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Disclosure of amyloid imaging results to research participants: Has the time come?

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Abstract

Amyloid imaging is becoming an increasingly popular tool in clinical research on Alzheimer's disease. In early studies, questions of whether to disclose amyloid imaging results were largely mooted by the immature state of the science. Lack of clarity as to what constituted a positive scan and what a positive scan meant from a prognostic or diagnostic perspective required investigators to advise research participants that, because their scans could not be meaningfully interpreted in a clinical sense, individual research scan results would not be disclosed. With a focus on the most widely used research tracer, Pittsburgh Compound B (PiB), we consider how advances in amyloid imaging are raising new questions about the appropriateness of withholding research results from study participants. We conclude that, although it remains advisable to withhold amyloid scan results from cognitively normal participants, it is no longer reasonable to uphold policies that unilaterally advise research participants with documented cognitive impairment that their PiB scans are uninterpretable. We outline circumstances that we believe compel investigators to provide research participants with the option of receiving their PiB scan results in a carefully managed fashion. Our findings can potentially be generalized to research involving all validated amyloid tracers.

Keywords

Amyloid; Neuroimaging; Mild cognitive impairment; Research ethics; Human subjects; Positron emission tomography; Biomarkers; Alzheimer's disease

The proliferation of human amyloid imaging research and associated accumulation of evidence for what constitutes a positive versus a negative research scan are raising unprecedented questions about the appropriateness of disclosing individual research results to research participants, particularly those who do not yet have a clinical diagnosis of Alzheimer's disease (AD). Given that approximately 25% of cognitively normal research participants and >50% of those with mild cognitive impairment (MCI) are amyloid-positive (for review, see Klunk [e1]), the question of whether to disclose such results has implications for a significant proportion of those who volunteer for amyloid imaging research. Disclosure of amyloid imaging results also is relevant to the 5%–10% of clinically diagnosed AD patients in trials who are found to be amyloid-negative [e1]. In this study we describe the conditions under which we believe investigators are obligated to present to participants the option of receiving the results of amyloid imaging research scans. Although our findings have implications across studies with all validated amyloid imaging tracers—and may also apply to studies of other in vivo amyloid biomarkers—we center our

discussion on experience with Pittsburgh Compound B, as it is the most widely studied radiotracer.

1. Amyloid imaging in human subjects of research

Pittsburgh Compound B (PiB) is a radiotracer designed for use with positron emission tomography (PET) imaging to detect fibrillar amyloid (A β), a major component of the neuritic plaques associated with AD in the human brain[e2,e3]. Approximately a decade ago, PiB research expanded from animal studies to investigations involving human subjects [e4,e5]. In addition to establishing safety, initial studies were performed in persons with AD and were aimed at demonstrating an in vivo pattern of amyloid deposition that closely matched that expected from previous postmortem studies [e6,e7]. Eventually, it became possible to directly correlate these in vivo findings with postmortem neuropathology in the same individuals and it became increasingly clear that the in vivo PiB PET signal was a good representation of postmortem pathology [e5,e8–e12]. Cognitively normal participants were included in these early studies as presumed amyloid-negative controls. Although this proved to be the case in essentially all cognitively normal control participants <50 years of age, cases of amyloid-positive controls began to appear with some frequency (~20%–50%, depending on age and apolipoprotein E gene status) in older research participants [e13–e16]. After the initial focus on participants with AD and cognitively normal controls, the third major category of participants to be included in amyloid imaging research studies applied to those with mild cognitive impairment (MCI) [e17–e24]. As previously noted, approximately one-half to two-thirds of those with MCI were found to be amyloid-positive [e1].

2. Development of reliable methods for classification of positive and negative scans

The finding that cognitively normal subjects could appear to have brain amyloid by PiB PET scans was consistent with previous postmortem studies [e24,e25]. In addition, this finding required that reliable methods be developed to distinguish cognitively normal controls with and without significant amyloid deposition. In the context of the present topic, virtually all arguments for the release of research results to human subjects require that validity of scientific findings be established [e26–e28]. As such, questions of whether and when to release PiB research scan results to participants in early human studies were mooted by the immature state of the science of amyloid imaging. Throughout the past decade, respect for human subjects and their right to basic information about the findings of the research was typically achieved by informing potential subjects, at the time of enrollment, that PiB research scans cannot be meaningfully interpreted in a clinical sense and, therefore, individual results would not be disclosed.

This practice now requires reconsideration. As noted, one *sine qua non* is the ability to accurately classify the amyloid scan itself as positive or negative. Considerable research has been devoted to accurately detecting amyloid positivity using PiB PET by both quantitative [e4,e13,e15–e18,e20,e22,e29–e41] and visual-read approaches [e30,e32, e42–e46]. Much progress has been made and it has been shown that the quantitative and visual-read approaches correlate well with each other [e32,e45,e46], and both correlate well with postmortem amyloid histopathology [e5,e9–e12]. The aforementioned methods were often focused on defining amyloid positivity in cognitively normal controls, where the task is most challenging. Although the possibility of an inconclusive PiB scan remains, MCI and AD patients who are amyloid-positive are usually highly and obviously positive, making the likelihood of an inconclusive PiB scan small in these groups. Therefore, if we accept this position that we can dichotomize PiB scans as positive and negative with sufficient accuracy, the focus then becomes whether or not this information contains meaningful

clinical information for an individual research participant with a clinical diagnosis of MCI or AD. If so, then respect for human subjects of research means that it may be no longer reasonable to uphold policies that unilaterally advise research participants with documented cognitive impairment that their PiB PET research scans are uninterpretable. Consequently, there is a pressing need to revisit the issue of what, if any, circumstances compel an investigator to disclose individual PiB scan results to research participants.

