Preclinical Alzheimer Disease and the Electronic Health Record

Balancing Confidentiality and Care

Seth A. Gale, MD, Judith Heidebrink, MD, Joshua Grill, PhD, Jonathan Graff-Radford, MD, Gregory A. Jicha, MD, PhD, William Menard, BA, Milap Nowrangi, MD, Susie Sami, MA, Shirley Sirivong, BA, Sarah Walter, MSc, and Jason Karlawish, MD

Correspondence
Dr. Gale
sagale@bwh.harvard.edu

Neurology® 2022;99:987-994. doi:10.1212/WNL.0000000000201347

Abstract

Because information technologies are increasingly used to improve clinical research and care, personal health information (PHI) has wider dissemination than ever before. The 21st Century Cures Act in the United States now requires patient access to many components of the electronic health record (EHR). Although these changes promise to enhance communication and information sharing, they also bring higher risks of unwanted disclosure, both within and outside of health systems. Having preclinical Alzheimer disease (AD), where biological markers of AD are identified before the onset of any symptoms, is sensitive PHI. Because of the melding of ideas between preclinical and "clinical" (symptomatic) AD, unwanted disclosure of preclinical AD status can lead to personal harms of stigma, discrimination, and changes to insurability. At present, preclinical AD is identified mainly in research settings, although the consensus criteria for a clinical diagnosis may soon be established. There is not yet adequate legal protection for the growing number of individuals with preclinical AD. Some PHI generated in preclinical AD trials has clinical significance, necessitating urgent evaluations and longitudinal monitoring in care settings. AD researchers are obligated to both respect the confidentiality of participants' sensitive PHI and facilitate providers' access to necessary information, often requiring disclosure of preclinical AD status. The AD research community must continue to develop ethical, participant-centered practices related to confidentiality and disclosure, with attention to sensitive information in the EHR. These practices will be essential for translation into the clinic and across health systems and society at large.

From the Department of Neurology (S.A.G.), Center for Brain/Mind Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Neurology (J.H.), the University of Michigan, Ann Arbor, MI; Institute for Memory Impairments and Neurological Disorders (J.G., Shirley Sirivong), University of California Irvine; Department of Neurology (J.G.-R.), Mayo Clinic, Rochester, MN; Department of Neurology (G.A.J.), Sanders-Brown Center on Aging, University of Kentucky, Lexington; Memory and Aging Program (W.M.), Butler Hospital; Division of Geriatric Psychiatry and Neuropsychiatry (M.N.), Department of Psychiatry, Johns Hopkins University School of Medicine; Brain Health and Memory Center (Susie Sami), University Hospitals, Cleveland Medical Center; Alzheimer's Therapeutic Research Institute (S.W.), University of Southern California; and University of Pennsylvania (J.K.), Departments of Medicine, Medical Ethics and Health Policy, and Neurology, Penn Memory Center.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Competing interests are noted. These include protecting the privacy of research participants and sensitive health information and making clinically relevant research information available to providers who are caring for these persons. Several strategies are available to enhance protection of confidentiality and enable selective access to sensitive information outside of research. The guidelines about how to manage specific types of preclinical AD research data (i.e., prioritizing what to exclude from the EHR given associated risks of potential harms to participants) may be helpful to researchers.

The article processing charge was funded by Alzheimer Clinical Trials Consortium, NIA, NIH.

Glossary

AD = Alzheimer disease; **ARIA** = amyloid-related imaging abnormalities; **CoC** = certificate of confidentiality; **EHR** = electronic health record; **GDPR** = General Data Protection Regulation; **PHI** = personal health information.

Years before the symptomatic stages of mild cognitive impairment or dementia, the pathologic changes of Alzheimer disease (AD)—the most common cause of these syndromes—appear and can be detected using biological marker (biomarker) tests. Discoveries of molecular brain imaging and CSF and plasma assays are revolutionizing the definition of AD. The field is moving toward an entirely biological framework, where diagnoses will likely involve determining sequential, pathologic changes of amyloid, tau, and neurodegeneration.[1,2] Preclinical AD describes a stage where biomarkers indicate the diagnosis of AD in the absence of symptoms.[3,4] Preclinical AD could be understood as an early disease, even as health systems, patients, and society begin to embrace it as an asymptomatic stage.

