Partners in FTD Care

A quarterly newsletter for healthcare professionals

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DETECTING AND DIAGNOSING FTD

Until approved biomarkers exist to support the accurate diagnosis of frontotemporal degeneration (FTD), diagnoses will continue to rely on comprehensive assessments by skilled and knowledgeable clinicians. But such assessments are notoriously difficult to obtain – on average, getting an FTD diagnosis takes 3.6 years following the onset of symptoms. And those symptoms can overlap with other, more common conditions, ranging from Alzheimer's and Parkinson's disease to conditions such as depression or bipolar disorder.

This issue of *Partners in FTD Care* focuses on aspects of FTD detection and diagnosis that can be particularly challenging for primary care clinicians, highlighting the need to improve FTD diagnosis to positively impact care and accelerate treatment research. Additionally, the issue lists resources that can assist with detection, help to differentiate FTD from psychiatric disorders, and discuss the importance of family involvement in assessment. It also includes an interview with a physician diagnosed with an FTD disorder who acknowledges it took far too long, even though he worked in healthcare.

AFTD is working to expedite accurate FTD diagnoses, giving families more valuable time to better manage the disease, learn about potential genetic risks, consider research participation, and plan for their future.

IN THIS ISSUE

THE SCIENTIFIC IMPERATIVE OF ACCURATE FTD DIAGNOSES: IMPROVING CARE AND ACCELERATING TREATMENT RESEARCH

In 2021, AFTD hosted an Externally Led Patient-Focused Drug Development (PFDD) meeting. Established by the U.S. Food and Drug Administration (FDA) in 2012, PFDD meetings ensure that the experiences of people impacted by specific diseases are incorporated into the FDA's decision-making on drug approval. During the 2021 AFTD-hosted meeting, people with lived experience of FTD repeatedly told the FDA about the importance of accurate and timely diagnoses:

> *"After she had cognitive testing, her doctor said, 'Nothing was wrong.' Yet, she was prescribed Namenda and Aricept."*

> *"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."*

> *"Early diagnosis is what's really helped us. And then he was enrolled in a clinical trial with a drug that really brought back his sense of humor, his ability to be affectionate."*

> *"She did receive a diagnosis, but it was already at the later stages of FTD…It's similar to what other people have said, really. It took us a long time to get a diagnosis. And by the time she did, we were basically told that there's not a lot you can do now, other than good luck."*

FTD, with its heterogeneous symptoms that can mimic a host of other disorders, can be difficult for healthcare professionals to diagnose, with the average diagnostic process taking 3.6 years on average, with visits to three or more doctors not uncommon.[1]

