HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2026 March 01.

Published in final edited form as:

Stroke. 2025 March ; 56(3): 758–776. doi:10.1161/STROKEAHA.124.045903.

WMH Contributions to Cognitive Impairment: Rationale and Design of the Diverse VCID Study

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Abstract

As awareness of dementia increases, more individuals with minor cognitive complaints are requesting clinical assessment. Neuroimaging studies frequently identify “incidental” WMH, raising patient concerns about their brain health and future risk for dementia. Moreover, current U.S. demographics indicate that nearly 50% of these individuals will be from diverse backgrounds by 2060. Racial and ethnic minority populations bear a disproportionate burden of vascular risk factors magnifying dementia risk. Despite established associations between WMH and cognitive impairment, including dementia, no study has comprehensively and prospectively examined the impact of individual and combined MRI measures of white matter injury, their risk factors, and comorbidities on cognitive performance among a diverse, non-demented, stroke-free population with cognitive complaints over an extended period of observation. The Diverse Vascular Cognitive Impairment and Dementia (Diverse VCID) study is designed to fill this knowledge gap through 3 assessments of clinical, behavioral, and risk factors; neurocognitive and MRI measures; fluid biomarkers of Alzheimer’s disease, vascular inflammation, angiogenesis, endothelial dysfunction; and measures of genetic risk collected prospectively over a minimum of three years in a cohort of 2,250 individuals evenly distributed among Americans of Black/African, Latino/Hispanic, and non-Hispanic White backgrounds. The goal of this study is to investigate the basic mechanisms of small vessel cerebrovascular injury, emphasizing clinically relevant assessment tools and

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[*]A list of all Diverse VCID investigators is given in the Appendix

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developing a risk score that will accurately identify at risk individuals for possible treatment or clinical therapeutic trials, particularly individuals of diverse background where vascular risk factors and disease are more prevalent.

INTRODUCTION

SCOPE OF THE PROBLEM

Vascular contributions to cognitive impairment and dementia (VCID) include a spectrum of disability that arise from vascular injury to the brain, ranging from questionable cognitive impairment to dementia[1–3]. Critical clinical features required for VCID diagnosis include subjective complaints or impairment on neuropsychological assessment in at least one cognitive domain, and a history of clinical stroke or presence of sufficient vascular disease by neuroimaging[2,4,5]. Currently, molecular mechanisms linking vascular disease and cognitive disorders in VCID are not well understood but are hypothesized to reflect an aging neurovascular unit assailed by biological insults from cerebrovascular and possibly neurodegenerative disease processes.

While progress has been made towards understanding VCID, there are multiple reasons to increase population diversity in the study of VCID. By 2060, racial and ethnic minority populations (defined as racial and ethnic groups other than non-Hispanic white) will represent 45% of the U.S. population aged ≥65 years[6]. Due to a history of social and structural racism, social determinants of health affect minority populations disproportionately, resulting in highest rates of age-related chronic conditions, such as Alzheimer's disease and related dementias (ADRD) [7,8]. For example, older Black/African and Hispanic/Latino Americans are about twice as likely to have dementia as older non-Hispanic (NH) White Americans[8,9]. It is also estimated that Black/African and Hispanic/Latino Americans suffer with dementia 3–3.5 years longer than White individuals[7,8]. Importantly, the impact of vascular disease on dementia risk may be magnified in Black/African and Hispanic/Latino Americans through a greater burden of vascular risk factors as the prevalence of diabetes is 1.2 times higher for Black/African and 1.5 times higher for Hispanic/Latino American than NH White males[10]. Similarly, the prevalence of stroke for Black/Africans is nearly twice that of NH White males[10]. A higher prevalence of vascular risk factors and disease also likely explain why vascular pathologies more commonly contribute to clinical dementia among Black/African and Hispanic/Latino Americans [11–13].

Increased volumes of cerebral white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) defined as increased white matter signals on T2 FLAIR imaging are a well-recognized marker of VCID reflecting cerebral small vessel disease[5,14]. Evidence indicates increased odds of large WMH burden are associated with hypertension (OR,1.70, 95% Cl [1.23–2.23]) [15] even among diverse cohorts[16–18]. Further evidence indicates that WMH burden is associated with cognitive impairment, cognitive decline (OR, 1.27, 95% Cl [1.08–1.48]) [19], and incident dementia (OR, 2.24, 95% CI [1.31–3.77]) [20] among non-Hispanic White cohorts as well as cognitive decline in Latinos[21]. Studies, reviewed below, that examine ethnoracial differences in risk factors for, and outcomes of, WMH are limited,

indicating further need to study diverse cohorts to understand the full impact of WMH on dementia risk to society.

As awareness of dementia increases, more individuals with minor cognitive complaints are requesting clinical assessment. Neuroimaging studies frequently identify “incidental” WMH, raising patient concerns about their brain health and future risk for dementia. Despite established associations between WMH and cognitive impairment, including dementia, no study has comprehensively and prospectively examined the impact of individual and combined MRI measures of white matter (WM) injury, their risk factors, and comorbidities on cognitive performance among a diverse, non-demented, stroke-free population with cognitive complaints over an extended period of observation. The Diverse Vascular Cognitive Impairment and Dementia (Diverse VCID) study, funded by the National Institute of Neurological Disorders and the National Institute on Aging, is designed to fill this knowledge gap through assessment of clinical, behavioral, and risk factors, neurocognitive and MRI measures, fluid biomarkers of Alzheimer’s disease (AD), vascular inflammation and endothelial dysfunction, and measures of genetic risk collected prospectively over three years to develop a profile of risk for future dementia. Development and validation of a risk profile could be the first step in development of prevention strategies or therapeutic interventions with the hope of reducing US population burden of dementia.

DEFINITION & EPIDEMIOLOGY

Initially identified on MRI in 1986 as “…incidental lesions of uncertain clinical significance associated with cerebrovascular risk factors[22]”, WMH are defined as increased signal in the WM on T2 weighted MRI sequences, particularly FLAIR imaging[14]. WMH are a common consequence of the aging process [23,24], increasing exponentially in volume with age. Significant sex differences also have been reported, with females usually having higher volumes as a proportion of intracranial volume as compared to men (OR 1.1, 95% CI [0.8–1.5]) [24].

