Montgomery, R. M. (2025). Retinal Nerve Fibre Layer Thinning and Ganglion Cell Complex Degeneration in Parkinson's Disease: Emerging Biomarkers for Neurodegeneration and Cognitive Decline; Scottish Science Society, Vol 1; Issue 1; p(1-16).

# Retinal Nerve Fibre Layer Thinning and Ganglion Cell Complex Degeneration in Parkinson's Disease: Emerging Biomarkers for Neurodegeneration and Cognitive Decline

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DOI:10.62162/SSSP117411

## Abstract

Parkinson's disease (PD) is characterised by progressive neurodegeneration extending beyond the central nervous system to affect retinal structures. Recent advances in optical coherence tomography (OCT) have revealed significant alterations in retinal nerve fibre layer (RNFL) thickness and ganglion cell complex (GCC) integrity in PD patients, suggesting potential biomarker applications for disease monitoring and progression assessment. This comprehensive review examines the current evidence for RNFL thinning and ganglion cell layer degeneration in PD, evaluating their correlation with visual disturbances, cognitive decline, and disease progression whilst assessing their potential as non-invasive biomarkers for clinical practice. A systematic analysis of recent literature was conducted, focusing on spectral-domain OCT studies investigating retinal structural changes in PD patients compared to healthy controls. Particular attention was given to meta-analyses, longitudinal studies, and investigations correlating retinal changes with clinical outcomes. Consistent evidence demonstrates significant RNFL thinning in PD patients, particularly in the inferior quadrant, with mean thickness reductions of approximately12-15 µm compared to controls. Ganglion cell-inner plexiform layer (GCIPL) thinning shows even greater sensitivity, with parafoveal GCIPL demonstrating twice the rate of degeneration in PD patients compared to controls. These changes correlate significantly with visual acuity, cognitive function, and disease severity, whilst appearing early in the disease course, often preceding clinical manifestations. RNFL and GCIPL measurements represent promising non-invasive biomarkers for PD diagnosis, progression monitoring, and cognitive decline prediction. The correlation between retinal neurodegeneration patterns and clinical outcomes supports the integration of OCT assessments into routine PD management protocols. Future research should focus on establishing standardised measurement protocols and validating these biomarkers across diverse populations and disease stages.

Keywords: Parkinson's disease, retinal nerve fibre layer, ganglion cell layer, optical coherence tomography, biomarkers, neurodegeneration, cognitive decline, visual hallucinations

# 1. Introduction

Parkinson's disease (PD) represents one of the most prevalent neurodegenerative disorders globally, affecting approximately 1% of individuals over 60 years of age and manifesting as a progressive condition characterised by motor symptoms including bradykinesia, tremor, rigidity, and postural instability (Dorsey et al., 2007). First described by James Parkinson in 1817 as "shaking palsy," the understanding of PD has evolved considerably, revealing its multisystem nature that extends far beyond the classical motor manifestations to encompass a broad spectrum of non-motor symptoms, including visual disturbances, cognitive impairment, and autonomic dysfunction (Abd Hamid et al., 2021). The pathological hallmark of PD involves the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, accompanied by the accumulation of α-synuclein protein aggregates known as Lewy bodies (Braak et al., 2003). However, emerging evidence suggests that the neurodegenerative process in PD extends beyond the central nervous system to affect peripheral structures, including the retina, which shares embryological origins with the brain and may serve as an accessible window into central nervous system pathology (London et al., 2013).

The retina, as an extension of the central nervous system, contains dopaminergic neurons and is susceptible to the same pathological processes that characterise PD (Archibald et al., 2009). Dopamine plays a crucial role in retinal function, particularly in the modulation of visual processing through horizontal, amacrine, bipolar, and ganglion cells (Witkovsky, 2004). The presence of dopaminergic dysfunction in the retina of PD patients has been demonstrated through various neurophysiological studies, revealing alterations in visual processing that may precede or accompany motor symptoms (Bodis-Wollner, 2009). These findings have prompted extensive investigation into the structural integrity of retinal layers using advanced imaging techniques, particularly optical coherence tomography (OCT), which provides high- resolution, non-invasive assessment of retinal architecture (Huang et al., 1991).

