ARTIFICIAL INTELLIGENCE, PRECISION MEDICINE, AND NEURODEGENERATIVE DISEASE:

A Giving Smarter Guide

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OCTOBER 2024

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FOREWORD

After decades of frustration, the tide has finally begun to shift in the fight against neurodegenerative disorders. The first few disease-modifying treatments were recently approved by the Food and Drug Administration. New tools, such as affordable "-omics" sequencing and nano-scale microscopy, have allowed researchers to generate massive new datasets from diverse human populations. With these puzzle pieces falling into place, the time is right to rethink traditional approaches to neurodegeneration research and the delivery of care for patients in need.

The 10,000 Brains Project is a US-based philanthropic initiative that seeks to accelerate the use of artificial intelligence (AI) in the fight against neurodegenerative diseases. We envision a world where AI-enabled tools are widely used to deliver more personalized diagnostics and treatment strategies for all types of neurodegeneration patients, which is the key to ending the global scourge of these diseases.

AI can be a uniquely powerful tool for grappling with the daunting complexities of neurodegenerative diseases. However, it will not achieve its full potential unless it is properly guided and supported. We commissioned this Giving Smarter Guide to cut through the hype surrounding AI and to create an actionable roadmap for maximizing its impact within the neurodegeneration research community.

We hope that our funding partners and other stakeholders will use this report to focus their efforts on the highest impact AI-enabling projects. By working together, we can minimize waste and redundancy while accelerating progress toward better diagnostics, treatments, and clinical support tools for all neurodegenerative disorders.

We are deeply grateful to the talented Milken Institute team that undertook this study and produced the report. We are similarly indebted to the dozens of subject matter experts who generously contributed their insights and ideas to it. This project would not have been possible without the Rainwater Charitable Foundation and the Robertson Foundation, who generously co-funded it with us and served with us on the steering committee.

There is a tremendous amount of work still left to do, but it's an extremely exciting time to be a supporter of neurodegeneration research. We hope that you'll join us on this important journey: Together, we can eradicate neurodegenerative disease in our lifetime.

Patrick Brannelly
CEO, The 10,000 Brains Project

EXECUTIVE SUMMARY

Neurodegenerative diseases (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS), affect more than 50 million people worldwide. NDs are complex disorders that cause progressive and debilitating cognitive and physical decline. They are difficult to diagnose, complicated to treat, and have no cures. The World Health Organization estimates that by 2040, NDs will be second only to cardiovascular disease as a cause of death in developed countries, overtaking cancer-related deaths. But by bringing the principles of precision medicine—an approach to tailoring disease prevention and treatment according to the characteristics of a disease *and the individual with the disease*—and the power of artificial intelligence (AI) to the forefront of research and discovery across NDs, there is significant potential to transform this landscape in less than a decade.

AI advances represent an area of untapped potential for leveraging data across NDs to develop precision medicine approaches informed by biology. Here, AI refers to the broad discipline of devising machines and systems that can solve problems in an "intelligent manner." Because they can process information at a rapid pace, AI tools can be game-changers for researchers who are building a biological understanding of complex NDs by integrating massive, multimodal datasets from diverse human subjects (e.g., genomics, neuroimaging, cognitive assessments, and movement measures). Interpreting these robust signatures—whether shared across the ND spectrum (i.e., pan-ND signatures), specific to a single disease or subset of diseases, or unique to individual patients—will accelerate progress in (1) identifying mechanisms for disease prevention, (2) ensuring early and accurate diagnosis, and (3) developing and assigning precision treatment strategies for all patients with NDs.

Areas of Opportunity in ND Research

Disease Prevention

The development of an ND begins decades before clinical symptoms appear. Once a patient starts to experience symptoms, the effects of available treatments may be limited. AI can help shed light on how aging, genetics, environmental exposures, medical history, and other factors interact to cause NDs. These tools can then identify patients at the highest risk of developing an ND, and indicate which interventions may have neuroprotective effects that delay disease onset, decrease the severity of disease, or even prevent ND development.

Early and Accurate Diagnosis

Delayed diagnosis limits the window for effective treatment. AI can assist in diagnosis by identifying biomarkers—biological molecules found in blood or other body fluids or tissues—that are signs of a normal or abnormal process, or of a condition or disease, and disease signatures. Biomarkers can be used to support the differential diagnosis of NDs that have similar early signs or symptoms and, potentially, even diagnose a condition before symptoms are manifest. This can extend the therapeutic window by enabling access to drugs that might slow progression and/or mitigate symptoms of some NDs.

Drug Development and Personalized Treatment

ND is characterized by heterogeneity of symptoms, time to onset, and overall trajectory. Patients are likely to derive the most benefit from therapeutics tailored to their current stage of disease. AI can help stratify patients into treatment groups to enable precision treatment approaches. It can also identify and validate specific drug targets across and within disease subsets.

AI tools can accelerate the design of de novo therapies and the repurposing of targeted therapies to pinpoint drugs with the highest probability of regulating the underlying biological pathways, such as gene expression or protein signatures, which may contribute to pathogenesis or underlie disease progression for each group. AI models can also be developed to predict whether therapeutics will cross the blood-brain barrier, bind specifically to pathological targets involved in NDs, enhance protective pathways to slow progression, reveal how molecular modifications can improve existing candidate molecules, and more.

The number of publications spanning AI, ND, and precision medicine doubled from 2020 to 2023. Titles including terms such as *precision medicine-guided diagnoses*, *artificial intelligence for dementia genetics and omics*, and *artificial intelligence and open science in discovery of disease-modifying medicines* reflect the excitement around the potential for AI to enable rapid implementation of precision medicine in NDs. Not only does AI have a unique potential to drive ND precision medicine, but a funding analysis performed by the Milken Institute has demonstrated that only three federally funded research projects (3 percent) at the intersection of AI and ND address more than one neurodegenerative disease (pan-ND), clearly demonstrating that cross-indication funding—which is critical to enabling ND precision medicine—is missing and should be prioritized. Now is the time to leverage exciting new technologies to bring NDs into the precision era.

Leveraging AI to Drive Progress in ND: Philanthropic Opportunities

The opportunities outlined in this Giving Smarter Guide were informed by a thorough review of the scientific literature, examination of public and private funding patterns, and structured interviews with more than four dozen subject matter experts and other key stakeholders across the ND and AI ecosystems. These stakeholders include foundations, advocates, researchers, clinicians, data scientists, and industry members. Through this deep due-diligence effort, the Milken Institute Science Philanthropy Accelerator for Research and Collaboration (SPARC) identified six high-priority opportunities spanning four broad areas where philanthropic investment and partnership could have a transformative impact:

Data Quality, Infrastructure, and Access

1. **Expand neurodegenerative disease data diversity.** Fill the gaps in existing datasets in terms of participant diversity, disease type, and data modality (e.g., sequencing data, imaging data).

2. **Ensure data accessibility and quality, and develop supportive infrastructure.** Leverage existing data platforms and infrastructure to build a federated data ecosystem and support data curation and utility across the ND landscape.

Training an Interdisciplinary Workforce

3. **Bridge training in neuroscience and computational biology.** Support the training of computational neuroscientists through programs that support cross-functional training on real-world AI-ND projects.

Artificial Intelligence Implementation

4. **Support AI-enabling resource development and validation of AI tools.** Encourage pan-ND initiatives and pilot studies that develop AI tools with the potential for translational impact, and build an ecosystem that supports the storage, validation, and recommendation of datasets and algorithms for AI-based research.

Ethics Standards and Support

5. **Protect people and their data.** Develop and adhere to the highest standards for protecting participants and their data, emphasizing the specific protections necessitated by the additional complexities of AI that requires vast amounts of data and cross-institutional collaboration and analysis.

6. **Ensure equitable AI benefits.** Ensure that AI analyses, applications, and access to AI tools integrate a diverse participant set so that findings benefit the wider population, regardless of socioeconomic status, location, race, education, and other features.

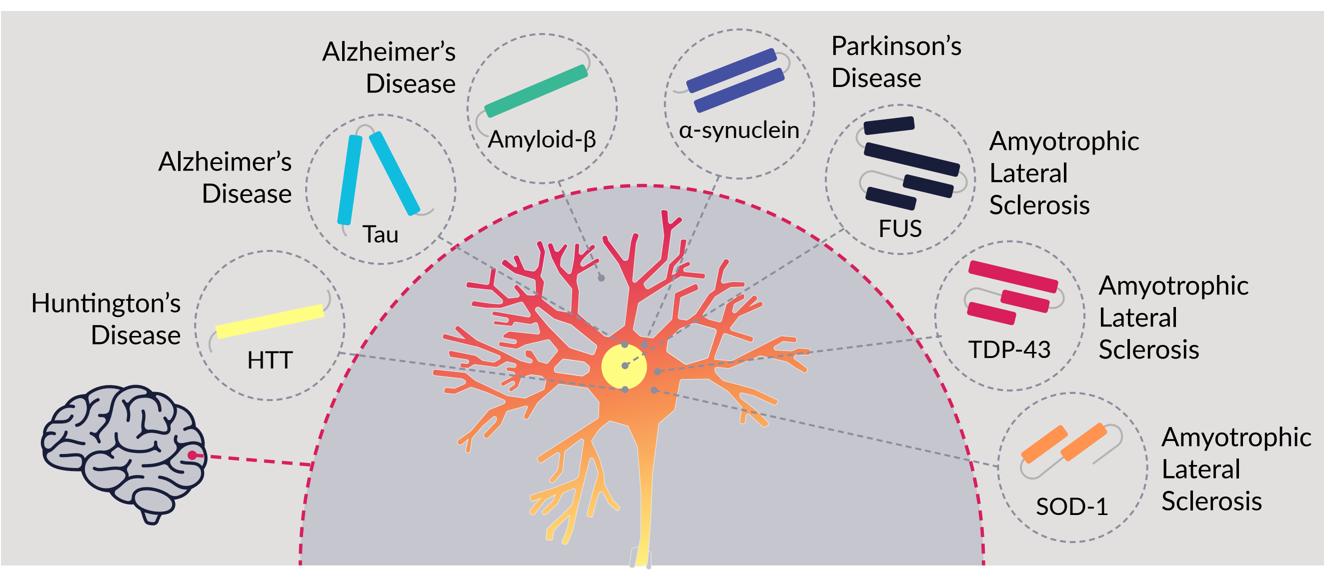
OVERVIEW OF NEURODEGENERATIVE DISEASE

Characteristics and Epidemiology

Neurodegenerative diseases (NDs) are complex disorders that cause progressive and debilitating cognitive and physical decline as well as changes in behavior and mood. Treatment options across NDs are woefully inadequate. NDs affect more than 50 million people worldwide, causing impacts on brain and nervous system functions ranging from mild to severe (Nichols et al. 2022). These conditions are more likely to develop over time; therefore, aging populations are the most susceptible. Estimates already place the impact of NDs at approximately 15 percent of the global population (Feigin et al. 2020). And, as people worldwide live longer thanks to improvements in nutrition, sanitation, and health care, the proportion of the population impacted by ND is likely to increase rapidly unless progress advances toward better treatments or cures.

While specific NDs vary by symptomatic profile and the underlying subset of cells affected, as a class they share some commonalities. For example, most NDs are marked by a proteinopathy component, whereby adverse protein aggregation occurs in the brain (Moda et al. 2023). Aggregation of misfolded proteins—including but not limited to amyloid-β, tau, TAR DNA-binding protein 43 (TDP-43), and α-synuclein—is seen in NDs such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) (Duran-Aniotz et al. 2022) (Figure 1).

