Cure MAPT FTD FDA Patient Listening Session - May 23rd, 2025

Overview

On May 23, 2025, members of the MAPT FTD patient community held a Patient Listening Session with the U.S. Food and Drug Administration (FDA). Approximately 35 FDA staff attended, to listen and learn from families who have faced multiple impacted generations of genetic FTD caused by mutations on the MAPT (microtubule associated protein Tau) gene. Despite being discovered in 1998, and decades of active research participation, we remain without clinical trials or treatments.

The session opened with Dr. Bradley Boeve, neurologist at the Mayo Clinic in Rochester, MN, providing a clinical overview of MAPT FTD and explaining how it relates biologically and medically to Alzheimer's Disease, Parkinson's Disease, and other forms of FTD. Seven members of the MAPT FTD patient community shared their stories - including four who have tested positive for a pathogenic MAPT variant and have a 98% chance of developing FTD. All speakers described the burden and struggle to provide long term care for their loved ones with FTD including their parents, spouses, children, siblings, aunts and uncles. These deeply personal stories were bolstered by the presentation of survey data indicating that the Cure MAPT FTD patient community already has a high research participation rate, is extremely eager to take part in clinical trials, and is willing to take on a high level of risk to participate.

Key Highlights

In their patient testimony and in a formal letter submitted to the FDA, Cure MAPT FTD presented the following key findings and requests of the FDA:

- As applicable therapies are approved for Alzheimer's Disease and other Tauopathies (e.g. Tau-targeting therapies, gene therapies, or therapies targeting neuroinflammation) allow sponsors to expand indication labelling to encompass MAPT FTD.
- Encourage sponsors to facilitate clinical trial consent and participation by integrating care partners into the clinical trial process.
- Encourage sponsors to expand Tau-targeting clinical trials for Alzheimer's disease and other Tauopathies to include MAPT FTD patients and asymptomatic mutation carriers.
- Allow use of natural history data as a comparator in clinical trials to determine treatment efficacy without requiring a placebo group or a large patient population.
- Encourage sponsors to include known asymptomatic MAPT mutation carriers in clinical trials and drug labeling, similar to how individuals with genetic Alzheimer's Disease are being included.

- MAPT FTD patients and asymptomatic carriers are desperate for a cure and are willing to assume moderate to high levels of risk.
- In absence of a disease-modifying therapy, encourage sponsors to look for opportunities to treat high-priority symptoms.

Session Objectives

The MAPT FTD community requested this Patient Listening Session to educate and increase awareness within the Agency about the autosomal dominant MAPT genetic variations of FTD, by both providing a scientific overview and also sharing the lived experience of MAPT FTD patients and caregivers. Additionally, the organization provided insight into the group's perspectives on trial involvement, risk willingness, and considerations for clinically meaningful outcomes, while highlighting the challenges inherent in conducting studies using smaller populations in the rare disease space. While many MAPT family have actively participated as much as possible in related longitudinal research studies where appropriate, there are **no forthcoming clinical trials specifically aimed at treating the MAPT variant.**

Attendees

FDA Attendance: Staff from a total of 17 different offices/divisions, across 4 FDA Centers attended the session:

Office of the Commissioner (OC): 2 offices
- OC/OEA/PES: Office of External Affairs/Public Engagement Staff (organizer)
- OC/OCMO/OPT: Office of the Chief Medical Officer/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER): 4 offices
- CBER/OCBQ/DBSQC/QAB: Office of Compliance Biologics Quality/ Division of Biological Standards and Quality Control /Quality Assurance Branch
- CBER/OCD: Office of the Center Director
- CBER/OTP/OCE/DCEGM/GMB2: Office of Therapeutic Products / Oncology Center of Excellence/Division of Clinical Evaluation General Medicine/General Medicine Branch 2
- CBER/OTP/PSPS: Office of Therapeutic Products/Policy and Special Projects Staff

Center for Drug Evaluation and Research (CDER): 6 offices
- CDER/OND/ODES/DCOA: Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON: Office of New Drugs/Office of Neuroscience
- CDER/OND/ON/DNI: Office of New Drugs/Office of Neuroscience/Division Neuroscience I
- CDER/OND/ORDPURM/DRDMG: Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBII: Office of Translational Science/Office of Biostatistics/Division of Biostatistics II
- CDER/OTS/OB/DBIII: Office of Translational Science/Office of Biostatistics/Division of Biostatistics III

Center for Devices and Radiological Health (CDRH): 5 offices

- CDRH/OPEQ/OHTI/DHTIB: Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IB
- CDRH/OPEQ/OHTI/DHTIC: Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IC
- CDRH/OPEQ/OHTIII/DHTIIIA: Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology 3A
- CDRH/OPEQ/OHTIII/DHTIIIB: Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology 3B
- OSPTI/OEID/DPCD: Office of Strategic Partnerships and Technology Innovation/Division of Patient Centered Development

Non-FDA Attendees
- Reagan Udall Foundation
- National Institutes of Health (NIH)
- NIH/NCATS – National Center for Advancing Translational Sciences
- NIH/NINDS – National Institute of Neurological Disorders and Stroke
- Cure MAPT FTD Members

Supporting Organization Attendees
- The Association for Frontotemporal Dementia (AFTD)
- Alzheimer's Association
- Concussion Legacy Foundation
- Cure PSP

Financial Disclosures

CURE MAPT FTD does not have any financial interests to disclose for this Patient Listening Session. None of the speakers participating in the session have any financial interests to disclose for the Patient Listening Session, including Dr Bradley Boeve, as stated in his recorded remarks.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects Cure MAPT FTD's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of MAPT mutations causing FTD, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire FTD patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Session Outline

Full speaker testimonies located in the appendix of this summary

Opening Statement - Linde Jacobs, RN

Cure MAPT FTD is a nonprofit organization created by impacted family members to mobilize and raise awareness of the MAPT genetic mutations causing Frontotemporal Dementia (FTD), assisting a global network of families, and advocating for clinical trials with the ultimate goal of finding a cure. The organization created a centralized space for researchers, clinicians, other non-profit partners, and industry to locate families impacted by MAPT mutations and to work in a proactive approach to lead further development of therapeutic potential through our three main pillars: advocacy, awareness and connection. MAPT mutations lead to dysfunction in the protein Tau, causing FTD as well as other Tauopathies: Alzheimer's Disease, Progressive Supranuclear Palsy, Corticobasal Syndrome, Parkinson's Disease, and Multiple System Atrophy. When considering Tau therapeutic development, it is important to note that a therapy that targets Tau may benefit many diseases, not just one. However, most clinical trials focus solely on one disease. **So even though many diseases share the same protein dysfunction, with the same terminal trajectory, only some patients are indicated for interventions to try to stop the process, while other diagnoses, often including rarer ones such as MAPT FTD, have no access to options that could potentially save their lives—ones that are stopped in the prime of their lives.** Once a therapy is approved for use, it might be assumed that patients with related diseases could access the drug through off-label prescription; unfortunately, **most victims of these illnesses must rapidly transition to federally funded payors for their health care (Medicare, Medicaid, etc.) soon after diagnosis, and these payors specifically exclude any off-label treatments from coverage**.

