Commissioned Paper on Defining Different Types of Dementia

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INTRODUCTION

Loss of cognition as people age is common and is often a consequence of one or more brain pathologies that accumulate over mid- to late-life. Cognitive loss occurs on a continuum. Cutpoints along that continuum distinguish cognitive impairment from no cognitive impairment, and dementia from mild cognitive impairment (MCI). These are clinical syndromes that reflect the severity of cognitive impairment and its clinical consequences. The causes of MCI and dementia are numerous and complex and reflect the number, distribution, and combinations of underlying brain pathologies. Further, these myriad pathologies accumulate in brains that vary in their ability to tolerate them. Alzheimer's Disease and Related Diseases (ADRD) represent a set of diseases defined by their underlying pathologies. Clinical criteria for these diseases often but do not always identify cases with the pathology of interest. Thus, the current term Alzheimer's disease (AD) in the most recent diagnostic criteria refers to pathologic AD by autopsy or biomarkers. The term Alzheimer's dementia and Alzheimer's cognitive impairment refers to clinical syndromes thought to be a consequence of the pathology. For clarity, the term Alzheimer's dementia for the clinical syndrome will be used throughout and AD will refer to pathologic disease despite this being a very recent development.

This paper first reviews clinical criteria for common syndromes that are thought to reflect the common causes of cognitive impairment and dementia, detection of dementia, and progression of cognitive impairment. It next reviews pathologic criteria for the common diseases and illustrates the complexity of the causes of Alzheimer's dementia. This is followed by the implications of the complexity of the disease for diagnostic classification and in the next section for understanding the relation of risk factors for ADRD to dementia. The final section provides recommendations regarding future research.

PART I. CLINICALLY DIAGNOSED ADRD

Syndromes of Mild Cognitive Impairment (MCI) and Dementia

The clinical diagnoses of dementia, MCI, and Alzheimer's disease (AD) were revised in 2011 by a committee sponsored by the National Institute on Aging and the Alzheimer's Association (NIA/AA) (Albert et al. 2011; McKHann et al., 2011; Sperling et al., 2011). The NIA/AA criteria entailed no substantive changes to clinical criteria for dementia relative to the prior criteria published in 1984 (McKhann et al., 1984). Both MCI and dementia required objective loss of cognition with evidence of impairment on a mental status test. In addition, dementia required the presence of functional impairment as a consequence of the loss of cognition. The diagnosis of MCI required a concern about cognitive loss reported by the subject or informant, objective evidence of impairment in one or more areas of cognition, e.g., memory, reasoning or judgement, language, and no evidence that cognition impairs social or occupational function (Albert et al., 2011). This information should be obtained by history and mental status testing.

The diagnosis of dementia required cognitive impairment as outlined for MCI that must entail at least two areas of cognition and be sufficiently severe that it impacts social and/or occupational function (McKhann et al., 2011). This too is obtained by history and mental status testing.

While this paper focuses on cognitive impairment, the defining feature of cognitive impairment and dementia, there is also great interest in neuropsychiatric symptoms

such as depressive symptoms, apathy, anxiety, agitation and irritability signs (Geda et al., 2008; Lyketsos et al., 2002; Okura et al., 2010, Zhao et al., 2016). Less appreciated but also common are motoric manifestations such as frailty and parkinsonian signs (Buchman et al., 2013; Louis et al., 2005). These additional clinical manifestations of MCI and dementia also contribute to functional impairment.

MCI Due to AD and Alzheimer's dementia

The 1984 criteria for Alzheimer's dementia fundamentally required dementia by the criteria above with progressive cognitive decline with two or more areas of impairment one of which had to be episodic memory (McKhann et al., 1984). Thus, the algorithm was: is cognitive decline progressive? If yes, is dementia present? If yes, was episodic memory impaired? If yes to all, then the diagnosis was Alzheimer's dementia. Thus, if dementia was not present Alzheimer's was not present. There were also criteria for possible Alzheimer's dementia. This included both atypical presentations of dementia as well as possible dementia which is what eventually evolved into MCI.

