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Translational Article

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Translational

Considerations in the Design of Clinical Trials for Cognitive Aging

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What will it take to develop interventions for the treatment of age-related cognitive decline? Session V of the Summit provided perspectives on the design of clinical trials to evaluate promising but unproven interventions, and some of the steps needed to accelerate the discovery and evaluation of promising treatments. It considered strategies to further characterize the biological and cognitive changes associated with normal aging and their translation into the development of new treatments. It provided regulatory, scientific, and clinical perspectives about neurocognitive aging treatments, their potential benefits and risks, and the strategies and endpoints needed to evaluate them in the most rapid, rigorous, and clinically meaningful way. It considered lessons learned from the study of Alzheimer's disease, the promising roles of biomarkers in neurocognitive aging research, and ways to help galvanize the scientific study and treatment of neurocognitive aging.

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On October 5–6, 2010, the National Institute on Aging and the McKnight Brain Research Foundation hosted their second Cognitive Aging Summit. Researchers from a range of scientific disciplines were asked to consider progress, opportunities, challenges, and strategic directions in the characterization, study of, and treatments for those cognitive declines attributable to the aging brain—and to place special emphasis on those neurocognitive changes that are not directly attributable to age-related brain disorders like Alzheimer's disease (AD) and cerebrovascular disease (CVD). In one session, four speakers and two discussants were provided perspectives related to the design of clinical trials to evaluate promising but unproven interventions for the treatment of cognitive aging. Their power point presentations are available at www.fnih.org/events/cognitive-aging-summit. In this article, we review those perspectives.

Researchers employ a range of strategies to characterize the biological and cognitive changes associated with normal aging (whether or not they are related to the development of age-related disorders) and translate them into the discovery and clinical development of new treatments. In the second section, Dr. R.D.B. discusses the strategy that she and her colleagues have used to discover key determinants of cognitive aging using preclinical models and translate these findings into promising treatments to sustain neurocognitive processes during aging. She indicates that the depletion of estrogen and other ovarian hormones is a cardinal feature of aging in

women, how her research team has characterized the effects of depleting ovarian hormones on mitochondrial bioenergetics, and how they have demonstrated the ability of estrogen treatment to maintain mitochondrial bioenergenic capacity in both wild-type mice and a transgenic mouse model of AD. Her laboratory is developing alternative estrogen treatments to sustain age-related neurocognitive processes and reduce the risk of age-related neurodegenerative disorders without increasing the risk of breast or uterine cancer.

With the advent of these and other investigational treatments for cognitive aging, regulatory agencies and researchers have begun to consider the clinical trial strategies needed to evaluate these treatments in the most rapid, rigorous, and clinically compelling way. In the third section, we summarize the U.S. Food and Drug Administration (FDA) perspective on the clinical development of drug treatments for cognitive aging, as articulated during the conference by Dr. R.K., Director of Neurology Drug Products for the FDA's Center for Drug Evaluation and Research. He indicated that FDA approval of a drug to treat the cognitive decline of normal aging is possible, that the drug sponsor would need to demonstrate the drug's clinically meaningful cognitive effects using appropriate outcome measures, that the drug would need to be extremely safe (such that its potential benefits outweighed its risks), and that the relevant social and ethical issues would need to be considered along the way.

As researchers begin to discover promising treatments for cognitive aging, it would be helpful to identify those individuals at highest risk for subsequent cognitive decline (ie, those at risk for "unsuccessful cognitive aging" and, thus, most likely to benefit from an effective treatment). It would also be helpful to determine the extent to which a treatment's effectiveness is related to the presence of underlying AD and/or cerebrovascular pathology. In the fourth section, Dr. R.C.P. and his collaborator S.N. consider some of the lessons learned from the study of AD. For instance, Dr. R.C.P. and his colleagues originally developed clinical and neuropsychological criteria to predict subsequent cognitive decline in patients with mild cognitive impairment (MCI), and Dr. S.N., Dr. R.C.P., and their colleagues have begun to investigate neuropsychological criteria to predict subsequent rates of decline in cognitively normal older adults. They also note the potential to use brain imaging and other biomarkers of AD (and CVD) to help determine the extent to which the trajectory of cognitive decline is associated with the presence or absence of underlying brain pathology.

