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Perspective

Recommended cognitive outcomes in preclinical Alzheimer's disease: Consensus statement from the European Prevention of Alzheimer's Dementia project

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Abstract The Horizon 2020/IMI European Prevention of Alzheimer's Dementia (EPAD) project will undertake large-scale proof-of-concept trials in predementia Alzheimer's disease (AD). Within EPAD, the monitoring of cognitive trajectories in the preclinical period will constitute a central outcome measure; however, there are currently no clear guidelines as to how this should be achieved as most measures have been developed for the period around dementia diagnosis. The EPAD Scientific Advisory Group for Clinical and Cognitive Outcomes identified appropriate cognitive measures based on a literature search covering both cognitive correlates of preclinical brain changes from imaging studies and cognitive changes observed over time in nondementia population cohorts developing incident dementia. These measures were evaluated according to the following criteria: validity, coherence with biomarker changes, psychometric properties, cross-cultural suitability, availability of alternative forms, and normative data limited practice effects. The resulting consensus statement provides recommendations for both future drug trials and research into preclinical Alzheimer's disease.

Keywords: Alzheimer's disease; Preclinical; Cognition; Neuropsychology

1. Background

Increasing evidence from both epidemiologic and biomarker studies suggests that not only does exposure to the principal risk factors for late-onset Alzheimer's disease (AD) occur earlier in life [1,2], but also that pathophysiological changes may also be observed in genetically at-risk persons many decades before dementia onset [3–6]. These findings suggest firstly that Alzheimer's disease may be a clinically silent disorder of mid-life whose terminal phase is characterized by dementia [7] and secondly that the preclinical stages of the disease may constitute an earlier and potentially more effective window for intervention. It is against this background of our changing conceptualization of AD that the European Prevention of Alzheimer's Dementia (EPAD) program was initiated in

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2015 [8]. This project is currently developing a platform for large-scale proof-of-concept trials in predementia AD. Cognitive loss is the central defining feature of AD, and the reason for which treatment is sought; AD without behavioral consequences being of little clinical interest. The tracking of cognitive trajectories in the predementia period thus constitutes a central outcome measure. The principal dilemma in this context is that current theoretical models of predementia change extrapolated from multiple clinical observations [9,10] have hypothesized that the biomarker changes which commonly characterize AD occur long before cognitive changes; the latter being detectable only around the time immediately preceding the diagnosis of AD dementia. Although a more recent model derived from empirical observations has suggested that cognitive decline begins up to a decade before dementia diagnosis with acceleration after increase in amyloid-beta accumulation [11], there is little current knowledge of either the scope of these preclinical cognitive changes or the most appropriate testing procedures for capturing them.

Within the EPAD Project, an International Scientific Advisory Group (SAG) has been constituted to explore this largely uncharted territory and to advise on the feasibility of capturing preclinical cognitive signals by reference to an evidence-based analysis of existing observations and neuropsychological knowledge of the likely behavioral correlates of predementia brain changes. The consensus meetings aimed further to identify appropriate clinical domains in relation to probable distance from dementia diagnosis and to recommend suitable testing procedures. The outcome of the work undertaken by this group as presented here will not only underpin the outcome measures used within this large European trials platform but may also inform future clinical research into predementia AD by filling current gaps in our knowledge of this important area.

2. Methods

2.1. The clinical and cognitive outcomes Scientific Advisory Group

The group was constituted with the principal aim of advising on appropriate cognitive outcomes for both a longitudinal cohort study from which high AD-risk participants could be recruited, and for proof-of-concept trials targeting persons with preclinical and prodromal Alzheimer's disease. Within the context of the EPAD project, prodromal Alzheimer's dementia is considered to be the period immediately before Alzheimer's dementia diagnosis characterized by mild cognitive impairment (MCI) and preclinical as a preceding clinically silent phase with both phases being additionally characterized by abnormalities on AD-related biomarkers. The group members are K.R., M.R. (co-chairs), B.A., J.H., J.Ka., J.K., and C.R. C.W.R. is co-coordinator of EPAD and principal investigator of the EPAD Longitudinal Cohort Study (LCS) [8] providing linkage between the advisory group and the overall study design. Group members were selected on the basis of their academic qualifications in neuropsychology and/or behavioral neurology, international track record in cognitive research, experience in clinical trials in AD, competence in psychometrics and biostatistics, and experience in AD neuropsychological test development. The EPAD project will have two settings where research participants will be tested, the EPAD LCS and the EPAD proof-of-concept (PoC) study. The cognitive data captured in the EPAD LCS will be used as run-in data for the PoC, and hence, the LCS cognitive outcome represents the primary outcome for the PoC study. For this reason, the work of the clinical and cognitive outcomes Scientific Advisory Group (CCO-SAG) was heavily scrutinized by the entire EPAD consortium.