Figure 1: Protein Aggregates in Neurodegenerative Diseases



Source: Eftekharzadeh, Hyman, and Wegmann (2016)

Other mechanistic features, such as oxidative stress, neuroinflammation, mitochondrial dysfunction, apoptosis, and glutamate toxicity, have been linked to NDs (Buga and Oancea 2023; Grel et al. 2023; Dailah 2022; Lewerenz and Maher 2015; Zhang et al. 2023). More than two dozen NDs are known, from the more common Alzheimer's to far rarer conditions, such as Creutzfeldt-Jakob disease, and more-recently characterized diseases, such as limbic-predominant age-related TDP-43 encephalopathy (LATE). They are often cataloged within larger groups, including:

- **Dementia-type diseases:** Progressive loss of neurons in the brain that can impact thinking, memory, reasoning, personality, mood, and behavior. Diseases in this category include Alzheimer's disease, frontotemporal dementia, Lewy body dementia, and LATE.
- **Parkinsonism-type diseases:** Loss of the neurons regulating coordination and muscle movements. This includes Parkinson's disease and other forms of parkinsonism.
- **Demyelinating diseases:** Loss of myelin, the fatty-protein sheath that insulates and protects nerve cells in the brain and spinal cord, allowing electrical impulses to travel quickly and efficiently between them. Demyelination adversely impacts the sending and relaying of nerve signals. Diseases in this category include multiple sclerosis and neuromyelitis optica spectrum disorder.
- **Motor neuron diseases:** Death of neurons that control movement. Examples of motor neuron diseases include amyotrophic lateral sclerosis and progressive supranuclear palsy.
- **Prion diseases:** Fast-spreading brain damage caused by protein misfolding. Creutzfeldt-Jakob disease is the most common disease in this category.

Table 1 summarizes similarities in etiology, risk factors, and, in some cases, genetic factors and symptom presentation among three of the more common NDs representing three different categories of NDs.

Table 1. Characteristics of a Small Subset of Neurodegenerative Diseases

Neurodegenerative Disease	Alzheimer's Disease	Amyotrophic Lateral Sclerosis, also called Motor Neuron Disease	Parkinson's Disease
Common Symptoms and Progression	Dementia, including memory loss, personality changes, and difficulties with problem-solving. Progression results in difficulty performing basic tasks. AD is fatal approximately 3–11 years post-diagnosis as the result of brain damage or secondary conditions associated with primary symptoms.	Cramping, twitching, loss of motor control in limbs, weakness and fatigue, slurred speech. Progression results in difficulty breathing and swallowing, projecting vocalizations, muscle paralysis, and dementia-like symptoms. ALS is fatal approximately two to five years after diagnosis as the result of difficulty breathing or paralysis.	Impaired movement (twitching, shaking, difficulty controlling motor functions) and non-motor functions (sleep, autonomic functions, cognition, depression, hyposmia, constipation). Progression involves worsening of the symptoms above until individuals cannot stand or walk unaided due to leg stiffness.

Neurodegenerative Disease	Alzheimer's Disease	Amyotrophic Lateral Sclerosis, also called Motor Neuron Disease	Parkinson's Disease
Diagnosis and Assessment	Assessment battery to rule out other causes of memory loss and cognition; tau positron emission tomography (PET); ADAS-COG for cognition; diagnostics for AD include amyloid PET, cerebrospinal fluid (CSF) Aβ 42/40, CSF p-tau 181/Aβ 42, CSF t-tau/Aβ 42, blood-based biomarkers, or combinations of these.	A battery of tests to rule out other potential causes. Neuroimaging and blood, urine, and CSF samples to explain symptoms until all have been excluded and only ALS remains; Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), which stratifies severity, for functional assessment.	A battery of tests including neurological and physical exams and a medical history review. Often, other assessments, including neuroimaging via PET and MRI, are used to rule out potential alternatives or support previous results.
Brief Epidemiological Statistics	Comprises 60–80 percent of dementia cases. 127 new yearly cases per 100,000 individuals. Women have a higher likelihood of developing AD. An estimated 55 million individuals globally have AD, including at least 6.5 million in the US.	1.6 new yearly cases per 100,000 individuals. Estimated 20,000 people living with ALS in the US. 10–15 percent diagnosed with ALS also receive an FTD diagnosis.	5–35 new yearly cases per 100,000 individuals. Second most common ND. Estimated 500,000 people living with PD in the US.
Contributing Genetics and Other Underlying Biological Factors	Over 70 risk genes have been identified, including mutations in *Amyloid Precursor protein (APP), MAPT, APOE4* isoform of APOE, *Presenilin 1 (PSEN1)* and *Presenilin 2 (PSEN2).* Protein aggregates composed of beta-amyloid (amyloid plaque) and tau (tau tangles).	Mutations in *C9orf72*/C9orf72; *SOD1*/SOD1; *MAPT*/Tau *TDP-43*/TDP-43; *FUS*/FUS. Amyloid deposits from TDP-43, C9ORF72 dipeptide repeats (DPRs), phosphorylated high molecular weight neurofilament protein (pNFH), rho guanine nucleotide exchange factor (RGNEF), FUS, and tau.	Mutations in *Alpha(α)-synuclein*/alpha-synuclein; *Parkin*/Parkin; *Pink1*/PTEN-induced kinase 1; *PGC-1$^{\alpha}$*/PGC-1 alpha. Alpha-synuclein build-up in Lewy bodies.
Genetic Susceptibility	Approximately 40–80 percent of cases are influenced by genetic factors. Fewer than 5 percent of cases are caused by a single genetic mutation that is transmitted through families.	About 5–10 percent of cases are genetic, and 90 percent are sporadic with no known family history.	About 10 percent of cases are linked to a genetic cause.

Sources: Sheppard and Coleman (2020); Jack et al. (2024); Masrori and Van Damme (2020); Khan and De Jesus (2024); Poewe et al. (2017)

Although NDs share similarities, they demonstrate a range of symptoms, and each disease impacts different brain regions and cell types. For example, FTD is categorized by the degradation of neurons in the frontal and anterior temporal lobes, contributing to unique clinical features, including disinhibition (the inability to withhold an inappropriate or unwanted behavior), apathy, loss of empathy, and compulsions (Magrath Guimet, Zapata-Restrepo, and Miller, 2022). In ALS, by contrast, motor neurons in the brain and spinal cord become diseased and die, leading to progressive muscle loss and paralysis. Notably, there are diagnostic criteria for a disease subtype with features of both ALS and FTD—ALS frontotemporal spectrum disorder (ALS-FTSD) (Jo et al. 2020; Strong, Donison, and Volkening, 2020)—which emphasizes that definitive and differential diagnosis is not simple in NDs.

Etiology

Mechanisms linked to neurodegeneration comprise a range of biological processes, although few have been identified as sufficient to cause disease. Most NDs have a component of genetic susceptibility, but not all cases are defined by a specific gene mutation.

Even known genes confer little risk individually and are instead thought to act in concert with other mutations as well as environmental and lifestyle factors. Moreover, the genetic background of NDs can differ across ethnic groups; for example, a specific type of apolipoprotein E (APOE), a protein involved in the metabolism of fats, is associated with AD risk. People who carry two copies of this protein type, APOE ε4, and are of European descent have a higher risk of developing AD than people of African, Hispanic, or Japanese descent. Adding complexity to this finding, specific mutations of APOE that are found more commonly in certain ethnicities can increase the risk of developing AD up to threefold (Le Guen et al. 2023).

Some mechanisms are consistently associated with a range of NDs. Appreciating the extent to which these pathological mechanisms—and combinations of pathological mechanisms—contribute to neuronal death is important for identifying the critical factors that lead to the development of NDs. Pathological mechanisms are complex and are likely to change throughout disease progression; some that are commonly identified in association with a range of NDs include the following:

- Disruption of signaling pathways that regulate cell division and metabolism are associated with the pathogenesis of various NDs, including PD, AD, and HD (Rai et al. 2019).
- Altered mitochondrial function and increased oxidative stress are linked to PD, AD, HD, and ALS (Alqahtani et al. 2023).
- Alternative gene splicing generates unique RNA products and protein isoforms from a single gene with different functions. Dysregulated alternative splicing has been broadly implicated in the development of NDs including AD, ALS, FTD, and PD (Nikom and Zheng 2023).
- Lysosomal dysfunction associated with genetic mutations (e.g., C9orf72, GRN, MAPT, TMEM106B) or aggregation of TDP-43 or tau proteins is an important disease mechanism in FTD and ALS (Root et al. 2021).
- Persistent neuroinflammation involving microglia and astrocytes has been associated with AD, PD, and ALS (Bevan-Jones et al. 2020).

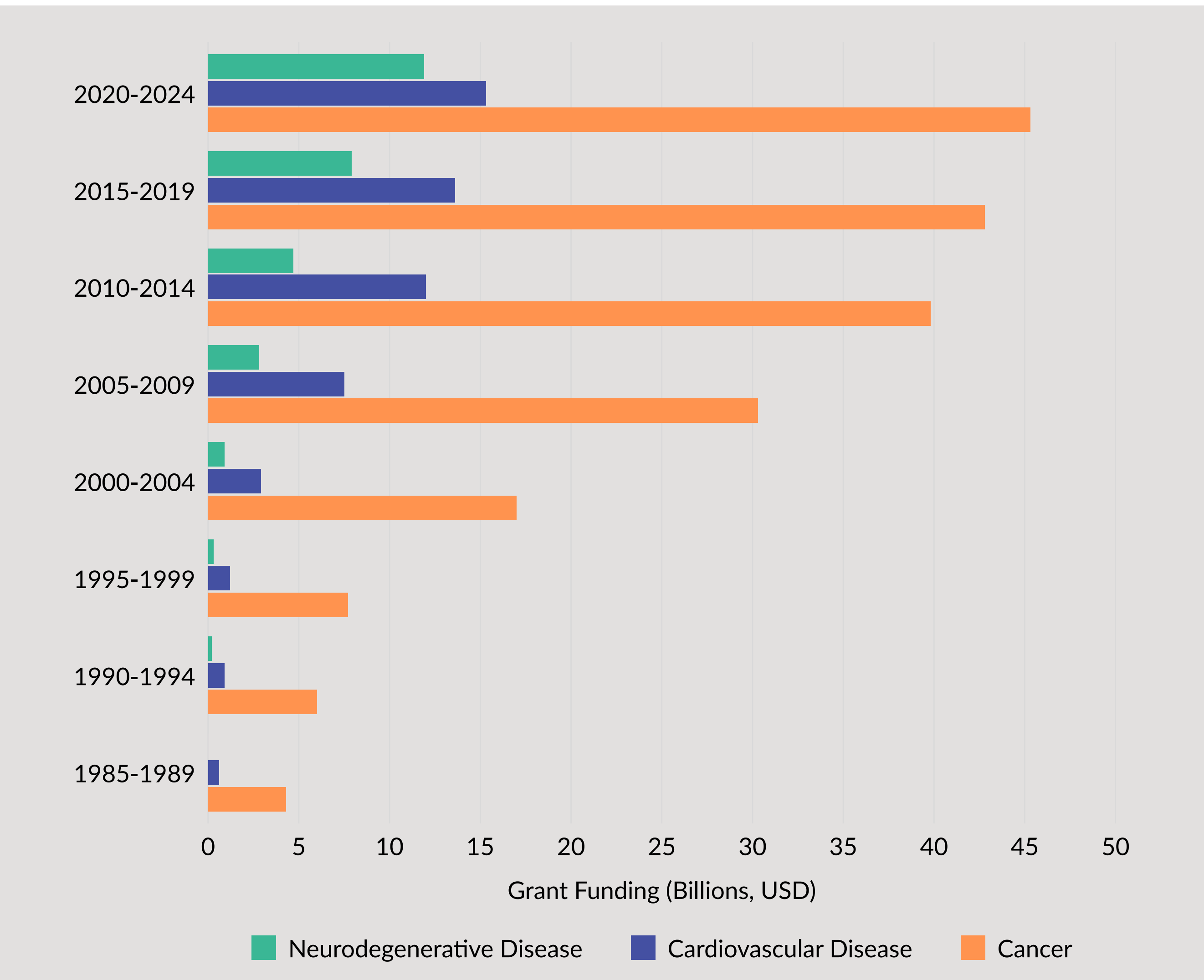
Additionally, environmental and lifestyle factors integrate in a complex interplay with identified genetic and pathological features, which can contribute to disease (Perneczky 2019). Some demographic groups are differentially susceptible to developing a specific ND. For example, women are more likely than men to develop AD (Podcasy and Epperson 2016), and people who suffer head injuries, such as traumatic brain injuries, may develop many forms of ND at higher rates (Smolen, Dash, and Redell 2023). Decades of epidemiologic studies from global populations have associated pesticide exposure, farm work, or rural residence with an increased risk of PD (Simon, Tanner, and Brundin 2020). These are just a few of the identified risk factors, and it is likely that many more will emerge with continued analysis of large-scale data specifically focused on identifying early risk factors.