Preclinical AD, while distinct from symptomatic stages, can be thought of as the start of the AD continuum. Diagnosing preclinical AD is not presently standard of care in clinical practice. Ongoing research seeks to define predictors and discover treatments to slow disease progression. At present, obtaining CSF and PET scans for evaluating AD biomarkers in cognitively normal individuals is primarily limited to the context of clinical research. AD biomarker tests have been essential in determining eligibility for secondary "prevention" trials, where results that suggest a risk of developing symptoms are used as inclusion criteria.[5,6]

As long as preclinical AD remains a research and not a clinical construct, researchers, providers, and patients-as-participants face a set of complex, ethically charged opportunities and challenges. Many of these relate to the recording of research results in electronic health records (EHRs).

Opportunities and Risks With the EHR in Preclinical AD Trials

Electronic health records are increasingly used to systematize the collection of patient health information in a digital format.[7] EHRs have a similar utility in research. In conjunction with clinical trial management systems and other platforms in research, EHRs can facilitate scheduling, organize study visits, execute study procedures, and acquire and view study data.

The EHR is the main digital interface with the health system used by preclinical AD research teams for both observational and interventional trials. Researchers can order study tests, such as brain MRI and PET scans, through the EHR. Depending on the parameters for EHR access, these orders and test results may be viewable in the EHR. In preclinical AD drug trials, for example, the EHR may be used for the ordering and administration of the research drug. Research-equipped pharmacies and study teams rely on the EHR to place drug orders, verify order accuracy by multiple parties, and execute and document the drug administration protocols. Even more routine study visits, inclusive of physical examinations or interviews, may require scheduling through an EHR and uploading of a participant's informed consent documents.

The EHR provides at least 3 opportunities for research. First, it creates a single platform to be the "container" of all personal health data within a health system, whether from care or research. This centralization of data allows for easy accessibility and cross-utilization between providers and researchers. For example, a subset of investigational AD drugs can cause side effects, such as amyloid-related imaging abnormalities (ARIA) detected on MRI. Because ARIA can have both immediate and longer-term implications for care, access to research MRIs could be clinically actionable in both emergent and nonemergent scenarios.[8] Notably, observational studies may generate less clinically actionable information than interventional trials, each with potentially different needs to facilitate access to providers. Second, the use of an already deployed clinical EHR for preclinical AD trials is often more cost-efficient and feasible for a research site than establishing a separate, research-only digital platform. Finally, integrating preclinical AD research into the EHR is an opportunity for the AD research community to be part of the larger effort toward patient-oriented clinical research and person-centered care. This is a shift that will require ongoing re-evaluation of the more traditional ways that researchers, clinicians, and patient-participants view separations between research and care activities.[9]

OpenNotes, the 21st Century Cures Act, and AD Biomarker Disclosure

Recent legislation presents a challenge to using the EHR for research. In the United States, for example, since April 2021, the 21st Century Cures Act requires patient access to 8 types of clinical notes. Efforts supported by the international OpenNotes movement have already led to ready access to personal EHR data for an estimated 50 million individuals in the United States and Canada.[10-12] Across the world, research to better understand stakeholders' perspectives on, and sociocultural and legal implications of, patient access to EHRs is underway, including in Scandinavia, Japan, and Chile, among other regions and countries.[13-15] Allowing patients access to their health information facilitates patient autonomy but also challenges traditional communication regarding care, especially in the delivery of AD biomarker test results.[10] Historically,

disclosure of this type of information, such as a radiology result that indicates a tumor, has been clinician-mediated, providing time to ensure education and contextualized understanding of the results. With legal requirements to allow individuals immediate access to their EHR, it is a reality that AD biomarker results may sometimes be viewable without concurrent clinician counseling. When disclosure occurs without clinicians, risks for negative outcomes are likely greater. Added research will be needed to instruct opportunities to streamline disclosure processes, including opportunities to reduce or perhaps someday eliminate the role of the clinician. Relatedly, data such as research MRI reports that are viewable by patient-participants in the EHR and include findings of a drug's adverse effects risk unblinding the participant.

Although EHRs present opportunities to enhance coordination and efficiency in research and patient-centered integration of research and care, their use also poses risks to the security and privacy of health information.