Age-related WMH burden is exacerbated by vascular risk factors, particularly hypertension[15], but may also accompany AD [25–27]. Age and disease-related differences in WM injury, however, extend beyond the presence of WMH lesions. Early studies using diffusion tensor imaging (DTI) identified subtle changes in normal appearing WM surrounding WMH[28]. More recent studies extend these findings to indicate that WMH are part of a continuum of WM injury[29]. These studies identified an area of subtle injury associated with reduced fractional anisotropy (FA) on DTI termed “WMH penumbra” [30]. Longitudinal assessment confirms that this area is prone to WMH extension with time[29], affected by the number of vascular risk factors[31], and associated with faster cognitive decline[32]. More recent studies using “Free Water (FW) [33]” show even greater sensitivity to differences in WM integrity as part of the cascade of physiological changes leading to WMH[34] that correlate with baseline as well as change in cognition and functional ability[35]. WMH, therefore, are only the apparent manifestation of a more diffuse injury process involving WM due to vascular and degenerative processes. Understanding the full spectrum of white matter injury, therefore, creates the opportunity to better understand the underlying mechanisms by which white matter injury leads to cognitive impairment

CLINICAL SIGNIFICANCE

WMH influence brain and cognitive health, even during middle life [36,37]. In later life, progression of WMH is associated with declines in both memory and executive function, [32] and extensive WMH predict incident MCI, stroke and dementia [20].

Significance by location—Cerebral WM is highly organized, reflecting connections between specific brain regions[38] associated with specific cognitive syndromes when injured[39,40]. Initial studies of WMH on brain structure and function suggested an effect on frontal systems[41] with later work indicating that this influence was independent of WMH location[42], due in part to the highly correlated nature of WMH development[43]. More recent work, however, found significant differences in both volume and distribution of WMH according to degree of cognitive ability[25]. Further work showed similar spatial relationships between the degree of cognitive impairment and regional fractional anisotropy (FA) measures[44], indicating that broad areas of WM microstructure are affected in neurodegenerative conditions. Another study extended these observations to include regional cortical gray matter measures and vascular comorbidity to assess the relative contributions of these pathologies on the identified spatial distributions of WMH and altered FA[26]. The concept of posterior WMH associated with cortical degeneration has been recently confirmed by an MRI study of autosomal dominant AD patients[27] and neuropathological work showing that tau burden is correlated with parietal WM lesions in patients with AD[45,46]. This evidence points to the heterogeneous causes of WMH indicating important differences in pathophysiology by location as recently confirmed in a study of over 3,000 individuals[47] where posterior WMH, particularly in the splenium of the corpus collosum, were significantly associated with cerebral amyloid burden and WMH in more anterior tracts were associated with vascular risk factors.

Advances in neuroimaging using tract-based WM measurements[48,49] have the potential to identify specific brain systems most affected by WMH. In a study[50] exploring the influence of tract based WMH volumes on regional cortical gray matter and cognition, five tracts were identified as particularly vulnerable to WMH occurrence. Results showed a primary role for atrophy of temporal and parietal cortices on memory, whereas degeneration of specific WM tracts, particularly the forceps major and minor, were associated with speed of information processing, findings that have been confirmed by a larger study[51]. These data suggest that anatomical connections between frontal and occipital cortices, passing through the forceps major and minor via the corpus callosum, have associated age-related abnormalities in WM microstructure and are important for executive functioning, including processing speed[52–54] (e.g. $\beta = -0.143$, se= 0.018 <.001 for association between WMH in forceps major and attention and executive function[51]).

In summary, these data show regional and possibly tract specific effects of WM injury affecting specific brain systems. Further evidence indicates regional differences in the pathophysiology of WM injury such that vascular disease may more strongly affect anterior WM tracts and AD pathology, more posterior. More thorough understanding of extent, etiology and location of WM injury, therefore, could lead to a more precise approach to understanding the biology of vascular cognitive impairment.

Significance in diverse populations—As the US elderly population becomes increasingly diverse, it is imperative that research studies address cognitive health among these individuals. A recent systematic review of the literature that investigated the prevalence of ethnic and racial differences in WMH burden amongst diverse groups in the US, identified 23 unique articles from 16 distinct cohorts of which 94% were prospective, longitudinal studies that included community-based populations[55].

The earliest report from the ARIC study, used a semi-quantitative rating scale of WMH severity and found that hypertension was associated with increased odds of WMH, and that this association was stronger in Black/African than White Americans after adjusting for age, sex, smoking, diabetes, and total cholesterol[56]. A follow-up study from the CHS cohort which also focused on Black/African and White Americans, similarly, concluded that WM grade was significantly greater among Black/African Americans [57].

Recent studies, however, have more carefully considered differences in vascular health and life-style factors that could contribute to WMH burden amongst diverse populations. Though there is no consensus as to what these cardiovascular risk and life-style factors may be, the literature suggests that age and the presence of hypertension are the factors most strongly associated with WMH burden[15]. When accounting for these factors, ethno-racial differences appear to diminish [15,58]. Other studies show stronger associations between cardiovascular risk factors and WMH in Black/African [16,59–61] and Hispanic/Latino [60,62,63] as compared to White Americans, which are believed to be driving the observed WMH differences. A WHICAP study examined racial differences in the distribution of WMH adjusting for group differences in age, sex, education and self-reported history of vascular risk factors and disease [59]. The researchers concluded that Black/African Americans had a greater WMH volume associated with vascular risk and disease that partially explained ethno-racial differences. Another study confirmed slight cross-sectional increases in WMH volume of parietal WM amongst Black/African as compared to White Americans even after adjustment for vascular risk factors, that became non-significant with longitudinal measurement[64]. These results suggest that disparities in health factors (and possibly treatment) likely contribute to previously reported excess burden of WMH in Black/African and to a lesser extent Hispanic/Latino Americans.

In conclusion, overall results of the review indicated heterogeneity in all aspects of data collection and analysis, limiting the ability to run meta-analyses or draw definitive conclusions[55]. General observations suggest increased vascular risk on Black/African American populations contributes to greater WMH burden in that population. These findings indicate a need for a standardized approach to investigating WMH in efforts to measure its clinical impact on diverse populations.