2.2. Description of the work program

Both research and clinical trials in AD have been highly heterogeneous in their choice of clinical and cognitive outcomes and even more diverse in the type of measures used to capture and quantify them. This heterogeneity has reflected not only the constant evolution of scientific knowledge about brain functioning and its functional correlates but also commercial interests, personal preferences, subject tolerance, and concerns over acceptability to regulatory authorities. Within this context, the EPAD project presented two further challenges:

1. The outcomes refer to a wider range of preclinical markers extending to a greater distance from clinical AD diagnosis than has been attempted in previous trials
2. That given competing industrial interests, the outcome measures should be seen to be scientifically objective and unlikely to favor a specific trial sponsor

Given these issues, it was considered essential to base the work of the group on established research with evidence-based recommendations founded on an objective review of current knowledge in the area of preclinical behavior and its measurement. It was agreed to work from empirical evidence only and not personal test preferences despite the extensive clinical experience of group members, drawing up tables to permit comparisons across tests and defining a priori criteria for test selection. The work of the SAG was thus divided into four distinct phases:

1. A review of publications relating to cognitive changes in the predementia period was carried out (Mortamais et al. 2015 submitted) based on the PubMed database using MeSH terms and keywords from previous reviews (preclinical, Alzheimer, neuroimaging, positron emission tomography, amyloid beta, cognition, cognitive, and neuropsychological tests). The studies examined demonstrated either cognitive correlates of preclinical brain changes from imaging studies or

cognitive changes observed over time in nondementia population cohorts developing incident dementia diagnosed by internationally recognized algorithms. Only studies referring specifically to the preclinical phase were included; prodromal groups were also excluded unless they were mixed prodromal/preclinical. Studies using only screening tests and not recognized cognitive tests targeting specific cognitive functions were excluded.

2. By reference to the literature review, the cognitive domains were identified which showed changes within the trajectory from first biomarker changes (preclinical AD) to MCI here referred to as prodromal AD.
3. To determine which neuropsychological tests best demonstrate changes in these domains in the predementia period and compare them according to their relative discriminability and psychometric properties according to the following criteria:
   a. Validated in relation to either preclinical, apolipoprotein status, or amyloid levels
   b. Psychometric properties (temporal reliability, normality of score distributions, and so forth)
   c. Cross-cultural suitability
   d. Availability of validated alternative forms
   e. Availability of normative data
   f. Limited practice effects
4. To make recommendations for neuropsychological testing within the predementia period which would be appropriate for clinical trials.

3. Results

3.1. A review of current knowledge relating to cognitive changes in the predementia period

The search revealed both cross-sectional and longitudinal studies. Although the longitudinal studies were more likely to capture a preclinical decline, the follow-up periods were highly varied (6 months to decades); however, where results were inconsistent between cross-sectional and prospective studies, we gave priority to longitudinal findings. The term "preclinical" was found to be defined in many different ways across studies and was therefore limited by the SAG to studies of normally functioning persons considered to be at high risk of AD due to either (1) being an autosomal dominant AD mutation carrier, (2) at genetic risk for late-onset AD (Apolipoprotein E ε4 carriers), (3) amyloid load, (4) presence of suspected non-Alzheimer pathology (neurodegeneration markers without evident amyloidosis), or (5) subsequently developing incident AD within prospective studies. These at-risk groups clearly have different probabilities of evolving toward dementia but are complimentary. Prospective population studies with incident cases of AD have the highest certainty of having covered a preclinical phase but are often limited by the range of cognitive tests used and long periods between follow-up so that date of onset can only be estimated as falling between a certain number of years. APOEε4 carriers have been intensively studied in terms of imagery, biomarkers, and cognitive testing but have in many studies not been followed up to diagnosis, and furthermore, it has long been recognized that a significant number of AD cases do not carry the allele [12], and whereas brain biomarker studies have provided intensive phenotyping, the follow-up periods have tended to be short. The review revealed above all else the great heterogeneity in definitions of cognitive domains, the cognitive tests used, study design, and adjustment variables, such that meta-analysis was considered inappropriate.

A concern of the SAG was that the neuropsychological tests which have been principally used in preclinical AD research have been those previously used to differentiate MCI and early dementia and may be less sensitive to behavioral correlates of very early biomarker change. There has been a tendency to focalize in particular on the episodic memory functions of the hippocampal formation while neglecting its other pivotal roles, notably in spatial navigation, spatial memory, and the integration of spatial location with episodic memory [13] which are directed in particular by the posterior hippocampal, entorhinal cortex, precuneus, and retrosplenial cortex; the regions in which both tau and Aβ pathology both initially co-occur [14–16]. The studies considered were therefore extended to include research within the cognitive neurosciences which had developed cognitive measures of these specific brain areas but not necessarily directed toward diagnosis of dementia.

