TACKL-PRED:

TACKLing the challenges of PREsymptomatic sporadic Dementia

Project Pitch:

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Institute of Medical Science UNIVERSITY OF TORONTO

U of T NEUROLOGY

Sunnybrook HEALTH SCIENCES CENTRE

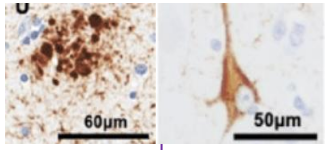
CCNA Canadian Consortium on Neurodegeneration in Aging

CCNV Consortium canadien en neurodégénérescence associée au vieillissement

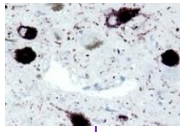
ONDRI

Late-onset Sporadic Dementia Has Many Causes

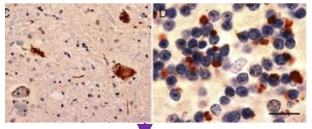
Alzheimer's Disease Continuum
(pre-clinical AD, MCI, AD)



Parkinson's-Lewy Body Diseases Continuum
(PD, PD-MCI, PDD, DLB)



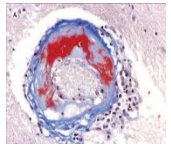
Frontotemporal Dementia-Amyotrophic Lateral Sclerosis Continuum
(FTLD-tau, FTLD-TDP, FTLD-FUS)



Amyloid-β and Tau

α-Synuclein

Tau / TDP-43 / FUS



Mixed disease

The most prevalent proteinopathies underlying dementia can frequently co-exist in the same individual as "mixed disease".

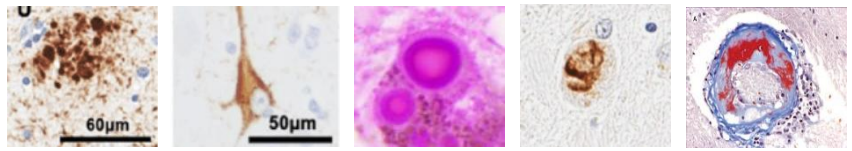
(Kapasi et al, 2017; Robinson et al, 2023; Schneider et al., 2007, 2012; Pantoni, 2010; DeJesus-Hernandez et al., 2011)

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment, PD, Parkinson's disease; PDD, PD dementia; DLB, dementia with Lewy bodies; TDP-43, TAR DNA binding protein 43; FTLD, frontotemporal lobar degeneration.

Challenges of Mixed Pathologies

These proteinopathies and cerebrovascular pathologies frequently coexist, even among patients diagnosed with a single specific form of dementia in life.

These findings serve to challenge the classic neurodegenerative disease distinctions.



Amyloid-β ± Tau ± α-Synuclein ± TDP-43 ± SVD (among others)

Diagnostic challenges | Therapeutic challenges | Patient outcomes

(Black et al., 2009; Lam et al., 2013; Rahimi and Kovacs, 2014; Snowdon et al., 1997)

The elucidation of underlying relationships across neurodegenerative disorders may offer a novel investigative approach to better understand shared risk leading to mixed pathologies.

