Precision Medicine in Alzheimer Disease & Neurodegenerative Disorders

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- Precision Medicine
- Biomarkers
- Treatment benefit
Alzheimer Disease

Definite Alzheimer's disease must be pathologically confirmed by autopsy or brain biopsy showing neurofibrillary tangles and senile plaques.

• Precision Medicine
**Precision Medicine**

Key elements of precision medicine:
1) Comprehensive risk assessment to identify underlying factors
2) Utilizing tools for preclinical detection of pathophysiological processes
3) Molecularly tailored intervention

“Personalized profile” based on metabolomics as well as other clinical and lifestyle data will be used to predict the patients’ responses to specific treatments and thus help select the best treatment regimens.

Metabolomics (2016) 12:149
DOI 10.1007/s11306-016-1094-6
Key elements of precision medicine are classification by risk, surveillance for preclinical disease, and alignment of an expanding repertoire of treatments with the molecular drivers of disease.

Am J Pathol 2016, 186: 500-506

Precision Medicine Approach

A Multimodal Biomarker Model of ADRD

Together these modalities can support a precision medicine approach to therapeutics
Precision Medicine

Alzheimer’s Disease & Related Dementias (ADRD)

Cognitive Disorders

Movement Disorders

Alzheimer’s

Parkinson’s

Alzheimer’s - AD (amyloid)

Parkinson’s - PD (α-synuclein)

Precision Medicine - Comorbid Approach

Economic Consequences of Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Annual Costs Per Patient ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's Disease</td>
<td>5000 (PD)</td>
</tr>
<tr>
<td>AD + Parkinson's Disease</td>
<td>35000 (PD + Cognition)</td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>30000 (AD)</td>
</tr>
<tr>
<td>AD + Alzheimer's Disease</td>
<td>40000 (AD + Parkinson's)</td>
</tr>
</tbody>
</table>

(adapted from Murman, 2003 and Vossius, 2011)
Precision Medicine Approach

Type 2 DM and AD

- A misfolded protein present in type 2 diabetes mellitus (T2DM) can exacerbate the aggregation of amyloid-β (Aβ)
- Both diseases feature misfolding and aggregation of proteins, resulting in Aβ deposition in the brains of individuals with AD, and the aggregation of islet amyloid polypeptide (IAPP) within the pancreas in individuals with T2DM

Cognitive deficits in preclinical AD models are triggered by Aβ-mediated neuroinflammation and insulin resistance, mitochondrial dysfunction, and impaired hippocampal ERK-dependent memory.

It is potential clinical relevance to define patient populations potentially responsive to mechanistically distinct insulin sensitizer therapies.
Fig. 1. Model of the clinical trajectory of Alzheimer’s disease (AD). The stage of preclinical AD precedes mild cognitive impairment (MCI) and encompasses the spectrum of presymptomatic autosomal dominant mutation carriers, asymptomatic biomarker-positive older individuals at risk for progression to MCI due to AD and AD-dementia, as well as biomarker-positive individuals who have demonstrated subtle decline from their own baseline that exceeds that expected in typical aging, but would not yet meet criteria for MCI. Note that this diagram represents a hypothetical model for the pathological-clinical continuum of AD but does not imply that all individuals with biomarker evidence of AD-pathophysiological process will progress to the clinical phases of the illness.

R.A. Sperling et al. / Alzheimer’s & Dementia - (2011) 1–13
NIA/Alz Assn Classification of AD

Preclinical AD → MCI Due to AD → Probable AD → Pathophysiological Proved AD

Types 1, 2, 3 with increasing Biological and Cognitive (mild) Abnormalities

Likelihood of AD Determined by Amyloid and Neurodegeneration Biomarkers

Diagnosis Supported by Course & Biomarkers or Mutation

Clinical and Pathology Criteria Met

Jack C et al; Sperling R et al; Alberts M et al; McKhann G et al. Alz Dementia 2011