Disclosure of Sensitive Information

The harms of unwanted disclosure of personal identifying information in the EHR are amplified when the health information is considered sensitive. In the United States, for example, the federal Health Insurance Portability and Accountability Act treats all identifiable health information as sensitive and equally deserving of protection under its Privacy Rule, although individual states and health systems have historically treated data as *more* sensitive when it poses high personal risks, including mental health and genetic information. These risks are not speculative and include stigma and discrimination.[13] Each of these risks are relevant to disclosure of AD biomarker results for preclinical AD.[14]

Study participants with preclinical AD are generally concerned about the confidentiality of written research records and these concerns are magnified with EHRs, given the greater accessibility and therefore greater risk of unwanted disclosure.[15] Research information revealing preclinical AD status can enter the EHR through several means. For example, biomarker status might be included in the narrative of progress notes or be written directly on a study consent form that is uploaded to the EHR. Preclinical AD trial titles often include terms such as "Alzheimer disease" or "preclinical Alzheimer disease." Despite some EHR system-based measures to minimize access to information by nonstudy team users, such as masking information behind a digital research "flag" (indicator), AD biomarker status might be revealed through the title of a study on the flag or through a hyperlink to the title.

Risks of Stigma, Discrimination, and Change to Insurability

Although preclinical AD trials bring novel scientific opportunities, they also bring novel risks. The defining biomarkers for both preclinical AD and "clinical" (symptomatic) AD are the same. This heightens the risk that an AD biomarker result will be erroneously equated with clinical AD. Even if the biomarker results are inaccessible, simply disclosing through the EHR that a participant is enrolled in a study that references AD may create confusion that the individual suffers from cognitive impairment or dementia.

Biomarker results could also be misinterpreted as signifying inevitable and severe decline. This in turn may lead to stigma whereby people stereotype, patronize, or avoid individuals with preclinical AD. Personal and social consequences of stigma can include social withdrawal, interpersonal stress, depression, and threats to personal identity, such as loss of dignity.[16] The stigma attached to AD seems mainly to be a consequence of the public's expectation of its prognosis as terminal and as inextricably linked to profound disability.[17] Discriminatory behavior in health care settings has included, for example, family physicians keeping "professional distance" from those with AD by avoiding treatment, resulting in poor communication about symptoms, therapeutic nihilism, and feelings of helplessness.[18,19]

Finally, unwanted disclosure of preclinical AD biomarkers could lead to discrimination by insurers, particularly long-term care insurers, because these individuals may be more likely than persons without biomarkers to need long term-care services and supports.[13,20] Laws governing the privacy and security of personal data, including health information, are different around the world, with varying regulations on data disclosure and impacts on the individual's rights. The European Union's General Data Protection Regulation (GDPR) law, for example, implemented in 2018, requires organizations to obtain "explicit consent" from "data subjects" for the processing of any personal health data; compliance has presented challenges for insurance carriers. The GDPR also affirms many individual rights, including the right to access one's medical record when "data are being processed," even while "data controllers" in the EU can limit this right in certain circumstances and access does not have to be free of charge nor provided immediately ("without delay"), as is required by the 21st Century Cures Act in the United States.[12,21] Furthermore, the GDPR does not establish a framework to prevent discrimination resulting from the processing of personal data.[21] Brazil's Lei Geral de Proteçao de Dados law and South Africa's Protection of Personal Information Act, both implemented in 2020, provide a similar legal framework as the GDPR and equally do not address the mitigation of potential harms stemming from sharing of personal health information.[22-24]

In the United States, current laws also do not provide meaningful protection from discrimination by long-term care insurers based on biomarker information, although there are protections against discrimination based on genetic information.[20] There are legal protections in place to protect sensitive information broadly in publicly funded research, but the reality of this protection is less clear. As of 2017, all participants in biomedical research that is funded even partially

by the NIH are covered by a Certificate of Confidentiality (CoC). The CoC attests that disclosure of names or any information, documents, or biospecimens to anyone not connected to the research is prohibited.[25] It does permit disclosure in certain circumstances, including when it is "necessary for the medical treatment of the individual, with consent." Researchers can request a CoC from NIH for health-related studies that are not funded by NIH or another HHS agency. Obtaining a CoC and informing research participants about its protections reflects a person-centered approach to research. A CoC can also serve as a legal buttress to help ensure institutional support to secure protection of sensitive information within a local IT/EHR infrastructure. In sum, individuals with preclinical AD could experience various unintended harms associated with a disease they are at risk for developing but do not have.

