MILKEN INSTITUTE

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Frontotemporal Dementia

A GIVING SMARTER GUIDE

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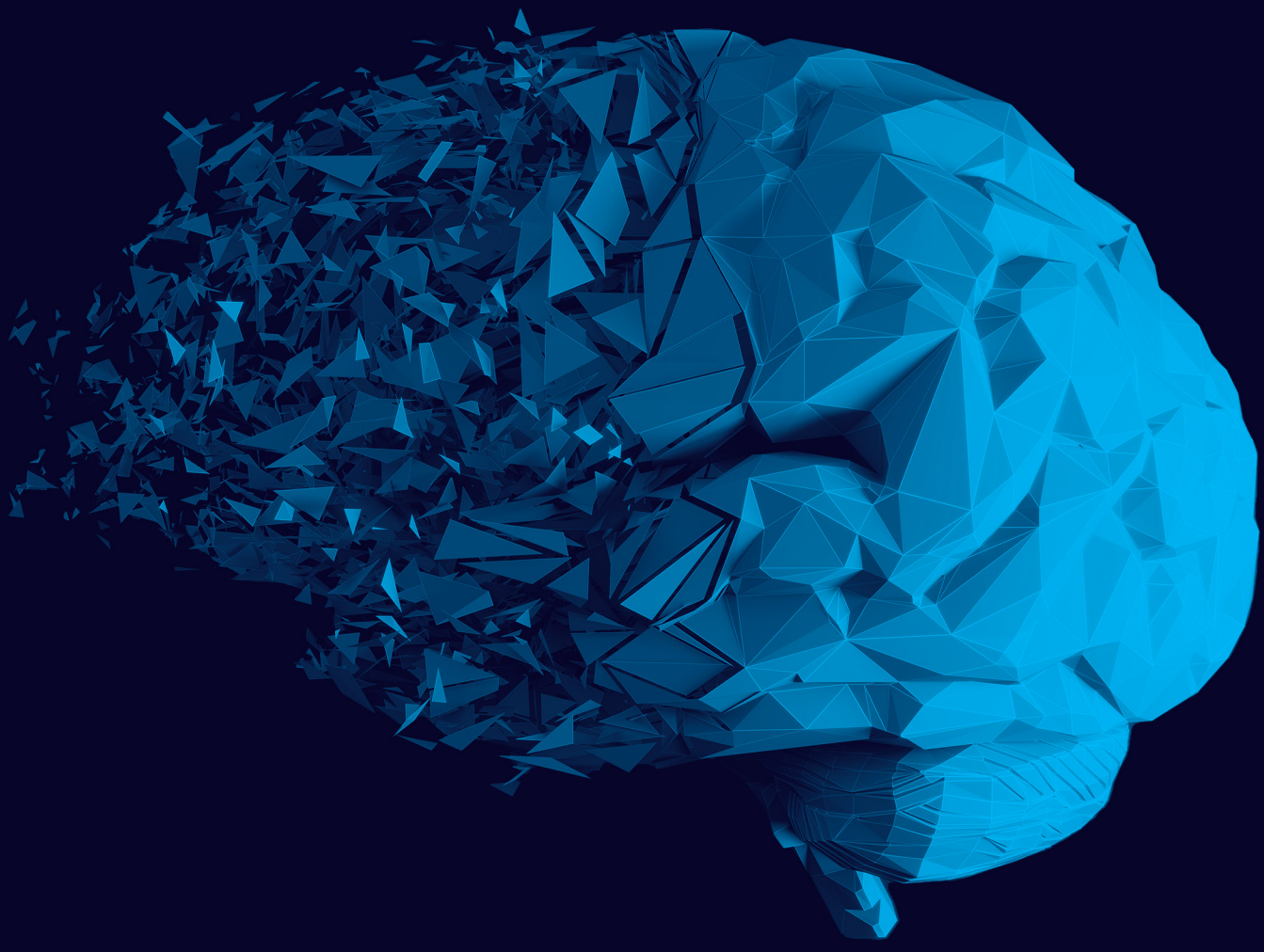


ABOUT US

About the Milken Institute

The Milken Institute is a nonprofit, nonpartisan think tank focused on accelerating measurable progress on the path to a meaningful life. With a focus on financial, physical, mental, and environmental health, we bring together the best ideas and innovative resourcing to develop blueprints for tackling some of our most critical global issues through the lens of what's pressing now and what's coming next.

About MI Philanthropy

MI Philanthropy advances the strategic deployment of philanthropic capital to create a better, more equitable world.

FOREWORD

Five years ago, John Kissick—our father, husband, a brilliant financial mind with a giving spirit—was diagnosed with frontotemporal dementia (FTD). Actually, he was initially diagnosed with Alzheimer's disease. Only months later, after tremendous persistence, was the diagnosis pinpointed to FTD.

At the time, we surmised that the next few years would be challenging. Talk about an understatement. Watching him slip away, month after month and year after year, has been one of the most excruciating experiences of our lives.

FTD is different from what people usually think of when they hear the word "dementia." FTD impacts behavior, personality, and language, with symptoms such as apathy, disinhibition, social withdrawal, loss of empathy, repetitive behaviors, and difficulty speaking. We witnessed our father and husband shift from a charismatic leader who could light up a room of friends, family, and strangers to someone who physically and mentally retreated from life. Now, he spends hours blankly staring, struggling to utter even a single word.

FTD is not for wimps. For families, the diagnosis of FTD is fraught with confusion. It begins with the inability to identify the underlying cause of baffling symptoms. Then, if properly diagnosed, families are forced to grapple with the agonizing fact that FTD treatment is non-existent. Many families, including our own, isolate in search of answers as they grapple with this brutal new reality.

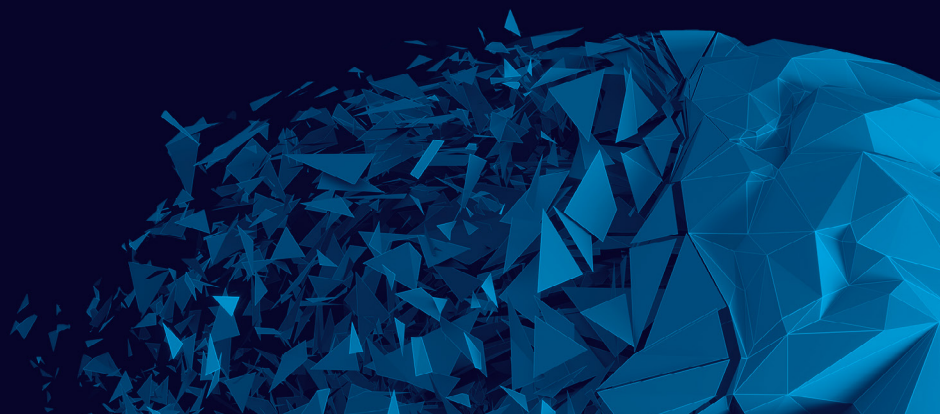
Today, our family is stepping forward to share our story publicly, offering our time and our resources to help beat down the enormous barriers to FTD progress. We are determined to galvanize the resources and leaders needed to make further headway against FTD and, hopefully, all neurodegenerative diseases. Maybe not in time for John, but for all the other families who will be dealing with FTD and related diseases in years to come. We are optimistic they will have an easier journey with a few more tools in the toolbox and a better outlook.

This report is a first step forward. We know that if John were able, he would have led the charge with us to confront and hopefully cure FTD once and for all. He faced the world with brilliance, compassion, determination, humility, and purpose. We follow in his footsteps. If you are reading this report, we know you are of like-mind and spirit, and already part of the team to fight FTD.

Thank you for joining the road ahead.

Kathy, Kasey, and Ryan Kissick

Kissick Family Foundation



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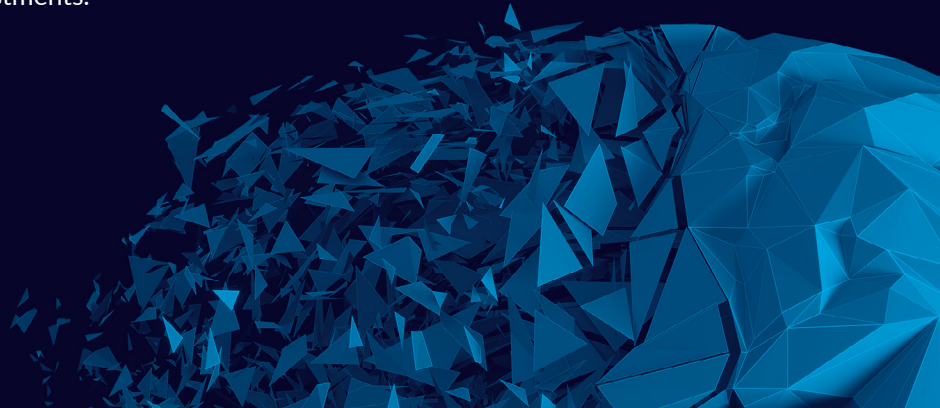
EXECUTIVE SUMMARY

Frontotemporal dementia (FTD), also referred to as frontotemporal lobar degeneration (FTLD), refers to a family of neurodegenerative conditions that cause changes in behavior, mood, executive function, language, memory, and motor function. As many as 30,000 people are living with FTD in the United States at a given time, although the true prevalence is likely much higher as FTD is often misdiagnosed as a psychiatric or another neurodegenerative condition. The average life expectancy for someone with FTD is only about 7.5 years after symptoms begin. FTD symptoms worsen over time due to progressive deterioration of the brain's frontal and temporal lobes, and people living with FTD eventually need full-time care as the disease progresses. Although drugs and other approaches can help manage FTD symptoms, the US Food and Drug Administration (FDA) has not approved any FTD-specific treatments.