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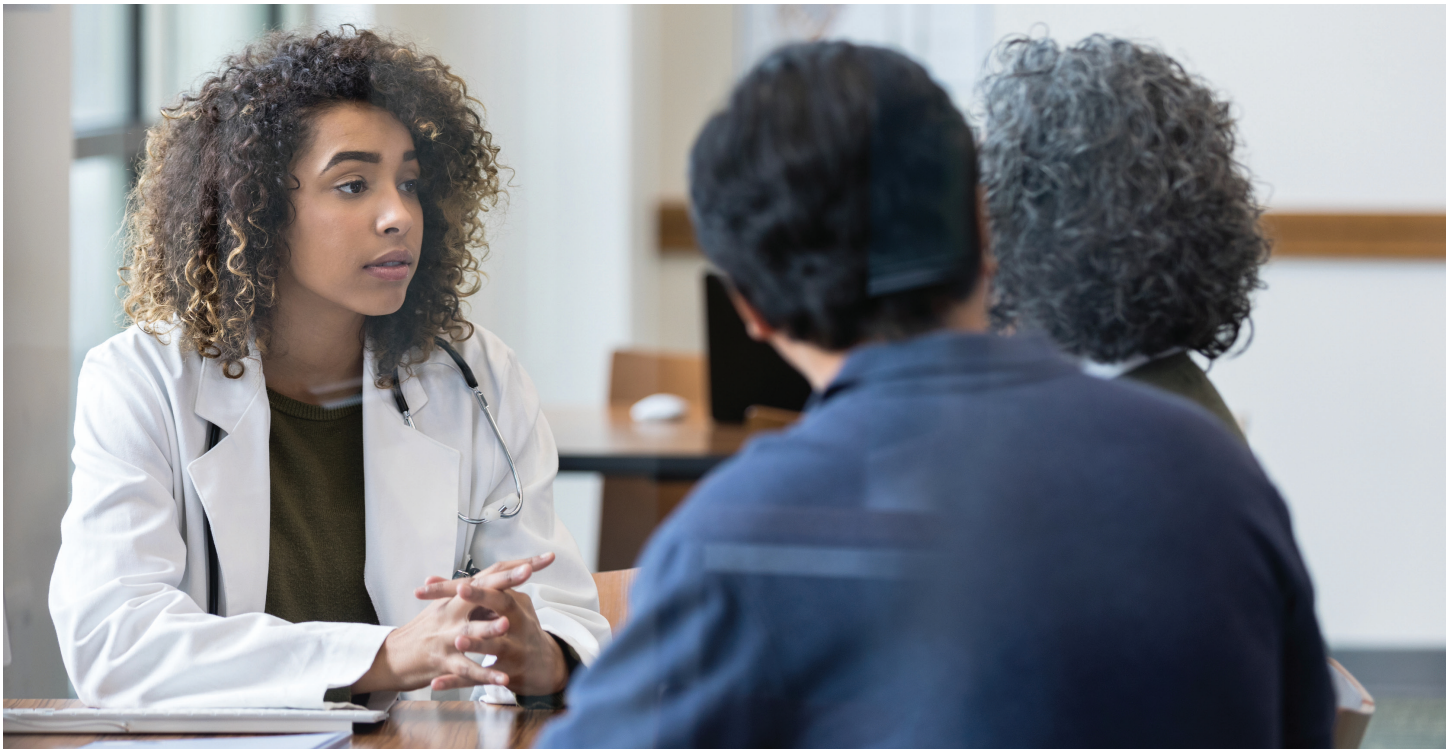

Research from AFTD found that 44% of survey respondents reported having received an initial diagnosis that differed from FTD, including Alzheimer's, Parkinson's disease, anxiety, depression, or bipolar disorder, as well as menopause or mid-life crisis.[2] In addition to causing families frustration and stress, misdiagnoses also mean that people with FTD are deprived of appropriate supportive care and may be receiving interventions that are contraindicated for FTD. Medication approved for Alzheimer's disease, for example, can be ineffective or even exacerbate cognitive and behavioral symptoms when given to someone with FTD pathology.[3,4]

With the emerging availability of FTD clinical trials, accurate diagnoses are even more critical. Current clinical trial options for people with FTD include symptomatic as well as disease-modifying therapies, spanning the spectrum of FTD clinical phenotypes. If clinical trials enroll people with the wrong diagnosis and underlying pathophysiology, researchers cannot determine if treatment effects, or lack thereof, are due to the intervention or to the heterogeneity of the participant pool.

This issue holds true across dementia research. According to Dr. Jeffrey Cummings of the Cleveland Clinic, "up to 25% of families have been told their loved one has Alzheimer's disease and they don't…which also means that up to 25% of people participating in some type of clinical trial don't actually have Alzheimer's disease."[5] In a rare disease like FTD where researchers recruit much smaller sample sizes, individual variability has a significant impact on the data. Many current clinical trials are focused on FTD caused by specific genes or on the underlying pathophysiology, underscoring the importance not only of an accurate clinical diagnosis, but of genetic status and potential pathology as well.[6] Further, for people to feasibly participate in clinical trials for FTD, their FTD diagnosis must be made early on in disease progression. Many people report that by the time a diagnosis was received, their loved one's FTD was too far progressed to make research participation possible.

There are, therefore, a number of reasons that timely access to accurate FTD diagnoses is critical. However, healthcare professionals' hesitancy to disclose dementia diagnoses are well-documented. The 2019 World Alzheimer Report noted that 62% of healthcare providers worldwide consider dementia a normal part of aging.[7] A 2015 study commissioned by the Alzheimer's Association found that disclosure rates (the percentage of persons diagnosed and families told about a diagnosis that was documented in their medical records) for Alzheimer's (45%) and other dementias (27%) were far below those of those of other medical conditions, including cancer (84-96%) and Parkinson's disease (72%).[8]

While there is no single diagnostic test, diagnosis typically includes a medical history and neurological examination, neuropsychological testing, neuroimaging, and blood tests.

