NEHI Network for Excellence in Health Innovation

Diagnosing Hope: The New Era of Alzheimer's Disease Treatment Hinges on Innovations in Diagnostics

A NEHI Report

October 2023

Contents

Acknowledgments

Authors

- **Thomas E. Hubbard, MPP**
  Senior Vice President of Policy Research, Network for Excellence in Health Innovation (NEHI)
  thubbard@NEHI-us.org
- **Lauren E. M. Bedel, MPH**
  Senior Health Policy and Program Associate, NEHI
  lbedel@nehi-us.org
- **Barrett Laird**
  Policy Intern, NEHI
- **Ashley Francis**
  Policy Intern, NEHI

Additional Project Team

- **Wendy Warring, JD**
  President and CEO, NEHI
  wwarring@NEHI-us.org
- **Steve Herskovitz**
  Vice President of Marketing and Member Engagement
  sherskovitz@nehi-us.org
- **Cristy Taylor**
  Chief of Staff, NEHI
  ctaylor@nehi-us.org

Layout and Design

- **Lilly Middleton**
  Marketing and Communications Specialist, NEHI
  lmiddleton@nehi-us.org

About This Report

This report was produced by NEHI following key stakeholder interviews and a stakeholder roundtable held at the Kaiser Permanente Center for Total Health on May 25, 2023. Financial support for this project was provided by Eisai Inc., Eli Lilly & Company, and Genentech Inc.

Representations and views expressed herein are solely those of NEHI staff and not necessarily those of the project participants and sponsors.

NEHI wishes to thank its roundtable panelists and subject matter experts for their participation, advice, and counsel. They are:

- **Hannah Mamuszka, MS**, Alva10
- **Joel Braunstein, MD, MBA**, C2N Diagnostics
- **Elizabeth Somers,** Eisai Inc.
- **Laura Cohen, JD & Adam Phipps, MBA**, Eli Lilly & Company
- **Brian Carey, JD**, Foley Hoag LLP
- **Hartmuth Kolb, PhD**, Janssen/Johnson & Johnson
- **Linda K. McEvoy, PhD**, Kaiser Permanente Washington Health Research Institute
- **Hampus Hillerstrom, MEcon, MBA, MSc,** LuMind IDSC Foundation
- **Claire Levesque, MD**, formerly Point32Health
- **Anil Nasta, MD & Cassandra Ricci**, Roche Diagnostics

About NEHI

NEHI is a non-profit, unbiased organization with members, including providers, hospitals and health systems, pharmaceutical and biotech companies, medical device, and technology providers, as well as associations and consultants. Through interdisciplinary collaboration and with our members' guidance, we research and examine tough and timely health care innovation issues from multiple, often divergent, perspectives. We then address policy and adoption challenges to promote the value of innovative products and processes.

Executive Summary

A New Era in Alzheimer's Disease Care Has Begun

A new era has begun with recent 2023 FDA approval of Leqembi, and the expected approval of donanemab, new drug therapies that remove a brain protein (amyloid-beta proteins accumulating as plaques) implicated in Alzheimer's disease.

The new therapies are disease-modifying therapies. They are likely to be more effective the earlier they are administered in the progression of a patient's disease.

Thus, it will be critical for patients, caregivers, and clinicians to:

- Initiate early screening for dementia
- Verify that patients have Alzheimer's disease and not other forms of dementia
- Detect the presence and the progression of amyloid plaques among patients with Alzheimer's who are eligible for anti-amyloid therapies

The Health Care System Now Faces a New Challenge: Accurate and Cost-Effective Testing for Alzheimer's Disease at Greater Scale.

Relatively few Americans are evaluated for dementia and Alzheimer's disease today, and most at a point when signs and symptoms of dementia are already evident.

The new anti-amyloid therapies may spur demand for screening and diagnosis that can only be met with a major scale-up in capabilities for testing, including clinician training, improved access to testing and testing facilities, and supportive payment.

Equity is a challenge in its own right: racial-ethnic disparities in Alzheimer's prevalence and in access to screening and diagnosis are well documented – factors that could drive new disparities in access to treatment.

The First Step: Overcoming Barriers to Uptake of CSF Analysis and PET Imaging

Currently the two best-validated and well-accepted modes of diagnosis for amyloid-related Alzheimer's disease are analysis of cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging. Innovations in both modes have improved their precision.

But Medicare coverage of PET imaging to detect amyloid has been limited to one image per patient per lifetime, conducted as part of studies under the Medicare Coverage with Evidence Development (CED) program. Medicare now intends to reverse this policy, but regional Medicare contractors will make final coverage decisions which may vary across the regions.

PET imaging facilities are also unevenly distributed throughout the U.S., creating barriers to access for rural residents, uninsured and poorly insured Americans.

Access to well-trained providers is especially important for uptake of CSF testing, a relatively inexpensive form of testing administered by lumbar punctures (spinal taps) that patients are often hesitant to accept.

Beyond CSF and PET: Expanding the Diagnostic "Toolbox" Will Be Crucial to Enable Testing on a "Right Test, Right Time, Right Patient" Basis and to Effective Use of New Therapies

Innovations now available and in development will be crucial in order to enable health care providers to screen and diagnose patients on a "right test, right time, right patient" basis.

Non-intrusive testing and highly scalable testing, including testing performed in primary care, will be essential to deliver cost effective testing for:

- Earliest feasible detection of dementia
- Differentiating Alzheimer's disease from other forms of dementia
- Pinpointing the presence of amyloid plaques among patients with Alzheimer's disease
- Tracking the progression of disease and patient's response during and after drug therapy
- Triggering referrals to more advanced or complex testing and to specialty health care, whenever warranted at every step in the journey.

Ultimately, innovations in testing may offer the promise of Alzheimer's detection before patients exhibit signs and symptoms of disease. Research has shown that disease may begin up to 25 years before symptoms appear.

Two Different but Complementary Sets of Tools Are Found in the Expanding Diagnostic Toolbox

Innovations are apparent in the two fields of dementia and Alzheimer's screening and diagnosis used in patient care today (See *Table Two*):

- ***Assessments of cognition and behaviors (neurobehavioral assessment).*** Innovations in development include digital assessment (data collection via digital devices and data analysis through artificial intelligence techniques) that may deliver objective measurement of Alzheimer's onset and progression.
- ***Detection of biochemical biomarkers.*** The first in an expected series of blood-based tests for Alzheimer's biomarkers are now available and more are in active development. As these tests are further validated and adopted, they offer capabilities for biomarker screening that could begin in primary care, trigger efficient referral to other modes of testing and to monitoring of disease progression, and refer patients to CSF analysis and PET. Identification of new, advanced biochemical biomarkers for CSF and PET is also highly active.

Amyloid Plaques Are Not the Only Pathology of Alzheimer's Disease- In Time, Early Detection of Tau Proteins and Other Pathologies Will Be Essential for Effective Treatment

Abnormal formations of tau proteins (tau tangles) in the brain, inflammation in the brain, and interaction of Alzheimer's disease with vascular dementia and other conditions contribute to as many as eight dominant pathobiological pathways of Alzheimer's disease.

In the long-term effective use of Alzheimer's disease therapies, including anti-amyloid drugs and anti-tau therapies now in development, will hinge on diagnostics that detect multiple pathologies.

Innovations in PET, CSF analysis, and blood tests are now providing estimates of both amyloid and tau concentrations in the brain.

The Emerging Need for "Right Test, Right Time, Right Patient" Portends a Paradigm Shift in Dementia Screening and Diagnosis in Three Phases

- ***In Phase One policy and practice must enable clinicians to make broader use of existing FDA approved or regulated tests.*** This includes early and recuring cognitive behavioral assessment with standard tests such as the Mini Mental State Examination and the Montreal Cognitive Assessment, coupled with neuropsychological testing, early uptake of blood-based testing, and appropriate referral to CSF analysis, PET, and other imaging modalities when warranted. Greater awareness of the need for early screening among patients, caregivers, and clinicians will be necessary if patients with amyloid-related Alzheimer's disease are to be identified at points most susceptible to treatment.
- ***In Phase Two novel digital assessment tools will be introduced as they become available,***

coupled with broader use of blood-based biomarker tests to complement or trigger referral to CSF analysis and neuroimaging. Persons with Down syndrome are at extremely high risk for Alzheimer's disease: Phase Two should hasten an urgent transition to configuring Alzheimer's diagnostics to meet the characteristics of their disease.

- ***Phase Three will be a longer-term transition to pre-clinical detection of Alzheimer's disease*** among patients who show no symptoms, including routine assessment among patients with a known genetic risk such as Down syndrome, or an inherited genetic risk. New protocols should include routine monitoring of patients on active anti-amyloid therapies and others that may emerge to treat pathologies such as tau tangles. Improving capabilities in machine learning and other artificial intelligence techniques may also enable the integration of data from cognitive-behavioral assessments and biochemical biomarker testing to yield more accurate and comprehensive information for clinicians on the individual patient's Alzheimer's disease pathway.

There are multiple implications for U.S. health care policy from the impending paradigm shift in dementia screening and Alzheimer's disease diagnosis. We present an overview in "Implication for Alzheimer's Disease Policy," at the conclusion of this paper.

A New Era in Alzheimer's Disease Care Has Begun

On July 6, 2023 the U.S. Food and Drug Administration granted traditional approval for the first time in its history to an anti-amyloid treatment for Alzheimer's disease. (Leqembi received accelerated approval status the prior January.)[i] A second anti-amyloid treatment could also receive traditional approval within the year.[ii] Amyloid plaques formed from abnormal deposits of beta-amyloid proteins in the brain are common in persons diagnosed with Alzheimer's disease. The new class of anti-amyloid monoclonal antibody therapies are disease modifying therapies that do not promise to cure the disease, but to slow down or arrest the patient's mental and physical decline by clearing the brain of amyloid plaques and excess amyloid proteins likely to produce plaques. Most drug treatments previously approved by the FDA target symptoms of advanced Alzheimer's disease, such as depression and irritability. The monoclonal antibody therapies are the first of what could be many potential disease-modifying Alzheimer's therapies in the future.

Treatment will likely be most effective at early stages of disease progression. Amyloid proteins occur naturally in the brain and perform essential functions in brain cells: it is abnormal expressions of amyloids that are associated with Alzheimer's disease. Abnormal amyloid formations and amyloid plaques can occur years before a patient begins to suffer from symptoms of Alzheimer's disease, such as memory loss and other signs of dementia. Recently published research suggests that the very earliest brain pathologies associated with Alzheimer's disease can start as much as 25 years before the onset of cognitive deficits.[iii] Thus, the effectiveness of the new anti-amyloid therapies will depend crucially on the ability of clinicians to detect abnormal amyloid formations as early as possible in the brain. Patients who are at the earliest stages of pathological amyloid formation are likely to benefit the most from anti-amyloid therapy, while patients at later stages are less likely to benefit and could be exposed to unnecessary risk.

Early detection and diagnosis of disease will be essential. Early detection and diagnosis of Alzheimer's disease looms as an essential step in effective treatment of the disease, and not only for effective use of the new anti-amyloid reaching the market today. While abnormal formations of amyloid are thought to be the first step towards progression of Alzheimer's and the eventual onset of severe forms of dementia, the course of the disease among individual patients, (that is, the underlying pathology of Alzheimer's disease), is complex and variable. Abnormal formations of amyloid can lead to abnormal formations of tau proteins, another naturally occurring protein in the brain, and to inflammation in the brain and other pathologies. At some point in the future these non-amyloid pathologies may also be subject to treatment with new therapies, creating new urgency around development of diagnostic tests that detect more than pathology at a time. (Anti-tau therapies are in active development already.)[iv]

Ultimately, realizing the full potential of new and oncoming treatments may hinge on early and even pre-clinical detection of Alzheimer's disease. The development of anti-amyloid disease modifying therapies for Alzheimer's disease is often represented as a true paradigm shift in medical care for the disease. But the full potential of new therapies will be realized if an equally significant paradigm shift occurs in the early detection and diagnosis of the disease, including detection of Alzheimer's disease at a pre-clinical stage, before signs and symptoms of Alzheimer's appear in patients.

This became more apparent less than two weeks after the FDA's July 6th approval of Leqembi. On July 16th a joint working group of the National Institute on Aging and the Alzheimer's Association released updated guidelines for diagnosis of Alzheimer's disease. Previous guidelines issued by the working group were directed only at Alzheimer's disease research. The July 6th guidelines are now directed at both research and clinical treatment of the disease. The new guidelines call for a new paradigm of Alzheimer's screening and diagnosis in which patients who do not appear to have signs or symptoms of Alzheimer's disease are tested for underlying biochemical biomarkers of the disease nonetheless. (The proposed guidelines also recognize that the Alzheimer's disease biomarkers that are currently available are not perfectly predictive of an individual patient's prognosis. Continuing and intensive research is still necessary to guide appropriate treatment to appropriate points in each patient's progression.)[v]

For now, early detection of amyloids and amyloid plaques will be the key priority for effective treatment. Many researchers suspect that abnormal formations of the amyloid-beta protein are the first pathologies that develop in the brains of patients with Alzheimer's disease.* Hence the heavy investment in anti-amyloid therapies that is now yielding Leqembi, donanemab, and other drug candidates still in development. This means that early detection of amyloids will be a key factor in effective treatment with anti-amyloid therapies.

---

* While excess amyloids and the formation of amyloid plaques are thought to be the first manifestations of Alzheimer's disease, the precise origins of Alzheimer's disease in the brain are not completely known, and likely vary from patient to patient. Risk factors that may trigger the onset of Alzheimer's disease include patient history of smoking and cardiovascular disease, and the presence of genetic mutations associated with high prevalence of the disease, including genetic mutations associated with Down syndrome and inherited genetic mutations such as the APOE4 mutation.

What Are Amyloid Proteins and Amyloid Plaques?

