PhD studentship
Funded by the
NIHR Maudsley Biomedical Research Centre

Project Catalogue

Biomarkers and Genomics

Studentship to commence October 2018
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Introduction

Welcome to the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC) project catalogue for potential candidates wishing to commence a PhD in October 2018 – we hope you will find a project which interests you.

The Maudsley BRC is a collaboration between the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King’s College London – the largest collection of researchers in Europe investigating mental disorders, and the South London and Maudsley NHS Foundation Trust – a leading mental health trust with a long tradition in joining clinical and academic excellence. Most Maudsley BRC researchers, staff and students are based at the IoPPN at the King’s College London Denmark Hill campus which is adjacent to the Maudsley Hospital. Within this setting we offer the opportunity to join a thriving group of interdisciplinary researchers with internationally recognised supervisors and we ensure our students benefit from an understanding of the context of their research, producing scientists with a strong translational ethos.

The Maudsley BRC is dedicated to developing better treatments for people with mental and neurological disorders, which collectively cause most of the disease burden in Western societies. Within the BRC we offer projects which are clinically relevant and attempt to bring new innovation to help treat people with mental disorders, dementia and other neurological conditions. This is the most exciting field in biomedical science, the least researched, the most important. And we offer an opportunity to gain research training in a vibrant and exciting centre where doctoral students are highly valued members of our team.

We hope we can look forward to receiving your application.

Professor Matthew Hotopf
Director
Maudsley Biomedical Research Centre

Professor Richard Brown
Training Lead
Maudsley Biomedical Research Centre
NIHR Maudsley Biomedical Research Centre (BRC)

NIHR Biomedical Research Centres are funded to support people and/or patient-focused early translational (experimental medicine) research, the aim of which is to translate discoveries from basic/discovery science into clinical research, and through to benefits for patients, the health system and for broader economic gain.

On September 16 2016 the Secretary of State for Health announced that the Department of Health has awarded £66 million funding over the next five years to the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry, Psychology & Neuroscience at King’s College London.

The award represents a substantial uplift in funding compared to the previous BRC funding round, and demonstrates the government’s continued commitment to the current NIHR Maudsley BRC, allowing the research centre both to build on its current work and expand into new areas including substance use, obesity, pain and mobile health technology.

The expanded NIHR Maudsley BRC will bring together scientists, clinicians, mental health professionals, service users and carers, to improve clinical care and services across the field of mental health. The investment in the NIHR Maudsley BRC will allow research into ground-breaking treatments and care for mental health and dementia.

NIHR Maudsley BRC Strategy

There are four major elements to the NIHR Maudsley BRC strategy for the coming 5 years, reflected in aims of the 17 themes:

- **Precision psychiatry**: Bringing together insights from cognition, behaviour, genomics and brain imaging, we will develop biologically-informed strata of psychiatric syndromes, with the ambition to develop and provide more individually tailored treatment

- **Novel therapeutics**: Using the access to our large databases, electronic consent for contact procedures, and our dedicated experimental medicine Clinical Research Facility (CRF), we will undertake trials of new pharmacological, neuromodulation and psychological treatments

- **Translational informatics**: By using our bespoke natural language processing algorithms and ‘smart agents’, we will use informatics to influence treatment choice, increase adherence, improve health behaviours and increase patient empowerment, all of which will benefit patient outcomes and service delivery

- **Mental/physical interface**: We will decrease the 15 years of life lost to serious mental illness by using informatics to identify, prioritise and track the treatment of those with comorbid mental and physical disorders
**Clinical disorder focused research themes**

Seven clinical disorder focused research themes cover mental health and dementia from cradle to grave:

- Affective Disorders and Interface with Medicine
- Child and Neurodevelopmental Disorders
- Dementia and Related Disorders
- Lifestyle Substance Use & Harms (Substance Use)
- Obesity, Lifestyle and Learning from Extreme Populations (Obesity)
- Pain and headache
- Psychosis and Neuropsychiatry

**Technology and methodology focused research themes**

Seven technology and methodology focused research themes develop and deploy new approaches to clinical problems:

- Bioinformatics and Statistics
- Biomarkers and Genomics
- Clinical and Population Informatics
- Mobile Health
- Neuroimaging
- Patient and Carer Involvement and Engagement
- Translational Therapeutics