Fortunately, there are tools to aid clinicians in the accurate diagnosis of FTD. While there is no single diagnostic test, diagnosis typically includes a medical history and neurological examination, neuropsychological testing, neuroimaging, and blood tests. As a significant subset of FTD is caused by autosomal dominant genes, healthcare providers should consider genetic counseling for persons with suspected FTD. In addition, natural history studies are uncovering promising neuroimaging, serum, and CSF biomarkers that may soon have diagnostic utility.[9,10] Finally, it is critical to communicate FTD diagnosis in a manner that can be understood by both the person with FTD and their family. Consider a person-centered approach to such disclosure, one that includes building rapport, tailoring your language, involving the care partner, and following up to ensure the family understood the information you provided.[11,12] ■

AFTD INTERVIEW: SETH L. STERN, MD

Dr. Seth Stern is living with a diagnosis of primary progressive aphasia, a form of FTD that gradually erodes one's ability to both speak and understand spoken and written language. In May 2023, Dr. Stern, a former obstetrician/gynecologist, told the story of his diagnosis to the Wall Street Journal*, which published a feature story about him entitled "Something Was Wrong with Dr. Stern. It Took Five Years to Figure Out." AFTD spoke with Dr. Stern in July 2023 to learn more; an edited version of that conversation appears below.*

AFTD: What were the most concerning early symptoms – the things that made you think something's wrong?

Dr. Stern: Initially it was word-finding. I couldn't think of the word "butter"; another time I couldn't think of the word for "washing machine." Then I started doing other things that were very unusual for me. I've been a surgeon for over 37 years, and I'm very particular: I dot my I's and cross the T's. But I started to do things that were both unusual and atypical. For example, I made coffee and forgot to put the mug under where the hot water comes out. Once I left my front door unlocked at night; once I got out of my car without turning it off.

In 2017, I started recording all these changes on my cell phone. That same year, I was seen by a neurologist who did both cognitive testing and an MRI, but nothing in my results was significant. So I just concentrated on being more careful. I made sure I locked the door at night; when I used the stove I checked that all the dials were turned off. And I made sure that when I did surgery, I was right on par and even more careful.

Starting in July 2021, however, things really started to progress. Finding words and completing sentences got much more problematic, and things that had been very common for me started becoming much more difficult, specifically surgery. For me, doing surgery was always very relaxing. I would hum or sing throughout, and I didn't have to think about what I was doing from step to step; it was just automatic. But then I started finding that I had to think twice.

I had always loved going to the hospital and taking care of my patients. I would be one of the first people to come in and I would be one of the last to leave. But I started to develop apathy – I didn't have that desire to be there early or stay late. I starting asking the nurses, "What time do we finish?" or "How many more patients do we

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have left?" That was a big difference – going from being concerned about the patients to being, well, "What time am I finished today?" I just kind of lost that desire.

"I feel something is wrong, and I would like to have the [PET] scan done," Dr. Stern told his doctor.

At this point, I was again seen by the neurologist, who repeated a cognitive test on me; I scored 29 out of 30 questions correct. He did blood work and another brain MRI, but nothing came back significant at all. He said to me, "You seem OK. The only thing left to do is the PET scan, but you don't really need it because you seem to be doing fine." I said, "No, I feel something is wrong, and I would like to have the scan done." I had the brain scan in April 2022, and it showed significant changes in the frontotemporal regions. The neurologist called me later – he didn't even tell me in person – and said that I have FTD, I need to be seen by a neurocognitive specialist, and have a good life.

This news was very, very upsetting. My overall plan was to continue to practice medicine another 10-15 years... instead I retired in May 2022.

AFTD: Was it helpful to get a diagnosis, or would you rather have not known?

Dr. Stern: It's funny – if I hadn't gone for the PET scan, I wouldn't have known I had FTD, and I could have continued to do what I was doing: seeing patients, doing surgery. So knowing at least was beneficial in that nobody got hurt. Unfortunately, finding out – especially with this condition which has no medical or surgical treatment, or cure – is difficult, because you're now living with a time limit, and in x number of years the dementia will progress and significantly worsen, and my lifespan will be much shorter than desired. That's very, very hard to live with. It's not unusual for me to think about it daily.

On the other hand, getting a diagnosis allowed me to make plans for my future health care needs. I made sure that my health proxy, my will, and my financial investments were all taken care of. And I have started to educate others about FTD and other neurodegenerative disorders.

