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PERSPECTIVE

Gaps in biomedical research in frontotemporal dementia: A call for diversity and disparities focused research

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Abstract

Frontotemporal dementia (FTD) is one of the leading causes of young-onset dementia before age 65, typically manifesting as abnormal behavior (in behavioral variant FTD) or language impairment (in primary progressive aphasia). Although FTD affects all populations across the globe, knowledge regarding the pathophysiology and genetics derives primarily from studies conducted in North America and Western Europe.

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Globally, biomedical research for FTD is hindered by variable access to diagnosis, discussed in this group's earlier article, and by reduced access to expertise, funding, and infrastructure. This perspective paper was produced by two professional interest areas of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) and discusses the field's current status on the cross-cultural aspects of basic and translational research in FTD (including that focused on epidemiology, genetics, biomarkers, and treatment). It subsequently provides a summary of gaps and needs to address the disparities and advance global FTD biomedical research.

KEYWORDS
biomarkers, cultural diversity, epidemiology, ethnicity, frontotemporal dementia, genetics, infrastructure

1 | INTRODUCTION

The term frontotemporal dementia (FTD) is generally used as an umbrella term for three canonical syndromes with heterogeneous clinical presentations affecting behavior or language: the behavioral variant of FTD (bvFTD) and the aphasia syndromes, semantic variant primary progressive aphasia (svPPA) and nonfluent variant PPA (nfvPPA).[1,2] FTD occurs in all races, ethnicities, and nationalities, but much of our knowledge about the clinical manifestations and the epidemiology, neuropathology, genetics, and pathophysiology stems from research in case–control or family cohorts of predominantly European descent.

Given that the main behavioral and/or language symptoms of FTD are deeply rooted in culture-sensitive domains, one can appreciate the complexity of defining, recognizing, diagnosing, and articulating care across an ethnoculturally diverse landscape. The FTD field is currently engaged in efforts to resolve cross-cultural barriers in the definitions, boundaries, and measurement of behavioral and language dysfunctions and build clinical care and research capacity in low-resource areas.[3] There remains much work to do to address disparities in the access and equity of care worldwide. In addition, efforts are needed to clarify ethnocultural questions in the research that informs the development of diagnostic technologies (particularly biomarkers) and novel treatments, but progress will necessarily rely on improvements in case detection, local expertise, infrastructure, and resources.[4–6]

The majority of basic and translational science on FTD disorders is focused heavily on individuals of European descent, and, to lesser extent, individuals from Japan. In other words, the work has been conducted primarily in high-income countries where public interest is higher, and expertise and funding are more readily available. Although it is reasonable to propose that the underlying *downstream* biological dysfunctional pathways to FTD syndromes are not likely to differ widely between population groups, it is to be expected that these pathways are influenced by genetic background and socio-economic factors, which are highly variable across populations and cultures. It is important to capture all variation in clinical features, socio-economic variables, pathology, and genetics *within* populations to properly support diagnosis, prognosis, and treatment *across* populations.

The Frontotemporal Dementia and the Diversity and Disparities Professional Interest Areas (PIA), supported by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), established a workgroup bringing together international expertise for the purpose of examining and addressing questions about diversity and equity in current FTD research and care. The groups' first article addressed gaps in clinical care and research.[3] This article aims to examine the current state of basic science and translational research with a cross-cultural lens, considering gaps in the resources needed to support clinical care and research globally. We conclude by describing the next steps and putting forward recommendations for future research as a call for action for the FTD field.

2 | UPDATE ON SOCIOCULTURAL FACTORS INFLUENCING FTD RECOGNITION AND DEVELOPMENT AND VALIDATION OF DIAGNOSTIC TOOLS ACROSS THE GLOBE

Our earlier article[3] provides a detailed discussion of the cross-cultural challenges of defining, identifying, and measuring FTD when the perception of dysfunction is influenced across regions by wide array of social norms, explanatory systems, and language characteristics. We emphasized the limited awareness of bvFTD and PPA in many regions, the limited availability of culturally appropriate diagnostic tools, and the disparities worldwide in care. The action steps suggested included the development of a best practice manual for FTD diagnosis, sensitive tests validated in local context, formal partnerships and exchange programs between established centers in developed regions and clinical programs in low- and middle-income countries (LMICs), and improvement of accessibility to care and treatment (e.g., by incorporating community involvement and remote/digital assessments). Significant updates since our last report include a step-by-step guide created by a workgroup of the International Neuropsychological Society on

how to implement guidelines of the International Test Commission to translate or adapt cognitive tests to different linguistic and cultural groups,[7] as well as the development of digital applications for recognition of speech and language markers (e.g., TELL app[8]). In addition, an international network for cross-linguistic research on brain health ('Include') was launched through the Global Brain Health Institute (GBHI, USA)[9] to improve global equity of access to language-based research, which has the potential to impact the diagnosis of PPA. Finally, research cohorts across the globe (South America, Southeast Asia, China) have united as the Frontotemporal Prevention Initiative (FPI).[10] These efforts demonstrate the growing collaborative efforts to address the need for appropriate FTD recognition, treatment development, care delivery, and access to diagnosis and care across the globe.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature on diversity and disparities in biomedical research (epidemiology, genetics, biomarkers, and treatment) for frontotemporal dementia using traditional sources (e.g., PubMed).
2. **Interpretation**: Experts from the Diversity and Disparities and the Frontotemporal Dementia Professional Interest Areas of the International Society to Advance Alzheimer's Disease and Treatment (ISTAART) outline critical gaps in knowledge of how underlying disease markers, such as structural and social determinants of health, genetic factors, and fluid, imaging, or pathology biomarkers are shared or different in FTD in ethnoracial diverse groups.
3. **Future directions**: Future research should be supported by increasing enrollment of patients from underrepresented groups and improving infrastructure for biomedical research in underrepresented populations globally, through (1) dedicating funding for research, (2) expanding research expertise, (3) protecting research time for physicians, and (4) developing more accessible equipment and methodology for (bio)marker analyses.

3 | EPIDEMIOLOGY

3.1 | Frequency and life expectancy

During the last three decades, the frequency of FTD has been described in more than 30 population-based studies from around the world.[4] Over half the studies were conducted in Europe or North America, several in Japan, and nearly all incidence data were derived from European/North American populations.[11] A 2016 review of population-based studies of FTD documented a point-prevalence range of 0.01–4.6 per 1000 persons, and an incidence range of 0.0–0.3 per 1000 person-years.[6] Prevalence and incidence rates were low in these studies, and varied widely across regions, reflecting differences in methods, expertise, and resources.[4] Population-based studies of FTD and other neurodegenerative diseases are challenging because case definition and systematic ascertainment of symptoms are difficult and the expertise and resources that are required are limited or scarce in many areas[4–6] (discussed in our earlier article,[3] and below in the Infrastructure and Outreach Needs section).

Studies from other parts of the world have also reported low frequency in the reference populations. For example, FTD prevalence ranged at ≈0.2% and accounted for 1.5%–2.8% of all dementia cases in four studies conducted in Brazil, Peru, and Venezuela.[12] On the other hand, a large study conducted in Japan, which focused on young-onset dementias, found FTD to be the third most frequent cause (9.4%) after Alzheimer's disease (AD) and vascular dementia. In a survey of 200 FTD patients from 16 clinics in South Korea,[13] 103 subjects presented with language variants (mostly svPPA), and these individuals were older than those with bvFTD. There were no differences in sex distribution, education, or duration of symptoms in the FTD groups. Studies on FTD prevalence are scarce in Africa and the Middle East. We found one study from Nigeria, in which a review of hospital records was undertaken. The authors identified four individuals with FTD from 108 cases of dementia seen over a 10-year period.[14] The few small population-based studies assessing dementia prevalence in different parts of Turkey focused on all-cause dementia or AD and did not provide FTD-specific rates.[15–17] A single-center study conducted in Oman found that 9.5% of 116 dementia cases were due to FTD,[18] which represents the only data from the Middle East we have been able to find. A recent report of 1%–2% prevalence of "dementia" in countries classified as Arab did not offer data specific to FTD in the region.[19] Likewise, data on FTD frequency in First Nations people/Indigenous Australians/Aboriginal and Pacific Islanders is very limited. According to the 2021 Australian census, the prevalence of conditions such as dementia (not otherwise specified), heart disease, and stroke were high in people born in Polynesian countries,[20] with dementia prevalence being about 3–5 times higher in First Nations people relative to frequencies in the Australian mainland.[21] In a nationwide study of young-onset dementia prevalence in New Zealand, case ascertainment for FTD prevalence relied on data extraction from medical records.[22] Estimates proved unreliable due to diagnostic deficiencies; over 60% of cases were recorded as "unspecified dementia." However, Māori and Pacific populations in New Zealand have been shown to have a higher prevalence of young-onset and late-onset dementia compared to populations of European descent.[22,23] To our knowledge, there are no studies of FTD diagnosis in the other Pacific Islands.

