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Screening with biomarkers for the early detection of Alzheimer's disease

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Recruiting

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Overall study status
Ongoing

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Condition category
Nervous System Diseases

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Alzheimer's disease and other diseases affecting the brain cause memory decline and other changes leading to dementia. The number of people with dementia is already high and is expected to increase markedly during the next decades. Lifestyle changes can reduce the risk of dementia, particularly in people with increased risk. Also, there are some new medicines that can slow down memory loss. It is important to diagnose Alzheimer's and other conditions that cause dementia as soon as possible. This way, people can make changes to lower their risk. Today, the only way to reliably diagnose Alzheimer's disease is to have an expensive and generally not available imaging scan of your brain, or by testing the fluid around your brain after a procedure called a lumbar puncture. There is a need to find simpler tests for people to access easily. This study will explore a number of relevant tests that can be performed in people's homes to help us diagnose Alzheimer's disease. To prevent and treat AD, it is important to gain a deeper understanding of the key factors that influence it. This study will address these important issues by measuring key risk markers (e.g., memory function and hearing, genes, gut microbiome (bacteria living in the gut), blood, brain activity, and mood) over 4 years in adults over the age of 50 years through an online or in-clinic study.

Who can participate?
Older adults aged 50 years and above who are at risk of memory decline and dementia based on other risks including memory decline, lifestyle and medical factors.

What does the study involve?
The study will include digital assessments such as online memory and hearing tests. Other assessments will include giving saliva, stool and finger prick samples. Some people may also undergo brain scans, lumbar puncture and assessment of brain activity. Guidance will be provided with all assessments and kits to allow participants to complete the assessments smoothly.

What are the possible benefits and risks of participating?
Participants will be taking part in an important research study that could provide valuable new knowledge about new ways to detect people at increased risk for AD.
All researchers have received training in the importance of confidentiality and data protection as

per the General Data Protection Regulation (GDPR) (2018) and GCP guidelines, and are made aware of University-specific regulations in handling confidential information. Each participant will have a single identifier (the study participant number). Identifiable personal data (names, addresses, dates of birth) will be recorded and stored separately. This data is needed for patient contact and to send biomarker kits to participants. Only delegated research team members will have access to this information. Digital Data files will be stored on the University of Exeter Servers and on the Institute of Psychiatry, Psychology, and Neuroscience's server in a shared folder to which only the study team will have access. Data for analysis will be provided in an anonymous format. De-identified data will be shared across the PREDICTOM research team for data analysis.

Consent is given in an informed manner, which has also been used successfully to date within the PROTECT infrastructure (https://www.protectstudy.org.uk/). Consent requires participants to complete individual tick boxes for all consent items, a second full consent item, and then a final confirmation of consent which appears on a separate pop-up page on the website. this process avoids participants consenting in error. All consent will be recorded electronically, time- and date-stamped and accompanied by the minimum required personal data to comply with data protection regulations.

Participants may find the cognitive tests challenging. The researchers will reassure participants and explain that these tests are designed to be hard because if they were too easy they would not be able to give useful information about their cognitive abilities.

This study protocol combines established markers like MRI with new ones such as lumbar puncture and optional imaging assessments. It also includes potential markers like fingerprick blood tests that aren't fully validated yet in this population. Alongside traditional clinical and cognitive assessments, this comprehensive approach helps us effectively establish markers for change. Similar studies show that this population is highly motivated to participate in such research, despite the study's intensity. The study participants are able to remain sufficiently committed to remain engaged throughout the study procedures, despite taxing study demand.

Study procedures will be discussed with the research team (study coordinator, nurse and study doctor), similar to a consent process, providing detailed information on each study procedure. The researchers will allow plenty of time to explain and administer the study procedures, and clinic staff at each site will ensure that participants do not feel rushed and understand fully what is happening and why.

Participants will be asked to complete two forms of blood tests (fingerprick tests using an at-home testing kit) and venous blood in the clinic. Whilst this does involve a minor invasive procedure, it is quick and relatively pain-free.

There is a small risk that some people may find certain questions in the memory tests difficult to answer or distressing. All of these tasks will be done at home on their own. Some of the questionnaires include questions about mental health, which may be distressing for some participants, who should contact their general practitioner (GP) or Samaritans (https://www.samaritans.org) if they are worried about their mental health. Mind’s website at www.mind.org.uk has useful resources to help you cope if you are feeling anxious, worried or isolated.

A lumbar puncture (LP) is essential for the collection of cerebrospinal fluid (CSF). The procedure involves introducing a needle to the spine allowing for access to take a sample of CSF. A lumbar puncture is generally a safe procedure, however, as with all medical procedures there is a small risk of side effects. Some people may experience swelling and lower back pain in and around the area where the needle was inserted. The pain normally disappears on its own after a few days or it can be treated with standard pain-relief medication and it’s normally nothing to worry about. A headache is another possible side effect of LP, which can last up to a week. The headache can usually be treated with similar painkillers. Before consenting to a LP, a study doctor will help the participant to understand what this procedure involves and any potential risks associated with it. Any questions and concerns that the participant may have will be also addressed. This procedure will be performed by a clinician (physician or trained specialist nurse) with specific training and

experience in administering the procedure. To minimise any discomfort the LP will be performed on a separate day to the rest of the study procedures.

