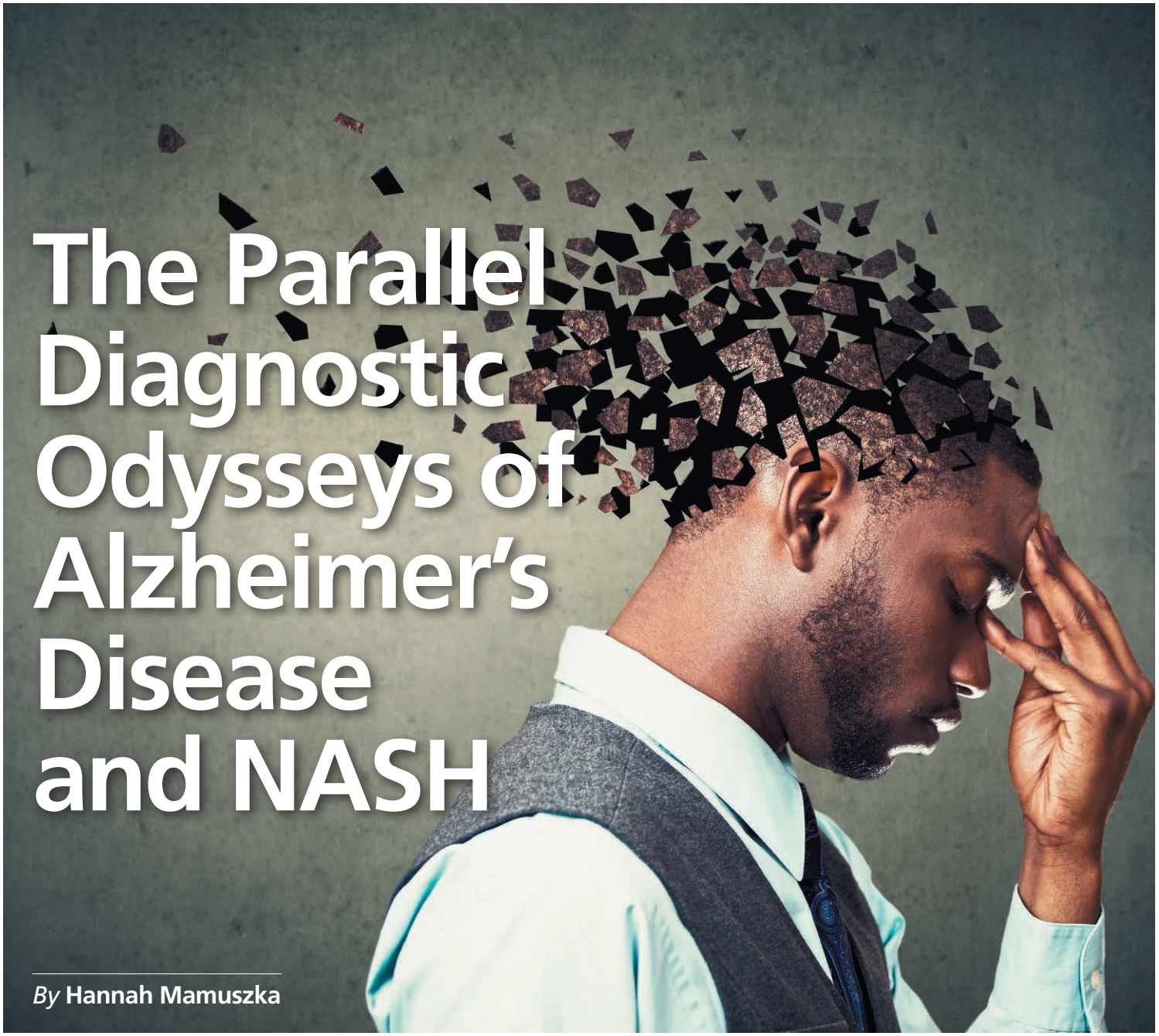


# The Parallel Diagnostic Odysseys of Alzheimer's Disease and NASH

*By* **Hannah Mamuszka**



## What do Alzheimer's disease and NASH have in common?

- Devastating diseases that affect millions of people every year
- No screening diagnostics to diagnose in early stages
- No effective therapeutic options
- Huge costs to our healthcare system that will continue to grow

Alzheimer's Disease is well known as a disease that causes dementia, though it is still poorly understood from a scientific perspective. Maybe your parents or your grandparents had it, like my grandfather did, and you watched them fade away in devastatingly slow motion. It is a disease most fear, and despite huge investment over the past 20 years, there are currently no therapeutic options that slow it's progression.