Amyloid precursor protein (APP) is one of the many proteins that build the human brain and central nervous system. APP is highly concentrated within the neuron tissues found in the brain, spine, and nerves.[vi] When APP splits, it separates into two peptides, soluble amyloid precursor protein (SAPP) and amyloid beta peptide.[vii] The buildup of amyloid beta protein can trigger a sequence of events that lead to nervous system inflammation and the breakdown of neurons.[viii] When amyloid beta proteins build up in the brain, they form amyloid plaques.[ix] Amyloid plaques form between neurons, blocking cell communication and compromising neuron functions.[x] Amyloid plaque buildup leads to inflammation and apparently is also implicated in abnormal production of tau proteins, another brain-building protein. Abnormal formations of tau proteins (tau tangles) lead to further breakdown of neurons and hinder cell communication.[xi]

A typical human brain contains billions of neurons and shrinks in size with age.[xii] In people with Alzheimer's disease, neuron cell death occurs more rapidly.[xiii] An underlying characteristic is brain shrinkage due to neuron deterioration beginning in the parts of the brain implicated in memory.[xiv] As a result, the most commonly identified first signs of Alzheimer's disease include forgetfulness and memory loss.[xv] Amyloid beta and tau proteins are both naturally occurring in the brain;[xvi] however, amyloid plaque buildup leads to the overproduction of tau tangles, followed by neuron cell death and the brain decreasing in size.[xvii] As a result, amyloid beta proteins are strongly implicated in the development of Alzheimer's disease.

Researchers postulate that there are seven stages of Alzheimer's disease, with Stage One occurring well before the presentation of symptoms.[xviii] However, modern-day diagnostic criteria only identify the disease after significant brain deterioration.[xix] The relationship between amyloid beta protein and Alzheimer's disease provides helpful insights regarding processes in the brain that signify the onset and progression of Alzheimer's and the need for intervention.[xx] The preponderance of amyloid beta proteins and amyloid plaques in many patients with Alzheimer's disease has also made amyloids a major target of research and development of therapies and diagnostics, including the new anti-amyloid therapies now reaching approval by the FDA.[xxi]

The Health Care System Now Faces a New Challenge: Accurate and Cost-Effective Testing for Alzheimer's Disease at Greater Scale

Relatively few Americans are evaluated for Alzheimer's disease today. A recent estimate suggests that only 16 percent of adults over the age of 65 are routinely screened for Alzheimer's and other forms of dementia.[xxii] The Medicare program encourages physicians to perform a cognitive assessment as part of the free (no out-of-pocket cost) annual wellness visit offered to Medicare beneficiaries. A 2020 study of data from 2011-2019 suggested substantial room for increasing uptake of cognitive assessments in the wellness visit. Only about half of Medicare beneficiaries reported that they had made use of the wellness visit, although the rate of patient uptake had increased steadily since 2011. Fewer than a third of beneficiaries had received a structured cognitive assessment (such as assessment with the Mini Mental State Examination or the Montreal Cognitive Assessment), although some beneficiaries may have been assessed by direct observations conducted by the physician. Beneficiaries of Medicare Advantage plans were more likely to have received cognitive assessments than beneficiaries of traditional, fee-for-service Medicare: possibly a reflection of more effective promotion of preventive care services under Medicare Advantage.[xxiii]

Findings from peer-reviewed literature suggest that patients and caregivers often avoid screening due to fear or denial that the patient is suffering from dementia, and from the perception among patients, caregivers and clinicians that little can be done therapeutically to arrest the patient's decline.[xxiv] Persons with a family history of Alzheimer's disease are more likely to access or be offered screening although, here again, in the absence of effective therapies, clinicians have debated both the clinical utility and the ethics of screening when an apparently positive finding of the disease could cause distress, not only to the patient, but to other family members who may discover their risk for the disease as a result. The U.S. Preventive Services Task Force has made no recommendation to support uptake of cognitive assessment for persons over 65 years of age, citing insufficient evidence of benefits and of potential harms.[xxv] (Despite the Task Force's stance, Medicare still encourages clinicians to administer cognitive assessments during annual wellness visits, as noted above.)

Earlier and more frequent screening will impose new demands on primary care. Demand for dementia screening may now increase as patients and caregivers become aware of the new anti-amyloid therapies. This represents an added, if necessary, burden on primary care physicians and primary care teams given the current, relatively low rates of screening. The most commonly used cognitive assessments (the Mini Mental State Examination or MMSE, and the Montreal Cognitive

Assessment, MoCA), are performed by clinicians in face-to-face encounters with patients, and typically take 10-15 minutes to administer. Clinicians must also be trained on the use of cognitive assessment tools.

As of now there are no clinical practice guidelines in common use that call for screening of asymptomatic patients who present with no signs or symptoms of Alzheimer's disease or other dementias, with the exception of patients at a known familial or genetic risk. Cognitive assessments are naturally limited to the detection of signs and symptoms. The newly released clinical diagnosis criteria released by the National Institute on Aging and Alzheimer's Association Workgroup is the first call to design guidelines around pre-clinical detection of Alzheimer's disease, based on the increasing evidence that pathologies of Alzheimer's can begin years before symptoms appear, (up to 25 years in advance, as noted above.) The new criteria call for classifying the progression of Alzheimer's disease in seven stages that begin with a Stage Zero (for persons with a "deterministic gene" for Alzheimer's, such as persons with Down syndrome), and a Stage One that classifies individuals who are asymptomatic but test positive for biomarkers of Alzheimer's disease. (See ***Table One***)

While they are not yet used in standard-of-care practice today, the Clinical Trials on Alzheimer's Disease Task Force, a panel of European and American experts on ongoing innovations in Alzheimer's disease research, anticipates that blood-based biomarker tests will become standard diagnostic tools for pre-clinical detection of Alzheimer's disease. Blood-based tests will allow primary care physicians to make an early diagnosis of the disease without referral to a specialist in memory disorders.[xxvi] The Task Force also anticipates that, before primary care physicians resort to administering a blood-based test, digital cognitive evaluation tests could be administered to indicate which patients are candidates for further evaluation with blood tests. Digital cognitive assessments will offer the advantage of returning results that are objective measurements.

Uptake of emerging diagnostic innovations will raise the probability that patients will be effectively treated – but does not guarantee it. The combined effect of these new forms of testing should be to increase the probability that a patient will be appropriately diagnosed and recommended for therapies (anti-amyloid, and other therapies that may emerge such as anti-tau therapies) at a point when they are most likely to be effective. Just how rapidly this probability can be raised will remain subject to the rate of progress in the scientific understanding of Alzheimer's disease.

While rapid progress has been made in recent years, precise understanding of the association between early, asymptomatic presence of biomarkers of Alzheimer's disease and the onset and path of progression of Alzheimer's disease in any given patient is not well understood at present. In the

words of the NIA-AA Workgroup, "the degree of cognitive/functional impairment does not follow in lock step with biological Alzheimer's disease severity - i.e., a range of possible relationships between biological Alzheimer's disease stage and clinical stage will be found across the population."[xxvii]

As a result, intensive research to characterize patients' susceptibility to Alzheimer's disease and the likely trajectory of their disease will be as essential to ensuring the effectiveness of new Alzheimer's therapies as detection of the disease at the earliest stages. Ongoing research on the application of machine learning and other forms of artificial intelligence (AI) may yield the most promising applications. Ultimately, machine learning from diverse data sources, including biomarker data, imaging analysis, and data from cognitive assessments may achieve an integration of data sources that will further characterize the eight pathobiological pathways of Alzheimer's disease enumerated by the NIA-AA Workgroup, and move Alzheimer's disease diagnosis and therapy closer to precision therapy and personalized care.[xxviii]

Alzheimer's disease policy must prepare the way for uptake of diagnostic innovations to ensure that existing challenges – such as disparities and inequitable access to Alzheimer's care – are not exacerbated. Without careful advance preparation within the health care system these promising advances towards pre-clinical detection of Alzheimer's disease and precision diagnosis could well exacerbate the challenges already evident in today's Alzheimer's care, such as the challenges of equitable access, patient convenience and cost cited above.

Racial-ethnic disparities pertaining to Alzheimer's disease and other dementias are wide: the prevalence of Alzheimer's disease and other dementias in Black Americans is estimated to be as much as twice as high as the rate found in white Americans of the same age. The prevalence of Alzheimer's and other dementias is as much as two percentage points higher in older Hispanic Americans compared to white peers, (12.2% vs. 10.3% among persons aged 65 years or older.)[xxix] Similar racial-ethnic disparities are evident in health care services for dementia, including diagnostic services for patients with Alzheimer's disease and other dementias.[xxx] Black, Hispanic and other minority groups are also historically underrepresented in clinical research on Alzheimer's disease, which indicates that research on characterizing Alzheimer's among these groups and identifying pathways to precision treatment through utilization of tools such as AI will be a particular challenge.

Even with adequate health insurance coverage, patients today face hurdles to accessing diagnostic procedures for Alzheimer's and other dementias.[xxxi] PET imaging facilities tend to be concentrated among major medical centers and teaching hospitals, leaving gaps in convenient access for patients living in rural communities.[xxxii] If past is precedent, as innovative and advanced forms of Alzheimer's detection and diagnosis (such as blood-based biomarker testing and use of AI-enabled analysis)

uptake will still tend to concentrate in major medical centers, in communities with the most highly trained clinicians, and be accessible first to patients who can bear the cost (through insurance, out-of-pocket spending, or both) of advanced diagnostic procedures.

Gaps in insurance coverage and in reimbursement are a final challenge. The imperative to detect Alzheimer's disease at early stages will be a challenge for Medicare and for other health insurance plans in the years ahead. Testing to determine patients' eligibility for anti-amyloid therapy is an immediate challenge since testing to confirm the presence of amyloid biomarkers is required for eligibility following a clinical diagnosis of mild cognitive impairment or mild dementia due to Alzheimer's disease. Several gaps in coverage and in reimbursement for professional and laboratory services must be overcome.

- ***Medicare:*** As noted, Medicare is dropping a decade-long policy that restricts patient access to PET imaging for amyloid detection, but final coverage policies will be left to regional Medicare administrators who also determine coverage on CSF analysis. Fifty percent or more of PET imaging is delivered as a hospital outpatient service. Medicare reimburses PET imaging on a "packaged" basis in which all costs of the imaging visit, including the cost of imaging agents such as PET radiotracers, are paid at one fixed rate representing average costs. This policy has dissuaded hospitals, particularly rural hospitals with limited financial resources, from offering PET imaging for detection of amyloid, since amyloid imaging agents are comparatively higher-cost than radiotracers (radiopharmaceuticals) used for other conditions, and demand historically for amyloid PET imaging has been significantly lower than demand for imaging of other conditions. Medicare is now reconsidering packaged payment for hospital outpatient PET imaging given the continuing introduction of novel PET imaging agents for Alzheimer's disease and other conditions.[xxxiii] Medicare reimbursement for CSF analysis is general insufficient for the services rendered because claim processing is largely based on generic coding methodology. Medicare coverage for blood-based biomarker testing is still largely undetermined.
- ***Commercial payers:*** Amyloid PET imaging is not widely covered by commercial payers, and a majority of payers do not yet cover CSF biomarker testing. As with Medicare, commercial coverage of blood-based biomarker testing is still largely undetermined. While the vast majority of commercially-insured patients are not of Medicare-eligible age, the increasing evidence that pathologies of Alzheimer's begin many years in advance of symptoms means that commercial plans will face increasing demand to underwrite screening and diagnosis.
- ***Medicaid:*** State Medicaid programs face similar gaps in coverage for diagnostic services for Alzheimer's disease. Moreover, as the insurer of the largest number of children in the U.S. and a major insurer of persons with disabilities, including Down syndrome, Medicaid will also face an

increasing need to underwrite access to appropriate screening and diagnosis for Alzheimer's disease.

Table One: National Institute on Aging-Alzheimer's Association: Revised Clinical Criteria for Alzheimer's Disease

Stage 0 Asymptomatic, deterministic gene	No evidence of clinical change. Biomarkers still in the normal range		
Stage 1 Asymptomatic, biomarker evidence only	Performance within expected range on objective cognitive tests	No evidence of recent cognitive decline or new symptoms	
Stage 2 Transitional decline: Mild detectable change, but minimal impact on daily function	Normal performance within expected range on objective cognitive tests	Decline from previous level of cognitive or neurobehavioral function, that represents a change from individual baseline within past 1-3 years, and has been persistent for at least 6 months • May be documented by evidence of subtle decline on longitudinal cognitive testing which may involve memory or other cognitive domains but performance still within normal range • May be documented through subjective report of cognitive decline (SCD) • May be documented with recent onset change in mood, anxiety, motivation not explained by life events	Remains fully independent with no or minimal functional impact on daily life activities (ADL)
Stage 3 Cognitive impairment with early functional impact	Performance in the impaired/ abnormal range on objective cognitive tests	Evidence of decline from baseline, documented by the individual's report or by observer (e.g. study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments	Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex activities of daily life, i.e., may take more time or be less efficient but still can complete, cither self-reported or corroborated by observer
Stage 4 Dementia with mild functional impairment	Progressive cognitive and mild functional impairment on instrumental ADL with independence in basic ADL		
Stage 5 Dementia with moderate functional impairment	Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance		
Stage 6 Dementia with severe functional impairment	Progressive cognitive and severe functional impairment on dependence for basic ADs		

From the National institute on Aging-Alzheimer's Association Revised Clinical Criteria for Alzheimer's Disease, July 15, 2023, *https://aaic.alz.org/nia-aa.asp*

The First Step: Overcoming Barriers to Uptake of CSF Analysis and PET Imaging

As of now, there are two standard modes for detecting amyloid formations in patients: analysis of cerebrospinal fluid (CSF) collected from a lumbar puncture (otherwise known as a spinal tap), and brain imaging conducted with FDA-approved positron emission tomography (PET). Repeated innovations have rendered both modes of detection highly predictive of the presence of amyloids and amyloid plaques, but they have seen limited use in the U.S. before now. In the absence of effective anti-amyloid therapies, findings from amyloid detection have been perceived to be of limited usefulness (i.e., limited clinical utility) for many patients. As a result, insurance coverage for both procedures has been restricted, most notably by Medicare, the source of health insurance for the vast majority of older Americans and most Americans with Alzheimer's disease.

