April 29, 2023

GUIDANCE FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

Biomarker Disclosure Guidance

There has been a rapid expansion of biomarker tests for Alzheimer's disease (AD) and AD Related Dementias (ADRD). These tests include imaging, cerebrospinal fluid (CSF), and plasma measures that assess amyloid and tau pathologies and neurodegeneration and are often performed at NIA-funded Alzheimer's Disease Research Centers (ADRCs).

Research participants understandably want to learn their biomarker results. Studies are therefore incorporating biomarker disclosure. Disclosure of biomarker results achieves a number of inter-related goals including demonstrating respect for participant well-being and self-determination, enhancing recruitment and retention, and reflecting a changing clinical practice, which now includes the approval of the first disease-modifying therapies for AD and the requirement of biomarker testing to identify appropriate candidates for these treatments.

The framework below builds upon the extant literature in biomarker disclosure.[e.g., 1-5] The guidelines are designed to be brief, practical, and anticipate that the validity and clinical value of biomarker tests will continue to be developed and refined.

The guidance recognizes that ADRCs maintain their own protocols, including how biomarkers may be collected and analyzed, and that ADRCs make their own decisions about what biomarkers should be returned to which participants. The following principles can assist ADRCs in making these decisions.

General principles.

- Scientific validity is a prerequisite for biomarkers to be disclosed to research participants.[6] Results should be replicable and interpretable, and investigators must make a compelling case that there are adequate data to support disclosure (i.e., how to describe results and their meaning to participants). (Figure 1)
- The more the research conditions resemble clinical practice (a participant's diagnostic label and the biomarker test are accepted in clinical practice), the more disclosure is warranted.
- Participants should make an informed decision about whether they want to learn their result. Investigators should exercise discretion if there are concerns that disclosure is not appropriate for an individual.
- The study of biomarkers has biases, the sources of which include the use of participants that predominantly represent non-Hispanic, White, healthy, and highly educated volunteers. Disclosure approaches should be equitable, but also acknowledge that scientific validity and value may be limited for participants from underrepresented groups.
- Biomarker disclosure is work for investigators. ADRCs must plan accordingly to address this labor need. The burden of disclosure may impact decisions whether to disclose.

- Decisions related to whether to disclose biomarkers at ADRCs will involve individual participant-level considerations, biomarker-specific considerations, and center-level considerations.

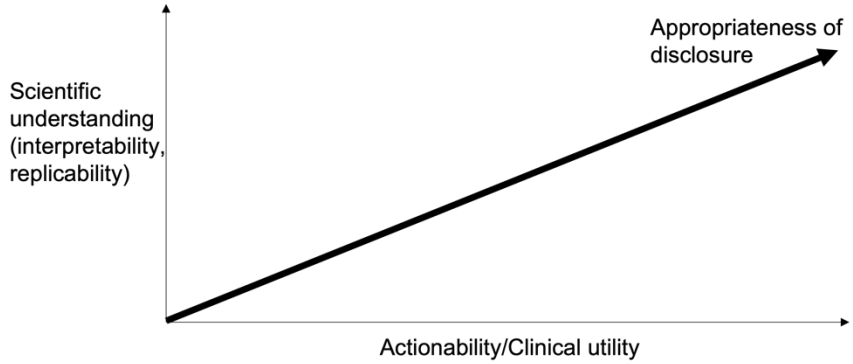

Figure 1. Disclosure's relationship to scientific validity (interpretability and reliability) and clinical value.

<u>What to disclose.</u>

- Ethical criteria support disclosure of biomarker results that are valid, interpretable, and actionable.[4] Other justifications for disclosure include research designed to instruct current or future clinical practice.
- Some biomarkers have regulatory approval (e.g., FDA) for clinical use. Biomarkers used for clinical care that are obtained similarly in research participants require justification for withholding results from participants.[4]
- Limitations in data should be recognized when developing disclosure materials and processes. These may include limited longitudinal data to instruct long-term outcomes and bias in the study samples that inform disclosure materials, such as underrepresentation of particular groups to whom disclosure will be performed.
- Disclosure protocols should specify and justify the manner in which results are disclosed, including whether numeric values (compared to categorical outcomes) are returned to participants and how results are framed or contextualized. While approaches that are currently used clinically are an obvious opportunity to justify an approach, they may not be the only approach. For example, biomarker data are frequently provided in clinical practice as a binary category outcome (e.g., positive/negative; elevated/not elevated), but biomarker measures are often continuous. Additionally, it may be possible to provide individualized risk estimates that incorporate not only the biomarker but also other key variables such as age, sex, race or ethnicity.
- To date, most biomarker tests have provided information about the probability that AD contributes either to the causes of cognitive impairments or to the risk of developing cognitive impairments. Most results disclosed have been a single result at one point in time. Biomarker disclosure research and practices should recognize a future that includes multiple biomarkers, including markers of AD as well as other causes of dementia, and longitudinal testing and measures of neurodegeneration. Disclosure of more complex results as well as changing biomarker results over time should be considered.

