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A conceptual framework and ethics analysis for prevention trials of Alzheimer Disease

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ABSTRACT

As our understanding of the neurobiology of Alzheimer Disease deepens, it has become evident that early intervention is critical to achieving successful therapeutic impact. The availability of diagnostic criteria for preclinical Alzheimer Disease adds momentum to research directed at this goal and even to prevention. The landscape of therapeutic research is thus poised to undergo a dramatic shift in the next 5–10 years, with clinical trials involving subjects at risk for Alzheimer Disease who have few or no symptoms. These trials will also likely rely heavily on genetics, biomarkers, and or risk factor stratification to identify individuals at risk for Alzheimer Disease. Here, we propose a conceptual framework to guide this next generation of pharmacological and non-pharmacological clinical pursuit, and discuss some of the foreseeable ethical considerations that may accompany them.

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1. Introduction

It has been estimated that in 2010, there were 36 million people worldwide living with dementia, and the costs associated with dementia were US $604 billion (Alzheimer's Disease International, 2010). As the population overall ages over the next several decades, both the prevalence and cost of neurodegenerative diseases such as Alzheimer Disease (AD) and others that lead to dementia can be expected to increase dramatically. Although there have been considerable advances in understanding the associated neurobiology and pathological processes, an effective disease-modifying treatment remains elusive. Indeed, the disappointing results of

Abbreviations: Aβ, amyloid beta; AD, Alzheimer Disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; API, Alzheimer Prevention Initiative; APOE, apolipoprotein E; BioM+, biomarker-positive; BioM−, biomarker-negative; CSF, cerebrospinal fluid; DIAN, Dominantly Inherited Alzheimer Network; EOFAD, early-onset familial Alzheimer Disease; FDA, Food and Drug Agency; MRI, magnetic resonance imaging; PET, positron emission tomography; PiB-PET, [^{11}C]Pittsburgh compound B positron emission tomography; REVEAL, Risk Evaluation and Education for Alzheimer's Disease.

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several anti-amyloid trials for AD over the past several years have lead to significant reconsideration of the strategies that have been undertaken (Extance, 2010; Opar, 2008).

One of the most important issues in developing an effective intervention for AD relates to timing of the intervention to create the optimal therapeutic window. Pharmacological intervention too late in the disease process may be ineffective given the extent of existing, irreversible neurodegenerative change (Sperling et al., 2011a). Given that the neurodegenerative changes in AD begin many years before symptom onset, biomarkers that reflect the in vivo neuropathological processes have the potential to guide the early interventions needed to achieve treatment efficacy (Dubois et al., 2010). The dominant models of biomarker changes in AD, for example, suggest that amyloid beta (Aβ), a key component of neuritic plaques, begins to aggregate in the brain many years before the onset of any clinical symptoms of AD, and such deposition can be reliably measured with amyloid PET imaging and CSF Aβ assays (Jack et al., 2010; Sperling et al., 2011a). The growing importance of biomarkers and early intervention for AD were key themes in a series of recent papers with revised diagnostic criteria for AD (McKhann et al., 2011), mild cognitive impairment (Albert et al., 2011), and preclinical AD (Sperling et al., 2011a). Clinical trials for AD in the future will therefore undoubtedly be poised to enroll asymptomatic or presymptomatic subjects, and will incorporate biomarkers to define patient populations, evaluate target engagement, pharmacodynamic effects, and surrogate outcomes.

The purpose of this paper is to provide a conceptual framework that anticipates the range of prevention trials for AD that are foreseeable within the next 5–10 years, and to consider the related ethical challenges on the horizon.

2. A conceptual framework for prevention trial designs for Alzheimer Disease

We illustrate a conceptual framework for future prevention trials for AD in Fig. 1. The framework organizes information in a manner that has heuristic value by highlighting obvious similarities and differences among possible trial scenarios. Some principles can be generalized across different samples; others are unique to certain samples only. The approach is designed to enable broad-based and efficient guidance as well as trial-by-trial analysis.

The first component of the figure focuses on stratification of genetic risk for AD (Boxes A, B, and C). The group with the highest genetic risk would be autosomal dominant mutations of the amyloid precursor protein gene, the presenilin-1 gene, or the presenilin-2 gene. Penetrance of these mutations is almost 100% (Hsiung and Sadovnick, 2007). The majority of individuals with early-onset familial Alzheimer Disease (EOFAD) carry one of the