**Cross cutting themes**

Three cross cutting themes provide enabling infrastructure:

- BioResource
- Clinical Research Facility
- Training and Capacity Development
**Biomarkers and Genomics**

**Lead: Professor Cathryn Lewis**

The theme delivers analytical expertise in genomics, particularly in the methodology, analysis and implementation of polygenic risk scores (PRS), allowing us to exploit the potential of genomic medicine and multimodal biomarkers to predict progression, prognosis, and treatment response across a range of psychiatric disorders. The theme complements the laboratory and recruitment/recall infrastructure provided by our BioResource cross-cutting theme. A data-driven approach to psychiatry will enable us to move genetic discoveries from research towards patient care, integrating diverse data sources to develop multimodal predictive models that inform diagnosis and treatment.

**Aims**

1. Determine how to use polygenic risk scores (PRS) to predict clinical outcomes for psychiatric disorders and
2. Evaluate the most cost-effective combination of PRS with neuroimaging, -omics, and cognitive biomarkers to increase the power of predictive models
3. Identify novel pharmacogenetic variants of therapeutic response and adverse effects
4. Translate genetic findings into novel therapeutics and drug repositioning opportunities using large-scale genetic data and novel pathway analysis methods
Institute of Psychiatry, Psychology and Neuroscience

The Institute is organised into three academic divisions, each comprised of a number of cognate departments. Each Division includes academics and researchers from diverse scientific disciplines, working closely with colleagues across the faculty and our national and international partners:

- **Division of Academic Psychiatry** comprises 6 departments: Addictions Sciences; Forensic & Neurodevelopmental Science; Child & Adolescent Psychiatry; Old Age Psychiatry; Psychological Medicine and Psychosis Studies (https://www.kcl.ac.uk/ioppn/divisions/academic-psychiatry/index.aspx)

- **Division of Psychology & Systems Science** comprises 4 departments: Biostatistics & Health Informatics; Health Service & Populations Research; Social Genetic & Developmental Psychiatry; Psychology; (https://www.kcl.ac.uk/ioppn/divisions/psychology/index.aspx)

- **Division of Neuroscience** comprises 4 departments: Basic & Clinical Neuroscience; Neuroimaging; Developmental Neurobiology; Wolfson Centre for Age-related Diseases (https://www.kcl.ac.uk/ioppn/divisions/neuroscience/index.aspx)

Successful applicants for this studentship will be registered for their MPhil/PhD with King’s College London and will be based in the same department as their first supervisor at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN).

**Please note:** The final choice of project and project details are agreed after successful interview.
Projects

When applying for the NIHR Maudsley Biomedical Research Centre PhD studentship in the Biomarkers and Genomics theme, please ensure you state your two preferred PhD projects from those listed in this catalogue only**. These should be listed in order of preference and include the number that is assigned to the project and the project title.

For example:

1. BGEN-2.04 Towards personalised medicine for antidepressant drugs: a machine learning approach
2. BGEN-2.01 Exploring genetic similarities and differences between depressive disorder and depression as a normal human experience

**Important:** With your application, in addition to the personal statement, please upload a separate single-side A4 document listing your first and second choice projects with a statement explaining why you have chosen your first choice project and why you would like to take this forward as a PhD (maximum 300 words).

**If you wish to apply for one or more of the other studentships we are currently advertising, please upload a separate A4 sheet for each studentship you are applying for, stating your preferred project choices from those advertised with the studentship, and a statement about your first choice project (see above). Please ensure each sheet clearly indicates which studentship you are applying for and lists only projects advertised for that particular studentship.**

If you wish to discuss a project before you apply, you will find supervisors' names and their contact details listed with each project in this catalogue.

Further information about project supervisors can be viewed in the King’s College London Research Portal. Under Researchers, type the name of the person you wish to view information about.

