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REVIEW ARTICLE

Applications of artificial intelligence and bioinformatics methodologies in the analysis of ocular biofluid markers: a scoping review

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Abstract

Purpose This scoping review summarizes the applications of artificial intelligence (AI) and bioinformatics methodologies in analysis of ocular biofluid markers. The secondary objective was to explore supervised and unsupervised AI techniques and their predictive accuracies. We also evaluate the integration of bioinformatics with AI tools.

Methods This scoping review was conducted across five electronic databases including EMBASE, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science from inception to July 14, 2021. Studies pertaining to biofluid marker analysis using AI or bioinformatics were included.

Results A total of 10,262 articles were retrieved from all databases and 177 studies met the inclusion criteria. The most commonly studied ocular diseases were diabetic eye diseases, with 50 papers (28%), while glaucoma was explored in 25 studies (14%), age-related macular degeneration in 20 (11%), dry eye disease in 10 (6%), and uveitis in 9 (5%). Supervised learning was used in 91 papers (51%), unsupervised AI in 83 (46%), and bioinformatics in 85 (48%). Ninety-eight papers (55%) used more than one class of AI (e.g. > 1 of supervised, unsupervised, bioinformatics, or statistical techniques), while 79 (45%) used only one. Supervised learning techniques were often used to predict disease status or prognosis, and demonstrated strong accuracy. Unsupervised AI algorithms were used to bolster the accuracy of other algorithms, identify molecularly distinct subgroups, or cluster cases into distinct subgroups that are useful for prediction of the disease course. Finally, bioinformatic tools were used to translate complex biomarker profiles or findings into interpretable data.

Conclusion AI analysis of biofluid markers displayed diagnostic accuracy, provided insight into mechanisms of molecular etiologies, and had the ability to provide individualized targeted therapeutic treatment for patients. Given the progression of AI towards use in both research and the clinic, ophthalmologists should be broadly aware of the commonly used algorithms and their applications. Future research may be aimed at validating algorithms and integrating them in clinical practice.

Keywords Artificial intelligence · Machine learning · Bioinformatics · Ophthalmology · Biomarkers · Aqueous humor · Vitreous humor

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Key messages

What is known:

- AI methodology is well suited to analyzing biofluid markers that are readily accessible in the ophthalmology patient population.

What is new:

- AI can accurately diagnose disease, support understanding molecular etiologies, and guide individualized targeted therapeutic treatment.
- Most AI tools are investigational and have not yet been deployed in a clinical setting.

Introduction

Biomedical research has experienced a paradigm shift as artificial intelligence (AI) analysis has become more prevalent. As AI-based tools are deployed clinically, the applications are projected to expand [1-3]. Both ophthalmology and early AI tools having a strong focus on image based diagnosis, causing ophthalmology to emerged at the forefront of clinical AI applications [4, 5].

As AI applications mature beyond imaging, AI analysis of omics data also represents great promise; advanced analytical tools such as AI can uncover meaningful relationships between clinical characteristics and the complex, highly dimensional data found in molecular etiologies such as genomics, lipidomics, metabolomics, and proteomics [6]. These molecular etiologies can be easily access in ophthalmology. Patients with ocular conditions undergo frequent procedures in clinical and surgical contexts, allowing for relatively easy access to biofluids such as serum, plasma, tears, aqueous humour, and vitreous humour that present opportunities for large omics datasets to be analyzed using AI [7].

AI analysis of these biofluid markers have varied applications in ophthalmology. The variability in methodologies reflects the wide range of applications, including pathogenic exploration [8, 9], diagnosis [10, 11], guidance of treatment selection [7, 12], and definition of distinct disease subtypes [13, 14]. Selection of an AI algorithm is highly dependant on a studies goals or the intended clinical application, as AI algorithms have diverse functions. = For example, supervised learning is a machine learning (ML) technique that learns to map an input to an output using example input–output pairs, called the training set, that have been defined by an expert [15]. Supervised AI algorithms can subsequently predict analogous outcomes or classify cases in a new data set, the test set. Supervised AI algorithms include artificial neural networks (ANN), support-vector machines (SVM), and discriminant analyses (DA). In contrast, unsupervised AI requires no example input–output pairs, and can determine patterns in a data set based on similarities or differences [16]. Unsupervised AI is particularly valuable in the analysis of highly dimensional and large data sets, with examples including hierarchical cluster analysis and principal component analysis (PCA). Finally, bioinformatics applications such as Gene Ontology (GO) translate complex biomarker profiles or findings into interpretable data (Table 1) [17].

Given the variability in applications of AI to analyze biofluid markers and the wide spectrum of AI algorithms utilized, understanding how best to deploy each algorithm and how to consider biofluids in ophthalmology practice and research is challenging. This study summarizes the types of AI and bioinformatics used in biofluid marker analysis in ophthalmology, with a focus on methodological considerations. We also explore how research has strategically deployed these analysis techniques for common and unique use-cases. Finally, we describe the AI algorithm parameters, the goals of AI application, commonly accessed biofluids, and identify areas for future investigations.

Methods

This study was conducted in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [18, 19]. The protocol was prospectively registered in PROSPERO (reg. CRD42020196749). Ethics approval from our Institutional Review Board was not required given this is a review of previously published studies. Given the large quantity of papers identified on this topic, a scoping review was deemed to be most appropriate for characterizing literature that used AI algorithms for biofluid marker analysis in ophthalmic conditions. This preliminary exploratory assessment was undertaken to determine the potential size and scope of available research literature. As all ophthalmic conditions

Table 1 Summary of common classes of artificial intelligence used in the analysis of ocular biofluid markers. The information presented in this table was gathered from a number of the included studies and augmentative papers [73-80]

AI Algorithm	Algorithm Activities	Classification	Strengths	Limitations
DA	Generalization of Fisher's linear discriminant that determines a linear combination of features to characterize ≥ 2 items. Used for dimensionality reduction or for linear classification. Assumptions include normal data distribution, homogeneity of variances/covariances, correlations between means and variances, and independent data (random sampling)	Supervised	• Simple, fast, and easy to implement • Can analyze multiple dependant variables • Can be used alongside other algorithms for dimensionality reduction	• Assumptions can be limiting • Other algorithms can have better accuracy • Other algorithms can be easier to interpret • Requires a relatively large quantity of data for accuracy
PCA	Variation of the Pearson Correlation Coefficient. Computes principal components of a dataset using change of basis and disregards the remaining data. Assumptions include normal data distribution, correlation between features, data that uses the same unit/scale of measurement, and few outliers in the data	Unsupervised	• Removes correlated features (principal components are independent) • Easy to use • Improves accuracy of other algorithms via dimensionality reduction • Reduces overfitting • Easy to visualize	• Challenging to interpret as principal components are linear combinations of original data • Information is lost following algorithm activities
Random forest	A group of AI that use ensemble learning to classify items using decisions trees (with random forest typically being more accurate). Assumptions include continuous input data and a discrete target variable	Supervised	• High accuracy • Allows input from many predictor variables • Estimates contribution of predictor variables • Accurate when data is missing	• Prone to overfitting, especially in noisy datasets • Biases towards predictors with multiple levels
ANN	Collection of nodes called artificial neurons that receive and process signals. The signals are transmitted as numbers, with neurons being about accept multiple inputs and outputting a non-linear function that is the sum of the inputs	Supervised	• Can model nonlinear relationships • Very flexible in their application • Massive computational power and ability to analyze large data sets • Estimates contribution of predictor variables • Can be highly accurate if trained correctly	• Require a large training set • Require significant computing resources • Challenging to assess complete algorithm activities and outputs, leading to "black box"
SVM	Supervised algorithms for data classification, regression, and outlier detection. They can perform linear classification or non-linear classification (using the kernel trick)	Supervised	• Effective for highly dimensional data sets, including when the number of dimensions is greater than the number of samples • Memory efficient • Can be adapted for many different tasks and data sets	• Can be prone to overfitting for some activities • Less suitable for large data sets • Difficult to interpret—require an additional calculation (cross validation) to provide probability estimates, which is expensive and time consuming
KNN	Nonparametric algorithm that is used for classification and regression. The input consists of the k closest training examples and assumes that similar things are close together. Although has no assumptions, KNN requires some way to approximate the distance between two data points	Supervised	• Easy to implement • Algorithm requires little change to apply to different data sets • Versatile algorithm	• Can be slow in larger data sets • Data needs to use the same unit/scale of measurement • Very sensitive to outliers • No way to correct for missing values

Table 1 (continued)

AI Algorithm	Algorithm Activities	Classification	Strengths	Limitations
Hierarchical cluster analysis	A type of cluster analysis that groups objects that are similar (thus close together) into clusters. This process involves repeated calculation of distance between objects and between clusters. Hierarchical cluster analysis can employ both a "bottom-up" approach, in which each item starts in its own cluster, or a "top-down" approach in which all observations start in one cluster. Outputs data as a dendogram	Unsupervised	• Easy to implement • Dendogram is easy to interpret	• Can be slow in larger data sets • Order of the data impacts the final results • Very sensitive to outliers
GO	Structured, controlled vocabularies and classifications used in the annotation of genes, gene products, and sequences. Maps biomarkers or pathways into genomic data to make it more easily interpretable	Bioinformatics	• Produces data on functional processes • Can predict gene function	• Available annotation might affect results and conclusions, so analysis method is very important
Pathway analysis	Characterization of a pathway (such as a metabolic or proteomic pathway) and its biological function. There are many different databases that are used for pathway analysis, each with their own advantages and disadvantages	Bioinformatics	Tool dependant	Tool dependant

Acronyms: *AI* = artificial intelligence; *ANN* = artificial neural network; *DA*=discriminant analysis; *GO*=gene ontology; *KNN*=k-nearest neighbors algorithm; *PCA*=principal component analysis; *SVM*=support vector machine

were surveyed, the literature was highly heterogenous, varying by study design, outcome measures, and omics discipline. Numerous AI algorithms and bioinformatics tools were also examined. Scoping reviews are particularly useful in such broad and complex areas that have not been reviewed comprehensively. We sought to create a database of papers that use AI to analyze biofluid markers in ophthalmology, that can be subsequently analyzed in different ways such as grouped by disease state..

Search strategy

A search strategy was developed following an extensive literature review and consultation with an experienced librarian. Five electronic databases including Embase, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science were comprehensively searched from inception to August 11, 2020. The search was updated on July 14, 2021, to capture articles published between these dates. No language or study design restrictions were placed on the search. To ensure search sensitivity, free-text and Medical Subject Heading (MeSH) terms of the respective databases pertaining to the concepts of "ophthalmology" and "AI/bioinformatics" and "proteomics, metabolomics, lipidomics" were included in the search strategy. The complete search strategy is contained within Appendix A. Each of the included studies' references were hand searched for relevant articles that were not captured in the initial database searches.

Selection criteria

Study inclusion criteria were: (1) original peer-reviewed study; (2) biofluid marker concentrations were analyzed, notably lipidomics, metabolomics, or proteomics from serum, plasma, tear fluid, vitreous humour, aqueous humour, or ophthalmic biopsy; (3) study population had intra-ocular ophthalmic conditions, a systemic disease affecting intra-ocular structures/physiology, or were well (in the case of exploratory studies). Study exclusion criteria were: (1) non-ophthalmic conditions; (2) extra-ocular ophthalmic conditions (e.g. strabismus); (3) ophthalmic disease only affecting pediatric patients (e.g. retinopathy of prematurity); (4) studies utilizing non-human subjects (animal studies, in-vitro studies), post-mortem samples, or enucleated eyes; (5) studies restricted to non-biofluid markers (imaging); (6) studies restricted to genomic or transcriptomic biomarkers; (7) abstracts, non-peer reviewed articles, reviews, systematic reviews, meta-analysis; (8) studies using only regression analysis. Note, studies combining AI analysis of biofluid markers with other types of data, such as imaging, were included. However, AI algorithms applied within software used to produce the raw data (e.g. pre-processing the spectra in mass spectrometry) were not included. For the purposes of this manuscript, the definition of AI remains broad, as there is no consensus about the definition of AI within the scientific community. Notably, statistical methods such as regression analysis are often considered a basic form of AI, but discussion of them has been omitted from this manuscript as they are ubiquitous in modern research.

Abstracts and titles were screened for inclusion by two independent reviewers in the first stage of screening. In the subsequent stage of screening, the full manuscript texts were screened by two independent reviewers. Conflicts between reviewers in these stages were resolved by a third independent reviewer. Covidence (Melbourne, Australia) was used to manage manuscript files and study eligibility status.

Data collection and extraction

One reviewer performed data extraction for each study using standardized data collection forms, with 10% of the extractions verified by a second independent reviewer to ensure agreement and consistency between data extractors. Key data extracted from each article included country of publication, disease of interest, study objective, types of AI used, AI algorithm accuracy, biofluid analyzed, and significant findings.

Synthesis of evidence

Descriptive synthesis of evidence was undertaken for the included studies. The characteristics of the included papers were described, including the diseases studied, the biofluids analyzed, and the AI algorithms deployed in analysis. The AI and bioinformatics methodologies utilized in the included papers were summarized. Algorithm accuracy is also explored in the results, although no calculations were applied to the accuracy measurements given the variability in reporting. No formal risk of bias assessment was performed [20].

Included studies were categorized according to study objectives into the following categories: 1) Diagnosis or prognosis; 2) Identifying characteristics; 3) Treatment decisions; and 4) Exploratory. Studies characterized as "Diagnosis or prognosis" sought to either diagnose disease or predict progression using AI. "Identifying characteristics" studies detailed exploration of biomarkers with the goal of exploring the pathogenic mechanisms or factors that contribute to disease progression. Among the "Treatment decisions" studies, the objective was to predict outcomes following treatment selection or guide selection of therapeutic or surgical options using biomarkers. Finally, in the "Exploratory" studies, there was an untargeted exploration of biomarkers with no specific disease of interest; for example, a study with the goal of describing the proteomic profile of the aqueous humour in a healthy patient.

