# Frontotemporal Degeneration (FTD): A Voice of the Patient Report

AFTD's Externally Led Patient-Focused Drug Development Meeting on FTD March 5, 2021



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Submitted for consideration pursuant to section 569C of the Federal Food, Drug, and Cosmetic Act to: Center for Drug Evaluation and Research (CDER) U.S. Food and Drug Administration (FDA)

Hosted by The Association for Frontotemporal Degeneration (AFTD)



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Frontotemporal Degeneration (FTD): A Voice of the Patient Report

# A Voice of the Patient Report: Frontotemporal Degeneration

Meeting date: March 5, 2021 • Report date: October 27, 2021

This report was prepared by The Association for Frontotemporal Degeneration (AFTD) as a summary of the input shared by people living with FTD, their family members, and care partners during a virtual Externally Led Patient-Focused Drug Development meeting and associated pre-meeting and post-meeting engagement activities. Participant input has been summarized by the authors to represent the comments and themes that emerged from the meeting process. This report does not represent any consensus among participants or the broader population of those living with FTD and does not include all possible perspectives.

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#### **Disclosures**

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#### Contact

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### DEDICATION

This report is dedicated to all who have lost a loved one to FTD and to all who are dedicated to addressing this disease. We share your hope for a world with compassionate care, effective support, and a future free from FTD.

FTD is a devastating diagnosis that can leave individuals and entire families feeling confused and isolated. Our EL-PFDD meeting and this report, however, are tangible evidence of a larger community united in the quest to improve diagnosis, advance quality of care and quality of life, and develop disease-modifying treatments for people facing this disease. We owe a debt of gratitude to what is emerging as a global community. Your efforts are vital.



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# **Executive Summary**

**Frontotemporal degeneration (FTD)** refers to a group of related progressive neurodegenerative disorders that disproportionately affect the frontal and temporal lobes of the brain, causing heterogeneous symptoms involving changes in personality, behavior, language, thinking, motor functioning, mood, and memory. FTD is the most common young-onset dementia, with a likely under-estimated prevalence of 60,000 cases in the United States today.

On March 5, 2021, people living with an FTD diagnosis, care partners, and caregivers participated in an Externally Led Patient-Focused Drug Development meeting (EL-PFDD) to describe their experiences with the FTD disorders. They discussed the diverse yet universally challenging daily impacts of FTD and shared perspectives on current and future approaches to treatment. Due to the COVID-19 pandemic, the meeting was held virtually. This format allowed increased participation by individuals from all regions of the United States, people living in other parts of the world, and people who would not have been able to travel to an in-person meeting.

This meeting was conducted by The Association for Frontotemporal Degeneration (AFTD) under the auspices of the U.S. Food and Drug Administration (FDA) EL-PFDD initiative, designed to help FDA regulators understand the experiences and priorities of people living with diseases such as FTD disorders. This enhanced understanding can inform the riskbenefit assessment of new drug candidates, as well as guide key regulatory decisions throughout the various stages of drug development, approval, and post-approval marketing.

In preparation for the EL-PFDD meeting on FTD, 1,241 people living with FTD, their care partners, caregivers, and family members completed the FTD Insights Survey, conducted in partnership between AFTD and the FTD Disorders Registry. Real-time polling questions were also used throughout the meeting to engage attendees and guide discussion. The EL-PFDD meeting was organized into two sessions. During the first, participants described the lived experience of FTD. In the second session, participants described their experiences seeking and receiving treatment, and shared their priorities for the development of novel treatments.

Pre-meeting survey responses, testimonials, panel discussions, comments, and live polling generated important information on the daily impacts of FTD and current treatments. Key themes are summarized below.

#### Devastating impact of FTD symptoms

- The heterogeneity of FTD is striking, with varied symptoms across FTD diagnoses and within a given disorder.
- Across FTD disorders, participants share an experience of wide-ranging and devastating impacts on every dimension of their lives.

#### Difficulty obtaining reliable FTD diagnoses

 There are significant challenges associated with obtaining FTD diagnoses, including repeated misdiagnoses.

#### **Impact of familial FTD**

 There is an enormous cross-generational toll that autosomal dominantly inherited FTD can have on a family, including the difficult choices at-risk family members face about whether to learn if they carry a disease variant.

#### Lack of effective treatment for FTD

- The lack of effective therapies symptomatic or disease-modifying – causes widespread frustration and concern.
- Treatment combinations are often experimented over the course of years, sometimes helping to temporarily mitigate specific symptoms.
- Side effects are common and often exacerbated by inappropriate prescription of drugs approved for other conditions (e.g., Alzheimer's disease).



Executive Summary, cont'd.

• Many are willing to risk side effects to try a new treatment for this, to-date, terminal diagnosis.

#### **Research participation**

• There is an overwhelming desire to participate in research to advance treatment options, although

some procedures and trial designs can challenge participation.

A recording of this public meeting can be viewed here: **www.theaftd.org/patient-focused-drug- development**.

# Introduction

#### Setting the Stage

On March 5, 2021, The Association for Frontotemporal Degeneration (AFTD) conducted a virtual Externally Led Patient-Focused Drug Development (EL-PFDD) meeting, an opportunity for people impacted by frontotemporal degeneration (FTD) to speak directly to representatives from the U.S. Food and Drug Administration (FDA). By offering first-hand testimony on the lived experience of FTD and treatment options, participants provided important perspectives to guide FTD therapeutic development, risk-benefit analyses, and key regulatory decisions by the FDA. See **Appendix 1** for meeting agenda.

A total of 25 speakers covering the full range of FTD disorders provided insights from their own experiences living with an FTD disorder or caring for someone who does (see Appendix 2 for meeting speakers). A steady stream of callers and online commenters contributed additional insights and testimonies. More than 550 individuals attended. including people living with an FTD diagnosis; care partners, who collaborate with the person diagnosed in enacting their care plan, and caregivers, who provide care for those unable to care for themselves (together the largest share of participants); individuals with at least one biological relative who is living, or has lived, with an FTD diagnosis; and people with a professional interest in FTD (see Appendix 3 for meeting participant demographic information).

The meeting opened with a short presentation by Dr. Michelle Campbell of the FDA's Center for Drug Evaluation and Research (CDER), followed by an overview of the FTD disorders from Dr. Bradford Dickerson of Harvard Medical School.

The first session focused on health effects and daily impacts while the second focused on current and future treatment approaches, including perspectives on both sporadic and familial causes of FTD. Each session began with pre-recorded panelist testimonials, followed by real-time polling and audience discussions moderated by James Valentine, an attorney formerly of the FDA, and Susan L-J Dickinson, AFTD's Chief Executive Officer (see Appendix 4 for meeting discussion questions). Following the meeting, participants and others affected by FTD were able to contribute additional comments online for a 30-day period. Real-time polling questions guided the discussions and captured descriptive information on those participating virtually. A full list of these questions is available in Appendix 5.

In preparation for this meeting, AFTD and the FTD Disorders Registry conducted a pre-meeting FTD Insights Survey with over 1,200 complete responses from person diagnosed, past and current care partners, and family members. Data from this survey helped to structure the EL-PFDD meeting, and the results have been used throughout this



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Introduction, cont'd.

report to supplement the narrative testimonials. More information on this survey is available in the appendices, including the methodology of the survey (**Appendix 6**), a list of survey questions (**Appendix 7**), and demographics of survey respondents (**Appendix 8**).

#### Frontotemporal Degeneration Overview

The FTD disorders are a closely related group of disorders, which in aggregate are considered an orphan disease. Common features include degeneration of the frontal and temporal lobes of the cerebral cortex and progressive atrophy of key neuroanatomical networks anchored in these regions (particularly those associated with social-emotional behavior and language). For more detailed information about FTD, see **Appendix 9**.

The FTD disorders vary in clinical presentation, pathology, and etiology. Diagnoses are based on clinical presentations, which include the following:

- **Behavioral variant FTD (bvFTD)**: The most common form of FTD, bvFTD is characterized by personality changes, apathy, and a progressive decline in appropriate social behavior, judgment, self-control, and empathy. Additional symptoms may include disinhibition, emotional blunting, compulsive or ritualistic behaviors, and changes in eating habits.
- FTD with amyotrophic lateral sclerosis (FTD-ALS): FTD and ALS can co-occur as a combination motor and cognitive disorder. In addition to changes in behavior, personality, and language skills, individuals with FTD-ALS may have difficulty walking, standing, using their hands, speaking, swallowing, or breathing.
- Corticobasal syndrome (CBS) or corticobasal degeneration (CBD): CBS/CBD is marked by degeneration of the brain's frontal and temporal lobes, as well as regions associated with initiating, controlling, and coordinating movement. In addition to motor symptoms, people with CBS/CBD may experience changes in behavior and language skills.

- **Primary progressive aphasia (PPA)**: PPA is characterized predominantly by the gradual loss of the ability to speak, read, write, and understand what others are saying.
  - o **nonfluent/agrammatic variant (nfvPPA)**: A form of PPA in which individuals progressively lose speech abilities yet can still recall the meanings of individual words.
  - o **semantic variant (svPPA)**: A form of PPA in which individuals progressively fail to grasp the meanings of words.
  - o **logopenic variant (lvPPA)**: A form of PPA in which individuals have difficulty finding words when they are speaking.
- **Progressive supranuclear palsy (PSP)**: PSP primarily affects movement. Initial symptoms are often stiffness in the axial muscles as well as the neck and trunk, along with poor balance and increasingly frequent falls.

The FTD disorders usually manifest from the outset as one of the distinct FTD types described above, although diagnostic uncertainty typically persists well after initial evaluation. FTD generally advances to involve various cognitive, behavioral, or motor domains and loss of independence, and then progresses to mild, moderate, and, finally, severe stages of dementia.

In terms of etiology, the FTD disorders may be of unknown ("sporadic FTD") or may run within families ("familial FTD"). A significant subset of familial cases of FTD are genetic in nature. Even in individuals with no family history, however, there is a risk of a new ("de novo") genetic variant. The FTD disorders are further complicated by the variation in age of onset and rate of clinical progression, factors that need to be considered when identifying appropriate clinical trial endpoints.

People with FTD often (but do not uniformly) lack insight into their own condition. This anosognosia can occur at the earliest stages of disease or as the condition worsens, with highest prevalence in bvFTD.



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As reported by current caregivers in the FTD Insights Survey, only 22% of individuals with bvFTD are mostly or fully aware of their symptoms, compared to 52% of individuals with other FTD disorders (see **Figure 1**, below). This potential lack of insight highlights the importance of caregiver report and collaboration in clinical and research evaluations and interventions. Epidemiologists estimate the prevalence of the FTD disorders in the United States at approximately 60,000, but this estimate is widely believed to be low. Access to accurate, timely diagnosis is a challenge for this rare, heterogeneous disorder with a typically young age of onset and no specific clinical criteria or diagnostic tests (Coyle-Gilchrist et al., 2016; Finger, 2016).



#### Figure 1. Are people diagnosed with FTD aware

of their symptoms? n= 549 Data from current care partners only. bvFTD group (n=369) includes diagnoses of behavioral variant frontotemporal degeneration and Pick's disease. Other group (n=180) includes PPA (svPPA, nfvPPA, lvPPA), PSP, CBS/ CBD, FTD with ALS or neuron disease, and unknown diagnoses. Data are available broken down by specific diagnoses, but the patterns represented in the graphs held within the smaller diagnostic groups.



# Session 1: Health Effects and Daily Impacts

#### Introduction

Meeting participants described living with FTD as a confusing, bewildering, and frustrating journey. For many, the uncertainty starts early. Families endure years of misdiagnosis and correspondingly inappropriate treatments, in addition to the impact of symptoms on important relationships and finances.

Gail, a caller from Florida and former caregiver to her husband, who had bvFTD, noted:

"He was diagnosed at 50, though his symptoms started in his forties. It took us seven years to get a diagnosis."

Aisha from Georgia, who cares for her mother with bvFTD, described the impact of initial misdiagnoses:

"Diagnosis took a couple of years and ranged from generic stress to menopause-related anxiety and depression, during which time her symptoms remained untreated and continued to become more extreme."

In the FTD Insights Survey, more than 50% of respondents reported that the person diagnosed saw three or more doctors before receiving an accurate diagnosis, and 44% reported having received a different diagnosis initially, including Alzheimer's or Parkinson's disease, anxiety, depression, or bipolar disorder, as well as menopause or mid-life crisis. Notably, considering the education level of survey respondents (74% had a bachelor's degree or higher), it is likely this group of respondents had more healthcare literacy, clinical resources, and access to medical specialists than the general population. Many individuals face additional barriers to receiving timely and accurate diagnoses, which have downstream effects on access to appropriate treatment. Day to day, symptoms and function can vary. Looking ahead, many people are told upon diagnosis only that the disorder is fatal and that nothing can be done to manage it.

Dan, who was diagnosed with bvFTD in 2019, described what was he was told by clinicians about the disorder:

"PET scans, MRIs, labs, and spinal tap confirmed sporadic behavior variant, frontotemporal dementia diagnosis. Treatment: none. Prognosis: fatal. Symptoms: progressive."

#### **First Symptoms**

While the majority of meeting participants and FTD Insights Survey respondents indicated the onset of symptoms between ages 50 and 59, many testimonials reflected the experience of earlier onset. Caregiving can even fall to parents, an experience unique amongst dementias.

Dawn from Illinois cares for her daughter, who started exhibiting changes in personality and behavior in her 20s, but spent two years seeking a diagnosis:

"She was diagnosed at the age of 29, but the actual [symptoms began at] 27. We didn't actually realize, because she was diagnosed with postpartum depression and then psychosis...due to her young age, it was not on their radar that she could have dementia."

The first indication that something is wrong varies widely across FTD disorders (see **Figure 2**, next page).



#### Session 1: Health Effects and Daily Impacts, cont'd.



Figure 2: First indication of something wrong, as reported by persons diagnosed and caregivers in the FTD Insights Survey. bvFTD includes bvFTD and Pick's disease (n=629). PPA includes PPA with no type reported, IvPPA, svPPA, and nfvPPA (n=228), PSP + CBD includes PSP, CBD, and CBS (n=77). FTD-ALS includes FTD-ALS and FTD with motor neuron disease (n=48). Respondents are allowed to select all that apply. "Other" response options included changes in spatial reasoning (e.g., judging distances, perceiving objects), delusions or hallucinations, "I'm not sure," a specific difficulty in everyday life [write in response], and other [write in response].

First symptoms can also vary within each FTD disorder. For example, among FTD Insights Survey respondents with PSP and CBD (n=77) whose hallmark symptoms involve movement, 58% reported motor dysfunction as the first sign something was wrong, meaning nearly half of that group experienced different initial symptoms. Write-in responses further highlight the array of first symptoms across FTD disorders, including vulnerability to "scams," extreme paranoia, getting lost in familiar places, getting in multiple car accidents, difficulty multitasking, changes in handwriting and spelling, and incontinence.

Dan, a former nurse practitioner and county coroner who was eventually diagnosed with bvFTD, described his experience of first symptoms this way:

"I believe I was the first one to notice something was not right. My main job at work was sitting with families with a loved one who was near death or who had just died. I considered myself a compassionate person. I started to forget to chart on patients or would just not show up to visits that were scheduled...It was more important for me to go gamble after work than care about what I missed that day."



Session 1: Health Effects and Daily Impacts, cont'd.

Some individuals first experience changes in thinking, which can include deficits in decision making or judgment, problem solving, planning, organizing, and paying attention.

James, whose father declined rapidly and died from FTD-ALS, described how his father's first symptoms manifested as memory and judgment changes:

"He started to make bad decisions financially, taking on loans that weren't needed. As these symptoms developed, he became disoriented and confused more easily, often getting lost in places he knew very well. In a matter of months, he went from walking and talking to being unable to feed himself."

Al's wife, initially diagnosed with PPA and Alzheimer's, was diagnosed with CBD upon autopsy. He described her early symptoms:

"The symptoms that first appeared were quite subtle. When asked a simple yes or no question, she would often answer with the opposite response she was intending. She also would do [poorly] socially and mostly listened without contributing to group conversations. Phone conversations were shorter and more one-sided than before."

Jennifer, a former high school English teacher and media specialist who was diagnosed with PPA in 2017, described her first symptoms:

"... I started to slur my words, or mix up the front and back of words...I often think of words, but then I put them in the wrong places. Sometimes, I would not know the difference between the tense I was supposed to use... As an English teacher, that is something you know down pat."

#### Most Troublesome Symptoms

As FTD spreads to different regions of the brain, symptoms advance to a wide range of additional impairments. Constant changes mean that families need to continuously adjust their strategies for coping. This also presents a challenge in determining intervention effectiveness and establishing standardized clinical trial endpoints, as trajectory of changes in symptom type and severity differ across and within FTD types.

Post-meeting, a participant left the following comment regarding changes in his wife's PSP symptoms:

"My beloved wife of 45 yrs began experiencing [symptoms] of PSP in 2014 with significant fatigue-she felt a sense of being slowly 'poisoned,' and by 2016 there were the beginning of balance abnormalities if fatigued."