Experimental measures developed within cognitive psychology laboratories designed to specifically target analysis of allocentric and egocentric space, and sensitive to change in the posterior hippocampus, entorhinal cortex, and parietal areas were thus examined by the group on the basis that they may be better able to detect very early biomarker changes than currently used testing methods. Preliminary research with these tests has already indicated a much higher sensitivity in this context than many currently used cognitive tests, being able to differentiate for example mild cognitive impairment with and without CSF biomarker changes, and AD from early frontotemporal dementia [17,18].

3.2. Determination of cognitive domains likely to be affected along the trajectory from biomarker change to MCI

Previous studies which were able to show differences in cognitive performance in the preclinical period were subsequently classified by cognitive domain. Given that cognitive tests are non-specific (that is they are sensitive to capacities other than the one they may have been specifically designed, for example, an episodic verbal memory test will also depend on auditory and/or visual attention, visuospatial analysis, executive functions) a given cognitive domain was only considered to be implicated if demonstrated by more than one testing procedure independently of other

cognitive functions. Overall significant differences between normal and preclinical participants could be detected in the following domains: attention, information processing time, working memory, verbal and non-verbal episodic memory, paired associate learning, visuospatial analysis, semantic retrieval capacity, verbal and non-verbal reasoning, and various components of prefrontal functioning often collectively referred to as executive functions (conceptual knowledge, conceptual shifting, cognitive control).

The hypothetical distance from dementia diagnosis was taken as defined within the relevant publications, corresponding to either time-to-diagnosis from baseline in prospective studies or the time between current age and recorded age of onset in a parent. The group observed that whereas almost all cognitive domains appear to differentiate preclinical groups within 5 years to dementia diagnosis [19,20] in preceding decades fewer cognitive domains show sensitivity, with episodic memory, executive skills, information processing speed, and visuospatial analysis being of greater importance [21,22]. This suggests that the selection of cognitive tests for a given study may need to take into account probable distance from dementia onset if this can be estimated.

3.3. Determining which tests show ability to demonstrate changes in these domains in the preclinical period and comparing them according to their relative discriminability and psychometric properties

Within each cognitive domain, previous studies have used a very wide range of testing procedures. The ability of these tests to demonstrate preclinical differences in either biomarker positive persons or future cases of clinically diagnosed dementia not only varied greatly between tests but also the same test was found to vary in discriminability between different studies. For example, the CVLT was found to differentiate persons with high or low amyloid load when the Pittsburgh compound B uptake index was used but not in studies assessing amyloid through visual ratings [23,24].

From the very large panel of testing procedures which have been used and shown to produce a signal in preclinical cohorts, SAG members discussed and compared the relative merits of different tests according to validation criteria, psychometric properties, cross-cultural suitability, availability of alternative forms, availability of normative data, and practice effects. On the basis of these criteria, a final list of tests was selected which was felt to adequately cover all domains likely to be implicated (Table 1). Each test was required to meet the first validity criterion and then scored by group members (yes/no) according to each of the other criteria, which were considered secondary. Cross-cultural suitability was subjectively assessed according to the clinical experience of the group. The different ratings given by members were compared, and where several tests were considered equally performant, further criteria were considered (alignment with imaging markers, ceiling and floor effects, providing both accuracy and processing time measures, validation of computerized versions, possibility of easily creating parallel forms if these did not exist). In addition, tests were chosen with consideration for whether a test would integrate well within a total battery administration time of around 1 hour. The decision process took into account both scientific and pragmatic considerations. For example, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) version of several types of test was chosen for some domains given that while being psychometrically equivalent to other tests of the same function, they already provided multiple parallel forms and cross-cultural validation in most European languages. Similarly, several tests were chosen from NIH examiner above similar and equally performant tests due to availability of validated computerized versions.

3.4. Recommendations for neuropsychological testing within the predementia period which would be appropriate for population and clinical research, as well as clinical trials

The final cognitive domains and corresponding tests listed below were selected by the CCO-SAG to provide an evidence-based combination of procedures highly likely to detect preclinical AD changes across time within the context of the EPAD clinical trials. These tests are presently all available in validated computerized format and will be integrated within a single battery for use in both the EPAD longitudinal cohort study and proof-of-concept trials. The tests were agreed by the entire EPAD consortium including all academic and EFPIA (European Federation of the Pharmaceutical Industries and Associations) representatives.

1. Reaction time/information processing speed/conceptual shifting/selective attention
   a. Flanker (NIH examiner/toolbox)
      The Eriksen flanker task is a set of response inhibition tests used to assess the ability to suppress responses that are inappropriate in a particular context. The target is flanked by nontarget stimuli which correspond either to the same directional response as the target (congruent flankers), to the opposite response (incongruent flankers), or to neither (neutral flankers). In the tests, a directional response (usually left or right) is assigned to a central target stimulus. Various forms of the task are used to measure information processing and selective attention.
   b. Coding (RBANS)
      The coding test is a measure of brief, focused, visual attention, visual scanning and processing speed. The subject must rapidly draw simple designs associated with a specific number. Accuracy and speed are recorded.

