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Early detection tools for Alzheimer's disease: a multi-site observational study

Submission date 20/08/2026	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 11/09/2026	**Overall study status** Ongoing	
Last Edited 11/09/2026	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims

Alzheimer's disease is often diagnosed late, which makes it harder to provide effective support. The AD-RIDDLE project is developing a "toolbox" of digital tests and blood samples to help identify the disease as early as possible. This study aims to see how well these tools work in everyday healthcare settings and if they can help doctors provide better care for their patients. We want to test these tools across a wide range of people, from those with no memory symptoms to patients already being seen at specialist clinics.

Who can participate?

We are looking for volunteers aged 40 years and over. This includes both people from the general population with no known memory concerns, and patients who are being seen at a memory clinic to investigate changes in their cognition or memory. To participate, you should be comfortable using a smartphone, tablet, or computer.

What does the study involve?

Participation involves completing digital memory and thinking tests on your own device or that provided to you in clinic. You will also provide a blood sample to check for specific markers related to brain health. For those being seen at a clinic, you may also undergo routine medical assessments, such as brain scans or a lumbar puncture, as part of your standard clinical care. We will also ask questions about your general health and lifestyle.

What are the possible benefits and risks of participating?

There may be no direct medical benefit to you personally, but your participation is vital for improving how Alzheimer's is detected and managed for others in the future. The risks are very low. Giving a blood sample may cause minor bruising. Digital tests are non-invasive but require some time and focus. Clinical procedures, such as a lumbar puncture or brain scan, may be performed if they are already part of your routine medical care. In some cases, you may be invited to undergo these procedures specifically for the study; however, this is entirely voluntary and you can choose not to participate in these additional tests. These procedures may cause minor discomfort, such as temporary headaches.

Where is the study run from?
The project is led by Region Stockholm and Karolinska Institutet in Sweden. It is a large European collaboration involving hospitals and clinics in six countries: Finland, Italy, the Netherlands, Spain, Sweden, and the United Kingdom.

When is the study starting and how long is it expected to run for?
January 2024 to December 2028

Who is funding the study?
This project has received funding from the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101132933. The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, EuropaBio, MedTech Europe and Vaccines Europe.

Who is the main contact?
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For UK-specific inquiries: Prof. Lefkos Middleton, l.middleton@imperial.ac.uk

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Study information

Scientific Title

Real-world Implementation, Deployment, and validation of early Detection tools and Lifestyle Enhancement for Alzheimer’s Disease (AD-RIDDLE): a multi-site observational study

Acronym
AD-RIDDLE

Study objectives
The AD-RIDDLE project addresses the need for scalable tools for early Alzheimer's disease (AD) detection in real-world settings. AD-RIDDLE includes a set of harmonised real-world studies testing blood-based biomarkers-BBMs and digital cognitive assessments-DCAs in diverse settings, from general populations to primary care and memory clinics. AD and dementia-related diseases are complex and heterogeneous. Timely diagnosis requires an orchestrated multi-step process starting in primary care settings and subsequently involving multiple specialised assessments. There is substantial between- and within-country variation in the division of tasks and responsibilities between primary and secondary care. This is further dependent on which specialty is assigned primary diagnostic and therapeutic responsibility in a specific country or region within a country. This variation requires a more flexible approach to real-world testing of BBMs and DCAs. Different DCAs and BBM assays may be tested at different study sites, and one site may choose to test multiple DCAs and BBM assays. Although a broad range of BBMs (including exploratory ones) will be measured from collected plasma samples, a central focus will be on p-tau217-based assays.

The primary and secondary objectives are to validate BBMs and DCAs for AD diagnosis in memory clinic populations where an appropriate reference standard (i.e., CSF or PET) can be used for AD pathology confirmation. For validation purposes, “memory clinic populations” refers to study participants recruited directly from memory clinics, and/or from primary care or general populations, who have been referred for further assessments in memory clinics. “Memory clinic” refers to any secondary or tertiary care clinic qualified to comprehensively assess, diagnose, and treat cognitive problems. Such clinics may be located within different specialities in different countries or regions, e.g. Neurology, Geriatrics, or Psychiatry. Each study site will decide the appropriate categorisation of their recruitment settings based on the site- or country-specific healthcare system organisation.