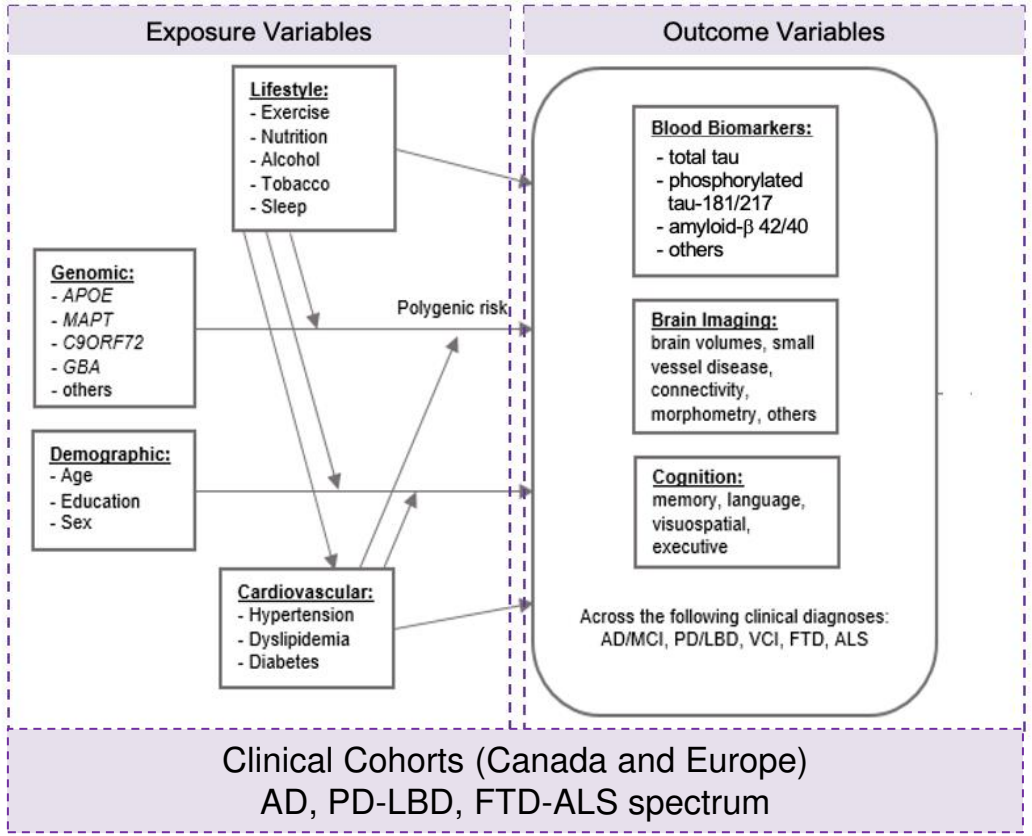
Images: Pantoni, 2010; Chung et al, 2021; Murry et al, 2014

Abbreviations: TDP-43, TAR DNA binding protein 43; SVD, cerebral small vessel disease

Aim 1

To identify how genomic / age / education / sex / cardiovascular (GAESC) risk factors together impact neuroimaging, blood biomarker, and cognitive / behavioural endophenotypes *across* neurodegenerative diseases (that is, irrespective of the clinical diagnosis), including that in an autopsy-proven subset.

(This will be done with diagnosis blinded to the data analytics team)