Where is the study run from?
South London and Maudsley NHS Trust (UK)

When is the study starting and how long is it expected to run for?
November 2023 to April 2028

Who is funding the study?
1. European Union Horizon Europe
2. COCIR
3. EFPIA
4. EuropeBio
5. MedTechEurope
6. Vaccines Europe

Who is the main contact?
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Study website
https://www.helse-stavanger.no/en/predictom/

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
339758

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 339758

Study information

Scientific Title
PREDICTOM: Evaluation and validation of a biomarker screening platform to identify risk of Alzheimer's disease at point of care

Acronym
PREDICTOM

Study objectives
Alzheimer’s disease (AD) and related disorders are associated with staggering costs and suffering. While there is yet no cure, the first disease-modifying therapies (DMT) have been approved by the FDA. Importantly, these medications are only considered to be effective if initiated in early-stage (MCI and mild dementia) amyloid confirmed AD.

Accurate and practical methods to screen for Alzheimer's disease are really important. Right now, tests like examining cerebrospinal fluid (CSF) or using brain scans (MRI and PET) are quite good at detecting Alzheimer's, but they are invasive, expensive, and not widely available.

However, there are some exciting developments in less intrusive methods. Recently, there have been advancements in using blood tests, digital cognitive assessments, MRI scans, electrical brain activity tests (EEG), and even studying the microbiome (bacteria in the gut) as potential markers for Alzheimer's. These newer approaches show a lot of promise and have been shown to be effective in various studies. This includes digital tests, different types of imaging (structural and functional), and markers found in both CSF and blood.

This progress is crucial because it could lead to simpler, more accessible, and less expensive ways of identifying Alzheimer's disease early on, making it easier for more people to benefit from early intervention and treatment.

However very little is known about the performance of these markers in real-life primary care settings or in community-based cohorts. Given the expected increase in demand and the strain on specialist health resources, there is an urgent need to test the accuracy, feasibility and safety of these markers in primary care and to identify which of them could be collected remotely. Interestingly, technological development, including digital cognitive testing and blood-based biomarkers, suggests the possibility that the diagnostic process can start in people's homes, allowing for an early, accurate and cost-efficient diagnostic triaging process, and can contribute to optimal patient stratification to determine benefit-risk profiles for different treatments. Ultimately, such technologies may allow us to move from a “diagnose and treat” to a “predict and pre-empt” model of care, enabling stratification to personalized drug and lifestyle interventions, which would allow people with AD to live independently for longer.

This project aims to identify the best combination of biomarkers for early disease detection, leveraging data analysis and machine learning techniques.

There is therefore an urgent need to establish diagnostic markers, tools and procedures that can identify specific diseases in people at increased risk or with very early signs of AD and other diseases leading to dementia at the point of care. The aim of this study is to deploy a set of multimodal biomarkers and clinical diagnostic procedures that can be administered in people’s homes or in primary care. The validation of individual or combined biomarkers may allow for a precision-medicine approach to allocate people to early intervention. Validation of predictive biomarkers requires large-scale sampling, particularly early in the triage process, to identify the most accurate and meaningful markers of decline. This presents a challenge for traditional in-clinic assessment due to the practical limitations involved in recruiting several thousand individuals for in-person visits. Digital and online technology, combined with remote biological sampling offers a valuable solution to this issue, enabling mass assessment and sampling to be performed at scale. Precision medicine approaches can then be applied to triage only the highest priority participants or patients for more costly, time-consuming in-clinic assessment.

Ethics approval required
Ethics approval required

Ethics approval(s)
Submitted 06/03/2024, Wales REC 4 (Health and Care Research Wales Castlebridge 5 Cardiff, Cardiff, CF11 9AB, United Kingdom; +44 (0)2922 941119; Wales.REC4@wales.nhs.uk), ref: 24/WA/0069

Study design
Multicentre observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)

Community, Home, Internet/virtual, Telephone, Other

Study type(s)
Diagnostic, Screening

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Alzheimer's disease, dementia

Interventions
Objective:
The primary objective is to test the accuracy of individual and combinations of novel biomarkers, collected remotely and in primary care clinics to diagnose AD.

Research questions:
Primary research question:
What is the accuracy of a novel biomarker screening platform at point-of-care to diagnose early AD?

Secondary research questions:
1. What is the feasibility and acceptability of biomarker collection methodologies at point-of-care?
2. What are the most sensitive, accurate and practical biomarkers for use in predicting cognitive decline at point-of-care?
3. What is the most cost-efficient combination of biomarkers for prediction of cognitive decline at point-of-care?
4. What is the predictive accuracy of biomarker combinations for other relevant disorders, including vascular cognitive impairment and Lewy body disease?

Design:
This is a multicentre, international biomarker diagnostic cohort study consisting of two consecutive cohort phases:
Cohort 1: Up to 4000 people with a mildly increased risk of AD (1) will perform home-based (Level 1) computerized cognitive testing, digital biomarker collection, including a hearing test, and remote biomarker collection (e.g., saliva for genetics and epigenetics, stool microbiome and finger-prick blood biomarker test) using standardized operationalized procedures.
Cohort 2: 615 participants were selected from Cohort 1 on the basis of biomarker results indicating a high (n = 415) or low (n = 200) risk of AD or related disorder. Participants will undergo more comprehensive biomarker collection in a clinic setting (Level 2: EEG, blood, hearing, MRI) followed by a final diagnostic evaluation to confirm or rule out a diagnosis of AD using established biomarkers (CSF, plasma, and amyloid PET [Level 3]) in accordance with the most recent National Institute on Aging-Alzheimer’s Association (NIA-AA) criteria (https://aaic.alz.org/releases_2023/new-alzheimers-diagnostic-criteria-unveiled.asp). Participants will also be staged as cognitively normal, subjective cognitive impairment and MCI based on established criteria. Participants included within M24 will complete a follow-up visit after 12 months.