Longitudinal publications relating to risk factors for WMH in diverse cohorts are even less common. One study examined longitudinal associations between MRI measures and cognition in a diverse cohort followed an average of 5.3 years[63]. In a multivariable model, rate of global gray matter atrophy was the strongest predictor of cognitive decline in Whites and Black/African Americans and rate of temporal lobe atrophy added incremental explanatory power in White Americans. Baseline WMH volume was the strongest predictor

of cognitive decline in Hispanic/Latino Americans and made an incremental contribution in White Americans. The MRI patterns observed in the White American group appeared to suggest a greater influence of AD. In contrast, cognitive decline in Black/African and Hispanic/Latino Americans was most uniquely attributable to global gray matter change and baseline WMH, respectively. The study concluded that "Brain changes underlying cognitive decline in older adults are heterogeneous and depend on fixed and modifiable risk factors that differ based on ethnicity and race[63]." This hypothesis is supported by studies that show an increased prevalence of vascular disease at post-mortem in Black populations[11] and a predominance of vascular disease among Hispanic/Latino populations[12,63]."

Diverse VCID, therefore, will contribute to further understanding of these effects through comprehensive prospective clinical and biomarker assessment in a large diverse cohort, potentially clarifying current uncertainties regarding the influence of racial and ethnic differences in vascular risk and vascular brain injury on cognition.

PATHOPHYSIOLOGY

The earliest studies of community based older individuals identified age and vascular risk factors, particularly hypertension, most strongly associated with WM injury[23,24,65,66]. [23,24,65,66]. More recent studies, however, indicate that WMH also results from AD degeneration[45,46] and differs in etiology by location[67], as previously reported using MRI [44], leading to a more nuanced view of WMH pathophysiology[45,46]. While we recognize that other medical illnesses such as multiple sclerosis[68], migraine[69] and rare genetic diseases such as CADASIL[70] are associated with WMH in various forms, these are generally not major contributors to WMH among older, community dwelling individuals at risk for future dementia. In this section, we discuss evidence from two fields of research that support both genetic and systemic influences on the extent of individual WMH burden commonly seen in community-based studies of older individuals.

Genetic Influences—WMH are highly heritable[71,72] and, therefore, are ideal endophenotypes for genetic studies that can be used to identify novel injury pathways. Transcriptomic and epigenetic studies of WMH versus normal WM in brain[73] and circulating leukocytes[74,75] find a broad array of biological systems affected by WMH. Large GWAS studies have also identified single nucleotide polymorphisms (SNPs) reflecting genes and pathways that influence WMH burden in multiple and diverse communities[76–80].

The most recent GWAS of 50,970 older community-dwelling individuals identified 27 WMH loci of which 18 were novel[81]. Additional gene-based tests yielded 49 significant associations ($P<2.8\times10^{-6}$), of which 13 were outside previously identified GWAS loci. Notably, about half of identified WMH risk loci were associated with higher blood pressure levels, underscoring the importance of blood pressure as a major risk factor for WMH. WMH risk loci also reflected novel molecular pathways not mediated by known vascular risk factors. These include pathways involved in cell membrane structure and representing core components of the extracellular matrix, all belonging to the matrisome, inflammatory, and glial proliferative pathways and pathways related to AD. Functional studies of the chr17q25.1 locus, the strongest genetic risk factor for WMH, point to the

role of *TRIM47*, encoding an E3 ubiquitin protein ligase [82]. Importantly, WMH genetic risk was associated with altered WM integrity among young adults, suggesting that biological pathways contributing to WMH at an older age may already have a significant impact on brain microstructure in early in life or, alternatively, that there may be a significant overlap between pathways involved in WMH development and those influencing brain maturation or both[81].

Systemic Inflammation and Endothelial Dysfunction—A recent review by Wardlaw et al. [83] emphasized the multifactorial pathogenesis of WMH and concluded, "…despite the risk factor association, immunohistochemical and gene expression microarray studies suggesting a role for ischemia, hypoxia, or hypoperfusion, studies also show immune activation, blood-brain barrier (BBB) dysfunction, altered cell metabolic pathways, and glial injury [73,84–86] which may also reflect systemic vascular injury affecting many organs including the brain[87,88]." Neuroimaging studies support hypothesized BBB dysfunction by showing leakage of gadolinium into WMH[89] and transudation of blood solutes[34], but the mechanism for BBB dysfunction is unclear. Endothelial dysfunction leading to BBB dysfunction is increasingly thought to play a pivotal role in subcortical vascular disease, as exemplified by inherited endotheliopathies such as CADASIL and RVCL[90]. Potential causal pathways of WMH in these diseases include regulation of vascular tone, fibrinolysis, inflammation, and angiogenesis[91]. Because cerebral endothelial cells are at the interface between the systemic circulation and the brain, they are likely to play a central role in the pathogenesis of WMH. Several potential circulating factors with putative connections to WM injury have been proposed, but the field has been hampered by variable cohorts, lack of longitudinal studies, focus on only single circulating factors, and the need for specific markers of brain (versus systemic) endothelial dysfunction[92]. Diverse VCID offers the opportunity to prospectively examine the impact of emerging systemic measures on WM pathology[91,93–96]. Because cerebral endothelial cells are at the interface between the systemic circulation and the brain, they are likely to play a central role in the pathogenesis of WMH.

CASCADE HYPOTHESIS OF VASCULAR BRAIN INJURY

It is likely that a cascade of factors leads to WMH and infarction (Figure 1).
This hypothetical graphic is based on evidence that vascular risk factors increase central vascular resistance[34] affecting blood-brain barrier constituents through various mechanisms, including endothelial stress and inflammation[94,97], leading to blood-brain barrier dysfunction and increased interstitial fluids. Transudation of inflammatory factors or other toxins, therefore, could result in myelin injury and the formation of WMH[34]. Genetic susceptibility[71] likely also plays a role in the injury process. Importantly, this hypothetical process does not exclude potential contributions to interstitial fluid accumulation and brain injury via reduced glymphatic clearance[98]. By measuring circulating inflammatory and endothelial factors, Diverse VCID is ideally positioned to test this hypothesis.

TIME COURSE OF VASCULAR BRAIN INJURY

Elevated systolic blood pressure or the presence of hypertension is the strongest predictor of WMH volume among common risk factors[15]. Hypertension increases in prevalence nearly

linearly with age among White Americans[99] and is further increased among African/Black and Hispanic/Latino Americans[100]. Data from the Framingham Heart Study indicates that hypertension and the increased vascular stiffness associated with hypertension are associated with increased WMH and subtle diminution in cognitive ability among individuals 40 years of age on average[37,101] emphasizing the important role of nonamyloid processes as early risk factors for cognitive decline and future dementia, when at a later age, other pathologies, particularly AD, become more prevalent[102] and contributory. This hypothesis will be prospectively examined in Diverse VCID.

