Journal of
Personalized Medicine

MDPI

Review

The Eye as a Window to Precision Psychiatry: A Scoping Review of Ophthalmic Biomarkers for Personalized Diagnosis, Prognosis, and Treatment of Mental Disorders

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Abstract

Background/Objectives: To map the literature on ophthalmic biomarkers in psychiatric disorders and evaluate their potential relevance to precision psychiatry. **Methods**: A scoping review was conducted following Joanna Briggs Institute methodology and reported per PRISMA-ScR. PubMed/MEDLINE was searched for studies published from January 2000 onwards. Eligible studies investigated retinal structural or vascular biomarkers, eye-tracking measures, pupillometric parameters, or electroretinography in psychiatric populations, high-risk cohorts, or studies examining psychiatric phenotypes. Data were extracted on study characteristics, biomarker modality, psychiatric population, and precision psychiatry applications. **Results**: One hundred and fourteen studies were included: eye-tracking ($n = 91$), retinal structural and vascular imaging ($n = 11$), pupillometry ($n = 11$), and electroretinography ($n = 5$); four studies spanned two modalities and are counted under both. Eye-tracking represented the largest and most diverse evidence base, spanning autism spectrum disorder, schizophrenia spectrum disorders, psychosis-risk states, attention-deficit/hyperactivity disorder, and anxiety disorders. Across modalities, ophthalmic biomarkers were investigated for diagnostic classification, risk stratification, prognostic assessment, treatment monitoring, and treatment-response evaluation. Retinal imaging studies identified structural and microvascular alterations associated with psychiatric conditions, while electroretinography and pupillometry provided evidence for neurophysiological and autonomic correlates of psychopathology. Major research gaps included methodological heterogeneity, limited multicenter validation, predominance of cross-sectional designs, and insufficient evidence for individual-level prediction. **Conclusions**: Ophthalmic biomarkers represent a promising area of psychiatric biomarker research. Eye-tracking currently constitutes the most extensively investigated modality, while retinal imaging, electroretinography, and pupillometry remain at earlier stages of development. Future research should prioritize standardization, longitudinal validation, multicenter replication, and multimodal biomarker integration to clarify their potential role in precision psychiatry.

Keywords: precision psychiatry; ophthalmic biomarkers; eye-tracking; retinal imaging; electroretinography; pupillometry; schizophrenia; autism spectrum disorder; risk stratification; personalized medicine

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Academic Editor: Takahiro Nemoto

Received: 20 September 2026
Revised: 13 November 2026
Accepted: 18 November 2026
Published: 23 November 2026

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1. Introduction

Despite substantial advances in neuroscience and psychopharmacology, psychiatric diagnosis and treatment remain largely dependent on clinical symptomatology rather than objective biological markers. Current diagnostic frameworks group patients according to symptom clusters that may encompass heterogeneous neurobiological mechanisms. Consequently, individuals with the same diagnosis often exhibit markedly different clinical trajectories, treatment responses, and functional outcomes. This heterogeneity contributes to prolonged diagnostic uncertainty and variable treatment effectiveness. Precision psychiatry has emerged in response to these limitations, aiming to improve clinical decision-making through the integration of biological, clinical, environmental, and digital data. Central to this approach is the identification of biomarkers capable of supporting individualized diagnosis, prognosis, patient stratification, and treatment selection. Recent reviews have highlighted biomarker discovery as a major priority for the advancement of precision psychiatry and personalized mental healthcare [1,2].

Although neuroimaging, genomics, and electrophysiological methods have generated promising findings, their implementation in routine psychiatric practice remains hindered by cost, complexity, and limited accessibility. Consequently, there is growing interest in alternative sources of objective biomarkers that are non-invasive, scalable, and clinically feasible. Among these, ophthalmic biomarkers have attracted increasing attention because they provide direct access to neural and vascular tissues that share developmental and functional characteristics with the brain [3,4].

The eye, and particularly the retina, represents a unique opportunity for biomarker research in psychiatry. Embryologically derived from the neural tube, the retina is widely considered an extension of the central nervous system. Retinal neurons, glial cells, and microvascular structures share important anatomical and physiological features with cerebral tissues, making retinal assessment a potential surrogate marker of central nervous system pathology [5]. As a result, retinal alterations may reflect neurodevelopmental, neurodegenerative, vascular, inflammatory, and neurotransmitter-related changes implicated in psychiatric disorders [3,6].

Advances in ophthalmic technologies have enabled detailed and non-invasive assessment of retinal structure and function. Optical coherence tomography (OCT) can quantify retinal nerve fiber layer and ganglion cell layer thickness with high resolution, while OCT angiography (OCTA) provides information regarding retinal microvascular integrity [7,8]. Fundus imaging permits the evaluation of retinal vascular architecture and vascular health, whereas electroretinography (ERG) allows functional assessment of retinal neuronal activity and neurotransmission [9]. The potential value of these technologies in psychiatry is supported by accumulating evidence of retinal structural and functional abnormalities in schizophrenia spectrum disorders and other psychiatric conditions.

In addition to retinal imaging, functional ocular measures have emerged as promising biomarkers. Eye-tracking paradigms can objectively quantify abnormalities in attention, visual processing, saccadic control, and social cognition, while pupillometry provides indices of autonomic regulation, cognitive effort, and emotional processing. These measures are inexpensive, reproducible, and increasingly amenable to integration with digital phenotyping and machine-learning approaches. Their potential utility as transdiagnostic biomarkers has generated growing interest across multiple psychiatric disorders, including schizophrenia, autism spectrum disorder, ADHD, mood disorders, and anxiety disorders [10,11].

The literature examining ophthalmic biomarkers in psychiatry has expanded substantially over the past decade but remains fragmented across different psychiatric diagnoses, ophthalmic modalities, and methodological approaches. Studies have investigated retinal structural alterations, retinal vascular changes, electrophysiological measures, eye-

movement abnormalities, and pupillary responses, often within isolated diagnostic groups. Despite increasing recognition of the eye as a potential source of biomarkers for psychiatric disorders, a comprehensive overview of these findings within the framework of precision psychiatry remains lacking [3,7].

The objective of this scoping review is therefore to map the breadth and extent of research concerning ophthalmic biomarkers in psychiatric disorders and to evaluate their potential contribution to precision psychiatry. Specifically, the review aims to: (i) identify the ophthalmic technologies and biomarker modalities investigated in psychiatric populations; (ii) summarize evidence regarding their diagnostic, prognostic, predictive, and disease-monitoring utility; (iii) examine emerging applications of artificial intelligence and machine learning in ophthalmic biomarker research; and (iv) identify current methodological limitations and priorities for future investigation. By synthesizing evidence across structural, vascular, electrophysiological, and oculomotor domains, this review seeks to clarify how ophthalmic biomarkers may contribute to the development of individualized, biomarker-driven psychiatric care [1,11].

2. Materials and Methods

2.1. Aim and Framework

This scoping review sought to map and synthesize the current evidence regarding the use of ophthalmic biomarkers in psychiatric disorders and to evaluate their potential contribution to the emerging field of precision psychiatry. The primary research question is what ophthalmic biomarkers have been investigated in psychiatric disorders, and how may they contribute to personalized approaches to diagnosis, prognosis, treatment selection, and disease monitoring. To address this overarching aim, several secondary questions were explored. Specifically, the review examined which ophthalmic technologies are most frequently employed, including retinal imaging modalities, eye-tracking, pupillometry, and electroretinography; which psychiatric disorders have been most extensively studied; and which ophthalmic biomarkers show the greatest potential as diagnostic tools. In addition, the review assessed the current evidence for biomarkers associated with disease prognosis and progression, as well as those capable of predicting treatment response or therapeutic outcomes. Given the growing emphasis on computational approaches in precision medicine, particular attention will be paid to the incorporation of artificial intelligence and machine-learning methodologies in ophthalmic biomarker research. Finally, the review identified key scientific, methodological, technological, and implementation barriers that currently limit the translation of ophthalmic biomarkers into routine psychiatric practice, thereby highlighting priorities for future research and clinical development. The review followed PRISMA-ScR [12] (Figure 1, File S2), Joanna Briggs Institute methodology [13] while the protocol has been registered with the Open Science Framework at https://osf.io/vtg6m/ (created on 30 August 2026).

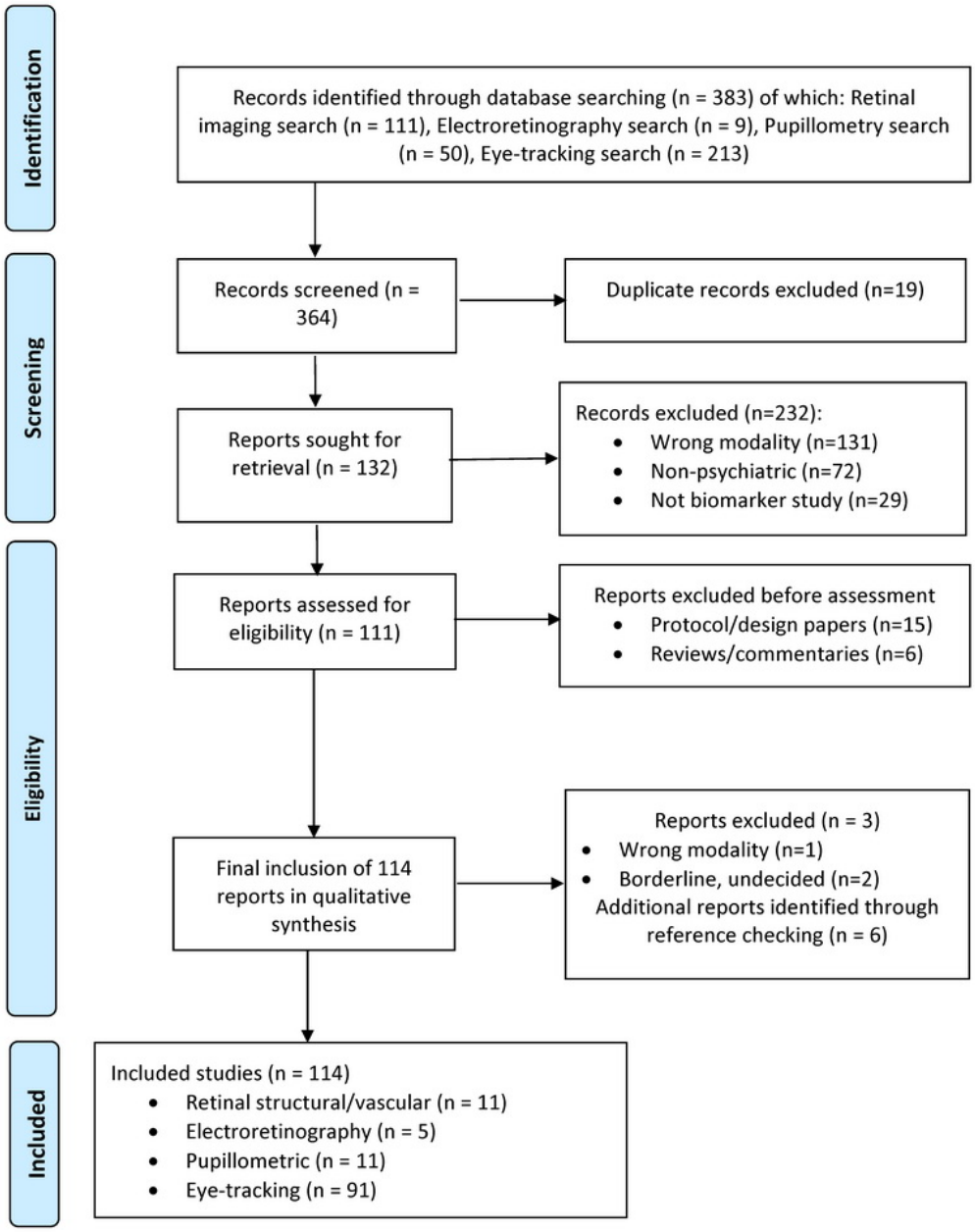

Figure 1. PRISMA flow diagram of the study selection process.