Principal Biomarkers in AD Diagnosis

- Amyloid (Aβ) related
  - CSF Aβ1-42 levels
  - Amyloid imaging
- Neuronal injury / neurodegeneration
  - MRI atrophy
  - FDG PET hypometabolism
  - CSF tau and p-tau
Cell Death and Neurodegeneration Lead to Brain Atrophy Detectable by MRI

Jagust W. Alz Dem 2006; 2: 36-42

MCI with High Amyloid Burden Represents an Early Stage of AD and Predicts Progression to AD Dementia

Preclinical Stages of AD

<table>
<thead>
<tr>
<th>Stage</th>
<th>A-beta Accumulation*</th>
<th>Neurodegeneration**</th>
<th>Very Subtle Cognitive Decline***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>3</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

*(+) a-beta imaging or decreased CSF a-beta  
** AD pattern on FDG PET or cortical thinning, volume loss on MRI, elevated CSF tau or p-tau  
***Do not meet criteria for MCI

Sperling R et al; Alz Dementia, 2011

Biomarkers in a diagnostic framework
Commonly analyzed biomarkers in Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Amyloid hypothesis</th>
<th>Genomic and non-genomic factors</th>
<th>Other CSF Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amyloid beta 42 peptide</td>
<td>• Gene mutations APP, PS1 and PS2</td>
<td>• Aβ oligomers</td>
</tr>
<tr>
<td>• Tau / p-tau proteins</td>
<td>• Apolipoprotein E</td>
<td>• ALZAS protein</td>
</tr>
<tr>
<td>• General agreement that MCI and AD are accompanied by decreased levels of Aβ42 in CSF and an increase in tau-p-tau in CSF</td>
<td>• TOMM40</td>
<td>• BACE1</td>
</tr>
<tr>
<td>• The use of Aβ42 and tau in combination can be used to confirm the diagnosis of probable AD based on cognitive decline and can be used to enrich clinical trial populations</td>
<td>• Homocysteine</td>
<td>• Clusterin</td>
</tr>
<tr>
<td>• Attempts to correlate plasma levels of Aβ and tau with stages of AD have provided inconsistent data, and plasma Aβ42 does not appear to represent a useful supporting biomarker to help the diagnosis of AD</td>
<td>• Genetic mutations can be used in an accurate predictive manner where a family history of AD exists</td>
<td>• Isoprostanes</td>
</tr>
<tr>
<td></td>
<td>• ApoE cannot be used as a predictive marker since a large number of positive subjects do not develop AD</td>
<td>• Proteomic</td>
</tr>
<tr>
<td></td>
<td>• TOMM40 is a protein encoded by the TOMM40 gene; alleles of this gene have been statistically associated with an increased risk of developing late-onset AD</td>
<td>15/17 panel</td>
</tr>
<tr>
<td></td>
<td>• Elevated blood homocysteine levels are associated with greater risk of developing AD; reduction of homocysteine levels is accompanied by decreased brain atrophy and improved cognition</td>
<td>• Ubiquitin</td>
</tr>
</tbody>
</table>

Source: C.R. Jack Jr. et al., Alzheimer’s & Dementia 2018; 14: 535-562
Genetics of Alzheimer’s disease

Alzheimer’s disease: 2 types of AD: EOAD (familiar) & LOAD
EOAD (familiar): Genetic background well defined
3 genes in EOAD: APP, PSEN1 and PSEN2

Modified from Bird et al. 1999
• An approach for disease prevention and treatment that is personalized to an individual’s specific pattern of genetic variability, environment and lifestyle factors, has emerged.

• AD is a polygenic and multifactorial clinical entity in which hundreds of defective genes distributed across the human genome may contribute to its pathogenesis.

• Diverse environmental factors, cerebrovascular dysfunction, and epigenetic phenomena, together with structural and functional genomic dysfunctions, lead to amyloid deposition, neurofibrillary tangle formation, and premature neuronal death, the major neuropathological hallmarks of AD.