The major advance in the diagnosis of Alzheimer's dementia in the 2011 NIA/AA criteria was the recognition of the continuum of AD from a pathophysiologic process to MCI to dementia with explicit recognition of MCI due to AD (Albert et al. 2011; McKHann et al., 2011; Sperling et al., 2011). Thus, a clinical diagnosis of Alzheimer's no longer required the presence of dementia. This was the culmination of data from multiple sources over the past three decades demonstrating the presence of AD pathology in persons without dementia and without cognitive impairment (Bennett et al., 2005; Bennett et al., 2006; Jack et al., 2008; Katzman et al., 1988;

Knopman et al., 2003; Morris et al., 1996; Morris et al., 2009). There was also an explicit

recognition of the presence of a preclinical phase of AD; although the paper stopped short of

calling this phase Alzheimer's, opting instead for pathophysiologic process of AD (Sperling et

al., 2011). Thus, the clinical diagnosis of Alzheimer's still required the presence of cognitive

impairment.   The criteria were published in series of three papers, one for dementia and

dementia due to AD, a second for MCI including MCI due to AD, and a third defining the

pathophysiologic process of AD. A major difference in the Alzheimer's dementia criteria from

earlier criteria was the recognition that it could have non-amnestic presentations whereas prior

criteria required impaired episodic memory. While non-amnestic presentations are found in

tertiary care clinics where relatively young persons can present with a number of different non-

amnestic signs and symptoms such as visuospatial impairment and primary progressive aphasia

(Putcha et al., 2019; Villain et al., 2019), the predominant feature of early Alzheimer's dementia

remains progressive amnesia. In addition to clinical criteria for Alzheimer's dementia, the

NIA/AA criteria also offered research criteria that incorporated neuroimaging and biofluid

biomarkers. This aspect of the criteria were considered a research agenda with forward looking

research criteria that required future validation.

In addition to the diagnoses widely used in the neurology field, the psychiatry field has a

different diagnostic classification system. Much of the psychiatric dementia literature uses the

diagnoses introduced in 1994 in the Diagnostic and statistical manual of mental disorders, 4th ed

(DSM-IV) (American Psychiatric Association, 1994). The DSM-IV diagnosis of dementia

required a deficit in memory and one other cognitive domain. If gradually progressive a

diagnosis of dementia of the Alzheimer's type was made. The DSM-5, in 2013, added mild

neurocognitive disorder similar to MCI which could be due to AD, and major neurocognitive

disorder similar to dementia (American Psychiatric Association, 2013).

<center>Vascular Cognitive Impairment (VCI)</center>

Criteria for VCI were adopted by a working group by the American Heart

Association/American Stroke Association (Gorelick et al., 2011). These supplanted earlier

criteria for vascular dementia (Roman et al., 1993). The major stride forward with the new

criteria was incorporating increasing evidence that cerebrovascular disease often co-existed with

AD in the brain and therefore was not the sole cause of dementia but instead made a contribution

to cognitive impairment (Schneider et al., 2009; White et al., 2016). Thus, the emphasis on the

contribution of vascular disease to cognitive impairment rather than vascular dementia. VCI

characterizes all forms of cognitive deficits from MCI to dementia with a contribution from

cerebrovascular disease. However, the criteria rely on the temporal relation between a vascular

event, e.g., stroke and the cognitive deficits. Increasing evidence suggests that a variety of

different vascular pathologies contribute to cognitive impairment in the absence of a vascular

event (Arvanitakis et al., 2016; Kapasi et al., 2018). These pathologies include macro- and

micro-scopic and watershed infarctions, atherosclerosis, arteriolosclerosis.

The DSM-IV criteria for vascular dementia also requires a temporal relation between

cerebrovascular disease and cognitive loss (American Psychiatric Association, 1994). The DSM-

5 goes further and states "that cerebrovascular disease is the dominant if not exclusive pathology

that accounts for the cognitive deficits," (American Psychiatric Association, 2013).

