The study [1] explored links between Parkinson's disease (PD) and various health conditions using German health insurance data from 138,345 PD cases and 276,690 controls over 10 years. It found that factors like brain injury, alcohol misuse, diabetes, and hypertension increase PD risk, while early signs include loss of smell and restless legs syndrome. The study’s reliance on insurance records and lack of genetic data were limitations, highlighting the need for further research to better understand these connections and develop early detection tools.

Schrag, A., Bohlken, J., Dammertz, L., Teipel, S., Hermann, W., Akmatov, M. K., ... & Holstiege, J. (2023). Widening the spectrum of risk factors, comorbidities, and prodromal features of Parkinson disease. *JAMA neurology*, *80*(2), 161-171.

The paper by Han et al. [2] examined how diabetes severity affects Parkinson's disease (PD) risk using data from over 2.3 million people in Korea. They found that more severe diabetes—measured by factors like insulin use, duration, and complications—was linked to a higher risk of PD, with the most severe cases having nearly three times the risk. While the study relied on claims data and couldn’t fully explore all diabetes-related factors, it highlighted the importance of controlling diabetes to reduce PD risk and suggested closer neurological monitoring for high-risk patients.

Han, K., Kim, B., Lee, S. H., & Kim, M. K. (2023). A nationwide cohort study on diabetes severity and risk of Parkinson disease. *npj Parkinson's Disease*, *9*(1), 11.

This study [3] highlights the pivotal role of glial neurotrophic factor (GDNF) as an early biomarker for Parkinson's disease (PD). Using ELISA, it revealed significantly diminished serum GDNF levels in PD patients (34.66 pg/ml) compared to controls (73.56 pg/ml), correlating with disease progression. Despite a limited sample and exclusive focus on GDNF, the findings underscore its potential in early neurodegeneration detection and the importance of expanding research to encompass additional biomarkers for enhanced diagnostic precision.

Isroilovich, A. E., Jumanazarovich, M. R., Muxsinovna, K. K., Askarovhch, M. B., & Yunusovuch, N. O. (2022). The Role And Importance Of Gliah Neurotrophical Factors In Early Diagnosis Of Parkinson Disease. *Texas Journal of Medical Science*, *5*, 1-6.

This review [4] presents two groundbreaking frameworks, NSD-ISS and SynNeurGe, redefining Parkinson's disease through biological markers like α-synuclein rather than clinical symptoms. Advanced tools, such as seed amplification assays (SAA) and α-synuclein immunostaining, are pivotal but risk overlooking co-pathologies like tau or amyloid-beta. The study advocates for broader pathological integration to enhance precision medicine and refine diagnostic frameworks.

Kalia, L. V., Berg, D., Kordower, J. H., Shannon, K. M., Taylor, J. P., Cardoso, F., ... & Fung, V. S. (2024). International parkinson and movement disorder society viewpoint on biological frameworks of parkinson's disease: current status and future directions. *Movement Disorders*, *39*(10), 1710-1715.

This paper [5] revealed genetic variants in 13% of Parkinson’s patients, including 9% without traditional risk factors. Dominant mutations were found in GBA1 (7.7%) and LRRK2 (2.4%). While advocating for universal genetic testing, the study highlights disparities in counseling access and inadequately represented of diverse groups, emphasizing the need for inclusive precision medicine to advance genetic insights.

Cook, L., Verbrugge, J., Schwantes-An, T. H., Schulze, J., Foroud, T., Hall, A., ... & Alcalay, R. N. (2024). Parkinson’s disease variant detection and disclosure: PD GENEration, a North American study. *Brain*, *147*(8), 2668-2679.

