Received: 27 November 2024 | Revised: 13 February 2025 | Accepted: 14 February 2025

DOI: 10.1002/alz.70082

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Developing digital health technologies for frontotemporal degeneration

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Abstract

Frontotemporal degeneration (FTD) is a rare neurodegenerative disease in which patients can present with cognitive, behavioral, motor, and speech impairment.

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Funding information
Fond de recherche du Québec – Santé; Rainwater Charitable Foundation; Bluefield Project to Cure FTD; National Institute on Aging, Grant/Award Numbers: AG068753, AG07265, AG062109, RF1AG077557, K23AG061253, 1K99AG073510-01, R01AG077472, P30AG066518, U2CAG054397, U19AG063911; American Heart Association, Grant/Award Number: 20SFRN35360180; Alzheimer's Drug Discovery Foundation, Grant/Award Number: 201902-2017835; Gates Ventures; Department of Defense, Grant/Award Number: W81XWH-20-1-0531; Association for Frontotemporal Degeneration; Veteran's Health Administration Research and Development, Grant/Award Number: No. IIR 17-144

Currently, there are no approved therapies available to slow or halt disease progression. Detection and monitoring of patient symptoms is challenging for this heterogeneous disease and has negatively impacted progress in FTD clinical trials. Rapid technological advancements can promote the development of digital health technologies (DHTs) capable of capturing even the most subtle clinical impairments. DHTs are computing platforms being designed to measure meaningful aspects of disease onset and progression. Here we present some of the numerous tools currently being developed to measure changes in the functional domains that become impaired in FTD, challenges faced by developers, and a proposed roadmap for developing fit-for-purpose DHTs that will aid in the development of effective therapies for FTD.

KEYWORDS
dementia, diagnostics, digital health technologies, disease progression and monitoring, frontotemporal degeneration, neurodegeneration

Highlights

- DHTs are being developed to assess FTD onset and progression.
- Tool developers must overcome numerous challenges in creating effective applications.
- Guidance to tool developers aims to benefit FTD drug development and patient care.

1 | INTRODUCTION

Human behaviors can be highly complex and require coordinated interaction between multiple neural systems. Language, executive, social-emotional, and motor neural networks are all essential for effective communication and locomotion, sleep, and daily human interactions. With current advancements in digital technologies, processing of digital data generated from various sensors has become much more feasible at scale. This allows for the development of digital markers for neurodegenerative conditions where the hallmark of impairment involves highly complex human behaviors. Digital technologies can allow us to quantify previously unquantifiable behaviors and complement clinic-based assessments for persons with neurodegenerative diseases by quantifying those behaviors in the home environment. Some of these tools provide objective and quantifiable measures at the earliest stages of disease that cannot be detected by current traditional methods.[1] Despite these potential benefits, the deployment of digital tools for both healthcare and research purposes has proven challenging. Few have had success at securing regulatory approval for use,[2] and none have yet had a significant impact on either patient management or candidate therapeutic evaluation.

The preponderance of behavioral symptoms and progressive nature of frontotemporal degeneration (FTD) suggest that digital health technologies (DHTs) may be especially beneficial to FTD research and clinical practice. On May 18 to 20, 2022, the Association for Frontotemporal Degeneration (AFTD) held the first annual Holloway Summit to focus the collective expertise of the FTD and other neurodegenerative disease research communities on the topic of digital assessment tools for FTD. Speakers and attendees spanned academic clinician-scientists, industry trialists, tool developers, patient advocacy groups, dementia family advocates, regulators, and leaders from related fields such as Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and autism spectrum disorders (ASDs). This paper outlines the motivation and rationale for developing digital tools for clinical assessment of FTD and summarizes the collective insights and recommendations from summit participants. These are offered as a guide to accelerate the development of digital measures for FTD that (1) improve diagnosis and management and (2) quantify the safety and efficacy of therapeutic interventions.

1.1 | FTD

FTD is a group of disorders characterized by localized atrophy in the frontal and temporal lobes, resulting in a range of symptoms with significant individual variability and rate of progression. Broadly, these symptoms affect six functional domains: behavior (i.e., motivation and drive, decision-making, social comportment, apathy); language; cognition (executive dysfunction, social cognitive deficits); motor speech; motor locomotion; and activities of daily living (ADLs) (Table 1). Impairments in these domains present as various clinical phenotypes. In contrast to the cognitive profile of Alzheimer's disease, cognitive impairment in FTD typically fits a unique profile involving multiple non-amnestic cognitive domains. FTD phenotypes are defined with

TABLE 1 Recommendations to accelerate FTD digital tool development.

1. **Develop** a **conceptual framework for FTD disorders** and define clear gaps in management.
2. Follow regulatory guidance to define measurable goals that are clinically meaningful to patients and families.
3. **Learn from related fields and disease-agnostic resources to avoid duplicating efforts in tool development**.
4. Monitor evolving regulatory expectations and communicate with regulatory bodies early in the course of tool development.
5. Consider diversity of clinical populations including ethnocultural, linguistic, and socioeconomic backgrounds.
6. **Generate** digital **data repositories** designed **for harmonization** across centers and fields.
7. Strive for **standardization and responsible data-sharing infrastructure**. Adopt existing standards for collection of DHT data whenever possible.

Integrate opinions from key stakeholders including **patients and care partners in selection and identification of DHTs**.