Other Dementias

Criteria exist in both the neurology and psychiatry literature for several of the more rare and difficult to diagnose dementias including Dementia with Lewy Bodies (DLB), and Behavior variant Fronto-Temporal Degeneration (bvFTD) (American Psychiatric Association, 2013; McKeith et al., 2017; Rascovsky et al., 2011). A recent dementia review provides a table that characterizes the key clinical and pathologic features that distinguish between AD, VCI, DLB, and bvFTS (Arvanitakis et al., 2019). Unfortunately, the criteria for these more rare dementias are unwieldy and virtually impossible to implement reliably in community-based settings outside a tertiary care clinic.

There are other even more rare causes of dementia such as Creutzfeld-Jakob disease (CJD). However, this is very rare and in most cases rapidly progressive dementia (Manix et al., 2015). It affects about 500 Americans a year and surveillance is done by the Centers for Disease Control (https://www.cdc.gov/prions/cjd/occurrence-transmission.html).

Other conditions such as limbic-predominant age-related TDP-43 encephalopathy (LATE) and suspected non-Alzheimer's disease pathophysiology (SNAP) can only be diagnosed with biomarkers or at autopsy (Burnham et al., 2016; Nelson et al., 2019).

Detection of Dementia

Dementia is an acquired loss of cognition relative to an earlier time in life. Cognition is made up of several partially dissociable cognitive abilities. The classical approach documents episodic memory typically by ability to encode and recall a story and or list of words; language,

or semantic memory, typically by naming and fluency; and executive function such as perceptual speed and working memory (ability to hold and manipulated information in short-term memory stores). Brief mental status tests performed on the participant include the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Mini-Cog, and Addenbrooke's Cognitive Examination III (ACE-III) and mini-ACE; there are also informant-based diagnostic tools that incorporate functional impairment such as the Clinical Dementia Rating (CDR), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), and AD8 (Arevalo-Rodriguez et al., 2015; Beishon et al., 2019; Chan et al., 2019; Davis et al., 2015; Harrison et al., 2015; Hughes et al., 1982; Larner et al., 2015). These tests vary in their ability to detect dementia and are generally insensitive for detection of the earliest stages of cognitive decline.

By definition (i.e., convention), cognitive impairment requires a loss of cognition relative to a prior time in life. Information such as education and occupation are often used as anchors to set expectations for performance to serve as a basis for a judgement of decline. For dementia to be present, the loss of cognition must be of sufficient severity that it interferes with social and/or occupational function. From a research standpoint, the latter criteria are problematic in general, and are particularly problematic when applied to diverse populations.

First, a wide range of abilities can lead to loss of function in older persons besides loss of cognition, including loss of vision, hearing, balance, strength, and dexterity, in addition to other medical conditions such as heart failure and pulmonary disease. It is often beyond the ability of a clinician to isolate the effects of cognition on loss of function in older persons with multiple co-morbidities. Further, the types of functions queried are typically basic and limited instrumental activities of daily living. For example, the CDR, published more than 35 years ago, remains among the mostly widely used dementia rating scales to document functional impairment

(Hughes et al., 1982). One component is personal care with impairment starting with "needs prompting." For others, questionable impairment is based on the prompt and directed to an informant. However, functional impairment from a third party observer may not be obvious (Watson et al., 2005).

A related issue is that loss of abilities does not take into account the fact that a key feature of early Alzheimer's cognitive impairment is the inability to learn new information. Thus, the ability of interest may be one that was not gained rather than one that was actually lost. For example, one study found that only 60% of older study participants without dementia used the internet (James et al., 2013). About a third of those with internet access did not use it and a third with internet access did not use email. Why do older persons have such difficulty incorporating new technology into their daily lives? Also related is that financial resources can dictate the kinds of higher level activities available to people and this can differ in diverse populations.

Another issue relates to cognitive function tests which are needed to document cognitive impairment. Brief tests are not sensitive very mild cognitive deficits. Detailed tests operate differently in diverse populations. This measurement invariance means that the same tests are not measuring the same thing in different groups (Blankson et al., 2015). Finally, some investigators advocate for strict age adjustment (Beeri et al., 2006). This is problematic as it allows the mean level of cognition to be lower in older persons artificially limiting the number of persons who can be affected and forcing impairment needed for dementia to be worse for each additional age. Such age adjustments are not done for other chronic conditions, e.g., hypertension, obesity, which can be present in the majority of the population at higher ages.

