Confidentiality in preclinical Alzheimer disease studies

When research and medical records meet

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ABSTRACT

Clinical trials to advance the diagnosis and treatment of Alzheimer disease (AD) may expose research subjects to discrimination risks. An individual enrolled in a research study that uses positive test results from amyloid PET imaging or CSF measures of β -amyloid 42 as inclusion criteria has biomarkers indicative of AD pathology. If insurers and employers learn this information, it could expose subjects to discrimination. Unfortunately, current legal and regulatory mechanisms are not sufficient to protect against harms that have significant consequences for subjects. Existing law that prohibits employment and insurance discrimination based on genetic status does not apply to amyloid biomarkers or any other biomarkers for neurodegenerative diseases. Gaps in legal protections fail to protect research subjects from discrimination by long-term care and disability insurers. This risk is particularly concerning because individuals with AD dementia ultimately need long-term care services. To maximize subject protections and advance valuable research, policymakers, investigators, and research institutions must address shortcomings in the design of the electronic medical record, revise laws to limit discrimination, and develop practices that inform research participants of risks associated with loss of confidentiality. **Neurology® 2014;82:725-729**

GLOSSARY

ACA = Affordable Care Act; **AD** = Alzheimer disease; **ADA** = Americans with Disabilities Act; **AE** = adverse event; **CLASS** = Community Living Assistance Services and Supports; **EMR** = electronic medical record; **GINA** = Genetic Information Non-discrimination Act; **HIPAA** = Health Insurance Portability and Accountability Act.

Diagnosing and treating Alzheimer disease (AD) before disabling cognitive impairments occur is critical to reducing its substantial personal and societal burdens. The hypothesis that abnormal test results from amyloid PET imaging or CSF measurements of β -amyloid 42 are indicators of preclinical AD has inaugurated clinical trials to test anti-amyloid drugs in subjects who have these biomarkers.¹ If investigators use amyloid status as an inclusion criterion, those enrolled in their studies would necessarily be assumed to be at increased risk of AD dementia. These study designs present ethical and legal challenges related to a unique and novel risk. Research data are increasingly incorporated into research subjects' medical records. Thus, any subsequent disclosures of the subject's medical record would include information that the individual tested positive for β -amyloid, a pathologic marker of AD. As a result, subjects who provide a social good of advancing research on AD diagnosis and treatment may be at risk of employment or insurance discrimination.

Unlike potential and similar risks associated with disclosing genetic markers, existing laws and policies that prohibit insurance or employment discrimination do not apply to nongenetic test results such as amyloid biomarkers. Additional gaps in legal protections fail to protect research subjects from discrimination by long-term care insurers, a particularly harmful risk to individuals whose disease foretells needing long-term care services.

HOW DISCLOSURE OCCURS IN THE ELECTRONIC MEDICAL RECORD A research subject's medical record may incorporate information related to research participation through 2 ways. First, the record may document amyloid tests as an imaging or other laboratory result. In EPIC, a common electronic medical record (EMR)

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system, disclosure of either a biomarker test order or its result can be substantially minimized using a “sensitive order class” that allows only the investigator and designees to view the order for and result of a test. Researchers should use this feature as a standard practice to protect subjects from a loss of confidentiality.

Second, research results may become part of clinical care records of care a subject received as a result of the research study. For example, if the subject experiences an adverse event (AE) that requires an emergency room visit or clinical follow-up, the documentation of that care will include information about the patient’s participation in a clinical intervention trial that targets brain amyloid. This medically appropriate documentation of the AE effectively discloses that the person has a biomarker of preclinical AD.

Insurers and employers may access medical records for purposes of underwriting or hiring practices. When disclosures are made for permissible purposes, neither the Health Insurance Portability and Accountability Act (HIPAA) nor a Certificate of Confidentiality prevents access to research information that is part of the medical record. HIPAA protects against the unlawful release of a patient’s EMR to entities for purposes unrelated to treatment.² Under HIPAA, there are allowances for disclosure of records to employers and insurers.³ Given this, unless the record is otherwise redacted, a subject’s research-related results may be disclosed to an employer or insurer.