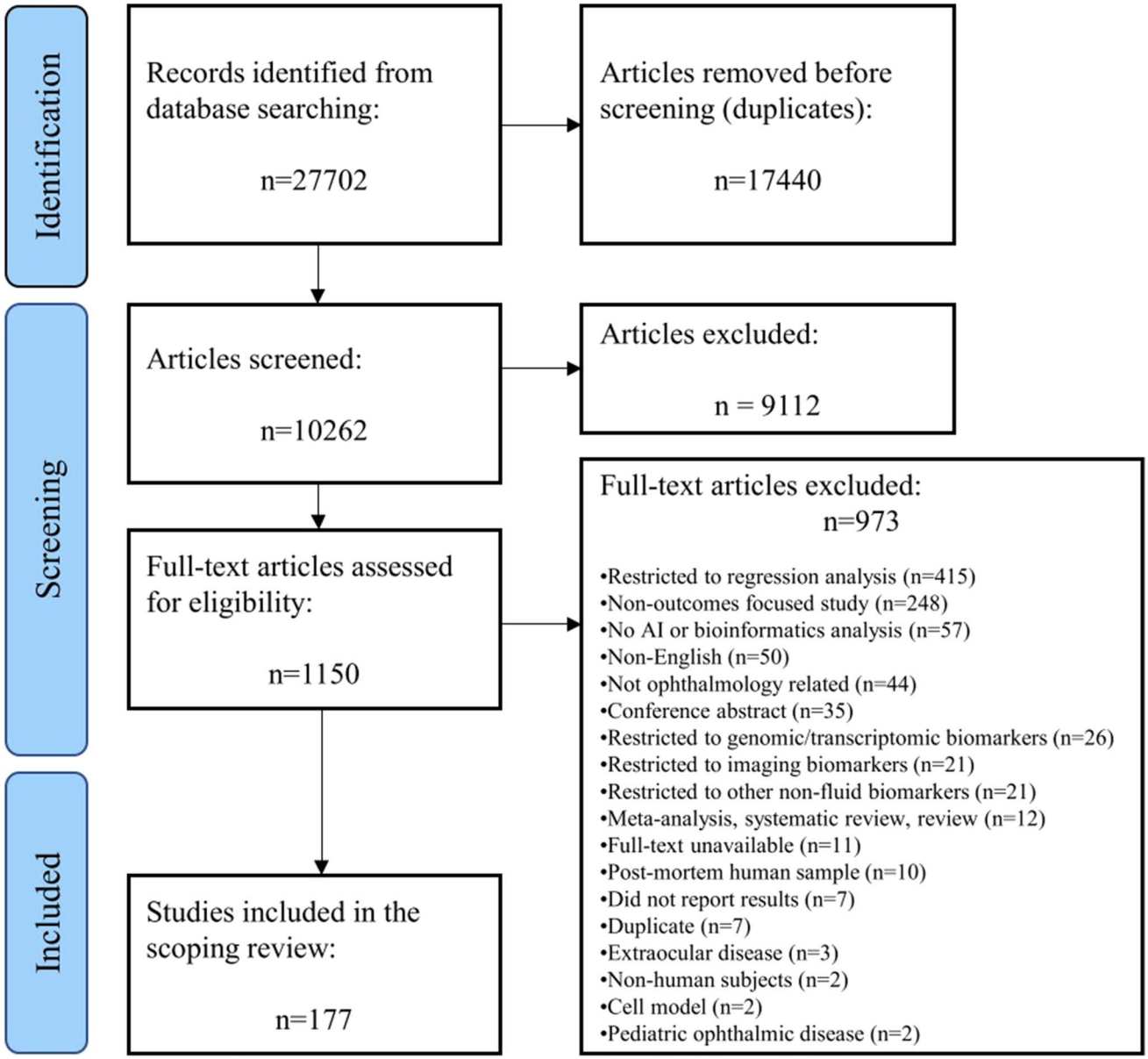

Fig. 1 PRISMA flowchart diagram for study identification and selection

Results

The included studies utilized heterogeneous methods, and had highly variable findings and objectives. Firstly, a summary of the characteristics of the studies included is presented. Next, the methodologies and aims of AI algorithms are assessed by dividing them into supervised and unsupervised AI. Commonly encountered applications as well as unique examples are presented to illustrate their use in investigating various ophthalmological conditions. Then, their predictive accuracy is appraised. Finally, the most common biofluids and significant biomarkers are summarized.

Study characteristics

A total of 10,262 articles were found in the literature search after deduplication, and 177 studies met inclusion criteria (Fig. 1). The complete list of included papers and study characteristics is contained in Appendix B. There was a global distribution of included studies, with the largest proportion of studies being performed in China (27%), the USA (17%), Germany (8%), Japan (5%), Singapore (5%), and Spain (5%). In total 31 countries were represented. The most commonly studied ocular diseases were diabetic eye diseases, with 50 papers (28%) focusing on diabetic

Table 2 Characteristics of artificial intelligence and bioinformatic analyses of biofluid markers by ophthalmic disease

AI algorithm	Total (n)	Ophthalmic Disease n (%)					
		DR/DME	Glaucoma	AMD	Dry Eye Disease	Uveitis	Other
		50 (28.2)	25 (14.1)	20 (11.3)	10 (5.6)	9 (5.1)	63 (35.6)
Discriminat Analysis	58	13	11	7	2	2	23
PCA	48	11	6	10	1	4	16
Random forest	31	14	5	2	0	3	7
Artifical Neural Network	25	6	5	1	2	2	9
Support Vector Machine	24	9	6	3	0	1	5
Decision tree	15	4	1	2	0	2	6
K-Nearest Neighbors Algorithm	8	2	1	1	0	2	2
Deep learning	3	2	1	0	0	0	0
KEGG	39	3	6	6	3	1	20
Hierarchical cluster analysis	38	4	5	5	1	5	18
Gene Ontology	36	2	5	1	5	1	22
Pathway analysis	18	1	3	5	0	2	7

Studies that used multiple types of AI algorithm contributed multiple counts to the values contained within the table

Acronyms: *AI* = artificial intelligence; *AMD* = age-related macular degeneration; *DME* = diabetic macular edema; *DR* = diabetic retinopathy; *KEGG* = Kyoto Encyclopedia of Genes and Genomes; *OSD* = ocular surface disease; *PCA* = principal component analysis;

retinopathy (DR), proliferative DR, and diabetic macular edema (DME). Glaucoma was explored in 25 studies (14%), age-related macular degeneration (AMD) in 20 studies (11%), dry eye disease in 10 studies (6%), and uveitis in 9 studies (5%). 63 studies explored other ocular diseases. The majority of studies (97, 55%) were classified as "Identifying characteristics", while 53 (30%) were classified as "Diagnosis or prognosis", 17 (10%) as "Treatment decisions", and 10 (6%) as "Exploratory".

AI characteristics

Table 1 summarizes the activities, strengths, and weaknesses of the commonly used algorithms of included papers. A summary of how often these algorithms are deployed and which disease they are used to study is contained in Table 2. Supervised learning was used in 91 papers (51%), unsupervised AI was used in 83 (46%), and bioinformatics in 85 (48%). Ninety-eight papers (55%) used more than one class of AI (e.g. > 1 of supervised, unsupervised, bioinformatics, or statistical techniques), while 79 (45%) used only one. Study sample sizes ranged from 1 to 19,084, and the number of inputted variables in analyses ranged from one to thousands. A common analysis pathway employed in the included studies was first to perform dimensionality reduction using unsupervised techniques such as PCA, followed by supervised learning, such as discriminant analysis, to differentiate between cases and controls, followed by bioinformatics analysis, such as pathway analysis, to output information about the biological processes implicated. Similarly, bioinformatics tools were often deployed with unsupervised techniques to translate groups of biomarkers into information regarding biological processes or pathways, for which treatment targets or disease etiology could be inferred.

Supervised AI

Supervised AI was the most commonly used class of AI. Discriminant analysis was used in 58 (33%) papers, making it the most commonly used supervised learning technique. Other common supervised algorithms were random forest (31, 18%), ANN (25, 14%), SVM (24, 14%), and decision trees (16, 9%). Most often, the application of these algorithms was to differentiate cases of ophthalmic disease detection from controls, using input variables that were either proteomic, metabolomic, or individual proteins in combination with demographic, genomic, or imaging markers. These tools were implemented to diagnoses a wide range of ophthalmic diseases such as DR [21, 22], glaucoma [23, 24], and uveitis [25]. Other predictive applications included discriminating between different diseases or diseases subtypes [26] and prediction of long-term risk of progression of an ophthalmic condition [27, 28].

Supervised AI was also used to determine the most influential biomarkers on an algorithm's predictive value, thereby implying possible biological significance of the biomarker

in disease. During the learning process, the supervised AI was trained on expert graded data in order to identify differentially expressed biomarkers between cases and controls in various ophthalmic diseases [29–34]. Notably, as humans are required to classify data in the training set, there is potential for error if samples are incorrectly classified. Among the included studies there was inconsistent reporting of the diagnostic guidelines used to classify data, the processes for training the supervised AI, the size of the test and training sets, and the specific algorithm activities. This could have introduced error into a substantial portion of the studies, reducing the external validity of their findings and compromising study reproducibility.

Unsupervised AI

PCA was the most widely used unsupervised technique, found in 48 papers. Also commonly used were hierarchical cluster analysis (38) and k-means clustering (4). PCA was a highly versatile algorithm, and was commonly deployed both alone and in conjunction with supervised AI. PCA was implemented within a large proportion of ML studies, as it was often applied as a step prior to a second ML analysis. In these instances, it was applied in order to determine in an unassuming manner whether the disease and control groups are distinguishable based on the biomarkers applied, and identify/remove confounding factors and outliers causing the disease and control groups to cluster in an unexpected manner [23, 35–41]. When deployed in this way, the results often determined how the data would be best applied in the final predictive AI model of the study, taking into account the levels of importance of certain biomarkers, and confounding factors [23, 35–41]. PCA was also used as a comparator model amongst AI algorithms to determine the algorithm that outputs the highest predictive accuracy, achieving the highest accuracy in contexts with highly complex datasets. Finally, several studies utilized PCA to identify biomarkers of interest within discriminative principal components, which were then subsequently analyzed by ontological methods to understand the implications for specific molecular pathways [41–44].

Hierarchical cluster analysis was almost always used with other forms of AI analysis. For example, biomarkers of interest were identified via clustering, and the strength of relationships subsequently compared using techniques such as discriminant analysis or regression [34, 45, 46]. Other forms of clustering analyses were also commonly used as a tool alone or in tandem with ontological analysis, and were deployed to (1) determine whether biomarker profiles can distinguish experimental and control groups in an unsupervised fashion, (2) identify molecularly distinct subgroups that may not have been anticipated, and (3) objectively cluster a disease cohort into distinct subgroups that are useful for prediction of the disease course. In use case (2) these algorithms enabled the identification of characteristic biomarkers and then the translation of these markers into meaningful pathways; for example, Zhavoronkov determined that TGF-b was elevated in primary open angle glaucoma patients using hierarchical cluster analysis, and linked the biomarker to pro-fibrotic pathways leading to extracellular matrix remodeling in trabecular meshwork and lamina cribosa using pathway analysis [47]. Often heatmaps were used in tandem with hierarchal cluster analyses to visually depict the most up- or downregulated proteins or protein clusters in a given patient group of patients [48–50]. Heatmaps were, in a small number of instances, used without a cluster analysis, still providing a visual guide to biomarker patterns but without an objective assignment of statistically distinct groups. K-means clustering was used to cluster a disease cohort into distinct subgroups [51, 52]. In this use case, cluster analyses were particularly useful in defining subgroups that shared common characteristics in disease states that may be fairly heterogeneous in underlying etiology.

Bioinformatics

There were many protein/metabolite/gene ontology tools utilized for both defining the functional or structural groups, and for conducting the pathway analyses themselves. These included Kyoto Encyclopedia of Genes and Genomes (KEGG), MetaboAnalyst, REACTOME, STRING, PANTHER, DAVID, and SWISSPROT. KEGG was the most commonly used, found in 39 studies. In some cases, as opposed to using gene ontology (GO) to identify changes in pathological groups, a number of studies including Aretz et al. (2013) and Dor et al. (2019) applied GO functional annotation in order to characterise the most prominent functional pathways in healthy human vitreous and tear fluids respectively [53, 54]. In another unique use case, Velez et al. (2017) utilized hierarchical clustering and pathway analysis to identify the most prominent therapeutic targets for individual cases of neovascular inflammatory vitreoretinopathy [55]. This group chose and implemented effective pharmacologic therapies for individual patients based on their most prominently dysregulated proteins and pathways, allowing for direct clinical application of findings [55].

AI Predictive accuracy

Amongst the identified studies, AI was often used to differentiate disease status from controls, or to predict disease subtype. Quantitative outcomes expressing the efficacy of a given predictive model were presented in multiple ways, which included percentage accuracy, percentage sensitivity and specificity, or area under the curve (AUC) of a receiver operator characteristic (ROC) curve—a total of 82 papers (46%) reported accuracy.

Accuracies of AI tools used in each study are contained in Appendix B. A number of studies, particularly those studying patients with diabetic retinopathy (DR), stated an aim to optimize predictive accuracy for DR detection [22, 56, 57]. Some studies also compared different predictive AI algorithms to maximize accuracy [26, 58–60]. While summarizing the accuracies of these models is made challenging by their differing objectives, and variable accuracy reporting, many of the models described achieved strong levels of accuracy, with AUCs over 0.85, and accuracy, sensitivity, and specificity over 90%. While no definitive trends in accuracy emerged between different AI algorithms, ANNs, random forest models, and decision trees tended to exhibit the highest level of accuracy. The majority of analyses implemented validation methods such as training and test samples or tenfold cross validation to ensure that the estimated accuracy was highly unlikely to be a result of chance. Several studies applied AI algorithms with the alternative goal of determining the most influential biomarkers on accurate prediction. This required the use of algorithms that expressed the relative importance or rank of inputted variables in the model, with random forest, k-means clustering, and PCA algorithms facilitating this goal.

