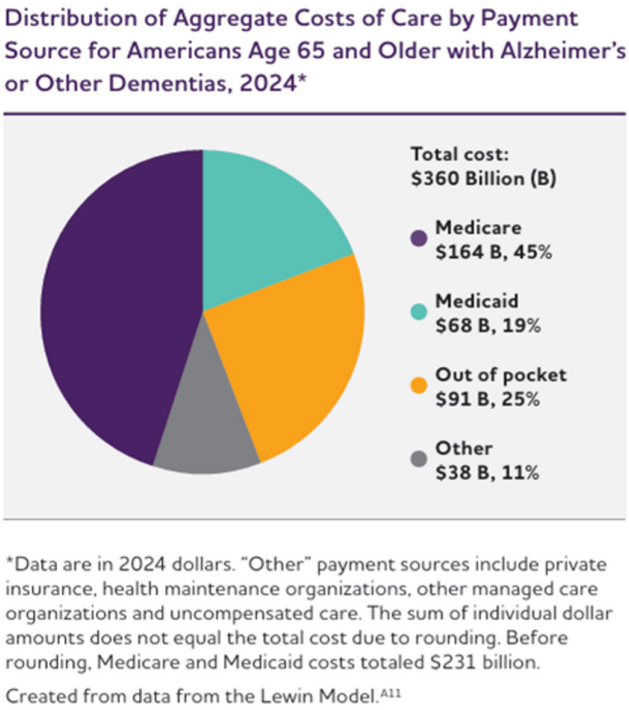

Figure 1. Sources of payment for care of Alzheimer's disease and related dementias (patients aged 65+ years) (Ref: Alzheimer's Association's "2024 Alzheimer's Disease Facts and Figures Special Report" p. 71)

Appendix A
Estimating the population eligible for disease-modifying therapy for Alzheimer's disease

The scale of change that will be needed to meet patient demand for treatment of Alzheimer's disease will be determined by the size of the patient population eligible for approved treatments. Determining the size of this population begins with estimates of the population that is diagnosed today with mild cognitive impairment and mild dementia due Alzheimer's disease but must also take into consideration findings from research on the underlying prevalence of Alzheimer's disease pathology among adults. Final estimations must account for the several factors that may rule out a patient's eligibility for treatment, even if the patient has confirmed pathology for the disease.

Table A
Table A presents estimates on the number of American adults thought to have MCI or mild dementia due to Alzheimer's disease, and the subset of these adults who are reported to have seen a doctor, and to have a confirmed case of Alzheimer's pathology. (Adapted from Spargo et al 2023; 2030 estimates as calculated by NEWDIGS)

Estimates of U.S. Population Aged 60 Years and Over	Base Year	2030 est.
Dementia due to Alzheimer's disease-Mild	1,650,488 (2021 est)	2,145,634
Mild Cognitive Impairment due to Alzheimer's disease	9,871,296 (2021 est)	12,832,685
Dementia due to Alzheimer's disease-Mild (Patients who see a doctor)	738,803 (2019 est)	960,444
Mild Cognitive Impairment (Patients who see a doctor)	1,184,556	1,539,923
Dementia due to Alzheimer's disease-Mild (Patients who see a doctor and have amyloid-beta positivity)	620,850 (2022 est)	807,105
Mild Cognitive Impairment (Patients who see a doctor and have amyloid-beta positivity)	666,646 (2022 est)	866,640
Total Patients with either condition who see a doctor and have amyloid-beta positivity	**1,287,496 (2021 est)**	**1,673,745**

Estimates of patient eligibility for anti-amyloid disease modifying therapy

Recently published estimates of the treatment eligible population include the following:

Arbanas, et al, JAMA Internal Medicine, May 11, 2023: Approximately 85,687 to 216,536 Medicare beneficiaries (per 2019 data) may be eligible for treatment with lecanemab (Leqembi/Eisai-Biogen). Patient eligibility restricted to clinical trial inclusion parameters.

Pittock et al, Neurology, November 7, 2023: Eight (8) percent of patients with MCI or mild dementia due to Alzheimer's disease found eligible for lecanemab (Leqembi) treatment. Patient eligibility confined to clinical trial criteria. With eligibility expanded to patients with MCI but no additional cognitive criteria, eligibility increases to 17.4 percent of patients with MCI or mild dementia.