In research settings, a detailed cognitive assessment that includes formal neuropsychological setting is required. Often these are two stage designs. Stage one includes a

brief screening examination to identify potential cases. Stage two is often a stratified random sample, or just screen failures, selected for more detailed testing. Even here slight methodological approaches can produce disparate results. Two examples of studies that used the "silver standard" diagnostic process of in home assessment neuropsychological testing, an informant interview and in one case an in-home evaluation by a neurologist and in the other a case conference to illustrate potential difficulties with implementing accepted diagnostic criteria for dementia and Alzheimer's dementia.

The Chicago Health and Aging Project (CHAP) is a population based study in three adjacent communities on Chicago's south side (Evans et al., 2003). The second is the Study Design Aging Demographics and Memory Study (ADAMS) which uses the Health and Retirement Study (HRS) as the sampling frame (Plassman et al., 2008). In 2003, incidence data from CHAP were used to estimate Alzheimer's dementia prevalence in the USA. The estimate came to about 5.4 million persons over age 65 using 2000 census data (Hebert et al., 2003). Four years later, data from ADAMS was used to estimate Alzheimer's dementia prevalence. The estimate came to 3.4 million dementia cases over age 71 in the USA (Plassman et al., 2007). This included 2.4 million cases of Alzheimer's dementia, less than half the number from CHAP. Both investigative teams subsequently analyzed the data jointly to identify sources of variability (Wilson et al., 2011). The authors concluded that "when a diagnosis of AD excludes persons meeting criteria for vascular dementia, when not all persons with dementia are assigned an etiology, and when a diagnosis of dementia requires an informant report of functional limitations, the prevalence is substantially lower and the diagnosed cases most likely have a relatively higher level of impairment."

Trajectory of Cognitive Decline

A brief cognitive screening instrument can be used to assess longer term change with large sample sizes (Piccinin et al., 2013). However, more detailed change and change in different cognitive domains requires more detailed measures over time. Methodological approaches need to consider random variability (three data points make a line as two data points cannot distinguish true change from random change) and practice effects (Ferrer et al., 2004).

Most data on the trajectory of ADRD are from clinic-based prevalence studies. These studies should be interpreted with caution as persons that come to the attention of the health care system for dementia differ from those that do not. For example, one study found differences in the types and severity of different dementia pathologies for AD, VCI, LBD and FTD in autopsies from community-based studies vs. clinic-based studies (Schneider et al., 2009). In addition, rate of cognitive decline among clinic persons with AD is rapid and inversely related to age (Wilson et al., 2000). By contrast rates of decline are much slower in community-based studies and directly related to age in the East Boston study (Wilson et al., 1999), but unrelated to age for incident AD in CHAP (Weuve et al., 2018). In the biracial CHAP, incident AD in Blacks is twice that of white; however, there were no racial differences in decline for incident AD with a global measure of cognition based on four cognitive tests despite large level differences in cognition at basesline (Wilson et al, 2010). By contrast, when examined with more granularity with a detailed cognitive battery tapping into multiple domains repeated annually, decline in semantic memory, perceptual speed, and visuospatial ability was slower in Blacks and in semantic memory and perceptual speed the effect was stronger in older participants (Wilson et al., 2015). Decline in episodic and working memory was not related to race. Finally, there is

limited data on ethnic differences in cognitive trajectories in older Latinx persons. One study with a detailed cognitive battery tapping into multiple domains repeated annually found no differences in level of or change in cognition (Wilson et al., 2016).

Given the large level differences in cognition across race and potentially ethnicity it's important to ensure that dementia prevalence differences are not an artifact.

There is essentially no data on incidence, prevalence or cognitive decline in rural populations in the USA.