Share data back with study participants, when possible, as appropriate and in line with regulatory limitations.

Develop accessible platforms for sharing of DHT data and identify resource needs for precompetitive efforts.

Earn the trust of the patient community and healthcare providers by proactive consideration of future potential uses or risks to such emergent technology.

current clinical criteria[3,4] and include a behavioral variant (bvFTD) and forms of primary progressive aphasia (PPA). Early behavioral signs of disease can be especially elusive and include things like loss of motivation, apathy, and subtle changes to language and communication.[5] These disorders are heterogeneous, rare, and difficult to detect in early stages. This can delay diagnosis and patient recruitment for clinical trials.

Motor syndromes can involve the pyramidal (ALS) or extrapyramidal motor systems (e.g., progressive supranuclear palsy and corticobasal disease).[6–8] Clinical phenotypes have been loosely linked to underlying pathology, mainly of the tau or transactive response DNA-binding protein 43 types, and genetic associations have been identified as well. Familial FTD (f-FTD) is recognized in 20% to 30% of cases.[9,10] Previous studies in large f-FTD cohorts, including the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) and the Genetic FTD Initiative (GENFI), suggest that language and executive functions may be among the earliest cognitive domains affected by the disease predating symptom onset by up to 8 years.[11–13] FTD is a common cause of young-onset dementia (<65 years of age).[14] The financial burden of FTD exceeds that of dementia in older cohorts,[15] in part because patients are often a part of the workforce and have parental responsibilities at diagnosis.[16]

There are currently no approved therapies to slow or stop FTD progression; however, several clinical trials targeting specific FTD-related neuropathologies are under way (e.g., DNL593/TAK594, INFRONT-3, upliFT-D, Veri-T-001, NCT04220021, ASPIRE, PROCLAIM, and others). A major obstacle facing these trials is the paucity of reliable clinical assessment tools to capture disease progression, which determine the efficacy of a therapeutic candidate. The Food and Drug Administration (FDA), the governing regulatory body for investigational therapeutics in the United States, requires demonstration of clinical improvement or stability in order to approve new treatments. There is an urgent need for reliable, valid, objective, reproducible, and inexpensive measures to track patient response during treatment trials. Imaging and biofluid markers, like cortical atrophy on structural MRI and elevated neurofilament light chain in cerebrospinal fluid (CSF), are important for initial diagnosis. However, their use in tracking disease progression is highly limited because they are often impossible to perform, invasive, unreliable, and expensive. These tests also do not provide information on the clinical status of the participant.

Clinical impairments are especially hard to quantify in FTD because they manifest in highly complex linguistic features (e.g., grammar complexity) or elusive behaviors (e.g., limited intonation or apathetic responses). Clinicians often rely on subjective or highly limited assessments of dysfluency (subjective impression of dysfluent speech), postural instability (pull test), or behavioral observations. In turn, it can be challenging to quantify neurological deficits such as impaired speech and gait in an objective and reproducible way.[17] Thus, the use of digital speech analysis and accelerometers can provide much more detailed and quantifiable measures of subtle changes to these vital human functions. Leveraging advances in digital technology could represent an alternative approach to the development of more accessible and cost-effective assessments. For example, methods to collect and analyze natural speech, a highly complex clinical behavior that can track pathological features in an objective and quantifiable way,[18] could be the basis of speech-language digital assessments that are low-burden, non-invasive, highly reproducible, and widely accessible.

1.2 | Introduction to DHTs

DHTs use sensors and advanced computing platforms for healthcare and clinical research.[19] They can measure how an individual functions or provide insight into underlying biological or pathological processes. In the context of drug development, the FDA categorizes digital measures or endpoints as either clinical outcome assessments (COAs) or biomarkers. According to the FDA, COAs are defined as measures that directly quantify what matters most to individuals, including how they feel.[19,20] Biomarkers are defined by the FDA as characteristics that indicate normal biological processes, disease pathways, or treatment responses. Assessing clinical outcomes and measuring a clinical biomarker can both be done via sensors. When a sensor-containing device is used to assess clinical outcomes or measure a biomarker, it then becomes a DHT. DHTs can also be treated as digital endpoints or COAs when applied to the measurement of how patients feel and function and can be linked to clinically meaningful aspects of health.[21,22] It

is critical to define whether a DHT will be categorized as a biomarker or COA, as this will influence the regulatory strategy.[21]

The development and validation of robust and reliable DHTs require the collaboration of diverse experts and a stepwise process analogous to the development of fluid, imaging, and other conventional laboratory-derived biomarkers.[23–25] Digital biomarkers and COAs serve purposes similar to those of their conventional counterparts,[26] with roles in diagnosis, monitoring, and prognosis of disease.[27] For diabetes, the blood biomarker HbA1C serves a role in clinical trials and disease management. The main difference between conventional biomarkers and digital measures is that digital measures are generated directly from data collected by digital sensors without needing to collect human tissue.[28] Examples of digital measures that could be useful in neurodegenerative diseases include body movement, geolocation, and speech parameters. They may involve active completion of a specific task, or they may be assessed passively. In the latter situation, sensors collect data continuously or periodically while users are engaged in their normal daily activities. These methods have their benefits and drawbacks in terms of introducing bias, promoting patient engagement, and preserving privacy.[29]

