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Baseline transcriptomic predictors of cognitive trajectories in Parkinson's disease

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Cognitive decline in Parkinson's disease (PD) is a critical unmet need with limited predictive markers. By linking baseline blood transcriptomes to subsequent cognitive outcomes, we identified molecular signatures that precede and anticipate decline. Baseline profiles already distinguished patients who later developed mild cognitive impairment or dementia, revealing early deficits in synaptic transmission, mitochondrial function, and calcium homeostasis. Strikingly, autonomic pathways emerged as central hubs. In the prodromal phase, gastrointestinal inflammation and mucosal barrier dysfunction were enriched and remained active through early decline. With progression, signatures shifted toward cardiovascular autonomic dysfunction, including impaired blood flow regulation, orthostatic hypotension, and hypertrophic cardiac responses, which dominated in advanced stages. This stagewise transition from gut inflammation to cardiovascular autonomic failure provides a mechanistic framework linking systemic dysfunction to cognitive trajectories in PD. Our findings highlight autonomic dysfunction as a driver of PD cognitive decline and nominate stage-specific biomarkers and therapeutic targets across the gut–immune–endothelium and cardiovascular autonomic axes.