Major molecular pathways involved in LOAD etiology that were identified by genomic study

<table>
<thead>
<tr>
<th>Gene</th>
<th>Molecular pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE, SOR1, CLU, CR1, PICALM, BIN1, ABCA7, CASS4, PLD3</td>
<td>Amyloid pathway</td>
</tr>
<tr>
<td>CLU, CR1, EPHA1, ABCA7, MS4A4A/MS4A6E, CD33, CD2AP, HLA-DRB5/DRB1, INPP5D, MEF2C, TREM2/TREM2</td>
<td>Immune system/Inflammation</td>
</tr>
<tr>
<td>APOE, CLU, ABCA7, SOR1</td>
<td>Lipid transport and metabolism</td>
</tr>
<tr>
<td>CLU, PICALM, BIN1, EPHA1, MS4A4A/MS4A6E, CD33, CD2AP, PTX2B, SOR1, SLC24A4/RN43, MEF2C</td>
<td>Synaptic cell functioning/endocytosis</td>
</tr>
<tr>
<td>BIN1, CASS4, FERMT2</td>
<td>Tau pathology</td>
</tr>
<tr>
<td>PTX2B</td>
<td>Cell migration</td>
</tr>
<tr>
<td>MEF2C, PTX2B</td>
<td>Hippocampal synaptic function</td>
</tr>
<tr>
<td>CELF1, NME8, CASS4</td>
<td>Cytoskeletal function and axonal transport</td>
</tr>
<tr>
<td>INPP5D</td>
<td>Microglial and myeloid cell function</td>
</tr>
<tr>
<td>FBXL7</td>
<td>Phosphorylation-dependent ubiquitination</td>
</tr>
</tbody>
</table>

Figure 1. Potential pathways of susceptibility genes involved in the pathogenesis of AD.

Figure 1. Rare and common variants contribute to Alzheimer’s disease risk. Figure updated and modified from (149).
APOE Genotypes in the General Western Population

- 3/3, 67%
- 3/4, 20%
- 2/4, 3%
- 4/4, 2%
- 2/3, 8%
- 2/2, 1%

ApoE4 25%

Senarong et al. BMC Neurology 2013, 13:3
http://www.biomedcentral.com/1471-2377/13/3

Table 7 ApoE gene status

<table>
<thead>
<tr>
<th>ApoE gene (N=302)</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2E2</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>E2E3</td>
<td>42</td>
<td>13.9</td>
</tr>
<tr>
<td><strong>E2E4</strong></td>
<td>11</td>
<td>3.6</td>
</tr>
<tr>
<td>E3E3</td>
<td>189</td>
<td>62.6</td>
</tr>
<tr>
<td>E3E4</td>
<td>55</td>
<td>18.2</td>
</tr>
<tr>
<td>E4E4</td>
<td>3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ApoE4 22.8%
ApoE4+

The data are estimated from a logistic model. Amyloid PET positivity was defined as a standardized uptake value ratio of 1:4 or greater. The estimated age at which 90% (the dashed horizontal line) of the population is positive is 57 years (IC: 53-61 years) for APOE ε4 carriers and 64 years (IC: 62-66 years) for APOE ε4 noncarriers.

Genetic based biomarker risk algorithm

Fig. 1. GBRA AD-risk algorithm. Flowchart and Tables show the process for the generation of the risk assessment for MCI due to AD using the GBRA. Risk of high or low is assigned based on APOE genotype, TOMM40/523 genotype, and current age. Abbreviations: GBRA, genetics-based biomarker risk algorithm; AD, Alzheimer’s disease; APOE, apolipoprotein E; TOMM40, translocase of outer mitochondrial membrane 40 homolog; MCI, mild cognitive impairment.