In the fifth section, Dr. D.M. considers the kind of cognitive measurements that will be needed to evaluate treatments for cognitive aging. He indicates how modern psychometric methods could be used to help characterize the most sensitive and suitable cognitive and functional endpoints for assessment of interventions to prevent cognitive decline, including the decline that occurs in the absence of MCI or dementia.

In the sixth section, Dr. P.S.A challenges the cognitive aging research community to further clarify the magnitude and clinical age-related cognitive declines, including those that are not directly attributable to preclinical AD or cerebrovascular pathology. He argues that this information is critically needed to help determine whether the potential benefits of an investigational treatment for cognitive aging would outweigh its potential risks.

In the last section, Dr. E.M.R. offers several recommendations to help accelerate the discovery and evaluation of treatments to improve cognitive performance and/or slow down the brain and cognitive changes associated with aging in normal older adults. He suggests how biomarkers could help characterize the brain changes associated with normal aging and the predisposition to age-related disorders like AD, some of the factors that influence these changes, and discovery promising new treatments. Finally, he recommends ways to help galvanize the scientific study and treatment of neurocognitive aging.

Cognitive Aging and Translational Research: Strategies to Sustain Neurological Function

In this section, Dr. R.D.B. describes the strategy employed by her laboratory to develop alternative estrogen treatments to sustain age-related neurocognitive processes and reduce the risk of age-related neurodegenerative disorders.

Although declines in cognition during aging are well recognized, a substantial degree of variability in the rate and trajectory of cognitive function is clearly documented (1). A major determinant of the functional trajectory of the aging brain is its bioenergetic capacity and continued reliance upon glucose as its primary fuel source (reviewed in Yao *et al.* (2)). The brain, which accounts for ~2% of body weight, consumes 25% of whole-body glucose to generate adenosine triphosphate (ATP) required for brain function. Of all the ATP generated in brain, 75% is required for synaptic transmission. To put this into a quantitative context, by some estimates, the brain is using 30–50 mM ATP/g/min (reviewed in Yao *et al.* (2)). Because of the magnitude of ATP demand required to drive and sustain synaptic transmission (whether induced by external stimuli or intrinsic to default networks), changes in the capacity and efficiency to generate ATP in brain will be first apparent in those circuits and functions with greatest bioenergetic demand (reviewed in Brinton (3,4)).

One clear hallmark of normal aging in men and women is reproductive senescence. This phase of aging is a multifactorial process with a high degree of interpersonal variability and subject to a host of beneficial or detrimental influences (1). As such, reproductive senescence is an illustrative example of both the aging process and of modifiers of aging. Although both men and women undergo reproductive senescence, the timing and profile of their reproductive senescence differs. Women undergo a systematic dismantling of reproductive capacity characterized by three distinct phases that occur over a 5- to 7-year time frame with completion on average by the age of 51 (1). In contrast, men, while experiencing a decline in testosterone by the mid 30s, can remain reproductively capable until death (1).

