The precision medicine future in neurodegenerative diseases

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Introduction

The neurodegenerative disease (NDD) treatment market has emerged as one of the most interesting markets, commercially and clinically, fueled by accelerating global aging, rising prevalence of NDDs, innovations in diagnostic and testing technologies, advancements in therapeutics, and increasing disease awareness. In this article, we illustrate why this market is at the precipice of an evolution and discuss a number of forward-looking considerations in applying precision medicine approaches to NDDs. These considerations include:

- Greater disease understanding as in oncology (e.g., amyloid-driven pathology is akin to early-stage cancer, and tau-driven pathology is similar to late-stage metastatic cancer)

- Similarities between cancer and NDD in their heterogeneity and need for personalized treatment (e.g., using Immuno-Oncology therapy as a backbone treatment in cancer versus amyloid-based treatment in NDD)

- Multifactorial considerations in NDD where comorbidities such as diabetes, inflammation, and metabolic disorders play a contributing role to the development and progression of NDD and serve as potential treatment targets

- Innovative diagnostic approaches such as serum-based testing (leveraging emerging, biological biomarkers), digital biomarkers, and retina scan, among others, to enable accessible, noninvasive means for risk identification, early detection, diagnosis, and monitoring

- Application of precision medicine to improve current treatment—giving patients the right drug (e.g., choosing the right backbone therapy to combine with other agents), at the right dose (e.g., personalized dosing of amyloid targeting treatment to avoid Amyloid Related Imaging Abnormality [ARIA]—amyloid-related imaging abnormalities), at the right time (e.g., adjust prescribed regimen depending on factors such as patient demographics, disease stage, and comorbidities).

This thought leadership article incorporates insights and hypotheses sourced from in-depth interviews with neurologists from major academic and medical institutions across the U.S. (n=7), U.K. (n=5), and Germany (n=5); in-depth interview campaign commenced in September and ended in October 2022.

Why precision medicine in NDD is similar to that in oncology

Cancer is a heterogeneous disease characterized by a wide spectrum of pathologies that differ among patients and sometimes makes traditional treatments ineffective. With the evolution of precision medicine and advances in imaging and molecular "omic" profiling, however, doctors can now apply the diagnostic and care continuum beyond just diagnosis and treatment selection, to provide prognostic assessments, prescribe personalized combined therapy options, and monitor treatment efficacy in real time to help improve outcomes.[1, 2]

NDDs like Alzheimer's are very similar to cancer as they are highly heterogeneous and manifest in a wide spectrum of symptomologies and pathologies. For much of modern medicine, clinical neurological evaluation of behavioral and cognitive symptoms of dementia pooled most patients into the Alzheimer's bucket. However, as technological innovations with imaging and in vitro diagnostics have advanced, detection of biomarkers such as amyloid and tau have helped doctors and scientists better understand the biological drivers of dementia and enabled more precise differentiation of the spectrum of clinical dementia. However, the real challenge, unlike in oncology, is that there was no disease-modifying treatment for dementias until the approval of Aduhelm. The lack of effective therapies cascades into less urgency in improving diagnostic methodologies (e.g., less invasive procedures) and potentially slower innovation that would otherwise drive earlier and more accurate detection. Several paradigm-shifting questions include: Can the same precision medicine approaches that drastically changed the tide in the fight against cancer be applied to NDDs for earlier and more defined diagnostic differentiations? Could these same approaches enable us to provide personalized, multipronged treatments that look beyond the traditional drivers of disease? In addition, can the application of the precision medicine continuum to NDDs drive stakeholders in the space to innovate advanced diagnostics and treatments?

These are just a few of the questions into which we will dive deeper to present a better understanding of the current NDD precision medicine landscape as well as future insights. Given significant public health and economic burdens, unprecedented global aging crisis, and multiple failures in dementia therapeutic research and development (R&D), we need to consider new ways in applying precision medicine in the future to transform how NDDs are detected, diagnosed, and treated. Biopharma and diagnostic companies can apply relevant learnings from oncology and collaborate to innovate therapeutic and testing options for NDDs.

Early detection and better disease stratification are key

Dementia is a broad term for a range of specific medical conditions, including Alzheimer's, Lewy Body disease, frontotemporal dementia, and vascular dementia, among others, that can cause a loss of memory and cognitive impairment severe enough to interfere with daily functioning.[3] While Alzheimer's Disease is the dominant form of dementia (accounting for approximately 70 percent of all cases[4]), the disease can only be definitively diagnosed postmortem using biopsy. This is further exacerbated by shared symptoms and mixed pathologies that overlap with other forms of dementia and the fact that many patients may have pathological changes decades before symptoms onset.

Today's diagnostic continuum for dementia relies upon traditional neurological examination, clinical evaluations, imaging, and sometimes in combination with biomarker diagnostics and IVD modalities to help verify diagnosis and distinguish the different forms of dementia.

Although the NDD diagnostic continuum has come along with the help of better imaging and biomarker testing, challenges in earlier detection and disease differentiation remain significant unmet needs in enabling appropriate patient care. For example, detection tools such as imaging tests are costly (and often not reimbursed), whereas CSF testing is too invasive to be performed routinely on patients for screening purposes.

