

# Prospects for Prediction

## Ethics Analysis of Neuroimaging in Alzheimer's Disease

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**ABSTRACT:** This article focuses on the prospects and ethics of using neuroimaging to predict Alzheimer's disease (AD). It is motivated by consideration of the historical roles of science in medicine and society, and considerations specifically contemporary of capabilities in imaging and aging, and the benefits and hope they bring. A general consensus is that combinations of imaging methods will ultimately be most fruitful in predicting disease. Their roll-out into translational practice will not be free of complexity, however, as culture and values differ in terms of what defines benefit and risk, who will benefit and who is at risk, what methods must be in place to assure the maximum safety, comfort, and protection of subjects and patients, and educational and policy needs. Proactive planning for the ethical and societal implications of predicting diseases of the aging brain is critical and will benefit all stakeholders—researchers, patients and families, health care providers, and policy makers.

**KEYWORDS:** neuroimaging; Alzheimer's disease; aging; prediction; neuroethics

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## INTRODUCTION

The progressive deficits characterizing dementia in Alzheimer's disease (AD) ultimately destroy judgment and communication abilities. The deficits are particularly difficult to detect in early stages,<sup>1</sup> and true confirmation of this form of neurodegenerative disease is elusive without postmortem histological examination of the brain for neuronal loss, neurofibrillary tangles, and senile plaques. A consequence of the subtlety of these changes is that diagnostic criteria are conservative and diagnosis is delayed until there is significant functional disability (Diagnostic Statistical Manual IV, 1994). Given the late age of onset of AD and a growing elderly American population, the public health burden of this disease is significant. Estimates of the prevalence of Americans suffering from the condition today vary between 1.5 and 4 million, with projections increasing steadily through 2050.<sup>2,3</sup> Despite recent therapeutic advances, available treatments at present are aimed primarily at slowing progression of the disease rather than halting it completely or reversing its progression.

Imaging is one among a few tests, such as genetic markers, cerebrospinal fluid, and demographic risk factors that may predict AD. Original genetic studies in the early 1990s, for example, associated one gene that encodes apolipoprotein E with the disease. APOE is a plasma protein that binds and transports cholesterol.<sup>4</sup> The presence of the type 4 allele (estimated to occur in about 25% of the AD population)<sup>5</sup> is widely viewed as a risk factor. However, many individuals affected by AD do not have the allele, and others who do inherit it do not manifest AD. The development of imaging biomarkers and a discussion of accompanying ethical challenges are the focus of the present article.

## ROLES FOR CURRENT IMAGING CAPABILITIES AND IMAGING BIOMARKERS ON THE HORIZON

Neuroimaging techniques are poised to transform the process of diagnosis, prediction, and clinical management of AD and related dementias. The role of magnetic resonance imaging (MRI) and positron emission tomography (PET) in the diagnosis of dementia and investigation of cognitive impairment has been discussed at length by Knopman *et al.*<sup>6</sup> and Albert *et al.*<sup>7</sup> ([www.alz.org/Research/Papers/Imaging\\_consensus\\_report.pdf](http://www.alz.org/Research/Papers/Imaging_consensus_report.pdf)). Currently, neuroimaging essentially serves the purpose of excluding alternate potential etiologies for cognitive dysfunction. For the future, there are three particularly important roles that neuroimaging may play: (1) increasing the sensitivity and specificity in diagnosing AD; (2) predicting who is likely to develop AD in the nondemented population; and (3) replacing clinical outcome measures in therapeutic trials (i.e., surrogate measures that have no direct relationship to a patient's clinical state but are presumed to substitute for

a clinically important measure). With respect to diagnosis, current accuracy is already highly sensitive and specific as compared to the neuropathological standard. In contrast, there is much work needed to predict who will develop AD in the nondemented population. As a surrogate outcome measure in studies evaluating new treatments, neuroimaging has great potential to reduce the length and cost of clinical trials because it can be collected long before current clinical outcome measures are available. The 5-year public-private Alzheimer's disease neuroimaging initiative (ADNI) is an example of ongoing validation trial toward this goal<sup>8</sup> (<http://www.loni.ucla.edu/ADNI>).