The Financial Burden of Neurodegenerative Disease

The risk of dementia increases exponentially with age, affecting 13.9 percent of people aged 71 or older. Notably, disproportionate effects of ND are seen in women and disadvantaged ethnic groups (especially Black and Hispanic people) and those with lower socioeconomic status and levels of education (Gooch, Pracht, and Borenstein 2017).

Over the last three decades, considerable federal investment has been made in support of cancer and cardiovascular disease research (Figure 2): $183 billion and $53 billion, respectively. These investments have yielded therapeutic benefits that have positively impacted health and survival. However, less support—$28 billion in the last three decades—has been dedicated to ND research, and, as more people survive diseases such as cancer, the result is an aging population in which NDs are becoming more common, but therapeutic gains have been limited. The number of individuals diagnosed with NDs has climbed considerably over the last 30 years, and the burden of neurodegenerative conditions is expected to double, at least, over the next two decades (Van Schependom and D'haeseleer 2023).

Figure 2. National Institutes of Health Grant Funding for Cancer, Cardiovascular Disease, and Neurodegenerative Disease from 1985 through 2024



Source: Milken Institute analysis of reporter.nih.gov (2024)

The cost of care increases dramatically with the disabilities associated with NDs. The need for daily care, supervision, and assistance burdens families and the health-care system. The total *annual* cost of purchased care and informal home care for each patient ranges from $45,805 to $61,525 (Hurd et al. 2013). NDs affected nearly 6 million Americans and were responsible for 270,000 deaths and, notably, 3 million disability-adjusted life years (Thorpe, Levey, and Thomas 2021), a measure of the overall burden of disease over time: One disability-adjusted life year is equal to one lost year of full health (Cao and Ho 2020). An assessment performed by the Partnership to Fight Chronic Disease concluded that ND costs exceeded $655 billion a year in medical expenses and economic losses in the US in 2021 (Thorpe, Levey, and Thomas 2021).

There are limited economic-impact data that span NDs, with most studies focusing primarily on individual diagnoses (Figure 3). AD is the most common ND, and its economic impact alone is significant. In 2019, the global economic burden of AD and related dementias (ADRDs) was estimated at $2.8 trillion and is projected approximately to double in each upcoming decade ($4.7 trillion in 2030, $8.5 trillion in 2040, and $16.9 trillion in 2050) (Nandi et al. 2022).

Figure 3. Economic Impact of a Subset of Neurodegenerative Diseases

Alzheimer's Disease and Related Dementias	Parkinson's Disease	Amyotrophic Lateral Sclerosis
Cost of Care		
$352B in annual direct costs	$54.7B in annual costs to the US	$1.2B in annual costs
$58B in Medicaid costs	$26.8B in direct medical costs	$2M in single-patient costs over 10 years
$179B in Medicare costs	$27.9B in indirect, non-medical costs	
$75B in out-of-pocket		
Caregiver Burden		
15.3B hours annually for unpaid caregiving	$6.9B $6.9 billion in unpaid caregiving	1 out of 4 patients and families experienced debt or had to borrow money due to ALS treatment or caregiving
70% of the lifetime cost of care is the responsibility of families of individuals with ADRDs	22 Hours a week for unpaid caregiving	1 in 10 lost health insurance coverage in the course of disease

Source: Thorpe, Levey, and Thomas (2021) and ALS Association (2024)

DRIVING PRECISION MEDICINE FOR NEURODEGENERATIVE DISEASE

Precision medicine is an approach to treatment that focuses on understanding and treating disease by integrating multimodal data to make decisions tailored to individual patients (MacEachern and Forkert 2021). Successful precision medicine initiatives require four key components:

- an understanding of the underlying biology of a disease;
- identification and grouping of specific subsets of patients based on their biology;
- disease biomarkers to facilitate diagnosis, track progression and treatment response, and inform inclusion in most relevant clinical trials; and
- therapeutics developed to address the disease state specific to each individual at each stage of disease.

The ND landscape could be transformed through research that focuses on precision medicine and addressing key unmet needs: early and accurate diagnosis, drug development and personalized treatment, and disease prevention.

Detection, Diagnosis, and Monitoring

Precision medicine approaches hold great promise for improving the screening, detection, and diagnosis of NDs. Diagnosing an ND requires multiple invasive, time-consuming, and expensive neurological, cognitive, and functional assessments administered by a physician to rule out other explanations for symptoms. In some cases, neuroimaging techniques and analysis of biofluids, such as blood and cerebrospinal fluid (CSF), can be used to confirm a diagnosis. In other cases, as seen with ALS and FTD, a range of variable symptoms may result in misdiagnosis, particularly in the early stages of the disease process. Notably, even when diagnostic options are available, imaging techniques are expensive and time-consuming, and CSF extraction is invasive.

Most importantly, these diagnostic methods are utilized only in patients in whom symptoms have already manifested. AD and FTD often impact cognitive function (presenting as mild cognitive impairment) and mood years before diagnosis. In the case of PD and ALS, which primarily impact movement, there are often discernible symptoms, such as constipation, muscle twitching, or frequent falls, that occur prior to diagnosis (Baldacci et al. 2019; Hampel et al. 2022; Logroscino, Urso, and Savica 2022; Masrori and Van Damme 2020; Samara et al. 2021). In all of these NDs, cellular pathology (e.g., amyloid plaques or tau tangles) and associated neuronal damage begin decades before symptoms develop, and, by the time of diagnosis, degeneration is already advanced.

Discovery and validation of biomarkers and other diagnostic technologies—including digital technologies, such as wearables and voice assessment—are needed to lower the cost and effort thresholds for assessing NDs and enable faster and more accurate diagnoses. The most useful diagnostics and biomarkers for precision medicine would be widely accessible, minimally invasive, cost-effective, sensitive, and accurate. Importantly, with sufficient sensitivity, they will also offer utility for screening and early detection and enable multiple evaluations over time (Van Schependom and D'haeseleer 2023), thus enabling disease monitoring.

Therapeutic Development

While improvements in precision diagnostics represent a critical need, their functional utility will be limited until disease-modifying therapeutics are available for NDs. Disease-specific therapeutics have been approved for use in AD, PD, and ALS, though these therapeutics are largely effective only if administered early in the disease course, and only a subset of individuals will derive benefit from the treatments. Central nervous system drugs are notoriously difficult to develop, with lower success rates and longer development timelines than other classes of drugs (Mohs and Greig 2017). Despite some recent high-profile therapeutic approvals in the ND space—including lecanemab for AD and tofersen for ALS—far too few disease-modifying treatments are available for this class of disease.

Disease Prevention

As with any condition, delaying or preventing disease is the most significant opportunity to reduce the burden. Prevention for NDs poses unique challenges as it requires a detailed understanding of the biology of the disease, extensive epidemiological studies, and identification of patients at risk of developing NDs before symptom onset, which can lag decades behind pathological changes.

Certain individual characteristics—including genetics, life experiences, environmental exposures, and neurobiological parameters—are associated with a heightened risk of neurodegeneration. Several large-scale dementia prevention programs are in progress to understand these potential factors better and to determine factors that may prevent ND development. Most such trials have shown limited benefit, but a recent study performed with the UK Biobank cohort identified positive effects of physical, lifestyle, and social factors on reducing the risk for dementia (Singh et al. 2023). These results suggest that additional assessment of cohorts and a better understanding of the underlying biological mechanisms of risk and protective factors could enhance our ability to identify and apply preventive measures.

AI AS A PRECISION MEDICINE TOOL

To construct the necessary framework for applying precision medicine across NDs, the field needs high-density, multidimensional, and longitudinal datasets from large, diverse populations. Analysis tools that can rapidly process these high-volume data streams into interpretable findings are essential to delivering individualized recommendations for patients with NDs. Rapidly integrating, analyzing, and understanding these data from various sources is only possible with the use of AI, which enables next-generation computational biology tools (Tang et al. 2019).

Computational biology is an interdisciplinary field at the nexus of biology, big data, and computer science. It involves modeling or simulating biological systems by analyzing experimental data to identify patterns and draw inferences that are beyond the capabilities of human researchers alone (Toma and Concu 2021; Nguyen and Wang 2020). Computational approaches are a powerful means to mine and analyze large amounts of biological and clinical information, and, in turn, integrating new data can improve the performance of computational tools. Incorporating these tools across the biomedical ecosystem can further scientific understanding of foundational biological mechanisms, advance translational research, revolutionize the identification of therapeutic targets, and accelerate drug development.

AI Case Studies in ND

Early Prediction

The damage to or loss of neurons in NDs probably begins several years before diagnosis. It makes late intervention challenging and treatment less effective. AI is increasingly being leveraged to identify individuals at early, presymptomatic points who may be likely to develop disease (Yao et al. 2023). Researchers are developing AI algorithms that can identify subtle and early signs of disease based on brain imaging, often before clinical symptoms manifest (Amoroso et al. 2018; 2023).

Disease Progression

AI also has the potential to predict patterns of disease progression in distinct groups of patients, thus enabling the identification of those most in need of assistance or intervention. A recurrent neural network algorithm was developed to identify AD patients likely to experience more severely impaired functioning between provider visits based on a range of features, including assessment of daily life functions, depression, general health, and other factors (Wang, Qiu, and Yu 2018).

Screening and Monitoring

Digital technologies such as wearables have the potential to serve as noninvasive tools to screen for NDs. An early example of digital technology for detecting PD incorporates an audio recording device or a breathing belt to detect specific signals to correlate with assessments of PD severity using AI (Yang et al. 2022). Innovative efforts are also focused on the use of voice as a biomarker of health in clinical care to assist in screening and diagnosis of diseases, including NDs.

Target Identification

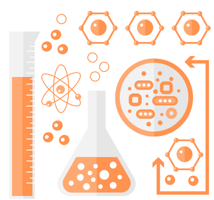
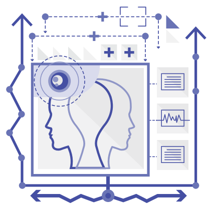
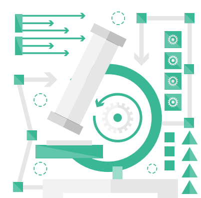
Before therapeutics can be developed for NDs, therapeutic targets involved in disease pathology must be identified. Target identification is often performed by characterizing and understanding vast quantities of information about genes, proteins, transcripts, and other cellular mechanisms—an approach collectively referred to as "omics" —which are integrated with computational tools. The commercial AI product, NetraAI, has been used to identify novel pathways involved in ALS (Geraci et al. 2024).

AI Applications in Neurodegenerative Disease

Although AI technologies have been under development for decades, most AI use for biomedical purposes has occurred in the last 20 years, following advancements in high-performance computing and the development of deep learning algorithms capable of performing analyses that detect complex patterns and relationships in massive data sets (Kaul, Enslin, and Gross 2020). Application of AI to NDs is even more in the fledgling stage, with the first published applications of AI in ND—specifically AD and PD—having occurred less than 15 years ago (Gerardin et al. 2009; Frizzell et al. 2022). Early examples of AI applications in ND research serve as proof of concept for their potential use to promote precision medicine in NDs.

Importantly, certain data types are currently underutilized in ND research because they are difficult to access, or they are not collected or stored in a usable format. Applying AI to these data types can unlock vast amounts of information, transforming the data into rich resources for research. As researchers integrate AI into their data collection and analysis processes, a wider variety of data types will become critical assets, offering more opportunities for breakthrough discoveries (Figure 4).