Biofluids and significant biomarkers

Serum was the most commonly accessed biomarker, used in 53 studies (30%). Aqueous humour was analyzed in 30 studies (17%), tears in 25 (14%), plasma in 18 (10%), vitreous humour in 17 (10%), and tissue biopsy in 12 (7%). The most common biopsy locations were cornea, pterygium, and conjunctiva. Combinations of biofluids were used in 16 (9%) studies. The complete proteomic profile was examined in 82 (46%) of studies, the metabolic profile studied in 39 (22%), and the cytokine profile studied in 7 (4%). Given the expansive nature of some of the studies included, significant biomarkers found ranged from none to thousands. In some of the studies with thousands of significant findings, the identified biomarkers were not detailed completely, making compilation of significant biomarkers for each disease challenging [36]. Additionally, while some biomarkers were implicated in the development, progression, or treatment of a specific disease over multiple studies, for most significant findings there was conflicting evidence presented in other studies. The biomarkers and pathways implicated in diabetic eye disease, glaucoma, AMD, ocular surface diseases, and uveal diseases are summarized in Table 3.

Discussion

The current scoping review summarizes the methods of AI and bioinformatics as they have been applied for analysis of ocular biofluid markers. The database of studies presented could be further analyzed for specific disease states and types of AI. With ophthalmology being at the forefront of medical AI development, it is important that ophthalmologists be aware of these developing technologies and remain mindful of the possibility that these technologies could be incorporated into clinical practice in the near future.

One of the most self-evident advantages of bioinformatic methods in proteomic and metabolomic studies, particularly overexpression/enrichment analyses, is that they provide specific insights into the complex molecular mechanisms and actions occurring in a pathological or physiological state [42, 61]. This can be advantageous for genomic and transcriptomic data, but as RNA concentrations are not always precisely proportionate to the amount of protein produced, proteomic analysis could provide more specific insight on the level of action of specific mechanisms. In ophthalmology, there is the particular advantage of conducting pathway analyses on vitreous or aqueous fluid samples to provide insight on the specific dysregulations that are occurring in the organ of interest [12, 27, 43]. Data from detailed fundoscopic or optical coherence tomography images could greatly complement bioinformatic data, providing insight on both the micro- and macroscopic pathologies occurring. Pathway analyses are also advantageous in very small patient samples, or in rare diseases, as they do not require the same power that is needed for AI algorithm accuracy [55]. However, as pathway analyses indicate significantly altered molecular pathways but do not make predictions, the results only serve as indicators for further investigation in the population of interest. Finally, Velez et al. [55] demonstrated the application of bioinformatics for individualized therapeutic management if applied to a patient's proteome.

One of the most effective ways to approach any predictive hypothesis in the included studies was the comparison of accuracies of multiple algorithms, assuming each one was designed and implemented properly, to see which model performed best with the given biofluid markers and patient population. In many instances in the included literature, it was observed that a random forest model outperformed other tested models in accuracy, and in particular cases even outperformed ANNs, which are often thought to be the most accurate predictive tools [59, 62]. It is unclear why random forest models consistently exhibited slightly better accuracy than other algorithms, but merits further investigation, and is worth consideration of inclusion when implementing future biofluid marker studies. Broadly, ANNs and decisions trees also had strong predictive accuracy. PCA was often used with supervised AI, in part because it can improves accuracy of other algorithms via dimensionality reduction. They are also very easy to implement for a wide variety of uses.

Interestingly, despite a multitude of AI models over many applications demonstrating strong predictive accuracy, no definitive characteristic biomarkers emerged for

Table 3 Implicated biomarkers and pathways in common ophthalmic diseases

Disease	Biomarkers	Pathways
DR/DME	Over 350 of unique biomarkers were implicated in the development, progression, treatment, and prediction of morbidity for all subtypes of DR and DME. There were many differentially expressed biomarkers identified between studies, although other studies presented conflicting evidence for almost all identified biomarkers. Unsurprisingly, the most commonly implicated biomarkers in DR/DME development were HbA1c and glycemic level	Over 150 of pathways were implicated in the development, progression, and treatment DR and DME. Given the complexity and heterogeneity of the studies included, a summary of the involved pathways is beyond the scope of this table
Glaucoma	Over 175 unique differentially expressed biomarkers were found across all glaucoma subtypes. Glycemic level, TGF-β1, alanine, glutamine, leucine, taurine, hypoxanthine, and sorbitol were all found to be significantly associated with POAG by more than one study, with glutamine being the most commonly implicated (three studies). HbA1c and VEGF were implicated in NVG development, while no studies found a common biomarker for NTG or PACG	Over 75 biological pathways implicated in POAG development. Pathways over multiple studies included the glycolytic pathway, inflammation, autoimmune mechanisms, extracellular matrix-receptor interaction, cellular transport, cell–cell signalling, and signal transduction. No pathways were identified over multiple studies for PACG, NTG or NVG by multiple studies
AMD	Over 250 markers found to be significantly associated with AMD development. The most commonly implicated biomarkers were cholesterol, CRP, and serum triglycerides. Notably, other included studies presented conflicting findings and indicated that these biomarkers were not associated with AMD development	Over 70 pathways associated with AMD development were identified. Pathways identified over multiple studies included oxidative stress, the glycerophospholipid pathway, 2-oxocarboxylic acid metabolism, ABC transportation, protein digestion and absorption, and mineral absorption
OSD	Over 50 markers were found to be significantly associated with dry eye, Sjögren's syndrome, and Meibomian Gland Dysfunction. Biomarkers implicated in dry eye included apolipoprotein, haptoglobin, annexin 1, Glutathione S- transferase, lipocalin-1, prolactin inducible protein, lysozyme C, lactotransferrin, cystatin S, and mammaglobin-b, proline rich protein across 5 studies. There was little overlap between biomarkers reported in association with keratoconus and other corneal disease development	Dysregulation of lipid metabolic processes, oxidation reduction, cytokine production, transportation, and immune response pathways were associated with dry eye and meibomian gland dysfunction. TNF-a signalling, B cell survival, Krebs cycle, oxidative stress, inflammation and complement coagulation were implicated in Sjögren's Syndrome. Commonly reported pathways associated with keratoconus developed were dysregulation of apoptosis, oxidative stress, response to vitamin D, and angiogenesis
Uveal diseases	The number of individual biomarkers analyzed varied from 1 to 4,386 per study with over 50% of studies analyzing < 10. There was very little overlap in the biomarkers found to be significant between studies for each condition, with the only commonly identified biomarker being lactate dehydrogenase in 50% of the uveal melanoma studies	Greater than 10 biological pathways were implicated in uveitis development, but none were confirmed over multiple studies. Novel pathways discovered included sucrose metabolism, phenylalanine metabolism, pyruvate metabolism, purine metabolism, tyrosine metabolism, vitamin B6 metabolism, branched-chain amino acid biosynthesis, ascorbate metabolism, the tricarboxylic acid cycle, glycolysis-diverting pathways, and arginase pathway. No biological pathways were identified in uveal melanoma

Acronyms: *AMD* = age-related macular degeneration; *CRP* = c-reactive protein; *NTG* = normal tension glaucoma; *NVG* = neovascular glaucoma; *OSD* = ocular surface disease; *PACG* = primary angle closure glaucoma; *POAG* = primary open angle glaucoma; *VEGF* = vascular endothelial growth factor

most diseases. As noted above, most studies found biomarkers significantly associated with disease development, progression, or treatment, but few were confirmed by other studies and conflicting findings were often found. As such, AI tools remain valuable for predictive applications, but have shown restricted utility in exploration of disease etiology. AI tools should be adept at such applications, but a number of issues in the included studies prevent strong

levels of agreement between studies. The complete activities of the algorithms were rarely explained, also known as a "black-box" approach [61]. Further, the rationale for AI algorithm selection was often excluded. As such, studies with analogous objectives, participants, and data sets could be using wholly different selection parameters for biomarker, and variation in AI activities could cause disagreement in biomarker significance. Many studies did not describe their patient population in detail, which could have led to factors such as demographics, comorbidities, lifestyle, or medication use altering their biomarker profiles. For example, all of the patients recruited by Li et al. were unrelated Chinese Han individuals who were recruited from the Zhongshan Ophthalmic Center, which could theoretically influence their distinct biomarker profiles [63]. There was also intrinsic variability in the biomarker profiles of clinically similar patients [45]. Additionally, biofluid extraction techniques varied significantly between studies, with differing location of biomarker extraction and small quantities of biofluid analyzed; volumes of ocular biofluids extracted ranged from 25 to 1000uL. While small volumes technically fall within the range that is acceptable for analysis, small aliquots can be susceptible to changes in the microenvironment, an issue made worse by differences in storage technique, sample handling, and the dilution of samples for analysis. Future efforts should describe analytical methods in detail and comprehensively describe the study population. Our group has previously published systematic reviews of AI analysis of biofluid markers in AMD [64], glaucoma [65], corneal disease [66], uveal disease [67], and retinal occlusive disease [68].

Although not within the scope of this review, it is worth acknowledging that regressions are argued to be the simplest form of ML, although this is controversial [69]. Regressions are highly restricted, simple, supervised prediction models [69]. Although less powerful and useful in highly complex datasets, they should not be discounted if they are the appropriate method for a simple question with a relatively small number of input variables. Over 40 articles in the current review included logistic regressions, either to use as comparator models against the other AI models tested or to quantify associations determined by other AI methods. Regressions were able to achieve accuracies that were often comparable to other types of AI, in some instances achieving a higher (but not statistically significant) area under the curve than a compared ANN [70]. Limitations of this review include the restriction to English language papers only. While a more focused systematic review could have explored these concepts in more depth, the database of studies we have created in this study will allow for this in future research. While a more focused systematic review could have explored these concepts in more depth, the database of studies we have created in this study will allow for this in future research.

The studies included in this scoping review are varied both in terms of their methodology and their objectives. Numerous studies provide examples of AI tools that could be directly applied to clinical practise following further development and investigation. For example, AI tools can support diagnosis of glaucoma, either in a screening context or to augment a clinicians own decision making [71, 72]. Automated AI tools could enable glaucoma screening at primary care facilities or low resource settings, leading to early diagnoses and the subsequent improvement of outcomes and efficient use of specialist time. Alternatively, AI tools could be used to predict responsiveness to anti-VEGF therapy in the setting of wet AMD, potentially sparing a patient countless uncomfortable injections or supporting the preservation of their vision [12]. While an exhaustive list of potential clinical applications is beyond the scope of this—or any other—manuscript, AI has the potential to transform clinical ophthalmology. However, it is crucial to note that none of the included studies include a clinical proven application of AI.

Conclusion

AI and bioinformatic analyses offer major advantages in understanding and treating ophthalmic diseases. When used in conjunction with biofluid markers as input variable, they provide improvements in detection of disease, understanding mechanisms of molecular etiologies, and an ability to provide individualized targeted therapeutic treatment for patients. However, despite the promise of application of AI in tools that have diagnostic or prognostic power, none of these tools have been directly integrated or tested in clinical workflow. Therefore, most AI-based applications using ocular biofluids are still in the translational stage and have not yet proven a clear use in clinical trials. Additionally, it is important to consider the role of these tools in a clinical context to ensure their thoughtful implementation and reduce poor technical understanding or inappropriate use [3]. There are many AI algorithms currently being utilized in ophthalmology, and selecting a tool appropriate for the intended task is crucial. Given the progression of AI towards use in both research and the clinic, ophthalmologists should be broadly aware of the commonly used algorithms and their applications. Future directions include the development of robust, open-source algorithms that make use of both biofluids and imaging variables to make predictions regarding disease exploration, diagnosis or prognostication. Furthermore, it is imperative to determine validation models and evaluate approaches to clinical deployment. A cost-effective analysis of implementation in clinical practice as well as training for ophthalmologists on their use may increase clinical acceptance.

Appendix A

Search strategy utilized for five electronic databases (EMBASE, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science).