- Biomarker disclosure should be described in study protocols and approved by an IRB.

To whom to disclose?

- Research participants at ADRCs span a spectrum from persons who are cognitively unimpaired to persons who are cognitively and functionally impaired. The decision to disclose and, if so, the approaches to disclosure are likely to differ across this spectrum.[3]
- The state of the scientific knowledge, implications of specific results, and clinical utility are likely to differ for participants with cognitive impairment (MCI and dementia), compared to those unimpaired (subjective cognitive impairment and cognitively unimpaired). Similarly, the desire for biomarker results, suitability for disclosure, and reactions to results will differ between impaired and unimpaired participants.
- Investigators must consider the appropriateness of biomarker disclosure to an individual. Some individuals may not be ready to receive biomarker results or may, in the judgment of the investigator, be at risk for harms such as catastrophic reaction. These risks may not preclude biomarker disclosure, but do warrant adequate resources (time, clinical skills, referral resources) to enact a person-centered approach.
- ADRCs should develop guidelines for biomarker disclosure to individuals who lack capacity to consent for themselves. Disclosure of biomarkers to legally authorized representatives and other surrogates is generally acceptable in scenarios that closely resemble clinical care. Assurance of participant assent must be considered.
- It is imperative that participants from underrepresented groups are included in biomarker and disclosure research. Educational materials and communication methods should be culturally sensitive and acknowledge the limitations of existing knowledge when disclosing results to persons who identify with groups that have been historically underrepresented in research, including biomarker research.[7]

Who should disclose?

- Though occurring in the context of research, disclosure is an interaction that is clinical in nature. Information valuable to the participant's health is being delivered. The persons performing disclosure must have the knowledge and skills to answer questions about meaning and outcomes and to assess for potential participant reactions and needs. Qualities include:
    - comfort assessing psychological well being
    - comfort and ability/experience with discussing the diagnosis of cognitive impairment.
- Study-specific trainings for NIA-funded multisite studies (e.g., A4 Study, AHEAD Study, ADNI4)[8] are available and provide valuable resources.
- ADRCs could engage thought leaders in the field or participate in cross-ADRC collaborations to conduct disclosure training. ADRC leaders may wish to protocolize training.
- In addition to the expertise necessary to perform disclosure, expertise in analyzing and interpreting biomarker test results will be essential to permit appropriate biomarker result disclosure.

- Disclosure may introduce added work for study teams, which includes the time necessary to complete the disclosure process, to follow-up with participants, and potentially to provide longer term referral and/or counseling.

<u>How to disclose.</u>

- Guidance exists in the literature for developing a process to disclose biomarker results. There are 5 overall steps[1-3]
    1. *Determine participant appropriateness for biomarker disclosure.* Research participants must be evaluated for their suitability for biomarker disclosure. This includes ensuring that disclosure does not produce unacceptable risk of harm.
    2. *Perform pre-test education and informed consent.* Culturally sensitive education is key to informed consent and appropriate opting-in to biomarker disclosure. Education must include the limitations of the current state of knowledge around a specific biomarker test, related to the test overall as well as the specific implications of the test in subgroups to which the participant may belong. Consent should include the potential risks of biomarker disclosure. Risk of psychological distress may be minimized by adherence to a strict disclosure protocol, but other risks such as medicolegal risks and stigma should also be addressed.
    3. *Test administration*. Most guidelines indicate that biomarker testing should be performed on a day separate from education and consent, as well as separate from result disclosure. This separation provides important opportunity for the participant to change their mind about learning their result.[1]
    4. *Returning test results*. Results should be delivered by a qualified and trained individual (see above) in an interactive form, such as in-person, videoconference, or telephone, that allows adequate opportunity for discussion (see Box). Departures from these ideal circumstances warrant study for potential impact on safety and effectiveness of the disclosure process.
    5. *Post-disclosure follow-up.* ADRCs should ensure participant safety after disclosure. At minimum recipients should be given contact information for any follow-up questions. Little data is available regarding the long-term impact of biomarker disclosure.