2.2. Eligibility Criteria

The review is guided by the Joanna Briggs Institute (JBI) Population–Concept–Context (PCC) framework [13]. The elements are the following:

2.2.1. Population

This review considered studies involving individuals with psychiatric disorders across the lifespan. Eligible populations included patients diagnosed with schizophrenia spectrum disorders, major depressive disorder, bipolar disorder, anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, personality disorders, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, substance use disorders, and other psychiatric conditions according to established diagnostic criteria. Individuals at clinical, familial, or developmental risk of these conditions (for example, clinical high-risk states, offspring and siblings of affected individuals, and infants at elevated likelihood of autism) and non-clinical samples in which ophthalmic measures were examined in relation

to later psychiatric symptoms or outcomes were also eligible. Studies including healthy control groups were also eligible where ophthalmic biomarkers were compared between clinical and non-clinical populations. Studies of non-psychiatric populations, including studies of psychological outcomes in people with primary eye disease, were excluded. No restrictions were applied regarding age, sex, geographical location, or healthcare setting.

2.2.2. Concept

The concept of this scoping review is the use of ophthalmic biomarkers as potential tools for precision psychiatry. Ophthalmic biomarkers were defined as objectively measurable structural, vascular, physiological, or functional ocular parameters that may reflect neurobiological processes relevant to psychiatric disorders and contribute to diagnosis, risk stratification and early detection, prognosis, patient stratification, treatment prediction, or disease monitoring. Eligible biomarkers included retinal imaging measures obtained through optical coherence tomography (OCT), OCT angiography (OCTA), and fundus imaging, as well as functional assessments derived from eye-tracking and oculomotor recording, pupillometry, and electroretinography (ERG). The review sought to map the extent, nature, and clinical applicability of these biomarkers across different psychiatric disorders, with particular emphasis on their potential role in personalized and biomarker-driven psychiatric care.

2.2.3. Context

The review was conducted within the context of clinical and translational psychiatry, reflecting the growing interest in precision medicine approaches to mental health care. Eligible studies included those involving individuals with psychiatric disorders such as schizophrenia spectrum disorders, major depressive disorder, bipolar disorder, anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, obsessive-compulsive disorder, post-traumatic stress disorder, personality disorders, and substance use disorders. Studies were included regardless of geographical location, healthcare setting, or patient age group, provided they investigated ophthalmic measures (retinal imaging, electroretinography, eye-tracking, or pupillometry) in relation to psychiatric phenotypes or clinically relevant outcomes. Original human studies published from 2000 onwards were eligible. Reviews, commentaries, editorials, and protocol or design papers without results were excluded, as were studies of non-psychiatric populations, studies of other ophthalmic or neurophysiological measures, and studies in which the ophthalmic measure served only as an outcome of treatment rather than as a biomarker. The review aimed to capture evidence from both established and emerging ophthalmic technologies that may facilitate the development of objective biomarkers for individualized psychiatric assessment and treatment.

2.3. Search Strategy

A systematic search of PubMed/MEDLINE was conducted to identify studies evaluating ophthalmic biomarkers in psychiatric disorders. To improve specificity and reduce retrieval of studies in which psychiatric diagnoses were incidental rather than the focus of biomarker research, four separate search strategies were developed according to ophthalmic modality: (1) retinal imaging (optical coherence tomography [OCT], OCT angiography [OCTA], retinal and fundus measures); (2) eye-tracking and oculomotor measures; (3) pupillometry and pupillary response measures; and (4) electroretinography (ERG). Each strategy combined a psychiatric population block with a modality-specific block. The population block was identical across all four strategies and combined controlled vocabulary (MeSH terms) with free-text terms restricted to the title/abstract fields for

psychotic disorders, mood disorders, anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, substance use disorders, eating disorders, personality disorders, and general psychiatric terms. The modality blocks combined MeSH terms and title/abstract terms specific to each technique. In the eye-tracking strategy, records on eye movement desensitization and reprocessing and rapid eye movement sleep were excluded. No biomarker-related concept terms and no publication-type, abstract-availability, or language filters were applied, so that eligibility was determined at screening rather than by search filters. The search was limited to studies published from 1 January 2000 onwards. Search strings are provided in Supplementary File S1. The retinal imaging search yielded 111 records, the eye-tracking search 213 records, the pupillometry search 50 records, and the electroretinography search 9 records, resulting in a total of 383 records. After removal of 19 records retrieved by more than one search, 364 unique records were screened on title and abstract.

2.4. Study Selection and Data Extraction

All records identified through the database searches were imported into a reference management software and screened for duplicate entries, which were removed prior to review. Two reviewers independently screened titles and abstracts against the predefined eligibility criteria. Potentially relevant records subsequently underwent full-text assessment for inclusion. Any disagreements arising during the screening or eligibility assessment stages were resolved through discussion and consensus, with consultation of a third reviewer when necessary. The study selection process was documented and reported using a PRISMA flow diagram (Figure 1).

2.5. Assessment of Study Characteristics

In accordance with the objectives of a scoping review and the recommendations of the Joanna Briggs Institute methodology for scoping reviews, no formal risk-of-bias or certainty-of-evidence assessment was conducted. Instead, methodological and study characteristics relevant to the interpretation of the evidence were extracted and summarized. These included study design, sample size, participant characteristics, psychiatric diagnosis, ophthalmic modality evaluated, comparator groups, outcome measures, and precision psychiatry application. Additional characteristics, such as longitudinal follow-up, adjustment for potential confounding factors, and the use of validation cohorts, were recorded when reported. These data were used to describe the breadth, and methodological diversity of the evidence base, since the aim of this review was to map the extent, nature, and characteristics of the available literature rather than to establish the effectiveness or diagnostic accuracy of specific biomarkers.

2.6. Data Synthesis

Extracted data were synthesized descriptively in accordance with the objectives of the scoping review. Studies were grouped according to ophthalmic biomarker modality, including retinal imaging (OCT, OCTA, and fundus imaging), eye-tracking, pupillometry, and electroretinography. Within each modality, findings were further organized by psychiatric disorder and by potential clinical application, including diagnostic, prognostic, predictive, and disease-monitoring utility. Results were presented in summary tables and accompanied by a narrative synthesis highlighting major findings, methodological trends, evidence gaps, and opportunities for future research. Given the heterogeneity of study designs, populations, outcome measures, and biomarker definitions, no quantitative synthesis or meta-analysis was undertaken.

3. Results

3.1. Study Characteristics

A total of 114 unique studies were included. Eye-tracking accounted for the largest proportion ($n = 91$), followed by retinal structural and vascular biomarkers ($n = 11$), pupillometry ($n = 11$), and electroretinography ($n = 5$). Four studies combined two modalities and are counted under both: one combined retinal imaging with pupillometry, and three combined eye-tracking with pupillometry. Most studies employed cross-sectional case-control designs, while only a minority used longitudinal or interventional designs. The literature was concentrated in autism spectrum disorder and schizophrenia spectrum disorders **, with smaller numbers of studies in attention-deficit/hyperactivity disorder, anxiety, mood, personality, and substance use disorders.

3.2. Retinal, Structural and Vascular Biomarkers Search

Eleven studies investigated retinal structural and vascular biomarkers across psychotic disorders, schizophrenia spectrum disorders, bipolar disorder, major depressive disorder, borderline personality disorder, obsessive-compulsive disorder, autism spectrum disorder (ASD), substance use disorder and attention-deficit/hyperactivity disorder (ADHD) (Table 1). The studies employed optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA), and retinal videomicroscopy to assess retinal microstructure, photoreceptor and choroidal parameters, vessel density, choroidal vascularity and retinal thickness parameters and one ADHD study paired OCT with pupillometry. All studies used cross-sectional or prospective case-control or comparative designs. Where group sizes were reported they ranged from 25 to 74 participants, and no study had a multicenter or population-based design. Healthy controls were included in all investigations, and several studies matched groups for age and sex.

Table 1. Characteristics of Included Studies Investigating Retinal Structural and Vascular Biomarkers in Psychiatric Disorders.

Author (Year)	Psychiatric Population	Sample Characteristics	Retinal Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Bannai et al. (2024) [14]	Psychotic disorders	Patients with psychotic disorders and healthy controls	Structural retinal biomarkers	OCT	Cross-sectional case-control	Retinal layer abnormalities were associated with psychotic disorders and correlated with clinical and neuroimaging parameters.	Diagnostic biomarker; disease severity marker
Boudriot et al. (2024) [15]	Schizophrenia spectrum disorders (SSD)	SSD patients and healthy controls	Structural retinal biomarkers	OCT and OCTA	Cross-sectional case-control	Altered retinal microstructure and electro-physiological abnormalities were associated with disease severity and polygenic risk burden.	Diagnostic biomarker; patient stratification

Table 1. *Cont.*

Author (Year)	Psychiatric Population	Sample Characteristics	Retinal Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Tarakcioglu et al. (2020) [16]	Attention-Deficit/Hyper-activity Disorder (ADHD)	Children with ADHD compared with age-matched healthy controls	Retinal vascular biomarkers	OCTA	Cross-sectional case-control	Most OCT angiography parameters, including foveal avascular zone area and perimeter, did not differ significantly. However, significant differences were observed in parafoveal retinal thickness, which was positively associated with treatment duration, suggesting a possible influence of methylphenidate on retinal tissues.	Diagnostic biomarker; developmental biomarker
Icoz et al. (2026) [17]	Major depressive disorder (MDD), newly diagnosed	50 patients with newly diagnosed MDD and 50 age- and sex-matched healthy controls	Structural and vascular (choroidal) retinal biomarkers	OCT (choroidal vascularity index)	Prospective comparative case-control	Choroidal thickness, optic disc measures and peripapillary RNFL did not differ between groups. Luminal choroidal area and choroidal vascularity index were lower in MDD at both subfoveal and peripapillary sites.	Diagnostic biomarker
Xiao et al. (2025) [18]	MDD and borderline personality disorder (BPD)	35 MDD patients, 36 BPD patients and 36 healthy controls	Structural and vascular retinal biomarkers	OCT and OCTA	Case-control (three-group)	Macular vessel density, RNFL and central retinal thickness were reduced in both MDD and BPD versus controls. Reductions in the foveal area, RNFL and central retinal thickness were greater in BPD than MDD and tracked BPD symptom severity. RNFL and central retinal thickness discriminated BPD (AUROC 0.625 and 0.695).	Differential diagnosis (MDD vs. BPD); diagnostic biomarker