There have been limited survival studies across ethnocultural groups. In a South Korean study of survival in 121 patients with FTD syndromes, a majority (67.8%) had bvFTD, 20.7% had svPPA, and the rest had FTD with amyotrophic lateral sclerosis (FTD-ALS), and nfvPPA.[24] Fifty-four (44.6%) died during follow-up. The median duration from onset to death was 9.6 years, with median durations of

3, 6.6, 9.8, and 11.3 years for FTD-ALS, nfvPPA, bvFTD, and svPPA, respectively. On the other hand, a systematic review of studies of FTD mortality conducted in China reported a median survival of 14 years from illness onset in the 35 bvFTD cases.[25] A worldwide comparison of FTD survival rates is not available, and data on FTD disease trajectories are lacking for many LMICs.[4] It is anticipated that there would be wide variation in survival estimates, as the reported age at disease onset in FTD varies largely across geographical areas.[5] This variation also influences reports on estimates of prevalence and incidence. Furthermore, presentations of FTD syndromes, and their recognition, and diagnosis are influenced by ethnocultural factors.[4]

3.2 | Effects of structural and social determinants of health and risk factors

There is growing recognition of the importance of structural and social determinants (S/SDOH) as risk factors for neurodegenerative diseases,[26] but this area remains critically understudied in FTD research.[27] Studies focused on patients of European descent have shown associations between educational attainment and brain function in patients with FTD,[28,29] and with cognition and gray matter volumes in pre-symptomatic carriers of FTD pathogenic variants.[30] Occupational characteristics, such as complexity and skill demand, have also been shown to be significantly associated with atrophy patterns,[31] brain metabolism,[32,33] and survival[34] in patients with FTD. No comparable data for S/SDOH and FTD are available for populations of non-European descent. Education and occupation are widely recognized proxies of cognitive reserve. However, most studies examining this in non-European FTD populations are conducted in small cohorts in specific settings,[35,36] making the final results preliminary and not generalizable to the reference population. A recent study conducted in Australia[35] investigated the clinical profiles (using tests specific to the English language), their interactions with S/SDOH, and the brain magnetic resonance imaging (MRI) correlates of associations pertaining to cognitive reserve in 107 bvFTD patients who had diverse cultural and linguistic backgrounds (Australian monolingual English speakers, non-Australian/English-first language speakers, and English-not-as-first-language speakers). Comparisons were made to cognitively normal monolingual English speakers. The participants who were English-not-as-first-language speakers had lower verbal performance scores (likely due to cultural bias in the testing) but had higher cognitive reserve and more intact frontal-temporal regions in imaging.[35] S/SDOH are essential to study in all disease stages, since individuals living with FTD without strong social support become increasingly vulnerable. A small preliminary study conducted in San Francisco (USA) showed that FTD patients (N = 13) who had low social support had a higher risk for unstable housing, homelessness, and incarceration, events with a potential adverse impact on prognosis.[36] The extent to which this vulnerability was linked to ethnocultural background or generalized beyond the San Francisco area is unclear. However, it is important to examine the impact of S/SDOH in different geographic regions and ethnocultural groups, to determine how to tailor psychosocial interventions and programs of care.

Studies conducted primarily in individuals of European descent have shown an association between FTD and lifestyle factors such as diet and physical activity. Evidence suggests a physiological connection between adipose tissue (storing body lipids including triglycerides and free cholesterol) and the central nervous system; it has been proposed that secreted adipokine factors cross the blood–brain barrier and trigger inflammation and oxidative stress in the brain. It is also noted that changes in feeding and dietary habits are a signal feature of FTD.[37] Metabolic alterations, including hormone C-peptide increase, adipokine visfatin reduction, and adipokine resistin increase, have been reported in the serum of patients with FTD versus control individuals.[38] At least one study, conducted in Italy, linked risk for young-onset dementia (in a sample of 30 AD and 8 FTD patients) to dietary habits, showing higher risk in those consuming dairy products and sweets and lower risk in those whose diets emphasized fish and vegetables.[39] Benefits of an active lifestyle have also been observed longitudinally in carriers of FTD pathogenic variants.[40,41] Carriers of pathogenic variants in *C9orf72*, *MAPT*, and *GRN* who had high levels of physical activity had less cognitive and functional decline and larger brain volumes than carriers with lower levels of physical activity.[41] Individuals living with FTD who were more engaged in social and leisure activities exhibited less loss of cortical thickness (based on MRI).[40]

3.3 | Effects of vascular disorders

Cerebrovascular disease has been shown to occur alongside AD and related dementias,[42] and may contribute in its own right to cognitive dysfunction. Cardiovascular disorders are among the most common factors associated with dementia risk. Little is known of the effects of vascular factors on FTD frequency, morbidity, and mortality in patients of non-European descent; results from the few studies to date have yielded mixed results.

Results from a hospital-based case–control study conducted in Argentina that assessed cardiovascular risk factors in 200 individuals with FTD and 100 healthy control subjects showed that diabetes mellitus was significantly more common in the FTD patients.[43] A larger study of 168 FTD cases (93% non-Hispanic White, 2.4% African American, 3% Asian, 1.8% multiracial) from the U.S. National Alzheimer's Coordinating Centers (NACC) showed faster cognitive decline in individuals who had hypertension and hypercholesterolemia. On the other hand, higher body mass index (BMI) and years of smoking were associated with a slower cognitive decline among FTD patients.[44] Another study using NACC data studied 391 individuals with neuropathological diagnosis of bvFTD and found that those with concomitant cerebrovascular pathology were significantly older at onset of cognitive decline and at time-of-death and had higher rates of hypertension and stroke than those without cerebrovascular disease.[45] Together, these data indicate a complex relationship between cardiovascular factors and FTD risk.

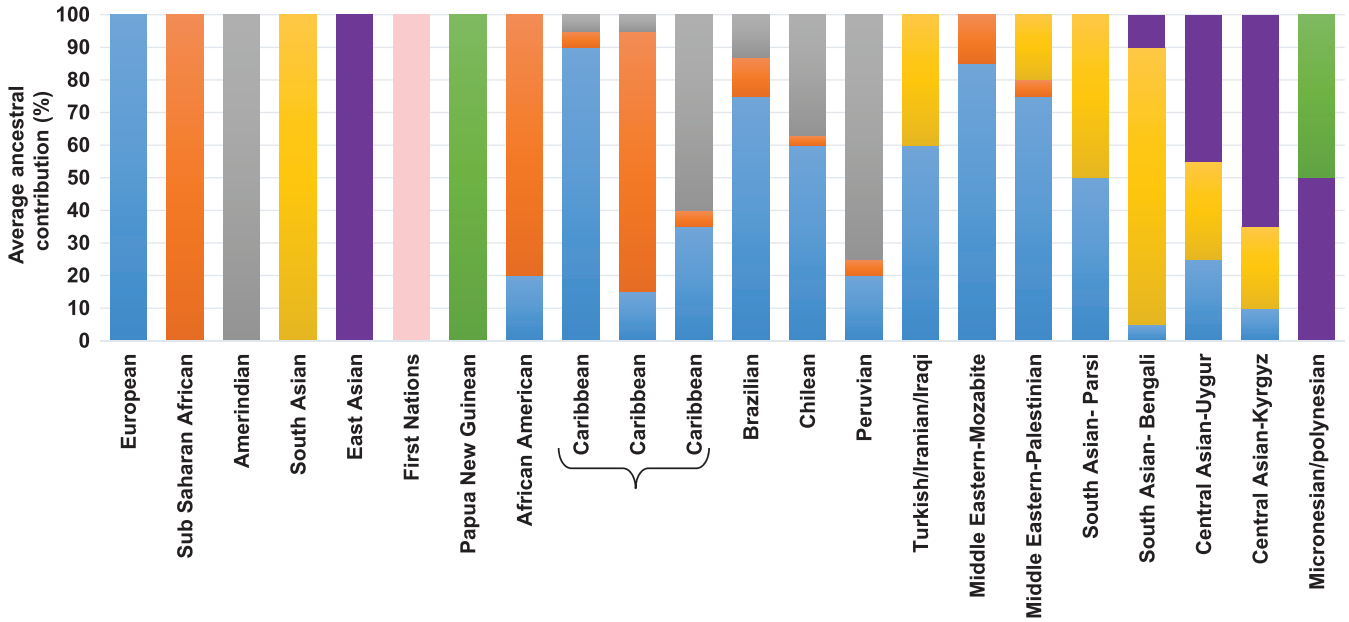

FIGURE 1 Contributions of major genetic ancestries to large world populations and example population groups representing variability, on average. Blue = European ancestry, Orange = African ancestry, Gray = Amerindian (U.S.) ancestry, Yellow = South Asian ancestry, Purple = East Asian Ancestry, Pink = First Nations (Australia) ancestry, Green = Papua New Guinean ancestry.