Embase

1. (ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo?r" or "vitreous fluid" or vitreo* or "aqueous humo?r" or "aqueous fluid" or tears or ((tear or lacrimal) adj fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or ?????????opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis adj3 "anterior chamber")).tw.
2. ("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera?nostic? or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm? or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neur??al) adj (cluster* or learning or learner? or classifi* or network?)) or "k-nearest neighbo?r?" or "naive bayes" or (decision adj (tree? or forest? or jungle?)) or "random forest?" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) adj1 (regression? or model?)) or bioinformatic? or "gene ontology" or "Kyoto Encyclopedia of Genes and Genomes" or "KEGG" or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*))).tw.
3. (Proteomic? or proteome? or metabolomic? or metabolome? or lipidomic? or lipidome? or "?????inflammatory protein?" or "?????inflammatory marker" or cytokine? or interleukin? or lymphokine? or monokine? or interferon? or "colony stimulating factor?" or chemokine? or "growth factor?" or "necrosis factor?" or "chemotactic protein?" or "adhesion molecule?" or "adhesion protein?" or "matrix metalloproteinase-2" or myeloperoxidase? or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin? or ((hemoglobin or haemoglobin) adj1 (a1c or glycated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))).tw.
4. ophthalmology/
5. eye/ or anterior eye chamber/ or anterior eye segment/ or aqueous humor/ or exp conjunctiva/ or exp cornea/ or eye fundus/ or eyeball/ or exp lens/ or ocular blood vessel/ or ophthalmic artery/ or optic disk/ or palpebral fissure/ or posterior eye chamber/ or posterior eye segment/ or exp retina/ or exp sclera/ or sphincter pupillae muscle/ or tenon capsule/ or trabecular meshwork/ or exp uvea/ or vitreous body/
6. lacrimal fluid/
7. eye disease/ or exp accommodation disorder/ or exp conjunctiva disease/ or exp cornea disease/ or exp dry eye/ or exp eye burning/ or exp eye chamber disease/ or exp eye discharge/ or exp eye discomfort/ or exp eye edema/ or exp eye infection/ or exp eye inflammation/ or exp eye injury/ or exp eye irritation/ or exp eye jaundice/ or exp eye malformation/ or exp eye pain/ or exp eye redness/ or exp eye swelling/ or exp eye toxicity/ or exp eye tumor/ or exp glaucoma/ or exp intraocular hemorrhage/ or exp intraocular pressure abnormality/ or exp lens disease/ or exp ocular albinism/ or exp ocular fibrosis/ or exp ocular pruritus/ or exp ocular surface disease/ or exp optic nerve disease/ or exp photophobia/ or exp pupil disease/ or exp retina disease/ or exp sclera disease/ or exp uvea disease/ or exp visual disorder/ or exp vitreous disease/
8. exp vitrectomy/
9. exp phacoemulsification/
10. exp trabeculectomy/
11. personalized medicine/
12. theranostic nanomedicine/
13. algorithm/
14. exp clustering algorithm/
15. artificial intelligence/
16. exp machine learning/
17. "decision tree"/
18. bioinformatics/
19. exp regression analysis/
20. discriminant analysis/
21. gene ontology/
22. proteomics/ or comparative proteomics/ or immunoproteomics/ or exp pharmacoproteomics/ or phosphoproteomics/ or proteogenomics/ or secretomics/
23. proteome/
24. metabolomics/
25. metabolome/
26. lipidomics/
27. lipidome/

28. exp cytokine/
29. exp cell adhesion molecule/
30. myeloperoxidase/
31. "tissue inhibitor of metalloproteinase 1"/
32. "tissue inhibitor of metalloproteinase 2"/
33. brain derived neurotrophic factor/
34. exp angiopoietin/
35. exp "peptides and proteins"/ec [Endogenous Compound]
36. biological marker/ec [Endogenous Compound]
37. 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10
38. 2 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
39. (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay).tw.
40. (35 or 36) and 39
41. 3 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 40
42. 37 and 38 and 41
43. limit 42 to conference abstracts
44. limit 42 to animal studies
45. limit 44 to human
46. limit 42 to "review"
47. 44 not 45
48. 42 not (43 or 46 or 47)

Medline

1. (ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo?r" or "vitreous fluid" or vitreo* or "aqueous humo?r" or "aqueous fluid" or tears or ((tear or lacrimal) adj fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or ?????????opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis adj3 "anterior chamber")).tw.
2. ("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera?nostic? or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm? or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neur??al) adj (cluster* or learning or learner? or classifi* or network?)) or "k-nearest neighbo?r?" or "naive bayes" or (decision adj (tree? or forest? or jungle?)) or "random forest?" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) adj1 (regression? or model?)) or bioinformatic? or "gene ontology" or "Kyoto Encyclopedia of Genes and Genomes" or "KEGG" or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*))).tw.
3. (Proteomic? or proteome? or metabolomic? or metabolome? or lipidomic? or lipidome? or "?????inflammatory protein?" or "?????inflammatory marker" or cytokine? or interleukin? or lymphokine? or monokine? or interferon? or "colony stimulating factor?" or chemokine? or "growth factor?" or "necrosis factor?" or "chemotactic protein?" or "adhesion molecule?" or "adhesion protein?" or "matrix metalloproteinase-2" or myeloperoxidase? or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin? or ((hemoglobin or haemoglobin) adj1 (a1c or glycated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))).tw.
4. exp Ophthalmology/cl, di, dg, ec, pd, px, sn, sd, su, th, td, ed, es, hi, is, mt, og, rt, st [Classification, Diagnosis, Diagnostic Imaging, Economics, Pharmacology, Psychology, Statistics & Numerical Data, Supply & Distribution, Surgery, Therapy, Trends, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Radiotherapy, Standards]
5. eye/ or exp anterior eye segment/ or "anterior capsule of the lens"/ or conjunctiva/ or meibomian glands/ or exp "pigment epithelium of eye"/ or exp posterior eye segment/ or exp retina/ or sclera/ or tenon capsule/ or exp uvea/
6. Tears/
7. eye diseases/ or cogan syndrome/ or exp conjunctival diseases/ or exp corneal diseases/ or exp eye abnormalities/ or exp eye diseases, hereditary/ or exp eye hemorrhage/ or exp eye infections/ or exp eye injuries/ or exp eye manifestations/ or exp eye neoplasms/ or exp lens diseases/ or exp ocular hypertension/ or ocular hypotension/ or exp optic nerve diseases/ or exp pupil disorders/ or exp refractive errors/ or exp retinal diseases/ or exp scleral diseases/ or exp uveal diseases/ or exp vision disorders/ or vitreous detachment/
8. Vitrectomy/ae, ec, ed, es, hi, is, mt, mo, nu, px, rh, st, sn, td [Adverse Effects, Economics, Education, Ethics, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends]
9. Phacoemulsification/ae, cl, ec, ed, hi, is, mt, mo, nu, px, rh, st, sn, td [Adverse Effects, Classification, Eco-

nomics, Education, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends]
10. Trabeculectomy/nu, px, rh, st, sn, td, ae, cl, ec, ed, hi, is, mt, mo [Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends, Adverse Effects, Classification, Economics, Education, History, Instrumentation, Methods, Mortality]
11. Precision Medicine/ae, cl, ec, es, hi, is, mt, mo, nu, px, st, sn, td [Adverse Effects, Classification, Economics, Ethics, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Standards, Statistics & Numerical Data, Trends]
12. Theranostic Nanomedicine/
13. exp algorithms/
14. Neural Networks, Computer/
15. Decision Trees/
16. exp Regression Analysis/
17. Discriminant Analysis/
18. exp Proteomics/cl, ec, ed, es, hi, is, mt, og, st, sn, td [Classification, Economics, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Trends]
19. Proteome/
20. exp Metabolomics/cl, ec, ed, es, hi, is, mt, og, st, sn, td [Classification, Economics, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Trends]
21. Metabolome/
22. exp Cytokines/
23. exp Cell Adhesion Molecules/
24. Matrix Metalloproteinase 2/
25. Peroxidase/
26. "Tissue Inhibitor of Metalloproteinase-1"/
27. "Tissue Inhibitor of Metalloproteinase-2"/Brain-Derived Neurotrophic Factor/
28. exp Angiopoietins/
29. Gene Ontology/
30. exp Proteins/
31. exp Peptides/
32. Biomarkers/
33. (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay).tw.
34. (31 or 32 or 33) and 3
35. 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10
36. 2 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 30
37. 3 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 35
38. 36 and 37 and 38
39. limit 39 to animals
40. limit 40 to humans
41. 40 not 41
42. limit 39 to "review articles"
43. 39 not (42 or 43)

Web of science

1. (TI = (ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo$r" or "vitreous fluid" or vitreo* or "aqueous humo$r" or "aqueous fluid" or tears or ((tear or lacrimal) NEAR/1 fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or *opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy. tw. or (paracentesis NEAR/3 "anterior chamber")) or AB = (ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris.tw. or "vitreous body" or "vitreous humo$r" or "vitreous fluid" or vitreo* or "aqueous humo$r" or "aqueous fluid" or tears or ((tear or lacrimal) NEAR/1 fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis NEAR/3 "anterior chamber"))) AND
2. (TI = ("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera$nostic* or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm$ or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neural or neuronal) NEAR/1 (cluster* or learning or learner$ or classifi* or network$)) or "k-nearest neighbo$r*" or "naive bayes" or (decision NEAR/1 (tree$ or forest$ or jungle$)) or "random forest$" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) NEAR/1 (regression$ or model$)) or bioinformatic$ or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*))) OR AB = ("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera$nostic* or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm$ or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neural or neuronal) NEAR/1 (cluster* or learning or learner$

or classifi* or network$)) or "k-nearest neighbo$r*" or "naive bayes" or (decision NEAR/1 (tree$ or forest$ or jungle$)) or "random forest$" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) NEAR/1 (regression$ or model$)) or bioinformatic$ or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*)))) AND

3. (TI = (Proteomic$ or proteome$ or metabolomic$ or metabolome$ or lipidomic$ or lipidome$ or "*inflammatory protein$" or "*inflammatory marker" or cytokine$ or interleukin$ or lymphokine$ or monokine$ or interferon$ or "colony stimulating factor$" or chemokine$ or "growth factor$" or "necrosis factor$" or "chemotactic protein$" or "adhesion molecule$" or "adhesion protein$" or "matrix metalloproteinase-2" or myeloperoxidase$ or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin$ or ((hemoglobin or haemoglobin) NEAR/1 (a1c or glycated or glycosylated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration$ or level$ or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))) OR AB = (Proteomic$ or proteome$ or metabolomic$ or metabolome$ or lipidomic$ or lipidome$ or "inflammatory protein$" or "inflammatory marker" or cytokine$ or interleukin$ or lymphokine$ or monokine$ or interferon$ or "colony stimulating factor$" or chemokine$ or "growth factor$" or "necrosis factor$" or "chemotactic protein$" or "adhesion molecule$" or "adhesion protein$" or "matrix metalloproteinase-2" or myeloperoxidase$ or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin$ or ((hemoglobin or haemoglobin) NEAR/1 (a1c or glycated or glycosylated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration$ or level$ or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))))

Cochrane central register of controlled trials (CONTROL), cochrane database of systematic reviews

1. ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo*r" or "vitreous fluid" or vitreo* or "aqueous humo*r" or "aqueous fluid" or tears or ((tear or lacrimal) NEXT fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or *opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis NEAR/3 "anterior chamber")
2. "precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera*nostic* or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm* or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neural or neuronal) NEXT (cluster* or learning or learner* or classifi* or network*)) or "k-nearest neighbo*r*" or "naive bayes" or (decision NEXT (tree* or forest* or jungle*)) or "random forest*" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) NEXT (regression* or model*)) or bioinformatic* or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*))
3. Proteomic* or proteome* or metabolomic* or metabolome* or lipidomic* or lipidome* or "*inflammatory protein*" or "*inflammatory marker*" or cytokine* or interleukin* or lymphokine* or monokine$ or interferon* or "colony stimulating factor*" or chemokine* or "growth factor*" or "necrosis factor*" or "chemotactic protein*" or "adhesion molecule*" or "adhesion protein*" or "matrix metalloproteinase-2" or myeloperoxidase* or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin* or ((hemoglobin or haemoglobin) NEXT (a1c or glycated or glycosylated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration* or level* or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))
4. MeSH descriptor: [Ophthalmology]
5. MeSH descriptor: [Eye]
6. MeSH descriptor: [Tears]
7. MeSH descriptor: [Eye Diseases]
8. MeSH descriptor: [Vitrectomy]
9. MeSH descriptor: [Phacoemulsification]
10. MeSH descriptor: [Trabeculectomy]
11. MeSH descriptor: [Precision Medicine]
12. MeSH descriptor: [Theranostic Nanomedicine]
13. MeSH descriptor: [Artificial Intelligence]
14. MeSH descriptor: [Algorithms]
15. MeSH descriptor: [Neural Networks, Computer]
16. MeSH descriptor: [Decision Trees]

17. MeSH descriptor: [Regression Analysis]
18. MeSH descriptor: [Discriminant Analysis]
19. MeSH descriptor: [Proteomics]
20. MeSH descriptor: [Metabolomics]
21. MeSH descriptor: [Proteins] explode
22. MeSH descriptor: [Peptides]
23. MeSH descriptor: [Biomarkers]
24. concentration* or level* or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay
25. (#21 or #22 or #23) and #24
26. MeSH descriptor: [Cytokines]
27. MeSH descriptor: [Cytokines]
28. MeSH descriptor: [Matrix Metalloproteinase 2]
29. MeSH descriptor: [Peroxidase]
30. MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-1]
31. MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-2]
32. MeSH descriptor: [Brain-Derived Neurotrophic Factor
33. MeSH descriptor: [Angiopoietins]
34. MeSH descriptor: [Anterior Eye Segment]
35. MeSH descriptor: [Anterior Capsule of the Lens]
36. MeSH descriptor: [Axial Length, Eye]
37. MeSH descriptor: [Pigment Epithelium of Eye]
38. MeSH descriptor: [Posterior Eye Segment]
39. MeSH descriptor: [Retina]
40. MeSH descriptor: [Sclera]
41. MeSH descriptor: [Tenon Capsule]
42. MeSH descriptor: [Uvea]
43. MeSH descriptor: [Asthenopia]
44. MeSH descriptor: [Cogan Syndrome]
45. MeSH descriptor: [Conjunctival Diseases]
46. MeSH descriptor: [Corneal Diseases]
47. MeSH descriptor: [Eye Abnormalities]
48. MeSH descriptor: [Eye Diseases, Hereditary]
49. MeSH descriptor: [Eye Hemorrhage]
50. MeSH descriptor: [Eye Infections]
51. MeSH descriptor: [Eye Injuries]
52. MeSH descriptor: [Eye Manifestations]
53. MeSH descriptor: [Eye Neoplasms]
54. MeSH descriptor: [Lens Diseases]
55. MeSH descriptor: [Ocular Hypertension]
56. MeSH descriptor: [Ocular Hypotension]
57. MeSH descriptor: [Optic Nerve Diseases]
58. MeSH descriptor: [Pupil Disorders]
59. MeSH descriptor: [Refractive Errors]
60. MeSH descriptor: [Retinal Diseases]
61. MeSH descriptor: [Scleral Diseases]
62. MeSH descriptor: [Uveal Diseases]
63. MeSH descriptor: [Vision Disorders]
64. MeSH descriptor: [Vitreous Detachment]
65. #1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64
66. #2 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
67. #3 or #19 or #20 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
68. #65 and #66 and #67