PART II. PATHOLOGICALLY DIAGNOSED ADRD

Pathological Diagnosis of AD

The NIA/AA workshop that developed clinical criteria for Alzheimer's dementia and MCI due to AD in 2011 also had a working group for pathologic AD (Hyman et al., 2012). The fundamental definition relied on the density and distribution of the two major pathologies, neuritic plaques and neurofibrillary tangles. The details were updated relative to prior criteria in 1997 (Hyman et al., 1997) to reflect a better understanding of the molecular bases for these histopathologic changes. However, the fundamental criteria were unchanged.

New NIA/AA Framework for AD

In 2018 a new AD Framework was published based on another NIA/AA workshop (Jack et al., 2018). This controversial framework now defines AD based on biofluid or neuroimaging

biomarkers, or brain pathology, regardless of its clinical consequences. In other words, the Framework offers no revision to the 2011 clinical criteria for MCI due to AD and Alzheimer's dementia defined above. Rather, it eliminates the awkward "pathophysiologic process of AD" and instead uses AD to refer strictly to the pathology without any consideration of its effects on cognition. The clinical criteria in the absence of biomarker evidence of AD was termed Alzheimer's clinical syndrome (or Alzheimer's dementia, Alzheimer's cognitive impairment). This completes the separation of the pathology of AD from its clinical consequences. This is similar to distinguishing between cerebrovascular disease and stroke or atherosclerotic heart disease separate and myocardial infarction. The main driver of the new criteria was the need to provide an AD regulatory path to approval for interventions aimed at AD pathology in asymptomatic people (Lopez Lopez et al., 2019; Sperling et al., 2014; Wang et al., 2019). These studies are attempting to treat asymptomatic persons with AD.

The framework was based on a prior paper that described an A/T/N (amyloid/tau/neurodegeneration) descriptive classification system for AD (Jack et al., 2016). Current biomarkers are based on Positron Emission Tomography (PET) or cerebrospinal fluid. With the exception of F18 PET amyloid tracers which are approved by the Food and Drug Administration for use in highly select cases, the PET tau and the CSF amyloid and tau measures are only available for research. Thus, these biomarkers are currently only deployable in an Academic Medical Center clinical research program. However, progress with blood based biomarkers promises to allow their large scale use in community-based studies in the near future (Bateman et al., 2019; Mattsson et al., 2015).

Relation of Other ADRD Pathologies to Alzheimer's Dementia

To date, about a dozen different brain pathologies in addition to AD are known to be associated with Alzheimer's dementia. These include a variety of cerebrovascular diseases, cortical Lewy bodies, tar-binding protein 43 (TDP-43), and hippocampal sclerosis (Arvanitakis, et al., 2016; Dawe et al., 2018). Importantly, many brain pathologies cannot be measured during life. Data from two community-based cohort studies with more than 1000 brain autopsies were used in an attributable risk model for Alzheimer's dementia (Boyle et al., 2019). AD (i.e., pathologic AD) accounted for about a third of Alzheimer's dementia cases at death. Seven other brain pathologies accounted for another third of cases. The remaining third was unaccounted for.