Please note: The final choice of project and project details are agreed after successful interview.
BGEN-2.01 Exploring genetic similarities and differences between depressive disorder and depression as a normal human experience

Primary Supervisor: Professor Cathryn Lewis
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Project Description

Background: Depression is an experience common to all humans, usually linked to some loss in the real or imaginary domain. Sadness, pain, anger, bouts of crying, and a depressed mood are considered normal during a period of bereavement or after some stressful event like a serious physical illness, but, when severe or chronic, the same experiences are considered symptoms of mental illnesses, for example of Major Depressive Disorder (MDD). Understanding whether genetically there is a continuum between these “normal” experiences and depression as a disorder will have important implications in our conceptualization of psychiatric diagnose (currently based on recordings of symptom lists) and the design of new therapeutic interventions.

Novelty and Importance: This project will build on the progress that has been made in our understanding of the genetic underpinning of depression through genome-wide association studies (GWAS). It will link large clinical datasets such as the Psychiatric Genomics Consortium MDD working group (Cathryn Lewis is the co-Chair) with general population data with rich phenotypic information, including physical health (UK Biobank).

This project will explore the genetics of emotional symptoms beyond the diagnostic boundaries of MDD and other affective disorders. Depression will be examined with genetic studies in the general population and stratified by physical and other mental disorders. Potential common genetic predisposition will support the trial of treatments for MDD in depression as a symptom.

Primary aim(s): To understand and measure the extent of genetic predisposition to depression and other symptoms (e.g. low energy and motivation, hopelessness, guilt, psychomotor retardation, emotional lability, explosive behaviour) in the general population and subpopulations where depression is a common symptom (e.g. patients with severe and debilitating physical illnesses).

Planned research methods and training provided: Trying to distinguish between depression as a normal experience from depression as a mental illness has a series of technical challenges, to be investigated as part of this PhD project:

- Depression is a common feeling, that everyone has experienced at some point in life. There is a need to identify and describe any qualitative differences between this experience and the depression experienced in the context of MDD.

Continued on next page
As the priority in GWAS studies has been large sample sizes at the expense of deep phenotyping, the PhD student will need to do data mining in large datasets and devise novel and efficient methods of extracting the relevant data.

There is a possibility of new data collection funded by the NIHR, which will allow the PhD student to participate in the study design to collect data relevant to the project.

Training will be provided in the statistical analysis of genetic and clinical data. The supervisors have an ideal background in statistics, statistical genetics and psychiatry (the lead supervisor from a Mathematics background, while the co-supervisor is a Psychiatrist who performs research in statistical genetics).

**Objectives / project plan:**

**Year 1:** Training in data management and genetic analysis, familiarization with available datasets, selection of relevant phenotypes, applications for data access.

**Year 2:** GWAS, polygenic score analysis and genetic correlation studies of depression and other emotional phenotypes in the general population and subpopulations at high risk of emotional symptoms (physical and other mental disorders).

**Year 3:** Validation of the above findings in new collection of clinical data, including questionnaires designed to disentangle emotional symptoms. Publications and write-up of thesis.

**Two representative publications from supervisors:**


**Keywords:** Statistics; Genetics; Depression; Genome-wide association studies; GWAS; Psychiatry;

**BRC Theme/s:** Affective Disorders and Interface with Medicine
Biomarkers and Genomics
BioResource
BGEN-2.02 Developing and applying polygenic risk score methodology for stratified medicine

Primary Supervisor: Dr Paul O’Reilly
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Second Supervisor: Dr Evangelos Vassos
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Project Description

Background: While clinicians and researchers are acutely aware that a disease diagnosis can mean very different things for different patients, there has been surprisingly little explanation for this ‘disease heterogeneity’ in terms of the underlying biology. However, genetics is now beginning to shed light on the different biological causes of psychiatric disorders, with particular profiles of shared genetic aetiology between disorders and putative risk factors emerging. Therefore, this is the perfect time to exploit genetics to stratify patients according to differential disease aetiology and test whether this could lead to improved outcomes over using broad disorder categories.