Table 1. *Cont.*

Author (Year)	Psychiatric Population	Sample Characteristics	Retinal Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Sivri et al. (2025) [19]	Obsessive-compulsive disorder (OCD), paediatric	33 children and adolescents with OCD and 45 healthy controls	Structural retinal biomarkers	OCT	Cross-sectional case-control	Central macular thickness was significantly lower in OCD. Ganglion cell complex thickness was lower but not significantly different. No correlation between OCT measures and symptom scales (MOCI, SCARED).	Exploratory diagnostic and developmental biomarker
Li et al. (2024) [20]	Autism spectrum disorder (ASD)	58 children with ASD and 53 typically developing (TD) children, aged 6–13	Structural and vascular retinal biomarkers	OCT and OCTA	Comparative case-control	Ellipsoid zone (cone photoreceptor) thickness was increased and large-calibre arteriovenous measures of the inner retina were reduced in ASD. Changes were more marked in the left eye than the right.	Early diagnostic biomarker
Kulu et al. (2021) [21]	Multiple Substance Use Disorder	30 patients with MSUD and 30 healthy controls	Structural retinal biomarkers	OCT	Cross-sectional case-control	Macular thinning and retinal nerve fibre layer alterations were detected in patients with substance use disorder.	Diagnostic biomarker; biological phenotyping
Orduna-Hospital et al. (2021) [22]	Bipolar disorder (BD)	25 BD patients (25 eyes) and 74 healthy controls (74 eyes)	Structural retinal biomarkers	OCT (Spectralis Posterior Pole 64-cell grid)	Cross-sectional case-control	RNFL (parafoveal cells) and ganglion cell layer (perifoveal cells) thickness differed from controls. Thinning correlated inversely with illness duration. Selected RNFL and GCL cells predicted BD status in logistic regression.	Diagnostic biomarker; disease-duration marker
Aslan et al. (2020) [23]	Attention-deficit/hyper-activity disorder (ADHD), newly diagnosed	32 children with ADHD and 43 age-matched healthy controls	Structural retinal biomarkers with pupillary function	OCT and pupillometry	Cross-sectional case-control	Mean pupillary velocity was significantly higher in both eyes in ADHD. Right-eye pupillary velocity correlated positively with RNFL thickness ($r = 0.339$).	Diagnostic biomarker; combined retinal and pupillary marker

Table 1. *Cont.*

Author (Year)	Psychiatric Population	Sample Characteristics	Retinal Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Lee et al. (2013) [24]	Schizophrenia	30 patients and 30 age-matched controls	Structural retinal biomarkers	SD-OCT	Cross-sectional case-control	Significant thinning of RNFL, macular thickness, and macular volume was observed, correlating with duration of illness.	Diagnostic biomarker; disease progression biomarker

ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; AUROC = area under the receiver operating characteristic curve; BD = bipolar disorder; BPD = borderline personality disorder; GCL = ganglion cell layer; MDD = major depressive disorder; MSUD = multiple substance use disorder; OCD = obsessive-compulsive disorder; OCT(A) = optical coherence tomography (angiography); RNFL = retinal nerve fibre layer; SD-OCT = spectral-domain optical coherence tomography; SSD = schizophrenia spectrum disorder; TD = typically developing.

The studies illustrate three retinal biomarker domains. Seven studies investigated retinal structural alterations using OCT or OCTA in psychotic disorders [14], schizophrenia spectrum disorders [15,24], bipolar disorder [22], obsessive-compulsive disorder [19], substance use disorder [21], and ADHD [23]. They reported retinal layer abnormalities associated with disease burden, illness duration, and neurobiological risk, and in bipolar disorder selected RNFL and ganglion cell layer measures predicted diagnostic status. One study examined retinal vascular biomarkers in children with ADHD using OCTA [16]; most vascular parameters, including foveal avascular zone area and perimeter, were similar between groups, but significant differences in parafoveal retinal thickness were observed and were associated with methylphenidate treatment duration. Three studies assessed combined structural and vascular measures in major depressive disorder [17,18], borderline personality disorder [18], and ASD [20]. Choroidal vascularity index was lower in major depressive disorder, macular vessel density and RNFL were reduced in both major depressive disorder and borderline personality disorder (more so in the latter, tracking symptom severity), and ASD showed increased ellipsoid zone thickness with reduced inner-retinal arteriovenous measures.

3.3. Electroretinographic Biomarkers Search

Table 2 presents the included studies investigating electroretinographic biomarkers in psychiatric disorders. Four studies investigated the potential role of electroretinography (ERG) as a biomarker in psychiatric disorders, encompassing established psychiatric illness, mood-state–dependent psychopathology, and individuals at elevated risk for future mental disorders. Sample sizes ranged from modest case-control cohorts to larger high-risk observational studies. Full-field electroretinography was the most commonly employed modality, assessing rod and cone function, retinal response amplitudes, and response latencies. Included study designs comprised cross-sectional case-control studies, longitudinal treatment-monitoring investigations, and cohort studies evaluating vulnerability to psychiatric illness. Comparator groups included healthy controls, diagnostic comparison groups, and unaffected high-risk individuals. Collectively, these studies suggest that retinal electrophysiological abnormalities may reflect neurobiological processes relevant to diagnosis, disease monitoring, and risk stratification.

In psychotic disorders, ERG abnormalities were reported in comparison with patients with bipolar disorder, supporting the view that retinal electrophysiological dysfunction may reflect alterations in central nervous system functioning and neurotransmission and indicating that retinal electrophysiological measures may have potential utility for differ-

entiating psychiatric phenotypes [25]. Evidence for the prognostic value of ERG emerged from a cohort of offspring at familial high risk for schizophrenia or bipolar disorder [26]. Distinct retinal response profiles were identified, and individuals exhibiting abnormal ERG patterns were significantly more likely to demonstrate cognitive impairment, suggesting that retinal electrophysiological alterations may precede the onset of clinical illness and contribute to risk stratification efforts. These findings suggest that ERG measures may have utility as objective pathophysiological markers in psychotic disorders.

In seasonal affective disorder, patients demonstrated different retinal response modulation profiles following exposure to three different light conditions for 1 h (10,000, 100 and 5 lux), suggesting retinal dysfunction in both the depressed and euthymic states [27]. A separate study found a state-dependent retinal electrophysiological alteration following either treatment or seasonal change [28]. These observations indicate that ERG parameters may function as state-dependent biomarkers capable of monitoring illness activity and treatment response.

In autism spectrum disorders, researchers demonstrated that GABA-dependent retinal response to light is altered compared to typically developed (TD) participants [29]. While in baseline condition a-wave amplitudes in response to single white flashes were more prominent in ASD, administration of a GABA agonist was associated with a decrease in the a-wave amplitude in ASD, but an increase in TD.

Table 2. Characteristics of Included Studies Investigating Electroretinographic Biomarkers in Psychiatric Disorders.

Author (Year)	Psychiatric Population	Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Lavoie et al. (2009) [28]	Seasonal affective disorder (SAD)	Retinal electrophysiological biomarker	Photopic and scotopic electroretinography (ERG)	Longitudinal case-control study with treatment follow-up	Patients with SAD ($n = 22$) showed lower cone ERG maximal amplitude and reduced rod sensitivity compared with healthy controls ($n = 16$) during fall/winter. Following 4 weeks of light therapy, cone and rod ERG function normalized; between-group differences were also absent during summer assessment, supporting a state-dependent retinal electrophysiological alteration.	State/monitoring biomarker; treatment-response biomarker
Hébert et al. (2020) [25]	Schizophrenia/Bipolar disorder	Electrophysiological retinal biomarkers	Full-field ERG	Cross-sectional case-control	Patients with schizophrenia exhibited abnormalities in retinal electrophysiological responses, suggesting retinal dysfunction and altered retinal neurotransmission associated with the disorder.	Diagnostic biomarker; pathophysiological marker

Table 2. *Cont.*

Author (Year)	Psychiatric Population	Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Huang et al. (2024) [29]	Autism Spectrum Disorders (ASD)	Retinal electrophysiological biomarker	Photopic ERG	Cross-sectional case-control	At baseline, the a-wave amplitudes in response to single white flashes were more prominent in ASD, relative to typically developed (TD) participants while administration of a GABA agonist was associated with a decrease in the a-wave amplitude in ASD, but an increase in TD	Diagnostic biomarker; pathophysiological marker
Gagné et al. (2011) [27]	Seasonal Affective Disorder (SAD)	Electrophysiological retinal biomarkers	Photopic and scotopic ERG	Longitudinal case-control	Patients with SAD demonstrated different retinal response modulation profiles following exposure to three different light conditions for 1 h (10,000, 100 and 5 lux), suggesting retinal dysfunction in both the depressed and euthymic states.	Monitoring biomarker; treatment-response biomarker; state marker
Peredo et al. (2020) [26]	Offspring at familial high risk for schizophrenia or bipolar disorder	Electrophysiological retinal biomarkers	Full-field ERG	Observational cohort with cluster analysis	Two distinct retinal response profiles were identified. Individuals exhibiting abnormal ERG profiles were more likely to belong to the subgroup with greater cognitive impairment, suggesting ERG as a potential biomarker of susceptibility to major psychiatric disorders.	Risk stratification biomarker; prognostic biomarker; susceptibility biomarker

ASD = Autism Spectrum Disorder; ERG = electroretinography; GABA = gamma-aminobutyric acid; SAD = seasonal affective disorder; TD = typically developing.

3.4. Pupillometric Biomarkers Search

Table 3 presents the included studies investigating pupillometric biomarkers in psychiatric disorders. One study investigated pupillary light reflex parameters before and after treatment in individuals with major depressive disorder [30], whereas the second employed task-evoked pupillary responses to threat-related stimuli within a randomized controlled trial of attention-bias modification for transdiagnostic anxiety disorders [31]. Both studies used pupillometry as an objective measure of autonomic, cognitive, and emotional processing and focused primarily on monitoring symptom-related changes and treatment effects rather than diagnostic classification. Collectively, the evidence suggests that pupillary dynamics may provide objective indices of autonomic, cognitive, and emotional processes relevant to psychiatric symptomatology and its modification through treatment.

Table 3. Characteristics of Included Studies Investigating Pupillometric Biomarkers in Psychiatric Disorders.

Author (Year)	Psychiatric Population	Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Bär et al. (2004) [30]	Major Depressive Disorder	Pupillometric biomarkers	Pupillary light reflex (PLR) assessment	Case-control study with treatment follow-up	Major depressive disorder was associated with alterations in pupillary light reflex parameters, indicating autonomic nervous system dysregulation. Changes in pupillary responses following treatment suggested that pupillometric measures may be sensitive to clinical state and therapeutic effects.	Monitoring biomarker; treatment-response biomarker; state marker
Woody et al. (2020) [31]	Transdiagnostic anxiety disorders	Pupillometric biomarkers	Task-evoked pupillary responses during attention-bias modification	Randomized controlled trial	Pupillary responses to threat-related stimuli were assessed before and after attention bias modification. Changes in pupillary dynamics reflected alterations in attentional and emotional processing associated with treatment.	Treatment-response biomarker; monitoring biomarker; cognitive-affective biomarker
Bast et al. (2025) [32]	Autism spectrum disorder	Pupillometric and arousal-regulation biomarkers	Eye-tracking with pupil-size measurement	Randomized controlled trial	Baseline pupil size was associated with reactive joint attention and mediated group differences. Early intervention increased joint attention and improved later social responsiveness.	Monitoring biomarker; treatment-response biomarker; mechanistic biomarker
Del Valle Rubido et al. (2020) [33]	High-functioning autism spectrum disorder and Asperger syndrome	Social pupillometric biomarkers	Pupillometry during social cognition tasks	Cross-sectional case-control	Pupillometry differentiated ASD from healthy controls and was proposed as a candidate biomarker for stratification and outcome prediction in ASD trials.	Diagnostic biomarker; patient stratification biomarker
Cohen et al. (2019) [34]	Youth at risk for depression onset	Pupillary reactivity biomarkers	Pupil dilation during emotional face processing	Longitudinal cohort study	Elevated pupil dilation significantly predicted future onset of major depressive episodes and improved prediction beyond conventional risk factors.	Prognostic biomarker; risk stratification biomarker
Jochum et al. (2016) [35]	Alcohol withdrawal syndrome	PLR biomarkers	Infrared pupillometry	Case-control with repeated measurements	Acute alcohol withdrawal was associated with abnormal pupillary autonomic regulation that improved after treatment.	Monitoring biomarker; state biomarker

