ALZCan: A Statistical Machine Learning Based Framework to Predict Future Onset of Alzheimer's Disease Using Genome-Wide Association Analyses, Polygenic Risk Scoring, and Multiple Neuroimaging Modalities (rs-fMRI, FDG-PET, Florbetapir-PET)

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Alzheimer’s affects 44 million people worldwide but has no preventive cures. This study created a novel methodology for Alzheimer’s (AD) and Mild Cognitive Impairment’s (MCI) early detection using data from the Alzheimer’s Disease Neuroimaging Initiative. Genome-Wide Association Analyses considered 14 million+ interactions between 608,586 SNP genetic variants and 23 disease endophenotypes linked to AD pathology; including Cerebrospinal Fluid protein levels, Florbetapir-PET (407 scans) beta-amyloid plaque levels, FDG-PET (427 scans) cerebral metabolic activity, and Resting-State fMRI (678 scans) functional network connectivity metrics computed using ICA, signal cross-correlation, and graph-rendering algorithms. The weighted additive effect of a subject’s multiple SNP variants, along with discovered SNP effect sizes on AD endophenotypes from association results, were utilized to compute 23 Polygenic Risk Scores per subject. With just a subject’s demographic info, cognitive scores, APOE-e4 (greatest genetic risk factor) allele dosage, and SNP Genotype Data for polygenic risk scoring, ALZCan’s gradient boosting ensemble machine learning engine differentiated between AD, MCI, and Healthy Controls with 98.10% diagnostic accuracy; and predicted onset of AD and MCI 12, 24, and 36 months into the future with 3-way prognostic accuracies of 91.72%, 85.38%, and 70.67%. By combining polygenic risk scores for risk prediction, intervention, and personalized medicine with machine learning for discovering patterns amongst high-dimensional genomic and neuroimaging datasets close to AD’s underlying etiology and progression, ALZCan revolutionizes Alzheimer’s screening, enabling prevention of further irreversible neurodegeneration and cognitive decline via early therapeutic intervention.

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