Greater-Bay-Area Healthy Aging Brain Study-Informed consent form

You are invited to participate in this study because you are eligible for enrolment in the Greater-Bay-Area Healthy Aging Brain Study. The researcher will explain the contents of the informed consent form to you. The researcher will not force you to participate in this study, so please read this informed consent form carefully and make your decision about whether or not to participate in the study based on your physical and mental condition. If you are participating in another study, please inform your study doctor or the researchers. The content/nature, risks, and other important information about this study are listed below:

1. Why was this study conducted?

Dementia is mainly caused by Alzheimer's disease (AD, 60-80%), and clinical symptoms include memory loss, mood and behavioural changes, language dysfunction and disorientation, etc. Aβ and tau proteins are the two main pathological features of AD. Scientific studies have shown that a large number of irreversible neurodegenerative lesions are already present in the middle and late stages of AD, thus missing the optimal time to intervene, and therefore intervening as early as possible in the pathogenesis of AD is the key to controlling the continued deterioration of the disease. abnormal changes in Aβ and tau proteins can be detected 15-20 years before the onset of clinical symptoms of AD. 30% of the cognitively normal older adults aged 70 years and older have a large amount of Aβ and tau protein in the cerebral cortex, which is already present. The cerebral cortex has already accumulated large amounts of Aβ proteins, and cognitive function will decline dramatically in the coming years. Our team focuses on quantitative analysis of Aβ and tau proteins in the brain and plasma of cognitively older adults using PET and MRI molecular imaging and electrochemiluminescence to assess the risk of Alzheimer's disease and to provide early prevention and treatment.

2. Who are we?

We are the research team of the "Greater-Bay-Area Healthy Aging Brain Study". The team leader, Dr. Guo Tengfei, is a Special Researcher at the Shenzhen Bay Laboratory, an Assistant Professor at the Peking University Shenzhen Graduate School, a PhD supervisor. Completed his PhD degree in Technical University of Munich, Germany, under the supervision of Prof Markus Schwaiger, member of the

German Academy of Sciences, and completed his postdoctoral training at the University of California, Berkeley/Lawrence National Laboratory under the team of Professor William Jagust. After years of accumulation and practice, Dr Guo is familiar with how to quantitatively analyse Aβ protein, tau protein, neurodegeneration and cognitive function in elderly people based on neurocognitive scoring, biochemiluminescence technology, PET/MRI brain imaging, therefore applying these to analyse the characteristics of the pathogenesis of AD in its early stage and its evolutionary pattern deeply. Dr Guo returned to China in December 2020 and joined Shenzhen Bay Laboratory (SBL) full-time as a researcher and independent PI, and formed a team to conduct scientific research on neurodegenerative brain diseases in the elderly in China. The team focuses on the early diagnosis and intervention of Alzheimer's disease (AD) using multimodal medical imaging. Currently, the team is working with a number of renowned hospitals in China to recruit cognitively unimpaired middle-aged and elderly volunteers from Guangdong, Hong Kong and Macao to conduct scientific research on neurodegenerative brain diseases.

3. How many people will take part in this study?

Approximately 1,400 elders between the ages of 55-85 (including 55 and 85) will participate in this study. Of these, participants aged 55-60 years must have a history of dementia in their immediate family (parent or sibling) and qualify for Subjective cognitive decline (SCD).

4. What is included in this study?

1. Study design

This project is a non-randomised, natural history, non-treatment, observational longitudinal research project. We will build on the initial screening by following participants over time for clinical presentation/cognitive performance, plasma biomarkers, gut microbes, salivary microbes, molecular imaging of the brain, and analysing genetic profiles through blood collection. We will conduct research on abnormal characterisation of AD-related pathological features and evolutionary patterns based on these data.。

2. Main inclusion and exclusion criteria

Inclusion Criteria：

1) Male or female, between the ages of 55-90 years (participants aged 55-60 years must fulfil the criteria of having a history of dementia in the immediate family (parent or sibling) and meet the criteria for SCD).
2) Have a score of less than 6 on the Geriatric Depression Scale.