The development of robust and reliable DHTs involves analytical stages where the sensor technology itself is developed and verified against a set of criteria pre-specified by engineers and computer scientists. Further analytical validation evaluates the performance of the technology and/or algorithm to measure, detect, or predict relevant physiological or behavioral metrics.[30] Clinical validation is the final stage where extensive research in the clinical population is done to validate the link between a digital biomarker and the clinical condition. Adaptation of the DHT is often needed to design fit-for-purpose tools that are more accurate and precise in clinical populations. This feedback loop of repeated clinical and analytical validation is described as the V3 (verification, analytic validation, and clinical validation) framework.[24,25] Ongoing efforts aim to extend this framework to address human factor testing and the use of digital measures for clinical, regulatory, and payer decisions. Other resources for guidance on these important developmental stages are being considered and addressed in regulatory documentation.[19,31,32]

Algorithm development and validation across different conditions should be conducted in line with device/sensor development. These algorithms are often device/sensor agnostic, which makes them much more reliable and versatile. One important aspect of the analytical validation of any algorithm designed to capture clinical manifestation of disease is testing its performance across different conditions: in-clinic versus at-home, across different tasks, or with passive data collection. Recent advancements in artificial intelligence (AI) methodologies will most certainly enhance algorithmic development. This is true throughout medical research, including the FTD space. To promote translation of AI methodologies from academia into clinical trials and clinical care, researchers may consider analyses in a certified quality management system or through the use of federated learning approaches.[33] Software developers should familiarize themselves with current regulatory guidance, which is still, in part, under development.[34,35] These guidelines provide a comprehensive list of risks and considerations that are particular to machine learning (ML)/AI model design and implementation in clinical settings. Acknowledging and addressing these concerns and expectations from regulators early on is vital for future acceptance of novel AI algorithms. As these developments are very recent, they were not the focus of the discussions at the first Holloway Summit, and at present we are not aware of major developments of AI algorithms for the clinical assessment, screening, or diagnosing of FTD. However, we expect this to change as AI models are improving and gain impact.

1.3 | DHTs as clinically meaningful assessments for FTD and other neurodegenerative disorders

Current research efforts on DHTs for FTD include acoustic and lexical features while speaking, speed and pattern of movement while walking, Global Positioning Systems (GPS) markers of daily routines, and much more. Some of these measures are sensitive to neurodegeneration in general, while others are highly specific to certain types of disorders.

Quantification of speech or gait parameters, for example, provides objective and reliable measures of aphasia (i.e., language impairment) and postural instability. These two common neurological impairments are not only a hallmark of some neurodegenerative conditions but also highly impactful in the clinical setting. However, it can be challenging to quantify neurological deficits such as impaired speech and gait in an objective and reproducible way.[17]

In FTD, early behavioral signs of disease can be especially elusive and include loss of motivation, apathy, and subtle changes to language and communication.[5] Detecting these subtle maladaptive behaviors (e.g., impaired communication) can serve as an entry point in identifying whether an individual may develop detrimental FTD symptoms. Digital tools can improve and accelerate early diagnosis of FTD by providing accessible, low-cost-low-burden yet highly sensitive and precise measurements of functioning and behavior.

In recent years we have seen an increase in research investigating digital markers in neurodegenerative conditions. Though many studies have reported promising initial results, few projects have progressed to the stage of clinical validation. At the Holloway Summit, participants, many of whom are involved in the study and development of such DHTs, discussed the various barriers to progression of research and development and ways to overcome them. Their insights are summarized here and conceptualized into a framework that is aimed at supporting researchers from academia and industry in their pursuit of advancing their preliminary findings to the development of tangible DHTs that will benefit the field.

2 | CURRENT STATE OF DHT DEVELOPMENT FOR FTD

A variety of digital tools can measure the specific symptomologies present in FTD. FTD symptoms can be categorized into several domains: cognition, behavior, language, speech, swallowing, and motor functions (Table 1). In addition to quantification of performance in

specific domains, digital tools can be employed for more general functional assessments. Recent advances in DHTs have allowed researchers to observe individuals with mild cognitive impairment (MCI) structuring their days differently than those with normal cognition,[36,37] home-based digital biomarkers that correlate with *post mortem* neurodegenerative pathologies,[38] and digital biomarkers used in clinical trials that are capable of significantly reducing needed sample sizes.[39,40] In this section, we discuss the digital tools currently under development for FTD disorders and related neurodegenerative diseases and describe their utility in evaluation of the aforementioned functional domains, their advantages and shortcomings.

2.1 | Automatic speech analyses

Speech can be captured in the clinic via active tasks or through passive monitoring of conversation in naturalistic settings.[41] The purpose of recording speech determines the type of tasks used, the timing and frequency of their elicitation, and the minimum quality of signal required for analysis.[42,43] Individuals with FTD can present with a heterogeneous combination of speech and cognitive-linguistic impairments, ranging from motor-based apraxia-like symptoms, to semantic, grammatic, and pragmatic deficits.[44] To capture the potential progression of these symptoms and signs, a communication assessment battery incorporating tasks that fall along a continuum of motor and cognitive complexity is proposed.[45] Motor stimuli include tasks devoid of meaning across languages such as sustained vowels and syllable repetition (diadochokinesis). These become more complex motorically and linguistically when real words are used such as counting or days of the week.[46] More cognitively demanding tasks draw on other components of communication such as reading, memory, or novel thought generation. These can include contemporaneously produced language such as conversation, picture description, or story retelling.