Scientific knowledge of FTD has been driven primarily by research into types of FTD that are linked to a genetic mutation, and several therapeutics for genetic FTD are making their way through the clinical trial pipeline. However, much less is known about the majority of FTD cases that cannot be attributed to known genetic mutations, referred to as sporadic FTD. Emerging research suggests that some molecular mechanisms are common to both genetic and sporadic forms of the disease, and additional study is needed to better resolve all types of FTD.

Although overall public funding for neurodegenerative conditions has risen over the past decade, growth in public awareness and funding for adjacent conditions such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS) have outpaced that for FTD. The public funding environment has contributed to an FTD field with fewer researchers focusing on FTD compared to other neurodegenerative conditions, as well as insufficient awareness of FTD within the medical community and the broader public. The FTD community benefits from having several active and committed private funders who have provided critical support, particularly focused on accelerating understanding of and therapeutic options for genetic forms of FTD. However, additional support is needed across the FTD research field to resolve the basic biology of the disease, develop and validate biomarkers that can be used to diagnose and track disease progression more effectively, and develop novel therapeutics for genetic and sporadic forms of FTD. FTD sits at the nexus of multiple neurodegenerative diseases, including Alzheimer's disease and ALS, which means scientific progress in FTD will likely generate breakthrough discoveries for other neurodegenerative conditions.

The Kissick Family Foundation partnered with MI Philanthropy to analyze and understand the state of the FTD research ecosystem and identify where philanthropic investments could be deployed to overcome barriers to scientific progress. This Giving Smarter Guide presents the results of this partnership and outlines four philanthropic opportunities that private funders should leverage to achieve maximum impact for the FTD community. Philanthropy is more nimble, more flexible, and more risk-tolerant than other forms of research capital, enabling rapid testing and advancement of novel and creative ideas. Philanthropic funding can signal to other private and public funders where greater support is needed, galvanizing activity and catalyzing further progress in FTD. This report is written to help orient funders who are new to the FTD field and underscore successful strategies on which existing stakeholders could double down to maximize the impact of their investments.



Philanthropic Opportunities to Address System-Wide Barriers

The opportunities presented in this report were informed by an extensive review of the scientific literature, an analysis of public and private funding patterns in the FTD field, and conversations with dozens of experts from around the world. MI Philanthropy has identified four philanthropic opportunities that could dramatically accelerate progress for people living with FTD:

1. **Improve the understanding of all FTD types.**

   Over the past decade, scientific understanding of FTD has been driven by studies focused on genetic forms of the disease, which account for approximately 40 percent of individuals living with FTD. The study of genetic FTD has enabled a better understanding of the mechanisms that cut across multiple types of FTD, but greater attention is needed to identify other inherited forms and resolve non-inherited forms of the disease, and to develop better treatments for all types of FTD. Engaging researchers with diverse expertise who can apply multiple scientific approaches across FTD disease models is necessary to improve the understanding of all forms of FTD comprehensively.

2. **Accelerate development of biomarkers for FTD diagnosis and therapeutic development.**

   Current approaches to diagnose and measure FTD progression are time-consuming, expensive, inaccessible for most people, and still do not lead to a definitive diagnosis of the disease. More support is needed to develop and validate a toolbox of reliable and specific biomarkers to meet these needs. These resources would streamline clinical care for individuals living with FTD and improve the therapeutic landscape by engaging more industry partners in FTD drug development and more FTD patients in clinical research studies.

3. **Increase patient engagement across the FTD ecosystem.**

   Engagement of FTD patients and their families is necessary across the entire research spectrum—from discovery and basic research conducted using patient-provided samples and data to participation in clinical trials of new therapeutics. People living with FTD experience significant hurdles to participating in research opportunities, while scientific and clinical research studies struggle to identify and retain enough study participants to meet their scientific and regulatory goals. Sustained philanthropic support would empower and enable patients of all backgrounds to participate in research and to build out FTD research infrastructure within research centers to meet the needs of additional study participants. These efforts would increase productivity and capacity within the FTD research ecosystem and enable more patients to actively engage in resolving FTD.

4. **Raise FTD awareness and support.**

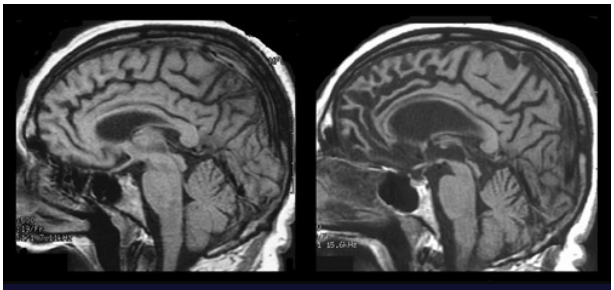
   Low awareness of FTD contributes to diagnostic delays and misdiagnoses. FTD symptoms are variable and can be confused with other conditions. FTD also suffers from a social stigma because this disease changes behavior and diminishes one's ability to self-advocate. Broad dissemination of information about FTD is crucial to ensure that doctors and the public can recognize early signs of the disease and identify clear pathways to support individuals living with FTD and their families. Also needed is philanthropic investment to build and launch a cohesive strategy to generate a strong FTD knowledge base within the general population and among clinicians and policymakers. Such a campaign would drive additional interest, funding, and progress for the FTD space.

OVERVIEW OF FTD

Clinical Features and Epidemiology of FTD

Frontotemporal dementia (FTD) is an umbrella term used to describe a diverse range of brain conditions characterized by progressive degeneration of the brain's frontal and temporal lobes. The brain's frontal lobe is responsible for executive functioning, which includes a person's ability to plan, make decisions, pay attention, and control impulses, among other actions. The temporal lobe is responsible for processing auditory information and forming new memories. The various forms of FTD impair these and other cognitive abilities. Although symptoms of FTD differ considerably among people, most people experience changes in behavior, mood, executive function, language, and motor function.

Figure 1: Progressive brain atrophy in FTD.



Two MRIs of the same person with FTD. The image on the right was taken four years after the image on the left and reveals marked reduction in brain volume.

Source: *Adapted from Honig et al., 2003.*

Diagnosing FTD is challenging and requires a combination of methods, including physical examination, behavioral assessments, brain imaging, genetic testing, and family medical history. Like most other neurodegenerative diseases, a definitive diagnosis of FTD can only be made upon death after autopsy. Challenges in diagnosis are further compounded by the tendency of FTD to affect people earlier in life than other forms of dementia, often leading to initial psychiatric diagnoses and treatments. FTD is thought to be the most common form of dementia in people under the age of 60, with the average age of onset between ages 45 and 65. Although FTD is not considered fatal, its worsening symptoms require full-time care, and the average life expectancy is about 7.5 years after symptom onset.

The clinical features of FTD are correlated with a progressive loss of brain tissue, which can be observed through clinical imaging methods such as magnetic resonance imaging (MRI, Figure 1). In successive scans over multiple years, researchers have identified that brain volume loss correlates with FTD progression. Importantly, brain atrophy can be detected early in a person's clinical disease course, and patterns of brain volume loss can aid in the diagnosis of different FTD subtypes, highlighting the importance of early imaging to facilitate early intervention.

There are *at least* five subtypes of FTD; the five most common FTD variants are briefly described in Box 1. Symptoms overlap a great deal among subtypes, although the specific locations of brain volume loss tend to differ. For example, behavioral variant FTD (bvFTD) is associated with shrinkage throughout the frontal and temporal lobes, while more localized patterns of brain loss are seen in variants of primary progressive aphasia (PPA).

BOX 1: OVERVIEW OF FTD SUBTYPES

Behavioral Variant FTD (bvFTD) is the most commonly diagnosed form of FTD. People with bvFTD may show a lack of impulse control, poor decision-making, apathy, unhealthy eating habits, agitation, and/or compulsive or perseverative behaviors. Often, patients cannot recognize their behavior as different or inappropriate. bvFTD is often misdiagnosed as a psychiatric illness.