Disease Overview

- Dr. Brad Boeve, MD - Behavioral Neurologist,Mayo Clinic,Rochester, MN
- Link to video
- Summary: full transcript available in Appendix

Dr. Brad Boeve, a neurologist at the Mayo Clinic, presented a comprehensive overview of Frontotemporal Dementia (FTD) caused by mutations in the *MAPT* gene (Microtubule Associated Protein Tau), a major monogenic cause of frontotemporal lobar degeneration (FTLD). This form of FTD is a progressive, highly penetrant neurodegenerative disorder with onset often occurring in midlife, leading to substantial functional, emotional, legal, and financial consequences for patients and families.

Clinically, *MAPT*-associated FTD falls within a spectrum of syndromes under the FTLD umbrella, including behavioral variant FTD, primary progressive aphasia, corticobasal syndrome, and progressive supranuclear palsy. These conditions are driven by selective neurodegeneration in frontal and temporal brain regions, frequently due to accumulation of misfolded Tau proteins. Approximately 30–40% of all FTLD cases have a strong genetic underpinning, with *MAPT*, *GRN*, and *C9ORF72* representing the most common causative genes.

Dr. Boeve emphasized the severe diagnostic delays many patients face—often years—due to misdiagnosis or misattribution of symptoms to psychiatric or psychosocial causes. These delays contribute to a protracted "diagnostic odyssey," delaying access to appropriate care and clinical research opportunities.

Despite being the first FTD-related gene discovered (1998), *MAPT* remains significantly underrepresented in therapeutic development. Unlike *GRN* and *C9ORF72*, which are currently the focus of multiple clinical trials, *MAPT* has seen only one small trial to date, which was discontinued. There are currently **no FDA-approved therapies** for FTD of any subtype, including MAPT-driven disease.

Dr. Boeve highlighted the urgent need for regulatory engagement to facilitate clinical trial development for MAPT-related FTD. Advances in biomarker research—including blood and CSF assays, advanced neuroimaging, and genetic testing—are improving diagnostic precision and readiness for trial enrollment. However, regulatory support is needed to translate these advancements into treatment options.

He concluded by acknowledging the contributions of advocacy organizations and research partners and urged the FDA to recognize *MAPT*-associated FTD as a critical area of unmet medical need deserving of targeted therapeutic development pathways.

Speaker Summaries

Speaker 1: Linde Jacobs, RN: Asymptomatic positive mutation carrier, former carepartner

Linde shared a personal and generational story of loss, resilience, and advocacy shaped by MAPT FTD. For 40 years, her family has endured the disease's devastating progression across multiple generations; her grandmother, mother, aunts, and uncles have all succumbed to FTD, each diagnosed in their early 50s. Now, Linde and her sisters—who all tested positive for the MAPT mutation—face the same future. Despite decades of suffering, no treatments or MAPT-specific clinical trials have been made available to her family, only symptomatic management. Linde, a mother of two young children, refuses to passively await decline. Instead, she has participated in more than 20 research studies and become an active advocate for change. Her message is urgent: action must be taken now, while momentum in Tau research is growing.

- Encourage sponsors to pursue expanded indication labeling for new Tau-targeting therapies, allowing them to include MAPT FTD in addition to Alzheimer's and other Tauopathies.
- Create clear regulatory pathways for including MAPT FTD in clinical trial indications, recognizing that many Tau drugs were developed using MAPT FTD models.
- Understand the financial impact: federal insurance programs like Medicare do not cover off-label use, making access impossible unless MAPT FTD is explicitly included in approved labeling.
- Accelerate inclusion of genetically confirmed MAPT carriers into prevention trials, particularly those focused on early biomarkers, before symptoms appear.

Speaker 2: Gil Chorbajian: Carepartner to his wife, with two at-risk children

Gil's powerful narrative follows a husband caring for his wife, who is the fourth generation in her family affected by MAPT FTD which took his father-in-law decades ago and now threatens her siblings and daughters. Since her diagnosis in 2020, the family's life has been transformed by FTD's relentless decline: she is now non-verbal, fully dependent, and unrecognizable from the vibrant woman she once was. Their two daughters, now in college, began caregiving as teenagers and face their own uncertain genetic futures. Despite her decline, her family fights on her behalf, participating in research, educating medical professionals, raising funds, and preparing for brain donation. But the reality remains stark: in nearly 30 years, there has been no meaningful advancement for MAPT-specific FTD treatments—not even a single meaningful clinical trial targeting the mutation.

- Prioritize clinical trials targeting MAPT FTD—a high-need, high-impact genetic form of dementia.
- Allow at-risk and asymptomatic carriers to participate in prevention-based drug trials, using biomarkers to detect and intervene before symptoms emerge.
- Enable families to take calculated risks in clinical research, because for them, doing nothing is the greatest risk of all.

Speaker 3: Susan Dunbar: Asymptomatic positive mutation carrier, currently surpassed typical age of onset

Susan's emotional narrative is shared as a 67-year-old woman who tested positive for the MAPT gene mutation, placing her at high risk for FTD symptom onset. This disease has haunted her extended family for generations. Having lost her mother, sister, aunt, uncle, cousins, and maternal grandfather to FTD—many in their 50s or 60s—she now lives with the knowledge that she may follow the same path. After receiving her genetic results at age 62, she retired early, moved to be near her children and grandchildren, and began participating in longitudinal FTD research. Despite the fear and grief of her diagnosis, she has chosen to focus on living meaningfully, while actively contributing to science. Her story is both a warning and a call to action. The MAPT mutation has devastated four generations of her family, and now she fears for her children and grandchildren. She urges the FDA to help close the gap in treatment equity, and to accelerate the pathway from biomarker detection to early intervention, before the disease steals more futures.

- Prioritize research and treatment development for MAPT-related FTD, a highly penetrant, genetically defined, and tragically underfunded condition compared to Alzheimer's.
- Support preventive therapies targeting Tau pathology, the core mechanism of MAPT FTD, which may halt or delay symptom onset in known gene carriers.
- Enable access to clinical trials for asymptomatic MAPT carriers using biomarker-based approaches, so interventions can begin before irreversible brain damage occurs.
- Ensure future FDA-approved Tau-targeting therapies include MAPT FTD in their indication labels, not just Alzheimer's disease, to ensure equitable access for patients, especially those reliant on Medicare or other public insurance, which do not cover off-label use.

Speaker 4: Marian Grems: Multigenerational carepartner to spouse and two affected children

Marian's narrative spans more than 60 years of heartbreak caused by MAPT FTD in one family. It begins with her father-in-law, who showed early symptoms decades ago, and continues through the devastating effects on her husband, son, daughter, and now the looming risk for her granddaughters. Her husband's nine-year battle with behavioral variant FTD destroyed his personality, empathy, and dignity, ending his career and profoundly impacting their family life and financial security. Their three children lost a father who was once a guiding, supportive presence. Tragically, her son later developed FTD, facing symptoms that included Parkinsonian-like immobility and legal troubles before dying at just 45. Her daughter, a cancer survivor, was diagnosed with MAPT FTD, threatening the health and future of her two teenage daughters, who now live with the fear of inheriting the gene. The granddaughters express the pain of seeing their mother change, losing joy, independence, and emotional connection, and worry about their own genetic risk.