Novelty and Importance: This project will be the first to use the full information of genome-wide common variation, in the form of polygenic risk scores and genetic pathways, to attempt to stratify a sample of individuals with a highly heterogeneous diagnosis (e.g., schizophrenia, depression) into subsets of more homogenous individuals that share similar aetiology. The method produced from this project could illuminate the search for the aetiology underlying a range of psychiatric disorders, and when applied to treatment-response data could guide the application of drugs so that patients get the most appropriate treatments for them. We also plan to apply the method to predict what diagnoses individuals are most likely to suffer from following their first admission at a psychiatric hospital. This is of paramount importance since being able to identify, for example, which individuals who first present with unspecified psychosis are most likely to go on to develop full-blown schizophrenia or the likelihood for patients with a first admission for depression to develop bipolar disorder, could be extremely important for prevention. Therefore, this project aims to have impact in three key areas of medicine: understanding disease, treatment, and disease prevention.

Primary aim(s):
1. Develop a polygenic disease-stratification method for application to disease, treatment and first-episode data. The method will require tailoring the polygenic risk score approach for disease stratification and exploiting statistical or machine learning clustering techniques appropriate for polygenic risk score data.
2. Design a study for testing the performance of the disease-stratification method.
3. Test the performance of the polygenic disease-stratification method versus leading alternatives (i.e. clinical diagnoses and subcategorization).
4. Apply the method to a range of disease cohorts, including those available locally at the BRC/SLAM, as well as external data that we have access to such as from the Wellcome Trust Case-Control Consortium and UK Biobank.
5. Apply the method to treatment-response pharmacological data to identify groups of individuals with different response to treatment caused by differing biological aetiology.
6. Apply the method to data on individuals following first admission at the South London and Maudsley (SLAM) and attempt to predict future diagnoses of the individuals using longitudinal data available in the BRC.
7. Refine the polygenic disease-stratification method as appropriate for the specific real data settings of 4-6.
Planned research methods and training provided: The student will be employing the latest statistical genetics techniques and methods, in particular those relating to polygenic risk scores, as well as contemporary statistical methods and machine learning, such as clustering algorithms. The student will also be trained in the nuances of psychiatric disorders required for the project. The supervisors have an ideal background in statistics, statistical genetics and psychiatry (the lead supervisor from a Mathematics background, while the co-supervisor is a Psychiatrist who performs research in statistical genetics).

Objectives / project plan:
Year 1: The focus of Year 1 will be the following primary aims:
1. Develop a polygenic disease-stratification method for application to disease, treatment and first-episode data. The method will require tailoring the polygenic risk score approach for disease stratification and exploiting statistical or machine learning clustering techniques appropriate for polygenic risk score data.
2. Design a study for testing the performance of the disease-stratification method.
3. Test the performance of the polygenic disease-stratification method versus leading alternatives (i.e. clinical diagnoses and subcategorization).

Year 2: The focus of Year 2 will be the following primary aims:
3. Complete testing the performance of the polygenic disease-stratification method versus leading alternatives (i.e. clinical diagnoses and subcategorization).
4. Apply the method to a range of disease cohorts, including those available locally at the BRC/SLAM, as well as external data that we have access to such as from the Wellcome Trust Case-Control Consortium and UK Biobank.
5. Apply the method to treatment-response pharmacological data to identify groups of individuals with different response to treatment caused by differing biological aetiology.

Year 3: The focus of Year 3 will be the following primary aims:
6. Apply the method to data on individuals following first admission at the South London and Maudsley (SLAM) and attempt to predict future diagnoses of the individuals using longitudinal data available in the BRC.
7. Improve and refine the polygenic disease-stratification method as appropriate based on the results/findings from the real data applications of aims 4-6.

Two representative publications from supervisors:

Keywords: Genetics; Statistics; Psychiatry; Genome-wide association studies; GWAS; Disease stratification;

BRC Theme/s:  Bioinformatics & Statistics
Biomarkers and Genomics
Clinical & Population Informatics
BioResource

This project also links into many of the Clinical disorders research themes (see page 5)
BGEN-2.03  Telomeres, Twins and Translational Medicine

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Project Description

Background:  Faster biological ageing has been associated with multi-systemic vulnerability to psychiatric disorders (e.g. childhood depression), cognitive dysfunction, and ageing-related disease. Telomeres are stretches of DNA at the end of chromosomes which become shorter as our cells divide, and their length is commonly used as a marker for biological age. We plan to conduct a series of studies to understand genetic and early environmental contributions to telomere length, and its relationship to early psychiatric disease symptoms and cognitive ability. We further plan to identify blood-based factors (e.g. lipid subtypes) causally related to telomere length regulation, with the aim of identifying novel anti-ageing drug targets.