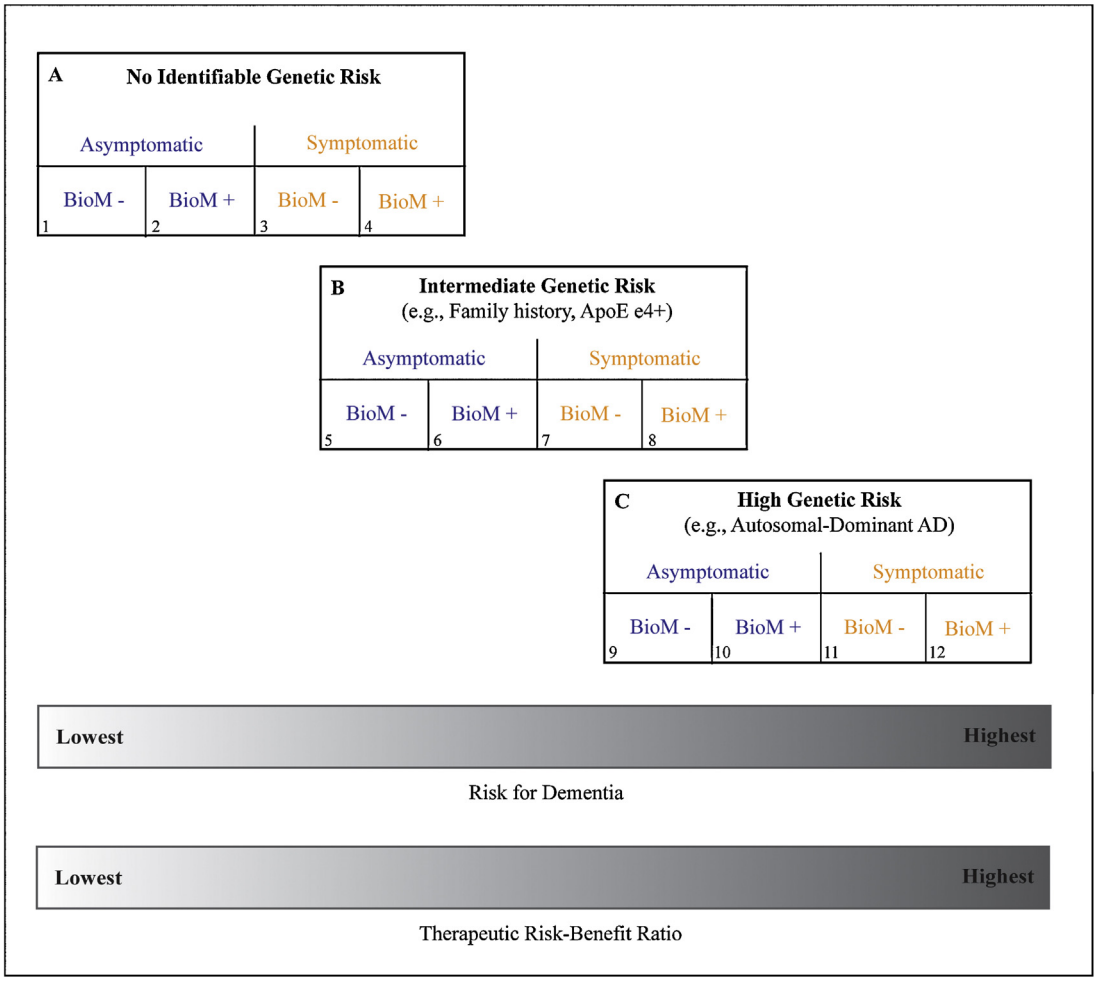

Fig. 1. Conceptual framework anticipating AD prevention trials. Large samples (Boxes A, B, and C) are differentiated on the basis of genetic risk. The overlap between the three boxes is for heuristic purposes only and is not meant to imply any precise degree of risk. Groups within each box are differentiated by the presence of clinical symptoms (blue for asymptomatic and orange for symptomatic). Stratification illustrates individual status as positive or negative for biomarkers (BioM). The lower portion of the figure illustrates the degree of risk for dementia for the samples and groups. Superimposed on the framework are therapeutic risk-benefit ratios as a function of risk category.

three known genes that cause autosomal dominant AD, with biochemical products of each of these genes implicated in its neuropathology (Bekris et al., 2010). These genes play a role in the abnormal processing and aggregation of Aβ in the brain. Individuals with an affected parent have a 50% chance of having the mutation, and penetration is almost 100% (Bekris et al., 2010). In addition, predicted differences in the levels of Aβ and tau can be detected in EOFAD mutation carriers during the preclinical state (Ringman et al., 2008). The group with intermediate genetic risk has factors such as a positive family history of AD, or the presence of at least one e4 allele of the APOE gene. The third group has no identifiable heightened genetic risk for AD.

Within each of the three groups we differentiate individuals with (orange text) and without (blue text) overt clinical symptoms. Given the push for early points of intervention, clinical trials will most likely involve individuals without any detectable symptoms of AD at trial onset. We also distinguish between individuals who are positive (BioM+) or negative (BioM−) with respect to biomarkers associated with AD. There are a number of in vivo biomarkers that indicate the presence of the neuropathology of AD. In an asymptomatic individual these biomarkers are seen as representing the disease in situ in its preclinical phase. These biomarkers include CSF levels of Aβ, total tau or tau isoforms, as well as amyloid PET imaging which reflects aggregated forms of Aβ. Furthermore it is also possible through in vivo biomarkers to identify downstream effects of the evolving pathology of AD in structural MRI volumetric brain measurements of atrophy. Prevention trials will use such biomarkers in one or two ways: either as part of the inclusion criteria for entry into a trial, as a surrogate outcome measure, especially in those trials that involve asymptomatic individuals at trial onset, or both. While there are no surrogate biomarker measures that are tightly correlated to therapeutic response at present, the likelihood of their discovery justifies thinking about them imminently.

We have arranged the samples and associated groups in Fig. 1 along two gradients presented in the bottom of the figure. The first gradient refers to the risk of developing AD, ranging from lowest to highest. The second refers to the definition of a therapeutic risk-benefit ratio that ranges from lowest to highest. To highlight how these two gradients interact, consider the use of a novel anti-amyloid drug as an example: although it may be more satisfactory to administer such a drug in trials involving individuals at higher risk for AD (e.g., Box C), it would be less acceptable to do so in healthy individuals who have no symptoms or only positive biomarkers of AD (e.g., Box A). In contrast, non-pharmacological interventions, such as diet and exercise regimens, entail far less therapeutic risk; the magnitude of benefit of such interventions may decrease, however, as symptoms or higher levels of biomarker positivity for AD develop.

The boundaries and degrees of overlap among the different samples and groups displayed in Fig. 1 are for heuristic purposes only; they are not meant to imply any degree of precision or risk. More specific risk estimates are available, and the precision of these estimates will continue to improve as the understanding of predictive risk for AD is refined. The data published on estimated risk curves for AD in first-degree relatives of AD patients from the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study (Cupples et al., 2004) are useful examples. This was a randomized trial in which control subjects received risk estimates for AD on the basis of age, gender, and family history of AD; subjects in the intervention group received risk estimates for AD based on the same information, plus their APOE genotype. These data can be used to determine risk estimates for individuals: for a 65-year-old male in the control group, for example, the remaining risk for developing AD by the age of 80 years is 11.5%; for a 65-year-old male who knows that he possesses an e3/e4 APOE genotype, the remaining risk to develop AD by the age of 80 years is 21.8% (examples from Cupples et al., 2004). Undoubtedly, the risk-based calculus between the estimated degree of predictive risk for AD with the estimated degree of therapeutic risk will change from trial to trial and will depend on a wide range of factors. Formalized procedures for making these calculations are still lacking, but they will be essential to gauge their application. One critical question that must be addressed, for example, is where the line that defines a favorable benefit-risk ratio within an intervention trial falls.