Genetic tests (e.g., APOE4, presenilin mutations) can help identify probability of disease development among individuals who have a family history, yet its predictability is debatable, and its potential benefits may be outweighed by other unintended consequences such as anxiety and stress. Ultimately, even with all the advances that today's diagnostic continuum provides, their utility is limited without the most important tool of all: a disease-modifying treatment.

> "
> The biggest hurdle in any dementia is patients have pathological changes years before they have any symptoms. Treatments will theoretically work better if we intercept the disease early.
>
> —Neurologist at a top ranked academic center in the U.S.

NDDs are more than just brain diseases and require multifactorial clinical considerations

Since Alois Alzheimer's first public reporting of Alzheimer's Disease in 1906, no disease-modifying treatment has been approved for dementia until 2021. Despite initial excitement about the approval of Aduhelm[5], mixed clinical data, a lack of clarity on real-world benefits, and high launch price contributed to suboptimal commercial performance by the drug.

Recent positive data of lecanemab (27 percent slow down of cognitive decline and robust amyloid clearance), which was approved by the FDA as the second-ever amyloid based Alzheimer's drug, and donanemab (superior amyloid clearance compared to Aduhelm) suggest that targeting amyloid may likely play a role as a disease-modifying approach.[6, 7, 8, 9] Meanwhile, negative top-line result of gantenerumab[10], that showed less amyloid clearance, while disappointing, also suggests amyloid has a role given the drug removed less amyloid plaque than anticipated. To date, evidence collectively indicates that amyloid-based therapy may not be the only or dominant treatment option, especially given its limitations [Exhibit 1].

> **Exhibit 1. Limitations of amyloid antibody therapy**
> - Treatment may not be efficacious if patients have had more advanced disease with corresponding neuronal deaths
> - The classic side effect of ARIA is too burdensome for many patients
> - Amyloid antibody clinical trial outcome may not be specific, as enrolled patients may have different/additional pathologies outside of Alzheimer's (e.g., vascular dementia)

> **There is a clear process that makes amyloid toxic. What it is actually is something we need to explore further.**
>
> —Neurologist at a top-ranked medical center in the U.K.

> **We need to retrospectively look at amyloid anitbody-treated patients who may have less-than-optimal responses or ARIA. The theory that patients may have had high baseline inflammation is one we need to explore.**
>
> —Neurologist at a top-ranked medical center in the U.S.

While amyloid may play a role in the development of dementias such as Alzheimer's Disease, the heterogeneity of dementias likely requires multifactorial clinical considerations. This is underscored by the observation that many asymptomatic patients have a buildup of proteins such as amyloid, tau, and/or alpha-synuclein, yet other symptomatic patients have no gross pathological changes within the brain.

> **There is such a high percentage of dementia patients who have long-standing depression. This may be separate from amyloid or an additive factor. We may need to think about how to treat those patients differently.**
>
> **All my dementia patients have some sort of metabolic dysregulation, especially with glucose control. That theory has been more and more studied over time.**
>
> —Neurologist at a top-ranked academic center in the U.S.

In addition to amyloid, tau, and alpha-synuclein, the next wave of emerging considerations such as metabolic dysfunctions, mental health, inflammation, mitochondrial dysfunction,

environmental factors, and gut microbiome, among others, point to the renewed understanding that NDDs are more than just brain diseases:

- Metabolic dysfunction is hypothesized to play a role in both the development of Alzheimer's Disease and, more broadly, dementia (especially vascular dementia). Given the vast majority of patients with dementia have cardiovascular conditions, it is possible that dementia is more of a systemic disease that is multifactorial and not just limited to the brain.

- A large percentage of dementia patients have cardiovascular conditions and stroke. Emerging theories suggest that dementia may be more of a microvasculature disease rather than macrovascular disease, but these need to be further explored.

- Mental health disorders may play a more prominent role in the development of dementias than previously thought. Although there's a clear correlation between patients having long-standing depression and developing dementia, the exact biology and pathophysiology is still unclear. Some emerging hypotheses suggest that long-term depression may lead to brain atrophy, which in turn causes dementia itself. Additionally, long-term treatment with antidepressants can increase serotonin levels, which is thought to be potentially pro-inflammatory.

- Inflammation is thought to play a critical role in the development of dementia—most if not all NDD patients have some sort of baseline inflammation in the brain. While recent studies are showing the role inflammation plays in driving the symptoms of NDDs,[11, 12] further elucidation of the inflammatory pathway in NDDs and its role in disease worsening is required. Further to this, there needs to be a greater understanding of the role of baseline inflammation versus amyloid/tau in driving NDD symptomology.