VASCULAR INJURY AND NEURODEGENERATION

Vascular risk factors are also associated with accelerated cerebral atrophy[103], even when very mild[41] or well controlled[104]. Similarly, CADASIL, is commonly associated with cerebral atrophy that drives clinical symptomatology[105]. Moreover, incident WM infarcts in CADASIL are associated with regional cortical thinning [106]. Additionally, WM tracts with a high prevalence of WMH are associated with regional atrophy among non-demented individuals[50] and vascular risk factors lead to reductions in cortical thickness in areas commonly presumed only to be affected by AD[107], further supporting evidence that brain atrophy is a prominent feature of vascular disease. Combining ATN and vascular biomarkers with regional and longitudinal atrophy measures in Diverse VCID will further clarify the timing and impact of these processes on regional atrophy measures.

CO-OCURRING VASCULAR AND ALZHEIMER DISEASE

Evidence reviewed above indicates that vascular risk factors lead to a broad spectrum of WM injury, infarction, brain atrophy, and cognitive impairment. While WMH also accompany AD [25–27] and may mediate the cognitive impact of AD pathologies, particularly among individuals with genetic mutations for AD, studies examining individuals with normal cognition or MCI find that WMH and infarction are negatively associated with cognition, even among individuals with high amyloid burden [108–112]. Moreover, the influence of WMH on cognition may be equal to that of AD pathology among cognitively normal individuals or those with mild cognitive impairment[109,113–115], reaffirming the importance of vascular factors on cognitive aging and transition to dementia, particularly among diverse communities[3,12]. The relationship between AD and CVD biomarkers, however, is complex[116] with some studies suggesting the effects are independent[108,109,114] or additive[113,115]. In addition to the major goal of developing a risk profile for dementia, Diverse VCID is uniquely poised to further examine the combined influences of vascular risk factors, vascular disease and vascular genetics along with genetic influences and plasma measures of Alzheimer's pathology on cognition.

GOALS OF DIVERSE VCID

While a number of community based studies have examined the impact of WMH on cognition among diverse communities (see Farkhondeh et al. [55] for review), prospective studies of dementia risk in diverse communities are limited (see Hu et al. [19] for review), and we are not aware of any clinical studies specifically designed to prospectively quantify the impact of the entire spectrum of WM injury on dementia risk, particularly among non-demented diverse populations where WMH burden is known to be higher[59]. The

significance of studying the clinical impact of WM injury is buoyed by the fact that dementia risk scales emphasize the role of vascular risk in dementia prediction[117,118] and that effective treatment of vascular diseases in later life[119] could lessen the population burden of dementia[120]. Yet, a complete understanding of WMH as markers of vascular brain injury contributing to cognitive complaints and possibly vascular cognitive impairment requires a comprehensive determination of a broad spectrum of WM injury associated with vascular risk. It also requires a better understanding of mechanisms leading to WMH formation and progression, and examination of the combined effects of WMH and neurodegenerative pathologies, in particular AD[27,108,109,113]. Additionally, examination of social cultural, comorbid health conditions and genetic influences should be studied as potential moderators or mediators[115].

Diverse VCID will address these gaps in scientific knowledge through 1) examining risk factors for WMH, including medical illness, lifestyle, and genetic influences; 2) examining the impact of overall burden, specific location and evolution of WMH on cognition using a comprehensive neuropsychological test battery[121], incidental clinical impairment, MI, Stroke, and death; 3) examining the moderating effects of genetic influence and risk factor treatment; 4) accounting for co-occurring AD pathologies; 5) investigating systemic and brain mechanisms leading to WMH formation and impact on cognition with the primary goal of building and validating a risk profile to assist clinicians in the assessment and potential treatment of WMH to prevent cognitive decline and transition to dementia. While the primary goal of Diverse VCID is to develop a risk profile for future dementia, further understanding of the multiple factors that contribute to dementia incidence[122] will also be examined. Given recent data showing that the impact of vascular risk factors on dementia can be modified by effective treatment in later life[119] potentially lessening the population burden of dementia[120], developing a profile that can identify specific risk factors and their impact of dementia, might lead to future precision medical treatments aimed at mitigating the impact of VCID, thereby lessening population dementia risk (Figure 2).

Overall study design and timeline—Diverse VCID is a prospective, observational study designed to enroll 2,250 individuals evenly distributed among Americans of Black/African, Latino/Hispanic, and non-Hispanic White backgrounds. To enable reliable risk predictions for each group, we are oversampling Black/African and Latino/Hispanic participants and thus, this sample will not be truly representative of US demographics. We expect, however, results from this study will allow us to achieve the goal of better predicting the impact of incidental WMH on future cognitive impairment for diverse individuals who generally have a higher prevalence of risk factors for VCID.

Individuals will be selected based on the presence of cognitive complaints[123,124], or mild cognitive impairment[125] who have not had a clinical stroke and can fully participate in the study. The project recognizes and shares methodologies with existing NINDS VCID programs, Discovery[126] and Mark VCID[127,128] along with experience in recruiting and evaluation of individuals from diverse background through the NIA Alzheimer's disease centers program[129].

Initial site selection was based on 1) experience in recruiting individuals of diverse backgrounds into clinical research and 2) the ability to obtain and submit structured research evaluations to the National Alzheimer's Disease Coordinating Center. Additional sites will be added according to recruitment needs and available expertise. Figure 3 summarizes the locations of current recruitment sites, Cores, and Scientific Collaborators.

The study timeline consists of a baseline evaluation with two follow-up visits 12–18 months apart. Evaluations include detailed clinical assessment in English or Spanish, including cognition, clinical diagnosis, comprehensive vascular risk and vascular disease assessment, functional assessment, blood sampling, and MRI at each evaluation (Figure 4).

Key enrollment criteria include 1) adults between the ages of 65–90, 2) Cognitive Complaint of decline in memory or thinking over the last three years, 3) who must be able to have an MRI to detect the presence of WMH abnormalities seen on FLAIR imaging, and 4) whose race, and ethnicity is non-Hispanic White, Black/African, or Hispanic/Latino American.

Participant Recruitment and Retention—Recruitment and retention of a diverse participant cohort is essential to the success of Diverse VCID, and many new and innovative techniques will be employed as reviewed by a separate publication. This section summarizes the general principles of our approach.