3. Clinical relevance of positive and negative amyloid PET scans

The findings just described with regard to AD patients and amyloid-positive control subjects, and to an even greater extent the issue of amyloid-positive and -negative participants with MCI, raise serious questions of what should be told to research participants and what can be ethically with-held from them. Although the data beginning to accumulate suggest that amyloid-positivity in cognitively normal control participants may be a poor prognostic sign [e10,e22,e47–e49], it seems to remain sound practice to tell cognitively normal participants that their amyloid scans cannot be interpreted in a clinically useful manner in individual cases and so they will not be informed of the results of their scan. This view is widely held in the AD/aging research community at present.

Another practice that seems very supportable is the revelation of amyloid PET scan results to a person clinically diagnosed with AD dementia. Although the vast majority of patients diagnosed with clinical AD in expert centers will have a positive PiB PET scan that may not add relevant information [e1], the amyloid-negative scans discovered in 5%–10% of clinically diagnosed AD patients would carry important clinical information. Recent recommendations for diagnostic criteria include dementia patients with negative amyloid PET scans in the category “Dementia—unlikely due to AD” [e50]. This practice is supported by the postmortem data showing a close correspondence between in vivo PiB PET and histopathology [e5,e8–e11]. In fact, the first U.S. Food and Drug Administration (FDA)-approved amyloid PET tracer, [F-18]florbetapir, was approved for the specific indication that a negative scan “reduces the likelihood that any cognitive impairment is due to AD” [e51]. Thus, a negative amyloid PET scan is likely to change the diagnosis and treatment of a person thought to have AD dementia prior to the scan.

Although a consensus may be easier to achieve at these two ends of the cognitive spectrum, intermediate levels of cognitive impairment such as MCI have not yet yielded the same degree of consensus in the field. Longitudinal clinical studies have shown that not all MCI subjects progress to clinical AD and a sizeable proportion may revert to normal cognition [e52–e56]. Likewise, neuropathologic studies have shown that not all MCI subjects have the pathologic hallmarks of AD in their brains [e57,e58]. Taken together, this implies that some MCI subjects will progress to AD and some would either not progress, would normalize, or would develop a different neurodegenerative disorder. The ability to predict which MCI subjects are more or less likely progress to clinical AD is of obvious importance and has great relevance for the individual subject. Early longitudinal follow-up studies support the presence of high PiB retention as a sensitive predictor of progression to clinical AD, with over half of all PiB-positive MCI cases converting to clinical AD in up to 3 years [e19,e21–e23,e59–e61]. Conversely, PiB-negative MCI subjects progress to clinical AD in the short term far less frequently, at rates of 7% [e22] to 17% [e59], which are similar to those expected in the general population of older adults [e62]. This suggests that PiB PET testing may provide information that is clinically relevant for distinguishing progressive from non-progressive MCI.

4. Regulatory guidance on disclosing research results and implications for amyloid imaging studies

The issue of releasing research results is a relatively recent focus of attention in the literature on human subjects' protection. Alleging that the Code of Federal Regulations (CFR) does not provide comprehensive guidance on the rights of individuals to access their research records, in 1999 a National Bioethics Advisory Commission (NBAC) panel on research involving human biologic materials undertook an analysis of the issue [e26]. The NBAC's analysis culminated in a recommendation that research results be carefully disclosed to human subjects when the following three conditions are met: (a) the findings are scientifically valid and confirmed; (b) the findings have significant implications for the subject's health concerns; and (c) a course of action to ameliorate or treat these concerns is readily available [e26]. These recommendations predate the development of amyloid imaging, but provide a logical starting point for our discussion as they have been central to related deliberations concerning the disclosure of research results for other AD biomarkers, like genetic tests.

4.1. Condition A: Validity of scientific findings

Although the NBAC did not distinguish between releasing individual-level results and aggregate findings of research, subsequent commentators have generally done so. Regarding the release of aggregate results, the requirement that research findings are valid and confirmed has generally been interpreted by investigators and ethicists to require that results be peer-reviewed prior to disclosing findings to participants (e.g., Fernandez and colleagues [e63]). Proponents of disclosing individual-level research results, particularly in the context of genomic research, have interpreted the requirement for scientific validity or confirmation to mean that tests on serum or tissue specimens be conducted in a Clinical Laboratory Improvement Amendments-approved laboratory. Several commentators have noted the ambiguity surrounding confirmation of scientific validity for other forms of individual research results [e64–e66]. In the context of PiB PET, we assert that the validity of a scan result for an individual with MCI or AD can be assured by requiring that positivity be established through either quantitative or qualitative (visual) ratings using a method that has been peer-reviewed. The practice of explaining what a positive, negative, or indeterminate PiB scan result may mean for a participant will likely involve going beyond the disclosure of current study results to provide participants with a lay version overview of results from previously published research and/or consensus statements from professional organizations. Without this second overlay of information, the disclosure of individual PiB scan results would pose unwarranted risks. For example, one may be falsely reassured by a negative PiB scan result if the discloser did not emphasize that cognitive impairment may be due to a non-AD dementia process. As Fernandez and colleagues underscored, the possibility of harm for some research participants does not justify withholding the offer to share research results. We contend that, when the possibility of harm is foreseeable, investigators assume an additional responsibility—that of minimizing such harm.