- Expand clinical trials to include families affected by genetic MAPT FTD across generations. The disease devastates multiple family members with varied symptoms and ages, requiring flexible, inclusive trial criteria.
- Prioritize early intervention research and preventive trials for presymptomatic carriers, especially young at-risk individuals like the granddaughters. Early treatment could preserve identity, function, and family bonds before irreversible decline.
- Incorporate caregiver perspectives into trial designs and assessments. Families experience profound emotional, financial, and physical burdens that must be acknowledged in research.
- Recognize the urgency for effective treatments to prevent the ongoing generational loss. Hope depends on timely FDA action to enable access to promising therapies.

Speaker 5: Ansel Dow: Asymptomatic positive mutation carrier

Ansel provided a multigenerational account of one family's devastating experience with MAPT FTD that has claimed the lives of six out of nine siblings in one generation and now threatens the next. He is a confirmed MAPT mutation carrier, as is his younger brother, and both have grown up surrounded by the trauma, caregiving burden, and emotional toll of FTD. His mother, a formerly vibrant and nurturing parent, is now symptomatic and in advanced decline. The disease began impacting their family as early as age 37 in one aunt and took years to diagnose. Another aunt has served as a full-time caregiver since 1995, a role that has required increasing sacrifices as the disease progressed. The psychological and emotional trauma of caregiving during childhood is highlighted—children were forced to become caregivers without understanding the disease, enduring confusion, isolation, and grief. Despite all of this, the family has committed themselves over the last 15 years to FTD research participation, clinging to science as their only hope.

- Include presymptomatic MAPT mutation carriers in clinical trials. They are ready to participate in any trial and take on risk because time is running out, and early intervention is essential before irreversible damage occurs.
- Design clinical trials that enable caregiver input as symptomatic individuals may struggle to complete tasks or communicate clearly, so caregiver observation and reporting must be integrated into trial protocols.
- Recognize the urgency of clinical trial access for MAPT FTD families as the impact of this disease is catastrophic across generations, and the window for preventive or disease-modifying interventions is narrow. Action now is essential.
- Adapt trial protocols to the unique challenges of studying FTD as it differs from other neurodegenerative diseases; protocols must reflect its early behavioral symptoms, long disease duration, and emotional and logistical strain on families.

Speaker 6: Erin B: Carepartner to husband, with two at-risk children

This narrative tells the story of a once-thriving attorney and devoted father who began showing symptoms of Frontotemporal Dementia (FTD) at just 37 years old. Misdiagnosed for years with Young Onset Parkinson's Disease, his true diagnosis—MAPT mutation-related FTD—came too late to change his treatment course. His rapid cognitive, behavioral, and physical decline has left his family devastated, especially his young sons, who are now growing up without the father they once knew. Despite these challenges, the family has prioritized research participation; he enrolled in the ALLFTD study and other research initiatives in hopes of helping others, especially his children, who each face a 50% genetic risk of inheriting the same devastating condition.

- Recognize MAPT FTD as a distinct and urgent medical need by promoting the inclusion of MAPT FTD patients in drug development pipelines, particularly for Tau-targeting therapies.
- Enable and encourage clinical trial access for asymptomatic and symptomatic MAPT mutation carriers, including those misdiagnosed or underrepresented due to atypical or early-onset symptoms.
- Support expanded clinical trial criteria that allow individuals like this man who actively sought out research despite diagnostic confusion, to contribute meaningfully to treatment development.
- Understand that families are ready to take on risk, in time, energy, and personal cost, to contribute to science and access therapies that might change the course of disease for future generations.

Speaker 7: Annika R: Asymptomatic positive mutation carrier, current carepartner for mother

This is the story of a family profoundly changed by MAPT Frontotemporal Dementia (FTD), beginning with a high-achieving, community-driven mother who began showing symptoms at age 48. Once a devoted parent and successful executive, she gradually lost empathy,

developed compulsive behaviors, and became emotionally distant—symptoms that were initially mistaken for depression. Over time, she lost the ability to parent, function independently, or show awareness of her condition. Her daughter, then a teenager, took on a caregiving role that has continued into adulthood.

Now 28, she recently tested positive for the MAPT gene mutation, confirming that FTD is in her future as well. She juggles the emotional and logistical demands of caring for her mother while preparing for her own potential decline. Both have had the opportunity to participate in longitudinal research studies, but no disease-modifying treatments exist, and no clinical trials have been available to carriers like her.

- Allow asymptomatic MAPT gene carriers to participate in clinical trials, especially those focused on prevention and early intervention.
- Support biomarker-based research to identify and track early signs of disease before symptoms begin, which could enable true disease prevention.
- Recognize the urgency and willingness of families to participate in high-risk trials because for them, the greater risk is doing nothing.
- Disclosure of the community survey results surrounding trial participation and risk willingness (see Appendix).

FDA and Advocate Discussion/Questions

Question, FDA:
What is your level of risk for severe adverse events (related to any trials, medications or therapies, such as cancer)?

Answer, Cure MAPT FTD:
Speaker 1- LJ: Speaking as someone from the community, when we understand that some day FTD is going to take our life, if we can stall the process, or do something to intervene prior to that happening, or slow things down to give us more quantity and quality of life, that is still the risk that many of us are willing to take. FTD is going to be the ending chapter so if we can have an opportunity for maybe something else being the ending chapter, I would say that our community is more than willing to participate in any trials.

Speaker 5- AD: I would add that as a presymptomatic gene carrier, I would much rather die of organ failure or of cancer going through an investigational treatment than die of FTD;that is certainly a risk I would be willing to take.

Speaker 3-SD: I would agree with that as well.

Closing Thoughts

As we close, we want to express our deep gratitude for the FDA's time and attention. On behalf of the MAPT FTD community—patients, families, and caregivers—we ask for your partnership and leadership in accelerating progress for this devastating disease. Our asks are simple, but the impact would be profound, and could change the trajectory of our families' future generations.

1. As new therapies are approved for Alzheimer's disease and other Tauopathies, such as Tau-targeting drugs, gene therapies, or treatments for neuroinflammation, we urge the FDA to **allow sponsors to expand indication labeling to include MAPT FTD**. This would ensure that our community's access to FDA approved therapies, and avoid hurdles trying to obtain off-label approvals through insurers.
2. We ask you to encourage sponsors to **integrate care partners directly into the clinical trial process.** For MAPT FTD, care partners are essential for consent and participation, and their involvement will make trials more accessible and meaningful.
3. We urge you to **encourage sponsors to expand Tau-targeting clinical trials beyond Alzheimer's and other Tauopathies, to include MAPT FTD patients and asymptomatic mutation carriers**. This will accelerate discovery and bring hope to more families.
4. Given the rarity of MAPT FTD, we ask that the FDA **allow the use of natural history data as a comparator in clinical trials, rather than requiring a placebo group or large patient populations**. This will make trials more feasible and efficient.
5. We ask the FDA to **encourage sponsors to include known asymptomatic MAPT mutation carriers in clinical trials and drug labeling**, just as is being done for genetic Alzheimer's disease. Early intervention could be transformative.
6. Please recognize that MAPT FTD patients and asymptomatic carriers are desperate for a cure. **Our community is willing to assume moderate to high levels of risk**, given the severity and inevitability of this disease.
7. In the absence of disease-modifying therapy, we urge you to **encourage sponsors to develop and test treatments that target the highest-priority symptoms**—those that most impact daily life and dignity.

"We are ready to take risks for the chance at hope. Please help us ensure that MAPT FTD patients and families are not left behind."