Patients tested by CSF analysis or PET imaging in the past were most likely tested at points when symptoms and signs of Alzheimer's disease were already evident, and thus at a point beyond the early stages of the disease, not to mention a pre-clinical stage.

In a major development, Medicare is expanding patient access to PET imaging for detection of amyloid. On October 13, 2023, Medicare formally removed its longstanding National Coverage Determination that restricted Medicare beneficiaries to one PET image per lifetime for amyloid detection and a corresponding requirement that imaging for amyloid detection be conducted within studies registered under Medicare's Coverage with Evidence Development (CED) program.[xxxiv] Reversal of the one CED-related image per lifetime rule was widely viewed as an essential step that will enable physicians to determine the eligibility of individual patients for treatment with Leqembi and other anti-amyloid therapies approved by the FDA in the future, and to enable monitoring of patients for their response to therapy.

Yet major near-term challenges still remain: challenges of equitable access, patient convenience, and cost. Lumbar punctures for CSF analysis and PET imaging are typically ordered by neurology specialists. There is a significant shortage in neurologists throughout the U.S. that was characterized as a "grave threat" to neurological care well before the launch of anti-amyloid therapies.[xxxv] PET imaging requires patient access to imaging facilities that are not evenly distributed throughout the country, thus creating barriers to care in rural areas and other medically underserved communities, and persistent racial, ethnic, and socioeconomic disparities in care.[xxxvi] Moreover, at present both procedures are ordered by specialists. At present, the costs of the procedures are

high enough to inhibit repeated or overly frequent use to detect or monitor Alzheimer's disease.† Use of both modes as the sole methods to detect and monitor beta-amyloid formations among patients, and in greater patient volumes, thus poses a fiscal challenge to Medicare, potential out-of-pocket cost burdens to patients and families, and may invite imposition of utilization management constraints. Sole reliance on PET imaging and CSF analysis for detection of amyloid at very early stages of Alzheimer's disease may have limitations given the scale of screening that may be required as therapies reach the market, and impractical for screening patients who manifest no signs or symptoms of Alzheimer's disease to determine pre-clinical formation of amyloid, or for other signs of neurodegenerative disorders.

† Costs of PET imaging and CSF analysis (via lumbar puncture) for Alzheimer's disease vary considerably according to the setting in which they are delivered, and by region of the country, but informal estimates solicited by NEHI range from about $1000 to $5000 for PET imaging, and from $500 to $3000 for CSF analysis.

Beyond CSF and PET: Expanding the Diagnostic 'Toolbox' Will Be Crucial to Enable Testing on a 'Right Test, Right Time, Right Patient" Basis and to Effective Use of New Therapies

Over time, the challenge of scaling-up cost-effective screening and diagnosis can be met by innovations in diagnostics that will give clinicians more options to offer the best test at the right time for individual patients. *Table One* enumerates several categories of innovation in Alzheimer's diagnostics that are in active development. They are designed to enable detection of declines in patient cognition and functional abilities, as well as other biochemical biomarkers of Alzheimer's disease. Successful development of a range of these innovations, including policy to expedite validation, approval, and adoption, may prove critical to identifying patients most likely to respond to the new class of anti-amyloid therapies and delivery of therapy at scale and in the most cost-effective manner.

Digital biomarker assessment is a non-invasive approach that could enable greater detection and monitoring of patients seen in primary care. Current tests of cognition (such as the MMSE and MoCA) are subject to ongoing enhancements, including administration of the tests over digital devices that collect and store data for further analysis. Analysis of this digitally collected data will enable application of advanced techniques, such as machine learning, that may differentiate signs of Alzheimer's disease from other forms of dementia and identify patterns of Alzheimer's disease progression. Digital data collection and advanced analytical techniques are also enabling research into new biomarkers of Alzheimer's disease that yield objective measurement of changes in patient cognition and function, in contrast to the subjectively measured findings from current cognitive tests. Promising areas of research on digital biomarkers include data (collected by digital device) on changes in patient movements (gait and mobility), speech and language patterns, eye movements, and sleep patterns. While research and development of digitally enabled screening and diagnostic tests is highly active, digital biomarkers and digitally enabled tests remain to be validated, approved, and made available for general clinical use.[xxxvii]

Blood-based testing will be a key complement to standard testing in the near-to midterm. Blood-based testing for Alzheimer's disease has begun to move into clinical use, albeit with some limitations. Blood-based assays for Alzheimer's offer the promise of testing that can be administered routinely, including routine administration in primary care practice. Innovative testing of whole blood, blood plasma or blood serum is very active and has already yielded at least one commercially available

blood test for detection of amyloids.‡ The NIA-AA Workgroup anticipates that blood tests will be the testing mode most likely to enable pre-clinical detection of Alzheimer's disease in patients, although a full complement of blood-based tests have not yet been validated and approved for clinical use. Expert consensus on acceptable standards for test accuracy (test sensitivity and specificity) are still in flux.[xxxviii] Nevertheless, use of these tests can still serve as a trigger for referral to CSF analysis, PET, and other forms of neuroimaging that clinicians may feel are warranted for individual patients. Innovative improvements in CSF analysis and PET imaging are also underway. The FDA has approved PET imaging for tau tangles as well as amyloid plaques, and FDA-approved assays for CSF analysis are now capable of testing multiple markers of Alzheimer's disease at once and rendering a ratio of relative concentrations of biochemical biomarkers.§

Amyloid Plaques Are Not the Only Pathology of Alzheimer's Disease: In time, Early Detection of Tau Proteins and Other Pathologies Will Be Essential for Effective Treatment

Much remains to be discovered about the causes and the progression of Alzheimer's disease among individual patients, as noted earlier. But research findings make clear that there is no single cause for all forms of the disease, and that the disease can take very different paths from one patient to another, along what Alzheimer's researchers now describe as the "Alzheimer's Continuum."[xxxix]

Research suggests that there are at least eight "pathobiological pathways" along the Alzheimer's Continuum. The disease may or may not progress from excess beta-amyloids and growth of amyloid plaques in the brain, to growth in tau proteins (another naturally occurring protein) that leads to tangled formations of tau (tau tangles), to inflammations of the brain, as well as interactions with other degenerative conditions that may co-occur with Alzheimer's disease, such as vascular dementia. The suspected major pathways of Alzheimer's disease are captured in what is known as the ATN Framework[xl] in which distinct pathways of disease encompass beta-amyloid formations ("A), tau and tau tangles ("T), and neuroinflammation ("N").¶

---

‡ The PrecivityAD test (C2N Diagnostics, Inc, St. Louis MO) was introduced in late 2020 as the first commercially available blood-based test for amyloids. A second blood-based test for amyloids, the AD-Detect Amyloid Beta 42/40 Ratio test (Quest Diagnostics), was introduced in May 2022. (See BrightFocus Foundation, " Alzheimer's Blood Tests – What You Need to Know in 2023," accessed August 8, 2023)

§ The FDA approved tests from Roche Diagnostics for simultaneous detection of amyloids and tau proteins in CSF in June 2023, (See Andrea Park, " Roche nabs FDA nod for another pair of CSF biomarker tests for Alzheimer's disease," Fierce Biotech, June 28, 2023)

¶ The NIA-AA Workgroup has recommended a new version of the ATN Framework, the ATNISV Framework, to

Biomarker detection of non-amyloid pathologies will be essential to development, testing and use of new therapies to treat tau tangles and other non-amyloid pathologies of Alzheimer's disease. Seventy percent or more of drug therapies currently in development for treatment of the disease are targeted at clearing tau proteins and tau tangles from the brain, or targeted at other pathologies of Alzheimer's disease that may unfold during or after the formation of beta-amyloids and amyloid plaques – or even before brain degeneration due to amyloids.[xli]

Ultimately, effective treatment of Alzheimer's disease may entail administration of multiple therapies in highly personalized sequences, necessitating parallel diagnosis and monitoring of multiple biomarkers. Eventually the treatment of Alzheimer's disease may be administered through personalized sequencing of differing therapies, or through combination therapies, akin to the use of combination therapies now seen in treatment of some cancers. This will increase the need for diagnostic tools capable of detecting multiple biomarkers of multiple pathologies of Alzheimer's disease at one time.

---

incorporate additional or added dimensions of Alzheimer's disease that are detected from additional biomarkers of inflammatory/immune mechanisms ("I"), vascular brain injury (V) and synucleinopathy (S), degenerative conditions that include Parkinson's disease and Lewy body dementia. (See NIA-AA Revised Clinical Criteria for Alzheimer's Disease, accessed July 28,2023 at https://aaic.alz.org/downloads2023/NIA-AA-Revised-Clinical-Criteria-AAIC-2023.pdf)

The Emerging Need for 'Right Test, Right Time, Right Patient' Testing Portends a Paradigm Shift in Dementia Screening and Diagnosis

Our history with dementia, including Alzheimer's disease, is one in which dementia is acknowledged most often at a point when a patient's memory loss and other signs and symptoms are already obvious. For patients and their caregivers, the best plan of action is enrollment in the best dementia care they can access and afford.

This may remain the best plan of action for many patients in the months and years ahead while Real World Data is collected on the performance of new Alzheimer's disease therapies, data that will guide effective use with patients. But looking ahead, the success of new anti-amyloid therapies, and the non-amyloid therapies (such as anti-tau therapies) that may follow will be closely tied to the launch of innovative tests for detection and diagnosis of Alzheimer's disease, including tests for signs and symptoms (cognitive behavioral assessments and other neurobehavioral assessments) and tests for pathologies of Alzheimer's that originate in the brain itself.

In contrast, the future of Alzheimer's disease treatment hinges on a major paradigm shift in Alzheimer's detection and diagnosis in which clinicians, patients and caregivers discuss cognitive decline more openly, test for dementia earlier than the norm today, on a greater scale, and when necessary test for biochemical biomarkers and the patient's cognition and functional abilities at multiple points along the patient's Alzheimer's disease journey. Testing will be necessary for at least five outcomes:

1. Early detection of biomarkers of neurodegeneration,[**]
2. Early differentiation of biomarkers to distinguish Alzheimer's disease from other neurodegenerative conditions such as vascular dementia (a differential diagnosis),[††] followed by;

** Including early and routine testing of individuals with a known genetic predisposition to Alzheimer's disease, such as individuals with Down syndrome or an inherited predisposition to the disease.

†† "The four most common age-related brain pathologies that underlie cognitive impairment or dementia in elderly persons are Alzheimer's disease, cerebrovascular disease (CVD, including vascular dementia), limbic associated TDP-43 714 encephalopathy (LATE), and Lewy body disease." (See NIA-AA Proposed Guidelines on Alzheimer's Disease Diagnosis, p.24) The extremely high prevalence of Alzheimer's disease among persons with Down syndrome has led researchers to designate the disease as Down syndrome-associated Alzheimer's disease (DS-AD), as distinct from Alzheimer's disease associated with inherited genetic mutations (familial Alzheimer's disease, or FAD), and sporadic Alzheimer's disease (sAD), the form most common among older adults. New Alzheimer's disease diagnosis guidelines

3. Early differentiation or characterization of underlying pathologies of Alzheimer's in the brain, such as beta-amyloid plaques, tau tangles and neuroinflammation,
4. Monitoring of biochemical biomarkers throughout a patient's course of treatment, such as through treatment with multiple therapies,
5. Monitoring of cognitive and neurobehavioral assessments throughout the patient's life Alzheimer's disease.

proposed by the National Institute on Aging and the Alzheimer's Association would designate a "Stage Zero" of Alzheimer's disease that applies to a pre-symptomatic stage among persons with an extremely high likelihood of eventual progression into later stages of the disease, including persons with Down syndrome. Other forms of dementia that are considered to be non-Alzheimer's but can be co-occurring are Parkinson's disease and Lewy body dementia, both of which have recently been relabeled in a disease category termed Neuronal Synuclein Diseases. (See NIA-AA Revised Clinical Criteria, page 8)

The High Risk of Alzheimer's Disease among Persons with Down Syndrome

Down syndrome (also referred to as Trisomy 21) is a developmental disorder in which people are born with an extra copy of chromosome 21.[xlii] This extra copy of chromosome 21 influences the physical characteristics, physical health, and intellectual capacity of persons with Down syndrome, and it also renders them more susceptible to Alzheimer's disease.[xliii] Chromosome 21 carries the amyloid precursor protein (APP) known to be associated with the development of Alzheimer's disease.[xliv] Consequently, the risk of developing Alzheimer's disease among individuals with Down syndrome is greater than that of the general population; only 11% (6.7 million) of people 65 and older in the US have Alzheimer's as compared to 60% of people with Down syndrome of the same age group.[xlv] Since people with Down syndrome have an additional APP-carrier site in their brains, they are more susceptible to amyloid beta buildup and the onset of Alzheimer's disease.[xlvi]

Some researchers classify Down syndrome-related Alzheimer's as a separate but similar disease (so-called DS-AD) due to differences in the neurobiological and behavioral presentations.[xlvii] For example, a common first sign of dementia in a typical patient is forgetfulness, but the caregivers of people with DS denote personality and behavioral changes as first signs.[xlviii] Consistent with these behavioral markers, DS-AD begins in the frontal cortex, whereas the "sporadic AD" found among non-Down syndrome persons tends to begin in the entorhinal cortex and hippocampus.[xlix] Furthermore, studies show that most individuals with Down syndrome develop AD-related brain pathology much earlier than the general population. More specifically, people begin to develop DS-AD by their 40s and 50s, whereas the general population develops Alzheimer's disease in their 60's.[l]

The relationship between Down syndrome and Alzheimer's disease is complex. First, due to the presence of intellectual disability in individuals with Down syndrome, Alzheimer's disease can be more difficult to diagnose.[li] To facilitate diagnosis, caretakers and clinicians must begin documenting baseline behaviors in individuals with Down syndrome prior to age 40.[lii] Adding to the complexity, most individuals with Down syndrome develop amyloid plaques and tau tangles by their 40s, but not all people with Down syndrome develop Alzheimer's disease.[liii] More research is necessary to determine why this occurs.