The framework in Fig. 1 captures the existing language of prevention trials as they relate primarily to genetic risk factors. One might alternatively construct similar figures taking into account other known risk factors for dementia and AD including vascular risk factor scores (Kivipelto et al., 2005), education, social setting and other factors as a risk stratified model is constructed within a trial design.

According to traditional terminology (Feldman and Jacova, 2007), trials involving individuals within all 'asymptomatic' boxes (i.e., those with blue text) are classified as primary prevention trials; trials involving individuals within all 'symptomatic' boxes (i.e., those with orange text) are classified as secondary prevention trials. The majority of published prevention trials for AD to date have used this terminology. The language of prevention trials is evolving, however, and some researchers are now using the presence of biomarkers to define the boundaries for primary and secondary prevention trials (Sperling et al., 2011b). According to newer terminology, both primary and secondary prevention trials involve individuals who are asymptomatic (i.e., all boxes with blue text): the key distinction is the presence or absence of biomarkers. Primary prevention applies to individuals within Boxes 1, 5, and 9; in contrast, secondary prevention trials apply to individuals within Boxes 2, 6, and 10. Presumably, trials involving individuals within all symptomatic boxes (i.e., those with orange text) would be classified as tertiary treatment under this newer terminology.

When viewed this way, there will be a clear impact of shifting the definitions of prevention trials on participant eligibility and on the duration and cost of future prevention trials for AD. Indeed, it is reasonable to anticipate that many prevention trials will focus on preventing the onset of clinical symptoms in individuals with evidence of AD pathology (i.e., secondary prevention according to the newer terminology). The hope is that future trials that select individuals based on biomarker profiles will be more targeted, and therefore, require fewer subjects than those of the past. On the other hand, trials involving asymptomatic individuals will need to be longer in duration in order to determine clinical efficacy, leaving open a range of issues related to long-term exposures and the human exposures necessary to support such research, particularly in preclinical individuals.

There are currently two prevention trials in development that will involve individuals at risk for EOFAD: the Alzheimer Prevention Initiative (API) (Reiman et al., 2010) and the Dominantly Inherited Alzheimer Network (DIAN) (Bateman et al., 2011). Some individuals will be enrolled up to 15 years before the expected age of symptom onset, using the time point of mean age of onset of the family's Alzheimer's disease or that individual's parent symptom onset as the reference time point. Using this same benchmark, other individuals who are as far as 10 years after this expected age of symptom onset will also be enrolled. Given the certain risk for AD, individuals with EOFAD in the API and DIAN trials would be classified into Box C of Fig. 1.

Another new planned prevention trial, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease trial, will involve approximately 1000 subjects who are cognitively normal but who have been identified as being amyloid positive via PET imaging. In this trial, which is a part of the Alzheimer Disease Cooperative Study, individuals who have a pathological signature of amyloid

pathology will be randomly assigned to a to-be-determined drug arm or placebo arm for a three-year period. Subjects in this trial will be over the age of 70 years to boost the possibility of detecting changes in cognitive measures over the time course of the trial. Individuals with a family history, one or more e4 alleles of the APOE gene, or subjective complaints will be enrolled, but such risk factors will not be required. Thus, subjects in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease trial will be classified into either Boxes 2 or 6 in Fig. 1 depending on whether or not genetic risk factors are present. The fact that subjects in this trial will be over the age of 70 also highlights that age is one of the most consistent risk factors for AD.

Each of these three trials is classified as a secondary prevention trial according to the new prevention terminology. Given the unprecedented nature of these trials, investigators from each have formed the Collaboration for Alzheimer's Prevention to harmonize trial design and protocols as much as possible. The conceptual framework developed here is meant to augment discussion of the ethical considerations that are unique to these trials within the larger context of future prevention trials for AD as well as drawing on previous prevention trials for AD such as those with Ginkgo biloba (DeKosky et al., 2006), non-steroidal anti-inflammatory drugs (Meinert et al., 2009), and estrogen plus progestin (Shumaker et al., 2003).

This framework also applies to non-pharmacological intervention trials in older adults, including exercise. Consider two such non-pharmacological studies for illustrative purposes. Erickson et al. (2011) conducted a 12-month intervention study involving 120 healthy older adults between the ages of 55 and 80. Subjects randomly assigned to the aerobic exercise condition showed statistically significant improvements in spatial memory as well as increases in anterior hippocampal volume compared to a control condition that involved stretching and toning exercises. In terms of biomarkers, the hippocampal volume measurements in this study were an outcome measure; subjects were not selected on the basis of these measurements. Accordingly, the subjects would be initially classified in Box 1 (No identifiable genetic risk: Asymptomatic; Biomarker negative or unknown).

Lautenschlager et al. (2008) conducted a single-blind randomized trial of a 6-month physical activity intervention in 170 subjects with memory problems, defined subjectively or objectively. Subjects in the physical activity group showed statistically significant benefits compared to a usual care control group on the cognitive subscale of the Alzheimer's Disease Assessment Scale that was maintained for up to 12 months following the intervention. In addition, the magnitude of benefit was significantly greater in non-carriers of the APOE e4 allele. These study participants would be classified in the symptomatic compartments of Boxes A (those without an APOE e4 allele) and B (those with at least one APOE e4 allele). Future studies will likely stratify individuals with genetic risk along CSF or imaging measures of biomarkers to further delineate treatment response across the various samples shown in Fig. 1.

3. Ethical considerations

The broad approach that we have used to conceptualize the future of prevention trials reflects some ethical challenges inherent to the state of the art in dementia research today, and allows us to anticipate others. Some of these challenges are generalizable to all trials; others are more trial-specific. The analysis draws upon and extends key principles guiding bioethical analysis (Beauchamp and Childress, 2009; Emanuel et al., 2000), and revolves around three themes: (1) scientific validity, (2) benefits and risks, and (3) diagnostic disclosure and accidental findings. The elements of the analysis are mapped in Fig. 2 as thematically organized ethics themes and alongside the traditional phases of clinical trials. The trial phases correspond to common practice as described by the ICH Expert Working (ICH Expert Working Group, 1997).