<u>Appendix:</u>

Dr. Brad Boeve: Full FTD Disease Overview Video Transcript

Dr. Brad Boeve, a neurologist at the Mayo Clinic in Rochester, Minnesota, was invited to provide an overview of Frontotemporal Dementia (FTD) associated with mutations in the *Microtubule-Associated Protein Tau* (MAPT) gene. In his presentation, Dr. Boeve outlined the clinical features of frontotemporal lobar degeneration (FTLD), the role of MAPT mutations, the lengthy diagnostic journey many patients face, and the significant unmet needs in treatment and care.

He began by explaining the clinical heterogeneity of FTLD, which encompasses multiple syndromes, including the behavioral variant of FTD (bvFTD), FTD with ALS, ALS alone, primary progressive apraxia of speech, three variants of primary progressive aphasia, corticobasal syndrome, and progressive supranuclear palsy. Each syndrome is associated with

degeneration in specific brain regions and is typically linked to abnormal accumulations of Tau, TDP-43, or other misfolded proteins.

Dr. Boeve noted that approximately 30–40% of FTLD cases have a strong genetic component. Among the genetic contributors, *MAPT* mutations are well recognized as a cause of bvFTD and are also implicated in other related syndromes. He highlighted the three most common genetic causes of familial FTD—*MAPT*, *GRN* (progranulin), and *C9ORF72*. While *MAPT* was the first of these discovered (in 1998), it remains underrepresented in clinical trials despite decades of knowledge.

The MAPT gene now has over 100 known variants, most of which are pathogenic and nearly fully penetrant. Individuals carrying a pathogenic mutation in MAPT have more than a 98% chance of developing symptoms if they live long enough, with onset sometimes as early as the 20s or 30s and typically before age 70.

Dr. Boeve described the "diagnostic odyssey" that many individuals with FTD endure. He explained that symptoms are often misinterpreted for years, frequently being mistaken for psychiatric conditions such as depression, bipolar disorder, or schizophrenia, or for life events like a midlife crisis. In many cases, it is a major incident—such as a legal issue, financial mistake, or personal crisis—that prompts recognition of a deeper problem. Even after a patient sees a primary care physician, referrals to neurology specialists familiar with FTD can take additional time, further delaying diagnosis. Once properly diagnosed, families must then face the added challenge of managing the disease, for which no FDA-approved treatments currently exist. Dr. Boeve shared that a patient's journey to diagnosis is often long and emotionally taxing, and that some families have depicted it as a confusing and painful maze.

The impact of MAPT-related FTD is profound. Patients and families face emotional hardship, financial stress, and in some cases, involvement with the criminal justice system due to behaviors driven by the disease process. Community stigma and misunderstanding are also common. Dr. Boeve emphasized the personal toll this disease takes, noting that in over 25 years of clinical experience, he has encountered many stories from families that are heartbreaking and emotionally difficult even for seasoned clinicians.

The socioeconomic burden of FTD is substantial. Although older data estimated direct annual per-patient costs at $120,000, current figures are likely much higher. These costs far exceed those associated with Alzheimer's disease, in part because FTD often strikes individuals in their prime working years. As a result, both the patient's income and the income of caregiving family members are frequently lost, amounting to combined financial losses of up to $200,000 per year in some households.

Dr. Boeve reviewed several ongoing challenges and unmet needs in the field. While early and accurate diagnosis remains inconsistent, it has improved significantly with increased public awareness and education, often led by advocacy organizations. Biomarker development has also advanced, including the use of blood and CSF protein assays, MRI, PET, and more refined molecular imaging techniques. Genetic testing for MAPT and other genes is now widely available. These diagnostic tools hold promise for earlier identification and tracking of disease progression. However, the most urgent unmet need is therapeutic development. While multiple

clinical trials are currently underway for *GRN* and *C9ORF72*, only one small trial has been conducted in MAPT mutation carriers—and that study was discontinued prematurely due to lack of efficacy in a related Tauopathy.

Dr. Boeve stressed the critical importance of initiating clinical trials specifically for MAPT-associated FTD. He emphasized that despite MAPT being the earliest discovered genetic cause of FTD, it remains the most underserved in therapeutic research. This, he noted, was one of the key reasons for engaging with the U.S. Food and Drug Administration.

He concluded by acknowledging the collaborative efforts of advocacy groups such as Cure MAPT FTD and the Association for Frontotemporal Degeneration, as well as long-standing research support from the National Institutes of Health. Dr. Boeve expressed deep gratitude for the opportunity to share these insights and reiterated his commitment to advancing knowledge and treatment for MAPT-related FTD.

In-Depth Survey Results: Community Survey Results

These survey responses come from 44 responses from MAPT affected individuals, asymptomatic carriers, care partners and family members, living in 30 US states, UK and Canada. Everyone was aged 18 or over.

1. Our MAPT FTD community is ready and interested to participate in any clinical trial available to us. We already actively participate in research, 70.5% participate in observational research up to 4 times per year.
2. When asked how important it was in participating in a clinical trial, 83.3% responded “Extremely important” when responding for themselves, and 68.75% when responding for “a loved one.”
3. What is the level of risk that individuals and families affected by MAPT FTD are willing to take in order to participate in a clinical trial? Over half of respondents - 52.3% - are willing to take on a moderate risk, meaning they would participate in trials where there's a chance of moderate adverse effects, as long as safeguards and monitoring are in place. Even more powerfully, 20.5% of respondents are willing to take on high-risk trials—those with serious uncertainties or the possibility of lasting harm, such as gene editing or first-in-human studies. This level of commitment underscores how urgent the need is for options, even experimental ones.
4. What are the specific types of risks that MAPT FTD families and individuals are willing to take in order to participate in a clinical trial? The most accepted risk, by over 70% of respondents, is uncertainty about a treatment’s effectiveness. This tells us that people aren’t demanding guarantees—they just want a chance. Next, 59% said they would accept mandated behavior or lifestyle changes—things like dietary restrictions or abstaining from alcohol—if it meant they could participate in a trial. This shows not only commitment but also adaptability. Over half—56.8%—are willing to undergo uncomfortable medical procedures, such as blood draws and lumbar punctures, which many MAPT FTD individuals are already regularly subject to with participation in observational research.
5. What could we do to motivate someone to join a high-risk clinical trial? The top motivator, cited by 59% of respondents, is lab results showing the potential for significant benefit, like

slowing disease progression. People want some evidence, even if early, that the trial might actually make a difference. More than half of respondents—52%—say they'd be more likely to join if the trial is run by a highly respected team or institution. Credibility matters, especially when the stakes are so high. And 50% emphasized the importance of clear communication about risks, benefits, and time commitment. (Other factors like guaranteed access to the treatment (no placebo), preserving eligibility for future trials, and reasonable logistics, such as visit length, travel distance, and cost reimbursement, were less influential, but still meaningful.)

6. If a new therapy could alleviate one or more FTD symptoms, which symptoms are the highest priority to treat? Three symptoms emerged as the top priorities, each selected by 56.8% of respondents:

Disinhibition and lack of self-control: This includes socially inappropriate behaviors, which can be distressing for both patients and families.
Impaired judgment: This symptom often leads to significant safety concerns and challenges in daily life.
Primary progressive aphasia: The decline in language skills is particularly devastating, as it affects communication and relationships.

"I am very willing to undergo a clinical trial, no matter what it offers." This is the MAPT FTD community: hopeful, informed, and incredibly willing to participate.