3) **Have a chaperone (immediate family member or carer) who maintains contact for at least 10 hours per week and who can accompany the participant to the testing site to take the test.**
4) Have visual and auditory acuity (including normal corrected visual and hearing acuity) adequate for neuropsychological testing.
5) Good general health, with no other diseases expected to interfere with the study.
6) Participants are not pregnant, breastfeeding, or of childbearing potential (i.e., women must be two years post-menopausal or had infertility surgery).
7) Willing and able to participate in longitudinal biomarker and imaging studies.
8) Modified Hutchinsky Ischaemia Score less than or equal to 4.
9) Completion of 9 or more years of education or a good work history (sufficient to exclude mental retardation).
10) Must speak Mandarin fluently
11) Be willing to undergo multiple 3T MRI brain imaging scans and at least two PET molecular imaging scans.
12) Agree to have blood collected for genomic analysis (including GWAS sequencing and other analyses), AD risk and protective genes APOE, APP, PSEN1, PSEN2, ABCA7, CLU, BIN1, SORL1, PICALM, ACE, ZCWPW1, ADAM10, BACE1, BDNF, HMGCR, BCHE, TLR4, PPP2R1A, CDK5RAP2, klotho testing and biospecimen bank storage.
13) Consent to collect blood for biomarker testing.
14) Consent to share genomic data and biomarker samples.
15) Tested using Scale A (Delayed Paragraph Memory) of Logical Memory II of the modified version of the Wechsler Memory Scale (out of 25), with the following score requirements in combination with education level:
    ① ≥ 9，with more than 16 years of education.
    ② ≥ 5，8-15 years of education
    ③ ≥ 3，0-7 years of education
16) MMSE score between 24-30.
17) Licensed medication stability for at least 4 weeks if on medication.

① Stable doses of antidepressants with no significant anticholinergic side effects (if they are currently adequately treated for depressive symptoms and have no history of major depression within the past year).

② Estrogen replacement therapy is permitted.

③ Ginkgo is permitted but discouraged.

④ No use of psychoactive medications for at least 4 weeks prior to screening (e.g., antidepressants, neuroleptics, chronic anxiolytics, or sedative-hypnotics are excluded).

18) Participants with familial autosomal dominant inheritance may participate in enrolment without age restriction.

Exclusion Criteria：

1) **Participants with cognitive impairment who are not accompanied by an immediate family member who cannot sign the informed consent form at the same time cannot be enrolled.**
2) Any major neurological disease such as Parkinson's disease, multiple infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumour, progressive supranuclear palsy, epilepsy, subdural haematoma, multiple sclerosis, or history of major head trauma with persistent neurological deficits or known structural brain abnormalities.
3) Have an MRI brain scan performed during the screening process that reveals infection, infarction, or other focal lesion or the presence of multiple cavities or lacunae in key memory structures.
4) Any participant who is ineligible for an MRI scan, including the presence of a pacemaker, metal fragments or foreign objects in the eyes, skin or body.
5) Presence of major depression, bipolar disorder within the past year.
6) Psychotic features, agitation or behavioural problems within the last 3 months that may make it difficult to comply with the contents of the aggrement.
7) Current use of medication for Obsessive Compulsive Disorder or Attention Deficit Disorder.
8) Have a history of schizophrenia
9) A history of alcohol or drug abuse or dependence within the past 2 years.
10) Any significant systemic illness or unstable medical condition that may make longitudinal studies difficult to conduct.
11) Clinically significant abnormalities in B12 or TFTs may interfere with the study and low B12 will be exclusionary.
12) Current use of specific psychoactive medications (e.g., certain antidepressants, neuroleptics, chronic anxiolytics, or sedative-hypnotics).

Current use of warfarin or other anticoagulants such as dabigatran, rivaroxaban and apixaban (except for lumbar puncture).

13) Use of prohibited drugs.

14) Concurrent participation in other clinical studies that include neuropsychiatric

Participation in the "Greater-Bay-Area Healthy Aging Brain" study is strictly prohibited if the above conditions exist. Participants shall undertake to strictly check their own situation against the contents of this clause and ensure that they do not have the conditions mentioned above.

3. Study Timeline

The duration of this project is approximately 5 years (2021-2025). Participant screening and information enrolment will take place within six months, with a complete longitudinal follow-up period of 5 years (except for participants dropping out).

Pre-screening: The pre-screening is based on the principle of inclusion and exclusion criteria, and the enrollees are initially screened for subjectively reported information, such as age, education level, and willingness to participate in different programmes.