Table 1
Cognitive tests detecting change in the preclinical phase of AD

Test	Cognitive domain	Test–retest reliability (r)	Parallel forms	Preclinical criteria*
Four Mountains Test† [17]	Allocentric spatial orientation spatial memory	Assessed with retest at 28 days. Cohen's d statistic = 0, indicating no practice effect with that test interval	Multiple	Amyloid burden and APOEε4
(Rey) Auditory-verbal learning test [25]	Verbal episodic memory	0.6–0.7	1	Amyloid burden
Benton visual retention test [26]	Visual episodic memory	Number correct = 0.57 number of errors = 0.53–	1	Prospective to AD diagnosis
California verbal learning test [27,30]	Verbal episodic memory learning	0.82 for learning trials, 0.88 for long delay recall, 0.86 for recognition	1	Prospective to AD diagnosis brain biomarkers
Category fluency† [28]	Semantic processing planning	≥0.7 for short (e.g., 1 week) as well as long (e.g., 5 years) intervals	Multiple	Prospective to AD diagnosis
Coding (RBANS)† [29]	Episodic memory/psychomotor speed	0.83 (39-week interval)—practice effect: Cohen's d = 0.34	4	Amyloid burden
Digit ordering test [31]	Working memory			Amyloid burden
Digit span (RBANS)† [32]	Working memory	0.63 (39-week interval)	4	Amyloid burden
Digit span forward and backward WAIS [25]	Working memory	35 days interval. Average stability coefficient in the 0.80s		Amyloid burden
Digit symbol [25]	Episodic memory/psychomotor speed			Prospective to AD diagnosis
Dot counting NIH examiner† [33]	Working memory	6-item = 0.65	3	Prospective to AD diagnosis
East Boston memory test [30]	Episodic memory			Prospective to AD diagnosis
Face-names associations† [34]	Episodic memory/spatial and episodic memory binding	Interval of 1 year—FN—name, 0.49–0.61		Amyloid burden
Figure copy (RBANS)† [31,38]	Visuospatial analysis	0.54 (39-week interval)	4	Amyloid burden
Figure recall (RBANS) [38]	Episodic memory	0.55 (39-week interval)—practice effect: Cohen's d = 0.37	4	Amyloid burden
Flanker toolbox/examiner† [33]	Shifting/cognitive control	0.88	multiple	Prospective to AD diagnosis
Flanker RT examiner† [25]	Processing speed	0.92	multiple	Amyloid burden
Free and cued selective reminding test [35]	Episodic memory	Between alternate forms 0.48 to 0.85	4	Prospective to AD diagnosis
Isaac set test [37]	Semantic retrieval			Prospective to AD diagnosis Amyloid burden
Judgment of line orientation [30]	Visuospatial analysis	Results vary from 0.59 to 0.90 for retest reliability—no practice effect		Prospective to AD diagnosis
Letter fluency (RBANS)† [38]	Semantic retrieval	≥0.7 for short (e.g., 1 week) as well as long (e.g., 5 years) intervals		Amyloid burden
Line orientation (RBANS)† [38]	Visuospatial analysis	0.49 (raw scores; 39-week interval)—practice effect: Cohen's d = 0.11	4	Amyloid burden
List learning (RBANS)† [38]	Episodic memory	0.52 (39-week interval)—practice effect: Cohen's d = −0.10	4	Prospective to AD diagnosis, Brain biomarkers
List recall (RBANS)† [38,39]	Episodic memory	0.60 (raw scores; 39-week interval)—practice effect: Cohen's d = −0.16	4	Brain biomarkers
List recognition (RBANS)† [38,39]	Episodic memory	0.27 (raw scores) (39-week interval)—practice effect: Cohen's d = 0.30	4	Brain biomarkers
Face/name associations† [40]	Episodic memory			
One card learning cogstate [41,42]	Visual memory			Brain biomarkers
Picture naming (RBANS)† [38,39]	Language/semantic processing			Amyloid burden

Table 1
Cognitive tests detecting change in the preclinical phase of AD (*Continued*)

Test	Cognitive domain	Test–retest reliability (r)	Parallel forms	Preclinical criteria*
Raven's standard progressive matrices [30]	Visuospatial reasoning	0.50 (raw scores; 39-week interval)—practice effect: Cohen's d = −0.22	4	Brain biomarkers
Rey-Osterrieth complex figure test [43]	Visual episodic memory	From 0.70 to 0.90	no	Amyloid burden
Semantic fluency† (RBANS) [38,39]	Semantic retrieval			Amyloid burden
Story memory (RBANS)† [21,38,39]	Episodic memory	0.52 (39-week interval)—practice effect: Cohen's d = 0.03	4	Brain biomarkers
Story recall (RBANS)† [21,38,39]	Episodic memory	0.80 (39-week interval)—practice effect: Cohen's d = 0.42	4	Brain biomarkers
Supermarket trolley virtual reality† [18]	Egocentric space	0.72 (39-week interval)—practice effect: Cohen's d = 0	4	Brain biomarkers
Symbol digit modalities test [34,22]	Episodic memory/psychomotor speed	In progress	multiple	Amyloid burden
Trail making test [37]	Planning/shifting			Prospective to AD diagnosis
Visual attention cognito [44]	Working memory			Prospective to AD diagnosis
Wechsler memory scales		0.62 (1 month)	No	Prospective to AD diagnosis
Logical memory [43]	Episodic memory			
Logical memory II [33]	Episodic memory	0.7–0.8		Amyloid burden and APOEε4
Logical memory story A [29,43]	Episodic memory	0.7–0.8		Amyloid burden
Similarities test [36]	Conceptual knowledge	0.7–0.8		Prospective to AD diagnosis
Word list memory CERAD [45]	Episodic memory			Prospective to AD diagnosis