It is important to emphasize that not all individuals with Down syndrome will develop Alzheimer's disease, but the likelihood is significantly increased compared to the general population.[liv] Regular medical check-ups, cognitive assessments, and monitoring of cognitive function are essential for early detection and intervention in individuals with Down syndrome.[lv] Moreover, since the pathologies of Alzheimer's disease in persons with Down syndrome appear to originate and progress along different biological pathways from sporadic Alzheimer's disease, diagnostic tools for detecting and diagnosing Alzheimer's in the Down syndrome population must be adapted and tested specifically to meet the unique characteristics of the disease among the Down syndrome population.

Preparing for the Future of Alzheimer's Disease Diagnosis and Treatment

How will the health care system make this transition to a future in which testing for Alzheimer's disease is likely to be more frequent, and initiated much earlier than today, even at pre-clinical stages when patients exhibit no signs and symptoms of disease?

Can this transition be accelerated or expedited?

There is no sure-fire guarantee that any given test now in development for detection and diagnosis of Alzheimer's disease will reach successful validation and adoption. But the wide range of innovations in cognitive behavioral assessment, other neurobehavioral assessment techniques and in biochemical biomarker testing is reason for real optimism.[lvi]

The transition to the future of Alzheimer's detection and diagnosis can be envisioned as three phases.

PHASE ONE is the "here and now" phase of today. In this phase clinicians will remain heavily reliant on the current standards of screening and diagnosis, including:

- Greater awareness of the need for early dementia screening by primary care teams as awareness of new anti-amyloid therapies increases.
- Early and recurring cognitive behavioral assessment with tests such as the MMES and the MoCA, and neuropsychological testing.
- Early adoption of blood-based biomarker tests
- Diagnosis through analysis of CSF and neuroimaging with PET scanning for amyloids, and other modalities (such as neuropsychological testing and Magnetic Resonance Imaging) when warranted. CSF analysis and PET imaging provide different, but complementary sources of data on the patient's condition and are not substitutes for each other. Clinicians will need to rely on both forms of testing to achieve careful evaluation of patients.

PHASE TWO is an intermediate phase in which new tests are validated and adopted. These tests will begin to complement standard tests of cognition, patient behaviors, and biochemical biomarkers by offering options, including tests that can be used by non-specialists, such as primary care physicians and primary care teams. For example:

- Novel cognitive and neurobehavioral assessments, such as digital assessment tools and techniques that may yield objective measurement of the signs and symptoms of Alzheimer's

disease and other forms of dementia.

- A first generation of blood-based biomarker tests and other forms of non-invasive testing that may also be adaptable for administration by non-specialists and provide convenient and relatively inexpensive testing to complement more standard CSF analysis and brain imaging.

PHASE THREE will be a future state in which primary care teams and specialists have a wide range of testing tools and techniques that will enable:

- A transition to testing for Stage 1 Alzheimer's disease, a stage at which patients present no signs or symptoms of Alzheimer's disease (i.e., asymptomatic), but test for underlying biomarkers of disease. Transition to Stage 1 could be a step-by-step progression in which patients with identifiable risk factors (such as a history of smoking, a known genetic risk factor such as that faced by persons with Down syndrome, or patient populations subject to highly disparate rates of disease, such as Black and Hispanic Americans) are prioritized for testing.
- Routine monitoring of patients who receive active therapy, such as patients treated with the newly emerging anti-amyloid therapies.
- Integration of data from all types of testing (cognitive behavioral, other neurobehavioral, and biochemical biomarker testing combined) to yield more specific and personalized information on each patient's condition and generate guidance for administering therapies to the patients most likely to benefit, at points in the progression of disease when they are most likely to benefit.

Table Two: Innovations in Diagnostics for Screening and Diagnosis of Alzheimer's Disease

Cognitive and Behavioral Tests		
Test		**Description**
Cognitive Assessment		Questionnaire-based tests of memory and cognitive function. Examples include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).
Neurobehavioral Assessment		Tests for impairments to activities of daily living, mood, executive function, visual perception and other behaviors. They are often administered as part of a battery of tests in comprehensive patient assessments of the patient's dementia status.
Digitally Enabled Assessment		Standard cognitive assessments and other tests can be adapted for use with digital tools (such as tablets) and enhanced with computerized cognitive tasks
Digital Biomarkers		An emerging area of development. Digital biomarkers can be collected through tools such as smartphones, wearable devices, and home or office-based sensors. Subject to validation, digital biomarkers may include markers of patients' gait, mobility, speech, language patterns, eye movements, and sleep.
Biomarker Tests		
Method	**Test**	**Description**
Imaging	**Magnetic Resonance Imaging (MRI)**	A standard tool for visualizing changes in a patient's brain structure and volume that may be indicative of Alzheimer's disease, and to rule out other diseases such as cancer or stroke.
	Positron Emission Tomography (PET)	Short-lived radioactive "tracers" are injected into the patient, bind to molecules in the brain, and emit gamma rays detectable by the PET scanner. PET tracers are now capable of detecting amyloid plaque and tau tangle formations indicative of Alzheimer's disease. Discovery of other (non-amyloid, non-tau) biomarkers detectable by PET imaging, such as markers of brain inflammation, is an active area of research.
Fluid Biomarkers	**Cerebrospinal fluid (CSF) analysis**	Detects the proteins associated with Alzheimer's disease (such as amyloid-beta and tau proteins) that circulate in the brain and central nervous system. Laboratory analysis of CSF (collected by lumbar puncture, also known as a spinal tap) can isolate the type and volume of proteins associated with Alzheimer's disease to confirm a diagnosis and stage of progression of the disease. Discovery of other novel biomarkers of Alzheimer's disease detectable by CSF analysis is an active area of research.
	Blood-based biomarker test	Microarray device development is generating advancements in the design of blood-based tests for biomarkers of Alzheimer's disease such as amyloid-beta and tau proteins. Discovery of other novel biomarkers detectable in whole blood, blood plasma or serum is an active area of research.
Genetic Testing	**Genetic tests**	Capable of identifying several specific gene variants and genetic mutations that are linked to an elevated susceptibility for the onset of Alzheimer's disease. Individuals who possess certain specific variants of the APOE gene can be at risk for late-onset Alzheimer's disease, while several rare, inherited genetic mutations are associated with elevated risks for earlier onset.
Analytical Approaches		
Test		**Description**
Artificial intelligence		Application of AI-enabled techniques to detection and diagnosis of Alzheimer's disease is now underway in several forms, although not yet in extensively validated or widespread use. AI algorithms can be applied to analysis of existing modalities (such as MRI, PET, CSF analysis, and to cognitive assessments) analysis) to gain greater precision and accuracy in findings. Application of Natural Language Processing to analysis of patient speech is a promising area development. Application of AI algorithms to integrated data sets (data from cognitive and behavioral, assessment, imaging, fluid and blood testing, and other biomarkers) is seen as a promising future pathway to early detection and long-term tracking of the progression of Alzheimer's disease and its underlying brain pathologies.

Implications for Alzheimer's Disease Policy

There are many near to long-term implications for health policy arising from oncoming innovations in Alzheimer's disease detection and diagnosis.

From a Phase One (near term) perspective:

- ***Heightened demand for cognitive assessment.*** The relatively low rate of cognitive assessment among older Medicare patients suggests a need for a scale-up of assessments in primary care and has prompted calls to implement performance incentives paid to clinicians for administration of cognitive assessments.[lvii] While most persons at-risk for Alzheimer's disease will likely be Medicare beneficiaries, commercial and insurance and Medicaid policy should adapt to cover assessments of persons with high specific risks, (persons with Down syndrome, persons with inherited risks, etc.)
- ***Increased need for clinician training in cognitive assessment.*** With or without new incentives for clinicians, patient and caregiver demand for cognitive assessments may well increase with greater public awareness of the new anti-amyloid therapies. However, a shortage of clinicians trained in cognitive assessment represents a bottleneck to greater access by patients.[lviii]
- ***Overcoming barriers to equitable access – and absorbing the increased cost of CSF analysis and PET imaging needed to support appropriate use of anti-amyloid therapies.*** Until more scalable and potentially less expensive testing options (such as blood-based biomarker testing) become widely available and serve to "funnel" patient for needed follow-up to PET imaging and CSF analysis, both PET and CSF analysis will remain the essential methods for amyloid-beta diagnosis among patients, and for monitoring patients who receive anti-amyloid therapy. Substantial barriers to equitable access to PET imaging remain, including uneven distribution of PET facilities throughout the U.S. that disadvantages rural patients and rural clinicians.[lix] Increased demand for both services will be a challenge for both traditional, fee-for-service Medicare and for the Medicare Advantage plans that now cover over 50 percent of all Medicare beneficiaries.[lx]
- ***Achieving consistent policy on coverage of diagnostics for dementia and Alzheimer's disease.*** As awareness of new Alzheimer's therapies and demand for patient evaluation increases, so does the need for consistent and predictable policies on coverage of screening and diagnosis. Medicare has delegated decisions on expanded coverage of PET imaging for amyloid-beta to its regional Medicare Administrative Contractors (MACs). The MACs also set coverage policy for CSF analysis. Policies set by the MACs should ensure equitable access

throughout the country, as should policies set by Medicaid and commercial insurance that will govern access for persons under age 65 who are at risk for Alzheimer's disease, (such as persons with Down syndrome or with inherited risks.) Meanwhile, blood-based biomarker tests are novel diagnostics that will require new and consistent policy. Ultimately, payers and providers need to prepare for cost-effective coverage of screening and diagnostic testing (such as blood testing and novel cognitive-behavioral assessment) to detect pre-clinical Alzheimer's disease.

From a Phase Two (intermediate or mid-term) perspective:

- ***New urgency surrounding the launch and uptake of blood-based biomarker testing.*** The high prevalence of Alzheimer's disease and the relatively high cost of purchasing and administering new therapies creates new urgency for the development, validation, and approval of new tests that are highly accurate and support safe use of therapies. A high priority is continued introduction of blood-based tests and other biomarker testing that will complement standard testing with new options that are non-invasive, relatively inexpensive, and capable of administration by non-specialists.
- ***Acknowledging rapid innovation in laboratory-developed tests (LDTs) for Alzheimer's disease as a factor in Clinical Laboratory Improvement Amendments (CLIA) reform.*** Many such tests are now marketed (or likely will be marketed) as LDTs regulated under the CLIA. The FDA oversees validation of LDTs under a policy of discretionary enforcement, a policy that the FDA has now signaled it will tighten in the coming months.[lxi] The FDA should give careful consideration to how heightened enforcement of its CLIA responsibilities will influence the rate of innovation for blood-based biomarker tests, and other innovative tests for Alzheimer's disease and other forms of dementia at a time when the introduction of new, FDA-approved therapies will increase the need for highly scalable and non-intrusive diagnostics for Alzheimer's disease.
- ***Acting on the urgency to adapt diagnostics to address the unique characteristics of persons with Down syndrome and others at high-risk.*** Careful consideration should also be given to expanding the validation, approval, and uptake of tests that address the unique and urgent requirements of patients at high risk for the onset of Alzheimer's disease. As noted, persons with Down syndrome are at exceptionally high risk for Alzheimer's disease, but as a rule the development of novel tests has not included evaluation of the disease as manifest among persons with Down syndrome, or adapted tests to so that they yield results that will guide safe and effective administration of new therapies among the Down syndrome population.[lxii]

- ***Optimizing the usefulness of the CMS-required registry of anti-amyloid therapy.*** CMS has reiterated that it will cover new, anti-amyloid monoclonal antibody therapies under a CED regimen in which data will be collected to generate Real World Evidence on the safety and effectiveness of the therapies. CMS intends to modify its CED, however, Medicare will not require formal CED clinical trials but will require prescribing physicians to enter a limited amount of data into registries. As of this writing, it is unclear whether data collected by the registries will support findings on how the use of screening and diagnostic testing – including specific types of testing – was utilized by the prescribing physicians. Real World Data on the use of the new therapies will be an invaluable resource for investigating how new and more precise diagnostic testing can improve the likelihood of success in treating patients with available therapies. CMS should initiate (or be given the resources to initiate) a strategy for rigorous evaluation of data from the CED registries and other data sources that may be available to shed light on the best use of innovative diagnostics.
- ***Acknowledging the need for expediting coverage of Breakthrough Devices for Alzheimer's disease detection and diagnosis as a factor for reconsideration of Medicare's Transitional Coverage of Emerging Technologies initiative.*** Notably, CMS also intends to apply an approach similar to Coverage with Evidence Development towards adoption of a select number of medical devices, but laboratory-developed diagnostic tests will not be eligible for the program as currently proposed. CMS released its proposal for a re-launched Transitional Coverage for Emerging Technologies (TCET) pathway on June 22, 2023.[lxiii] Under the TCET program approximately five medical devices, previously approved by the FDA as Breakthrough Devices, will receive Medicare coverage, conditioned on development of post-approval data on the devices' effectiveness (Real World Evidence, RWE) that will support definitive coverage. Novel diagnostic tests for Alzheimer's Device have received Breakthrough Device designation from the FDA in the past and more are likely in the future. Their inclusion in the TCET pathway should be considered given the heightened importance of early and accurate detection and diagnosis of Alzheimer's disease.
- ***A heightened need for development of longitudinal data and Real World Evidence.*** Real World Evidence on the impact of screening and diagnosis of Alzheimer's disease, particularly the impact of early detection and diagnosis, will be crucial for a rigorous assessment of new Alzheimer's disease therapies, as repeatedly noted above. To that end, development of longitudinal data that links the use of diagnostics to patient outcomes – including data that could be generated through the Medicare registry on anti-amyloid therapies, and potentially on an extension of the Transitional Coverage for Emerging Technologies (TCET) pathway – will also be crucial for development of a base of evidence to support evaluation by the U.S. Preventive Services Task Force (USPSTF). A positive recommendation by the USPSTF (i.e., an

evidence grade of A or B) is necessary to trigger mandatory coverage by commercial, employer self-funded, and other health plans regulated under the Affordable Care Act.[lxiv]