FTD Insights Survey respondents were asked to report all symptoms the person diagnosed has experienced over time (see **Figure 3**, next page). While all major symptom domains were experienced to some degree across the FTD disorders, prevalence differed. As expected, individuals with PSP and CBS/CBD reported higher rates of motor symptoms compared to those with PPA, while individuals with PPA reported the highest incidence of language symptoms.



#### Session 1: Health Effects and Daily Impacts, cont'd.



Figure 3.

**Figure 3. What symptoms has the person diagnosed experienced?** *Combined responses of people diagnosed with FTD, as well as current and past caregivers. Symptoms experienced merges responses from "What was the first indication something was wrong?" and "Since the first symptom(s), what other symptoms have developed?" If a respondent endorsed the same symptom for both survey questions, the response was only counted once; however, both survey questions allowed respondents to select all that apply. bvFTD includes bvFTD and Pick's disease (n=629). PPA includes PPA with no subtype reported, lvPPA, svPPA, and nfvPPA (n=228), PSP + CBD includes PSP, CBD, and CBS (n=77). FTD-ALS includes FTD-ALS and FTD with motor neuron disease (n=48)* 



Session 1: Health Effects and Daily Impacts, cont'd.

In addition, FTD Insights Survey respondents were also asked to note the one symptom domain they find most distressing (see **Figure 4**, below). These include what symptoms the person diagnosed finds most troublesome as well as what care partners find most troublesome.



**Figure 4. What symptoms are most distressing?** Responses to question "What symptoms, if any, distress you the most?" as posed to people diagnosed (n= 148) and care partners (n=601). Respondents could select one option. Language = speaking, finding words, understanding, knowing the meaning of objects. Behavior and Personality = repetitive or compulsive behavior, rigid routines, acting differently or inappropriately in social situations, and changes in relationships. Memory = remembering recent events, learning new information. Thinking = solving problems, making judgments, organizing. Motor = tremor, balance, performing movements. Mood = anxious, not interested, depressed, irritable, emotional outbursts. Sleeping and eating/drinking = not sleeping through the night, bad dreams, sleeping too much, cravings, alcohol intake, weight gain. Other = a specific difficulty in everyday life, I'm not sure, or other. No distress = I am not distressed by symptoms [people diagnosed]/I am not distressed by his or her symptoms [care partners]



Session 1: Health Effects and Daily Impacts, cont'd.

FTD symptoms are not always distressing to the person diagnosed, particularly if that person has anosognosia. On the FTD Insights Survey, persons diagnosed and care partners were asked to reflect on what the person diagnosed finds most distressing. Six percent of persons diagnosed reported no distress caused by symptoms compared to 31% of current and past care partners who believe the person diagnosed is not distressed by any symptoms. These differences may reflect the level of functioning of those able to complete the survey and differences in anosognosia.

#### Language

On the FTD Insights Survey, 27% of people diagnosed reported being most distressed by language symptoms and 82% of respondents reported the presence of some language symptoms (99% of those with PPA). These symptoms not only cause frustration and confusion but can also undermine effective diagnosis, treatment, and symptom management, because a person living with an FTD diagnosis may have difficulty reporting their needs to others. Of respondents who reported language impairment, challenges included finding the right word (86%), speaking (70%), writing (65%), understanding long sentences (63%), reading (60%), and identifying familiar objects (42%).

Helen described the pain of how her husband Geoff's PPA manifests primarily as a wide range of language-related symptoms:

"I have watched the steady deterioration in his language. The ability to find words, his reducing vocabulary, slower listening processing time, the ever-reducing appetite for emailing, telephoning, reading, and speaking. His vocabulary is now just a handful of words. There is an almost total lack of understanding of the spoken or written word." **Sandy** from Washington, who lives with bvFTD, submitted the following written comment to convey the struggles associated with her language symptoms:

"[bvFTD] is like word vomit. Can't control what I'm saying, but by others looks not good. Me arguing at doctor's appointments. I'm embarrassed after the fact, but not really know all what I said. Then apathy towards the whole event, that was unheard of for me. Processing slow, halted more frustrating for me and others."

Jennifer from Alabama noted how her PPA language symptoms have worsened:

"Sometimes when I try to speak, nothing comes out. Sometimes, it's guttural sounds that come out, or nothing at all. Even when the words are in my mind, I can't get them to come out of my mouth. Sometimes, it feels as if my mind is buffering."

### Thinking

Fourteen percent of FTD Insights Survey respondents diagnosed with FTD report cognitive impairments as being the most distressing symptom, and 77% of respondents reported symptoms related to thinking. Of those who report symptoms related to thinking, they specified problems with decision making and judgment (91%), problem solving (88%), planning (83%), organizing (80%), and paying attention (79%).

Kacy from Texas, whose mother lived with bvFTD for 14 years, reported how the disorder affected her mother's judgment and decision making:

"If she was in the car with me and I was driving, I could be at a red light and she would say, 'Well, you can just go. Nobody's here.' And that's just not something my mom would ever say. And it makes you wonder, what else is off in her mind?"



Session 1: Health Effects and Daily Impacts, cont'd.

Jill from New York relayed the story of her late husband Deven, who was posthumously diagnosed with bvFTD.

"Deven was connecting with people online... Strangers from Ghana, Nigeria, and elsewhere asked Deven for money, and he said yes again and again and again. Deven disregarded increasingly strident warnings from me and from other family and friends. He made and repeatedly broke promises to stop hemorrhaging what became thousands of dollars to his online friends."

#### Memory

Fourteen percent of FTD Insights Survey respondents diagnosed with FTD indicated that memory impairment was the most concerning symptom, with some degree of memory deficit experienced by 58% of respondents. For people living with an FTD diagnosis, short-term memory loss interferes with one's ability to remember very recent events, as well as to perform simple tasks (e.g., brewing coffee or making tea) or more complicated but familiar tasks, such as driving a car or shopping for groceries. Such memory impairments can also diminish a person's insight into their own disabilities, which can place immense strain on the person's care partners and family members, lead to poor decision making, and exacerbate the difficulty of identifying and managing symptoms. Of those who reported symptoms related to memory, they cite problems remembering recent events (83%), remembering names of new people (68%), remembering names of friends and family (57%), and remembering the way around familiar streets (50%).

Aisha from Georgia described the impact of her mother's bvFTD memory challenges:

"One day, she was driving home from a routine doctor's appointment when she suddenly had no idea where she was or where she was going. Thankfully, she called my father and he guided her home. In 2009, my mother took a job at a local retailer. For the first time in her life, she quit a job when she was unable to retain any of the training. She was humiliated, and her confidence was crushed."

Bobby from Florida also reported the significant consequences of memory impairments:

"The impact on my life has been affected by my loss of memory, to the point of surrendering my driver's license, loss of my job, and taking my independence."

#### **Motor and Movement**

Ten percent of survey respondents with an FTD diagnosis reported motor/movement symptoms being the most distressing; however, 69% of respondents noted some presence of physical symptoms (90% of those with PSP or CBS/CBD). Those who reported such symptoms specified challenges associated with worsening balance (81%), difficulty writing (68%), weakness (60%), difficulty walking (60%), tremors (58%), and difficulty swallowing (40%). Additional motor symptoms reported included diminished energy levels, difficulty shifting positions, getting in and out of a car, and controlling urination and bowel movements, as well as reduced hand-eye coordination and an inability to feed oneself.



Session 1: Health Effects and Daily Impacts, cont'd.

Carmelo from Texas described how his wife Sherry, a former professional chef and avid traveler who lives with a diagnosis of PSP, began experiencing motor symptoms in 2018:

"Sherry would have difficulty with balancing and movement, things like getting in and out of the car were becoming a challenge for her. She had a pretty serious fall that required her to get stitches...She owned her own business as a professional chef. When she could no longer cut vegetables due to difficulty with her hand-eye coordination, she decided to close her business."

Amanda from Texas described her recently diagnosed husband's difficulties with movement:

"The falling, the balance, the hand-eye coordination. I've had more emergency room [visits] because...he still thinks he can do things and...he drilled through his own hand. He's falling. Something happens almost on a daily basis that'slike a catastrophe."

Scott from Oregan's wife had svPPA for 3.5 years before she died. He described the influence of her movement symptoms on her life:

"The impact of her activities was really in her ability to initiate activity, even tell herself to stand up, to go do something, to freezing at the coffee maker, freezing at any number of daily activities, having troubles with incontinence, personal care."

#### Mood

On the FTD Insights Survey, nine percent of respondents with an FTD diagnosis and 12% of caregivers reported being most distressed by mood symptoms, and 68% of respondents reported some presence of mood changes. This group noted challenges caused by anxiety (70%), irritability (61%), depression (59%), anger (47%), and emotional outbursts (46%).

James from California described the impact of svPPA on his mood:

"When I was failing to remember certain things, I would get quite depressed. And occasionally when I was having those problems and my family members were not recognizing that that was what was going on, I would get angry...they would get super scared that I was getting angry with them or that I would do something negative to them."

Bobby, a caller from Florida, noted his mood symptoms:

"My sleep patterns keep me up at night, wandering the house and the yard at night, and it creates high anxiety during the day because of lack of sleep. My anxiety is so high I no longer like to go into public places or family gatherings."

#### Sleep and Eating/Drinking

While only two percent of individuals on the FTD Insights Survey with an FTD diagnosis reported sleep and eating/drinking symptoms to be the most distressing symptoms, nearly half of respondents reported some changes in eating/drinking and sleep. These symptoms include cravings, increased alcohol intake, weight gain or weight loss, not sleeping through the night, having bad dreams, and sleeping too much.



#### Session 1: Health Effects and Daily Impacts, cont'd.

Dan from Colorado emphasized the distress he has experienced due to sleep issues from his FTD disorder, which involve shifting from "poor sleep" to "too much sleep." He described an interminable struggle to obtain much-needed rest:

"The sleep issues of dreams, nightmares, hallucinations have made sleep difficult and hard to get rest."

Julie from San Diego, who cared for a loved one with FTD, described the difficulties associated with her loved one's insatiable hunger:

"We had to put locks on our cabinets, pantry, and fridge. When we were eating meals, he would steal food off of other people's plates."

Several meeting participants described compulsive eating and drinking as particularly troublesome. Julie from San Diego shared that one of the biggest impacts of FTD has been her loved one's insatiable hunger:

"We had to put locks on our cabinets, pantry and fridge. When we were eating meals, he would steal food off of other people's plates."

#### **Personality and Relationships**

On the FTD Insights Survey, two percent of people diagnosed indicated personality and relationship impairments were the most distressing, while more than 15% of caregivers noted these domains were most distressing for them. Examples include lack of motivation (78%), not realizing their effect on others (78%), not caring about others' feelings (73%), and acting inappropriately (58%). While not the most distressing, 68% of respondents reported personality changes and 36% reported relationship changes. Several people living with an FTD diagnosis, and many care partners, described the aggressive behavior, apathy, irregular mood, and diminished impulse control that can result from the FTD disorders. Care partners and caregivers described their loved ones exhibiting stubbornness, rebelliousness, and defensiveness in inappropriate situations, and apathy in situations that would normally elicit concern or alarm—such as hurting a loved one's feelings, driving on the wrong side of the road, or causing a car accident. In many instances, changes like these strained personal relationships with friends and family, induced financial ruin, and in some cases led to physical danger and even violent death.

Dan from Colorado described FTD's effects on his relationships in profound, devastating ways:

"I long to not yell at my 17-year-old daughter in the evening for cooking me the wrong meal. ....[My wife] is now my guardian and caregiver. She doesn't know what Dan she'll be living with today...The isolation of the disease has made my dogs my best friends, and my true friends I had don't call anymore. People just don't know what to do with me."

Jill from New York relayed the story of her late husband Deven's behaviors that ultimately led to his death:

"Deven no longer seemed to care about anyone apart from the strangers he met online. They took precedence over family and friends, becoming more important to him, more trusted, and more predatory. Other than Deven's uncharacteristic gullibility with regard to their requests—which included enlisting him in criminal activity—he presented as cognitively intact. He blogged eloquently. He won a national education award for outstanding work as a school librarian."



Session 1: Health Effects and Daily Impacts, cont'd.

Deven would later be evicted from his Bronx apartment. He lived in his car for a while before selling it and using the money to live in a cheap hotel room. When the hotel evicted him for nonpayment, Deven moved into the homeless shelter where he was stabbed to death. Deven was still in the early stages of FTD, having lived outside of his previous home for only 17 months when he was killed.

Amanda D., who belongs to a family that carries an autosomal dominantly inherited FTD variant, described the trauma of growing up with her father given his mood and personality symptoms, and her fear that she would develop similar symptoms and traumatize her own son in turn:

"It was not safe, physically, psychologically, to be around [my dad] alone as a child. He had violent outbursts and was a dangerous driver, and [said] just deeply hurtful words that children shouldn't have to hear...I think if I had the lack of empathy that my dad had as a result of the disease, that lack of insight, that would be traumatic for my son."

#### **Delusions and Hallucinations**

Delusions (firm beliefs held despite contradictory evidence) and hallucinations (sensory experiences in the absence of external stimuli) can also be present in FTD and complicate the diagnosis between FTD and a primary psychiatric disorder. While only 3% of care partners and 1% of people diagnosed cited delusions and hallucinations to be the single most distressing symptom type on the FTD Insights Survey, 20% of respondents noted the presence of delusions or hallucinations, particularly among those with bvFTD (29.3%) and FTD-ALS (27%). Additionally, 16% of meeting attendees and 35% of FTD Insights Survey respondents noted being prescribed antipsychotic mediations. When present, these symptoms can be extremely troublesome. Amanda from Texas described her husband's delusional beliefs and the impact on his behavior:

"There's been paranoia where he thought that I was after him, I was going to leave and take off with the kids so he disappeared with my children for 10 days, going from hotel to hotel, thinking people were after him."

#### **Global Impact of Symptoms**

One constant is that across all FTD types and respondent types, individuals report a relentless deterioration in functioning at home, in the community, and interpersonally. The continually changing and worsening array of symptoms in cognitive, behavioral, and physical domains exacerbates the impact on daily living. These detrimental effects include loss of career and corresponding normal daily structure. Failure to manage the household and increasing dependency on others are significant issues for both persons diagnosed with FTD as well as their care partners.

Dorian from Maine described the case of her son Matthew, who first began showing symptoms at age 20 and was diagnosed with bvFTD at 28:

"Matthew was an athlete, an Eagle Scout, served a church mission, worked out six days a week, ran marathons, and was active in sports and socially. I started getting phone calls about Matt's behavior, showing up at job sites, meetings, and rehearsals on the wrong data or wrong time, inappropriate conversation, asking for rides when class already started."

She reported that Matthew went from being independent to requiring 24/7 1:1 care in a matter of months.



#### Session 1: Health Effects and Daily Impacts, cont'd.

Cindy, diagnosed with bvFTD, described the impact of her symptoms on her daily life:

"Employed as an accountant, I struggled during tax season. I could do the forms fine, but putting them into the correct order left me befuddled... at the end of that tax season, I was fired."

Matthew described the impact of bvFTD symptoms on his wife's activities of daily living:

"She was twice let go from her position as an insurance broker. From there, we began to notice her lack of attention to personal hygiene, as well as a shockingly apparent lack of empathy for those closest to her."

Aisha from Georgia described the profound challenges she faces in providing care for her mother, who has lived with a diagnosis of FTD since 2013:

"Before FTD, my mother was a supportive wife to her high school sweetheart husband of more than 40 years, a proud and protective mother of a sickly only child, and an active member of her church...She seems to understand that she can no longer do the things she once did..."

Young-onset FTD can have especially harsh impacts on families with children or teenagers in the home. The sudden or gradual inability of a parent to perform his or her duties; the stress, confusion, and uncertainty surrounding journeys of misdiagnoses; the occurrence of embarrassing or inappropriate parental behaviors; and the need for familial role reversals can all severely impact the health and stability of a young family system. Impaired social cognition, which is a common feature of all FTD disorders, can also compound and add to these stressors. Amanda from Texas spoke about how her husband's FTD symptoms, which include odd behaviors and motor symptoms (falling, loss of balance and of handeye coordination), affect their children:

"We still have school-aged children. Both of them are in middle school... One of the hardest things is for my children to have to see this and understand what's happening. He doesn't want to admit anything's happening or going on."

Matthew described how his wife Lisa, diagnosed with bvFTD at 43, experienced profound thinking changes that affected their family:

"Watching her get up and abruptly walk out of the room just as the kids were showing her the report card was both heartbreaking and painful to witness. This was not the loving, tender, and compassionate mother the children and I once knew."

FTD Insights Survey respondents reported that loss of independence and difficulty communicating impacted their daily lives more than any other symptoms. Meeting participants described similarly devastating impacts of these symptoms. Symptoms of the FTD disorders make it difficult to manage home activities, such as paying bills and managing finances, keeping track of appointments, managing medications, performing household chores, preparing meals, managing communications, and maintaining daily hygiene.