Ethical Issues Involved With Biomarker Disclosure in Preclinical AD

Researchers conducting preclinical AD trials face ethical issues related to disclosure and confidentiality.[26,27] Basic principles to provide a framework for AD researchers to understand their obligations and enact practical measures include respect for participants' autonomy and welfare.

An overarching ethical principle to guide researchers in their responsibilities to individual participants is "respect for participants"[28] or "respect for persons." This principle has mostly been centered on the recognition of individuals' autonomy regarding all aspects of study participation.[29] Investigators should consider individual dignity, integrity, privacy, and vulnerability of research participants. Researchers have an obligation to respect participants' autonomy in decisions that relate directly to and stem from their study participation.

Respect for autonomy involves deferring to participants' informed decision to not enroll in a study when the personal risks outweigh the study's potential benefits. Informed consent by trained researchers, for example, must address any biomarker or genetic risk information that will be disclosed with enrollment. This includes a contextualized discussion of potential risks to psychological health with attainment of this knowledge and disease risk implications for genetic relatives. In preclinical AD clinical trials, there is rarely an option to enroll but "not to know;" at least 1 ethical analysis has not supported the need for blinded enrollment.[30] Regarding data privacy and security, researchers themselves must have detailed knowledge of the data processing and storage plan. Consented participants should be able to understand precisely how personal data will be used, where it will be stored, who it will be shared with now and in the future, and how it will be accessed. Conceivably, within the limits of an EHR's functionality, participants could dictate what kind of users (e.g., only study team personnel or only preidentified medical care providers) they are comfortable with having access to sensitive information. Alternatively, the research teams' approach and the extent to which they and the institution can protect participants' sensitive health information within the EHR should be presented through the informed consent process and documented in the consent form.[31] It is of importance that participant engagement in preferences about the methods of privacy protection does not alleviate an institution from its overall responsibility to make all efforts to protect confidential information.

Respect for participants' overall welfare and well-being[28] entails beneficence by actions to avoid individual harms and to maximize benefits. Individual harms related to knowledge of preclinical AD status include potential disclosure outside of the research team. Consent forms should describe the specific, predictable study situations where care providers would be optimally served by accessing the participant's research data. Examples include acute medical situations, particularly ones with direct neurologic care implications and when participants are emergently ill with limited capacity. Nonstudy clinicians such as emergency providers should have immediate access to relevant trial (e.g., MRI images with known prior abnormalities or the mechanism of action of investigational drugs). In this conception of welfare, the protection of a participant's safety and allied efforts to ensure optimal medical outcomes from research over time become more important than protecting sensitive information from unwanted disclosure.

Respect for participants' welfare and well-being also includes protecting an individual's privacy by keeping sensitive information confidential. Given the risk of melding ideas about clinical AD with preclinical AD and so the potential for stigma and discrimination, steps should be taken to keep preclinical AD status confidential from everyone except providers who may need relevant information to address urgent medical concerns.

Recommendations for Preclinical AD and the EHR

EHRs differ across research institutions. Equally, there are differences in institutional policies on the management of electronic research and clinical data and protection of sensitive personal information. In multicenter trials, the risks of unwanted disclosure may be magnified because centers' different EHRs may be governed by dissimilar protection practices, affecting disclosure risks when data are accessed centrally. Risks also accrue if robust security measures are not in place for the data platforms themselves, including for hyperlinks within the EHR to external databases. Although these factors make it difficult to offer broad, technically detailed, EHR-specific recommendations, there are general strategies to apply to local systems to enhance the protection of

sensitive information. This work should consider the specific types of information in preclinical AD research (i.e., brain MRI images, AD biomarker results, and study title) because these carry different levels of risk with unwanted disclosure. These differences in the risk of harm from specific data are relevant to researchers and their IT teams because it may be necessary to prioritize which data to segment or to focus security measures on if there is limited feasibility to make technical modifications to an employed EHR. Ideally, developing a "Best Practices," reasonable use framework for protection of sensitive research information is the goal. Such a model will, ultimately, guide how best to protect sensitive AD-related information in clinical care.