Table 3. *Cont.*

Author (Year)	Psychiatric Population	Biomarker Type	Ophthalmic Modality	Study Design	Main Findings	Precision Psychiatry Application
Daluwatte et al. (2013) [36]	Autism spectrum disorder	PLR biomarkers	Infrared pupillometry	Case-control	Children with ASD demonstrated atypical PLR responses and autonomic abnormalities compared with controls.	Diagnostic biomarker; physiological biomarker
Silk et al. (2007) [37]	Child and adolescent major depressive disorder	Emotional pupillary reactivity biomarkers	Pupillometry during emotional word processing	Case-control	Depressed youth exhibited altered pupil dilation to emotional stimuli that correlated with symptom severity and ecological measures of affect.	Diagnostic biomarker; severity biomarker
Anderson et al. (2006) [38]	Autism spectrum disorder (ASD)	Pupillary response biomarkers; social-attention biomarkers	Pupillometry and eye-tracking	Case-control study	Children with ASD exhibited pupillary constriction to children's faces, whereas control groups demonstrated pupillary dilation. Pupillary and visual-scanning measures differentiated ASD from developmental-delay and typically developing controls and correctly classified a high proportion of participants.	Diagnostic biomarker; patient stratification biomarker; early-indicator biomarker
Kojima et al. (2004) [39]	Panic disorder	PLR biomarkers	Infrared pupillometry	Comparative case-control study	Patients with panic disorder exhibited altered PLR regulation during stress-inducing audiovisual stimulation.	Diagnostic biomarker; autonomic biomarker
Aslan et al. (2020) [23]	Attention-Deficit/Hyperactivity Disorder (ADHD)	Pupillometric biomarkers; autonomic biomarkers	Pupillometry with OCT correlation analysis	Cross-sectional case-control study	Children with ADHD ($n = 32$) demonstrated significantly higher pupillary velocities than healthy controls ($n = 43$). Pupillary velocity was positively correlated with retinal nerve fibre layer thickness, suggesting an association between autonomic pupillary function and retinal structural characteristics in ADHD.	Diagnostic biomarker; physiological biomarker; neurodevelopmental biomarker

ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; MDD = major depressive disorder; OCT = optical coherence tomography; PLR = pupillary light reflex; RNFL = retinal nerve fibre layer.

In major depressive disorder, alterations in pupillary light reflex parameters were reported, indicating disturbances in autonomic nervous system regulation. Furthermore, pupillary measures changed following treatment, suggesting that pupillometry may be sensitive to fluctuations in clinical state and therefore useful for monitoring treatment response over time. This positions pupillary light reflex measures as potential state-dependent biomarkers rather than stable diagnostic markers [30].

In a randomized controlled trial involving individuals with transdiagnostic anxiety disorders, pupillary responses to threat-related stimuli were assessed before and after attention bias modification. Pupillary dynamics changed across the intervention period, reflecting alterations in attentional and emotional processing mechanisms targeted by

treatment. These findings support the utility of pupillometry as an objective measure of cognitive-affective processing and therapeutic response [31].

3.5. Eye-Tracking Biomarkers Search

Table 4 presents the included studies investigating eye-tracking biomarkers by psychiatric disorders. Supplementary Table S2 provides more details per individual reference. Eye-tracking constituted the largest and most diverse biomarker category identified in this review, encompassing 91 studies across autism spectrum disorder (ASD), schizophrenia spectrum disorders, psychosis-risk states, attention-deficit/hyperactivity disorder (ADHD), and anxiety disorders. The evidence spans the full precision psychiatry continuum, including diagnostic classification, risk stratification, prognosis, treatment monitoring, and prediction of clinical outcomes. Most studies employed cross-sectional case-control designs, although several longitudinal, interventional, and randomized studies were identified. Sample sizes varied substantially, ranging from small exploratory cohorts to multicenter biomarker validation initiatives. Eye-tracking measures included gaze allocation, biological motion preference, face-processing tasks, smooth pursuit, antisaccades, predictive saccades, oculomotor inhibition and countermanding, visual scanpaths, exploratory eye movements, and gaze-following paradigms. Healthy controls were commonly included as comparator groups, while several studies examined familial-risk or clinical high-risk populations. (Supplementary Table S2).

Table 4. Summary of Eye-Tracking Findings by Psychiatric Disorder.

Disorder	Included Studies	Principal Eye-Tracking Findings	Potential Precision Psychiatry Applications
Autism Spectrum Disorder (ASD)	[32,33,38,40–72]	Altered gaze patterns, impaired gaze following, reduced preference for biological motion, abnormalities in face processing, social attention deficits, and impaired oculomotor control. Several studies demonstrated the feasibility of deriving objective autism biomarkers from eye-tracking metrics. Further studies reported reduced fixation on the eyes and other social stimuli, atypical pupillary responses, atypical volitional oculomotor control, and an atypical developmental trajectory of fixation on the eye region. Infants and siblings at elevated likelihood of ASD showed atypical early social attention and visual orienting, and unaffected siblings showed gaze measures consistent with a broader autism phenotype. Gaze measures helped to distinguish ASD from conduct disorder, developmental coordination disorder, Rett syndrome, fragile X syndrome and Williams syndrome, and index-based and machine-learning models achieved classification of ASD.	Diagnostic classification; early-risk detection; patient stratification; prognosis of social outcomes; treatment monitoring; treatment-response assessment; biomarker validation; screening (including low-cost, tablet-based tools); differential diagnosis; developmental and symptom-severity tracking; candidate efficacy endpoints for clinical trials; endophenotypes
Schizophrenia Spectrum Disorders	[54,73–110]	Abnormal exploratory eye movements, impaired smooth pursuit, antisaccade deficits, and broader oculomotor dysfunction. Findings were associated with clinical course, familial risk, and genetic loading. Smooth-pursuit and antisaccade measures behaved as trait-like, familial markers in patients and relatives, and were related to genotype, medication, illness stage, working memory and neural correlates. Several studies found these measures were not specific to schizophrenia across psychosis, bipolar and schizoaffective disorders, and one study reported negative findings for pursuit as a vulnerability marker. Multivariate, biotyping and machine-learning approaches improved classification and patient stratification.	Diagnostic biomarkers; endophenotypes; prognostic biomarkers; risk stratification; differential diagnosis; pharmacodynamic and medication-effect biomarkers; genetic-risk markers; patient biotyping

Table 4. *Cont.*

Disorder	Included Studies	Principal Eye-Tracking Findings	Potential Precision Psychiatry Applications
Clinical High-Risk for Psychosis	[78,111–113]	Eye-movement abnormalities predicted subsequent transition to psychosis and reflected longitudinal changes preceding illness onset. However, antisaccade measures did not predict conversion within two years in one large cohort, although antisaccade deficits in ultra-high-risk individuals were proposed as possible predictive markers in another.	Prognostic biomarkers; risk stratification; prediction of conversion to psychosis; risk stratification with limited predictive value for transition in some cohorts
Attention-Deficit/Hyperactivity Disorder (ADHD)	[31,110,114–120]	Impaired pro- and antisaccadic performance, altered inhibitory control, and broader oculomotor abnormalities relative to healthy controls. Eye-tracking differentiated ADHD from ASD and ASD + ADHD groups. Adults, including partially remitted cases, showed longer antisaccade latencies, more anticipatory and direction errors, and impaired countermanding. Deficits were greater in the combined than the inattentive subtype and improved with methylphenidate, and adolescents showed impaired gaze pursuit. A multimodal model including oculomotor measures reached AUC 0.892. Antisaccade errors were shared with bipolar disorder, and oculomotor anticipation was examined in youth-onset psychosis and ADHD.	Diagnostic biomarkers; objective assessment of attentional and inhibitory dysfunction; patient stratification; subtype stratification; treatment-response assessment; differential diagnosis from bipolar disorder; multimodal classification
Anxiety Disorders	[121,122]	Distinct gaze allocation patterns toward emotionally salient stimuli and altered attentional bias to threat-related information. In socially anxious adolescents, attention bias switched between vigilance and avoidance within individuals, and clinician-rated severity explained bias to adult but not adolescent faces.	Monitoring biomarkers; treatment-response biomarkers; patient stratification; stimulus selection for biomarker research
Major Depression and Trauma-Related Disorders	[123,124]	Women with remitted recurrent major depression showed lower sustained attention to happy faces than comparison groups. In soldiers assessed before deployment, shorter fixation on fearful faces predicted PTSD symptoms and longer fixation on sad faces predicted depressive symptoms.	Risk markers for recurrence; predictive biomarkers of vulnerability; patient stratification
Borderline Personality Disorder	[125]	Patients showed more and faster initial fixation changes to the eyes of angry faces, with greater amygdala activation. Both normalised after intranasal oxytocin.	Pharmacodynamic biomarkers; treatment-response biomarkers
Substance Use Disorder (cocaine)	[126]	Treatment responders showed poorer antisaccade accuracy at faster response times than non-responders, on cocaine-cue trials only.	Predictive biomarkers of treatment response

The strongest body of evidence was observed in ASD. Multiple studies demonstrated that abnormalities in gaze patterns, biological motion perception, face processing, gaze following, and oculomotor control can distinguish individuals with ASD from typically developing controls. Several investigations further explored eye-tracking as a biomarker-development tool, including the creation of objective autism risk indices and the validation of candidate biomarkers for use in clinical trials. Longitudinal studies also showed that eye-tracking measures may predict subsequent social outcomes and capture treatment-related changes, supporting both prognostic and monitoring applications. Gaze measures also helped to distinguish ASD from conduct disorder, developmental coordination disorder, and genetic syndromes such as Rett, fragile X, and Williams syndrome, and infant-sibling studies identified atypical early social attention and visual orienting before diagnosis.

In schizophrenia spectrum disorders, eye-movement abnormalities were consistently reported across exploratory eye movements, smooth pursuit, and antisaccade paradigms. These deficits were associated with clinical course, familial risk, and schizophrenia-related phenotypes, suggesting that oculomotor dysfunction may represent both a diagnostic biomarker and a potential endophenotype. Smooth-pursuit and antisaccade measures behaved as trait-like, familial markers in patients and relatives, and were related to genotype, medication effects, and illness stage. Several studies found they were not specific to schizophrenia, with similar abnormalities in bipolar and schizoaffective disorders, and

machine-learning and biotyping approaches improved classification and stratification. Notably, one longitudinal study demonstrated that eye-movement characteristics predicted transition to psychosis among individuals at clinical high risk, highlighting the potential role of eye-tracking in early identification and risk stratification.

Evidence in ADHD indicated impaired pro- and antisaccadic performance and broader oculomotor abnormalities relative to healthy controls, supporting the use of eye-tracking measures as objective indicators of attentional and inhibitory dysfunction. Adults, including partially remitted cases, also showed antisaccade abnormalities and impaired countermanding. Deficits were greater in the combined than the inattentive subtype and improved with methylphenidate, and antisaccade errors were shared with bipolar disorder. Similarly, studies involving anxiety disorders demonstrated distinct gaze patterns toward emotional stimuli, suggesting that eye-tracking may provide useful markers of attentional bias and symptom-related cognitive processing.

