Alzheimer's disease biomarkers and the tyranny of treatment

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Summary

Advances in treatment are changing not only the therapeutic options for patients with Alzheimer's disease; they're also changing their diagnostic options. Technologies to detect amyloid such as PET imaging and blood or CSF testing now have a central role in Alzheimer's disease care. Notably, this role has been made possible by regulatory approval and coverage by payers of therapies. Access to treatments and the diagnostic tests needed to prescribe them is encourageing but it reveals a problem. These tests are tailored to the needs of the therapies, not to the needs of patients. Patients and families need to understand the causes of their impairments and their prognosis. This requires access to the best available diagnostic tests and this access should not depend on the availability of treatments. These tests should be used to their fullest capacity to inform patients of the causes of their cognitive impairments and their prognosis. Unfortunately, compared to diagnostic testing, treatment options are overvalued. We call this problem the tyranny of treatment.

Keywords: Alzheimer; Biomarker

Until recently, Alzheimer's disease—among the most frequent causes of dementia—was a diagnosis of exclusion. A clinical evaluation of a person with dementia ruled out the many non-neurodegenerative causes and brain diseases other than Alzheimer's. The diagnosis was therefore qualified as "probable Alzheimer's disease." Probable only became definite at death, if a post-mortem examination showed the hallmark pathologies of amyloid plaques and neurofibrillary tangles. The discovery of biomarkers of Alzheimer's are fast retiring this approach into history.

Biomarkers of Alzheimer's disease are powerful tools. For patients being evaluated for cognitive problems, biomarkers permit clinicians to assign an etiological diagnosis. This information can result in changed diagnoses and treatment choices, as was the case for more than a third of patients with Mild Cognitive Impairment (MCI) or dementia in one large practice-based study of amyloid PET.[1] Biomarkers can also provide important information about prognosis. In patients with MCI, numerous studies demonstrate a strong association of positive amyloid PET imaging biomarker tests (amyloid being one of the two hallmark pathologies of Alzheimer's disease) with the outcome of progression to dementia.[2–4] Information provided by biomarkers also has value to patients and families; to help them move past a diagnostic phase and into an active phase of disease management.[5]

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And yet, as powerful as these tools are, their clinical use around the world has been highly limited.[6–8] In the US, for example, amyloid PET imaging has been available for over two decades. Ten years ago, however, the Centers for Medicare and Medicaid Services (Medicare), the US national health insurance for persons 65 years and older, declined to cover the test, deeming it unable to pass its evidentiary bar of "reasonable and necessary" for patient care.[9,10] In July of 2023, Medicare changed its mind. It announced it will pay for the scan.[11] Why the change?

One of the key reasons was the availability of a new treatment. In that same month, the US Food and Drug Administration (FDA) granted "full approval" to one anti-Aβ immunotherapy (lecanemab, Leqembi®, Eisai) for the treatment of persons with Alzheimer's disease in the MCI or mild dementia stages. Another (donanemab, Eli Lilly) has subsequently been granted approval. Other nations' regulatory authorities have yet to weigh in.

Patients need treatments, but the central premise of this essay is these treatments are vastly overvalued compared to diagnosis and prognosis and this overvaluation does not well serve patients and their families.

Treatment drives diagnosis

In 2012, Eli Lilly's florbetapir (Amyvid®) became the first amyloid PET ligand to secure US FDA approval for clinical use.[12] The argument to move amyloid imaging into routine practice was that the prognostic significance of the scan warranted coverage for persons with

cognitive impairment. The clinicians who petitioned Medicare told vivid stories of patients who wanted to know whether they had the earliest signs and symptoms of Alzheimer's disease. Those who did, who learned a "positive" amyloid PET scan foretold dementia, set to work to get their health and personal affairs in order.[5,13] A "negative" scan, in contrast, offered reassurance.[5] Medicare, however, didn't endorse the value of diagnosis and prognosis.

What's notable is that the medical profession didn't either. Alternative technologies, specifically spinal fluid testing for Alzheimer's biomarkers, offer near identical diagnostic and prognostic information and have been available for as long as amyloid imaging. But medicine, at least in the United States, had little interest in pushing for the widespread adoption or uptake into clinical practice of these tests. Nor did professional societies and advocacy groups. There was no push for widespread adoption and uptake of spinal fluid assessments of Alzheimer's biomarkers.