The other, NASH (non-alcoholic steatohepatitis, or fatty liver disease that leads to liver failure), you may have not heard of, but statistically you are much more likely to already have, and you should know and ask your primary care physician about it. NASH, and its predecessor, NAFLD (non-alcoholic fatty liver disease) indicate the liver is in the early stages of failure. It is estimated* that between 30-40% of the US population has NAFLD, 3-8% have NASH, and 1.5-2% have liver cirrhosis[3] (*estimated, because we don't screen for NASH; more on that below). NASH is now the leading cause of liver failure and liver transplant in the United States and has been an underdiagnosed comorbidity linked to severe COVID-19, ICU stays and death. In fact, NASH is the comorbidity with the highest association with death from COVID-19 in the United States.[1]

Both Alzheimer's Disease and NASH are debilitating diseases that affect millions of Americans every year (about 5.8M people living with Alzheimer's Disease and 10M people living with NASH), although no one actually knows if those numbers are accurate because we don't have standard-of-care screening diagnostics or coverage

policies that accurately diagnose either disease. And that is where the problems with both of these diseases start – we don't know who actually has them until it's too late to treat them.

Both diseases require a lot of treatment and management in the later stages, as both are progressive and debilitating and can ultimately be fatal. With Alzheimer's Disease, patients begin to lose the ability to recall simple things, like why they were going to the grocery store. Alzheimer's Disease ends when the nerve connections in the brain are destroyed to the point where patients can't move, feed themselves, or swallow. Eventually, complications from the decline of brain functions lead to death. With NASH, which has four stages starting with NAFLD, patients are largely asymptomatic until their liver begins to fail or they are diagnosed with liver cancer. Too often, by the time the liver failure or cancer is diagnosed, it is too late to treat them, other than with liver transplant for a lucky few. NASH is now the primary cause for liver transplant in the US.[2]

Neither disease has effective treatment options that have been approved by the FDA or any other global regulatory body that dramatically impact the progression of the disease. However, it is not that the pharmaceutical industry doesn't recognize the unmet need and hasn't been working on therapies; it's just that they haven't applied the lessons we have learned from oncology drug development and applying them to these big diseases.

Neither Alzheimer's Disease or NASH are one 'disease', in the same way that patients are no longer treated for 'cancer,' but for EGFR+, ALK-negative, non-small cell lung carcinoma, neither Alzheimer's Disease or NASH is one 'disease.' Abundant data has shown that both diseases are pathologically, genomically, and genetically different, yet no biomarker stratification tools have been implemented as a way to differentially diagnose and therapeutically manage these patients. Because of that, we are stuck. Trials for drugs in both diseases have been hampered in regulatory review by low overall response rates coupled in some cases with high adverse event rates, and no biomarkers used to segment the populations into responders vs non-responders, adverse event likely vs not.

In addition to causing significant disability, Alzheimer's Disease is the fifth-leading cause of death among those over 65, and the sixth leading cause of death overall in the United States. Yet, we have no diagnostic tools to screen for Alzheimer's Disease before symptoms become serious and no therapeutic interventions to stave off the loss of memory function. Why? Part of the requirement for coverage of a diagnostic – meaning that it gets paid for in our healthcare system, which is a requirement for broad use- is demonstration of 'clinical utility.'

Clinical utility for a diagnostic is defined as a test that changes the medical management of a patient population, and improves their care. Without any therapeutic options to improve care, it is not possible to demonstrate clinical utility of a diagnostic to diagnosis Alzheimer's Disease. But without a diagnostic that diagnoses early Alzheimer's Disease, we can't have any therapeutics for those patients, because we can't diagnose. The key reason Alzheimer's Disease has been so difficult to treat is because the early symptoms of memory complaint are difficult to distinguish from other memory issues, that can be the result of many unrelated factors.

Developing diagnostics to accurately diagnose Alzheimer's Disease and distinguish it from other subjective memory complaints (including confounding factors from diabetes, issues related to nutrition and hydration, complications from medications, and other factors) is complicated, expensive, and requires a lot of data (and money to develop that data). To be clinically useful, the data needs to include a longer term plan to track outcomes, meaning that you are able to confirm that later on in the patient progression that you accurately diagnosed a patient with Alzheimer's, either before they had symptoms or early in the disease. The ideal test for Alzheimer's disease would be early in the patient's experience with memory loss, or even before, with the ultimate intention to determine interventions to prevent the disease from progressing.

The challenge with developing these tests is significant, and comes in the market – who is going to pay for them? In the US healthcare system, we do not value paying for 'information' that does not have clinical utility. But since there are no approved therapeutics, there isn't anything meaningful to change with an accurate early diagnosis of Alzheimer's Disease, so diagnostic developers, even those with excellent data, have not been able to get the funding to commercialize the diagnostics that diagnosis and distinguish early Alzheimer's Disease from other memory complaints, because no one will pay for the test without clinical utility. Investors cannot fund commercialization of diagnostic tests that aren't going to be paid for.