Although brain imaging is not currently applied in a clinical context for diagnosing AD except as a means of ruling out other causes of dementia, such as strokes or tumors, it has been widely accepted that benefits would accrue to patients and individuals at risk with improved assessment of brain integrity; structural and functional imaging are likely candidates since they may provide more direct information than inferences based on behavior, genetics, or other systemic indicators, such as CSF metabolites.<sup>9</sup> As described in this volume and elsewhere, early detection of the disease has been a major focus of a variety of neuroimaging techniques, including fMRI, structural MRI, and PET. Recently, these techniques have also been found to be useful in monitoring cognitive and pathological progression of the disease, as well as monitoring response to clinical intervention and treatment.<sup>10-14</sup>

## MEETING ETHICAL CHALLENGES

With each new technique comes the burden of validation against current standards for diagnosis and disease state monitoring. The consensus report on the use of MRI and PET for Clinical Diagnosis of Dementia<sup>7</sup> provides guidelines based on the state-of-the-art and scientific research. This consensus report was developed to extend the current clinical standards as described by the American Academy of Neurology Guidelines<sup>6</sup> for the use of neuroimaging in clinical diagnosis. With each new application of a technique, there are ethical implications that must be addressed. To complement the other articles in this volume, the editorial board invited us to report on our examination of these implications. To do so, we explored them systematically according to five major themes:

1. overall medical and social consequences of predicting AD using functional neuroimaging,
2. differentiating different clinical subtypes of AD,
3. scanning protocols and modalities,
4. research and clinical ethics issues, and
5. key issues for education, counseling, and communication.

Our discovery and recommendations follow.

### ***Overall Medical and Social Implications of Predicting AD Using Functional Neuroimaging***

As described previously<sup>5</sup> for genetic testing, the potential value of predicting AD must be considered in the context of the meaning of the disease for those affected and those around them. Unintended consequences and counseling further emerged as key areas under this theme.

#### *Meaning of Disease*

- For predictive imaging, the meaning of disease will depend on the specificity of testing tools that are used.
- Changing technologies are going to have an impact on the nosology of the disease, for example, how the professional community classify it and assess significance.
- The value addition of imaging alone compared to other tools in the context of prediction is not clear-cut. A combination of different technologies—genetic testing, proteomics, and imaging interacting in different ways—is likely to achieve the best definition and predictions about AD and related diseases.
- AD may be increasingly viewed as a syndrome rather than a single disease. Advances in technology may lead to its further differentiation. As technologies become powerful and more predictive, the professional community can anticipate a proliferation of subclassifications of the syndrome.
- As presymptomatic testing becomes available, it is likely that people who are actually healthy now and will not manifest the disease for a long period of time will still be included within the classifications. This suggests the acute need for the development and introduction of early and effective interventions.
- It is imperative that research is conducted not only on the development of technology but on how it will be best used clinically and integrated with current health care practices.

#### *Unintended Social, Economic, and Ethical Consequences*

A number of areas on which predictive imaging will have an impact may face unintended consequences. They are:

##### *Health Insurance*

In the current health care system in the United States:

- Requirements by insurers for predictive testing must be articulated and vetted.

- Insurers could ask clients directly to take the test or, if there are laws that restrict that, they can ask people to voluntarily take tests or provide results of tests. If clients refuse to do so, insurers may act on that information. This is one strategy available to insurance companies for not violating certain legal restrictions.

### *Stigma*

Because people live in a cognitively centered world, any information that raises questions about cognitive status of an individual may stigmatize that individual:

- Predictive imaging may expand the pool of disease to people who are much younger, and therefore expand the pool that is stigmatized.
- Both earlier prediction and stigma have the potential to reduce quality of life, including autonomy and the privilege to drive, and other daily functions.
- There may be medical discrimination against people at risk, for example, with respect to eligibility for organ transplantation.

We recognized that in spite of any stigma, some people will have psychological solace from the biologic information.

### *Health care disparities*

Testing might exacerbate existing disparities, largely through access.

- If predictive imaging becomes commercialized, those who cannot afford tests may not be able to get them.
- If some interventions have a high impact on behavior—such as the demonstration that physical or cognitive exercise reduces risk—then knowing about that risk might affect behavior. Then those who cannot afford to pay out of pocket for these tests will not have those kinds of incentives.

### *Counseling*

A great deal of expertise will be required of clinical providers who offer predictive imaging services. In this respect, a cohort of specialists may emerge especially since, recalling counseling in the history of genetic testing, guidelines fell away as primary care providers could not possibly keep up with demand.