In 2020, seven years after Lilly failed to convince Medicare to cover amyloid imaging, the company received FDA approval for flortaucipir (Tauvid®), a tau PET imaging agent (tau tangles are the second hallmark Alzheimer's pathology). Clinicians now had the ability to image both pathologic markers required for the definitive diagnosis of Alzheimer's disease. Perhaps sobered by their experiences with amyloid imaging, Lilly didn't perceive a business model for diagnosis and prognosis and chose not to seek Medicare coverage.

What changed Medicare's decision to cover amyloid testing was the FDA's approval of lecanemab. Medicare will cover the cost of a scan as part of a workup to determine whether a patient with MCI or mild stage dementia is eligible for anti-amyloid treatment. This decision is entirely sensible. The drug targets amyloid and was tested in persons with evidence of it.

Clinicians are now enthusiastic about ordering Alzheimer's biomarker tests. Clinicians developed appropriate use guidelines for anti-amyloid prescriptions that required biomarker testing (PET or spinal fluid).[14,15] Yet, biomarker testing is constrained to persons who meet the clinical criteria for treatment. The message is implicit, but it is loud and clear. Treatment drives diagnosis.

Treatment and biomarker coexist in a kind of looping effect. The biomarker signifies the need for a treatment. The treatment in turn shapes how we use the biomarker. Anti-amyloid treatments promote talking about amyloid as either "positive" or "negative." A positive test warrants treatment. The results of a study of donanemab suggest when the test becomes negative, treatment can be stopped.[16] An emerging idea from that same study of donanemab is that a tau scan may inform treatment decision making. A person with a "positive" tau scan has, compared to a person with a negative scan, a greater risk of decline and so the benefits of treatment are more compelling. This is the promise of precision medicine.

One major driver of this is business. A vast biopharmaceutical industry develops, tests and markets therapeutics. It openly speaks of drugs as "blockbusters," a term that originally described the power of a bomb to destroy a city-block and was then taken up by Hollywood studios to describe films with spectacular production costs and even more spectacular revenues. Notably, Biogen had this vision of financial success with aducanumab, the first approved but no longer marketed anti-Aβ immunotherapy, initially pricing it at $56,000 per year.[17]

Together, the combination of clinicians' enthusiasm to do something for their patients and a business model for a treatment are propelling Alzheimer's biomarkers into clinical practice. Hence this essay's title[18]—treatment dominates. Treatment, which we think of as following diagnosis, in fact drives diagnosis. It is a monarch.

Something is missing

There is absolutely nothing wrong with the practice of precision medicine. Patients need treatments. What's wrong is what's missing. Patients also need a diagnosis, an answer to *what's wrong with me?* And they should have this question answered even if there is no treatment or the patient is not eligible for treatment because for example, she has moderate stage dementia.

In neurological diseases such as Alzheimer's, ALS and Huntington's, diagnosis means an explanation of symptoms. Patients also want to know what to expect in the future, or prognosis. A core concept in the care of individuals with neurological disease is helping patients understand "how long" and "how well."[19] Having answers to these questions helps patients and their families take other important and meaningful actions, like seeking support and adjusting long-term plans for residence, finances, and care. Unfortunately, much of the nomenclature and vocabulary we have to talk about biomarkers is driven by the values that compel treatments—not prognosis.

The story of tau PET imaging illustrates this. The FDA approved label for tau PET is uninformative to answer "how long" and "how well." It indicates a visual read outcome of "negative" or "positive," the latter is equivalent to roughly Braak stage V/VI. The true clinical value of tau PET is unrealised. It could inform a clinician to help patients and families understand their condition by explaining symptomatic presentation with regional specificity of pathological disease burden. It could instruct the probability and pace of disease progression.[20]

Consider a person diagnosed with Alzheimer's disease whose history is of notable problems with speech. They have the logopenic primary progressive aphasia

label. Tau imaging would show uptake in their temporal lobe region that explains why their speech is hesitant. The spread of that tau would inform the course of their disease.[20] Moreover, earlier stage presentations of tau pathology (significantly below Braak V/VI) offer important prognostic information.[21] The "positive/negative" regulatory nomenclature may be good for signifying the need for treatment. A more complete nomenclature would include the diagnostic range of tau PET outcomes and so greatly enhance the value of the tool.

All of this leads up to a striking irony about the treatment of Alzheimer's disease. Absent a cure, treatment is in fact about prognosis. For many common and chronic diseases, such as cancer or heart disease, prognosis is about how much time until the end of life, until death. But with Alzheimer's and other neurodegenerative diseases that cause dementia, the time to death is morally problematic. We don't prescribe treatments to live longer with dementia. We prescribe treatments to reduce the pace of disability and to maintain a healthy mind.