3.1. Scientific validity

Identification of therapeutic targets: Issues related to scientific validity require consideration across all clinical trial phases. After a therapeutic target and agent have been selected during the early phases of drug development, drug trial investigators need to define criteria for ascertaining target engagement, as well as the dose range for safety and putative efficacy. Recent failed anti-amyloid treatments illustrate some of the problems inherent in not adequately establishing the early-stage pharmacodynamics effects of a drug on biomarkers of interest and doses to advance into larger trials (Aisen, 2009; Extance, 2010). In the example of the γ-secretase modulator tarenflurbil, the drug continued into Phase II and III trials despite the absence of a robust effect on CSF levels of Aβ in Phase I trials (Aisen, 2009; Extance, 2010). Ideally, the degree of biomarker effect such as Aβ lowering for clinical effects would be known but this is not the case presently. The absence of such a benchmark is a serious limitation to current study designs and creates risks inherent in the current development of amyloid lowering treatment. In the case of CSF measures of Aβ, how much reduction will need to be demonstrated before moving onto Phase II and III trials?

Studies of the similarities between Down's syndrome and AD by Wan et al. (Wan et al., 2009) and of the novel single nucleotide polymorphism mutation in the APP gene (A673T) among Icelanders by others (Jonsson et al., 2012) suggest that reductions in Aβ of less than 50% could have substantial benefits in delaying disease onset or progression, however this requires extrapolation to other settings. Absent definitive human data, extrapolations are made from animal models. Bateman and Klunk (2008) highlight the fact that, in mice, decreases in γ-secretase activity of 30–50% have been associated with reduced amyloid pathology as long as those decreases were maintained over the lifetime. Once signs of AD pathology are present, however, substantial decreases in γ-secretase activity of even 95% are insufficient to prevent further progression of amyloid pathology. Although these results are potentially important, results obtained in animal models cannot be taken today to generalize to human efficacy. Researchers will have to grapple with the difficult question of scientific validity in this context before human trials are initiated, including developing objective and theoretically relevant decision trees about how to interpret early trial results through to proof of confidence ahead of moving to larger clinical research programs in later phase II and beyond.

Outcomes measures: Absent a surrogate biomarker to gauge treatment efficacy, the identification of appropriate primary outcome measures in asymptomatic individuals poses an immediate challenge. Clinical measures that are sensitive and specific to change over time in individuals without overt symptoms at trial onset, and who may not develop symptoms for many years remain the gold standard. The difficulties of identifying such clinical measures should not be underestimated, however, as distinguishing normal aging from mild cognitive impairment in persons that are destined to progress to dementia is itself a challenging task. Biomarkers may be helpful, but to date are unproven for longitudinal evaluation.

Researchers will also have to anticipate the degree of change in these measures that can be reasonably expected over the long term. Recently published longitudinal data on CSF biomarkers from the Alzheimer's Disease Neuroimaging Initiative (ADNI) highlight this imperative. The ADNI data show a small change in CSF levels of Aβ-42 and total tau over a 12-month period of less