↑ *APOE*-ε4 dose

ANALYSIS 2

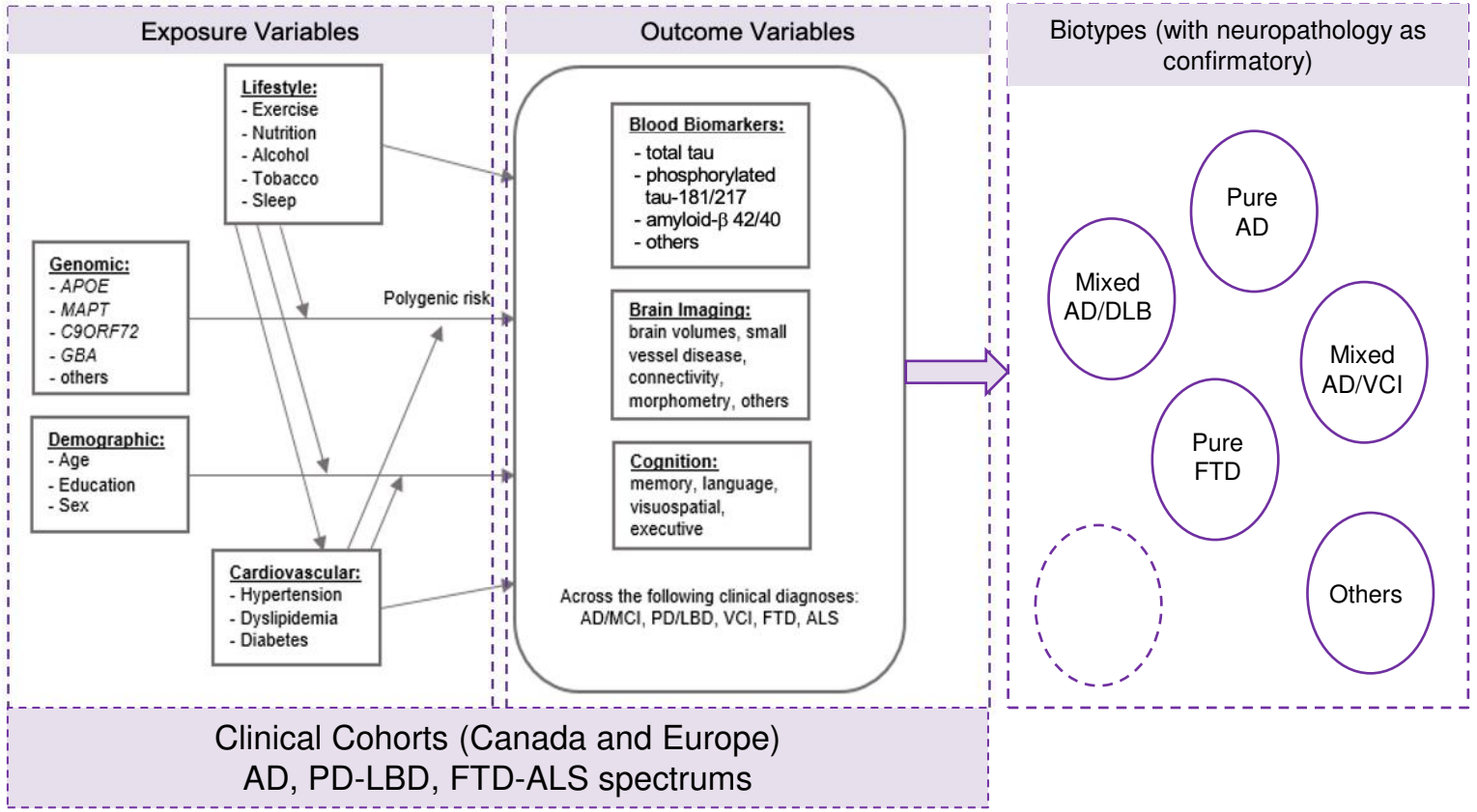
POLYGENIC RISK SCORES

↑ Hippocampal atrophy across the dementia spectrum

Aim 2

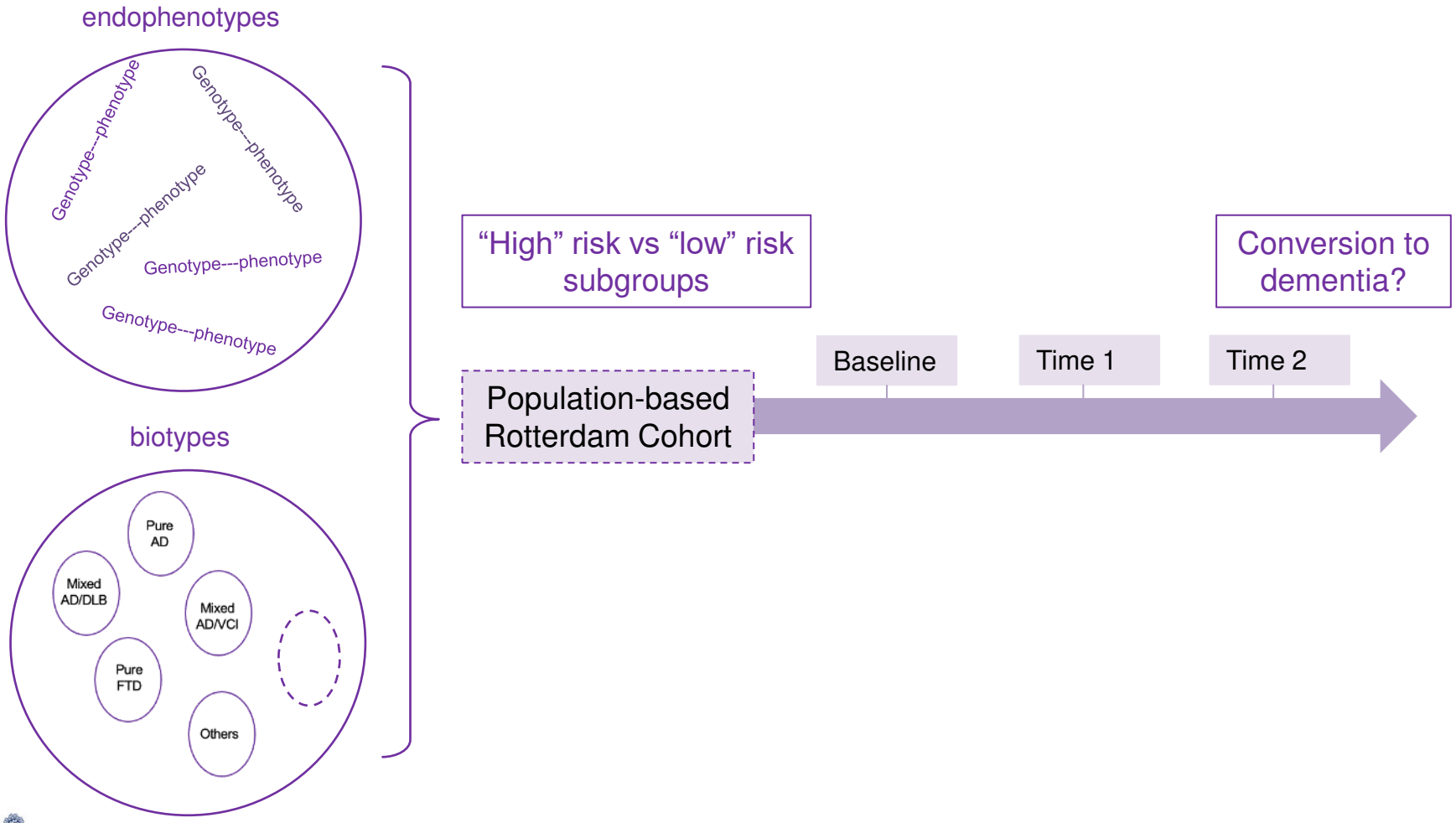
To determine how results from Aim 1 may facilitate re-classification of patients into dementia biotypes (e.g., mixed vs pure) based on their particular risk factor-phenotype profiles

(Original diagnoses will be unblinded at this stage for comparative purposes)