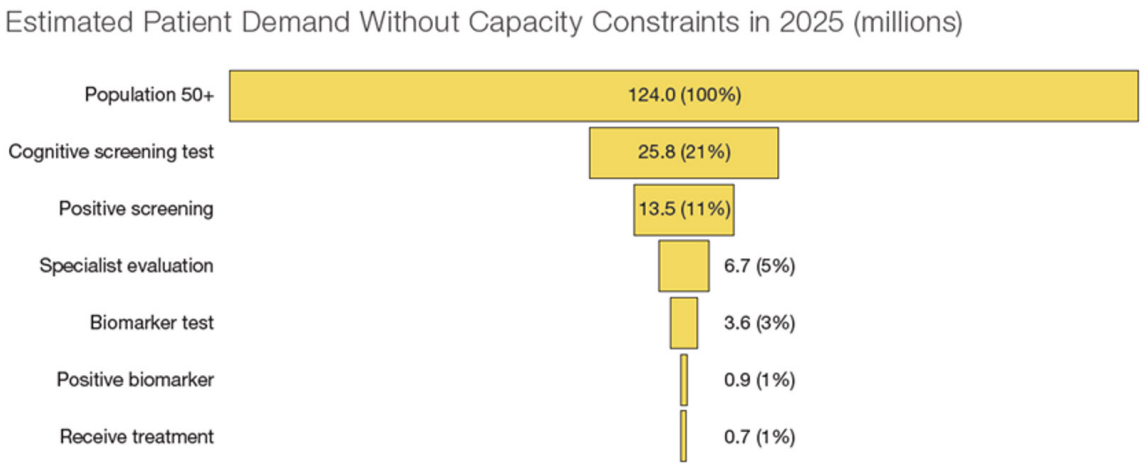

Figure 2. Estimated patient demand for alzheimer's disease-modifying therapy without health system capacity constraints (Figure 3 of RAND Research Report, January 2024).

Appendix B
Modifiable risk factors of Alzheimer's disease and primary care

Numerous risk factors are correlated with the onset of Alzheimer's disease and other dementias.

A recent review of risk factor research identified fifteen modifiable risks factors, (as distinct from non-modifiable risk factors such as genetic predispositions to the disease.) Fifteen distinct risk factors, as experienced over a person's lifetime, may influence an individual's risk of Alzheimer's disease:[2]

- Physical activity
- Alcohol use (level of
- Social engagement
- Hypertension
- Hearing and vision
- Diabetes
- Hyperlipidemia
- Weight
- Smoking history
- Stress and depression
- Sleep
- Medication use (e.g. avoidance of medications with anticholinergic properties)
- Cognitive stimulation and level of education
- Prevention of brain trauma or toxic insults to the brain
- Diet

A standing commission of The Lancet (The Lancet Commission on Dementia) concluded in 2024 that interventions to reduce modifiable risk factors for dementia are effective to varying degrees throughout the life course, (i.e. from early to late in life.)[3] In fact interventions to improve vascular health, (such as smoking cessation, and medical interventions to control hypertension and LDL ('bad') cholesterol may have played a role in reducing the age-specific incidence of dementia over the last fifty years. (In other words, a lower rate of dementia onset is evident in age cohorts compared to historical rates, although increasing life expectancy in the U.S. and other countries has led to a higher number of persons living to an age at which dementia appears.) A long-term reduction in the rate of growth in Medicare spending, compared to previous estimates, has been attributed in part to improvements in cardiovascular health among aging Americans.[4] The Lancet Commission estimates that 49 percent of dementias could be averted or delayed but for the burden of modifiable risk factors.

