Power to the participants: Perspectives and considerations for disclosing amyloid status to healthy research volunteers

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Objectives

• Review amyloid in context of Alzheimer’s disease research
• Discuss implications of amyloid disclosure in research
• Introduce PREDICT Amyloid Disclosure study
  • Steps to support participants
Disclosures

• Financial:
  • NIA support through RO3 and PREDICT supplement
  • No financial gain from disclosing amyloid

• Professional:
  • Physician seeing memory patients 2 days per week

• Personal:
  • Family history of AD in father
Thank you to...

- Lindsay Clark, PhD
- Sterling Johnson, PhD
- Claire Erickson, MPA
The definition of Alzheimer’s disease

• Alzheimer’s disease is the cause of a patient’s MCI or dementia
  • Diagnose MCI or dementia first
  • Determine cause is Alzheimer’s disease based on clinical factors

• Alzheimer’s disease is AT(N)
  • Identify the biological changes of amyloid and tau accumulation in the brain
  • Study cognitive performance and relationship of ATN and various factors to those changes

The clinician
• Diagnoses patients
• Focus on management of symptoms and care planning

The scientist
• Identifies pathology
• Focus on understanding disease process and studying interventions
Alzheimer’s disease through the lens of biomarkers
A new research framework

Table 4
Descriptive nomenclature: Syndromal cognitive staging combined with biomarkers

<table>
<thead>
<tr>
<th>Biomarker Profile</th>
<th>Cognitive stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cognitively Unimpaired</td>
</tr>
<tr>
<td>A+ T(N)^+</td>
<td>normal AD biomarkers, co cognitively unimpaired</td>
</tr>
<tr>
<td>A^+ T(N)^+</td>
<td>Preclinical Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A+ T(N)^+</td>
<td>Preclinical Alzheimer’s disease</td>
</tr>
<tr>
<td>A+ T(N)^+</td>
<td>Alzheimer’s and concomitant suspected non-Alzheimer’s pathologic change, cognitively impaired</td>
</tr>
<tr>
<td>A+ T(N)^+</td>
<td>non-Alzheimer’s pathologic change, cognitively unimpaired</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.

NOTE. Formatting denotes three general biomarker “categories” based on biomarker profiles: those with normal AD biomarkers (no color), those with non-AD pathologic change (dark grey), and those who are in the Alzheimer’s continuum (light grey).
Alzheimer’s disease has a sequence of events:

1. **Amyloid**
2. **Tangles**
3. **Brain cell death**
4. **Mild cognitive impairment**
5. **Dementia**
Amyloid is central to Alzheimer’s disease

- Beta-amyloid 1-42
  - Abnormal product from a normal process
  - Forms into plaques outside of the neuron
  - It is necessary but not sufficient
  - Amyloid increases one’s risk for AD & cognitive impairment

http://dev.nsta.org/evwebs/1539p2/Alzheimer/default.html
Presence of amyloid is a risk factor for decline

Beta-amyloid and cognitive decline in late middle age: Findings from the Wisconsin Registry for Alzheimer’s Prevention study

Alzheimer’s & Dementia 12 (2016) 805-814
### Presence of amyloid is a risk factor for decline

<table>
<thead>
<tr>
<th>Study</th>
<th>Year and Journal</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Roe et al. Neurology. 2013 May. | • AB+ CNs have greater risk of progression on CDR  
• HR 3.80 | |
| Rowe et al. Ann Neurol. 2013 Dec. | • AB+ CN have greater risk of progression to MCI and dementia  
• HR 4.8 for progression to cognitive impairment over 3 years | |
| Harrington et al. Alzheimers Dement. 2017. | • AB+ CN exhibit greater decline in episodic memory testing over 6 years  
• Similar findings to Lim et al. Brain. 2014. | |
| Papp et al. Neuropsychology. 2016. | • AB+ CN exhibit early changes in semantic fluency | |
| Petersen et al. Jama Neurol. 2016 | • AB+ CN have greater cognitive decline over 2.7 years  
• Multi-domain decline | |
PREDICT Study: Amyloid + Tau = decline