Primary Progressive Aphasias (PPA) affect parts of the brain necessary for generating and understanding language and typically presents with loss of speech or language. There are at least three different subtypes of PPA.

FTD with Amyotrophic Lateral Sclerosis (FTD-ALS) or FTD with Motor Neuron Disease (FTD-MND) frequently leads to symptoms similar to bvFTD, followed by muscle weakness and loss of muscle function. Greater than 10 percent of people living with FTD will also receive an ALS diagnosis, and up to 50 percent of people with ALS will experience behavioral symptoms of FTD.

Corticobasal Degeneration (CBD) usually begins with changes in behavior, language, and/or executive function then progresses to a loss of motor function that resembles Parkinson's disease. Motor symptoms include muscle stiffness, slow movement, and lack of limb control.

Progressive Supranuclear Palsy (PSP) progresses more gradually than some of the other forms of FTD and often begins with impaired eye movements and/or stiffness in the muscles of the neck and trunk. Other motor, behavioral, and executive symptoms emerge over time, including poor balance and frequent falls, difficulty swallowing, slurred speech, declining executive function, and personality changes.

Worldwide, an estimated 36 million people are thought to be living with FTD. However, the disease is widely believed to be underdiagnosed and undercounted, especially as FTD diagnosis is delayed by an average of three years from symptom onset. Several population-based studies have investigated the prevalence and incidence of FTD, but estimates across studies are widely variable, likely due to differences in the populations studied and methodologies used. FTD is considered a rare disease, with an estimated 20,000–30,000 people living with FTD at any one time in the United States and approximately 3,000 people developing the disease each year. Men and women appear to be diagnosed at equal rates.

However, little is known about the FTD diagnosis rate across distinct racial and ethnic groups. More accurate epidemiological data will require the development of more specific diagnostic tools and approaches.

Causes and Risk Factors

In many cases, FTD's precise causes are unknown, but family history is the strongest known risk factor. Up to 40 percent of identified FTD cases can be linked to known and inherited genetic mutations or variants; this proportion is unusual among neurodegenerative diseases, which tend to be either fully genetic (e.g., Huntington's disease) or rarely inherited (e.g., Alzheimer's disease). The remainder of FTD cases (60 percent) are referred to as *sporadic*, meaning there is no known family history of the disease. Sporadic FTD can refer to one or a combination of the following: FTD caused by a genetic mutation that is not inherited

(i.e., familial) in nature, FTD caused by a familial mutation that has not yet been identified or characterized, or FTD caused by environmental or other life events.

Traumatic brain injury (TBI) is another known risk factor for FTD because the frontal lobe is especially vulnerable to head trauma. A Norwegian study found that individuals with a known head injury were three times more likely to develop FTD than the general population. Likewise, military and veteran populations are more likely to develop neurodegenerative diseases—including FTD—than the general population. Although conclusive studies of lifestyle, disease comorbidity, and behavioral risk factors in FTD are limited, associations with type-2 diabetes, obesity, hypertension, and stroke have been reported, suggesting a possible link to cardiovascular health. Anxiety and autoimmune disease have also been reported to increase the risk of developing certain types of FTD.

A more complete understanding of the biological causes of FTD is necessary to improve clinical outcomes for people affected by the disease. Scientists and clinicians continue to work toward an understanding of FTD by studying the connection among genes, proteins, cellular functions, brain pathology, and neurological symptoms (Box 2).

BOX 2: BIOLOGY REFRESHER

Genes: Regions of DNA, or genetic code that enable specific functions.

Proteins: Molecules within cells that perform a variety of functions. The structure of a protein is the result of our genes, and genetic mutations can change protein shape and function.

Cellular functions: Coordinated processes performed by proteins that sustain the life of cells. These include activities such as energy production, waste removal, molecular transport, and intracellular communication.

Brain pathology: Development of disease in the brain caused by impaired cellular function, protein aggregation, and/or abnormal cell death. Abnormal cell death leads to physical brain shrinkage.

Neurological symptoms: Changes in behavior, movement, mood, personality, or bodily function as a result of changes in the brain. Because the brain is central to who we are and how our bodies work, neurological disease can cause wide-ranging symptoms.

FTD Disease Pathways

Researchers use genetic association in disease to gain footholds to understanding its biology. Three prominent genetic mutations have been linked to inherited forms of FTD: *chromosome 9 open reading frame 72* (C9orf72), *granulin* (GRN), and *microtubule associated protein tau* (MAPT). Each mutation accounts for between 5 percent and 10 percent of total FTD cases and affects biological processes, including cellular structure and maintenance, communication between neurons, and regulation of the immune system. Table 1 describes the function of each of these three genes, along with their associated FTD subtypes. Dozens of other disease-causing genes have also been identified, but most of these are rare.

Without a clear family history or genetic link, it is difficult to identify individuals with non-inherited, or

Table 1: An Overview of FTD Gene Associations

GENE	PROTEIN PRODUCT	CELLULAR FUNCTIONS	ASSOCIATED FTD SUBTYPES
C9orf72	C9orf72	Neuronal communication Cellular waste Immune regulation	Behavioral variant FTD FTD with ALS
GRN	Progranulin	Cellular waste Immune regulation	Behavioral variant FTD Nonfluent variant PPA Corticobasal Degeneration
MAPT	Tau	Neuron structure and stability Neuronal communication	Behavioral variant FTD Semantic variant PPA Progressive supranuclear palsy

Source:

sporadic, FTD until the disease is quite advanced. Furthermore, poorly defined sporadic FTD patient populations have challenged efforts to understand the heterogeneous drivers of nongenetic FTD.

However, the genes involved in genetic FTD have served as an entry point for understanding sporadic FTD, and the three most common FTD-linked genetic mutations have helped illuminate candidate pathological mechanisms. Scientists are increasingly focused on understanding how the causes and biology of genetic FTD may be relevant to non-inherited forms of the disease as well. Some of the known molecular mechanisms that cut across several genetic mutations in FTD and are relevant in sporadic FTD include the following:

- Protein aggregation: Abnormal accumulation of certain proteins in the brain is a common feature in many neurodegenerative conditions, including FTD. Although aggregation is central to most, if not all, cases of FTD, the specific protein affected can differ across individuals.
- Cellular waste: The lysosome is a cellular compartment that breaks down unwanted materials, but when the lysosome is impaired, these unwanted materials accumulate, potentially leading to cell damage and death. Lysosomal function has been linked to several FTD-relevant genes, and understanding this compartment could, in turn, better our understanding of FTD.
- Neuroinflammation: Typically, neuroinflammation is a protective process that helps the brain respond to injury and other threats. However, persistent neuroinflammation can lead to neurodegeneration. Immune cells, both inside and outside the brain, have been implicated in FTD.

Researchers can use multiple scientific approaches to resolve the underlying biology of FTD, including research with human sample-derived stem cells, animal models of FTD, and cutting-edge data science or machine learning technologies (Box 3). These and other methods are proving necessary to fully understand the complexity of pathways implicated in all forms of FTD.

BOX 3: DIVERSE SCIENTIFIC APPROACHES TO STUDY FTD BIOLOGY

Human sample-derived stem cell models (e.g., induced pluripotent stem cells, or iPSCs, and three-dimensional brain organoids) are powerful tools to study cellular functions in FTD and develop therapeutics because they contain the exact genetic makeup of the person from which they were derived. These in vitro models can be used to draw comparisons across different individuals with FTD as well as identify key differences in their disease biology.

Animal models are critical experimental tools that researchers use to interrogate underlying disease mechanisms. Scientists can manipulate specific molecules, cellular components, or multicellular networks in these models to better understand how these factors contribute to FTD pathology and disease.

Computational research methods, such as data science and machine learning, can be an especially powerful means of studying FTD. These methods allow researchers to identify patterns among forms of FTD and integrate multiple types of data, enabling the discovery of associations between molecular changes, pathology, and clinical manifestations.

Similarities between FTD and Other Neurodegenerative Conditions

FTD is one of many neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and ALS. All neurodegenerative diseases are characterized by a progressive loss of neurons and brain function, which leads to high overlap in clinical symptoms and the underlying molecular biology of these diseases, suggesting that scientific discovery in one disease will facilitate progress in others. Key differences among the diseases can also be helpful for research; for example, the unusual proportion of genetic FTD compared to other neurodegenerative diseases, which tend to be either fully genetic (e.g., Huntington's disease) or rarely inherited (e.g., Alzheimer's disease), has enabled progress in the FTD field toward understanding FTD by using genetic-based tools that are less applicable to other diseases.