3.4 | Effects of head trauma

Antecedent head trauma has been found to be more frequent in FTD when compared to AD or controls in European descent cohorts in Finland,[46] The Netherlands[47] and the NACC database (USA),[48] and individuals with a positive history of head trauma had an earlier age at onset.[46,48] To our knowledge, there are no reports pertaining to patients of non-European descent. One of the factors proposed to explain that this association is the reduction of plasma levels of progranulin, due to increased proteolysis by a post-trauma inflammatory response.[49] This reduction mimics the loss-of-function state characteristic of the pathogenic variants in the progranulin gene (*PGRN*). Similarly, increased proteolysis of TAR DNA-binding protein (TDP-43), encoded by the FTD gene *TARDBP*, after head trauma, leading to its mis-localization and aggregation, was proposed as a mechanism to explain the greater occurrence of FTD among affected individuals in a Taiwan cohort.[50]

4 | GENETICS

Understanding the genetic determinants of disease facilitates the identification and investigation of the underlying biological and pathological substrates and pathophysiological mechanisms of the disease process. The knowledge can be leveraged as diagnostic tests and accelerates discovery of novel therapeutic approaches. Genomic studies of FTD often include other entities in the FTD clinical spectrum (e.g., ALS and FTD-ALS) due to syndromes sharing pathological type (defined by tau, TDP-43, or FUS, EWSR1 and TAF15 (FET) protein inclusion bodies).

The corpus of genetic studies in FTD has described associations in patients of European descent, such that there is sampling bias in the identification of FTD genes and estimates of frequencies of pathogenic variants in current known FTD genes— *MAPT* (encoding microtubule-associated protein tau), *GRN* (encoding progranulin), and *C9orf72*—which together account for a large majority, and the much less common *TARDBP*, *VCP*, *FUS*, *CHMP2B*, *SQSTM1*, *UBQLN2*, or *TBK1*. Genetic analyses conducted in North America and Western Europe have scant inclusion of other population groups. As illustrated in Figure 1, many large population groups (e.g., African American, Latin American, Central Asian populations) in these regions are admixed and have variable proportions of main continental genetic ancestries (e.g., European, African, Amerindian, and South and East Asian). Although the pathogenicity of the known causal variants is unlikely to be affected by genetic ancestry, a comprehensive understanding of the ancestral background is important for appreciating the impact or "need to screen" of these in other population groups that differ in their ancestry contributions. Of note, reliance on the main continental ancestries listed above oversimplifies the wide variation in haplotypes that exists between different subcontinental populations. As we embrace a precision medicine approach, genetic data will inform novel targets for the prevention and treatment of FTD. The inclusion of samples from a wide variety of ancestral backgrounds is critical for the identification of other genetic associations with FTD, thereby narrowing the gap in health disparities, and ensuring that discoveries benefit all populations equally. Here we review what is known about the genetic determinants of FTD in diverse populations from Latin American, African, Middle Eastern, Asian, and Oceanian samples.

Depending on the availability of methodology and expertise, many reports included candidate gene screening only and are

therefore incomplete in the assessment of variant frequency across all known genes. Of the six identified non-Asian studies with data available beyond the candidate genes (whole exome, whole genome, or larger gene panel through next-generation sequencing [NGS]), all had received funding from UK or USA foundations or governmental institutions. Twelve Asian studies with NGS data were supported by national or government institutions in countries considered high-income countries (China, $n = 8$; South Korea, $n = 2$; and Singapore and Taiwan $n = 1$ each). A summary of referenced reports, methodology, studied genes, and identified variants, as well as funding sources, is available in Table S1.

4.1 | South America

Genomics research in Latin American populations has been limited. Our understanding of the genetic basis of FTD in the Latin American population stems from a small number of studies reviewed in two articles,[51,52] and relies primarily on variants and populations of mainly European origin. The frequency of *C9orf72* expansion carriers varies in the different Latin American regions. In an Argentinian cohort, the overall frequency in FTD expansion carriers was 18.2% ($n = 9/33$) and accounted for 37.5% of all familial FTD cases ($n = 6/16$).[53] In a Brazilian cohort ($N = 67$ FTD, 39 FTD-ALS), *C9orf72* expansions accounted for 7% of familial FTD cases ($n = 1/14$) as well as 50% of familial and 17.6% of sporadic FTD-ALS cases.[54] *C9orf72* expansions have also been described in case reports from Argentina, Brazil, Chile, and Colombia ($n = 1/197$).[55–59] Although these cohorts have limited power due to their size, a preliminary comparison of expansion frequencies shows similar distributions to those of both predominantly Southern European cohorts (4%–30% of familial and 4%–22% of sporadic FTD[60]) and predominantly Western and Northern European cohorts (25% of familial and 6% of sporadic FTD[61]). This is consistent with their partial European ancestry. Pathogenic variants in *MAPT* were observed in a large Argentinian family with bvFTD,[62] in a Brazilian FTD study ($n = 2/76$[63]), and in a Colombian cohort ($n = 4/197$[58]). *GRN* pathogenic variants were identified in 9.6% of cases from the same Brazilian cohort ($n = 7/76$[63]), one family in Colombia[58] and one patient of Caribbean origin.[64] Other less common FTD-related genetic variants in *TBK1*, *TARDBP*, and *VCP* have also been reported in case studies.[51,52,58,65–68]

Although there is large variation in ancestral proportions in these different Latin American countries, variant carriers in these studies likely inherited the variants on a European ancestral background. Identifying the ancestral background of variants is important to determine the recurrence of disease-causing variants across ancestries. Colombia is an exemplar in South America, where we are beginning to learn more about FTD genetics across different ancestral backgrounds. For example, only a few *C9orf72* expansion carriers have been reported in Colombia, compared to Brazil and Argentina.[58,69] The roughly ≈60% European ancestry in Colombia is attributed mostly to southern European colonization, whereas Brazil and Argentina experienced a remarkable surge in *both* northern and southern European immigration in the early twentieth century. These differences in demographic history and gene influx patterns could contribute to differences in pathogenic variant frequency distributions in these populations. The European ancestry–biased search for pathogenic variants in patients and families with FTD becomes evident in admixed populations. For example, The Admixture and Neurodegeneration Genetic Landscape (TANGL) study in Colombia[58] evaluated genomes from 900 individuals with AD ($N = 376$), FTD-ALS ($N = 197$), young-onset dementia not otherwise specified ($N = 73$), and cognitively unimpaired participants, and identified several pathogenic variants in AD- and FTD- related genes. Although the search for pathogenic variants in AD-associated genes showed variants of multiple ancestral origins in the *PSEN1* gene, the pathogenic variants identified in *MAPT*, *GRN*, *C9orf72*, *TARDBP*, and *TBK1* resided in European haplotypes. However, in the search for variants in ALS-associated genes, researchers identified several likely pathogenic variants in patients with FTD phenotypes, predominantly in Native American haplotypes.[58] Collectively, these findings highlight the importance of including diverse and admixed populations in genetic research to identify and understand the genetic factors that cause and contribute to the risk for FTD spectrum disorders in non-European populations.[70]

4.2 | Africa and the Middle East

Few studies have assessed the frequency of FTD-related genetic variation in African and Middle Eastern populations. A small FTD study in Turkey ($N = 28$) reported three carriers of *C9orf72* expansions and one carrier each of pathogenic variants in *MAPT* and *GRN*.[71] A larger cohort report from Turkey ($N = 175$) identified five bvFTD and FTD-ALS patients carrying (likely) pathogenic variants in *MAPT*, *GRN* (2x), *VCP*, and *TARDBP*.[72] Some Turkish cohorts are also included in the larger GENetic FTD Initiative (GENFI) consortium, which mostly encompasses European and Canadian samples.[10] A South African study of Black and mixed-race patients with ALS ($N = 103$, of which 6 had ALS-FTD) identified seven carriers of the *C9orf72* expansion.[73] In addition, a case report identified a *MAPT* pathogenic variant in an African American individual with FTD.[74] In a cohort of 78 unrelated Iranian ALS patients, one patient with sporadic ALS and their relative with clinical findings suggestive of early-stage FTD had the *C9orf72* pathogenic expansion, whereas none of the FTD index patients ($N = 3$) were carriers.[75] Furthermore, one case report from Iran described a homozygous carrier of *MAPT* p.R406W with FTD with Parkinsonism.[76] Single carriers of pathogenic variants in *TBK1*, *TARDBP*, and *CHMP2B* have also been reported in South Africans of African, Afrikaner (predominantly descended from Dutch settlers), and mixed-race background with ALS or FTD.[73,77] However, none of these studies specifically address the genomic ancestry of these variants.