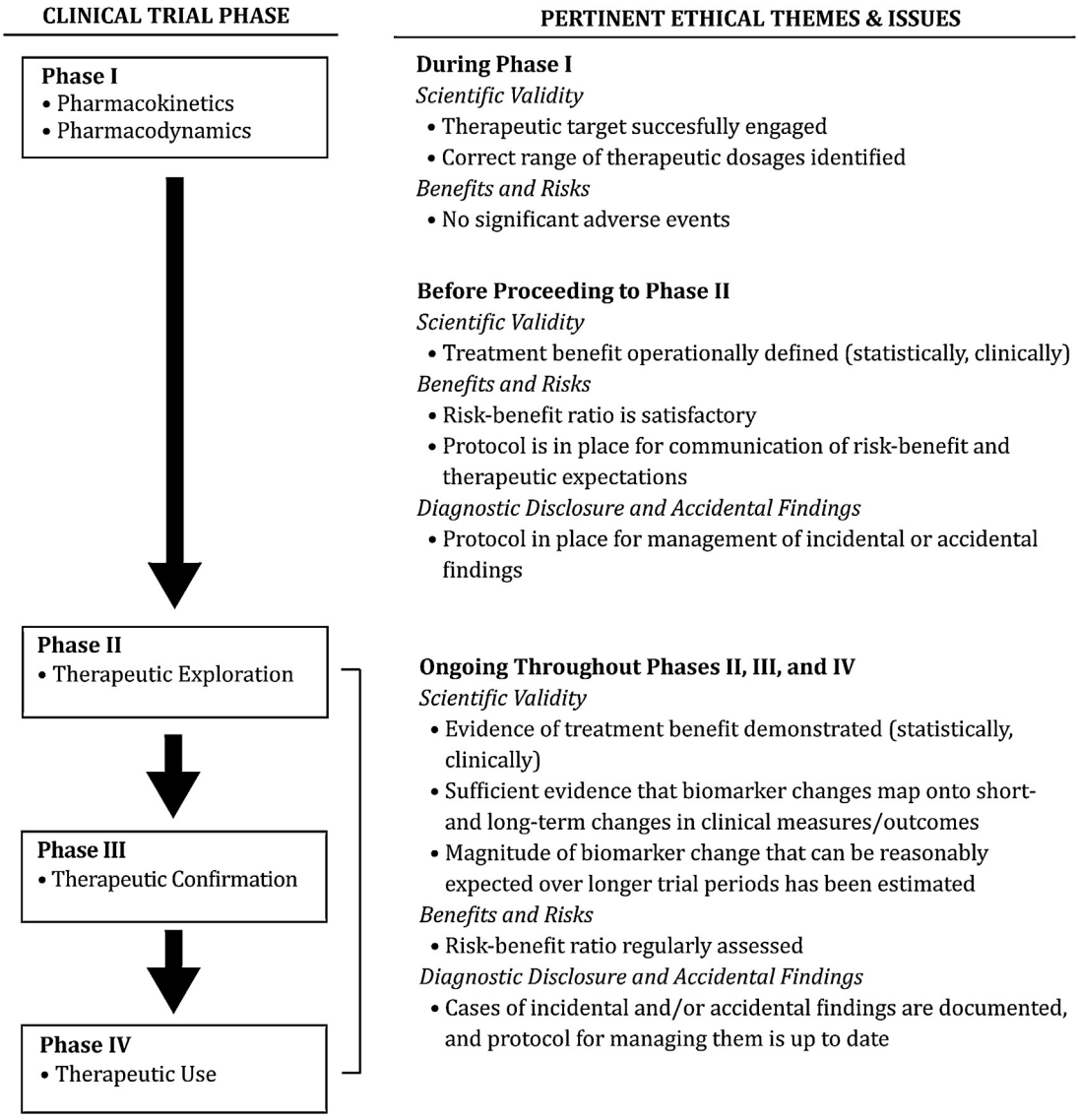

Fig. 2. Mapping of key ethical themes onto clinical trial phases.

than 1% (Petersen et al., 2010), making the detection of statistically significant treatment effects in an insidious condition such as AD no small feat.

Clearly, more work needs to be done with respect to ensuring the best methodology is used, and not just the best biomarker candidates. The future therapeutic landscape for AD is largely uncharted; the research community will not be able to proceed as it has in the past with the cholinesterase inhibitors when efficacy was determined on the basis of 3- or 6-months clinical trials. Early futility assessments in future prevention trials will be essential to see whether biomarker and cognitive outcome measures are related and moving in the right direction. In addition, the biomarker data generated by the ADNI provides an opportunity to estimate the range of possible effect sizes for longitudinal changes in biomarkers. These estimates should be used for subsequent power analyses.

Researchers have also examined the ability of [^{11}C]Pittsburgh compound B positron emission tomography (PiB-PET) scans to detect changes in amyloid deposition in the brain over time in different clinical populations (Quigley et al., 2011). Other similar imaging markers, such as the F-labeled tracers flutemetamol and florbetapir, exist but PiB-PET has been the most intensely investigated.

On the one hand, although the PiB-PET studies have provided useful information, a number of challenges remain to be addressed before widespread use of such imaging can be widely adopted, especially with respect to monitoring therapeutic outcome. There are issues, for example, of how much amyloid deposition occurs at various stages of the disease and whether or not such technology can reliably detect these changes over time. Several PiB-PET studies have reported little or no increase in amyloid deposition over periods of 1–2 years in cognitively normal individuals, patients with mild cognitive impairment, and mild AD (Engler et al., 2006; Jack et al., 2009; Scheinin et al., 2009). The stabilization of amyloid deposition is consistent with the hypothesis that such deposition occurs very early in the disease and leads to a cascade of neurodegeneration (Quigley et al., 2011). In addition, there is ongoing work to establish tau ligands for PET imaging and these may move the field forward.

On the other hand, using a different analytic approach, Vlassenko et al. (2011) performed repeated PiB-PET scans over a 2.5-year period in cognitively normal individuals. These authors reported that the amount of amyloid deposition was greater in those individuals who had elevated amyloid levels at baseline, and they interpreted these results as evidence of the development of 'preclinical' AD. Unfortunately, however, this study did not employ

any clinical measures to verify such claims. Indeed, the presence of increased levels of amyloid deposition in cognitively normal individuals does raise an important issue with respect to the specificity of PiB-PET imaging. The percentage of cognitively normal individuals with heightened levels of amyloid deposition ranges from 10 to 30% (Quigley et al., 2011), similar to the number of individuals with significant levels of AD pathology at autopsy (Jack et al., 2010). Is this simply an issue of choosing appropriate cut-off values for pathological levels of amyloid deposition? If so, what thresholds will define clinical validity across different stages of the disease, across different individuals, and across different diagnostic/research centers? These considerations will need to be addressed in constructing trials and informing the consent process and lexicon used in discussion with research participants.

Bateman and Klunk (2008) discussed the possible scenarios to consider with respect to the outcome of early Phase II trials employing both clinical and biomarker outcome measures. When there is evidence of biomarker improvement and clinical benefit, the decision to move forward with further and larger trials should be straightforward, notwithstanding that the risk-benefit ratio is considered as part of defining clinical benefit. Similarly it is unlikely there will be grounds to proceed when both types of measures fail to show any improvement or benefit. It becomes more problematic when one of the other two outcome scenarios occurs. This will be particularly challenging in early trials where sample sizes are generally insufficient to detect effect sizes beyond those that are very large. In turn, when there is improvement on biomarker measures but no clinical benefit, one must keep in mind the limitation of the power within the trial to detect statistically significant clinical benefits. Investigators may interpret the lack of a clinical benefit as being a null finding, and therefore ambiguous. It is possible that a larger, more statistically powerful, trial aimed at demonstrating clinical efficacy may still demonstrate clinical benefits, however, the parameters to guide such a decision should be anticipated and thought through as part of a development plan with a guiding decision tree prior to unblinding of early trials. In the example of limited populations such as genetic mutations, the resource of affected families is more limited and not easily expanded for larger trials. The anti-amyloid drug tramiprosate is an interesting case of a mixed result where biomarker and clinical results were not convergent. In an early phase II trial the medication reduced CSF levels of Aβ in AD patients, however, there was no clinical efficacy at that time nor was there any such benefit seen in larger Phase II trials (Aisen, 2009). A similar example can be found in the case of bapineuzumab, with promising early trial results for lowering of brain amyloid levels without clinical benefit (Rinne et al., 2010). These examples underscore some of the potential problems with scientific validity and the consequential exposures that will occur in preclinical trials where agents and decision-making are similar in this population as in the fully affected mild to moderate AD populations.