- Before any test is offered clinically for which counseling will be needed, the validity of the test, including psychometric reliability and sensitivity, must be in place. Quality assurance analogous to CLIA laboratory

guidelines may be one response to this recommendation. We note that the American Academy of Neurology currently vets tests and identifies those that are ready. Professional institutions have a responsibility to continue to meet and help clarify standard of care in this area.

- Since AD has a significant component of heritability and individuals with a first-degree relative and an ApoE4 allele are believed to have a 40% lifetime risk of developing AD, physicians should be aware of the implications for family members who may be present when testing results are disseminated. Physicians who convey test results to patients should be prepared to field questions from family members concerned about their own risk.

### *Clinical Populations for Screening*

Any discussion of the ethical issues at play for screening imaging for AD must take into account two important facts. The first is that treatments for AD currently have limited effectiveness and the disease is fatal. The second is that even the best imaging test will be prone to some degree of false positive and false negative results. The ethical issues pertaining to which clinical populations should be tested will depend largely on whether or not a definitive treatment becomes available. The screening of certain populations and the accompanying ethical issues will vary depending on whether such a treatment is effective at stemming the progression of AD or can actually reverse the pathologic changes and cure patients. Similarly, there will be a separate set of ethical questions if a treatment is developed that can prevent the disease from occurring when given to presymptomatic subjects. With these important caveats in mind we consider four specific scenarios for clinical screening as follows:

#### *Screen All Individuals for AD When They Reach 65 Years of Age*

- Imaging tests could be added to the panoply of other screening tests (e.g., colonoscopy, mammogram) that are recommended as people grow older. The greatest concern for this scenario is that, even with prevalence rates approaching 10% in this age range,<sup>15</sup> there will be a significant number of false positives. In screening for AD, the benefit of a follow-up confirmatory biopsy or other gold standard procedure does not exist because brain biopsy is too risky. As such the imaging test may be the most definitive measure available and the one on which treatment decisions will be based.
- If relatively benign and effective treatments are developed, a relatively larger percentage of false positives in this scenario can be tolerated. However,

initial clinical trials of the  $\beta$ -amyloid vaccine, in which 6% of vaccinated patients developed a meningoencephalitis,<sup>16</sup> serve to remind us that (potentially) potent therapies are rarely completely benign.

### *Screen Patients Who Already Have Some Mild Cognitive Impairment*

- The true prevalence of AD in the mild cognitive impairment population will be greater than in a sample of subjects without cognitive complaints. The positive predictive value of the test (the probability that a positive result is a true positive) will increase, giving clinicians greater confidence that a potentially potent but toxic treatment is being given to patients who actually have pathology.
- The rate at which cognitive and functional decline is likely to occur may be projected from this population.
- A downside to this scenario is that the AD pathology in this cohort of patients is already more advanced and may prove less amenable to treatment.

### *Screen Asymptomatic Individuals with Risk Factors*

The scenario to screen asymptomatic individuals with risk factors, such as family history, ApoE genotype, older age, or some combination of these variables, analyses represents the most typical of the cost-benefit analyses made by physicians considering testing a patient for a particular disease. Many patients and their families in this scenario may find it useful, in terms of planning for the future, to know with some certainty that the cognitive loss they are already suffering is due to AD. At the level of intervention, a physician might encourage or limit treatment, such as with a cholinesterase inhibitor, especially for an AD patient with limited means or multiple other medical conditions that can be treated more effectively. However:

- Given the lack of definitive treatment, the clinical value of making a diagnosis of AD is considerably reduced.
- Given the relatively slow course of the pathology and the persistent social stigma surrounding AD, there is more potential harm in making the diagnosis of AD in asymptomatic individuals who may not become ill for another 5 to 15 years.

### *Screen Everyone Who Wants a Scan*

A great deal of variability exists among consumers in the desire to be tested. This variability will exist as long as treatments are lacking, but will likely

diminish as treatments become available. In light of this, and for this scenario as well as the others described above:

- Methods are needed for guaranteeing confidentiality of results.
- Guidelines are needed for defining who should have access to results of testing when they are purchased for reasons that are not medically indicated.
- Research is needed to assess the impact of results on personal liberty, self-image, job security, and patient-physician and family relationships.
- Currently unregulated methods for direct consumer advertising or direct physician advertising for imaging would benefit from professional self-regulation and guidelines for best practices.<sup>17</sup>

We further note that the greater predictive power combined with the growing number of people with AD might be the brick that breaks the back of the current health care system.