The advent of spectral-domain OCT has revolutionised the ability to quantify retinal layer thickness with unprecedented precision, enabling researchers to detect subtle changes in

retinal nerve fibre layer (RNFL) thickness and ganglion cell complex (GCC) integrity (Schuman et al., 1995). The RNFL, composed of unmyelinated axons of retinal ganglion cells, represents a critical component of the visual pathway that may be particularly vulnerable to neurodegenerative processes (Inzelberg et al., 2004). Similarly, the ganglion cell layer and inner plexiform layer, collectively referred to as the ganglion cell complex, contain the cell bodies and dendrites of retinal ganglion cells and may provide complementary information about retinal neurodegeneration (Mwanza et al., 2012).

Recent meta-analyses have consistently demonstrated significant RNFL thinning in PD patients compared to age-matched controls, with the most pronounced changes observed in the inferior quadrant (Chrysou & Jansonius, 2019). Chrysou and Jansonius conducted a comprehensive meta-analysis of spectral-domain OCT studies, revealing that PD patients exhibit significant thinning of inner retinal layers, with effect sizes comparable to those observed in other neurodegenerative conditions such as multiple sclerosis and Alzheimer's disease (Chrysou & Jansonius, 2019). The consistency of these findings across multiple studies and populations suggests that retinal changes represent a fundamental aspect of PD pathophysiology rather than an epiphenomenon.

The clinical significance of retinal changes in PD extends beyond mere structural alterations to encompass functional implications that may directly impact patient quality of life. Visual symptoms are commonly reported in PD, including difficulty reading, double vision, reduced contrast sensitivity, and complex visual hallucinations (Armstrong, 2015). These symptoms have traditionally been attributed to central visual

processing deficits; however, accumulating evidence suggests that peripheral retinal dysfunction may contribute significantly to visual impairment in PD patients (Nowacka et al., 2015). The correlation between RNFL thickness and visual acuity observed in several studies supports this hypothesis, indicating that structural retinal changes have direct functional consequences (Elanwar et al., 2023).

Perhaps most intriguingly, recent longitudinal studies have revealed associations between retinal neurodegeneration and cognitive decline in PD, suggesting that retinal changes may serve as biomarkers for cognitive deterioration (Murueta-Goyena et al., 2024). The work of Murueta-Goyena and colleagues demonstrated that parafoveal ganglion cell-inner plexiform

layer (GCIPL) thinning rates were twice as high in PD patients compared to controls, with slower progression patterns paradoxically associated with more rapid cognitive decline (Murueta-Goyena et al., 2024). This counterintuitive finding suggests that retinal neurodegeneration patterns may reflect underlying disease mechanisms and provide insights into individual patient prognoses.

The potential for retinal imaging to serve as a biomarker in PD is particularly compelling given the urgent need for objective measures of disease progression and treatment response (Marek et al., 2011). Current clinical assessments of PD rely heavily on subjective rating scales and clinical observations, which may be influenced by various factors including medication effects, examiner variability, and patient cooperation (Goetz et al., 2008). In contrast, OCT measurements provide objective, quantitative data that can be obtained rapidly and non-invasively, making them attractive candidates for routine clinical monitoring (Petzold et al., 2017).

The segmentation of RNFL boundaries requires precise identification of the internal limiting membrane and the interface between the RNFL and ganglion cell layer (Ishikawa et al., 2005). Modern OCT systems employ sophisticated algorithms that utilise intensity gradients and morphological features to automatically detect these boundaries, though manual correction may be necessary in cases with poor signal quality or anatomical variations (Tan et al., 2009). Quality control measures are essential to ensure reliable measurements, including assessment of signal strength, centration accuracy, and the absence of motion artefacts or segmentation errors (Schuman et al., 1996).