Clinical research recruitment is most successful when rooted in culturally relevant priorities, provides specific benefits/incentives, and 'gives back' tangible local services to the community[130]. UC Davis is a national leader in minority recruitment and retention due to its commitment to community-based participatory research (CBPR) principles[131]. From this and other experience, the Diverse VCID team has identified three overarching personal beliefs that influence choice to participate in clinical research: 1) Culturally Relevant Priorities, 2) Altruistic Interests, and 3) Self-preserving Interests. Individuals with *culturally relevant priorities,* view participation in clinical research as a form of social justice, particularly in the face of racial health disparities and the history of exclusion in research. *Altruistic participants* are focused on the next generation and seek to contribute to research to contribute to potential treatments for the next generation. Individuals with *self-preserving interests* usually seek medical results and/or access to high-quality medical testing through research participation. Diverse VCID recognizes the need to understand individual motivation to participate in research and will use this as a foundation for community dialogue about health and disease to motivate recruitment. Understanding the reason why Black/African and Hispanic/Latino community members participate in research will help us to address underrepresentation in science that has plagued previous studies of VCID. Gaining new insights into the barriers and facilitators of minority participation will significantly enhance recruitment and support the attainment of our goal of 750 participants per ethnoracial group.

The Diverse VCID Recruitment and Retention Core (RRC) is composed of neuropsychologists, a population neuroscientist, and a neuroanthropologist who are leaders in the field of Black/African and Hispanic/Latino American aging studies and have extensive experience with outreach, recruitment, and engagement of diverse clinical research

participants. In addition to adopting CBPR methods, the RRC has created (and will continuously update) a catalog of e-tools to facilitate precision engagement available to all sites, with particular focus on best practices for engaging Black/African and Hispanic/Latino American older adults. Materials will greatly enhance participating centers' existing recruitment efforts using novel digital media outreach tools (MORRE Toolbox; Table 1). These e-tools will promote efficient use of core resources by maximizing its engagement with communities of color by tailoring its messaging to the interests of specific subpopulations identified in market analysis.

Retaining participants over the life of the study and repeatedly measuring study outcomes will maximize the likelihood that Diverse VCID will be sufficiently powered for discovery (See Supplemental Materials for specifics). High retention rates can be maintained through strategic communication from study coordinators, appreciation events, and digital media. Strategic communication tools will be developed by the RRC in collaboration with recruitment centers who have also developed effective strategies to recruit and retain underrepresented communities. Strategies and template scripts will be disseminated through the MORRE Toolbox, and through monthly study coordinator meetings led by the RRC. Well-structured annual participant appreciation events will be at the heart of our retention effort. Each event reviews the current state of research with the greatest implications for the communities of interest as well as a review of Diverse VCID study objectives and progress to date. The goal will be to engage in meaningful discussions with participants about study progress and their role in making it a success. Additionally, highlighting young investigators associated with the study and emphasizing Diverse VCID's contribution to training the next generation of medical researchers helps make participants' contributions more tangible. To further maximize continued study engagement, the RRC is creating a media environment that supports healthy aging, accommodates disability, and celebrates diversity. A web designer, and media professional is creating a welcoming and easy-to-use media environment that emphasizes the unique gift of time and effort that each participant contributes. We are most successful with a web presence celebratory of cultural differences, and emphasizing how research participation supports healthy aging in their community and contributes to a national dialogue about race, equity, and disease prevalence. We have found that themes of cultural diversity created an *esprit de corps* among many participants and motivated their adherence to study protocols. Much of this media environment is created in an online newsletter that engages participants and potential participants in familiar social media forums like Facebook. We will focus on meaningful health related topics and will also evaluate media content to help improve and refine our health-education delivery to specific communities. Finally, all recruitment and retention materials will be made available through a data-sharing portal on the Diverse VCID website to enhance local site efforts.

Clinical Assessment—Clinical assessment is designed to meet two essential goals of the project. First, to detect and quantify the degree of cognitive impairment of the participants at baseline and over time, as well as potentially understand the etiology of cognitive decline, if present. Second, to assess potential modifiers or mediators of the relationship between WM injury and our cognitive and medical outcomes. Accordingly, all participants will receive clinical assessment according to UDS 3.0[121,132] with the addition of a list learning memory

task consistent with the MarkVCID study[128], and evaluation of everyday function (ECog) as a functional outcome predictive of decline. In addition, each participant will be asked to fill out a detailed questionnaire regarding health history specific to vascular disease, along with others regarding diet[133], sleep[134], and exercise[135]. From these measures, we will derive Life's Essential Eight[136] and Framingham Cardiovascular risk[137] scores. The details of the clinical assessment are further described in the Supplemental Materials.

Biomarkers—Diverse VCID will extensively use blood and imaging-based methods (Table 2) to assess many biomarker outcomes, both conventional and innovative. These markers will be maintained and analyzed by the Repository Core.

MRI biomarkers:

Sequence development: MRI is the gold standard tool for defining vascular brain injury[5,14,138] and will be used extensively in Diverse VCID to assess the spectrum of WM injury at baseline and over time in relation to cognition. MRI is also a key measure of neurodegeneration[139,140]. [139,140]. In addition to providing harmonized, state-of-the-art MRI acquisitions, Diverse VCID will also provide summary measures of vascular and degenerative brain injury to address the aims of this project as well as to share with contributing sites in support of their collaboration as outlined in the Supplemental Materials.

Advanced measures: In addition to standard MRI measures, we will quantify the spectrum of WM injury using tract-based principal components analysis (PCA) and convolutional neural network (CNN) approaches to predict WMH patterns associated with baseline and change in diagnosis and cognitive decline[141]. Our CNN approach will further extend baseline predictions to estimate the location and amount of *future* WMH burden associated with vascular and AD risk factors as well as cognition and cognitive trajectories as part of our precision medicine approach to identify at-risk individuals. In addition, we will make continuous associations between WMH and cognition via projection charts. These charts associate WMH volume as a function of age. The associations with cognition are then projected via color maps and isocontours. These isocontours are then associated with memory scores to give age-adjusted estimates.

Another innovative approach to MRI analysis will be the implementation of biomechanical modeling of WMH pathology. The spatially heterogeneous mechanical environment of the brain stems from locally varying cellular microstructure that can represent various biological processes. Biophysics-based modeling enables predicting mechanical and mechanobiological brain behavior in the presence of uncertainty to material properties, model parameters, and experimental data and has been used to model AD pathology[142]. We will develop and validate a multi-fidelity, data-driven, biophysics-based computational framework to predict WMH growth in the aging brain and deliver personalized predictions of WM lesion changes.