<table>
<thead>
<tr>
<th>GBRA risk group</th>
<th>CSF levels (ADNI)</th>
<th>Imaging (ADNI)</th>
<th>MMSE**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aβ42***</td>
<td>t-tau**</td>
<td>SUVR*</td>
</tr>
<tr>
<td>High</td>
<td>157.15 ± 37.8</td>
<td>36.70 ± 1.23</td>
<td>1.90 ± 0.36</td>
</tr>
<tr>
<td>Low</td>
<td>195.59 ± 46.7</td>
<td>28.17 ± 1.38</td>
<td>1.52 ± 0.37</td>
</tr>
</tbody>
</table>

Abbreviation: GBRA, genetics-based biomarker risk algorithm; CSF, cerebrospinal fluid; ADNI, Alzheimer’s Disease Neuroimaging Initiative; MMSE, mini-mental state examination; Aβ42, amyloid-beta; t-tau, phosphorylated tau; CDR, clinical dementia rating; ADRC, Alzheimer’s Disease Research Center; SUVR, standardized uptake value ratio.

NOTE: *P < .05; **P < .001.
• 3 genes carrying a higher burden of protein-truncating and missense predicted damaging variants in Alzheimer disease (AD) cases as compared to controls:
  • TREM2,
  • SORL1, and
  • ABCA7.

SORL1 gene

SorLA: a protector against AB secretion, SORL1 encodes SorLA, a key protein involved in the processing of the amyloid-beta (Aβ) precursor protein (APP) and the secretion of the Aβ peptide, SORL1: aggregating protein-truncating (PTV) and predicted damaging missense variants

SORL1 mettaanalysis: a significant enrichment in PTVs with ORs of 12.29 (95% confidence interval = [4.22-35.78]) among all AD cases and 27.50 [7.38-102.42] among EOAD cases

SORL1 variants in familial AD

<table>
<thead>
<tr>
<th>Mutations (protein)</th>
<th>Goldman Score</th>
<th>Gender</th>
<th>Age of onset (yr)</th>
<th>Current age (yr)</th>
<th>Additional features of DAT</th>
<th>APOE Other genetic studies (negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gly1817Val</td>
<td>3</td>
<td>Female</td>
<td>58</td>
<td>72</td>
<td>None</td>
<td>4.4 C9orf72, PSI</td>
</tr>
<tr>
<td>Splice-site</td>
<td>Male</td>
<td>53</td>
<td>70</td>
<td>85</td>
<td>Apathy, behavioral problems</td>
<td>3.3 NGS dementia panel, C9orf72</td>
</tr>
<tr>
<td>Gly3270Lys</td>
<td>Female</td>
<td>64</td>
<td>72</td>
<td>None</td>
<td>C9orf72</td>
<td></td>
</tr>
<tr>
<td>Gly852Ala</td>
<td>Female</td>
<td>66</td>
<td>72</td>
<td>None</td>
<td>C9orf72</td>
<td></td>
</tr>
<tr>
<td>Arg1702Met</td>
<td>Female</td>
<td>70</td>
<td>85</td>
<td>None</td>
<td>C9orf72</td>
<td></td>
</tr>
<tr>
<td>Asn1809Ser</td>
<td>Female</td>
<td>72</td>
<td>76</td>
<td>Prior chronic depression, irritability</td>
<td>4.4 C9orf72</td>
<td></td>
</tr>
<tr>
<td>Asp2065Val</td>
<td>Female</td>
<td>60</td>
<td>72</td>
<td>Parkinsonism</td>
<td>4.4 NGS dementia panel, C9orf72</td>
<td></td>
</tr>
</tbody>
</table>

*Deceased. NGS dementia panel includes 18 genes (see text).
Whole-exome sequencing in 20,197 persons for rare variants in Alzheimer’s disease

19 cases carrying rare SORL1 loss-of-function variants among 6,965 cases vs a single loss-of-function variant among 13,252 controls (P = 2.17 9 10e8 ; OR: 36.2 [95% CI: 5.8–1493.0]). Age-at-onset was 7 years earlier for patients with SORL1 qualifying variant compared with noncarriers.