We can detect pathology before symptoms

70-year old woman with no notable cognitive symptoms

MRI  Plaques  Tangles

N  A  T
Modifiable risk factors of Alzheimer’s disease

- **Depression**
  - RR = 1.85
  - 21 Studies

- **Midlife Hypertension**
  - RR = 1.61
  - 21 Studies

- **Midlife Obesity**
  - RR = 1.60
  - 14 Studies

- **Smoking**
  - RR = 1.59
  - 13 Studies

- **High Cholesterol**
  - RR = 1.54
  - 13 Studies

- **Diabetes**
  - RR = 1.47
  - 21 Studies

- **Inflammation**
  - RR = 1.45
  - 5 Studies

- **Physical Inactivity**
  - RR = 1.39
  - 7 Studies

- **Kidney dysfunction**
  - RR = 1.39
  - 9 Studies
Modifiable risk factors

RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES

EVIDENCE PROFILES
Physical activity interventions
Tobacco cessation interventions
Nutritional interventions
Interventions for alcohol use disorder
Cognitive interventions
Social activity
Weight management
Management of hypertension
Management of diabetes
Management of dyslipidaemia
Management of depression
Management of hearing loss
**Finnish Geriatric (FINGER) study to Prevent Cognitive Impairment**

- 2-year study
- 1260 adults ages 60–77 years
- Multi-domain intervention:
  - Diet
  - Exercise
  - Cognitive training
  - Vascular risk monitoring

Improved cognitive performance

Amyloid and known risk factors lead to greater cognitive decline

Amyloid positivity & high blood pressure (or obesity) are associated with greatest decline on memory measure

Amyloid + vascular risk factors = faster decline
Why disclose amyloid status?

Clinical trial enrollment

Research participants want personal data [1]

Researchers believe disclosing has value [2]

Opportunity for risk-reducing behavioral change

Why not disclose amyloid status?

- Lack of clear individualized predictive power
- No curative and disease modifying treatment
- Potential increased risk of psychosocial symptoms
- Impact on longitudinal studies
APOE disclosure in AD research

2004

• REVEAL Study

NEJM 2009

• Disclosure of APOE to adult children of patients with AD

Alz & Dem 2015

• A randomized non-inferiority trial of condensed protocols for genetic risk disclosure of Alzheimer’s Disease
APOE disclosure direct to consumer

- 2006: Creation of 23andMe
- 2007-2015: 23andMe shares raw genetic data, including APOE, PSEN1/PSEN2/APP
  - No health risk reports shared
- 2017: FDA approved application for APOE testing
  - Health risk reports shared
APOE disclosure in AD research

- Health Behavior Changes after Genetic Risk Assessment for Alzheimer’s Disease: The REVEAL Study
- Associations between self-referral and health behavior responses to genetic risk information
- Long-term follow up study on disclosing APOE to promote healthy lifestyles in Finland
Review of 8 prior amyloid disclosure studies

• Sample size ranged: 11 to 133

• Participants
  – 5/8 focused on cognitively unimpaired older adults
  – 3/8 focused on MCI and/or dementia
  – 1/8 focused on caregiver perspectives

• Locations
  – 5/8 in the US
  – Other locations: Japan, Belgium, Australia

• Disclosure protocols varied

• Methodology varied: quantitative, qualitative, and mixed
Key findings – Cognitively unimpaired

- AB+ were not surprised (1,4), reported anxiety at interview but no increased levels of depression, anxiety, stress, subjective sense of memory impairment (1,2,5)
- AB+ did not show avoidance or reported risk of self harm (1,2)
- AB+ reported making positive health and lifestyle changes (1)
- AB- reported relief (1,2) and were less likely to make health and lifestyle changes (1,3)
- Most participants understood scan results (3)
- Most participants had subclinical levels of distress related to learning result (3)
- All participants shared result with others (3)

- Varied understandings and uncertainties of meaning of risk (4)
- Desire to have a specific risk and degree of elevation (4)

(5) Wake et al. International psychogeriatrics. 2018
Key findings – Cognitively impaired

• Most participants recalled “the gist”
• Emotional responses were mixed
• Most shared result with family
• Experienced advantages & disadvantages of disclosure depended on result & timing
• Multiple reasons to undergo the exam
• Participants felt need to engage in future planning
• Felt relieved learning results
• Felt information gained was a major benefit
• No negative aspects

(3) Taswell et al. Ment Health Fam Med. 2018
Overall conclusions

• AB-
  – feeling relieved
  – adequate comprehension of scan result meaning
  – no test-related distress
  – no mood changes
  – most shared results with family members
  – less likely to initiate lifestyle change

• AB+
  – feeling unsurprised
  – mixed feelings on results
  – minority of unimpaired demonstrated inadequate understanding of scan result meaning
  – some had test-related distress
  – no mood changes on a clinically significant level
  – some shared results with family members
  – more likely to initiate lifestyle change
What do research participants think?

