Towards individualized risk profiling in patients with mild cognitive impairment

Parallel Session Prediction
Grand challenge

Alzheimer’s disease
• 47 million worldwide
• High costs
• Caregiver burden

Grand challenge:
• Find treatments
• Arrange care

Timely + accurate diagnosis essential to allow choices, arrange care, choose medication, prevent crises later in disease process
Improved diagnosis

Novel diagnostic tests amongst largest research success

- **MRI**
  - Cerebral atrophy
  - Hippocampal atrophy

- **CSF**
  - Amyloid beta + tau

- **PET**
  - Amyloid PET

- Alzheimer pathology *in vivo* (accurate diagnosis)
- Alzheimer pathology before dementia (MCI)

- # MCI in memory clinics ↑
Patient journey

Memory complaints/ worry
General Practitioner refers to memory clinic

How to decide which test?
Best application of test
How to combine different tests?

What about the patient?
What does test result mean for my patient?

How to explain?
ABIDE Alzheimer Biomarkers In Daily practice

Goal: translate available knowledge about MRI, CSF, PET diagnostic tests to daily practice

- Public-private consortium
- Special focus on MCI
- Involvement local professionals
- Involvement patients + caregivers

2015 - 2018
ABIDE: goals

Before diagnostic tests
- Optimal use of tests
- After diagnostic tests

Involve patients

Involve professionals
Individualized risk prediction

If not dementia but MCI, than diagnosis becomes prognosis..
MRI + CSF in MCI: what do results mean?

Amsterdam Dementia Cohort: 525 MCI

MRI: medial temporal lobe atrophy + whole brain atrophy
CSF: Amyloid beta + tau
Taking into account age, gender, MMSE

- care ~ research
- broad informed consent
- standardized protocol
- wealth of data
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total n=525</th>
<th>MCI stable n=324</th>
<th>MCI progressors n=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67±8</td>
<td>66±8</td>
<td>69±8</td>
</tr>
<tr>
<td>Sex (F)</td>
<td></td>
<td></td>
<td>92(47%)</td>
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<tr>
<td>education</td>
<td></td>
<td></td>
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<tr>
<td>MMSE</td>
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<tr>
<td>Follow-up</td>
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<tr>
<td>CSF biomarkers</td>
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<td></td>
<td></td>
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<tr>
<td>Abeta</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tau</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On group level, we know:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• age↑-progression↑</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• cognition↓-progression↑</td>
<td></td>
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<tr>
<td>• atrophy ↑-progression↑</td>
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<tr>
<td>• CSF abeta↓-progression↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CSF tau↑-progression↑</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NWBV</td>
<td>1417±80</td>
<td>1433±80</td>
<td>1391±73</td>
</tr>
</tbody>
</table>

But what to tell the next patient who comes into the office?
### Patient characteristics

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<tr>
<td><strong>Sex (F)</strong></td>
<td>210(40%)</td>
</tr>
<tr>
<td><strong>education</strong></td>
<td>5±1</td>
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<tr>
<td><strong>MMSE</strong></td>
<td>27±2</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>2.4±1</td>
</tr>
<tr>
<td><strong>CSF biomarkers</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Abeta</strong></td>
<td>674±298</td>
</tr>
<tr>
<td><strong>Tau</strong></td>
<td>477±309</td>
</tr>
<tr>
<td><strong>NWBV</strong></td>
<td>1417±80</td>
</tr>
</tbody>
</table>

→ Predictive modelling

But what to tell the next patient who comes into the office?

\[ HR = \frac{\exp(\sum B \cdot X)}{\exp(\sum B \cdot X)} \]
Prognosis

Case:
- Female 60 year
- MMSE=24
Risk
  1 year 16%
  3 year 58%

MRI: moderate atrophy
CSF: normal
**Prognosis**

**Case:**
- Female 60 year
- MMSE=24

**Risk**
- 1 year 16%
- 3 year 58%

**MRI:** moderate atrophy

**CSF:** normal

**Risk**
- 1 year 2%
- 3 year 15%

• Validation ~ ADNI freely available → very helpful
Prognosis

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- Female 60 year
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MRI: moderate atrophy
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Risk model provides individualized prognosis. Especially useful to re assure if markers normal. Next steps: (1) develop model bridging different data sets (2) develop tool to support communication
ADappt: interpretation + communication

For professionals

www.alzheimercentrum.nl/professionals/adappt/
ADappt: support prediction

Communication sheet to facilitate communication with patients

Hurdles:
• Legal; CE mark/ medical device legislation/ etc
• Store data yes/ no? Even more complicated
• Firewalls hospitals

Patient wants:
• Own image
• Comparison to normal
→ Bridge data sets/ methods
Next steps & lessons learned

Individualized risk modeling
- Validation; build ‘supra model’ bridging methods and continents
- Extend model; other markers
- Ethical/ social; does a patient want to know the risk? (does professional think the patient should not want to know the risk)
- Lesson learned: data are necessary. Lots of data. Truly longitudinal data.

Online tool:
- Implementation into practice more difficult than anticipated: CE mark, hosting, IP, business model, further development, …
- Practical use in hospital IT environment (fire walls..)
- Lesson learned: easily available ELSI helpdesk would be most helpful!
What we did not do yet, but should be next step

Translate from tertiary setting to average Alzheimer patient
→ taking into account that average does not exist! (one size does not fit all; personalized medicine)

Model not only dementia, but outcomes that matter, i.e. PRO’s
→ foundation for patient-orchestrated care

Model modulation individualized risk predictions by (future) preventive interventions (lifestyle, medication).
→ large, longitudinal, representative datasets needed.
ABOARD

Our mission: to jumpstart Personalized Medicine for Alzheimer’s disease by preparing for and investing in effective, efficient and patient-orchestrated diagnosis, prediction and prevention.

To achieve this mission, we need all ABOARD!

Broad consortium
• Public-private
• Research–industry–care–society
• Advised by Health RI

One of the main goals:
• Set-up nationwide database
  • with focus on PRO’s

• Anticipated: >100 DSA’s, >100 medical ethical committees, professionals without time
  • what is needed; light-weight rules&regulations, facilitators not barriers, ELSI support
  • Patient at steering wheel