Blood-based biomarkers: Multiple emerging biomarkers have been reported in cross-sectional studies including large national studies such as MarkVCID[93–95]. Diverse VCID will extend cross-sectional findings by generating longitudinal datasets enabling cognitive stage-dependent analyses of inter-related biomarkers for pathway analysis and construction

of risk prediction models that could apply to multi-ethnic populations across diverse genetic and socioeconomic status.

Inflammation: We have shown that an aggregate serum measure of peripheral inflammatory markers centered on IL-18 signaling is associated with a 2-fold risk of having WMH and a 10% increase in silent cerebrovascular injury [94]. Importantly, there is substantial evidence that rates of inflammation vary among racial and ethnic groups [143,144], perhaps driving observed differences in cerebral small vessel disease and neurodegenerative pathologies. To address this knowledge gap, we will perform longitudinal assessments of serum levels of an IL-18-mediated inflammatory network[94]. We expect longitudinal variation in serum inflammatory biomarkers to serve as modifiers of the effect of WM lesion topography, volume, progression, and demographic variables on rates of cognitive impairment.

Innate Immunity: The role of innate immunity has been well established in vascular disease with the observation of lipid-laden macrophage depositions in atherosclerotic plaques and complement activation in small and large vessel disease[145,146]. Innate immunity through complement activation is also recognized to modulate neurodegenerative disease and is an active area of therapeutic development[147]. Complement factors can deposit on cell surfaces, forming membrane attack complexes leading to cell lysis, escalation in inflammation, and opening of the BBB[148]. Exosomes are a powerful tool for complement activation studies since exosomes form from the plasma membrane of their host cells and carry molecules from their cell surface and the surrounding microenvironment[149]. We have shown that plasma-derived endothelial exosomes can capture brain-specific endothelial changes affecting BBB integrity, with strong associations with WM disease and cognitive impairment[93,150,151]. More recently, we showed that in individuals with WM disease of presumed vascular etiology, EDE cargo demonstrates complement activation within classical and alternative pathways[95].

In this project, we will quantify an endothelial inflammation biomarker comprised of two key complement factors, Bb and C3b, from EDEs to test the association of therapeutically important endothelial innate inflammation to WM injury and cognitive impairment across diverse backgrounds.

Angiogenesis: Circulating angiogenic factors including multiple members of the vascular endothelial growth factor (VEGF) family have been implicated in cerebral blood flow regulation. Recently, the VEGF family member, placental growth factor (PlGF) has demonstrated sensitivity as a biomarker for vascular cognitive impairment with elevated levels associated with functional cognitive impairment as well as vascular brain injury by MRI[96]. Given this evidence, Diverse VCID will measure PlGF.

Plasma AD Biomarkers: In post-mortem studies, underlying neurodegenerative pathologies are concurrent with cerebrovascular disease in up to 70% of subjects[11,152]. Recent studies of diverse subjects find that mixed diagnoses with contributing AD and CVD pathologies are more common in Hispanic and Black decedents than non-Hispanic Whites with dementia in our cohort[11,12]. It is imperative, therefore, to assess biomarkers of both underlying AD pathology and non-AD specific brain injury. Given that Black/African Americans are less

likely to participate in clinical research involving lumbar puncture[153], we chose plasma measures such as amyloid beta 40 and 42, p-tau 181, neurofilament light and glial fibrillary acid proteins, that may contribute to and modify the trajectories of cognitive decline (Supplemental Materials) to reduce barriers to participation of diverse individuals.

Genetics: Genome-wide association studies in large population-based cohorts have made headway in defining the genetic landscape of WMH [81], stroke [154,155], dementia [156] and other VCID-related phenotypes and provide an opportunity to estimate an individual's genetic risk for these traits by deriving polygenic risk scores (PRS). Methodological developments and increased GWAS diversity improve PRS accuracy and portability[157,158]. We will derive PRS for WMH and VCID-relevant conditions and risk factors to evaluate their ability to improve the precision of predictive models for WMH risk and trajectories.

Supporting Current and Future Research through the Data Management and Statistics Core

Data Management: Diverse VCID will obtain a wide range of clinical and biological information from participating sites. A master database record will be created that contains basic information for each participant, including forms collected, current contact information, and vital status. Data confidentiality is ensured by password-protected secure WEB SSL-based access. This system allows for ease in data input, tracking, site specific reporting and data sharing for interested scientists as described in the Supplemental Materials.

Facilitating scientific discovery: Diverse VCID supports the innovative research efforts of approximately 11 laboratories. To facilitate the success of these funded investigators, the Statistical Core will create extracted datasets containing relevant variables. Creating a resource sharing and publications and ancillary study subcommittee will further support research.

Resource Sharing Subcommittee (RSS): The RSS will develop and implement policies and protocols for data and biosample sharing. The protocols can link existing resource infrastructures such as the Alzheimer's Disease Centers Program, the National Alzheimer's Coordinating Center, Stroke Net, etc. In addition, the RSS will oversee the stewardship of the resource at the project's closeout, working with the leadership committee to transition the resources to NIH-designated repositories (e.g., BioSEND).

Publication and Ancillary Studies Subcommittee (PASS): The PASS will review publications and ancillary proposals, prioritizing high-impact research manuscripts and ancillary proposals that may complement the Diverse VCID project major goals while avoiding overlap. The overall role of this subcommittee is to encourage scientific productivity while adhering to high standards in methodology and content. Investigators, especially junior investigators, both within and outside the project, will be encouraged to contribute to the publication process actively and in the submission of ancillary proposals that will maximize scientific output and use of the resources generated by the project.

A precision medicine approach to WMH and VCID—Our approach to developing the prediction models will follow the model-building steps described in the Supplemental Materials, with slight modifications. We will start with developing prediction models for incident dementia based on regression methods. We will treat sex as a biological variable in all regressions and results will be reported in aggregate and stratified by sex.

In addition to this standard approach to building prediction models, machine learning techniques, including CNN, support vector machines, and ensemble methods, such as bagging, boosting, and random forests, will also be used to develop potential models by training models to predict those that progress to dementia from those that do not[159]. K-fold cross-validation will be used to develop and validate these models.

We will evaluate the performance of the predictive models using calibration measures, how closely the outcomes predicted by a given model approximate the observed outcomes, and discrimination, the ability of each model to correctly distinguish between individuals who do and do not develop the outcome[160–162]. Standard measures of predictive accuracy, including sensitivity, specificity, positive predictive value, and negative predictive value, will also be assessed. Model performance will be compared across the different risk models to decide on a final prediction model that will be used to define the risk score.