2 List adapted from Krivanek and Gale, "Promoting successful cognitive aging: a ten year update," Journal of Alzheimer's Disease, April 2021
3 Livingston et al, "Dementia prevention, intervention and care: 2024 report of the Lancet standing commission," The Lancet, July 31, 2024
4 Cutler et al, "Explaining the slowdown in medical spending growth in the elderly population," Health Affairs, February 2019

However, systematic review of dementia research studies suggests that, in most instances, interventions to reduce modifiable risk factors have little or no impact on dementia symptoms suffered by patients with a diagnosed dementia; that is, among patients suffering from dementia that is already progressing. While interventions to reduce social isolation and increase physical activity may improve quality of life among some patients and their caregivers, they are not effective as treatment for Alzheimer's disease symptoms or symptoms of other forms of dementia.[5]

The research reviewed by the Lancet Commission and others underscores the important role that primary care plays in supporting good, evidence-based health practices that may reduce dementia risk over the decades of adulthood. For example, primary care teams are responsible for providing the blood pressure, cholesterol and blood glucose care that most adult patients receive, and thus for care correlated with dementia risk, including the risk of Alzheimer's disease. At the same time, intensifying medical care for patients who have an already-progressing dementia will represent an expansion of core capabilities for most primary care practitioners.

5 Lancet Commission, op cit; page 39

Appendix C
Alzheimer's disease staging

The U.S. Food and Drug Administration employs a six-stage model of Alzheimer's disease onset and progression to evaluate Alzheimer's drugs and diagnostics (see chart below), a model that tracks the continuum of AD disease progression. The FDA has approved use of the currently approved anti-amyloid therapies (Leqembi and Kisunla) for patients diagnosed with mild cognitive impairment or mild dementia, and with confirmed presence of abnormal amyloid in the brain. Thus FDA approval extends to patients deemed at Stage Three and Stage Four of Alzheimer's disease, although patients at Stage Two may be also be deemed to exhibit signs of mild cognitive impairment with detectable presence of abnormal amyloid. Patients at Stages Five and Six (overt dementia at moderate and severe stages) may well remain beyond the current/near-future treatment protocols.

Diagnostic criteria for early Alzheimer's disease: FDA recommendations on staging of Alzheimer's disease

(From U.S. Food and Drug Administration, Early Alzheimer's Disease: Developing Drugs for Treatment, Guidance for Industry, Draft Guidance March 2024)

Stages	Characteristics of the stage	Description
Stage One	Patients with characteristic pathophysiological changes of AD but no evidence of clinical impact	These patients are truly asymptomatic with no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures. The characteristic pathophysiological changes are typically demonstrated by assessment of various biomarker measures.
Stage Two	Patients with characteristic pathophysiological changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures or subjective complaints of mild cognitive symptoms but no functional impairment	This may be considered a transitional stage in which slight cognitive symptoms first appear. The emergence of subtle functional impairment signals a transition to Stage 3
Stage Three	Patients with characteristic pathophysiological changes of AD, generally more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment	The functional impairment in this stage is not severe enough to warrant a diagnosis of overt dementia. This stage roughly corresponds with the syndrome of "mild cognitive impairment"; however, it is noted that the term "mild cognitive impairment" may also encompass patients in late Stage 2 or early Stage 4.

Stages	Characteristics of the stage	Description
Stage Four	Patients with overt dementia - mild	This diagnosis is made as functional impairment worsens from that seen in Stage 3.
Stage Five	Patients with overt dementia - moderate	
Stage Six	Patients with overt dementia - severe	

Appendix D
Dementia, mixed etiologies, and co-occurring conditions of Alzheimer's disease

Dementia and mixed etiologies

The term 'dementia' encompasses a group of brain disorders that have multiple potential underlying diseases or etiologies, and these complications may be challenging for PCPs to assess. At the same time, PCPs are particularly well-placed to identify cognitive changes in their patients, as well as common co-morbidities and risk factors for the development of AD. Alzheimer's disease is the most dominant form (about 80 percent) of dementia, but other etiologies include vascular dementia, Lewy body syndrome, and frontotemporal dementia are also present. Moreover, related dementias may be co-occurring with Alzheimer's disease and the onset of one disease may influence the progression of another, resulting in patients classified with Alzheimer's disease and mixed etiologies. As improved diagnostic tools become accessible, PCPs will be able to identify amyloid accumulations independently, especially by using blood biomarker testing. However, PCPs will also have to judge when a more thorough assessment is required and refer these patients to specialists.