From a Phase Three (long term) perspective:

- ***Acting on the need to develop, test and promote models of comprehensive dementia care.*** In the long-term, the arrival of a "full toolbox" of cognitive, neurobehavioral, and biochemical biomarker tests for Alzheimer's disease will necessitate change in the standard of care and in the models of care delivery for older patients and patients at special risk for the disease. Early testing, recurring testing, and testing with multiple modes of testing (modes of cognitive, other neurobehavioral, and biochemical biomarker testing and monitoring) will introduce new tasks into clinical practice that are expected to fall heavily on primary care teams because of the persistent shortage in geriatric and neurology specialists throughout the country. If fully realized this transition will require new and increased clinician training, new standards for evidence-based practice and performance metrics, and payment models that support these expanded duties.[lxv]
- ***Reconsidering the prevailing payment policy on diagnostic testing.*** Multiple new forms of testing for Alzheimer's disease may pose a challenge to current policy on the reimbursement of diagnostics. As noted, Medicare reimbursement of laboratory testing, including PET imaging, conducted as a hospital outpatient service is reimbursed on a "packaged" basis which inhibits hospitals from offering novel forms of PET imaging, including PET imaging for amyloid-beta plaques. Medicare is now reconsidering the packaged payment policy, including adoption of packaged payment policy that will accommodate reasonable use of novel diagnostics. With the launch of new, anti-amyloid drug therapies for Alzheimer's disease, new policy is needed to support the new paradigm of earlier and more frequent patient testing for the onset and progression of Alzheimer's disease across an entire "pathobiological pathway."

  Ultimately, the availability of a greater number of tests could enable a "right test, right time, right patient" approach to screening and diagnosis that will yield more precise decisions for patients on appropriate dementia services and, for Alzheimer's patients, more precise determination of patients who are likely to benefit from new therapies, and lay the groundwork for eventual value-based approaches to Alzheimer's care.
- ***Acting on the greater urgency for equitable access to the full range of screening and diagnostic tools and tests.*** Racial, ethnic, and socioeconomic disparities are widespread

in the prevalence and detection of Alzheimer's disease. While the high rate of innovation in Alzheimer's diagnostics is welcome news, it could also widen existing disparities if traditional early adopters of innovation, such as major medical centers, take the lead in utilization of new testing and health care policy fails to spread access more evenly, or if health benefits coverage does not extend to patients (such as Black and Hispanic Americans) in which Alzheimer's disease is disproportionately present. Policies for equitable access to innovation will be needed to guide patients toward the best available forms of therapy and dementia care.

Conclusion

The pace of scientific research on Alzheimer's disease and other forms of dementia is accelerating. It is revealing Alzheimer's as a disease with complex origins and paths of progression that are highly variable among patients. Much work remains to be done to develop a range of therapies that will help patients on a "right therapy, right time, right patient" basis. It is increasingly clear that this goal will not be reached unless clinicians are equipped with a range of tools for dementia screening and Alzheimer's diagnosis that enables them to offer patients and caregivers options for the "right test, at the right time, for the right patient." It will require significant shifts in standards of dementia care and payment policy to make this capability accessible to all who need it, and to do so equitably. Policymakers, patient advocates, payers, providers, and diagnostic test developers can and should prepare for this paradigm shift now.

NEHI Alzheimer's Panel, May 25, 2023: Key Takeaways

On May 25, 2023, NEHI hosted a public roundtable at the Kaiser Permanente Center for Total Health in Washington DC at which stakeholders from across the healthcare industry discussed the coming impact of innovation in diagnostic tests and tools on Alzheimer's disease diagnosis and treatment. Panelists and audience members represented patient and caregiver advocates, clinical researchers, diagnostic device developers, the biopharma industry, insurers, and clinicians.

Panel One: New and Oncoming Innovations in Diagnostics for Alzheimer's Disease

Tom Hubbard, Senior Vice President of Policy Research at NEHI, moderated the first panel which featured the following individuals:

- Joel Braunstein, MD, MBA, Founder and CEO, C2N Diagnostics
- Hampus Hillerstrom, MEcon, MBA, MSc, President and CEO, LuMIND IDSC Foundation
- Hartmuth Kolb, PhD, Vice President of Neuroscience Biomarkers and Imaging, Janssen/ Johnson & Johnson
- Linda K. McEvoy, PhD,Principal Investigator, Adult Changes in Thought (ACT) Study at the Kaiser Permanente Washington Health Research Institute; Professor Emerita, University of California San Diego Herbert Wertheim School of Public Health & Human Longevity Science
- Anil Nasta, MD, Physician; Disease Area Partner – Core Lab, Central Nervous System, Medical and Scientific Affairs, Roche Diagnostics

See **Appendix A** for biographical information on the panelists.

The first panel at the May 25 roundtable focused on new and oncoming diagnostic tests and tools and how future utilization of these innovations is likely to change the way in which we screen for, diagnose, and treat Alzheimer's disease. New and oncoming innovations include innovations for screening and assessment of patient cognition and behavior (neurobehavioral testing) and for detection and monitoring of biochemical biomarkers of Alzheimer's disease (i.e., pathologies within the brain).

Standard cognitive tests today include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), both of which are validated, questionnaire-based tests used for screening. Oncoming innovations that may serve as complementary or confirmatory tests include

digital cognitive assessment tools, such as tools for analysis of patients' speech and gait patterns that can be registered via smartphone and analyzed for signs of Alzheimer's disease or other dementias through machine learning techniques.

Standard biomarker testing today includes analysis of cerebrospinal fluids (CSF) collected by lumbar puncture, and positron emission tomography (PET) imaging of the brain to detect abnormal brain structures associated with amyloid plaques. Oncoming innovations include further validation of biomarkers detectable by CSF analysis and PET imaging and blood-based testing for amyloids and other signs of Alzheimer's pathology such as tau proteins. Blood-based tests now in development or reaching the health care market are mostly focused on the detection of amyloids and amyloid plaques, the same target as the emerging Alzheimer's disease therapies such as Leqembi (approved in July 2023), Aduhelm (approved in June 2021), and donanemab (widely expected to receive FDA approval by late 2023 or early 2024). However, other tests in development are expected to detect amyloids, tau proteins, tau tangles, and other biomarkers of Alzheimer's disease, such as signs of brain inflammation. As data from biomarker testing is integrated with data from cognitive and neurobehavioral assessment, a more precise view of a patient's condition will be achieved that will give clinicians greater certainty as to the most clinically appropriate course of treatment to offer patients, whether an anti-amyloid therapy, therapies not-yet fully developed that target tau tangles, or other pathologies, or combinations of all these pathologies.

As described by Dr. Hartmuth Kolb of Johnson & Johnson, development of a wider range of tests, from non-intrusive and comparatively inexpensive cognitive testing (e.g., digital diagnostics) to more advanced biomarker testing, will enable clinicians to "rule in" a diagnosis of Alzheimer's disease, as differentiated from other forms of dementia, and "funnel" patients with Alzheimer's on to a sequence of tests, administered when deemed clinically prudent, that will give ever more precise findings of the patient's underlying pathologies, as well as his or her cognitive and behavioral status. "We need to think about what... test [people] could get first," Dr. Kolb said. "They could then get into this whole 'funnel' of testing."

At the same time, even though newly emerging tests and tools represent major advances in screening, diagnosis, and treatment of Alzheimer's disease, significant work remains to be done. Panelists generally agreed that more research and data collection is needed to create standards for clinically effective use of new and still-developing diagnostic tools, particularly among under-studied populations. In addition, standardizing clinician awareness of and education on these innovative tests and tools will support an increase in access to diagnosis and treatment for individuals who could benefit from early and accurate detection of Alzheimer's disease.

Expand the generalizability of Alzheimer's screening, diagnostic, and therapeutic effectiveness to underrepresented populations

There is a paucity of data that shows the effectiveness of anti-amyloid Alzheimer's therapies on underrepresented populations. This includes underinsured and uninsured populations as well as individuals with co-morbidities (e.g., cerebrovascular disease). This also encompasses populations with intellectual and developmental disabilities, such as the Down syndrome community—although as panelist Hampus Hillerstrom, CEO of the LuMIND IDSC Foundation pointed out, "people with Down syndrome… have a 90% chance of getting Alzheimer's in their lifetime... We still need to play catch up in terms of the anti-amyloid drugs that had recent approvals and are nearing approvals. Zero people with Down syndrome were included in those trials. [Clinicians] are not willing to prescribe these medications without safety data in the Down syndrome population. So, we have to play catch up there as soon as possible with safety trials in the Down syndrome population. And, at the same time, work on cutoff values for the Down syndrome population with these different assays, blood biomarkers, so that we are not left behind on that front [too]... We are talking about this enormous need in our population."

A lack of data across populations limits the generalizability and use of new diagnostics and therapies; without data, we cannot understand how well these tests, tools, and treatments will work on individuals within these populations and more importantly, the potential ways in which these innovative methods can improve individuals' quality of life. Panelists agreed that because of this obvious lack of Real World Evidence, physicians are and will continue to be less inclined to administer or prescribe such diagnostics and therapies to their patients. It will be incredibly important to design long-term cohort studies that include under- and unrepresented populations in order to produce data that provide meaningful information on a) the effectiveness of these newly developed diagnostic tests and therapies across different populations, and b) transformations to individuals' quality of life. Principal Investigator of the ACT Study at the Kaiser Permanente Washington Health Research Institute, Dr. Linda K. McEvoy reinforced her point noting that, "there is quite a bit of research that needs to be done, I think, before we can really comfortably move [diagnostic tests and tools] into a clinical realm and understand how... valid [they're] going to be, and how predictive [they're] going to be."

Furthermore, new data on the effectiveness of Alzheimer's screening, diagnostic, and therapeutic effectiveness among under- and underrepresented populations will help us begin to identify individuals at risk for Alzheimer's prior to the onset of symptoms and provide us the ability to classify types of Alzheimer's disease (a topic that was also discussed during the second panel). "We have

solutions today that address and improve clinical outcomes in the patients that are experiencing symptoms, which is where the initial problem is, and where the primary focus needs to be because once we can alleviate and address some of those gaps, we can then start moving upstream," explained Dr. Joel Braunstein, Founder and CEO of C2N Diagnostics. "The issues around upstream assessment are much more complicated in many ways because now you have information that becomes known to the person. How does it impact their social status? How does it impact their risk? The risks of insurance bias? What does it mean for their professional work-life environment? When does it become a disclosure issue? There are a lot of issues that have to be addressed. But we know that we have effective drugs today that we need to be able to enable patients to get timely and proper access to,… validate there, build the care pathways that show you can improve outcomes by early detection, and then start applying these lessons learned to the earlier stages where you can, long-term, prevent a disease."

Standardize clinician awareness of and education on innovative tests and tools for Alzheimer's

The mere existence of new diagnostics and therapies for Alzheimer's does not translate to a change in physician prescribing behaviors (i.e., the clinical utility of the test, tool, or therapy). Many physicians serve patient populations with chronic and/or co-occurring diseases and conditions and are not able to remain up to date with newly emerging technologies and treatments. This presents an issue, as described above, as clinical trials for Alzheimer's generally exclude individuals with co-occurring conditions, therefore limiting the generalizability of screening, diagnostic, and therapeutic options. In this way, it will be important to produce new data on the effects of new diagnostics and treatments across different populations that can be shared with clinicians to increase awareness of the existence of such tests and tools. This data will also be necessary to be able to provide education on how to not only access and administer new tests, tools, and therapies, but also when to apply them; as additional methods for screening, diagnosing, and treating Alzheimer's across different populations become available, physicians will need to understand the differences between the different care pathways and when to utilize one over the other. "Along with the technical side of biomarkers, we really have to attack [diagnostics] from the [primary care physician] setting," Dr. Anil Nasta, a physician and Disease Area Partner at Roche Diagnostics, stated. "A lot of community neurologists…. aren't necessarily focusing on Alzheimer's disease. They might be focusing on MS [and] other conditions... So, getting them involved with this [and] spreading the message...will be incredibly important."

It is also important to standardize clinician awareness and education on innovative tests and tools in Alzheimer's to increase individual and patient trust in healthcare providers. We live in an age where individuals have access to data and information pertaining to new screenings, diagnostic tools, and

therapies and are willing to bring these innovative tests and tools to the attention of their healthcare provider for potential use in their care journey. In this way, it is likely that individuals will begin to—if they have not already—approach their provider about screening and diagnostic tools for Alzheimer's disease given their respective family history or if they are experiencing symptoms they believe could be related to the disease. Clinicians will therefore need to obtain a basic understanding of the options when it comes to screening for, diagnosing, and treating Alzheimer's disease and be able to share their knowledge with their patients.