Regional analysis of RNFL thickness provides valuable insights into the spatial distribution of neurodegeneration in PD (Raza et al., 2011). The peripapillary region is typically divided into four quadrants (superior, inferior, nasal, and temporal) or eight sectors for more detailed analysis (Budenz et al., 2007). Studies have consistently demonstrated that the inferior quadrant shows the most pronounced thinning in PD patients, though the underlying mechanisms responsible for this regional vulnerability remain incompletely understood (Altintaş et al., 2008).

## **1.1** Ganglion Cell Complex Evaluation Techniques

The assessment of ganglion cell complex integrity represents a complementary approach to RNFL evaluation, providing information about the cell bodies and dendrites of retinal ganglion cells rather than their axons (Curcio & Allen, 1990). The ganglion cell-inner plexiform layer (GCIPL) complex is typically measured within the macular region, where ganglion cell density is highest and the contribution of other retinal layers is minimised (Zeimer et al., 1998). Macular cube scans covering a 6×6 millimeter area centred on the fovea provide comprehensive coverage of the ganglion cell-rich region whilst maintaining sufficient resolution for accurate layer segmentation (Mwanza et al., 2011).

The relationship between retinal changes and visual hallucinations in PD represents another area of significant clinical interest. Visual hallucinations occur in approximately 20-40% of PD patients and are associated with increased morbidity, accelerated cognitive decline, and reduced quality of life (Fénelon et al., 2000). While the pathophysiology of visual hallucinations in PD remains incompletely understood, several studies have suggested associations with retinal structural changes, particularly thinning of inner retinal layers (Elanwar et al., 2023). However, this relationship remains controversial, with some studies failing to demonstrate significant correlations between retinal thickness and hallucination severity (Nowacka et al., 2015).

The temporal relationship between retinal changes and PD onset represents a critical consideration for biomarker development. Several studies have suggested that retinal alterations may be detectable in the early stages of PD, potentially even in the prodromal phase before motor symptoms become apparent (Beach et al., 2014). This possibility is supported by post-mortem studies demonstrating α-synuclein deposition in retinal tissues of PD patients, suggesting that retinal pathology may parallel central nervous system changes (Bodis-Wollner et al., 2014). If confirmed, early retinal changes could facilitate earlier diagnosis and intervention, potentially improving long- term outcomes for PD patients.

This comprehensive review aims to synthesise the current evidence regarding RNFL thinning and ganglion cell complex degeneration in PD, with particular emphasis on their potential as biomarkers for disease monitoring and cognitive decline prediction. By examining the methodological approaches, clinical correlations, and future directions in this rapidly evolving

field, we seek to provide a foundation for the continued development and implementation of retinal biomarkers in PD care (Poewe et al., 2017).

