Patient Stratification in Alzheimer’s Disease: Opportunities and Challenges

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Disclosures

- Carla Abdelnour has received lecture fees paid by a commercial entity (honoraria) in the last 3 years from Zambon, F. Hoffmann-La Roche Ltd, Schwabe Farma Ibérica S.A.U., and Nutricia.
- Federica Agosta serves as Section Editor of NeuroImage: Clinical and received compensation for consulting services and/or speaking activities from Philips, Novartis, Biogen Inc, and F. Hoffmann-La Roche Ltd.
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The prevalence of Alzheimer’s disease and other dementias is growing and so will the societal burden across the world

AD is a complex, progressive, neurodegenerative disease associated with cognitive, functional, and behavioural changes, spanning decades\(^1\).\(^2\)

Globally, an estimated \textbf{50 million people} are living with Alzheimer’s disease and other dementias\(^4\)

- 62\% are women\(^3\)
- 38\% are men\(^3\)

There has been a dramatic increase in the numbers of individuals living with AD and other dementias since 1990, due to ageing and population growth\(^3\)

By 2050, the number of people living with dementia could be over \textbf{150 million}\(^4\)

Due to the limited scope for disease prevention and the currently limited availability of effective disease-modifying treatments, the burden on caregivers and healthcare systems devoted to care of the elderly will increase rapidly\(^1\)

\(^1\)AD, Alzheimer’s disease.
Current patient experience in Alzheimer’s disease

Patient presentation to PCP and referral to specialist for more specific testing

Differential diagnosis from other conditions, sometimes using biomarkers

Disease characterization/staging, not usually based on biomarkers

Symptomatic treatments and lifestyle interventions

Monitoring and management of disease progression

Experiences can differ based on country guidelines, access to healthcare and diagnostics, clinician preference, and individual factors

PCP, primary care physician.
Potential role of patient stratification in Alzheimer’s disease

**Patient stratification**

Divides one group of patients into subgroups based on particular disease features and characteristics.\(^1\)

**Uses**

To identify individuals who could experience greater benefit and/or less risk from treatment options,\(^2\) either in clinical trials or routine clinical use of DMTs.

**Our research**

In January 2021, clinicians and AD experts met to discuss patient stratification in AD, which was informed by a qualitative literature review.

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AD, Alzheimer’s disease; DMT, disease-modifying treatment.
Methods for patient stratification

There are a variety of methods for patient stratification to identify people who will experience greater benefit and/or less risk from treatment.
Proposed patient experience in AD with stratification for a DMT


Patient presentation at PCP and referral to specialist for more specific testing

Differential diagnosis from other conditions, sometimes using biomarkers

Disease characterization/staging, using biomarkers

Not a DMT Candidate

Symptomatic treatments and lifestyle intervention

Monitoring and management of disease progression

DMT Candidate

DMT treatment and lifestyle intervention

Increased monitoring (imaging, fluid, or digital biomarkers) to assess appropriate response

AD, Alzheimer’s disease; DMT, disease-modifying therapy; PCP, primary care physician.

Patient stratification for differential diagnosis

- Family and/or medical history
- Family observations of change
- Cognitive, physical, and/or neurological testing
- MRI and/or PET testing
- General blood testing
- CSF testing

Biomarkers are not routinely used for diagnosis, but will be increasingly important to diagnose patients with Alzheimer’s disease.
Disease characterization to identify patients for DMT treatment

Most DMTs in development target early AD, so appropriate staging of disease severity along the AD continuum will be critical for identifying candidates for DMTs

AD pathology and risk of progression may be characterized using a variety of factors:

- **Genetic risk factors**
  - Familial AD genes, APOE ε4

- **Biomarkers**
  - CSF, Aβ, Tau

- **Neurodegeneration**
  - MRI, CSF

Treatment pathways can be tailored to the individual, and people at risk of adverse events can be identified to optimize safety planning.

Aβ, beta-amyloid; AD, Alzheimer’s disease; APOE, apolipoprotein E; CSF, cerebrospinal fluid; DMT, disease-modifying treatment; MRI, magnetic resonance imaging.

Considerations for people eligible for DMT treatment

Eligibility
- DMTs targeting Aβ only given to patients with Aβ accumulation
- Alignment with approved label and appropriate use criteria, reflecting clinical trial population
- Inform on limitations/absence of data in underrepresented groups

Communication
- Potential adverse events, e.g. ARIA
- Burden of administration and monitoring
- Costs of DMTs clarified before starting treatment

Not all patients will qualify for treatment with a DMT, so it is critical to identify the ones who could experience greater benefit and/or less risk

Aβ, beta-amyloid; ARIA, amyloid-related imaging abnormalities; DMT, disease-modifying therapy.
Challenges and opportunities for patient stratification

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<tr>
<th>Challenges</th>
<th>Opportunities</th>
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<tr>
<td>Biomarker availability and application varies by country¹</td>
<td>Increase education for PCPs and specialists</td>
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<tr>
<td>Stigma against patients and/or caregivers²</td>
<td>Increase education for the public</td>
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<td>Misdiagnosis or poor coordination of the diagnostic process²</td>
<td>Population-based prevention methods to reflect local cadences</td>
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<tr>
<td>The cost of diagnostic testing may be prohibitive³</td>
<td>Shift in resources and tasks to support earlier intervention</td>
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<td>Identifying appropriate factors for stratification¹,³</td>
<td>Increase understanding of potentially unmeasured factors</td>
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Many challenges need to be overcome to support patient stratification both in clinical trials and in clinical routine.

PCP, primary care physician.
Conclusions

Patient stratification is an important tool in AD treatment, which takes into consideration demographics, cognitive and functional status, biomarker assessment, genetics and other risk factors.

Biomarkers will be integral for patient stratification to identify individuals with underlying target pathology who may be at the early stages of symptomatic AD.

Patient stratification can help identify individuals at risk for adverse events so they can receive appropriate monitoring.

Addressing challenges to patient stratification must happen now to identify patients who will benefit the most from emerging DMTs.

AD, Alzheimer’s disease; DMT, disease-modifying treatment.
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