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Barriers to identifying residents with dementia for embedded pragmatic trials: a call to action

Running title: Barriers to identifying residents with dementia for ePCTs

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The continued lack of progress in translating efficacious, evidence-based interventions into real-world settings has been an area of increasing focus over the last 10 years. This implementation gap is also found in the translation of nonpharmacological interventions for people living with Alzheimer's disease or other dementias (ADRD) and their care partners.[1] While efficacious interventions exist, few have demonstrated effectiveness or sustainability under real-world testing. In response, the National Institute on Aging (NIA) has made a significant investment in bridging the implementation gap by funding the **IM**bedded **P**ragmatic **A**lzheimer's disease and Related Dementias **C**linical **T**rials (IMPACT) Collaboratory.[2] The mission of the IMPACT Collaboratory is to build national capacity to conduct pragmatic clinical trials of nonpharmacological interventions for people with ADRD and their care partners.

One key feature of embedded pragmatic trials is to enroll all participants who are likely to be recommended to receive the intervention when it becomes part of usual care. In order to enroll participants in large pragmatic trials, we first need to be able to accurately identify the target population. Adequate screening optimally relies on use of available data sources as reliance on clinician or researcher screening is frequently infeasible at scale. In October 2020, the NIA IMPACT Collaboratory Technical Data Core sponsored a virtual workshop entitled "Future Priorities for Identifying People with Dementia from Digital Health Data for Embedded Pragmatic Clinical Trials".[3] Over 50 research and policy experts convened to share best-practice, validated algorithms for identifying people with ADRD and their limitations. The goals of the workshop were to assess the current state of the field, clarify directions for future work, and prioritize

immediate and long-term goals. In this call to action, we summarize three major barriers to identifying people with ADRD that need to be addressed to equitably and accurately target eligibility and enrollment for future pragmatic trials (Table 1).

1) Creating more equitable and ethical algorithms:

Despite disproportionately high prevalence and burden of ADRD, historically excluded and minoritized groups including African American/Black, Hispanic/Latino, Native American/Alaskan Native, socioeconomically disadvantaged, and rural dwelling Americans are more likely than whites to have a delayed diagnosis[4] and lack of access to evidence-based care.[5] The utility of diagnosis-based algorithms to detect ADRD among these populations is hindered by disparities that produce systematic differences in care and utilization patterns that lead to higher rates of delayed or missed diagnosis, and under-utilization of outpatient and specialty care.[6] These differences have implications for the availability and utility of structured data elements that are predominantly leveraged in automated or semi-automated screening algorithms, such as diagnostic codes or medications. As a result, structured data elements alone are likely inadequate for pragmatic trials whose objectives necessitate identifying individuals with undetected dementia or to achieve sufficient algorithmic fairness and equipoise among historically underrepresented populations.

Despite probable differences in underlying data availability, few validation studies have evaluated data element sufficiency or differential algorithm performance across historically underrepresented populations. Lack of familiarity with best practices in

algorithmic fairness as well as missing and inaccurate data on race, ethnicity, and language preferences in electronic health record (EHR) data likely contribute to the absence of these studies.[7] It has been suggested that incorporation of unstructured (i.e. narrative text) data elements may help augment both broad and sub-population specific limitations of structured data elements which risk masking and/or reinforcing disparities in ADRD detection and enrollment into pragmatic trials.[8] While few validation studies have incorporated unstructured data elements, most have utilized diagnostic terminology and/or been carried out in research cohorts that have previously undergone neuropsychological evaluation, limiting their utility for pragmatic trials.[9, 10] Preliminary derivation studies of broader unstructured clinical data elements, encompassing terminology descriptive of both cognitive and non-cognitive (i.e. behavioral, functional) symptomatology common in ADRD may prove useful in broadening capture of dementia cases, but have not been validated in diverse cohorts.[8] It is likely that these data elements may also be subject to a frequency effect, based both on engagement in the care system and type of utilization, as frequency of unstructured documentation varies considerably across setting and intensity of care episodes.

Using predominantly text-based algorithms to better identify underdiagnosed patients for enrollment in pragmatic trials raises additional ethical concerns. One in five patients with an ADRD diagnosis are unaware that they have the disease.[11] That proportion likely nears 100 percent when using text-based algorithms to identify people with likely dementia. Researchers need to better understand the risk-to-benefit ratio of informing someone that they have a terminal disease with the potential benefit of receiving a behavioral intervention targeting management of symptoms. Inequities of

the current healthcare system are likely to be carried over into the data on which algorithms are developed. While there are multiple benefits to using algorithms – such as the ability to rapidly identify large numbers of patients for enrollment in trials – there are risks as well, such as the risk of perpetuating disparities in access to research[12] and potentially efficacious treatments and enrollment of people who do not know they have the disease.