Motor speech outcomes are focused on elements of communication such as voice quality, vocal tract dynamics, sound articulation, and prosody.[47–53] These features are measured objectively via acoustic analysis and can be derived across various tasks. In contrast, speech features relating to language and cognitive domains may include acoustic signals such as intonational range,[47] but also measures derived from transcribed text. The latter include measures of syntax, word morphology, parts of speech, and discourse and are derived with the use of advanced ML/AI tools, natural language processing, and large language models.[53,54] Applying automated speech analysis technologies to recordings of other traditional neuropsychological tasks can also reveal additional richness. For example, fluency tasks (e.g., letter fluency, category naming fluency) are highly sensitive tasks that are often performed at the bedside as part of neuropsychological assessments. However, traditional scoring only includes total correct word count. Applying automated speech-language analyses to recorded fluency tasks can not only automate and standardize scoring but also provide additional metrics such as semantic and phonetic distances between consecutive words and reaction times. Such metrics could reveal more subtle deficits than is captured by total correct word count, especially during repeated evaluations of the same subject.[55]

2.2 | ORCATECH – a home-based assessment for FTD

Performance on routine daily tasks (e.g., eating, cleaning) declines as an individual develops cognitive impairments such as those observed in FTD (e.g., impaired judgment, planning/organizing, mental flexibility, and decision-making). These functional deficits are observed across FTD subtypes. Functional assessments can provide us with information on how individual are performing their daily tasks. Digital technologies for executive-functional assessments can improve our ability to monitor changes in daily function and the patient's response to treatment.

The Oregon Center for Aging & Technology (ORCATECH) home-based technology platform has been developed over the last 2 decades. It is supported by federal, industry, and foundation funding, including the recently completed Collaborative Aging Research using Technology (CART) initiative. The ORCATECH platform includes multiple sensors and devices placed throughout the home and worn by participants to monitor key aspects of health and wellbeing such as mobility, sleep, socialization, physiology, and cognition. In-depth descriptions of the technology platform have been previously published.[56,57] Dozens of manuscripts highlight the utility of the ORCATECH platform in aging and cognitive research (for a complete list: https://www.ohsu.edu/oregon-center-for-aging-and-technology/publications). The ORCATECH platform has been applied in aging, cognition, and Alzheimer's disease research; however, the functional domains assessed by the platform naturally translate to other conditions. Accordingly, the ORCATECH platform is currently also being utilized in research studies for cancer,[58] frailty, PD, and FTD. Preliminary findings in FTD provide support for the feasibility and sustainability of conducting comprehensive in-home passive data research in FTD.[59,60]

2.3 | Ignite app project

While multiple digital cognitive batteries have been developed for other neurodegenerative diseases,[61] none had previously been designed with FTD specifically in mind. The GENFI set out to develop a tablet-based set of tasks (called Ignite) that would tap into different elements of executive function and social cognition but would also be able to test other cognitive domains shown to be abnormal in FTD. The overall battery consists of 12 tests, many with subtasks at different levels of difficulty. Within executive function, testing of inhibitory control, mental flexibility, working memory, and decision-making is performed, while in social cognition, emotional processing and theory of mind are assessed. The app has been tested in healthy controls and in GENFI participants, with versions across multiple languages already available (www.genfi.org/ignite).

2.4 | ALLFTD remote app project

Smartphone usage is on the rise around the globe, and these devices appear to be a viable solution for deploying remote assessments of cognition and motor functioning. The clinical heterogeneity of FTD justifies the development of a uniquely comprehensive smartphone battery.[62] The ALLFTD research consortium is a multicenter observational study of sporadic and familial FTD. ALLFTD investigators partnered with Datacubed Health (www.datacubed.com) to develop the ALLFTD-mApp on Datacubed Health's Linkt platform, which is suitable for Android and iOS smartphones. The platform incorporates neuroeconomical principles to keep patients engaged and promote adherence. The app includes questionnaires for the participants and their study partners as well as neuropsychological tasks that measure a range of cognitive domains, including processing speed, attention, executive functioning, and memory. The app also includes motor speech and language tasks (e.g., picture description) that can be administered to patients. Patients' verbal responses to tasks are recorded and stored as raw audio files. Additional language tests, including measures of naming and semantic retrieval, and a figure copying test have also been developed for the platform. To quantify the range of motor deficits that present in FTD, the app includes a finger-tapping test to evaluate motor dexterity and speed and tests of gait and balance that leverage the phone's accelerometer and gyroscope to collect raw six-direction positional data every 10 ms while patients walk or balance. Finally, to evaluate whether phone usage reflects behavioral changes in FTD, the app collects metadata such as battery life, step count, and location data.

The ALLFTD mApp has been deployed through the ALLFTD consortium since March 2021. Remote digital data collection using this application has been feasible in a multicenter research consortium and acceptable to participants with a variety of diagnoses.[62] Cognitive tests deployed through the ALLFTD mApp have strong associations with gold-standard neuropsychological tests and brain imaging measures, high accuracy for differentiating FTD from controls, and moderate to excellent test–retest reliability when administered remotely in participants' homes.[63] Qualified investigators can request ALLFTD mApp data through the ALLFTD consortium (https://www.allftd.org/data).