4.3 | Asia

C9orf72 pathogenic expansions are rare in both North and Southeast Chinese cohorts ($N = 20–120$), with studies identifying no[78–80] or very

few carriers[81–83] in their samples. These studies did not specifically examine the surrounding haplotype, but others in Chinese ALS cohorts identified the expansion on a non-European haplotype.[84] Similarly, frequencies of pathogenic variants in *MAPT* and *GRN*, are relatively low, although typically higher than observed for *C9orf72* expansions; *MAPT* (n = 2/110[81], n = 1/52[78], n = 2/82[79], n = 1/29[80], n = 2/204[83], n = 8/49[85]) and *GRN* (n = 2/110[81], n = 1/52[78], n = 1/82[79], n = 1/29[80], n = 2/204[83], n = 1/49[85], case reports of 6 and 1 carriers[86,87]). Strikingly, other FTD-related variants, identified in *CHCHD10*, *TBK1*, *VCP*, and *TARDBP*, for example, have been associated with FTD syndromes in China (reviewed in[88], and described in reports from Southeast China[79,81,89,90] and North China[83,85]) at seemingly higher frequencies than in other populations. This is especially true for variants in *TBK1* (n = 2/90[91], n = 1/110[81], n = 1/29[80], n = 5/204[83], and a case report[92]).

C9orf72 repeat expansions have been identified in one ALS-FTD patient from India across two available studies,[61,93,94] whereas no expansions were observed in Korean (N = 75, N = 107, N = 72[95,97]) or Japanese (N = 473[98], N = 38[99]) cohorts. Recent studies in an ethnically diverse Malaysian cohort (N = 101) and a mixed Singapore/Philippines cohort (N = 59) reported a *C9orf72* pathogenic expansion in one Malay patient with a family history of FTD-ALS[100] and in three bvFTD and four nfvPPA patients.[101] Pathogenic *MAPT* variants were not identified in one Indian (N = 116[102,103]) and two Korean (N = 75, N = 3[95,104]) reports, whereas single carriers of variants were identified in Korea (n = 1/72[97]), Taiwan (case report[105]), Japan (case report[106], n = 1/38[99]), and Singapore/Philippines (n = 1/59[101]). *GRN* pathogenic variant carriers were observed in one of two Indian (n = 1/116[107] and n = 0/86[103]), one of three Korean (n = 1/107[96], n = 0/3,[104] and n = 0/75[95]), two Japanese (n = 1/38[99], case report[108]) studies, one Singaporean (n = 4/59[101]) study, as well as in a case report from the Philippines.[109] One *TBK1* pathogenic variant carrier was described in a case report from India.[110]

4.4 | Oceania

Genetic studies in Australia generally only include individuals of European ancestry, not First Nations people/Indigenous Australians/Aboriginal and Torres Strait Islanders or Pacific Islanders.[111–115] Because many of the individuals of European ancestry are descendants of British inhabitants, we would expect variant frequencies to be similar to that observed in Great Britain. The frequency of FTD-related variants in New Zealand has not been investigated, and the occurrence in the Indigenous Māori population is unknown. A *MAPT* pathogenic variant has been described in a large New Zealand family of European ancestry, in association with the bvFTD syndrome.[116] Two *C9orf72* expansion carriers were identified in a small ALS study; neither was reported to have FTD.[117] To our knowledge, no studies have investigated FTD-related variation in the Pacific Islands.

4.5 | Impact of AD and risk genes in non-European populations

It is noteworthy that variants in AD-related genes have been reported in patients with a FTD syndrome. These include *PSEN1* variants in South America[118,58] and *TREM2* homozygous or (compound) heterozygous carriers in South America[119,120] and Turkey.[121] Because these reports of AD variants have also been seen in European ancestry FTD cohorts, analyses of these genes in cohorts of differing ancestry and/or in-depth characterization of the phenotype in the carriers are needed to clarify the relationship of these variants to FTD and AD phenotypes.

The search for FTD risk-conferring or protective variants requires large data sets of cases and controls to perform association studies with sufficient power to detect those variants with lower risk effects. The most recent genome-wide association analyses in cohorts of European ancestry—by far, the most significant resource in the FTD genetics space— encompasses ≈2200 FTD cases.[122] A smaller association study in 515 European FTD patients with confirmed TDP-43 pathology, representing a more homogenous patient cohort, identified a protective locus in *TMEM106B*.[123] In order for these analyses to be performed in populations with different or mixed ancestries, large cohorts will need to be assembled around the world. Identifying the ancestral background of risk-conferring or protective variants is also important to determine the recurrence of these variants across ancestries as well as to assess differential risk effects of the same risk variant depending on ancestry (as is seen for apolipoprotein E (*APOE*) ε4 in AD[124]).

Taken together, our understanding of FTD genetics in diverse populations is growing. Thus far, existing research focuses primarily on *C9orf72*, *MAPT*, and *GRN*, the three most common genes identified in European-descent FTD cohorts, and data from non-European groups are often limited to smaller cohorts or subgroup analyses within larger, predominantly European cohorts. For known pathogenic variants, it is often not determined whether these originate from a European ancestor or are recurrent in other ancestries. In addition, whether the ancestral background of the particular variant influences FTD risk or clinical expression in its own right remains to be determined. Unfortunately, lack of access to genetic testing (research or diagnostic) in many regions has led to two intertwined issues. The inability to test often means there is no molecular evidence to support a diagnosis. If there is the ability to perform genetic screening, insufficient reference genomic background data in that same population/ancestry group severely limits the interpretation of observed variants or associations. As a result, efforts to establish a reference and/or disease context genome for all ancestries is a *sine qua non* for comprehensive genetic screenings in all populations. Furthermore, the identification of novel variants in known genes or potential disease-causing variants in novel loci requires follow-up functional analyses (e.g., using cell models or animal models) studying the (aberrant) effect of the variant(s) and their potential interaction with environmental factors to fully determine their impact on disease development. As with other biomedical

research arms described in this article, these kinds of analyses require considerable funding, infrastructure, and functional genomics training and expertise, which are not available everywhere, even in institutes with genetic screening capability.

5 | BIOMARKERS

A biomarker is a quantifiable characteristic of a biological process (either physiological or pathological) that can be objectively measured in vivo.[125] For the study of neurodegenerative diseases, the main biomarker modalities are fluid, imaging, pathology, and genetic (described above). In FTD, biomarkers can be used for four primary purposes: (1) to support the diagnosis by identifying key pathophysiological changes and differentiating persons living with FTD from those with other neurodegenerative and non-neurodegenerative diseases (i.e., diagnostic markers), (2) to estimate the risk or speed of progression of a particular disease (prognostic markers), (3) to monitor progression or response to therapy (theragnostic markers),[126] and (4) to characterize relevant aspects of disease pathophysiology (i.e., in vivo etiologic diagnosis from identification of abnormal protein aggregation). Much work with biomarkers so far has focused on their utility for differentiating FTD disorders from other neurodegenerative syndromes. In the last decade, biomarkers have demonstrated tremendous diagnostic and prognostic potential in FTD and other neurodegenerative dementias,[127] paving the way for precision medicine approaches.[128] However, several challenges obstruct the widespread implementation of biomarkers in routine clinical practice.[129] These barriers include accurate definitions of significant covariates for the interpretation of biomarkers, ethnic and genetic diversity, patient burden, resource and processing time, and affordability.