A Certificate of Confidentiality provides only minimal additional protections. Certificates prohibit researchers from forced disclosure of identifiable sensitive information (e.g., substance abuse) gathered during research.⁴ They are not a presumed protection for every study. Researchers must submit an application and be awarded a Certificate. The impetus of Certificates stems from concerns that judicial bodies or other interested entities could force researchers to disclose research data, including illegal activity. Certificates may be useful for

protecting research subjects from employers and insurers who specifically request data related to a subject. However, even if a researcher obtained a Certificate, protections provided by Certificates do not extend once research results are part of the subject’s medical record.

HIPAA and Certificates of Confidentiality leave a gap in privacy protections. Researchers need a tool to redact information related to research participation when requested by third parties. Such a tool would prevent information gathered during research from being disclosed with other nonresearch-related information. However, such a tool is not available and may not be sensible because research information related to an AE is clinically relevant. Even with a tool to redact information, which may not successfully protect sensitive information in all circumstances, risks remain of disclosure and subsequent discrimination in either employment or insurance.

DISCRIMINATION IN INSURANCE Health, life, and long-term care insurers may have an interest in using biomarkers in underwriting practices. Current legal mechanisms are not sufficient to protect subjects enrolled in research on the basis of biomarkers or genetic markers from discrimination by insurers (see the table). Beginning in 2014, the Patient Protection and Affordable Care Act (ACA) will prohibit health insurers from discriminating against an individual based on a preexisting condition.⁵ Whether these provisions will prevent discrimination against individuals with preclinical AD, a condition that has yet to be clinically validated, is uncertain. An additional provision prohibits health insurers from discriminating against individuals based on their participation in medical research.⁶ To qualify for protections under this provision, the clinical trial must be an investigation to prevent, detect, or treat cancer or “another life-threatening disease or condition.” The provision goes on to define “life-threatening disease or condition” as “any disease or condition from which the likelihood of death is probable unless the course of

Table Summary of the scope of legal protections to prevent employment and insurance discrimination in persons who have either genetic markers or biomarkers for developing Alzheimer disease dementia

	Protection from employment discrimination		Protection from discrimination by health insurers		Protection from discrimination by life insurers		Protection from discrimination by long-term care insurers	
	Genetic markers	β-Amyloid biomarkers	Genetic markers	β-Amyloid biomarkers	Genetic markers	β-Amyloid biomarkers	Genetic markers	β-Amyloid biomarkers
Americans with Disabilities Act ^{4,7}	Uncertain ^a	Uncertain	No	Uncertain	No	No	No	No
Affordable Care Act ⁶	No	No	Yes	Possible ^b	No	No	No	No
Genetic Information Nondiscrimination Act ⁷	Yes	No	Yes	No	No	No	No	No

^aThe Equal Employment Opportunity Commission (EEOC) does not directly address genetic disposition. However, the EEOC has interpreted the 2008 amendment to the Americans with Disabilities Act to broaden the definition of disability in favor of coverage.

^bAffordable Care Act provisions to limit discrimination in health insurance for persons with a preexisting condition start in 2014. Whether these provisions will apply to the concept of preclinical Alzheimer disease is uncertain—the analysis is complicated by the fact that preclinical biomarkers have yet to be validated and thus may not qualify as a preexisting condition.

the disease or condition is interrupted.” AD is life-threatening, but it is unclear whether AD is within the intention of the definition. Additionally, the protections do not prohibit discrimination based on the disclosure of information gathered during research, but merely discrimination based on enrollment.

There are no protections under the ACA relevant to long-term care or disability insurance. At its passage, the ACA included the Community Living Assistance Services and Supports (CLASS) Act.⁷ This provision sought to create an option for individuals to purchase long-term care insurance through a public option. Under the CLASS Act, individuals would have been able to buy into a long-term care insurance plan even if they had preexisting conditions. The CLASS Act was, however, repealed in early 2013. As a result, the ACA fails to protect research subjects from discrimination by long-term care insurers or provide additional options for those who seek to purchase long-term care insurance once learning that they test positive for AD biomarkers.