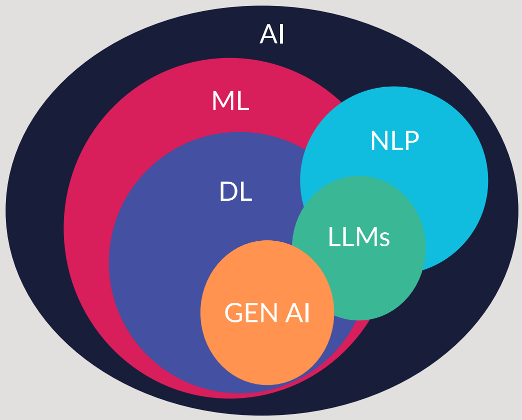
Figure 4. High-Potential Data Types

	 **Biomedical Data**	 **Medical Images**	 **Histopathological Images**	 **Physiologic Signals**
Data Source Examples	Electronic health records: medical history, medications, allergies, immunization status, laboratory test results	CT, X-ray, MRI, PET	Digitized, stained, and processed brain slice slides	ECG, PPG, EEG, arterial pressure, voice, breath
Current Data Limitations	Complex and heterogeneous EHR data are often incomplete and difficult to search and analyze.	Extraction and analysis of data is time-consuming and can be inaccurate due to noise, bias, and human error.	Manual interpretation of slides is laborious, requires expertise, and is only semiquantitative with interrater variability.	Wearables produce large volumes of data that are impractical to analyze manually.
Opportunities for AI to Unlock Data	Natural language processing can be used to extract information from EHR data and reformat them for machine learning. ML can be applied to develop predictive models or classifiers to improve disease diagnosis, risk assessment, and disease progression.	AI algorithms can correct image distortion and reduce noise to improve imaging quality, identify patterns or features in medical images that are difficult for humans to detect, and extract imaging data and analyze them much faster than humans alone.	AI allows for faster and more consistent interpretation of huge sets of digitized slides. AI can identify subtle patterns and morphological changes better than the human eye, enable deeper phenotyping, and perform large-scale tissue biomarker studies.	AI algorithms enable efficient analysis of raw data that extracts meaningful information and discovers hidden patterns in a semi-automatic way to identify early signs of disease.

Source: Lin et al. (2020); Scalco et al. (2023); Go (2022); Zhao et al. (2023)

AI refers to the broad discipline of creating machines and systems that enable the integration, analysis, and understanding of complex data from various sources. AI can perform a wide range of tasks, such as making predictions to solve problems in an "intelligent manner." Various terms are used to describe different aspects of AI, and the meanings of these terms are fluid, as the field is continuously evolving (Figure 5).

Figure 5: Artificial Intelligence Overview



- **Artificial Intelligence**
- **Machine Learning (ML):** Subset of AI that has systems that learn information and adapt this learning as more data are presented (with minimal intervention from humans). ML models are trained to use large amounts of information to make simple linear predictions and "learn" to iteratively improve.
- **Deep Learning (DL):** A type of ML that requires very large datasets and uses layers of algorithms to generate artificial neural networks (interconnected nodes or neurons) to process data and identify patterns, similarly to how the human brain functions.
- **Generative AI:** Any AI system that generates new content based on learnings obtained from data.
- **Natural Language Processing (NLP):** Subset of AI that enables machines to understand human language by combining computer science, linguistics, and ML. Computer programs are trained to translate text across different languages, respond to commands, summarize large volumes of text and complete speech-to-text dictation. Examples include virtual assistants (e.g., Siri, Alexa) and chatbots that utilize LLMs (e.g., ChatGPT).
- **Large Language Models (LLMs):** Type of ML/DL model that can perform NLP tasks like generating text (and hence can also be a form of generative AI). LLMs are foundation models, which are trained on large amounts of textual data, can capture complex patterns in language, and generate responses to prompts or queries.

ML/DL tools are predictive statistical models that continue to evolve, learn, and improve as new data become available. These tools have applications across many industries, including self-driving cars, speech/voice recognition, and computer vision techniques such as image classification. DL models can predict more complex relationships than ML models so are useful in understanding complex biological systems.

Source: Milken Institute synthesis, "Transformative Computational Biology: A Giving Smarter Guide," Milken Institute (April 2024), page 3.

AI Ethical Considerations

AI requires large datasets to be effective, and the process of collecting and sharing data requires significant care and consideration of ethics. Moreover, applying AI to human data requires evaluating how the data are used, how accurately the data used to train AI models represent the patient population, and how findings will ultimately impact human health. The ability to implement AI technologies in various populations is linked to the trust and perceived capabilities of the technology (Steerling et al. 2023). AI introduces thorny questions about who is responsible when an AI-based technology inadvertently harms a patient (Cestonaro et al. 2023).

A goal for AI use for precision medicine is to inform patient care and therapeutic strategies more rapidly. Clinicians who use AI for patient care will want to understand how and why it is making recommendations—or at least be assured that it has been extensively evaluated for safety—before using it to inform patient care. Unless ethical standards are developed and implemented in concert with AI development, there is a risk that they will be addressed too late, eroding trust in a technology that could have enormous potential if applied within a robust ethical framework.

Participant Protections

Participant protection is a key component of ethical data collection, sharing, and use. It should begin with an effective informed consent process, one in which participants truly understand what they are agreeing to and, as a result, can explain what data are being collected and how they will be used. Data privacy is understandably a concern for research participants and their family members. As emphasized by the National Institutes of Health (NIH) Office of Scientific Data Sharing, "respect for and protection of participant privacy is the foundation of the biomedical and behavioral research enterprise." Privacy involves protecting the research participant's right to control the information that is collected, used, and shared, and with whom the information is shared.

Effective consent addresses participants' concerns about the scope and volume of data being collected and ensures that participants are not unduly motivated by the desire to share their data out of an understandable hope for immediate personal benefit (Manti and Licari 2018). Critically, consented research participants are equally frustrated when their data are not deployed and analyzed appropriately; the majority of patients want to share their electronic health records (EHRs) and biospecimens for research (Kim et al. 2019). Consents must be thoughtfully designed to allow for sharing data, while providing participants with confidence that their information will be protected and neither they nor their family members will be harmed or identified.

When advanced technology like AI is involved, the informed consent process can become more complicated because there is additional, often complex, information that the provider must convey to the patient. Certain questions need to be answered, for example: How much information should be shared about the technology to ensure sufficient understanding of the consent? How specific or general should consents be about the purpose of the AI and the extent to which it may or may not directly impact patient care? Are any additional risks pertaining to patient privacy sufficiently addressed?

The patient must understand and consider this additional information as part of the decision-making process. As AI rapidly advances, it is important to establish national guidelines to help institutions manage consent and responsibly share data, ensuring both participant protection and research progress.

Specifically, beyond the data protections that have been an area of intense scrutiny since participant data started to be used for research, AI requires additional considerations (Ratwani, Bates, and Classen 2024). In this burgeoning field, we are only beginning to understand the ethical implications of AI use to analyze participant data and ultimately serve as a tool to support clinical decisions, but some include:

- **Enacting the appropriate level of trust in AI:** Both mistrust of and too much trust in AI can lead to detrimental impact when AI is used in a health-care setting. Mistrust, from either patient or clinician, can mean that the technology may not be used, even when it has a high potential to benefit a patient. On the other hand, when AI is overly trusted, decisions may be made without appropriate vetting, or AI systems may be set as sole contributors to health-care decisions or processes that, if not monitored properly over time, could lead to flawed decision-making. The Biden administration's executive order on the safe, secure, and trustworthy development and use of artificial intelligence recommends a structured testing effort to find flaws and vulnerabilities in an AI system in collaboration with developers of AI as a mechanism for engendering trust and ensuring that trust is validated (Biden 2023).

- **Data privacy:** Artificial intelligence requires unprecedented amounts of data, which in turn necessitates the maintenance and sharing of large data repositories. The collection and sharing of large volumes of data increase the risk of privacy breaches, which makes its security even more crucial. Additionally, the data used for AI applications usually has to be uploaded to cloud servers for processing, introducing an added risk of data compromise.

- **Health-care professional complacency:** Once AI systems are put in place and demonstrate efficacy and benefit, there is a potential for the AI system to become the sole decision-maker, instead of one tool within a larger clinical toolbox used to assist in clinical decision-making. For example, an AI system designed to detect sepsis identified only 7 percent of 2,552 patients who ultimately had the condition. Although the hospital was able to diagnose sepsis through other methods, the initial reliance on AI caused delays in administering antibiotics (Wong et al. 2021). AI should complement, not replace, other tools used to make clinical decisions or contribute to patient care.

Diversity and Inclusion

One of the major concerns regarding biomedical research, including the application of AI and precision medicine to ND, is that the results will be one more tool selectively benefiting those of a certain race, class, and education level. Participants may worry about discriminatory interpretations of their data (Price and Cohen 2019). It is critical to ensure that access to the benefits of research is distributed equitably and that planning starts early in the research process. Social outreach plans, which feature training, counseling, and medical care, are critical components of study design.

Bias is an additional concern that arises when AI is applied to participant data. Bias has been defined as any trend or deviation from the truth in data collection, analysis, and interpretation that can result in false conclusions (Simundic 2013).

While AI has the potential to offer a more objective approach to research by relying on algorithms instead of human judgment, completely eliminating bias is extremely challenging. Bias can be introduced at any stage of the research process and can vary in degree. For example, because AI is trained on data generated by people, bias can be incorporated unless it is explicitly mitigated during the data collection phase. With rigorous research planning and conduct, it is possible to minimize and acknowledge biases that cannot be removed.

Data acquisition from nonrepresentative or incompletely represented populations is a common bias that results from the use of local, more medically engaged, or more easily available populations and can be difficult to mitigate. It is challenging to account equitably for all global populations. Some resource-poor health institutions lack the infrastructure to collect all needed data types, such as neuroimaging or various omics, leaving gaps in those types of data for certain populations (Mollura et al. 2020). Even when the desired data types can be collected, they may be subject to biased collection techniques. For example, cognitive assessments may have performance differences attributed to confounding variables, such as the ability to read a form or hear a study administrator (Reynolds, Altmann, and Allen 2021).

Early and frequent consideration of ethical concerns can reduce harm to participants and improve benefits to patient communities. Importantly, thoughtful ethics can help to avoid the development of AI tools that result in adverse outcomes and erode trust in AI.

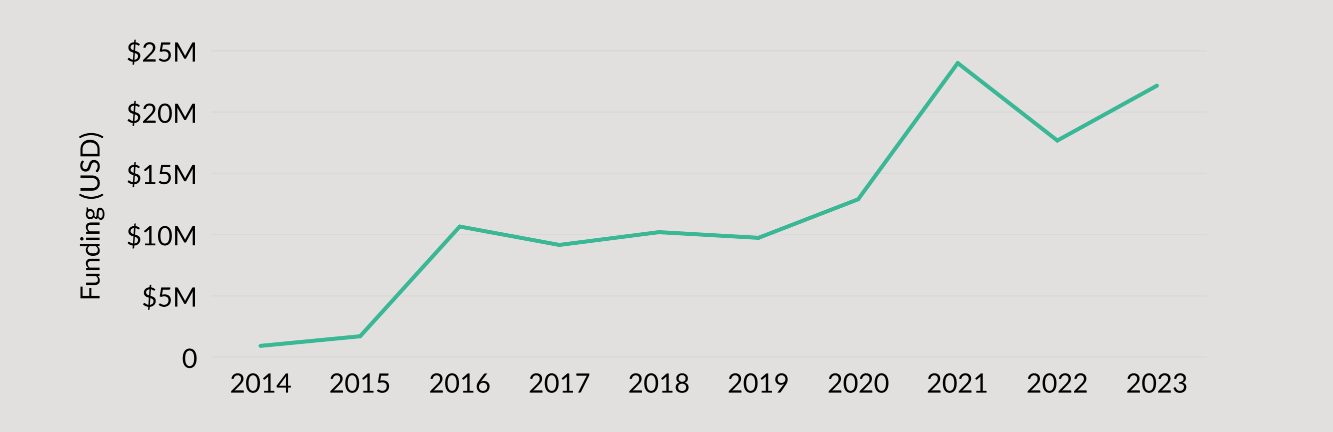
RESEARCH FUNDING FOR AI APPLICATION IN NEURODEGENERATIVE DISEASE

To better understand the needs and opportunities for research funding at the intersection of AI and neurodegenerative disease research, Milken Institute SPARC performed a funding assessment of public and private capital going to this space. The purpose of this analysis is not to provide an exhaustive list of funders, but rather to identify trends and funding priorities in the field over time. Most AI in ND research in the US is funded by the federal government through the NIH and, more specifically, by the National Institute on Aging (NIA). Details on the methodology for federal funding analysis are provided in the Appendix of this document. In addition to public funding, private funding sources were also explored.