Alzheimer's disease and co-occurring conditions

The role of the primary care provider will continue to be a central, integrative point of care for AD patients, and for AD patients with comorbidities. A recent systematic review of studies indicates that approximately seventy (70) percent of Alzheimer's patients suffer from clinical hypertension, while twenty (20) percent or more suffer from dyslipidemia, cardiovascular diseases, type 2 diabetes, hearing loss, depression, or combinations of these conditions.20 Most recently, vascular stresses or 'vascular aging' is now considered a likely contributor to the onset and progression of Alzheimer's disease, most likely caused by neuronal damage due to impaired blood flow to the brain.[xxxviii] Primary care physicians and their teams are the front-line of medical care for the most common chronic conditions, including hypertension, cholesterol control and, in many instances, for control of type 2 diabetes. The primary care physician's familiarity with a patient's chronic conditions may also provide insight to judge the suitability of disease modifying treatment for patients with Alzheimer's disease, and to counsel patients on initiation and maintenance of therapy, in conjunction with treatment for a patient's panel of chronic conditions.

Appendix E
Pre-clinical Alzheimer's disease

Pre-clinical Alzheimer's Disease (PCAD) is a state in which a patient tests as cognitively normal, but pathology indicative of Alzheimer's disease is present in the brain. Stage One of the Alzheimer's disease staging system recommended in FDA guidance describes patients at this stage as having "characteristic pathophysiological changes of Alzheimer's disease but no evidence of clinical impact." (See Appendix B)

Recent research suggests that patients at the PCAD stage are at markedly elevated risk for the onset of Alzheimer's disease in comparison to patients who are cognitively normal but have no detectable Alzheimer's pathology in the brain. By some estimates the lifetime risk of progression to Alzheimer's disease at age 65 among persons with abnormal amyloid concentrations is about 30 percent.[6] But ongoing studies suggest that Alzheimer's risk among pre-symptomatic persons rises markedly with age. Risks also rise with the presence of one or two copies of the ApoE4 genetic variant and with rising levels of AD biomarkers, especially the tau protein. This suggests that it has become possible technologically to identify patients at elevated, near or mid-term risk for symptomatic Alzheimer's disease.

By way of example: a 2017 study of participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) found that 32 percent of patients 75 years and older with abnormal, but pre-symptomatic amyloid concentrations had developed symptoms of mild cognitive impairment within four years, as compared to 15 percent of patients with normal amyloid. Limited data suggested that 88 percent of individuals with elevated amyloid progressed to MCI within ten years, as compared to 29 percent of individuals with normal amyloid.[7] A 2020 study of ADNI participants aged 55 to 88 found that 34 percent of amyloid positive individuals progressed to MCI within 8 years, as compared to 10 percent of individuals who initially tested as amyloid negative.[8] A 2024 analysis of participants in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study (the A4 Study) found that in excess of 50 percent of asymptomatic individuals testing in the highest third of scores for the biomarker pTau217 (a biomarker of both amyloid and tau levels) progressed to Alzheimer's disease within 4.5 years, a risk level roughly 4 times higher than the risk faced by individuals without elevated amyloid levels.[9]

In sum, asymptomatic individuals who test with abnormal levels of amyloid in the brain do not categorically develop Alzheimer's disease before dying of other causes, but their likelihood of progressing into symptomatic AD is several times higher than the risk faced by individuals without elevated amyloid levels.

6 Brookmeyer and Abdalla, "Lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease," Alzheimer's Dementia, August 2018

7 Donohue, et al, Alzheimer's Disease Neuroimaging Initiative, " Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons," JAMA, June 13, 2017

8 Shen, et al, Alzheimer's Disease Neuroimaging Initiative, "Plasma amyloid, tau, and neurodegeneration biomarker profiels predict Alzheimer's disease pathology and clinical progression in older adults without dementia," Alzheimer's Dementia, September 24, 2020

9 Sperling et al, "Amyloid and tau prediction of cognitive and functional decline in unimpaired older individuals: Longitudinal data from the A4 and LEARN Studies, Journal of Prevention of Alzheimer's Disease, July 2024