Screening: Enrollees who pass the pre-screening will be further determined to be eligible through the screening stage, and those who are eligible will undergo an informed consent session. Screening is carried out in the following order: 1) informed consent; 2) screening assessment items listed in the project flow chart, except MRI; 3) MRI examination; 4) interpretation of MRI results (by a medical professional); and 5) full verification of inclusion and exclusion criteria.

Initial visit: the initial visit began after all screening assessments were completed and was conducted within 28 days of screening, with the entire initial visit controlled to be completed within 2 weeks. The initial visit included cognitive, functional, and behavioural assessments, review of medications and adverse events, Aβ PET molecular imaging scan, tau PET molecular imaging scan, and blood collection. The project flow chart provides a list of items for the initial visit. Participants and staff should be aware of the following at the initial visit: 1) an overnight fast (at least 6 hours) is required prior to the blood draw; and 2) cognitive assessment should be performed 24 hours prior to the blood draw.

Longitudinal follow-up: Starting from Day 1 of the initial visit, follow-up visits will be conducted every 12 months. Follow-up items (see item flow chart for details) include cognitive, functional and behavioural assessments, review of medication history and adverse events and MRI scan. Blood collection will be performed

annually, and MRI and PET molecular imaging scans will be performed every two years. 20% amyloid-negative and 80% amyloid-positive participants will be randomly selected to undergo two Tau PET molecular imaging scans.

If you agree to participate in this study and sign the informed consent form, you will undergo a "screening" process to confirm your suitability to participate in this study according to the following protocol, which describes the complete project process:

Project Flow Chart

Clinical visit name	**Screening**	**Initial visit**	**Clinical Follow-up visit**	**Telephone Checks**
Explaining the study and obtaining informed consent	X			
Demographics, family history, inclusion and exclusion criteria	X			
history, physical examination, neurological examination, modified Hutchinsky ischaemia score	X			
Vital signs	X	X	X	
Height	X			
Laboratory screening (haematology, chemistry panel, urine test, B12, TSH)	X			
Genotyping		X		
Mini-mental State Examination (MMSE)	X		X	
Logical Memory I and II	X		X	
Montreal Cognitive Assessment (MoCA)		X	X	
Symbol Digit Modalities Test		X	X	
Digit Span Test		X	X	
Wechsler Verbal Fluency		X	X	

(Animal)				
Shape Connectivity Test (TMT)		X	X	
Auditory Vocabulary Learning Test (AVLT)		X	X	
Geriatric Depression Scale	X		X	
Clock Drawing Test		X	X	
Neuro Psychiatric Inventory (NPI) / (NPI- q telephone call)		X	X	X
ADAS-Cog 13 (Delayed Recall and Digit Elimination)		X	X	
Clinical Dementia Rating Scale (CDR)	X		X	
Collection of plasma biomarkers		X	X	
DNA and RNA sample collection		X	X	
Stool collection (gut microbiological testing)		X	X	
Saliva collection (oral microbiological testing)		X	X	
Concomitant medications	X	X	X	X
Adverse events	X	X	X	X
Diagnostic Summary	X	X	X	
3T MRI Molecular Imaging	X		X	
Aβ PET Molecular Imaging		X	X	
ECG		X	X	
Tau PET molecular imaging		X	X	

5. How long will this study last?

This study will last for 5 years (2021-2025) and participants who meet the inclusion and exclusion requirements will be offered follow-up testing, all longitudinal follow-up testing will be done on an informed and voluntary basis.

You may choose to withdraw from the study at any time without losing any of the benefits you would otherwise receive. However, if you decide to withdraw from

the study in the middle of the study, we will conduct a final check-up after you have decided to withdraw from the study, taking into account your safety concerns, and we will discuss the timing and programme of this final check-up with you.

6. What are the potential risks of participating in this study?

（1）PET

The major risks associated with PET are radiation exposure associated with injection of radiotracer and CT. Venipuncture, placement of intravenous catheters, and radioisotope injections also carry a smaller risk (pain, bruising, or painful infiltration after a failed injection). Because the amount of chemical entering the body is very small, approximately 4.2 x 10-8 mg/kg body weight, which is much smaller than that of conventional medications, no abnormal reactions have been reported in all domestic and foreign literature to date.