### *Scanning Modalities*

Efforts to improve the quality of imaging technologies are ongoing in a variety of domains, notably by increasing the availability of techniques and comfortable, well-validated clinical applications.

#### *Patient Comfort*

- Making techniques maximally comfortable, fast, and efficient is essential to enable patients, who have difficulty tolerating medical procedures, to be evaluated. This includes rapid acquisition protocols that will make it easier for patients to remain still enough to undergo the procedures.

#### *Standardization of Acquisition and Analysis Protocols*

- Standardization of acquisition and analysis protocols is vital to the replicability of data across sites, equipment, and software. Performing identical procedures does not ensure that acquisition routines result in comparable image quality with respect to parameters such as signal to noise.
- Quality assurance data should be collected on a regular basis.

#### *Cost Reduction in Acquisition and Analysis*

The information contributed by neuroimaging techniques must improve in a manner that justifies its cost by increasing sensitivity and specificity of differential diagnosis for decision making.



- At the present time, only relatively few, elite centers are capable of performing reliable volumetric analyses on structural MRI images. PET imaging of radioligands is expensive. If neuroimaging begins to play a larger role in routine clinical standard of care in AD, cost-effectiveness must be demonstrated.<sup>18</sup> Early diagnosis that enables earlier treatment that in turn delays the placement of a patient in a nursing home is one measure of cost reduction.<sup>19</sup>
- Increased patient numbers and procedures will justify acquisition operations costs for more medical centers.

### *Validation Studies for Diagnostic/Treatment Decision Making*

#### *Individual Patients*

- The majority of current studies of imaging techniques involve comparisons of groups of well-characterized subjects, but clinical decisions must be made for individuals. Standardized, reproducible protocols in which sensitivity and specificity of different measures are well established will be crucial in making decisions for individual patients.<sup>20-22</sup>
- Practices of disclosure of positive test information will need to take into account the nature of the experimentally or clinically validated test as well as the volunteer who may or may not wish to be informed of results.

#### *Diversity of Ethnicity and Age*

Normative measures generated from one gender, ethnic, or age group may not generalize to all.

- Diverse populations should be included in all development efforts and this information should be routinely reported in normative samples.
- Clinical trials will be enriched by expanding study cohorts to include older adults in whom treatments that act on AD pathology are likely to show an effect.

#### *Populations with Comorbid Disease*

- Patients in communities with inadequate preventive care often are at risk for comorbid illnesses, such as substance abuse, head injury, or vascular disease. Decision rules based on individually presenting diseases do not always easily apply. To enable generalization to these populations, studies are needed to assess the impact of comorbidities on decision-making rules.

### *Predictive Validity and Priorities for Imaging*

Unless an imaging biomarker has been tested to assess whether it is associated with later change through prospective longitudinal studies, it should be used with extreme caution.

- Errors in prediction could result in situations in which patients who need medication are denied it and patients who cannot benefit from medication are exposed to its risks.
- Once positive predictive value is achieved clinical trials over clinical management are favored as a priority given the information trials bring to clinical treatment of many patients.

### *Surrogate Markers for Speed and Cost-Effectiveness of Clinical Trials*

#### *Surrogate Markers Are Viewed to Have Significant Potential Benefit.*

- Effective surrogate measures from MRI or PET that predict early clinical benefit would accelerate the pace of clinical trials.
- Surrogate biomarkers that are more sensitive and specific to the clinical progression of AD than current clinical measures<sup>23</sup> will yield more power to detect treatment effects and the need for fewer participants in clinical trials.

### *Incidental Findings in Predictive Neuroimaging*

Findings of possible clinical significance are detected in the brain both in clinical workup and in research. Previous studies of incidence suggest that the rate of occurrence of such findings is about 1–2% in the general population<sup>24</sup> and the data suggest that it may be substantially higher in older cohorts.<sup>25</sup>

- As reported elsewhere,<sup>26</sup> embedded in research imaging studies should be the anticipation of such findings and a protocol in place for managing them.
- In clinical medicine, findings are followed up routinely, although the rising cost-benefit ratio as in genomic testing has become a source of concern.<sup>21</sup>
- In the case of predictive imaging, however, much remains to be learned about functional anomalies. Current recommendations pertain only to anatomical images obtained for research and as yet, not to single subject metabolic measures.
- The greatest risk lies in misclassifying a finding as a positive indicator of disease.