Key to reproductive aging in women is the decline in the ovarian hormones, estrogen, and progesterone. Both ovarian hormones, and particularly estrogen, significantly promote glucose driven mitochondrial bioenergetics (3,4). The essential role of mitochondria in cellular bioenergetics and survival has been well established (reviewed in Yao et al. (2)). Furthermore, mitochondrial dysfunction has been suggested to play a pivotal role in neurodegenerative disorders, including AD (reviewed in Yao *et al.* (2)). Estrogen promotes the coupling of glycolysis to oxidative phosphorylation by increasing the activity of glycolytic enzymes, including hexokinase, phosphofructokinase, and phosphoglycerate kinase, and the expression and activity of proteins involved in oxidative phosphorylation, including pyruvate dehydrogenase, aconitase, and ATP synthase (3,4). In contrast, loss of ovarian hormones, due to either reproductive senescence or to removal of the ovaries, induced a significant decline in glucose driven ATP generation and a shift to utilization of less efficient energy fuels in brain, ketone bodies (3,4). Surgical removal of the ovaries in young female rodents can induce impairment of mitochondrial function and bioenergetic capacity comparable to the aged brain (reviewed in Brinton (4)). Estrogen treatment, initiated at the time of the removal of ovaries or during the transition leading to reproductive senescence (perimenopause in the human), prevents decline in mitochondrial bioenergetic function in brain of both normal and transgenic Alzheimer's mouse models (reviewed in Brinton (3,4)). Consistent with findings in the animal model, menopause is associated with a decline in brain metabolism in women, whereas women who received hormone therapy sustained brain metabolism (reviewed in Brinton (3,4)). Furthermore, mitochondrial deficits and associated deficits in brain metabolism are significant risk factors for developing MCI and AD (reviewed in Yao et al. and Brinton (2–4)).

If decline in the bioenergetic capacity of the brain is an early or precipitating event in the development of age-associated cognitive decline and subsequent neurodegenerative disease, then sustaining the function and efficiency of glucose transport and metabolism, aerobic glycolysis, and oxidative energy production in brain is a reasonable therapeutic strategy (2). Preventing or treating the bioenergetic deficits that can cause or contribute to decline in the most bioenergetically demanding function of the brain, cognition, requires a systems biology therapeutic approach. From a prevention perspective, estrogen is a bioenergetic system regulator, which promotes multiple critical components of the entire system, from substrate supply to metabolism to catalysis and ATP generation (reviewed in Brinton (3,4)). Because estrogen promotes and sustains the entire bioenergetic system of the brain, we are developing brain selective estrogen alternatives, Phyto-β-SERMs, and NeuroSERMs that target promote the action of estrogen in brain without proliferative action in the uterus or breast (5,6) and which meet FDA approved indications for hormone therapy interventions, relief of vasomotor symptoms, treatment of vulvar and vaginal atrophy, and prevention of bone loss population.

From a clinical trial design perspective, targeting cognitive decline in normally aging women during the menopausal transition may have several advantages. Chief among them is a neurologically normal population with a risk of age-associated cognitive decline. Furthermore, there are well-characterized indicators of entry into the transition. Although there is an abundance of data indicating that a subpopulation of women experience cognitive deficits associated with menopausal transition (reviewed in Yao et al. and Brinton (2–4)), cognitive decline is not an FDA approved indication for hormone therapy for either women or men. However, the population of neurologically normal women undergoing the menopausal transition as part of normal aging who experience cognitive deficits could serve as a proof of concept study population to evaluate cognitive changes associated with aging, biomarker validity, and endophenotypes at risk for age-associated cognitive diseases such as Alzheimer's.

An FDA Perspective on the Approval of Drugs to Treat the Cognitive Decline of Normal Aging

This section summarizes the FDA perspective provided in Dr. R.K.'s presentation at the 2010 Cognitive Aging Summit. The legal definition of a "drug" not only includes those "articles included in the diagnosis, cure, mitigation, treatment, or prevention of disease" but also "articles (other than food) intended to affect the structure or any function of the body …" A drug does not need to treat a "disease" for regulatory agency approval. Still, the statutory standard of effectiveness requires "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." Thus, an approved label would need to describe the drug's clinically meaningful cognitive effects—whether that means a meaningful improvement in some aspect of cognitive performance in older people, slowing or delaying cognitive changes unrelated to the risk of age-related disorders like AD, and/or reducing the risk of age-related disorders. In general, the sponsor would need to demonstrate clinically meaningful cognitive effects using appropriate outcome measures and one would need to provide an adequate and accurate description of the cognitive "syndrome" being treated. Because a treatment's potential benefits must be weighed against its risks, a drug would need to be extremely safe for it to be considered for use in the general population. Among the relevant issues, one would need to consider benefits versus risks, including the magnitude of the clinical benefit, what is known or not known about potential risks, and the percentage of exposed individuals unlikely to receive any benefit. (Greater risks may be acceptable for a treatment shown to significantly reduce the risk of developing the symptoms of an age-related disorder like AD if the treatment is limited to individuals known to be at high risk for developing AD symptoms.)