AFTD: What would you say about how long it took to get a diagnosis? It took a number of years. Do you wish you would have known sooner rather than later?

Dr. Stern: I was dealing fairly well with my day-to-day activities until the middle of 2021, when things progressed dramatically. From there I was diagnosed in less than a year. But I'm a doctor and a surgeon. For the average person out there who doesn't personally know neurologists, they may face the problem of having a physician who is not really educated about FTD. Or they may have family members who tell them, "Oh, you're just getting older; some decline is expected." Or there's no neurologist where they live, and they have to drive 100 to 200 miles to see one. Or their insurance doesn't cover the tests they need. All of these are different, unfortunate, and complicating issues.

"Getting a diagnosis allowed me to make plans for my future health care needs," Dr. Stern said.

Having someone to participate in your care, or to represent you when you go to these medical appointments, is very beneficial. So was the fact that I kept a diary to record my changes. And if I had not pushed for that PET scan, it wouldn't have been done. If patients don't have someone with them when they are being seen or evaluated, they could easily be swayed not to undergo necessary testing. That person can tell the doctor, "Look, he or she is experiencing such-and-such – this is why we're here." Personally, I know that if I didn't insist that there was a problem, my FTD would not have been diagnosed. ■

DISTINGUISHING BEHAVIORAL VARIANT FTD FROM PSYCHIATRIC DISORDERS

Distinguishing behavioral variant FTD (bvFTD), the most common FTD subtype, from psychiatric diagnoses (such as depression, bipolar disorder, or schizophrenia) can be extremely difficult. Many symptoms – disinhibition, apathy, loss of empathy – are common to both bvFTD and certain psychiatric disorders, leading doctors to initially diagnose the latter until a person's bvFTD gradually reveals itself. Getting an accurate diagnosis is crucial, however, because of bvFTD's drastically different prognosis, the differences in disease management, disease-specific needs for family counseling and caregiver education, and financial and long-term planning. It is also critically important to accurately identify bvFTD as early as possible so that persons diagnosed can consider potential participation in clinical trials, and learn about genetic causes of FTD.[13]

Diagnosing bvFTD remains challenging because of the limited accuracy of neuroimaging in the early disease stages and the absence of biomarkers, and therefore relies on clinical assessment.[13] The diagnostic criteria for a probable diagnosis of bvFTD requires evidence of atrophy in the frontal and/or temporal lobes of the brain as seen on MRI, along with the presentation of three of the following six symptoms: behavioral disinhibition, apathy without sadness, loss of empathy, executive dysfunction, hyperorality, and compulsive behaviors. A progressive disease, bvFTD can onset in subtle ways that are often first identified by family members.

Some questions clinicians can ask when attempting to differentiate bvFTD from psychiatric disorders are:

- At what age did the symptoms begin?
- Are there cognitive symptoms? Are they getting worse?
- Is the individual with symptoms falling frequently or complaining of muscle weakness?
- Are symptoms occurring late in life for the first time?

- Is the family presenting with increased distress?
- Is the individual with symptoms showing a lack of insight into their health changes?

If bvFTD is suspected, refer the person with symptoms to a neurologist or other neurological specialist, such as a neuropsychiatrist, neuropsychologist, or behavioral neurologist. FTD specialists can be found on the AFTD website.

To learn more, watch "Distinguishing bvFTD from Psychiatric Disorders," a presentation delivered by Ted Huey, MD, at the 2022 AFTD Education Conference. Dr. Huey is the Director of the Memory and Aging Program at Butler Hospital, affiliated with the Warren Alpert Medical School at Brown University.

To learn more about the diagnostic criteria for bvFTD, download AFTD's Diagnostic Checklists. ■

DETECTING AND DIFFERENTIATING DEMENTIA SYMPTOMS EARLY

The first step toward an accurate diagnosis for those experiencing frontotemporal degeneration (FTD) symptoms is early recognition by the person and/or their family that something is wrong, leading to a timely appointment with their doctor for an assessment. This gives the doctor the opportunity to evaluate symptoms in relation to an established cognitive and behavioral baseline. Early assessment – which will ideally include a close family member, who can speak more objectively to any changes detected in the person experiencing symptoms – can help differentiate between FTD and other dementias, such as Alzheimer's.