4.2. Condition B: Implications of findings for subject's health concerns

Condition B, that the findings have significant implications for a participant's health concerns, may have particular relevance in the context of MCI. For participants with clinical AD, the diagnosis of dementia is already in place and positive scans offer an additional piece of evidence for a diagnosis that has already been disclosed on the basis of a clinical exam, neuropsychological testing, and other brain imaging. Although some individual participants with AD may see great value in knowing their positive scan results, it is difficult to argue these positive scan results have "significant implications for a participant's health concerns" in the context of an existing AD diagnosis. However, as discussed earlier, the

negative scan results that are expected in 5%–10% of clinically diagnosed AD patients would hold significant implications. Persons with MCI, on the other hand, are living with marked uncertainty about their prognosis. Although a negative or indeterminate scan result may not attenuate such uncertainty, a positive scan result may afford an individual the opportunity for a better understanding of their prognosis. Of relevance to indeterminate scans, it is worth noting that a survey of 504 participants in AD-related research and Medicare beneficiaries found that the overwhelming majority (89%) want to know the results of studies using their stored biologic samples, even if the results are of uncertain clinical significance [e67].

Arguments in favor of disclosing research results are grounded in the basic assumption that respect for persons means that individuals have the right to receive the results of the research that they have made possible. We maintain that of even greater significance is respecting the right of a participant to decide individually whether or not to receive their own research results. Respecting these individuals means acknowledging and supporting their right to determine whether they are willing to receive information when counseled in advance regarding the level of certainty associated with such results. We also interpret respect for persons to imply an obligation to give participants the option of receiving either individual or aggregate study results, or both. In the context of research on cognitive impairment, our argument is vulnerable to the criticism that a cognitively impaired person, even at the MCI level, may lack the capacity to fully understand his or her test results and/or their implications. We maintain that if an individual has been determined capable of consenting to a PiB scan study, barring a significant change in cognitive status, then that individual should be capable of a basic understanding of the research test's outcome. In the event of a significant decline in cognitive status, then the individual's study partner or proxy of record would become the primary recipient of the option to learn of the results, with the patient's level of involvement determined by considering their desire for and capacity to appreciate such information.

4.3. Condition C: A course of action is readily available

The final requirement put forth by NBAC, that research results be disclosed when there exists a readily available course of action to ameliorate or treat concerns raised by research results, is deserving of careful consideration. Although AD is neither curable nor preventable with current therapies, a broad view of what it means to develop AD requires consideration of how the disease affects quality of life. We maintain that, because advance planning can be undertaken to promote quality of life in advanced AD, a position requiring the availability of a medical intervention to alter or arrest the underlying AD pathology would be untenable. Recognizing that the lack of a cure or prevention for AD is a valid concern and may indeed deter some individuals from choosing to learn their test results, we believe that, following the precedent of genetic testing protocols [e68,e69], a clear discussion of what actions one may and may not be able take based on one's test results should be a central component of the informed consent process. Under this model, the participant's personal definition of a meaningful course of action becomes the guiding determinant of whether to disclose results.

A similar argument, albeit not specific to a particular research test or disease process, has been put forth by the U.S. Department of Health and Human Services (DHHS) [e70]. In response to the NBAC report, DHHS raised concerns that the requirement for Conditions B and C may preclude investigators from complying with the Health Insurance Portability and Accountability Act (HIPAA) privacy regulation, which grants individuals the right to access information about themselves that is generated in a research context[e71]. DHHS acknowledges that research participants may have varying personal perspectives on what information is of significance to their own health and recommends further analysis of this

issue. As demonstrated herein, amyloid imaging research with symptomatic individuals provides a very useful context for such an analysis.

5. Conclusions and future directions

Advances in amyloid imaging raise vexing questions about the circumstances under which investigators should disclose individual research results. We have argued that the return of validated amyloid imaging results may be particularly relevant to persons with MCI and in those patients with amyloid-negative AD, but not for cognitively normal individuals. Given that the disclosure of amyloid status to research participants with MCI would require multiple safeguards to minimize the potential for harm, a wide range of stakeholders, including research participants, investigators, and regulators, should be engaged in subsequent steps to address this issue. Comprehensive pre-disclosure counseling and carefully managed disclosure session results will be necessary to ensure that individuals with MCI or AD dementia who are considering receiving their amyloid imaging results are equipped with the information and support required to make such a decision.

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