*Amyloid burden = one or more studies showed the cognitive measure was able to differentiate levels of amyloid accumulation; APOEε4 = one or more studies has shown that the cognitive test is able to differentiate persons with and without an APOEε4 allele; prospective to AD diagnosis = one or more studies has shown that the test is able to significantly identify the group of non-symptomatic participants in a prospective study who are given an AD dementia diagnosis at follow-up; brain biomarkers = one or more studies has shown an association between test performance and a brain biomarker change.
†Testing procedures selected for EPAD.

2. Verbal episodic memory
   a. List learning (RBANS)
      List learning measures rote verbal memory for unrelated information. The subject hears a list of 10 unrelated words and must repeat the words back to the examiner. The word list is presented to the examinee a total of four times evaluating ability to learn verbal information after repeated exposure. After a delay with intervening tasks, the task is repeated over three further trials.
   b. Story memory (RBANS)
      The task measures memory for conceptually related verbal information. The subject hears a story that is two sentences in length and must repeat the story back to the examiner. The subject hears the story two times to assess learning. After a delay with intervening tasks, the story is recalled to assess long-term verbal memory encoding and retrieval.
3. Visuospatial analysis
   a. Figure copy (RBANS)
      The figure copy task requires the copying of a complex geometric design from a model implicating visuospatial reasoning, attention to visual details, motor programming, and to a lesser degree, organization, and fine-motor ability. The figure is redrawn without prior warning after a delay from memory to measure long-term free recall for conceptually related visuospatial information and incidental memory (i.e., memory for information that was encoded without specific effort to do so.
   b. Line orientation (RBANS)
      The line orientation task assesses ability to correctly identify the angle and spatial orientation of lines in two-dimensions. The subject is presented with 13 lines fanning out in different directions which they are required to differentiate according to angle.
4. Language
   a. Picture naming (RBANS)
      The picture naming task measures confrontation naming skills. This is a direct assessment of expressive language skills often impaired in global and specific types of aphasia, specifically dysnomia. The subject is shown 10 drawings of common objects and asked to name each one. The drawings are simple line drawings to avoid any perceptual confusion that more complex drawings may create.

b. Semantic fluency (RBANS)
The semantic fluency task measures the subject's ability to retrieve and express words using a semantic prompt. This is a direct assessment of expressive language skills and semantic access. The examinee is asked to say as many words as possible associated with a specific category of objects within a fixed time limit.

5. Working memory
   a. Digit span (RBANS)
   The digit span subtest is a measure of auditory registration and brief focused attention requiring simultaneous retention of letter order both forward and backward. The subject listens to a series of digits read out by the examiner at one per second (e.g., 2–9) and is asked to repeat the digits in reverse order.
   b. Dot counting (NIH EXAMINER/Toolbox)
   This verbal working memory task is presented on a computer screen as a mixed array of green circles, blue circles, and blue squares, and the subject is instructed to count all the blue circles on the screen and remember the final total. The examiner then switches the display to a different mixed array of green circles, blue circles, and blue squares. The subject is instructed to count the blue circles in the new display. The number of different displays presented to the examinee in each trial increases from two to seven over six trials. After counting the blue circles on all the displays presented within a trial, the subject recalls the total number of blue circles in each of the different displays in the order in which they were presented.
6. Allocentric space: Four Mountains Task (University College London and Cambridge University)
   This test assesses linkage between the episodic and spatial functions of the hippocampus which permits representation of spatial information in an allocentric form and hence encoding of the context in which events occur. Computer-generated landscapes comprised of four hills (of varying shape and size) surrounded by a distant semicircular mountain range are presented with a sample image for 10 seconds following which the subject is immediately presented with four alternative images, one of which (the target image) shows the same topography as the sample image, seen from a novel viewpoint, from which they must identify the target image by pressing a key. Non-spatial features (lighting, vegetation, weather conditions) of both target and foil landscapes are varied between presentation and testing, such that transient local features of the image cannot be relied on to solve the task.
7. Paired-associate learning: Favorites (NIH examiner/toolbox)
   The face word associative memory task is a behavioral version of a cross-modal associative memory test based on an fMRI task that pairs pictures of unfamiliar faces with common words. The test is a refinement of the Face-Name Association test, requiring the more difficult task of learning associations with random words from two categories, thus reducing ceiling effects in normal populations. The test consists of an initial learning phase, immediate cued recall, delayed cued recall, facial recognition, and a multiple choice recognition trial.
8. Navigation in egocentric space: Virtual reality supermarket trolley (Cambridge University)
   This test which is sensitive to deterioration in the precuneus, retrosplenial cortex, and entorhinal connections measures egocentric spatial orientation (as opposed to allocentric space) through presentation of 14 video vignettes in an ecological virtual supermarket from a first-person perspective. A route through the supermarket in which the participant is behind the trolley involves series of 90° turns, and at the end, the subject is required to point in the direction of the entry.