Appendix B

Table 4 Characteristics of all studies identified

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Acar [81], 2020	Netherlands	AMD	Identifying characteristics	Unsupervised: PCA Statistical method: Univariate logistic regression, linear regression	Not reported	Plasma	Metabolic profile	146 metabolites Pathways: Involved in large and extra-large HDL subclasses, VLDL, amino acid 73, citrate, complement activation
Adav [16], 2019	Singapore	PACG	Identifying characteristics	Unsupervised: Hierarchical clustering (Gene Pattern) Bioinformatics: GO	Not reported	Aqueous humor	Proteomic profile	773 proteins (501 up-regulated, 272 down-regulated) Pathways: Platelet degranulation, dysregulation of endocytic, exocytosis, secretion mechanisms, immune system components, oxygen homeostasis, extracellular membrane dynamics
Agasing [82], 2020	USA	NMOSD	Treatment decisions	Unsupervised: Hierarchical clustering Statistical method: Binomial generalized linear model	Not reported	Plasma	Proteomic profile	91 proteins of which 26 were significantly elevated in NMOSD vs healthy: CXCL9, CXCL10, CXCL11, MCP-3/CCL7 Pathways: Type I interferons, T helper 17, aquaporin 4
Agrawal [83], 2017	UK	Ocular tuberculosis	Diagnosis or prognosis	Supervised: Bayesian latent class model	Positive predictive value = 58.7%, negative predictive value = 56.1	Plasma	Angiotensin converting enzyme	Weak discrimination between TB and non-TB groups based on various models including ACE
Ahlqvist [84], 2018	Sweden	DR, PDR	Diagnosis or prognosis	Unsupervised: Hierarchical clustering, k-means clustering Statistical method: Cox regression and logistic regression	Not reported	Plasma	Glutamate decarboxylase antibodies, HbA1c, alanine transferase, ketones, serum creatinine, glucose	Used in clustering model: Glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance
Ahlqvist [84], 2020	Sweden	DR, PDR	Diagnosis or prognosis	Unsupervised: Hierarchical clustering, k-means clustering	80% concordance	Plasma	glutamate decarboxylase autoantibodies, HbA1c, glucose, C-peptide	Used in clustering: Glutamate decarboxylase autoantibodies, age at diabetes onset, HbA1c, BMI, homoeostatic model assessment 2 estimates of β-cell function and insulin resistance
Alabdulwahhab [21], 2021	Saudi Arabia	DR	Diagnosis or prognosis	Supervised: LDA, SVM, random forest, ranger random forest	Ranger random forest: accuracy 86%, the rest were lower accuracy	Plasma	HbA1c	HbA1c
Anjana [85], 2020	USA	NMOSD	Treatment decisions	Unsupervised: Hierarchical clustering Statistical method: Binomial generalized linear model	Not reported	Plasma	Proteomic profile	91 proteins of which 26 were significantly elevated in NMOSD vs healthy: CXCL9, CXCL10, CXCL11, MCP-3/CCL7 Pathways: Type I interferons, T helper 17, aquaporin 4

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Apreutesei [15], 2018	Romania	POAG	Identifying characteristics	Supervised: ANN (feed forward neural network—multilayer perceptron, Jordan Elman Network type)	Accuracy = 95%	Serum	HbA1c, glycemic level	None
Aqrawi [86], 2017	Norway	Sjogren's Syndrome	Identifying characteristics	Bioinformatics: GO, DAVID, STRING	Not reported	Tears, saliva	Proteomic profile	Biomarkers: 500 proteins Pathways: Innate immunity, cell signalling, would repair, TNF-a signalling, B cell survival, protein folding and metabolism
Aretz [53], 2013	Germany	Exploratory	Exploratory	Bioinformatics: GO, DAVID, PANTHER	Not reported	Vitreous humor	Proteomic profile	Biomarkers: 262 proteins Pathways: Structural, transport, binding proteins, complement and coagulation, growth hormones
Bai [87], 2010	China	NMO	Diagnosis or prognosis	Bioinformatics: SWISSPROT protein database and MASCOT, pathway analysis	Not reported	Cerebrospinal fluid	Haptoglobin, transthyretin, APOE, APOA1, neurofilament, pigment epithelium-derived factor	Biomarkers: Haptoglobin, transthyretin, APOE, APOA1, neurofilament, pigment epithelium-derived factor Pathways: Prostaglandin synthesis and angiogenesis, inflammation, cholesterol transport
Bancks [51], 2019	USA	DR	Diagnosis or prognosis	Unsupervised: k-means clustering	Not reported	Serum	HbA1c, glucose	HbA1c
Barba [35], 2010	Spain	PDR	Exploratory	Supervised: PLS-DA Unsupervised: PCA	PLS-DA: Sensitivity = 86%, specificity = 81%	Vitreous humor	Metabolic profile	Lactate, glucose, ala- nine, valine, glutamine, acetate, leucine, isoleucine, succinate
Barbosa Breda [23], 2020	Belgium	Glaucoma (NTG, POAG)	Diagnosis or prognosis	Supervised: LDA, SVM Unsupervised: PCA Statistical method: multivariate regression	LDA: AUC = 9.91 SVM: AUC = 0.93	Aqueous humor, serum	Metabolic Profile	Alanine, N-acetylglutamate, lysine, glutamine, glutamate, valine, V-hydroxybutyrate, glutamine, a-ketoglu- terate, lysine, creatine, phosphocreatine, creatinine, a-ketogluterate, glucose, taurine, betaine, glucose, Ha of amino acids
Bennett [88], 2011	Austria	Cataract	Exploratory	Bioinformatics: iTRAQ, GO	Not reported	Aqueous humor	Proteomic profile	Biomarker: 198 proteins Pathways: Binding, inhibition of proteolytic activity, inflammatory and immune response, transport
Beutgen [10], 2019	Germany	POAG	Diagnosis or prognosis	Supervised: ANN—feed forward neural network (multilayer perceptron)	AUROC: 0.875, Sn 81%, Sp 93%	Serum	Serological antibody profile	Biomarkers: CALD1, PGAM1, VDAC2, HSPD1, VIM Pathways: Apoptosis, cell–cell and cell–matrix adhesions, autoimmunity, glycolytic pathway
Beutgen [89], 2021	Germany	POAG, NTG, PXG	Diagnosis or prognosis	Unsupervised: k-means Bioinformatics: GO	Not reported	Serum	Serological antibody profile	Biomarkers: HSPA1A, HSPD1, YWHAZ, VDAC2, PGAM1, ENO2 Pathways: mRNA processing, protein folding, Serum coagulation and apoptosis pathways
Blighe [36], 2020	UK	DR	Identifying characteristics	Supervised: Random forest Unsupervised: PCA Statistical Method: penalized regression	PCA: AUC = 0.80 Penalized regression: AUC = 0.74 Random forest: AUC = 0.84	Serum	400 laboratory parameters	Biomarkers: hematocrit, BUN, urinary albumin potassium urinary nitrate, glucose, iodine etc
Bocca [37], 2018	France	Optic atrophy	Identifying characteristics	Supervised: PLS, OPLS-DA, Biosigner ML algorithm that includes PLS-DA, random forest, SVM Unsupervised: PCA	PLS: 73.6% predictability OPLS-DA: 80.3% predictability Biosigner: accuracy > 85%	Serum	Metabolic profile	Biomarkers: Xanthine, hypoxanthine, inosine, urocanate, choline, phosphocholine, glycerate, 1-oleoyl-rac-glycerol, rac-glycerol-1-myristate, aspartate, glutamate, cystine Pathways: Purine, lipid metabolism, AA pathway

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Bocca [38], 2021	France	LHON	Exploratory	Supervised: OPLS-DA Unsupervised: PCA	Accuracy = 55% for OPLS-DA	Serum	Metabolic profile	Inosine, C5 H4 N4 O_3.83, Acetoacetate, Methylhistidine, Taurine, Glutamate, C8 H8 O3 _9.62, Pipecolate, Nicotinamide, Fumarate Choline, Hippurate, C10 H13 N5 O5 _3.81
Bonacini [48], 2020	Italy	Uveitis	Identifying characteristics	Unsupervised: hierarchical clustering Bioinformatics: GO, PANTHER, REACTOME	Not reported	Aqueous humor	Proteomic profile	Biomarker: IL-6, IL-10, G-CSF, IFNy, MCP, IL-7, IL-8, MIP-1a, TNFa, eotaxin, Pathways: Interleukin-10 signalling, granulocyte and leukocyte chemotaxis
Burgess [71], 2015	USA	POAG	Exploratory	Unsupervised: Two-way hierarchical cluster analysis, Bioinformatics: Pathway analysis (MetaboAnalyst), KEGG	Not reported	Serum	Metabolic profile	Pathways: Galactose metabolism, fructose and mannose metabolism, steroid hormone biosynthesis
Cao [22], 2021	China	NPDR	Diagnosis or prognosis	Supervised: ANN, random forest, SVM, xgradient-boosting (XGB) Statistical method: Linear regression	ANN: AUC = 0.72 SVM: AUC = 0.75 XGB: AUC = 0.82 Linear regression: AUC = 0.72	Serum	Proteomic profile	DGF-BB, leptin, ANG-1, TIMP-1, RANTES, TIMP-2, ENA-78, angiostatin, CXCL16,VEGFR2, IL-10, ANGPTL4, bFGF, VEGFR3, HB- EGF, IL-12p40, IGF-1, IL-17, I-309, LIF
Chan [90], 2008	Taiwan	DR	Diagnosis or prognosis	Supervised: ANN, C5.0	C5.0: C5.0: sensitivity 58%, specificity 748% ANN: sensitivity 59%, specificity 99%	Serum	Unclear (various laboratory parameters)	Creatinine
Chiang [91], 2021	Taiwan	DR	Identifying characteristics	Bioinformatics: STRING	Not reported	Aqueous humor	Proteomic profiling	Biomarkers: Apolipoprotein A-I (APOA1), serotransferrin (TF), keratin type I cytoskeletal 9 (KRT9), keratin type I cytoskeletal 10 (KRT10), podocan (PODN), matrix metalloproteinase 13 (MMP13), growth factor receptor-bound protein 10 (GRB10), brain-specific angiogenesis inhibitor 1-associated protein 2 (BAIAP2), selenoprotein P (SEPP1), cystathionine beta-synthase (CBS), and retrotransposon gag domain-containing protein 1 (RGAG1) Pathway: Nutrition transport, reorganization of microstructures and extracellular matrix (ECM) in retina and retinal Serum vessels, angiogenesis, anti-oxidation and neuroprotection
Christakopoulos [92], 2019	Denmark	Idiopathic macular hole	Exploratory	Unsupervised: Hierarchical clustering Bioinformatics: STRING	Not reported	Vitreous humor	Proteomic profiling	Biomarkers: Brillin- 1, tenascin, prolargin, biglycan, opticin, collagen alpha-1(II) chain, protein-glutamine gamma-glutamyl- transferase 2, fibronectin, filamin-A, collagen alpha-2(IX) chain, spectrin alpha chain, transforming growth factor beta induced protein ig–h3, dihydropyrimidinase—related protein 3, endoplasmin, glutamate dehy- drogenase 1 Pathways: Nucleotide metabolic process, skin development, keratinization, cornification, glomerular basement membrane development.

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Csosz [7], 2018	Hungary	POAG	Treatment decisions	Unsupervised: Hierarchical cluster analysis, pathway analysis Bioinformatics: GO Statistical method: Linear regression	Not reported	Tears	Proteomic profile	IL-6, MMP1
Curnow [25], 2005	UK	Uveitis	Diagnosis or prognosis	Supervised: random forest Unsupervised: Hierarchical average-linkage clustering	Accuracy = 100% for random forest idiopathic uveitis vs controls	Aqueous humor	IL-1beta, -2, -4, -5, -7, -8, -10, -12, -13, -15, TNFalpha, IFNy, CCL2 (MCP-1), CCL5 (RANTES), CCL11 (Eotaxin), TGFbeta2, and CXCL12 (SDF-1)	IL-6, IL-8, CCL2, IL-13, TNFa, IL-2
Curovic [93], 2020	Denmark	DR	Diagnosis or prognosis	Statistical method: partial correlation network analysis, multivariate linear regression	Not reported	Serum	75 metabolites	Biomarkers: creatinine and myoinositol, but also glyceryl-glycoside, 4-hydroxybenzeneacetic acid, and fumaric acid Pathways: kidney function-related, glucose metabolism, fatty acids
Dagliati [94], 2018	Italy	DR	Diagnosis or prognosis	Supervised: NBC, SVM, random forest Statistical method: Logistic regression	1) Accuracy = 0.777, Sn = 0.820, Sp = 0.730 at 3 years 2) Accuracy = 0.743, Sn = 0.790, Sp = 0.685 at 5 years 3) Accuracy = 0.666, Sn = 0.606, Sp = 0.745 at 7 years	Serum	HbA1c	HbA1c
de Almeida Borges [29], 2020	Brazil	Keratoconus, pterygium, graft vs host disease	Identifying characteristics	Supervised: PLS-DA Unsupervised: Cluster analysis Bioinformatics: KEGG	1) AUC = 0.85–0.993 in keratoconus group using PLS-DA 2) AUC = 0.792–0.990 in pterygium group using PLS-DA 3) AUC = 0.941–0.997 in graft vs host disease group using PLS-DA	Tears	Proteomic profile	Biomarkers: 7 in keratoconus group, 29 in pterygium group, and 79 in graft vs host disease group Pathways: Estrogen signalling pathway in pterygium, complement and coagulation cascades in graft vs host disease
Dor [54], 2019	Switzerland	Exploratory	Exploratory	Bioinformatics: DAVID, GO, KEGG, STRING	Not reported	Tears	Proteomic profile	Biomarkers: 1351 proteins, including 2 unique peptides. 39% 36 of the lacrimal proteins were enzymes, with high numbers of dehydrogenases, 37 phosphatases, kinases and ligases. Immunoglobulins, serpins and 14–3-3 domains 38 proteins were also abundant Pathways: Glycolysis, ATP-dependent 6-phosphofructokinase, and complement and coagulation cascades
Duong [13], 2021	Korea	PDR, DR	Identifying characteristics	Unsupervised: PCA Bioinformatics: GO, STRING	Not reported	Vitreous humor	Proteomic profile	Biomarkers: 20 proteins, including kininogen-1, serotransferrin, ribonuclease pancreatic, osteopontin, keratin type II cytoskeletal 2 epidermal, and transthyretin in the DR group and prothrombin, signal transducer and activator of transcription 4, hemoglobin subunit alpha, beta, and delta in the PDR group Pathways: Complement and coagulate cascades in both DR and PDR, n thyroid hormone synthesis pathway in PDR

