ETHICAL ISSUES IN THE USE OF NEW DIAGNOSTIC BIOMARKERS AND FUTURE COMBINATION THERAPIES FOR AD

Serge Gauthier, C.M, MD, FRCP C
McGill University Research Center for Studies in Aging
Douglas Mental Health University Institute
Conflict of interest

• Clinical trial support from Lilly and Roche in DIAN-TU, TauRx, Lundbeck
• DSMB member of ADCS, ATRI, API, Eisai
• Scientific advisor to Affiris, Boehringer-Ingelheim, Lilly, Servier, Sanofi, Schwabe, Takeda, TauRx, Roche
OUTLINE

• Who is at risk of progression to AD?
• Biomarkers allow for risk assessment for progression to AD
• Biomarkers allow for enrolment in clinical trials
• Possible combination therapies
• Ethical considerations
STAGING OF AD: THE GLOBAL DETERIORATION SCALE (Reisberg)

1. no complaints no impairment
2. complaints but no impairment (SCI)
3. early cognitive impairment (MCI)
4, 5. mild to moderate dementia
6, 7. severe dementia
STAGING OF AD: THE GLOBAL DETERIORATION SCALE (Reisberg)

1. no complaints no impairment
2. complaints but no impairment (SCI)
3. early cognitive impairment (MCI)
4, 5. mild to moderate dementia
6, 7. severe dementia
OUTLINE

• Who is at risk of progression to AD?
• Biomarkers allow for risk assessment for progression to AD
• Biomarkers allow for enrolment in clinical trials
• Possible combination therapies
• Ethical considerations
AD Progression

Kadir, Marutle et al. Brain 2010
Relationship between “abnormality” and CDR of 1.0


-30 -25 -20 -15 -10 -5 0

Biomarker magnitude

-30 -25 -20 -15 -10 -5 0

Time (years)

Aβ deposition
Hippocampal volume
Episodic memory
Grey matter volume
Non-memory

abnormal

normal

cut-off

CDR 1.0

non-demented
demented
OUTLINE

• Who is at risk of progression to AD?
• Biomarkers allow for risk assessment for progression to AD
• **Biomarkers allow for enrolment in clinical trials**
• Possible combination therapies
• Ethical considerations
# Diagnostic Criteria for Preclinical AD Using Biomarkers

(Modified from Sperling et al, 2011)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Aβ</th>
<th>Neuronal Injury</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic cerebral amyloidosis (ACA)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACA + evidence of neuronal injury (NI)</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ACA + NI + subtle cognitive decline</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
“The concept of a biomarker-defined pre-symptomatic stage of AD provides a foundation for early-stage clinical trials”

“Asymptomatic individuals with amyloid-β accumulation in the brain show faster cognitive decline than similar individuals without amyloidosis”
OUTLINE

• Who is at risk of progression to AD?
• Biomarkers allow for risk assessment for progression to AD
• Biomarkers allow for enrolment in clinical trials
• Possible combination therapies
• Ethical considerations
PATHOLOGIES ASSOCIATED WITH AD

AGE

30
40
50
60
70
80
90
100

β-amylloid deposition

Microglial activation

NFTs

Neuronal loss

Symptoms
COMBINATION Rx IN AD

• So far anti-amyloid monotherapy has not helped in a clinically meaningful way
• Combination of anti-amyloid drugs are being considered (ex. BACE inhibitor and antibodies)
• Combinations of an anti-amyloid drug and an anti-tau phosphorylation drug should be considered
Socio-economic considerations of combination Rx in AD
Tomaszewski et al, JPAD 2015

• Tuberculosis, HIV/AIDS and breast cancer are useful models to work out the costs of combination therapies in common diseases

• WHO’s Access Framework facilitates assess to essential medicines: rational selection, affordable prices, sustainable financing, reliable health & supply systems
OUTLINE

• Who is at risk of progression to AD?
• Biomarkers allow for risk assessment for progression to AD
• Biomarkers allow for enrolment in clinical trials
• Possible combination therapies
• Ethical considerations
Currently unresolved issues with very early diagnosis of AD

- Risk of false positive diagnosis
- Social stigma
- Risk of catastrophic reaction
- No proven long-term treatments
- Additional costs for tests
- Burden on memory clinics
POSSIBLE FUTURE SCENARIO 1

• An anti-amyloid drug is effective in 35% of patients in prodromal AD before age 80
• A positive amyloid biomarker is required for Rx coverage (CSF or PET)
• Safety MRIs are needed for the first three months of Rx
• The Rx is stopped when patients reach CDR1.
POSSIBLE FUTURE SCENARIO 2

• A combination of anti-amyloid and anti-tau drugs is effective in 50% of patients with prodromal or mild dementia due to AD, all ages
• Same biomarker restrictions and monitoring
• The Rx is stopped when patients reach CDR2
CONCLUSION

• Caution in knowledge transfer between exploratory biomarkers of AD and clinical testing, diagnosis and treatment
• Particularly true in asymptomatic persons
• Disclosure of individual tests results for research participants should be restricted to clinically relevant information
• Optimism for the near future!