5.1 | Current status of biofluid biomarker research

Several cerebrospinal fluid (CSF)[130] and blood[131–133] measures of phosphorylated tau have shown promise for discounting AD pathology in patients presenting with FTD syndromes.[130–133] Specifically, plasma phosphorylated tau at threonine 181 (p-tau$_{181}$), 217 (p-tau$_{217}$), and 231 (p-tau$_{231}$) is elevated in AD but not as much in FTD syndromes.[131,134] The p-tau/amyloid beta (Aβ)$_{1-42}$ ratio and p-tau$_{217}$ are elevated in CSF of pathology-confirmed AD patients but not FTD patients.[130,135,136] Neurofilament light (NfL) chain levels are elevated in plasma of FTD patients, particularly those cases with TDP-43 pathology and ALS.[137,138] However, NfL has low specificity because CSF levels are also elevated in several other neurodegenerative and non-degenerative conditions (e.g., stroke, HIV infection, Huntington's disease, and other dementias).[138,139] NfL levels have also proven useful for predicting disease progression and survival in several FTD syndromes,[140–144] including in carriers of pathogenic variants in *C9orf72*, *MAPT*, or *GRN*.[145,146] Most biofluid biomarker studies have incorporated clinic-based samples with limited racial and ethnic diversity. Even in AD research, contemporary research on biomarkers across racial and ethnic groups has been limited by small sample sizes and cohort selection biases.[147–151] A recent analysis of AD biomarkers in a large and ethnoculturally diverse cohort (with 393 African American and 975 Hispanic AD cases and controls) suggested consistent results across population groups in the discriminatory power of AD plasma markers, particularly p-tau$_{181}$, between AD cases and controls.[152] Overall, the diagnostic and prognostic value of biofluid biomarkers in FTD needs to be established in representative, community-based, and ethnoracially diverse cohorts to determine applicable cutoff points for interpretation.

Changes in the levels of the disease-associated proteins progranulin and dipeptide (Gly-Pro [GP]) repeat, encoded by *GRN* and *C9orf72* intronic repeat expansion, respectively, have also been used in FTD clinical trials as exploratory response markers.[153,154] For example, an antisense oligonucleotide poly(GP) was used as a target engagement biomarker in a C9orf72-specific Phase1/2 trial for FTD and ALS due to the *C9orf72* repeat expansion. Development of more sensitive "omics" technologies to identify posttranslational modifications along with novel neurodegenerative biomarkers such as changes in exosomal composition, neurofilament chains, microRNAs, small noncoding RNAs, and changes in neurotransmitters and their regulators may help improve diagnostic capability.[155]

5.2 | Current status of imaging biomarker research

Most FTD imaging biomarker research (including MRI and tau or amyloid-PET [positron emission tomography]) has been conducted in Western Europe and North America, in cohorts comprising mainly non-Hispanic individuals of European descent, although some data are available from high-income Asian countries, such as Japan.[156] Imaging biomarkers have had little development in other population groups. The inherent sample bias limits the generalizability of neuroimaging findings through different mechanisms,[157] including differences in: (1) brain structure, (2) disease pathophysiology, (3) S/SDOH, comorbid conditions, and vascular risk factors. For instance, in a study conducted in the USA, consistent brain volume loss, determined by MRI, was observed equally among non-Hispanic White (N = 47), Hispanic (N = 22), and African American (N = 13) dementia patients, based on the Mini-Mental State Examination (MMSE), compared to cognitively unimpaired individuals (N = 70, 55, 59, respectively).[158] However, a larger total brain volume in Hispanic participants compared to non-Hispanic White or African American individuals has been reported; this difference seemed unrelated to cognitive status.[158] Similarly, higher levels of brain amyloid measured by PET scan were reported in African American relative to non-Hispanic White non-cognitively impaired individuals (45:55) in the Atherosclerosis Risk in Communities (ARIC) cohort.[159] These preliminary data indicate significant baseline ethnocultural differences for these imaging biomarkers. Greater collaboration among various FTD cohort studies is needed to address the confounding effects of ethnocultural background in the disease process.

5.3 | Current status of pathology studies

As with other biomarker studies described here, the vast majority of neuropathological studies involving large cohorts investigated non-Hispanic White samples. There are a limited number of brain banks outside of North America or Europe; a recent 2022 review[160] and information on Alzforum indicate that >85% of brain banks are located in those two regions, with few numbers in Latin America (Brazil, Colombia, Peru), Africa (South Africa), Oceania (Australia, New Zealand), and Asia (China, India, Japan). Obvious limiting factors for establishing a brain bank (representing all populations from the area) include the high cost of infrastructure and equipment, the need for experienced neuropathologists in the center, and the lack of clinical experts for the diagnosis. Equally important, however, are the barriers against organ (brain) donation in many cultures and/or religions.[161–165] These factors also influence the interpretation and limit generalization of preliminary data from the brain banks found in these regions.

A study from the Brazilian Biobank for Aging Studies in 1092 individuals older than 50 years of age at death (≈30% reported as "non-Whites") identified only four individuals with FTLD-TDP and eight with FTLD-tau.[166] It has been suggested on the basis of neuropathological data from the NACC that FTD is less frequent in African American individuals than in non-Hispanic White individuals[167]; but the analyses were limited by the much lower autopsy rate in the African American patients with dementia (N = 110 vs 3500 non-Hispanic White). AD-related neuropathology analyses in North American cohorts showed a higher prevalence of mixed brain pathologies (AD+Lewy bodies or AD+infarcts) in African Americans (70%) relative to non-Hispanic White individuals (50%) with dementia.[168,169] In addition, higher levels of cerebrovascular disease pathology sufficient to contribute to dementia were observed in African American (n = 14/35 = 40%) and Hispanic AD patients (n = 16/28 = 54%) than in the non-Hispanic White (n = 101/360 = 28%) cases.[168,169] These data point to the importance of lifestyle choices and cardiovascular risk factors for dementia in non-White groups.

5.4 | Considerations of cost of biomarkers for low- and middle-income countries

The high cost, resource-intensive requirements, demand for specialists, and poor scalability of both CSF and imaging biomarkers (especially those using radiotracers) create nearly insurmountable barriers for the implementation of modern methods in routine clinical practice, particularly in LMICs and geographically remote regions.[170] Although blood biomarkers show promise as reliable and "affordable" biomarkers with huge potential to improve FTD diagnosis and recognition worldwide,[171] their attractiveness derives from comparison to the gold standard. However, the requirement for reagents and specialized analytic instruments still represents a significant cost for many LMICs, whether it be for research purposes or use in routine clinical practice. From an infrastructure perspective, the electrical/power grid in many countries cannot sustain continuous supply, resulting in rolling blackouts that would make sample storage, especially long-term storage in −80°C freezers, impossible. This challenge with preserving samples for processing limits the widespread accessibility to LMICs, particularly in geographically distant locations. Transportation of samples is also dependent on the availability of wet and dry ice to preserve samples for processing and the quality of transit networks and hubs. To address some of these issues, efforts to simplify sample processing, such as work evaluating the accuracy of blood biomarkers from a blood spot (on paper), which does not require ample refrigeration space and specialized transport, are currently in progress in several dementia consortia.

Specific diagnostic markers of FTD have not yet been developed and thus are far from being implemented in clinical practice or research. When developed and properly validated, blood-based biomarkers will have tremendous value as relatively affordable tools to improve access to FTD diagnosis worldwide. Progress in blood biomarkers for other neurodegenerative diseases raises hope that these challenges are temporary.[172] Once more robust biomarkers for FTD are established and widely available, additional efforts will have to be made to secure sufficient representation of ethnoracial diversity in validation studies so that context-specific baseline and disease risk- and prognosis-supporting cutoff values can be determined in all patient groups.

6 | TREATMENT

As described previously in the clinically focused article by this workgroup and in other reports,[3,173,174] clinical trials for persons with FTD have been conducted primarily in North America, Western Europe, and Australia. The 2019 ISTAART perspective paper reporting on demographics of participants in AD research studies describes <5% participation of people of non-European descent in clinical trials.[148] Although increased focus in the last 5 years on inclusion of diverse populations has improved the representativeness within North America and Europe, significant barriers cause continued underrepresentation of other ethnocultural groups from the rest of the world.[175,176]

We reported on general issues (site location, inclusion/exclusion criteria, time commitment and flexibility, gender bias, and funding of trials[177]) and FTD-specific issues (such as language proficiency for non-invasive speech and language interventions) in our earlier article.[3] This section discusses more invasive, "basic science" therapies, including neuromodulatory interventions and gene therapy approaches. Although these approaches are not influenced directly by cultural or language differences affecting the availability or efficiency of treatments, as they are for non-invasive inventions, they are still only offered at highly specialized centers (mostly in North America, Western Europe, and Australia) and to a smaller, homogenous subset of patients due to the high cost and high-level technical resources and skills required to implement these treatment options. In addition, because these interventions are more invasive and specialized, they

may seem intimidating to many and would require higher levels of trust in the provider and health literacy in the participants.