APOE/TOMM40 genes
APOE/COMT
APOE/BDNF
APOE/KIBNA
confer dementia risk
(but not MCI risk)
Spanish MCI and HC

Performance in **language and memory** tasks between carriers and non-carriers of BIN1, CLU, and CR1 variants and a trend toward **poor cognitive** performance for PICALM, GWAS_14q, SORL1, and PVRL2 variants; the APOE and TOMM40 variants were not associated with poor cognitive performance.
• Genetics and treatment response

• The therapeutic response to conventional drugs (cholinesterase inhibitors, multifactorial strategies) is genotype-specific.

• Genomic factors potentially involved in AD pharmacogenomics include at least five categories of gene clusters:
  
  (1) genes associated with disease pathogenesis;
  (2) genes associated with the mechanism of action of drugs;
  (3) genes associated with drug metabolism (phase I and II reactions);
  (4) genes associated with drug transporters;
  (5) pleiotropic genes involved in multifaceted cascades and metabolic reactions.
• The effect of APOE ε4 on onset age of autosomal dominant AD was confirmed in large pedigrees

• Up to 75% of individuals heterogeneous for APOE ε4 do not develop AD during life, and up to 50% of people with AD do not carry the high-risk ε4 allele

• In a Columbian kindred carrying the PSEN1 p.E280A mutation, a protective haplotype was recently identified through whole genome sequencing. This haplotype, associated with a 10-year delay in onset age, harbors a missense mutation in the CCL11 gene encoding eotaxin-1.53

• The mutation p.R406W in MAPT, a known causal gene for FTLD, has repeatedly been reported in pedigrees with a clinical presentation of AD. Mutations in two other FTLD genes, GRN and C9orf72, have also been described in clinical AD cohorts. It may be important to include screening of these genes in the genetic diagnostic work-up of high genetic load AD patients

• Gene–environment interactions and epigenetic changes can also result in significantly different disease outcomes
Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

METHODS
In a double-blind study, we evaluated subjects with the amnestic subtype of mild cognitive impairment. Subjects were randomly assigned to receive 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for three years. The primary outcome was clinically possible or probable Alzheimer's disease; secondary outcomes were cognition and function.

RESULTS
A total of 769 subjects were enrolled, and possible or probable Alzheimer's disease developed in 212. The overall rate of progression from mild cognitive impairment to Alzheimer's disease was 16 percent per year. As compared with the placebo group, there were no significant differences in the probability of progression to Alzheimer's disease in the vitamin E group (hazard ratio, 1.02; 95 percent confidence interval, 0.74 to 1.41; P=0.91) or the donepezil group (hazard ratio, 0.80; 95 percent confidence interval, 0.57 to 1.13; P=0.42) during the three years of treatment. Prespecified analyses of the treatment effects at 6-month intervals showed that as compared with the placebo group, the donepezil group had a reduced likelihood of progression to Alzheimer's disease during the first 12 months of the study (P=0.04), a finding supported by the secondary outcome measures. Among carriers of one or more apolipoprotein E4 alleles, the benefit of donepezil was evident throughout the three-year follow-up. There were no significant differences in the rate of progression to Alzheimer's disease between the vitamin E and placebo groups at any point, either among all patients or among apolipoprotein E4 carriers.

CONCLUSIONS
Vitamin E had no benefit in patients with mild cognitive impairment. Although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment, the rate of progression to Alzheimer's disease after three years was not lower among patients treated with donepezil than among those given placebo.

Figure 1. Kaplan–Meier Estimates of the Rate of Progression from Mild Cognitive Impairment to Alzheimer's Disease (AD).
Panel A shows the survival estimates in all three groups during the three-year study. Panel B shows the results of pre-specified comparisons involving zolets at 6 months (P=0.004) and 12 months (P=0.04). Panel C shows the effect of APOE4 carrier status on the rate of progression to Alzheimer's disease, and Panel D shows the effect of treatment among APOE4 carriers. Comparisons were adjusted for multiple comparisons with the use of the Hochberg method.