Panel Two: The Implications of Innovative Diagnostics for Alzheimer's Disease Policy and Practice

Tom Hubbard (NEHI) moderated a second panel featuring the following individuals:

- Brian Carey, JD, Attorney and Partner, Foley Hoag LLP
- Claire Levesque, MD, Retired Chief Medical Officer of Commercial Products; Point32Health; Former Alzheimer's Researcher
- Hannah Mamuszka, MS, Founder and CEO, Alva10
- Adam Phipps, MBA, Associate Vice President, US Government Payer Strategy/Alzheimer's Diagnostics and Therapies, Eli Lilly & Company

The panelists framed the discussion around the evolving understanding of Alzheimer's disease as one that has an early, pre-symptomatic onset, likely has multiple causes that are highly particularized to the individual patient, and takes different trajectories of progression among different patients, including differing progressions of symptoms and disabilities and differing progressions of underlying brain pathologies. Ultimately the end goal of innovation in Alzheimer's disease diagnostics is a goal in which recurring testing and monitoring of patients will lead to the most effective choices of treatment (as treatments become available) and, equally important, the most effective dementia services for individual patients, their families, and caregivers. To realize this vision, clinicians will need to have recourse to accurate, scalable, and cost-effective screening and diagnostic tests of patient cognition, quality of life, and of underlying biomarkers, throughout the course of the patient's life with Alzheimer's disease.

To that end, panelists also discussed the challenges that this evolving vision poses for coverage and reimbursement of Alzheimer's screening and diagnosis, as well as the regulatory oversight of screening and diagnostic methods. By examining both coverage and reimbursement, which are heavily intertwined, panelists and audience members were able to begin to highlight major—and often conflicting—barriers to accurate and timely care.

We note that FDA approval and CMS coverage of Leqembi (Eisai/Biogen) were not yet released at the time of this discussion. Similarly, the CMS proposal to remove its National Coverage Determination on amyloid-beta PET imaging that limited eligible beneficiaries to one scan per lifetime was not yet released. We discuss this in more detail below.

Redefine how we talk about Alzheimer's disease

Many of the panelists noted that they hope to see an evolution in how we talk about Alzheimer's disease, similar to how our references to cancers have evolved. Rather than using Alzheimer's as an "umbrella term," it will be important to recognize, diagnose, and treat distinct types of Alzheimer's (e.g., amyloid-beta vs. tau) and stratify individuals at risk as well as those who have been diagnosed with the disease. This point reinforced the first panel's discussion on the need to collect additional data on different populations. "I fully believe that in the—hopefully—not too distant future, we're going to think about Alzheimer's in the same way that we think about cancer," said Hannah Mamuszka, Founder and CEO of Alva10. "As... one umbrella term that we use that is really a whole bunch of different diseases and different pathologies and different genotypes that we're going to treat with different, exquisitely developed drugs. And we're going to use diagnostic tools to find those patients. But the first thing we have to do is separate out the Alzheimer's and the non-Alzheimer's patients from the beginning." This additional data and broader use of diagnostic tools will allow us to identify those at risk for different types of Alzheimer's (and to differentiate it from non-Alzheimer's forms of dementia) and ultimately allow for the development of diagnostic screening tools that can be applied prior to the onset of any symptoms. Furthermore, advancing data interoperability will assist providers and payers in making decisions regarding screening, diagnosing, treating, and monitoring individuals.

Another point of agreement throughout was the need to define and identify "pre-symptomatic" or "asymptomatic" individuals. In an ideal world, rather than waiting for the individual to begin to show common symptoms of early Alzheimer's (e.g., some form of mild cognitive impairment), individuals should be screened while still asymptomatic, or prior to developing common symptoms that would suggest the individual may develop Alzheimer's.

Transform screening for Alzheimer's disease

Most care delivered to patients today remains reimbursed under a fee-for-service model. The panel discussed the idea of a value-based care approach to Alzheimer's screening, which could be monitored using key performance indicators and quality metrics. At present, incentives to screen for

Alzheimer's are often lacking among both patients and providers. Some patients do not wish to know whether they may develop Alzheimer's, given that there are few approved therapies that will prevent the disease from progressing. Similarly, many providers do not wish to screen, knowing that the result of the screening will likely not affect the patient's treatment course.

In addition, a more holistic view must be adopted when it comes to screening and treating individuals. Often, other diseases produce symptoms that present as cognitive impairment (e.g., depression, thyroid imbalances, etc.). Being able to concretely identify individuals with and without Alzheimer's (i.e., differentiate Alzheimer's from other forms of dementia) will signify major advancement in this space. For those who are definitively diagnosed with Alzheimer's, however, the individual and their family/caregiver(s) will require a team of individuals who can assist across the care journey, from the screening physician to the specialist, and beyond. "We actually need a team. And that's not what we do well right now [as a country]. We need that team to follow along with [the individual] and not fragment [their] care," argued recently retired CMO of Commercial Products from Point32Health and former Alzheimer's researcher, Dr. Claire Levesque. "When somebody's disease has progressed past what the PCP can do... how does the neurologist take over or the geriatric doctor or whomever it might be? And then how does it transfer over? All of those timeframes when somebody is transferring care are incredibly vulnerable times. And that's when people fall apart... So, fixing a lot of those transitions will be important. And we have to remember, the patient can't advocate for themselves because they have a memory problem. We put a huge burden on the family to advocate for every bit of this..." Adopting a medical home model to ensure gaps in care are closed and/or that the care is not placed solely on the caregiver will be crucial to providing comprehensive care to the individual and their family, including care coordination that makes appropriate treatment choices as treatment options become available.

Furthermore, it is imperative to remember that the most important aspect of treatment and support for individuals with Alzheimer's is that it must improve their quality of life. "We have to make sure that there's validation of the therapeutics of the non-therapeutic interventions that improve quality of life because that's what it's about," said contributor Ian Kremer, Executive Director of the Leaders Engaged on Alzheimer's disease (LEAD) Coalition. "It's about quality of life. It's not about the efficacy of a drug or efficacy of a non-drug intervention. It's, 'What does it do for a person and for the people in their ecosystem?' So, being able to test matters, but also being able to detect and diagnose matters."

Continue to reassess CMS coverage policies upon FDA approval of therapies and monitoring for Alzheimer's

Panelists also noted the tension between FDA approval of new therapies and gaps in subsequent Medicare coverage of the therapies. Aduhelm was referenced throughout the conversation as a novel Alzheimer's therapy that received FDA approval but received highly restricted overage by Medicare (covered only for individuals enrolled in specific clinical trials) as well as by most commercial health plans due to limited data on benefits and reports of adverse side effects. Since the time of the panel, Leqembi received both FDA approval and wider CMS coverage than Aduhelm. However, options for monitoring patients and their response to the new therapy still appeared limited.

After the May 2023 panel, CMS also announced its intent to remove its National Coverage Determination (NCD) that limited patients to one PET imaging session per lifetime for the detection of amyloid-beta plaques associated with Alzheimer's disease. The prior coverage determination severely limited the ability to monitor individuals engaged in anti-amyloid therapies. By removing the NCD, CMS would eliminate the "one scan per lifetime" determination, and "allow local [Medicare Administrator Contractors (MACs])] to make coverage determinations regarding the use of this imaging technique to include covering more than [one] scan per patient's lifetime and use within or outside the context of a CMS-approved study." Adam Phipps, Associate Vice President of US Government Payer Strategy/Alzheimer's Diagnostics and Therapies at Eli Lilly & Company described the rarity of NCDs and how treatments, tests, and tools are typically covered when an NCD isn't involved. "National Coverage Determinations are actually pretty rare," Phipps said. "CMS only does seven or eight National Coverage Determinations per year, across everything that they do. From a coverage standpoint, [the treatment or test in question] will be allowed to be handled like a normal pathway at the local level with the MACs and maybe Medicare Advantage plans... [who will be] able to handle that through their own, normal processes that they use."

While retracting the amyloid-beta PET imaging NCD will remove a major barrier to monitoring individuals engaged in anti-amyloid treatments for Alzheimer's, Attorney and Partner at Foley Hoag, Brian Carey, predicted that leaving coverage decisions to the local level could create confusion that may still restrict access to diagnostic and screening tests, noting that regions require varying depths of clinical evidence and may set differing levels of reimbursement. "Some regions of the country have very specific rules where you have to show analytical and clinical validity. You have to have publications on clinical utility... all that takes quite a long time," said Carey. "Other regions of the country don't really have any policies. So, it's unclear if [diagnostic tests are] paid for or not paid for.

Some claims get paid, some claims don't. But there's not much reliability on it. And there's a whole separate process for how they are priced, which has a lot of... regional variability until it goes to a national process."

Medicare's new policy treats PET imaging for amyloid-beta in the same manner as PET imaging for the detection of tau proteins associated with Alzheimer's disease. As panelist Adam Phipps pointed out, Medicare has covered PET imaging for tau under regional coverage policies from the beginning although, unlike amyloid-related Alzheimer's disease, there are no anti-tau therapies approved for treatment as of yet (anti-tau therapies are in active development).

Harmonize FDA approval and CMS coverage policies

FDA approval and CMS coverage policies (i.e., payment and reimbursement) often do not occur concurrently (although the approval and coverage of Leqembi occurred nearly simultaneously) and therefore create challenges for providers and payers who may wish to offer newly approved treatments, and for patients who have limited, if any, treatment options. Narrowing the gap between the approval timeline and coverage policy announcements could serve to eliminate potential gaps in care.

Therein lies a chicken and egg dilemma in which Medicare and other health plans generally do not cover diagnostics until diagnostic developers prove analytical validity (detecting what you claim to be detecting), clinical validity (what you are detecting is meaningful to the patient), and clinical utility (the physician using the diagnostic test or tool believes it and that this knowledge affects how they care for their patient). Clinical utility is very difficult to prove in the absence of meaningful treatment and care options. As new anti-amyloid and, eventually, anti-tau and possibly other therapies become available, there will be an increasing need to harmonize or closely coordinate FDA approval of new diagnostics with Medicare's capability to cover new tests for appropriate use.

Appendix A: May 25, 2023, NEHI Roundtable Panelist Biographies

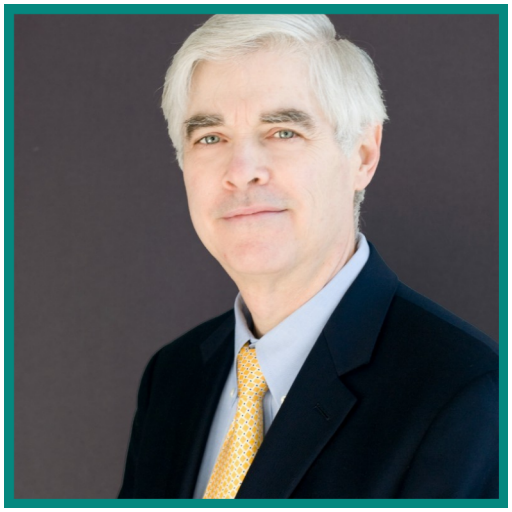
The Coming Impact of Innovation in Diagnostic Tests and Tools on Alzheimer's Disease and Dementia Screening, Diagnosis, and Treatment

Thursday, May 25, 1:00PM – 4:30PM ET

Kaiser Permanente Center for Total Health, Convergence Center

Tom Hubbard, MPP (Moderator)

Senior Vice President of Policy Research, Network for Excellence in Health Innovation (NEHI)



Tom Hubbard leads NEHI's projects on coverage and payment for innovative biopharmaceuticals, comparative effectiveness research policy, Real World Evidence, medication management, and patient medication adherence. Mr. Hubbard leverages his policy and technology experience to examine ways the country's health care system can be transformed, focusing on the promotion of medical innovation and the improvement of quality and efficiency in clinical care.

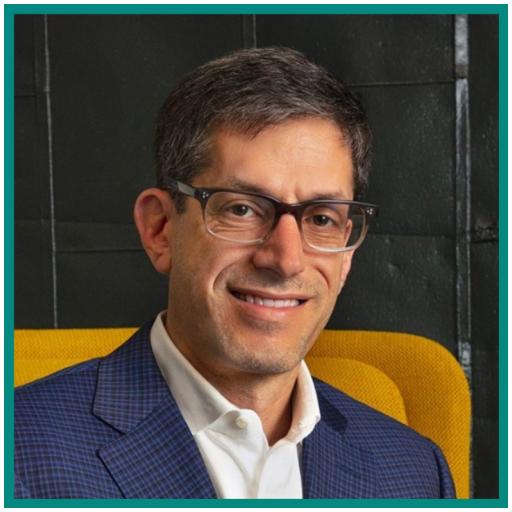
Mr. Hubbard came to NEHI after seven years at the Massachusetts Technology Collaborative (MTC), where he led industry-focused projects and supervised the annual publication of the MTC Index of the Massachusetts Innovation Economy. His work has included supervising the I-495 Technology Corridor Partnership, an industry-municipal collaboration on growth, and leading projects on broadband deployment, federal research funding advocacy, and nanotechnology.

Previously, Mr. Hubbard served as Executive Assistant for Economic Affairs to U.S. Senator John Kerry, as Deputy Director of Development for Massachusetts Governor Michael Dukakis, and as Director of Community Development and Planning for the City of Gardner, Massachusetts.

Mr. Hubbard graduated from Harvard College and holds a master's in public policy from Harvard's Kennedy School of Government.

Panel One: Oncoming Innovations in Alzheimer's Diagnostic Tests & Tools

Joel Braunstein, MD, MBA
Founder and CEO of C2N Diagnostics



Dr. Braunstein is Co-Founder and CEO of C2N Diagnostics and has led the company's growth and commercial efforts since its inception. Dr. Braunstein has played a senior executive role in numerous emerging life sciences companies since 2004. He received his M.D. with Highest Distinction from Northwestern University Medical School in 1996. Subsequently, he trained in internal medicine at the Brigham and Women's Hospital, Harvard Medical School, and was a Fellow in Cardiovascular Medicine and Robert Wood Johnson National Clinical Scholar at the Johns Hopkins Medical Institutions. Additionally, he completed an MBA with management and health policy focus and maintained an Assistant Professorship in Cardiology at Johns Hopkins University. In 2010, he was named a Distinguished Alumnus of Johns Hopkins University.