Federal Funding at the Intersection of AI and ND Research

In the last 10 years (fiscal years [FY] 2014–2023), the NIH and Department of Defense funded 105 unique extramural research project grants at the intersection of AI and ND. The cumulative total value of these grants was nearly $119 million, and the average project award amount was just over $1 million. Annual funding for projects leveraging AI to address ND has been trending upward over the last decade, ranging from less than $100,000 in 2014 to a peak at just under $24 million in 2021 (Figure 6).

Figure 6. Federal Funding at the Intersection of Neurodegenerative Disease and Artificial Intelligence



Source: Milken Institute analysis of reporter.nih.gov (2024)

While multiple NIH institutes and centers have supported AI in ND research over the last decade, the NIA is the largest funder. Between FY2014 and FY2023, NIA sponsored 69 percent of all such grants and provided 78 percent of the total research dollars. While the nearly $22 million of the NIA budget dedicated to AI research in 2023 is a significant number, it is a minor proportion (0.5 percent) of an overall institute budget of more than $4.4 billion in FY 2023 alone. The second-largest funder of AI in ND research projects was the National Institute of Mental Health, which provided $8.7 million (7.4 percent of total NIH research dollars devoted to AI and ND) (Table 2).

Table 2. Federal Funding for Artificial Intelligence and Neurodegenerative Disease Research from FY2014 to FY2023

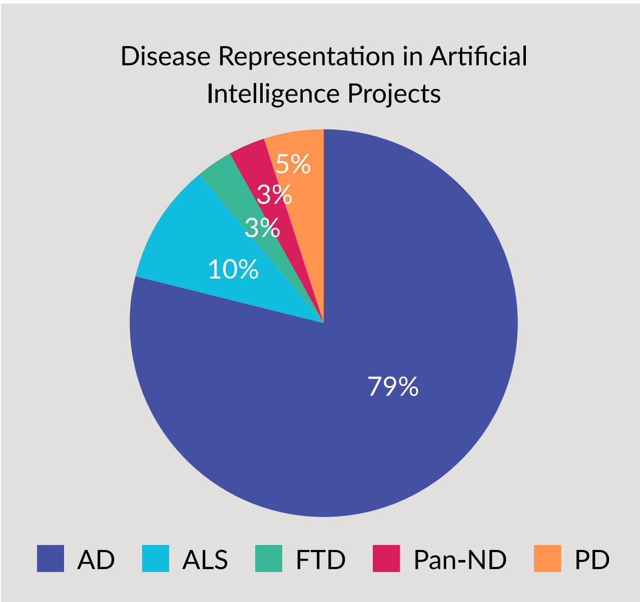
NIH Institute/Center	Grant Counts (%)	Total Funding (%)
National Institute on Aging	76 (69.1)	$92,919,390 (78.0)
National Institute of Mental Health	5 (4.5)	$8,756,878 (7.4)
Department of Defense	8 (7.3)	$7,136,851 (6.0)
Other (AHRQ, ATSDR, NCI, NIBIB, NIDCD, NINDS combined)	*16 (14.5)*	*$10,273,257 (8.6)*
Total	**105 (100.0)**	**$119,086,376 (100.0)**

Note: AHRQ = Agency for Healthcare Research and Quality, ATSDR = Agency for Toxic Substances and Disease Registry, NCI = National Cancer Institute, NIBIB = National Institute of Biomedical Imaging and Bioengineering, NIDCD = National Institute on Deafness and Other Communication Disorders, NINDS = National Institute of Neurological Disorders and Stroke

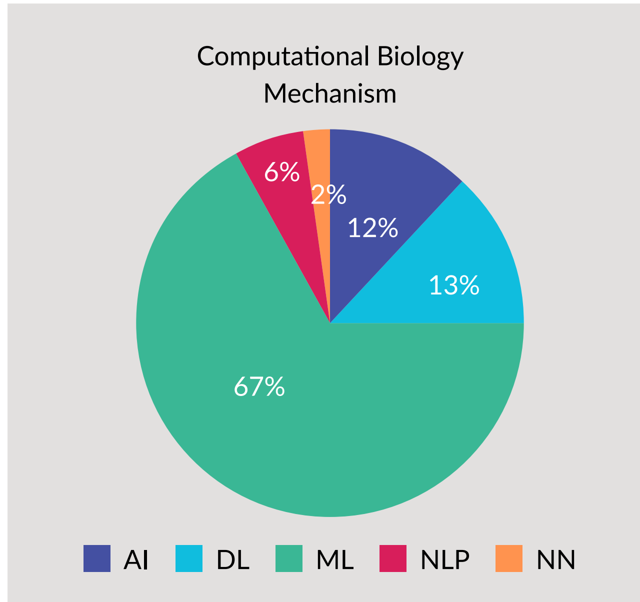
Source: Milken Institute analysis of reporter.nih.gov (2024)

Understanding funding trends is pivotal for driving advancement in the field. Most NIH extramural AI in ND research funding between FY2014 and FY2023 addresses AD (79 percent of all projects funded). Machine learning (67 percent of all projects) is the most common AI approach (Figure 7). The emphasis on AD is likely driven by several factors that include the number of patients impacted by the disease, dedicated advocacy that has driven federal funding for Alzheimer's and dementia research, and consortia and infrastructure that enable efficient and coordinated collection and sharing of a range of data types.

Figure 7: Characteristics of Federally Funded ND/AI Projects



Note: NIH-funded artificial intelligence projects at the intersection of AI and ND most frequently address AD (n=86). They very rarely assess FTD (n=3) or cross more than one ND (n=3).



Note: NIH-funded artificial intelligence projects focused on NDs most frequently employ machine learning (n=70). Neural networks are the least frequently AI technology used in AI/ND projects (n=2). In 12 percent of projects, a specific subtype of AI was not indicated. DL=deep learning, ML=machine learning, NLP=natural language processing, NN=neural networks.

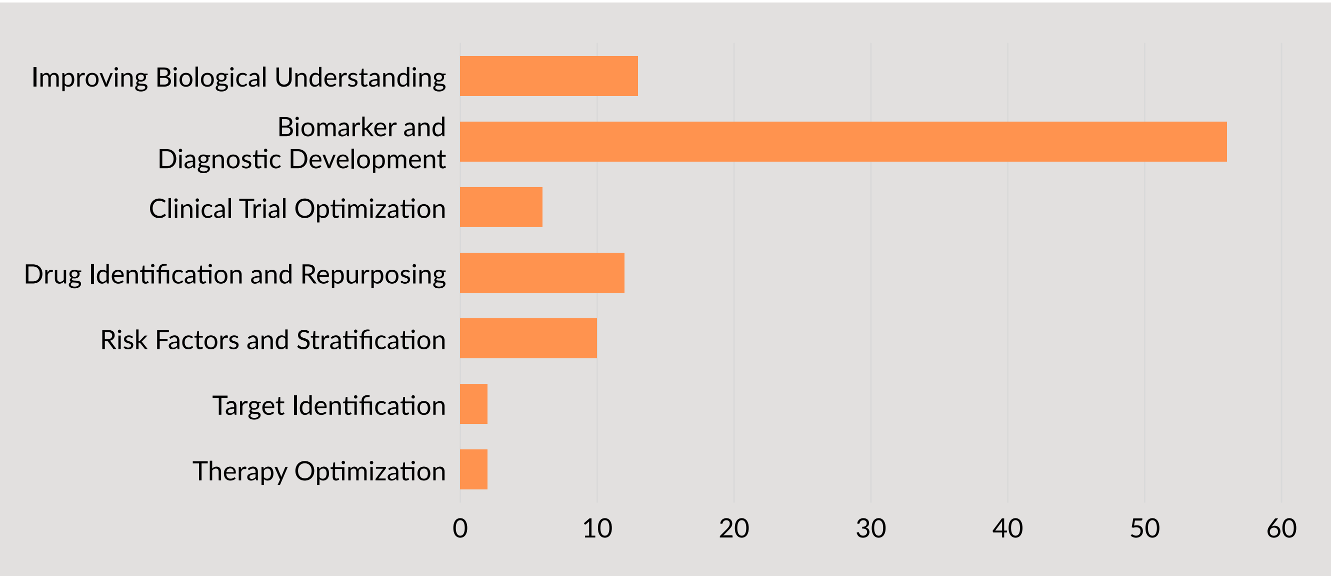
Source: Milken Institute analysis of reporter.nih.gov (2024)

Notably, only three projects (3 percent of the total) address more than one neurodegenerative disease (pan-ND). Two of these projects are focused on building research tools that can be implemented across dementias. The third is focused on developing a method to quantify cognitive function in AD, FTD, and a progressive type called dementia with Lewy bodies (DLB).

AI has the potential to drive biological understanding across complex NDs by integrating massive, multimodal datasets (e.g., genomics, proteomics, neuroimaging, cognitive assessments, movement measures). For example, AI can perform tasks like pattern recognition and prediction to identify signatures of disease. These signatures may be shared across the ND spectrum (i.e., pan-ND signatures), specific to a subset of diseases, specific to a single disease, specific to a subset of patients within a disease, or unique to individual patients. Using AI to tease apart these nuances will accelerate progress in areas of opportunity to drive ND precision medicine, including (1) identifying mechanisms for disease prevention, (2) ensuring early and accurate diagnosis, and (3) developing and assigning personalized treatment strategies for all patients with NDs.

In the last decade, no federally funded research projects have aimed to utilize AI to pursue the implementation of precision medicine across more than one ND. Over half of all projects in this analysis (n=56) are focused on the development of biomarkers and/or diagnostics required for precision medicine (Figure 8). Target identification and therapy optimization are not areas of especially strong investment at this time. However, rapid advancement in the understanding of disease mechanisms, risk factors, and patient stratification will lead to the creation of biomarkers and diagnostics that may help to enable better drug development in the near future.

Figure 8. Federally Funded Project Contributions to Precision Medicine Goals



Source: Milken Institute analysis of reporter.nih.gov (2024)

In addition to the extramural project funding included in the analysis above, program grants and cooperative agreements focused on supporting AI in ND research account for $13 million and $31 million, respectively (see the Appendix for a listing of these grants).

As ethics is a critical consideration across AI in ND research, SPARC performed an additional analysis of NIH funding, including an “ethics” search term. This search revealed that very limited federal funding supports research on ethics in relation to AI and NDs.

Research projects funded at the intersection of ethics, AI, and NDs account for less than $500,000 of funding. Most funding efforts within this space support training programs that integrate an ethics component. Additional funding is committed to centers at individual institutions that support research efforts within the institution. The most significant source of funding is just over $9 million over fiscal years 2022 and 2023 to support the Bridge2AI Voice program, which is building an ethically sourced bioacoustics database to understand how voice may be applied as a biomarker of health.

Private Funders Supporting Research at the Intersection of AI and ND Research

Private funding tends to focus on a specific disease area, platform, or technology. In ND programs, even when AI-focused grants are funded, they usually represent only a small portion of the overall funding portfolio. Likewise, platform- or technology-focused foundations will rarely emphasize a single disease area but will instead apply the technology across a range of applicable diseases. There are four nonprofit organizations for which the overlap between AI and ND research is particularly strong or that have a stated goal that specifically notes this intersection (Table 3).