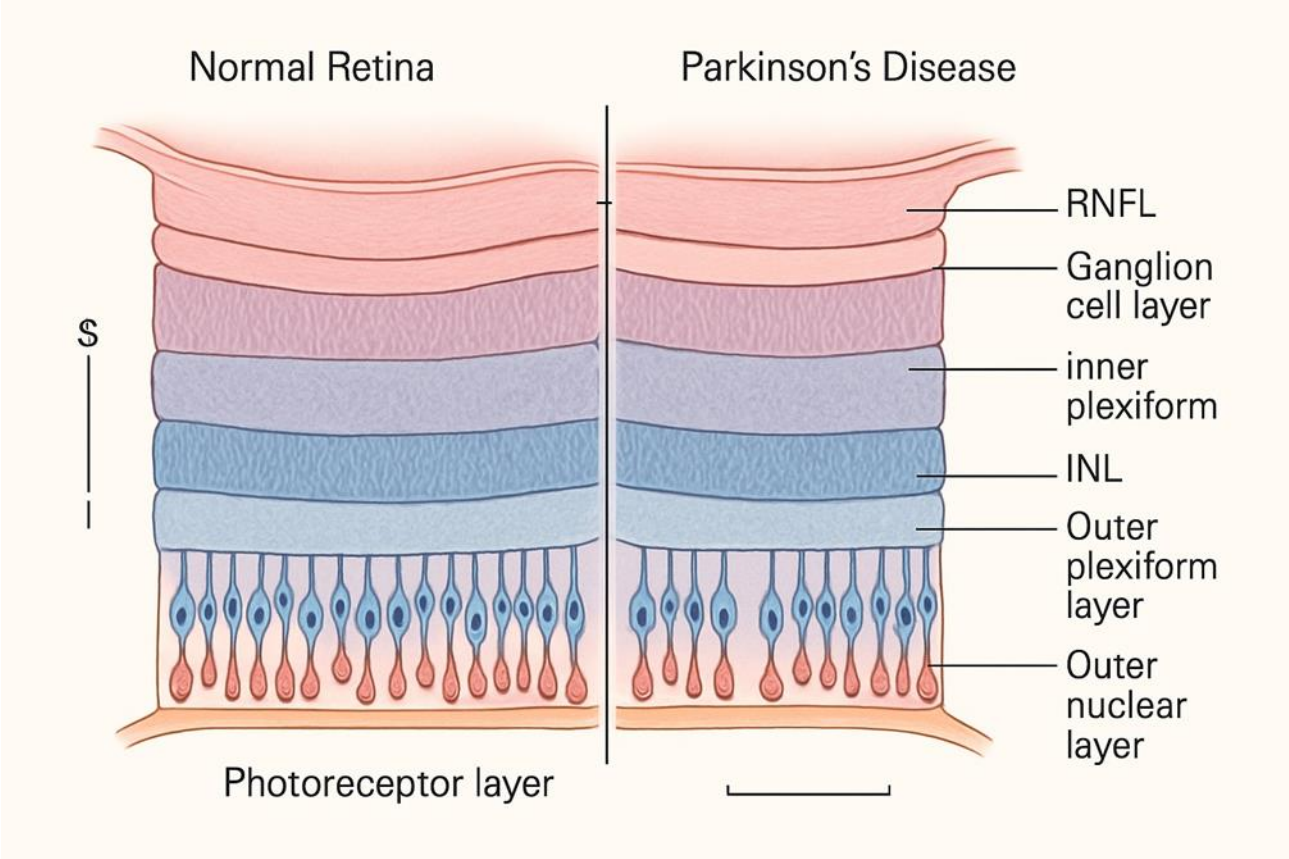


Figure 1. Comparative cross-sectional anatomy of retinal layers in normal individuals (left) and Parkinson's disease patients (right). The diagram illustrates the characteristic thinning of the retinal nerve fibre layer (RNFL) and ganglion cell layer observed in PD patients. Key retinal layers are labelled, including the inner nuclear layer (INL), inner and outer plexiform layers, outer nuclear layer, and photoreceptor layer. Scale bar
represents 50 μm. The visible reduction in RNFL and ganglion cell layer thickness in PD demonstrates the structural basis for retinal biomarker development.

# 2.Methodology

## 2.1ptical Coherence Tomography Principles and Applications

Optical coherence tomography represents a revolutionary imaging modality that has

transformed the assessment of retinal structure in neurodegenerative diseases, including Parkinson's disease (Fujimoto et al., 2000). The fundamental principle of OCT relies on low-coherence interferometry, utilising near-infrared light to generate high-resolution cross-sectional images of biological tissues with axial resolution approaching 1-3 micrometers (Drexler & Fujimoto, 2008). This exceptional resolution capability enables precise quantification of individual retinal layers, including the retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC), which are of particular interest in PD research (Hood et al., 2013).