#### Session 1: Health Effects and Daily Impacts, cont'd.

Caroline from Ohio cares for her 43-year-old daughter Karen, a business owner who lost the ability to manage her finances:

"She was not able to handle any finances, [or] pay her bills. So consequently, we had to bring her home, shut down her Pilates studio and take care of everything financially."

Carmelo from Texas, whose wife Sherry lives with a diagnosis of PSP, described how painful it has been for Sherry to lose her independence:

"She now uses a walker to move about the house, and she needs help with little things like getting in and out of the shower. She doesn't like to call me for help and has kept her independent and determined spirit...It really hits home what PSP does to someone."

Drew from Minnesota described his loved one's lack of independence:

"We have full-time caregivers seven days a week. This is to help her take and plan her medication, but also to drive her to her appointments, help her with household chores and perhaps most importantly, to socialize with her and watch her. She can't cross the street or even cook on her own anymore."

Similarly, survey respondents and meeting participants described how symptoms of the FTD disorders can make it difficult to perform activities outside of the home, especially driving a car, grocery shopping, running errands, working, engaging in physical activity, and attending school. A participant left the following comment in the wake of the EL-PFDD meeting regarding his wife, who has a PSP diagnosis:

"She had been a wonderful student and practicing medical doctor with a memory unrivaled. This disease has taken her from a remarkable ability to understand and apply complex solutions to medical problems and has left her apathetic, unable to walk or stand, entirely dependent upon me for mobility and all activities of daily life."

Cindy from Arizona cares for her husband with FTD and described the impact of the disorder on both of their abilities to work:

"He can't follow directions very well. He can't work and I've had to quit work and stay home and seek part-time employment. And I kind of have to manage everything...I've had to make some adjustments around the house for safety reasons."

Symptoms of the FTD disorders also impact a person's ability to participate in interpersonal or social activities. FTD Insights Survey respondents reported several such activities that are especially affected, including attending social gatherings, participating in conversations, interacting with new people, maintaining friendships, playing a game like cards or chess, being intimate with a spouse or partner, and caring for children or grandchildren.



Session 1: Health Effects and Daily Impacts, cont'd.

Al, whose wife Judith died from PPA in 2017, described how her social engagement and communication skills were affected by her condition:

"When asked a simple yes or no question, she would often answer with the opposite response she was intending. She also withdrew socially and mostly listened, without contributing, to group conversations. Phone conversations were shorter and more one-sided than before."

Rita from Maryland cared for her mother who had a bvFTD diagnosis. She shared the impact of her mother's symptoms on her social connections:

"She loved to talk and laugh and be with her friends... and then began to get very confused and really increasingly stepped away from doing that... Now we know that it really became very difficult for her to process and to understand what was happening."

Teresa from Arizona described her fears of how FTD could limit her ability to connect with her family:

"I know that as my disease progresses, I'm going to lose my voice and I'm not going to be able to tell my child that I love her."

#### **Concerns About the Future**

FTD Insights Survey respondents and meeting participants all expressed concerns about how their FTD disorders may impact the future for themselves and their families. When asked to identify their top three worries about the future, meeting participants indicated that their biggest fear was the stress of not knowing how the disease will progress, followed by the possibility of losing the ability to communicate, and losing identity or sense of self. Lower-ranked but still significant concerns included losing the ability to swallow, losing mobility or the ability to walk, and damaging family relationships. Substantial proportions of FTD Insights Survey respondents who regard themselves as being at heightened risk for FTD reported that their risk status has influenced their future plans, particularly in regard to financial planning (86%); lifestyle choices such as diet, exercise, and hobbies (85%); and having children (38%).

Anne, a meeting participant who carries an FTD genetic variant that she inherited from her father, expressed concern about her financial future, echoing worries expressed in the FTD Insights Survey results:

"I didn't plan on being sick like this, so I didn't plan financially for this. My father had FTD, so I have the genetic component. I'm not really worried about what's going to happen. I already know what's going to happen."

Another meeting participant named Pedro resonated with the real-time polling results, stressing his family's top concern for the future:

"What's coming down the path for us with the disease? It's hard to get visibility into how the disease is going to progress."



# Session 2: Current and Future Approaches to Treatment

#### Introduction

During Session 2, which focused on current and future approaches to treating FTD disorders, participants described painful odysseys in search of effective therapies. Many participants recalled years of misdiagnosis and ineffective treatment, followed by many more years of experimenting with various treatment combinations in an attempt to mitigate some of the worst symptoms. The absence of effective therapies, combined with a lack of knowledge about FTD among many clinicians, are the primary factors that leave families to manage through a series of symptom-by-symptom approximations to treatment, relying on interventions designed to treat other conditions. With the inability of people diagnosed to monitor or shape their own behavior, family caregivers and others must learn nuanced behavioral interventions with little professional training or hands-on support to help. Many people report the most effective treatment is learned by experiences of other caregivers through peer support groups.

#### Treatments

Participants living with an FTD diagnosis catalogued many classes of medicines they have been prescribed to help manage their symptoms, including antidepressants, Alzheimer's disease medications (i.e., anticholinergics or cognition-enhancing drugs), antipsychotics, anxiolytics or benzodiazepines, mood stabilizers, sedatives, anticonvulsants, and Parkinsonian drugs (i.e., dopamine promoters), as well as marijuana (see **Figure 5**, next page). As reported by care partners, the prevalence of prescription medication use is consistent across moderate, severe, and profound levels of impairment.

Meeting participants described how various treatment options have helped them to relieve symptoms: escitalopram reduced anxiety, temazepam mitigated nighttime disturbances, Zoloft helped to regulate mood and behavior and reduce pacing, Haldol helped control aggression and obsessions, and Myrbetriq helped control nighttime incontinence. Most of these benefits, however, were fleeting.



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Figure 5

#### Figure 5. Past use of prescription medications as reported in the

**FTD Insights Survey.** *n*=841. Results include reports from individuals with an FTD diagnosis (*n*=89), current care partners (*n*=422), and past care partners (*n*=330) who indicated that they had taken prescription medications. Survey also included response option "I prefer not to say" (only endorsed in *n*=1). Free text from the "Other" category is available as well as data broken down by diagnosis, and reports from current care partners can be broken down by disease severity level. Respondents are allowed to select all that apply.

Meeting participants highlighted various drawbacks to current treatment regimens, especially ineffectiveness and side effects, as well as number of pills or other medications needed per day, high cost, limited availability or accessibility of treatments, and level of effort or time needed to adhere to treatment regimens. Some also reported that treatments can worsen FTD symptoms. For instance, nearly half of FTD Insights Survey respondents indicated that they or their loved one had been prescribed cognitionenhancing drugs, despite evidence to contraindicate their use, including lack of benefit and evidence that they exacerbate behavioral symptoms of the FTD disorders.

Dorian, whose son Matthew died of bvFTD, described her family's desperate journey to seek effective treatments. Matthew began to show symptoms of neurodegeneration during his 20s and was diagnosed with bvFTD at 28. Medication dosages, combinations, and delivery systems were constantly adjusted to help manage Matthew's symptoms; he was prescribed Depakote for his seizures and anxiety, sertraline for his obsessive-compulsive behaviors, and clonidine for his anxiety and lack of impulse control. He also took trazodone and oxycodone to help reduce his tremors and melatonin to improve his sleep.



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Dorian described a desperate and painful journey of changing from one ineffective medication to another:

"Meds offered short-lived and fluctuating relief and we were constantly adjusting the dosages every three months or less. All were imperfect tools, but the only tools we had. None impacting the underlying pathology. None of the medications Matthew was prescribed ever managed his impulse control."

Melissa from Oregon described her family's struggle to find appropriate treatment for her late father:

"His disease had progressed enough that he was accepted into a care home... We worked daily with a geriatric psychologist to figure out what cocktail of meds would help and dosages were increased frequently."

Brandon from California became a primary caregiver for his mother when he was 19. A VCP genetic variant runs in his family:

"Her symptoms have constantly been progressing and changing so we've constantly been evaluating the medications that she's been taking, making adjustments to her dosages...It's a constant struggle to gauge the benefit of an antipsychotic or a mood stabilizer or a sleep medication with the negative effects that it has at the same time." Halima, a geriatrician from Maryland spoke about her father, who has been diagnosed with PPA:

"When thinking about drawbacks of our current treatment approaches: side effects I think is the biggest, also number of pills, as well as questions of effectiveness."

People living with an FTD diagnosis and their families often seek symptom relief using various nonpharmaceutical treatments, such as speech therapy for PPA and physical or occupational therapy for FTD with motor symptoms. Many FTD Insights Survey respondents had tried at least one of the following treatment approaches: exercise (48%), speech/language therapy (42%), support groups (35%), physical therapy (33%), diet modification (31%), meditation (20%), and occupational therapy (16%). Some report physical therapy improved mobility; exercise improved sleep; speech therapy and communication aids such as Oxford Picture Dictionary and picture books helped to maintain communication skills; and Alpha-Stim, intravenous immunoglobulin, and meditation helped with anger management. While a comprehensive interdisciplinary care team would be ideal, such care is costly and inaccessible to many.

Similarly, meeting participants described varying degrees of success attributed to other nonpharmacological interventions, such as modifications to their home, neurofeedback, biofeedback memory aid tools (e.g., Play Attention), light therapy, and electrotherapy. Participants repeatedly stressed that strategies for managing symptoms rarely if ever provided long-term relief.

Meeting participants' testimony revealed a common theme: namely, the lack of official medical guidance or standards for treatment drive those living with an FTD diagnosis and their families to search creatively, and in many cases desperately, to find ways of temporarily managing the most troublesome



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symptoms of the FTD disorders. The approaches that achieve results usually only provide temporary respite, which leads families on long, frustrating journeys in search of genuine, long-term relief.

Bob from Alabama, who cares for his wife Charlotte, described their struggle to manage her communication symptoms:

"We tried speech therapy early on and it can help with short-term benefits, maintaining communication...I had to explain the disease to the therapist who knew stroke aphasia, but not PPA. We tried the Lingraphica communicator, which generates speech, but it was too slow functioning...These strategies work for [her] somewhat to manage, but they don't really change this disease."

Ed from California illustrated the frustration caused by the search for symptom relief for his wife, who has a C9orf72 variant:

"They were experimenting a lot with different medications...It became hard to know the difference between what's the disease and what's the side effect of the drug that she's on right now." When considering whether to try a new medication, FTD Insights Survey respondents reported weighing factors such as a doctor's opinion, the invasiveness of the treatment (e.g., spinal tap delivery), potential interaction with other medications, and the ability to take the medication at home.

Despite universal frustration with finding appropriate and long-lasting treatment options, meeting participants reported some degree of progress based upon the current treatment regimen (see **Figure 6**, below), reflecting that even small improvements can be clinically and personally meaningful and that people may continue to use medications if they appear to offer even a slight alleviation of symptoms.

Wanda highlighted the need to expedite treatment development:

"Three, four months, for my family is an eternity. So please, urgency is important."

# Figure 6.

**Figure 6. How well does the current regimen control important symptoms of the condition?** *Asked of meeting participants during live polling, n=113* 





#### Session 2: Current and Future Approaches to Treatment

#### Autosomal Dominantly Inherited FTD

A significant minority of families affected by the FTD disorders transmit an autosomal dominant diseasecausing variant across generations. Individuals in these families often know what it means when the first symptoms of FTD appear. For them, the FTD disorders are a nightmare that has affected generations of their family members, including the dread of recognition upon receiving a diagnosis, and the fear felt on behalf of the next generation, who are at risk of carrying an FTD variant. Each individual in a family with a genetic variant also faces questions about if and when to undergo genetic testing as well as the risks and benefits of participating in clinical trials. There are many families in which genetic loading is not known or discussed amongst all family members. Of FTD Insights Survey respondents who reported a positive family history or genetic variant, 40% have undergone genetic testing.

Cindy, who was diagnosed with bvFTD in 2011 at the age of 58, described how FTD has taken the lives of her grandmother, her mother, her aunt, and her uncle. It was not until several of her relatives had died from the disease that her neuropsychiatrist diagnosed Cindy with FTD and realized that autosomal dominantly inherited FTD was running through her family. Cindy fears for the children in her family:

"I would willingly participate in any research studies or drug trials, even if there is a risk to my life. I am that desperate to have this disease end with me... FTD has now taken a family member in every decade. I pray that this disease can end with me." Hannah, a police officer in the U.K., illustrated the amplified trauma of genetic FTD:

"With my dad's diagnosis came another blow, it was genetic. I debated over having the test, but I realized that I could live better with the result, whatever it was. Then, I was given the bad news. I am to suffer the same fate as my dad, giving my children a 50% chance too. I look at my children every day, as they run and play with their friends, knowing that I am responsible for this brutal condition potentially affecting them, and that kills me."

Whether familial or sporadic, individuals experience the same heterogeneous range of initial symptoms, report the same kinds of symptoms as most burdensome, search constantly for effective treatments and switch for years from one ineffective option to another, and face grave uncertainty about how the disease will progress.

#### A Commitment to Clinical Trials

Meeting participants who belong to families with a known FTD variant acknowledged that their hereditary risk presents a special opportunity to learn about the disease at (and before) onset, as well as to develop and test early intervention strategies. Many expressed willingness to obtain genetic testing and to participate in clinical trials to develop symptomatic therapies, prevent or slow the progression of the disorder, or target the underlying causes.

Helen described her husband Geoff's participation in the Genetic Frontotemporal Dementia Initiative (GENFI) observational study and other clinical trials:

"He has never refused any type of intervention, including multiple lumbar punctures. He likes to know he's doing good, even if it is for others."



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Hannah, who has lost several family members to FTD and who has tested positive for an FTD genetic variant, emphasized the need for treatments that impact the disease before it becomes too advanced:

"I actively participate in the GENFI study. And for me, the priorities for treatment are to stop people losing themselves to this condition. I personally would not want treatment that extends my life or slows the deterioration once I've reached certain clinical stages."

Wanda, whose family has a history of progranulin variants, also expressed her eagerness to participate:

"Families are ready, we're willing, we're ready to go...across the branches, it looks a little different in every individual. But if the treatments could be broad enough to capture a lot of the behaviors, would just be wonderful. I would just encourage the FDA: Go, don't sit on anything." **Jessica** from the U.K., who shares a C9orf72 variant with her FTD-diagnosed mother, shared her insights about research:

"I'm obviously doing everything I can in my power to help fight this. I want researchers to know...and the panel that sit on the board for the FDA, I want them to know that I am available and use me. And, if you can help find biomarkers by testing on me, then I'm available."

Geoff, Hannah, Wanda, and Jessica's willingness to participate in FTD clinical trials was shared among meeting participants across all sessions. Respondents to the FTD Insights Survey reported a strong willingness to participate in clinical trials to help obtain more effective treatments (see **Figure 7**, below).

### Figure 7.

Figure 7. Rate your willingness to participate in a clinical trial to develop an FTD treatment. n=328. Results broken down by those with a current FTD diagnosis (n=132) and at-risk relatives (n=196). Data are also available for current care partners. Results suggest that the majority (>75%) of individuals diagnosed with FTD and at-risk relatives would be willing

to participate in clinical trials to develop an FTD treatment





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Among at-risk family members who responded to the FTD Insights Survey, 70% are willing to obtain genetic testing to determine whether they are approaching the onset of FTD symptoms, if such testing is needed to participate in a clinical trial.

Of those willing to participate in research, FTD Insights Survey respondents reported an openness to procedures including blood samples (93%), genetic testing (86%), MRI scans and EEG recordings (82%), PET scans (77%), skin biopsies (76%), answering detailed questions (70%), and lumbar punctures (42%). However, perceptions of willingness differed across caregivers and persons diagnosed. For example, 98% of individuals diagnosed with FTD said they would be willing to answered detailed questions; only 50% of care partners believed their family member with FTD would be willing to do so. This difference likely reflects a combination of anosognosia, differences in believed capabilities, and a selection bias of persons diagnosed able and willing to complete the FTD Insights Survey.

Echoing the determination described by many panelists and participants during this session of the meeting, a substantial proportion of pre-meeting survey respondents (i.e., 20 to 40%) expressed a willingness to risk rare but serious side effects to try a new treatment, as reflected in **Figure 8**, below.



### Figure 8.

#### Figure 8. Percentage of people willing to risk rare but serious side effects to try a new

**treatment for an FTD disorder.** *n*=1100. "Which, if any, of the following rare but serious side effects would NOT prevent you from choosing a new treatment? Select all that apply." Results include individuals with a current diagnosis of FTD, at-risk relatives, current care partners, and past care partners. The pattern did not differ depending on respondent type. Data are available broken down by respondent group.



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James, whose father has FTD and who has a family history of C9orf72 variants, described the complexity of decisions around genetic testing and research participation:

"Before participating in any future new drug trial, I would want to clearly understand the likely benefits, such as furthering knowledge or effectively treating the condition. I would consider genetic testing for the carrier gene, if it were beneficial for this study. However, I would want to understand what these benefits are."

Some meeting participants and survey respondents described reluctance to participate in research, particularly when they or their loved ones are at later stages of the disease.

