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Life Science Tools & Diagnostics

Alzheimer's – A Large, Untapped Dx & Bioprocessing Opp w/ a Lot of Unknowns

In this report, Nephron's Tools & Dx and Health Policy teams join forces to provide a comprehensive overview on the clinical need and market potential in Alzheimer's for our coverage. We expect this topic will increase in importance throughout 2023, with Eisai/Biogen's Leqembi PDUFA scheduled for 7/6 and recent Phase 3 results reported for Lilly's donanemab. **We think it is prudent to have modest expectations relative to a significant TAM**. The opportunity is important for our Dx coverage of the labs (DGX/LH) and bioprocessing (AVTR, DHR & TMO).

Diagnostics/Labs Opportunity: **There is a significant opportunity to innovate blood-based tests to screen and monitor for Alzheimer's**. This is a potential win-win-win-win. Pharma companies are incentivized to have strong testing solutions to identify early-stage AD patients. Payors are incentivized to ensure that high-cost therapies are only utilized by patients most likely to benefit from them. There is patient demand to understand risk of Alzheimer's and potential eligibility for novel therapies. Diagnostic tests are under development to meet the market need. **That said, there is also significant uncertainty around exactly how this will play out**. Blood tests will need to compete with the current standard of care (PET and CSF), which have obvious drawbacks such as cost and access. Guidelines have also not yet been established to include novel tests. Finally, current Medicare reimbursement is at levels which raise questions about commercial viability. We see both opportunity and risk when it comes to the outlook for Medicare coverage and reimbursement over the next three to five years for new diagnostic tests.

In our Diagnostics coverage, we think the national labs (Quest and LabCorp) stand to benefit over time as operators of IVD tests developed. Quest has also innovated their own LDT, AD-Detect, for beta/amyloid status that could offer a unique blood-based alternative to PET/CSF. **There are several IVD manufacturers developing tests, notably Roche and Quanterix (QTRX, not covered).** Roche is developing a two-pronged workflow of tests to screen for Alzheimer's disease. Quanterix is arguing for differentiated quality in detection of protein biomarkers used in Alzheimer's, leveraging its ultra-sensitive Simoa immunoassay platform.

We think potentially the most compelling commercial opportunity for our Diagnostics coverage is monitoring of patients on therapy, which we size at $200mm in our base case. Patients on therapy could need to get multiple tests per year – as a baseline upon starting treatment, and then follow-up tests to monitor disease progression. **For screening, our base case forecast for Alzheimer's testing is $400mm annually**. The market potential is obviously much more significant in terms of the # of patients who could get screened, though there is also significant uncertainty around guidelines and reimbursement which limit visibility into adoption.

Bioprocessing Opportunity: **Alzheimer's has long been one of the big biologics opportunities**. Given the size of the patient population and manufacturing intensity of monoclonal antibodies, the total addressable market is sizable and largely untapped. **Despite all of the promise, the category has a history of under-delivering**. Experts we interact with are skeptical of the size of the short-term contribution to sales. **Our top-down and bottom-up analysis suggests that AD can add 0.5-1% to industry bioprocessing sales for several years**. The forecast supports long-term demand dynamics for suppliers such as Thermo Fisher and Danaher (amongst others), leaders in upstream and downstream bioprocessing. **We view the contribution as supportive of LT biologics growth, but it won't save the day from ST de-stocking risk.**

Please see important disclosures at the end of this report.

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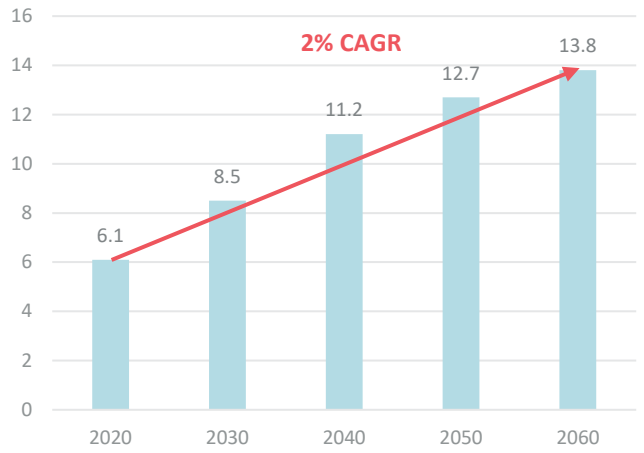
Overview on Alzheimer's Disease (AD)

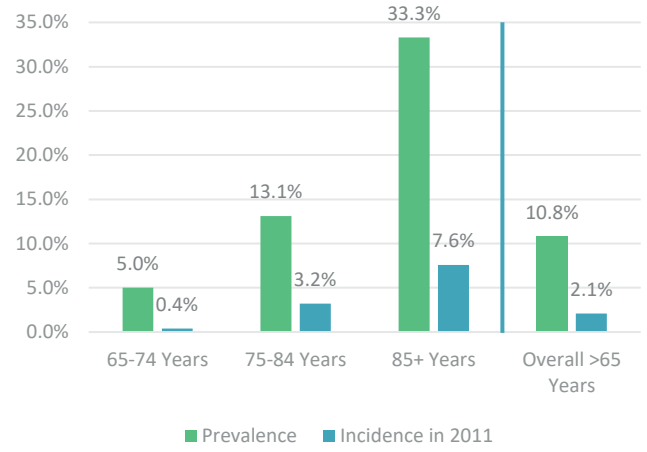
There are 6.7mm Americans living with Alzheimer's in 2023. Most Alzheimer's patients are elderly and eligible for Medicare. Symptoms of the disease can first appear after age 60, and the risk increases with age. Younger people may get Alzheimer's, but it is less common**. The prevalence rate for individuals >65 years of age is estimated at 11%, while the incidence rate is roughly 2%**. The prevalence is expected to rise to 14mm by 2060. Studies indicate people >65 years of age live 4-8 years after a diagnosis of AD, though some live as long as 20 years. Alzheimer's is the sixth leading cause of death in the United States. The costs to treat Alzheimer's are estimated at $159-$215bn.

Fig. 1: Estimated Prevalence of Alzheimer's by Decade (MM)



Source: Alzheimer's Association, Nephron Research

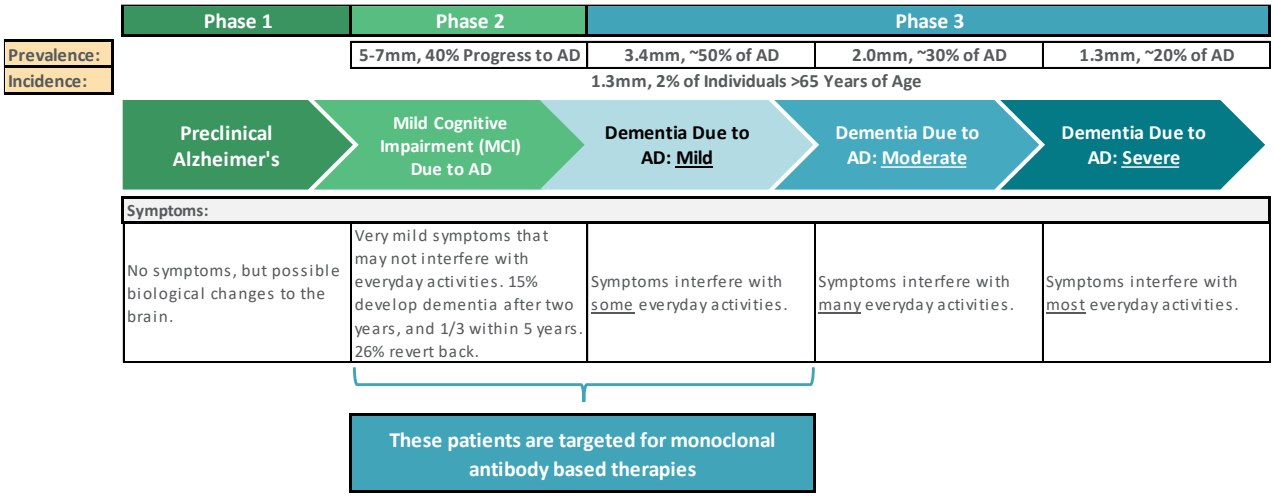
Fig. 2: Prevalence & Incidence of Alzheimer's by Age Group



Source: Alzheimer's Association, Census Bureau, Nephron Research

Alzheimer's is a progressive disease, beginning with mild memory loss – known as Mild Cognitive Disorder (MCI). It is estimated 5-7mm Americans live with MCI, 40% of which will progress to AD over time. **Brain changes include the accumulation of abnormal proteins beta-amyloid and phosphorylated tau, as well as the degeneration of neurons**. As time passes, more neurons are damaged and more areas of the brain are affected. **Novel therapies to slow the progression of AD target patients with MCI or mild AD, where patients have the greatest likelihood to benefit.**

Fig. 3: Progression of Alzheimers and Estimated Market Sizes (MM)



Source: Alzheimer's Association, Census Bureau, NIH, Nephron Research

The Diagnostics Opportunity in Alzheimer's

Diagnosing Alzheimer's is a significant issue for the industry. Up to 75% of people living with symptoms of Alzheimer's have not been diagnosed. It is believed that genetics may play a role in developing Alzheimer's, in addition to lifestyle (diet, alcohol consumption and smoking status). Changes in the brain can begin years before symptoms begin.