To reiterate, FDA approval of a drug to treat the cognitive decline of normal aging is possible. The drug sponsor would

need to demonstrate the drug's clinically meaningful cognitive effects using appropriate outcome measures. The drug would need to be extremely safe (such that its potential benefits outweighed its risks). Finally, relevant social and ethical issues would need to be considered during and after the approval process. A "drug" does not need to treat a "disease" for regulatory agency approval. Still, any approved label would need to describe the drug's clinically meaningful cognitive effects—whether that is a meaningful improvement in some aspect of cognitive performance in older people, slowing or delaying cognitive changes unrelated to the risk of age-related disorders like AD, and/or reducing the risk of age-related disorders. In general, one would need appropriate outcome measures to demonstrate the clinically meaningful cognitive effect. Except in those known to be at extremely high risk for a preventable age-related disorder like AD, the drug should be extremely safe. Because any treatment's potential benefits must be weighed against its risks, a drug would need to be extremely safe for it to be considered for use in the general population.

Biomarkers for Aging Studies: What Have We Learned From AD?

In this section, Drs. R.C.P. and S.N. suggest lessons from the study of AD for the scientific study of cognitive aging, the prediction of subsequent cognitive decline, and the evaluation of cognitive aging treatments.

The field of AD research is embracing a theoretical model that postulates certain pathophysiologic events occurring in the development of AD (7). In particular, this model postulates that the amyloid protein is misprocessed and laid down early in the cascade of events and can be detected currently by either amyloid imaging or cerebrospinal fluid measures on Aβ42. It is likely that these events occur in the preclinical stages of the disease process. Next, after the amyloid has been deposited, there develops a neuronal injury, which can be detected by several modalities, structural magnetic resonance imaging (MRI), positron emission tomography with fluordeoxyglucose positron emission tomography (FDG PET), or cerebrospinal fluid tau levels. It is likely that this neuronal injury occurs in the early symptomatic state when individuals are in the MCI phase of the disease process. Only later does one start to see clinical manifestations of these early pathophysiologic events, and initially, memory impairment typically develops followed by other cognitive difficulties culminating in functional impairment. At this point, one labels the disease process as dementia because there is an impact of the cognitive changes on daily activities.

Although this model does not necessarily apply to normal cognitive aging, there may be lessons to be learned from this approach. In particular, if one was to design a clinical trial for healthy cognitive aging, a variety of factors would need to be considered including appropriate dependent measures, duration of trials, sample size refinement, use of surrogates, and the mechanism of action of the underlying therapy. Consequently, to the extent that any of these measures might relate to processes operative in AD, this comparison might be appropriate. For example, it is possible that, even in a trial of healthy cognitive aging, one could use MRI volumetric measures as an outcome. In a similar fashion, perhaps FDG or amyloid PET or perhaps fluid biomarkers in the cerebrospinal fluid, plasma or serum might be relevant. Finally, genetic predisposition can help subclassify participants for a healthy cognitive aging trial.

Recent research on certain cognitive endophenotypes could be relevant. A study investigating the gene *KIBRA* noted a relationship with human memory performance in typical aging (8). As such, if this or other genetic features could be used to subclassify participants, greater power and efficacy might be built into the trial.

Recent research on successful aging may also shed light on the issue of designing trials for normal cognitive function. Successful aging does not have an accepted clinical definition at present, but several models have been proposed. In the Mayo Clinic Study of Aging and Alzheimer's Disease Patient Registry, subjects have been recruited over a number of years and followed longitudinally for their cognitive outcomes. Although a certain proportion of these participants ultimately develop MCI and AD, there is another subgroup that remains essentially clinically stable throughout the course of aging. In general, one can envision three trajectories through cognitive aging: successful aging, typical aging and impaired aging leading to MCI, and dementia.