Helen, who has cared for her 57-year-old husband Geoff since he was confirmed to carry an FTD-causing progranulin variant, had this to say about Geoff's decision to obtain genetic testing and participate in FTD clinical trials:

"I believe that every FTD sufferer has a trial tipping point. If a trial intends to suspend or slow disease progression, at what point does participation remain acceptable?... I ask, 'If Geoff could be suspended at this point of progression and be like this for the next 20 years, would that be what he or I want?""

Of those with a negative perception of clinical trials, they cited issues like the person with FTD having to undergo unpleasant tests, side effects, not knowing individual or overall study results, being put in a placebo group, and the physical and emotional toll. In addition, there is a need to determine whether the person diagnosed or a study partner will be responsible for navigating the logistics of research participation in addition to the daily challenges of FTD. FTD Insights Survey respondents noted concerns with how FTD symptoms makes study participation difficult:

"Patient refuses to talk, leave the home or get dressed."

"No invasive tests - flu shot requires a bear hug."

"This patient [is] too far advanced to participate properly in clinical trials."

Other respondents reported feeling like it was too late or burdensome for their loved one to participate:

"25 years ago I would have agreed - now I just want this to end."

"My life was turned upside with my husband's illness. Our family has been through enough. Enough is enough."

"My spouse is too far into the disease."

Despite concerns, respondents to the FTD Insights Survey representing the range of FTD disorders shared hope for what impact new treatments may have with respect to improving their ability to communicate, maintain independence, achieve higher-quality relationships with family and friends, and control emotions and behavior (see **Figure 9**, next page).



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Figure 9.

**Figure 9.** What I would want most in a treatment for FTD would be for it to improve [select all that apply]. *n*=982. Results include responses from currently diagnosed individuals and current/past care partners. Other response options included "Hold a job" and "Other."

Meeting participants stressed the urgent need for research and treatments. When ranking treatment targets, meeting participants noted an interest in drugs to slow or stop the progression of the disease (25%), help with language and communication (19%), enhance thinking and decision making (19%), and improve behavior (16%).

A participant who has the same C9orf72 variant as his father left the following post-meeting comment:

"I am 35, the changes are not yet visible but are already happening in my brain, I will soon be at a point of no return. If experts in research into this field believe the treatment may prevent the disease, I would be happy to try anything." Teresa, who has a diagnosis of FTD, emphasized the pressing need for appropriate treatment:

"... for the FDA to listen to us and to realize that this is an immediate need, because I don't have forever."



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#### **Benefit-Risk Assessment Framework for FTD**

Over the past several years, the FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains the FDA's rationale for its regulatory decision. In the Framework, the Analysis of Condition and Current Treatment Options rows summarize and assess the severity of the condition and therapies available to treat FTD. The assessment provides an important context for drug regulatory decision making, including valuable information for weighing the specific benefits and risks of a particular medical

product under review. The input provided by people diagnosed with one of the FTD disorders and their loved ones through the FTD EL-PFDD meeting and survey comments will inform the understanding of the Analysis of Condition and Current Treatment Options for this disease.

The information in the top two rows of the proposed framework for FTD, below, draws from various sources, including what was discussed at the FTD EL-PFDD meeting. This proposed framework contains the kind of information that, if it is anticipated, could be included in a framework completed for a drug under review for bvFTD, PPA, FTD-ALS, CBD, or PSP. Each FTD disorder be addressed individually (bvFTD, PPA, FTD-ALS, CBD, or PSP). The information in these tables may be adjusted over time as understanding of FTD disorders improves or new therapies emerge.



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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<b>bvFTD</b> is progressive and fatal. It is the most common form of FTD. This FTD type is characterized by progressive atrophy in the frontal and anterior regions of the brain leading to alterations in complex thinking and behavior. Personality changes, apathy/emotional blunting, and progressive decline in socially appropriate behaviors are often notable. Additional symptoms may include disinhibition, compulsive or ritualistic behaviors, and changes in eating habits. Changes in executive functioning may lead to poor financial decisions or on-the-job mistakes that ultimately lead to occupational disability. The affected person often has poor insight into their condition, making the changes particularly distressing and difficult to manage for caregivers and care partners. One individual diagnosed with bvFTD stated, "The most concerning thing for my family was the changes in my mood and behavior that were bizarre. My ability to screen my words and jokes was gone." A daughter shared about her father, "on many occasions he attempted to exit the car while it was still moving down the road." Another reported, "With bvFTD, you lose the essence of who you are." As the condition progresses, additional symptoms emerge, including language and motor symptoms, and, ultimately, death.	bvFTD accounts for approximately 60% of people living with FTD. At early stages of disease, burdensome symptoms often relate to personality changes, emotional dysregulation, and impaired judgment. Significant impacts include altered social relationships, marital difficulties, job problems, damage to financial well-being, legal problems, drug and alcohol abuse, and the ability to live independently. People diagnosed with bvFTD have a poor prognosis; as bvFTD progresses, additional symptoms typically arise, leading to impairment across all domains of functioning and activities of daily living. Like all FTD types, bvFTD is progressive and fatal. Survival duration varies, but reviews point to an average of eight years between onset and death (Kansal et al., 2016, Onyike et al., 2013).
Current Treatment Options	There are no FDA approved treatments for bvFTD. Off label use of selective serotonin reuptake inhibitors (SSRIs) may help some persons with bvFTD manage symptoms of agitation, irritability, and lack of motivation. Other management strategies include exercise, diet, alcohol avoidance, a daily routine, and peer support. Drugs to help with sleep may be prescribed, as well as antipsychotic medications when needed to address behavior control. Prescription for anti-cholinergic medications is common, despite some evidence to contraindicate their use. More than half of FTD Insights Survey respondents reported that no intervention they have tried for bvFTD has had a positive impact on the person diagnosed.	There is a need for effective and tolerable FDA- approved therapies to treat bvFTD. In the search for effective treatments, many pursue drug therapies that are ineffectual or exacerbate symptoms. This pernicious illness calls for the development of both symptomatic and disease-modifying treatments as there is a clear and significant unmet medical need for people living with bvFTD. Across all FTD types, however, affected individuals and family members often report that disease-modifying therapies to slow progression may not offer perceived benefit once the disease is progressed. One meeting participant noted "If he could be suspended at this point of progression and be like this for the next 20 years, would that be what he or I want?" In the FTD Insights Survey, seventy percent of respondents expressed hope that a future treatment could restore [continued next page]

#### Behavioral Variant FTD - bvFTD



# Session 2: Current and Future Approaches to Treatment

Dimension	Evidence and Uncertainties	<b>Conclusions and Reasons</b>
Current Treatment Options		their independence while more than half hope that a treatment could enhance their interpersonal relationships, communication skills, and ability to control emotions and behavior.



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Dimension	Evidence and Uncertainties	Conclusions and Reasons	
Analysis of Condition	PPA is progressive and fatal. Affected individuals exhibit a gradual impairment of language, including speech, reading, writing, and comprehending what others are saying. People can have difficulty producing movements of their lips and tongue and their speech may be labored, while others become completely mute. While language is the hallmark symptom of PPA, on the FTD Insights Survey, more than half of participants with PPA reported experiencing changes or dysfunction in thinking and decision-making, memory, mood, and personality. In addition, nearly half of FTD Insights Survey respondents reported changes in thinking as a first indication that something was wrong. Research on PPA classifications is ongoing. Currently, clinicians recognize three types of PPA: • <b>nonfluent/agrammatic variant (nfvPPA)</b> : A form of PPA in which individuals progressively display disrupted language production (e.g., shorter phrase structure, omission of grammatical morphemes) and labored speech, yet retain the meaning of individual words. • <b>semantic variant (svPPA)</b> : A form of PPA in which individuals progressively fail to grasp the meanings of words, have trouble recognizing faces of familiar people and have difficulty understanding the emotions of others. In addition, disinhibited, rigid and compulsive behaviors eventually develop. While most remain relatively unconcerned about their condition, some individuals retain insight and focus on their deficits and may be at risk of suicide. • <b>logopenic variant (lvPPA)</b> : A form of PPA in which individuals have difficulty finding words, resulting in frequent pauses while speaking. People with lvPPA, however, generally recall the meanings of words, unlike other types of PPA. Of the three PPA types, lvPPA is most commonly – but not always – associated with Alzheimer's disease pathology, which creates additional challenges in diagnosis and treatment trials. <b>[continued next page]</b>	PPA primarily affects speech and language, particularly at early stages of disease. These communication issues impact the ability to maintain employment, socialize, to participate in activities with others, to engage in everyday household activities like meal preparation, and, notably, to communicate one's needs and wants. People with PPA may eventually become completely nonverbal. Losing language skills can be extremely isolating and have severe psychological impacts. Other functional domains are impacted as well, including behavior, cognition, and movement. The disease is progressive and ultimately fatal. Individuals with PPA typically live for an average of seven years following diagnosis, although years of survival is highly variable (Grossman, 2010).	

#### Primary Progressive Aphasia - PPA



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### Session 2: Current and Future Approaches to Treatment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
s of Condition, cont'd.	A friend of someone diagnosed with PPA observed, "Phone conversations were shorter and more one-sided than before."	
	A person diagnosed said, "I started to slur my words or mix up the front or back of words." One woman reported, "Now, sometimes when I try to speak, nothing comes out. Sometimes it's a guttural sound that comes out, or nothing at all. Even when the words are in my mind, I can't get them to come out of my mouth."	
Analysi	As the condition progresses, additional language domains are impacted and the distinction between PPA types is blurred. In advanced stages of PPA, additional symptoms emerge, including cognitive, behavior, and motor symptoms, and, ultimately, death.	
Current Treatment Options	There are no FDA-approved treatments for PPA. Antidepressants may be used to treat depression and anxiety associated with PPA. Non-pharmaceutical treatment options can include speech-language therapy, but as the disease progresses, speech-therapy interventions lose any effectiveness. Psychotropic medications may be used to treat sleep or behavioral issues. Less than a quarter of FTD Insights Survey respondents reported any intervention having a positive impact on the person with PPA.	Treatment options for PPA are few and difficult to tolerate. People living with PPA need treatment that will restore some level of verbal communication. Additionally, treatments that would slow the disease progression would be helpful. One husband said, "We need a way to slow this disease down if a cure cannot be found." More than 90% of FTD Insights Across all FTD types, however, affected individuals and family members often report that disease-modifying therapies to slow progression may not offer perceived benefit once the disease is progressed. Survey respondents noted a desire for medication that would improve the ability to communicate and 70% expressed hope that a future treatment would allow the person diagnosed to

### Primary Progressive Aphasia - PPA, cont'd.



### Session 2: Current and Future Approaches to Treatment

### FTD and Amyotrophic Lateral Sclerosis (Lou Gehrig's disease) - FTD-ALS

AFTD thanks the ALS Association for their feedback on this table.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	FTD-ALS is progressive and fatal. In people with FTD-ALS, the disorders co-occur as a combination of motor and cognitive problems, among other domains. Clinical manifestations of FTD-ALS include muscle weakness, difficulty breathing, loss of muscle tissue, muscle contractions, and difficulty swallowing which can lead to choking and aspiration. Speech may be slowed and slurred. In addition to these hallmark symptoms of ALS, people with FTD-ALS demonstrate impairments in executive functioning, behavior, and language, among other domains. Symptoms are heterogeneous. In the FTD Insights Survey, the first reported sign something was wrong was most likely be changes in personality, followed by relationships, mood, and motor disturbances. Respondents to this FTD-focused survey reported further changes or dysfunction in language, thinking and decision-making, movement, personality, memory, mood, behaviors, sleep, and eating/ drinking. People affected with FTD-ALS typically have a <i>C9orf72</i> gene variant which is inherited in an autosomal dominant manner, meaning a carrier's children each have a 50% chance of inheriting the variant, leading to multiple generations of disease impact. FTD-ALS is progressive, generally leading to the loss of the ability to walk and reliance on ventilator support for breathing. A family member reported, "In a matter of months, he went from walking and talking to being unable to feed himself." Another, "Within a very short time, months rather than years, my father required a wheelchair, a hoist, downstairs accommodation with an appropriate bed, and assistance to wash and clean." He added, "My mother became a full-time caregiver with little to no respite. My mother struggled with the lack of information that caregivers had available to them, often making her own choices with care provision." As the condition progresses, additional symptoms	FTD-ALS is a debilitating and life-threatening condition that impacts the ability to perform everyday activities such as walking, speaking, and eating. Progression is rapid; loss of independence can arise within months. The swift progression of impairment across functional domains often leads to a requirement of full-time care. Difficulty with swallowing and chewing impair the person's ability to eat and can lead to choking and potentially lead to aspiration pneumonia. The FTD-related behavioral, thought, and personality changes can add complexity in implementing ALS standard of care interventions and adaptive equipment. It can also contribute to severe distress for caregivers and families. The clinical symptomatology is highly heterogenous and may differ between and within families, which leads to an unpredictable pattern and age of onset of clinical manifestations. The disease is progressive and ultimately fatal. The most common cause of death in FTD-ALS is respiratory failure. FTD-ALS has a poor prognosis with a median survival rate of approximately 2.5 years from disease onset (Kansal et al., 2016; Onyike et al., 2013).

Return to


### Session 2: Current and Future Approaches to Treatment

#### Dimension **Evidence and Uncertainties Conclusions and Reasons** There is no cure for FTD-ALS, a fatal, progressive There is a clear unmet medical need for disease disease. There are FDA-approved treatments to slow modifying treatments to stop progression of this the progression of symptoms in a subset of persons debilitating and fatal illness. Some treatments are diagnosed with ALS, including Riluzole and Radicava. available for the ALS component of FTD-ALS. No Other drugs may be prescribed to individuals with treatments exist for the cognitive and behavioral **Current Treatment Options** FTD-ALS to relieve specific symptoms, such as muscle symptoms and those symptoms can, in turn, spasticity and cramping, but many symptomatic hinder the implementation of ALS standard-oftreatments are ineffective. Often people try supportive care treatments. A care partner noted, "He is interventions for the movement symptoms, such receiving treatment for his ALS symptoms, but as braces, walkers, and thickened liquids for easier there's been no treatment for his FTD symptoms." swallowing. On the FTD Insights Survey, 100% of Across all FTD types, however, affected individuals persons diagnosed and 50% of their care partners. and family members often report that diseasereported that no intervention tried to date has had a modifying therapies to slow progression may not offer perceived benefit once the disease is positive impact on the person diagnosed. progressed. Ninety percent of respondents on the FTD Insights Survey expressed hope that future treatments could allow the person diagnosed to have more independence in everyday life. More than half indicated a desire for interventions to address communication skills, interpersonal relationships, and the ability to control emotions and behavior.

### FTD and Amyotrophic Lateral Sclerosis (Lou Gehrig's disease) - FTD-ALS, cont'd.



### Session 2: Current and Future Approaches to Treatment

### **Corticobasal Degeneration - CBD**

AFTD thanks CurePSP for their feedback on this table.

Dimension	Evidence and Uncertainties	<b>Conclusions and Reasons</b>
Analysis of Condition	<b>CBD</b> is progressive and fatal. It is marked by degeneration of the brain's frontal and temporal lobes, as well as regions associated with initiating, controlling, and coordinating movement. CBD primarily affects movement, such as the inability to make hands, arms, or legs carry out the desired motion. In the most common clinical subtype of CBD, called corticobasal syndrome (CBS), people exhibit slow movements and difficulty completing familiar activities. Those affected may experience involuntary muscle contractions and sustained abnormal limb postures, often on just one side of the body. In addition to motor changes, the majority of individuals with most CBD subtypes describe experiencing dysfunction in language, memory, thinking and decision-making, personality, mood, behavior, and sleep. On the FTD Insights Survey question asking about the first indication that something was wrong, many reported changes in motor and spatial reasoning but half noted changes in mode. As the disease progresses, more symptom domains become affected, eventually leading to death.	CBD affects a person's ability to carry out many activities of daily living, including opening a door; operating the television, computer or telephone; or completing tasks such as cooking. A person with CBD gradually loses the ability to live and function independently and becomes dependent on the help of others. The disease is progressive and ultimately fatal. Death in CBD is, on average, 6.5 years following diagnosis, caused by pneumonia or other complications, such as sepsis or pulmonary embolism (Armstrong et al., 2013; National Institute of Neurological Disorders and Stroke, 2019).
Current Treatment Options	There are no FDA approved treatments for CBD and there is no way to slow the progression. Benzodiazepines and some antiepileptic drugs may help with dystonia and myoclonus. Many of the deficits may respond to nonspecific symptomatic medications. Other treatments include changes to diet, exercise, occupational therapy, speech therapy, physical therapy for gait and balance concerns, and the use of assistive and orthotic devices. On the FTD Insights Survey, people diagnosed and care partners overwhelmingly reported that no interventions, medical or non-medical, have had a marked impact on the affected individual.	Treatments are urgently needed to slow or halt the disease progression. There is an additional need for symptomatic relief, particularly to address the movement symptoms. Across all FTD types, however, affected individuals and family members often report that disease-modifying therapies to slow progression may not offer perceived benefit once the disease is progressed. One hundred percent of FTD Insights Survey respondents noted a desire for future treatment that would allow the person diagnosed to function independently.