3.6. Studies Appearing in More than One Table, and Cross-Modality Retrieval

The four modality-specific searches were not mutually exclusive, and studies were assigned to a table according to the ophthalmic measures they analyzed, not the search that retrieved them. Nineteen records were retrieved by more than one search and were counted once after deduplication.

Four included studies appear in two tables because they analyzed two modalities. Aslan et al. [23] which combined optical coherence tomography with pupillometry in children with ADHD, appears in Table 1 (retinal imaging) and Table 3 (pupillometry). It was retrieved by both the retinal imaging and the pupillometry searches. Bast et al. [32], Del Valle Rubido et al. [33] and Anderson et al. [38] combined eye-tracking with pupillometry in autism spectrum disorder and appear in Table 3 (pupillometry) and Table 4 (eye-tracking). All three were retrieved by both the pupillometry and eye-tracking searches. Each of these studies is counted once in the total of 114 included studies but is tallied under both of its modalities.

Several studies were retrieved by the search for one modality but belong to another. Four electroretinography studies [26–29] were identified by the retinal imaging search and are reported in Table 2. The first three were also retrieved by the ERG search. Huang et al. [29] was retrieved only by the retinal imaging search. Two smooth-pursuit eye-movement studies in schizophrenia [74,93] were identified by the retinal imaging search and are reported in Table 4. Müller et al. [60] and the Autism Biomarkers Consortium study [66] were retrieved by both the pupillometry and eye-tracking searches and are reported in Table 4 only, because their principal measures were gaze-based. Six included studies were not retrieved by any search and were identified through reference checking.

4. Discussion

4.1. Retinal Structural and Vascular Biomarkers

Although the evidence base for retinal structural and vascular biomarkers was comparatively small, the included studies illustrate the broad biological potential of retinal assessment within precision psychiatry. Structural retinal measures derived from OCT and OCTA identified abnormalities in psychotic disorders and schizophrenia spectrum disorders, supporting the hypothesis that retinal architecture may reflect neurodevelopmental or neurodegenerative processes occurring elsewhere in the central nervous system. In parallel, retinal vascular studies demonstrated alterations in microvascular structure and perfusion, particularly in ADHD and population-based cohorts, suggesting that retinal vascular health may provide insight into systemic and neurovascular mechanisms relevant to psychiatric illness.

A notable strength of retinal imaging is its ability to provide objective, quantitative, and non-invasive measures of neuronal and vascular integrity. Unlike eye-tracking paradigms, which predominantly assess cognitive and behavioral processes, retinal imaging offers direct biological correlates that may be linked to underlying pathophysiological mechanisms. This distinction is particularly important in precision psychiatry, where biologically informed stratification of patients remains a key objective. The incorporation of retinal vascular biomarkers further expands this framework by acknowledging the growing evidence implicating microvascular dysfunction, inflammation, and cardiometabolic factors in psychiatric disorders.

Nevertheless, the retinal imaging literature remains at an early stage of development. Most studies were cross-sectional and focused on group differences rather than longitudinal prediction. Replication across independent cohorts remains limited, and there is currently insufficient evidence to determine whether retinal structural or vascular measures can reliably predict clinical outcomes, treatment response, or disease progression at the individual patient level. Future studies should prioritize longitudinal assessment, multimodal biomarker integration, and the establishment of normative reference datasets before clinical implementation can be considered.

4.2. Electroretinographic Biomarkers

Electroretinography (ERG) represents a distinct ophthalmic modality that provides objective assessment of retinal neurophysiology and neurotransmission. The included studies suggest that ERG abnormalities may be detectable across different stages of psychiatric illness, including established schizophrenia, affective disorders, and populations at elevated familial risk.

Unlike retinal imaging, which primarily evaluates structure and vascular integrity, ERG captures dynamic retinal function. Abnormal retinal electrophysiological responses observed in schizophrenia support the hypothesis that retinal dysfunction may reflect broader disturbances in neural signaling and neurotransmitter systems. Similarly, findings from seasonal affective disorder demonstrated that ERG parameters change alongside clinical state and normalize following treatment, suggesting potential utility as state-dependent biomarkers. Most notably, altered ERG profiles in offspring at familial risk for schizophrenia or bipolar disorder were associated with greater cognitive impairment, raising the possibility that retinal electrophysiological abnormalities may precede overt psychopathology and contribute to risk stratification.

From a precision psychiatry perspective, ERG is notable because it spans multiple biomarker domains, including diagnosis, prognosis, disease monitoring, and susceptibility assessment. However, the current evidence remains limited to a small number of studies with relatively modest sample sizes. The extent to which ERG abnormalities are disorder-specific or represent transdiagnostic markers of neural dysfunction remains unclear. Large prospective studies are therefore required to establish reproducibility, temporal stability, and clinical utility before ERG-based biomarkers can be incorporated into routine psychiatric assessment.

4.3. Pupillometric Biomarkers

The pupillometry literature identified in this review was limited but conceptually important. The included studies demonstrated that pupillary responses capture aspects of autonomic regulation, emotional processing, and cognitive-affective functioning that are highly relevant to psychiatric disorders. Altered pupillary light reflex responses in major depressive disorder suggest the presence of autonomic nervous system dysregulation, while

changes in task-evoked pupil responses during treatment for anxiety disorders indicate sensitivity to cognitive and emotional processes targeted by intervention.

This limited available evidence suggests that pupillometric measures may have potential utility for monitoring clinical state and treatment-related changes. Compared with retinal imaging and ERG, pupillometry assesses dynamic physiological processes that may change over relatively short periods in response to symptom fluctuations or treatment effects. Consequently, pupillary measures may prove useful in the future for tracking illness state, assessing therapeutic response, and evaluating cognitive-affective mechanisms underlying psychiatric symptoms. A large number of the studies that were assessed for inclusion and rejected were in fact studies using pupillometry as a tracker during therapy rather than diagnosis.

Despite these potential advantages, the current evidence base is extremely limited, and no studies identified robust diagnostic or prognostic applications. Furthermore, pupillary responses are influenced by numerous factors, including age, medications, lighting conditions, fatigue, and autonomic status, which may complicate interpretation if not carefully controlled. Future studies should investigate pupillometry in larger clinical populations and determine whether integrating pupillary measures with other ophthalmic and neurobiological biomarkers can enhance predictive performance. Such work may help define a role for pupillometry within multimodal precision psychiatry frameworks, particularly for treatment monitoring and measurement-based care.

4.4. Eye-Tracking Biomarkers

Eye-tracking constituted the largest and most diverse biomarker category identified in this review, encompassing 18 studies across autism spectrum disorder (ASD), schizophrenia spectrum disorders, psychosis-risk states, attention-deficit/hyperactivity disorder (ADHD), and anxiety disorders. The evidence spans the full precision psychiatry continuum, including diagnostic classification, risk stratification, prognosis, treatment monitoring, and prediction of clinical outcomes. Unlike other ophthalmic measures, the eye-tracking literature contributes evidence across virtually all precision psychiatry domains, including diagnostic classification, early-risk detection, patient stratification, prognosis, prediction of transition to psychosis, treatment monitoring, and treatment-response assessment. Nevertheless, substantial methodological heterogeneity exists across paradigms, outcome measures, and study populations.

Table 4 presents a summary of findings by psychiatric disorder. The strongest body of evidence was observed in ASD. Multiple studies demonstrated that abnormalities in gaze patterns, biological motion perception, face processing, gaze following, and oculomotor control can distinguish individuals with ASD from typically developing controls. Several investigations further explored eye-tracking as a biomarker-development tool, including the creation of objective autism risk indices and the validation of candidate biomarkers for use in clinical trials. Longitudinal studies also showed that eye-tracking measures may predict subsequent social outcomes and capture treatment-related changes, supporting both prognostic and monitoring applications. Eye-tracking measures have been used not only to differentiate affected individuals from healthy controls but also to identify infants and young children at elevated risk, predict later social functioning, evaluate response to intervention, and support large-scale biomarker validation initiatives. Gaze measures also helped to distinguish ASD from conduct disorder, developmental coordination disorder, and genetic syndromes such as Rett, fragile X, and Williams syndrome, and unaffected siblings showed gaze patterns consistent with a broader autism phenotype. Combined eye-tracking and pupillometry studies reported atypical pupillary responses, and index-based and machine-learning models achieved classification of ASD, including in a six-center study

of 499 young children [55]. This progression from biomarker discovery to clinical trial implementation suggests that eye-tracking currently has its greatest maturity within ASD research. Consequently, ASD may provide a model for the development and validation of ophthalmic biomarkers in other psychiatric disorders.

In schizophrenia spectrum disorders, eye-movement abnormalities were consistently reported across exploratory eye movements, smooth pursuit, and antisaccade paradigms. These deficits were associated with clinical course, familial risk, and schizophrenia-related phenotypes, suggesting that oculomotor dysfunction may represent both a diagnostic biomarker and a potential endophenotype. Smooth-pursuit and antisaccade measures behaved as trait-like, familial markers in patients and their relatives, and were related to genotype, medication effects, illness stage, and working memory. However, several studies found these measures were not specific to schizophrenia, with similar abnormalities in bipolar and schizoaffective disorders, and one reported negative findings in relatives. Multivariate, biotyping, and machine-learning approaches improved classification and patient stratification. Notably, one longitudinal study demonstrated that eye-movement characteristics predicted transition to psychosis among individuals at clinical high risk, highlighting the potential role of eye-tracking in early identification and risk stratification.

Evidence in ADHD indicated impaired pro- and antisaccadic performance and broader oculomotor abnormalities relative to healthy controls, supporting the use of eye-tracking measures as objective indicators of attentional and inhibitory dysfunction. Antisaccade abnormalities and impaired countermanding were also found in adults, including partially remitted cases. Deficits were greater in the combined than the inattentive subtype and improved with methylphenidate, and a multimodal model including oculomotor measures reached an AUC of 0.892. Antisaccade errors were shared with bipolar disorder, indicating limited diagnostic specificity. Similarly, studies involving anxiety disorders demonstrated distinct gaze patterns toward emotional stimuli, suggesting that eye-tracking may provide useful markers of attentional bias and symptom-related cognitive processing.

Evidence outside these disorders was sparse and preliminary, with one or two studies per condition. In remitted recurrent major depression, reduced sustained attention to happy faces was associated with recurrence risk, and in soldiers assessed before deployment, gaze bias toward fearful and sad faces predicted later post-traumatic stress and depressive symptoms. In borderline personality disorder, heightened initial fixation on the eyes of angry faces normalised after intranasal oxytocin, and in cocaine use disorder, antisaccade performance differed between treatment responders and non-responders. These findings suggest broader transdiagnostic and treatment-related applications but require replication.

Eye-tracking emerged as the most extensively investigated ophthalmic biomarker modality and the only modality represented across multiple precision psychiatry domains. Unlike other ophthalmic measures, the eye-tracking literature contributes evidence across virtually all precision psychiatry domains, including diagnostic classification, early-risk detection, patient stratification, prognosis, prediction of transition to psychosis, treatment monitoring, and treatment-response assessment (Table 5). Nevertheless, substantial methodological heterogeneity exists across paradigms, outcome measures, and study populations. Further standardization and replication in larger longitudinal cohorts will be necessary before eye-tracking biomarkers can be incorporated into routine psychiatric practice.

Table 5. Precision Psychiatry Domains Represented by Eye-Tracking Studies.