Study length:
36 months from the inclusion of the first participant to the final assessment of the last participant

Target population:
Adults aged over 50 years with an increased risk of AD

Setting:
Participants will be living in the community and recruited, screened, and consented through a study-specific digital research platform using established online procedures or through in-person screening and consenting. The cohort will be supported online and through clinical settings. Cohort 1 involvement will be achieved through the use of a computer, tablet, or smartphone at home or in the clinic, combined with remote biofluid sampling. Cohort 2 assessments will take place in clinical settings.

Withdrawal from study:
In the event that a participant chooses to withdraw from the study or no longer meets study eligibility criteria, they will have the option to retain or destroy any identifying data stored within the study (e.g., email address, telephone number, home address). This option will be given at the point of withdrawal. A name and the first four alphanumeric characters of the postcode will be retained to ensure a record of consent is kept, according to data protection requirements. All anonymised data will also be retained.

Available digital registries:
Participants will be recruited through existing online and digital research registries which have consent for re-contact. These include:
1. PROTECT-UK and PROTECT-Norge: Both PROTECT registries will be screened for existing participants fulfilling the eligibility criteria. Participants will be invited by email to register for the PREDICTOM study through a nested study on their PROTECT dashboard.
2. Swiss Brain Health Registry (https://www.bhr-suisse.org/en) (Geneva)
3. 'Clinique du Docteur Memo' digital Clinic (DocteurMemo.fr) (Quairnel)
Participants from the non-PROTECT sites will be approached by research teams at the local sites and be guided to visit the PREDICTOM study website. Please see Appendix 1 for further information on the participant recruitment from each site.

Primary and Secondary care settings:
Participants will be recruited through primary care (GP clinics or equivalent) and secondary care (memory clinics or equivalent) settings. Clinical staff at these centres will be informed about PREDICTOM and asked to present the study to relevant potential participants, including providing material and online resources for them for further reading and opportunities to contact study staff for pre-screening and consenting if appropriate.

Consent:
In accordance with ethical research standards and regulatory requirements, potential participants who meet inclusion criteria will provide written and/or electronic informed consent prior to any research study activities after having ample time to consider their participation and Informed consent form (ICF) before signing. The study information sheets will provide them with clear information about the purpose of the study and participant activities. It will be clearly stated that participation in the study is voluntary and that they may withdraw at any time without consequence. Their personal information will be kept confidential, as required by law,

and data that is shared externally will be de-identified. Participants may nominate an informant to provide support and complete informant-based questionnaires. A dedicated informant consent form will be completed.

Participants from the UK, Norway and France will follow established digital consent procedures. Participants from other sites including Spain, Belgium, Switzerland and Germany will follow pen-and-paper consent in line with ethical requirements at these sites, followed by digital consent on the PREDICTOM platform.

Standard pen-paper consent:
In sites providing in-person pen-and-paper consent, participants will be provided with the Participant Information Sheet and will have the opportunity to ask any questions with a member of the research team. They will be informed about the potential risks and benefits of participation. After reviewing and agreeing to the terms of the consent form, participants will provide a signed consent. They will be given a copy of this consent form for their use.

Online consent process:
Centres in Norway, the UK and France will conduct consent through a validated, ethically approved online consent process in addition to any pen-and–paper consent. Consent items will involve giving consent for re-contact to enable recruitment to Cohort 2 and for sharing data from individual sites with the PREDICTOM consortium.

The online consent process involves the following steps:
1. Participants will access the Participant Information Sheet (PIS)/ Informant Information Sheet (IIS) following registration. The information sheet will be presented in online and printable format, and study subjects will be required to tick a box to confirm they have read and understood the relevant document. They will be provided with study helpdesk contact details to ask any questions they have about taking part.
2. Participants will then be presented with a new website page with each consent item in the Informed Consent Form (ICF). Depending on their role in the study (participant or informant) the study subject will be presented with the applicable ICF. They will have to tick each item individually which activates a button to allow them to proceed to a new website page.
3. On the new website page, participants/informants will then tick a further tick-box to confirm they consent to take part in the study which activates a button that they must select to continue. This process ensures consent cannot be given in error.
4. Consents are time- and date-stamped electronically and stored on the study database, linked to study ID and pseudo-anonymised to allow for linkage to personal details in the event this information is required for future contact.

Data collection and processing:
Participants will complete a range of screening questionnaires and digital assessments including test batteries and questionnaires, followed by biofluid collection (These are briefly explained below, please see Appendix C for more details). If convenient, the testing procedures can be divided and performed on different days.

Digital assessments:
All participants will complete a series of online assessments through the PREDICTOM digital platform. Sites in the UK, Norway and France will complete the test batteries at home without supervision, or with telephone or online support if needed. At sites where participants are consenting in the clinic (Spain, Belgium, Germany and Switzerland), participants will complete the online procedures on the PREDICTOM platform in a quiet, private room at the clinic. These digital assessments will include a set of questionnaires and digital battery tests that will be

presented on the participant dashboard in the sequence described below. Participants will be given the opportunity for frequent breaks in between assessment sessions but will be encouraged to complete each assessment type in full.