The following resources are provided to support the timely recognition and assessment of FTD symptoms in the primary care setting.

AFTD WEBINARS

AFTD HEALTHCARE PROFESSIONAL EDUCATION WEBINAR: DIFFERENTIATING BEHAVIORAL VARIANT FTD FROM ALZHEIMER'S AND OTHER DISORDERS

This February 2023 AFTD webinar was presented by FTD expert Howard Rosen, MD, a behavioral

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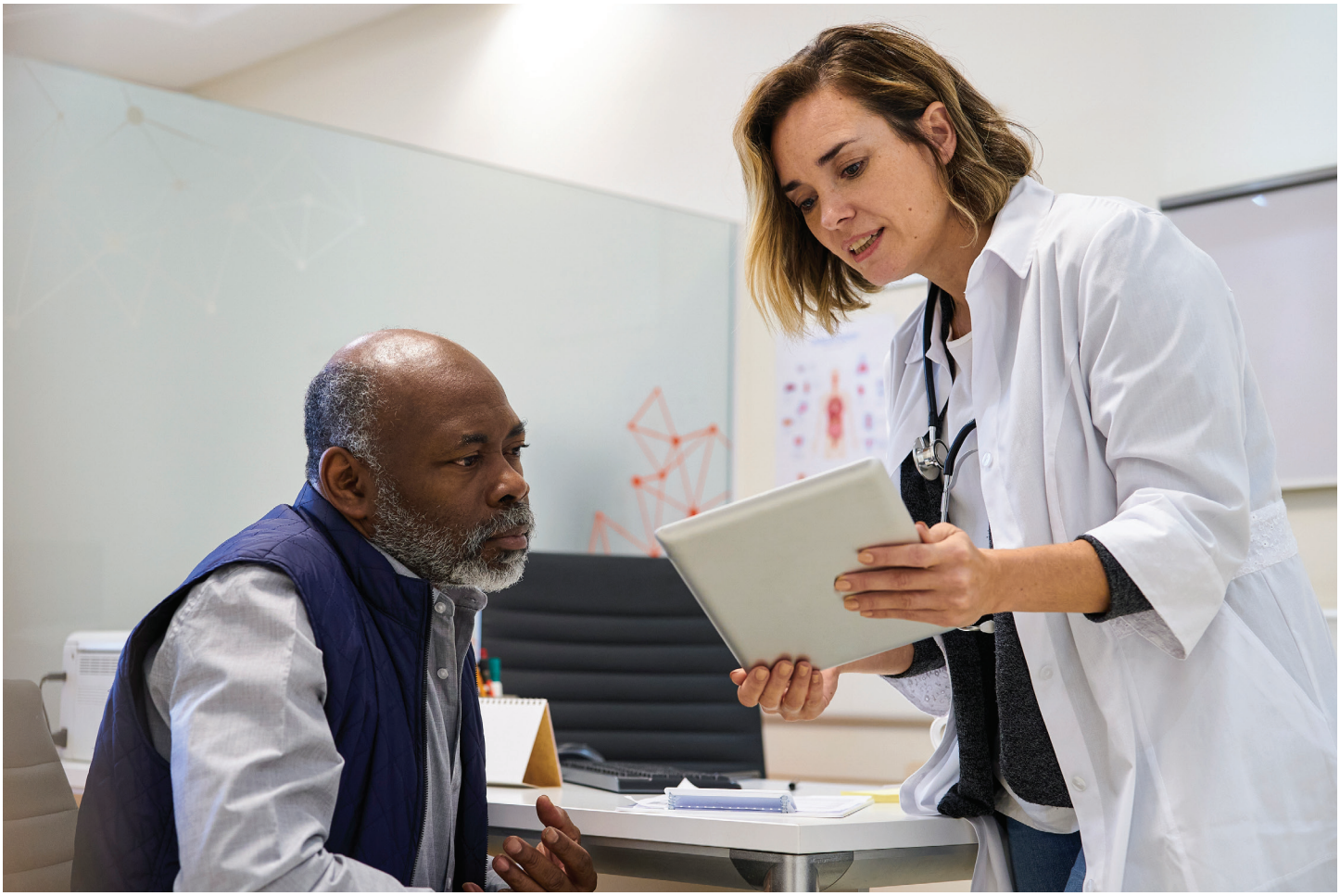

neurologist and the associate director of the Alzheimer's Disease Research Center at the University of California, San Francisco. Here, he presents a clear approach to understanding bvFTD and diagnosing and differentiating it from Alzheimer's disease, other dementias, and psychiatric conditions.