Relation of ADRD Pathologies to Trajectories of Cognitive Decline

In the same dataset described above, brain pathologies were linked to change in multiple cognitive domains measured annually over up to a quarter century. First, nearly 250 different unique combinations of brain pathologies were found to contribute to cognitive decline (Boyle et al.., 2018). Pathologic AD alone was present in fewer than 6% of cases and no single pathology or combination was present in more than 6% of persons. Moreover, nearly 100 combinations were present in a single individual. Second, the variance of cognitive change explained by each pathology, including AD pathology, varied from a low of about 20% to 100% depending on the presence of co-morbid pathologies. This is 20-100% of the variance that is explainable which is less than half of the person-specific variability of decline (Figure 1).
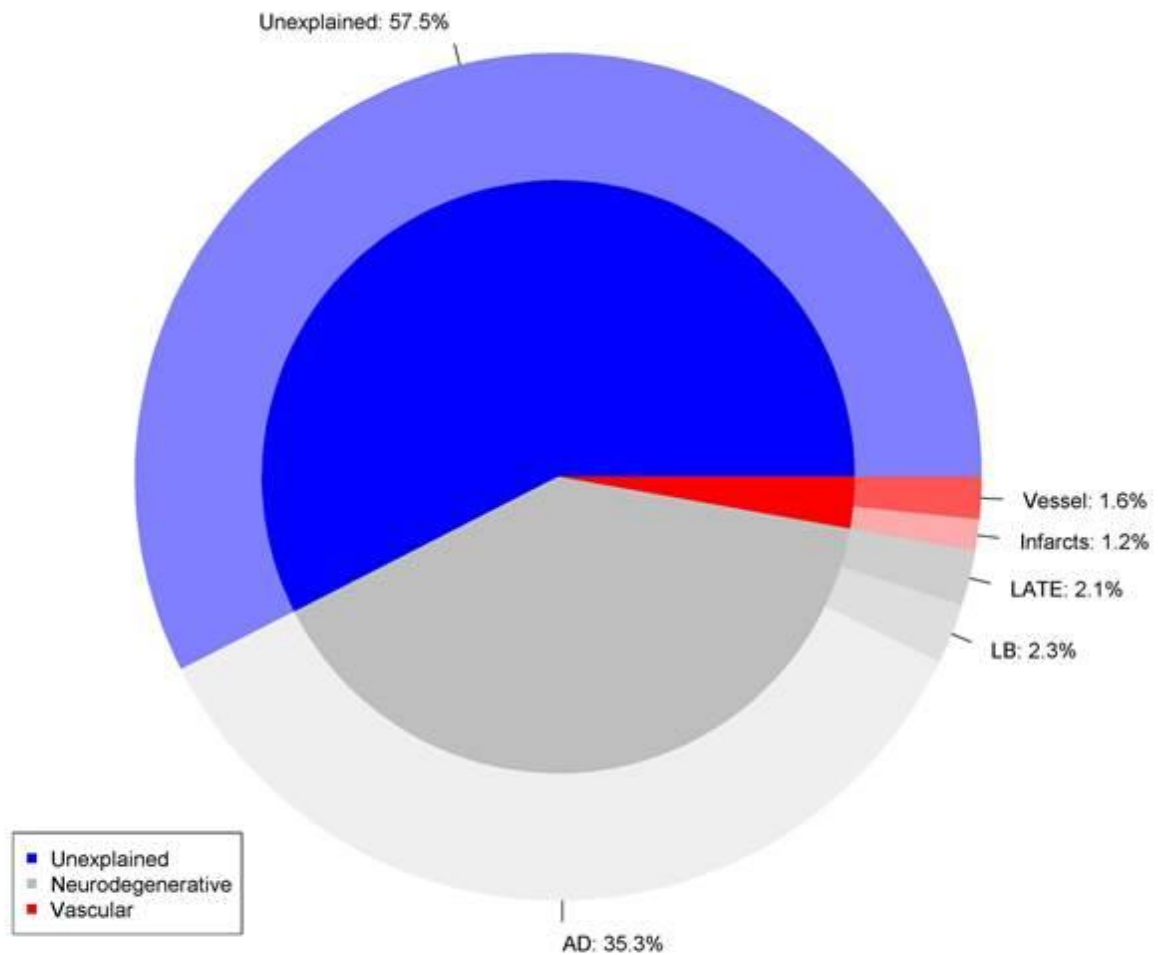
Figure 1. Contributions of different pathologies to the person-specific variability of cognitive decline over up to 25 years of annual cognitive data prior to death among decedents in the Religious Orders Study or Rush Memory and Aging Project. [AD=pathologic AD; LB=cortical Lewy bodies; LATE= Limbic-predominant age-related TDP-43 encephalopathy; infarcts=macrospcopic cerebral infarctions; vessel=atherosclerosis].

