The challenges and ethical issues of returning results of amyloid and tau status to subjects

Jason Karlawish, MD

University of Pennsylvania

Penn Memory Center

Returning AD Biomarker Research Results
Some cases to ponder

- An ADC cohort gives feedback on clinical assessments of cognition and the consensus diagnosis.
- It does not provide feedback on results of research scans: MRI, PET, etc.
- Ms. A, Mr. D, and Ms. C have been cohort participants for a number of years.
- As part of the study, each has an amyloid PET scan….

Returning AD Biomarker Research Results
Some cases to ponder

- Ms. A. carries consensus diagnosis of AD dementia. She appreciates this as, “I have Alzheimer’s.”

- Mr. D. carries consensus diagnosis of AD dementia. He appreciates this as “I have Alzheimer’s.”

- Ms. C carries consensus diagnosis of MCI, amnestic plus other. She appreciates this as “I don’t have Alzheimer’s.”

Returning AD Biomarker Research Results
Some cases to ponder

- Ms. A. carries consensus diagnosis of AD dementia. She appreciates this as, “I have Alzheimer’s.”
  - ***elevated, or positive, amyloid***
- Mr. D. carries consensus diagnosis of AD dementia. He appreciates this as “I have Alzheimer’s.”
  - ***not elevated, or negative, amyloid***
- Ms. C carries consensus diagnosis of MCI, amnestic plus other. She appreciates this as “I don’t have Alzheimer’s.”
  - ***elevated, or positive, amyloid***

The looming value of tau imaging adds complexity to the above anticipated incidental findings.

Ethics Guidance for the Return of Research Results

- Beneficence and reducing harm to the subjects
- Resources
- Respect for persons

Presidential Commission. Anticipate and Communicate: Ethical Management of Incidental And Secondary Findings in the Clinical, Research, and Direct-to-Consider Contexts. 2013.

Ethics Guidance for the Return of Research Results

- Beneficence and reducing harm to the subjects
  - relationships with the subjects
  - analytic validity: accuracy of the result
  - clinical validity: truth of the result
- Resources
  - the ability to obtain a clinical read & deliver the results
- Respect for persons
  - do they know they can / cannot receive results, especially *anticipated incidental findings*
    - e.g. sometimes the scan can show a person with “AD” doesn’t have AD (defined by biomarkers)

Ethics Guidance for the Return of Research Results

The logic of clinical purpose:

- The more a study is designed to change clinical practice, the more the study should conform to clinical practice
  - in the diagnosis of persons with dementia and MCI, biomarkers have an emerging role in diagnosis

Ethics Guidance

Recommendation 11: During the informed consent process, researchers should convey to participants the scope of potential incidental or secondary findings, whether such findings will be disclosed, the process for disclosing these findings, and whether and how participants might opt out of receiving certain types of findings.

Recommendation 12: Researchers should develop a plan to manage anticipatable incidental findings, including but not limited to those findings known to be significant and clinically actionable (and, when relevant, analytically valid and clinically valid). The plan should be reviewed and approved by an institutional review board.

Presidential Commission. Anticipate and Communicate: Ethical Management of Incidental And Secondary Findings in the Clinical, Research, and Direct-to-Consider Contexts. 2013.

Proposals for MCI and dementia stages

Cohort studies that follow persons with MCI & dementia:

- Consider….
  - analytic validity: accuracy of the result
  - clinical validity: truth of the result
  - resources: the ability to obtain a clinical read and to deliver the results
  - relationships with the subjects
- Have data fields that record whether the subject knows her gene and biomarker results
  - *even if that cohort study does not return results*

Q2: Have you ever learned the result of a PET (Position Emission Tomography) scan that measures brain amyloid? This may also have been referred to as an "amyloid PET scan" or "brain amyloid scan."

☐$_1$ Yes
☐$_2$ No [If no, skip to Q3]

Q2a: If yes, what was your amyloid PET scan result?

☐$_1$ "Elevated" or "Positive"
☐$_2$ "Not elevated" or "Negative"
☐$_3$ I don't know

Q2b: Did your amyloid PET scan result indicate that you have an increased risk for developing Alzheimer's disease dementia?

☐$_1$ Yes, my amyloid PET scan result indicated an increased risk for Alzheimer's disease dementia

☐$_2$ No, my amyloid PET scan result did not indicate an increased risk for Alzheimer's disease dementia

☐$_3$ I don't know

Q2c. Is there another term you would use to describe your amyloid PET scan result? If so, please write it in the box below:

Q3: Have you ever learned the result of a spinal fluid test that measures amyloid? This may also have been referred to as a "CSF" (cerebrospinal fluid) test, "LP" (lumbar puncture), or "spinal tap."

☐$_1$ Yes
☐$_2$ No [If no, skip to end of section]

Disclosing Amyloid imaging results

"Suppose the FDA approves PET amyloid imaging with florbetapir. Would you support a policy that allows you to tell ADNI participants with mild cognitive impairment their amyloid imaging result?"

ADNI physician-researchers (N=68)

- 84% support (definitely or probably)
- 3% unsure
- 13% do not support (definitely or probably)

Disclosing Amyloid imaging results

"Suppose the FDA approves PET amyloid imaging with florbetapir. Would you support a policy that allows you to tell ADNI participants with normal cognition their amyloid imaging result?"

ADNI physician-researchers (N=68)

- 56% support (definitely or probably)
- 18% unsure
- 26 % do not support (definitely or probably)

Ethics Guidance for the Return of Research Results

The logic of clinical purpose:

- The more the study is designed to change clinical practice, the more the study should conform to clinical practice
- Competent hence professional medicine proceeds by progressive consensus within the profession
  - preclinical AD trials have a role in changing clinical practice

Points to Consider

- Some studies are telling cognitively unimpaired persons their AD biomarker result
  - REVEAL-SCAN
  - A4
  - EARLY
  - Generation2

Points to Consider

- We need to recognize that our subjects have many ways to learn their AD biomarker results, whether in the study we are doing, we want them to know them or not
- Knowledge of AD gene and biomarker results may have independent effects on
  - outcomes such as cognition and well-being
  - how people interpret symptoms
  - how they think about their future
  - willingness to participate in studies.

Proposals for cognitively unimpaired

Cohort studies that follow persons with cognitive aging

- Consider….
  - analytic validity: accuracy of the result
  - clinical validity: truth of the result
  - resources: the ability to obtain a clinical read and to deliver the results
  - relationships with the subjects
- Have data fields that record
  - whether the subject knows her gene and biomarker results
  - understand the preclinical AD disease experience

Proposals for cognitively unimpaired

- Clinical trials: In the case of a clinical trial that uses an AD biomarker result to determine eligibility to receive the intervention, if the results of the clinical trial would lead a practitioner to order the biomarker test as part of the decision whether to prescribe the drug, then (1) the study should tell subjects their biomarker result, and (2) the study should study the “disease experience”