In-Depth Speaker Narratives

Speaker 1: Linde Jacobs: Asymptomatic positive mutation carrier, former carepartner

Linde comes to this meeting not just as a member of Cure MAPT FTD, but as someone whose life has been intricately shaped by generations of family devastated by MAPT FTD. For the past 40 years, her family has endured the relentless progression of this disease, yet never once were they given the opportunity to participate in a clinical trial or offered a treatment to halt the decline—only medications to manage symptoms. After testing positive as a MAPT mutation carrier at the age of 33, she finds herself facing seemingly impossible odds. FTD is guaranteed to be a part of her future. But rather than wait for the disease to erode the best parts of who she is, she chooses to fight for possibility. As the future face of FTD, she is desperate to prevent the flaw in her genome from stealing her future, her identity, and her ability to raise her children into adulthood.

FTD has haunted her family since her birth. Her grandmother began exhibiting symptoms in the early 1990s—drastic personality changes, hoarding, and a withdrawal from social life. Once a vibrant community member, her grandmother became a recluse. Initially diagnosed with Pick's disease, the diagnosis remained only probable until her death and autopsy in 2006 confirmed it as FTD. Beverly spent over 15 years with the disease, the last five immobilized, non-verbal, and incontinent. Since then, all four of her grandmother's children have received the same terminal

diagnosis in their early 50s. One uncle now lives in a locked memory care unit, another is incarcerated, her aunt requires 24-hour in-home care, and her mother has passed away.

Just three years after her grandmother's death, her daughter—this advocate's mother—began showing signs at age 50. Subtle at first, symptoms like sleep disturbances, anxiety, and word-finding difficulties were dismissed by her physician as menopause or stress. But her condition escalated—marked by disinhibition, emotional volatility, and eventually criminal behavior. Allison went from a respected physical therapist to someone unrecognizable—neglecting hygiene, overindulging in alcohol and sugar, accumulating arrests, and falling victim to scams. Despite a strong family history and her daughter's nursing background, a correct diagnosis of MAPT FTD wasn't received until 2018—after eight painful years. Her mother passed away in 2021.

Only four weeks after her mother's death, the advocate received confirmation that the genetic curse continued with her. Her sisters soon followed with testing, also testing positive. This means all six children between them now face the same cruel genetic coin toss. These children are her reason to continue fighting—though she often wonders if not knowing might have been easier. She desperately hopes that a breakthrough will come in time to change their futures, that MAPT FTD will no longer be a terminal sentence but a treatable condition.

In the three years since learning of her positive status, she has immersed herself in the scientific world—desperate for signs of progress. She has participated in over 20 research studies, trying to contribute to science and position herself for early access to interventions. Already, MRI scans show volume loss in her white matter—the silent beginning of the disease—even as she remains outwardly symptom-free. The damage is underway, and no treatment exists to intervene. It feels like she is treading water, waiting for a life jacket that may never come.

Her plea to the FDA is simple but urgent: to encourage sponsors to include expanded indication labeling and prescribing allowances that encompass MAPT FTD as therapies are approved for Alzheimer's disease and other Tauopathies. She has personally appealed to pharmaceutical companies developing Tau therapies to consider families like hers. While recognizing the complexity of treating a rare, genetic disease like MAPT FTD—with small patient populations and variable presentation—she notes that many Tau-targeting therapies were developed using MAPT FTD mouse models. The science is already connected.

Momentum in Tau research is building, and now is the time to act. She urges the FDA to create pathways that allow sponsors to extend indication labeling to include MAPT FTD. While insurance policy is beyond FDA's scope, it's critical to understand that most families affected by this disease eventually rely on federal insurance programs like Medicare. These programs do not cover off-label medications, making access to new treatments financially impossible for many, even if approved.

That is why the primary request—expanded indication labeling—is so vital. It would open a pathway for physical and financial access to lifesaving medications for MAPT FTD families. She respectfully asks the FDA to consider this approach as new Tau therapies move through trials and into approval.

Until that day comes, she will continue to fight—for her family, for her children, and for all who carry this burden—until she no longer can.

Speaker 2: Gil Chorbajian: Carepartner to his wife, with two at-risk children

His father-in-law died in 1995 from what is now understood to be MAPT Frontotemporal Dementia (FTD), three years before he met his wife. Unbeknownst to her at the time, she had inherited the mutated MAPT gene from her father and is now walking the same devastating path. She represents the fourth generation of her family to suffer from this disease.

What makes this story especially tragic is that, nearly three decades after her father's death, there is still no treatment for FTD—let alone a cure—and not a single clinical trial specifically targeting the MAPT mutation. This means that the prognosis her father faced in the early 1990s is essentially the same one his wife received thirty years later. That is why he is speaking out—because this must change.

Before his wife's diagnosis, the letters "FTD" reminded him of flowers. That changed on March 17, 2020—the day a neurologist sat across from them and said, "Frontotemporal Dementia." As the doctor described the condition of his wife's brain using words like *atrophy* and *shrinkage*, he understood—though his wife could not—that their lives had just been altered forever.

He began reading everything he could about the disease but quickly lost momentum. In the world of FTD, there was a vacuum of hope: no experimental drugs, no promising preclinical trials, and, most devastatingly, no survivor stories. He realized they were in a battle against an undefeated opponent—one not content merely to win, but to crush everything in its path.

Her diagnosis came just as the pandemic began. He remembers wondering whether it might be more merciful for her to succumb to COVID-19—then immediately reprimanding himself for having the thought. But the reality of FTD is such that these intrusive questions creep in, whether invited or not.

In a strange twist, the pandemic provided a temporary silver lining. It allowed him to transition from a full-time office job to working from home so he could better monitor his wife. But after 18 months, the dual demands of employment and caregiving became too much. He moved to a part-time position of 15–20 hours per week, then to one requiring just 15–20 hours per month. Finally, four years after her diagnosis, he stopped working altogether to care for her full-time.

Their current life is unrecognizable from the one they lived before FTD. His wife can no longer bathe or dress herself, and she is incapable of performing even basic personal hygiene tasks. She is non-verbal. Cooking, driving, managing finances, and even simple conversations are now distant memories. Sometimes he has to remind himself that those things were once part of their daily life.

She no longer knows his name, their daughters' names, or even her own. While her body remains physically functional, her soul and spirit seem sealed away—unreachable.

Pinpointing the date of her diagnosis is easy. Pinpointing the moment she slipped away is far more elusive. It feels as though she quietly left the room when no one was watching.

Gone is the woman who laughed at his jokes, organized neighborhood block parties, served as PTA president, ran marathons, generously donated during the holidays, and showed up for anyone in need. The loss is enormous.

But FTD does not affect only one person. It radiates outward, impacting countless lives.

Consider her mother, who lost a husband to this disease and is now reliving that nightmare with her daughter. She recently learned that her middle son—his wife's brother—has also been diagnosed with MAPT FTD. A third sibling turns 50 this year and may be on the cusp of developing symptoms if he, too, carries the mutation.

Then there are their two daughters, now in college. They were just 14 and 15 when their mother was diagnosed. In a matter of months, they transitioned from children to caregivers. They have bathed their mother, taken her to appointments, and helped her in the bathroom—offering the kind of care their mother once provided to them. They carry this burden while also grappling with their own uncertain genetic futures.