Domain	Studies Contributing Evidence
Diagnostic Biomarkers	[38,41,43,47,48,50–52,54–56,58–60,65,66,70,74,75,77,83,87,90,94,104,107,109,114–117,119,120]
Risk Stratification/Early Detection	[44–47,49,55,68,71,76,78,91,111–113,123]
Prognostic Biomarkers	[32,33,58,73,78,111,113,124,127]
Treatment-Response Biomarkers	[32,40,41,61,79,84,86,97,100,118,121,125,126]
Monitoring Biomarkers	[40,41,48,59,87,100,121]
Patient Stratification and Differential Diagnosis	[33,53,54,57,63,64,67,69,81,83,86,103,108–110,118,121–123,128]
Endophenotypes	[42,64,74,76,80,82,85,88–90,92,94–96,98,99,101,102,104,106,120]
Biomarker Validation	[66,77]

From a precision psychiatry perspective, eye-tracking biomarkers possess several advantages. They are non-invasive, relatively inexpensive, repeatable, and capable of generating highly quantitative data. Furthermore, many eye-tracking variables can be collected using standardized paradigms and are readily amenable to computational analysis and machine-learning approaches. These characteristics make eye-tracking particularly attractive for patient stratification, longitudinal monitoring, and integration into multimodal biomarker models combining neuroimaging, genetic, digital phenotyping, and clinical data. Overall, the current evidence suggests that eye-tracking biomarkers are uniquely positioned among ophthalmic measures to contribute across the full precision psychiatry pathway, including early-risk identification, diagnostic classification, patient stratification, prognostic assessment, treatment monitoring, and treatment-response prediction. However, further standardization, longitudinal validation, and demonstration of clinical utility at the individual-patient level will be necessary before widespread implementation in routine psychiatric practice.

Nevertheless, important limitations remain. Substantial heterogeneity exists across studies with respect to paradigms, outcome measures, hardware platforms, participant characteristics, and analytical approaches. Replication across independent cohorts remains inconsistent, and relatively few studies have established clinically meaningful thresholds capable of informing real-world decision-making. Moreover, many investigations have focused on group-level differences rather than individual-level prediction, which remains the ultimate goal of precision psychiatry.

4.5. Cross-Modality Findings

Table 6 presents a cross-modality synthesis of the findings in this review.

Table 6 demonstrates that the various ophthalmic biomarker modalities occupy distinct but complementary positions within the precision psychiatry framework. Eye-tracking emerged as the most mature and versatile modality (91 of the 114 included studies), with evidence supporting nearly every stage of the clinical pathway, including early-risk identification, diagnostic classification, patient stratification, prognostic assessment, treatment monitoring, and prediction of clinically relevant outcomes. This breadth is particularly evident in autism spectrum disorder, where eye-tracking biomarkers have progressed from discovery and risk stratification to multicenter validation initiatives and evaluation in clinical trials, and in schizophrenia, where oculomotor abnormalities have been repeatedly identified as candidate endophenotypes and predictors of illness trajectory [66,129,130]. Eye-tracking evidence also extends to ADHD, anxiety, depression, post-traumatic stress, borderline personality disorder, and substance use disorder.

Table 6. Cross-Modality Synthesis of Ophthalmic Biomarkers for Precision Psychiatry.

Modality	Disorders Studied	Principal Biomarker Targets	Diagnostic Utility	Prognostic Utility	Risk Stratification	Treatment Response/ Monitoring	Level of Maturity
Eye-Tracking	ASD (including infants and siblings at elevated likelihood), schizophrenia and psychosis spectrum, clinical high-risk and ultra-high-risk states, ADHD, anxiety disorders, major depression, PTSD, borderline personality disorder, bipolar disorder, substance use disorder	Social attention, gaze patterns, gaze following, fixation to the eyes, smooth pursuit, antisaccades, predictive saccades, oculomotor inhibition, exploratory eye movements, attentional bias	Strong	Moderate-Strong	Strong	Moderate	High
Retinal Structural Biomarkers	Schizophrenia spectrum and psychotic disorders, bipolar disorder, major depression, borderline personality disorder, ASD, obsessive-compulsive disorder, substance use disorder	RNFL thickness, ganglion cell layer thickness, macular parameters, retinal microstructure, ellipsoid zone (photoreceptor) thickness, choroidal thickness	Moderate	Limited	Limited	Limited	Moderate
Retinal Vascular Biomarkers	ADHD, ASD, major depression, borderline personality disorder	Vessel density, foveal avascular zone, choroidal vascularity index, inner-retinal arteriovenous measures	Emerging	Limited	Limited-Moderate	Limited	Emerging
Electroretinography (ERG)	Schizophrenia, bipolar disorder, seasonal affective disorder, ASD, familial high-risk populations	Rod and cone function, a-wave amplitude, light-response modulation, retinal electrophysiology, retinal neurotransmission	Limited-Moderate	Limited	Limited-Moderate	Moderate	Emerging
Pupillometry	Major depression (including youth and those at risk), anxiety and panic disorders, ASD, ADHD, alcohol withdrawal	Pupillary light reflex, task-evoked and emotional pupillary responses, pupil velocity and size, autonomic regulation	Limited-Moderate	Limited-Moderate	Limited-Moderate	Moderate	Emerging-Moderate

'Maturity' reflects the breadth of the identified evidence base, including number of studies, diversity of psychiatric disorders examined, representation across precision psychiatry domains, and presence of validation studies. These categories were generated descriptively by the review authors and do not represent a formal evidence-grading system. ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; ERG = Electroretinography; PTSD = post-traumatic stress disorder; RNFL = retinal nerve fibre layer.

Retinal structural and vascular biomarkers occupied a different translational niche, primarily contributing to biological phenotyping and diagnostic research. Retinal imaging studies across psychotic, mood, neurodevelopmental, obsessive-compulsive, and substance use disorders have demonstrated that retinal microstructural and vascular alterations may reflect neurodevelopmental, neurodegenerative, and microvascular processes implicated in psychiatric disorders [14,15,17,18,20]. The retina's accessibility and shared developmental origin with the central nervous system make these measures particularly attractive as objective biological markers, although current evidence remains largely cross-sectional and focused on group-level associations rather than individualized prediction.

Electroretinography occupies an intermediate position within the biomarker landscape. By assessing retinal neurophysiology directly, ERG provides information that is complementary to structural and vascular retinal imaging. The available studies suggest potential applications in disease characterization, monitoring of clinical state, and identification of individuals at elevated psychiatric risk. Importantly, ERG findings in high-risk offspring and seasonal affective disorder indicate that retinal electrophysiological measures may be

sensitive to both vulnerability and dynamic changes associated with illness course and treatment [26–28]. A study in autism spectrum disorder further showed that retinal responses change with pharmacological (GABAergic) modulation [29], although the ERG evidence base remains small and has not been validated.

Pupillometry appears particularly promising for measurement-based psychiatric care. The identified studies in depression, anxiety, autism spectrum disorder, ADHD, and alcohol withdrawal suggest that pupillary responses capture autonomic and cognitive-affective processes that fluctuate with symptom severity and therapeutic intervention. Consequently, pupillometry may be better suited to monitoring clinical state and treatment response than to diagnostic classification, although a longitudinal cohort showed that pupil dilation predicted later depressive episodes in at-risk youth [34]. This interpretation is also consistent with broader pupillometry literature, which emphasizes the relationship between pupil dynamics, emotional processing, attentional allocation, and cognitive effort [131,132].

Taken together, the findings suggest that no single ophthalmic modality currently fulfills all requirements of an ideal precision psychiatry biomarker. Rather, each modality contributes unique information regarding different dimensions of psychopathology. Eye-tracking presently shows the greatest degree of translational development among the ophthalmic modalities identified in this review, whereas retinal structural and vascular biomarkers, ERG, and pupillometry provide complementary biological and physiological information that may enrich patient characterization. The most promising future direction therefore lies in multimodal biomarker frameworks that combine ophthalmic measures with neuroimaging, genetics, electrophysiology, and digital phenotyping to improve prediction, stratification, and personalized treatment selection. Similar multimodal approaches have already been proposed within autism biomarker consortia and schizophrenia biomarker research, where integration across modalities is increasingly viewed as essential for achieving clinically meaningful predictive performance [66].

4.6. Computational and Machine-Learning Approaches

Predictive and machine-learning modelling was reported almost exclusively in eye-tracking studies. Machine-learning models were applied to autism, schizophrenia spectrum and psychosis-risk samples, including random-forest prediction of transition to psychosis from baseline eye-movement measures (accuracy 0.78) [111], multivariate pattern classification of psychosis from smooth-pursuit measures (balanced accuracy 64%, confirmed in independent samples) [83], and supervised classification of autistic adults from kinematic and eye-movement features (accuracy 70–78%) [70]. Index-based and regression models derived from eye-tracking measures achieved higher discrimination for autism within single samples (AUC 0.85–0.91) [47,48,65], whereas a multicenter evaluation reported sensitivity of 71% and specificity of 81% [55]. A multimodal regression model combining near-infrared spectroscopy and oculomotor measures reached an AUC of 0.89 for ADHD [117], and cluster-based biotyping integrating eye-movement and other biomarkers was replicated in psychosis [81]. No retinal, electroretinographic, or pupillometric study applied machine learning; these modalities reported conventional ROC or regression estimates [18,22,34]. Reported performance tended to decline as validation became more rigorous, and external validation in independent samples was uncommon.

4.7. Conceptual Heterogeneity of Ophthalmic Biomarkers

An important conceptual challenge identified during this review concerns the heterogeneous use of the term “biomarker.” Some studies investigated biomarkers as indicators of diagnosis, whereas others focused on risk stratification, treatment monitoring, disease progression, endophenotypes, or mechanistic insights into psychopathology. Conse-

quently, ophthalmic biomarkers should not be viewed as a homogeneous category. Rather, different modalities may serve different functions within a precision psychiatry framework. Eye-tracking measures were most frequently evaluated as diagnostic, prognostic, or risk-stratification tools, whereas retinal imaging primarily contributed biological phenotyping information, pupillometry was mainly investigated as a state and monitoring marker, and ERG occupied an intermediate position spanning diagnostic, prognostic, and monitoring applications.

4.8. Limitations of the Cross-Modal Evidence Base

Several limitations should be considered when interpreting the cross-modality evidence summarized in this review. First, the available literature is highly imbalanced across modalities, with eye-tracking accounting for the majority of included studies, whereas retinal structural and vascular biomarkers, electroretinography (ERG), and pupillometry were represented by relatively small evidence bases. This asymmetry limits direct comparison between modalities and increases the likelihood that apparent differences in clinical maturity reflect differences in research investment rather than true differences in biomarker performance. The more advanced state of eye-tracking research is partly attributable to large multicenter initiatives and dedicated biomarker-development programs, which are largely absent for the other modalities [66,127].

Second, substantial heterogeneity was observed across study populations, psychiatric diagnoses, ophthalmic technologies, outcome measures, and analytical approaches. Even within the same modality, studies frequently employed different paradigms and endpoints, making direct comparison challenging and precluding quantitative synthesis. This limitation was particularly evident in the eye-tracking literature, where measures of gaze behavior, social attention, smooth pursuit, antisaccades, and exploratory eye movements were often treated as distinct biomarker constructs. Similar methodological variability has been identified as a major obstacle to biomarker qualification and reproducibility [129,130].