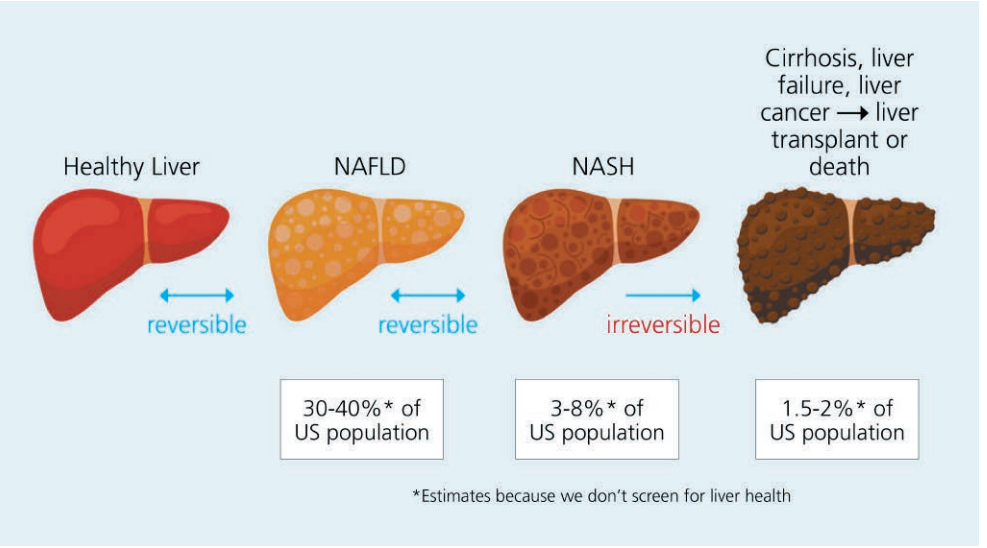



**Figure 1:** NASH progression

On the other side, we have the pharmaceutical industry, who has tried valiantly for years and spent billions of dollars trying to develop therapies that will mitigate the effects of Alzheimer's Disease with no approvals, yet repeatedly resists using biomarkers to stratify patients for response in their regulatory submissions. As one pharmaceutical executive once described it, "...the Alzheimer's Disease market is a $10B/year market right out of the gate. No one wants to be the one who limits that to $2B (by using a diagnostic that stratifies the population)."

Now on to NASH. NASH is the end stage of a disease that starts with NAFLD and progresses through four stages of NASH. Both NAFLD and NASH are largely asymptomatic, so patients are unaware that they are in the early stages of liver failure. NASH has overtaken hepatitis as the leading cause for liver transplant in the US, and is related to type II diabetes and obesity, which are extraordinarily prevalent in the US (42% of US adults are obese according to a February 2020 CDC report). There are also patients who are not