In the Mayo Clinic Study of Aging, cognitive function is assessed in four cognitive domains: memory, executive function, language, and visuospatial skills. Two or three individual cognitive tests are used to characterize a given cognitive domain, and normative data are available from our population on the individual measures, which then can be translated into normative data for the cognitive domains (9).

Dr. S.N. proposed three models of successful aging and assessed them with respect to their ability to predict outcomes (10). Model 1 used the top 10% of cognitive function using a global composite score of the cognitive measures score. Model 2 required all four cognitive domain scores to be in the upper 50% of the total distribution. Model 3 used a reversal strategy of age-associated memory impairment, whereby performance was gaged relative to normal performance of younger individuals. A total of 560 participants were evaluated in these three models, and 56 participants conformed to Model 1, 76 participants to Model 2, and 34 participants to Model 3. The models were then assessed with respect to their ability to predict survival. Model 1 was successful after the survival figures were adjusted for age, gender, and education ($p = .04$). Model 2 was not successful after the same adjustments at predicting survival ($p = .49$). Model 3, however, after adjustment, was able to predict survival, as well ($p = .04$).

Next, the models were assessed for their ability to predict cognitive impairment in the future. Using this type of survival analysis, Model 1 was able to predict subsequent cognitive

decline after adjustments for age, gender, and education ($p = .02$). Model 2 approached significance after adjustment and was nearly significant ($p = .06$). However, Model 3 was not successful after adjustment of predicting cognitive decline ($p = .38$).

As such, depending on the particular model that is chosen, successful aging criteria can be generated and validated against typical outcomes such as mortality and cognitive decline. Biomarkers that have been acquired in the study of AD may be useful in stratifying participants within various clinical classifications, such as successful aging, to further refine prediction models. This is a fertile area for future research.

Measurement Matters: Evaluating Interventions to Prevent Cognitive Decline

In this section, Dr. D.M. considers the psychometric challenges, methods, and endpoints needed to evaluate treatments to prevent the cognitive declines associated with aging and its disorders.

Cognitive decline in older populations is a major cause of disability that adversely impacts individuals, their families, their communities, and society in general. Intervention studies to identify effective treatments to prevent or slow cognitive decline are an important part of efforts to mitigate the adverse effects of cognitive decline. Measurement of cognitive function is central to the assessment and treatment of older persons experiencing cognitive decline. Sensitive measurement across the full range of cognitive ability is critical for early identification that can lead to intervention to prevent irreversible brain injury as well as for monitoring the natural course of cognitive change and response to prevention and treatment interventions.

There are a number of challenges for measuring cognition in intervention studies. First, tests must be able to track change from normal function to dementia. This is not trivial because normal function spans several standard deviations, particularly in demographically diverse populations, so that an effective test must have consistently high reliability across a broad range of ability. Second, floor and ceiling effects can prevent effective measurement. Ceiling effects are common in neuropsychological tests and limit sensitivity to early manifestations of disease. Floor and ceiling effects also result in nonlinear measurement, which means that the measured change may not accurately reflect true change. Of greatest concern, a person may actually be declining, but test scores do not change appreciably because of measurement limitations. This kind of nonlinear measurement has been well-documented for widely used tests of global cognition including the Mini-Mental State Examination (11) and the Alzheimer's Disease Assessment Scale—Cognitive (12).

Psychometric methods have progressively evolved because the pioneering efforts at intellectual assessment beginning in the early 20th century. The development of theory and methods related to item response theory beginning the 1950s provides an important foundation for improving measurement of cognition in treatment studies. Traditional psychometric methods provide limited information about a measure's reliability and validity for a specific use. In particular, a high global reliability coefficient does not necessarily mean that there will be high measurement precision in different ranges of ability. For example, the Mini-Mental State Examination and Alzheimer's Disease Assessment Scale—Cognitive have high global reliability coefficients but have limited ability to detect early decline in individuals with high premorbid abilities. Modern psychometric methods associated with item response theory yield comprehensive information about reliability or precision of measurement across the entire ability continuum and can help to identify these problems.