### Session 2: Current and Future Approaches to Treatment

### Progressive Supranuclear Palsy - PSP

AFTD thanks CurePSP for their feedback on this table.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<b>PSP</b> is progressive and fatal. Motor dysfunction may be the initial presenting symptom, manifested as difficulty with balance, increased falling, an unsteady gait, and slow movements. First symptoms can also be stiffness in the axial muscles as well as in the trunk and neck, but then may progress to other bodily systems, including the ability to aim the eyes or blink, to swallow safely, and to produce comprehensible speech. Many people also report inappropriate behaviors such as disinhibition, emotional incontinence, apathy, anxiety, depression and emotional blunting. Cognitive symptoms, such as impaired concentration, decision making, mental flexibility, spatial reasoning, problem solving, organizing, reasoning, and planning are often cited. On the FTD Insights Survey, the majority of respondents reported problems with language, personality, and mood. One husband reported about his wife, "her ability to balance has progressively deteriorated. I have installed bars around the bathroom so she can move about, but she still needs help with things like getting in and out of the shower." Another noted, "the most upsetting part of my wife's experience with PSP is her loss of independence."	PSP is a disease that severely impacts movement and then progresses to affect other functional domains. The inability to walk influences every aspect of a person's life and falls can have sequelae with significant health consequences. Isolation due to loss of mobility can have psychological impacts and lead to depression and anxiety. Most people with PSP develop severe speech and swallowing problems; the most common cause of death in PSP relates to aspiration pneumonia or the inability to swallow. In addition to motor symptoms, people diagnosed often experience dysfunction in language, personality, mood, cognition, and behavior, all of which significantly impact people's lives. The disease is progressive and fatal. The median survival duration of PSP patients is 6-8 years from onset (dell'Aquila et al., 2013; Chiu et al., 2010).
Current Treatment Options	There are no FDA approved treatments for PSP. Levodopa-related medications may be tried to help with slowness, stiffness, and balance, but their efficacy is modest and brief in most cases. Botulinum injections may help those struggling to open their eyelids. Physical therapy can help with balance and muscle control and is the main tool in reducing falls and maximizing engagement in daily activities. Exercise may help flexibility, conditioning, mood, and bowel function but the risk of falls limits its use. Speech and swallowing therapy may help temporarily. On the FTD Insights Survey, nearly three quarters of people diagnosed with PSP reported that no intervention to date has significantly impacted their life.	There continues to be a great unmet medical need for people living with PSP. Disease-modifying and symptomatic treatments are urgently needed. Across all FTD types, however, affected individuals and family members often report that disease- modifying therapies to slow progression may not offer perceived benefit once the disease is progressed. Nearly 90% of FTD Insights Survey respondents noted a desire for medication that would improve the ability to maintain independence and to communicate. More than half reported hope that future treatments could enhance the ability to communicate and the quality of interpersonal relationships.



Frontotemporal Degeneration (FTD): A Voice of the Patient Report

# Conclusion

Participants throughout this meeting and survey highlighted the devastating impacts of the FTD disorders on diagnosed persons as well as families and caregivers. They described painful journeys involving misdiagnoses, worsening and evolving symptoms, isolation, loss of independence, and constantly evolving efforts to treat this progressive fatal disease with off-label medications or nonpharmaceutical options. While symptoms are heterogeneous, there is a common experience of symptoms' devastating impact on daily functioning, interpersonal relationships, and independence. Participants note special challenges related to sporadic type - for example, difficulty finding others who understand their condition - as well as familial type, where individuals must manage their at-risk status. They universally stressed the urgency of finding new treatments, both to manage symptoms and to cure the underlying disease.

People with FTD and their significant others overwhelmingly expressed interest in participating in clinical trials and considering new treatments, but noted concerns regarding degree of invasiveness, potential efficacy, and logistics involved in participation. Research challenges include accounting for heterogeneity in symptom presentation and course combined with widespread and progressive functional impairments. Recruitment and retention for these rare disease trial designs will benefit from broad inclusion criteria and recognition that symptom presentation and insight vary across people, disease state, and even in a single individual over the course of a day. Potential anosognosia, as well as other symptoms that affect a diagnosed person's ability to self-report, point to the need to consistently include care partner and caregiver reports. In addition, the heterogeneous presentation of symptoms and course presents opportunities and obstacles with respect to clinically meaningful trial endpoints, as well as the need for outcome assessments that are broad enough to capture all presentation types and sensitive enough to detect individual changes. Innovative trial designs are critical to recruiting enough individuals to power a study, particularly to evaluate potential therapies that target specific, ultra-rare subsets of this rare disease.

With no available long-term effective options, participants stressed the need to develop and approve therapies as quickly as possible, even if treatment gains may be small. Respondents noted that they and their family members are currently in distress and the only available symptomatic treatments work temporarily, if at all. Many expressed an openness to participating in research to expedite the development of treatment options, even risking severe side effects. Participants implored representatives from the FDA to act quickly given the notable unmet medical need.

Aisha summarized the urgent plea to clinical researchers and regulatory agencies:

"Frontotemporal dementia is the cruelest, most unrelenting disease that completely strips its victims of their identity and robs families of a piece of their soul. We need relief, and it cannot come soon enough."



# Appendix 1: Meeting Agenda

#### FTD EL-PFDD Meeting Agenda March 5, 2021 10:00 am – 3:30 pm ET

Time	Торіс	Subtopic	Leader	Number of presenters
10:00 am	Welcome		AFTD Representative	1
10:10 am	Invited FDA speaker		Michelle Campbell, PhD, Center for Drug Evaluation and Research (CDER)	1
10:20 am	FTD clinical overview		Bradford Dickerson, MD, Harvard Medical School	1
10:35 am	Introduction and meeting overview		James Valentine, JD, MHS (HPM), moderator; and Susan Dickinson, MSGC, CEO (AFTD), co-hosts	2
10:40 am	Remote demo	ographic polling		
	Session 1: He	alth Effects and Daily Impacts		
10:45 am		Pre-recorded panelist testimonials		5 @ 5 min each
11:10 am		Moderated audience discussion and remote polling		
12:25 pm	Lunch			
	Session 2: Current and Future Approaches to Treatment			
12:55 pm	Moderator opening		James Valentine	
1:00 pm		Panel 2A – Perspectives on Sporadic FTD	Pre-recorded panelist testimonials	5 @ 5 min each
1:25 pm		Moderator-led transition		
1:30 pm		Panel 2B – Perspectives on Genetic FTD	Pre-recorded panelist testimonials	5 @ 5 min each
1:55 pm		Moderated audience discussion and remote polling		
3:15 pm	Meeting summary		Larry Bauer, RN, MA, HPM	1
3:20 pm	Next steps & closing remarks		Susan Dickinson, AFTD	1
3:30 pm	Adjourn			

# **Appendix 2: Meeting Speakers**

#### Panel 1 - Health Effects and Daily Impacts



Aisha A. – Aisha lives in Georgia and helps her father provide care for her mother, who was diagnosed with behavioral variant FTD in 2013. Before her FTD symptoms began interfering with daily tasks, Aisha's

mother was an accomplished businesswoman and a talented vocalist, and lived with a desire to help others. When reflecting on aspects of her mother's progressive changes, Aisha recalls episodes when her mother became disoriented, began having violent outbursts and hallucinations, and slowly lost the ability to perform daily tasks. Additionally, the family experienced many frustrating years of incorrect diagnoses and medical prescriptions that did little to alleviate her mother's symptoms. Some medications came with significant side effects that only made the family's situation more challenging. Aisha describes FTD as *"the cruelest, most unrelenting disease that completely strips its victims of their identity"* and urges that *"relief cannot come soon enough."* 

Jill B. – Jill, a writer and editor, lives in New York. She bravely shares details about her late husband's journey with behavioral variant FTD, which was diagnosed after his death at the age of 62. Jill remembers Deven as a fiercely intelligent individual, an avid reader, and someone with a quirky sense of humor. Shortly after winning a national award honoring his work as a librarian, Deven's behavior and personality began to radically shift, and his relationship with Jill and their son deteriorated quickly. Jill recalls that Deven's long-time friendships also began to unravel, but that he formed new relationships with strangers and gave away large sums of money in blatant financial scams. Without any awareness that these changes were caused by an underlying pathology, Deven moved to New York City, where his inability to make sound decisions

ultimately cost him his life. Jill hopes that sharing Deven's story will highlight the need to have more awareness about the devastating impact FTD can have on a person and their family, as well as the urgent need for disease-modifying interventions and therapies. *"This insidious disease demands attention. It demands research dollars, it demands treatment,"* said Jill.

**Carmelo G.** – Carmelo is an attorney who lives in Texas and is a full-time care partner for his wife of 38 years, Sherry. In 2017, when Sherry was 62 years old,



they started noticing that she was having difficulty with her balance, coordination, and movement. Following visits with a series of specialists, Sherry was diagnosed with progressive supranuclear palsy in 2018. Eventually, as her symptoms continued to impact her physical abilities. Sherry had to close her culinary business, which she had started 14 years earlier after receiving her degree in culinary arts from the Ritz Escoffier in Paris, France. Following her diagnosis, Carmelo and Sherry enjoyed several trips to South America until her symptoms and physical limitations became too overwhelming. Carmelo says that today, Sherry rarely leaves her bedroom and prefers to keep visitors to a minimum. While her memory and mental abilities remain strong, her lack of mobility and loss of independence are most upsetting. "Sherry was never one to back down from a challenge," said Carmelo. "If by some miracle her symptoms could be reversed, I know she would pick right up doing all the things she loved and enjoyed before."



Frontotemporal Degeneration (FTD): A Voice of the Patient Report

### **Appendix 2:** Meeting Speakers



Dan K. – Dan lives in Colorado with his wife, Lisl, and their youngest of three children. When Dan was in his late 40s, he began to notice a concerning lack of empathy, new forgetfulness, and inability to focus on

and retain important details. As a nurse practitioner and county coroner, Dan's career relied on all these skills and more. His family life was suffering as well, because of changes to his behavior and emotional responses, including being prone to angry outbursts, consuming too much alcohol and food, and impulsive spending. Following his diagnosis of behavioral variant FTD in 2018 when he was 48 years old, Dan immediately retired, guit driving, and relinguished control of the family's finances. He recognizes the impact FTD has had on himself and his family, and wishes for medications or therapies that could help him manage his symptoms and improve his daily quality of life. "I long not to yell at my 17-year-old daughter in the evening for making the wrong meal," Dan said. "My wife and I have to choose joy daily to not allow this disease to conquer us."



Jenn L. – Jenn lives in Alabama with her husband, Chris, and their six children. Prior to her diagnosis of primary progressive aphasia in 2017, Jenn had worked as a high school educator for 17 years and was an active community

volunteer, alongside balancing her children's busy schedules. Keeping a journal of her progressive symptoms has helped Jenn recall changes in her abilities and personality leading up to her diagnosis, including spelling and grammatical errors atypical of an English teacher, changes in her handwriting and letter inversions, and overwhelming anxiety when faced with crowds and loud noises. She describes slowly losing the ability to perform everyday tasks, such as doing the laundry or making meals, and how she has had to relearn patterns and adapt to the progressive challenges of the disease. Often, Jenn feels as though she is just hanging on and fears what will happen "when I get to the bottom." Though she is often frustrated and saddened by the changes she continues to face, Jenn says that she and her family have decided to celebrate her good days and to cherish their time together.



### Frontotemporal Degeneration (FTD): A Voice of the Patient Report

### Appendix 2: Meeting Speakers

### Panel 2A - Perspectives on Sporadic FTD

**Dorian B.** – Dorian lives in Maine where she is an occupational speech therapist specializing in dementia care. In 2011, Dorian's son Matthew was diagnosed with behavioral variant FTD at the age of 28. She offers examples



of the devastating changes in Matthew's behavior, personality, and abilities leading up to his diagnosis. Dorian suspects that Matthew was beginning to experience early symptoms of FTD when he was 20 years old, and that the disease eventually impaired his athleticism, his technical and mechanical skills, and his gregarious personality. As his symptoms progressively worsened, an ever-changing protocol of medications did little to counteract Matthew's impulsivity, hyperactivity, and obsessive-compulsive tendencies. When Matthew lived in a full-time care facility, Dorian worked tirelessly with the staff to augment his care whenever new behaviors would become harmful or destructive. Today, Dorian volunteers as a support group facilitator, sharing her son's experience with other families as they face their personal journeys with FTD. She hopes that sharing Matthew's story will drive greater awareness about the need for tools, therapies, and treatments that can effectively manage the multiple symptoms experienced by persons diagnosed with FTD. "I couldn't help my son, but I am here because maybe, just maybe I might be able to help someone else's child."



Matt D. – Matt lives in Canada with his three young children and is a caregiver for his wife, Lisa, who was diagnosed with behavioral variant FTD in 2013 when she was 43 years old. After Lisa was relieved of her position as an insurance broker for a second time in 2011. Matt and his children noticed more episodes when she was listless and uninterested in the family, lacked empathy, and was not attending to her personal hygiene. Additionally, Matt recalls Lisa repeatedly lying, secretly spending excessive amounts of money, experiencing auditory hallucinations, and having angry outbursts toward their children. Since her diagnosis in 2013, Lisa has been placed on an ever-changing list of medications to help manage her symptoms, with little effect. Matt longs for a treatment that would allow Lisa, who became nonverbal in 2018, to be able to communicate with him and their children and to be able to more fully experience being a wife and mother again. "A treatment that would allow the brain but a few brief moments of sheer exhilaration, joy, and empathy to be able to cherish these special moments would help to erase the painful memories our three children will forever have of what should've been special [...] occasions with their mother," said Matt.



### Frontotemporal Degeneration (FTD): A Voice of the Patient Report

### Appendix 2: Meeting Speakers

AIP. – Al and his wife had been married for nearly 50 years when Judy was diagnosed with primary progressive aphasia and Alzheimer's disease in 2014. He recalls that her symptoms were subtle at first, and mainly consisted of momentary lapses in the ability to communicate and a general withdrawal from socializing and participating in large groups. Following a



neuropsychological evaluation that showed deficits in Judy's short-term memory, language skills, visual perception, and executive functioning, she willingly gave up driving. Medications that had shown some promise for persons with Alzheimer's disease had little effect on Judy's early symptoms, and as the disease progressed, she started to have trouble focusing on details, struggled to feed herself, and became incontinent. An adjustment in her prescriptions either provided little help or caused deleterious side effects. Al chose to keep Judy at home, though her condition required him to hire professional support to help with her daily care, including administering multiple medications. Eventually, Judy's condition progressed to the point where she was admitted to hospice care, once in 2016 and again in 2017. Judy "passed the morning of April 19th, our daughter's birthday," Al said. "There were no medications or treatments that slowed the progression or alleviated any of the symptoms. It would be my hope that one day, that would not be the case."

**Bob B.** – Bob lives in Alabama with his wife Charlotte who is living with primary progressive aphasia. About nine years ago, Bob says Charlotte began having difficulty with communication and understanding



conversations on television, leading them to seek more information from neurology specialists in their area. Following Charlotte's diagnosis in 2013 at the age of 64, they eagerly pursued enrolling in clinical trials and studies to help slow the progression of her symptoms. Like many persons with FTD, Charlotte was prescribed medications to address individual symptoms without much improvement in her ability to communicate with others. Today, Charlotte is still able to manage her personal care and can cook simple meals while closely following a recipe. While she is nonverbal, she communicates to others through mobile text and tries to retain her language skills through adaptive learning. Bob understands that this disease, without specific treatments to address the cause of it, will progress and that Charlotte's abilities will continue to change. "For us, smiles and laughter are rare," Bob said. He added that "I want her here as long as possible, but she's frustrated and in pain. We need better treatments."



### Appendix 2: Meeting Speakers



Melissa F. – Melissa, who lives in Oregon, relates dramatic and emotional details of her father's diagnosis with FTD. Today, Mark lives in a full-time care facility in Hawaii and, due

to the many medications he is prescribed, often sleeps throughout the day. Though he was diagnosed with FTD in 2018 at the age of 71, Melissa believes her dad has been exhibiting the symptoms of the disease since his 50s. She recalls episodes of Mark - once a guiet, gentle, and compassionate husband, father, and grandfather - becoming violent and combative with his wife, suspicious of outsiders, and a danger to himself and others due to compulsive behaviors and lack of awareness, all compounded by excessive alcohol consumption. Melissa and her family struggled for many years to help control the worst of Mark's symptoms, including changing combinations and doses of medications to help alleviate his anxiety, compulsive behaviors, and agitation. Short of leaving Mark nearly sedated, the medications do little to improve Mark's quality of life. Melissa describes FTD as "a disease of the family" that has caused her mother, as Mark's caregiver, to endure years of emotional trauma. By sharing Mark's protracted struggle with FTD, Melissa and her family are hopeful there will be a future where treatments are available to help persons diagnosed retain their true personalities and capabilities for longer periods of time. "This brutal disease has taken so much from our family, and we wish for no one else to ever suffer the pain of it."