Preliminary studies of the ALLFTD mApp suggest that passively collected data about smartphone use behaviors are associated with clinical functioning in FTD. For example, in the ALLFTD cohort, participants with prodromal or symptomatic frontotemporal lobar degeneration (FTLD) demonstrated less change in battery percentage (a proxy for less phone usage) than those without symptoms, and less battery use was associated with worse cognitive test results, more neuropsychiatric symptoms, and smaller brain volumes.[64]

2.5 | Measurement of social interaction

Assessing social interactions could provide important insights into FTD disease processes and patient clinical status. They can also be leveraged to quantify caregiver burden, which has been an important topic frequently addressed at FTD centers. Questionnaires have traditionally been used to assess social interactions, for example, the Social Interaction Scale.[65] An objective digital method would be preferable, and it has been proposed that a proxy for social interaction would be proximity to consumer electronic devices that emit Bluetooth beacon messages.[66] For example, if each person is carrying a mobile phone that has its Bluetooth module turned on, then the number of different Bluetooth IDs detected during a day and the duration of such contact could indicate social interactions. The applicability of this approach is limited by several factors, including the huge number of Bluetooth beacons people may encounter by smart devices that are not carried by individuals, the possibility that individuals do not have their Bluetooth enabled on their device, and the variability in support for the relevant Bluetooth protocols on different devices. Dedicated hardware for tracking social interactions can overcome these problems, but social interaction is only measured between individuals wearing a suitable device, such as a bracelet or dedicated transmitters that are placed in the environment. Such an approach may be appropriate for measuring social interactions with caregivers and family members in the home.[67]

3 | CURRENT CHALLENGES IN DEVELOPING DIGITAL TOOLS FOR FTD

The FTD research community continues to face challenges related to timely and accurate diagnosis, disease heterogeneity, symptoms that complicate travel or research participation, and more. Though many DHT studies report promising solutions to these challenges, no tools have yet been developed to reach validated use in clinical research or care. Below we summarize some of the most prominent challenges for DHT development for neurodegenerative disease in general and FTD specifically.

3.1 | Validation of digital tools against gold-standard clinical measures

To validate a DHT, researchers are typically expected to compare it against the gold standard clinical measurement. Unfortunately, the current clinical measures of FTD symptoms and behaviors are limited and somewhat subjective. For example, apathy is consistently reported in up to 80% of FTD cases and is also recognized as an important and meaningful early sign of the disease. A digital measure of intonational range in speaking has been developed as a potential proxy for apathy.[52] However, it has proven challenging to correlate this finding with currently available rating scales for apathy, in part because clinical methods for detecting and measuring apathy are limited.[68,69] There is no magic solution to this problem. However, this does not relieve the researcher and developer of digital measures of the need to use the current gold standard to test the association between a new digital measure and apathy. Other ways to test this association can also be

considered, especially with the concurrent development of additional digital tools to estimate the degree of apathy (e.g., *ActiviDaily*[70]).

3.2 | Impaired insights on self-reporting

Determining clinical meaningfulness in FTD is complicated by the prevalence of anosognosia, or lack of awareness of one's condition, particularly in bvFTD. This lack of insight is a hallmark symptom of FTD and is not necessarily an artifact of disease progression and severity. Anosognosia can result in significant differences between caregiver or observer reports and the reports of patients, many of whom may not recognize the presence of symptoms.[5,71]

3.3 | Variability in disease progression

Variability in disease progression is a common feature of all neurodegenerative conditions and one that complicates DHT development. Variability manifests temporally, where rate of disease progression is not necessarily linear, and also in the quality of clinical behavior change over the course of the disease. For example, measuring semantic impairment in semantic variant primary progressive aphasia (svPPA) may be confounded in later stages of disease where semantic diversity is so impaired that it becomes harder to detect significant improvements or deterioration. Though this poses a challenge, one can also regard it as an advantage. With DHTs, there is potential for greater dimensional space, which allows for the development of a large and more diverse array of measures from a single test or tool that would be sensitive to early or late stages of disease. As an example, consider the high dimensionality of speech and language. The number and type of digital speech and language markers are enormous, including hundreds of measures easily extracted from an audio recording. These features may be attributed to the acoustic signals or to the lexical content of a sample. Some of these digital measures are likely more sensitive in the early stages of disease, perhaps even in subclinical or prodromal stages,[72] where even experienced clinicians cannot detect signs of the disease. Such tools would be particularly important in guiding inclusion criteria or outcome measures for preventive clinical trials in genetic carriers at risk of developing of FTD. Other speech measures sensitive in later stages of overt clinical disease may help gauge response to treatment.

3.4 | Device hardware and embedded software considerations

Clinical trials require consistent methods, but updates to smartphones and updated cellular device iterations have the potential to render studies, and even data collected at different times in the same study, non-comparable to one another.[41,73] There is an ever-changing landscape of sensors and embedded software that defines sensor operability (e.g., sampling rate, filtering). Some clinical trials address this issue by standardizing the devices used in a particular clinical study. However, this is an expensive and potentially wasteful solution.[74] It also does not solve the problem of comparing data from different studies or the practical demands of using devices in clinical practice. Some trials have adopted a bring your own device (BYOD) strategy, which requires that patients use their personal cellular device's sensors to record digital outcomes. While it is impossible to achieve uniformity in hardware, managing risks from heterogeneous devices and software upgrades is an important consideration in DHT development. Developers should consider the sustainability of required maintenance services and troubleshooting in the short and long terms. For wearable devices, including consumer devices (e.g., Apple Watch), and clinical-grade devices (Actigraph), researchers must consider variables related to battery life, accuracy and precision of sensor data, access to raw data, and user experience. When considering the development of a new digital tool, research consortia should consider the potential for data harmonization across studies. For example, ALLFTD and GENFI are planning to swap digital applications and evaluate whether data are consistent across different technologies as well as the different countries of origin of research participants.