Early diagnosis is critical for treatment. Evidence shows that therapeutics work best when patients have mild disease. Alzheimer's patients who have been diagnosed wait 2.8 years on average before starting treatment, during which disease progresses and they may no longer benefit from treatment.

There is a significant benefit for both pharma companies and payors to enable earlier diagnosis. For pharma, early diagnosis can help build a funnel of potential patients eligible for therapy. For payors, testing can be used as a gatekeeper to ensure that only the patients most likely to benefit from treatment get reimbursed.

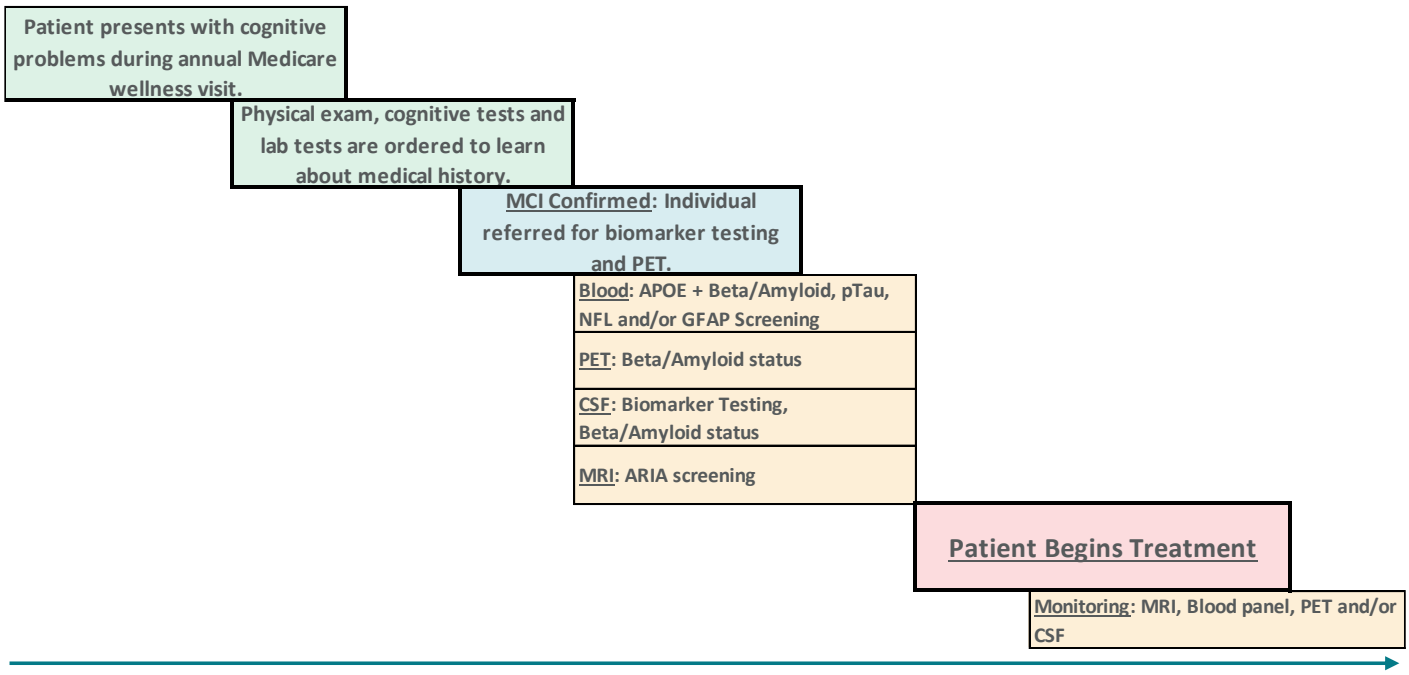
The Alzheimer's Diagnostics Workflow

Patient diagnosis begins with a clinical assessment of the patient. Physicians and specialists gather information on patient symptoms, family history, and lifestyle factors to establish a baseline for diagnosis. This can include cognitive and neuropsychological testing to objectively measure cognitive abilities and identify any patterns of decline.

- **Today, the standard of care for the official diagnosis of Alzheimer's includes neuroimaging techniques such as positron emission tomography (PET) and MRI**. These tools visualize the brain structure and can detect abnormalities associated with Alzheimer's. Imaging can also rule out other potential structural issues outside of Alzheimer's. In terms of cons, there is a limited availability of imaging centers (around 2K) and imaging can be expensive (around $5K).
- **Patients can also confirm status through biomarker status based on cerebrospinal fluid (CSF) sampl**es. The process of getting a spinal tap is painful for patients and requires a specialist. From the sample, labs can test for biomarkers such as pTau and beta/amyloid status.
- **There are additional innovative tests under development based on blood samples to measure biomarkers for Alzheimer's**.
- **Patients also undergo a cognitive assessment test** – the most common tools among providers include the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Exam (MMSE) and the Clinical Dementia Rating (CDR) Scale).

Today, blood testing augments the workflow. Screening tests can work as a funnel for PET/CSF, offering a lower cost and less invasive method of screening. Blood testing can relieve the burden/cost on the number of patients potentially looking to get imaged (though positive results will need follow-up imaging). Medicare beneficiaries also face coverage hurdles when it comes to PET scans that detect beta amyloid. Under a current national coverage policy, Medicare only covers one PET scan for detecting beta amyloid per lifetime of a Medicare beneficiary. While CMS will likely expand coverage for PET scans in patients seeking a confirmatory diagnosis for Alzheimer's, there will still be concerns about access and out of pocket costs for beneficiaries. There is currently no rule-in screening test which is blood based. **That said, there are diagnostics under development which hope to replace imaging altogether**. This will take clinical trials and FDA approval to prove that out. This would significantly improve access & workflow efficiency.

Fig. 4: Potential Workflow for Identification of Alzheimer's Patients for Treatment



Source: Alzheimer's Association, Nephron Research

Alzheimer's Biomarkers of Interest

- **1) APOE4 Status**: The E4 allele of the apolipoprotein E (APOE) gene has been identified as a major genetic risk factor for AD. APOE provides the blueprint for a protein that transports cholesterol in the bloodstream. It encodes a protein that plays a key role in cholesterol metabolism and has been found to increase the risk of developing AD. **There are six possible APOE pairs based on three alleles of the gene (e2, e3 or e4) received from each parent**. Individuals who inherit two copies of the e4 form have an -12x risk of getting Alzheimer's, while those who inherit just one have about a 3x risk. Individuals with two copies of e4 can also face higher risk of side effects from monoclonal antibodies targeted at slowing the progression of Alzheimer's disease. For example, the Veterans Administration set a coverage policy for lecanemab earlier this year that excludes coverage for VA beneficiaries with two copies of the e4 gene. Having the e2 form may decrease your risk, while e3 is neutral. **Not all carriers of the gene go on to develop Alzheimer's**.

- **2) Phosphorylated Tau (pTau) Protein**: Accumulation of an abnormal form of the protein tau (called tau tangles) *inside* neurons is associated with Alzheimer's. pTau can be measured from PET or CSF/blood samples and it is believed that higher levels of pTau are associated with greater progression of the disease There are multiple versions, including pTau-181 & 217. LLY stratified patients by tau levels in its Phase 3 Trailblazer-Alz2 study for its monoclonal antibody donanemab.

- **3) Beta-Amyloid Status**: Accumulation of the protein fragment beta-amyloid (known as beta-amyloid plaque) into clumps *outside* of neurons is associated with early stages of Alzheimer's. beta-amyloid status can be measured from PET or CSF/blood samples. PET scans are the most common modality for measuring beta-amyloid, although there are limitations in how Medicare covers the scan for patients seeking a diagnosis of Alzheimer's (one scan per lifetime and part of a clinical registry).

- **4) Glial Fibrillary Acidic Protein (GFAP)**: GFAP is involved with many important neurological processes, including cell communication and the functioning of the blood brain barrier.