Clinical studies in AD may seek to recruit individuals who are retired, near retirement, may have already invested in insurance, or may be eligible for Medicare. However, Medicare only provides limited coverage for long-term care services. Medicare provides coverage for long-term care hospitals providing acute care for extended periods, but only provides coverage for limited services in skilled nursing facilities.⁸ This will likely be insufficient coverage for individuals with a chronic condition such as AD dementia. Additionally, relying on public options to provide coverage for those who become ineligible for private health insurance would create an unjustified societal burden.

The Genetic Information Nondiscrimination Act⁹ (GINA) prohibits discrimination by insurers or employers based on genetic information. GINA protects individuals with known genetic markers who have not demonstrated “disease manifestation” of a condition that is consistent with the genetic marker. For example, GINA protects an individual who tests positive for carriage of an *APOE* $\epsilon 4$ allele, unless they are experiencing symptoms consistent with AD. Protections likely extend to individuals enrolled in a study with genetic markers as inclusion criteria. However, GINA protections do not encapsulate discrimination based on biomarkers because they are not “genetic information.” Instead, a biomarker may be categorized as a “disease manifestation.” If positive biomarker test results do indicate “disease manifestation,” then individuals who are genetically predisposed to AD and test positive for a biomarker would also be excluded from protections under GINA. Extending legal protections, such as those in GINA and some state laws, to individuals with other presymptomatic or asymptomatic markers could provide initial protections to research subjects with positive biomarker status.

Additional limitations prevent GINA from providing needed protections for individuals with early indicators of AD, either genetic disposition or biomarkers indicating disease pathology. Protections under GINA do not extend to long-term care or disability insurers. Fewer than 20 states prohibit discrimination by life, disability, or long-term care insurers based on genetic information without actuarial justification.¹⁰ The gaps in legal protections relevant to insurance discrimination emphasize a need for legal amendment. Extending protections to individuals who test positive for asymptomatic biomarkers comes with policy concerns. Providing blanket protections to individuals who are presumed to be at the asymptomatic stage of AD may unfairly expose insurers to adverse selection by consumers who may be informed of their high risk status.¹¹ Insurers need regulatory policies that allow them to use relevant health information for underwriting that is not discriminatory and also not cost prohibitive.

Potential protections for research subjects at risk of discrimination include amending GINA to extend to individuals with disease biomarkers. Extending protections under the ACA for research subjects to include protections from discrimination based on information gathered or disclosed as part of the research study would promote research enrollment and recognize the social good provided by subjects. However, neither ACA nor GINA provides protections relevant to long-term care insurance, leaving a critical gap. Individuals with AD biomarkers and genetic markers will likely require and thus benefit from insurance for long-term services. Providing insurance for these individuals would reduce personal and societal burdens related to financing long-term services. In repealing the CLASS Act, Congress created the Commission on Long-Term Care to develop a comprehensive plan for long-term care needs. The Commission has a unique opportunity to develop solutions for discrimination against individuals with preexisting conditions and asymptomatic individuals who test positive for biomarkers. We recommend that the Commission and policymakers give special consideration to individuals who learn of their biomarker-positive status while enrolled in clinical studies.

DISCRIMINATION IN EMPLOYMENT The potential protections under the Americans with Disabilities Act (ADA) may provide sufficient protections to limit discrimination by employers. However, the definition of “disability” has never been tested in case law relating to protecting asymptomatic individuals with disease biomarkers. The ADA¹² prohibits employers from discriminating on the basis of disability, defined as “a physical or mental impairment that substantially

limits one or more of the major life activities.” Following amendments to the ADA in 2008, “impairment” includes a physical or mental impairment that is a “physiological disorder or condition affecting one or more body systems.” Among other conditions, the Equal Employment Opportunity Commission identified HIV infection, an asymptomatic condition, as a presumed disability because it limits the immune system. Like HIV, which limits the immune system, preclinical AD pathology limits the function of the neurologic system. Such a determination will require proof that a positive biomarker test result indicates neurologic damage, proof that will come in large part from clinical trials that enroll biomarker-positive, asymptomatic persons.