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i. Drabo et al, "Longitudinal analysis of dementia diagnosis and specialty care among racially diverse Medicare beneficiaries," Alzheimer's Dementia, November 2019

ii. Drabo, op cit

iii. Milbank Memorial Fund and The Physicians Foundation, "No One Can See You Now: Five Reasons Why Access to Primary Care Is Getting Worse (and What Needs to Change): The Health of U.S. Primary Care- 2024 Scorecard Report," February 28, 2024

iv. Rajan et al, "Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020-2060)," Alzheimer's Dementia, December 2021

v. A 2019 survey by the Alzheimer's Association found that nearly all primary care physicians waited for patients or their loved ones to bring up concerns about cognition. See Alzheimer's Association, (2019), 2019 Alzheimer's disease facts and figures, Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 15 (3), 321-387

vi. Donohue, et al, Alzheimer's Disease Neuroimaging Initiative, "Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons," JAMA, June 13, 2017. See also: Shen, et al, Alzheimer's Disease Neuroimaging Initiative, "Plasma amyloid, tau, and neurodegeneration biomarker profiles predict Alzheimer's disease pathology and clinical progression in older adults without dementia," Alzheimer's Dementia, September 24, 2020 . and Sperling et al, "Amyloid and tau prediction of cognitive and functional decline in unimpaired older individuals: Longitudinal data from the A4 and LEARN Studies, Journal of Prevention of Alzheimer's Disease, July 2024

vii. See Liu, et al, op cit; also see Ball et al, "A framework for addressing Alzheimer's disease: Without a frame, the work has no aim,": Alzheimer's Dementia, April 2023.

viii. The Rand Corporation 2024 study modeled wait times for patients seeking diagnosis and treatment of dementia, especially for appointments with dementia specialists. See Jodi L. Liu, Lawrence Baker, Annie Chen, Jessie Wang, Federico Girosi. "Detection and Geographic Variation in Health System Capacity for Alzheimer's Disease–Modifying Therapies" Rand Corp. Jan 30, 2024: p.10. https://www.rand.org/content/dam/rand/pubs/research_reports/RRA2600/RRA2643-1/RAND_RRA2643-1.pdf.

ix. Marketing of Aduhelm has been discontinued

x. Cummings et al, "Alzheimer's disease drug development pipeline: 2024," Alzheimer's Dementia, April 24, 2024

xi. Clinical trials of Leqembi and Kisunla continue to test dosage levels and dosage sequencing that may improve patient tolerability, safety and improved effectiveness.

xii. PR Newswire, January 13, 2025:"FDA accepts Leqembi (lecamenab-irmb) Biologics License Application for subcutaneous maintenance dosing for the treatment of early Alzheimer's disease."

xiii. Palmqvist S, Tideman P, Mattsson-Carlgren N, Schindler SE, Smith R, Ossenkoppele R, Calling S, West T, Monane M, Verghese PB, Braunstein JB, Blennow K, Janelidze S, Stomrud E, Salvadó G, Hansson O. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. JAMA. 2024 Oct 15;332(15):1245-1257. doi: 10.1001/jama.2024.13855. PMID: 39068545; PMCID: PMC11284636.

xiv. See RAND Corporation study, op cit

xv. Liu, et al, "Detection rates of mild cognitive impairment in primary care for the United States Medicare population," Journal of Prevention of Alzheimer's Disease, October 24, 2023

xvi. Lang et al, "Prevalence and determinants of undetected dementia in the community: A systematic literature review and a meta-analysis," BMJ Open, February 3, 2017

xvii. Patients who self-report a perception of memory loss, confusion or cognitive difficulties can be characterized clinically as subject to 'subjective cognitive decline,' and these perceptions often trigger pro-active outreach by a patient or caregiver to a PCP or PCP team.