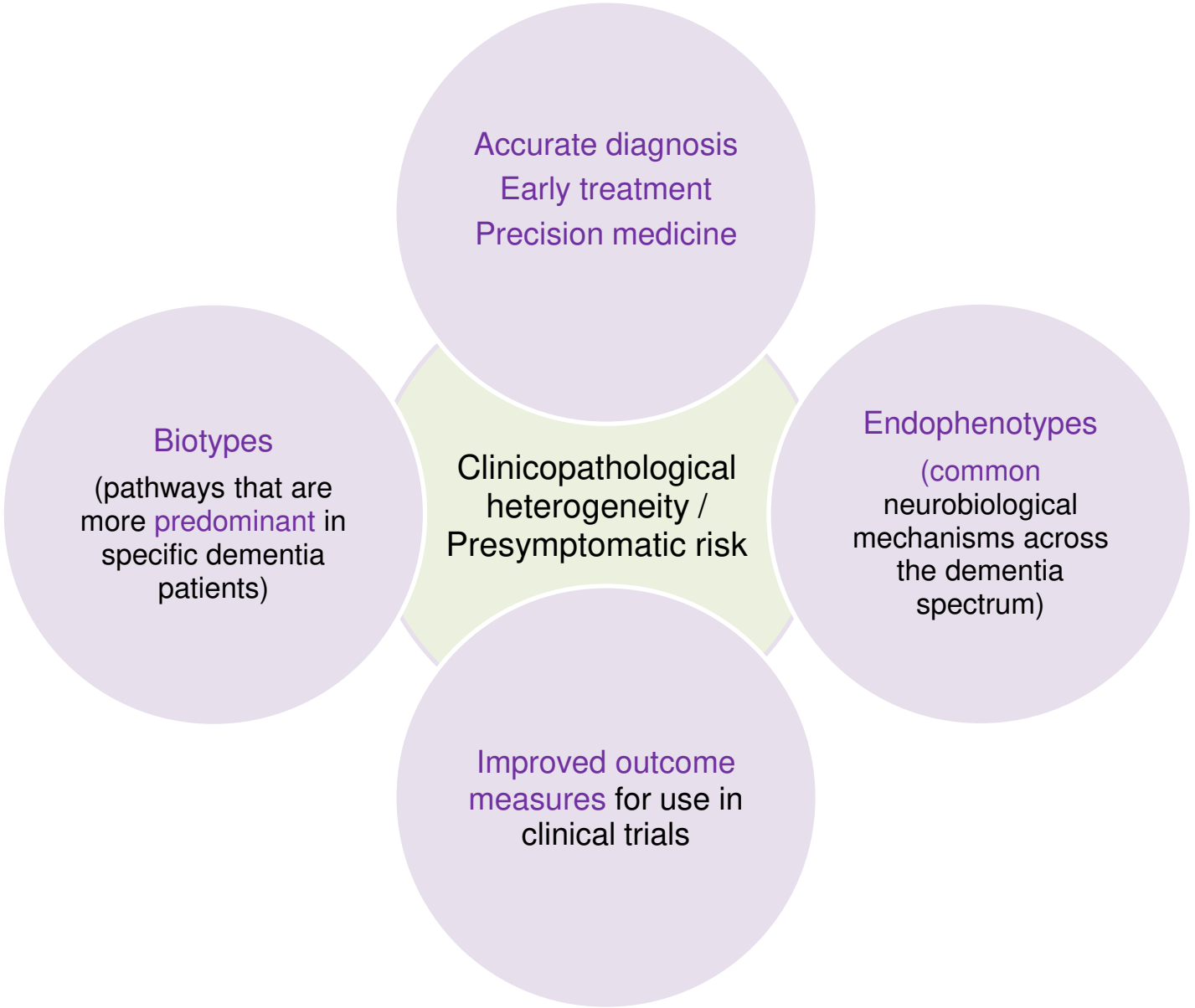


Aim 3

To apply the risk factor-phenotype profiles and biotypes identified in Aims 1 and 2 to the 'at risk' Rotterdam population-based cohort to see how they determine presymptomatic risk for dementia.



Relevance


Accurate diagnosis
Early treatment
Precision medicine
Biotypes
(pathways that are more predominant in specific dementia patients)
Clinicopathological heterogeneity / Presymptomatic risk
Endophenotypes
(common neurobiological mechanisms across the dementia spectrum)
Improved outcome measures for use in clinical trials

Successes and Challenges

- Successes:
  - Comprehensive dataset (multi-site, multinational collaboration) – harmonization across Canadian cohorts
  - Combined analytical expertise and knowledge exchange
  - Broaden the scope of our proposed data analyses (large sample, “real world” patients, clinical cohort and an independent population-based cohort)
  - Analyses are underway currently
- Challenges:
  - One year delay to get DESCA agreement finalized because of legal hold-ups
  - Data sharing between Canada and Europe

Dissemination of Results

- Specific research questions and preliminary analyses: TACKL-PRED investigator meetings
    - Toronto, Canada (September 11-12, 2023)
    - Brno, Czech Republic (Nov 14-15, 2024)

- National and international conferences
- High-impact peer-reviewed journals
- Academic institutions and research hospitals
    - Healthcare Professionals
    - Patient and Caregiver Groups
    - Policy Makers
    - General Public
- Social media
- TACKL-PRED Patient Advisory Committee

TACKL-PRED Investigators Meeting, November 14-15, Brno, Czech Republic

Thanks

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