- Given the importance of mitochondria to support neuronal activity and guard against antioxidative damage, mitochondrial dysfunction has been hypothesized as a driver of NDD.[13, 14] To this end, animal models and postmortem materials from NDD patients support the theory that mitochondrial dysfunction is an early feature among Alzheimer's and Parkinson's patients. There is more of a clear correlation in mitochondrial dysfunction and Parkinson's to date, but further studies are looking into the role it may play in broader dementia.
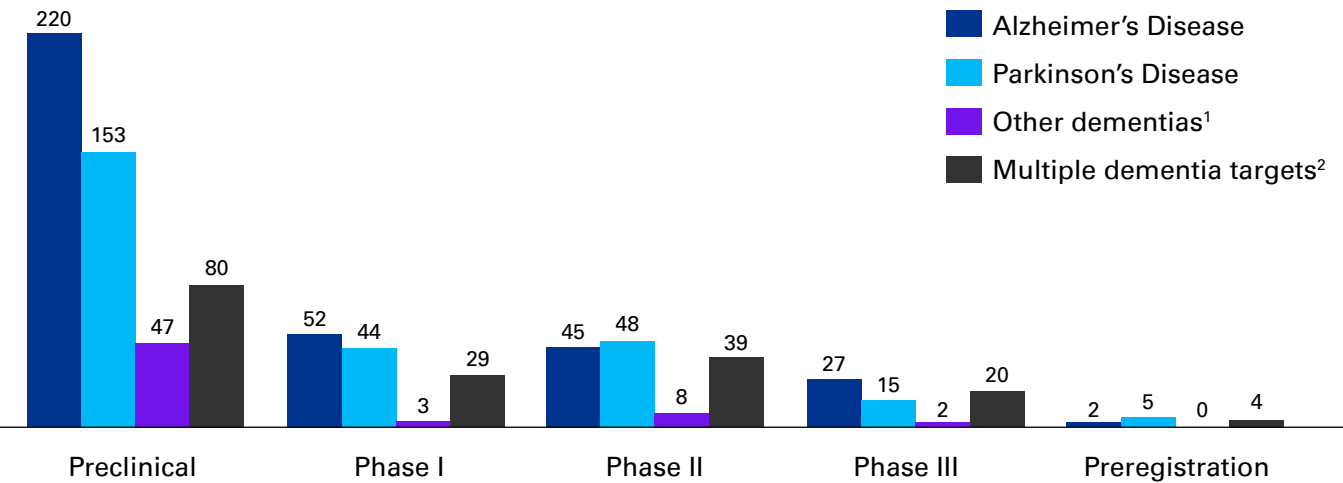
- There has been increasing literature and hypotheses that environmental factors such as contaminants and viral infection toxins may contribute to the development and progression of dementia.[15, 16, 17] As an analogous example, it has been shown that being infected by particular viruses may in fact lead to the pathogenesis of diseases such as multiple sclerosis.[18] It is perhaps not surprising that similar theories are emerging in the development of dementia. It may be the case that COVID-19 in the long run can increase dementia rates given the neurological changes in some patients, and is something that should be closely monitored for long-term correlation.

- Finally, there's been an increased interest in the role that gut and specifically the microbiome may play in the development of dementia.[19, 20] While the precise mechanism is unclear, it is well known that microbiome dysfunction can lead to the pathogenesis of Parkinson's Disease.[21] Further studies are needed to understand the potential role microbiome plays in the development of dementia and whether microbiome can help potentiate the effect of treatments.

Given these observations, it is perhaps not surprising that NDDs are underdiagnosed today, and will continue to be so unless their heterogeneous nature is being considered during drug and testing development by biopharma and diagnostic companies.

In light of recent positive Phase 3 lecanemab data from Eisai and Biogen, and biopharma's inherent interest in developing NDD treatments, we expect there to be a healthy pipeline of clinical assets potentially coming onto the market in the future. Indeed, pipeline analysis reveals a large number of later stages, amyloid, tau, and alpha-synuclein-based assets, with most targeting Alzheimer's Disease, followed by Parkinson's and other dementias [Exhibits 2 and 3].
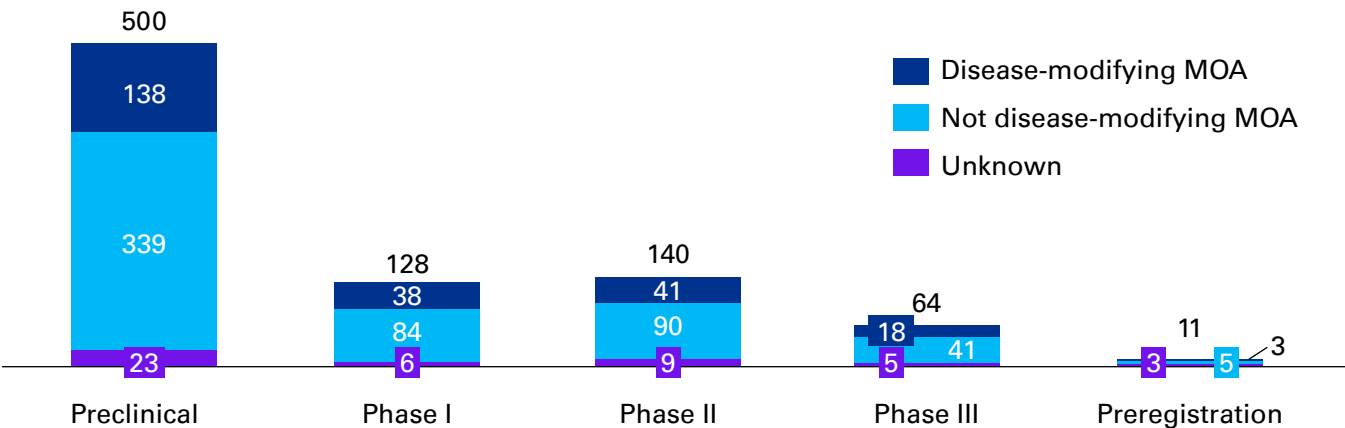
Exhibit 2. Number of pipeline assets targeting Alzheimer's, Parkinson's, and other dementias[1]

Legend:
- Alzheimer's Disease
- Parkinson's Disease
- Other dementias[1]
- Multiple dementia targets[2]

Preclinical: 220, 153, 47, 80
Phase I: 52, 44, 3, 29
Phase II: 45, 48, 8, 39
Phase III: 27, 15, 2, 20
Preregistration: 2, 5, 0, 4

1) Includes assets targeting Lewy body, frontotemporal, vascular, and AIDS-related dementias
2) Includes assets that target a combination of Alzheimer's, Parkinson's, and/or other dementias
Source: Informa and KPMG analysis, data accessed in September 2022

- Given the commonality among different dementia conditions, it's not surprising that many assets are targeting multiple indications.
- Alzheimer's and Parkinson's currently have the highest number of assets in the clinical pipeline.