Our view is that a combination of biomarkers is likely going to be necessary for diagnosing and monitoring Alzheimer's patients. Evidence has shown that APOE status is indicative for both efficacy and safety of therapies, while Lilly's TRAILBLAZER-ALZ 2 results were stratified by their level of Tau. Beta/Amyloid also has clear clinical significance given that is the fundamental thesis behind therapies under development. **A sensitive test will be required given that only patients with MCI or mild AD are being targeted for use with monoclonal antibody treatments**.

Under a national coverage decision by Medicare, CMS requires that patients have confirmed presence of beta amyloid pathology as a condition of being eligible for the class of monoclonal antibodies such as lecanemab and donanemab. On 6/22/2023, CMS in releasing details on a registry requirement noted that patient information will include, "Results of the individual's amyloid positron emission tomography (PET) scan, cerebrospinal fluid (CSF) test, or other amyloid test." See below for more discussion on coverage of diagnostic tests to detect and monitor the progression of Alzheimer's disease.

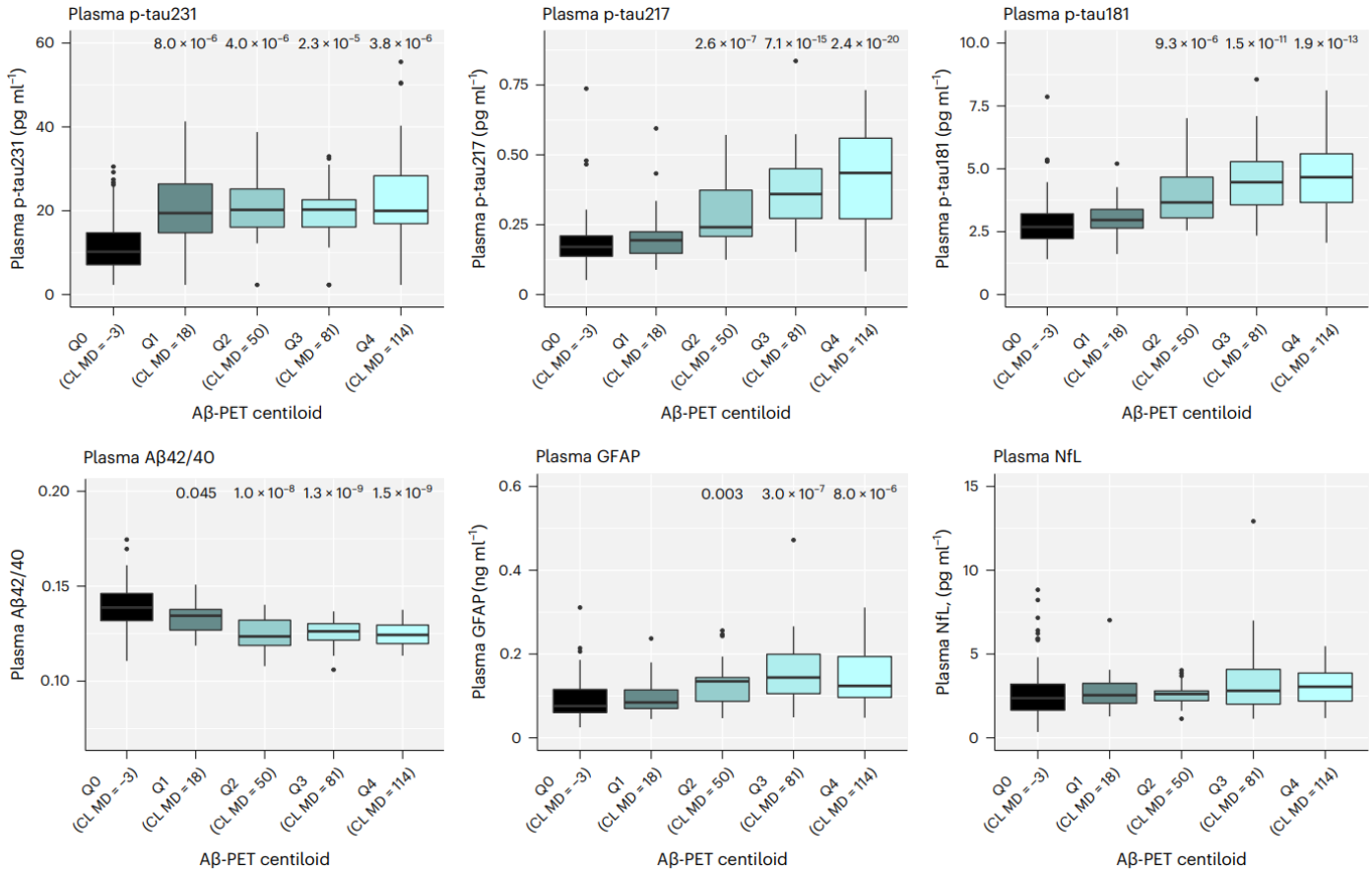
Fig. 5: Alzheimer's Dx Lab CPT Codes and Medicare Pricing

Test	CPT	Method	Medicare Rate	Description
Generic Codes				
pTau-181 and pTau-217	83520	IA	$17	Measurement of phosphorylated Tau in plasma. Excessive phosphorylation has pathophysiological consequences.
Neurofilament Light Chain	83520	IA	$17	NfL is a neuron-specific protein released, elevated levels may reflect injury and neurodegeneration - and are associated with beta-amyloid and tau.
Beta Amyloid 42/40 Ratio	83520 x2	IA	$35	Measurement of Beta-Amyloid 42/40 ratio from CSF
GFAP	88342	IA	$102	A class-III intermediate filament majorly expressed in astrocytic glial cells in the central nervous system.
APOE	81401	PCR	$137	Genotype results for E4 variant supplement information for clinical diagnosis of Alzheimers
Proprietary Codes				
Quest AD-Detect	0346U	LC MS/MS	TBD, $93.26 Prelim Gapfill	Measurement of Beta-Amyloid 42/40 ratio from plasma. CMS initially proposed $20 pricing before finalizing a gapfill decision in November 2022.
C2N Dx PrecivityAD	X082U	LC MS/MS	TBD	Combination of Beta-Amyloid 42/40 ratio and APOE proteotype detection from blood samples.
Fujirebio Lumipulse G Bamyloid Ratio (1-42/1-40)	0358U	IA	TBD	Based on CSF, positive result is consistent with PET per FDA approval

Source: CMS, Nephron Research

In December 2022, there was an interesting study published in Nature Medicine, "Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring." The study promoted pTau-217 as a leading biomarker. Relative to beta/amyloid, pTau-181 and pTau-231, "Only longitudinal increases of p-tau217 were also associated with clinical deterioration and brain atrophy in preclinical AD… These findings support the differential association of plasma biomarkers with disease development and strongly highlight p-tau217 as a surrogate marker of disease progression… **The main finding of this study, which compared several state-of-the-art plasma biomarkers in early stages of AD, was that the longitudinal trajectory of plasma p-tau217, but not other candidate biomarkers, was closely related to disease progression.**"

Fig. 6: Associations between plasma biomarkers and Aβ-PET in BioFINDER-1 (cohort 1)