A substantial portion of the field focused its efforts on the amyloid cascade hypothesis, highlighted by the identification of pathogenic mutations in APP, PSEN1, and PSEN2. This approach led to human clinical trials potentially decreasing the production or aggregation of Aβ or enhancing Aβ clearance from the brain.
Hypothesis on passive immunization works in AD

Three mechanisms postulated:

- Direct effect of antibody on amyloid β
  - Dissolution
  - Neutralization of Aβ oligomers
- Amyloid β specific antibodies lead to
  - Plaques with Fab domain
  - Microglial cells with Fc domain
  - Antibodies bind to amyloid plaques, triggering microglia activation and infiltration of tissue

The peripheral sink hypothesis: Administration of amyloid β specific antibodies

Efflux of Amyloid β from brain to blood

Neurology 73 15 December, 2009

New Treatments:
SURPRISES WITH ANTI-AMYLOID IMMUNOTHERAPY

CD3 T-cell meningeal response to AN-1792
Vasculitis
Posterior Reversible Encephalopathy Syndrome (PRES)
Intra-cerebral Microhemorrhage
Accelerated Brain Atrophy
Development of Bapineuzumab

Bapineuzumab is a humanized anti-Aβ monoclonal Ab that binds to all toxic forms of Aβ. A significant side effect, called vasogenic edema (VE) or amyloid related imaging abnormality (ARIA), was discovered.

**VE** increase with increase of bapineuzumab dose

<table>
<thead>
<tr>
<th>Bapineuzumab dose cohort</th>
<th>VE rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 mg/kg</td>
<td>3.2 %</td>
</tr>
<tr>
<td>0.50 mg/kg</td>
<td>0 %</td>
</tr>
<tr>
<td>1.00 mg/kg</td>
<td>10.0 %</td>
</tr>
<tr>
<td>2.00 mg/kg</td>
<td>26.7 %</td>
</tr>
</tbody>
</table>

10 of 12 VE cases occurred in ApoE4 carriers with a higher rate observed in ApoE4.

<table>
<thead>
<tr>
<th>ApoE status</th>
<th>VE rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE4 carriers</td>
<td>13.5 % (10/74)</td>
</tr>
<tr>
<td>Non ApoE4 carriers</td>
<td>4.3 % (2/47)</td>
</tr>
</tbody>
</table>

**VE rate** increases with ApoE4 gene dose: 4.3% with 0 copy → 33.3 % with 2 copies

The phase III trials’ intent-to-treat populations: iv infusions of bapineuzumab

- 658 patients in the treatment group (0.5 mg/kg infused 6 times every 13 weeks) and 432 patients in the placebo group for the APOE4 carrier group; for the APOE4 noncarrier group.
- There were 621 patients in the treatment group (0.5 mg/kg or 1.0 mg/kg infused 6 times every 13 weeks; patients were divided equally among these 2 doses) and 493 patients in the placebo group.
- Results of these studies showed no clinical improvement in ADAS-Cog or DAD for both the APOE4 carrier and noncarrier groups.
- There was a measurable difference between the treatment and placebo groups in global amyloid burden and reduction of CSF tau protein in the APOE4 carrier group and a reduction in CSF tau protein in the high-dose APOE4 noncarrier group; otherwise, there were no other improvements noted, including no change in brain volume loss.
- **Vasogenic edema** occurred in **15%** of patients in the APOE4 carrier group and in **9%** and **4% of the high-dose and low-dose APOE4 noncarrier treatment groups** respectively.
- The edema was symptomatic in approximately 2% of those who developed it.
ApoE4 and therapeutic target in Alzheimer Disease

Fig. 2 Schematic presentation of the apoE4-driven mechanisms involved in AD pathology

Safieh et al. BMC Medicine (2019) 17:64
https://doi.org/10.1186/s12916-019-1299-4
Thank You For Your Attention