Exhibit 3. Number of pipeline assets[1] by mechanism of action (MOA)

Legend:
- Disease-modifying MOA
- Not disease-modifying MOA
- Unknown

Preclinical: 500 (Disease-modifying MOA: 138, Not disease-modifying MOA: 339, Unknown: 23)
Phase I: 128 (Disease-modifying MOA: 38, Not disease-modifying MOA: 84, Unknown: 6)
Phase II: 140 (Disease-modifying MOA: 41, Not disease-modifying MOA: 90, Unknown: 9)
Phase III: 64 (Disease-modifying MOA: 18, Not disease-modifying MOA: 41, Unknown: 5)
Preregistration: 11 (Disease-modifying MOA: 3, Not disease-modifying MOA: 5, Unknown: 3)

1) Includes assets that target a combination of Alzheimer's, Parkinson's, and other dementias
Source: Informa and KPMG analysis, data accessed in September 2022

Not surprisingly, assets targeting emerging pathologies such as inflammasomes are also observed.

- While there's a high unmet need for disease-modifying treatments, additional symptomatic treatments, such as those that address cognitive and behavioral symptoms, are needed.
- An evolution in the pipeline looking at additional pathological conditions would also be required to address the heterogeneous nature of NDDs.

Innovative diagnostic approaches are on the horizon

There is a need for new technologies to identify and diagnose patients earlier and more easily. Given recent advancements in therapeutic options, we expect to see lockstep diagnostic and testing innovations to screen, identify, diagnose, and monitor different forms of dementias.

For screening and early identification, innovative modalities such as digital biomarkers and retinal imaging are on the horizon. Retinal imaging, such as the optical coherence tomography angiography, could be a low-cost, noninvasive approach to readily capture retinal blood vessel changes and could identify amyloid plaque deposits on the retina, phenomenon that may reflect early pathological features in the brain. Digital biomarkers, such as fine motor movement and speech characteristics, can harness advances in consumer-grade mobile and wearable technologies to provide yet another highly accessible, population-based means for early risk identification. These approaches, along with others that leverage artificial intelligence, can help improve early detection among those who are at an increased risk and to support follow-up diagnosis at the population level.
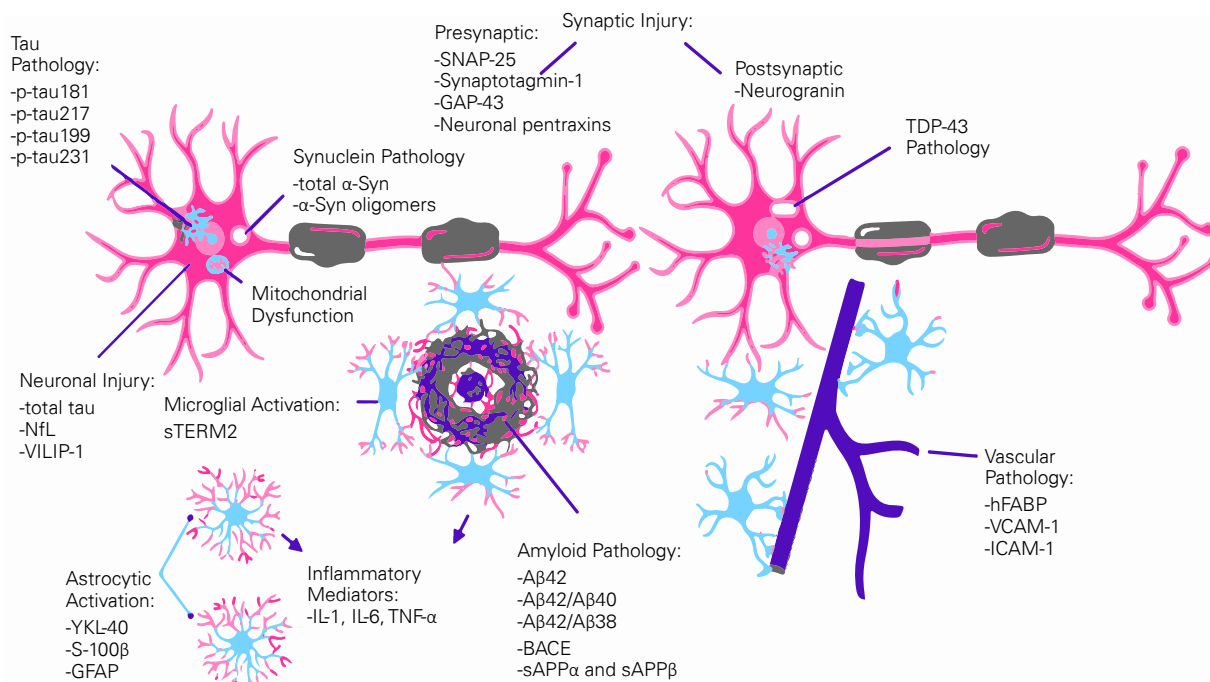
Ongoing studies are also discovering and validating a broader set of emerging biomarkers that can help better differentiate and diagnose different NDDs [Exhibit 4]. While amyloid ratios have historically been used, biomarkers such as P-Tau 181 and P-Tau 217 might be better markers of dementia diagnosis and progression. Leading experts in the field are also starting to look at neurofilament light chain (NfL) and TREM-2 levels as markers of neuronal injury and/or inflammation.