Box: Sample approach to biomarker disclosure

- Conduct disclosure in-person or virtually (with consideration of whether study partner presence is required)
- Discuss whether participant continues to want their result(s)
- Assess participant's current understanding of test implications before providing results
- Assess participant's psychological readiness to receive results
- Provide test results
- Assess participant's initial reaction to results and connect them with additional resources if needed
- Provide written information regarding interpretation of test results
- Follow up with participant ~1 week after results provided

- In cases where biomarker tests have already been performed, some of these steps may be abbreviated, but the essential elements should not. For example, participants with existing biomarker results should still undergo thorough education, counseling and consent, including having time to process the provided educational information and change their minds before individual biomarker results are disclosed.
- Investigators should exercise caution related to the use of electronic medical records and the potential for unwanted disclosure to the participant or others.[9]
- Model phrases and language to adapt in delivering biomarker information are available in the literature.[3] Disclosure approaches should recognize the variation in culture, education, and beliefs among ADRC participants. Processes should also be adjusted for the participant population based on whether and what type of symptoms they are experiencing.
- Charts, illustrations, and examples of biomarker results, including from the participant's own biomarker test (e.g., an amyloid PET scan image) may be helpful to explaining biomarker results. Participants benefit from written summaries of results.
- A justification for disclosing biomarkers is to instruct future practice. This justification requires collection of data, ranging from participant willingness to receive individual results to reactions to the information and longitudinal impact of knowing results. This will likely often include collecting data from a co-participant.

Conclusions

- Biomarkers have transformed the ways clinicians and researchers define, measure and talk about AD/ADRD. Systems are needed to return results to research participants. The above guidance is a starting point for ADRCs to consider and develop these systems.
- ADRC approaches to biomarker disclosure will need to change iteratively, as new biomarkers are developed and discoveries reveal greater understanding of clinical outcomes related to these tests.
- The field needs to support the science of disclosure. ADRCs are well positioned to contribute to this knowledge through rigorous assessment of the frequency and predictors of participation in biomarker disclosure and careful characterization of disclosure impact and outcomes among diverse participants.

April 29, 2023

References

1. Harkins K, Sankar P, Sperling R, et al. Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. *Alzheimers Res Ther*. 2015;7(1):26. doi:10.1186/s13195-015-0112-7
2. Lingler JH, Butters MA, Gentry AL, et al. Development of a Standardized Approach to Disclosing Amyloid Imaging Research Results in Mild Cognitive Impairment. *J Alzheimers Dis*. Mar 8 2016;52(1):8. doi:10.3233/JAD-150985
3. Largent EA, Grill J, O'Brien K, Wolk D, Harkins K, Karlawish J. Testing for Alzheimer Disease Biomarkers and Disclosing Results Across the Disease Continuum. *Neurology*. Jan 31 2023;doi:10.1212/WNL.0000000000206891
4. Grill JD, Karlawish J. Disclosing Alzheimer Disease Biomarker Results to Research Participants. *JAMA neurology*. Jul 1 2022;79(7):645-646. doi:10.1001/jamaneurol.2022.1307
5. Lingler JH, Sereika SM, Butters MA, et al. A randomized controlled trial of amyloid positron emission tomography results disclosure in mild cognitive impairment. *Alzheimers Dement*. Sep 2020;16(9):1330-1337. doi:10.1002/alz.12129
6. National Academies of Sciences Engineering, and Medicine. *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm*. 2018.
7. Ketchum FB, Erickson CM, Chin NA, et al. What Influences the Willingness of Blacks and African Americans to Enroll in Preclinical Alzheimer's Disease Biomarker Research? A Qualitative Vignette Analysis. *J Alzheimers Dis*. 2022;87(3):1167-1179. doi:10.3233/JAD-215521
8. University of Pittsburgh Biomarker Disclosure Toolkit. https://www.adrc.pitt.edu/for-researchers/biomarker-disclosure-toolkit/
9. Gale SA, Heidebrink J, Grill J, et al. Preclinical Alzheimer Disease and the Electronic Health Record: Balancing Confidentiality and Care. *Neurology*. Sep 30 2022;doi:10.1212/WNL.0000000000201347