2) Validating algorithms across settings:

Algorithms - of any kind - are imperfect. Algorithms to identify PLWD and their care partners for pragmatic trials are particularly challenging, given the underdiagnosis of dementia in most care settings, issues with the underlying data itself and its variability, and the vicissitudes inherent in implementation. Validation across multiple systems can address these issues for algorithms[13] that identify (or phenotype) PLWD; however, these validation studies are rarely performed. Most studies using EHR data to define diagnostic- or text-based algorithms do not provide enough detail to allow for replication. To combat this problem, standardized reporting guidelines have been proposed[14] and repositories for validated algorithms have been built. Repositories include the Phenotype Knowledge Base, or PheKB, (phekb.org) repository and the PhenX repository, among others. Selecting an algorithm is not enough; validating the algorithm for the local setting is required. We need to provide guidance, not only to help researchers choose amongst validated algorithms, but on how to conduct validation analyses in their research setting. While some validation approaches are complex, there are rapid, lightweight approaches which could be employed by most researchers.[15] For

example, an iterative approach during initial algorithm implementation where the researcher manually validates small numbers of patients to estimate current accuracy and adjusts the algorithm until the estimated precision is sufficient for the full validation can help avoid major errors. With this guidance, evidence of algorithm validation in the study setting could become a standard requirement of pragmatic trial proposals. Validation became particularly critical during the coronavirus pandemic when patterns of utilization, on which these algorithms were built, dramatically changed.

3) Longitudinal, cross-setting data integration:

Attendees noted the need for longitudinal data with complete and accurate outcome ascertainment. For example, almost 30% of people with dementia in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory Distributed Research Network (DRN) were lost to follow-up within a year due to leaving a participating MA plan.[16] Researchers expressed a need for tokenization, similar to the NIH GUID project,[17] to follow unique individuals across data sets. Accomplishing this goal will require greater collaboration from insurance companies, healthcare systems, and federal data partners to access data for clinical research. One of the goals of the IMPACT Collaboratory will be to advocate for the availability of high-quality, longitudinal data sets to all dementia researchers conducting pragmatic trials.

Tracking individuals across existing claims- and EHR-based data sources is a good start, but we also need our longitudinal data sets to integrate different types of information. Quality of life outcomes, which are highly valued outcomes for people with

ADRD and their caregivers,[18] are often not present in EHR data. Equally absent are details about social support and receipt of social services, despite the significant impact on health outcomes for people with ADRD and their caregivers.[19] Researchers would also benefit from integration of biomarker data, such as those collected by the National Alzheimer's Coordinating Center Uniform Data Set (UDS).[20]

While many promising and high-performing algorithms to identify people with ADRD were presented throughout the workshop, discussion centered on the need to validate these algorithms in underdiagnosed populations and across healthcare settings. In response to these needs, the IMPACT Collaboratory plans to: support researchers testing the equity of existing algorithms through pilot funding and support; provide guidance to pragmatic trialists on algorithm selection and how to rapidly validate their algorithms prior to funding submission; and enable use of longitudinal, cross-setting data sources, such as Medicare claims data, for use by investigators in the planning and evaluation phases of their embedded, pragmatic trials. While much interdisciplinary research remains to be done on identifying ADRD populations through the use of algorithms, their use has the potential to improve care of ADRD patients by enabling large, embedded pragmatic clinical trials that aim to reduce the implementation gap and bring efficacious nonpharmacological interventions to all people living with ADRD.

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Conflicts of Interest:

All of the authors are members of the Technical Data Core, contributed in all phases of writing this manuscript and none have conflicts. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1. Identifying PLWD for Pragmatic Trials: Barriers and Potential Action Steps

Need	Barriers	Potential action steps
Creating more equitable and ethical algorithms	• Historically underrepresented populations are less likely to have access to care and receive a timely ADRD diagnosis • Pragmatic trials which rely on structured data elements, including diagnoses, to identify potentially eligible persons will fail to achieve equity in enrollment	• Validate existing algorithms in underrepresented populations • Develop algorithms that incorporate unstructured data to better capture underrepresented PLWD, with the appropriate ethical considerations related to identification
Validating algorithms across settings	• Variation in implementation results in differential documentation of ADRD diagnoses and symptoms across clinical settings • Cross-setting validation studies are rarely performed	• Leverage existing repositories to document existing algorithms • Provide guidance to researchers on how to choose between existing algorithms and how to conduct rapid validation of algorithms in their trial setting, prior to funding
Longitudinal, cross-setting data integration	• High rates of loss to followup as PLWD exit a given healthcare system, resulting in incomplete outcome ascertainment • Few data sets linking EMR and claims-based data sources. • Most existing longitudinal data sets missing quality of life, caregiver / social support, and biomarker information	• Create a tokenization, similar to the NIH GUID project, to follow unique individuals across data sets. This will require collaboration from insurance companies, healthcare systems, and federal data partners to access data for clinical research.

Abbreviations: PLWD, people living with dementia; ADRD, Alzheimer's Disease and Related Dementia; EMR, electronic medical record; NIH, National Institutes of Health; GUID, Global Unique Identifier