AFTD HEALTHCARE PROFESSIONAL EDUCATION WEBINAR: TREATMENT OF BEHAVIORAL VARIANT FRONTOTEMPORAL DEGENERATION

Dr. Simon Ducharme, a neuropsychiatrist, researcher, and expert specializing in FTD, presents the treatment considerations for bvFTD symptoms as well as non-pharmacological approaches for disease management in this April 2023 AFTD webinar. He also discusses pharmacological treatments for common behavioral symptoms such as apathy, agitation, anxiety, and obsessive-compulsive behaviors, as well as the lack of evidence for approved Alzheimer's treatments in FTD.

DIAGNOSTIC CRITERIA FOR FTD SUBTYPES

- bvFTD – Rascovsky, K, Hodges, JR, Knopman, D, Mendez, MF, et al. Sensitivity of revised diagnostic criteria for the behaviourial variant of frontotemporal dementia. *Brain*. 2011 Sept; 134:2456 – 2477.
- PPA – Gorno-Tempini, ML, Hillis, AE, Weintraub, S, Kertesz, A. Classification of primary progressive aphasia and its variants. *Neurology*. 2011 March 15; 76: 1006 – 1014.
- PSP – Höglinger, GU, Respondek, G, Stamelou, M, Kurz, C, et al. Clinical diagnosis of progressive supranuclear palsy: the Movement Disorder Society criteria. *Movement Disorders*. 2017 Jun; 32: 853-864.
- CBD – Armstrong, MJ, Litvan, I, Lang, AE, Bak, TH, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013; 80: 496 – 503.
- FTD-ALS – Strong, MJ, Abrahams, S, Goldstein, LH, Wooley, S, et al. Amyotrophic lateral sclerosis-frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. 2017 Jun 12; 18: 153-174.

AFTD DIAGNOSTIC CHECKLISTS

These checklists are designed for both families and physicians to identify and discuss the symptoms for the two most common types of FTD: behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA). Also available in Spanish. Visit theaftd.org/what-is-ftd/ftd-diagnostic-checklist to download.

ADDITIONAL RESOURCES

ASSESSMENT OF COGNITIVE COMPLAINTS TOOLKIT FOR ALZHEIMER'S DISEASE: INSTRUCTION MANUAL

Developed by the California Alzheimer's Disease Centers, a statewide network of 10 dementia care Centers of Excellence, this toolkit provides primary care providers with the tools necessary to diagnose Alzheimer's disease and identify other cognitive disorders like FTD, requiring specialty referral. This guide provides a useful summary of the major neurodegenerative disorders with a summary of the primary clinical features that can help to distinguish them.

UCSF HEALTHCARE PROVIDER'S GUIDES FOR FTD DISORDERS

These disorder-specific guides provide clinicians with guidance for diagnosis and management of bvFTD and the nonfluent and semantic variants of PPA. ■

ANOSOGNOSIA AND THE IMPORTANCE OF INCLUDING FAMILY CAREGIVERS IN EVALUATION

People with FTD may exhibit a symptom called anosognosia – a lack of recognition, insight, or awareness of their own condition – and can therefore be a poor historian of their changing behavior and personality. Family caregivers – spouses, partners, and other family members who best know the person with FTD – are therefore essential to any comprehensive FTD evaluation. Due to anosognosia, family caregivers can at times be better equipped to accurately describe the ways their loved one has changed, when their symptoms began, and how those symptoms have progressed.

During an evaluation, clinicians should be aware that reports from family caregivers may not align with self-reporting from the person experiencing FTD symptoms, and that this can be due to their anosognosia. Clinicians should also note that they themselves may not observe anything "wrong." Early symptoms of FTD such as apathy or disinhibition can be subtle; additionally, persons with FTD can present as "normal" in brief encounters such as doctor's appointments. Family caregivers and others who know the person well are better positioned to describe symptoms exhibited at home or in other public settings, and that may deviate from their usual conduct (including aggression, apathy, or inappropriate/uninhibited behavior).

Family caregivers and others who know the person well are better positioned to describe symptoms exhibited at home or in other public settings.