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Fan [95], 2021	China	DR	Diagnosis or prognosis	Supervised: ANN, Bayesian network, chi-squared automatic interaction detector, classification and regression tree, quick unbiased efficient statistical tree, discriminate model, ensemble model	1) ANN: AUC = 0.725 ± 0.142, accuracy = 0.812 ± 0.091 2) Chi-squared automatic interaction detector: AUC = 0.818 ± 0.161, accuracy = 0.875 ± 0.053 3) Bayesian network: AUC = 0.749 ± 0.179, accuracy = 0.978 ± 0.031 4) Discriminate*: AUC = 0.832 ± 0.086, accuracy = 0.799 ± 0.055	Serum	Diabetes profile (HbA1c, dyslipidemia)	HbA1c, dyslipidemia
Fernández [96], 2019	Spain	DE	Identifying characteristics	Unsupervised: PCA, k-Means cluster analysis, Bayesian Information Criterion Statistical method: Logistic regression	AUC = 0.7545–0.9545, Sn = 0.8000–100.00, Sp = 0.6765–0.9655 using logistic regression. Different "clusters" of DE disease had different predictive accuracy	Tears	Proteomic profile, demographic and clinical	Biomarkers: EGF, CX3CL1/fractalkine, IL-1Ra, IL-6, CXCL8/IL-8, CXCL10/IP-10, CCL5/RANTES, VEGF, MMP-9
Fernández [97], 2020	Spain	Refraction	Diagnosis or prognosis	Unsupervised: Hierarchical cluster analysis, k-means cluster analysis Statistical method: Logistic regression	AUC = 0.75, Sn = 81.8% (95% CI 65.7–97.9), Sp 77.3% (95% CI 59.7–94.7)	Tears	Cytokine profile	Biomarkers: Epidermal growth factor, interferon-gamma, IL-1b, IL-1RA, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL17A, IP-10, MCP-1, regulated on activation, normal T cell expressed and secreted, TNF-a, MMP-9
Gao [12], 2020	Singapore	nAMD	Treatment decisions	Supervised: PCA Unsupervised: OPLS-DA Bioinformatics: Pathway analysis Statistical method: Logistic regression	AUROC = 0.762	Serum	Metabolic profile	Biomarkers: LysoPC (18:2), PS (18:0/20:4), glycerophosphocholine Pathways: Glycerophospholipid metabolism alteration
González [30], 2014	Spain	DE, Meibomian gland dysfunction	Identifying characteristics	Supervised: ANN (multilayer perceptron neural network) Statistical method: Local regression, nonlinear iterative partial least squares	Accuracy = 89.3%	Tears	Proteomic profile	Not reported
Grus [98], 1998	Germany	Grave's ophthalmopathy	Diagnosis or prognosis	Supervised: DA, ANN (probalistic neural network)	Accuracy = 96.3	Tissue biopsy (extraocular muscle),	Proteomic profile	Not reported
Grus [99], 2001	Germany	DME	Identifying characteristics	Supervised: DA	Not reported	Tears	Proteomic profile	Not reported

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Grus [100], 2005	Germany	Refraction	Identifying characteristics	Supervised: ANN (multiple-layer feed-forward network), DA	1) Sn = 0.90, Sp = 0.95 in study 1 to recognize the typical pattern of a contact lens wearer with ANN 2) Accuracy = > 90% in study 3 to recognize participants as typical contact lens wearers with ANN	Tears	Proteomic profile	2000 + proteins
Grus [101], 2005	Germany	DE	Identifying characteristics	Supervised: ANN (multiple-layer feed-forward network), DA	AUC = 0.93, Sn = ~0.90, Sp = ~0.90 using ANN with 7 protein panel	Tears	Proteomic profile	Biomarkers: Nasopharyngeal carcinoma-associated proline-rich protein, proline-rich protein 4, alpha-1-antitrypsin (c-terminal fragment), proline rich protein 3, calgranulin A, two more unidentified proteins Pathways: Inflammation, protective functions
Grus [31], 2008	Germany	POAG	Identifying characteristics	Supervised: DA, ANN	AUC = 0.941, Sn = 0.90, Sp = 0.87	Aqueous humor	Proteomic profile	Human transthyretin
Guha Mazumder [102], 2017	USA	DR	Identifying characteristics	Supervised: SVM, LDA Unsupervised: PCA Bioinformatics: KEGG	1) Accuracy = 70–94.9%, Sn = 0.700–0.917, Sp = 0.828–0.963 using SVM to distinguish control from DR 2) Accuracy = 72.7–93.9%, Sn = 0.0.714–0.933, Sp = 0.737–0.944 using SVM to distinguish diabetes from DR 3) Accuracy = 78.3–91.7%, Sn = 0.714–0.929, Sp = 0.806–0.931 using linear SVM to distinguish control form diabetes from DR	Serum	Proteomic profile	Biomarkers: ribitol, glycerophosphocholine, uridine diphosphate N-acetyl glucosamine, lipids, β-sheet-containing proteins Pathways: Neoangiogenesis, vascular fragility, vascular asymmetry, and neuroretinal degeneration
Guo [103], 2014	China	Acute anterior uveitis	Identifying characteristics	Unsupervised: PCA Bioinformatics: KEGG, METLIN database, HMBD database	Not reported	Plasma	Metabolic profile	102 metabolites detected, and 33 were identified Pathways: Starch and sucrose metabolism, phenylalanine metabolism, pyruvate metabolism, purine metabolism, tyrosine metabolism, Vitamin B6 metabolism, amino acid metabolism, carbohydrate metabolism, lipid metabolism
Hall [104], 2015	USA	Sjogren's syndrome	Identifying characteristics	Unsupervised: Hierarchical cluster analysis Statistical method: Logistic regression	Not reported	Tissue biopsy (labial salivary glands)	Interferons	Biomarkers: Interferon level, interferon-1, interferon-2 Pathway: Inflammation
Han [9], 2020	China	wAMD	Identifying characteristics	Supervised: PCA Unsupervised: OPLS-DA Bioinformatics: KEGG	Not reported	Aqueous humor	Metabolic profile	Biomarkers: Deoxycarnitine, N6,N6,N6-trimethyl-L-lysine, glycine betaine, itaconic acid, cis-aconitate, 5-aminopentanoic acid, norleucine, L-phenylalanine, carnitine, γ-glutamylglutamine, hetisine, 3-phenyllactic acid, LPC 18:2, coumaroyl agmatine, N-acetylhistidine, creatine, N-fructosyl isoleucine, L-proline Pathways: Carnitine-associated mitochondrial oxidation pathway, carbohydrate metabolism pathway, activated osmoprotection pathway

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Huang [105], 2018	China	DE	Identifying characteristics	Bioinformatics: GO, STRING	Not reported	Tears	Proteomic profile	Biomarkers: Lactotransferrin, lysozyme, lipocalin 1, zinc-alpha-2-glycoprotein, secretoglobin, family 2A, member 1, deleted in malignant brain tumors 1, lacritin, proline rich 4, transferrin, keratin 1, polymeric immunoglobulin receptor, complement component 3, S100A8, S100A9, orosomucoid 1, Annexin A1, Immunoglobulin J polypeptide, heat shock 27 kDa protein 1 Pathways: Transfer/carrier proteins, hydrolyses, enzyme modulators, signaling molecules, inflammatory response, biosynthesis of IL-8, activation of the host immune response and the inflammatory response
Hysi [32], 2019	UK	Glaucoma	Identifying characteristics	Supervised: Random forest Statistical method: Mendelian randomization	Not reported	Serum	Metabolic profile	O-methylascorbate (Vitamin C metabolite), carnitine, phenylacetylglutamine
Igarashi [26], 2021	Japan	POAG, SOAG, PXG	Diagnosis or prognosis	Supervised: Random forest, SVM, LASSO	1) AUC = 0.675 or 0.607 for POAG vs control 2) AUC = 0.729 or 0.747 for SOAG vs control 3) AUC = 0.966 or 0.967 for PXG vs control 4) AUC = 0.670 or 0.694 for POAG vs SOAG 5) AUC = 0.913 or 0.860 for POAG vs PXG 6) AUC = 0.834 or 0.854 for SOAG vs PXG All models use LASSO, and the first AUC uses autotaxin, TGF-β1, TGF-β2, and TGF-β3 as inputs while the second uses only autotaxin and TGF-β3	Aqueous humor	Autotaxin, and TGF-B levels	Autotaxin, TGF-β1, TGF-β3
Indini [106], 2019	Italy	Metastatic melanoma	Treatment decisions	Supervised: ANN	Not reported	Serum	Complete Serum count, demographic and clinical data	Lactate dehydrogenase level
Ing [70], 2019	Canada	GCA	Diagnosis or prognosis	Supervised: ANN Statistical method: Logistic regression	1) AUROC = 0.867, accuracy = 0.780–0.794, Sn = 0.525–531, Sp = 0.904–0.951 for logistic regression* models 2) AUROC = 0.860, accuracy = 0.760–0.819, Sn = 0.602–0.695, Sp = 0.838–0.891 for ANN models	Serum	ESR, CRP, platelet level	ESR, CRP, platelet level
Iomdina [17], 2020	Russia	POAG	Identifying characteristics	Bioinformatics: GO, PANTHER, KEGG	Not reported	Tissue biopsy (sclera)	Scleral proteome	Vimentin, angiopoietin-related protein 7, annexin A2, serum amyloid P component, serum albumin, thrombospondin-4

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Ji [107], 2015	China	Cataract	Identifying characteristics	Bioinformatics: GO, STRING	Not reported	Aqueous humor	Proteomic profile	77 proteins Pathways: vascular smooth muscle contraction, long-term potentiation, salivary secretion, phototransduction, neurotrophin signaling pathway, melanogenesis, protein digestion and absorption GnRH signalling, olfactory transduction, gastric acid secretion, insulin signalling, complement and coagulation cascades, amino sugar and nucleotide sugar metabolism, Chagas disease, amoebiasis, glioma, Alzheimer's disease, Leishmaniasis, tuberculosis, staphylococcus aureus infection, prion diseases, lupus, pertussis, phosphatidylinositol signaling, ECM-receptor interaction, calcium signalling, actin cytoskeleton regulation, phagosome, focal adhesion, oocyte meiosis
Ji [33], 2018	Korea	Grave's ophthalmopathy	Identifying characteristics	Supervised: OPLS-DA Bioinformatics: Pathway analysis	1) AUC = 0.931, Sn = 0.787, Sp = 0.875 for control vs Grave's ophthalmopathy AUC = 0.845–0.935 for control vs Grave's ophthalmopathy vs Grave's with no eye involvement	Serum, tissue biopsy (orbital adipose or connective tissues)	Metabolic profile	Biomarkers: 37, including glucose, pelargonic acid, fumaric acid, gluconic acid, glycerol, mannose, threose, pentadecanoic acid, pyruvate, and 2-(4-hydroxyphenyl)ethanol Pathways: Sugar metabolism, including galactose metabolism, starch metabolism, pentose phosphate pathway, glycerolipid metabolism, amino-sugar metabolism

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Ji [108], 2019	Korea	DE	Treatment decisions	Bioinformatics: GO, KEGG, STRING	Not reported	Tears	Proteomic profile	Biomarkers: 54 proteins for cyclosporin A, 105 proteins for diquafosol tetrasodium Pathways: Innate and adaptive immune responses, cellular detoxification, hydrogen peroxide catabolism, vesiclemediated transport, defense response, regulation of cell death, MAPK cascade, complement activation, lipid transport, calcium-ion and lipid binding, enzyme activity, glycoprotein biding, serine-type endopeptidase activity, cell adhesion, chaperone binding
Jiang [49], 2020	China	Grave's ophthalmopathy	Identifying characteristics	Supervised: PLS-DA Unsupervised: Hierarchical cluster analysis Bioinformatics: GO, KEGG, STRING, Clusters of Orthologous Groups, EuKaryotic Orthologous Groups, REAC enrichment analysis	Not reported	Tears	Proteomic profile	83 proteins Pathways: Immune system, metabolism, programmed cell death, vesicle-mediated transport, neuronal system and extracellular matrix organization
Jin [109], 2019	China	DR	Identifying characteristics	Supervised: OPLS-DA Unsupervised: PCA	AUROC = 0.725–918, which varied depending on biomarker used	Aqueous humor	Metabolic profile	Biomarkers: Ascorbate, citrate, creatine, dimethylamine, formate, glucose, isobutyrate, lactate, succinate, 2-hydroxyisovalerate, 2-hydroxybutyrate, 2-oxoisocaproate, and amino acids including alanine, asparagine, glutamine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, tyrosine, threonine, valine, and 2-aminobutyrate Pathways: Alanine, aspartate, and glutamate metabolic pathway, aminoacyl-tRNA biosynthesis, propanoate metabolism, nitrogen metabolism, D-glutamine and D-glutamate metabolism, cyanoamino acid metabolism, citrate cycle, valine, leucine and isoleucine biosynthesis, beta-alanine metabolism, glycolysis, pyruvate metabolism
Joachim [110], 2005	Germany	POAG, NTG	Identifying characteristics	Supervised: DA	Not reported	Serum	Ocular antibody profile	Complex antibody patterns, especially retinal against antigens
Joachim [111], 2007	Germany	POAG, PXG	Identifying characteristics	Supervised: DA	Not reported	Aqueous humor	Ocular antibody profile	Heat shock protein 27, α-enolase, actin, GAPDH
Jurnyczyk [112], 2017	UK	Multiple sclerosis, aquaporin-4-antibody NMOSD, myelin oligodendrocyte glycoprotein-Ab disease	Identifying characteristics	Supervised: OPLS-DA Unsupervised: PCA	Accuracy = 73–100%	Plasma	Metabolic profile	Biomarkers: Scyllo-inositol, high density lipoproteins, low density lipoproteins, histidine, glucose, lactate, alanine, formate, leucine, myo-inositol Pathways: Demyelination, inflammation, Serum brain barrier breakdown, disruptions to energy metabolism
Kahkoska [113], 2019	USA	DR	Identifying characteristics	Unsupervised: k-means cluster analysis Statistical method: Regression	Not reported	Serum	Diabetes profile (HbA1c, glucose, lipids, creatinine, cystatin), demographic and clinical data	HbA1c, glucose, lipids, creatinine, cystatin