The evolution from time-domain to spectral-domain OCT has significantly enhanced imaging speed and resolution, enabling the acquisition of detailed retinal maps within seconds whilst minimising motion artefacts that could compromise measurement accuracy (Wojtkowski et al., 2004). Spectral-domain OCT systems typically operate at wavelengths between 800-870 nanometers, providing optimal penetration through ocular media whilst maintaining high contrast between different retinal layers (Povazay et al., 2002). The automated segmentation algorithms incorporated into modern OCT systems facilitate rapid and reproducible measurement of layer thicknesses, though manual verification remains essential to ensure accuracy, particularly in cases with retinal pathology or poor image quality (Garvin et al., 2009).

## 2.2.Retinal Nerve Fibre Layer Assessment Protocols

The assessment of RNFL thickness in PD research follows standardised protocols that have been refined through extensive validation studies (Tewarie et al., 2012). Peripapillary RNFL measurements are typically obtained using circular scans centred on the optic disc, with a standard diameter of 3.4 millimeters corresponding to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (Early Treatment Diabetic Retinopathy Study Research Group, 1991). This scanning pattern provides comprehensive coverage of the RNFL as it converges towards the optic nerve head,

**OCT IMAGING**

RNFL and GCIPL measurements

**DATA ANALYSIS**

thickness guantification
regional analysis

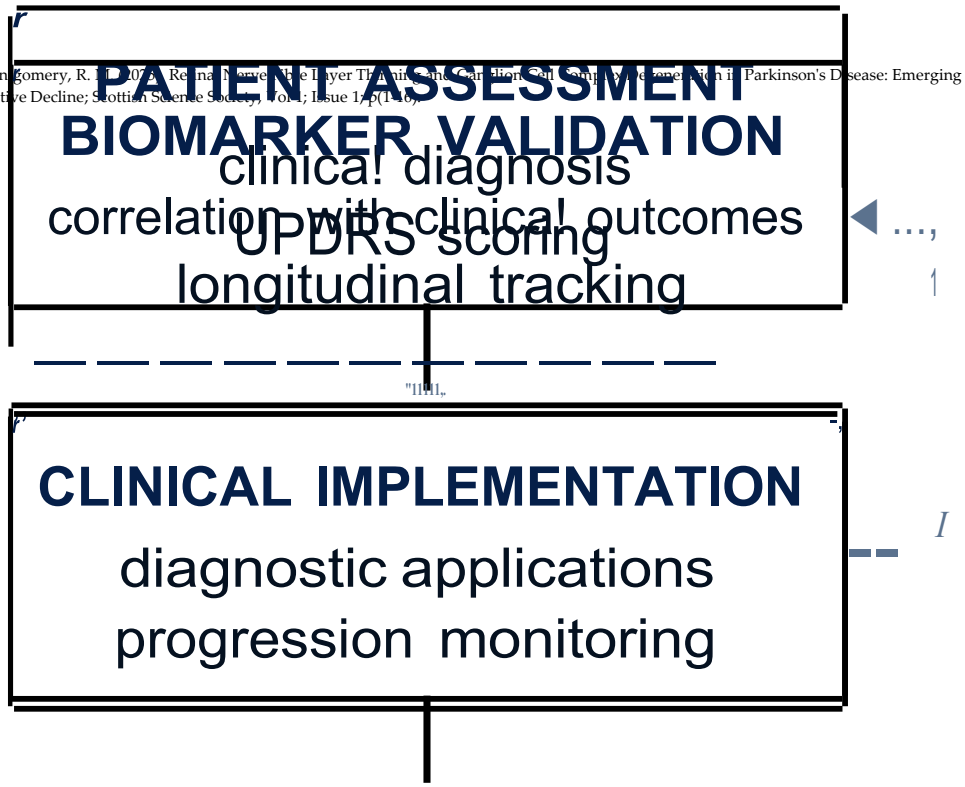
PATIENT ASSESSMENT
BIOMARKER VALIDATION
clinical diagnosis
correlation with clinical outcomes
UPDRS scoring
longitudinal tracking
CLINICAL IMPLEMENTATION
diagnostic applications
progression monitoring

**Figure 2.** Systematic workflow for the development and validation of retinal biomarkers in Parkinson's disease. The process begins with comprehensive patient assessment including clinical diagnosis and UPDRS scoring, followed by standardised OCT imaging to measure RNFL and GCIPL parameters. Data analysis involves thickness quantification and regional analysis, leading to biomarker validation through correlation with clinical outcomes and longitudinal tracking. The feedback loop from clinical implementation back to biomarker validation ensures continuous refinement and optimisation of the biomarker approach.