FLAME cognitive test battery (14) (30 minutes): FLAME is a validated computerized neuropsychology battery with utility for clinical trials focusing on cognition with key memory, attention and executive function assessment. The FLAME battery tests are presented in a set sequence according to the paradigm validated in the published FLAME cognitive composite measure which has proven sensitivity for detecting cognitive status and change over time (14). The tests include measures such as picture recognition, self-ordered search task, Paired Associate Learning Task, Digit Span task, Simple and Choice Reaction Time, Digit Vigilance and Verbal Reasoning.

Banking Task for Activities of Daily Living (5 minutes): Participants will perform the 'banking app' which assesses a key aspect of Activities of Daily Living (ADL). The test presents participants with a virtual automated teller machine on-screen. They are provided with a four-digit PIN and an amount of money and given the task to enter the PIN and withdraw the "virtual" money before confirming their action. The test measures the number of attempts needed, duration of the task and accuracy.

Online Hearing Screening (10 minutes): An online self-administered hearing screening test will be performed. The participants will be asked a series of questions about subjective hearing complaints, associated conditions such as pain, vertigo or tinnitus, and in which environments they experience hearing difficulties if any. Next, participants will be instructed on how to perform the test and use headphones if available and increase the volume of their device to the maximum available level. Each ear will be tested individually on four different frequencies: 500Hz, 1000Hz, 2000Hz and 4000Hz. For each frequency for each ear, the participant will be presented with a scale of 12 volume levels and instructed to start at 1 and continue one level until the participant can barely hear the tone. This will continue throughout the remaining frequencies. If no headphones are available, an option to use the available speakers will be present, reducing it to only testing both ears at the same time over the four frequencies. If hearing aids are used, participants are asked to remove them for the test. The hearing test will provide a qualified indication of whether the participant has a meaningful hearing loss or not but is not a validated test.

Eye-tracking (MIRA) (3 minutes): Participants will complete an eye-tracking test which measures eye movements during a short task. Participants are asked to either follow the moment of an on-screen avatar or avoid watching an avatar. Their gaze is monitored through software linked to a webcam built into the computer or Android tablet to identify prosaccade and antisaccade eye movements that are associated with cognitive health. Participants will be encouraged to log on after the baseline assessment session to complete this task up to five times over five weeks.

BrainCheck (15 minutes): Participants will complete the BrainCheck Cognitive Battery, a comprehensive and advanced cognitive assessment tool designed to provide detailed insights into an individual's cognitive abilities and functions. The current study protocol will utilise the Braincheck Assess which offers evaluation of various cognitive domains including simple and complex visual attention (Trail making A and B), executive function (Digit-Symbol Substitution and Stroop) and memory (Immediate and Delayed word recognition).

Altoida (15 minutes): Participants will complete the Altoida Digital Biomarker Assessment which consists of a mobile software application on an Apple iPad/smartphone. The app guides the user through several motoric and augmented reality tasks. The software is based on machine learning

that simulates conducting activities of daily living, providing an objective measure of cognitive ability. The Altoida assessment evaluates cognitive and functional impairment through easy-to-use exercises such as tapping and tracing shapes, as well as placing and locating virtual objects. These assessments will require the participant to be in an ambulatory position. To complete the augmented reality assessment, the participant will need to hold the device with the non-dominant hand angled at approximately 60° and complete each activity using the index finger of the dominant hand.

Demographics: Participants will provide their age (date of birth), gender (expanded question for inclusivity), ethnicity, marital status, education level and employment status.

Self-reported questionnaire set (52 minutes): Participants will complete the following questionnaires to provide self-reported information on their health, lifestyle and medical risk factors:
1. Medical history and risk factors: Participants will be asked to provide information about existing medical conditions using multi-select questions and to report key medical status including height/weight (for BMI calculation), history of traumatic brain injury and hearing loss.
2. Family History of Dementia Scale: A short questionnaire that captures immediate family members' diagnoses of brain conditions including dementia, Parkinson's disease, motor neurone disease, epilepsy, normal pressure hydrocephalus, and psychiatric conditions including depression, schizophrenia, bipolar disorder, and anxiety.
3. Subjective Cognitive Decline: A 24-item questionnaire that captures a subjective report of current cognitive status.
4. Lifestyle risk factors: Participants will complete a composite lifestyle risk questionnaire that will capture key modifiable risk behaviours including level of physical activity, smoking status, alcohol use, social activity and isolation behaviour.
5. Mental health: Participants will complete the well-established Patient Health Questionnaire (PHQ-9), and General Anxiety Disorder (GAD-7) questionnaire.
6. Loneliness: Participants will complete a brief 3-item loneliness scale, The UCLA 3-item Loneliness scale.
7. Function: Participants will nominate an informant to complete the well-validated Amsterdam IADL Questionnaire short version (A-IADL-Q-SV), consisting of 30 items (18). Optional: Informants to complete a proxy assessment of function in a broad range of daily activities.

Feasibility questionnaire (10 minutes): Participants will be asked to complete a brief feedback questionnaire to capture their experience of completing the PREDICTOM protocol, including the biofluid collection. This questionnaire will be presented for completion after all digital and biofluid assessments are complete. It will employ tick-box and free text responses to capture the ease of use of the kits, accuracy of instructions and willingness to complete remote tests of this nature in the future.