Table 3. Nonprofit Organizations Supporting AI in ND Research

Organization	Organization Overview	Project Types
The 10,000 Brains Project	The 10,000 Brains Project is a 501(c)(3) philanthropic initiative that seeks to accelerate the use of AI in the fight against ND. The 10,000 Brains Project provides leadership, expertise, and financial support to ensure that the medical research community can rapidly adopt this exciting new technology for maximum impact.	The 10,000 Brains Project conducted a comprehensive assessment of the current state of AI in neurodegeneration research. This eight-month project was a rigorous, unbiased, due-diligence step that identified key gaps in the current ecosystem, potential barriers to progress, and specific areas where funders can have the greatest impact. Projects have not yet been initiated in accordance with the strategy.
Allen Institute	The mission of the Allen Institute is to understand the principles that govern life and advance health. The Allen Institute's creative and multidimensional teams focus on answering some of the biggest questions in bioscience. They accelerate foundational research, catalyze bold ideas, develop tools and models, and openly share their science to make a broad, transformational impact on the world.	The Allen Institute supports large-scale, multidisciplinary project teams who, within the neurodegenerative disease space, are leveraging computational biology in addition to other techniques to develop innovative approaches to combat age-related dementia.
Chan Zuckerberg Initiative (CZI)	CZI was founded in 2015 to help solve some of society's toughest challenges. In its work in science, in education, and within communities, CZI pairs technology with grantmaking, impact investing, and collaboration to accelerate the pace of progress toward its mission. CZI works at the intersection of philanthropy and technology while supporting movement and capacity-building to achieve progress across focus areas with a diversity, equity, and inclusion lens.	The CZI Neurodegeneration Challenge Network brings new people into the field, encourages communication among researchers studying different diseases, and supports interdisciplinary networks of scientists, physicians, engineers, and computational scientists. Less than 1 percent of the current funded portfolio applies AI to ND research. CZI is currently developing its strategy to engage AI in ND basic science research.
International Neurodegenerative Disorders Research Center (INDRC)	Founded in 2021, INDRC brings together leading experts from the fields of ND and AI to achieve breakthroughs in the treatment and prevention of AD and other NDs.	Active and planned research projects: • Center for Artificial Intelligence and Quantum Computing in System Brain Research • Detecting unrecognized cognitive impairment and dementia • Assessing the issue of drug responders/nonresponders in clinical trials and drug repurposing

Source: Milken Institute (2024)

A non-exhaustive list of other nonprofit organizations that fund data generation, tool development, and/or research at the intersection of AI and ND can be found in the Appendix.

OPPORTUNITIES FOR PHILANTHROPY TO ACCELERATE ND RESEARCH

The daunting complexity within and across NDs requires the scientific community to develop fundamentally new approaches that can augment the understanding of disease biology and patient subgroups. Most ND research and development efforts take place in silos with a singular focus on a specific ND. AI can break down these silos and identify the key nuances, commonalities, and differences among ND patients that will improve diagnosis, support the prediction of prognosis, and aid in developing novel treatment strategies. Although federal funding for AD research has increased substantially in recent years, NDs such as FTD, ALS, and PD have not seen similar increases. As importantly, there are very few federally funded projects that leverage AI across multiple NDs—and most are not focused on AI in pursuit of precision medicine.

These funding gaps present a range of opportunities for philanthropy to supplement and complement traditional funding strategies. Because philanthropic investment is flexible and risk-tolerant—able to fund collaborative and aspirational projects and promote innovation—there is a significant opportunity for philanthropy to reshape the AI/ND research landscape by establishing sorely needed infrastructure and supporting the development of new skills through cross-training. There is also an important role for philanthropy in forming new collaborative networks that bring neuroscientists, data scientists, computational biologists, ethicists, and industry players to the table to pursue common goals. SPARC has identified four particularly important areas where philanthropies can help to break down silos and accelerate the efficient implementation of AI in ND research.

Data Quality, Infrastructure, and Access

Precision medicine requires enough data to account for biological differences among members of a population to resolve specific biological signatures. Before researchers can apply precision medicine across NDs, the field needs high-density, multidimensional, and longitudinal datasets from large, diverse populations. The ability to process multimodal, disease-agnostic data will improve scientific understanding of the biology of neurodegeneration, distinguishing the contributors that might be targetable across and within individual NDs. These diseases are heterogeneous and complex; novel data management allows researchers to embrace this complexity by identifying both shared and distinctive pathological features of various NDs.

Specifically, the ND field would benefit from a complete understanding of the factors that differentiate neuronal vulnerability across NDs and mechanisms critical for progressive cell death. The integration of multiple data types from across NDs—e.g., clinical, imaging, molecular—has the potential to unravel these biological mechanisms driving progress toward addressing areas of critical need, including disease prevention, early and differential diagnosis, target identification for drug development, and discovery of companion biomarkers to promote precision medicine.

The ND data landscape is complex and constantly expanding. Researchers have indicated that finding useful datasets is one of the most significant and earliest challenges to applying AI to ND research, especially across diagnoses. In addition to making data findable, accessible, interoperable, and reusable, metadata (that fully describe each data set) are critical to using AI effectively for precision medicine. Data silos must be broken down, and any data collected moving forward should be robust, including annotations that capture their context and provenance.

The opportunities outlined below aim to resolve issues with current datasets so that they can be more effectively leveraged to the greatest impact. They also describe the generation of new datasets that will fill data gaps and set the standard for prospective data collection for use in AI.

Opportunity 1. Ensure Data Accessibility and Quality and Develop Supportive Infrastructure

Need: Data are siloed, and access is limited.

Opportunity: There is an overwhelming consensus that data should be shared, with more funders making open data a requirement for their grantees. However, within the current incentive framework at institutions, data sharing may not be seen as a high priority. It requires significant time and effort to prepare and distribute data, which is challenging for investigators, even if they want to share their data. This also means that the development of user-friendly data portals and sharing infrastructure have not been a high priority for funders or researchers. Importantly, even when data are made usable and shared, end-users are faced with the challenge of identifying the appropriate data to enable their studies.

All funders have a role to play in ensuring that the data collection efforts they support foster a scientific environment that allows fair accessibility. Across ND, many funders actively support clinical and human research data-collection efforts. While many of these initiatives have a single disease focus, working to ensure that the data are collected and stored in a way that allows the broader research community to access and reanalyze the data will increase its scientific value.

An even more significant opportunity that needs to be considered early and often is how global data-sharing platforms can be developed and accessed. Data diversity can be assured only if there are solutions for storing data from diverse populations around the world, including lower-resourced countries. Moreover, the system should not only enable data submission but also empower global data access so that all talented researchers can access the data needed to answer their research questions. This requires funders to work with grantees and partner funding organizations focused on other NDs to develop and use platforms that allow global sharing. It also requires consent from study participants for their data to be used in broader, cross-disease, cross-institutional, and international research.

Opportunity 2. Expand Neurodegenerative Disease Data Diversity

Need: There are diversity, disease, and data-type gaps in the existing ND data landscape.

Opportunity: The data ecosystem for NDs is constantly changing. Emphasis should be placed on collecting new data that will fill specific gaps better to enable AI in cross-ND studies. Rare NDs, more diverse participants, and novel data types should be prioritized (Table 4). Data collectors do not necessarily need to increase the number of cohort studies, since they may be able to fill data gaps in existing studies that are built around standardized data collection and sharing principles. New data can be gathered according to specified standards that bridge the divide between the promise of computing power and the provision of high-quality data.

The current paradigm of ad-hoc aggregation and curation of data needs to be replaced with what Chung and Jaffray (2021) referred to as a "metadata supply chain," in which:

- observations are made in context,
- the quality of an observation is captured in context,
- provenance links insights to observations, and
- data governance is granular and consistent with the needs of the demand.

Funding with an expectation of meeting set standards in data collection and sharing will increase the data's utility.

Table 4: High-Priority Data Needs

<table>
<tr><th>Data Category</th><th colspan="3">Data Opportunities</th></tr>
<tr><td>Rare ND Data</td><td colspan="3">Diseases that either meet the definition of a rare disease, affecting fewer than 200,000 people in the US, or for which insufficient data are collected and shared. This can include, but is not limited to:
Amyotrophic lateral sclerosis
Ataxia telangiectasia
Cockayne syndrome
Creutzfeldt-Jakob disease
Familial dysautonomia
Huntington disease
Mucopolysaccharidosis type III
Niemann-Pick disease type C
Progressive supranuclear palsy</td></tr>
<tr><td>Participant Diversity</td><td>Participants from regions including, but not limited to:
Africa
Asia
Latin America</td><td>Participant representation from the US
Disadvantaged groups
Low socioeconomic status
Women</td><td>Disease status
Earlier stages (presymptomatic, initial symptoms, etc.)
Healthy controls</td></tr>
<tr><td>Novel or Underrepresented Data Types</td><td>Tissue data
Blood-based omics
Digital neuropathology
Epigenomics
Metabolomics
Proteomics</td><td>Physiologic signals
Breath
Eye movements
Voice
Wearables</td><td>Patient data
Exposures
Imaging
Longitudinal clinical data</td></tr>
</table>

Source: Milken Institute (2024)

Training an Interdisciplinary Workforce

In ND research, the use of AI requires an uncommon combination of interdisciplinary expertise across neuroscience, biology, computer science, and data science. Not enough individuals are being trained across these diverse skill sets. Further, collaborations between laboratories that perform computational research ("dry labs") and traditional "wet labs" with the capabilities to validate AI-based discovery in cellular and animal systems are difficult to develop and sustain. This is due to challenges in identifying appropriate cross-discipline funding and partners who have the time and expertise to support these new types of projects.

Philanthropic funding can help expand interdisciplinary training programs and build new cohorts of AI experts in the life sciences. An influx of individuals with this expertise will demonstrate the value of cross-disciplinary AI work and encourage institutions to develop positions and training infrastructure of their own.

Opportunity 3. Bridging Training in Neuroscience and Computational Biology

Need: There are too few individuals with expertise that includes computational biology and neuroscience, limiting meaningful AI work in NDs and hindering the development of a case for institutions to support such expertise.

Opportunity: Universities are experimenting with various initiatives to further encourage interdisciplinary studies, but additional, formalized programs are needed to address the challenge of building a workforce that effectively spans ND and computational biology. Funders can build or leverage an existing training framework to target specific career stages.

A key priority of this training at the baccalaureate or master's level is integrating projects within the coursework that allow students to gain firsthand experiences with using AI to answer research questions. Supporting trainees at this level would expand the pipeline of individuals with cross-disciplinary expertise and an interest in ND.

For doctoral students and postdoctoral fellows, there is a unique and important opportunity to integrate AI training into active ND research projects. Training should focus on providing these young investigators with cross-laboratory experiences that allow them to utilize skills and answer questions from their primary labs through supported time in laboratories focused on work in a different discipline. For example, funders can support young neuroscientists who have developed a hypothesis in a traditional wet lab to further test their ideas as part of a collaborative project in a computational laboratory.

Multiyear support for independent researchers within five years of starting their own labs could help researchers solidify their cross-disciplinary expertise and ensure that investigators with strengths across computational biology and neuroscience are encouraged to remain in the academic environment. Funders could provide support at this stage to make academic pay scales more competitive with industry and incentivize research that spans AI and ND.

In addition to formal training, interdisciplinary expertise needs to be brought into the current research ecosystem. Funding to support long-term, collaborative work and cross-pollination of expertise will increase the use of AI in ND research and build the case for the utility of interdisciplinary expertise in addressing complex research problems.

Artificial Intelligence Implementation

Analytical tools that can rapidly process high-volume data streams into interpretable findings are essential to delivering precision recommendations for patients with NDs. Rapidly integrating, analyzing, and understanding such data from various sources is possible only with the use of computational tools.

Opportunity 4. Support AI-Enabling Resource Development

Need: Existing funding mechanisms do not sufficiently support computing resources or the development of AI tools; a lack of validation or maintenance can limit the utility of promising tools.

Opportunity: While data availability and a skilled workforce are important prerequisites, the advancement of AI in ND ultimately depends on the development, validation, and ongoing availability of powerful new AI-based tools with demonstrated translational and clinical impact. Success will depend on the ability of researchers and clinicians to access and trust the outputs of those algorithms so they can be certain that they are applying the most appropriate approaches.

Powerful computing infrastructure and funding support are needed to process the tremendous amount of data required for the application of AI at scale. Infrastructure will also be necessary to store, maintain, and share AI models with the field. This infrastructure should be flexible and scalable enough to adapt to future changes that could impact the way data or technologies are used in research or the delivery of patient care.

Philanthropy is uniquely positioned to build partnerships and support the development of an AI-centered ND research ecosystem. To achieve this, philanthropy can develop and promote a federated data ecosystem that is designed to meet the needs of the global AI community. Philanthropy can also provide financial support for computing and validation studies for new tools.