# 3.Discussion

## 1.2 Clinical Significance and Biomarker Potential

The accumulating evidence for retinal nerve fibre layer thinning and ganglion cell complex degeneration in Parkinson's disease represents a paradigm shift in our understanding of the disease's systemic nature and offers unprecedented opportunities for developing objective biomarkers (Abd Hamid et al., 2021). The consistency of findings across multiple independent studies, different populations, and various OCT platforms strongly suggests that retinal changes represent a fundamental aspect of PD pathophysiology rather than an incidental finding (Chrysou & Jansonius, 2019). The magnitude of these changes, with RNFL thickness reductions of 10-15 micrometers and GCIPL thinning rates twice those observed in healthy controls, approaches the effect sizes observed in established neurodegenerative biomarkers, supporting their potential clinical utility (Murueta-Goyena et al., 2024).

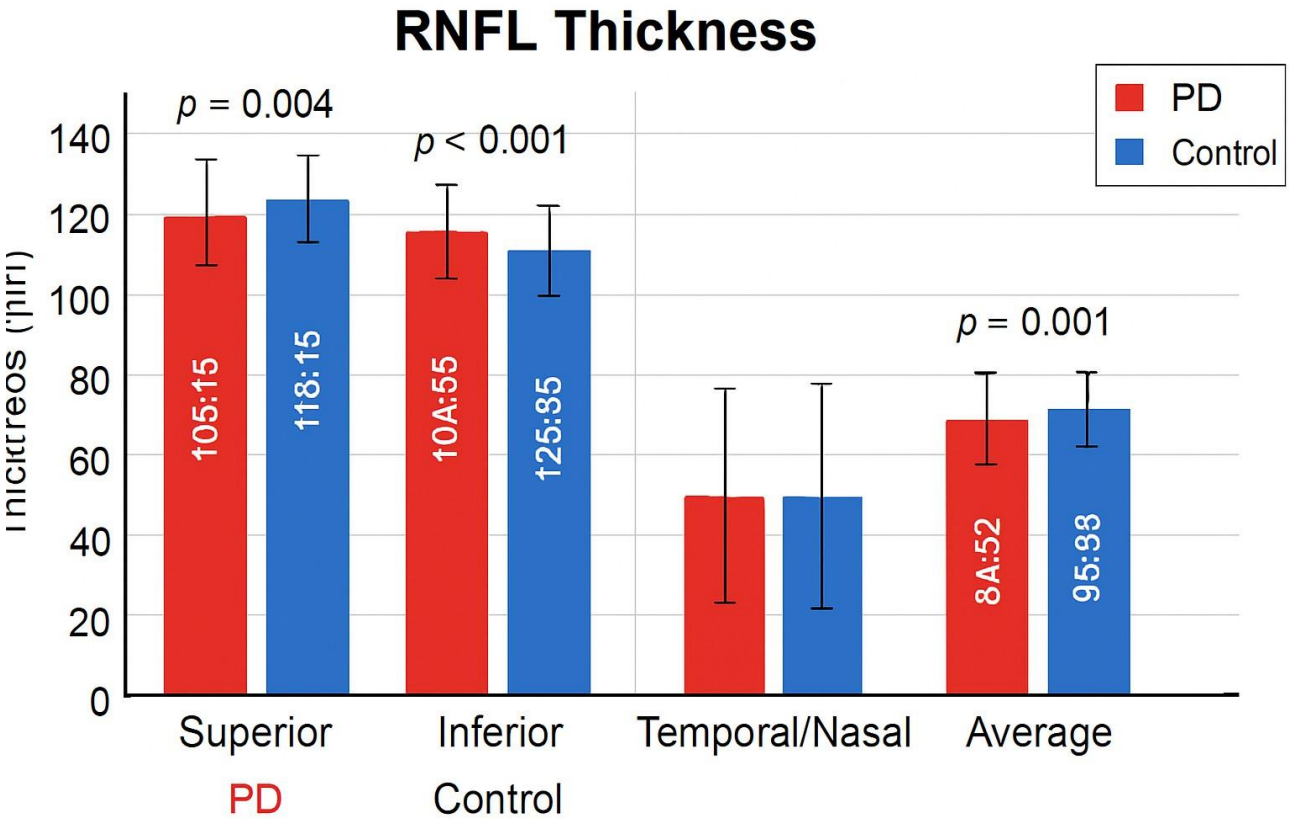


**Figure 3.** Comparative analysis of retinal nerve fibre layer (RNFL) thickness measurements between Parkinson's disease patients (red bars) and healthy controls (blue bars) across different retinal quadrants. Data derived from Abd Hamid et al. (2021) showing statistically significant reductions in RNFL thickness in PD patients, with the most pronounced changes observed in the inferior quadrant ($p < 0.001$). Error bars represent standard deviation. Statistical significance levels are indicated above each comparison. The consistent pattern of RNFL thinning across all measured regions supports the potential utility of these measurements as biomarkers for PD.

The temporal relationship between retinal changes and disease progression represents a critical consideration for biomarker development. The observation that retinal alterations may be detectable in early-stage PD, potentially even before motor symptoms become clinically apparent, suggests that OCT assessments could facilitate earlier diagnosis and intervention (Beach et al., 2014). This possibility is particularly compelling given the growing recognition that neuroprotective therapies may be most effective when initiated early in the disease course, before extensive neuronal loss has occurred (Athauda & Foltynie, 2015). The work of Murueta-Goyena and colleagues,