Assuming that participants received the Aβ PET and tau PET scans in this programme, the maximum annual equivalent dose received would be 16.53 mSv. These doses are equivalent to approximately 6 years of living background radiation. These doses are far below the GB18871-2002 National Standard of the People's Republic of China, "Basic Standard for Protection Against Ionising Radiation and for the Safety of Radiation Sources", which requires a cumulative effective dose of 50 mSv per year.Therefore, the risk of radiation doses received by the participants in this study is low and is comparable to the risk of daily radiation.

For male participants, taking part in this study may damage your sperm and cause harm to the child you conceive during the study. This damage is currently unpredictable. If you are sexually active, you must agree to use medically recognised contraception during the study and for several months afterwards (please specify the time if possible). Please inform your partner of this risk to the unborn child. She should be aware that if she becomes pregnant, you will need to inform your study doctor immediately and she should inform her doctor immediately.

In order to minimise the risk of unnecessary radiation exposure to you, the project re-emphasises that you will not be able to take part in a PET imaging scan if you are:

1) You will not be able to participate in the PET scan if you are a male participant and you are pregnant.

2) You will not be able to participate in the PET scan if you are a pregnant woman or a woman who may become pregnant during the PET study.

We will not be liable for any unforeseen effects of your participation in the PET scan if you have deliberately concealed or misrepresented the facts.

（2）MRI

All participants will be rigorously screened by the MRI to ensure that you do not have any medical contraindications to MRI, including metal foreign bodies in the brain, eyes or pacemaker. There is a slight risk of anxiety due to the claustrophobic environment and noise. Any participant who feels anxious when entering the MR

scanner will be removed from the scanner and the MR technician conducting the scan will provide them with reassurance and the option to continue or terminate the study. You will not be forced to complete tests if do not like. If anti-anxiety medication is required to complete the MRI scan, this will be decided by the site clinician in consultation with the site manager.

（3）Blood testing

Risks of having blood drawn include pain from the needle or fainting from having blood drawn.

（4）Cerebrospinal fluid

Although lumbar punctures are generally considered safe, some risks do exist.

These include:

Headache after lumbar puncture. About 25% of patients who undergo a lumbar puncture develop a headache as a result of fluid leaking into nearby tissue after the puncture. The headache usually begins within a few hours to two days and may be accompanied by nausea, vomiting, and dizziness. The headache usually occurs while sitting or standing and is relieved by lying down. Headaches may last from a few hours to a week or more after a lumbar puncture. Back discomfort or pain. You may feel pain or pressure in your lower back. The pain may spread to the back of your legs. Bleeding. Bleeding may occur near the puncture site or in the epidural space (rare)

（5）Other

There may be undetected or unanticipated adverse events, and you are encouraged to contact the site manager promptly for any discomfort you experience during the study, whether or not it is related to the study.

Drug Interactions:

For safety reasons, you must tell the researcher with whom you are matched with all prescription medications, herbal products, over-the-counter medications, vitamins, and health supplements such as natural supplements that you are taking prior to the start of the study. Please also be sure to tell your study partner before you need to take any of these medications during the study. We will also investigate your medication use during the screening phase.

7. What are the benefits of participating in the study?

If you agree to participate in this study and pass the screening, you will receive:

(1) Health check-ups worth about RMB 18,000 per year, which include a series of check-ups such as: cranial PET imaging, cranial MRI imaging, blood tests, intestinal flora tests, cognitive function assessment, risk gene tests and ECG.

(2) Professional long-term follow-up, annual cognitive function and blood index examination, and imaging examination every 2 years.

(3) Professional guidance from clinicians on brain protection and active health.

(4) Priority participation in subsequent clinical trials on cognitive impairment related diseases.

8. What happens to the data collected from me?

We will keep your research records confidential as required by law. Our relevant laws provide for privacy, data and security of authorised access. Information about your research will be represented by a unique number and the coded information will be stored securely in the Shenzhen Bay Laboratory. Your identity will not be disclosed when the research information and data obtained from this study are published in scientific conferences or scientific journals. However, your records may be reviewed to ensure that the study complies with relevant laws and regulations. The reviewers include the relevant national regulatory authorities and the Medical Ethics Committee of Shenzhen Bay Laboratory.