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Karpati [52], 2018	Israel	DR	Identifying characteristics	Supervised: Random forest Unsupervised: k-means cluster analysis Statistical method: Logistic regression	Accuracy = 99.8% of random forest to predict clusters	Serum	HbA1c	HbA1c
Ke [114], 2021	China	High myopia	Identifying characteristics	Supervised: OPLS-DA Unsupervised: PCA Bioinformatics: KEGG	AUC = 0.59–0.71 depending on the metabolite used, with alanine being the highest	Serum	Metabolic profile	Biomarkers: Alanine, mannose, itaconic acid, aconitic acid, O-acetylserine 1, phthalic acid, abietic acid, salicin, citric acid, aminomalonic acid, palmitoleic acid, conduritol b epoxide, shikimic acid, 4-hydroxyphenylacetic acid, hesperitin, anandamide, oxalacetic acid, oxalacetic acid, pimelic acid, 2-ketoadipate, N-ethylmaleamic acid Pathways: Citrate cycle, selenoamino acid metabolism, alanine, aspartate and glutamate metabolism, glycolysis or gluconeogenesis, glyoxylate and dicarboxylate metabolism, cysteine and methionine metabolism, biotin metabolism
Kersten [115], 2019	Netherlands	AMD	Identifying characteristics	Supervised: sPLS-DA Statistical method: Logistic regression	1) AUROC = 0.71 using complete metabolic profile 2) AUROC = 0.66 using complete metabolic profile plus derived variables such as ratios of metabolites	Serum	Metabolic profile	Glutamine, glutamate, glutaminolysis, phosphatidylcholine diacyl C28:1 (PC aa C28.1)
Kim [116], 2001	Korea	Grave's ophthalmopathy	Identifying characteristics	Unsupervised: Cluster analysis	Not reported	Serum	Thyroid markers (TSH, thyrotropin receptor antibodies, IgG	Thyrotropin receptor antibody epitopes
Kim [117], 2014	Korea	Pterygium	Identifying characteristics	Bioinformatics, GO, DAVID	Not reported	Tissue biopsy (pterygium)	Proteomic profile	Biomarkers: 230 proteins, including aldehyde dehydrogenase, dimeric NADP-preferring, protein disulfide-isomerase A3, peroxiredoxin-2 Pathways: structural molecule activity, nucleotide binding, cytoskeletal protein binding, peptidase activity, guanyl ribonucleotide binding, structural constituent of eye lens, glycosaminoglycan binding, phosphotransferase activity, structural molecule activity, peptidase activity, identical protein binding, carbohydrate binding, protein binding, bridging, glycosaminoglycan binding, polysaccharide binding, oxidoreductase activity, acting on peroxide as acceptor, antioxidant activity, integrin binding, growth factor binding

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Kouassi Nzoughet [118], 2020	France	w	Identifying characteristics	Supervised: OPLS-DA, PLS-DA, random forest, SVM, LASSO Unsupervised: PCA	1) LASSO: 100 models, with 75% having AUC of > 0.8 2) ROC = 0.9301 for controls, 0.8243 for glaucoma, using a panel of eight metabolites 3) Accuracy = 73.7% for PLS-DA with nicotinamide and N-acetyl L-leucine 4) Accuracy = 71.1% for SVM with nicotinamide and N-acetyl L-leucine	Serum	Metabolic profile	Nicotinamide, hypoxanthine, xanthine, 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, N-acetyl-L-Leucine, arginine, RAC-glycerol 1-myristate, 1-oleoyl-RAC-glycerol, cystathionine
Kowalczuk [119], 2018	Switzerland	Central serous chorioretinopathy, RD	Identifying characteristics	Bioinformatics: Panther, KEGG, GO	Not reported	Subretinal fluid	Metabolic profile, proteomic profile	Biomarkers: 291 proteins and 651 metabolites Pathways: acute phase response signaling, LXR/RXR and FXR/RXR Activations, complement system, glycolysis, gluconeogenesis, coagulation system, atherosclerosis signaling, IL-12 signaling and production of macrophages, clathrin-mediated, endocytosis signaling which are involved in o glycolysis/ gluconeogenesis, inflammation, alternative complement pathway, cellular adhesion, biliary acid metabolism, and glucocorticoid and mineralocorticoid systems
Kramann [120], 2011	Germany	Refraction	Identifying characteristics	Supervised: DA, ANN	Not reported	Tears	Proteomic profile	Complex proteomic signature, including cystatin-1, lipophilin-A precursor, lysozyme C precursor, calgranulin-A
Kuiper [121], 2017	Netherlands	AMD, idiopathic non-infectious uveitis, primary vitreoretinal lymphoma, rhegmatogenous RD	Diagnosis or prognosis	Supervised: Decision tree, KNN Unsupervised: Hierarchical cluster analysis Statistical method: SMOTE	1) AMD: accuracy = 87.20%, Sn = 0.8570, Sp = 0.8750 2) Idiopathic non-infectious uveitis: accuracy = 76.70%, Sn = 0.5550, Sp = 0.9310 3) Rhegmatogenous RD: accuracy = 78.72%, Sn = 0.8460, Sp = 0.8529 4) Primary vitreoretinal Lymphoma: accuracy = 97.87%, Sn = 0.8880, Sp = 1.0000 Overall model: accuracy = 86.67%, Sn = 0.7940, Sp = 0.9250	Aqueous humor	Proteomic profile	IL-10, IL-21, ACE
Laíns [122], 2018	USA	AMD	Identifying characteristics	Unsupervised: PCA Bioinformatics: KEGG Statistical method: Multivariate logistic regression	1) AUC = 0.80 (95% CI 0.71–0.90) using 87 metabolites 2) AUC = 0.71 (95% CI 0.59–0.85) using only demographic and clinical data	Plasma	Metabolic profile	87 differentially expressed metabolites (48 across all AMD stages), including linoleoyl-arachidonoyl-glycerol, stearoyl-arachidonoyl-glycerol, oleoyl-arachidonoyl-glycerol, 1-Palmitoyl-2-arachidonoyl-GPC, 1-stearoyl-2-arachidonoyl-GPC, adenosine Pathways: Glycerophospholipid pathway

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Laíns [123], 2019	USA	AMD	Identifying characteristics	Unsupervised: PCA Bioinformatics: KEGG Statistical method: Multivariate logistic regression	1) AUC = 0.725 for baseline model including only demographic covariates 2) AUC = 0.745 for all metabolites plus elastic net model including baseline + metabolites selected using elastic net regression with all metabolites 3) AUC = 0.789 for AMD/Control model including baseline + metabolites identified in the logistic regression 4) AUC = 0.815 for: stage + 2eye model including baseline + metabolites identified in the permutation-based cumulative logistic regression Note that the above are combined patient cohorts, and individual patient cohorts were also reported	Plasma	Proteomic profile	28 metabolites, including those from the lycerophospholipid, purine, taurine, hypotaurine, nitrogen metabolism pathways
Lee [56], 2021	China	DR	Diagnosis or prognosis	Supervised: Random forest Bioinformatics: KEGG Statistical method: Cox regression, Poisson regression, Gaussian regression	1) AUC = 0.9065 using regularized and weighted random forest model 2) AUC = = 0.8557 using random forest 3) AUC = 0.7671 using Cox regression	Serum	Diabetes profile (HbA1c, total cholesterol, low density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride)	HbA1c, total cholesterol, low density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride
Li [14], 2014	China	Rhegmatogenous RD, proliferative vitreoretinopathy	Identifying characteristics	Supervised: PLS-DA Unsupervised: PCA	Not reported	Vitreous humor	Metabolic profile	Biomarkers: 4-oxoproline, 3-ethylmalate, L-carnitine, creatinine, urea, creatinine, D-glucuronolactone, valine, phenylpyruvate, lactate, uric acid, threonate, homoisocitrate, leucine, cyromazine, 3-methylhistidine, isoglutamine, hypoxanthine, citrate, glycerate, allantoate, 5-Hydroxykynurenamine, ascorbate, 2-oxoglutarate, D-glyceraldehyde, tyrosine, succinate, inosine, phenylalanine, tryptophan, linoelaidic acid Pathways: 31 including histidine metabolism, purine metabolism, urea cycle, glycolysis, tyrosine metabolism, phenylalanine metabolism, citrate cycle
Li [63], 2016	China	nAMD, polypoidal choroidal vasculopathy	Identifying characteristics	Supervised: OPLS-DA Unsupervised: PCA Bioinformatics: KEGG	ROC > 80 for LPA (18:2), LPC (20:4), PC (20:1p/19:1), SM (d16:0/22:2), PAF (35:4), PC (16:0/22:5) and PC (18:1/20:4) metabolites	Serum	Lipid profile, demographic and clinical data	41 lipids, including 19 phosphatidylcholines, 8 sphingomyelins, 4 lysophosphatidic acids, 3 platelet-activating factors, 3 lyso-PCs, 2 sphingosines, 1 phytosphingosine, 1 phosphatidylethanolamine Pathways: glycerophospholipid metabolism, sphingolipid metabolism, ether lipid metabolism, glycerolipid metabolism

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Li [124], 2020	China	Grave's ophthalmopathy	Treatment decisions	Bioinformatics: KEGG, DAVID, STRING	Not reported	Tissue biopsy (orbital connective tissues)	Orbital fibroblast profile	Biomarkers: IL-1β, TGF-β1 Pathways: fibrosis, inflammation
Li [125], 2020	China	DR	Identifying characteristics	Unsupervised: PCA Statistical method: Principal component regression, logistic regression	AUC = 0.88 (95% CI 0.78–0.99)	Serum	n-6 polyunsaturated fatty acids	Linoleic acid, γ-linolenic acid, eicosadienoic acid, dihomo-γlinolenic acid and arachidonicacid
Linghu [126], 2017	China	Pterygium	Identifying characteristics	Bioinformatics: GO, KEGG, DAVID	Not reported	Tissue biopsy (pterygium, conjunctiva)	Proteomic profile	Biomarkers: 156 proteins including MMP10 and CD34 Pathways: cellular component organization or biogenesis, cellular process, localization, biological regulation, response to stimulus, developmental process, multicellular organismal process, biological adhesion, locomotion, metabolic process, immune system process, nitrogen metabolism, hematopoietic cell lineage, focal adhesion, complement and coagulation cascade
Liu [127], 2019	Greece	Conjunctivitis	Identifying characteristics	Bioinformatics: STRING	Not reported	Serum	Vascular adhesion protein-1 related proteomic profile	Biomarkers: C-reactive protein, hemoglobin subunit β, vascular adhesion protein-1, A-albumin, enolase, immunoglobulin heavy constant mu, interferon regulatory factor-1,serum amyloid A2 protein Pathways: hydrogen peroxide catabolic, positive regulation of t-cell, oxygen transport, peroxidase activity, calmodulin binding, TAP2 binding, platelet activation, regulation of cell shape
Liu [128], 2021	China	POAG	Treatment decisions	Bioinformatics: GO, KEGG Statistical method: Linear regression	Not reported	Aqueous humor	Proteomic profile	97 total proteins involved in glutathione metabolism (GSTP1), inflammation, immune responses, growth and development, cellular movement and vesicle-mediated transport

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Liu [59], 2021	China	DME	Treatment decisions	Supervised: SVM, decision tree, random forest, deep learning (AlexNet, Visual Geometry Group 16, FResNet18) Statistical method: LASSO	1) Central foveal thickness training set: AUC = 0.8 for AlexNet, 0.82 for VGG16, 0.79 for ResNet18, 0.81 for Ensemble CNN, 0.87 for LASSO, 0.89 for SVM, 0.82 for decision tree, 0.88 for random forest, 0.90 for ensemble model 2) Central foveal thickness external validation set: AUC = 0.94 3) Best corrected visual acuity training set: AUC = 0.74 for AlexNet, 0.74 for VGG16, 0.66 for ResNet18, 0.77 for Ensemble CNN, 0.78 for LASSO, 0.75 for SVM, 0.68 for decision tree, 0.79 for random forest, 0.80 for ensemble model 3) Best corrected visual acuity external validation set: AUC = 0.81	Serum	Diabetes profile (HbA1c, glucose, hemoglobin), optical coherence tomography imaging	HbA1c, glucose, optical coherence tomography imaging
Liu [129], 2021	Singapore	Refractive surgery, DE	Identifying characteristics	Bioinformatics: GO, DAVID	Not reported	Tears	Proteomic profile, neuromediator profile	Biomarkers: 49 proteins inckuding tear mucin-like protein 1, substance P levels Pathways: Leukocyte migration, wound healing, humoral immune response, apoptosis, negative regulation of endopeptidase activity, extracellular structure organization
Luo [46], 2017	China	wAMD	Identifying characteristics	Supervised: PLS-DA Unsupervised: PCA, hierarchical cluster analysis Bioinformatics: KEGG	Not reported	Plasma	Metabolic profile	Biomarkers: N-Acetyl-L-alanine, N1-Methyl-2-pyridone-5-carboxamide, L-tyrosine, L-phenylalanine, L-palmitoylcarnitine, L-methionine, L-Arginine, isomaltose, hydrocortisone, biliverdin Pathways: biosynthesis of amino acids, aminoacyl-tRNA biosynthesis, biosynthesis of antibiotics, central carbon metabolism in cancer, protein digestion and absorption, biosynthesis of plant secondary metabolites, 2-oxocarboxylic acid metabolism, glucosinolate biosynthesis, mineral absorption, ABC transporters, biosynthesis of alkaloids derived from shikimate pathway, biosynthesis of plant hormones, biosynthesis of alkaloids derived from ornithine, lysine and nicotinic acid, phenylalanine, tyrosine and tryptophan biosynthesis