> **NfL is akin to C-reactive protein in inflammation—it is nonspecific but speaks to ongoing neuronal death. TREM2 is really interesting and should be studied further.**
>
> **—Neurologist at a top-ranked university in Germany**

Exhibit 4. Illustration of existing and emerging CSF NDD biomarkers

Tau Pathology:
-p-tau181
-p-tau217
-p-tau199
-p-tau231

Presynaptic:
-SNAP-25
-Synaptotagmin-1
-GAP-43
-Neuronal pentraxins

Synaptic Injury:

Postsynaptic
-Neurogranin

TDP-43 Pathology

Synuclein Pathology
-total α-Syn
-α-Syn oligomers

Mitochondrial Dysfunction

Neuronal Injury:
-total tau
-NfL
-VILIP-1

Microglial Activation:
sTERM2

Vascular Pathology:
-hFABP
-VCAM-1
-ICAM-1

Astrocytic Activation:
-YKL-40
-S-100β
-GFAP

Inflammatory Mediators:
-IL-1, IL-6, TNF-α

Amyloid Pathology:
-Aβ42
-Aβ42/Aβ40
-Aβ42/Aβ38
-BACE
-sAPPα and sAPPβ

Source: "Biomarkers: Our Path Towards a Cure for Alzheimer Disease," Biomarker Insights, Tarawneh R, November 25, 2021

Yet one of the biggest obstacles that remains is to identify and diagnose patients years before any symptoms present—urgency and willingness to receive screening and testing are often the rate-limiting step in getting patients "through the door," and technological innovations (e.g., serum-based blood testing) that alleviate access concerns may help reduce patients' hesitation and drive more testing engagement with different stakeholder groups. Development of novel serum-based blood biomarker testing has ramped up over the years, and several exciting approaches have emerged [Exhibit 5].

While there are mixed opinions on whether serum-based biomarkers are viable to be used as a sole testing approach, innovation in this space will help expand the arsenal of diagnostic and monitoring options for providers and patients.

Exhibit 5. Emerging serum-based biomarker tests

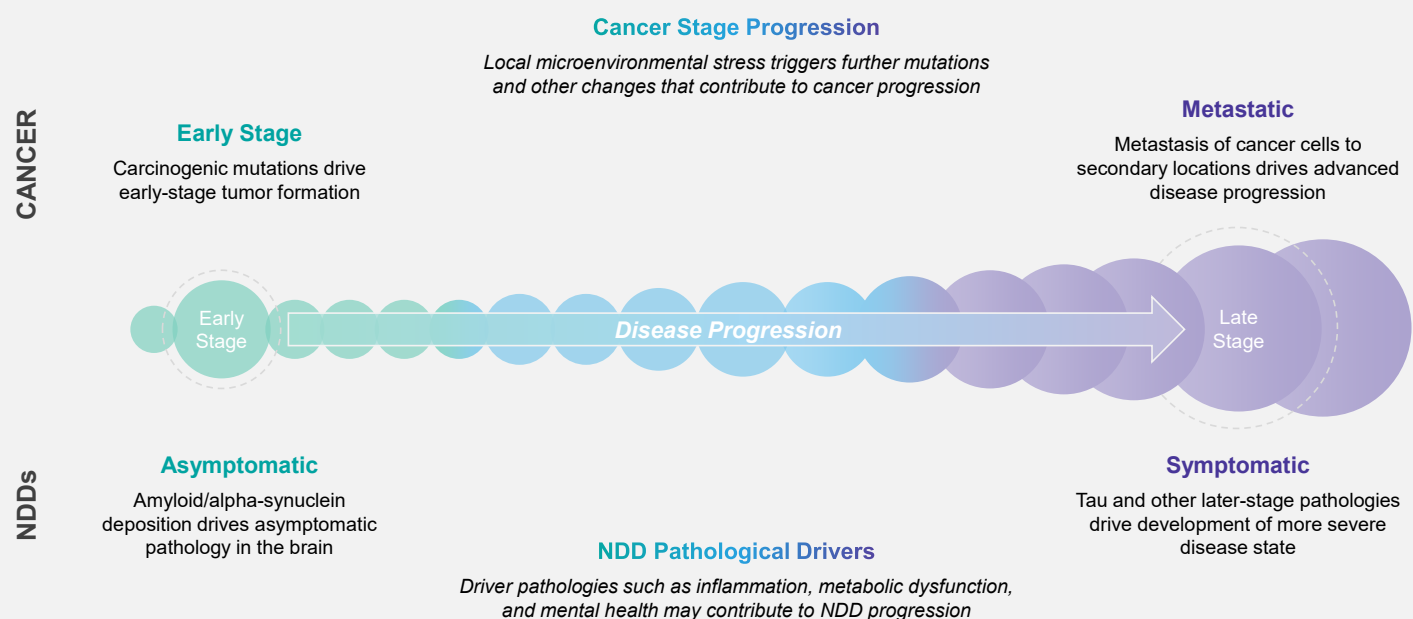| Products/Services	Technologies	Company name	Country
PrecivityAD	IP-MS	C2N Diagnostics	U.S.
Universal Screening Test	qRT-PCT	DamiR Bioscience	U.S.
Simoa	ELISA	Quanterix	U.S.
Elecsys Amyloid Plasma Panel	ELISA	Elecsys (Roche)	U.S.
SOBA-AD	Oligomer Peptide Binds	AltPep	U.S.
genoSCORE-LAB	Genetic analysis	CytoX	U.K.
ABtest-IA ABtest-MS	ELISA Mass Spectrometry	Araclon Biotech	Spain
Amyblood	ELISA	ADx Neuroscience/ EUROIMMUN (a PerkinElmer company)	Belgium/Germany
AlzoSure	U-p53AZ Antibody	Diadem SpA	Italy
Olink Target	Immunotherapy + PCR	O-Link Proteomics	Sweden
Amyloid MS	IP-MS	Shimadzu	Japan
HISCL	CLEIA (HISCL)	Sysmex/Eisai	Japan
IMR Reagent	Immunotherapy + Magnet therapy	MagQu	Taiwan
MDS - OA Test	ELISA	PeopleBio	South Korea