Biofluid collection:
Biofluid Collection Coordination (details are provided in the Appendix)
Participants will complete three self-supported biofluid sampling protocols. Individual sample kits for the collection of saliva (Muhdo), stool (Norgen Biotek), and finger prick blood samples (Capitainer) will be provided by the manufacturers as pre-prepared kits including instructions and all the necessary components for at-home sampling. Local sites will consolidate the kits into a single, comprehensive PREDICTOM Cohort 1 kit for each study participant.

The research team operating at the local site will oversee the distribution of the PREDICTOM Cohort 1 kits to the study participants. To ensure proper tracking and data management, individual kit IDs will be assigned to the participant ID generated by the PREDICTOM platform.

Local sites will maintain site-specific records of participant and kit IDs using a standardised format to enable the centralisation of data. Participants will receive their PREDICTOM Cohort 1 kit either through the post (UK and Norway) or in the clinic (France, Germany, Brussels, Spain and Switzerland). Site staff will be available to support the sample collection process through a dedicated helpdesk at each site. After successfully completing their sample, participants will return their kits to the local site using pre-prepared addressed envelopes. Sites will track the receipt of samples, batching and transferring of samples to analysis laboratories.

Finger prick blood test for biomarker analysis:
Participants will complete two finger-prick blood tests to enable measurement of neurodegeneration biomarkers p-tau217, GFAP and NfL. Capillary blood is extracted via a macro lancet needle from the index fingers of both hands. The CapitainerTM device accurately measures 50uL of whole blood which is dried onto two filter cards that are protected from contamination within the device. Once the Capitainer® cards reach the laboratory, the dry blood spots are resuspended and extracted for analysis for GFAP, p-tau, and NfL on the single molecular array (Simoa) system. Samples will be discarded post analyses.

Saliva collection for epigenetic and genetic analysis:
Saliva collection will be undertaken for genetic and epigenetic testing through the assessment of DNA methylation patterns. Participants will provide a saliva sample in a pre-prepared tube which will be sent for analysis through the post. Genomic and epigenetic profiles will be analysed by Muhdo Health, an established commercial consumer-facing platform, and their laboratory partner (Eurofins in Denmark) using the Illumina Infinium platforms: Global Screening Array BeadChip for genomic and MethylationEPIC chip for epigenetic profiling. Samples will be discarded after analyses.

Microbiome stool test:
Stool collection for microbiome analysis will be performed by participants at home using the Stool Nucleic Acid Collection and Preservation System (NorgenBiotek). The sample is stabilised in the kit and participants will return it in a study self-addressed envelope. DNA will be extracted from stool samples provided by study participants and the microbial composition determined following next-generation sequencing. Microbiome data will be analysed and correlated to (meta) data collected to identify key species linked to gut health. Samples will be discarded after analyses.

Data curation and harmonisation:
All data from Cohort 1 will be collated in the cloud-based PREDICTOM platform on Microsoft Azure servers. This will contain all digital biomarker data in addition to flagged data from genetic and blood biomarker analysis for pre-determined thresholds or dementia risk. Data will be extracted and checked for quality either by the individual providers of the tests (Epigenetics, blood biomarkers) or by a central data management team. All data will be pseudonymised under a single participant ID and uploaded to a central database for analytics.

Algorithm development:
A three-tiered classification system will be developed, with operationalized definitions of normal, abnormal, and borderline for each individual diagnostic marker and the combinations.

Feedback for participants and clinicians
A key outcome of PREDICTOM is to provide a convenient, accessible, and easy-to-understand system for feedback of the results to participants and primary care providers. The precise technology and solution for providing this feedback will be developed as part of the PREDICTOM programme but will not be available for use during the Cohort 1 phase. Participants

will be given the option of receiving individualised feedback after Cohort 1 has completed, regardless of whether or not they are progressing to Cohort 2. This will be an optional consent item and participants will be able to change their preference at any time.
Within this study, individual feedback will only be provided for the biomarkers listed below. Other biomarkers are not currently clinically verified and so will not be provided due to the ethical issues raised by providing data from tools that do not have full clinical validation. Feedback will be provided as a report that will be emailed to the participants. Site staff will be available to discuss the feedback and any implications for onward assessment on a case-by-case basis.
1. DNA and epigenetics feedback: Participants will be offered the opportunity to register for the Muhdo app to access their DNA and epigenetics results. If they wish to accept this then they will provide explicit consent for site staff to enter the participant's name and contact information into the Helix portal. The participants will then be given instructions for downloading the Muhdo app to access their data.
2. Blood-based biomarkers -finger prick blood test
3. Cognitive tests
4. Hearing

Study Procedure for Cohort 2 (Levels 2 & 3)

Recruitment for Cohort 2:
Participants will be recruited from Cohort 1. Eligible participants will be identified by screening a centralised pseudonymised dataset from Cohort 1 using the thresholds described in the below section. Participants fulfilling the criteria for high and low risk and each site will be selected and sites will be informed of eligible participant IDs for recall. In the event that a participant does not wish to continue to Cohort 2 the next eligible participant will be selected from the central database. Participants will be approached by email, letter or telephone, provided with the Participant Information Sheet and invited to book a telephone call to discuss the Cohort 2 study.