[6] This study inspects the burden of neurological disorders in Europe by operating data from the Global Burden of Disease Study 2017. In the EU28, 13.3% of disability-adjusted life years (DALYs) and 19.5% of mortality was observed for by neurological disorders, including stroke, Alzheimer’s disease, and Parkinson’s disease, assigning them third after cardiovascular diseases and cancer. During hasty mortality rates decreased, the burden of neurodegenerative diseases expanded owing to elderly demographics. Disparities across the span of countries in health consequences, determined by healthcare systems and demographic factors, are brought to attention by the study. It does not disregard the need for greater investment in risk-reduction strategies, vigorous public health strategies, and research on therapeutic treatments to reduce the rising burden of neurological disorders.

Deuschl, G., Beghi, E., Fazekas, F., Varga, T., Christoforidi, K. A., Sipido, E., ... & Feigin, V. L. (2020). The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. *The Lancet Public Health*, *5*(10), e551-e567.

[7] A closed-loop system integrating body-mounted sensors through automated processes levodopa delivery to confront the challenges of Parkinson’s disease management is visualized in this paper. The authors detail ongoing challenges in levodopa therapy, such as fluctuating efficacy and a narrowing therapeutic window, and advise on biosensor integration and machine learning algorithms for real-time tracking health indicators and adjusted therapies based on individual needs. These technologies, even though encouraging, are mainly in the experimental stage and involve substantial clinical validation. The review emphasizes the radical possibility of such innovations to enhance excellence of life for Parkinson’s patients while admitting the difference between concept and real-world use.

Teymourian, H., Tehrani, F., Longardner, K., Mahato, K., Podhajny, T., Moon, J. M., ... & Wang, J. (2022). Closing the loop for patients with Parkinson disease: where are we?. *Nature Reviews Neurology*, *18*(8), 497-507.

[8] In this experimental setup, double-blind phase 2 trial, the therapeutic value of deferiprone, an iron chelator, was investigated in people in the early stages of Parkinson's disease. Cerebral iron levels were reduced by deferiprone; nevertheless, it was tied with worsened motor symptoms when compared with the placebo, accompanied by significant adverse side effects such as agranulocytosis and neutropenia. Performed over 36 weeks with 372 participants, the study emphasizes a discrepancy between biochemical and clinical outcomes, triggering concerns about the therapeutic potential of chelation therapy in Parkinson’s disease. The observations, notwithstanding the robust design, highlight boundaries in efficacy and safety, focusing on the need for ongoing analysis into other disease-modifying treatments.

Devos, D., Labreuche, J., Rascol, O., Corvol, J. C., Duhamel, A., Guyon Delannoy, P., ... & Moreau, C. (2022). Trial of deferiprone in Parkinson’s disease. *New England Journal of Medicine*, *387*(22), 2045-2055.

[9] This paper offers an in-depth analysis of Parkinson’s disease, focusing on its escalating incidence, diverse symptoms, and primary genetic and environmental influences. The disease's multifaceted nature is emphasized by the authors, who note various subtypes and the potential for individualized healthcare strategies. Diagnosis remains clinical, depending on motor symptoms such as bradykinesia and non-motor indicators, while definitive validation can only be made posthumously. Current treatments, primarily levodopa and team-based care, do not influence disease progression, even though directed at symptom relief. The review covers active experiments on gene-targeted therapies and disease-modifying strategies, pointing out shortcomings like the lack of initial diagnostic signs and effective treatments. Its strength lies in aggregating recent research and expert opinions.

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *The Lancet*, *397*(10291), 2284-2303.

The paper [9] explores advances in discovering Parkinson's disease biomarkers using modern "-omics" approaches like proteomics and metabolomics. Potential biomarkers, like microRNA in cerebrospinal fluid and metabolic patterns in plasma, show promise but aren’t yet ready for use in clinics. The complexity of Parkinson's and inconsistent methods make progress challenging. However, initiatives like the Parkinson’s Progression Markers Initiative (PPMI) are working to standardize research and improve diagnostic tools. While no numerical accuracy values are provided, the paper acknowledges the lack of clinically validated biomarkers.

Barker, R. A., Björklund, A., Gash, D. M., Whone, A., Van Laar, A., Kordower, J. H., ... & Lang, A. E. (2020). GDNF and Parkinson’s disease: where next? A summary from a recent workshop. *Journal of Parkinson's disease*, *10*(3), 875-891.

This [10] systematically reviews the potential of exergaming in Parkinson's disease (PD) rehabilitation. It evaluates 64 studies, including randomized clinical trials (RCTs) and pilot studies, focusing on the use of devices like Microsoft Kinect and Wii Balance Board to improve motor and cognitive functions. The findings reveal that exergames match or surpass traditional rehabilitation approaches, delivering enhanced improvements in motor functions and cognitive domains like focus and executive processing. The limitations encompass inconsistencies in study designs, absence of uniform outcome metrics, and inadequate follow-up strategies. Future research should prioritize incorporating advanced sensors, refining task-specific interventions, and implementing comprehensive patient evaluation methods to achieve clinical standardization.

Garcia-Agundez, A., Folkerts, A. K., Konrad, R., Caserman, P., Tregel, T., Goosses, M., ... & Kalbe, E. (2019). Recent advances in rehabilitation for Parkinson’s Disease with Exergames: A Systematic Review. *Journal of neuroengineering and rehabilitation*, *16*, 1-17.

This review explores metabolomics as a tool for uncovering biomarkers and metabolic pathways in Parkinson's disease. Techniques like NMR and MS analyze metabolites in various samples, revealing alterations in amino acids, lipids, and oxidative stress pathways [11]. Some biomarkers show high accuracy in distinguishing PD cases, but challenges like incomplete metabolome coverage and inconsistent validation remain. Integrating multiple platforms and sample types could improve diagnostic and therapeutic advancements.

Shao, Y., & Le, W. (2019). Recent advances and perspectives of metabolomics-based investigations in Parkinson’s disease. *Molecular neurodegeneration*, *14*(1), 3.

Initiatives to develop disease-modifying therapies, featuring the targeting of alpha-synuclein poisonousness, the augmentation of mitochondrial function, and genetic interventions like resolving LRRK2 and GBA mutations, are covered in this document. The paper covers challenges such as the deficiency of credible biomarkers for treatment monitoring, variability in patient responses, and the influence of symptomatic effects on results in clinical trials. Thecriticality of identifying patient subgroups for targeted therapies is emphasized in the study, which also highlights the complexity of formulating interventions that address the root causes of disease [12].

Lang, A. E., & Espay, A. J. (2018). Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. *Movement Disorders*, *33*(5), 660-677.

An overview of the pathophysiology, epidemiology, and management approaches of PD is provided in this paper, emphasizing the gradual degeneration of dopaminergic neurons and the buildup of alpha-synuclein. It also discusses the imminent role of the gut microbiome in early non-motor symptoms [13]. The limitations include the absence of large-scale studies and the lack of effective disease-modifying treatments. The review highlights emerging fields of interest, such as gut microbiome research, and stresses the importance of thorough studies to pinpoint early indicators and observe disease progression.

Radhakrishnan, D. M., & Goyal, V. (2018). Parkinson's disease: A review. *Neurology India*, *66*(Suppl 1), S26-S35.

This paper evaluates biomarkers for early diagnosis and disease monitoring in Parkinson's Disease (PD). Motor and non-motor symptom-related biomarkers, including clinical, biochemical, neuroimaging, and genetic markers, are discussed. The paper does not overlook the relevance of multimodal biomarker combinations to improve diagnostic accuracy [14]. The lack of accuracy and awareness when using individual biomarkers is a key constraint. In research concentrating on Parkinson's, the increase in diagnostic reliability using the fusion of biomarkers could be explored.

He, R., Yan, X., Guo, J., Xu, Q., Tang, B., & Sun, Q. (2018). Recent advances in biomarkers for Parkinson’s disease. *Frontiers in aging neuroscience*, *10*, 305.

In this study, PD biomarkers are organized into imaging, biochemical, clinical, and genetic types, placing importance on early-stage detection to prevent progression [15]. Techniques like molecular imaging (DAT-SPECT and F-DOPA PET) are not overlooked for their diagnostic relevance. The scarcity of verified, extremely targeted biomarkers is pointed out in the report, with an emphasis on the merging of diverse biomarkers for improved sensitivity. Drawbacks are elevated costs and limited access to imaging tools. In a PD-oriented study, using imaging biomarkers could provide a strong diagnostic approach.

Lotankar, S., Prabhavalkar, K. S., & Bhatt, L. K. (2017). Biomarkers for Parkinson’s disease: recent advancement. *Neuroscience bulletin*, *33*, 585-597.

Neuroprotective strategies, encompassing dopamine replacement, surgical treatments like deep brain stimulation, and stem cell therapy, are noted in this overview [16]. It evaluates therapies for their restrictions, for example levodopa's motor complications and dopamine receptor agonists' non-motor unintended effects. Latest neuroprotective agents concentrate on dealing with oxidative damage, neural inflammation, and the misfolding of proteins. The significance of early intervention strategies and reliable biomarkers is highlighted in the article. These particular neuroprotective techniques could act as guidance for a paper on innovative treatment pathways for PD.

Sarkar, S., Raymick, J., & Imam, S. (2016). Neuroprotective and therapeutic strategies against Parkinson’s disease: recent perspectives. *International journal of molecular sciences*, *17*(6), 904.

The author [18] of the paper discusses the role of endolysosomal dysfunction in Parkinson's Disease and its inferences for understanding disease mechanisms. It emphasizes findings from genetic, cellular, and in vivo studies, particularly focusing on a novel mouse model lacking the Atp13a2 gene. This model duplicates certain neuropathological changes in behavior observed in human Kufor-Rakeb syndrome, such as protein aggregation and autophagic deficits. Accuracy metrics are not directly reported, as the study's focus is on mechanistic insights rather than diagnostic performance or therapeutic prediction.

Delenclos, M., Jones, D. R., McLean, P. J., & Uitti, R. J. (2016). Biomarkers in Parkinson's disease: Advances and strategies. *Parkinsonism & related disorders*, *22*, S106-S110.

The next paper [19] shows the potential of GDNF as a treatment for Parkinson’s. Although preclinical studies demonstrated its potential to regenerate dopaminergic neurons, clinical trials did not produce notable improvements in motor function. Challenges like poor GDNF distribution and late-stage patient selection limited success. However, ongoing research into better delivery methods and related factors like CDNF offers hope, with promising results in animal studies and early trials. Imaging-based metrics suggested a 32.5% treatment difference in dopamine uptake for GDNF-treated groups, but this did not correlate with clinical outcomes, limiting the "accuracy" of the treatment's functional benefits.

Kett, L. R., & Dauer, W. T. (2016). Endolysosomal dysfunction in Parkinson's disease: Recent developments and future challenges. *Movement Disorders*, *31*(10), 1433-1443.

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[20] The paper explores various biomarkers for Parkinson's disease (PD) targeted at early diagnosis, tracking progression, and analyzing treatment efficacy. Neuroimaging techniques like PET and SPECT, as well as flexible biomarkers such as neuromelanin antibodies and DJ-1 protein, are highlighted in the study. The paper admits weaknesses in the variability of biomarkers across individuals and the technical and financial challenges of advanced diagnostic methods, regardless of their potential. The findings point out the significance of using multi-dimensional approaches to improve early detection and monitoring, as no specific accuracy metrics have been presented.

Sharma, S., Moon, C. S., Khogali, A., Haidous, A., Chabenne, A., Ojo, C., ... & Ebadi, M. (2013). Biomarkers in Parkinson’s disease (recent update). *Neurochemistry international*, *63*(3), 201-229.