Novelty and Importance:  This multidisciplinary research project has the potential to identify early environments and drug targets capable of preventing premature ageing, and in determining if faster ageing shares common environmental and genetic risk factors with specific psychiatric/cognitive traits.

Primary aims are to determine:
(i)  Pro/anti-ageing environments in early childhood.
(ii) The genetic and environmental contributions to variation in telomere length, and its shared association with psychiatric/cognitive phenotypes.
(iii) If telomere length in childhood predicts psychiatric/cognitive phenotypes in late adolescence.
(iv) Pro/anti-ageing factors in blood using population genetics, and to validate their effects using an in vitro stem cell model.

Planned research methods and training provided:
(i)  Molecular biology (qPCR);
(ii) statistical and twin model-fitting analysis;
(iii) population genetic methods (LD score regression, polygenic risk scores, Mendelian randomization); (iv) in vitro stem cell work.
Objectives / project plan:

**Year 1:** (i) To assay telomere length in 500 monozygotic and dizygotic twin pairs from the Twins Early Development Study (~age 12), (ii) To establish heritability estimates of variation in telomere length, (iii) To determine if very early home environments predict telomere length by ~age 12, (iv) To determine if telomere length at ~age 12 predicts psychiatric disease symptoms and cognitive ability up to age 18.

**Year 2:** (v) For significant correlations between telomere length and psychiatric/cognitive phenotypes, we will use bivariate twin models to dissect genetic and environmental overlap. Where we observe significant shared heritability we will use polygenic risk scores and Mendelian randomization to determine the direction of effect. (vi) Using publically available GWAS summary statistics data we will determine genetic correlations between telomere length and circulating blood-based factors.

**Year 3:** (vii) We will test whether blood-based factors affect telomerase and telomere length as predicted using a stem cell model.

**Two representative publications from supervisors:**


**Keywords:** Telomeres; Twins; Population genetics; Translational medicine; Psychiatric disease;

**BRC Theme/s:** Affective Disorders and Interface with Medicine  
Child and Neurodevelopmental Disorders  
Psychosis and Neuropsychiatry  
Biomarkers and Genomics  
Clinical and Population Informatics  
Translational Therapeutics  
BioResource
BGEN-2.04  Towards personalised medicine for antidepressant drugs: a machine learning approach

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Project Description

Background:  Individuals with depression differ in their response to treatment with antidepressants. It has been estimated that at least 40% of variation is attributable to genetic factors. Clinical factors showed a moderate role in predicting treatment response. The development of algorithms integrating genetic and clinical factors to predict treatment outcomes in depression may enable clinicians to select optimal medication for each patient.

Novelty and Importance:  Developing algorithms for treatment personalization from large datasets is a challenging task for which traditional statistics had limited success. Problems arise when the number of predictors exceeds the number of individuals, there are missing data, variables are highly correlated and effect sizes are small. This PhD studentship will develop new algorithms to personalise antidepressant treatment based on Topological Data Analysis (TDA) a set of Multivariate machine learning techniques (MML) that have successfully been applied to precision medicine studies, but not yet in psychiatry. Algorithms will be applied to genetic and clinical data from 3899 subjects from two clinical trials (GENDEP, STAR*D) and three observational studies (MARS, MUENSTER, PRN-AMPS). This research may produce clinically relevant predictive models to guide clinicians in antidepressant treatment selection.

Primary aim(s):  To develop new MML algorithms that combine genetic with clinical variables to improve prediction of antidepressant treatment response at the individual level.

Planned research methods and training provided:

This PhD studentship will include an individualised training plan in methodology required for personalised medicine (e.g. statistical genetics, machine learning, longitudinal analysis of multivariate phenotypes and predictive modelling).

Objectives:

Year 1: Develop and implement free standing code of a method for predictors selection based on the mapper TDA algorithm.

Year 2: Develop and implement free standing code of a predictive algorithm based on the combination of a TDA method for predictors selection and a machine learning classifier.