Being able to characterize a test's sensitivity to change at all points on the ability continuum facilitates matching of the psychometric properties of the test to the measurement needs for a study. An intervention targeting early cognitive change will require tests that are sensitive to change across the broad range of normal and mildly impaired function. Modern psychometric methods can be helpful in identifying existing tests with desired properties but also can be used to develop new tests with improved measurement properties. This involves an iterative process in which new items are developed or existing items are combined to measure conceptually relevant abilities, empirical data is used to evaluate the psychometric properties of these tests, and the tests are progressively refined to achieve the desired psychometric goals. In this way, tests can be optimized for the intended measurement purpose and linear measures without floor and ceiling effects can be created to accurately track change. Measure development can be based on existing tests (13), and new tests can be created and tailored to specific measurement needs (14). An important caveat is that modern psychometric methods cannot compensate for an inadequate item pool, although they can be used to evaluate and systematically improve the utility of the item pool for the desired measurement purpose.

In conclusion, treatments for early cognitive decline are likely to be increasingly important in coming years as the aging population grows. Clinical trials to evaluate these treatments will be dependent on effective cognitive outcome measures. Traditional cognitive tests often have limited sensitivity at higher ability levels, which interfere with measuring the earliest cognitive changes that may be most amenable to treatment interventions. Modern psychometric methods can be used to characterize psychometric properties of existing tests, create improved measures from existing tests, and create new tests with desired measurement characteristics.

A Challenge to the Cognitive Aging Research Community

In this section, Dr. P.S.A. notes that the benefits of any drug treatment should outweigh its potential risks, and he

challenges researchers to further characterize the cognitive decline associated with normal cognitive aging they consider the development of investigational drug treatments for this condition.

In thinking about the development of therapeutic interventions, cognitive aging must be distinguished from age-associated diseases of cognition. The latter include AD as well as other neurodegenerative and vascular disorders associated with cognitive impairment; the later stages of such disease are marked by the loss of function associated with dementia. These disorders, among the most feared consequences of aging, clearly warrant major efforts at therapeutic intervention. On the other hand, it is not clear that cognitive aging should similarly be a target for drug development.

The manifestations of cognitive aging include slowed processing speed, constricted working memory, and word finding difficulties. These changes are obvious to most individuals past middle age and are certainly bothersome to many. But I have not seen compelling evidence that they impede function. Indeed, the literature suggests that these declines may be counterbalanced to an extent by aspects of cognition that improve with age, including wisdom and experience. In the absence of a specific disease affecting cognitive function, age-related cognitive decline may not significantly impair quality of life. An important requirement for drug approval is the demonstration that impact on symptoms provides clinically meaningful benefit. It is not yet clear that treatment of age-related decline can provide such benefit.

Aging, of course, has deleterious effects on most organ systems. Sarcopenia is an example of age-related dysfunction that can significantly impair capacity to maintain daily activities. But most would question the wisdom of pharmacotherapy for age-related sarcopenia; rather, physicians encourage exercise to build muscle strength and restore optimal function. Similarly, most physicians embrace recommendations to maintain brain function through cognitive exercise, but many would question drug development for this purpose. Even if a cognitive stimulant were shown to improve aspects of memory and processing speed in aging individuals, I believe that more evidence is needed to suggest that there would be clinically important benefits that would justify the risk of medication. In contrast to the enormous need to expend resources on the development of therapeutics to prevent or slow AD, drug development efforts targeting normal cognitive aging may be misguided.

For these reasons, Dr. P.S.A. argues that the field needs to provide more compelling evidence of the clinically meaningful nature of the cognitive declines associated with normal aging prior to targeting those declines with therapeutic interventions. At the same time, I would acknowledge the possibility that treatments targeting relevant aging processes, whatever they may be, might have the clinical benefit of reducing the risk of age-related disorders like AD and CVD.