And there are dozens of others: friends, neighbors, coworkers, aunts, uncles, cousins, in-laws—over 40 of whom are pictured as part of this story—each feeling their own version of this loss. Then there are those yet to be born, such as future grandchildren, who will never have the chance to know her.

To those who never met her, he would say that his wife was many things, but above all, she was a fighter. She never shied away from a challenge. Today, her family carries on her spirit and fights on her behalf.

They have enrolled her in multiple research studies, including the ALLFTD Study. They host medical students to give them firsthand insight into the realities of dementia. They've helped raise thousands for the Alzheimer's Association. Their eldest daughter has twice run the Philadelphia Half Marathon to benefit the Association for Frontotemporal Degeneration. And one day, they will make the ultimate contribution through brain donation.

Still, they want to do more. He says "they" because he knows his wife would want the same. She would go to any length to spare future generations—especially their daughters—from experiencing what she has. That's why he wants to make it abundantly clear: his family is willing to bear nearly any risk and overcome any obstacle to participate in drug trials that might move this research forward in a meaningful way.

He often reflects on the moment when his wife first learned her father was ill. He wonders whether she and her brothers considered their own risks back then. If they did, perhaps they found comfort in the hope that, by the time they were at risk, science would have progressed.

And while there has been some progress, it has not been nearly enough.

That is why he shares their story today—and why he is asking for help. Because his greatest hope is not for himself or even his wife, but for their daughters: that they may follow in their mother's footsteps in how she lived, not in how her life will end.

Speaker 3: Susan Dunbar: Asymptomatic positive mutation carrier, currently surpassed typical age of onset

She is 67 years old, the youngest of six children born over a span of 19 years. Her oldest sibling, a brother, passed away from heart complications at the age of 64. Three of her sisters are still living—aged 83, 75, and 70. None have shown symptoms of illness nor have they been tested. Each of them has children and grandchildren.

She has lost her mother, one sister, at least one aunt, one uncle, and several cousins to the devastating disease known as frontotemporal dementia (FTD). Her maternal grandfather and three of his siblings died in their 50s from what was once referred to as "hardening of the arteries of the brain"—now recognized as FTD. Her mother had five siblings. Two of her brothers died in their 40s of heart disease, but little is known about the medical histories of their descendants. Her mother's sister began exhibiting symptoms of FTD around age 60 and passed at 73. That sister had seven children: two of them—one son and one daughter—developed FTD and died at 67 and 63, respectively, leaving behind their own children and grandchildren. There is no known history of the remaining siblings.

Her mother began showing symptoms of behavioral variant FTD (BvFTD) around age 60. She began speaking of an old boyfriend who was coming to take her away. Her verbal filter disappeared, her empathy waned, and her emotional affect flattened. She once left a pan on the stove that caused a fire. The heartbreaking process of watching her mother slowly lose herself without ever truly saying goodbye was torturous. That, she says, is the unique cruelty of FTD—there is no definitive end, only a slow, painful withdrawal.

She remembers visiting her mother in a catatonic state, her eyes fluttering with nystagmus, and wondering if there was any remaining spark of recognition. Deep down, she knew there wasn't. During one such visit, she brought her 4-year-old son. When she broke down in tears, he asked what was wrong, never having known his grandmother before her illness. She explained to him that her mother's brain had taken her away—transforming her into someone who was both the same and not the same. He responded with hugs and kindness. Her mother died in 1997, at age 75, after contracting pneumonia. She was kept comfortable until the end.

Her sister began showing symptoms in her early 50s and passed away at age 65. It was her autopsy that confirmed the diagnosis of Pick's Disease. This sister had four daughters. Though she has tried to encourage their involvement in research and testing, none have chosen to participate. The eldest, now turning 60, may be showing early signs of the disease.

In 2019, at age 62, she was living in Syracuse, New York, and working as a nurse midwife—a role she found stressful at times but mostly joyful. She loved supporting women and helping to bring babies into the world. Knowing she had a 50% chance of inheriting the MAPT gene

mutation and that she was near or past the typical age of symptom onset in her family, she decided not to continue working if the future was uncertain.

That October, she and her husband traveled to the FTD Center at the University of Pennsylvania. Before testing, she obtained life insurance and underwent genetic counseling. The doctor agreed to deliver the results by phone since she lived in central New York. That call changed her life forever: she had tested positive for the MAPT gene mutation. The emotional toll was immediate and overwhelming. Her husband had to hold her up as they both wept, mourning the loss of their shared dreams of growing old together.

Learning that she would likely lose her cognitive abilities over time was horrifying. Perhaps even worse was the realization that each of her three children—and potentially her two grandchildren—had a 50% chance of inheriting the gene. She felt guilt, sorrow, and a deep sense of contamination. Telling her children was one of the hardest things she had ever done. Though they had anticipated the family meeting's purpose and tried to lighten the moment with handmade "Pick's Disease" crowns made of toothpicks, she still burst into tears with a mix of relief and pain.

Everything suddenly felt urgent. Her son, daughter-in-law, and grandchildren had recently moved to North Carolina, and she knew she needed to be near them. Within three months, she retired, sold her beloved home, and moved with her husband to the Asheville area.

The first year after the move was especially difficult. She experienced intense depression, cried frequently, and scrutinized every mistake or lapse in memory for signs of the disease. She knew the earliest symptoms were behavioral—loss of inhibition, empathy, and the emergence of compulsive actions. Yet over time, she realized that most of what she experienced were just normal "senior moments." After that first painful year, she began thinking about the disease less and focused more on living fully.

Her children have discussed undergoing genetic testing. She has mixed emotions about it. Her eldest is about to turn 40. If one of them tests positive, it would be like receiving her own diagnosis all over again—only worse—knowing she passed the mutation on. It's a possibility she's not sure she could emotionally endure. And if her child is positive, her grandchildren might be, too. A part of her wants her children to wait until after she is gone to get tested—a feeling she admits is selfish and cowardly. The thought weighs heavily on her heart.

Now, she is past the age of onset for all known symptomatic relatives. Even though she understands that the MAPT gene has near-complete penetrance, she doesn't dwell on it daily. It lingers in the background, but she remains active—exercising her body and mind—and prioritizes making lasting memories with loved ones.

Today, all three of her children live nearby, and they spend a great deal of time together. She has traveled with them and her husband to Greece, Hawaii, Montana, the Everglades, and Mexico, cherishing every shared experience and adventure.

Since 2020, she has participated in the University of Pennsylvania's ALLFTD longitudinal research study, traveling yearly from North Carolina for MRIs, cognitive assessments, and

bloodwork. Though the cognitive testing can be brutal and often makes her feel inadequate, the research team has reassured her that she is doing well. She also contributes to a three-year quarterly blood draw study that is nearing completion.

The thought of her children and grandchildren suffering from this devastating disease is almost unbearable. She urges the research community to prioritize investigations into FTD caused by the MAPT gene. While Alzheimer's research receives significant funding, FTD does not. If her descendants carry the mutation, she hopes that emerging research will lead to preventive treatments—particularly those targeting the Tau protein.

Speaker 4: Marian Grems: Multigenerational carepartner to spouse and two affected children

Her relationship with FTD began over 60 years ago, when she met her future father-in-law. He was nonverbal, prone to pinching, maniacal laughter, and often appeared without clothes.