Because of FTD's unique position at the nexus of multiple neurodegenerative diseases, some researchers and clinicians have speculated that discovering treatments for FTD could be the first domino to fall toward curing other neurodegenerative diseases.

Investment in FTD research may therefore have an outsized impact on neurodegenerative disease research more broadly.

A Need for Biomarkers to Diagnose and Measure FTD

To turn promising foundational research into clinical tools or treatments for FTD, the field needs accurate, specific, and valid methods to diagnose and measure FTD. A biomarker is an indicator of a medical condition or disease that a researcher or clinician can easily and reliably measure. Biomarkers can be used to diagnose a disease, monitor its progression, or measure responses to treatments. Biomarkers can be

molecules or chemicals measured from human samples (such as blood), changes in the brain observed through neuroimaging or electrical signals, or other data that provide insight into biological functions such as blood pressure readings. In FTD, biomarkers are needed to:

- Improve and accelerate accurate diagnosis. Biomarkers that can distinguish between FTD and other neurodegenerative or psychiatric disorders would enable earlier detection and diagnosis of the disease. Patients would receive earlier access to appropriate care, and participation in clinical research studies and therapeutic trials would improve.

- Provide more robust clinical trial measurements. Sensitive and accurate biomarkers are also needed to measure disease progression accurately and assess whether a treatment will likely be effective against the disease by engaging its intended therapeutic target. These biomarkers could enable clearer detection of changes in disease course by clinical researchers, which could lead to better and more precise outcome measurements for clinical trials. These tools would help engage industry and potential participants in clinical trials and increase the likelihood of regulatory approval for therapeutics and treatments.

The FTD field needs a toolbox of different biomarkers that can be used in various combinations to improve diagnosis, monitor disease progression, and eventually tailor treatments to an individual's specific pathology. Box 4 provides information on some promising biomarkers currently being studied for use in FTD.

BOX 4: THE BEGINNINGS OF A BIOMARKER TOOLBOX IN FTD

Numerous biomarkers will be needed to adequately diagnose and monitor the various forms of FTD. Below are some of the promising biomarker and diagnostic tools currently in development.

- **Neurofilament light chain (NfL**) is a molecular biomarker that is indicative of neurodegeneration. However, it does not indicate which kind of neurodegenerative disease a person has. NfL is currently being used as an indicator of the transition from the presymptomatic state to an active disease state in someone with a causal genetic variant associated with FTD.
- **Two forms of tau** can be detected and may reliably distinguish CBD from other forms of neurodegeneration.
- **Biomarkers for FTD with known genetic causes (C9orf72 or GRN)** may assist in diagnosis without the need for genetic testing, but their utility in monitoring disease progression is not yet clear.
- **Tau brain imaging** is useful in monitoring disease progression over time by measuring changes in brain volume and structure. Tracers, or chemicals that bind to aggregates of tau protein in the brain, are currently being developed to "show" whether and where tau concentrations are increased via brain imaging.
- **Speech-based biomarkers from devices** could be used remotely and cost-effectively to understand symptom changes and progression. FTD symptoms often include changes in speech patterns or diction, and assessing these and other criteria could provide additional insight into disease progression and effect on behavior.

Observational and Clinical Studies to Understand and Treat FTD

In addition to biomarkers, observational and clinical research studies are essential to improving the understanding of FTD and accelerating the development of FTD treatments. With observational and longitudinal studies, scientists can study the same individuals over time and systematically analyze data from a variety of FTD clinical courses. These studies enable the identification of similarities and differences between cases and potentially illuminate previously unknown therapeutic targets or biomarkers.

Longitudinal and observational studies can take many forms but often involve the collection and study of clinical data and patient samples, such as blood or cerebrospinal fluid (CSF), and comparisons of these data to other individuals in the same cohort. These large population-focused studies can also link tissue samples to rich clinical data, providing a comprehensive understanding of FTD in study participants. To be successful, these efforts also require substantial coordination, field-wide buy-in, and long-term financial support to ensure their stability.

Two prominent, ongoing observational studies in the FTD space are the US-based ALLFTD and UK-based Genetic Frontotemporal Dementia Initiative (GENFI). Together, these large clinical research studies have collected data and biological samples from nearly 3,000 individuals with FTD and their family members. ALLFTD and GENFI have started to work with FTD consortia around the world as part of the FTD Prevention Initiative, which aims to globalize the FTD research system. As part of this work, the group spearheads an initiative to collect and standardize clinical datasets from around the world into a single open-access database. Several other ongoing clinical studies are gathering biological samples and clinical data from the same individuals for use by the broader research community.

Clinical studies enable the testing of promising treatments for safety and efficacy with the goal of developing regulator-approved therapeutic options for patients. Although there are no FDA-approved medications that can stop, slow, or prevent FTD, several dozen clinical trials are underway to evaluate the safety and efficacy of new treatments and tools for FTD. As of June 2023, the US government's clinical trial database listed 87 clinical trials as currently active, 19 of which are evaluating different candidate treatments.[1]

Over the past several years, the Tau Consortium and the Bluefield Project, two philanthropically driven initiatives focused on accelerating progress in neurodegeneration, have helped advance 12 investigational treatments into clinical trials. Although these numbers are encouraging and show the outsized impact that a few dedicated organizations can have, the number of active trials in FTD is relatively low compared to other neurodegenerative diseases. ALS—which affects approximately the same number of individuals each year as FTD—currently has 178 clinical trials underway.[2] Experts in the field noted that, compared to those for ALS, FTD clinical trials suffer from a lack of clinical endpoints or measurable outcomes for clinical trials, and difficulty in recruiting trial participants. These challenges lead to less investment from pharmaceutical and biotechnology firms, and fewer clinical trials overall.

FINANCIAL LANDSCAPE OF FTD

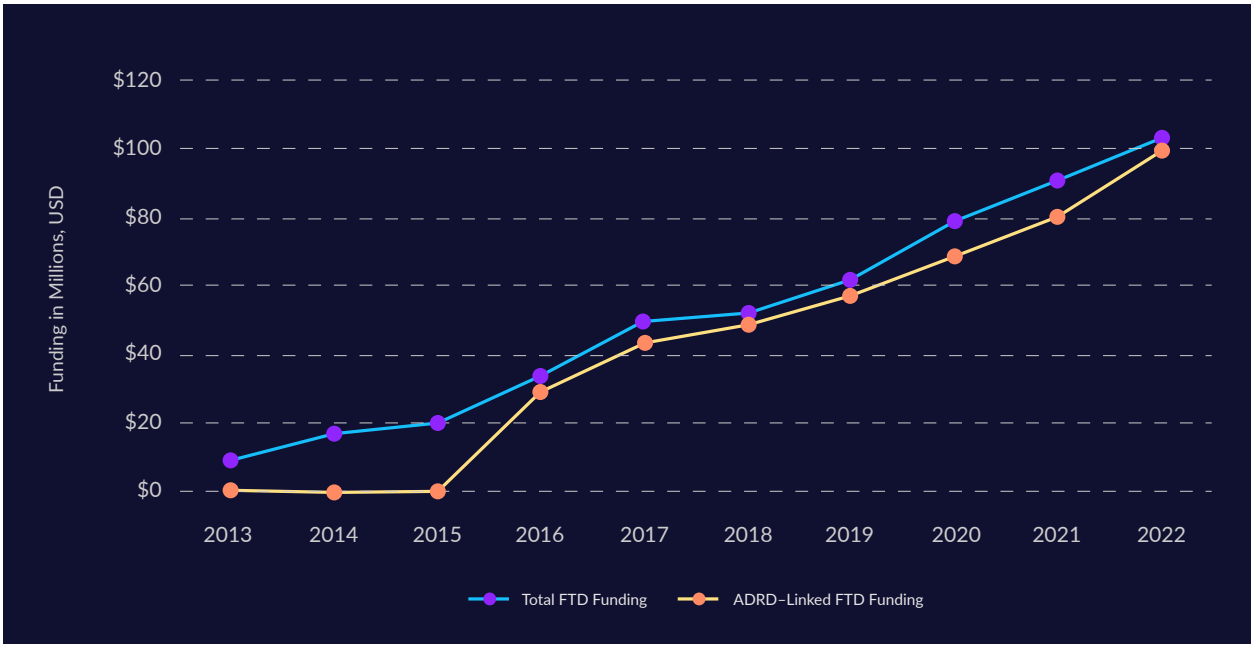
Although FTD has clear entry points for studying biology, the FTD field has experienced less visibility and research funding than other neurodegenerative conditions. Despite this overall trend, the field has benefited from prominent philanthropic initiatives that have had a significant impact, especially toward understanding and advancing promising therapeutics into clinical testing for genetic FTD. Increased, sustained support from public and private funders is needed to continue the development of treatment options for genetic FTD, improve the therapeutic landscape for sporadic FTD, and accelerate scientific discovery for all forms of the disease.