demonstrating that slower GCIPL progression patterns are paradoxically associated with more rapid cognitive decline, highlights the complex relationship between retinal

neurodegeneration and clinical outcomes, suggesting that progression patterns may be as important as absolute thickness measurements (Murueta-Goyena et al., 2024).

## 3.2Advantages of Retinal Biomarkers in PD

The potential advantages of retinal biomarkers in PD are multifaceted and address several critical limitations of current diagnostic and monitoring approaches (Petzold et al., 2017). The non-invasive nature of OCT examinations represents a significant advantage over other biomarker modalities, such as cerebrospinal fluid analysis or dopamine transporter imaging, which involve more complex procedures and potential risks (Marek et al., 2011). The rapid acquisition time for OCT scans, typically requiring only a few minutes per patient, makes them highly suitable for routine clinical practice and large-scale screening programmes (Schuman et al., 1995).

The objective, quantitative nature of OCT measurements provides a significant advantage over subjective clinical rating scales, which may be influenced by examiner variability, patient cooperation, and medication effects (Goetz et al., 2008). The high reproducibility of OCT measurements, with intraclass correlation coefficients typically exceeding 0.9 for RNFL and GCIPL thickness, enables detection of subtle changes over time that might not be apparent through clinical assessment alone (Budenz et al., 2005). This precision is particularly valuable for monitoring disease progression and assessing treatment responses in clinical trials, where objective outcome measures are essential for regulatory approval (Marek et al., 2011).

## 3.3Limitations and Future Directions

Despite the promising potential of retinal biomarkers in PD, several significant limitations and challenges must be acknowledged and addressed before widespread clinical implementation can be achieved (Petzold et al., 2017). The heterogeneity of PD presentations and progression patterns represents a fundamental challenge, as the disease encompasses a spectrum of phenotypes with varying rates of progression and patterns of involvement (Poewe et al., 2017). This heterogeneity may limit the sensitivity and specificity of retinal biomarkers, particularly in early-stage disease where changes may be subtle and overlap with normal age-related variations (Parikh

et al., 2007).