Most of these tests generate several scores such as correct and incorrect responses, response time, error type, field neglect, and so on, which should be selected according to the research protocol or drug trial in which they are used. Recommendations for principle outcome measures have therefore not been proposed.

4. Discussion

An international panel with recognized expertise in experimental and observational research as well as clinical trials in AD has made accepted recommendations for multi-domain testing based on current evidence derived from brain biomarker and population studies of preclinical AD and experimental cognitive psychology focusing on hippocampal structures. Although the advisory group has indicated domains of cognitive functioning and associated testing procedures which appear on the basis of previous research to appear sensitive to changes in preclinical AD, the choice of a primary outcome measure derived from these tests must be tailored to the drug target or research hypothesis of a given study. Within the EPAD project, for example, an RBANS total score has been taken as the primary outcome and the remaining tests as secondary outcomes, as this alternative represented the best compromise between sensitivity to change over time in a clinical range from preclinical to prodromal, statistical caveats, and regulatory body acceptability within a phase II trial. This may not necessarily be the best choice in other contexts.

Our recommendations are primarily intended for interventional clinical trials that involve investigational compounds, multimodal interventions, or products which not

only have to meet the rigors of good science but must also adhere to regulatory requirements and standard practices of pharmaceutical or biotechnology companies. Although there may be differences in trial design and implementation depending on the investigational product, the company, and the country or region for the investigation, there are actually some basic issues that generally should be adhered to or accounted for when investigating products that might treat or modify the disease course of AD. The patient population of interest has already been defined by EPAD as ranging from preclinical AD to prodromal or mild cognitive impairment due to AD. Although the identification of AD-related biomarkers at study start or baseline and their longitudinal course throughout the duration of the treatment phase will serve as an important parameter, it is quite clear that the primary or key efficacy outcome will be cognitive in nature. The first issue is to ensure that there is sufficient historical data for the primary cognitive tests showing the changes in the target patient population over what will be the treatment duration in terms of percentage and absolute change as well as the associated variance for the nontreated individuals or those that would receive the established standard of care. Access to cognitive testing performance data in relation to candidate biomarkers from existing studies will be essential for the calculation of sample sizes. The other two components required for the sample size calculation are the absolute or percentage change from baseline that would be considered as clinically meaningful as well as what minimal treatment effect or difference between a placebo or nontreatment group would be required for those receiving the investigational product over the treatment period. Both of these parameters will be specific to the actual cognitive testing that is used, and these data are required before the initiation of any clinical study.

Although there are numerous cognitive test instruments that have been used in many hundreds of studies, there are relatively few that have been carefully scrutinized and evaluated by the regulatory health authorities (HAs). Even those cognitive tests that have found their way into clinical trials of investigational products have often not been fully reviewed and/or critiqued by the HAs, as the trials were probably early in the compounds development and would have been viewed at best as exploratory or informative but not of registration or approval quality. Many of the cognitive assessments investigated in the earlier stages of AD depend on relatively small changes in such parameters as reaction time or speed of response, often in milliseconds or in one or two more items properly recalled. Both the HAs and their advisors who are usually key opinion leaders in the AD area are looking for assessments that have some degree of "face-validity" or would be viewed as clinically meaningful. Although the SAG has in the first instance attempted an objective evidence-based selection of outcomes, the above issues have also been kept in mind in final selection from multiple options targeting similar domains. While conducting good and ethical science must remain our highest priority, we should not lose sight of these key issues.

The EPAD project represents the largest single project to model disease in a preclinical and prodromal population with at least 6000 people due to enter EPAD-LCS. Evaluations of cerebrospinal fluid, blood and imaging biomarkers, genetic analysis, and other risk factor assessment will ensure full characterization of risk and deep biological phenotyping. The accurate assessment of cognitive and clinical expressions of these biological changes is of paramount importance to the success of the project. Accordingly, the EPAD CCO-SAG has conducted a thorough, un-biased, empirical review of all available literature in this area and constructed the EPAD cognitive evaluation now fully incorporated in the EPAD LCS and PoC protocols. In doing so, we believe we have made significant progress in delivering recommendations for cognitive outcome measures which may not only be of use in the design of future pharmaceutical trials in preclinical AD, but which may also be incorporated into epidemiologic and clinical studies of high-risk cohorts. The provision of tailored cognitive outcome measures appropriate for the long preclinical phase of AD will thus help advance our understanding of preclinical and prodromal dementia and hence accelerate the development and delivery of new, effective interventions for the prevention of Alzheimer's dementia.