EHR Strategies: Enhancing Protection of Sensitive Information

Three broadly presented EHR strategies can increase protection of sensitive preclinical AD research information. See Table 1 for a summary.

1. Institutions could create an EHR for research information with distinct users that is entirely separate from the clinical EHR. In this case, there should be a simple indication in the individual's clinical EHR that (1) the person is enrolled in a study, with the study team's contact information, but without study title or any details and (2) should care questions arise, the study team may be contacted to provide immediate information or access.
2. Institutions could dissociate research from clinical information within the same EHR, with a focus on separating the specific, sensitive research information that carries the greatest risk with unwanted disclosure (e.g., a study title which includes "Alzheimer disease"; amyloid PET imaging results; see Table 2 below).
3. With a single clinical/research EHR, institutions could implement access control measures for predetermined, sensitive research data that dissuade or prohibit easy access for typical EHR users. These so-called "break the glass" or similar features can act as either an impenetrable firewall or an interface that requires user-input justification for tracking when accessing specific data elements.[32,33] Access control systems are already used in some EHRs to limit and digitally track or prohibit access for certain records, such as those with mental health information or those of an institutions' employees.

Specific Preclinical AD Data

The likelihood and magnitude of harms from unwanted disclosure of preclinical AD research information varies depending on the kind of information (see Table 2). For example, if brain MRI data include only the date the images were acquired, and that they were acquired "for research" absent other details, there is a low risk that preclinical AD status will be disclosed. On the other hand, images accompanied with radiology reports that often include the study title and thus terms such as "Alzheimer disease" or "Preclinical Alzheimer disease" carry significantly higher risk of a larger, negative impact. These disease labels are also not essential to fulfill obligations to participant welfare and safety. In emergent care scenarios, the unlabeled research data are what are relevant for treating clinicians. Additional information, like potential interpretations of MRI findings given the study drug or procedures, could be provided directly and swiftly by the study team to clinicians, outside of the EHR.

Broadly speaking, narrative description of Alzheimer pathology or any mention of "Alzheimer disease" in the EHR is more likely than raw research data, such as MRI images or the numeric values of spinal fluid proteins, to divulge preclinical AD status.

To guide the implementation of privacy measures in the EHR, specific types of preclinical AD research data can be categorized into "low risk" or "significant risk" if included in the EHR. Table 2 presents a summary of these data types and categories. Although a basic assumption here is the use of an all-access, combined clinical/research EHR, these recommendations are relevant to any of the 3 EHR strategies mentioned above (and in Table 1).

Beyond the EHR: The AD Continuum and Clinical Care

The biomarker revolution in defining AD holds great promise and brings new challenges. Advances in AD diagnostics and therapeutics, along with biomarker-supported, predictive models of progression through the AD continuum, will continue to erode the separation between preclinical and clinical AD even further. Indeed, as preclinical AD enters clinical practice, the term may be retired. Identifying AD biomarkers in individuals without symptoms is already occurring in clinical care, and its scale will increase over time with the arrival of blood-based AD biomarkers.[34,35] Our systems of research protections must continue to adapt.

Researchers and supporting institutions who conduct studies in AD, including preclinical AD, have been charting new

Table 1 Three EHR Strategies to Enhance Protection of Sensitive Research Information

Create a research EHR entirely separate from the clinical EHR	Dissociate research from clinical information within the same (combined clinical/research) EHR	Implement access control measures for sensitive research information in a combined clinical/research EHR to dissuade or prohibit easy access

Abbreviations: EHR = electronic health record.