#### Panel 2B - Perspectives on Genetic FTD

Hannah M. – Hannah, a 37-yearold mother of two girls and a police officer in the United Kingdom, outlines her family's history with dementia, which in her lifetime



has affected her grandfather and her father. Hannah recalls that nearly five years ago, her family noticed subtle changes in her father's behavior. The affectionate, dependable, and active person they all knew gradually became withdrawn, uncommunicative, and insensitive, and made poor financial decisions. Over time, her father's inattention to certain details were becoming dangerous to himself and others, which had a profound impact on the lives of his family members. Hannah's father was diagnosed with FTD in 2017; in 2018, further testing confirmed it was caused by an inherited genetic variant. Worried about her own future, Hannah received genetic counseling and learned that she too would face a personal journey with FTD. Aware of what lies ahead, Hannah fears the possibility that the disease might also affect her daughters. "I live everyday feeling like a ticking time bomb," said Hannah. "It is too late for my dad, this totally cruel disease has taken him and his dad, and unless we stop it, it will take me and my kids too."



### **Appendix 2:** Meeting Speakers

Cindy O. - Cindy, who lives in North Carolina with her daughter, was diagnosed with behavioral variant FTD in 2011 when she was 58 years old. She can recall occasions as a teenager when her grandmother would get easily confused and behave inappropriately in social situations. Her grandmother, whose aunt had also passed away due to the effects of dementia, was eventually admitted to a hospital and diagnosed with dementia. Shortly before her grandmother passed away in 1998, Cindy's mother also started making guestionable financial decisions and inappropriate advances toward strangers. While her mother was diagnosed with Alzheimer's disease and put on medication to treat the disease, Cindy recalls that the medicine did little to improve the situation and that her mother complained that treatments made her feel worse. Eventually, Cindy noticed that she herself was starting to put clothes on incorrectly, was easily disoriented, and that as an accountant, was struggling with math and money. After she was initially diagnosed with Alzheimer's, a second doctor confirmed that Cindy had behavioral variant FTD and suggested that many of her family members had been similarly affected. Today, Cindy says she would willingly participate in clinical trials and studies, even at a risk to herself, to halt the devastation from progressing through successive generations of her family. "I am that desperate to have this disease end with me," Cindy said. "FTD has now taken family members every decade. It must end!"

Helen P. - Helen lives in the United Kingdom with her husband Geoff, who is 57 years old and is living with primary progressive aphasia related to a progranulin variant. Young-



onset dementia has affected several of Geoff's family members, including his mother, who passed away at the age of 66 and his grandmother, who died at 54 years old. Both family members had demonstrated the effects of corticobasal degeneration, though Geoff had always believed his mother had had Alzheimer's disease. Through a relative, Geoff learned that his family was impacted by an inherited genetic variant - something that he had been unaware of beforehand and that compelled him to seek genetic counseling. When Geoff learned that he would also be affected by the progranulin variant, they prioritized plans that they had made for the future and retired early from their careers. Helen also ensured Geoff was enrolled in the GENFI observational study in London and they continue to pursue clinical research participation opportunities. Helen remembers her husband as a gregarious, affectionate, and generous person who now mostly communicates with her through mime and single words. Today, she considers their relationship as one of companionship and caregiving and notes how their social world has shrunk considerably. When Geoff was able to verbally communicate with Helen, he said he would "rather die of anything else but this." Helen says that "inside I feel that I am just a widow in waiting."



Frontotemporal Degeneration (FTD): A Voice of the Patient Report

### **Appendix 2:** Meeting Speakers



James W. – James lives in London, England with his wife and two sons. He describes his family's generational struggle with FTD-ALS caused

by a variant in the C9orf72 gene, which he now understands is an inherited condition in his father's family. James recalls how his paternal grandmother was diagnosed with dementia and motor neuron disease, also known as FTD-ALS, and that she was cared for at home by James's mother and father until she passed away. Like many others who are diagnosed with FTD, James's father began making unsound financial decisions, became disoriented and confused more easily, and became lost in familiar places. He was diagnosed with FTD in 2008 when he was 65 years old, and it was not long until symptoms of ALS appeared. James remembers that within months, his father was unable to walk or feed himself. When his father was diagnosed in 2008, James enrolled in the GENFI observational studies, and though he has declined to learn his genetic status, he is amenable to participating in clinical trials that might have a significant impact on the disease's progression. Motivated by and concerned for his children's future, James is also aware that minimal progress in research now has the potential for major gains in the future. "I do not want my wife and children to be in the same position we were in when my father was diagnosed," said James.

#### Discussion Starters A.M. – Health Effects and Daily Impacts



#### Discussion Starters P.M. – Perspectives on Sporadic and Genetic FTD

Wanda S. Amanda D. Ed F. Halima A. Teresa W.

#### **Speakers**



#### Bradford Dickerson,

M.D. – Dr. Dickerson is Professor of Neurology at Harvard Medical School and Director of the Frontotemporal Disorders Unit at the Massachusetts General Hospital, an integrated

multidisciplinary unit dedicated to the highest level of care for people living with these conditions. He is also a behavioral neurologist in the MGH Memory Disorders Unit and runs a multidisciplinary team of 30 clinicians and scientists to study how memory, language, emotion, and social behaviors change in normal aging and for people with neurodegenerative disease, and to study new approaches to caregiving. Dr. Dickerson is also the Chair Elect of AFTD's Medical Advisory Council, which provides AFTD with the medical, scientific and research expertise necessary to advance our mission.



Frontotemporal Degeneration (FTD): A Voice of the Patient Report

### Appendix 2: Meeting Speakers



Susan L-J Dickinson, MSGC – Susan is AFTD's Chief Executive Officer (CEO), and joined AFTD in February 2008. A genetic counselor, she brings more than three decades of experience facilitating

communications among lay, scientific and medical communities. Under her leadership, AFTD has expanded dramatically in scale and impact, from a \$400,000 organization with a part-time staff of three to an \$8 million organization with 30 full-time staff. During her tenure, AFTD has expanded programs to meet and advocate for the needs of FTD families. and invested in specific strategies to advance FTD research and drug development, including four multiyear, multi-million-dollar research initiatives targeting FTD diagnosis and treatment. Ms. Dickinson also serves on the Advisory Council for the National Institute for Neurological Disorders and Stroke. She holds an M.S. in genetic counseling from Arcadia University and B.A. in biology and psychology from Swarthmore College.



#### Michelle Campbell,

**Ph.D.** – Michelle is a Senior Clinical Analyst for Stakeholder Engagement and Clinical Outcomes in the Division of Neurology Products with the FDA. As a reviewer on the Clinical Outcome Assessments

(COA) Staff with the FDA, Michelle advises the Office of New Drugs review divisions and other FDA centers by providing consultation and advice on clinical outcome assessment development, validation, and interpretation of clinical benefit endpoints in clinical trials to support drug development, labeling, and promotion. Additionally, the COA Staff leads and manages the Center for Drug Evaluation and Research's Clinical Outcome Assessment qualification program and engages with internal and external stakeholders to advance good scientific clinical outcome measurement standards and policy development.

James Valentine, JD, MHS - James is an Associate with the law firm Hyman, Phelps & McNamara where he assists medical product industry and patient advocacy organization clients in a wide range of regulatory matters, including new drug and biologic development and approval issues. Prior to his role with HPM, James worked in the FDA's Office of Health and Constituent Affairs (previously the Office of Special Health Issues), where he facilitated patient input in benefit-risk decision-making and served as a liaison to stakeholders on a wide range of regulatory policy issues. James administered the FDA Patient Representative Program, facilitated stakeholder consultations during the reauthorization of PDUFA and MDUFA, helped launch the Patient-Focused Drug Development program, and developed the FDA Patient Network.

Larry Bauer, RN, MA - As Senior Regulatory Drug Expert with the law firm Hyman, Phelps & McNamara, Larry provides counsel to drug manufacturers on a wide range of regulatory topics including Rare Pediatric Disease Designation requests, Orphan Drug Designation requests, Fast Track and Breakthrough Therapy Designation requests, drug development regulatory strategy, preparing regulatory submissions, and drafting regulatory policies and procedures. He has extensive experience in patient advocacy and has expertise in the planning and execution of Patient-Focused Drug Development meetings. Larry's experience includes 17 years at the National Institutes of Health, as well as working for the FDA as a regulatory scientist focusing on policy, education, and science related to rare disease drug development. He has participated in numerous internal and sponsor meetings related to the development and review of novel rare disease drugs, and serves on the National Organization for Rare Disorders (NORD) Advocacy Committee.



Frontotemporal Degeneration (FTD): A Voice of the Patient Report

# **Appendix 3: Meeting Participants**

More than half of meeting participants were current or past caregivers or care partners of individuals with FTD (see **Figure 10**, below). Of the people with FTD present or represented by a care partner or relative at the EL-PFDD meeting, approximately half identified as men, and half identified as women. Most were either 60 to 69 years of age or deceased, although substantial proportions of individuals currently living with FTD were 50 to 59 years of age or older than 70. A relatively small proportion were 49 years of age or younger. Most resided in the United States (ranging from the east coast to Hawaii). A limited but encouraging number of attendees joined from Canada, Mexico, and other countries around the world. Respondents represented all FTD disorders, including behavioral variant FTD (55%), primary progressive aphasia (13%), amyotrophic lateral sclerosis with FTD or motor neuron disease (10%), progressive supranuclear palsy (4%), and corticobasal syndrome (3%); six percent of respondents were unsure which type of FTD disorder they had.



**Figure 10. Meeting participant respondent type (n=210).** Responses reflect 56% of meeting participants who responded to this live polling question. Respondents could select all options that applied.



# Appendix 4: Meeting Discussion Questions

### Session 1 - Health Effects and Daily Impacts

- 1. OF ALL THE SYMPTOMS OF FTD, WHICH 1-3 SYMPTOMS HAVE THE MOST SIGNIFICANT IMPACT ON THE PERSON WITH FTD?
- a. Which symptoms most affect the individual now?
- b. Which symptoms were the most significant at other times in the individual's life?
- c. What were the first symptoms that you detected (where you suspected something was off, or when looking back after diagnosis you now believe to be FTD)?
- 2. HOW HAS FTD AFFECTED THE PERSON WITH FTD ON THEIR BEST AND WORST DAYS? Describe the best days and the worst days.
- 3. HOW HAVE THE INDIVIDUAL'S SYMPTOMS CHANGED OVER TIME? HOW HAS THE ABILITY TO COPE WITH THESE SYMPTOMS CHANGED OVER TIME?
- 4. ARE THERE SPECIFIC, PERSONALLY MEANINGFUL ACTIVITIES THAT THE INDIVIDUAL WITH FTD CANNOT DO AT ALL, OR NOT DO AS FULLY BECAUSE OF FTD?
- a. How does this affect relationships/friendships with others?
- b. How does it affect life activities (school/work, relationships, self-sufficiency, living situation, activities, etc.)?
- c. If you or your loved one could perform one activity that you currently are unable to, what would it be?

# 5. WHAT WORRIES YOU MOST ABOUT LIVING WITH FTD?

- a. What capabilities are you most concerned about potentially losing as the disease progresses?
- b. What frustrates you most about your or your loved one's condition?

Session 2 - Current and Future Approaches to Treatment

- 1. WHAT ARE YOU CURRENTLY (OR RECENTLY) DOING TO MANAGE FTD SYMPTOMS?
- a. Which specific FTD symptoms do the treatments address?
- b. How has this treatment regime changed over time and why?
- 2. WHAT ARE THE MOST SIGNIFICANT DOWNSIDES TO THESE FTD TREATMENTS AND HOW DO THEY AFFECT DAILY LIFE? (Examples of downsides may include bothersome side effects, going to the hospital for treatment, etc.)

#### 3. HOW WELL HAVE THESE TREATMENTS CONTROLLED FTD OVERALL?

- a. How well do these treatments improve the ability to do specific activities that are important in daily life?
- 4. ALONG THE PATHWAY TO A CURE, WHAT SPECIFIC THINGS WOULD YOU LOOK FOR IN AN IDEAL TREATMENT FOR FTD? WHAT FACTORS DO YOU CONSIDER WHEN MAKING DECISIONS ABOUT SELECTING A DRUG FOR PREVENTION OR TREATMENT?



# Appendix 5: Real-Time Polling Questions

Polling questions were used as a discussion tool during the live meeting. There were 291 individuals who participated in live polling. As people came and went throughout the meeting, each question was answered by between 96 to 175 people.

### **Demographic questions**

\*Note: Caregivers were instructed to answer subsequent questions on behalf of the person living with FTD\*

### 1. WHICH BEST DESCRIBES YOU?

SELECT all that apply

- a. I am diagnosed with FTD
- I have one biological relative with FTD (parent, sibling, grandparent, child, aunt or uncle related by blood)
- c. I have multiple biological relatives with FTD
- d. I am or was a care partner/caregiver for someone with FTD
- 2. WHERE DOES THE PERSON DIAGNOSED CURRENTLY (OR MOST RECENTLY) RESIDE?
- a. US Pacific time
- b. US Mountain time
- c. US Central time
- d. US Eastern time
- e. US Alaska time
- f. US Hawaii time
- g. Canada
- h. Australia
- i. Mexico
- j. Africa
- k. Asia
- I. Europe
- m. Middle East
- n. South America
- o. Other

- 3. WHICH BEST DESCRIBES THE GENDER IDENTITY OF THE PERSON WITH FTD?
- a. Male
- b. Female
- c. Gender non-conforming
- d. Prefer not to say
- 4. HOW OLD IS THE INDIVIDUAL WITH FTD?
- a. 29 years or younger
- b. 30-39 years of age
- c. 40-49 years of age
- d. 50-59 years of age
- e. 60-69 years of age
- f. Older than 70 years of age
- g. Deceased

#### 5. AT WHAT AGE WERE SYMPTOMS FIRST EXPERIENCED BY THE PERSON WITH FTD?

- a. 29 years or younger
- b. 30-39 years of age
- c. 40-49 years of age
- d. 50-59 years of age
- e. 60-69 years of age
- f. Older than 70 years of age

#### 6. HOW WOULD YOU DESCRIBE THE PERSON'S CURRENT LEVEL OF FUNCTIONAL IMPAIRMENT?

- a. Mild needs little to no assistance to perform daily activities
- b. Moderate needs assistance to perform most daily activities
- c. Severe needs full assistance to perform nearly all daily activities
- d. Profound can no longer perform daily activities and has limited mobility and ability to communicate
- e. Not applicable the person is deceased



Appendix 5: Real-Time Polling Questions, cont'd.