Source: Nature

Competitive Landscape: Roche, Quanterix, the Labs (DGX/LH) and More

A) Roche Diagnostics

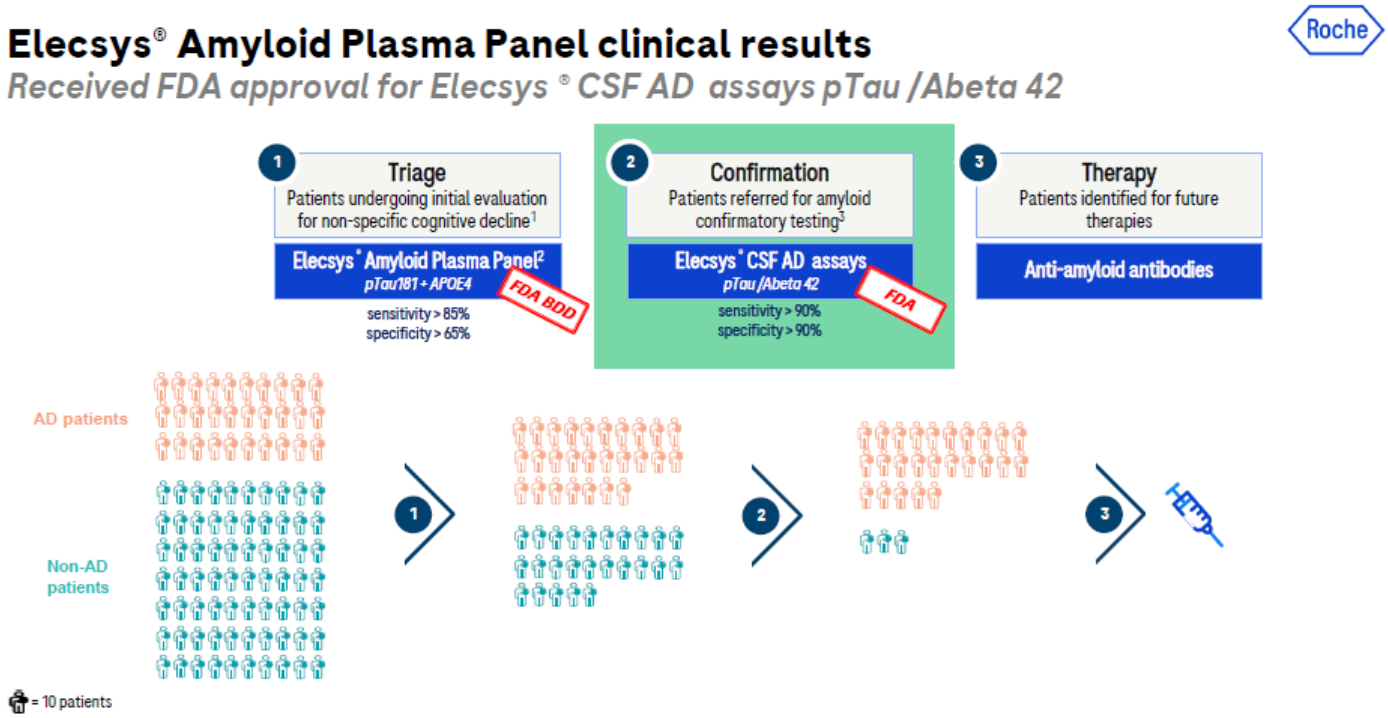
Roche is developing a two-pronged workflow of tests to screen for Alzheimer's disease.

- **1) Triage Test – the Elecsys Amyloid Plasma Panel**: To start, Roche is developing a Triage test to rule-out for Alzheimer's. **The test is intended for patients that have symptoms of cognitive decline, and physicians want to narrow that down to individuals suspected of Alzheimer's**. The test is based on a combination of two biomarkers from blood, phosphorylated Tau (pTau) 181 and apolipoprotein (ApoE) E4. The test will run on routine immunodiagnostics platforms, enabling broad access to testing for laboratories. Sensitivity will be >85%, but specificity will be low at >65% - so there will likely be a lot of false positives. **As such, positive tests will need to be confirmed (discussed next)**. Roche plans to run a confirmation study in order to get FDA approval for Alzheimer's screening, which will take at least a year. While the test will be available later this year with an RUO claim, it will likely be difficult for labs/physicians to get reimbursed. **We note that Roche announced a collaboration with Eli Lilly on 3/22/2023 for the development of their Elecsys Amyloid Plasma Panel (EAPP).**

- **2) Confirmation – the Elecsys CSF AD Assays**: Roche received FDA 510(k) clearance for its Elecsys beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys Phospho-Tau (181P) CSF (pTau181) assays in December 2022. **The two tests are based on CSF, and can be used by physicians instead of PET**

(the results are equivalent). The main drawback is that only specialists can perform CSF testing, and patients need anesthetics to manage the pain.

Fig. 7: Roche Alzheimer's IVD Blood Test Paradigm



Source: Company Documents

B) Quanterix (QTRX)

Quanterix is arguing for proprietary testing solutions and differentiated quality for the detection of protein biomarkers used in Alzheimer's. The company has developed its single molecule array technology, known as Simoa. The technology is focused on ultra-sensitivity of proteins that are very low in concentration in the blood. The company has a mix of research and translational customers today, hoping to bridge discoveries into clinical diagnostic usage.

Quanterix CEO Masoud Toloue recently commented on improving sensitivity in Alzheimer's to go up head-to-head with PET: "I think that we're going to be getting to a stage in the next year or two where a blood biomarker just isn't a screen... or an aid to a diagnostic, which goes into a PET test. I think in a couple of years, we'll have enough information and data and acceptance that the blood test replaces the PET scan. And there, I think a blood a biomarker, that's a multiplex could help." **A rule-in test would be the "holy grail" for Alzheimer's, but is also a very high clinical bar**.

Quanterix's initial Alzheimer's test is based on pTau-181. They are planning for an LDT launch in 2022, with a blood based IVD test in 2024. **The plasma pTau-181 biomarker is included as an endpoint for Eisai/Biogen's Leqembi.** Quanterix's pitch is differentiated quality vs the competition, though there are outstanding questions around reimbursement given current Medicare rate for Tau at $17 per test.

The upcoming read-out of the Bio-Hermes study could be a catalyst to help support the role of blood biomarkers in screening for Alzheimer's. The purpose of the study is to develop a biomarker database to see whether a meaningful relationship exists between digital tests, blood amyloid-beta, pTau and neurofilament biomarker levels and amyloid beta levels identified through PET images. The study recruited >1,200 patients across 17 sites with a diverse population. **The study was announced in**

April 2021, and included 11 biopharma, technology and non-profit partners. These include Lilly, AbbVie, Merck, the Alzheimer's Drug Discovery Foundation, and also Quanterix. Blood tests being compared include pTau 181, 217 and 231; amyloid-beta 42/40, and neurofilament light (NfL). Lilly will provide full genomic sequencing of each volunteer and a separate APOE gene test. **The study closed in November 2022,** and recently completed its first database lock in early June 2023.

Quanterix also has a multi-plex test under development which could further differentiate the company. The company has experience across all of the key biomarkers for Alzheimer's, including pTau-217, beta/amyloid 42/40 ratio, NfL and GFAP. **Development of the test was supported by funding from the Alzheimer's Drug Discovery Foundation (ADDF)**. The test will be validated in collaboration with Amsterdam UMC. The multi-site trial will look at thousands of diverse patients and compare imaging with Quanterix's multi-analyte blood test as part of a Phase 1b comparison. From there, the study will look at primary memory clinics and primary care sites as Phase 3 and Phase 4, which is expected to wrap-up around 2024. **With FDA approval, there could be an opportunity to earn differentiated reimbursement from CMS for a proprietary panel.** It is important to note that a reimbursement rate doesn't guarantee coverage by Medicare and provider buy-in via guideline inclusion will be an important factor in potential utilization.

Quanterix has a non-exclusive, worldwide license to Lilly's proprietary pTau-217 antibody technology for potential RUO use. The parties have also entered into a collaboration agreement, which establishes a framework for future projects focused on the development of Simoa immunoassays (including multi-plex biomarkers). **In 2022, Lilly presented data from the TRAILBLAZER-ALZ study at the Alzheimer's Association International Conference which utilized the Simoa HD-X platform and assays to measure pTau-217**. The study reported a significant reduction in plasma levels of phosphorylated tau protein after treatment with donanemab.

C) C2N Diagnostics - Private

C2N Diagnostics is a private molecular diagnostics company based in St. Louis, MO. The company's core technology is based on mass spectrometry to quantify protein biomarkers in neurological disorders. **The company has two tests on the market**:

- **PrecivityAD**: This is a blood test intended for patients with cognitive impairment to determine the presence of amyloid plaque in the brain. It provides quantitation of the Amyloid/Beta 42/40 ratio and detection of the APOE proteotype in blood samples. The test received FDA's Breakthrough Device Designation in January 2019. The test establishes an amyloid probability score that is used to estimate the likelihood of amyloid plaques in the brain. C2N received funding from NIH's National Institute of Aging for the initial development of the test. The company recently obtained a PLA code which is currently under consideration by CMS for reimbursement in 2024. CMS will announce in September a preliminary determination for how reimbursement will be established for the code, which will then be finalized in November. The company asked for the code to be paid based on the gapfill process, where local Medicare contractors set reimbursement next year that is used to calculate a national rate in 2025 based on a median rate from the contractors. The test is currently offered as an LDT, though does not currently have State of NY approval.
- **PrecivityAD2**: In November 2022, C2N Dx introduced its next generation assay. Similar to the original, the test is based on mass spectrometry, though it also looks at the ratio of pTau-217 and npTau-217 in addition to beta/amyloid.

D) Fujirebio – HU Group

Fujirebio is a subsidiary of HU Group, a publicly traded company headquartered in Japan (TSE 4544). The company offers the Lumipulse G β-Amyloid Ratio (1-42/1-40) test, which is an immunoassay

based test which runs on the company's Lumipulse G1200 system. The test is based on CSF samples. The company is pursuing CMS reimbursement for its PLA code, 0358U. Last week the company asked CMS to set reimbursement for the code at $260.50 based on a crosswalk to CPT 81500. CMS will issue a preliminary decision in September and final in November.