Source: "Alzheimer's diagnosis: Diagnosis market could evolve faster," UBS Global Research, Koike Y, June 28, 2021

How to move forward to personalize NDD treatment and improve outcomes

Evolution of NDD treatments will likely follow the personalized, precision medicine path in focusing on treating each individual patient rather than the perceived disease. Emerging evidence suggests that amyloid and tau are the drivers of early-stage and later-stage disease, respectively—amyloid or alpha-synuclein deposition during asymptomatic stages in the brain can be thought of as early-stage cancer, whereas other driver pathologies and tau accumulation contribute to disease progression and symptomology, mirroring the progression of stable, early-stage to advanced, metastatic-stage cancer [Exhibit 6].

Given this, we hypothesize amyloid and tau-based treatments can be part of the backbone for initial versus later-stage treatments. Tau-based treatments may also be better positioned in treating conditions such as Lewy Body dementia, where tau is a known driver of pathology. We would also expect to see more and more multimodal, personalized regimens in NDDs, leveraging backbone therapy such as anti-amyloid, tau, and/or alpha-synuclein antibodies delivered to patients in conjunction with one or a combination of therapeutic approaches that address adjacent morbidities [Exhibit 7].

Exhibit 6. Analogy of disease progression between cancer and NDDs

CANCER

Cancer Stage Progression
Local microenvironmental stress triggers further mutations and other changes that contribute to cancer progression

Early Stage
Carcinogenic mutations drive early-stage tumor formation

Metastatic
Metastasis of cancer cells to secondary locations drives advanced disease progression

Early Stage — *Disease Progression* — Late Stage

NDDs

Asymptomatic
Amyloid/alpha-synuclein deposition drives asymptomatic pathology in the brain

Symptomatic
Tau and other later-stage pathologies drive development of more severe disease state

NDD Pathological Drivers
Driver pathologies such as inflammation, metabolic dysfunction, and mental health may contribute to NDD progression