Decades later, she discovered that he and his estranged brother had been raised in an orphanage after their mother was institutionalized. His brother, two of his children, and one of their descendants died from early-onset dementia. Another family member is a presymptomatic carrier of the MAPT mutation.

Her husband began showing dramatic personality changes in his mid-40s. He became moody, withdrawn, obsessive, and his behavior grew increasingly abusive and unpredictable. Afterward, he expressed no regret or memory of his actions. It soon became clear that this was far more than a mid-life crisis.

He also became sexually inappropriate, frequently violating personal boundaries, and grew obsessed with tongues—once decorating the exterior of their home with eight large-faced decorations with exaggerated tongues, outside of any seasonal context like Halloween.

At work, his behavior further deteriorated. He annoyed coworkers by repeating stories incessantly, repeatedly called high-profile clients only to hang up, and struggled with simple tasks such as sending an email attachment.

At the age of 50—during what should have been his peak professional years—he lost his job. While this was not unexpected given the circumstances, what shocked the family was his complete obliviousness to the consequences of that loss.

During his nine-year journey with behavioral variant FTD (bvFTD), the family endured staggering anticipatory grief. FTD stripped him of purpose, empathy, dignity, and personality as both his cognitive and physical abilities declined.

Their financial security and hopes for a joyful retirement were destroyed, replaced with relentless challenges. But the most profound loss was felt by their three children.

The children's memories were clouded with embarrassment, unpredictability, and a lack of emotional connection. They lost the father who would have guided them, celebrated their triumphs, and supported them in dark times.

Five years after her husband's death, her heart was shattered again when her 40-year-old son began exhibiting hallmark FTD behaviors. Another FTD diagnosis was not part of their life plan. After losing his job, he relocated from Arizona to Ohio, where she became his caregiver.

His journey was distinct but no less tragic. It included a prolonged, costly divorce; Parkinsonian-like symptoms that left him frozen and immobile; and run-ins with law enforcement due to inappropriate interactions with dogs and children. He died at just 45.

Her daughter, a three-time cancer survivor, later began experiencing executive function difficulties. Torn between fears of cancer recurrence and neurodegeneration, they pursued genetic testing, which confirmed her worst fear: MAPT-related FTD. The long-standing mystery of familial dementia now had a name.

She had hoped their two granddaughters, aged 14 and 16, would be spared the pain of FTD. Her daughter, who had already battled non-Hodgkin's lymphoma, angiosarcoma, and triple-negative breast cancer, now faced yet another cruel adversary. And with her diagnosis came the painful reality that her daughters were at risk of carrying the MAPT mutation.

Her granddaughters shared their thoughts:

> *"FTD has changed our happy, fun-loving mom. She does really embarrassing things so it's hard to have our friends over. She can't follow simple directions and repeats herself. When we try to help her, she gets mad and pouts. She doesn't think anything is wrong with her.*
>
> *She doesn't laugh anymore. She spends lots of time in her room ordering brain health products—once making 21 purchases in two hours.*
> *We miss our mom! We miss her goodnight kisses and how she used to ask how our day was. We're scared we inherited the MAPT gene too."*

She spoke not only as a spouse, mother, and grandmother, but also as a voice for countless parents caring for adult children with genetic FTD. Each story is unique, yet all are bound by the shared heartbreak of watching a child lose their potential, identity, and future to this disease.

Losing a spouse or parent to FTD is devastating, but no word adequately captures the despair of losing a child in this slow, cruel way. Parents may be prepared to face the physical and emotional demands of caregiving—taking away car keys, helping with toileting, dressing, and absorbing financial burdens—but nothing prepares them for watching their child disappear, piece by piece.

She remains committed to doing whatever it takes: participating in trials, risking everything, and pushing past despair toward hope—a hope for a future free of MAPT-FTD.

Speaker 5: Ansel Dow: Asymptomatic positive mutation carrier

This individual's family is deeply affected by MAPT FTD. His mother developed the disease at a young age and is also a carrier of the gene variant, which means the disease is expected to affect them personally in the future.

The individual shared a photograph from their childhood, taken when they were six years old. At that time, the family lived in Eugene, Oregon. Their mother loved taking the children hiking and playing in the forest. She was described as caring, kind, and thoughtful. She came from a large family with nine siblings. Another photo, taken shortly after the individual's birth, shows a family reunion with many aunts, uncles, and cousins—highlighting the closeness of the extended family at that time.

Around the same period, the individual's aunt began showing symptoms of FTD. She became withdrawn and distracted. One alarming incident involved her 2-year-old son nearly drowning in a swimming pool while she sat nearby, unaware of the danger. The child was saved by his young sister. At only 37 years old, this aunt's symptoms marked the beginning of a long struggle to obtain a diagnosis. It wasn't until 1997—eight years later—that she was formally diagnosed with FTD.

Tragically, six of the nine siblings in that generation would go on to suffer from FTD. They lost their jobs, saw their marriages and relationships fall apart, were arrested, or went missing. Unaware of their genetic risk, they passed the MAPT variant on to their children. The individual, their younger brother, and several cousins are now presymptomatic carriers of the gene.

There are no recent family photos that include everyone together, as 1994 was among the last times the family gathered in full. The disease created rifts among the siblings, some of whom argued or became estranged. Others dedicated their lives to providing care for affected family members.

One aunt has served as the full-time caregiver to her sister since 1995. They have lived together in the same house for decades. Initially, the caregiver helped manage doctor's appointments. Over time, she took on more responsibilities—preparing meals, assisting with hygiene, and providing around-the-clock care. The sister now wears adult diapers, and certain areas of their home carry the odor of long-term illness and incontinence. Despite the progression of dementia, those affected often live long lives, placing an extended and heavy burden on caregivers.

The impact of growing up with a parent affected by dementia is different from that of adult caregiving. The trauma of losing a parent to cognitive decline in childhood is difficult to articulate. Children often must reverse roles, becoming caregivers without understanding why their parents are changing. Most people with FTD cannot explain or recognize their symptoms, creating confusion and isolation for their loved ones.

The individual also expressed fear about their own future, particularly regarding the possibility of passing on the gene to their future children—or burdening them with caregiving if symptoms develop. Their mother, after witnessing her sister's decline, once said she would rather die than live with dementia. The individual understands that sentiment, given the intense toll caregiving can exact on loved ones.

Despite these fears, their mother firmly believed that science and medical research were a source of hope. The family has participated in FTD longitudinal research for over 15 years. Photos from their recent annual visit to the Mayo Clinic show their ongoing commitment.

Studying symptomatic individuals like the individual's mother poses challenges: traveling is difficult, answering questions is hard, and focusing on tasks for more than a few minutes can be impossible. Caregivers are essential to this research, as they observe and report the day-to-day changes in behavior and function. Any future clinical trials for FTD treatments will need to rely heavily on caregiver input.

Both the individual and their brother are confirmed carriers of the MAPT FTD gene variant. They have expressed willingness to do anything necessary to support the development of a treatment. They are ready to take risks and participate in any test protocol, because for them, the stakes are extraordinarily high. Time is limited, and irreversible damage is on the horizon.

They urge those reviewing clinical trial protocols to consider the unique challenges involved in studying FTD and to act with urgency. For families affected by FTD, the need for effective treatments is not just important—it is life-saving.