Validation studies are an area of particular need. Computational biologists develop algorithms using clinical or experimental data (from patients or model systems). Validation of computational models usually means evaluating their performance in datasets beyond the one used for the original training cycle. Computational biologists often have the expertise to develop algorithms but may lack the relationships or access to data from disease-model systems to evaluate these algorithms across a variety of data sets.

Assessment of the validity of an AI algorithm to predict cellular processes is critical to reaching the ultimate goal of applying these algorithms in a clinical setting to impact patient care. Philanthropic funding can support projects that bridge computational labs and biological research labs and stimulate collaboration across these domains of expertise.

Ethics Standards and Support

The massive amounts of patient data required, as well as the iterative nature of AI, increase the need for attention to the ethical practice of AI in neurodegeneration. This must include careful monitoring of data stewardship, the development of algorithms, and the utilization of AI in research and clinical settings. Key ethical challenges associated with the use of AI for research and clinical care include patient privacy, informed consent, data ownership, data bias and fairness, methodological transparency, and accountability when AI is for patient-facing applications. Consistently incorporating ethics assessments will enable challenges to be addressed as early as possible and build trust in AI.

Opportunity 5. Protect People and Their Data

Need: Research participants provide their data with an understanding that such material will be used in an ethical manner, but ethics standards are often developed as an afterthought.

Opportunity: Ethical data collection recognizes that every data point comes from a human being. It acknowledges that the research could not be conducted without participant data and makes every effort to protect participants. Such protection begins with an effective informed-consent process. Existing consent models need to be reevaluated to understand the factors that are applicable to the adoption of AI tools and those that will need to be changed. Philanthropy can play a leadership role in producing standardized consenting tools that enable the use of patient data in AI applications for academic, industry, and medical use and are easily understood by patients.

Moreover, privacy breaches are an increasingly common challenge in the age of big data and AI. In some cases, it has even become possible to re-identify anonymous individuals in large datasets. Data privacy and security will remain serious ongoing concerns for members of the general public. Philanthropists can support the establishment of new methods to assess and mitigate risk in both academic research and the delivery of care. Philanthropies can play an important leadership role by stipulating that any work they fund in data science or AI meets the highest ethical standards and includes proactive input from trained ethicists.

Opportunity 6. Ensure Equitable AI Benefits

Need: A significant concern associated with AI application to biomedical research is that the results will preferentially benefit only a subset of the population.

Opportunity: If AI-based research and products are not reviewed with careful attention to ethics, the resulting tools may be biased and end up exacerbating existing imbalances in socioeconomic class, ethnicity, religion, gender, disability, or sexual orientation. Bias disproportionately affects disadvantaged and underrepresented populations, who are more likely to be subjected to algorithmic outputs that are less accurate or underestimate their need for care. Solutions for identifying and eliminating bias are critical for developing generalizable and fair AI technologies. Currently, funding that supports systemic ethics research is limited. Philanthropy has the flexibility to proactively support ethics research that is optimized for equitable outcomes and aggressively addresses historical disparities.

CONCLUSION

Artificial intelligence is rapidly impacting the biomedical space, increasing drug development efficiency, improving clinical care, and revolutionizing how the basic biology of complex diseases is understood. This Giving Smarter Guide summarizes the current and emerging trends at the intersection of artificial intelligence, neurodegenerative disease, and precision medicine. The proposed strategic philanthropic opportunities have the potential to revolutionize the diagnosis, treatment, and care of patients. The recommendations reflect spaces where major advances are needed and where philanthropy is uniquely positioned to take on a leadership role.

Artificial intelligence has undoubtedly generated a great deal of hype and even some misguided optimism among researchers and the general public. There will certainly be many setbacks and disappointments as the neurodegeneration research community gains more real-world experience in using AI to understand disease and treat patients. At the same time, there is little doubt that AI is enabling researchers to take exciting new approaches that were unimaginable just a few years ago. Researchers may finally have the tools needed to untangle the daunting complexities of neurodegenerative disease and match unique individuals to the right combinations of treatments. However, this once-in-a-generation opportunity to solve neurodegeneration will not come to fruition without strategic investments and ethical leadership from the philanthropic sector.

APPENDIX

Federal Funding Analysis Methods

NIH RePORTER

A search was performed within the NIH RePORTER database for projects from FY2014 to FY2023 that contained any of 56 possible pairings of seven “technical” terms (e.g., artificial intelligence) and eight “medical” terms (e.g., “neurodegenerative disease”) in the Project Title or Abstract.

Technical Terms	Medical Terms
Artificial Intelligence	Neurodegenerative Disease
Machine Learning	Alzheimer’s Disease
Deep Learning	Parkinson’s Disease
Generative AI	ALS
Large Language Models	Amyotrophic Lateral Sclerosis
Natural Language Processing	Lou Gehrig’s Disease
Neural Networks	FTD
	Frontotemporal Dementia

All related data were downloaded, the results sorted by Project Number and Project Title, duplicate Project Numbers were identified, and duplicates were removed.

Next, conditional formatting was applied to identify Project Titles that contained any one of the 56 possible pairs of terms *or* any of the 15 individual search terms noted above. All projects containing “ALS” as part of a word (e.g., “trials”) in the Project Title and not a stand-alone term were removed. Any projects that contained one or more of the 56 technical/medical word pairs in the Project Title were flagged for inclusion in the analysis. The remaining Project Titles (and where the project title was not definitive, the Project Abstract) were reviewed to determine which projects focused on the intersection of AI and ND. The final analysis assesses projects that include at least one technical and one medical term.

Congressionally Directed Medical Research Programs Database

All Congressionally Directed Medical Research Programs (CDMRP) projects from FY2014 to FY2023 were downloaded to account for the variability in search results based on the exact phrasing of queries (a problem that was not encountered with the NIH RePORTER database). All data were downloaded and sorted by Project Number and Title, and duplicate Project Numbers were removed. Of note, data downloaded from the CDMRP database do not include project abstracts, so projects at the intersection of AI and ND had to be identified by title.

Conditional formatting was applied to identify Project Titles that contained any one of the 56 possible pairs of terms or any of the 15 individual search terms noted above. All projects containing "ALS" as part of a word (e.g., "trials") in the Project Title and not a stand-alone term were removed. Any projects that contained one or more of the 56 technical/medical word pairs in the Project Title were flagged for inclusion in the analysis. The remaining Project Titles were reviewed to determine which projects focused on the intersection of artificial intelligence and neurodegenerative disease. The final analysis assesses projects that include at least one technical and one medical term.

Program Grants and Cooperative Agreements at the Intersection of AI and ND

Program grants are provided by the NIH for the support of a broadly based, multidisciplinary, often long-term research program that has a specific major objective or a basic theme. A program generally involves the organized efforts of relatively large groups, members of which are conducting research projects designed to elucidate the various aspects or components of this major objective. Each project supported through this mechanism should contribute or be directly related to the common theme of the total research effort. The NIH has provided $13 million via two program grants relating to AI/ND research in the last decade:

- **Stanford Alzheimer's Disease Research Center**—A four-year, $3,015,406 grant to develop a shared resource to facilitate and enhance research on AD and the spectrum of cognitive impairment associated with Lewy body pathology.
- **Massachusetts AI and Technology Center for Connected Care in Aging and Alzheimer's Disease**—A five-year, $9,966,452 grant to support a core that identifies, selects, advises, and helps to translate innovative pilot projects that use emerging AI-enhanced technologies to address clinically and societally unmet needs in AD.

Cooperative agreements involve high-priority research areas that require substantial involvement from the NIH program or scientific staff. Nine cooperative agreements totaling $31 million have been awarded in the last decade for the following projects:

- AIM-AI, an Actionable, Integrated and Multiscale genetic map of Alzheimer's disease via deep learning ($1,278,119, FY2023)
- Alzheimer's MultiOme data repurposing: artificial intelligence, network medicine, and therapeutics discovery ($2,389,614, FY2021–2023)
- Analytic methods for determining multimodal biomarkers for Parkinson's disease ($295,098, FY2014)
- Artificial intelligence strategies for Alzheimer's disease research ($3,595,852, FY2022–2023)
- Assessing Alzheimer's disease risk and heterogeneity using multimodal machine-learning approaches ($1,892,941, FY2021–2023)
- Causal and integrative deep learning for Alzheimer's disease genetics ($2,120,056, FY2021–2023)

- Genetics of deep learning-derived neuroimaging endophenotypes for Alzheimer's disease ($4,872,066, FY2021–2023)
- Machine-learning model validation for AD/ADRD ($378,750, FY2018)
- Ultrascale machine learning to empower discovery in Alzheimer's disease biobanks ($14,470,620, FY2020–2023)

Philanthropic Funders Whose Missions Align with AI/ND Research

The 10,000 Brains Project is a 501(c)(3) philanthropic initiative that seeks to accelerate the use of AI in the fight against neurodegenerative diseases. The 10,000 Brains Project provides the leadership, expertise, and financial support needed to ensure that the medical research community can rapidly adopt this exciting new technology for maximum impact.

The Allen Institute is an independent nonprofit bioscience research institute aimed at unlocking the mysteries of human biology through foundational science that fuels the discovery of new treatments and cures. Initially founded to map gene activity in the mouse brain, the institute's work quickly expanded to catalogue the constellation of cells and their connections in the mouse and human brain, along with deep research into the human immune system; inner workings of our cells; and identifying transformative, paradigm-shifting science around the world.

The Allen Institute for Artificial Intelligence (Ai2) is a nonprofit research institute founded in 2014 with the mission of conducting high-impact AI research and engineering in service of the common good. Headquartered in Seattle on the shores of Lake Union, Ai2 employs the world's best scientific and engineering talent in the field of AI, attracting individuals of varied interests and backgrounds from across the globe. Ai2 prides itself on the diversity and collaboration of its team and takes a results-oriented approach to complex challenges in AI. Ai2 has undertaken several ambitious projects to drive fundamental advances in science, medicine, and conservation through AI.

The Brain Research Foundation, as the nation's oldest brain research organization, has seen the impact that undesignated giving can have. Brain Research Foundation grants fund a broad scope of projects that help scientists explore a wide range of neurological disorders. The Brain Research Foundation exists to accelerate discoveries of the human brain by funding pioneering neuroscience research.

Chan Zuckerberg Initiative (CZI) was founded in 2015 to help solve some of society's toughest challenges. Across its work in science education and within communities, CZI pairs technology with grantmaking, impact investing, and collaboration to accelerate the pace of progress toward its mission. CZI works at the intersection of philanthropy and technology while supporting movement and capacity building to achieve progress across focus areas with a diversity, equity, and inclusion lens.

Cure Alzheimer's Fund is a nonprofit organization dedicated to funding research with the highest probability of preventing, slowing, or reversing Alzheimer's disease. Frustrated with the slow pace of research, the founders of the Cure Alzheimer's Fund applied their experience in venture capital and corporate start-ups to build an organization specifically designed to accelerate research, make bold bets, and eradicate the disease.

The Dana Foundation explores the connections between neuroscience and society's challenges and opportunities, working to maximize the potential of the field to do good. As of 2022, Neuroscience & Society became the Dana Foundation's dedicated focus. It embodies the spirit of open inquiry, collaborative research, and multidisciplinary thinking in service of the well-being of all people. The Dana Foundation advances neuroscience that benefits society and reflects the aspirations of all people. The foundation explores the connections between neuroscience and society's challenges and opportunities, working to maximize the field's potential to do good.

Gladstone Institutes is an independent, nonprofit life-science research organization located in the epicenter of biomedical and technological innovation in the San Francisco Bay Area. Gladstone has created a research model that disrupts how science is done, funds big ideas, and attracts the brightest minds to overcome unsolved diseases through transformative biomedical research.

International Neurodegenerative Disorders Research Center (INDRC), founded in 2021, brings together leading experts from the fields of ND and AI to achieve breakthroughs in the treatment and prevention of AD and other NDs.