Communication is key
- Disclosure done by an expert and face-to-face
- Emphasize risk not diagnosis
- Suggestions for action should be included

Post-disclosure care matters
- Time is needed for questions
- Monitoring post-disclosure is needed and follow up if necessary
- Support should be available
PREDICT Amyloid Disclosure Supplement

- Amyloid disclosure + personalized lifestyle plan
- Amyloid status
  - Age
  - Education level
  - Perceived risk of AD

Behavioral changes
- Study participation
- Psychosocial changes
- Disclosure process improvement

Supplement project to ongoing PREDICT amyloid/tau imaging study
Amyloid disclosure visit outline

1. Describe study, mail informational brochure and links to e-learning materials, and follow-up to schedule, participant reviews materials
2. Visit 1: Informed consent, screening, and amyloid quiz
3. Main Study: amyloid scan
4. Visit 2: Amyloid disclosure (6 weeks after scan)
5. Telephone Visit 1 (1-3 days after V2)
6. Visit 3: Personalized lifestyle plan (6 weeks after V2)
7. Telephone Visit 2 (1 month after V2)
8. Telephone Visit 3 (6 months after V3)
Personalized lifestyle plan visit

Discuss participant-specific AD modifiable risk factors
- Diabetes: fasting glucose and insulin
- Hypertension: blood pressure
- Obesity: BMI, waist-to-hip ratio
- Physical inactivity questionnaires
- Depression questionnaires
- Smoking questionnaires
- Education level

Discuss participant's other medical risk factors and current medications
- Lab values from WRAP visit:
  - Vitamin B12 & D
  - C-reactive protein
  - Cholesterol panel
- Co-morbid conditions:
  - Sleep apnea
  - Dyslipidemia
  - Coronary artery disease
  - Chronic kidney disease
- Current medications

Discuss lifestyle intervention to reduce modifiable risk factors
- Exercise
- Diet
- Sleep
- Stress reduction
- Cognitive engagement
- Socialization

Discuss personalized care plan by incorporating select lifestyle interventions
- Specific recommendations based on participant input
- Suggested activities or strategies based on research findings
- Pragmatic approach based on participant's motivation and health
- Structured plan using SMART goals and goal attainment scaling
Addressing Risk

1. **Screening**
   - 1. Strict exclusion criteria
   - 2. Use of clinical tools
   - 3. Matching expectations

2. **Education**
   - 1. Multiple formats of information
   - 2. Discussion with clinician
   - 3. Quiz

3. **Follow-up care**
   - 1. Personalized lifestyle counseling visit
   - 2. Telephone calls & in-person visits
   - 3. Clinical tools and access to clinicians

4. **Suicidality plan**
   - 1. **Participant safety comes first**
Suicidality Prevention Protocol

Standard Protocol

- Study coordinator – telephone call
- PHQ-9
- GAS
- CSSRS
- Interview
- IES-Intrusion
- INI-AD

Clinician – telephone call

Clinician – In person visit

Geriatric Psychiatrist – telephone call

Emergency Room

Connection to primary care

Safety plan

Counseling

Urgent Psychiatry visit
Concerns with disclosure

Lack of clinical validity of amyloid biomarkers
- Amyloid testing is not diagnostic of disease, its purpose is to identify pathology
- IDEAS has shown it may have a place in clinic

Lack of predictive value
- Brookmeyer 2018, Roberts 2018, Lingler 2015 and Okello 2009 provide relative risks

Lack of clinical utility (extent the biomarker affects management)
- Clinical utility in risk stratifying an individual
- High risk = Counseling, closer monitoring with labs & cognitive testing, deprescribing

Unclear if personal utility is enough
- People have a fundamental right to their personal data
Utility

Clinical utility

• Extent to which the biomarker test will affect clinical management and improve the individual’s health
• Drugs are not synonymous with clinical management

Personal utility

• Extent to which the biomarker test has the potential to effect change on a non-medical personal level

Considerations

• Current evidence does not support the fear of suggested risks
• Disclosure in healthy people is happening, focus needs to be on process and consequences
• Is there any other established risk factor being intentionally withheld from the public?
“Dementia Matters” explores Alzheimer’s disease research and caregiver topics for a general audience.

3 Ways to Listen!

Through your favorite podcast app on your smartphone.

Online at adrc.wisc.edu/dementia-matters

On the radio at 102.9 WMUU in Madison, Fridays at 4:00 p.m.
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Determining “elevated” vs “non-elevated” amyloid

Visual rating of PiB elevation (Johnson et al., 2014)

- ACTC color map that demarcates PiB levels SUVR > 1.1
- Rated on a 4-point scale. Only a rating of 3 (unambiguous amyloid binding in the cortex) is considered elevated.