xviii. Alzheimer's Association, "2019 Alzheimer's Disease Facts and Figures, see Special Report: Alzheimer's Detection in the Primary Care Setting: Connecting Patients and Physicians," March 2019

xix. See the Davos Alzheimer's Collaborative, Early Detection Blueprint, at www.dacblueprint.org

xx. Heintz et al, "Emerging collaborative care models for dementia care in the primary care setting: a narrative review," American Journal of Geriatric Psychology, March 2020

xxi. See recommendations of the UsAgainstAlzheimer's Brief Cognitive Assessment Work Group in Mattke, et al, "Expanding the use of brief cognitive assessments to detect suspected early -stage cognitive impairment in primary care," Alzheimer's & Dementia, January 2023; also see Ty et al, "Improving early detection of cognitive impairment and dementia," Milken Institute, December 2024. Recommendations fall into three major categories: (1) provide primary care clinicians with brief cognitive assessment (BCA) tools that meet optimal criteria for use; (2) integrate BCAs into routine health care workflows; and (3) revise or update reimbursement policies to encourage adoption of BCAs

xxii. Under FDA guidance issued in March 2024, Stage 2 Alzheimer's disease is defined as a stage in which "patients..(have) characteristic pathophysiological changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures or subjective complaints of mild cognitive symptoms but no functional impairment." See Appendix C for definitions within the FDA staging system.

xxiii. Center for Medicare and Medicaid Services (CMS), Cognitive Assessment & Care Plan Services, accessed at cms.gov/medicare/payment/fee-schedules/physician/cognitive-assessment, March 12, 2025

xxiv. See analysis of brief cognitive assessment uptake as a major rate limiting factor in patient diagnosis of AD and determination of eligibility for disease-modifying therapy: Liu, et al, "Modeling Early Detection and Geographic Variation in Health System Capacity for Alzheimer's Disease-modifying Therapies, " RAND Research Report, 2024

xxv. Mielke et al, "Recommendations for clinical implementation of blood-based biomarkers for Alzheimer's disease," Alzheimer's & Dementia, July 2024

xxvi. Chin et al, "Monoclonal anti-amyloid antibodies for the treatment of Alzheimer's disease and the hesitant geriatrician," Journal of the American Geriatrics Society, October 2023

xxvii. PR Newswire, FDA accepts Leqembi (lecanemab-irmb) Biologics License Application for subcutaneous maintenance dosing

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xxviii. For example see: Schafer et al,"Why Warfarin Should Be Managed in Primary Care," Annals of Family Medicine, July-August 2022 ; and Shrivastav et al, "Type 2 Diabetes Management in Primary Care: The Role of Retrospective, Professional Continuous Glucose Monitoring." American Diabetes Association/ Diabetes Spectrum, August 31, 2018

xxix. Alzheimer's Association 2024 Alzheimer's Disease Facts and Figures. Accessed online 3.25.25

xxx. Nandi, et al, "Cost of care for Alzheimer's disease and related dementias in the United States: 2016 to 2060," NPJ Aging, 2024, The estimate quoted is a base case estimate assuming 3 percent annual inflation.

xxxi. National Institute of Aging, "What Causes Alzheimer's Disease," website at https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-causes-alzheimers-disease#alzheimer accessed March 26, 2025

xxxii. Medicare Advantage plans utilize Hierarchical Conditions Categories (HCCs) to nuance what they pay a plan provider for an individual's covered care. Chronic conditions increase the health risk of a patient, thus impacting how much a Medicare Advantage plan will pay for your care. Providers assign medical codes based in part on the HCCs for any individual patient, leading to a risk-adjusted payment model for each patient. See What Are Hierarchical Condition Categories (HCC)? | Medicare and Insurance Costs | MedicareAdvantage.com Accessed online 3.25.25.

xxxiii. Medicaid and CHIP Payment and Access Commission (MacPac), "Issue Brief: Estimates of Medicaid Nursing Facility Payments Relative to Costs," January 2023

xxxiv. Mukamel et al, "Dementia care is widespread in US nursing homes; Facilities with the most dementia patients may offer better care," Health Affairs, June 2023

xxxv. Alzheimer's Association- Alzheimer's Impact Movement Fact Sheet, "Cost of Alzheimer's to Medicare and Medicaid," March 2024

xxxvi. Relatively rare forms of genetically influenced AD – so-called dominantly inherited Alzheimer's disease- does occur among persons younger than 65, but anti-amyloid drug therapy is not currently indicated for these patients.

xxxvii. Zissimopoulos et al, "The value of delaying Alzheimer's disease onset," Forum on Health Economics Policy, November 2014.

xxxviii. Avitan et al, "Towards a consensus on Alzheimer's disease co-morbidity?," Journal of Clinical Medicine, September 24, 2021