- 7. WHAT TYPE OF FTD HAS BEEN DIAGNOSED IN YOUR FAMILY? Select all that apply.
- a. bvFTD behavioral variant FTD, frontotemporal dementia
- b. CBD or CBS corticobasal degeneration or corticobasal syndrome
- c. FTD with ALS
- d. PPA primary progressive aphasia
- e. PSP progressive supranuclear palsy, or Richardson's syndrome
- f. Pick's disease
- g. FTD dementia no subtype specified
- h. I'm not sure

### Session 1 - Health Effects and Daily Impacts

- 1. WHICH OF THE FOLLOWING SYMPTOMS HAS THE PERSON WITH FTD EXPERIENCED? Select ALL that apply
- a. Language and communication
- b. Memory
- c. Thinking and decision-making
- d. Spatial (judging distances, perceiving objects)
- e. Personality
- f. Mood
- g. Motor and movement
- h. Eating or drinking
- i. Behavior
- j. Sleep
- k. Delusions or hallucinations
- I. Other

- 2. SELECT THE TOP 3 MOST TROUBLESOME FTD-RELATED SYMPTOMS EXPERIENCED BY THE PERSON WITH FTD. Select up to 3
- a. Language and communication
- b. Memory
- c. Thinking and decision-making
- d. Spatial (judging distances, perceiving objects)
- e. Personality
- f. Mood
- g. Motor and movement
- h. Eating or drinking
- i. Behavior
- j. Sleep
- k. Delusions or hallucinations
- I. Other
- 3. WHAT ARE THE MOST IMPORTANT ACTIVITIES OF DAILY LIVING THAT THE PERSON WITH FTD IS NOT ABLE TO DO INDEPENDENTLY DUE TO THE DISEASE? Select TOP 3
- a. Managing finances
- b. Preparing meals
- c. Housecleaning and home maintenance
- d. Communicating with others (use phone, email, converse)
- e. Connecting with others (relationships with family and friends)
- f. Attending school or having a job
- g. Driving, managing transportation
- h. Managing medications
- i. Physical activity (take a walk, exercise)
- j. Walking and moving from one position to another
- k. Feeding
- I. Self-care (dressing, personal hygiene)
- m. Continence and toileting
- n. Other



### Appendix 5: Real-Time Polling Questions, cont'd.

- 4. WHAT WORRIES YOU MOST ABOUT YOUR OR YOUR LOVED ONE'S CONDITION IN THE FUTURE? Select TOP 3
- a. Losing identity or sense of self
- b. Losing a job or career
- c. Losing friendships
- d. Damaging family relationships
- e. The stress of not knowing how the disease will progress
- f. Losing independence
- g. Losing mobility/ability to walk
- h. Losing ability to communicate
- i. Losing ability to swallow
- j. Developing respiratory issues
- k. Not being able to work and live as desired
- I. Losing financial security (retirement, savings, income)
- m. Becoming a burden to my family
- n. Other
- o. Not applicable the person is deceased

# Session 2 - Current and Future Approaches to Treatment

- 1. WHAT MEDICATIONS OR MEDICAL TREATMENTS HAS THE PERSON DIAGNOSED TRIED? Select ALL that apply
- a. Antidepressant (SSRIs or other)
- b. Anti-parkinsonian drug (levodopa/carbidopa)
- c. Transcranial stimulation
- d. Experimental medications as part of a clinical trial
- e. Riluzole or Rasagiline
- f. Drugs for anxiety (benzodiazapines or other)
- g. Medications for cognition (Aricept, Exelon, Namenda)
- h. Antipsychotics (Seroquel, Zyprexa)

- i. Mood stabilizers (Depakote, Lithium)
- j. Other medications
- k. I'm not sure
- I. I prefer not to answer
- m. Have not used medications or medical treatments
- 2. BESIDES MEDICATIONS, WHAT APPROACHES HAS THE PERSON DIAGNOSED USED TO HELP MANAGE THE SYMPTOMS OF FTD? Select ALL that apply
- a. Increased exercise
- b. Decreased exercise
- c. Modifications/accommodations at home
- d. Mobility aids (walker, wheelchair)
- e. Diet modifications
- f. Physical or occupational therapy
- g. Speech therapy
- h. Meditation, stress management
- i. Dietary supplements
- j. Cannabidiol (CBD) or cannabis
- k. Therapy/counseling
- I. Peer support group
- m. Alternative communication strategies (personalized cards, board, technology apps)
- n. Other
- o. Not doing anything to help manage symptoms
- 3. HOW WELL DOES THE CURRENT REGIMEN CONTROL IMPORTANT SYMPTOMS OF THE CONDITION?
- a. Not at all
- b. Very little
- c. Somewhat
- d. To a great extent
- e. Not applicable because no treatment being used



### Appendix 5: Real-Time Polling Questions, cont'd.

- 4. WHAT ARE THE BIGGEST DRAWBACKS OF YOUR CURRENT APPROACHES? Select up to three
- a. Not very effective
- b. Cost
- c. Limited availability or accessibility
- d. Number of pills/medications per day
- e. Side effects
- f. Worsened the symptoms of FTD
- g. Requires too much effort and/or time commitment
- h. Travel to hospital/clinic, or doctor to maintain prescriptions
- i. Other
- j. Not applicable as no treatment is being used

- 5. WHICH ASPECTS OF THE CONDITION WOULD YOU RANK AS MOST IMPORTANT FOR A POSSIBLE DRUG TREATMENT TODAY? Select TOP 3
- a. Language and Communication
- b. Memory
- c. Thinking and decision-making
- d. Spatial (judging distances, perceiving objects)
- e. Connecting with others
- f. Mood
- g. Motor and movement
- h. Eating or drinking
- i. Behavior
- j. Sleep
- k. Delusions or hallucinations
- I. Slow or stop progression of disease
- m. Other



# Appendix 6: Pre-Meeting FTD Insights Survey Methodology

The core features and structure of the FTD Insights Survey were based on surveys distributed at previous FDA-led PFDD meetings, along with existing surveys designed and used by the FTD Disorders Registry (FTDDR) (https://ftdregistry.org/) and GENFI. Survey development was guided by AFTD, along with input from the FTDDR, and FTD experts, including both clinicians and researchers. The survey covered several broad areas related to the diagnostic journey, disease symptoms and their impacts on daily life, experiences with past treatments, and hopes for future treatments, as well as perceptions of research and willingness to participate in future studies. Pilot versions of the survey were distributed to individuals diagnosed with FTD and their care providers to ensure that the full spectrum of disease symptoms, experiences, treatments, and preferences were represented. The survey was designed to capture information relevant to each of the various, heterogenous clinical presentations of FTD.

Given the tremendous impact that FTD has on the family, and the effects that FTD can have on the ability of the person diagnosed to complete the survey independently, the current survey was designed to be completed by persons diagnosed, relatives of diagnosed individuals, and/or care providers. The survey also captured experiences and opinions of individuals who are at increased risk for developing FTD by virtue of their genetic status or family history.

The survey used branching and skip logic to include appropriate questions for each type of respondent. Twenty-three questions were mandatory for progressing through the survey; however, the total number of survey questions therefore varied across respondents. Survey items were grouped into eight broad areas in the following order: **1**) respondent demographic characteristics, **2**) FTD family history and/or genetic risk status (up to 10 items), **3**) caregiving (up to 5 items), **4**) disease symptoms and their impact on the lives of persons diagnosed (up to 20 items), **5**) experience with past treatments (up to 7 items),



6) hopes for future treatments (6 items),
7) perspectives on research (up to 5 items), and
8) willingness to be involved in future research (up to 19 items).

An Institutional Review Board assessed study parameters and confirmed exempt status. Eligibility for participation was geographically bounded to the United States, Canada, and the United Kingdom. Participation in the UK was covered by the GENFI study protocol. The survey was distributed through a variety of channels that included email invitations to the AFTD and FTDDR constituent lists, newsletter notices, and social media posts. These promotional materials were also provided to allied patient advocacy organizations for dissemination.

The survey was completed in full by 1,796 individuals during the six-month period of October 2020 through March 2021, to allow for data collection before and after the EL-PFDD meeting. The data included in this report are from a data-freeze on October 30, 2020, at which time 1,616 individuals had initiated the survey, 1,241 (77%) of whom completed the survey. 11% (n=132) of surveys were completed by individuals diagnosed with FTD, and 89% (n=1,109) by relatives and care providers. Responses were received from individuals living in the U.S. (90%), the UK (6%), and Canada (4%).

When interpreting results from the FTD Insights Survey, some factors should be considered. The survey respondents were disproportionately female, highly educated, and Caucasian relative to the general U.S. population. As a result, the caregivers and care partners who chose to participate likely do not fully reflect the breadth of people and families affected by FTD. There was variability in



### Appendix 6: Pre-Meeting FTD Insights Survey Methodology, cont'd.

responses depending on respondent type (i.e., person diagnosed, caregiver) and diagnosis; when data are pooled some of these differences may be masked. In addition, it is our understanding through decades of knowledge in this field that the people diagnosed with FTD who had the insight and resources to complete the survey very likely represent a highly functioning subset of all individuals diagnosed. Finally, participants self-reported their diagnoses. Often, FTD diagnoses are confirmed or changed at autopsy; therefore it is possible that self-reported diagnoses on the FTD Insights Survey do not accurately reflect the underlying pathology.



# Appendix 7: Pre-Meeting FTD Insights Survey Questions



The following questions were used to generate the graphs provided in this report. Many additional questions and data are available by request from the FTD Disorders Registry.

#### **RESPONDENT TYPE:**

Which best describes you? [asked of all survey respondents]

Select all that apply.

- □ I am diagnosed with FTD
- I have a close biological relative with FTD (parent, sibling, grandparent, aunt or uncle related by blood)
- □ I am or was a primary or secondary caregiver for someone with FTD

#### **FTD DIAGNOSIS:**

What is your current FTD diagnosis? [asked of people diagnosed]

What is the person's current FTD diagnosis? [asked of current caregivers/care partners/family members]

What was the person's FTD diagnosis? [asked of past caregivers/care partners/family members]

- bvFTD behavioral variant FTD, frontotemporal dementia, or FTD dementia
- CBD or CBS corticobasal degeneration, or corticobasal syndrome
- □ FTD with ALS (amyotrophic lateral sclerosis), or FTD with MND (motor neuron disease)
- PPA primary progressive aphasia (no subtype given)
- nfvPPA nonfluent agrammatic variant aphasia, or progressive nonfluent aphasia (PNFA)

- svPPA semantic variant aphasia, or semantic dementia
- IvPPA logopenic aphasia, or logopenia
- PSP progressive supranuclear palsy, or Richardson's syndrome
- Pick's disease
- 🗌 I'm not sure

#### AGE:

How old are you? [asked of people diagnosed]

How old is the person diagnosed with FTD currently? [asked of current caregivers/care partners/family members]

[drop down > 18 - 100]

#### SEX:

**Please indicate your sex.** [asked of people diagnosed]

What is the sex of the person diagnosed with FTD? [asked of current caregivers/care partners/family members]

🗌 Male

Female

#### **COUNTRY OF RESIDENCE:**

What is your country of residence? [asked of people diagnosed]

What is the country of residence of the person diagnosed with FTD? [asked of current caregivers/ care partners/family members]

US

🗌 Canada	1
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🗆 UK



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

#### **EDUCATION:**

What is your highest level of schooling completed? [asked of people diagnosed]

What is the highest level of schooling of the person diagnosed with FTD? [asked of current caregivers/ care partners/family members]

- □ No formal schooling
- □ Elementary or Middle School
- 🗌 High School Diploma
- □ Associate Degree
- College / Bachelor's Degree
- Master's Degree
- Doctoral Degree

### **RACE/ETHNICITY:**

Which best describes your race/ethnicity? [asked of people diagnosed]

Which best describes the race/ethnicity of the person diagnosed with FTD? [asked of current caregivers/care partners/family members]

- □ American Indian or Alaskan Native
- 🗌 Black / African American / African British
- 🗌 East Asian
- □ Hispanic / Latino
- Indian
- Middle Eastern
- □ Native Hawaiian or Pacific Islander
- White / Caucasian
- More than one race
- Other\_\_\_
- Prefer not to answer

#### **EMPLOYMENT:**

Are you currently employed? [asked of people diagnosed]

Is the person diagnosed with FTD currently employed? [asked of current caregivers/care partners/family members]

- □ Yes full-time
- □ Yes part-time
- 🗌 No

#### FUNCTIONAL IMPAIRMENT:

How would you describe the person's current level of functional impairment? [asked of current caregivers/ care partners/family members]

- Mild (Needs little supervision to perform daily activities)
- Moderate (Needs supervision to perform most daily activities)
- Severe (Needs full supervision to perform nearly all daily activities)
- Profound (Can no longer perform daily activities and has limited mobility and ability to communicate)

#### FIRST INDICATION SOMETHING WRONG:

How would you describe the first indication that something was wrong? [asked of all respondents]

Changes in [select all that apply]:

- □ Language (speaking, finding words, understanding, knowing the meaning of objects)
- Memory (remembering recent events, learning new information)
- Thinking (solving problems, making judgments, organizing)
- □ Spatial (judging distances, perceiving objects)
- Personality (acting differently or inappropriately in a social situation)
- □ Relationships (getting along with others)

responses continue next page



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

- □ Mood (anxious, not interested, depressed, irritable, emotional outbursts)
- □ Motor (tremor, balance, performing movements)
- □ Eating or drinking (cravings, alcohol intake, weight gain)
- □ Behavior (repetitive or compulsive behavior, rigid routines)
- □ Sleep (not sleeping through the night, bad dreams, sleeping too much)
- □ Delusions or hallucinations
- □ A specific difficulty in everyday life
- □ Other \_\_\_\_\_
- I'm not sure

### SUBSEQUENT SYMPTOMS:

Since the first symptom(s), what other symptoms have developed? [asked of all respondents]

### Changes in [select all that apply]:

- □ Language (speaking, finding words, understanding, knowing the meaning of objects)
- Memory (remembering recent events, learning new information)
- Thinking (solving problems, making judgments, organizing)
- □ Spatial (judging distances, perceiving objects)
- Personality (acting differently or inappropriately in a social situation)
- □ Relationships (getting along with others)
- Mood (anxious, not interested, depressed, irritable, emotional outbursts)
- □ Motor (tremor, balance, performing movements)
- Eating or drinking (cravings, alcohol intake, weight gain)
- □ Behavior (repetitive or compulsive behavior, rigid routines)

- □ Sleep (not sleeping through the night, bad dreams, sleeping too much)
- □ Delusions or hallucinations
- Other \_\_\_\_\_
- I'm not sure

### **TYPES OF LANGUAGE PROBLEMS:**

What type(s) of language problems have you experienced? [asked of people diagnosed who reported the development of language symptoms]

What type(s) of language problems has the person diagnosed with FTD experienced? [asked of current caregivers/care partners/family members who reported the development of language symptoms]

Difficulty with [select all that apply]:

- □ Understanding single words
- Understanding long sentences
- □ Speaking
- Finding the right word
- Reading
- Writing
- □ Knowing what a familiar object is or how it is used
- Other \_\_\_\_\_

### **TYPES OF MEMORY PROBLEMS:**

What type(s) of memory problems have you experienced? [asked of people diagnosed who reported the development of memory symptoms]

What type(s) of memory problems has the person diagnosed with FTD experienced? [asked of current caregivers/care partners/family members who reported the development of memory symptoms]

Difficulty with [select all that apply]:

- Recent events
- Names of friends and family
- □ Names of new people
- $\hfill\square$  My way around familiar streets
- Other \_\_\_\_\_



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

### **TYPES OF SPATIAL PROBLEMS:**

What type(s) of spatial problems have you experienced? [asked of people diagnosed who reported the development of spatial symptoms]

What type(s) of spatial problems has the person diagnosed with FTD experienced? [asked of current caregivers/care partners/family members who reported the development of spatial symptoms]

Difficulty with [select all that apply]:

- □ Trouble judging distances
- □ Bumping into objects
- □ Confusion with left versus right
- Misperceiving things (for example, mistaking a coat rack for a person)
- Other \_\_\_\_\_

### **TYPES OF THINKING PROBLEMS:**

What type(s) of thinking problems have you experienced? [asked of people diagnosed who reported the development of thinking symptoms]

What type(s) of thinking problems has the person diagnosed with FTD experienced? [asked of current caregivers/care partners/family members who reported the development of thinking symptoms]

Difficulty with [select all that apply]:

- Problem solving
- Decision making and judgment
- Planning
- □ Organizing
- □ Paying attention
- Other \_\_\_\_\_

# TYPES OF PERSONALITY/RELATIONSHIP PROBLEMS:

What type(s) of personality or relationship problems have you experienced? [asked of people diagnosed who reported the development of personality or relationship symptoms]

What type(s) of personality or relationship problems has the person diagnosed with FTD experienced? [asked of current caregivers/care partners/ family members who reported the development of personality or relationship symptoms]

Select all that apply.

- Not being interested in the same activities as before
- □ Not being interested in my friends and family
- □ Lack of motivation
- □ Not caring about others' feelings
- □ Not realizing the impact of my behavior on others
- Not appreciating humor in things that others find funny
- Offending others with comments or jokes
- $\hfill\square$  Not getting along with others
- □ Saying or doing things that I shouldn't say or do
- □ Difficulty taking another person's point of view
- $\hfill\square$  Talking in an aggressive way, shouting or yelling
- □ Hitting or trying to hit someone
- □ Acting inappropriately in some social situations
- □ Not wanting to bathe or keep a neat appearance



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

### **TYPES OF MOOD CHANGES:**

What type(s) of mood changes have you experienced? [asked of people diagnosed who reported the development of mood changes]

What type(s) of mood changes has the person diagnosed with FTD experienced? [asked of current caregivers/care partners/family members who reported the development of mood changes]

Select all that apply.

- Feeling depressed
- □ Feeling anxious
- Feeling angry
- □ Feeling irritable
- □ Having emotional outbursts
- Other \_\_\_\_\_

### **TYPES OF MOVEMENT PROBLEMS:**

What type(s) of movement problems have you experienced? [asked of people diagnosed who reported the development of movement problems]

What type(s) of movement changes has the person diagnosed with FTD experienced? [asked of current caregivers/care partners/family members who reported the development of movement problems]

Select all that apply.