Hampus Hillerstrom, MEcon, MBA, MSc
CEO, LuMind IDSC Foundation

Hampus Hillerstrom is President and CEO of LuMind IDSC Foundation, a non-profit organization empowering families with Down syndrome, including his 9-year-old son Oskar. Previously, he co-founded and served in executive roles at Proclara Biosciences, a biotech company developing novel treatments for Alzheimer's and other conditions. Hampus also worked at biotech venture capital firm HealthCap, pharma company AstraZeneca, and investment bank Lazard. Hampus holds a master's in economics from University of St. Gallen, an MBA from Harvard Business School, and an MSc in Health Sciences and Technology from MIT/Harvard Medical School.

Hartmuth Kolb, PhD

Vice President of Neuroscience Biomarkers and Imaging, Janssen/Johnson & Johnson

Hartmuth's expertise includes the development of PET tracers for all therapeutic areas and the development of precision medicine approaches in Neuroscience. He serves as co-chair of the Neuroscience Steering Committee of the Foundation of National Institutes of Health (FNIH) Biomarkers consortium. At Janssen, Hartmuth's lab developed a p217Tau blood test that detects the presence of Alzheimer's pathology in patients. Prior to Janssen, he was head of Siemens Biomarker Research, where he and his team developed PET tracers using Click Chemistry. The PHF-Tau PET tracer [18F]-T807 (aka "Flortaucipir", "Tauvid") was recently approved by the U.S. Food and Drug Administration (FDA) to image a distinctive characteristic of Alzheimer's disease (AD) in the brain called tau pathology. Before joining Siemens, he was Vice President of Chemistry at Coelacanth Corporation, where he worked with K. Barry Sharpless on pioneering Click Chemistry, for which Sharpless received the 2022 Nobel Prize in Chemistry. Hartmuth began his career in industry at Ciba-Geigy after receiving his doctorate in Organic Chemistry from the Imperial College of Science, Technology and Medicine, London.

Linda K. McEvoy, PhD

Principal Investigator, Adult Changes in Thought (ACT) Study, Kaiser Permanente Washington Health Research Institute

Professor Emerita, University of California San Diego Herbert Wertheim School of Public Health & Human Longevity Science

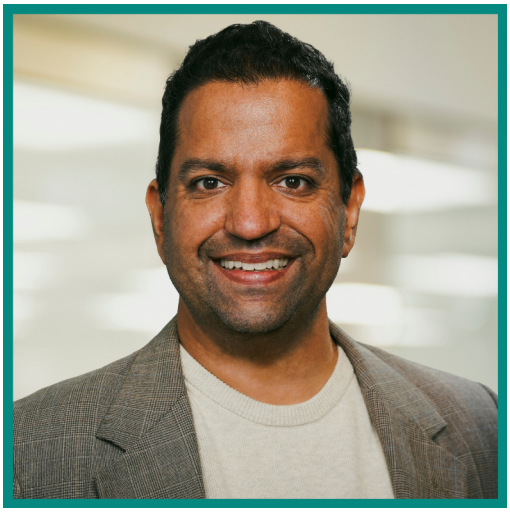
Linda K. McEvoy, PhD, is an experimental psychologist and neuroscientist with acquired expertise in aging epidemiology. She is a senior investigator at Kaiser Permanente Washington Health Research Institute (KPWHRI) and professor emerita at the University of California San Diego. Dr. McEvoy's research is focused on improving understanding of factors throughout the life course that affect cognitive and brain health in aging. She conducts research on longitudinal cohort studies Including the Alzheimer's disease Neuroimaging Initiative,

the Rancho Bernardo Study of Healthy Aging, the Vietnam Era Twin Study of Aging, the Women's Health Initiative Memory Study, and most recently, the Adult Changes in Thought (ACT) Study. Her goals are to identify genetic, health, and behavioral risk factors for age-related cognitive decline and dementia, and biomarkers for prediction of dementia risk. Along with her colleagues, Dr. McEvoy has identified neuroimaging signatures that predict risk of cognitive decline, mild cognitive impairment and dementia, even among cognitive healthy middle-aged adults. She aided in the development of polygenic scores for age-specific prediction of Alzheimer's disease risk, and has shown how the combination of imaging, fluid, and genetic markers improve risk prediction. Her research has demonstrated how modifiable factors, such as diet, alcohol use, and physical activity affect brain health and cognitive aging. Dr McEvoy has published >160 original research manuscripts on cognitive function, aging, and dementia. She currently serves as a standing member of the Center for Scientific Review Adult Psychopathology and Disorders of Aging Study Section.

Anil Nasta, MD

Disease Area Partner – Core Lab, Central Nervous System, Medical and Scientific Affairs, Roche Diagnostics

Physician



Dr. Anil Nasta is a physician and board-certified by the American Board of Family Medicine and a former Clinical Assistant Professor of Medicine at Florida State University's School of Medicine. Dr. Nasta completed his residency in Family Medicine at the Institute for Family Health. He has practiced medicine in both hospital and office settings, primarily with the geriatric population. In addition to Dr. Nasta's clinical experience, he has extensive experience advising hospitals and hospital administrators on ways to improve patient care to reduce length of stay and readmission rates. At Roche Diagnostics, Dr. Nasta is a contributor to the medical and scientific affairs strategy for Roche's Alzheimer's disease diagnostic portfolio. In his free time, he enjoys spending time with his 19-month-old daughter, traveling, cooking, and staying up to date in medicine.

Panel Two: Implications of Innovative Alzheimer's Screening and Diagnosis for Clinical Practice and Payment Policy

Brian Carey, JD

Partner, Foley Hoag LLP

Brian has over two decades of experience advising a wide range of life sciences companies and healthcare providers on federal legal, regulatory, and legislative policy matters impacting novel technologies. As a Co-Chair of the Life Sciences Coverage & Payment Group, he has deep experience with assisting biopharma and medical technology companies on complex Medicare coverage and payment issues, and related billing and compliance issues for innovative technologies.

Brian regularly advocates on behalf of innovative technology developers and medical trade associations before the U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services, and U.S. Congress. His insights help investors appreciate regulatory risk and opportunity for new technologies.

In recent years, Brian has counseled leading clinical laboratory and molecular diagnostic companies on the evolving regulatory and reimbursement requirements for Laboratory Developed Tests (LDTs). In particular, he has extensive experience advising laboratories on coverage, coding, and payment pathways under the Protecting Access to Medicare Act of 2014 (PAMA).

Brian's extensive background in healthcare policy matters includes serving as a legislative aide to Senator Edward M. Kennedy. In that capacity, he worked in the Committee on healthcare, biotechnology, and food and drug legislation. Prior to Foley Hoag, Brian was an associate at Sullivan & Cromwell in New York, and he was a judicial law clerk for the Honorable Edward F. Harrington of the United States District Court of Massachusetts. Brian splits his time between the firm's Washington, D.C. and Boston offices.

Claire Levesque, MD

Former Chief Medical Officer for Commercial Products, Point32Health

Former Alzheimer's researcher, Boston University

Dr. Claire Levesque just retired from her role of Chief Medical Officer for Commercial Products at Point32Health (the parent company of Harvard Pilgrim Health Care and Tufts Health Plan). Her responsibilities included clinical leadership, medical management, and medical cost control. She worked with providers to develop member-centric programs to meet complex needs with a focus on health equity. She is a graduate of the University of Vermont College of Medicine and completed residency and fellowship training at the University of Virginia. Board certified in neurology, she specialized in the care of patients with dementia, intellectual disabilities and behavioral issues. Before starting at the health plan fourteen years ago, she was assistant professor of neurology at Boston University, founding and managing partner of a practice in the Boston area, president of the medical staff at a long-term acute care facility, and chief of neurology at a community hospital. Dr. Levesque has also published journal articles, book chapters, and short stories. Losing her husband to Alzheimer's disease has allowed her to see this condition from both a personal and professional view.

Hannah Mamuszka, MS

Founder and CEO, Alva10

Hannah Mamuszka is Founder and Chief Executive Officer at Alva10, which she founded in 2015 to spur change in healthcare to allow more patients better access to diagnostic technology. Hannah's career has spanned the laboratory and business sides of healthcare in both the pharma and diagnostics industries. Prior to Alva10, Hannah was VP of Exosome Diagnostics (acquired by BioTechne), where she led some of the earliest deals in the liquid biopsy space. Earlier in her career, she was Global Director of Pharmaceuticals Services for Oncotech, and then by acquisition, Exiqon (acquired by QIAGEN), where she built the Pharmaceutical

Services and Companion Diagnostics business in the US, Europe, and ROW. Prior to her time in diagnostics, she worked on the IND submission for VelcadeTM at Millennium Pharmaceuticals (acquired by Takeda). She started her laboratory career at the National Institutes of Health, holding laboratory positions in both the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Disease (NIAID). Hannah is a frequent speaker and writer on how to drive change in healthcare and is on the editorial board for the Journal of Precision Medicine, where she also writes a regular column on the challenges of implementing change in medicine. Hannah serves on the Board of Directors for Bionano Genomics (BNGO) and the University of North Carolina's Carolina Health Informatics Program (CHIP).

Adam Phipps, MBA

Associate Vice President, US Government Payer Strategy/Alzheimer's Diagnostics and Therapies, Eli Lilly & Company

Adam Phipps is the Associate Vice President of Government Strategy, Alzheimer's, at Eli Lilly and Company. He is responsible for Lilly's business strategy and implementation across all federal government segments for the company's Alzheimer's disease portfolio. He is responsible for coverage, coding, and payment for both diagnostic and therapeutic products for federally-insured patients. Adam is a veteran of Lilly's Alzheimer's business, having served in a variety of roles over the past decade. He has built expertise on a variety of CMS-related topics, including Part B policy, National Coverage Determinations, and Coverage with Evidence Development. Adam has been at Lilly since 2008, and his responsibilities have included provider marketing, brand payer marketing, sales leadership, and government strategy. He holds a Bachelor of Science from the University of Evansville and an MBA from the Indiana University Kelley School of Business.

References

[i] US Food and Drug Administration. FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval. FDA. Published July 7, 2023. Accessed August 15, 2023. https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval

[ii] Widera EW, Brangman SA, Chin NA. Ushering in a New Era of Alzheimer Disease Therapy. JAMA. 2023;330(6):503-504. doi:10.1001/jama.2023.11701

[iii] Walker KA, Chen J, Shi L, Yang Y, Fornage M, Zhou L, Schlosser P, Surapaneni A, Grams ME, Duggan MR, Peng Z, Gomez GT, Tin A, Hoogeveen RC, Sullivan KJ, Ganz P, Lindbohm JV, Kivimaki M, Nevado-Holgado AJ, Buckley N, Gottesman RF, Mosley TH, Boerwinkle E, Ballantyne CM, Coresh J. Proteomics analysis of plasma from middle-aged adults identifies protein markers of dementia risk in later life. Sci Transl Med. 2023 Jul 19;15(705):eadf5681. doi: 10.1126/scitranslmed.adf5681. Epub 2023 Jul 19. PMID: 37467317.; see also Abdullahi Tsanni, "These proteins could predict dementia risk decades before symptoms, new study suggests," STAT, July 19, 2023

[iv] Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2023;9(2):e12385. doi:10.1002/trc2.12385

[v] National Institute on Aging – Alzheimer's Association Revised Clinical Guidelines for Alzheimer's Disease, July 16, 2023, accessed at https://aaic.alz.org/nia-aa.asp

[vi] BioLegend. Amyloid Precursor Protein. Published 2023. Accessed July 18, 2023. https://www.biolegend.com/en-us/amyloid-precursor-protein ; National Cancer Institute. Nervous Tissue | SEER Training. Accessed July 18, 2023. https://training.seer.cancer.gov/anatomy/cells_tissues_membranes/tissues/nervous.html; OpenStax. 12.2 Nervous Tissue - Anatomy and Physiology 2e | OpenStax. Published April 20, 2022. Accessed July 18, 2023. https://openstax.org/books/anatomy-and-physiology-2e/pages/12-2-nervous-tissue

[vii] MedlinePlus. APP gene- amyloid beta precursor protein. Accessed July 18, 2023. https://medlineplus.gov/genetics/gene/app/

[viii] How Alzheimer's Changes the Brain.; 2017. Accessed July 18, 2023. https://www.youtube.com/watch?v=0GXv3mHs9AU; National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease; BioLegend. Tau Proteins. Published 2023. Accessed July 18, 2023. https://www.biolegend.com/en-us/tau

[ix] BioLegend. Amyloid Beta Processing. Published 2020. Accessed July 18, 2023. https://www.biolegend.com/en-us/videos/amyloid-beta-processing; How Alzheimer's Changes the Brain.; 2017. Accessed July 18, 2023. https://www.youtube.com/watch?v=0GXv3mHs9AU; National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[x] How Alzheimer's Changes the Brain.; 2017. Accessed July 18, 2023. https://www.youtube.com/watch?v=0GXv3mHs9AU

[xi] How Alzheimer's Changes the Brain.; 2017. Accessed July 18, 2023. https://www.youtube.com/watch?v=0GXv3mHs9AU; National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease; BioLegend. Tau Proteins. Published 2023. Accessed July 18, 2023. https://www.biolegend.com/en-us/tau

[xii] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[xiii] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[xiv] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[xv] PennMedicine. Stages of Alzheimers - Penn Medicine. Published December 31, 2020. Accessed July 18, 2023. https://www.pennmedicine.org/updates/blogs/neuroscience-blog/2019/november/stages-of-alzheimers