A broad range of exploratory analyses may be conducted based on data from all recruited participants from all types of populations and settings. While all recruited participants should preferably have both blood sampling for BBMs and DCAs, DCAs may be done without blood sampling where relevant. Exploratory analyses will cover a broad range of BBMs beyond p-tau217-based.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 23/04/2025, Medisch Ethische Toetsingscommissie (METC) Amsterdam UMC (De Boelelaan 1117, Amsterdam, 1081 HV, Netherlands; +31 (0)20-4445585; metc@amsterdamumc.nl), ref: 2025.0164

2. Approved 16/12/2025, Medisch Ethische Toetsingscommissie (METC) Amsterdam UMC (De Boelelaan 1117, Amsterdam, 1081 HV, Netherlands; +31 (0)20-4445585; metc@amsterdamumc.nl), ref: 2025.0920

3. Submitted 16/05/2026, Medisch Ethische Toetsingscommissie (METC) Amsterdam UMC (De Boelelaan 1117, Amsterdam, 1081 HV, Netherlands; +31 (0)20-4445585; metc@amsterdamumc.nl), ref: 2026.0245

4. Approved 13/01/2026, Comité de Ética de la Investigación con medicamentos del Parc de Salut MAR (Dr. Aiguader, 88, Barcelona, 08003, Spain; +34 (0)93 316 06 77; ceic-psmar@imim.es), ref: 2025/12270/I

5. Approved 12/04/2018, Comité de Ética de la Investigación con medicamentos del Parc de Salut MAR (Dr. Aiguader, 88, Barcelona, 08003, Spain; +34 (0)93 316 06 77; ceic-psmar@imim.es), ref: 2018/7805/I

6. Approved 21/11/2025, West of Scotland Research Ethics Committee 3 (Admin Building, Level 2 Gartnavel Royal Hospital 1055 Great Western Road, Glasgow, G12 XH, United Kingdom; +44 (0) 141 211 3600; ggc.WoSREC3@nhs.scot), ref: 25/WS/0163

7. Approved 28/11/2024, London-Harrow Research Ethics Committee (2 Redman Place Stratford, London, E20 1JQ, United Kingdom; +44 (0)20 7104 8000; harrow.rec@hra.nhs.uk), ref: 24/LO/0769

8. Approved 03/03/2022, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: 2021-05724-01

9. Approved 15/10/2025, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: 2025-06170-01

10. Approved 23/10/2019, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: 2019-04320, Amendments: 2022-04089-02; 2023-00171-02; 2024-00106-02; 2025-02486-02

11. Approved 20/10/2022, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: 2022-04893-01, Amendments: 2024-00105-02; 2024-01894-02; 2024-02647-02; 2025-08001-02

12. Approved 19/02/2025, Comitato etico regionale- CER Umbria (Ospedale S. Maria della Misericordia Piazzale Menghini, Perugia (Pg), 06156, Italy; +39 (0)75 578 4269; segreteriacerumbria@ospedale.perugia.it susarcerumbria@ospedale.perugia.it segreteriacerumbria.aosp.perugia@postacert.umbria.it), ref: CE-1838/25

13. Approved 18/02/2025, Comitato etico regionale- CER Umbria (Ospedale S. Maria della Misericordia Piazzale Menghini, Perugia (Pg), 06156, Italy; +39 (0)75 578 4269; segreteriacerumbria@ospedale.perugia.it susarcerumbria@ospedale.perugia.it segreteriacerumbria.aosp.perugia@postacert.umbria.it), ref: CE-3635/26

14. Approved 22/10/2025, Comitato etico regionale- CER Umbria (Ospedale S. Maria della Misericordia Piazzale Menghini, Perugia (Pg), 06156, Italy; +39 (0)75 578 4269; segreteriacerumbria@ospedale.perugia.it susarcerumbria@ospedale.perugia.it segreteriacerumbria.aosp.perugia@postacert.umbria.it), ref: CE-2989/25