- □ Tremor
- □ Tripping
- □ Falling
- □ Weakness
- □ Worsening balance
- Difficulty walking
- Difficulty writing
- □ Difficulty typing
- Difficulty performing familiar movements (buttoning or zipping clothing, tying shoelaces)
- Difficulty controlling hand or arm
- □ Feeling that my hand or arm is not my own

- □ Difficulty moving or blinking my eyes
- □ Difficulty swallowing
- Other \_\_\_\_\_
- **AWARENESS:**

Is the person diagnosed with FTD aware of his or her symptoms? [asked of current caregivers/care partners/family members]

- □ Yes
- Mostly
- A little bit
- Not at all
- 🗌 I'm not sure

#### **CURRENT DISTRESS:**

What symptoms, if any distress you the most? [asked of people diagnosed]

What symptoms, if any distress the person diagnosed with FTD the most? [asked of current caregivers/care partners/family members]

- □ I am not distressed by symptoms / He or she is not distressed by symptoms
- □ Language (speaking, finding words, understanding)
- Memory (remembering recent events, learning new information)
- Thinking (solving problems, making judgments, organizing)
- □ Spatial (judging distances, perceiving objects)
- Personality (acting differently or inappropriately in a social situation)
- □ Relationships (getting along with others)
- Mood (anxious, not interested, depressed, irritable, emotional outbursts)
- □ Motor (tremor, balance, performing movements)
- Eating or drinking (cravings, alcohol intake, weight gain)

responses continue next page



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

- Behavior (repetitive or compulsive behavior, rigid routines)
- □ Sleep (not sleeping through the night, bad dreams, sleeping too much)
- Delusions or hallucinations
- □ A specific difficulty in everyday life
- Other \_\_\_\_\_
- □ I'm not sure

### **PAST DISTRESS:**

What symptoms distressed you the most early in the illness? [asked of people diagnosed]

#### What symptoms distressed the person diagnosed with FTD the most early in the illness? [asked of current caregivers/care partners/family members]

- □ I was not distressed by symptoms / He or she was not distressed by his or her symptoms
- □ Language (speaking, finding words, understanding, knowing the meaning of objects)
- Memory (remembering recent events, learning new information)
- Thinking (solving problems, making judgments, organizing)
- □ Spatial (judging distances, perceiving objects)
- Personality (acting differently or inappropriately in a social situation)
- □ Relationships (getting along with others)
- Mood (anxious, not interested, depressed, irritable, emotional outbursts)
- □ Motor (tremor, balance, performing movements)
- Eating or drinking (cravings, alcohol intake, weight gain)
- Behavior (repetitive or compulsive behavior, rigid routines)

- □ Sleep (not sleeping through the night, bad dreams, sleeping too much)
- Delusions or hallucinations
- □ A specific difficulty in everyday life
- Other \_\_\_\_\_
- I'm not sure

### **ACTIVITIES AT HOME:**

Do symptoms make it difficult for you to do any of the following activities independently? [asked of people diagnosed]

Do symptoms make it difficult for the person diagnosed with FTD to do any of the following activities independently? [asked of current caregivers/care partners/family members]

Select all that apply.

- □ Perform daily hygiene (shower, groom, dress)
- Perform household chores (laundry, vacuum, clean)
- □ Prepare a meal (cook)
- Keep track of appointments
- □ Manage medications
- $\hfill\square$  Pay bills, organize financial or business files
- Do crafts
- Care for a pet
- ☐ Manage communications (use email, answer the phone, answer the door)
- Other \_\_\_\_\_
- I don't have difficulties doing these activities independently / No difficulties doing activities independently
- I'm not sure



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

### **ACTIVITIES OUTSIDE OF THE HOME:**

Do symptoms make it difficult for you to do any of the following activities outside of the home independently? [asked of people diagnosed]

Do symptoms make it difficult for the person diagnosed with FTD to do any of the following activities outside of the home independently? [asked of current caregivers/care partners/family members]

Select all that apply.

- □ Attend school
- □ Work
- □ Shop for groceries, run other errands
- Drive a car
- Use mass transit
- □ Engage in physical activity (take a walk, ride a bike, exercise)
- Other \_\_\_\_\_
- □ I don't have difficulties doing activities outside of the home independently / No difficulties doing activities outside of the home independently
- 🗌 I'm not sure

### **ACTIVITIES INVOLVING OTHERS:**

**Do symptoms make it difficult for you to do any of the following activities involving others?** [asked of people diagnosed]

Do symptoms make it difficult for the person diagnosed with FTD to do any of the following activities involving others? [asked of current caregivers/care partners/family members]

Select all that apply.

- □ Play a game like cards or chess
- □ Participate in conversations with family or friends
- Attend social or other gatherings where there will be more people
- □ Interact with new people in everyday life (in stores, on phone, etc.)

- □ Be intimate with a spouse or partner
- Maintain friendships
- □ Care for children or grandchildren
- $\hfill\square$  Care for a spouse or parent
- Other \_\_\_\_\_
- I don't have difficulties doing activities involving others / No difficulties doing activities involving others
- 🗌 I'm not sure

#### **BIOLOGICAL RELATIVES:**

How many of your close biological relatives (parent, sibling, grandparent, aunt, or uncle related by blood) have been diagnosed with FTD? [asked of respondents who endorsed being diagnosed with FTD or having a close biological relative with FTD]

- 0
- □ 1
- □ 2
- □ 3
- □ 4
- □ 5 or more

### FTD GENE:

**Do you carry the gene?** [asked of people diagnosed who endorsed having at least one close biological relative with an FTD diagnosis]

**Does your family carry a gene for FTD?** [asked of caregivers/care partners/family]

- 🗌 No
- I don't know
- □ I prefer not to answer
- □ Yes, the gene is C9orf72
- □ Yes, the gene is MAPT (tau)
- □ Yes, the gene is PGRN (progranulin)
- □ Yes, but I don't know which one
- □ Yes, it is another gene: \_\_\_\_\_



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

#### **GENETIC TESTING:**

Have you been tested to see if you carry a specific gene for FTD? [asked of respondents who endorsed having at least one close biological relative with an FTD diagnosis or an FTD diagnosis themselves]

- 🗌 No
- □ Yes

□ I prefer not to answer

### **PRESCRIPTION MEDICATION TAKEN:**

Have you ever taken a prescription medication to treat the symptoms of FTD? [asked of people diagnosed]

Has the person diagnosed with FTD ever taken a prescription medication to treat the symptoms of FTD? [asked of current caregivers/care partners/ family members]

Did the person diagnosed with FTD ever take a prescription medication to treat the symptoms of FTD? [asked of past caregivers/care partners/family members]

Select all that apply.

- 🗌 No
- 🗌 Yes
- 🗌 I'm not sure

#### **MEDICATION TYPE:**

Did you ever take any of the following types of medications to treat symptoms of FTD? [asked of people diagnosed]

Has he or she ever taken any of the following types of medications to treat symptoms of FTD? [asked of current caregivers/care partners/family members]

Did he or she ever take any of the following types of medications to treat symptoms of FTD? [asked of past caregivers/care partners/family members]

Select all that apply.

□ Anti-depressants (SSRIs or other)

For example: Celexa (citalopram), Eldepryl (selegiline), Lexapro (escitalopram), Luvox (fluvoxamine), Paxil (paroxetine), Prozac (fluoxetine), Trazadone, Wellbutrin (buproprion), Zoloft (sertraline)

□ Antipsychotic

For example: Abilify (aripiprazole), Seroquel (quetiapine), Zyprexa (olanzapine)

□ Anxyolitics / Benzodiazapines

For example: Xanax (alprazolam), Klonopin (clonazepam), Ativan (lorazepam)

Cognition-enhancing drugs

For example: Aricept (donepezil), Cognex (tacrine), Exelon (rivastigmine), Namenda (memantine), Razadyne (galantamine)

Anti-Parkinsonian drugs

For example: Amantadine, Carbidopa/levodopa

Mood Stabilizers

For example: Depakote/Depacon (valproate), Lamictal (lamotrigine), Lithium, Neurontin (gabapentin), Tegretol (carbamazepine)

Other \_\_\_\_

- 🗌 I'm not sure
- □ I prefer not to answer



### Appendix 7: Pre-Meeting FTD Insights Survey Questions, cont'd.

#### SIDE EFFECTS:

Which, if any, of the following rare but serious side effects would prevent you from choosing a new treatment? [asked of all respondents]

Select all that apply.

- □ Hallucinations
- Pneumonia
- □ Serious infection (sepsis)
- □ Changes in liver function or liver damage
- □ Changes in kidney function or kidney damage
- $\hfill\square$  Changes in heart function or heart damage
- □ Seizure
- Stroke
- Neuroleptic malignant syndrome (fever, confusion and muscle stiffness)
- □ Any life-threatening condition

#### **NEW TREATMENT:**

What I would want most in a treatment for FTD would be for it to improve [asked of all respondents]

Select all that apply.

- □ The ability to communicate
- ☐ The quality of relationships with family and friends
- ☐ The ability to maintain independence in everyday activities
- □ The ability to hold a job
- $\hfill\square$  The ability to control emotions and behavior
- Other: \_\_\_\_

#### **CLINICAL TRIAL WILLINGNESS:**

Please rate your willingness to participate in a clinical trial to develop an FTD treatment [asked of all respondents]

- □ Very Willing
- Willing
- Neutral
- Unwilling
- Very Unwilling

#### **APPROACHING ONSET:**

Would you be willing to know that you were approaching the onset of FTD symptoms in order to take part in a clinical trial? [asked of respondents who were not diagnosed with FTD but reported being at risk]

- □ Yes
- 🗌 No
- 🗌 I'm not sure



## Appendix 8: Pre-Meeting FTD Insights Survey Respondent Demographics

Age (Mean years)	61.7
Sex	
Female	76.4%
Male	23.6%
Race / ethnicity	
White / Caucasian	92.4%
Hispanic / Latinx	1.5%
East Asian	1.1%
Black / African American / African British	0.9%
American Indian or Alaskan Native	0.3%
Middle Eastern	0.2%
Indian	0.4%
Other	1.1%
More than one race	1.1%
Prefer not to answer	1.1%
Country of residence	
USA	90.4%
Canada	3.6%
UK	6.0%



Education*	
Doctoral Degree	8.3%
Master's Degree	29.1%
Bachelor's Degree	36.9%
Associate's Degree	12.8%
High School Diploma	12.7%
Elementary or Middle School	0.1%
Employment Status	
Unemployed	62.8%
Employed full-time	25.9%
Employed part-time	11.3%

Survey respondent demographic information.

Responses indicate demographic information of the person diagnosed with FTD (i.e., caregivers responded on behalf of the person diagnosed). \*= education data from USA and Canadian residents only; education data from UK residents collected in "years." Percentages calculated with N who responded to the specific question as the denominator.



**Figure 11: Survey respondent type.** N=1241. Incomplete and disqualified surveys were excluded from all analyses (N=375). Non-white racial/ethnic groups and rarer FTD phenotypes were not overrepresented in the excluded surveys. Risk status is not considered here, but data are available further broken down by risk status (i.e., increased risk for developing FTD) for the blue, green and red groups.







**Figure 12: Survey respondent diagnosis.** N=1241. Relatives who are not caregivers answer "What type of FTD has been diagnosed in your family?" bvFTD = behavioral variant frontotemporal dementia; PPA = primary progressive aphasia; FTD with MND = frontotemporal dementia with amyotrophic lateral sclerosis or motor neuron disease; PSP = progressive supranuclear palsy or Richardson's syndrome; CBD or CBS = corticobasal degeneration or corticobasal syndrome; svPPA = semantic variant primary progressive aphasia; nfvPPA = nonfluent / agrammatic variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; PPA = primary progressive aphasia.



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Appendix 8: Pre-Meeting FTD Insights Survey Respondent Demographics, cont'd.



**Figure 13. Survey respondent age versus functional impairment.** Mild = needs little supervision to perform daily activities (n=118); Moderate = needs supervision to perform most daily activities (n=194); Severe = needs full supervision to perform nearly all daily activities (n=127); Profound = can no longer perform daily activities, has limited mobility and ability to communicate (n=114). Box plots show median and interquartile ranges.



Appendix 8: Pre-Meeting FTD Insights Survey Respondent Demographics, cont'd.



### Figure 14: Survey respondent familial vs sporadic family history.

Data from individuals with a current FTD diagnosis and biological relatives of someone with an FTD diagnosis. Respondents who did not answer family history questions are not included here, even if they indicated having biological relatives at the beginning of the survey, unless they indicated that they were genetic variant carriers themselves or had a genetic variant in their family. "Familial" category defined as reporting >1 person in a family with an FTD diagnosis, and/ or reporting a genetic variant. "Sporadic" category defined as reporting only 1 person in the family with an FTD diagnosis (unless reporting a genetic variant per above).



# Appendix 9: Frontotemporal Degeneration and Treatments

Frontotemporal degeneration (FTD) represents a group of brain disorders caused by degeneration of the frontal and/or temporal lobes of the brain. FTD is also frequently referred to as frontotemporal dementia, frontotemporal lobar degeneration (FTLD), or Pick's disease. These differences in nomenclature, disparities between terminology describing clinical manifestations compared to pathophysiological states, and changing diagnostic criteria complicate the ability to accurately diagnose FTD as well as to conduct epidemiological and meta-analytic studies. Approximately 40% of people diagnosed with FTD report a family history of related disorders, with 10% representing an autosomal dominant transmission. The other 60% have apparent sporadic FTD with no identified affected family members (Sirkis et al., 2019; Ramos et al., 2020). Autosomal dominantly inherited FTD can result from variants in several known genes, including *MAPT* (tau), *progranulin*, and *C9orf72*. Other genes implicated in FTD include *VCP*, *CHMP2B*, *FUS*, *TARDBP*, *TBK1*, *CHCHD10*, *TREM2* and *CYLD* (Lok & Kwok, 2021).

A subset of respondents on the FTD Insights Survey who reported a family history of FTD and had undergone genetic testing shared their type of genetic variant (see **Figure 15**, below). Consistent with epidemiological studies, *C9orf72* was reported to be the most common amongst this relatively small subgroup of participants.



### Figure 15

**Figure 15. Known Genetic Variants.** *n*=75. Results only include those who answered "yes" to "Does your family carry a gene for FTD" or "Do you carry [an FTD] gene?" and had undergone genetic testing, which is a small subsample of the entire respondent group. Results include individuals with a current FTD diagnosis and biological relatives of someone with an FTD diagnosis. Genes noted in the "another gene" category include VCP, R159C, PPND, TBK1, and UBQin2.



### Appendix 9: Frontotemporal Degeneration and Treatments, cont'd.

On the cellular level, the FTD disorders are frequently characterized by protein pathologies in the brain, with 50% of FTD cases showing evidence of transactive response DNA-binding protein (known as TDP-43) pathology, 40% showing evidence of tau pathology, and 10% showing evidence of some other pathology (e.g., fused-in-sarcoma [FUS]).

In general, there is no clear 1-to-1 correspondence between the various FTD disorders and their clinical presentations, brain pathologies, and etiologies. **Figure 16** (below) represents the complex nature of the relationships among these different features of the FTD disorders. As a result of this complexity, there is a critical need for biomarkers that can differentiate among the various pathologies to aid both diagnosis and drug development for the FTD disorders.



**Figure 16. The complex relations among the clinical presentations, pathologies, and etiologies of the FTD disorders** (*Visual courtesy of Dr. Bill Seeley, University of California San Francisco, demonstrating Dr. Ian Mackenzie's harmonized scheme, Mackenzie, 2011*).


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### Appendix 9: Frontotemporal Degeneration and Treatments, cont'd.

Disease onset typically begins between the ages of 45 and 65, although onset can occur as young as the 20s and as late as the 80s. Due to this wide variance in onset, age does not correlate with disease severity.

#### **Treatments for the FTD Disorders**

Treatment options for the FTD disorders remain extremely limited, with no therapies currently approved by the FDA. Several studies have demonstrated that antidepressants can help to mitigate various FTD symptoms. Other medication classes that may be prescribed to help manage FTD symptoms include mood stabilizers and antipsychotics.

The genetic forms of FTD, although relatively uncommon, present an opportunity to develop FTD prevention therapies. Such clinical trials will not be possible in sporadic FTD cases until appropriate biomarkers are validated. People who carry FTDrelated variants manifest detectable changes within the brain and in biofluids, such as cerebrospinal fluid and plasma neurofilament light, well before symptom onset. The ability of novel therapies to modulate those changes could help researchers assess the effectiveness of such therapies to modify the course of disease.

# Challenges and Opportunities for FTD Drug Development

The field of FTD research and treatment development faces daunting challenges as well as promising opportunities.

People living with an FTD diagnosis need symptomatic therapies that prioritize the critical outcomes of functional independence and quality of life. Such treatments will continue to be needed even after the development of disease-modifying therapies.

Key challenges for therapeutic development include:

• Difficulty of identifying people affected during the early stages of these conditions, with an inability

to detect people affected by sporadic FTD before disease onset and complexity in predicting disease onset for people with genetic FTD.

- The heterogeneity of clinical and neuropathological features.
- The need for inclusion criteria and outcome measures for the different FTD disorders.

Overcoming such challenges will require biomarker development and advances in clinical trial design. Genetic forms of FTD represent an opportunity for testing early interventions, but trials will need to address practical challenges, including variations in age of symptom onset and in clinical presentation, as well as the fact that many potential participants do not want to know their genetic status. Advances in trial design (e.g., basket trials) could meet the challenge of heterogeneity, where each class of FTD neuropathology has a broad array of clinical presentations, such as the *C9orf72* FTD-ALS spectrum.

Despite the challenges, the commitment of the FTD community represents an opportunity. Many individuals expressed a strong willingness to participate in clinical trials to contribute toward the discovery of new drugs.

For example, Cindy, who was diagnosed with familial bvFTD in 2011 at age 58, affirmed:

"I would willingly participate in any research studies or drug trials, even if there is a risk to my life. I am that desperate to have this disease end with me."

Elaine, from England, called in to add:

"We hope that research will ultimately be the key to early diagnosis and treatment. If not for my husband, then for our son."



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## Appendix 11: Acknowledgements

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