Finally, we will assess the final risk score's validity using data from publicly available datasets such as the CHARGE cohorts[163]. We will generate 5-year risk scores for each participant in these cohorts and evaluate calibration and discrimination as outlined above. Although the actual risk score provides an estimate of the probability of incident dementia, we will also create a point-based score so that each year of age counts as an additional point. The final score is simply the linear combination of the points and the individual variables.

Summary: The Goal of Diverse VCID—In summary, Diverse VCID is the first study to prospectively recruit, assess, and retain a large, and diverse group of individuals with cognitive complaints or mild impairments in the presence of incidental WMH with the vision to improve cognitive health in at-risk individuals. The study is designed to comprehensively assess risk factors and biology of WM injury as a contributor to cognitive decline while also assessing the influence of Alzheimer's disease, a similarly common pathological process affecting cognition in later life. The goal is to investigate the basic mechanisms of small vessel cerebrovascular injury, emphasizing clinically relevant assessment tools and developing a risk score that will accurately identify an individual's risk for future cognitive impairment, with particular emphasis on those from diverse backgrounds who have a higher prevalence of vascular risk factors or disease. The mission of this project is to provide a valid predictive risk score that could be of future use to stratify patients into clinical trials aimed at mitigating the impact of vascular factors on dementia risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the Diverse VCID study (Diverse Vascular Cognitive Impairment and Dementia) research personnel and collaborators at the Administrative, Recruitment and Retention, Statistical and Repository Cores, and the Diverse VCID clinical performance sites. We particularly wish to thank Ms. Ayala, Ms. Flores-Marin, Ms. Crivello, Dr. Forloines and Ms. Roberts for their remarkable administrative support. Furthermore, we are grateful to our over 1,000 participants from diverse backgrounds who have already enrolled in this important study.

Sources of Funding

Diverse VCID study (Diverse Vascular Cognitive Impairment and Dementia) is jointly supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA) under award U19NS120384.

Disclosures

Charles DeCarli is supported in part by NIH grants P30 AG072972, U19NS120384, R01 AG075758, RF1 AG077639, and RF1 NS130659. He also serves as a consultant to Norvo Nordisk and Eisai Pharmaceuticals. Kumar B. Rajan is supported in part by NIH grants R01 AG058679, R01 AG 065359, U19 NS 120384, R01 AG 073627. Lee-Way Jin is supported in part by NIH grants U19 NS120384, P30 AG072972, RF1 AG071665, RF1 AG052132, RF1 AG056519, and P01 AG025532. David Johnson is supported in part by NIH grants P30 AG072972 and U19NS120384 as well as CA Dept of Public Health 18–10922, 22–10901 and 22–2948. Danielle Harvey is supported in part by NIH grants P30AG072972, U19AG024904 and U19NS120384 and is consultant to NervGen. Jason Hinman is supported in part by NIH Grants UF1NS100608, UF1NS100614, U19 NS120384 and U19NS115388. He is also employed by U.S. Department of Veterans Affairs, has stock holdings in Sage Cerebrovascular Diagnostics, serves as President for Sage Cerebrovascular Diagnostics, and has a patent pending for Serologic assay for silent brain ischemia licensed to Sage Cerebrovascular Diagnostics. Myriam Fornage is supported in part by NIH grants U19NS120384, R01AG075758 and UF1NS125513.

APPENDIX

Study Group: The Diverse VCID Investigators

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Nonstandard abbreviations:

AD	Alzheimer’s disease
ATN	amyloid, tau, neurodegeneration

BBB	blood brain barrier
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBPR	community-based participatory research
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CNN	convolutional neural network
DISCOVERY	Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery
DTI	diffusion tensor imaging
DVCID	Diverse vascular cognitive impairment and dementia study
ECog	evaluation of everyday function
EDE	endothelial-derived exosomes
FA	fractional anisotropy
FLAIR	fluid attenuated inverse recovery
FW	free water
GWAS	genome-wide association study
MarkVCID	Markers of Vascular Cognitive Impairment and Dementia
MORRE	memorable outreach, recruitment, retention, and engagement
MRI	magnetic resonance imaging
PASS	Publication and Ancillary Studies Subcommittee
PlGF	Placental growth factor
PRS	polygenic risk scores
RRC	Diverse VCID Recruitment and Retention Core
RSS	Resource Sharing Subcommittee
RVCL	Retinal Vasculopathy with cerebral leukoencephalopathy
SNPs	single nucleotide polymorphisms
VCID	vascular cognitive impairment and dementia
UDS	uniform data set
WHICAP	Washington Heights/Inwood Columbia Aging Project
WM	white matter

WMH white matter hyperintensities

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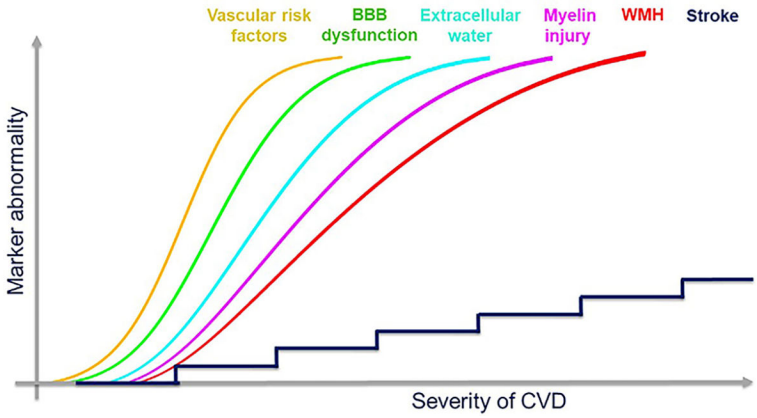

Figure 1. Hypothetical Pathological Cascade for Small Vessel Vascular Disease

The proposed cascade is based on evidence that systemic vascular disease affects cerebrovascular endothelium leading to a dysfunctional blood brain barrier (BBB) that results in fluid transudation into the cerebral interstitial space. It is further posited that this fluid is toxic to white matter constituents leading to diffuse changes in white matter microstructure, eventually resulting in WMH. This presumed continuous process differs—but shares some aspects of etiology—from the more stochastic event of stroke represented as the stepped line.