3.5 | Challenges related to application software and data management

DHTs can generate large volumes of data. Sharing and aggregating such data across studies can accelerate the development of urgently needed improvement in clinical care and research. However, such sharing and harmonization require careful consideration of how data are collected, transferred, and stored, along with their associated metadata.[75] Despite recent technological advances, there are multiple sources of variability in digital data,[76] and issues related to data standardization remain unresolved.[77] The earlier section on device hardware and embedded software highlighted the challenges that arise from rapid innovation in DHT hardware. Similarly, study information should be captured as metadata.[78] For example, when using a mobile application to collect digital cognitive test scores, the application should capture measures relating to users and how they use the device, similarly to data collection processes that occur in the ALLFTD mApp study.[62] Developers should also consider code and software that are easily accessible and that can be installed and compiled by different users. DHT developers in the FTD space can learn from successes in other fields, such as the Centiloid approach to standardizing amyloid positron emission tomography images from different manufacturers of scanners and radio tracers, as well as protecting the privacy of patients and risks associated with health data sharing.[79]

Policies related to data collection methods, governance, long-term curation, processing, sharing, and access are urgently needed for DHTs in development for neurodegenerative diseases like FTD. Developing and implementing data standards could help unify digital tool development across the research community and improve remote assessments for many clinical indications and in large, multicenter, clinical trials.

Recently proposed frameworks[78] are a good starting point. Additionally, incorporation of ML/AI tools for analysis should take into account recent publications from regulators on the ethics and trustworthiness of their use.[80]

Protection of patient privacy and rights must be proactively reinforced in the development of digital measures. Attention should be given to identifiable data such as the human voice. This is especially relevant in the FTD space, where the use of genetic information is more common than in other neurodegenerative conditions and where trials are often conducted on healthy mutation carriers. Thankfully, guidelines and legislation regarding protected health information (PHI) are widely established. However, industry, especially in the consumer technology world, often do not prioritize compliance with data protection laws such as the Health Insurance Portability and Accountability Act (HIPAA) of 1996 in the United States or General Data Protection Regulation (GDPR) in Europe. Education and best practice guidelines for the tech industry, when developing DHTs, are important to establish. This may also facilitate trust and cooperation between industry and academia in sharing patient data for collaborative studies. Closely associated with privacy considerations is the need for greater attention to cybersecurity, with recent publications for medical devices providing a helpful framework for ensuring robust cybersecurity in DHTs.[81] In addition, DHTs to detect the earliest onset of neurodegenerative disease, for example, using algorithms of speech patterns, are a high priority for researchers and clinicians to test preventive treatments and improve clinical care. Yet such tools are likely to be adopted by other industries such as health or long-term care insurance. Policies are needed to protect people from potential external harms, such as lost access to insurance coverage before clinical diagnosis.

3.6 | Considerations relating to patient engagement

As with any potential outcome measure, DHTs should be evaluated for whether their measurements of symptoms or functions match those that are most meaningful to patients. Regulatory perspectives on the methods for such evaluation can be found in the FDA's recent patient-focused drug development guidance series.[82] A leading example of such evaluations in neurology and DHTs is the Wearable Assessments in the Clinic and at Home in Parkinson's Disease (WATCH-PD) study focused on digital assessments in early-stage PD.[83] Researchers embarked on a novel strategy to align DHT measures with outcomes that are important to patients.[84,85]

Digital tools must also be user-friendly for patients and caregivers. Frequent sampling can facilitate patient engagement and increase the power of study outcomes, but it can also burden participants or caregivers. Gamification of digitized tests is often used to improve patient engagement and retention, as well as social and/or tangible rewards.[62] Simplifying graphical user interfaces and access to technical support is also helpful and should be encouraged. However, adherence will vary, including over the course of the disease. Researchers who solicit patient community feedback before, during, and after development of a tool will be better positioned to reduce participation burden and maximize retention.

Despite the recognized challenge with research participant compliance with remote DHT assessments, DHTs offer the potential to reduce the travel burden for FTD research and increase the number of people able and willing to participate in clinical research. People impacted by FTD (e.g., persons diagnosed, caregivers, spouses, children) have expressed a desire to be able to participate in research without the burden of traveling. Both people diagnosed and their care partners reported by survey that symptoms make it difficult to manage appointments, drive, and use mass transit, which can all impact the ability to travel to a clinical trial site. Among those diagnosed who reported an unwillingness to participate in clinical trials, 33% would be more likely to participate if a health professional could come to their home for some aspects of the study, and 44% would be more likely to participate if they could complete interviews and assessments from home using a computer or smartphone. The number of respondents willing to travel for a clinical trial site visit decreased as travel distance and frequency of visits increased. A number of respondents wrote in answers noting the impact of travel on the ability to participate in research, "My husband would likely refuse travel," "If he could participate and not have to travel so far," "If we could participate in something in our town, we'd be willing to do it monthly. If we had to drive a long distance or fly, we'd want more time between visits."[86]

3.7 | Socioeconomic and cultural considerations

Digital tools also face challenges in addressing cultural differences and barriers, particularly related to the devices themselves. For example, some people may consider continuous monitoring by wearable devices intrusive and distracting. Internet access may be limited in many households, especially in rural communities or based upon race or ethnicity.[87] Thus, digital tools should have offline ability to collect and store data temporarily. Developers should also consider automatic methods to transfer data and clean device storage. Access to technical support should be available to remote users (both healthcare providers [HCPs] and patients). Trust with participant communities must be both earned and established, particularly in communities of people from ethnocultural populations underrepresented in clinical research.