E) Amprion – Private

Amprion is a private molecular diagnostic company based in San Diego, California. The company has its proprietary SYNTap Biomarker Test that seeks to detect patients with an early diagnosis of both Lewy bodies and Alzheimer's disease. The test is based on CSF samples and detects abnormal forms of the alpha-synuclein protein that is associated with Lewy body.

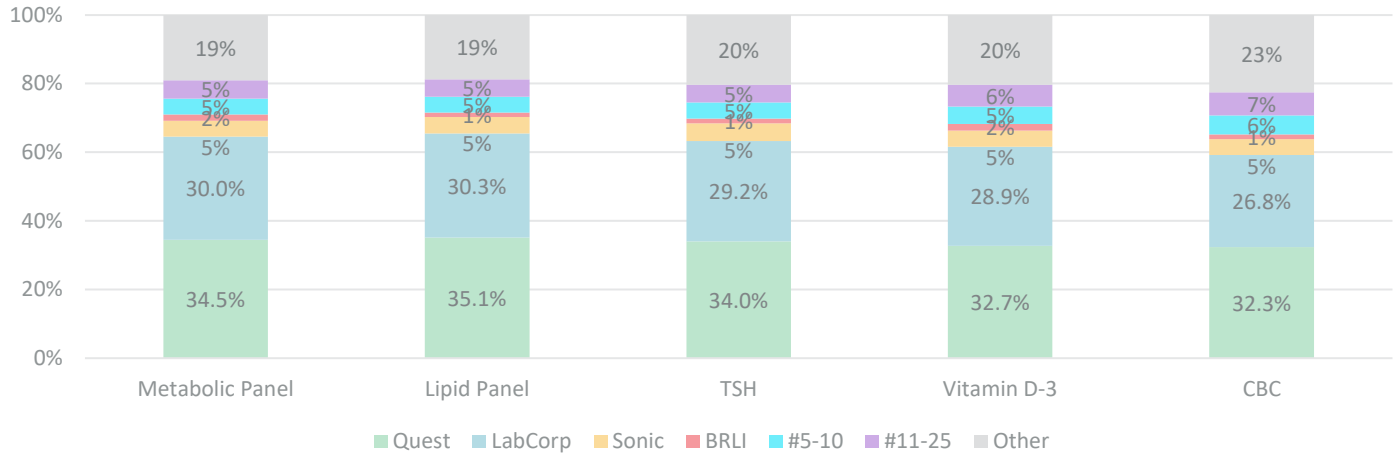
F) National Labs (DGX/LH) – IVD Beneficiaries Plus Quest LDT Innovation w/ AD-Detect

To start, Quest and LabCorp should be beneficiaries of all IVD tests developed by the diagnostics industry. Tests under development leverage commonly used immunodiagnostics systems. Looking at Medicare Part B claims data for 2021, for routine testing codes, LabCorp and Quest collectively have anywhere from 60-65% share of testing.

In addition, Quest has developed their own proprietary LDT for detection of amyloid beta, known as AD-DETECT. As noted earlier, the test is based on research that suggests the accumulation of amyloid beta in the brain is an early sign of the disease. **The test measures the ratio of beta-amyloid 42/40 using ultrasensitive HPLC MS-MS**. The test offers an alternative to PET imaging and CSF sampling. Performance is similar to that reported in literature for MS-based assays in CSF performed by Quest. **The test is currently undergoing a rate setting process by CMS known as gapfilling, where local contractors set payment this year and the median of the local rates becomes a national limitation amount for 2024. CMS issued a preliminary gapfill rate of $93 for the test.** A final rate will be issued later this year before going into effect Jan. 1. The company plans to make the test available via Quest Health, its consumer-initiated testing platform, likely at a premium to Medicare rates. As discussed in more detail below, we think commercial insurers and Medicare Advantage plans will be reluctant to cover the test in the near term. The consumer-initiated testing platform will provide a mechanism for patients to obtain the test outside of health insurance coverage.

A December 2022 study in Alzheimer's and Dementia showed that AD-DETECT could accurately differentiate PET-positive from PET-negative individuals (AUROC=.862), with sensitivity of 71%/specificity of 89%. The test would help provide access/cost relief from patients who would otherwise go to PET, HOWEVER in addition to insurance coverage restrictions noted above we think there is also an open question of whether doctors will view the results as interchangeable (and ultimately send patients to PET anyway). **Quest has additional studies underway comparing AD-Detect to CSF and PET**.

Fig. 8: 2021 Medicare Market Share for Routine Codes Amongst Independent Labs



Source: CMS, Company Documents, Nephron Research

Looking at the routine codes used for Alzheimer's testing, for 83520 (billed for pTau, beta/amyloid and NfL), Quest has 50% market share while LabCorp has 13% share. Share for 81401 (used for APOE) was lower, at just 1% for Quest and 0.2% for LabCorp, though we view this as a function of some labs using the code more aggressively (which has been the subject of regulatory scrutiny). **Insurers have historically been reluctant to cover testing for APOE, noting lack of guideline inclusion or national standards, inadequate data supporting testing or that the test would not alter a patient's clinical management**. We think coverage polices for commercially insured and Medicare Advantage beneficiaries will change to provide coverage of APOE testing in select patients as drugs gain full FDA approval.

Fig. 9: CPT 83520: Medicare Market Share in 2021

	83520		% Total
1	**Quest Diagnostics**	**395,352**	**50%**
2	**LabCorp**	**100,660**	**13%**
3	Cleveland HeartLab	18,890	2%
4	Morningstar Laboratories	15,866	2%
5	Boston Heart Dx	13,299	2%
6	Mayo Clinic	13,169	2%
7	RealTime Labs	12,534	2%
8	Sonic Healthcare	11,066	1%
9	Genesis Laboratory Mgmt	10,703	1%
10	Exagen Diagnostics	9,797	1%
11	EpicGenetics	6,964	1%
12	A2CL Services	6,693	1%
13	Genova Dx	6,013	1%
14	Mayo Collaborative Services	5,650	1%
15	Scripps Health	4,858	1%
16	Global Discovery Biosciences	4,812	1%
17	Washington University	4,338	1%
18	Health Network Labs	4,310	1%
19	MedScan Labs	4,081	1%
20	Prometheus Labs	4,077	1%
21	Regents of University	3,752	0%
22	Estoerix, Inc	3,489	0%
23	Bio-Reference Labs	3,375	0%
24	Mayo Clinical Arizona	3,348	0%
25	Diagnostic Laboratory Services	3,198	0%
26	LabTech Diagnostics	3,084	0%
27	North Shore LIJ	3,031	0%
28	TriCore Reference Labs	2,502	0%
29	Physicians Laboratory Services	2,382	0%
30	PathGroup Labs	2,287	0%
31	Diagnostics Solutions Lab	2,188	0%
32	University of Washington	1,996	0%
33	ARUP	1,938	0%
34	Associated Clinical Labs	1,695	0%
35	Professional Clinical Labs	1,384	0%
36	Matias Clinical Labs	1,364	0%
37	Compunet Clinical Labs	1,206	0%
38	International Medical Lab	1,113	0%
39	Interpath Lab	1,070	0%
40	Medical Labs of Eastern Iowa	1,034	0%
41	Other	91,124	12%
		789,692	**100%**

Source: CMS, Nephron Research

Fig. 10: CPT 81401: Medicare Market Share in 2021

	81401	Tests	% Total
1	Bio Choice Lab	52,389	49%
2	Advanced Dx Labs	5,914	6%
3	Elite Medical Lab Solutions	4,835	5%
4	Sonoran Desert Pathology Assoc.	4,615	4%
5	Biogen Labs	4,365	4%
6	Kingdom Health Laboratory Llc	4,035	4%
7	FIRST CHOICE LABORATORY LLC	3,791	4%
8	Axis Professional Labs Llc	2,280	2%
9	Pathema Gx Lab, Llc	1,684	2%
10	Advanta Labs, Llc	1,446	1%
11	Elite Clinical Laboratory, Inc	1,399	1%
12	Ek Advanced Laboratories Llc	1,398	1%
13	**Quest Diagnostics**	**1,084**	**1%**
14	Grey Stone Labs Llc	995	1%
15	SMA Medical	914	1%
16	Principle labs	893	1%
17	BioDesix	796	1%
18	Redwood Lab Services	626	1%
19	Independent Drug Test. & Forensic	596	1%
20	AdvaGenix	568	1%
21	Sval	512	0.5%
22	Brookside Clinical Lab	499	0.5%
23	Accu Reference Lab	490	0.5%
24	Advanced Bio Medical	477	0.4%
25	Microgen Health	433	0.4%
26	Medcomp Gx	422	0.4%
27	Bios Scientific	418	0.4%
28	K&S Clinical Diagnostics	401	0.4%
29	Paternity Testing Corp	390	0.4%
30	Gentox Lab Services	387	0.4%
31	Lehigh Valley Toxicology	345	0.3%
32	Claro Scientific Laboratories	334	0.3%
33	Altru Diagnostics	316	0.3%
34	DTR Labs	278	0.3%
35	Genetics Institute Of America Labo	254	0.2%
36	Silverpath, Inc.	245	0.2%
37	Igenomedx	242	0.2%
38	**LabCorp**	**240**	**0.2%**
39	Legacy Diagnostic Lab	232	0.2%
40	ApolloMdx	223	0.2%
41	Other	5,456	5%
		107,217	**100%**

