Alzheimer's Association International Conference (AAIC) 2022, July 31–August 4, 2022, San Diego, CA, USA, and Online

Roadmap to implementation of a fully automated blood-based biomarker test to facilitate diagnosis and treatment in early Alzheimer's disease

P4-21

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Introduction

- Alzheimer's disease (AD) is characterized by β-amyloid deposition (amyloid pathology) and tau pathology in the brain, with clinical symptoms including cognitive complaints or impairment.[1]
- Currently, AD is often diagnosed via a combination of patient history and cognitive assessments. Confirmatory tests for amyloid pathology, including positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarker assessment, may be performed, but their use is not universal, due to limited availability, invasiveness, and cost.[2–5]
- Robust and minimally invasive blood-based biomarker (BBBM) tests to facilitate AD diagnosis are needed and are currently under development.[6]
- Routine implementation of a fully automated BBBM test could streamline AD diagnosis,* facilitate referral decisions, reduce diagnosis times, and allow for timely decision for initiation of disease-modifying therapies (DMTs).

Objectives

- **To explore obstacles in the current AD diagnostic pathway.***
- **To examine the unmet needs that a BBBM test could fulfil.**
- **To outline the potential barriers to BBBM testing.**

*Results for "Current diagnostic pathways for Alzheimer's Disease – A comparison of six countries" are presented in poster P1-21, at this congress.

Methods

- Data were collected using quantitative (n=1,694 healthcare professionals [HCPs], including primary care physicians [PCPs], nurses, and specialists [geriatricians, neurologists, and psychiatrists]) and qualitative surveys (n=213 HCPs/payers), conducted in the following countries from October–December 2021:

China France Germany Spain UK USA

- By completing patient record forms (PRFs) alongside the surveys, HCPs provided data for 6,744 patients, including patient demographics, presenting symptoms, and diagnostic tests and procedures conducted and/or ordered.
- The inclusion criteria for HCPs were: familiarity with aspects of AD and diagnostic biomarker tools; see ≥3 (PCPs/nurses) or ≥5 (specialists) people with subjective/objective cognitive impairment and be involved in these individuals' diagnosis; ≥75% (PCPs/nurses) or ≥60% (specialists) time spent in clinical practice; board certified (USA only); can refer to patient records (excluding Spain).
- In addition, two virtual advisory boards were attended by a total of 10 participants (neurologists, PCPs, and clinical researchers) based in the USA and Europe (December 2021).

Results

Results from quantitative and qualitative surveys

- The surveys showed that, across all countries examined, the current AD diagnosis pathways are not standard (**Table 1**):
  - Between 18% (China) and 83% (France) of patients presented to primary care first with their symptoms, with the remaining patients presenting directly to secondary care.
  - Between 27% (Germany) and 58% (UK) of patients presenting to primary care were referred to secondary care.
  - Of the patients remaining in primary care, referral for PET or CSF analysis was rare, ranging from 6% (UK) to 30% (Spain).

Table 1. Percentages of patients who presented to primary care, were referred to secondary care, or remained in primary care and underwent confirmatory diagnostic tests (all countries).

	China %	France %	Germany %	Spain %	UK %	USA %
Patients presenting to primary care	18	83	57	79	78	58
Patients presenting to primary care and referred to secondary care	51	48	27	37	58	33
Patients remaining in primary care who underwent PET/CSF analysis	7	29	15	30	6	13

Values given are mean percentages of each country examined. Data are based on 6,744 PRFs: China, n=1,204; France, n=871; Germany, n=852; Spain, n=1,023; UK, n=1,056; USA, n=1,738 PRFs. Patients could be counted twice if referred to two specialties.

- There was a lack of consistency in the reasons given by PCPs when referring patients to secondary care or requesting confirmatory testing; this may place a high burden on specialists.
- When deciding whether to refer a patient to secondary care, 73% of PCPs reported basing their decision on cognitive assessment, whereas 35% based their decision on laboratory results (**Figure 1**).

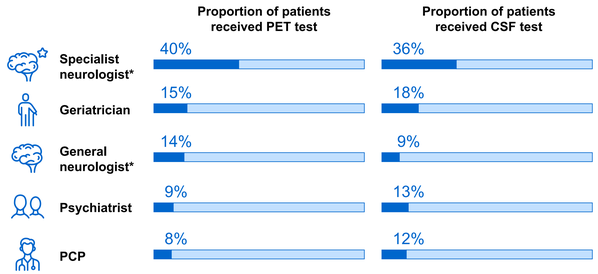
Figure 1. Percentages of PCPs considering the following patient information when deciding whether to refer a patient to secondary care (all countries).