Mind means consciousness, the stream of moment-to-moment experiences that emerge from bidirectional perceptions and interactions between a brain and its environment. Assembled together, those conscious experiences constitute identity. Neurodegenerative diseases such as Alzheimer's damage a brain and as a result impair a person's mind. The person struggles to experience the world. A person with logopenic variant primary progressive aphasia for example, struggles to communicate and so have shared experiences with close friends and family.

How well do we care for patients' minds? Arguably, not well. Access to well-funded person-centred care might include a dementia care coordinator, support with social integration and reducing social isolation, dementia-friendly exercise programmes, support for psychological/emotional well-being, in–home technology to keep people safer and respite and services for family carers. Unfortunately, these services and supports are often bundled under a label that describes them by what they aren't more so than what they are: "nonpharmacological treatments." In many countries, they are categorized as welfare not healthcare.

We also lack a language to talk about living with Alzheimer's disease. Time matters in Alzheimer's disease. The label transforms how people, both patients and caregivers, think about it. The diagnosis engenders in patients and families deep reflections over identity and how long it will be as it is now and what's needed to maintain it. People derive value from knowing biomarker information to instruct planning, including employment, financial, residential, and care decisions. These decisions are best informed not by binary categories (positive/negative or elevated/not elevated), but by information about how much time an individual has living with their current mind.

Looking toward the future

There is an urgency to this. Biomarker information may soon allow us to foretell to individuals with no symptoms at all the time remaining before dementia is apparent. These predictive models, or risk calculators, have been built around the premise that amyloid accumulates with a knowable time course to the onset of symptomatic Alzheimer's disease.[22,23] Multi-biomarker combinations that incorporate amyloid and tau may provide even better models to identify those at greatest immediate risk.[24] The performance of predictive models is improved when demographic information such as age and sex, as well as apolipoprotein E genotypes, are included.[25] Plasma assays that can do what has to this point required multiple PET scans will reduce the cost and increase access to these models.

Risk calculators may hold great promise for improving precision medicine for the mind, but will also require extensive education of clinicians and patients and families. There's an urgent need to determine the optimal ways to deliver risk information to maximise patient and family understandings and optimise behaviour outcomes.[26] A vast industry exists to move a treatment into practice. Not so for risk calculators.

Other areas of medicine (e.g., cardiovascular disease, osteoporosis, breast cancer) have incorporated risk calculators, with or without biomarker tests, often delivering opportunities for patients to self-assess their risk. Direct-to-consumer campaigns urging older individuals to "know their number," with specific scores being indicated with the need for disease delaying Alzheimer's treatments, are anticipated and are anticipated to bring great challenges.[27]

Whether Alzheimer's disease risk calculators will be equally informative across general populations is unknown. Their accuracy for individuals from minoritised groups, for example, will remain unclear until more data are available to understand whether and how race and ethnicity modify disease prevalence, genetic associations, and biomarker performance.[28,29] Moreover, race and ethnicity are social constructs and lifetime exposure to social determinants of health may differ substantially by nation.[29] Elucidating these relationships in one country may not necessarily inform relationships in others.[30]

Prognostic information prior to symptom onset has value for patients and families to plan, adjust, and prepare,[31] but it also has risks that include mislabeling, stigma, and discrimination. To label a person with Alzheimer's or another dementia-causing brain disease puts them at risk for discrimination in the workplace, the clinic, and the home.[32–34] To fully realise the power, opportunity, and impact of disease biomarkers, we must create global equitable dementia-friendly societies where the risks associated with the label of Alzheimer's and other dementia-causing diseases are eliminated. Society must also improve the care it provides older

Key messages

- Research advances are creating new tools to diagnose and treat Alzheimer's disease.
- These tools include diagnostic biomarkers and disease-targeting treatments.
- Unfortunately, these tests are tailored to the needs of the therapies, not to the needs of patients.
- We call this failure to value diagnosis and prognosis the tyranny of treatment.

people with brain diseases, not just in the clinic, but in the work place and in service industries where disease-risks manifest, such as banking.[35] We must recognise that biomarkers represent mile-markers on a journey taken not only by patients but by family members.[36,37]

New treatments for Alzheimer's disease rule the clinic. They're reshaping the landscape of care for patients living with or at risk for cognitive impairment. To fully realise the optimal impact of tremendous progress in dementia research, we must recognise the value that diagnosis and prognosis, in addition to treatment, have for the care of patients living with or at risk for dementia.

Only then will we break the tyranny of treatment and achieve a republic of care.

Contributors

The authors contributed equally to this manuscript. Both drafted, edited, and approved the final version.

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