[xvi] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease; Jagust W. Is amyloid-β harmful to the brain? Insights from human imaging studies. Brain. 2015;139(1):23-30. doi:https://doi.org/10.1093/brain/awv326

[xvii] BioLegend. Amyloid Beta Processing. Published 2020. Accessed July 18, 2023. https://www.biolegend.com/en-us/videos/amyloid-beta-processing; How Alzheimer's Changes the Brain.; 2017. Accessed July 18, 2023. https://www.youtube.com/watch?v=0GXv3mHs9AU; National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease; BioLegend. Tau Proteins. Published 2023. Accessed July 18, 2023. https://www.biolegend.com/en-us/tau

[xviii] PennMedicine. Stages of Alzheimers - Penn Medicine. Published December 31, 2020. Accessed July 18, 2023. https://www.pennmedicine.org/updates/blogs/neuroscience-blog/2019/november/stages-of-alzheimers

[xix] Alzheimer's Association. Earlier Diagnosis. Alzheimer's Disease and Dementia. Accessed July 18, 2023. https://alz.org/alzheimers-dementia/research_progress/earlier-diagnosis

[xx] BioLegend. Amyloid Beta Processing. Published 2020. Accessed July 18, 2023. https://www.biolegend.com/en-us/videos/amyloid-beta-processing; How Alzheimer's Changes the Brain.; 2017. Accessed July 18, 2023. https://www.youtube.com/watch?v=0GXv3mHs9AU; National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[xxi] BioLegend. Amyloid Beta Processing. Published 2020. Accessed July 18, 2023. https://www.biolegend.com/en-us/videos/amyloid-beta-processing; How Alzheimer's Changes the Brain.; 2017. Accessed July 18, 2023. https://www.youtube.com/watch?v=0GXv3mHs9AU; National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? Accessed July 18, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[xxii] 2019 Alzheimer's Disease Facts and Figures Report

[xxiii] Jacobson M, Thunell J, Zissimopoulos J. Cognitive Assessment At Medicare's Annual Wellness Visit In Fee-For-Service And Medicare Advantage Plans. Health Aff (Millwood). 2020 Nov;39(11):1935-1942. doi: 10.1377/hlthaff.2019.01795. PMID: 33136503; PMCID: PMC9517732.

[xxiv] Jacobson M, Joe E, Zissimopoulos J. Barriers to seeking care for memory problems: A vignette study. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2022;8(1):e12238. doi:10.1002/trc2.12238

[xxv] Owens DK, Davidson KW, Krist AH, et al. Screening for Cognitive Impairment in Older Adults. JAMA. 2020;323(8):757. doi:https://doi.org/10.1001/jama.2020.0435

[xxvi] Angioni D, Delrieu J, Hansson O, et al. Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done? A Report from the EU/US CTAD Task Force. J Prev Alzheimers Dis. 2022;9(4):569-579. doi:10.14283/jpad.2022.85

[xxvii] From the NIA-AA proposed guidelines, page 23;

[xxviii] Fabrizio C, Termine A, Caltagirone C, Sancesario G. Artificial Intelligence for Alzheimer's Disease: Promise or Challenge? Diagnostics (Basel). 2021;11(8):1473. doi:10.3390/diagnostics11081473

[xxix] Alzheimer's Association 2020 Facts and Figures

[xxx] Murchison CF, Kennedy RE, McConathy JE, Roberson ED. Racial Differences in Alzheimer's Disease Specialist Encounters Are Associated with Usage of Molecular Imaging and Dementia Medications: An Enterprise-Wide Analysis Using i2b2. J Alzheimers Dis. 79(2):543-557. doi:10.3233/JAD-200796

[xxxi] Waite S, Scott J, Colombo D. Narrowing the Gap: Imaging Disparities in Radiology. Radiology. 2021;299(1):27-35. doi:10.1148/radiol.2021203742

[xxxii] see also Waite S, Scott J, Colombo D. Narrowing the Gap: Imaging Disparities in Radiology. Radiology. 2021;299(1):27-35. doi:10.1148/radiol.2021203742

[xxxiii] See comments of the Society of Nuclear Medicine and Molecular Imaging and other commenters, submitted in response to proposed Medicare Hospital Outpatient Prospective Payment policy changes (CY 2024 Hospital Outpatient PPS Policy Changes and Payment Rates and Ambulatory Surgical Center Payment System Policy Changes and Payment Rates), accessed at https://www.regulations.gov/docket/CMS-2023-0120/comments

[xxxiv] Centers for Medicare and Medicaid Services, Medicare Coverage Database, National Coverage Analysis (NCA) Decision Memo: Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease, CAG-00431R, October 13, 2023, accessed at https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=308

[xxxv] Majersik JJ, Ahmed A, Chen IHA, et al. A Shortage of Neurologists We Must Act Now: A Report From the AAN 2019 Transforming Leaders Program. Neurology. Published online April 30, 2021:10.1212/WNL.0000000000012111. doi:10.1212/WNL.0000000000012111

[xxxvi] See Waite S, Scott J, Colombo D. Narrowing the Gap: Imaging Disparities in Radiology. Radiology. 2021;299(1):27-35; also Abner E, Jicha G, Christian W, Schreurs B. Rural-Urban differences in Alzheimer's disease and related disorders diagnostic prevalence in Kentucky and West Virginia. J Rural Health. 2016;32(3):314-320. doi:10.1111/jrh.12155

[xxxvii] Öhman F, Hassenstab J, Berron D, Schöll M, Papp KV. Current advances in digital cognitive assessment for preclinical Alzheimer's disease. Alzheimers Dement (Amst). 2021;13(1):e12217. doi:10.1002/dad2.12217

[xxxviii] See Angioni D, Delrieu J, Hansson O, Fillit H, Aisen P, Cummings J, Sims JR, Braunstein JB, Sabbagh M, Bittner T, Pontecorvo M, Bozeat S, Dage JL, Largent E, Mattke S, Correa O, Gutierrez Robledo LM, Baldivieso V, Willis DR, Atri A, Bateman RJ, Ousset PJ, Vellas B, Weiner M. Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done? A Report from the EU/US CTAD Task Force. J Prev Alzheimers Dis. 2022;9(4):569-579. doi: 10.14283/jpad.2022.85. PMID: 36281661; PMCID: PMC9683846.

[xxxix] Aisen PS, Cummings J, Jack CR, et al. On the path to 2025: understanding the Alzheimer's disease continuum. Alzheimer's Research & Therapy. 2017;9(1):60. doi:10.1186/s13195-017-0283-5

[xl] See National Institute on Aging – Alzheimer's Association Revised Clinical Guidelines for Alzheimer's Disease, July 16, 2023, op cit

[xli] Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2023;9(2):e12385. doi:10.1002/trc2.12385

[xlii] Centers for Disease Control and Prevention. Facts about Down Syndrome. Centers for Disease Control and Prevention. Published June 28, 2023. Accessed July 31, 2023. https://www.cdc.gov/ncbddd/birthdefects/downsyndrome.html

[xliii] National Institute on Aging. Alzheimer's Disease in People With Down Syndrome. National Institute on Aging. Accessed July 31, 2023. https://www.nia.nih.gov/health/alzheimers-disease-people-down-syndrome

[xliv] Centers for Disease Control and Prevention. Down Syndrome and Increased Risk for Alzheimer's. Centers for Disease Control and Prevention. Published December 20, 2022. Accessed July 31, 2023. https://www.cdc.gov/aging/publications/features/down-syndrome-alzheimers-risk.html

[xlv] Centers for Disease Control and Prevention. Down Syndrome and Increased Risk for Alzheimer's. Centers for Disease Control and Prevention. Published December 20, 2022. Accessed July 31, 2023. https://www.cdc.gov/aging/publications/features/down-syndrome-alzheimers-risk.html; Salehi A, Ashford JW, Mufson EJ. The Link between Alzheimer's Disease and Down Syndrome. A Historical Perspective. Curr Alzheimer Res. 2016;13(1):2-6. doi:10.2174/1567205012999151021102914

[xlvi] Centers for Disease Control and Prevention. Down Syndrome and Increased Risk for Alzheimer's. Centers for Disease Control and Prevention. Published December 20, 2022. Accessed July 31, 2023. https://www.cdc.gov/aging/publications/features/down-syndrome-alzheimers-risk.html

[xlvii] Alzheimer's Association. Down Syndrome and Alzheimer's Disease. Alzheimer's Disease and Dementia. Accessed July 31, 2023. https://alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/down-syndrome

[xlviii] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? National Institute on Aging. Accessed July 31, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[xlix] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? National Institute on Aging. Accessed July 31, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease; Alzheimer's Association. Alzheimer's Disease Facts and Figures. Alzheimer's Disease and Dementia. Accessed July 31, 2023. https://www.alz.org/alzheimers-dementia/facts-figures

[l] Centers for Disease Control and Prevention. Down Syndrome and Increased Risk for Alzheimer's. Centers for Disease Control and Prevention. Published December 20, 2022. Accessed July 31, 2023. https://www.cdc.gov/aging/publications/features/down-syndrome-alzheimers-risk.html ; Salehi A, Ashford JW, Mufson EJ. The Link between Alzheimer's Disease and Down Syndrome. A Historical Perspective. Curr Alzheimer Res. 2016;13(1):2-6. doi:10.2174/1567205012999151021102914

[li] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? National Institute on Aging. Accessed July 31, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[lii] National Institute on Aging. What Happens to the Brain in Alzheimer's Disease? National Institute on Aging. Accessed July 31, 2023. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

[liii] Alzheimer's Association. Down Syndrome and Alzheimer's Disease. Published online 2022.

[liv] Centers for Disease Control and Prevention. Down Syndrome and Increased Risk for Alzheimer's. Centers for Disease Control and Prevention. Published December 20, 2022. Accessed July 31, 2023. https://www.cdc.gov/aging/publications/features/down-syndrome-alzheimers-risk.html; Alzheimer's Association. Down Syndrome and Alzheimer's Disease. Published online 2022.

[lv] National Down Syndrome Society. Alzheimer's Disease & Down Syndrome. Accessed July 31, 2023. https://ndss.org/resources/alzheimers

[lvi] Here again see the recent reports of the CTAD and the July report from the NIA-AA Work Group.

[lvii] See Jacobson, op cit

[lviii] See Majersik, op cit

[lix] Centers for Medicare and Medicaid Services. Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431R) - Proposed Decision Memo. www.cms.gov. Published July 17, 2023. Accessed August 15, 2023. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=308

[lx] Marty Stempniak. "Alzheimer's drug could spur upward of $500M in new Medicare spending on imaging," Radiology Business, May 15, 2023, accessed at https://radiologybusiness.com/topics/medical-imaging/nuclear-medicine/alzheimers-drug-medicare-imaging-lecanemab-leqembi; Jessica Kim Cohen, "New Alzheimer's Drugs Poised to Drive Demand for Beta-Amyloid Testing if Reimbursement Improves," Precision Medicine Online, June 21, 2023, accessed at https://www.precisionmedicineonline.com/neurological-psychological-disorders/new-alzheimers-drugs-poised-drive-demand-beta-amyloid-testing

[lxi] See Office of Management and Budget, Pending EO 12866 Regulatory Review, July 26, 2023, accessed at https://www.reginfo.gov/public/do/eoDetails?rrid=325012; also James Boiani and Amy K. Dow, "What's on the Agenda? Laboratory Developed Tests Added to the Unified Regulatory Agenda Signals FDA Movement Toward New Regulatory Framework," Epstein Becker and Green LLC, June 29, 2023, accessed at https://www.ebglaw.com/insights/whats-on-the-agenda-laboratory-developed-tests-added-to-the-unified-regulatory-agenda-signals-fda-movement-toward-new-regulatory-framework/

[lxii] See Annalee Armstrong, "Alzheimer's meds are here. But for the Down syndrome community, it's still the 1980s," Fierce Biotech, March 1, 2023, accessed at https://www.fiercebiotech.com/biotech/down-syndrome-and-alzheimers-pharma-clinical-trials-safety-lecanemab

[lxiii] Lee Fleisher, MD; Steve Farmer, MD, PhD; Lori Ashby, MA; and Jonathan Blum, MPP, Centers for Medicare & Medicaid Services, "Transforming Medicare Coverage: A New Medicare Coverage Pathway for Emerging Technologies and Revamped Evidence Development Framework," June 22, 2023, accessed at https://www.cms.gov/blog/transforming-medicare-coverage-new-medicare-coverage-pathway-emerging-technologies-and-revamped

[lxiv] See current USPSTF recommendation of insufficient evidence at U.S. Preventive Services Task Force, op cit

[lxv] For background see Marc Agronin, MD, "Geriatric Mental Health and New Models of Dementia Care," PsyCom Pro, February 26, 2023, accessed at https://pro.psycom.net/geriatric-mental-health-and-new-models-of-dementia-care; national goals for development of Alzheimer's Disease and dementia care models can be viewed at the National Plan to Address Alzheimer's Disease (2021 Update), U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, December 27, 2023, accessed at https://aspe.hhs.gov/reports/national-plan-2021-update ; for a recent proposal for comprehensive reform of dementia care delivery and payment see the Milken Institute Alliance to Improve Dementia Care, "Scaling Comprehensive Dementia-Care Models," November 10, 2021, accessed at https://milkeninstitute.org/report/dementia-care-models-scaling-comprehensive; also of note – on July 31, 2023 the Centers for Medicare and Medicaid Innovation (CMMI) proposed a test of a new voluntary model of dementia care and payment, the "Guiding an Improved Dementia Experience (GUIDE) Model"; see Centers for Medicare and Medicaid Services, Guiding an Improved Dementia Experience (GUIDE) Model, July 31, 2023, accessed at https://innovation.cms.gov/innovation-models/guide