To find more nuanced patterns of cognitive trajectories, AD, LBD, TDP-43, Hippocampal sclerosis, and five indices of cerebrovascular disease (including amyloid angiopathy) were related to trajectories of episodic memory, the clinical hallmark of Alzheimer's dementia, semantic memory, working memory, and perceptual speed (Wilson et al., 2019). Each neurodegenerative marker was associated with lower episodic memory function beginning about 10 to 16 years before death. As time before death decreased, AD pathology, Lewy bodies, and hippocampal sclerosis were associated with impairment in other cognitive domains but the association of TDP-43 pathology with cognition continued to be mainly confined to episodic memory. This is due in part to terminal dedifferentiation in cognitive abilities (Wilson et al., 2012). As cognition worsens, the ability to dissociate different cognitive abilities is lost as different domains become increasing inter-correlated. Thus, after the onset of cognitive impairment it becomes increasingly difficult to find specific patterns of cognition associated with specific cognitive domains.

The authors also examined competing risk. Risk of cognitive impairment before death increased as the number of co-morbid pathologies increases (Yu et al., 2015).

<center>Resilience and Cognitive/Neural Reserve</center>

All physiologic systems have ways to maintain function despite injury or the development of pathologies. Brain reserve, neural reserve, and resilience have all been used to refer to this ability in the nervous system (Stern and Barulli, 2019). Several structural and functional indices have been identified that help maintain cognition or promote loss of cognition

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separate from brain pathologies (Bennett, 2017. Buchman et al, 2016; Stern et al, 2019; Yu et al., 2018). The effects of these indices can be additive or interactive.

Implications for Diagnostic Classification of ADRD in Community-Based Studies

The data illustrate that cognitive decline, Alzheimer's cognitive impairment, and Alzheimer's dementia typically results from the additive and interactive effect numerous brain pathologies and resilience indices. Nearly all of these indices are not measureable in living persons. Further, all of the common pathologies contribute to decline in episodic memory which is the clinical hallmark of Alzheimer's dementia. While most people with Alzheimer's dementia have pathologic AD, they also have other pathologies contributing to cognitive impairment. The result is that diagnostic classification outside of relatively younger persons in tertiary care centers is problematic, time consuming, expensive, and likely inaccurate.

PART III. RISK FACTORS FOR ADRD IN THE AGE OF THE NEW FRAMEWORK

Understanding the relation between exposures and outcomes are essential for improving public health and finding more robust therapeutics to improve the health and well-being of older persons (James et al., 2019). Risk factors for Alzheimer's dementia include a range of environmental and individual factors; the latter can be categorized as experiential, psychological, medical, and genetic. Given the combination of mixed pathologies and unexplained dementia, it is not surprising that many risk factors for Alzheimer's dementia are not related to AD pathology. Figure 2 highlights different pathways through which a risk factor could operate.