### *Therapeutic Benefits*

Although predictive neuroimaging has not yet reached its potential utility, we recognize future therapeutic benefits and procedures.

- To the extent that patients with various dementias will benefit differentially or experience different side effects from different medications, imaging in the future may enable selection of the optimal treatment or monitor progression more sensitively than is presently possible.
- It may become necessary to have secondary trials or repeated imaging of patients on medication after medications are released to the public.

### *Research and Clinical Ethics*

Neuroimaging research in AD raises a number of important well-known challenges in the domain of research ethics. These include issues such as informed consent, confidentiality, and privacy. The potential translation of neuroimaging research to clinical care intersects with a broader and significant number of potential ethical, legal, and social issues. In particular, it will yield sensitive personal information that will have to be handled with utmost ethical care. National and international laws and guidelines for research need to be carefully considered in the research design and recruitment phases of research given the current negative risk-benefit trade-off for individual AD volunteers often recruited from the pool of vulnerable volunteers (e.g., mentally disabled persons as alluded to in the Common Rule; Federal Policy for the Protection of Human Subjects; 45 CFR 46). Autonomy, cognitive privacy, and cultural sensitivity are of paramount importance. As stated in the *Belmont Report*, any participation of vulnerable volunteers, including patients with AD, should be based on the needs of science and for improving clinical care.

### *Subjects with Decisional Capacity*

Many people suffering from AD remain capable of understanding and deciding whether they want to participate in a specific research project.

- It is the responsibility of PIs to ensure that the best conditions are met for the volunteer to be fully informed of the risks and benefits (if any) of a study.
- The setting must be free of coercion either from members of the research team or others (e.g., family member, health care provider) who can exert undue influence on a volunteer.
- Whenever feasible, AD volunteers who can consent to research should be recruited before those who cannot.

### *Subjects with Limited Decisional Capacity*

Additional ethical complexity is created when volunteers cannot directly give informed consent either because they are declared legally incompetent in matters of research participation or lack the capacity to consent.

### *Availability of Advanced Directives for Research*

When a volunteer has written specific advanced directives<sup>27-29</sup> for research participation, such as a research living will, guidance is available about prior autonomous wishes. These may be wishes, such as the willingness to participate in minimal risk research only or not to participate in research involving scanners. The pure autonomy standard, that is, precedence of previously expressed autonomous judgments, should apply.

### *Absence of Advanced Directives for Research*

The absence of advanced directives for research is the likely case for most prospective research subjects. In the absence of specific directives:

- The volunteer may have designated, through a durable power of attorney, a proxy decision maker (sometimes called a research proxy) empowered to make research participation decisions. The decision lies in the hands of this formally designated research proxy based on the wishes of the volunteer and applicable legal provisions of the jurisdiction.
- In the absence of a research proxy, practices can vary depending on the circumstances and the applicable legal and regulatory context. An existing health care power of attorney may serve as a research decision maker. A legal guardian, i.e., a court-appointed legally authorized representative, or an informal decision maker (typically from the volunteer's family), may give consent for research participation. Following any of these options, the proxy decision maker should respect the previous wishes of the volunteer if known. Otherwise, when clear wishes are unknown, the proxy should use the best interest standard; that is, based on the values and prior wishes of the volunteer, judge what is in his or her best interests.
- When possible, the assent of the volunteer should be obtained even though assent is not a substitute for consent mechanisms. Signs of objection (dissent) from the volunteer should be considered a significant indication of refusal.

### *Shared Databases*

Large neuroimaging consortia studying AD have created data banks that require specific security and deidentification measures.

- Deidentification measures have become especially important given that some cranial features acquired during imaging could possibly be used to reidentify volunteers.<sup>30</sup> Risks related to the crossing of information and the limits of deidentification and anonymization are considerable, even if the most effective methods are used.
- Further complicating the issue of brain databases is the discovery of incidental findings on secondary analysis of the data. Some of these issues are familiar to other areas of research, such as genetics. Cross-fertilization of approaches and standards are highly relevant but the practices of obtaining consent in AD and addressing some of the newer issues in the context of neuroimaging are still evolving and call for empirically evaluated practices.