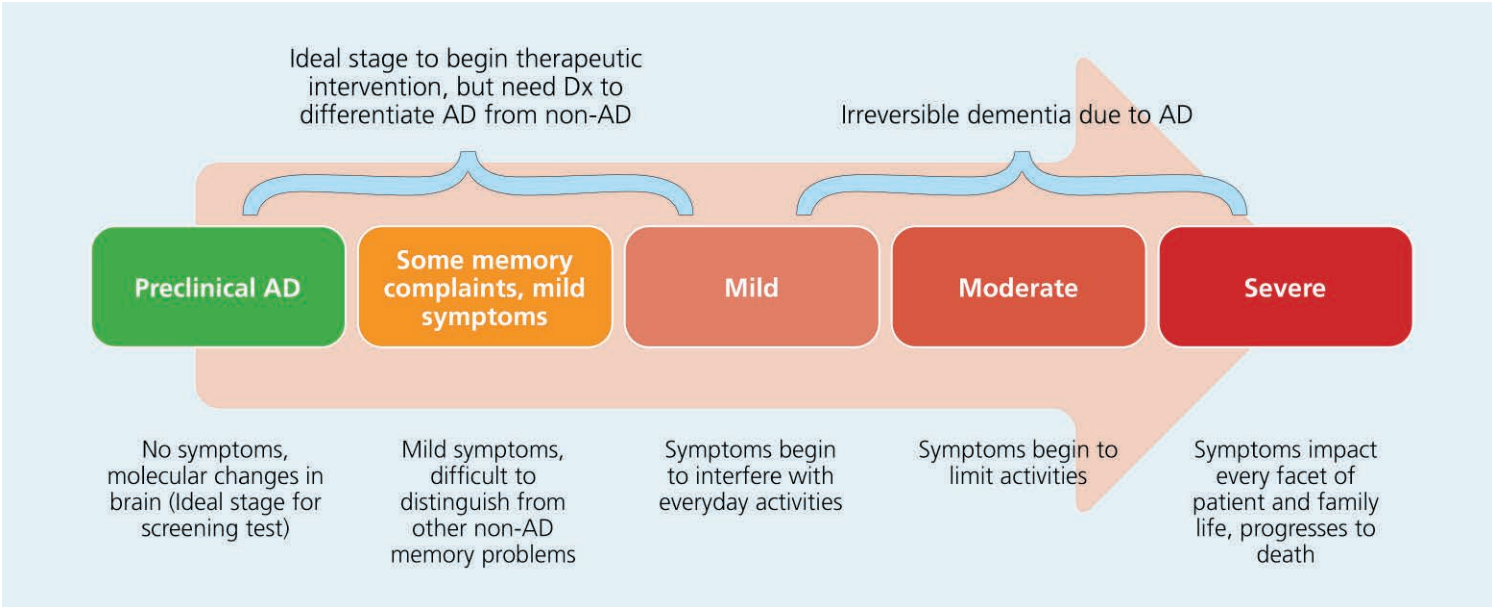



**Figure 2:** Where diagnostics and therapeutics could impact the course of Alzheimer's Disease



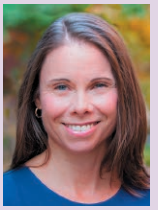
overweight and do not have type II diabetes and have NASH. In reality, because we don't screen for NASH, we don't know the true prevalence, which is almost certainly higher than the estimates.

The reasons for not screening for NASH has some similarities with Alzheimer's Disease. There are no currently approved therapeutics for NASH, with some recent late stage failures in 2020 dashing hopes of imminent treatment. But unlike Alzheimer's Disease, many patients with NASH could manage and improve their liver function (and correlating NASH status) through lifestyle modifications, including diet and exercise. However, payers don't see that as a clinical utility, because diet and lifestyle modifications are recommended for diagnoses that often accompany NASH (type II diabetes and obesity) and despite those diagnoses, the majority of patients are not able to treat their obesity or type II diabetes in this manner.

Diagnosing NASH is not trivial; the current 'gold standard' requires a liver biopsy. Even Medicare has admitted that liver biopsy is far from ideal, both because it misses between 25-30% of NASH and because it is painful and risky to the patient. Additionally, there are not enough hepatologists and pathologists in the US to biopsy everyone who would be 'under suspicion' of NASH, meaning we need to find other diagnostic tools. Fortunately, several less invasive options, including both imaging and blood-based testing, are in advanced development or early commercialization; however none of them are being readily paid for by either Medicare or commercial insurance.

In January 2021, at the most recent FDA meetings around NASH drug development, the FDA was discussing the need for better up front diagnostics for NASH, and was asking for proof in the form of data to move beyond pathology. The challenge with moving beyond pathology is that all the outcome data related to the therapeutics currently in development are in the control of the sponsors, i.e., the pharmaceutical companies running the trials. For years, they have resisted, by contractually blocking diagnostic developers, the best diagnostic technologies from being used in these trials, or for the diagnostic developers to be able to own the data rights. Without access to that data, it's challenging for diagnostic developers to prove the clinical utility of their tests either to the FDA or to payers. Without being able to prove clinical utility, it will be hard for these non-invasive diagnostics to be commercially viable.

It's clear that making progress in either of these diseases is going to require investment in the diagnostics that can be utilized at the beginning of the disease, so where do we go from here? The financial implications for the decisions that we make today will have a significant effect across our healthcare system. As a result, we need to accept that while diagnosing patients today may not lead to immediate therapeutic changes, we cannot improve care without the knowledge of who has early-stage diseases when they are more easily and effectively treated. We also need to understand the longer time horizons for evaluating outcomes and demonstrating value beyond the standard one-year window, as well as the need for those diagnostics to be paid for at the value they deliver to the healthcare system. Doing so now can encourage innovation and use to foster progress for diseases such as AD and NASH in the future. JoPM



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Hannah is Founder and Chief Executive Officer at Alva10, which she founded in 2015 to address the 'vicious cycle' of diagnostics- inadequate reimbursement leading to inadequate investment preventing promising diagnostic technology from impacting patient care. Alva10 partners with payers, employers, and diagnostic developers to develop diagnostic tools to address major areas of healthcare need, inefficient spending and poor patient outcomes.

Prior to Alva10, Hannah was VP of Exosome Diagnostics (acquired by BioTechne), where she led some of the earliest deals in the liquid biopsy diagnostic space. Earlier in her career, she was Global Director of Pharmaceuticals Services for Oncotech, and then by acquisition, Exiqon (acquired by QIAGEN). Prior to her time in diagnostics, she worked in drug development on 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 speaker and writer on healthcare technology and writes a regular column for the Journal of Precision Medicine on the challenges of implementing change in healthcare. Hannah serves on the Board of Directors for Bionano Genomics (BNGO) as well as on the Advisory Board for the Carolina Health Informatics Program (CHIP), a graduate program in health informatics at the University of Carolina at Chapel Hill.

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