Source: CMS, Nephron Research

Market Sizing: Several Huge Variables to Consider

There are several huge variables that will dictate the market opportunity in Dx & Bioprocessing:

A) Therapeutic Demand: Low Visibility into the Penetration of a Huge TAM

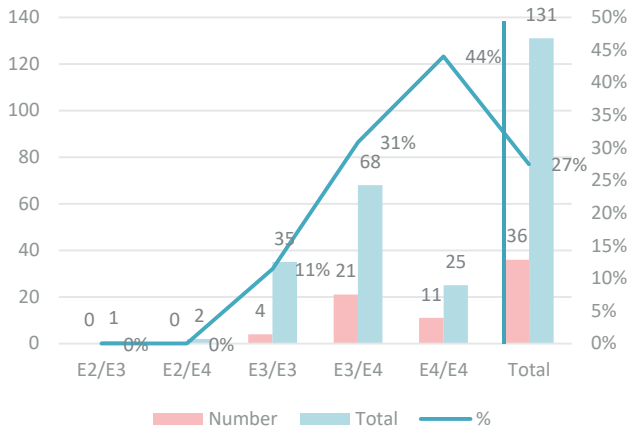
There is a significant debate around what role emerging therapies could play in the treatment of Alzheimer's. Eli Lilly's donanemab and Eisai/Biogen's lecanemab both aim to change the underlying biology of Alzheimer's by removing beta-amyloid from the brain. The thesis is that this could slow cognitive and functional decline in people living with early Alzheimer's. **There is an urgent need for better Alzheimer's treatments**. Patient's, caregivers and advocacy groups are all pushing for FDA approval and Medicare to expand access by dropping certain coverage requirements for monoclonal antibodies including donanemab and lecanemab. **The market itself is significant in size**. As noted earlier, there are 5-7mm Americans living with MCI and another 6.7mm living with Alzheimer's – a number that is also projected to grow significantly over the next decade.

That said, the long-held amyloid-beta hypothesis has also been the subject of significant criticism. There is a question of how efficacious the treatments actually are. Beyond that, it is worth noting that only about 40% of patients with MCI progress to Alzheimer's, and patients can have amyloid-beta plaque and still not get the disease!

The therapies also have drawbacks around cost and negative side effects, such as brain swelling, hemorrhaging and death. In Lilly's NEJM publication on Phase 2 results for Donanemab, APOE status was highlighted as a potential risk factor for ARIA. ARIA is amyloid related imaging abnormalities. ARIA represents abnormal differences seen in MRI of the brain in patients with Alzheimer's disease. **There are two types of ARIA: 1)** ARIA-E for cerebral edema, which involves the breakdown of the tight endothelial junctions of the blood-brain barrier and subsequent accumulation of fluid. This can lead to headaches, changes in mental state, confusion, vomiting, and nausea. **2)** ARIA-H refers to cerebral microhemorrhages. **Patients with an E4 allele had an elevated risk of ARIA-E**. Altogether, the rate of ARIA-E was 27%, however it was 31% in patients with an E3/E4 genotype and 44% in patients with an E4/E4 genotype. Conversely, it was just 11% amongst the 35 patients with an E3/E3 genotype.

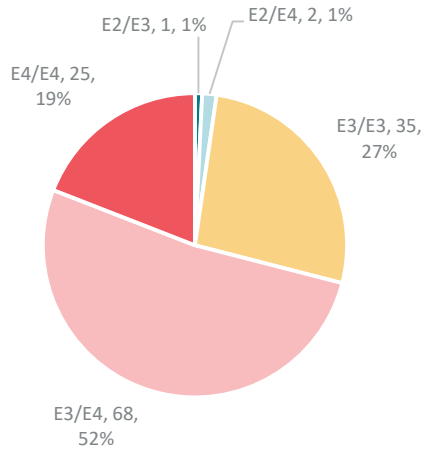
The data not only highlights the importance of APOE as a biomarker, but also potentially the limits for how broad the drugs can penetrate the market. In the study, >70% of patients had an E3/E4 or E4/E4 genotype. Lilly highlighted in their 5/3/2023 Phase 3 update that the death of two study participants was attributed to ARIA, and a third participant died after an incident of serious ARIA.

Fig. 11: # and Rate of ARIA-E Events by APOE Status



Source: NEJM, Nephron Research

Fig. 12: Mix of Donanemab Patients by APOE Genotype



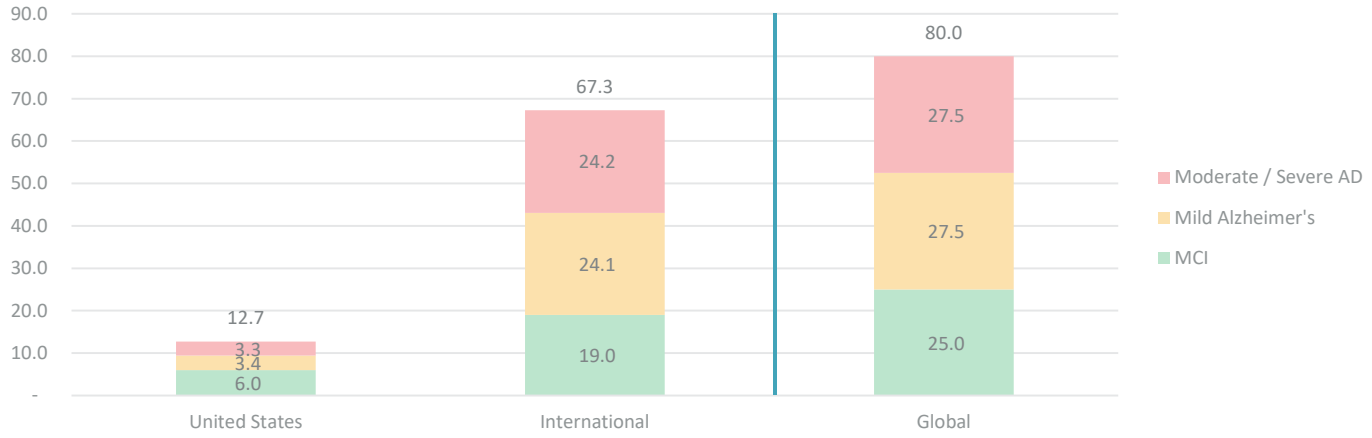
Source: NEJM, Nephron Research

B) Penetration: Only a Portion of the Sizable Population TAM Will Get Tested

The burden of Alzheimer's is sizable. Alzheimer's primarily impacts elderly individuals, with >60mm Americans and >700mm people worldwide >65 years of age. **We assume only a sliver of this population will be eligible for screening**. In the US, we think it is unlikely that guidelines would recommend anytime soon this as a standard screening test for all Medicare-eligible patients as part of their annual wellness visit. **The most obvious targets for testing are patients with MCI and mild AD**. The data has shown that these patients are most likely to benefit from treatment (the magnitude of which is certainly a matter of debate). Later stage AD patients have progressed too far to benefit from therapeutics, and thus the value of diagnostic testing is limited with the current class of drugs coming to market

In the US, there are roughly 9-10mm Americans with MCI or mild AD. Globally, we estimate there are >50mm people living with MCI or mild AD.

Fig. 13: Progression of Alzheimers and Estimated Market Sizes (MM)



Source: Alzheimer's Association, Census Bureau, WHO, Nephron Research

C) Guidelines: No Current Support for Alzheimer's Biomarker Testing

There is a significant debate around the appropriate diagnostics workflow for Alzheimer's patients to prepare for therapy. Clinical guidelines will be an important driver in adoption of tests.

NIH's National Institute of Aging has dated guidelines from 2011 on diagnosing Alzheimer's disease. For example, the guidelines don't recommend testing for APOE4 outside of a research setting, citing that carrying the E4 allele doesn't mean a person has or will develop the disease. Given the likely importance of understanding a patient's APOE status before treatment with a monoclonal antibody, we think it is only a matter of time before the guidelines are updated to reflect recent research.

