BRAIN IMAGING, BLOOD AND CEREBROSPINAL FLUID BIOMARKERS FOR DIAGNOSIS OF ALZHEIMER’S DISEASE

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TOPICS REQUESTED

- Current use of imaging/biomarkers in diagnosis
- Current use of imaging/biomarkers in research
- Distinguish FDA approved/non-approved diagnostic tests
- What should be considered as definitive for Social Security’s purposes???????
GENERAL USE OF TECHNOLOGY FOR DIAGNOSIS

• A century ago, all medical diagnosis was based on self-report/physical exam

• Widespread use of technology for diagnosis, early detection, risk assessment
  – Blood tests, imaging, EKG, etc

• Most diagnosis of neurological/psychiatric disorders based on self report/physical examination
  – Imaging/biomarkers have limited but growing use
CURRENT DIAGNOSIS OF ALZHEIMER’S DISEASE

- Clinical diagnosis
- Requires presence of dementia
- Growing recognition that AD pathology exists for many years prior to dementia
  - Asymptomatic phase
  - Mild symptoms, mild cognitive impairments
  - Dementia
IMAGING FOR DIAGNOSIS OF ALZHEIMER’S DISEASE

• Uses:
  – Diagnosis
  – Prediction of future decline/dementia (Research!)
    • early detection
    • Risk assessment
  – Clinical trials

• Imaging Modalities
  – Computerized tomography
  – MRI: many types of MRI scans
  – PET: FDG, amyloid scans
STRUCTURAL MRI
Normal Elderly Brain (FDA approved)
Alzheimer’s Atrophy

Age: 62
Sex: Male
Dx: AD Probable
Alzheimer’s Atrophy

Age: 87
Sex: Female
Dx: AD Probable
Frontal-Temporal Dementia (FTD)

Age: 52
Sex: Female
Dx: FTD
WMSH With Lacunes

Age: 80
Sex: Male
Dx: IVD
USE OF MRI

• Rules out other causes
  – Tumors, bleeding, multiple sclerosis etc
  – Suggests other causes of dementia
    • Frontotemporal dementia

• Provides confirmatory evidence
  – Atrophy of brain esp hippocampus: not diagnostic

• Many research uses
  – Emphasis on predicting future decline
  – Identifying AD pathology
POSITRON EMISSION TOMOGRAPHY (PET)

• Fluro Deoxyglucose PET: FDA approved
  – Widely used for cancer staging
  – Approved by CMS for ‘differentiating AD from FTD (long story)
    • Some evidence of widespread abuse/misuse
  – Not approved for Dx of AD
• FDG PET does help “rule in” AD
• Many research uses
Normal Aging vs. Alzheimer’s Disease
Positron Emission Tomography (PET)

Normal

AD
AMYLOID PET

• A technique to detect presence of amyloid plaques in the brain
  – Amyloid plaques = AD pathology (?)
• Carbon 11 Pittsburgh compound B
• Four commercially produced F18 amyloid agents: GE, Bayer, AstraZeneca, AVID
  – In phase 3
• Likely to be approved ‘to detect amyloid’
  – Diagnostic claims uncertain
PIB Imaging: Alzheimer’s Disease

FDG

PIB
FDA AND PIB PET
Frontotemporal Dementia
WHAT IS ROLE OF AMYLOID PET FOR DIAGNOSIS ETC?

• Currently undetermined
• Could be used to “rule out” AD pathology
• Could be used for early detection of AD pathology
  – A risk factor for cognitive decline/dementia
  – PIB+ seems to predict future decline/dementia
• Lots of research to do: will take years
BLOOD AND CSF BIOMARKERS

• Abeta amyloid (various species)
  – Measurement in CSF
    • Seems to have some diagnostic use
    • Use by some in clinical practice: not widespread
  – Measurement in blood: research value only

• Tau: a measure of neurodegeneration in CSF
  – May have clinical value: lots of research

• Other proteins: Blood and CSF

• RNA expression: Blood
### BIOMARKERS

John Trojanowski, Les Shaw, U Penn.

<table>
<thead>
<tr>
<th></th>
<th>Tau</th>
<th>αβ_{1-42}</th>
<th>P-Tau_{181P}</th>
<th>Tau/αβ_{1-42}</th>
<th>P-Tau_{181P}/αβ_{1-42}</th>
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<td><strong>AD (n=102)</strong></td>
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<tr>
<td>Mean±SD</td>
<td>122±58</td>
<td>143±41</td>
<td>42±20</td>
<td>0.9±0.5</td>
<td>0.3±0.2</td>
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<td><strong>MCI (n=200)</strong></td>
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<tr>
<td>Mean±SD</td>
<td>103±61</td>
<td>164±55</td>
<td>35±18</td>
<td>0.8±0.6</td>
<td>0.3±0.2</td>
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<td><strong>NC (n=114)</strong></td>
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<td>Mean±SD</td>
<td>70±30</td>
<td>206±55</td>
<td>25±15</td>
<td>0.4±0.3</td>
<td>0.1±0.1</td>
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</table>

p<0.0001, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC.

For AD vs MCI: p<0.005, Tau; p<0.01, αβ_{1-42}; p<0.01, P-Tau_{181P}; p<0.0005, Tau/αβ_{1-42}; p<0.005, P-Tau_{181P}/αβ_{1-42}. Mann-Whitney test
PIB vs CSF Biomarkers: Aβ

Total N = 55 (11 Control, 34 MCI, 10 AD)

Penn Autopsy Sample (56 AD, 52 Cog normal) 192 pg/ml
AMYLOID IMAGING VS CSF ANALYSIS

• Thus far CSF analysis ($300) seems to provide similar predictive information to amyloid imaging ($>3000)
• But there is resistance to lumbar puncture
• More research needed
• Public acceptance of LPs would be helpful
USING IMAGING/CSF BIOMARKERS TO DETECT AD IN HEALTHY normals

• Early data suggests that a substantial minority of healthy normal
  – + amyloid imaging
  – Low CSF amyloid
• These subjects may be at increased risk for cognitive decline and dementia
• Much important research to do
• Technologies will improve
DIFFUSION SPECTRUM IMAGING MEASURES BRAIN CONNECTIVITY
SUMMARY

• Currently MRI is approved
  – To rule out other causes of dementia
  – Also provide evidence in favor of Dx
• FDG PET approved AD/FTD
  – Also provides evidence in favor of Dx
• CSF analysis is used by some
  – For diagnosis risk assessment
• F 18 amyloid imaging has promise
  – Advantage over CSF?
• Much research to be done
NA-ADNI
Planned n=800
~60M USD

EU-ADNI
AddNeuroMed n=700
Pilot E-ADNI n=59
~8.6M Euro

J-ADNI
Planned n=600
4.7M USD / year

A-ADNI
N=1111; 286 MRI
2.5M USD

WW-ADNI
COSTS TO SOCIAL SECURITY

• Dementia already costs US economy over $120 billion/yr
• AD research is underfunded compared to heart disease (NHBL) and cancer (NCI)
• How could SS/CMS funds be used to support dementia prevention research?
• It would be useful to estimate the savings to SSN/CMS by treatment/prevention of AD