Public FTD Funding

Public funding is the primary source of support for FTD research. In the 10 years between fiscal years 2013 and 2022, the federal government provided more than $517 million for FTD research via the National Institutes of Health (NIH) (Figure 2A). The NIH supported 682 FTD projects during this time, with most projects spanning three to five years.

Federal FTD funding from the NIH rose during the FY2013–FY2022 period, reflective of broader trends in growing support for neurodegenerative diseases (Figure 2A).[3] By congressional mandate in 2012, NIH established the Alzheimer's Disease and Related Dementias (ADRD) spending category to significantly accelerate scientific and medical progress for neurodegenerative diseases. FTD is considered a related dementia by the ADRD categorization, and investment in FTD tied to ADRD funds accounts for the recent overall growth in federal FTD funding, beginning in FY2016 (Figure 2A). However, a notable proportion of support for FTD is related to its relationship to ALS. Over the past 10 years, approximately 40 percent of

Figure 2A: NIH Funding of FTD Research, FY13-FY22



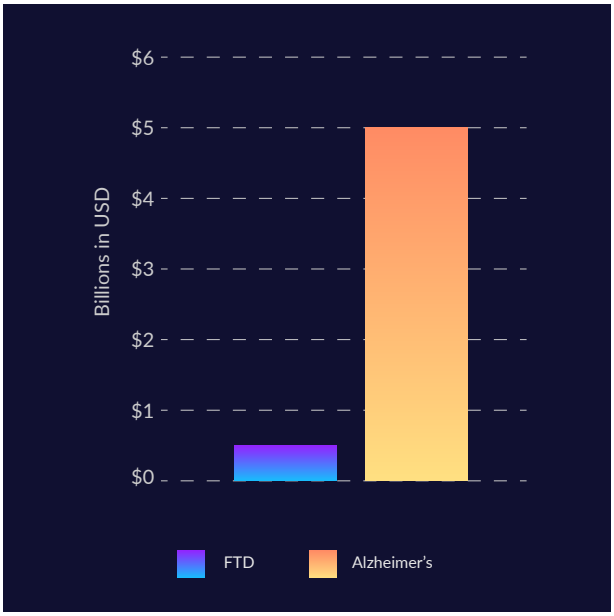
Source: *Milken Institute (2023)*

FTD funding went to projects that addressed both FTD and ALS (Figure 2B).[4]

Figure 2B: FTD and ALS Funding Relationship, FY13-FY22

Source: *Milken Institute (2023), using data from NIH Reporter (2013-2022)*

Figure 2C: FTD and Alzheimer's Disease ADRD Funding Comparison, FY16-FY22



Source: *Milken Institute (2023), using data from NIH Reporter (2013-2022)*

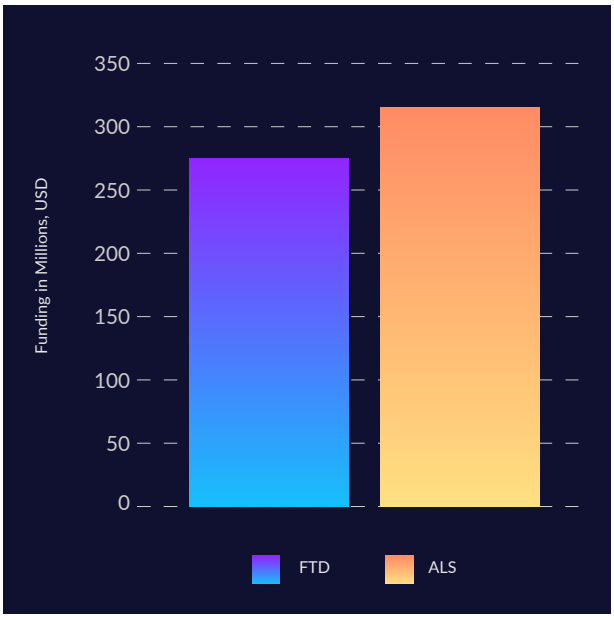
While this funding overlap is not inherently a problem given the close biological links between FTD and ALS, researchers have experienced this trend as a less favorable funding environment for research studies that seek to focus on either FTD or ALS alone. Approximately 15 percent of FTD patients also develop ALS, but around 40 percent of NIH funding for FTD research is linked to ALS.

FTD is funded at a lower level than other neurodegenerative conditions. Strikingly, over seven years, Alzheimer's disease research received more than 10 times more funding than FTD (Figure 2C).[5] The relative prevalence of FTD and Alzheimer's disease does not explain the funding disparity because Alzheimer's disease is around 40 percent more prevalent than FTD, with FTD being the third most common form of dementia, after Alzheimer's disease and Lewy body dementia. As the science underscores, neurodegenerative diseases exist on a spectrum, but FTD has seen disproportionately scarce funding compared to its more prevalent (Alzheimer's disease) and better-known neighbors (ALS).

Another manifestation of insufficient FTD funding is a relatively small pool of NIH-funded researchers who are developing and testing novel and innovative ideas. Compared to ALS, which has a similar prevalence to FTD, NIH funds about half the number of unique lead researchers working on FTD scientific projects (Figure 3A).[6] NIH is uniquely positioned to bring new researchers into the FTD ecosystem through early career awards and to provide the sustained support necessary for budding FTD professionals to build careers in the field. Philanthropy often plays this role in other fields.

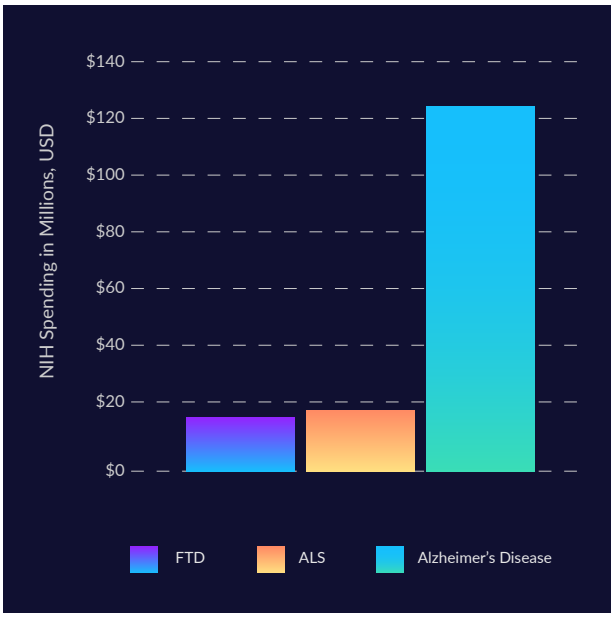
In the past 10 years, NIH provided slightly more than $15 million in awards for FTD early career researchers (Figure 3B).[7] This amount is similar to that awarded to early career investigators in ALS but is overshadowed by that of Alzheimer's

Figure 3A: Number of Unique Lead Researchers, FY13-FY22



Source: *Milken Institute (2023), using data from NIH Reporter (2013-2022)*

Figure 3B: Early Career Award Funding Across Neurodegenerative Conditions FY13-FY22



Source: *Milken Institute (2023), using data from NIH Reporter (2013-2022)*

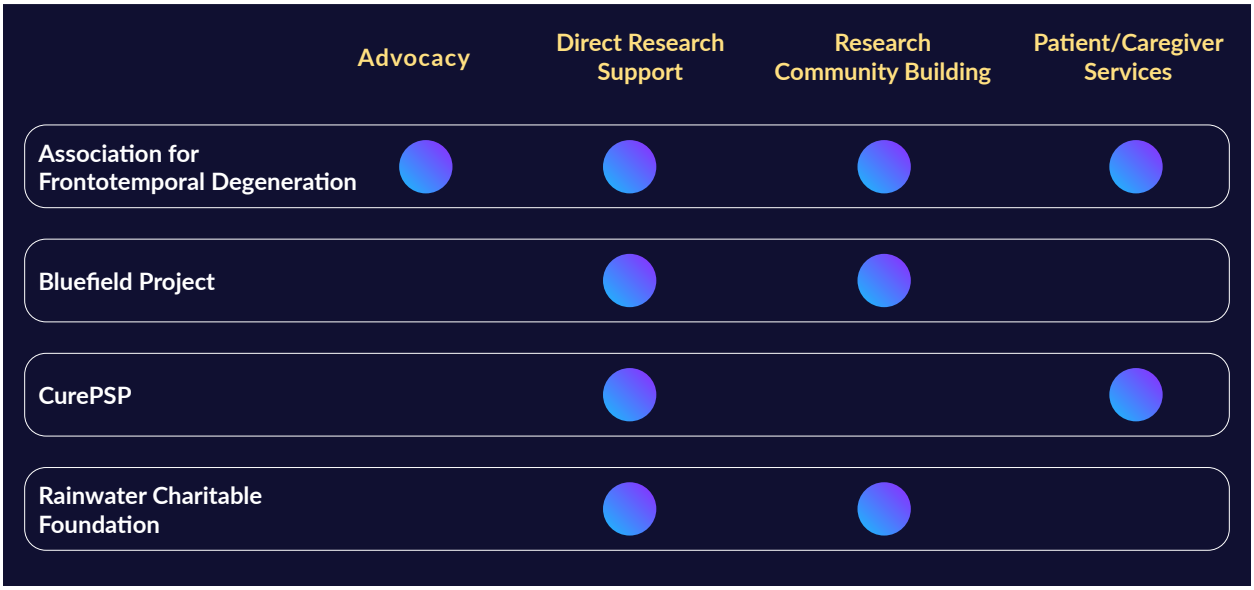
disease, which received more than $77 million for this pool of investigators in the same time frame. As noted earlier, these differences in funding are disproportionate to the number of people affected by these diseases. More support is needed here to ensure a healthy pipeline of FTD researchers who are passionate about making discoveries and developing new interventions for people living with FTD.