Illustrative

Exhibit 7. Therapy personalization – combining backbone and add-on therapies to maximize clinical outcomes
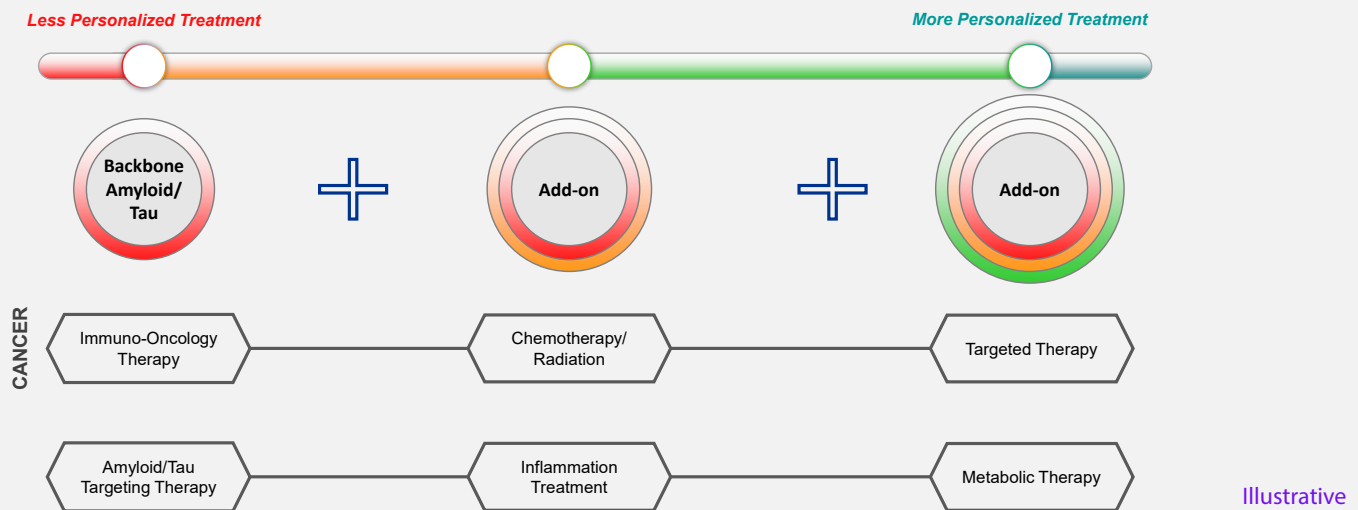
> **We have to be more flexible in how we treat patients moving forward; amyloid antibodies may work well for some patients, but it may not work for all and be enough by itself.**
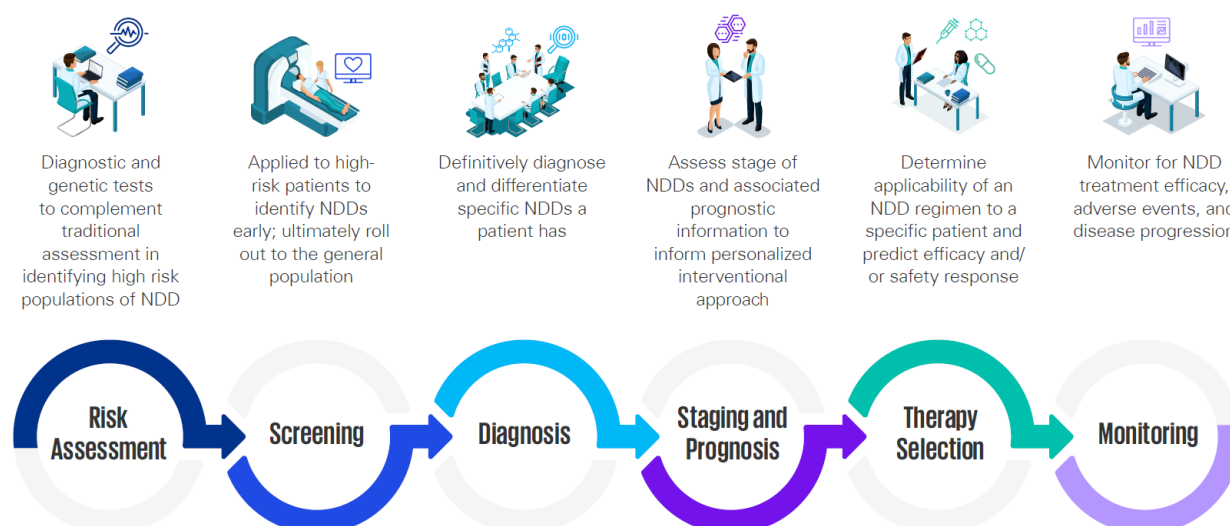> —**Neurologist at a top-ranked medical center in the U.K.**

This is akin to what is seen in oncology, where checkpoint inhibitors have become backbone therapy for types of cancers and treatments such as chemotherapy, targeted therapy, and/or other checkpoint inhibitors are added to maximize results. Some examples on addressing NDD adjacent morbidities include:

- Alzheimer's patients tend to have a high inflammatory state, both at the baseline as well as further exacerbated by the formation of amyloid plaques. Patients who have a high state of baseline inflammation could theoretically benefit from a low dose anti-inflammatory medicine such as Humira or Enbrel.

- One of amyloid targeting therapy's classic side effects, ARIA, is a primary reason patients are given a lower dose or need to stop treatment. Our hypothesis is that patients with a high level of baseline inflammation are more likely to develop ARIA. Theoretically, by giving a lower dose anti-inflammatory treatment, there is potential to lessen the effects of ARIA, thereby allowing patients to reap the full benefit of their anti-amyloid regimen. It may be worthwhile screening patients for inflammatory biomarkers in the future to help improve treatments.

- Many patients have a baseline of metabolic dysfunction caused by diseases such as hypercholesterolemia, hypertension, and diabetes. For these patients, therapies such as Glucagon-Like Peptide 1 (GLP-1, e.g., semaglutide), an anti-diabetic medication in development for Alzheimer's, could be a potential option, either as a stand-alone or combination treatment. While still under study, semaglutide could have disease-modifying effects among patients whose dementia is driven by metabolic dysfunction.

- Given the emerging role of the gut, optimizing the gut microbiome may help potentiate the effects of backbone and/or other therapies a patient is receiving. Emerging literature has shown that the gut microbiome plays a role in response to immunotherapy in cancer,[22, 23] and we hypothesize the same case may be true in NDDs.

- Psychedelics, which function via the reduction of inflammation, improvement in neuronal plasticity, and the rejuvenation of neurogenesis, represent another exciting, emerging class of therapeutics that can help augment current or backbone therapies to better treat dementias.