6.1 | Non-invasive brain stimulation trials in FTD

Non-invasive brain stimulation techniques (mainly transcranial direct current stimulation and transcranial magnetic stimulation) have been proposed as non-pharmacological interventions for FTD, especially for the language variants.[178,179] Most studies have been performed in Europe and North America. Although these techniques are still controversial, some studies suggest differences in ethnicity[180] or sex[181,182] in cortical excitability in cognitively healthy people or patients with neurodegenerative disease. These aspects could influence the stimulation parameters, and the success of treatment and should be taken into consideration in future studies.

6.2 | Potential for gene therapies

In the last decade, clinical trials using treatments targeting a genetic factor have been twice as successful as trials without a genetic target.[183,184] Of interest, although analyses in families with positive family history (up to 40% of FTD patients) are instrumental for identifying disease-causing genes, pathogenic variants in the FTD-related genes have been identified in both patients with positive family history and patients with sporadic FTD. This observation highlights a promising future for gene therapies in the FTD field for all patients carrying pathogenic variants in the genes with targeted therapies.

Current clinical trials registered in the United States (clinicaltrials.gov) include seven trials for patients carrying loss-of-function variants in *GRN* aimed at increasing levels of functional progranulin through the prevention of progranulin breakdown or full gene replacement. One clinical trial aims to reduce the presence of abnormal RNA molecules due to the *C9orf72* repeat expansion by using an antisense oligonucleotide, triggering its mRNA breakdown. Although these kinds of therapies have the potential to be non-discriminatory, because pathogenic variants in these genes have been reported across population groups and the treatment should technically apply to all carriers, six trials have sites in North America and Western Europe only, with only one of the *GRN* clinical trials also including study sites in Latin America and another being the only one also available in Australia (australianclinicaltrials.gov.au). It is important to note that successful gene therapy approaches are notoriously expensive, especially for rarer disorders (e.g., ≈$2 million US dollars (USD) for gene replacement or modulation treatment in multiple system atrophy, or $2.2 million USD for one course of fetal hemoglobin gene induction in sickle cell anemia). Combined with the poor accessibility to genetic testing in rural areas and LMICs,[176,185] the high cost and lack of access to the treatment itself outside North America and Western Europe indicates that much needs to be done to live up to the promise of gene therapy approaches for patients in all regions and ethnocultural groups.

7 | INFRASTRUCTURE AND OUTREACH NEEDS

Progress in FTD research requires the inclusion of a wide diversity of participants, advocates, physicians, and researchers for comprehensive and impactful analyses. It is imperative that participants in research are representative of the racial, ethnic, socioeconomic, sex, and gender distribution of all persons living with FTD. The biomedical field has made significant efforts to increase the ethnoracial representation of both individuals living with dementia and the research workforce, but much of that work has focused on AD research. Progress for the FTD community requires similar efforts directed at maximizing equity in the access to diagnosis, and in studies that characterize natural history, pathophysiology, clinical and biomarker measurements, and treatment development. These should employ strategies to increase the diversity of professional teams, expand their biomedical expertise and perspectives, and improve the education and literacy of all patient communities affected by neurodegenerative illnesses.[186]

7.1 | Limited clinical expertise and access to diagnosis

The scope of FTD-related clinical activity varies widely across regions and differs among ethnocultural groups, reflecting unevenness in the distribution of expertise, clinical and research resources, public health priorities, and sociocultural factors. Health inequity in access to screening and diagnosis exists for all neurodegenerative disorders.[187,188] FTD diagnosis is incredibly challenging given the varied nature of clinical presentations, limited awareness in medical and lay communities, low health literacy globally, and the uneven distribution of expertise and resources. Even in communities with adequate resources, time to FTD diagnosis is significantly delayed relative to that of AD.[189] FTD diagnosis often follows visits to multiple physicians (e.g., generalists, specialists, and neuropsychologists) and is frequently preceded by misdiagnosis and misdirection of care—as exemplified by the results of the FTD Insights Survey from the FTD Disorders Registry.[190,191] This problem is particularly pronounced in underserved and ethnocultural minority populations. Issues with diagnoses in these groups are twofold; a lack of culturally adapted diagnostic tools to identify potential culture/language-specific symptom presentation (discussed in our previous article[3]) and a lack of representation in the clinical workforce, that is, the scarcity of general neurologists, behavioral neurologists, neuropsychiatrists, and neuropsychologists with familiarity with the local community and its norms.[192,193] FTD presentations especially touch on communal characteristics in the social, cultural, and language domains. Therefore, diagnostic assessments by physicians with knowledge of the local population and culture are crucial. The underrepresentation of cultural diversity among clinical and research professionals contributes to a vulnerability to implicit and explicit biases in the diagnostic and care processes.[194]

A study from 2002 on the training and distribution of neurologists worldwide indicated large differences in the number of neurologists

among countries, ranging from 1 per ~6500 (Lithuania) to 1 per ~4.5 M (Pakistan) individuals.[195] Data on current clinical infrastructure and resources across the globe, however, are incomplete, as some of the information available is derivative, estimated, or purely anecdotal in nature, and might not represent the differences within larger geographic regions. Here, we describe available data, with the caveat that validated published resources are non-existent or limited for some areas.

7.1.1 | Europe

According to a report in 2019 from the European Academy of Neurology, ≈84,000 neurologists are registered in neurological societies in the greater European continent for ≈540 million individuals with (any) neurological disorder,[196] clearly indicating a shortage of the expertise. To our knowledge, data on the representation of individuals of non-European descent in the neurology field across Europe are unavailable. A 2023 report on representation in neurosurgery specifically attests to a low frequency of minority representation in leadership positions in all countries, with slightly better numbers for countries with long-established immigration from pertinent regions.[197]

7.1.2 | North America

In the United States, only about 350 (2.5%) of the 14,000 neurologists are African American, and 770 (5.5%) identified as Hispanic, based on a 2019 report.[198] Specific efforts, such as the Healthy Brain Initiative from the U.S. Centers for Disease Control and Prevention, the Alzheimer's Association, and the Health Resources and Service Administration (HRSA) funded Geriatric Workforce Enhancement Programs are in place to strengthen the competencies of professionals who deliver health care and other care services to persons living with dementia through interprofessional training and other strategies. In Canada, a recent survey by the Canadian Medical Association (2019) reported that there are only 1080 neurologists throughout the country. However, health care practitioner shortages do not affect Canadian populations equally.[199] Currently, organizations such as the National Collaborating Centre for Aboriginal Health, the Canadian Consortium on Neurodegenerative in Aging, and the Native Women's Association of Canada are attempting to address these systemic inadequacies by advocating for additional training for health care staff working with indigenous communities, increasing communication between on- and off-reserve practitioners, and providing culturally safe health care.[200,201]

7.1.3 | South America

There is a low level of awareness of FTD among professionals[202,203] and limited resources for training and inadequate diagnostic facilities (reviewed here[27]). For instance, a recent survey of Brazilian physicians showed that the main limitations in the diagnostic framework of FTD are limited access to genetic testing, PET imaging, and formal cognitive assessment.[204] Approximately 10% of the South American population is indigenous; the vast majority of this population lives in poverty and sometimes in isolation, complicating their access to education and health programs.[27,205] Specific programs such as the Latin American and Caribbean Consortium on Dementia (LAC-CD) are setting out programs to improve the training of health professionals, support multicentric clinical practice, develop protocol harmonization for clinical assessments, and validate these assessments in separate populations.

7.1.4 | Oceania

In Australia, cognitive/behavioral neurologists and specialized psychiatrists (old age psychiatrists and neuropsychiatrists) may assess and diagnose FTD. Recent modeling data have suggested that by 2034, there will be ≈896 neurologists for 638,024 initial and 1,269,112 review encounters, with significant shortfalls, particularly in regional Australia.[206] Similarly, in 2019, there were an estimated 3615 psychiatrists, with the majority (87.1%) working in metropolitan areas, compared to 72.2% of the Australian population living in major cities. There were 16.5 full-time equivalent (FTE) psychiatrists per 100,000 in major cities, compared to 6.7 FTE in regional and remote areas.[207] Data from 2014 indicated a shortfall of neurologists in New Zealand: there were a total of 36 FTE neurologists, giving a ratio of 1 FTE per 126,000 people.[208] In 2019, there were 634 psychiatrists registered in New Zealand, or 13 per 100,000 people.[209] Anecdotally, clinicians with expertise in FTD diagnosis are rare and difficult to access.