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RESEARCH IN CONTEXT

1. Systematic review: Recommendations for cognitive assessment in pre-dementia AD have been made by EPAD on the basis of a literature search and expert opinion.
2. Interpretation: Cognitive measures were selected on the basis of their sensitivity to pre-clinical AD, psychometric properties, and coherence with biomarker changes.
3. Future directions: The procedures are considered best practice for future clinical trials and research in pre-clinical AD.

References

[1] Ritchie K, Carrière I, Ritchie CW, Berr C, Artero S, Ancelin ML. Can we design prevention programs to reduce dementia incidence ? A prospective study of modifiable risk factors. BMJ 2010;341:3885–92.

[2] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819–28.

[3] Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci U S A 2004; 101:284–9.

[4] Scarmeas N, Habeck CG, Stern Y, Anderson KE. APOE genotype and cerebral blood flow in healthy young individuals. JAMA 2003;290:1581–2.

[5] Alexopoulos P, Richter-Schmidinger T, Horn M, Maus S, Reichel M, Sidiropoulos C, et al. Hippocampal volume differences between healthy young Apolipoprotein E e2 and e4 carriers. J Alzheimers Dis 2011;26:207–10.

[6] Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in Dominantly Inherited Alzheimer's Disease. N Engl J Med 2012;367:795–804.

[7] Ritchie K, Ritchie CW, Yaffe K, Skoog I, Scarmeas N. Is Alzheimer's disease really a disease of mid-life. Alzheimers Dement (N Y) 2015; 1:122–30.

[8] Ritchie CW, Molinuevo JL, Truyen L, Satlin A, Van der Geyten S, Lovestone Son behalf of the European Prevention of Alzheimer's Dementia (EPAD) Consortium. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. Lancet Psychiatry 2016;3:179–86.

[9] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.

[10] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an up-dated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16.

[11] Ritchie K, Carrière I, Berr C, Amieva H, Dartigues JF, Ancelin ML, et al. The clinical picture of Alzheimer's disease in the decade before diagnosis: clinical and biomarker trajectories. J Clin Psychiatry 2016; 77:e305–11.

[12] Ritchie K, Kotzki PO, Touchon J, Cristol JP. Characterisitics of Alzheimer's disease patients with and without ApoE e4 allele. Lancet 1996;348:960–1.

[13] Chen KH, Chuah LY, Sim SK, Chee MW. Hippocampal region-specific contributions to memory performance in normal elderly. Brain Cogn 2010;72:400–7.

[14] Nestor PJ, Fryer TD, Ikeda M, Hodges JR. Retrospelnia cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). Eur J Neurosci 2003;18:2663–7.

[15] Rowe CC, Ng S, Ackerman U, Gong SJ, Pike K, Savage G. Imaging beta amyloid burden in aging and dementia. Neurology 2007;68:1718–25.

[16] Khan UA, Liu L, Provenzano FA, Berman DE, Profaci CP, Sloan R, et al. Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. Nat Neurosci 2014; 17:304–11.

[17] Moodley K, Minati L, Contarino V, Prioni S, Wood R, Cooper R, et al. Diagnostic differentiation of mild cognitive impairment due to Alzheimer's disease using a hippocampus-dependant test of spatial memory. Hippocampus 2015;25:939–51.

[18] Tu S, Wong S, Hodges JR, Irish M, Piguet O, Hornberger M. Lost in spatial translation – A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. Cortex 2015;67:83–94.

[19] Jungwirth S, Zehetmayer S, Bauer P, Weissgram S, Tragl KH, Fischer P. Prediction of Alzheimer dementia with short neuropsychological instruments. J Neural Transm (Vienna) 2009;116:1513–21.

[20] Amieva H, Jacqmin-Gadda H, Orgogozo JM, Le Carret N, Helmer C, Letenneur L. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population based study. Brain 2005; 128:1093–101.

[21] Laukka EJ, Macdonald SW, Fratiglioni L, Bäckman L. Preclinical cognitive trajectories differ for Alzheimer's disease and vascular dementia. J Int Neuropsychol Soc 2012;18:191–9.

[22] Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before clinical diagnosis of Alzheimer's disease dementia. Neurology 2015;5:1–8.

[23] Perrotin A, Mormino EC, Madison CM, Hayenga AO, Jagust WJ. Subjective cognition and amyloid deposition imaging: a Pittsburgh Compound B positron emission tomography study in normal elderly individuals. Arch Neurol 2012;69:223–9.