615 participants selected from Cohort 1, of whom:
415 with a high risk of progression to dementia, i.e., a high risk of having a progressive brain disease.
200 with a low risk of progression to dementia, i.e., a low risk of having a progressive brain disease.

Cohort 2 registration & consent:
Participants will be invited to attend a research clinic at their PREDICTOM setting. They will have the opportunity to review the Participant Information Sheet, discuss the Cohort 2 study and ask any questions they have with a trained staff member. If they are willing to take part, they will complete a Cohort 2 Informed Consent Form using a pen-and-paper format. They will receive a copy of their consent for their records. Separate information sheets and consent forms will be available for the more invasive data collection methodologies including neuroimaging and cerebrospinal fluid sampling.

Level 2 data collection and processing:
Participants will complete the following data collection and sampling activities during one or more clinic visits. The ordering of procedures suggested below is a recommendation, these can vary depending on the local situation, (please see Appendices for additional details). Participants who complete this process before month 24 of the programme will be invited to return for a follow-up visit to repeat most of the data collection process for longitudinal data.

Cohort 2 assessments

Physical examination:
Physical examination, including neurological screening assessment (20 minutes)
Participants will undergo a short physician-led physical examination and interview to identify any co-morbid physical diseases that could affect cognition or biomarker results.

Cognitive assessment (15 minutes):
Participants will complete the Montreal Cognitive Assessment (MoCA) cognitive assessment (18), conducted by a trained clinical research staff member. The MOCA test is a widely used tool for assessing cognitive abilities. It consists of various tasks and questions that evaluate memory, attention, language, and other cognitive functions. Participants are instructed to respond to questions and perform tasks to the best of their ability.

Eye-tracking: augmented reality and virtual reality-based eye-tracking measurement (15 minutes):
Participants will complete a series of eye-tracking tasks using highly discriminative and novel eye-tracking features, such as micro-saccades and suites of saccadic eye movements. Smartphones and tablets will be used to conduct fun and engaging tests or games, building on previous experience with camera-based eye tracking. The tasks will include using Augmented Reality and Virtual Reality to measure eye movements while playing fast-paced games, focusing on unique and distinguishing eye features, like small eye movements.

Pure tone average hearing test (10 minutes):
A pure tone average (PTA) hearing test will be done at level 2 in the clinic with a tablet-based IEC 60645-1 certified system (hearTest by hearX). The system enables an easily deployable and validated bilateral audiogram to be done without a sound isolation chamber outside an audiology setting. The hearing assessment will be performed as an air conduction pure tone audiometry using calibrated headphones. This hearing assessment will include measurement of pure tone thresholds in the left and right ear at frequencies up to 16 kHz such as 500, 1000, 2000 and 4000 Hz, which will take less than 10 minutes. The test is pre-configured on the tablet and is fully automated when started. For each frequency a tone will be played with an increasing intensity until the participant indicates it is audible or until the test indicates potential deafness. The participant will be instructed to press the button on the tablet screen when a tone is audible, which will signal the test to continue to the next frequency until all frequencies have been completed upon which the test is done. The PTA test is intended to confirm the level of hearing loss first indicated by the hearing screening performed at level 1. Participants will receive a hearing assessment as part of study participation, which may reveal potential undiagnosed hearing loss. Participants without hearing assistive devices will be recommended to make arrangements for an audiologic examination if hearing loss is suspected (not covered by the study).

Blood sampling (10 minutes):
Venepuncture will be performed by a trained phlebotomist according to standardized procedures at local sites. This blood test will be performed to obtain a sample (plasma, platelet free plasma and buffy coat) to identify other potential diseases contributing to cognitive decline (routine tests for renal and liver function, thyroid function), to measure Alzheimer biomarkers (pTau, Aβ40, Aβ42, GFAP, NfL) and to develop and validate new markers (including microRNA biomarkers, protein biomarkers, glycans and protease activity).
Participants will also be supported to complete a further finger-prick blood test to provide test-re-test reliability with the sample taken in Cohort 1. This will follow the same process as described in section 5.6.2.

Electroencephalogram (EEG) (60 minutes):
Electroencephalogram (EEG) analysis will be used to measure electrical activity in the brain. Participants will wear a wireless headset with inbuilt small electrodes to detect the electrical impulses generated by the brain. Portable EEG devices will be used to monitor brain activity whilst executing four cognitive tasks including the Resting State EEG task, Visual attention and short-term memory task (VAT & VSTMT), Ekman faces task and Two-tone oddball task. The assessments will take place in a clinic with a trained research team member.

Magnetic Resonance Imaging (MRI) (1-2 hours):
A comprehensive neuroimaging MR protocol will be undertaken containing a set of standard sequences including T1-, T2-, T2-FLAIR-, SWI/T2*-, and diffusion-weighted imaging (DWI) weighted images, together with other advanced neuroimaging scans including resting-state fMRI, arterial spin labeling (ASL) and magnetic resonance spectroscopy (MRS). In a subset of 300-400 participants from centers with the same type of MRI scanner, a research MRI protocol consisting of motion-corrected, highly accelerated versions of the standard acquisitions and powered by deep-learning reconstruction and a fast, motion-robust, multi-contrast sequence in a single scan containing essential imaging contrasts will also be acquired. The detailed scanning protocols will be developed before the start of Level 2 assessments.