Only risk factor 1 is a risk factor for AD. Risk factor 2 is a risk factor for another disease that contributes to dementia. Risk factor 3 is a risk factor for another pathology that has yet to be discovered. Risk factor 4 results in neurodegeneration in the absence of a pathologic footprint. Finally, risk factor five modifies the relation of pathology to dementia rather than having a direct effect. All risk factors for dementia are important. However, as biomarkers and therapeutics improve, understanding the mechanism linking risk factors to dementia will acquire greater importance (Bennett et al., 2017).
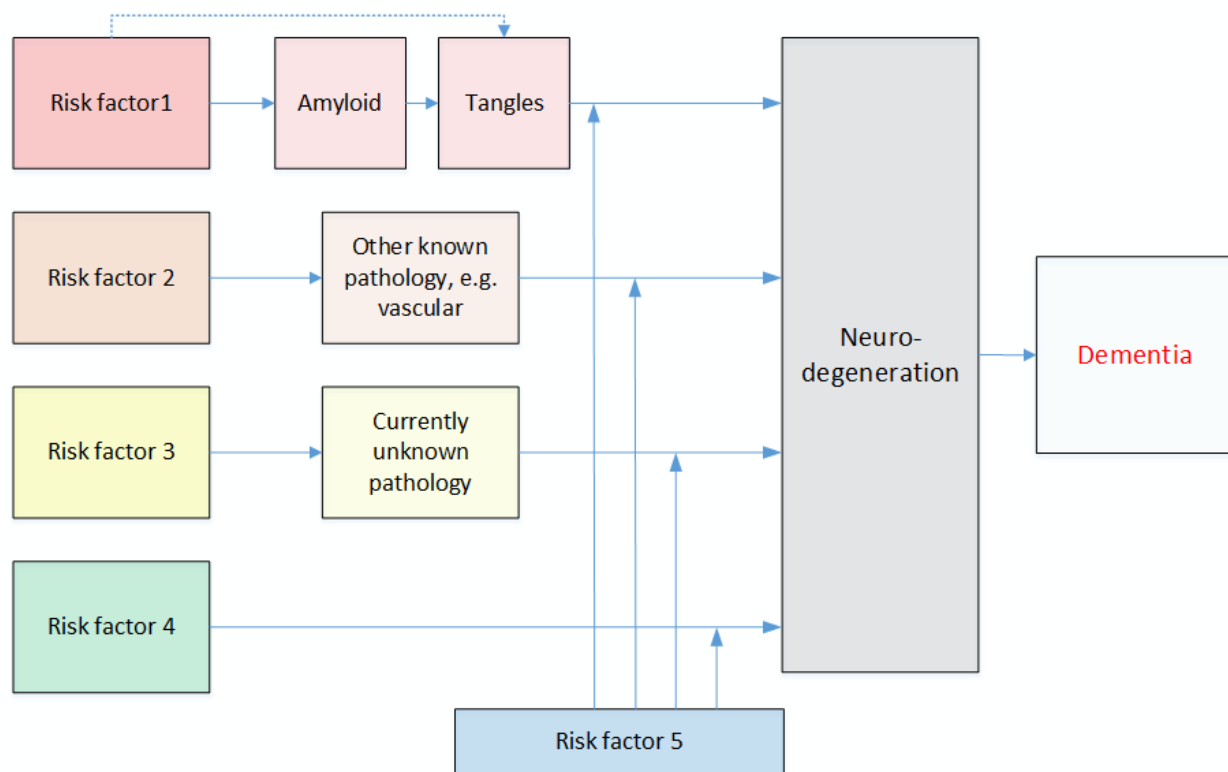

Figure 2. Hypothetical model illustrating potential pathways linking risk factors to dementia.

RISK IV. FUTURE AREAS OF RESEARCH

- Given the extent of mixed dementia and unknown causes, diagnosing specific causes of dementia is not resolvable at scale. While biomarkers are increasingly available they have limited utility at scale at this time. Blood based biomarkers will be available soon and these will be scalable. Generating population level data and understanding the association of environmental, socioeconomic status, and social risk factors with blood based biomarkers will be an important future area of research.

- Population level trends in cognitive health has been an important area of research. Given the rising inequality in life expectancy across the USA, much more work is needed in this space. There is a dearth of data on cognition and dementia prevalence and trends in rural and other areas experiencing declines in mortality. Getting more granular data on the effects of inequality on trends in cognitive impairment and dementia is an important future area of research.

- Limited information is available at the population level on cognitive trajectories especially in diverse populations. Given the level differences in cognition in diverse populations these data are needed. Life course epidemiology has long been a focus of research in this space and it should be expanded to better understand early and midlife cognition.

- Differences in rates of cognitive decline in diverse populations need to be confirmed and work needs to ensure it is not an artifact of measurement invariance.

- Information is needed on the relation of blood based biomarkers and cognitive trajectories in diverse populations.

- While a focus on cognitive trajectories needs to be expanded, for political reasons and for counting and trends it is important to continue to diagnose cognitive impairment, dementia

and Alzheimer's dementia in the future. This can be done efficiently. Other dementias are not worth the time and treasure in direct or opportunity costs.

- Generalizability and internal validity compete for resources and studies that maximize the former may not be the best place to accomplish risk factor associations beyond select social determinants. Population level data maximize generalizability. Risk factor associations with outcomes maximize internal validity. (The ultimate sacrifice of generalizability for internal validity are studies, typically of therapeutics, that randomize the exposure and blind all parties to the randomization.

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