Current cognitive impairment screening guidelines from the USPSTF received an Insufficient rating. The last final recommendation statement for "Cognitive Impairment in Older Adults: Screening" was published in February 2020. The guidelines focus predominantly on screening tests for cognitive impairment, and notes that a positive result can lead to blood tests, radiology examinations, and a medical and neuropsychologic evaluation to confirm the diagnosis of dementia and determine its subtype. The guidelines noted that there is insufficient evidence to recommend for or against screening. **While the emergence of new novel therapies for Alzheimer's could change the USPSTF's perspective in future guideline updates, we start off skeptical that the task force will recommend screening in patients without symptoms of cognitive decline.**

The American Academy of Neurology has also published guidance on detection of cognitive impairment during annual wellness visits. The statement was reaffirmed on 1/30/2021. They recommend just a cognitive assessment instrument.

D) Coverage & Reimbursement: Medicare Policies Could be a Barrier to Adoption

The good news for diagnostics tests for Alzheimer's in the United States is that, by far and large, they are only going to have to deal with one payor – Medicare.

The bad news is that we see hurdles for both coverage and reimbursement in Medicare.

Starting with Medicare coverage, there are limited written policies that are specific to diagnostic testing for Alzheimer's:

- **Beta amyloid detection**:
  - **PET Scans:** Medicare has a national coverage policy in place that restricts coverage of beta amyloid PET scans to one scan per lifetime for dementia patients and requires coverage as part of a coverage with evidence development study or registry. The agency is long overdue in issuing a coverage revision that we continue to believe will drop the lifetime limit and registry requirement.
  - **Blood-based tests:** Coverage will likely be left to local Medicare administrative contractors via either claims by claims determinations or coverage policies in the near term. **We wouldn't be surprised if local contractors seek to limit coverage of blood-based tests that receive proprietary lab codes (such as Quest's AD-Detect and C2N's PrecivityAD) until additional data is published and there is greater physician buy-in.**
  - **CSF testing:** CSF testing will likely be viewed as an alternative to PET scans in Medicare patients that are not able to obtain a scan. We see limited risk of coverage restrictions for patients that have mild cognitive impairment and are seeking a potential diagnosis for Alzheimer's. Providers will likely follow appropriate use criteria from the Alzheimer's Association when determining whether to perform a lumbar puncture/CSF testing for a potential Alzheimer's diagnosis.
- **pTau:** There is no national coverage policy that limits coverage for detection of pTau via a PET scan, CSF or blood-based tests. Coverage is left to local Medicare administrative contractors. We think this will continue to remain the case over the next couple of years as science evolves and new therapeutics and tests come to market. We believe CMS, the government agency that runs Medicare, probably won't have an interest in the potential political pressure that would be associated with developing a national coverage policy for pTau diagnostic tests.

We also believe Medicare coverage of diagnostic tests for Alzheimer's will be driven by FDA labeling of monoclonal antibody drugs. CMS indicated it plans to follow FDA labeling requirements when setting out coverage for Medicare patients under a national registry. The registry will collect patient information that includes results from an amyloid PET scan, CSF test or "other amyloid test," along with results from cognitive function testing. We think providers participating in the registry will likely follow FDA labeling, particularly in the early stages of utilization as we continue to learn more about the side effects and efficacy of drugs such as lecanemab and donanemab.

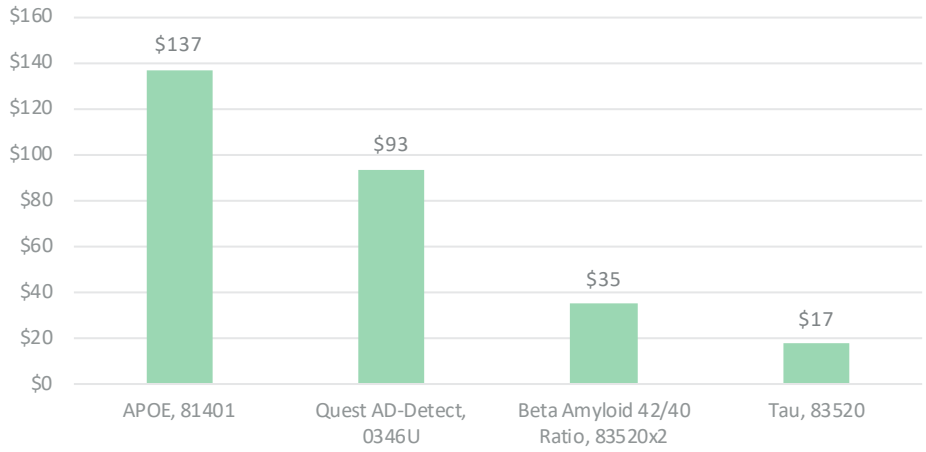
Current Medicare reimbursement is abysmal for Alzheimer's tests:

- **pTau** gets reimbursed under CPT 83520, which Medicare only reimburses $17(!). As a single analyte immunoassay test for Alzheimer's, it is difficult to see how that is commercially viable for either

IVD companies or the labs that run these tests. We think reimbursement is unlikely to improve in the near term under the Medicare clinical lab fee schedule, as we reiterate that Congress will likely continue to delay implementation of updated payment rates based on private payer data. This will likely keep payment flat over the next few years. Even in the event updated rates go into effect, we would be surprised if commercial insurers elected to pay more for the code.

- **Quest** recently had their AD-Detect test under PLA 0346U get a preliminary rate via gapfill at $93 per test. Despite dodging a bullet of getting reimbursed $24 (CMS' initial proposed this approach last year), we don't think that Quest is fully satisfied with the rate. The mass spectrometry based test is inherently more expensive to run than traditional IA tests. The preliminary $93 rate was driven by pricing from Palmetto's MolDX which used its private equitable pricing model to develop the rate. A final rate will be published in September by CMS.
- **One potential workaround is companies that develop proprietary multi-analyte tests**. Companies will need to go through the arduous CMS rate-setting process. As noted, Quanterix has discussed development of a multi-analyte test leveraging their Simoa platform. Roche's Triage test notably combines pTau with APOE.
    - **We see potential workarounds when it comes to coding and reimbursement both via proprietary laboratory analyses (PLA) codes and the creation of Category I CPT codes**. The AMA CPT Editorial Panel could create new Category I codes that detect tau and amyloid proteins, and APOE. Still, the coding process can be lengthy before it goes to Medicare for a reimbursement rate. Once the AMA approves a code, it goes to CMS for payment evaluation during its June/July lab meetings. The earliest a new Category I code could go into effect would be 2025. We note that CMS also has the option to create a new HCPCS code if it felt pressure to create a billing mechanism for a multi-analyte test. The next AMA CPT Editorial Panel meeting will take place in September, with the agenda released on July 14.

Fig. 14: Medicare Reimbursement for Common Tests



Source: CMS, Nephron Research

Market Sizing: A Prudent Base Case vs a Significant TAM

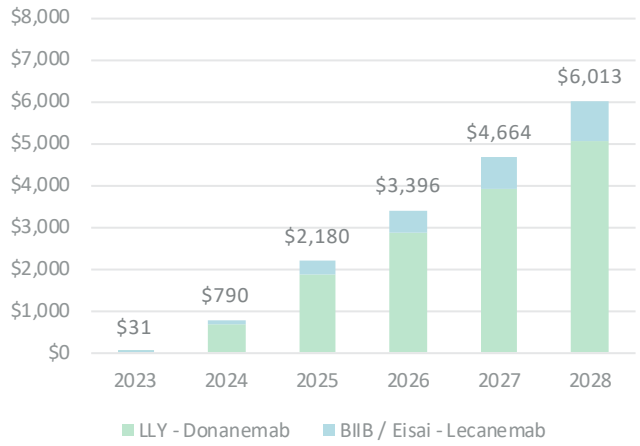
Bioprocessing: We Estimate a 0.5-1% Contribution to Sales for Several Years

Alzheimer's has long been one of the big opportunities for our coverage. Given the size of the patient population and manufacturing intensity of monoclonal antibodies, the total addressable market is sizable and largely untapped. **Despite all of the promise, the category has a history of under-delivering**. Experts we interact with are skeptical of the size of the short-term contribution to sales. **Our top-down and bottom-up analysis suggests that AD can add 0.5-1% to industry bioprocessing sales for several years**. The forecast supports long-term demand dynamics for suppliers such as Thermo Fisher and Danaher (amongst others), leaders in upstream and downstream bioprocessing.

From a top-down perspective, manufacturing costs are typically in the range of 15-20% of product sales. Within that, a good rule of thumb is that roughly 60% of the cost goes toward API (or 9-12% of product sales), and 40% goes toward drug product (or 6-8% of total) - including fill/finish, labelling and distribution.