Data are from 454 PCPs. "Cognitive score" included a low MMSE and/or MoCA test result; "patient history" included a family history of cognitive complaints or impairment, physical or behavioral changes over time, and/or mental ill health; "laboratory results" included abnormal blood test results of the following: vitamin B12, vitamin B9, folate, and/or TSH levels; "other criteria" included concerns and/or changes in behavior voiced by family members.

MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; TSH, thyroid-stimulating hormone.

- Specialist neurologists (those working in memory clinics) requested confirmatory diagnostic tests (PET or CSF analysis) for a higher percentage of patients (40% and 36% of patients, respectively) than PCPs (8% and 12% of patients, respectively) (**Figure 2**).

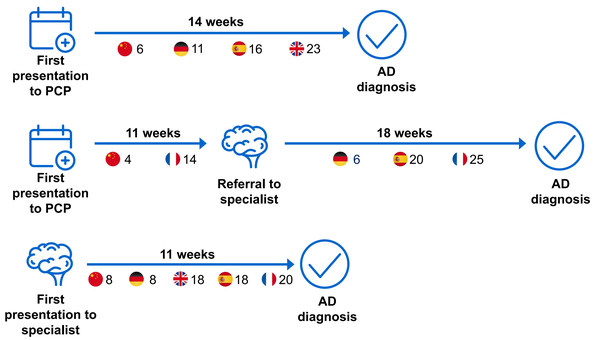
Figure 2. Percentages of patients referred for confirmatory diagnostic tests, by referrer type (all countries).



*Specialist neurologists work in memory clinics; general neurologists do not work in memory clinics. Data are based on 6,662 PRFs.

- A similar proportion of patients received a diagnosis of AD regardless of whether confirmatory diagnostic tests were carried out (**Table 2**).
- The mean time to receive a diagnosis of AD also varied between countries and pathways (**Figure 3**):
  - Patients waited between 6 weeks (China) and 23 weeks (UK) to receive a diagnosis of AD when presenting directly to primary care (mean of all countries: 14 weeks).
  - Patients referred to secondary care, waited a mean of 29 weeks to receive a diagnosis of AD.

Figure 3. Mean number of weeks for patients to receive a diagnosis of AD, depending on countries and pathways.



Patients presenting and remaining in primary care, n=1,475; patients presenting to PCP and referred to a specialist, n=1,038; patients referred by PCP to (and reported by) a specialist, n=453; patients presenting directly to a specialist, n=3,438. The numbers above the arrows indicate the mean number of weeks taken to receive a diagnosis of AD across all countries examined; the numbers to the right of the flag symbols indicate the mean number of weeks to receive a diagnosis of AD by country.

Table 2. Proportion of patients receiving each diagnostic outcome according to whether confirmatory diagnostic tests were carried out (all countries).

	PET and/or CSF carried out, %	Neither PET nor CSF carried out, %
AD diagnosis	31	27
Another dementia diagnosis	19	15
No diagnosis	8	6
Patient told to watch & wait	19	17

Data are based on n=6,744 PRFs: China, n=1,204; France, n=871; Germany, n=852; Spain, n=1,023; UK, n=1,056; USA, n=1,738 PRFs. Percentages in each column do not add up to 100% because other outcomes were possible but are not included.

Conclusions of the advisory boards

- The advisory boards concluded that:
  - A minimally invasive, patient-friendly BBBM test with a high negative predictive value (NPV >90%) and a moderate positive predictive value for amyloid pathology could act as a triage test to exclude patients not requiring downstream diagnostic testing, whilst freeing capacity and allowing timely intervention for other patients.
  - A BBBM test would be useful in both primary and secondary care and could guide the use of confirmatory diagnostic testing whilst streamlining the diagnostic pathway.

Conclusions

- **Heterogeneity in the AD diagnostic pathway across all countries examined presents a unique challenge.**
- **Use of confirmatory testing was limited yet inefficient, with only 31% of patients receiving a diagnosis of AD after undergoing confirmatory testing; this may limit access to DMTs.**
- **A BBBM test with a high NPV (>90%) could streamline the AD diagnostic pathway and accelerate diagnosis by reducing unnecessary confirmatory tests in patients without AD and prioritizing CSF and PET capacity, through immediate actionability in secondary care.**
- **Further evidence of the positive impact on patient outcomes and resources is needed to support reimbursement in primary care.**

References

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Acknowledgments and Disclosures

The authors thank Sophie Roth (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) for her contribution to generating the quantitative data used in the study.

This study was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland). Third-party medical writing assistance, under the direction of the authors, was provided by Anna King, PhD, of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland).