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Perspective

Translational Biomarkers for Early Diagnosis of Alzheimer's and Parkinson's Diseases

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DESCRIPTION

Neurodegenerative diseases such as Alzheimer's Disease (AD) and Parkinson's Disease (PD) are among the leading causes of disability and cognitive decline in aging populations. Despite extensive research, these disorders remain incurable, largely due to the difficulty of diagnosing them at early stages when therapeutic intervention could be most effective. Current diagnostic methods often rely on clinical symptoms that appear only after significant neuronal damage has occurred. This delay in detection significantly limits the potential for disease-modifying treatments. Translational research into biomarkers-measurable indicators of biological processes-offers a promising avenue to identify AD and PD in their preclinical or prodromal stages, enabling timely diagnosis and targeted intervention.

Biomarkers serve as crucial tools in bridging basic neuroscience discoveries with clinical applications. In Alzheimer's disease, hallmark pathological features include the accumulation of Amyloid-Beta (Aβ) plaques and tau neurofibrillary tangles in the brain. These processes begin years before cognitive symptoms emerge. Translational efforts have led to the development of Cerebrospinal Fluid (CSF) and blood-based biomarkers that reflect these underlying pathologies. Reduced CSF Aβ42 levels and increased phosphorylated tau (p-tau) and total tau are now recognized as reliable biomarkers for AD and have been incorporated into diagnostic criteria. More recently, advances in ultrasensitive detection technologies such as single molecule arrays (Simoa) have enabled the measurement of these proteins in blood, paving the way for non-invasive, accessible screening methods.

Similarly, in Parkinson's disease, the aggregation of alpha-synuclein in the form of Lewy bodies is a defining pathological feature. Translational research has identified several candidate biomarkers associated with alpha-synuclein pathology, mitochondrial dysfunction, and neuroinflammation. Oligomeric and phosphorylated forms of alpha-synuclein have been detected in CSF and, more recently, in peripheral tissues such as skin and saliva. Seed amplification assays like Real-Time Quaking-Induced Conversion (RT-QuIC) show promise in detecting pathological alpha-synuclein with high sensitivity and specificity, even before motor symptoms begin.

Neuroimaging biomarkers also play a significant role in early diagnosis and disease stratification. Positron Emission Tomography (PET) scans using radiotracers for amyloid and tau have greatly enhanced the visualization of AD pathology *in vivo*. In PD, Dopamine Transporter (DAT) imaging with Single-Photon Emission Computed Tomography (SPECT) can detect early dopaminergic deficits, even in individuals who are not yet clinically symptomatic. Functional and structural MRI techniques are increasingly used to assess brain atrophy, connectivity changes, and microstructural alterations associated with both AD and PD, contributing further to early detection efforts.

Genetic and transcriptomic biomarkers are another focus of translational research. Inherited mutations in genes such as *APP*, *PSEN1*, and *PSEN2* are associated with familial *AD*, while mutations in *SNCA*, *LRRK2*, and *GBA* are linked to familial PD. While these genetic forms represent a small fraction of total cases, their study has led to the identification of downstream molecular signatures that may be present in sporadic cases. Transcriptomic and proteomic profiling of blood and brain tissue has uncovered distinct gene expression and protein patterns that could serve as early indicators or predictive tools for disease risk and progression.

Despite these advances, challenges remain in translating biomarker discoveries into clinical practice. Variability in sample collection, processing, and analytical methods can affect reproducibility across studies. Standardization and validation in large, diverse cohorts are essential to ensure accuracy and generalizability. Additionally, ethical considerations must be addressed when implementing early diagnostic biomarkers, including psychological impacts, potential for discrimination, and implications for individuals with no available disease-modifying treatment.

The integration of multi-modal biomarkers-combining molecular, imaging, and clinical data-may offer the most comprehensive approach to early diagnosis. Machine learning and

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artificial intelligence tools are increasingly applied to large biomarker datasets to identify patterns predictive of disease onset and trajectory. These integrative approaches not only improve diagnostic accuracy but also support the development of personalized treatment strategies based on individual risk profiles.

CONCLUSION

Translational biomarkers hold immense promise for transforming the early diagnosis and management of Alzheimer's and Parkinson's diseases. By detecting pathological changes before the onset of symptoms, these biomarkers enable earlier intervention, improved clinical trial design, and the potential for more effective therapies. Continued investment in biomarker discovery, validation, and implementation will be critical to changing the trajectory of these devastating neurodegenerative diseases.