Private FTD Funding

FTD has an active private funding environment with several committed nonprofit organizations and philanthropic funders. These funders have provided critical support for accelerating the understanding of genetic FTD and brought a dozen therapeutics to clinical trials. More support is needed to ensure that these therapeutics are sufficiently tested and that new therapeutics are brought into the clinical trial pipeline to benefit a larger proportion of the FTD population. The Association for Frontotemporal Degeneration (AFTD), the Bluefield Project, CurePSP, and the Rainwater Charitable Foundation are the most prominent contributors of private and philanthropic funding to FTD research. A characterization of their activities can be found in Figure 4.

Rainwater Charitable Foundation supports the Tau Consortium, a scientific network that conducts research across the therapeutic spectrum for neurodegenerative conditions related to *MAPT* mutations, from underlying mechanisms of neurodegeneration to drug discovery to clinical trials. The Bluefield Project is a research consortium focused on progranulin-related FTD and supports research from biological studies to clinical trials, forming strategic partnerships to ensure that the discoveries can be translated into therapeutics. CurePSP focuses on PSP, a form of FTD that is usually sporadic but can also be caused by mutations in the *MAPT* gene. CurePSP's research portfolio covers sciences that seek to understand the basic biology of PSP and develop novel biomarkers for the disease. Finally, AFTD provides funding for several initiatives, including research grant programs. Most of its portfolio focuses on drug discovery and biomarker development.

Figure 4: Focus Area of Private FTD Funders



Source: *Milken Institute (2023)*

FY2020 provides a snapshot of funding from these four organizations, which combined provided $48 million in research grants and other types of support for FTD and other neurodegenerative conditions. Although these organizations have provided significant support for FTD research, most of the funding has been focused on genetic FTD. More information on each of these organizations can be found in the Appendix.

PHILANTHROPIC OPPORTUNITIES IN FTD

MI Philanthropy has identified four opportunities within the FTD field where thoughtful philanthropic investment could overcome barriers to scientific progress. Supporting any of these opportunities to grow and strengthen the FTD research ecosystem will help accelerate progress toward a healthy life for people living with FTD.

Opportunity 1: Improve the Understanding of All FTD Types

The FTD field has made substantial progress in understanding FTD linked to the three most prominent genes: *GRN*, *MAPT*, and *C9orf72*. These genes have provided a clear route to conduct detailed studies of molecular mechanisms and pathological pathways associated with FTD. However, there is still much to learn about the underlying biology of genetic FTD and a clear need to improve diagnostic tools and develop therapeutic interventions for individuals living with genetic FTD. Several therapeutics are advancing through the clinical trial pipeline to treat genetic forms of the disease, but the field needs more support to ensure that a diversity of treatments is approved and become available to all FTD patients.

Despite progress in the research of genetic FTD, the historic focus on relatively few FTD subtypes creates an unmet need for the 60 percent of patients who seem to develop the disease without a family history. Emerging scientific evidence suggests that genetic and sporadic FTD share common biological processes such as pathological protein aggregation, impaired cellular waste management, and neuroinflammation; further study of these cellular mechanisms will accelerate the discovery for all forms of FTD. Scientists must develop and employ a breadth of research models and approaches—including animal models, patient-derived cellular models, and postmortem tissue—to understand the biological complexity of FTD. More information on some of these approaches can be found in Box 3 in the *Overview of FTD* section above.

Basic science research findings are strongest and, therefore, most valuable when validated using multiple scientific approaches in multiple models before advancing therapeutic candidates through the research pipeline. Researchers with expertise across diverse scientific disciplines, including biochemistry, neurophysiology, immunology, data science, biotechnology, molecular biology, chemical biology, functional genomics, and others, are important to moving the field forward. Any effort to advance the fundamental understanding of FTD will be more likely to succeed with an intentional diversity of approaches and scientists.

To comprehensively improve the understanding of all forms of FTD, MI Philanthropy recommends directing funding to:

- **Support ongoing and new studies to resolve genetic FTD.** A continued commitment to understanding the function and impact of gene mutations associated with genetic forms of FTD will enrich the understanding of molecular pathways and cellular processes that may be relevant to multiple forms of the disease. Although therapeutics for some genetic forms of FTD (e.g., GRN-FTD) are at various stages of clinical development, these studies require additional funding to ensure that these drugs are appropriately tested. Therapeutic progress for other genetic forms of FTD (e.g., FTD associated with

the *C9orf72* mutation) has not progressed as far, which underscores the need for a sustained focus on genetic FTD.

- **Facilitate research into sporadic FTD.** Insights into genetic FTD have increased the field's understanding of biological pathways that appear common to multiple forms of FTD. Supporting research approaches that seek to understand several FTD types can accelerate progress toward effective therapeutic interventions for many living with FTD. The development of dedicated funding initiatives, such as grant programs and collaborative research funding models, to understand these common mechanisms through the lens of sporadic FTD will likely lead to more widely applicable therapeutic targets and benefits for more FTD patients than continuing with a dominant focus on genetic FTD alone.

- **Expand and diversify approaches and scientific disciplines engaged in the FTD field.** To fully understand the complexity of all types of FTD, the community of FTD researchers must grow, diversify, and be incentivized to bring multidimensional approaches to FTD research questions. Expertise is needed from scientists who can interrogate FTD across multiple model systems and apply research methodologies from disciplines including molecular biology, immunology, and data science.

Philanthropy is an effective tool for creating the conditions under which novel ideas and new approaches can thrive.

Opportunity 2: Accelerate Development of Biomarkers for FTD Diagnosis and Therapeutic Development

FTD is currently diagnosed using a variety of behavioral, cognitive, and neurophysiological assessments. The extensive battery of tests required for a clinical diagnosis of FTD is time-consuming, expensive, and inaccessible for many people. A toolbox of biomarkers is needed to diagnose FTD affirmatively and efficiently, assess disease progression, and measure treatment efficacy. Scientists are making rapid progress in developing a comprehensive battery of biomarkers, including those that can be measured in blood or other body fluids, such as NfL or Tau, as well as imaging and speech-based biomarkers, which could be used to monitor disease progression. These tools would help identify more people with FTD who could participate in clinical research, increase the accessibility of research studies by reducing geographic barriers to study participation, and incentivize more engagement from industry partners.

Biomarkers are an important part of clinical trials because they provide pharmaceutical and biotechnology companies with methods to measure whether the therapeutic target they are testing is effective at alleviating a patient's symptoms or slowing progression. Many promising therapeutics do not reach the clinical trial phase because few biopharma companies can accept the higher risk that comes with running a trial without a reliable and regulator-accepted means of measuring disease changes. Treatment-responsive biomarkers could encourage companies to coordinate and run more FTD clinical trials, allowing the field to test promising therapeutic options more rapidly.

To expedite the development and validation of biomarkers to address multiple needs in FTD, MI Philanthropy recommends directing funding to:

- **Expand access to remote and home-based testing to support biomarker development.** The extensive battery of tests required for a clinical diagnosis of FTD is time-consuming, expensive, and can be inaccessible for many people. Home-based biofluid sample collection and remote monitoring of speech, movement, and other modalities will enable researchers to collect data that can be used for biomarker development and validation more reliably and from more individuals by lowering barriers to participation in these types of studies.

- **Use data collected by related fields to accelerate progress across neurodegenerative diseases.** Because of the misdiagnosis of FTD and significant biological overlap with other neurodegenerative conditions, several adjacent neurodegenerative fields have collected data from FTD patients that can be mined to expand datasets and aid the search for promising biomarker and therapeutic targets. Additionally, linking FTD cohort study data to platforms in other neurodegenerative disease fields can help researchers better understand the similarities and differences between FTD and other diseases. Collaborations between FTD researchers and those working in related fields such as ALS and Alzheimer's disease can result in a better understanding of overlapping biology, improved biomarker development, and faster progress for all patients.