[24] Song Z, Insel PS, Buckley S, Yohannes S, Mezher A, Simonson A. Brain amyloid-beta burden is associated with disruption of intrinsic functional connectivity within the medial temporal lobe in cognitively normal elderly. J Neurosci 2015;35:3240–7.

[25] Hedden T, Oh H, Younger AP, Patel TA. Meta-analysis of amyloid –cognition relations in cognitively normal adults. Neurology 2013; 80:1341–8.

[26] Bilgel M, An Y, Lang A, Prince J, Jedynak B, Resnick SM. Trajectories of AD-related cognitive measures in a longitudinal sample. Alzheimers Dement 2014;10:735–42.

[27] Yotter RA, Doshi J, Clark V, Sojkova J, Zhou Y, Wong DF, et al. Memory decline shows stronger associations with estimated spatial patterns of amyloid deposition progression than total amyloid burden. Neurobiol Aging 2013;34:2835–42.

[28] Nutter-Upham KE, Saykin AJ, Rabin LA, Roth R, Wishart HA, Pare N, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. Arch Clin Neuropsychol 2008;23:229–41.

[29] Kennedy KM, Rodrigue KM, Devous MD, Hebrank AC, Bischof GN, Park DC. Effects of beta-amyloid accumulation on neural function during encoding across the adult lifespan. Neuroimage 2012;62:1–8.

[30] Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive Decline in Prodromal Alzheimer Disease and Mild Cognitive Impairment. Arch Neurol 2011;68:351–6.

[31] Duff K, Foster NL, Dennett K, Hammers DB, Zollinger LV, Christian PE, et al. Amyloid deposition and cognition in older adults: the effects of premorbid intellect. Arch Clin Neuropsychol 2013; 28:665–71.

[32] Doraiswamy PM, Sperling RA, Coleman RE, Johnson KA, Reiman EM, Davis MD, et al. Amyloid-assessed by florbetapir F 18 PET and 18-month cognitive decline. Neurology 2012;79:1636–44.

[33] Kramer JH, Mungas D, Possin KL, Rankin KP, Boxer AL, Rosen HJ, et al. NIH EXAMINER: Conceptualization and Development of an Executive Function Battery. J Int Neuropsychol Soc 2014;20:11–9.

[34] Rentza DM, Amariglioa RE, Becker JA, Freya M, Olsona LE, Frishea K, et al. Face-name associative memory performance is related to amyloid burden in normal elderly. Neuropsychologia 2011; 49:2776–83.

[35] Grober E, Sanders AE, Hall C, Lipton RB. Free and cued selective reminding identifies very mild dementia in Primary Care. Alzheimer Dis Assoc Disord 2010;24:284–90.

[36] Amieva H, Le Goff M, Millet X, Orgogozo JM, Peres K, Barberger-Gateau P, et al. Prodromal Alzheimer's Disease: Successive emergence of the clinical symptoms. Ann Neurol 2008;64:492–8.

[37] Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Int Neuropsychol Soc 2008;14:266–78.

[38] Karantzoulis S, Novitski J, Gold M, Randolph C. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Utility in Detection and Characterization of Mild Cognitive Impairment due to Alzheimer's Disease. Arch Clin Neuropsychol 2013;28:837–44.

[39] England HB, Gillis MM, Hampstead BM. RBANS Memory indices are related to medial temporal lobe volumetrics in healthy older adults and those with mild cognitive impairment. Arch Clin Neuropsychol 2014;29:322–8.

[40] Hampstead BH, Stringer AY, Stilla RF, Deshpande G, Hu X, Moore AB, et al. Activation and effective connectivity changes following explicit memory training for name-face pairs in patients with mild cognitive impairment: a pilot study. Neurorehabil Neural Repair 2011;25:210–22.

[41] Lim YY, Villemagne VL, Pietrzak RH, Ames D, Ellis KA, Harrington K, et al.for the Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group. APOE ε4 moderates amyloid-related memory decline in preclinical Alzheimer's disease. Neurobiol Aging 2015;36:1239–44.

[42] Ellis KA, Lima YY, Harrington K, Ames D, Bush AI, Darby D, et al.and the AIBL Research Group. Decline in Cognitive Function over 18 Months in Healthy Older Adults with High Amyloid-beta. J Alzheimers Dis 2013;34:861–71.

[43] Storandt M, Mintun MA, Head D, Morris JC. Cognitive decline and brain volume loss as signatures of cerebral amyloid peptide deposition identified with Pittsburgh Compound B. Arch Neurol 2009;66:1476–81.

[44] Ritchie K, de Roquefeuil G, Ritchie CW, Besset A, Poulain V, Artero S, et al. COGNITO: Computerized Assessment of Information Processing. J Psychol Psychother 2014;4:136.

[45] Riley KP, Jicha GA, Davis D, Abner EL, Cooper GE, Stilese N, et al. Prediction of preclinical Alzheimer's Disease: longitudinal rates of change in cognition. J Alzheimers Dis 2011;25:707–17.