Speaker 6: Erin B: Carepartner to husband, with two at-risk children

Her husband was in the prime of his life when he began developing symptoms of Frontotemporal Dementia (FTD) at age 37. At the time, he was climbing the corporate ladder as an attorney for one of the largest financial institutions, regularly speaking at legal seminars and mentoring other attorneys. He also volunteered on two city government boards, participated in school and church events, and served as chairman of a nonprofit board.

It took over five years to receive a completely accurate diagnosis. Initially, an orthopedic doctor attributed his decreased movements to nerve damage, followed by two nationally recognized neurologists diagnosing him with Young Onset Parkinson's Disease (YOPD). Even after genetic testing revealed an N279K mutation of the *MAPT* gene, his neurologist insisted his primary diagnosis remained YOPD and that his progression would align with that disease.

She became deeply involved with the Parkinson's Foundation and began to notice his cognitive decline was far more rapid than that of others with YOPD. Ultimately, his worsening speech and cognitive issues forced him to retire in April 2022 at the age of 40. The community lost a natural leader, skilled negotiator, and dedicated civil servant to this genetic mutation.

He was a devoted husband and father, with family always his top priority. Full of life, he enjoyed exercising, creating things for his sons, and constantly improving their home. When his symptoms began, their sons were just five and seven years old. He introduced them to his favorite childhood toys and delighted in spoiling them with train sets, Matchbox cars, wooden blocks, and more. He worked hard to keep them active—building a large sandbox on the patio and using jogging strollers, tagalongs, and trails for walks, runs, bike rides, and playground visits. He never missed a sports game or school activity and loved exposing his sons to new experiences—zoos, pools, museums, fishing, skiing, golf, pumpkin carving, sledding, even

building igloos. As a family, they enjoyed vacations to lake resorts, family cabins, Disney World, Disneyland, and various parts of Florida and California. Yes, that was even him standing on the water ski tube.

Now, he is a shell of the man he once was. Over the past two to three years, his executive functioning, speech, behavior, and movement have deteriorated significantly. He often cannot retain information, follow steps, or think rationally. His speech is frequently too soft or too fast to be understood—or entirely absent. He also confuses words. Conversations with him have become nearly impossible, which is especially hard for their oldest son, who used to have nightly one-on-one talks with his dad. Now, their sons either leave the room or ask their mother to interpret what he is saying, as he often repeats himself without understanding. Although he attempts to use an app to speak, he struggles with typing and focusing his eyes on the screen and keyboard.

His FTD manifests in ritualistic and paranoid behaviors—checking every closet before bed, repeatedly locking doors, and obsessively reviewing footage from numerous Ring cameras. These behaviors keep him up late at night, disrupting the family's sleep. He also exhibits hyperorality, consuming iced cookies and other sweets by the handful, leading to significant weight gain, and often licking plates and bowls clean. Hypersexuality is another symptom; he has signed up for dozens of dating and social media platforms, communicated with unknown women, and exchanged explicit photos—sometimes involving money.

His physical symptoms have worsened as well. Exposure to wind, light, or water causes his eyelids to close involuntarily, often requiring him to manually lift them open. He frequently loses balance—not while moving, but while standing still. He will try to catch himself while falling backward but is unable to, often crashing into a wall, countertop, or the floor.

He immediately enrolled in the ALLFTD study and any other research opportunities he qualified for, determined to help others. When he learned there was a 50% chance their sons might carry the same gene mutation, he committed to doing everything possible to contribute to research, find potential treatments, and one day, a cure. His sons mean everything to him, and he is devastated by the thought that this could affect their bright futures.

After receiving the genetic test results, he wrote the following letter to his sons:

> *"I am writing this 8 days after first learning about my diagnosis (of FTD). I am totally shocked at the diagnosis I just received. I could never have done life without each of you. Therefore, I totally understand if you each want to have children even if you have this gene mutation. It will be up to each of you to decide if you want to get tested and if you want to have children. I wanted each of you to go as far as you could in life before learning this news. I do not want it to hold you back! I led a very fulfilling life (and I am only 40 years old as I write this). I truly feel like I lived a King's life. I got to go to DC as an intern, flew around the country as an attorney. I had my dream job. I also married the woman of my dreams and had two amazing kids! I am with each of you as you go on this journey! Whatever you decide I support you 100%! I will always be with each one of you, and I love you always!"*

Their family remains committed to supporting his desire to make a difference—for their sons and for others—no matter the time, cost, or effort required.

Speaker 7: Annika R: Asymptomatic positive mutation carrier, current carepartner for mother

This is the story of how Frontotemporal Dementia (FTD) changed a family, beginning with the mother, who began showing symptoms at just 48 years old.

She was the main provider for her family and very active in her community. She grew her own vegetables, made soap from scratch, and volunteered on weekends, all while maintaining a successful career as a senior vice president at a Fortune 500 company and serving on the boards of several local nonprofits. She lived by the motto “treat others how you want to be treated,” and deeply instilled this value in her children.

In 2010, she lost her job, and this major life change triggered the onset of FTD symptoms. At first, her family thought she was struggling with depression. She seemed to lose interest in her children, and it appeared as if her empathy simply disappeared—she could no longer sense or respond to their feelings as she once had. New compulsive behaviors emerged, such as watching the same TV show on repeat for hours. Most shockingly, she developed a drinking problem, despite rarely consuming alcohol before. These changes were confusing and heartbreaking to her family, who did not realize at the time that these were early signs of FTD.

When her daughter was 16, the mother was arrested for a DUI and spent a night in jail. Even during such significant moments, she showed no guilt or sadness. FTD had flattened her emotions. She simply returned to her normal routine as if nothing had happened.

She stopped formally parenting, leaving her children somewhat to fend for themselves. Her son, struggling in school at age 12, convinced her to let him stay home every day, and he rarely returned. Her gullibility increased; she was easily persuaded to buy expensive supplements that she never used. She also lost the ability to navigate new places and was once missing for several hours in New York City before being found by a police officer. Since then, her family has not let her out of their sight.

Her family now supports her in many ways. Her daughter moved closer to home to help manage her care, and her husband adjusted his work schedule to work from home most days. She cannot safely drive and needs assistance with bathing and personal hygiene.

At 28 years old, the daughter has begun to consider her own future. Knowing she had a 50% chance of inheriting the disease, she was terrified for years to get tested. Would she lose her memory, empathy, and ability to function as her mother has?

A few months ago, with the support of her husband, she got tested and received a positive result. She now manages her mother’s care while confronting the reality that this disease is in her own future. Her mother is only 59 and may live for years with the disease, slowly losing her ability to function.

Furthering research and science in MAPT FTD is critical for both of them. They have participated in longitudinal studies for years. The daughter would do anything to keep her mother in the current state and prevent further decline. If the disease progresses, the family will have to make greater sacrifices, and the woman her mother once was will diminish even further. Despite her illness, the mother can still enjoy many things she loves, like singing to her favorite ’80s music and playing simple card games.

With a positive genetic result, the daughter is uniquely positioned to participate in clinical trials. As an asymptomatic carrier of MAPT FTD, she urges the FDA to allow individuals like her to participate in clinical trials. Studying such individuals using biomarkers could identify and track the disease before symptoms appear, opening the door to true prevention.

Though grieving the loss of her mother and facing the dark shadow of her own future, she remains vigilant, pleading for clinical trials that include people like her. They are ready, willing, and desperate for a chance, no matter the risk.