The influence of confounding factors on OCT measurements presents ongoing challenges for clinical interpretation (Savini et al., 2012). Age-related changes in retinal

thickness, refractive errors, axial length variations, and concurrent ocular pathology can all influence measurements and must be carefully considered when interpreting results (Varma et al., 1996). The potential effects of dopaminergic medications on retinal structure and function remain incompletely understood, though some studies suggest that levodopa therapy may influence retinal thickness measurements (Djamgoz et al., 1997).

The lack of standardised protocols and normative databases across different OCT platforms represents a significant barrier to clinical implementation (Giani et al., 2010). Variations in segmentation algorithms, measurement protocols, and reference standards between manufacturers can lead to systematic differences in measurements that complicate cross-platform comparisons and limit the generalisability of research findings (Wolf-Schnurrbusch et al., 2009). The development of universal calibration standards and cross-platform validation studies is essential for addressing these limitations.

# 4.Conclusion

The comprehensive body of evidence examining retinal nerve fibre layer thinning and ganglion cell complex degeneration in Parkinson's disease represents a significant advancement in our understanding of the disease's systemic nature and offers compelling opportunities for developing objective biomarkers for clinical practice. The consistent demonstration of RNFL thinning, particularly in the inferior quadrant, and accelerated GCIPL degeneration across multiple independent studies provides robust evidence that retinal neurodegeneration is a fundamental aspect of PD pathophysiology rather than an incidental finding.

The clinical significance of these retinal changes extends beyond mere structural alterations to encompass meaningful correlations with visual function, cognitive performance, and disease progression. The observation that parafoveal GCIPL thinning rates are twice as high in PD patients compared to controls, combined with the paradoxical finding that slower progression patterns are associated with more rapid cognitive decline, highlights the complex relationship between retinal neurodegeneration and clinical outcomes. These findings suggest that retinal

biomarkers may provide valuable insights into individual patient prognoses and guide personalised treatment approaches.

The potential advantages of retinal biomarkers in PD are substantial, including their non-invasive nature, rapid acquisition time, objective quantitative measurements, and widespread availability of OCT equipment. These characteristics make retinal biomarkers particularly attractive for routine clinical monitoring, large-scale screening programmes, and resource-limited settings where advanced neuroimaging may not be readily available. The high reproducibility of OCT measurements enables detection of subtle changes over time that might not be apparent through clinical assessment alone, providing valuable tools for monitoring disease progression and assessing treatment responses.

However, several significant challenges must be addressed before widespread clinical implementation can be achieved. The heterogeneity of PD presentations and progression patterns, the influence of confounding factors on OCT measurements, and the lack of standardised protocols across different platforms represent important limitations that require continued research and development efforts. The complex relationship between retinal changes and visual symptoms, particularly visual hallucinations, remains incompletely understood and warrants further investigation.

Future research priorities should focus on large-scale longitudinal studies to establish the temporal relationship between retinal changes and disease progression, the development of standardised protocols and normative databases, and the integration of artificial intelligence approaches to enhance diagnostic accuracy. The economic and regulatory implications of implementing retinal biomarkers in clinical practice require careful analysis to ensure cost-effective and responsible deployment of these technologies.

In conclusion, retinal nerve fibre layer and ganglion cell complex measurements represent promising biomarkers for Parkinson's disease that could transform clinical practice by providing objective, non-invasive tools for diagnosis, progression monitoring, and cognitive decline prediction. While challenges remain in translating research findings into clinical practice, the substantial potential benefits justify continued investment in this rapidly evolving field. The integration of retinal biomarkers into routine PD care protocols could ultimately improve patient outcomes, facilitate earlier intervention, and advance our understanding of this complex neurodegenerative disorder.

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