Third, most included studies were cross-sectional and focused on identifying group-level differences between psychiatric populations and controls. Consequently, evidence supporting longitudinal prediction, treatment selection, relapse forecasting, or individualized clinical decision-making remains limited. While several studies demonstrated promising prognostic or treatment-monitoring applications, few reported externally validated predictive models or clinically actionable performance metrics such as sensitivity, specificity, and predictive value [66,133].

Finally, the review included a broad range of psychiatric disorders, risk states, and non-clinical at-risk or relative samples, reflecting the exploratory nature of the field but also introducing conceptual heterogeneity. Many ophthalmic biomarkers may represent transdiagnostic indicators of cognitive, neurodevelopmental, autonomic, or microvascular dysfunction rather than disease-specific markers. Accordingly, current evidence is insufficient to determine the specificity of individual ophthalmic biomarkers for particular psychiatric diagnoses. Future research should prioritize standardized methodologies, multicenter validation, longitudinal designs, and multimodal biomarker integration to establish the clinical utility and generalizability of ophthalmic biomarkers within precision psychiatry [66,127].

4.9. Research Gaps

Table 7 presents an outline of the research gaps identified in this review.

Table 7. Mapping of Research Gaps to Findings Identified in the Present Review.

Research Gap	Review Finding(s) Identifying the Gap	Supporting Studies	Modalities Most Affected	Priority for Future Research
Limited standardization of acquisition and analysis methods	Considerable variation in eye-tracking paradigms (antisaccades, smooth pursuit, predictive saccades, biological motion, gaze following, face processing, social-preference tasks), pupillometric outcomes, ERG parameters, and retinal imaging metrics.	[17,27,37,47,54,56,66,76]	Eye-tracking, ERG, Pupillometry, Retinal Imaging	Develop consensus acquisition, processing, and reporting standards.
Predominance of small, single-center studies	Most studies relied on modest sample sizes and single-site recruitment. Large multicenter validation efforts were uncommon and were concentrated in autism eye-tracking research.	[16,27,28,55,73,75,118,128]	Retinal Imaging, ERG, Pupillometry	Conduct multicenter validation studies and collaborative research networks.
Limited longitudinal evidence	Most studies were cross-sectional. Longitudinal designs were observed primarily in psychosis-risk, depression-risk, treatment-response, and symptom-monitoring studies.	[28,30,34,41,111,124,127]	Retinal Imaging, Pupillometry, ERG, Eye-tracking	Prioritize prospective longitudinal cohorts.
Insufficient evidence for individual-level prediction	Most studies focused on group differences rather than clinically actionable prediction. Where individual-level performance was reported it was modest or unvalidated (for example, AUROC 0.63–0.70 for retinal measures in borderline personality disorder, and no antisaccade measure predicting conversion within two years in a clinical high-risk cohort).	[18,40,47,111,112]	All modalities	Evaluate individual-level prediction and externally validated performance metrics.
Evidence concentrated in a limited number of disorders	Most eye-tracking studies examined ASD and schizophrenia-spectrum disorders; mood, anxiety, personality, and substance-use disorders were each represented by only one to two studies. Retinal, ERG, and pupillometry evidence was similarly sparse outside selected conditions.	[30,31,66,73,121,123,125–127]	All modalities	Expand research to mood, anxiety, OCD, personality, and substance-use disorders.
Lack of normative reference datasets	None of the included studies established broadly applicable normative ranges for ophthalmic biomarkers.	All included studies	All modalities	Develop population reference datasets using standardized protocols.
Fragmented investigation of ophthalmic modalities	Retinal imaging, ERG, pupillometry, and eye-tracking were typically studied independently. Only a few studies combined two ophthalmic modalities (OCT with pupillometry, or eye-tracking with pupillometry), and no study comprehensively integrated all ophthalmic modalities.	[14,23,26,29,30,38,66]	All modalities	Investigate multiple ophthalmic modalities within shared cohorts.
Limited multimodal biomarker integration	Few studies combined ophthalmic measures with neuroimaging, genetics, electrophysiology, or digital phenotyping.	[15,29,66,69,70,76,81,90,117]	All modalities	Develop multimodal precision psychiatry frameworks.
Underutilization of machine learning and AI	Machine-learning and index-based modelling was encountered mainly in eye-tracking studies of autism and schizophrenia-spectrum disorders and in emerging psychosis-risk research, and was largely absent from retinal, ERG, and pupillometry studies.	[47,48,54,66,70,77,83,111,117]	Retinal Imaging, ERG, Pupillometry	Apply machine-learning and AI approaches to multimodal prediction and stratification.

Table 7. *Cont.*

Research Gap	Review Finding(s) Identifying the Gap	Supporting Studies	Modalities Most Affected	Priority for Future Research
Uncertain clinical implementation pathways	Few studies evaluated feasibility, scalability, cost-effectiveness, or integration into routine psychiatric workflows; feasibility was addressed mainly in autism eye-tracking screening studies.	[28,30,40,55,66,71]	All modalities	Conduct implementation and clinical utility studies.

AI = Artificial Intelligence; ASD = Autism Spectrum Disorder; AUROC = area under the receiver operating characteristic curve; ERG = Electroretinography; OCD = obsessive-compulsive disorder; OCT = optical coherence tomography.

The mapped research gaps suggest that ophthalmic biomarker research in psychiatry is entering a transitional phase, moving from biomarker discovery toward biomarker validation and implementation. Across modalities, numerous studies have demonstrated statistically significant associations between ophthalmic measures and psychiatric phenotypes; however, relatively few investigations have progressed to the level of external validation, longitudinal prediction, or clinically actionable decision support. This discrepancy was particularly evident in the eye-tracking literature, where promising findings regarding diagnosis, risk stratification, and treatment monitoring coexist with substantial methodological heterogeneity and limited standardization. Efforts such as the Autism Biomarkers Consortium for Clinical Trials illustrate the potential benefits of harmonized protocols and multisite validation frameworks for advancing biomarker readiness [66,72].

A second notable finding is the unequal maturity of the various ophthalmic modalities. Eye-tracking studies have expanded beyond simple case-control comparisons to encompass prediction of social outcomes, transition to psychosis, treatment response, and biomarker validation. In contrast, retinal structural and vascular biomarkers, pupillometry, and electroretinography remain largely concentrated in exploratory and early-validation stages. Consequently, the current evidence base is strongest for establishing biological plausibility and identifying candidate biomarkers, whereas evidence supporting routine clinical implementation remains limited. This imbalance highlights the need for larger prospective studies capable of determining whether the promising signals observed in smaller cohorts translate into robust and reproducible clinical tools.

The mapping process also revealed that research activity is concentrated within a relatively narrow range of psychiatric disorders, particularly autism spectrum disorder and schizophrenia spectrum disorders. Comparatively little evidence was identified for mood disorders, anxiety disorders, obsessive-compulsive disorder, personality disorders, or substance use disorders, each of which was generally represented by only a handful of studies per modality. As a result, the current understanding of ophthalmic biomarkers may reflect the priorities of existing research programs rather than the full spectrum of psychiatric illness. Expanding investigations into underrepresented conditions will be important for determining whether observed biomarker abnormalities are disorder-specific or reflect broader transdiagnostic processes.

Perhaps the most important gap from a precision psychiatry perspective is the scarcity of multimodal and individual-level predictive research. Most studies evaluated ophthalmic biomarkers in isolation and focused on group-level differences between patients and controls. A minority of eye-tracking studies reported classification or risk-index models, or combined eye-tracking with electrophysiology, neuroimaging, or pupillometry, but these were rarely externally validated. Yet the findings of this review suggest that different modalities provide complementary information regarding behavior (eye-tracking), autonomic regulation (pupillometry), retinal neurophysiology (ERG), and retinal structural or vascular integrity. Future advances are therefore likely to stem from integrated biomarker frameworks rather

than from any single ophthalmic measure. Combining ophthalmic biomarkers with neuroimaging, genetics, electrophysiology, and digital phenotyping may ultimately provide the predictive performance necessary to support individualized diagnosis, prognosis, and treatment selection in psychiatric care.

Although ophthalmic biomarkers are not yet ready for routine psychiatric practice, the accumulating evidence across eye-tracking, retinal imaging, electrophysiology, and pupillometry indicates that they may ultimately contribute valuable objective information within multimodal precision psychiatry frameworks, provided that current challenges relating to reproducibility, validation, and clinical implementation can be successfully addressed.

4.10. Future Research Directions

The findings of this scoping review indicate that ophthalmic biomarkers represent a promising but unevenly developed area of precision psychiatry research. Future investigations should prioritize the standardization of acquisition protocols, outcome measures, and reporting practices across ophthalmic modalities to improve reproducibility and facilitate comparison between studies. Particular attention should be paid to the harmonization of eye-tracking paradigms, retinal imaging parameters, pupillometric outcomes, and electroretinographic measures, as methodological heterogeneity emerged as a consistent limitation across the evidence base. The success of multicenter initiatives such as the Autism Biomarkers Consortium for Clinical Trials (ABC-CT), which implemented standardized acquisition procedures, quality-control processes, and harmonized analytic pipelines, demonstrates the feasibility and importance of such efforts [66,72].

A second priority is the expansion of multicenter and longitudinal research designs. Most identified studies were cross-sectional and conducted in single cohorts, limiting conclusions regarding biomarker stability, prognostic value, treatment response, and generalizability. Large prospective studies are needed to determine whether ophthalmic biomarkers can reliably predict clinically meaningful outcomes such as symptom progression, relapse, functional recovery, treatment response, or transition to psychosis. Existing longitudinal findings in psychosis-risk cohorts and autism biomarker research suggest that this approach is both feasible and potentially clinically informative [66,130].

The review also identified a marked concentration of research in autism spectrum disorder and schizophrenia spectrum disorders, with comparatively limited evidence for mood disorders, anxiety disorders, obsessive-compulsive disorder, personality disorders, and substance use disorders. Future work should therefore evaluate ophthalmic biomarkers across a broader range of psychiatric conditions and investigate whether observed abnormalities represent disorder-specific signatures or transdiagnostic markers of underlying neurobiological dysfunction. Such efforts are particularly important given growing interest in dimensional and mechanism-based approaches to psychiatric classification [66,129].

Another important research priority is the development of clinically relevant predictive models. Although many studies reported significant group-level differences, relatively few assessed individual-level prediction or provided externally validated measures of diagnostic, prognostic, or treatment-response performance. Future investigations should incorporate robust validation procedures and report clinically meaningful performance metrics, including sensitivity, specificity, calibration, and external validation. Emerging machine-learning studies in schizophrenia and autism demonstrate the potential of such approaches but also highlight the need for rigorous independent replication [77,133].

One promising future direction identified through this evidence mapping exercise is the integration of ophthalmic biomarkers within multimodal precision psychiatry frameworks. The findings of this review suggest that eye-tracking, retinal structural and vascular imaging, electroretinography, and pupillometry provide complementary information re-

garding behavioral, physiological, and neurobiological processes. Future research should therefore move beyond single-modality investigations and explore integrated biomarker frameworks combining ophthalmic measures with neuroimaging, genetics, electrophysiology, blood-based biomarkers, and digital phenotyping. Multimodal strategies have already been advocated within major autism biomarker initiatives and are increasingly viewed as necessary to achieve clinically meaningful stratification and prediction in psychiatric populations [66,72].