The fourth possible Phase II trial outcome is that of clinical benefit but no improvement on biomarker measures or divergent results. The Aβ immunization trial of AN1972 provides a basis for considering this possibility. The Phase II trial was terminated when 18 of 298 (6%) subjects in the drug group developed subacute meningoencephalitis (none of the 74 placebo controls developed this condition) (Orgogozo et al., 2003). A secondary analysis of 45 subjects who were classified as antibody responders demonstrated that despite greater brain volume decreases, the cognitive performance of these subjects actually improved (Fox et al., 2005). The explanation for this outcome of increased volumetric loss remains unknown, and runs against the a priori assumptions that a successful treatment would attenuate and not increase volumetric loss. It is a clear reminder that despite our best theorizing, biomarker and clinical measures may not always behave as expected.

The potential for circularity in using biomarkers both to determine subject eligibility for a trial and as an outcome measure to gauge efficacy for that trial is yet another challenge. The circular logic problem that arose historically in neuropsychology is an example: poor memory performance was used to identify people at risk for AD, who were then documented to have a greater than normal rate of converting to AD, which is defined itself by poor memory performance (Tuokko and Frerichs, 2000). The same problem may arise for the use of biomarkers when used as both inclusion criterion and outcome measure. Given that amyloid deposition is thought to occur very early in the disease process, before symptom onset, and that such deposition may reach a plateau relatively early in this process, care must be taken in designing future trials to not rely solely on the reduction of amyloid deposition as an outcome variable. A safeguard might be to avoid the selection of subjects for clinical trials on the basis of elevated levels of amyloid deposition, and then concurrently deploying this biomarker measure as the main outcome variable, without any reference to other clinical outcomes. This caution would guard against defining conversion to dementia on the basis of biomarker profiles of amyloid deposition. Alternative approaches could include measures that are potentially downstream in the neuropathological process including CSF tau or volumetric MRI measures. A designated panel of biomarkers is a consideration, provided that there is validation that they have predictable change over time. Biomarker development and understanding are in a dynamic state and protocols must incorporate such changes as they advance.

With respect to outcome measures, researchers typically distinguish between primary and secondary outcomes. It is important to make distinctions about the weight that ought to be attributed to each of these outcomes in the assessment of efficacy. Consider for example the clinical trial of vitamin E, donepezil, and placebo in MCI conducted by Petersen et al. (2005). The authors reported no significant differences among the three groups with respect to their primary outcome, progression to AD over three years. However, they did report significant improvement in the vitamin E and donepezil groups on several of their secondary outcome measures, which were the results from various cognitive tests. The amount of weight that ought to be attributed to these secondary outcomes in the absence of benefit on the primary outcome, however, is unclear given the number of statistical comparisons carried out to obtain these secondary results, and the associated increases the type I error rate. Similar concerns surround secondary or post hoc analyses for phenomena that were not identified for exploration a priori. Given that prevention trials will require long periods of data acquisition, new knowledge about disease processes will surely emerge during that time, and researchers will be prompted to probe them.

An additional concern relates to measures acquired from between-subjects versus within-subjects analyses of outcome. Given that intervention trials usually comprise at least a placebo and intervention group, and from more than one time point, researchers are able to examine group differences in the amount of change over time, as well as the amount of change within groups. While interpreting results when these analyses are in agreement can be straightforward, discordant results are naturally more difficult to rationalize. The exercise intervention study by Lautenschlager et al. (2008) is a case in point. These authors reported a significant difference between an exercise group and a placebo group in the degree of change on the ADAS-Cog over an 18-month period. However, the amount of improvement within the exercise group was not significant. Taken together, the results raise questions both about the most suitable methods to resolve

such inconsistencies as well as the best method by which to establish efficacy.

Regulatory challenges: The issue of using biomarkers as surrogate outcome measures becomes even more complicated when one considers that, at present, most regulatory agencies would not likely approve a treatment for AD based on biomarker data alone (Reiman et al., 2010). There are other medical conditions that are diagnosed and treated prophylactically on the basis of laboratory tests and biomarker data and it is reasonable to imagine that AD could be added to this list of conditions in the future (Jack et al., 2010). However, AD to date is considerably less well defined than, for example, Type II diabetes, hypertension, and osteoporosis. Furthermore, in some of these conditions where biomarker-based outcome measures are also employed, efficacy was first demonstrated using more clinically relevant primary outcomes, such as survival in diabetes (Nissen et al., 2005), hypertension (MRC Working Party, 1992), and fractures in osteoporosis (Shea et al., 2002). A language of benefit with respect to outcome measures for AD trials does not currently exist (Karlawish, 2009). Part of the scientific value of long-term trials that enroll individuals with little or no clinical symptoms is that they increase the understanding of how biomarkers respond to different treatment interventions, they inform how changes in these biomarkers map onto clinical responses in the short- and long-term, and they lead to benefit benchmarks that are vital for the success of future studies.

3.2. Benefits and risks

Consent and counseling: As with any medical condition, it is essential to weigh the benefits and risks associated with prevention trials for AD (Emanuel et al., 2000). The prospects of risks and benefits are always probabilistic in nature, and there are ethical issues related to how this type of information is presented to potential subjects. Since subjects in many of these trials will be asymptomatic at the time of enrollment, there is no real prospect of any immediate and direct benefits such as the reduction of symptoms. There exists the possibility, however, that a drug may be effective and mitigate symptoms in the longer term, but it will take years before the clinical meaningfulness of any benefits can be determined. This raises an important question of whether the potential for delaying symptom onset in the future can be considered a direct benefit, and how this information ought to be presented to subjects before enrolling into a prevention trial. The risks are of longer-term exposure without knowing the ratio at trial onset. In fact, risks could come to be seen sooner than benefits. Mitigating therapeutic misconception about the nature of the trial (treatment versus research) and minimizing the degree of therapeutic misestimation (overestimate benefit, underestimate risk, or both) that may occur during the consent process (Horng and Grady, 2003) are significant tasks and require dedicated consideration. Meaningful and regular counseling throughout the study and afterward will be important to meet this goal. One practical option is to have a third-party individual, who is independent of the study, review the consent process with all potential subjects, and to repeat this process over several sessions. There are practical considerations around the designation and deployment of such an individual so they continue to remain outside the vested interests of the trial.