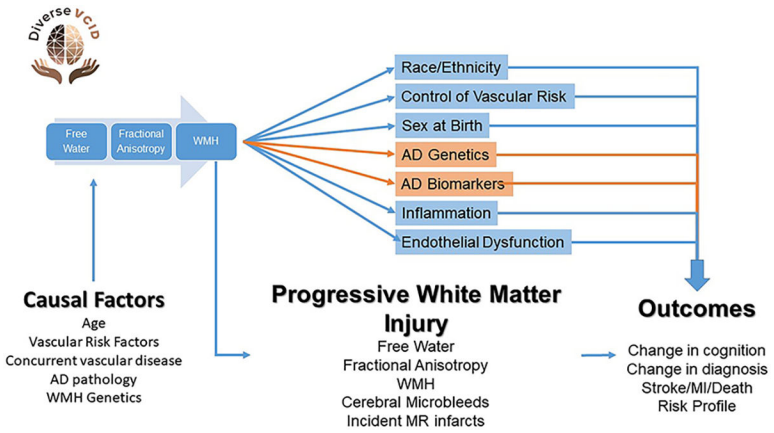

Figure 2. Overview of Diverse VCID Protocol

Diverse VCID addresses current gaps in scientific knowledge through 1) examining risk factors for WMH, including medical illness, lifestyle, and genetic influences; 2) examining the impact of overall burden, specific location and evolution of WMH on cognition, incidental clinical impairment, MI, Stroke, and death; 3) examining the effects of genetic influence and risk factor treatment; 4) accounting for co-occurring AD pathologies; 5) investigating systemic and brain mechanisms leading to WMH formation and impact on cognition and 6) building and validating a risk profile to assist clinicians in the assessment and potential treatment of WMH to prevent cognitive decline and transition to dementia. Whether a risk or resilience factor acts as a moderator, or a mediator is not *a priori* specified but will be assessed through our analyses to derive the risk profile. Orange colored factors indicate Alzheimer's disease (AD) related influences.

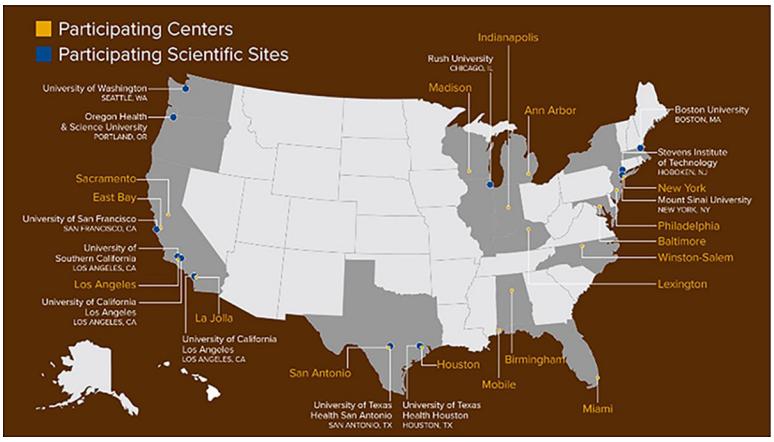

Figure 3. Diverse VCID Sites

Diverse VCID is comprised of 4 study cores (Administrative, Recruitment and Retention, Statistical, and Repository), 14 science and 17 clinical performance sites across the United States.

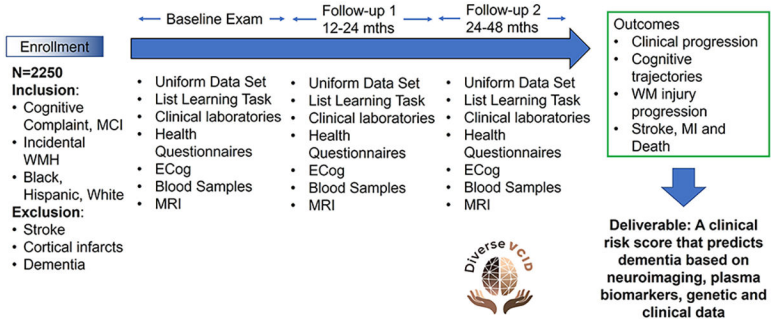

Figure 4. Diverse VCID Study Timeline

Adults between the ages of 65–90 self-identified as non-Hispanic White, Black/African or Hispanic/Latino Americans with cognitive complaints or mild cognitive impairment will be enrolled and assessed 3 times over approximately 3 years. Assessments will include detailed medical and neurological examination, health history, questionnaires, MRI, and blood sampling.

Table 1.

Memorable Outreach, Recruitment, Retention and Engagement (MORRE) Model

OUTREACH (Community focused messaging)	**RECRUITMENT (Directly answer participant questions)**	**RETENTION (Make opportunities to engage)**	**ENGAGEMENT (Well-defined tasks for CAB)**
Local Market Research & Digital Media Support	Culturally Relevant Priorities	Easy to Participate	Generate / Refine Community Outreach Topics
Video Shorts re CVD & Dementia	Altruistic Interests	Culturally Supportive Environment	Identify New Participant Pools
Infographics	Self-preserving Interests	Participants Check Ins	Snowball Recruitment
Themed Slide Decks	Video Shorts re Study Requirements	Web-Based Newsletter	Study Advocacy / Testimonials
Event Tracking DB, Tools & Reporting Templates		Appreciation Events	Engage Community Gatekeepers
Event Planning Support Docs		Participant Feedback	Community Engagement Studio (CES)

Precision Engagement: Appreciation that media needs to speak to a broad audience of participants with many specific needs based on who they are. Event content drives study engagement with speaking points that resonate with the challenges and questions that a particular audience member may have.

Table 2.

Diverse VCID Biomarkers

Standard MRI	Advanced MRI	Blood Based	Genetic
WMH volume, location, progression	Longitudinal Penumbra	Peripheral inflammation with IL-18 network	SNP/ApoE
Regional WM micro- structure (FA/FW)	WM injury Factor analysis	Innate immunity with endothelial exosomes	Whole Exome
Cerebral Microbleeds number/location	CNN quantification/ prediction	Angiogenesis with placental growth factor	AD PRS
Enlarged perivascular spaces Extent/location	WMH projection charts	Plasma AD markers of Abeta 40, 42, phospho-tau 181	WMH PRS
MR Infarcts presence/incidence/size/type/ location	Biomechanical modeling	Glial activation with GFAP	
Cerebral Blood Flow /Mean Transit Time		Neuronal Injury with Neurofilament lig ht	
Regional Gray matter volumes/thickness			
Central CSF volumes			
Signature ROI			