# Dlagnostic and prognostic precision (Algorithm) medicine for behavioral variant frontotemporal dementia

Published: 15-01-2021
Last updated: 08-04-2024

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Congenital and hereditary disorders NEC |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON55267

**Source**
ToetsingOnline

**Brief title**
DIPPA-FTD

### Condition

- Congenital and hereditary disorders NEC
- Neurological disorders NEC
- Psychiatric and behavioural symptoms NEC

**Synonym**
Behavioural variant of Frontotemporal dementia, bvFTD and Primary Psychiatric disorders

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum
**Source(s) of monetary or material Support:** in het kader van JPND

## Intervention

**Keyword:** Behaviour, Biomarkers, Frontotemporal dementia, Primary psychiatric disorder

## Outcome measures

### Primary outcome

Our goal is to provide an early, accurate diagnosis and a prognosis to patients

presenting with

adult onset behavioral changes between 45 and 75 years by:

1. Creating a diagnostic algorithm to differentiate between bvFTD and

late-onset PPD, using

clinical features including social cognition, neuroimaging patterns, genetic

and peripheral neuronal

markers.

2. Creating a prognostic algorithm for bvFTD and late-onset PPD using clinical

features including

social cognition, neuroimaging patterns, genetic and peripheral neuronal

markers.

3. Differentiating between the main FTD pathological subgroups (FTLD-tau and

FTLD-TDP) based

on biologically derived materials including neuron-derived exosomes and

cell-free DNA

**Secondary outcome**

- enable future patient stratification, trial design and personalized

treatments.

- Creation of animation movie and online precision medicine tool

- Usage of the animation movie and the online tool as communicaton tool to

stakeholders

# Study description

**Background summary**

The behavioural variant of frontotemporal dementia (bvFTD) is a common cause of early-onset
dementia with heterogeneity in underlying pathology, genetics, and natural course, demanding a
customized approach to predict individual prognosis and develop personalized treatments.
BvFTD is often mistaken for a primary psychiatric disorder (PPD), causing substantial diagnostic
delay of up to 6 years on average. Unlike with Alzheimer*s disease, reliable in vivo biomarkers
for FTD are not available yet. Recent research attention has been on genetic FTD (now known
to differ pathologically and often clinically); however, the critical challenge is how to diagnose
non-familial forms of bvFTD (which accounts for 80% of all cases) early in the disease course
and therefore distinguish it from late-onset psychiatric disorders that may mimic bvFTD, in order
to deliver relevant interventions and treatments. The creation of a diagnostic and prognostic
model of sporadic bvFTD is highly needed and crucial to enable performing precision medicine..
We selected the most promising results of our ongoing research, including neuropsychological
and social cognitive markers; neuroimaging- based classifiers; serum neurofilaments, plasma
neuronal derived exosome signatures, and cell free DNA. Our project will contribute towards an early and accurate

bvFTD identification, that is crucial for trial enrolment, whereas early PPD identification will lead
to the appropriate psychiatric treatments.

**Study objective**

In this project, we will combine cohorts from several countries into a comprehensive retrospective discovery cohort to examine the above-mentioned markers focusing on sporadic cases and PPD, in addition to a large number of
pathologically confirmed bvFTD and PPD cases. We will further collect a deeply phenotyped
prospective multi-national cohort to validate these markers, in addition to collecting postmortem
cases of clinically less well-defined bvFTD / PPD cases. We will use statistical modeling to
create the best diagnostic and prognostic model for non-familial forms of bvFTD and PPD. As a
subgoal we aim to determine underlying FTD pathology within the sporadic bvFTD group, to
enable eventual patient stratification.

**Study design**

Retrospective and prospective cohort study

**Study burden and risks**

The extra MRI and blood withdrawl are normally part of standard care. Therefore, there is enough experience to follow standard protocol to decrease the risk and burden to a minimum. The tests and questionnaires from the DIPPA-FTD Test battery are already part of neurological and psychiatric diagnostic care and science. The combination of these tests is new however. With this combination, we will create a specific questionnaire to distinguish late onset psychiatry from FTD. It is possible the primary caregiver will be asked to complete a few of the DIPPA-FTD Test Battery questionnaires about the patient. The patient will give informed consent approval. The primary caregiver will be asked informed consent on a separate form.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Retrospective cases
- possible and probable behavioural variant of Frontotemporal dementia (bvFTD) patients (meeting criteria of Rascovsky et al, 2011) or definite non familial/sporadic bvFTD cases .
- late-onset Primary Psychiatric cases (onset after 45 years);including Major depressive disorder, single/ recurrent/ persistent (ICD 10 F32, 33, 34), Bipolar disorder (ICD 10 F 31), Manic episode (ICD 10 F30), Schizophrenia, schizotypical disorder (ICD 10: F20, F21), Delusional disorder (ICD 10: F22), Schizoaffective disorder (ICD 10: F25) and Obsessive-compulsive disorder (ICD 10: 42) according to the DSM5 criteria. .

All above mentioned patients have undergone thorough clinical work-up, according to the respective national protocols, including neuropsychiatric examination, neuropsychological exam, MRI of the brain, DNA, and blood sampling. Follow-up duration was at least one year, and a substantial

proportion had a follow-up duration of two years or more.

2. Prospective clinical cohort.
We will enroll new cases with:
- possible and probable bvFTD (meeting criteria of Rascovsky et al, 2011)
- ambiguous cases (suspect of bvFTD, but not completely fulfilling criteria).
- late-onset PPD diagnosis; including Major depressive disorder, single/ recurrent/ persistent (ICD 10 F32, 33, 34), Bipolar disorder (ICD 10 F 31), Manic episode (ICD 10 F30), Schizophrenia, schizotypical disorder (ICD 10: F20, F21), Delusional disorder (ICD 10: F22), Schizoaffective disorder (ICD 10: F25) and Obsessive-compulsive disorder (ICD 10: 42) according to the DSM5 criteria.

All cases will be kept in follow-up and will have repeated clinical examinations, plasma sampling and MRI of the brain at baseline and after 1 year.

3. Pathologically verified cohort.
Dutch and Australian subjects are invited into brain donation programs.
In addition, we include pathologically verified patient cohort of FTD and PPD cases from the Netherlands and Australian Brain Banks (The Netherlands: FTLDtau, n=40; FTLD-TDP, n=54; schizophrenia n=13; bipolar disorder n=34; depression, n=40; Australia: FTLD-tau, n=112; FTLD-TDP, n=42; schizophrenia plus matched controls, n=37; depression plus matched controls, n=10). During the course of our project, we will keep collecting donated brains from subjects with FTD, PPD, and ambiguous cases.

### Exclusion criteria

- Mini-mental State Exam score (MMSE) no more than 18
- Traumatic brain injury
- Drugs or alcohol abuse
- Lack of reliable informant
- Familial form of bvFTD, defined as genetic or familial bvFTD
- Patient declined genetic testing offered as part of standard clinical practise

## Study design

### Design

**Study type:** Observational invasive
Masking: Open (masking not used)

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| Control: | Uncontrolled |
| Primary purpose: | Basic science |

### Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 09-09-2022 |
| Enrollment: | 150 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 15-01-2021 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 11-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 09-02-2023 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| CCMO | NL72988.029.20 |