The information and data collected by the team of researchers at Shenzhen Bay Laboratory and related to you will be used for scientific research, such as: the characteristics of the pathogenesis and evolution of AD, trials related to early diagnosis and treatment of AD, and so on. The data will be stored in paper or electronic form. In order to protect your privacy, none of these data contain your personal information, and if the research results are publicly released, your identity will remain confidential. By signing this consent form, you agree to the use of your data for the purposes described above. Your personal medical records, as well as a list of your name and code, will be kept permanently by Shenzhen Bay Laboratory to facilitate access to this information by reviewers (including relevant national regulatory authorities, Shenzhen Bay Laboratory Medical Ethics Committee, etc.). To the extent permitted by law, your personal information and medical records will not be disclosed. By signing this informed consent form, you agree on behalf of you that persons with legitimate reasons may have direct access to your medical records.

9. Research costs

Cognitive assessments, blood tests and imaging scans performed during the course of this project are free of charge.

10. In the event of a study-related injury

This study will purchase commercial accident insurance for you. If you suffer an injury as a result of your participation in this study, you will be compensated to a

certain extent in accordance with the law through the accident insurance purchased by Shenzhen Bay Laboratory. Please contact the project leader Guo Tengfei at 0755-26849264, and we will not be responsible for any injury caused by your own illness or fault.。

11. Refusal to participate or withdrawal from the study

Your participation in the trial is voluntary and you may refuse to participate or withdraw from the project in any way at any stage of the project without discrimination or retaliation, and your rights will not be affected.

If you have a serious adverse reaction, or if you feel that staying in the study is not in your best interest. We respect your choice, but we may ask you to have one last check-up before stopping the project.

12. Related Counselling

If you have any questions related to this study, please reach out to the contact person for this project, Siyuan Wang, telephone number: 0755-26849267.

If you have any questions related to your rights and interests, or if you would like to reflect your dissatisfaction and concerns about participating in this study, please contact the Ethics Office of the Medical Ethics Committee of Shenzhen Bay Laboratory at 0755-86724273.

Informative Statement

"I have informed the subject of the background, purpose, procedures, risks and benefits of the Greater-Bay-Area Healthy Aging Brain Study, given him/her enough time to read the informed consent form, discussed the study with others, and answered his/her questions about the study; I have informed the subject that he/she can contact (the investigator) at any time with questions about the study, and provided accurate contact information; I have informed the subject that he/she can contact the Ethics Office of the Shenzhen Bay Laboratory Medical Committee at any time with questions about his/her rights/interests; and I have provided accurate contact information. related issues and to contact the Ethics Office of the Shenzhen Bay Laboratory Medical Committee at any time when he/she encounters problems related to the study (the investigator) and to contact the Ethics Office of the Shenzhen Bay Laboratory Medical Committee at any time when he/she encounters problems related to his/her rights/interests, and I have provided accurate contact information; I have informed the subject that he/she may withdraw from the study at any time and without

any reason; and I have informed the subject that he/she will be provided with a copy of this Informed Consent Form, which will contain both his/her and my signatures. "

Signature of researcher obtaining informed consent Contact number Date

Informed Consent Statement

"I am a person with full capacity for civil behaviour. I have been informed of the background, objectives, procedures, risks and benefits of the research of the Greater-Bay-Area Healthy Aging Brain Study, and I fully understand the possible risks and consequences of participating in the Greater-Bay-Area Healthy Aging Brain Study. I am fully aware of the risks and consequences of participating in the Greater Bay Area Brain Health Programme and I voluntarily accept and assume the risks and consequences of participating in the Greater Bay Area Brain Health Programme. I have read this informed consent form in detail, and I confirm that I am not prohibited from participating in the study as stated in Article 4, Section 2 of this informed consent form, and that I will bear all the consequences of withholding or failing to inform the researcher of the relevant information about myself.

I voluntarily participate in this study and promise that the information I provide to the researcher and the results of laboratory tests are true and valid. I was given ample time and opportunity to ask questions and the questions were answered to my satisfaction. I was also told who to contact when I had questions, complaints, concerns, or wanted further information. I was informed that I could withdraw from this study at any time and without any reason. I was told that I would be given a copy of this informed consent form containing my signature and that of the researcher."

Signature of volunteer/family member Contact number Date