Therapy beyond the trial window: Where long-term treatment is eventually shown to be successful, what duty of provision does the researcher or sponsor have and for how long? How is this responsibility defined in the context of trials in which subjects may convert from an asymptomatic to symptomatic state? From a justice perspective, individuals with EOFAD have contributed to basic science research on AD for over 20 years, yet they have continued to be excluded from most of the clinical trials for AD (Bateman et al., 2011). On the other hand, it is very likely that many of these families would not be able to financially afford treatments that are found to be successful and subsequently brought to market. This issue will need to be addressed, and the target outcome will need to be clearly indicated in the informed consent process.

Unanticipated challenges: There will be a critical need to revisit the risk-benefit analysis iteratively during the course of the trial. The discontinuation of the phase II Aβ active immunization therapy (AN1792) trial due to the development of subacute meningoencephalitis in 6% of subjects in the treatment arm serves as a potent and sobering reminder of unanticipated adverse events (Orgogozo et al., 2003). The recent discussions surrounding amyloid-related imaging abnormalities (ARIA) serve as an example of how coordinated efforts of international experts, industry, and federal regulatory agencies can be used to overcome unanticipated challenges that arise in AD clinical trials (Schindler et al., 2011). In that instance the presence of MRI evidence of potential cerebral microhemorrhages and vasogenic edema in several clinical trials of amyloid-modifying therapies prompted the U.S. Food and Drug Agency (FDA) to propose more stringent recommendations for the conduct of clinical trials of these agents. An Alzheimer's Association Research Roundtable Workgroup was convened with expert input to review the relevant literature and propose recommendations around the issues of amyloid-related imaging abnormalities and clinical trials of anti-amyloid treatments. This work group published their findings (Sperling et al., 2011c), and the FDA modified their initial recommendations. Beyond the risks of emerging side effects, there will also be the needs to monitor death rates, and other unexpected morbidities. The development of Safety Monitoring Boards for trials with written charters and with outline plans for stopping rules are an important safeguard and consideration. Decisions within the charter need to address whether such Boards will monitor safety, efficacy, futility, the risk/benefit ratio, or all of these.

Trial design and consent: During any long trial period, new information about the understandings of disease processes and potential interventions are bound to occur, and investigators will need to conceptualize the process of consent as being dynamic rather than static. A dynamic process will need to be built into the trial design whereby subjects are regularly provided with new and evolving information about the disease and treatment intervention so that they can base their decisions about continuing in the study on the best available evidence over the long-term. The length of time that subjects are kept on a placebo when a given treatment intervention looks promising will also have to be minimized, especially for subjects who are at greatest risk for AD. Similarly, careful attention will need to be paid to the length of time subjects are kept on a treatment that is clearly not working, unnecessarily exposing them to potentially harmful side effects. The manner with which futility assessments are conducted during trials will require careful consideration by overseeing steering committees and principal investigators.

Given the push for early interventions in an insidious condition such as AD, access to long-term information about outcomes will be essential to establishing efficacy and safety. Will positive findings within a five-year trial period be sustained over time? Will unexpected adverse events arise in the future? How do researchers collect this type of long-term information beyond the duration of a prevention trial? In addition to considering these questions for the desired scenario of a positive trial, researchers will also have to think about whether and how they will access such information when trials are discontinued, such as in the case of futility reasons, or when subjects decide to withdraw from a trial. The process of consent can serve this purpose with different options for subjects:

(a) totally withdraw from the study and not allow any further data collection at all, or (b) withdraw from the study, but allow researchers to access information in the future such as death certificates. This approach would maintain respect for individual autonomy, while also allowing for the possibility of collecting important outcome data that would not have otherwise been collected.

3.3. Diagnostic disclosure and accidental findings

The principle of autonomy is a key feature of western approaches to and decision-making about participation in research. Community-based participatory research methods (Brief and Illes, 2010) that are more relevant to indigenous populations, however, would dictate that communities and participants have the right to determine, collaboratively with the researchers, if diagnostic disclosure is a prelude to entry into a clinical trial. How will these models be adopted in future prevention trials for AD? What provisions will be made for handling sensitive information, especially accidental disclosure? Today, the number of people who opt to undergo genetic testing for neurodegenerative diseases ranges from 8 to 20% (Meiser and Dunn, 2000; Steinbart et al., 2001), and the majority of individuals do not wish to know their genetic status. The risks that subjects in future trials will find out their genetic status through inference, or secondary findings not related to a primary study will need to be evaluated carefully as will the question of who will own and be responsible for these data and for providing this information.

To minimize treatment-related risks in the API study, the investigators plan to include EOFAD mutation carriers only in their randomized controlled trials; all non-carriers will be assigned to placebo, preventing unnecessary exposure of non-carriers to the potentially harmful adverse events of the novel treatments under study. One potential problem with this design, however, is that carriers assigned to the treatment arm may notice the onset of side effects that are associated with the drug, and may therefore infer that they are a carrier because only carriers will have a chance to receive the drug.

The DIAN (Bateman et al., 2011) study will not directly provide information on genetic status, but will refer subjects to relevant commercial agencies for further testing, per their interest to do so. Questions about the processes for covering costs for such additional testing in the latter model, and the management of subject reactions to learning carrier status have yet to be answered. While the actual genetic test may be done commercially, the provisions for counseling around the testing needs to be included.

New guidelines for genetic counseling in AD have recently been published and may provide insightful and helpful suggestions for the proposed trials in EOFAD (Goldman et al., 2011). Although the primary concern is with the disclosure of carrier status, clinically significant incidental findings on brain imaging can be expected in at least 2% of the population (Illes et al., 2006). The discourse around disclosure is extensive and turns largely on the actionability of a finding, although some writers have argued for subjects' fundamental right to know to ensure trust and reciprocity in research (Illes and Chin, 2007). Minimally, the possibility of such a discovery should be anticipated in the research protocol and articulated during consent (Illes et al., 2008) with provisions for how this will be handled.