When anosognosia is present, the person with FTD symptoms may become agitated or frustrated at their loved ones who voice their concerns to the doctor. When possible, talk separately with the person accompanying their loved one to let them speak freely and to reduce the risk of conflict. If this is not possible during the appointment, schedule a follow-up phone call, ask the person to complete a written questionnaire, or have them simply write down their concerns. ■

PARTNERS IN FTD CARE ADVISORS

The Partners in FTD Care initiative is the result of collaboration among AFTD, content experts, and family caregivers. Advisors include:

- **Sandi Grow, RN**, former FTD caregiver, AFTD Board member
- **Susan Hirsch, MA**, memory care/education specialist
- **Mary O'Hara, LCSW**, University of Colorado School of Medicine
- **Jill Shapira, PhD, RN**, retired

REFERENCES

1. Barker, M. S., Dodge, S. G., Niehoff, D., Denny, S., Dacks, P. A., Dickinson, S., ... & Wheaton, D. K. (2023). Living With Frontotemporal Degeneration: Diagnostic Journey, Symptom Experiences, and Disease Impact. *Journal of Geriatric Psychiatry and Neurology*, 36(3), 201-214.

2. Association for Frontotemporal Degeneration. (2021, October 27). *Frontotemporal Degeneration (FTD): A Voice of the Patient Report*. https://www.theaftd.org/wp-content/uploads/2021/10/AFTD_Voice-of-the-Patient-Report-10.27.2021.pdf

3. Gaugler, J. E., Ascher-Svanum, H., Roth, D. L., Fafowora, T., Siderowf, A., & Beach, T. G. (2013). Characteristics of patients misdiagnosed with Alzheimer's disease and their medication use: an ana2lysis of the NACC-UDS database. *BMC geriatrics*, 13(1), 1-10.

4. Irwin, D., Lippa, C. F., & Rosso, A. (2010). Effects of prescribed medications on cognition and behavior in frontotemporal lobar degeneration. *American Journal of Alzheimer's Disease & Other Dementias*, 25(7), 566-571.

5. Roche. (n.d.). Alzheimer's disease: the value of accurate diagnosis. Retrieved July 26, 2023, from https://www.roche.com/stories/alzheimers-disease-the-value-of-accurate-diagnosis

6. Tsai, R. M., & Boxer, A. L. (2016). Therapy and clinical trials in frontotemporal dementia: past, present, and future. *Journal of neurochemistry*, 138, 211-221.

7. Alzheimer's Disease International. (2019). *World Alzheimer Report 2019: Attitudes to dementia*. London: Alzheimer's Disease International.

8. Alzheimer's Association. (2015). Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia* 2015;11(3)332.

9. Gifford, Abbott, Nathan Praschan, Amy Newhouse, and Zeina Chemali. "Biomarkers in Frontotemporal Dementia: Current Landscape and Future Directions." *Biomarkers in Neuropsychiatry* (2023): 100065.

10. Heuer, H. W., Clark, A. L., Brushaber, D., Forsberg, L. K., Miyagawa, T., Staffaroni, A. M., Huey, E. D., Boeve, B., Rosen, H. J., Boxer, A. L., & Ascot Investigators. (2023). Phenoconversion and disease progression observed in mutation carriers of familial Frontotemporal Lobar Degeneration in the ALLFTD Consortium. *Alzheimer's & Dementia, 19*(S1).

11. King, A., & Hoppe, R. B. (2013). "Best practice" for patient-centered communication: a narrative review. *Journal of graduate medical education*, 5(3), 385-393.

12. Wollney, E. N., Armstrong, M. J., Bedenfield, N., Rosselli, M., Curiel-Cid, R. E., Kitaigorodsky, M., Levy, X., & Bylund, C. L. (2022). Barriers and Best Practices in Disclosing a Dementia Diagnosis: A Clinician Interview Study. *Health Services Insights, 15*, 117863292211418.

13. Ducharme, S., Dols, A., Laforce, R., Devenney, E., Kumfor, F., van den Stock, J., Dallaire-Théroux, C., Seelaar, H., Gossink, F., Vijverberg, E., Huey, E., Vandenbulcke, M., Masellis, M., Trieu, C., Onyike, C., Caramelli, P., de Souza, L. C., Santillo, A., Waldö, M. L., ... Pijnenburg, Y. (2020). Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. *Brain, 143*(6), 1632–1650.

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