- **Incentivize academic and industry collaboration to support therapeutic development.** Academic and industry scientists have differing motivations across the multiple phases of research to translate basic research findings into new therapies. Academic scientists tend to be focused on novel molecular discoveries that could be leveraged into new treatments, while industry scientists determine whether a potential target could be used to develop a marketable drug. Industry firms will be less likely to launch FTD clinical trials without biomarkers that can measure whether a target has been engaged. Working to develop discovery-focused strategies that incorporate potential clinically measurable endpoints early in the scientific process could accelerate engagement from both sectors. Philanthropy is catalytic in connecting academia with industry and supporting partners across the therapeutic development spectrum that are key to accelerating therapeutic development.

Opportunity 3: Increase Patient Engagement across the FTD Ecosystem

Patient engagement is critical for research at all stages to progress and benefit the most people living with FTD possible. At the basic science level, patient samples provide the platform for researchers to interrogate questions of FTD biology and molecular pathology. Biological and clinical data are incredibly important for developing and validating biomarkers, and engagement of FTD patients is critical for testing therapeutic interventions. However, patient engagement across all facets of FTD research has been consistently described as low. Throughout our due diligence and outreach to experts in the field, our team heard that once a person is informed that they or a loved one has been diagnosed with FTD, there is a "now what" feeling because there are few therapeutic options and limited or cumbersome research opportunities.

This phenomenon reflects a vicious cycle in which people diagnosed with FTD cannot easily engage in research studies while researchers across academia and industry struggle to recruit study participants. Research engagement is even more challenging for people who live far from specialty clinics and for people of non-Caucasian ancestry, who have been almost entirely omitted from clinical studies and therapeutic research trials. Empowering patients to participate in research and supporting the build-out of FTD research infrastructure within medical research centers will increase patient engagement and retention within the FTD research ecosystem.

To create more opportunities for patients to become part of the solution for FTD, MI Philanthropy recommends directing funding to:

- **Expand infrastructure to collect, share, and study patient samples and data**. While some institutions, researchers, and organizations have the infrastructure to collect, store, and use samples derived from people living with FTD, these resources are not universal, and expanding researchers' ability to study FTD using patient samples is imperative to driving progress. Additionally, the bureaucratic and logistical steps needed to donate samples and data are confusing and resource-intensive for patients. There is a clear need to streamline how individuals can participate in research studies that integrate clinical symptoms and biological features of FTD—as can only be done by studying patient-provided samples and data. To facilitate these discoveries, philanthropy can support collaborative efforts that enable effective and efficient sample and data collection and sharing. These efforts will help ensure that valuable patient-provided resources can be used for maximum scientific impact.

- **Connect academic researchers with existing medical systems to improve continuity of care and research**. Developing collaborations between academic or other research-focused institutions and large medical systems can bring FTD to the forefront for medical providers and help researchers identify and engage more individuals living with FTD. Medical clinics serve as an entry point for people experiencing FTD symptoms and represent an opportunity to connect FTD patients with dementia specialists, clinical trials, and other research opportunities. Facilitating connections between researchers and physicians can encourage better information flow between front-line medical teams and researchers to learn more about clinical manifestations of FTD and direct more FTD patients toward opportunities for improved care.

- **Ensure that diverse populations are involved in every study**. Historically, non-White populations have not been included in FTD research, which limits the ultimate utility of any discoveries made in the field. Research studies must include individuals from all backgrounds to gain a complete understanding of FTD because it is possible that FTD will manifest differently in different racial and ethnic groups and will require different considerations for measuring and treating the disease. Research initiatives should articulate and prioritize patient diversity as a goal.

Opportunity 4: Raise FTD Awareness and Support

When a person experiences new, troubling symptoms, they generally expect that clinicians will be able to recognize, diagnose, and address those symptoms. However, rare diseases put this notion to the test. Many clinicians will not have seen sufficient patients to have first-hand experience, and even specialists may only see some conditions occasionally.

FTD symptoms are widely variable and can result in behavioral changes that are often confused with psychiatric conditions. The field acknowledges the uphill battle to overcome the societal stigma of brain diseases that diminish people's ability to advocate for themselves. Advancing knowledge about FTD and its impact on individuals and families is necessary to overcome this stigma and encourage more engagement within the field.

Improved dissemination of information about FTD is needed to ensure that doctors can accurately identify and treat individuals living with FTD. Greater awareness of FTD by primary care physicians,

caregivers, and patients would enable them to better identify appropriate clinical trials and observational studies for people living with FTD and their family members to participate in. Higher levels of awareness would lead to the identification of more potential FTD clinical trial participants and boost the number of research samples available for scientists to use for their studies. Campaigns to raise FTD awareness should also target policymakers and other officials with the authority to increase funding levels or improve access to care for individuals living with FTD. Adjacent fields such as ALS have seen marked success in translating awareness into funding and policy changes that benefit the neurodegenerative and rare disease communities and can serve as a model that the FTD community could learn from.

To raise awareness of FTD, MI Philanthropy recommends directing funding to:

- **Leverage learnings from other fields to increase public awareness**. Adjacent rare disease fields, such as ALS, have seen tremendous success in raising awareness through coordinated and concerted efforts, including viral social media challenges, high-profile public figures with the disease, and vocal advocacy from the lived experience community. These campaigns have increased interest from private and public funders and generated increased levels of funding in the past decade. Although the success of awareness efforts from other fields cannot always be perfectly replicated, the FTD field could learn from and adapt the strategies used in ALS and other disease fields to raise overall awareness, which could lead to more scientific interest and funding in the field.

- **Develop broad and easily accessible FTD educational information and screening tools for primary care physicians and patients**. A primary care physician is often someone's first interaction with the medical care system, but medical professionals need improved screening tools to correctly recognize FTD symptoms early. Additionally, FTD symptoms can be mistaken for psychiatric or other neurodegenerative conditions, and developing screening tools for individuals who believe that they or a loved one is developing FTD could decrease time to diagnosis. Developing and disseminating simple and accessible educational information and screening tools that are based on validated FTD biomarkers should be prioritized so that primary care physicians and individuals can collectively reduce diagnostic delays for FTD and begin care sooner.

- **Launch a strategic campaign to increase awareness of FTD**. A strategic, concerted effort to make FTD a household acronym could have strong downstream effects. An awareness-building campaign should increase public knowledge of FTD to enable earlier recognition of symptoms, raise clinician proficiency in diagnosing and referring people with FTD to opportunities for research and treatment, and reduce societal stigma associated with dementias and other similar brain diseases. Increased awareness in the general and clinical populations can also help build momentum and political pressure for policymakers and other key decision-makers to implement widespread changes such as increasing FTD funding and improving access to care.

WHAT COMES NEXT

FTD is a devastating disease that is life-altering for everyone who is touched by the symptoms it causes. Symptoms that include changes in behavior, personality, memory, mobility, and more strike people in the prime of their lives, robbing them of their livelihoods, independence, and, ultimately, themselves. More work is needed to understand fundamental questions about how FTD arises and develops and how to slow, halt, or prevent the disease. The field needs reliable and accurate ways to diagnose, track, and treat FTD, but a lack of biological understanding, insufficient opportunities for patient participation, and low general awareness has slowed progress.

Looking across the FTD field, there are multiple reasons to be hopeful. Thanks to the dedication of funders, researchers, clinicians, industry partners, and patients, an increased understanding of genetic FTD has resulted in progress in therapeutic development with a dozen therapies in clinical testing. More work is needed to ensure that these therapies continue advancing through the clinical pipeline and make their way to all patients, and this will require a sustained commitment from all stakeholders. Although scientific understanding of sporadic FTD is less advanced, progress is being made to learn about the underlying mechanisms that cut across FTD subtypes. Leveraging knowledge of these mechanisms could help accelerate progress across the field. Several biomarkers are in development now that could soon be used to better diagnose patients, measure FTD progression, and assess whether therapeutics are working as intended.

Public funding for FTD has increased over the past decade, suggesting a growing interest in the space, and private funders have already contributed substantially to our understanding of FTD. However, more funding and attention are needed to overcome the hurdle of low public awareness, reduce stigma around the disease, and increase financial and other support for the FTD community.

Strategically deployed philanthropic capital can guide the changes the field considers necessary to advance scientific progress in FTD. Philanthropic investments can be deployed with speed and agility and galvanize increased interest and funding from other private and public funders. Strategic philanthropy can support the FTD field as it works to overcome the barriers in the space by improving knowledge about all types of FTD, supporting the development of biomarkers for improved diagnosis and treatment, increasing patient engagement across the ecosystem, and raising awareness and support for the condition. Investment in these areas will lead to significant scientific discovery and improve diagnosis, treatment, and quality of life for individuals living with FTD and their families.