Year 3: Validate the predictive algorithm internally and externally, in GENDEP, STAR*D, MARS, MUENSTER and PRN-AMPS datasets. Apply the developed algorithms to assess the role that
Towards personalised medicine for antidepressant drugs: a machine learning approach

Clinical and genetic variation plays in response to antidepressant treatment in GENDEP, STAR*D, MARS, MUENTSER and PRN-AMPS studies.

This project combines (a) the development of cutting-edge methods for treatment personalisation, using TDA as a novelty, plus (b) the practical application of the developed methods to a very relevant area, with a real potential to improve patients' health. We would welcome applications from students with a background in mathematics or other quantitative sciences (e.g. bioinformatics, computer science) and from biomedical with a strong commitment to developing statistical skills.

Two representative publications from supervisors:


Keywords: Antidepressant; Personalisation; Machine learning; Topological Data Analysis; Genetics;

BRC Theme/s: Affective Disorders and Interface with Medicine
Bioinformatics and Statistics
Biomarkers and Genomics
**BGEN-2.05** Novel biomarkers for dementia in Down syndrome, a genetic cause of Alzheimer’s disease

**Primary Supervisor:** Professor Andre Strydom  
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**Project Description**

**Background:** Cognitive decline and dementia is common in ageing individuals with Down syndrome (DS - trisomy 21) due to an extra copy of the amyloid precursor protein (APP) gene on chromosome 21, leading to Alzheimer’s disease (AD) brain pathology. DS can thus be viewed as a genetic form of AD. We have an active AD in DS biomarker programme, collecting both blood and CSF samples.

**Novelty and Importance:** DS is a critically important patient group for clinical trials of treatments to prevent and delay AD pathology and dementia symptoms, which could inform AD treatment in other patients. But they are currently excluded from trials due to lack of data on reliable fluid biomarkers of dementia progression. This proposal is to explore new AD fluid biomarkers in DS using cutting-edge methods including super-sensitive immunoassays (Simoa analyzer) and immuno-PCR. The results will have immediate impact by enabling early-phase clinical trials of new treatments to prevent or delay AD in DS.

**Primary aim(s):** To explore biomarkers for cognitive decline in DS (including amyloid beta (Aβ)1–42, total tau (T-tau), and phosphorylated tau (P-tau) as well as amyloid processing (AβX-38, AβX-40, AβX-42, soluble amyloid precursor protein (sAPP)α, and sAPPβ), neurodegeneration (neurofilament light), and pyroGlu-3 Aβ, a particularly sticky form of Amyloidβ believed to trigger plaque formation, by

1. Exploring cross-sectional relationships of CSF biomarkers with age and dementia status, and variation in genes implicated in amyloid processing such as APOE
2. Where possible, determining relationships between CSF and plasma biomarker levels
3. Exploring biomarker differences between DS, and samples from controls and sporadic AD cases

**Planned research methods and training provided:** The student will work within an established consortium (The LonDownS Consortium) with genetics, biomarker and clinical expertise for a unique opportunity to gain both laboratory skills (processing and storing samples, using assays) and clinical research skills (e.g. cognitive assessments) and as well as valuable transferable research skills (ethics, consent, regulatory issues).
BGEN-2.05  Novel biomarkers for dementia in Down syndrome, a genetic cause of Alzheimer’s disease

Objectives / project plan:

Year 1: Month 0 – 6 - training - research governance and ethics, cognitive assessments, phlebotomy. Month 6 – 12: work with LonDowns team on data and sample collection

Year 2: Training in laboratory techniques; ongoing data collection/ lab analysis

Year 3: Lab analysis to month 6; analysis/ write up month 7-12

Notable aspects: The student will have input from Probiodrug, a drug company based in Germany (funding for pilot work, assays, and training), and expert labs in London and Sweden.

Two representative publications from supervisors:

1: https://www.nature.com/nrn/journal/v16/n9/abs/nrn3983.html

2: https://doi.org/10.1016/j.freeradbiomed.2017.08.024

Keywords: Dementia; Down syndrome; Alzheimer’s disease; Biomarkers;

BRC Theme/s:  Child and Neurodevelopmental Disorders
Dementia and Related Disorders
Biomarkers and Genomics
Translational Therapeutics
BioResource
Clinical Research Facility