Communication about predictive risk will be particularly important in prevention trials that involve subjects who are biomarker positive. Consider that, by definition, subjects may be enrolled in a trial because they a priori meet entry criteria for higher than normal levels of amyloid deposition in the brain. Both the probabilistic nature that defines this risk for AD, as well as the fact that signs of significant amyloid deposition occur in 20–40% of cognitively normal adults, a portion of whom who may not go on to develop AD, will need to be properly and accurately explained (Jack et al., 2010). This will benefit from large and converging sets of data that have followed such individuals, information that is not currently available but will continue to accrue in the coming years. Prior work on the subjective construction and representation of risk surrounding genetic testing in Huntington disease provides foundational work for the problem at hand (Cox and McKellin, 1999) Although similar results may be present for EOFAD where the penetrance is almost 100%, the extent to which subjective constructions of risk for individuals who are at risk for late-onset, or sporadic forms of AD will likely be much more variable and diverge considerably more from the objectively determined risk for these individuals.

The REVEAL study (Green et al., 2009) has examined the effect of disclosing APOE genotype information to subjects who are adult children of individuals with late-onset AD. Subjects were randomly assigned to either the 'disclosure' (risk assessment based on age, gender, family history, and APOE genotype status) or to the 'nondisclosure' (risk assessment based on age, gender, and family history; no APOE genotype information provided) group. Individuals who were provided with APOE genotype information did not show evidence of significant psychological distress (e.g., anxiety and depression) over a one-year follow-up period. Questions about the long-term clinical usefulness of disclosing such information remain, however. Only half of the REVEAL subjects were able to accurately recall their lifetime risk and genotype information one year after receiving this information (Eckert et al., 2006). Additionally, subjects who were able to accurately recall information were significantly more likely to recall discrete information (i.e., genotype status) over probabilistic information (i.e., lifetime risk estimates).

Qualitative analyses based on in-depth interviews with a subset of 55 REVEAL study subjects confirm, and extend, these recall accuracy results (Lock and Hedgecoe, 2009). These investigators suggested that the information provided during the disclosure sessions did not tend to displace the common sense understandings of the study subjects. Such common sense understanding was consistent with the concept of 'blended inheritance', the idea that a person's genetic make-up is a blending of influences from each parent (which is inconsistent with our current scientific understanding of genetics). More work clearly needs to be done to determine optimal methods of educating individuals about their genetic risk for diseases such as AD. In Canada, the Tri-Council Policy Statement (Sections 8.3 and 8.4) specifies the importance of "provision for access to genetic counselors" in studies where genetic risk is involved (Canadian Institutes of Health Research et al., 2010, December).

The tendency to forget or misremember risk-based information, along with the demonstrated preference for recall of discrete over probabilistic information that was demonstrated in the REVEAL study will pose a formidable challenge for future AD prevention trials. Many of the biomarker measures that will be used to enrich enrollment of prevention trials, and to monitor therapeutic outcome will be continuous variables (e.g., CSF levels of Aβ or PiB-PET amyloid imaging). The prognostic information provided by these continuous measures is complex, and it will be difficult to explain such information to participants. One option, of course is to simply convert these continuous measures into dichotomous ones (e.g., amyloid-positive versus amyloid-negative), but there are methodological, statistical, and ethical concerns associated with doing this. First, there is still no consensus as to what the appropriate cut-off values are with respect to defining amyloid-positive for CSF and amyloid imaging measures. The variability of biomarker measurements amongst different labs adds to this concern (Mattsson et al., 2011). Second,

dichotomizing a continuous measure will substantially reduce the statistical power of the analysis (Cohen, 1983). Third, informing an individual of amyloid-positive status, may lead to an exaggerated sense of subjective risk for AD, and increase the likelihood that the person will participate in a prevention trial.

Most recently, the ADNI consortium was established. This is a special Working Group to provide guidance on the return of research results and incidental findings from Florbetapir imaging in studies of adult patients being evaluated for AD and other causes of cognitive decline, to patients and their families (http://www.adni-info-org). Florbetapir is a radioactive diagnostic agent for PET imaging of the brain that estimates Aβ neuritic plaque density. The group developed a consensus document with recommendations regarding which results from amyloid imaging should be returned, by whom they should be returned, and professional responsibilities for documenting disclosures. Beyond a review of guidance offered for disclosure of unexpected results from other domains of neuroimaging (Illes et al., 2008), the recommendations also took into consideration the results of a consent document analysis that revealed significant variability in the content of statements, and location in consent form about the return of research results across participating ADNI sites. The overall effort underscored the importance of proactive and careful management of return of results and incidental findings to ensure public trust, participation in research, and the integrity of research and researcher/clinician–patient relationships.

4. Conclusion

We have proposed a conceptual framework to anticipate the range of AD prevention trials on the horizon for the coming 5–10 years, and we have applied it to identify and address some expected ethical challenges. Consideration of scientific validity, benefits and risks, and diagnostic disclosure and accidental findings are the ethics starting points. Continued proactive analysis will serve to further evolve and inform the design, quality and meaningfulness of AD trials in the short- and long-term.

Disclosure statement

Drs. Kevin R. Peters, B. Lynn Beattie, and Judy Illes do not have any conflicts of interest to declare relating to the content of this paper. During the preparation of this paper and in the past 3 years, Dr. Howard H. Feldman has been a full-time paid employee of Bristol-Myers Squibb between January 2009 and December 2011 while on leave from the University of British Columbia. In the course of this employment with Bristol-Myers Squibb, he received salary, stocks and stock options. Within the past 3 years, he has also served as a paid consultant to Eli Lilly, Kyowa Kirin, and Nutricia, ICER, and has provided CME lectures sponsored by Janssen, and Novartis for which he has received honoraria. He has received travel funding from New York Academy of Sciences, NIH, Alzheimer Association Research Roundtable and Pfizer for attendance at meetings. He has had peer reviewed grant funding support from Canadian Institutes of Health Research and Pacific Alzheimer's Research Foundation and has served as Chair of the Alzheimer Society of Canada Biomedical Peer Review Panel (2012) and as co-Chair Leadership Council New York Academy of Science Alzheimer Research Initiative.

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HHF, KRP, BLB and JI discussed and developed the initial conceptual framework. KRP developed the first draft of the paper, which was critically revised by all four authors. All four authors reviewed the final version for submission.

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