The Michael J. Fox Foundation for Parkinson's Research (MJFF) is dedicated to finding a cure for Parkinson's disease through an aggressively funded research agenda and ensuring the development of improved therapies for those living with Parkinson's today. The MJFF exists for one reason: to accelerate the next generation of PD treatments, which means identifying and funding projects most vital to patients; spearheading solutions around seemingly intractable field-wide challenges; coordinating and streamlining the efforts of multiple, often disparate, teams; and doing whatever it takes to drive faster knowledge turns for the benefit of every life touched by PD.

The **New York Stem Cell Foundation** (NYSCF) aims to accelerate cures for the major diseases of our time through stem cell research. The NYSCF pursues its mission through three main avenues:

1) Accelerating Stem Cell Science at the NYSCF Research Institute: NYSCF Research Institute is an independent nonprofit accelerator that bridges the ongoing gap between research institutions and pharmaceutical and biotech companies by reducing the cost, time, and risk that historically have inhibited the development of new treatments and cures.

2) Supporting Leading Researchers Worldwide: NYSCF champions and convenes many of the world's top scientists and the broader stem-cell community with Postdoctoral Fellowship and Investigator Programs, as well as an annual conference and Initiative on Women in Science and Engineering.

3) Advancing STEM Education for Everyone: NYSCF democratizes access to science education for students and the public through the NYSCF Academy for Science and Society, which encompasses an internship program, Summer Immersive for high school students, lab tours, event programming, and more.

The **Rainwater Charitable Foundation** (RCF) is dedicated to sustainable solutions across all areas it serves. Over the years, RCF's funding has evolved to serve North Texas education and family economic security, medical research focused on neurodegenerative diseases, and initiatives in East Africa. RCF is guided by values of innovation, accountability, and collaboration. Members believe in using innovative solutions to tackle complex problems and that grantmaking should be held accountable for making a positive difference in people's lives. RCF strives to collaborate with like-minded organizations to achieve shared goals and create lasting change.

Representative Collaborative Data Networks

Data Collaboratives	Overview	Patient/Study Population	Dataset/Cohort Overview
Accelerating Medicines Partnership Parkinson's Disease	The Accelerating Medicines Partnership Parkinson's Disease (AMP PD) is a public-private partnership between the National Institutes of Health, multiple biopharmaceutical and life sciences companies, and nonprofit organizations. Managed through the Foundation for the NIH, AMP PD aims to identify and validate the most promising biological targets for therapeutics for Parkinson's disease.	Parkinson's disease	Cohorts include Global Parkinson's Genetics Program; Harvard Biomarkers Study; MJFF and NINDS BioFIND study; MJFF and NINDS Study of Urate Elevation in Parkinson's Disease, Phase 3; MJFF LRRK2 Cohort Consortium; NINDS Parkinson's Disease Biomarkers Program; MJFF Parkinson's Progression Marker Initiative; NIA International Lewy Body Dementia Genetics Consortium; Genome Sequencing in Lewy body dementia case-control cohort; NINDS Study of Isradipine as a Disease Modifying Agent in Subjects with Early Parkinson Disease, Phase 3.
Accelerating Medicines Partnership Program for Alzheimer's Disease	The Accelerating Medicines Partnership Program for Alzheimer's Disease (AMP AD) program is a precompetitive partnership among government, industry, and nonprofit organizations to transform the current model for developing new diagnostics and treatments for Alzheimer's disease.	Alzheimer's disease	The AMP AD dataset includes 68 cohorts representing more than 200,000 individuals. Data types include gene expression, proteomics, metabolomics, epigenetics, imaging, electrophysiology, clinical, and more. Brain, blood, induced pluripotent stem cells (iPSC), and cell line specimens are also available through AMP AD.

Alzheimer's Disease Data Initiative	The Alzheimer's Disease Data Initiative (ADDI) is a coalition of leading academic, advocacy, government, industry, and philanthropy organizations that recognizes the need for dementia researchers to find easier ways to share unpublished data, analytical tools, and scientific findings. These partners work together to accelerate progress toward new diagnostics, treatments, and cures in Alzheimer's disease and related dementias.	Alzheimer's disease and related dementias	ADDI has 15 cohorts and data from 21 clinical trials. Datasets include (but are not limited to) Alzheimer's Disease and Healthy Aging Data, Critical Path for Alzheimer's Disease Database, PREVENT Dementia Research Programme, European Prevention of Alzheimer's Dementia Project, the English Longitudinal Study of Ageing, and the GERAS Study.
Alzheimer's Disease Genetics Consortium	The Alzheimer's Disease Genetics Consortium is funded by a grant from the National Institute on Aging, an $18.3 million five-year research grant to conduct genome-wide association studies to identify genes associated with an increased risk of developing late-onset Alzheimer's disease.	Late-onset Alzheimer's disease	Whole genome sequence projects include the AGES Icelandic cohort, the Mexico 10/66 project, and TARCC Hispanic samples.
Alzheimer's Disease Sequencing Project	The Alzheimer's Disease Sequencing Project (ADSP) was initiated to understand the genetic architecture of Alzheimer's disease and related dementias. This project involves a large number of study participants from ethnically diverse populations and will capture and analyze common and rare genetic variation.	Alzheimer's disease and related dementias	The samples for the ADSP are obtained from well-characterized, ethnically diverse cohorts and datasets of individuals characterized for AD/ADRD diagnoses with biospecimens (DNA and/or other biomarkers and tissues). ADSP comprises more than 345 investigators and 62 institutions from across the globe. After five data releases, there are now over 136,000 whole genomes and nearly 20,000 whole exomes from 146 cohorts.
Answer ALS Data Portal	Answer ALS builds a clinical and in-depth biological picture of ALS. For each participant, the program generates longitudinal clinical data, whole-genome sequences, and multi-omics (transcriptomics, epigenomics, and proteomics) from induced pluripotent stem cell-derived motor neurons. These data and links to the associated bio-resources (patient-derived biofluids, iPSC lines) are made available to the global research community through the Answer ALS Neuromine Data Portal.	Amyotrophic lateral sclerosis	Answer ALS has collected clinical data on 1,200+ participants from both control and neurodegenerative disease populations. The current dataset totals more than 100 TB of data, including epigenomic, proteomic, and transcriptomic data.

Cohort Studies of Memory in an International Consortium	Cohort Studies of Memory in an International Consortium (COSMIC) is an international consortium to combine data from population-based longitudinal cohort studies to identify common risk factors for dementia and cognitive decline.	Aging, dementia, and cognitive decline	COSMIC has brought together 47 cohort studies of cognitive aging from 35 countries across six continents, with a combined sample size of almost 150,000 individuals.
Davos Alzheimer's Collaborative	The Davos Alzheimer's Collaborative (DAC) is building global cohorts to advance understanding of Alzheimer's among diverse populations. The data will provide the foundation for identifying new biomarkers and developing targeted treatments that work for people worldwide.	Alzheimer's disease	DAC has engaged cohorts from 26 countries to diversify the understanding of Alzheimer's and develop targeted treatments. So far, DAC has secured participation from 15 cohorts, yet to be announced.
Dementias Platform Australia	The Centre for Healthy Brain Ageing at the University of New South Wales Sydney is leading the establishment of Dementias Platform Australia (DPAU). DPAU will facilitate data sharing between Australian and international dementia researchers, significantly enhancing productivity and reusability of data from contributing research studies. Joining data across studies and modalities within one virtual space allows for the large samples and multimodal analyses required in the "omics" era.	Dementia	The DPAU Data Portal will bring together records of more than 150,000 people in 44 international population studies in a free-to-access resource. Current cohorts include Cohort Studies of Memory in International Consortium, Memory and Ageing Study, Sydney Centenarian Study, and Older Australian Twins Study.
Dementias Platform UK	Dementias Platform UK (DPUK) is a partnership linking 29 public, private, and third-sector organizations, with core funding from the Medical Research Council. Based at Oxford University, DPUK brings together expertise from universities, charities, and pharmaceutical and technology companies to enable crucial breakthroughs in dementia research.	Dementia	The DPUK Data Portal gives access to multimodal data from 63 population and clinical cohort studies representing 48 countries and comprising records of more than 3.5 million people. Available data include lifestyle information, cognitive test results, brain imaging, and genetics.

European Platform for Neurodegenerative Diseases	European Platform for Neurodegenerative Diseases (EPND) is a consortium of multidisciplinary educators, clinicians, researchers, and scientists committed to revolutionizing scientific breakthroughs in the effort to diagnose, treat, and prevent neurodegenerative diseases. With support from the Innovative Medicines Initiative, EPND is building a platform and community to fuel new discoveries in the field.	Neurodegenerative Disease	The EPND catalogue includes an extensive list of international studies across the neurodegenerative spectrum. The catalogue has more than 60 studies with metadata on participants, biosample collections, imaging, and cognitive data representing over 230,000 participants.
Image & Data Archive	The Image & Data Archive (IDA) is run by the Laboratory of Neuro Imaging at the University of Southern California Mark and Mary Stevens Neuroimaging and Informatics Institute. IDA provides tools and resources for deidentifying, integrating, searching, visualizing, and sharing a diverse range of neuroscience data and facilitates collaborations among scientists worldwide. Study investigators maintain complete control over data stored in the IDA while benefiting from a robust and reliable infrastructure that protects and preserves research data to maximize data collection investment.	Neuroscience	The IDA contains data collected from more than 156 studies focused on processes such as development, aging, and the progression of specific diseases. The studies include 102,134 subjects from 167 countries.
Multi-Partner Consortium to Expand Dementia Research in Latin America	Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat) fosters a consortium whose goal is to expand dementia research in Latin America and the Caribbean (LAC). The consortium aims to combine genomic, neuroimaging, and behavioral (clinical, cognitive, socioeconomic) data to improve dementia characterization and identify novel inroads to treat neurodegeneration in diverse populations. ReDLat will develop an innovative, harmonized, and cross-regional approach for two of their most prevalent neurodegenerative disorders: Alzheimer's disease and frontotemporal dementia.	Alzheimer's disease and frontotemporal dementia	ReDLat is establishing a first-in-class cohort anchored in six LAC countries (Argentina, Chile, Colombia, Brazil, Mexico, and Peru), compared to US samples (totaling more than 4,200 participants, including 2,100 controls, 1,050 AD patients, and 1,050 FTD patients), headed by world-renowned leaders in dementia research.

National Alzheimer's Coordinating Center	The National Alzheimer's Coordinating Center (NACC) functions as the centralized data repository, and collaboration and communication hub for the National Institute of Aging's Alzheimer's Disease and Research Centers Program.	Alzheimer's disease	NACC collects data from 37 active Alzheimer's Disease Research Centers across 26 states. The NACC database includes 48,600 participants' data, 7,565 neuropathology exams, and 180,000 clinical assessments.
National Centralized Repository for Alzheimer's Disease and Related Dementias	The goal of the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) is to support research focused on the etiology, early detection, and therapeutic development for Alzheimer's disease and related dementias. NCRAD is a national resource where clinical information and biological materials, such as DNA, plasma, serum, RNA, CSF, cell lines, and brain tissue can be stored and requested. NCRAD currently maintains samples from individuals with Alzheimer's disease and/or related dementias as well as healthy controls.	Alzheimer's disease and related dementias	67 studies with samples are banked at NCRAD, representing 118,000 subjects. 370,000 samples have been distributed by NCRAD for research.
Northeast Amyotrophic Lateral Sclerosis Consortium	The mission of the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) is to rapidly translate scientific advances into clinical research and new treatments for people with amyotrophic lateral sclerosis and motor neuron disease.	Amyotrophic lateral sclerosis	NEALS maintains and makes available the de-identified data from NEALS-affiliated trials, when possible. Currently there are six ALS trial datasets available to share with researchers.

Note: This list is not exhaustive. It includes an overview of some key data collaboratives and platforms that will evolve with time.

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ACKNOWLEDGMENTS

We sincerely thank the experts, scientists, clinicians, physician-scientists, policymakers, and government leaders working across AI, ND research, ethics, and data science for sharing their time and insights. This report would not have been possible without their willingness to speak with us about their work and the field at large. These discussions served as the basis for our understanding of the challenges and opportunity areas at the intersection of AI and ND that philanthropy can help to address.

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