Diagnostic validation assessments (“Level 3”):
All participants in Cohort 2 will undergo a second wave of assessments for confirmatory diagnostic testing of AD. These assessments will enable the local PI to make a provision diagnosis of AD or related condition which will be confirmed by a central diagnostic consensus committee, according to the most recent consensus criteria for AD (12). This diagnostic assessment protocol will involve the in-clinic assessments described below to detect established biomarkers of AD. The final diagnosis will be based on all available information.

At least one of the below biomarkers will be administered/collected.

Venous blood analysis:
Venous blood analysis using blood from venopuncture performed at Level 2 for analysis of AD marker (plasma ptau217).

Positron Emission Tomography (PET):
Positron Emission Tomography (PET) will be used to assess specific biomarkers associated with Alzheimer's disease in the brain, including the presence and patterns of beta amyloid plaques (tracers described in appendix) and, where available, tau tangles in the brain. A PET scan is a non-invasive imaging procedure that involves the use of a small amount of radioactive material to create detailed images of the brain.

Lumbar puncture cerebrospinal fluid sampling:
In participants who are willing to consent to a lumbar puncture, this will be performed in a hospital setting to obtain a CSF sample (12mL) for l analyses, focusing on abeta42, p-tau and total tau. For CSF sampling, local site SOPs will be applied for performing the actual lumbar puncture. CSF will be analysed locally using local cut-offs for most centres. If required, CSF will be sent to Gothenborg for analysis.

Sample size calculation:
Cohort 1 sample size:
The proportion of people with AD or related brain disorders entering Cohort 1 is estimated to be

15%. To confirm this proportion with an acceptable 95% CI with a margin error of +/-1.2% will require 3401 subjects. Considering the loss of participants due to dropouts the target sample size for Cohort 1 is therefore 4000 individuals for the core digital and cognitive assessments.

Cohort 2 sample size (Level 2 & 3):
Cohort 2 will be an enriched at-risk cohort consisting of those with clinical and biomarker evidence indicating an increased risk of dementia. The part of the study will recruit approximately 10% of the 4000 in cohort 1 who have the highest risk for AD and dementia, and a group with low risk. The proportion of people in Cohort 2 who are at risk of dementia is estimated to be 40%. This gives a 95% CI to detect a 40% frequency at a +/-4% margin error, allowing for a 10% drop-out. Furthermore, for the biomarker accuracy assessment (Level 3), for sensitivity and specificity of at least 80%, assuming a frequency of 40% for AD, 95% CI, and a margin error of +/-5%, a sample size of 615 is required. Accordingly, we will recruit 415 with high risk and 200 with low risk of AD or related disorders for Levels 2 & 3.

Description of statistical methods:
Statistical methods for individual analyses arising from the PREDITOM data will be designed according to the unique requirements of the analysis. The main final analysis is to compare each biomarker, and the combination of biomarkers for the final gold-standard diagnosis of AD, by calculating sensitivity, specificity, positive and negative predictive values, and area under the curve. The detailed analysis will be described in the Statistical Analysis Plan.

Intervention Type
Other

Primary outcome measure
1. Memory function measured through FLAME Cognitive test online at home baseline and within 12 months
2. Lifestyle factors measured through Lifestyle & Medical Risk Factors Questionnaire at home baseline
3. Family history of dementia measured through Family History of Dementia Scale Questionnaire at home baseline
4. Self-reported memory function changes measured through Subjective Cognitive Decline Questionnaire at home baseline
5. Mood measured through Patient Health Questionnaire at home baseline
6. Mood measured through General Anxiety Disorder (Anxiety) Questionnaire at home baseline
7. Loneliness measured through U-CLA 3 (Loneliness) Questionnaire at home baseline
8. Activities of daily living measured through ADL Amsterdam Participant and Informant (optional) Questionnaire at home baseline
9. Hearing measured through Hearing Screening Hearing test online at home baseline and follow up within 12 months
10. Memory function measured through eye tracking online task at home baseline
11. Memory function measured through Banking app task Cognitive test online at home baseline
12. Memory function measured through Altoida (augmented reality task) Cognitive test online at home baseline
13. Memory function measured through BrainCheck Assess Cognitive test online at home baseline
14. Feasibility of the PREDICTOM platform measured through questionnaire at home baseline
15. Biomarkers for dementia measured through saliva sample (genetics/epigenetics) sample kit at home baseline
16. Biomarkers for dementia measured through fingerprick blood test (biomarkers) sample kit at

home baseline and follow up within 12 months
17. Biomarkers for dementia measured through stool sample (microbiome) sample kit at home baseline
18. General wellbeing and function measured through physical examination in Clinic/hospital within 12 months
19. Memory function measured through Montreal Cognitive Assessment in Clinic within 12 months
20. Biomarkers for dementia measured through venous blood samples (biomarkers) in Clinic (blood draw) within 12 months
21. Brain activity changes measured through electroencephalogram (EEG) in Clinic (headset) within 12 months
22. Memory function measured through eye-tracking (augmented reality) in Clinic (device) within 12 months
23. Neurological changes measured by MRI (neuroimaging) in Clinic/hospital within 12 months
24. Neurological changes measured using amyloid PET scan (neuroimaging)* (optional) in Clinic /hospital within 12 months
25. Changes in cerebral spinal fluid measures through lumbar puncture (CSF biomarkers)* (optional) in Clinic/hospital within 12 months

