Systematic investigation of nominated candidate markers in CSF (and serum) for PD
CSF ALPHA-SYNUCLEIN IS NOT A GOOD DIAGNOSTIC AND PROGRESSION MARKER (ALONE)

We therefore need better diagnostic and progression marker
Due to the clinical heterogeneity / misdiagnoses etc. better biomarker OR a better biomarker panel needs to be identified and validated
IDENTIFICATION OF BIOMARKER CANDIDATES BY LITERATURE REVIEW FROM THE PD BIOMARKER DISCOVERY WORKSHOP

Potential PD Biomarkers for Evaluation in PPMI

- **Axonal Integrity:**
  - Neurofilament light chain (blood and CSF)
  - Neurofilament heavy chain
  - Tau, p-tau
  - Vlip-1

- **Synaptic Integrity/Function:**
  - Granins other than neurogranin
  - SNAP-25 and other SNARE-related proteins (Munc18-1, synaptoctrelin, syntaxin1a & 1b)
  - Neurotransmitter metabolites

- **Glial:**
  - YKL-40
  - GFAP, S100
  - TREM2
  - Cytokines/chemokines (Brit is investigating this)

- **LRRK2-Related:**
  - Exosomal LRRK2, total LRRK2, pS935 LRRK2
  - phospho-RABs
  - Mitochondrial DNA damage, secretion

- **GBA-Related/Lysosomal:**
  - Gcase activity (Tom is investigating this)
  - Other lysosomal proteins (LAMP-1, LAMP-2)

- **ECM and Other:**
  - Serpins (Serpin A1, Neitin G1)
  - Complement
  - UCL-1
  - Neurotrophic factors
SYSTEMATIC INVESTIGATION OF 8 (10) NOMINATED CANDIDATE MARKERS (ON COMMERCIALLY AVAILABLE PLATFORMS) FOR STATE, RATE, FATE AND TRAIT IN CSF (AND SERUM) OF

I: 500 CROSS SECTIONAL COHORT OF MOVEMENT DISORDERS
II: LONGITUDINAL (DENOPA, PPMI)

Step I (ongoing):
-Kassel cohort I:
Cross sectional, single center cohort
PD (n=139) and other movement disorders [Progressive Supranuclear Palsy (PSP; n=38), Multiple System Atrophy (MSA, n=15), Normal Pressure Hydrocephalus (NPH, n=36), Dementia with Lewy Bodies (DLB), other neurological controls (NC; n=195)]

Step II: best candidates validated longitudinal samples (DeNoPa, PPMI etc.)
SYSTEMATIC INVESTIGATION OF 8 (10) NOMINATED CANDIDATE MARKERS (ON COMMERCIALLY AVAILABLE PLATFORMS) FOR STATE, RATE, FATE AND TRAIT IN CSF (AND SERUM)

**Step I: cross sectional assessment of measurements**

<table>
<thead>
<tr>
<th>Nominator</th>
<th>Axonal integrity</th>
<th>Glial marker</th>
<th>α-Synuclein</th>
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<tbody>
<tr>
<td>Quanterix</td>
<td>NFL*</td>
<td>pNFH</td>
<td>YKL-40</td>
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<td>Proposed assays</td>
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<td>Eur immun</td>
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<td>matrix</td>
<td>CSF and Serum</td>
<td>CSF</td>
<td>CSF and Serum</td>
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<tr>
<td>NC vs. PD</td>
<td>CSF p&lt;0.05</td>
<td>CSF and serum p&lt;0.05</td>
<td>CSF and serum p&lt;0.05</td>
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</tbody>
</table>

* Quanterix Human Neurology 4-Plex (Quanterix): NFL, GFAP, UCHL-1 and tau protein

Ongoing analyses: Hb measurements in CSF (despite normal Erythrocyte count), S100 B analyses, correlation with Hoehn and Yahr stage in PD, reassessment of diagnoses, combined analyses
LONGITUDINAL COHORT: DENOPA

**Parkinson Patients**
- Baseline Analysis: n=159
- 2-year Follow-up: n=147
  - Drop-out: n=8 lost for follow-up, n=4 died
  - Other neurological disorders (OND) with Parkinsonism (n=24): PSP (n=4), MSA-P (n=4), essential tremor (n=3), vascular Parkinsonism (n=2), Corticobasal Degeneration (n=1), cerebellar tremor (n=1), unclear diagnoses (n=8)
  - n=123
    - Drop out: n=5 lost, n=1 died
  - 4-year Follow-up: n=117
    - Drop out: n=6 lost, n=7 died
  - 6-year Follow-up: n=104
    - Drop out: n=6 lost, n=7 died

**Healthy Controls**
- n=110
- n=107
- Drop-out: n=1 lost for follow-up, n=2 died
- n=106
- Drop out: n=2 lost, n=4 died
- n=94
- Drop out: n=6 lost, n=3 died

**REM Sleep Behaviour Disorder**
- n=36
  - Drop out: n=2 lost, n=0 died
  - n=20 (%)
  - Drop out: n=1 developed tremor
  - n=9 (%)

**Conversion**
- n=1
  - PD (n=2)
  - DLB (n=1)

**Autopsies**
- n=2 after 6-year Follow-up
  - PD (n=3)
  - MSA (n=1)
  - PSP (n=1)
  - NN (n=2)
LONGITUDINAL CSF NFL IN PD VS HC

CSF NFL baseline PD vs. HC: p<0.05
Slope PD vs. HC: p>0.05

<table>
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<tr>
<th></th>
<th>n</th>
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<th>24FU</th>
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<td>HC</td>
<td>100</td>
<td>47</td>
<td>30</td>
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<tr>
<td>total</td>
<td>235</td>
<td>130</td>
<td>81</td>
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</table>
CSF NFL is high in other neurological disorders (differential diagnoses of PD) and PD? Therefore CSF NFL in PPMI can help to identify other neurological/differential diagnoses. CSF NFL significantly correlates with MDS-UPDRS total (p=0.0091) and MDS-UPDRS III (p=0.00091).
No longitudinal difference in all three groups (p>0.05)