15. Approved 05/10/2025, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: Dnr 2025-03944-01

16. Approved 07/01/2026, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: dnr 2025-08173-01

17. Approved 24/02/2026, Itä-Suomen yhteistyöalueen alueellinen lääketieteellinen tutkimuseettinen toimikunta / The Regional Medical Research Ethics Committee of Eastern Finland Collaborative Area (Puijonlaaksontie 2, PL 1711, Kuopio, 70211, Finland; +358 (0)44 717 2102; tutkimuseettinentoimikunta@pshyvinvointialue.fi), ref: 46/13.00/2026

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19. Approved 14/11/2023, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: 2023-04708-01

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21. Approved 25/02/2026, Etikprövningsmyndigheten/Swedish Ethics Review Authority (Box 2110, Uppsala, 750 02, Sweden; +46 (0)10-475 08 00; registrator@etikprovning.se), ref: 2026-01100-02

Primary study design
Observational

Secondary study design
Cohort study

Study type(s)

Health condition(s) or problem(s) studied
Alzheimer’s disease (AD)

Interventions
AD-RIDDLE real-world testing is not a single study with multiple European sites and one centralised protocol to be strictly and uniformly applied at all sites. A one-size-fits-all approach does not recognize that different clinics will have differing needs and preferences. This protocol enables a more customised approach in which sites can choose from DCA and BBM options to suit their needs. For example, depending on healthcare system or clinic preference, one DCA tool may be preferable over another; one BBM may be incompatible with one setting yet be priority in another. As such, sites will have flexibility to assemble the set of ‘tools’ that are right for them. However, to ensure that cross-site analyses can be conducted, some common data requirements will be applied.

Participants are recruited from memory clinics and community settings across multiple European sites. The study procedures include digital cognitive assessments (Amsterdam-IADL, AUMC; BioCog, Lund university; CANTAB, Cambridge Cognition; cCOG, Combinostics; or neotiv, neotiv) and blood sampling with BBM measurements (p-tau217-based BBMs measured using Fujirebio Lumipulse or C2N PrecivityAD2 assays). In addition, the study will collect sociodemographic data (age, sex, education, self-reported ethnicity), clinical diagnosis (AD or other related disease), comorbidities (e.g. kidney diseases, diabetes, other), BMI, plasma creatinine, eGFR, medications (anti-amyloid treatment, cholinesterase inhibitors, memantine, other), amyloid-PET data or CSF AD biomarkers (Ab42, Ab40, t-tau, p-tau181) available as per standard clinical site procedures, cognitive measures (e.g. MMSE or MoCA, verbal list learning, symbol substitution test, animal fluency, other cognitive tests as available), APOE genotype (where available).

Data collection occurs primarily at baseline. A once yearly longitudinal follow-up of up to 2 years may include DCAs and/or BBMs where feasible according to standard clinical site procedures. The target sample size of 20000 reflects the total reach of the DCAs and BBMs combined.

Intervention Type
Other

Primary outcome(s)
1. Diagnostic accuracy of p-tau217-related blood-based biomarkers (BBM) measured using area under the curve (AUC), sensitivity, and specificity compared with AD pathology reference standard (CSF or amyloid-PET) and dementia expert diagnosis. at baseline (at the time of diagnostic work-up)

2. Diagnostic accuracy of digital cognitive assessments (DCA) measured using area under the curve (AUC), sensitivity, and specificity compared with clinical diagnosis (e.g. normal/SCI, MCI, dementia, established according to site-specific standard procedures) at baseline (at the time of diagnostic work-up)

Key secondary outcome(s)
1. Potential variation in diagnostic accuracy of p-tau217-related blood-based biomarkers (BBM) by cognitive status (SCD, MCI, dementia), presence of relevant comorbidities (e.g., kidney disease, diabetes, obesity), relevant medications, and time of day of sample collection (morning, noon, afternoon), measured using area under the curve (AUC), sensitivity, and specificity compared with AD pathology reference standard (CSF or amyloid-PET) at baseline (at the time of diagnostic work-up)

2. Change in diagnosis certainty self-reported by physicians after seeing p-tau217-related BBM results measured using questionnaire developed by Lund University at baseline (at the time of diagnostic work-up)