7.1.5 | Africa

According to the World Health Organization (WHO) 2004 report, in Africa, the number of neurologists per 100,000 population was 0.03, compared to 4.84 in Europe.[210] A continental-wide online survey conducted between March 2020 and August 2020 on the distribution and number of active neurologists in the African continent received responses from 50 of the 54 African countries; WHO data were used to adjust for the four non-respondents. Accordingly, until December 2020, there were a total of 4392 neurologists practicing on the African continent, among whom 3108 (70.8%) were from Egypt.[211] Over 31.5% of the countries had more than 11 neurologists, and 27 countries (50%) had between 1 and 10 neurologists. According to the survey, 10 African countries had no neurologists. Most African clinical/academic neurologists practice general clinical neurology out of necessity, because of the paucity of neurologists in most African countries.[211,212] To the best of our knowledge, there is no formal subspeciality training in behavioral neurology after completion of the general neurology training in Africa. However, the 5–6 year African neurology training programs have built-in competency development in behavioral neurology, and most neurologists can acquire additional

training experiences in their sub-specialty of interest through courses and programs by experts offered at meetings, seminars, and so on, as they continue to provide care and, in some cases, participate in research (personal communication Dr Rufus Akinyemi of the African Dementia Consortium, AfDC, and [213]). The AfDC[213,214] is poised to enhance epidemiological research into the subtypes of dementia in addition to enhancing training of African specialists for the diagnosis and care of people living with dementia and their families. In addition, the AfDC is working in concert with other established initiatives such as advocacy groups, to improve public awareness and destigmatization of AD and related dementias.

7.1.6 | Middle East

Little information is available describing access to diagnosis in the Middle East. Smaller reports in the last decade from different countries all paint a picture of extremely low numbers of professionals in the neurology field. Saudi-Arabia reports 848 neurology practicing physicians, equaling 1 in 42,500 citizens (2021),[215] Iran reports ≈950 neurologists, equaling 1 per 900,000 citizens,[216,217] Lebanon estimated ≈250 physicians (including *all* disciplines) per 100,000 (2023 report, no data on neurology field included),[218] whereas a 2022 report from the Ministry of Health in Israel estimates that 300 additional neurologists are needed for its population size.[219]

7.1.7 | Asia

In China, neurologists usually evaluate patients suspected to have dementia, and about 10% of the tier 3 hospitals have memory clinics. There are ≈2340 tier 3 hospitals with 96,000 neurologists and ≈2000 active dementia specialists. Only 0.10% of neurology outpatients are diagnosed with dementia in hospitals without memory clinics, whereas 0.41% are diagnosed with dementia in hospitals with memory clinics.[220] With a population of 1.5 billion, India has ≈2500 neurologists registered under the Indian Academy of Neurology, ≈12,500 psychiatrists, and fewer than 100 geriatricians. Only about 200 clinicians have received dementia training. There are ≈2700 neurologists in Indonesia for a population of 275 million, but only 20 dementia specialists and fewer than 50 functioning memory clinics. Indonesia and India have recently joined the global FPI.[10]

7.2 | Access to research expertise, funding, and resources

Most FTD research is conducted in high-income countries and mostly in individuals of European descent. Insufficient enrollment of racially and ethnically diverse participants limits the validation of research discoveries across genetic backgrounds and cultures. Latin America, Asia, and Africa are regions with high racial, ethnic, and socioeconomic diversity.

7.2.1 | North America/ Europe

Access to research expertise and resources. The North American and European research cohorts for FTD are over 95% non-Hispanic White[5] (see Table 1). From 2005 to 2021, the U.S. NACC data set—which includes individuals from the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) consortium[221]—had 94.4% of subjects with a primary diagnosis of FTD who were non-Hispanic White, compared to 83.2% of those with a primary diagnosis of AD (data provided directly by NACC, September 2021). The GENetic Frontotemporal Dementia Initiative (GENFI) includes research centers from Europe and Canada with expertise in familial FTD. In September 2022, 98.3% of GENFI participants identified as non-Hispanic White, 0.7% as mixed race, 0.2% as Black, 0.4% as Indian, and 0.4% as Other (data directly provided by GENFI, September 2022). As discussed in our previous article,[3] barriers to participation in research for racial and ethnic minority populations often include the location of the study site and time commitment. A recent NACC study assessing the risk of progression to cognitive impairment found that African American participants were more likely to be recruited using community-based strategies, whereas non-Hispanic White individuals were recruited primarily in clinics, evincing inherent selection bias.[222] Therefore, adjusted protocols to provide access to research for underrepresented populations need to be implemented. *Available research funding.* Although research sponsors such as the National Institutes of Health (NIH) and the Alzheimer's Association have increased their focus on the ethnocultural diversity of research populations, many of the funded awards from these institutes based in the United States are for AD-focused research. In addition, many of the projects are based in larger research/academic/health institutes in urban areas. Anecdotally, researchers in North American and in European countries are often required to address the inclusion of diverse populations (e.g., using culturally sensitive tools and purposeful recruitment across ethnocultural groups) in grant proposals to local funding agencies, although these requirements are generally not enforced after funding is awarded.

7.2.2 | South America

Access to research expertise and resources. Besides funding, difficulties with regulatory processes and socioeconomic status represent additional barriers to participation in research studies. Current programs such as LAC-CD[27,223,224] and the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat[70]) are aimed at setting up efficient communication among the stakeholders of dementia research in the region and driving recruitment of dementia patients throughout Latin America in their research studies. These consortia include researchers with considerable expertise in FTD on clinical and biomedical levels. *Available research funding.* Funding for research development has been limited in many countries in South America, where less than 2% of national public health budgets (the minimal percentage recommended by the Council on Health Research for Development) has been invested in research across disciplines.[225]

TABLE 1 Available data on number or frequencies of diverse representation in current consortia.

	NACC[a]			
	AD	FTD	Overall	GENFI
	N = 56185	*N* = 4190	*N* = 60375	FTD
American Indian /Alaskan Native	361 (0.6%)	4 (0.1%)	365 (0.6%)	–
Asian	1294 (2.3%)	63 (1.5%)	1347 (2.2%)	0.4% (Indian)
Black/African American	6412 (11.4%)	102 (2.4%)	6514 (10.8%)	0.2%
Hawaiian/Pacific Islander	50 (0.1%)	10 (0.2%)	60 (0.1%)	–
Other	1081 (1.9%)	30 (0.7%)	1111 (1.8%)	0.4%
Unknown	225 (0.4%)	26 (0.6%)	251 (0.4%)	–
Mixed	–	–	–	0.4%
White	46,762 (83.2%)	3955 (94.4%)	50717 (84.0%)	98.3%

[a]National Alzheimer's Coordinating Centers (NACC) data include participants from Alzheimer's Disease Research Centers and the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration. GENFI; GENetic Frontotemporal Dementia Initiative.

The LAC-CD[27,223,224] and RedLat[70] programs, focusing on dementia, including FTD,[27,70,223,225] are currently co-sponsored by institutes from North America (NIH, Alzheimer's Association, GBHI, etc.). Both programs are also supporting Latin American regional and international grant proposals. Other local efforts (e.g., TANGL) are also often supported by international grant funding through collaboration. To our knowledge, no FTD-specific efforts are present in South America.

7.2.3 | Oceania

The only active FTD research program in New Zealand is FTDGeNZ (The New Zealand Genetic FTD Study), a longitudinal study of presymptomatic biomarkers in a single European family with genetic FTD.[116] Funding for dementia research in New Zealand is limited. To our knowledge, there is no FTD research being conducted in the other Pacific Islands.

7.2.4 | Africa

Access to research expertise and resources. There is limited FTD research in Africa owing to a shortage of expertise and infrastructure and, until recently, low prioritization. Through local and international efforts (programs and funding), steps toward improving dementia care and research are now being undertaken. First, the AfDC[213] brought together health care professionals throughout Africa via local networking. Some of the AfDC neurologists and psychiatrists have received a behavioral neurology–enriched 1-year training curriculum through the GBHI programs at the University of California San Francisco (USA) and Trinity College Dublin (Europe). The AfDC consortium also collaborates with the North American NIH-funded Recruitment and Retention for Alzheimer's Disease Diversity Genetic Cohorts—Alzheimer Disease Sequencing Project (The DAWN Study) for recruitment and genomic analyses of AD and related dementia (including FTD) samples. So far, no cases of FTD have been reported from the AfDC sites in nine countries, although a total of 894 participants (including 424 AD patients) have been recruited and are undergoing multi-level adjudication of diagnosis (personal communication from Rufus Akinyemi, AfDC). Second, the Tau Consortium, a collaborative research program of the Rainwater Charitable Foundation (USA based), currently supports a recently developed multidisciplinary dementia research program in Northern Nigeria. This project, the Northern Nigeria Dementia Research Group (NNDRG), has brought together a team of neurologists, neuropsychiatrists, neuroscientists, internists, neuropsychologists, nurses, and medical laboratory technicians from six regional university, neuropsychiatric, and specialist hospitals to develop a carefully characterized population-based cohort, a tauopathy registry, local biomarker and genomic protocols, and a tissue repository. The NNDRG is in partnership with investigators at the University of Sussex (UK), the University of Pittsburgh, the Johns Hopkins University and Wake Forest University in the USA, and the Aga Khan University in Kenya. *Available research funding*. To our knowledge, local funding is very limited. The above programs are supported by the United States- or Europe-based government and private funding agencies.

7.2.5 | Middle East

To our knowledge, no info on research funding and resources is publicly available.

7.2.6 | Asia

Access to research expertise and resources. Funding and access to biomarkers and genetics are massive barriers to research in most Asian countries. There is limited availability of neuropsychologists, neuroimaging experts trained in dementia, and neurogeneticists. A dementia research working group in Thailand comprising experts in dementia from four university hospitals and two large tertiary care

hospitals formed the Collaborative Aging and Dementia Research Society Thailand (CART). They reported that 2.6% of 454 patients evaluated at a memory clinic received an FTD diagnosis.[226] Accurate diagnosis of FTD is a major first barrier for research in many Asian countries. For example, delay in the diagnosis of dementia, in particular FTD, has been reported from an urban hospital in India due to barriers at several levels (e.g., low FTD awareness, young onset, linguistic diversity).[227] *Available research funding*. Funding disparity exists within the Asian continent. Although governmental and national funding is available in high-income countries, most of the published research on FTD in LMICs is conducted in universities or tertiary hospitals, with funding from national or collaborative international grants.

7.3 | Access to FTD patient advocacy groups

Local patient advocacy groups can be instrumental in raising awareness to improve the recognition of FTD in general and resources available to patients specifically. These and other support groups for patients or caregivers exist in only a small number of countries.

8 | SUMMARY OF GAPS AND NEXT STEPS

In summary, much work remains to reduce the gaps in our knowledge of the mechanisms and pathways by which ancestral and ethnocultural background influences the risk factors, clinical expression, distribution, recognition, diagnosis, and treatment of FTD syndromes. It is just as important to characterize the unevenness in the distribution of the expertise and resources required to develop this knowledge, in order to bridge the gaps.

An accurate diagnosis is foremost and crucial for efficient recruitment for all types of research (biomarkers, genetics, treatment development, etc.). Unfortunately, this is a significant barrier in many regions and ethnocultural contexts, owing to low awareness, a dearth of expertise, and a lack of resources. It is critical to promote efforts that increase awareness of FTD in all regions and cultures, focusing on the general population as well as the clinical and research professionals. This will require various strategies, as different communication strategies will fit different contexts. It will be just as important to adapt the constructs, diagnostic approaches, and tools to local context—that is, to culture and language. Intentional international efforts and collaborative approaches are required for these activities. In our previous article,[3] we articulated several recommendations to improve recognition and clinical care and research for FTD across ethnoracial groups.

Many of the basic and translational science projects involve highly skilled personnel and the development, validation, and implementation of novel technologies—which require a considerable amount of time, training, and funds. The resource constraints of LMIC countries sharply limit their capacity for investments in health education, workforce training, and infrastructure development. For example, (89%) of the 613 FTD-related grants ($432,167,275) awarded between 1998 and 2008 were funded from the United States, and the remainder largely from Europe.[228] Limited detailed information is available to assess available funding worldwide and how it is implemented in reducing health disparities in FTD biomedical research. Evidence provided in the literature and through co-authors of this work corroborates the clear lack of sufficient funding available outside of the United States and Europe.

Many of the recommendations provided in our previous article on clinical considerations[3] are also relevant to the work to be done in the FTD basic and translational science spaces. There is growing recognition among researchers and policymakers of the need for broad ethnocultural representation in FTD research. International consortium programs—such as ALLFTD[221] and GENFI,[10] based in North America and Europe respectively, and Latin American populations (RedLat[70]) and Africa (AfDC[213])—recognize this need. The recently formed FPI[10] seeks to unite consortia around the world to foster international and cross-cultural collaboration. The FPI brings together groups from North America, Europe, South America and the Caribbean, Australia and New Zealand, Southeast Asia, China, Japan, and South Korea, in a timely effort to address this underrepresentation problem in FTD research. However, there is still a gap in worldwide reach (e.g., no presence in Africa, the Middle East, and Eurasia) and most research outside North America, Europe, Australia, and Japan is still in the foundational stages—addressing barriers to proper diagnosis and care, meeting the challenges of cohort building, and filling the pressing need for descriptive epidemiologic studies—and researchers continue to face infrastructure and funding challenges. Thus, it will be some time before their full participation in FTD basic science and translation research. Intentional action from the international FTD community is required to accelerate progress in these regions. In a timely development, the 2022 NIH draft recommendations for FTD research emphasized making high-priority investments in research to understand how ethnocultural and socioeconomic factors influence FTD risk, genetics, expression, natural history, pathophysiology and, in turn, the development of biomarkers and treatments.[229] This list supports that much work is still "in progress," especially in ethnoracial diverse groups. NIH acknowledges the work done by ALLFTD and FPI as having "achieved" setting up research structure and international trial networks. As discussed above, not all worldwide regions are included in those efforts and expanding efforts to all regions is a crucial aspect of the work to be done. Here we describe a few initial recommendations to start addressing these gaps.

Leveraging and expanding current funding: For any of the proposed recommendations on building expertise and resources and supporting research personnel, substantial funding will be needed. In the last 5 years, we have seen some dementia projects in Africa and South America take advantage of the resources available in North America and Western Europe through international collaborations. To make sure these efforts translate into sustainable capacity building at the local sites, subcontracts to the local sites, local management of funds to build infrastructure, as well as accountability are needed. Dedicated funding opportunities for LMICs, as well as efforts to assist LMIC researchers with obtaining independent funding from existing

agencies through grant writing workshops, translation services, and so on, will further increase the available funding for researchers in these areas, develop their capacity for designing projects, and foster their independence. To specifically address FTD research within already funded efforts, existing dementia consortia can establish FTD-specific workgroups to adapt protocols and identify gaps for FTD within their consortium.

Building research expertise: The aforementioned international collaborations are also being leveraged for advanced training for clinicians and scientists. However, most training resources require the trainees to relocate to North America and Western Europe—often never to return. In addition, there are limits on which regions trainees can come from and on the number of trainees. The development of additional formal partnerships and exchange programs between established centers in North America, Western Europe, Australia, and Japan, and programs in LMICs are needed to broaden and accelerate knowledge transfer, capacity-building, and infrastructure development across the globe. These programs should include clinical training (which could include implementation of genetic or fluid biomarker data in clinical practice) or laboratory training to generate these data, as well as a training focused on building bioinformatic, statistical, and computational analysis capacities in a research setting.

Supporting research personnel: In addition to providing for independent funding for projects and development of technical capacity, protecting time spent on research is an important aspect for researchers in LMICs. In many LMICs, much FTD research is performed by physicians committed to both clinical care and research. Funding to support salary for time spent on research would allow for more dedicated/protected time to advance research projects. To allow for improved dissemination of results globally, additional services such as translation and proofreading for manuscripts and reduced publication and journal access fees for LMIC researchers would further build international knowledge on FTD.

Developing and building resources for biomarker analyses in research and clinical settings: In parallel to increasing training programs and funding opportunities, the development of more accessible equipment or methodology would be instrumental in implementing the proposed analyses of epidemiological, genetic, fluid, imaging, and autopsy markers. Developing smaller, more portable, less energy-dependent equipment for running these assays would greatly increase their utility globally. Efforts to develop simpler genetic and blood biomarker analyses, such as analyses of blood spots on paper are underway, and would greatly reduce sample storage and transport needs.

We hope that the "status of the field" report, with respect to gaps and priorities for reflecting ethnocultural and diversity in FTD care and research, and the recommendations for international collaboration and capacity-building activities articulated here and in our earlier article,[3] will serve as a call to action and a stimulus for FTD research approaches, questions, and investments aimed at bridging the gaps, accelerating ongoing initiatives, and exploiting the opportunities that the richness of human diversity presents for FTD research.

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SUPPORTING INFORMATION

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

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