Some HCPs may take time to develop trust in new digital tools and adapt their practices to accommodate them. Developers should consider ways to earn such trust and to support HCPs and health systems in incorporating new digital tools into their clinical practices.

4 | DEVELOPING FIT-FOR-PURPOSE DIGITAL MEASURES – A ROADMAP

Many promising DHTs fail to advance beyond developmental stages. The causes of this may be diverse, but at least in part we suspect there is a knowledge gap between academia and industry and a need to update regulations to clarify the path for commercialization of digital tools and

measures. In this section, we propose a framework aimed at supporting researchers from academia and industry to bridge the gap from a promising DHT to one that is clinically validated.

4.1 | Emphasize end-user experience

To improve the incorporation of novel DHTs into clinical trials, researchers must develop measures that are user-friendly for patients, caregivers, and HCPs. Patients must be able to understand and complete digitized tasks. Caregivers must know when and how to assist, if needed. Creating a path of least resistance by minimizing patient stress and caregiver burden is essential. Additionally, HCPs should be educated and supported in how to easily access, view, and interpret digital data. Some DHTs may be deployed in a clinic environment by non-specialized HCPs or other staff. Others may be administered at home or collected passively. For stakeholders to accept a new DHT, it must demonstrate equivalence to the standard questionnaire, interview, or functional assessment while imposing a reduced burden of administration. Special attention should be given to end-user characteristics that are unique to FTD and may affect the use of DHT, such as apathy, disinhibition, and motor coordination. Developers should consider collecting qualitative data on user experience for DHTs through an exit interview or qualitative substudy to create the optimal end-user experience.

4.2 | Regulatory considerations

The FDA and the European Medicines Agency (EMA) have issued a wealth of guidance documents, frameworks, and public workshops on digital and remote health tools. The FDA and the EMA have endorsed the qualification of drug development tools as the path to seeking regulatory endorsement of DHTs for use in medical product safety and efficacy evaluation. Many digital tools take the form of a non-device clinical decision support software (CDS) for which the FDA is actively developing guidelines.[31] This is a major development because many digital tools for FTD meet the definition of a non-device CDS tool, and this opens a much faster route for commercialization.

The Breakthrough Device Program[88] enables research teams to engage with experts during the conception and development of medical devices, allowing for the integration of FDA feedback and advice in early stages. Additionally, the FDA has launched a dedicated program, the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot, under the Office of Drug and Evaluation Sciences for review of DHTs. This program aims to facilitate the development of novel approaches to drug development, and this includes DHTs and AI-based algorithms that could improve study designs and the success rate of clinical trials.

FDA also hosts a Digital Health Center of Excellence[89] led by the Center of Devices and Radiologic Health, which aims to advance health care through innovation in regulatory processes to ensure that effective and safe tools can be implemented in the clinic and clinical trials in a timely manner. Documentation is available to researchers within the FTD field and should be accessed early in research and development for maximal impact.

Other guidance series by the FDA, particularly that of the patient-focused drug development series,[82] are invaluable resources to develop and validate DHTs for use in the patient population.

4.3 | Resources for developers

The FTD research community should continue to gather and establish guidelines on approaches to accelerate digital tool development for FTD from a variety of sources, including regulatory agencies, associations, repositories, and other disease fields. Below are a few examples of such resources that could serve as valuable examples for the FTD community in developing digital assessment tools.

4.3.1 | DHT development and validation frameworks

The Critical Path for Parkinson's (CPP) Consortium was established as a program led by the Critical Path Institute with the goal of developing tools to quantify PD progression by harnessing the collective expertise of industry, academia, non-profit organizations, and government entities within the PD research field. Within the CPP Consortium is the Digital Drug Development Tools (3DT) initiative, which aims to advance the regulatory maturity of digital technologies in PD clinical trials targeting early stages of the disease. The 3DT initiative, along with industry collaboration, academic experts, and non-profit organizations, focuses on the WATCH-PD study and includes the use of remote wearable technology to assess both motor and non-motor symptoms including cognition. Preliminary results indicate that smartwatch technology can distinguish PD from healthy controls, even when PD patients are in early stages.[83] Under the advisement of global regulatory agencies and in partnership with patients, clinical validation has identified meaningful digital features that show change over time,[90] and the data have been shared with participants.[91] This example demonstrates how collaboration and convening expertise under the advisement of global regulatory agencies can lead to promising results for digital tools. Experts from academia and industry developing digital tools for FTD should consider replicating this strategy in the FTD space, which has much in common with PD.

Another resource is the Digital Medicine Society V3 framework,[24] which outlines and explains the typical verification, analytical validation, and clinical validation processes of biometric monitoring technologies. Verification refers to stratification of digital tool performance (accuracy and precision of measurement). Analytical validation involves evaluation of the capability of a digital health technology to measure, detect, or predict physiological or behavioral metrics. Clinical validation confirms the association of the new digital measure with a clinically or biologically meaningful function or state in the intended context of use. All of these criteria may be useful to DHT developers.