3. Usefulness of pTau217-related BBMs results rated by physicians before seeing CSF/PET results measured using questionnaire developed by Lund University at baseline (at the time of diagnostic work-up)

4. Usefulness of doing CSF/PET after pTau217-reated BBMs, rated by physicians after they see both BBMs and CSF/PET results measured using questionnaire developed by Lund University at baseline (at the time of diagnostic work-up)

5. Diagnostic accuracy of digital cognitive assessments (DCA) measured using area under the curve (AUC), sensitivity, and specificity compared with p-tau217-related BBMs at baseline (at the time of diagnostic work-up)

6. Diagnostic accuracy of digital cognitive assessments (DCA) measured using area under the curve (AUC), sensitivity, and specificity compared with other AD pathology markers (CSF, PET) at baseline (at the time of diagnostic work-up)

Completion date
31/12/2028

Eligibility

Key inclusion criteria
General inclusion criteria for all study participants:
1. Aged 40+ years (no upper limit)
2. Willing and able to provide informed consent
3. Able to read and speak the local language
4. It is preferable (but not compulsory) that the participants can identify a study partner who is an adult, has ongoing contact with the participant, and is willing and able to sign the study partner informed consent

Additional inclusion criteria for study participants contributing with data to primary and/or secondary objectives (validation of blood-based biomarkers [BBMs] and digital cognitive assessments [DCAs] in memory clinics):
1. General inclusion criteria are fulfilled
2. Patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI) or dementia who are evaluated for the first time at a secondary or tertiary memory clinic
3. After relevant clinical assessments, according to the treating physician, AD could be a potential cause of the symptomatology, and information about potential AD pathology will be relevant for patient management
4. An appropriate reference standard (i.e., CSF AD biomarkers and/or Aβ-PET) can be used for AD pathology confirmation
5. The participant is willing to use a touchscreen-based device or computer for completing digital cognitive assessments
6. Blood sampling (for BBMs)

Additional inclusion criteria for study participants contributing with data to preclinical AD-related exploratory objectives:
1. General eligibility criteria are met
2. At least 50 years of age
3. No substantial cognitive impairment
4. The participant is willing to use a touchscreen-based device or computer for completing DCAs and/or undergo blood sampling.

Healthy volunteers allowed
Yes

Age group
Mixed

Lower age limit
40 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
General exclusion criteria for all study participants:
1. Significant neurological, psychiatric or other conditions (e.g., hearing or vision impairment) hindering ability to complete study procedures according to clinical judgement
2. Impaired decision-making capacity that renders the individual incapable of consenting or completing study assessments, based on clinical judgement.

Additional exclusion criteria for study participants contributing with data to primary and/or secondary objectives (validation of BBMs and DCAs in memory clinics):
1. Participant cannot undergo lumbar puncture or Aβ-PET imaging, i.e.. no reference standard is available for AD pathology confirmation
2. CSF or Aβ-PET results older than 12 months cannot be used as pathology reference standard

Date of first enrolment
01/01/2024

Date of final enrolment
30/06/2028

Locations

Countries of recruitment
United Kingdom

England

Finland

Italy

Netherlands

Spain

Sweden

Study participating centre

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Sponsor information

Organisation
Region Stockholm

Funder(s)

Funder type

Funder Name
Innovative Health Initiative

Funder Name
Combinostics OY

Funder Name
Neotiv GmbH

Funder Name
Cambridge Cognition Ltd

Funder Name
Fujirebio Europe

Alternative Name(s)
Fujirebio Europe N.V., Fujirebio

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Belgium

Funder Name
C2N Diagnostics, LLC

Funder Name
Sanofi-Aventis Recherche & Developpement

Funder Name
Gates Ventures

Alternative Name(s)
Gates Ventures, LLC, The Gates Notes LLC

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Davos Alzheimer's Collaborative

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository (EPND/AD-Workbench).
The site specific datasets generated during and/or analysed during the current study will be available upon request from study site principal investigators.
Shared data will encompass the data dictionary and de-identified participant data only. Access is subject to the AD-RIDDLE legal framework.

IPD sharing plan summary

Available on request, Stored in non-publicly available repository