Table 2 Guidelines for EHR Management of Preclinical AD Research Information

Type of research information	Specific component of the information	Inclusion/ exclusion in EHR?	Rationale
	A "flag" indicating research participation (*with no other study-revealing information)*	✓	• Study titles typically include the term 'preclinical AD' (or 'AD'), disclosing sensitive biomarker status and/or potential for unwanted association with AD. • The flag and study team contact information allow for access to study information when needed for relevant care or with participant permission.
Progress (narrative) notes	Study team's contact information	✓	
	Title of the research study (trial); AD biomarker results; name of investigational product	✗	
Informed consent form (ICF)	Copy of the signed ICF	✗	• Consent forms include study titles, name of study drug/intervention, and key enrollment criteria (often AD biomarker status). • Verification of consent that procedures can be handled without risking inadvertent disclosure of sensitive information, e.g., through masked research documents, shared access outside of the EHR, or "hard-copy" documentation provided by the study team.
AD genetic testing	Date genetics samples obtained	✗	• Results are not immediately, clinically actionable. • Disclosure outside of the strict protocols developed to maximize participant comprehension and minimize negative consequences carries risk of negative psychological reaction and stigma. • Unwanted disclosure of genetic results may also have risks for biological family members.
	Testing results	✗	
Brain MRI scans	Date MRI conducted for research	✓	• Clinical EHR users should be able to view research MRI images, even if their interpretations may not reflect comprehensive knowledge of the research; scans may identify abnormalities that affect care decisions in emergent settings. • Avoiding the terms AD or references to preclinical AD in the reports or requisitions for tests is essential to protect participant confidentiality.
	Viewable images	✓	
	Radiology report or clinical interpretation (*with no reference to AD or preclinical AD)*	✓	
	Stated reason for MRI other than simple statement of "research purposes"	✗	
Brain FDG-PET scans	Date PET/CT conducted for research	✓	• Disclosure of results should happen following the strict protocols developed to maximize participant comprehension and minimize negative consequences. • For individuals without symptoms, viewing images would not directly affect clinical care. • Inclusion of scan date may have clinical relevance regarding radiation exposure for individuals with other research/clinical exposures.
	Scan (image files)	✗	
	Radiology report or clinical interpretation	✗	
Amyloid PET scans (AD biomarker)	Date PET conducted for research	✓	• Disclosure of results should happen following the strict protocols developed to maximize participant comprehension and minimize negative consequences. • For individuals without symptoms, viewing images would not directly affect clinical care. • Inclusion of scan date may have clinical relevance regarding radiation exposure for individuals with other research/clinical exposures.
	Scan (image files)	✗	
	Radiology report or clinical interpretation	✗	

Continued

Table 2 Guidelines for EHR Management of Preclinical AD Research Information *(continued)*

Type of research information	Specific component of the information	Inclusion/ exclusion in EHR?	Rationale
Tau PET scans (AD biomarker)	Date PET conducted for research	✓	• Disclosure of results should happen following the strict protocols developed to maximize participant comprehension and minimize negative consequences. • For individuals without cognitive symptoms, viewing images would not directly affect clinical care. • Inclusion of scan date may have clinical relevance regarding radiation exposure for individuals with other research/clinical exposures.
	Scan (image files)	✗	
	Radiology report or clinical interpretation	✗	
CSF tests (AD biomarker)	Date lumbar puncture conducted for research	✓	• Disclosure of results should only be performed following the strict protocols developed to maximize participant comprehension and minimize negative consequences. • The specific test results (levels/ratios of proteins) would not affect clinical care. • Inclusion of collection date may have clinical relevance if other laboratory tests are completed (e.g., CSF total protein, WBC counts).
	AD protein analysis results	✗	
Clinical laboratory tests	Dates samples collected	✓	• Safety laboratory test results may be directly, clinically relevant. • Results should not contain information that could lead to unblinding in a blinded study.
	Results	✓	
Study Medication/ Investigational Product (IP)	Dates medication dispensed or dates of infusion	✓	• Where needed, the date of study medication/IP administration may be included. • Including name of the IP may risk loss of preclinical AD status confidentiality. • Study team contact information or immediate access measures can be embedded for clinicians who need more information.
	Name of intervention or IP product	✗	
	Unblinding information (active or placebo)	✗	

✓ = "Low risk" for inclusion in the EHR; ✗ = "Significant risk" for inclusion in the EHR.

Abbreviations: AD = Alzheimer disease; EHR = electronic health record; WBC = white blood cell; IP = investigational product.

territory as they balance protection and disclosure of sensitive AD-related information. Inherent to this practice has been navigating the ethical obligations to patient-participants in biomarker disclosure and subsequent decision making. Efforts to develop ethical, patient-oriented research/clinical electronic interfaces seem especially important moving forward. We know that emerging AD therapeutics will have nontrivial side effects that will require easy access to clinical data and ongoing monitoring. Similarly, we anticipate that new medications and interventions meant to delay symptomatic disease will require intervention years before symptoms develop.

In this new era of earlier AD diagnoses, potentially disease-modifying treatments, and greater numbers of individuals in clinical care at every stage in the AD continuum, interactions between providers, patients, the health system, and society will be increasingly tested. Even with challenges as the field moves forward, however, the AD research community at this moment is well-positioned to continue to improve ethical, effective practices related to confidentiality and disclosure and to help guide the translation of experiences into the clinic and community.

Study Funding

This project was completed in partnership with the Alzheimer's Clinical Trial Consortium (ACTC), funded by a Cooperative Agreement from the National Institute on Aging, NIH (ACTC grant (NIH/NIA U24 AG057437, Aisen/Sperling/Petersen, Multi-PI).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* May 10, 2022. Accepted in final form August 19, 2022. Submitted and externally peer reviewed. The handling editor was Linda Hershey, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Seth A Gale, MD	Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content
Judith Heidebrink, MD	The University of Michigan, Ann Arbor, MI	Drafting/revision of the manuscript for content, including medical writing for content
Joshua Grill, PhD	University of California Irvine	Drafting/revision of the manuscript for content, including medical writing for content
Jonathan Graff-Radford, MD	Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content
Gregory A. Jicha, MD, PhD	University of Kentucky	Drafting/revision of the manuscript for content, including medical writing for content
William Menard, BA	Butler Hospital	Drafting/revision of the manuscript for content, including medical writing for content
Milap Nowrangi, MD	Johns Hopkins University School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content
Susie Sami, MA	University Hospitals, Cleveland Medical Center	Drafting/revision of the manuscript for content, including medical writing for content
Shirley Sirivong, BA	University of California Irvine	Drafting/revision of the manuscript for content, including medical writing for content
Sarah Walter, BSc	University of Southern California	Drafting/revision of the manuscript for content, including medical writing for content
Jason Karlawish, MD	Penn Memory Center	Drafting/revision of the manuscript for content, including medical writing for content

References

1. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
2. Hampel H, Cummings J, Blennow K, et al. Developing the ATX(N) classification for use across the Alzheimer disease continuum. *Nat Rev Neurol*. 2021;17(9):580-589. doi:10.1038/s41582-021-00520-w
3. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12(3):292-323. doi:10.1016/j.jalz.2016.02.002
4. Sperling RA, Karlawish J, Johnson KA. Preclinical Alzheimer disease-the challenges ahead. *Nat Rev Neurol*. 2013;9(1):54-58. doi:10.1038/nrneurol.2012.241
5. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? *Sci Transl Med*. 2014;6(228):228fs13. doi:10.1126/scitranslmed.3007941
6. Sperling R, Henley D, Aisen PS, et al. Findings of efficacy, safety, and biomarker outcomes of atabecestat in preclinical alzheimer disease: a truncated randomized phase 2b/3 clinical trial. *JAMA Neurol*. 2021;78(3):293-301. doi:10.1001/jamaneurol.2020.4857
7. Ozair FF, Jamshed N, Sharma A, Aggarwal P. Ethical issues in electronic health records: a general overview. *Perspect Clin Res*. 2015;6(2):73-76. doi:10.4103/2229-3485.153997
8. Johnson EA, Carrington JM. Clinical research integration within the electronic health record: a literature review. *Comput Inform Nurs*. 2020;39(3):129-135. doi:10.1097/CIN.0000000000000659
9. Sacristán JA. Clinical research and medical care: towards effective and complete integration. *BMC Med Res Methodol*. 2015;15:4. doi:10.1186/1471-2288-15-4
10. Largent EA, Bradbury AR. Bringing Alzheimer Disease Testing and Results Disclosure Into the 21st Century Cures Act. *JAMA Neurol*. 2022;79(3):219-220. doi: 10.1001/jamaneurol.2021.4851.
11. OpenNotes – patients and clinicians on the same page. Accessed April 1, 2022. opennotes.org/
12. 21st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program. Federal Register; 2020. Accessed April 1, 2022. federalregister.gov/documents/2020/05/01/2020-07419/21st-century-cures-act-interoperability-information-blocking-and-the-onc-health-it-certification.
13. Arias JJ, Karlawish J. Confidentiality in preclinical Alzheimer disease studies: when research and medical records meet. *Neurology*. 2014;82(8):725-729. doi:10.1212/WNL.0000000000000153
14. Shenoy A, Appel JM. Safeguarding confidentiality in electronic health records. *Camb Q Healthc Ethics*. 2017;26(2):337-341. doi:10.1017/S0963180116000931
15. Campos-Castillo C, Anthony DL. The double-edged sword of electronic health records: implications for patient disclosure. *J Am Med Inform Assoc*. 2015;22(e1):e130-e140. doi:10.1136/amiajnl-2014-002804
16. Stites SD, Rubright JD, Karlawish J. What features of stigma do the public most commonly attribute to Alzheimer's disease dementia? Results of a survey of the U.S. general public. *Alzheimers Dement*. 2018;14(7):925-932. doi:10.1016/j.jalz.2018.01.006
17. Stites SD, Gill J, Largent EA, et al. The relative contributions of biomarkers, disease modifying treatment, and dementia severity to Alzheimer's stigma: a vignette-based experiment. *Soc Sci Med*. 2022;292:114620. doi:10.1016/j.socscimed.2021.114620
18. Werner P, Giveon SM. Discriminatory behavior of family physicians toward a person with Alzheimer's disease. *Int Psychogeriatr*. 2008;20(4):824-839. doi:10.1017/S1041610208007060
19. Bacsu J, Mateen FJ, Johnson S, Viger MD, Hackett P. Improving dementia care among family physicians: from stigma to evidence-informed knowledge. *Can Geriatr J*. 2020;23(4):340-343. doi:10.5770/cgj.23.426
20. Arias JJ, Tyler AM, Oster BJ, Karlawish J. The proactive patient: long-term care insurance discrimination risks of Alzheimer's disease biomarkers. *J L Med Ethics*. 2018;46(2):485-498. doi:10.1177/1073110518782955
21. General data protection regulation (GDPR). 2018. gdpr-info.eu/
22. Buys M. Protecting personal information: implications of the protection of personal information (POPI) act for healthcare professionals. *S Afr Med J*. 2017;107(11):954-956. doi:10.7196/SAMJ.2017.v107i11.12542
23. Hunton Andrews Kurth's Privacy and Cybersecurity. South Africa's protection of personal information act, 2013, goes into effect july 1. *Natl L Rev*. 2020;X(181). Accessed May 12, 2022. https://www.natlawreview.com/article/south-africa-s-protection-personal-information-act-2013-goes-effect-july-1.
24. Tantleff A, Pierce S, Millendorf S. Brazilian government makes the LGPD effective imminently. *Natl L Rev*. 2020;X(254). Accessed July 5, 2022. https://www.foley.com/en/insights/publications/2020/09/brazilian-government-lgpd-effective-imminently
25. Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality. National Institutes of Health. September 7, 2017. Accessed May 8, 2022. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html
26. Piasecki J, Walkiewicz-Żarek E, Figas-Skrzypulec J, Kordecka A, Dranseika V. Ethical issues in biomedical research using electronic health records: a systematic review. *Med Health Care Philos*. 2021;24(4):633-658. doi:10.1007/s11019-021-10031-6
27. Evans B Much ado about data ownership. *Harv J L Technol*. 2011;1:69-130.
28. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA*. 2000;283(20):2701-2711. doi:10.1001/jama.283.20.2701
29. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. 1978.
30. Kim SYH, Karlawish J, Berkman BE. Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials. *Neurology*. 2015;84(14):1488-1494. doi:10.1212/WNL.0000000000001451
31. Dunlop BW. Should sensitive information from clinical trials be included in electronic medical records? *JAMA*. 2010;304(6):685-686. doi:10.1001/jama.2010.1117
32. Rezaeibagha F, Win KT, Susilo W. A systematic literature review on security and privacy of electronic health record systems: technical perspectives. *Health Inf Manag*. 2015;44(3):23-38. doi:10.1177/183335831504400304
33. Murray TL, Calhoun M, Philipsen NC. Privacy, confidentiality, HIPAA, and HITECH: implications for the health care practitioner. *J Nurse Pract*. 2011;7(9):747-752. doi:10.1016/j.nurpra.2011.07.005
34. Schindler SE, Bateman RJ. Combining blood-based biomarkers to predict risk for Alzheimer's disease dementia. *Nat Aging*. 2021;1(1):26-28. doi:10.1038/s43587-020-00008-0
35. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol*. 2022;21(1):66-77. doi:10.1016/S1474-4422(21)00361-6