4.3.2 | Data repositories

Data repositories, including ones focused on other disease indications, can also provide the FTD research field with insights on accelerating digital tools for FTD.

EverythingALS, a patient advocacy group for ALS, has developed a citizen-driven open-science platform to help researchers discover and evaluate biomarkers for ALS and ultimately improve patient experience within clinical trials. This platform curates Institutional Review Board (IRB)-approved patient data from hospital systems, laboratories, physicians, pharmacies, and insurance companies and provides these data to researchers, startups, and pharmaceutical companies to inform biomarker studies and clinical trials. Open-science platforms such as the EverythingALS database and the ALS Therapy Development Institute (TDI) can help accelerate biomarker discoveries by allowing many researchers to perform their own analyses simultaneously. Broad sharing of data in a similar platform within the FTD research community may accelerate similar studies for the FTD field. Existing repositories such as the Alzheimer's Disease Data Initiative (ADDI) include data on FTD along with other clinical causes of dementia and neurodegeneration.

TalkBank[92] is the largest open-access database of spoken language data in the world, having collected data from participants with various conditions affecting speech production, including dementia, aphasia, and ASD. These data – which are available in a standardized format – are being used globally by researchers to advance their studies and inform clinical trials. Spoken language data from TalkBank DementiaBank have been used by hundreds of groups internationally in a series of speech technology challenges[93] designed to maximize the ability of programs to classify samples as being from MCI, dementia, or healthy controls and to assess the progression of dementia longitudinally. Further recent efforts focus on the collection of high-quality audio data using a standardized protocol, including a wider variety of tasks and measures.[94] The TalkBank website includes examples of IRB consent forms for researchers seeking to approve protocols for patient data sharing in their institutions.

4.4 | Timeline for DHT development

Despite the ubiquity of health data captured from modern digital devices, validated DHTs for use in drug development are in the early stages of development across healthcare sectors. As described in Section 1.2, the US FDA qualifies DHTs for use as biomarkers or clinical outcome assessments through a rigorous review process. This includes a three-stage qualification process, of which no DHTs have yet to advance beyond the initial stage.[95] The EMA approved its first DHT for use as a primary endpoint in Duchenne muscular dystrophy clinical trials in 2023.

The timeline for DHT maturation within the context of neurodegenerative disease is subject to not only the technical complexity of clinical validation but societal and ethical bottlenecks as well.[96] One potential approach being proposed in PD aims to accelerate DHT development through the use of a new federated learning metanalytic framework.[33] Collaborative efforts across related neurodegenerative diseases on the challenges faced and viable solutions need to be communicated so that we can collectively advance the field.

5 | CONCLUSIONS

Optimization of DHTs for FTD clinical research could open the door to more inclusive, affordable, and well-powered clinical trial designs, which in turn could help to improve our understanding of FTD spectrum disorders, develop effective therapeutics, and improve delivery of care. However, the development of digital tools must include rigorous testing, stringent validation, and proactive ethical considerations. In this paper, we offered some guidance to improve the collaboration among academic, industry, and regulatory partners both within and beyond the fields of dementia to accelerate and optimize development and adoption of novel DHTs in FTD clinical trials and patient care.

ACKNOWLEDGMENTS

The ideas of this manuscript were brought forward at the inaugural AFTD Holloway Summit, an annual event made possible by the Holloway Family Fund at AFTD. The authors along with AFTD board member Kristin Holloway convened at the summit. The authors also disclose funding from Rainwater Charitable Foundation, and the Bluefield Project to Cure FTD. Specifically, RA: National Institute on Aging (NIA) – AG068753, AG07265, AG062109; American Heart Association 20SFRN35360180, Alzheimer's Drug Discovery Foundation 201902-2017835, and Gates Ventures. Dr. Ducharme receives salary support from the Fond de recherche du Québec – Santé. Dr. Staffaroni is supported by NIA RF1AG077557 and K23AG061253. Dr. Nevler is supported by the Department of Defense (W81XWH-20-1-0531) and the NIA (1K99AG073510-01). Dr. Dacks, Dr. Gleixner, and Dr. Niehoff received salary support from Association for Frontotemporal Degeneration (AFTD). Dr. Beattie is supported by the NIH–NIA; R01AG077472, NIH–NIA; P30AG066518, NIH; U2CAG054397, U19AG063911, Veteran's Health Administration Research and Development Award No. IIR 17-144.

CONFLICT OF INTEREST STATEMENT

Oregon Health & Science University (OHSU) and Z. Beattie have a financial interest in Life Analytics, Inc., a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU. Dr. Staffaroni provides consulting for Alector Inc., CervoMed, Eli Lilly and Company/Prevail Therapeutics, Passage Bio Inc., and Takeda Pharmaceutical Company and receives licensing fees as a co-inventor of smartphone cognitive tests. Dr. Hansen is an employee of Johnson & Johnson Innovative Medicine and may hold stock options or shares in the company but has no non-financial competing interests. All other authors have nothing to disclose. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Consent was not necessary.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nevler N, Niehoff D, Gleixner AM, et al. Developing digital health technologies for frontotemporal degeneration. *Alzheimer's Dement*. 2025;21:e70082. https://doi.org/10.1002/alz.70082