Based on Consensus sales forecasts for the therapeutics, we estimate Alzheimer's could represent an >$500mm sales opportunity for our bioprocessing coverage by 2028. This could add up to 1% to industry sales for several years.

Fig. 15: Consensus Forecast for Alzheimer's Tx ($MM)



Source: FactSet, Nephron Research

Fig. 16: Top-Down Analysis Suggests Up to 1% Contribution to Industry Growth for Several Years

$MM	Low	Mid	High
2028 Sales (Consensus)	$6,013		
Manufacturing % of Total	15.0%	17.5%	20.0%
Manufacturing Costs	**$902**	**$1,052**	**$1,203**
% Drug Substance	60%		
API Costs	**$541**	**$631**	**$722**
Per Year, '24->'28 (/4)	**$135**	**$158**	**$180**

Source: FactSet, Nephron Research

From a bottom's up perspective, we land in a similar spot – with a base case scenario of 100K patients equating to roughly $300mm of bioprocessing supplies by 2026, roughly 0.5% to industry growth per year.

- **Patient Population**: The target population is patients with MCI (5-7mm Americans) and mild AD patients (roughly half of the 6.7mm patients with AD). **As noted earlier, there are significant concerns about the efficacy and safety profile of new monoclonal therapies, and it is prudent to haircut this TAM**. The issues have led to calls for registry requirements to study usage of therapies in the field, which could limit adoption. **Our base case is based on 100K patients getting therapy**, consistent with Eisai's estimate by 2026.

- **Dosage**: For Eisai / Biogen's Leqembi, patients are expected to get dosed once every two weeks at 10mg/kg. Assuming the average American weighs 80kg, at our base case the total drug substance needed is 2.1mm grams.
- **Capacity**: Experts have quoted us grams per Liter in the range of 3-4 grams/L. Using the midpoint, it would equate to almost 600K Liters of capacity needed to manufacture therapeutics. At this level of manufacturing, we think it is likely to utilize stainless steel manufacturing.
- **Cost per Gram**: Experts have quoted us that a good rule of thumb is $100-$200 per gram.

Fig. 17: Bottoms-Up Analysis Suggests a >$300mm Bioprocessing Opportunity

	Low	Base	High
Population	25,000	100,000	250,000
Average Weight (kg)	80		
Dose (mg/kg)	10		
Doses per year	26		
Drug Substance (g)	**520,000**	**2,080,000**	**5,200,000**
Grams per Liter	3.0	3.5	4.0
Liters of Capacity Needed	**173,333**	**594,286**	**1,300,000**
Cost / Gram	$200	$150	$100
Bioprocessing Opp (MM)	**$104**	**$312**	**$520**

Source: Company Documents, Nephron Research

Diagnostics Monitoring: We Size at $200MM Base Case

We think potentially the most compelling commercial opportunity for our Diagnostics coverage is monitoring of patients on therapy, which we size at $200mm in our base case. Patients on therapy could need to get multiple tests per year – as a baseline upon starting treatment, and then follow-up tests to monitor disease progression. **We assume a range of 3-5 tests per year**.

The big variable that requires additional diligence is reimbursement and coding. Given the therapeutic dollars at stake for pharma and payors, there could be justification for a higher price point for a high-quality panel of markers (such as pTau, beta/amyloid, NfL and GFAP). Beyond traditional Medicare reimbursement, it is possible that pharma companies could subsidize testing. **Proprietary multi-plex tests could pursue their own PLA code, and make their case for higher reimbursement with CMS**. We will also likely see the creation of additional Category I CPT codes for multi-analyte tests. That contrasts with single biomarker tests, which face the hurdle of low Medicare reimbursement. There are examples of multi-plex protein biomarker tests priced in the hundreds of dollars. **We assume a wide range of $200-$1000 per test ($500 base case).**

Fig. 18: Diagnostics Monitoring Market Sizing

	Low	Base	High
Population on Tx	25,000	100,000	250,000
Monitoring Tests/Year	3.0	4.0	5.0
Tests	**75,000**	**400,000**	**1,250,000**
ASP	$200	$500	$1,000
Sales ($MM)	**$15.0**	**$200**	**$1,250**

Source: Company Documents, Nephron Research

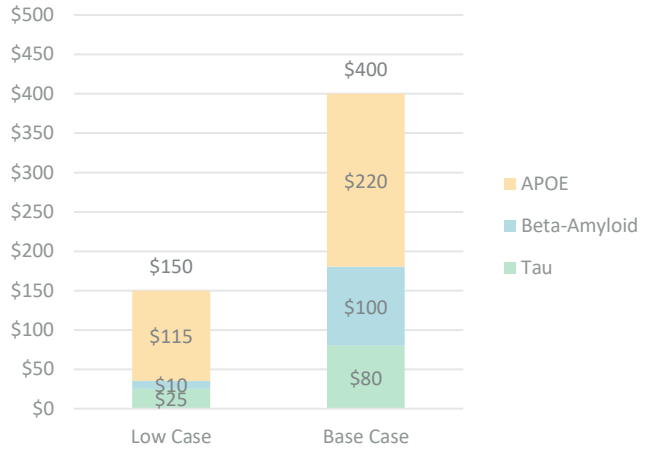
Screening: We Size a $400mm Base Case

For screening, our base case forecast for Alzheimer's testing is $400mm annually. This would add 0.5% to lab industry sales. The market potential is obviously much more significant in terms of the number of patients who could get screened, though there is also significant uncertainty around guidelines and reimbursement which limit visibility into adoption.

- **Population Screened**: Our base case assumes that testing targets the 9.4mm Americans living with MCI or mild Alzheimer's, a subset of the 61.6mm Americans >65 years of age.
- **Penetration**: In our base case, we estimate that half of individuals with MCI / mild AD are screened. That would be higher than the roughly 30% of Medicare-eligible patients who get an annual wellness check.
- **Pricing**: Our base case is predicated on current Medicare reimbursement for Tau ($17), Beta-Amyloid off of blood samples ($93) and APOE ($137).
- **Adoption of Tau ($80mm Base Case)**: In the screening population, we assume 100% compliance for Tau testing. The cost burden to the healthcare system is manageable, and the biomarker has clinical relevance based on therapeutic trial data. There is a clear need to understand a patient's biomarker status and how that changes over time.
- **Adoption of Beta-Amyloid ($100mm Base Case)**: In the screening population, we assume <25% compliance with beta-amyloid blood testing. Beta-amyloid has clear clinical relevance in AD. There are also several clear advantages for blood biomarkers in terms of cost, access and ease-of-use. That said, until tests can prove equivalence to PET scans, we think the bar is likely high to supplant imaging.
- **Adoption of APOE ($220mm Base Case)**: Given APOE is only required once in a lifetime, our analysis focuses on the 4.1mm seniors who age into Medicare annually. Our base case assumes 40% penetration of testing, which would be below historical adoption levels of mature Diagnostics we've seen in the range of 60-80%. There are an estimated 1.3mm new AD patients each year who would also have a reason to need to get tested. That said, we note only 20% of Medicare-eligible individuals have MCI or mild AD and have a reason to want to get tested.

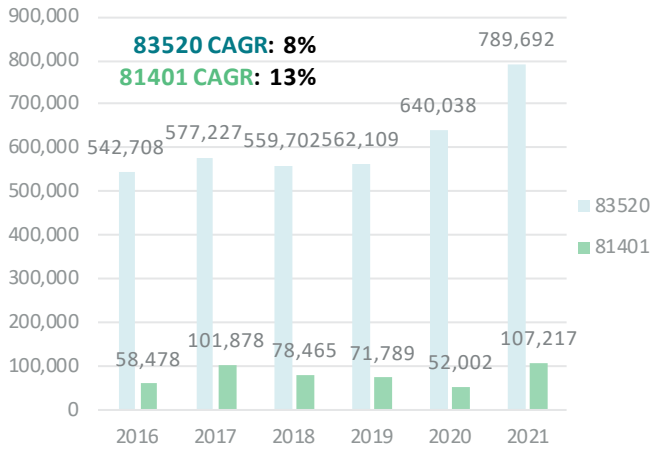
Putting our estimates in perspective, our base case assumes there are 4.7mm Tau tests run and 1.1mm blood-based beta/amyloid tests performed. Collectively, those 5.8mm tests compare to 790K tests ordered under CPT 83520 for Medicare patients in 2021. **For APOE, our 1.6mm test forecast compares to just >100K tests ordered under CPT 81401 in 2021**. Note that 81401 is ordered for multiple tests beyond APOE (it is a generic, level 3, molecular pathology procedure code).

Fig. 19: AD Screening: Nephron Low & Base Case ($MM)



Source: Nephron Research

Fig. 20: Medicare Utilization for CPT 83520 & 81401 by Year



Source: CMS, Nephron Research

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