Taken together, the evidence indicates that future progress will depend less on the identification of additional candidate biomarkers and more on the rigorous validation, standardization, and integration of existing ophthalmic measures into broader precision psychiatry frameworks. Importantly, the findings of this review suggest that future progress is unlikely to arise from any single ophthalmic modality in isolation. Rather, the most promising path forward involves multimodal biomarker platforms integrating retinal structural and vascular imaging, eye-tracking, pupillometry, and electroretinography with complementary biological and digital data sources. Such approaches may ultimately provide the predictive accuracy and biological specificity required to support diagnosis, risk stratification, prognosis, and personalized treatment selection in psychiatric practice. The principal priorities are the establishment of standardized acquisition and reporting frameworks, multicenter validation networks, and prospective longitudinal studies capable of demonstrating clinically meaningful prediction. Initiatives such as the Autism Biomarkers Consortium for Clinical Trials have shown that harmonized protocols, centralized quality control, and biomarker standardization are achievable and can substantially improve reproducibility [66,72]. Future advances may also be facilitated by developments in digital ophthalmology, including portable eye-tracking systems, smartphone-based retinal imaging, and remote monitoring technologies. These approaches may improve scalability and accessibility of ophthalmic biomarkers, although evidence supporting their application in psychiatric populations remains limited and requires further investigation.

Table 8 presents recommendations for future cross-modality research in ophthalmic biomarkers for precision psychiatry.

Table 8. Recommendations for Future Cross-Modality Research in Ophthalmic Biomarkers for Precision Psychiatry.

Priority Area	Current Limitation	Recommended Actions	Expected Impact
Standardization of Acquisition Protocols	Substantial variability in hardware, calibration procedures, task paradigms, and data-processing pipelines across studies.	Develop consensus protocols for eye-tracking, pupillometry, ERG, OCT/OCTA, and retinal vascular imaging, with harmonized operating procedures and quality-control standards.	Improved reproducibility, comparability, and multicenter scalability.
Core Outcome Measures	Lack of standardized biomarker endpoints within and across modalities.	Establish consensus-derived core outcome sets for each modality, including recommended acquisition parameters and reporting standards.	Greater consistency across studies and improved evidence synthesis.
Multicenter Validation	Evidence is dominated by single-center studies with modest sample sizes.	Create international collaborative networks to conduct prospective, multicenter biomarker validation studies.	Improved external validity and generalizability.
Longitudinal Cohort Studies	Most studies remain cross-sectional.	Conduct prospective studies examining symptom trajectories, treatment outcomes, functional recovery, relapse, and transition to psychosis.	Stronger evidence for prognostic and predictive applications.
Individual-Level Prediction	Emphasis on group differences rather than clinical prediction.	Prioritize predictive modeling and report classification performance metrics, including sensitivity, specificity, AUC, calibration, and external validation.	Greater clinical utility and decision-support potential.

Table 8. *Cont.*

Priority Area	Current Limitation	Recommended Actions	Expected Impact
Normative Reference Databases	Absence of age-, sex-, and population-specific reference ranges.	Develop large normative datasets across the lifespan using standardized protocols.	Facilitates interpretation at the individual patient level.
Dimensional Psychiatry Approaches	Studies are largely organized around categorical diagnoses.	Examine ophthalmic biomarkers in relation to dimensional symptom domains, cognition, social functioning, emotional processing, and neurodevelopmental traits.	Improved transdiagnostic applicability and patient stratification.
Integration of Retinal and Functional Measures	Most studies evaluate individual modalities in isolation.	Combine retinal structural imaging, retinal vascular biomarkers, eye-tracking, pupillometry, and ERG within the same cohorts.	More comprehensive characterization of neurobiological and physiological dysfunction.
Multimodal Biomarker Platforms	Single biomarkers may lack sufficient predictive accuracy.	Integrate ophthalmic biomarkers with neuroimaging, electrophysiology, genetics, blood-based biomarkers, wearable sensors, and digital phenotyping.	Enhanced prediction, stratification, and personalized treatment selection.
Machine Learning and Artificial Intelligence	Limited use of advanced predictive analytics.	Employ explainable machine-learning models and externally validated prediction algorithms that combine multimodal data sources.	Improved diagnostic and prognostic performance.
Clinical Trial Integration	Few biomarkers have been assessed as trial endpoints or stratification tools.	Evaluate ophthalmic biomarkers as enrichment markers, treatment-response endpoints, and stratification tools in psychiatric clinical trials.	Accelerated translation into clinical practice.
Regulatory Qualification Pathways	Few psychiatric ophthalmic biomarkers have progressed toward qualification.	Develop regulatory roadmaps and qualification programs supported by multicenter validation and standardized methodologies.	Facilitation of clinical implementation and acceptance.

AUC = Area Under the Curve, ERG = Electroretinography, OCT(A) = Optical Coherence Tomography (Angiography).

4.11. Limitations of This Review

The limitations of this review should be interpreted within the methodological framework of scoping reviews. The literature search was restricted to a single database (PubMed/MEDLINE) and to publications from 2000 onwards; other databases (such as Embase, PsycINFO, and Web of Science) and grey literature were not searched. Six of the included studies were identified through reference checking rather than the database searches, indicating that the search strategies did not capture all eligible literature. In addition, studies in which an ophthalmic measure served solely as an outcome of treatment, rather than as a biomarker, were excluded, which may under-represent evidence on treatment monitoring. In accordance with the Joanna Briggs Institute (JBI) methodology [13] and the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [12], the primary objective of this review was to map the extent, nature, and characteristics of the available evidence rather than to evaluate intervention effectiveness, determine diagnostic accuracy, or generate quantitative estimates of biomarker performance. Scoping reviews are specifically intended to identify key concepts, characterize existing evidence, and highlight knowledge gaps within a field. Consequently, no quantitative synthesis or meta-analysis was undertaken, and the findings should not be interpreted as evidence of the comparative superiority or clinical effectiveness of any specific ophthalmic biomarker modality.

A second limitation relates to the substantial heterogeneity of the included literature. Consistent with the broad exploratory purpose of a scoping review, studies varied considerably with respect to psychiatric populations, ophthalmic technologies, acquisition protocols, study designs, outcome measures, and analytical approaches. Such heterogeneity was particularly evident within the eye-tracking literature, where diverse paradigms were used to investigate oculomotor control, social attention, biological motion perception, face processing, and gaze behavior. Similar variability was observed across retinal imaging,

retinal vascular phenotyping, pupillometry, and electroretinography studies. As a result, direct comparison between studies and modalities should be interpreted cautiously.

The mapped evidence was also unequally distributed across psychiatric disorders. Most studies focused on autism spectrum disorder and schizophrenia spectrum disorders, particularly within the eye-tracking literature, while mood disorders, anxiety disorders, obsessive-compulsive disorder, personality disorders, and substance use disorders were comparatively underrepresented. Therefore, the resulting evidence map may reflect existing research priorities rather than the true distribution of ophthalmic biomarker utility across psychiatric conditions. The evidence base was also unequally distributed across modalities, with eye-tracking accounting for 91 of 114 studies, which limits direct comparison between modalities. The assignment of studies to precision psychiatry domains and the maturity ratings in Table 6 were made descriptively by the review authors and are not a validated grading system.

In keeping with JBI guidance for scoping reviews [13], a formal risk-of-bias assessment or certainty-of-evidence evaluation was not conducted. Critical appraisal is not a mandatory component of JBI scoping reviews, and the purpose of the present review was to characterize and organize the available literature rather than assess the methodological quality of individual studies or provide definitive recommendations for clinical practice. Accordingly, the findings should be viewed as descriptive and exploratory rather than confirmatory.

Potential publication bias must also be acknowledged. As with all evidence syntheses relying on the published literature, studies reporting statistically significant or positive findings may be more likely to be published and indexed than studies with null results. The mapped evidence may therefore overestimate the consistency or strength of associations between ophthalmic biomarkers and psychiatric outcomes.

Finally, many included studies were cross-sectional, conducted at single centers, and involved relatively modest sample sizes. Consequently, evidence supporting longitudinal prediction, treatment-response assessment, relapse forecasting, and individual-level clinical decision-making remains limited. Although several promising studies addressed risk stratification and prognostic applications, particularly in eye-tracking and pupillometry research, these findings require replication and external validation before broad clinical implementation can be considered.

Taken together, these limitations are consistent with the objectives of a JBI- and PRISMA-ScR-compliant scoping review, which is intended to identify, characterize, and map available evidence rather than establish definitive clinical conclusions. The findings should therefore be viewed as a foundation for future hypothesis-driven research, systematic reviews, and validation studies aimed at clarifying the role of ophthalmic biomarkers in precision psychiatry.

5. Conclusions

This scoping review mapped the available literature on ophthalmic biomarkers in psychiatry and identified evidence across four principal domains: retinal structural and vascular imaging, electroretinography, pupillometry, and eye-tracking. Collectively, the mapped evidence suggests that ophthalmic measures may provide objective biological, physiological, and behavioral information relevant to psychiatric disorders. However, the quantity, scope, and maturity of the evidence varied substantially across modalities.

Among the identified approaches, eye-tracking represented the most extensively investigated modality, with studies spanning autism spectrum disorder, schizophrenia spectrum disorders, psychosis-risk states, ADHD, and anxiety disorders, and, to a lesser extent, mood, trauma-related, personality, and substance use disorders. Eye-tracking was also the modality with evidence across the broadest range of precision psychiatry domains, including

diagnostic classification, risk stratification, prognostic assessment, treatment monitoring, treatment-response evaluation, and endophenotype characterization. In contrast, retinal structural and vascular biomarkers, electroretinography, and pupillometry were represented by smaller and comparatively less mature evidence bases, with current studies primarily focused on biomarker discovery, biological characterization, and early-stage validation.

Several recurring knowledge gaps were identified across modalities, including methodological heterogeneity, limited multicenter validation, a predominance of cross-sectional study designs, and insufficient evidence regarding individual-level prediction. The mapped literature was also concentrated within a relatively small number of psychiatric disorders, particularly autism spectrum disorder and schizophrenia spectrum disorders.

Consistent with the objectives of a scoping review, the findings of the present review highlight areas of research activity as well as important evidence gaps. Future research should prioritize methodological standardization, longitudinal validation, multicenter replication, and evaluation of multimodal biomarker frameworks. Such work will be necessary to determine the potential contribution of ophthalmic biomarkers to precision psychiatry and their possible future role in diagnosis, prognosis, patient stratification, and personalized mental healthcare.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jpm16120589/s1, Supplementary File S1: PubMed search strategies; File S2: PRISMA checklist; Table S1: Original studies identified during the search process and included in this review; Table S2: Characteristics of Included Studies Investigating Eye-Tracking Biomarkers in Psychiatric Disorders. Ref. [134] is citated in the Supplementary Materials.

Author Contributions: Conceptualization, G.D.F.; methodology, I.M.; writing—original draft preparation, I.M.; writing—review and editing, A.K. and G.D.F.; supervision, G.D.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ADHD	Attention-Deficit/Hyperactivity Disorder
AI	Artificial Intelligence
ASD	Autism Spectrum Disorder
AUROC	Area Under the Curve
BD	Bipolar Disorder
BPD	Borderline Personality Disorder
CHR	Clinical High-Risk
GCR	Ganglion Cell Layer
ERG	Electroretinography
MDD	Major Depressive Disorder
MSUD	Multiple Substance Use Disorder
OCD	Obsessive-Compulsive Disorder
OCT(A)	Optical Coherance Tomography (Angiography)

PLR	Pupillary Light Reflex
PTSD	Post-Traumatic Stress Disorder
RNFL	Retinal Nerve Fibre Layer
SAD	Seasonal Affective Disorder
SD-OCT	Spectral Domain-Optical Coherence Tomography
SSD	Schizophrenia Spectrum Disorder
TD	Typically Developing

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