Recommendations to Advance the Discovery and Evaluation of Treatments for Cognitive Aging

In this section, Dr. E.M.R. offers several recommendations to help advance the scientific understanding of neurocognitive aging and the discovery and evaluation of treatments for neurocognitive aging and its disorders.

When it comes to the development of treatments for neurocognitive aging, it would help to clarify exactly what one intends to treat. Potential indications include an improvement in cognitive performance, an attenuation in cognitive decline, and/or a reduction in the risk of an age-related disorder. Also critical to clarify is whom one intends to treat. A treatment intended to improve cognitive performance might do so in everyone, in those who experience age-related cognitive decline, whether or not they have preclinical biomarker evidence of AD, CVD, or another age-related disorder, or only in those with risk factors for or preclinical biomarker evidence of a particular disorder. Similarly, a treatment intended to improve cognitive performance might have the potential to do so in everyone who experiences age-related cognitive decline, whether or not they have preclinical biomarker evidence of one or more age-related disorders, or only in those with risk factors for or preclinical biomarker evidence of a particular disorder.

Of course, it would also help to demonstrate the treatment's clinical benefit. Among other things, the field currently lacks (i) sensitive and suitable cognitive and functional endpoints (to assess the cognitive changes associated with normal aging, alone or in combination with the preclinical stages of AD or CVD), evidence to suggest that a treatment's cognitive and/or functional effects are "clinically meaningful," and (ii) the evidence needed from rigorously performed randomized clinical trials to make a compelling case that the treatment's benefits outweigh its risks. To design the relevant randomized clinical trials, the field needs sample size estimates, taking into consideration the targeted research participants, the intended treatment duration, whether the treatment is intended to improve cognitive performance or to slow down or postpone the onset of cognitive decline.

At a more fundamental level, the field needs to further develop, test, and apply biomarkers of normal brain aging, including those unrelated to presymptomatic AD and CVD pathology, to further characterize modifiers of neurocognitive aging and clarify their relationship to the biomarker changes associated with age-related disorders like AD and CVD. Promising brain imaging measures of normal neurocognitive aging—including but not limited to declines in frontal glucose metabolism (15), gray matter and white matter integrity (16,17), and dentate gyrus blood volume (18)—could be used as endophenotypes (biological measurements more closely related to brain aging than cognitive decline itself) to evaluate factors that modify the rate of neurocognitive aging and whether they conspire with other risk factors in the predisposition to age-related brain disorders

(19). They could also be used to help clarify the extent to which putative cognitive aging treatments slow the processes associated with normal aging and/or the predisposition to age-related disorders. Because certain brain regions appear to be preferentially affected by normal aging processes, different brain regions could be compared in the same expired brain donors to further characterize the molecular substrates of normal aging, providing targets at which to aim new treatments (20).

Biomarkers could also be used to clarify the magnitude, pattern, and clinically meaningful nature of age-related cognitive decline in individuals without substantial evidence of AD and CVD pathology. If it could be shown, as many but not all researchers believe, that these cognitive declines are clinically meaningful, that information would help galvanize the study, as well as the discovery and evaluation of treatments for neurocognitive aging. Further, if it could be shown that slowing the biomarker changes associated with normal cognitive aging also slows down or postpones the onset of biomarker or clinical changes associated with age-related brain disorders, research and development of treatments that target normal aging processes would gain greater clinical relevance. Finally, biomarkers of normal aging and age-related disorders could be used to provide selection criteria, predictors of differential treatment response, and endpoints to help evaluate treatments for these conditions. For each of these reasons, there should be a concerted effort to further develop the biomarkers associated with normal aging, clarify the differential contributions of normal aging, AD and CVD to cognitive decline in older adults, and standardize these measurements for potential use in clinical trials.

In general, the field would benefit from a better understanding of the biological and cognitive changes associated with normal aging and how they conspire with other risk factors in the predisposition to age-related disorders; the further development and use of biomarkers to characterize the differential contributions of aging and age-related diseases to cognitive decline and the effects of cognitive aging treatments; and the development of clinically meaningful cognitive and biomarker endpoints to enable systematic evaluation of cognitive aging treatments.

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