### *Hype versus Clinical Hope*

To date, FDG-PET has been approved by the Centers for Medicare and Medicaid Services to help distinguish AD from frontotemporal dementia. However, no neuroimaging procedure is currently used to rule-in, that is, definitively diagnose AD. The predictive power of neuroimaging remains to be proven despite positive impressions fueled hopes for technology transfer and commercialization and marketing practices.

- Once sufficiently validated for clinical use, however, conflicts of interest and tensions between academia and the private sector, and possibly within large academic consortia can be expected to rise.
- In spite of the current limited application of neuroimaging to health care in AD, discussion of the ethics of predictive neuroimaging should be encouraged given the prospects for clinical translation and the potential pitfalls of unattended risks for all parties involved.

### *Education and Policy*

History predicts that the process of rolling out new technology, such as imaging, for an application such as detecting neurodegenerative disease, happens on a continuum. With off-label uses already in existence and active information dissemination throughout the media, Internet, and other sources, the full introduction of the technology can be anticipated. Working to maximize the generalizability of results is imperative. In the context of education and

policy, therefore, four major considerations are key: the content of education, education about research, driving forces in utilization, and professional responsibility.

### *Content of Education*

Key factors for education about the predicting AD with imaging are:

- Clarity about technical readiness and meaningfulness of data given a dynamic state of the art, breadth of uses including the use of imaging as an adjunct to clinical diagnosis and its predictive potential;
- Characteristics of imaging that differentiate this technology from others, including, for example, the potential to uncover latent disease;
- Relative degrees of specificity (e.g., genetic markers vs. individual brain regions), regulatory and access controlled at level of device;
- Individuality in methods and interpretation;
- Cost, time, invasiveness, and tempered promise.

### *Education about Research*

The group recognized the importance of K-12 science education as first priority for education about science in our society. Beyond this:

- Informed consent, incidental findings, privacy, access to data and sharing are key priorities.
- Elucidating natural caveats of neuroimaging research defined by the process of discovery, and different types of altruism that might underlie participation by volunteers for diagnostic and predictive imaging research are also key ethical and educational challenges.
- All relevant groups will benefit from education about neuroimaging research, including physician, specialty societies, advocacy, national and local level, the media, patients, families, caregivers, conservators, insurers, trainees, funders, and government officials, such as Congress and the CDC.

### *Utilization of Technology*

Many of the groups that represent cores for education also represent major driving forces in technology transfer and utilization.

- Constraints on utilization are access and cost, age of populations, time limitations of physicians, reimbursement for screening versus diagnosis, and ethnic differences.

- Advocacy groups can play a role in optimizing the transfer of technology into clinical use through objective education, dissemination of validated and vetted information, legislation, priority setting based on scientific and political pressure, and issue identification through short- and long-term planning.

### *Professional Responsibility*

#### *Professional Responsibility Spans Both Funders and Investigators*

- Even as regulations are developed, the burden still rests on individual physicians to adopt guidelines responsibly and to engage in professional self-regulation modeled, for example, by the American Academy of Neurology.<sup>6</sup>
- Sponsors of research should continue to invest and create mechanisms for knowledge transfer. Communications liaisons for large-scale programs can serve the knowledge transfer role effectively.
- Taking into consideration all the factors discussed in this report, investigators themselves bear a significant burden to operationalize plans for information dissemination and transfer results from research on predictive imaging.
- A policy equivalent to the Genetic Nondiscrimination Act for insurance, eligibility for services, and employment is viable and may be needed for brain imaging.

## CONCLUSION

The goal of predictive neuroimaging is to improve upon the human condition in neurodegenerative disease by providing reliable information about treatment outcome, rate of decline, and possibly therapeutic benefit to slow or even halt its relentless progression. These worthy goals are challenged by the still relatively immature state of the technology. Past events in the history of neuroscience and clinical medicine have taught us that such challenges must further take into consideration how culture and values differ in terms of what defines benefit and risk, and who will benefit and who is at risk. Methods must be set in place to assure not only maximum safety, comfort, and protection of subjects and patients, but also the educational and policy needs of all stakeholders.

We explored many issues here, resolved some, and left others open. Clearly, we also left many completely untouched. Overall, we conclude that as ethical paths are followed right alongside the development of powerful imaging tools, the future will hold ever-greater promise for AD patients and their families.

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