The future state of personalized medicine in NDDs

Exhibit 8. The future state of personalized medicine in NDDs

Risk Assessment	Screening	Diagnosis	Staging and Prognosis	Therapy Selection	Monitoring
Diagnostic and genetic tests to complement traditional assessment in identifying high risk populations of NDD	Applied to high-risk patients to identify NDDs early; ultimately roll out to the general population	Definitively diagnose and differentiate specific NDDs a patient has	Assess stage of NDDs and associated prognostic information to inform personalized interventional approach	Determine applicability of an NDD regimen to a specific patient and predict efficacy and/or safety response	Monitor for NDD treatment efficacy, adverse events, and disease progression

To realize the full potential of precision medicine and help improve outcomes for patients, biopharma and diagnostic companies must work together in tandem to develop next-generation disease-modifying treatments and cutting-edge diagnostic technologies. Much like how precision medicine approaches have evolved in oncology, NDDs are on the precipice of a similar evolution—the market will likely see realization of earlier diagnosis years before symptoms occur, stratification of patients based on symptoms and pathophysiology, targeted and efficacious therapies administered in combination, and advanced testing tools for monitoring to ensure optimal outcomes [Exhibit 8].

KPMG Deal Advisory & Strategy (DAS) provides a suite of services to support biopharma companies and diagnostic manufacturers in exploring long-term and lifecycle growth strategy within precision medicine in the neurology space. In addition, KPMG DAS provides clients with a broad suite of due diligence services (commercial, operational, financial) and advises on investments, divestitures, acquisitions, and carve-outs. For more information, contact your KPMG precision medicine leaders below.

Example engagements we support in the neurology precision medicine space include:

- R&D, clinical development, and new product strategy
- Early commercial planning and forecasting
- Pipeline asset forecast verification
- Commercial, financial, and operational due diligence supporting acquisition and divestiture of therapeutic assets and/or small-medium biopharma entities

- Organic and inorganic growth strategy analyzing precision medicine landscape in neurology
- Portfolio optimization strategy advising for investment decisions on clinical stage assets and in-market therapeutics products

References

1. "Promise of personalized omics to precision medicine," Wiley Interdisciplinary Reviews: Systems Biology and Medicine, Chen R & Snyder M, November 26, 2012

2. "Precision medicine and molecular imaging: new targeted approaches toward cancer therapeutic and diagnosis," American Journal of Nuclear Medicine and Molecular Imaging, Ghasemi M, Nabipour I, Omrani A, et al., November 30, 2016

3. "What is dementia?," alz.org, accessed September 2022

4. Dementia fact sheet, WHO, September 20, 2022

5. Aducanumab (marketed as Aduhelm) Information, FDA, July 8, 2021

6. Lecanemab confirmatory Phase 3 CLARITY AD Study met primary endpoint, showing highly statistically significant reduction of clinical decline in large global clinical study of 1,795 participants with early Alzheimer's Disease, Biogen, September 27, 2022

7. Fierce Pharma Asia—Eisai, Biogen's Alzheimer's win; Astellas, Pfizer patent fight; Sandoz plant sale, FiercePharma, September 30, 2022

8. https://investor.lilly.com/news-releases/news-release-details/lilly-shares-positive-donanemab-data-first-active-comparator

9. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment

10. Roche's antiamyloid antibody gantenerumab fails phase 3 in major blow to Alzheimer's ambitions, FierceBiotech, November 14, 2021

11. "A Proposed Hypothesis on Dementia: Inflammation, Small Vessel Disease, and Hypoperfusion Is the Sequence That Links All Harmful Lifestyles to Cognitive Impairment," Frontiers in Aging Neuroscience, Hakim A, April 29, 2021

12. "The Impact of Inflammation on Cognitive Function in Older Adults: Implications for Health Care Practice and Research," Journal of Neuroscience Nursing, Sartori A, Vance D, Slater L, and Crowe M, August 1, 2013

13. "Mitochondrial Dysfunction and Oxidative Stress in Alzheimer's Disease," Frontiers in Aging Neuroscience, Misrani A, Tabassum S, and Yang L, February 18, 2021

14. "Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances," Molecular Neurodegeneration, Wang W, Zhao F, Ma X, et al., May 29, 2020

15. "Potential involvement of Varicella Zoster Virus in Alzheimer's Disease via reactivation of quiescent Herpes Simplex Virus Type 1," Journal of Alzheimer's Disease, Cairns D, Itzhaki R, and Kaplan D, August 2, 2022

16. "Environmental Risk Factors for Early-Onset Alzheimer's Dementia and Frontotemporal Dementia: A Case-Control Study in Northern Italy," International Journal of Environmental Research and Public Health, Adani G, Filippini T, Garuti C, et al., October 29, 2020

17. "Are infections seeding some cases of Alzheimer's disease?," Nature, Abbott A, November 4, 2020

18. "Study suggests Epstein-Barr virus may cause multiple sclerosis, National Institutes of Health, Doctrow B, February 1, 2022

19. "The relationship between the gut microbiome and mild cognitive impairment in patients without dementia: a cross-sectional study conducted in Japan," Scientific Reports, Saji N, Murotani K, Hisada T, et al., December 18, 2019

20. "Dysbiosis, gut barrier dysfunction and inflammation in dementia: a pilot study," BMC Geriatrics, Stadlbauer V, Engertsberger L, Komarova I, et al., July 20, 2020

21. "Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation," NPJ Parkinson's Disease, Romano S, Savva G, Bedarf J, et al., March 10, 2021

22. "Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies," Journal of Hematology & Oncology, Lu Y, Yuan X, Wang M, et al., April 29, 2022

23. "Gut Microbiome and the Response to Immunotherapy in Cancer, Discoveries (Craiova), Stancu A, September 30, 2018

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