Secondary outcome measures
Health cost and service use measured by Resource in Dementia scale at baseline and within 12 months

Overall study start date
01/11/2023

Completion date
01/04/2028

Eligibility

Key inclusion criteria
Cohort 1:
1. Adults aged 50 years or above
2. Access to a computer (or touchscreen device) and the internet
3. Participant is willing and able to give informed consent for participation in the study
4. In the UK and Norway, already an active participant in the PROTECT-UK or PROTECT-Norge cohort respectively
5. Willing and able to visit one of the PREDICTOM research centres
6. Symptoms or risk profile indicating an increased risk of AD or related disorders, operationalized as having at least one of the below:
6.1. Subjective cognitive complaints
6.2. AD or dementia in a first-degree relative
6.3. At least one cardiometabolic disorder known to be a risk factor for dementia (e.g. diabetes, obesity, hypertension, hypercholesterolemia, cerebrovascular disease or coronary disease or peripheral arterial disease)

Cohort 2:
Criteria for high and low risk will be defined based on a machine learning algorithm based on retrospective data from existing datasets and refined with data from the Cohort 1 assessments and sampling. Thresholds will be set for high and low risk within a centralised dataset. The exact

algorithm will be developed and completed prior to the first participant completing Level 1 testing. Criteria will include:
1. Relative risk scores for each of the 12 modifiable risk factors from the Lancet Commission (1)
2. Family history of dementia.
3. APOE genotype
4. Cognitive test performance from Cohort 1 testing
5. Blood biomarkers from finger prick blood test performed in Cohort 1
6. Data from other relevant Level 1 tests.
7. Willing and able to give informed consent for the Cohort 2 protocol

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
50 Years

Sex
Both

Target number of participants
4615

Key exclusion criteria
1. An established diagnosis of dementia
2. Life-threatening physical disease
3. Active major psychiatric disorder which is inconsistent with being able to complete informed consent or perform the procedures
4. Unable to speak native tongue
5. Neurodevelopmental disorder, sensory or other physical impairment or other factor making the person unable to complete the study procedures
6. Major disabling stroke, e.g., clinically significant symptoms and/or functional impairment

Date of first enrolment
30/04/2024

Date of final enrolment
30/10/2025

Locations

Countries of recruitment
Belgium

England

France

Germany

Norway

Spain

Switzerland

United Kingdom

Study participating centre
South London and Maudsley NHS Foundation Trust
Institute of Psychiatry, Psychology & Neuroscience
16 De Crespigny Park
Denmark Hill
London
United Kingdom
SE5 8AB

Sponsor information

Organisation
Stavanger University Hospital

Sponsor details
Helse Stavanger HF
Stavanger
Norway
Postboks 8100
+47 (0)90748883
svein.skeie@sus.no

Sponsor type
Hospital/treatment centre

Website
http://www.helse-stavanger.no/en/Sider/default.aspx

ROR
https://ror.org/04zn72g03

Funder(s)

Funder type

Government

Funder Name
HORIZON EUROPE Framework Programme

Alternative Name(s)
Horizon Europe, Horizon Europe Programme, Framework Programme, Horizon Europe, EU Framework Programme, Horizon

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Funder Name
COCIR

Funder Name
European Federation of Pharmaceutical Industries and Associations

Funder Name
EuropeBio

Funder Name
MedTechEurope

Funder Name
Vaccines Europe

Results and Publications

Publication and dissemination plan
Protocol submitted to the Alzheimer's Association International Conference 2024

Intention to publish date

30/04/2025

Individual participant data (IPD) sharing plan

The study is being led by Helse Stavanger HF (Stavanger University Hospital), Norway. The dataset generated during the study will be stored in a database developed by the University of Exeter. The information collected via the study website will be transferred in encrypted form to two separate databases that are configured behind a firewall. The databases are operated by Microsoft Azure Norway (region west), which is located in Stavanger, and the University of Exeter. The storage system is structured so that it separates identifiable and non-identifiable information. A unique and personal code of 36 characters links you to your information. The University of Exeter has developed an online database to collect and process the information you provide, only approved database developers at the University of Exeter will have access to personally identifiable data through the master electronic database. All data collected will be de-identified and given a study code that will be linked to the data.

By participating in the project, participants also consent to de-identified information being stored, analysed, and processed by the researchers' partners, also abroad, as part of research collaboration and publication. The researchers will at all times use the partners who are most appropriate based on the purpose of the project. Currently collaborating research partners are the University of Exeter (UK), King's College London (UK), Univ Geneva (Switzerland), LMU Munich (Germany), University of Gothenburg (Sweden), Qairnel (France), Vrije Universiteit Brussel (Belgium), La Fe University/Fundacion Para La Investigacion (Spain) and other organizations such as Mudho Health Ltd, Siemens HealthCare Gmbh/Diagnostics, GE Healthcare, CERTH, Pharmacoidea, Novo Nordisk, Alzpath, Lygature, Icometrix, GN brainworks, Braincheck and Altoida. When cooperating with countries outside Norway, the researchers will set the same strict requirements for the protection of the information, and project manager Prof. Dag Årsland will ensure that your information is safeguarded in a safe manner. An updated list of partners can be obtained by contacting PREDICTOM support (by contacting the Chief Investigator Prof Dag Aarsland: dag.aarsland@kcl.ac.uk).

IPD sharing plan summary

Stored in non-publicly available repository