Without proof that a positive biomarker test indicates neurologic damage, protections may be extended to those “regarded as having such an impairment.” Under the ADA, an individual is “regarded as having such an impairment” if the individual can demonstrate that he or she has been discriminated against based on an actual or perceived disability. Unlike other definitions of disability, the analysis of these claims focuses not on whether the condition is a disability, but whether the individual can show that the employer acted “because of a perception of disability.”¹³ This application of the ADA requires that each claim of discrimination undergo an analysis of the employer’s actions. As a result, whether AD biomarkers constitute a disability under the ADA cannot be decided on a global basis for all subjects. This case-by-case application means the ADA cannot provide needed prospective protections for research subjects who test positive for AD biomarkers.

Until case law or the Equal Employment Opportunity Commission provides explicit guidance specific to biomarkers, a gap in protection remains for individuals enrolled in studies whose employers learn their research information. While legal mechanisms could provide certainty in protecting against discrimination, other measures may reduce the potential for discrimination. Employers’ interest in biomarker results may be tied to 2 relevant issues. First, an employee perceived to be more likely to develop symptomatic AD may affect employer-based insurance group premiums. This challenge may be resolvable through protections discussed related to insurance. Second, employers may weigh the potential for decreased work product and potential safety issues. Education programs for employers related to the current knowledge connecting AD biomarkers to symptoms may resolve erroneous perceptions that an individual who has an AD biomarker will demonstrate symptoms that affect performance in the near future.

ROLE OF STUDY DESIGN In addition to the legal and policy recommendations to protect research

participants, novel study designs may be helpful. One design is enrolling participants with negative amyloid status into a blinded, placebo-only cohort study that occurs simultaneously with the randomized trial of biomarker-positive subjects. This 3-arm design is, for example, the strategy used in the Dominantly Inherited Alzheimer Network trials testing drugs in persons with dominantly inherited AD. If it is known that a person is a subject of such a 3-arm study and the chance of assignment to the cohort study is known, then the certainty that any one subject is amyloid-positive is effectively 1 minus the chance of randomization to this group. Someone can estimate the chance that person is in fact biomarker- or gene-positive. The experience of AEs, especially those typical for study drug, would further inform this estimate.

Another approach is, before screening for amyloid status, implementing an education module for those who are interested in enrolling in the study. This is the approach taken in the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease Study. This module would inform potential research participants of the consequences of loss of confidentiality, including insurance eligibility and employment discrimination. This approach cannot protect individuals who do choose to enroll from discriminations as a result of loss of confidentiality, but it will assure that subjects accept these risks. Study design is not sufficient by itself to address risks of loss of confidentiality, even if design can mitigate some risks. Researchers should consider how design could incorporate protections for research participants while maintaining integrity and feasibility of study methodology.

CONCLUSION Current legal and regulatory mechanisms are not sufficient to protect against harms that could have very real consequences for subjects of preclinical AD trials. To maximize subject protections and advance valuable research, policymakers, investigators, and research institutions must address shortcomings in the design of the EMR, revise laws to limit discrimination, and disclose details of risks associated with loss of confidentiality. A review of GINA, ADA, and the ACA indicates that current laws fail to protect research subjects. Additional research is needed to evaluate the full spectrum of laws pertinent to employment discrimination and insurance eligibility, including state law and judicial interpretations of key provisions. Ultimately, without necessary protections, research subjects may be contributing to advancing clinical treatment of AD in a sad exchange for discrimination by employers and insurers.

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Jalayne J. Arias and Jason Karlawish: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, and accept responsibility for conduct of research and will give final approval.

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