APPENDIX

Key Stakeholders

This section summarizes key stakeholders in the FTD research field. These include organizations, large research projects, collaborations, and consortia, as well as other important resources that support the FTD community. Collectively, these entities are working to fill critical gaps in the understanding of FTD and its underlying disease mechanisms, as well as support individuals living with FTD and their caregivers. This is not a comprehensive list of ongoing work in the field but provides a snapshot of ongoing efforts.

ORGANIZATIONS SUPPORTING FTD

Association for Frontotemporal Degeneration

The mission of the Association for Frontotemporal Degeneration is to improve the quality of life of people affected by FTD and drive research to a cure. The organization and its partners work to advance research by coordinating grant programs, raising awareness, providing critical support and education for patients and caregivers, and advocating for those impacted by FTD.

Bluefield Project

The Bluefield Project is a research consortium focused on finding treatments for FTD caused by the dozens of known disease-causing mutations in the progranulin gene (*GRN*). It does this primarily through funding research across the discovery and drug development process and collaborating with others to accelerate research progress.

CurePSP

The mission of CurePSP is to raise awareness, build community, improve care, and find a cure for PSP, CBD, and multiple system atrophy. It provides families with resources and support services, spearheading education and outreach initiatives and investing in research. *Note: PSP and CBD are both forms of FTD.*

Rainwater Charitable Foundation

The Rainwater Charitable Foundation (RCF) is a private family foundation founded by Richard Rainwater in 1991. The foundation focused on supporting children, families, and education until 2009, when RCF also began investing in research on PSP and other tauopathies. RCF leads the Tau Consortium, a research consortium studying and developing treatments for tauopathies. RCF also hosts events for field stakeholders to connect and supports an FTD registry.

FTD RESEARCH INITIATIVES

AFTD and Target ALS Collaboration

In May 2020, Target ALS and AFTD announced $5 million in funding awards for work by six research teams to aid in the discovery of biomarkers and viable treatments for ALS and FTD, which overlap in genetic causes and biological mechanisms. The six collaborative projects will assess promising potential ways to detect and address ALS/ FTD pathology.

ALLFTD

ALLFTD is a comprehensive longitudinal clinical research study encompassing most subtypes of FTD. The overarching goal of ALLFTD is to understand the changes in brain function that occur because of disease progression and how those changes differ from normal aging. The study aims to identify reliable clinical measures and biomarkers to aid in clinical research, diagnosis, and treatment of FTD.

Clinical Research in ALS and Related Disorders for Therapeutic Development

The Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) is a consortium dedicated to advancing the field's understanding of the genetics of ALS as well as FTD, primary lateral sclerosis, hereditary spastic paraplegia, and progressive muscular atrophy. The project aims to advance therapeutic development by better understanding the relationship between genetics and clinical phenotype and discovering and developing biomarkers. In addition to the primary research, the consortium supports a small biorepository as well as a clinical research training scholarship in collaboration with the American Academy of Neurology and the American Brain Foundation.

FTD Prevention Initiative

The FTD Prevention Initiative is a project within GENFI that aims to globalize the FTD research system. This effort includes working with global pharmaceutical companies to help design better clinical trials for genetic FTD, as well as spearheading a promising initiative to collect and harmonize clinical datasets from around the world into a single open-access database.

FTD Registry

The FTD Registry provides a platform for the whole FTD community to learn about and share clinical research studies, as well as share de-identified data. The mission of the registry is to facilitate and advance FTD research and accelerate the development of treatments by providing tools and resources that (1) promote and support research participation, (2) enable access and sharing of data with researchers, and (3) amplify the patient and family voice in research.

Genetic Frontotemporal Dementia Initiative

The Genetic Frontotemporal Dementia Initiative (GENFI) is an observational study primarily focused on genetic forms of FTD in European and Canadian populations. The GENFI study enrolls participants 18 and older with FTD symptoms as well as presymptomatic gene carriers at risk of developing FTD. It has enrolled more than 1,400 people with the goal of answering the question: How do we better stratify people living with FTD? GENFI consists of several research cores, each with its own assessments and sample collections: Clinical, Neuropsychology, Imaging, Biomarkers, and Genetics. It also has a Participant Engagement Board that provides input on the study's progress and upcoming clinical trials.

National Alzheimer's Coordinating Center's FTD module

The National Alzheimer's Coordinating Center (NACC) was established in 1999 by the National Institute on Aging at the NIH to facilitate collaborative research. The center maintains a large database of standardized clinical and neuropathological research data. The focus of the NACC is Alzheimer's disease, but the database includes a subset of data from people living with FTD, as well as several training modules to help clinicians collect and utilize standardized datasets.

National Centralized Repository for Alzheimer's Disease and Related Dementias

National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) is a national resource where clinical data and biological materials, such as genetic material, blood, CSF, cellular research models, and brain tissue, can be stored and requested by other researchers. The goal of the repository is to support research on the causes of Alzheimer's disease and related dementias, including FTD, as well as advance early detection and therapeutic development. It maintains data and biological samples from diagnosed individuals as well as healthy controls. Data and samples from the ALLFTD project are available through NCRAD.

Neurofilament Surveillance Project

The Neurofilament Surveillance Project is an ancillary study to ALLFTD funded by 11 pharma and biotech companies and three nonprofits. It is managed by the Bluefield Project. The study evaluates the levels of NfL, a promising biomarker candidate, in the blood of people at-risk for or with familial FTD and their family members. To be eligible, participants must be from a family with pathogenic mutations in one of three known disease-causing genes: *C9orf72*, *MAPT* or *GRN*. The study began in 2020 and is projected to end in 2026.

PSP Genetics Consortium

Funded by CurePSP and the Tau Consortium, the PSP Genetics Consortium is a group of neurologists, geneticists, and other neuroscientists from the United States, United Kingdom, and Germany studying the underlying genetics of PSP. This multinational approach aims to search the entire human genome for genes linked to PSP and related disorders. The study aims to sequence and analyze 2,000 genomes.

Tau Consortium

The Tau Consortium was established and funded by the Rainwater Charitable Foundation to accelerate the development of new treatments for Alzheimer's disease, frontotemporal dementia, and other neurodegenerative diseases involving tau. The consortium provides financial support to research projects and helps funded investigators collaborate, engage strategic partners, and establish and share resources needed to accelerate research progress. Collaboration goes beyond traditional research partnerships to include external support for drug discovery, clinical trials, and intellectual property.

ENDNOTES

1. Clinical trial data were obtained on 6/13/23 from beta.Clinicaltrials.gov. Condition keywords were "Frontotemporal Dementia" AND "Frontotemporal Lobar Degeneration." Study statuses were limited to "Recruiting," "Active, not recruiting," AND "Enrolling by invitation."

2. Clinical trial data were obtained on 6/13/23 from beta.Clinicaltrials.gov. Condition keywords were "Amyotrophic Lateral Sclerosis" AND "Motor Neuron Disease." Study statuses were limited to "Recruiting," "Active, not recruiting," AND "Enrolling by invitation."

3. FTD funding data were obtained on 6/7/23 from NIHReporter for 2013–2022 using keywords "Frontotemporal Dementia" OR "frontotemporal degeneration" OR "frontotemporal lobar degeneration" OR "frontotemporal lobar dementia" or "FTD" OR "FTLD" OR "Pick's Disease" OR "PSP" OR "progressive supranuclear palsy" OR "corticobasal degeneration" OR "corticobasal syndrome" in funded project titles or grants. ADRD-linked FTD funding data were obtained using the same search terms and searching within "Alzheimer's Disease Related Dementias (ADRD)" AND the "Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)."

4. ALS funding within FTD was obtained on 6/7/23 by searching for "ALS" OR "Amyotrophic Lateral Sclerosis" OR "Motor Neuron Disease" in our NIHReporter FTD spreadsheet from 2013 to 2022.

5. Alzheimer's Disease funding data within ADRD were obtained on 6/7/23 from NIHReporter for 2016–2022 using keyword "AD" OR "Alzheimer's Disease" in funded project titles and the NIH Spending Categories "Alzheimer's Disease Related Dementias (ADRD)" AND "Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)."

6. FTD investigator data were obtained from NIHReporter for 2013–2022 using search criteria from endnote 1. ALS investigator data were obtained from NIHReporter for 2013–2022 using search criteria from endnote 2.

7. Early career award data were obtained from NIHReporter for 2013–2022. The disease specific keywords are the same as noted in previous endnotes. Each of the results was limited to activity codes "Fellowships (Fs)" AND" K09" AND" "K10" AND" Research Career Awards (Ks)" AND "Training Grants (Ts)."

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