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Lynch [130], 2019	USA	AMD, GA	Identifying characteristics	Bioinformatics: Pathway analysis Statistical method: Linear regression	Not reported	Plasma	Proteomic profile	AMD biomarkers: Vinculin, CD177 AMD pathways: Cargo trafficking to the periciliary membrane, FGFR3b ligand binding and activation, VEGF binds to VEGFR leading to receptor dimerization/VEGF ligand-receptor interactions, common pathway of fibrin clot formation GA biomarkers: Neuroregulin 4, soluble intercellular adhesion molecule-1 GA pathways: SHC1 events in ERBB4 signaling, PI3K events in ERBB4 signaling, SHC1 events in ERBB2 signaling, GRB2 events in ERBB2 signaling, nuclear signaling by ERBB4, NADE modulates death signaling, PI3K events in ERBB2 signaling, signaling by BMP, interleukin receptor SHC signaling, regulation of beta-cell development, regulation of commissural axon pathfinding by SLIT and ROBO, reversible hydration of carbon dioxide, tetrasaccharide linker, cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding, ERBB4
Lynch [131], 2020	USA	AMD, reticular pseudodrusen	Identifying characteristics	Bioinformatics: Pathway analysis Statistical method: Linear regression, Cox regression, univariate logistic regression	Not reported	Plasma	Proteomic profile	Biomarkers: TCL1A, CNDP1, lysozyme C, TFF3, RNAS6, SAP3 Pathways: Tumor necrosis factor binding, digestion and absorption, activin signaling, TGF-β family signaling
Maier [132], 2011	Germany	Corneal transplant immune reaction	Treatment decisions	Supervised: LDA Statistical method: Cox regression	Accuracy: ~ 100% using LDA analysis of IL-5, IL4, IL2, IFN-y, and age	Aqueous humor	Cytokine profile	IL-5, IL4, IL2, IFN-y (in the 3rd Cox analysis)
Marino [58], 2020	Brazil	Toxoplasmosis	Identifying characteristics	Supervised: Decision tree	1) Accuracy = 76% using decision tree analysis of CXCL9, CCL25, and GM-CSF to distinguish acute from chronic 2) Accuracy = 81% using decision tree analysis of CCL11 to distinguish from patients with and without ocular involvement* 3) Accuracy = 60% using decision tree analysis of CXCL12 and CXCL13 to distinguish from patients with and without ocular involvement in acute phase	Serum	Immune mediator panel	Biomarkers: 40 immune mediator panel, including CXCL9, CXCL10, GM-CSF, CCL25, CCL11, CXCL12, CXCL13, and CCL2 Pathways: Chemokines, cytokines, and growth factors involved in the activation, proliferation, and migration of inflammatory cells to injured tissues

Table 4 (continued)

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Mazumder [60], 2018	USA	DR	Diagnosis or prognosis	Supervised: SVM, PCA-LDA	1) Accuracy = 90.5%, Sn = 0.900, Sp = 0.927. for all features selected through forward feature selection model 2) Accuracy = 80.6, Sn = 0.700, Sp = 0.938 for normal vs DR 3) Accuracy = 91.9%, Sn = 0.882, Sp = 0.950 for diabetes vs DR*	Serum	Fourier transform infrared spectroscopy-based serum metabolomic spectral biomarkers	Biomarkers: Lipid signature, HbA1c, carbohydrate and polysaccharide content, total lipids. Not detailed completely
Menegay [133], 2008	USA	Climatic droplet keratopathy	Identifying characteristics	Bioinformatics: KEGG	Not reported	Tissue biopsy (cornea)	Proteomic profile	Biomarkers: 105 proteins, including annexin A2 and glyceraldehyde 3-dehydrogenase Pathways: glycolysis, pyruvate metabolism, propionoate metabolism, cell junction, cell cycle, focal adhesion, adherens junction, gap junction, actin cytoskeleton, Huntington's disease
Mirić [134], 2012	Serbia	Cataract	Identifying characteristics	Unsupervised: PCA Statistical method: Logistic regression	Not reported	Serum, tissue biopsy (lens)	Oxidative markers	Biomarkers: Glutathione reductase and glutathione S-transferase
Mitchell [45], 2018	USA	nAMD	Identifying characteristics	Supervised: PLS-DA, SVM, random forest Unsupervised: Hierarchical cluster analysis Bioinformatics: pathway analysis Statistical method: linear regression, linear models for microarray data, variable importance	Not reported	Plasma	Metabolic profile	Biomarkers: 159 metabolites Pathways: Carnitine shuttle pathway (fatty acid metabolism) and bile acid biosynthesis pathway
Moussallieh [135], 2014	France	NMO, multiple sclerosis	Diagnosis or prognosis	Supervised: PLS-DA Unsupervised: PCA	Sn = 0.943, Sp = 0.902 using scylloinositol and acetate PLS-DA model	Serum	Metabolic profile	Biomarkers: Glutamine, glutamate, lactate, lysine, scylloinositol, and acetate
Myer [136], 2020	USA	PXG, POAG	Identifying characteristics	Supervised: PLS-DA, SVM, ANN, deep learning Unsupervised: PCA Bioinformatics: KEGG	1) ANN*: accuracy = > 90%) 2) Deep learning: accuracy = > 80 3) SVM was unpredictable	Aqueous humor	Metabolic profile	L-arginine, L-lysine, L-tyrosine, 2,4-diacetamido-2,4,6-trideoxy-beta-L-altrose, N(6)-acetonyllysine, 1-aminocyclropropane-1-carboxylate, L-histidine, C6H9N4O3P, C6H13NO6, 5-hydroxypentanoate, propylene glycol, creatinine, 2-hydroxy-butyrate, 3-methyl-2-oxovalerate, propylene glycol, 3-hydroxy isovalerate, pyruvate, choline
Nättinen [137], 2020	Finland	Refractive surgery	Identifying characteristics	Bioinformatics: STRING, IPA	Not reported	Tears	Proteomic profile	Biomarkers: 747 proteins identified Pathways: Myeloid cells, phagocytes and leukocytes, inflammation, angiogenesis, viral infection, cell movement, cell death, energy production, tissue morphology

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Nezu [138], 2021	Japan	Acute retinal necrosis, endophthalmitis, virus-induced anterior uveitis, sarcoidosis, uveitis, vitreoretinal lymphoma, uveal melanoma, rhegmatogenous RD, PDR, epiretinal membrane, macular hole, RVO, RP, AMD, POAG, cataract with atopic dermatitis, cataract	Diagnosis or prognosis	Supervised: Random forest, linear SVM, decision tree, NBC, ANN (radial basis function)	Acute retinal necrosis: accuracy = 71% Endophthalmitis: accuracy = 91.6% Virus-induced anterior uveitis: accuracy = 92.6% Sarcoidosis: accuracy = 63.8% Uveitis: accuracy = 67.8% Vitreoretinal lymphoma: accuracy = 92.9% Uveal melanoma: accuracy = 68.3% Rhegmatogenous RD: accuracy = 85.5% PDR: accuracy = 74.0% Epiretinal membrane: accuracy 57.1% Macular hole: accuracy = 50.5% RVO: accuracy = 32.8% RP: accuracy = 67.8% AMD: accuracy = 59.9% POAG: accuracy = 86.7% Cataract with atopic dermatitis; accuracy = 59.8% Cataract: accuracy = 63.5% Note, each of these are the third prediction by the random forest model. 1st and 2nd predictions were less accurate. Each of the other algorithms yielded lower accuracy	Aqueous humor	Immune mediator profile	Biomarkers: 28 immune mediators were used in model construction
Nielson [139], 2015	Denmark	NMOSD, NMO spectrum disorders, multiple sclerosis	Identifying characteristics	Unsupervised: Hierarchical cluster analysis, PCA Statistical method: Logistic regression	1) AUC = 0.70 for model using Ig-G3 logistic regression model 2) AUC = 0.81 for model using Ig-K logistic regression model 3) AUC = 0.78 for model using Ig-L logistic regression model 4) AUC = 0.915 for four protein logistic regression model for discrimination between all included conditions* 5) AUC = 0.858 for NMO discrimination vs multiple sclerosis using 333 proteins in a logistic regression model	Urine	Proteomic profile	1112 proteins, of which 333 were shared among all subjects
Nusinovici [140], 2020	Singapore	POAG, PACG, DR, NDR, AMD, cataract	Identifying characteristics	Supervised: LASSO, GBM	Not reported	Serum	Metabolic profile, HbA1c	Many significant biomarkers, not detailed

Table 4 (continued)

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Ogunyemi [141], 2019	USA	DR	Diagnosis or prognosis	Supervised: KNN, SVM, ANN Statistical method: Logistic regression	1) Logistic regression: AUC = 0.752, Sn = 0.575, Sp = 0.794 2) SVM: AUC = 0.745, Sn = 0.656, Sp = 0.713 3) ANN: AUC = 0.754, Sn = 0.580, Sp = 0.800 These models are all internal validation set results using classifiers that take into account class-imbalances	Serum	Diabetic profile (HbA1c, dyslipidemia), demographic and clinical (sex, race, education, BMI, diabetes duration, co-morbidities such as hypothyroid)	HbA1c, dyslipidemia
Okrojek [142], 2009	Germany	Graves Ophthalmopathy	Diagnosis or prognosis	Supervised: DA, ANN	ROC: 0.99	Tears	Proteomic profile	Proteins between 3 000 – 20 000 Da (unspecified)
O'Leary [143], 2020	Switzerland	Graft vs host disease	Diagnosis or prognosis	Supervised: Random forest	AUC: 0.95	Tears	Proteomic profile	Lactotransferrin, Lysozyme C, Polymeric immunoglobulin receptor, Immunoglobulin J chain, Prolactin-inducible protein, Immunoglobulin heavy constant α1, Actin, cytoplasmic 1, Annexin A2, Glutathione S-transferase P, Phosphoglycerate mutase 1, Keratin type II cytoskeletal 6A, Pyruvate kinase PKM
Osborn [40], 2013	USA	nAMD	Diagnosis or prognosis	Supervised: PLS-DA Unsupervised: PCA, SVM Bioinformatics: KEGG, pathway analysis	Accuracy: 95.56%	Plasma	Metabolomic profile	Tripeptides, covalently modified amino acids, bile acids, vitamin D-related metabolites, tyrosine metabolism, sulfur amino acid metabolism, amino acids related to urea metabolism
Pan [144], 2020	China	POAG	Identifying characteristics	Supervised: OPLS-DA Unsupervised: PCA Bioinformatics: KEGG	AUC = 0.62–0.85 depending on metabolite used	Aqueous humor	Metabolic profile	Biomarkers: Glucose-1-phosphate, methylmalonic acid, N-cyclohexylformide 1, sorbitol, biotin, pelargonic acid, 2-mercaptoethanesulfonic acid 2, galactose 1, mannose 1, D-erythronolactone 2, dehydroascorbic acid 2, ribitol, D-talose Pathways: Biotin metabolism
Pavan [145], 2000	Croatia	DR	Diagnosis or prognosis	Supervised: Decision tree and rule analysis	Accuracy: 85.3%	Serum, Aqueous humor	Proteomic profile	Albumin, IgG, IFN-γ
Prior [146], 1993	USA	DR	Diagnosis or prognosis	Supervised: DA	Sensitivity: 96.9% Specificity: 59.4%	Serum	Protein	C-peptide
Qin [147], 2022	China	PACG	Diagnosis or prognosis	Supervised: PLS-DA Unsupervised: PCA	AUC: 0.8512	Plasma	Metabolomic profile	DHA, total saturated fatty acids
Romero [148], 2007	Spain	DR	Diagnosis or prognosis	Supervised: DA	Accuracy: 61.3–71.9%	Serum, urine	Proteins, Lipids	HbA1c, HDL, LDL, total cholesterol, triglycerides, albumin
Romero-Aroca [149], 2012	Spain	DR	Diagnosis or prognosis	Supervised: DA	Accuracy: 72.72–76.78%	Serum, urine	Proteins, Lipids	HbA1c, HDL, LDL, total cholesterol, triglycerides, albumin
Romero-Aroca [150], 2019	Spain	DR	Diagnosis or prognosis	Supervised: Random forest	Accuracy: 80.76%	Serum, urine	Proteins	HbA1c, albumin
Romero-Aroca [151], 2021	Spain	DR	Diagnosis or prognosis	Supervised: Random forest	Accuracy: 87.6%	Serum, urine	Proteins	HbA1c, albumin
Roybal [152], 2018	USA	Proliferative vitreoretinopathy	Identifying characteristics	Unsupervised: Hierarchal clustering Bioinformatics: Path analysis	Not reported	Vitreous humor	Proteomic profile	T-cell marker cytokines, profibrotic cytokines, cytokines downstream of mTOR activation, monocyte chemoattractant

Table 4 (continued)

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Safai [153], 2018	Denmark	DR	Diagnosis or prognosis	Unsupervised: PCA, K-means clustering	Not reported	Serum, urine	Proteins	HbA1c, C-peptide
Sandhu [154], 2020	USA	NPDR	Diagnosis or prognosis	Supervised: Random forest	AUC: 0.96	Serum	Protein	HbA1c
Sato [155], 2019	Japan	NV-AMD	Diagnosis or prognosis	Unsupervised: PCA, hierarchal clustering	Not reported	Aqueous humor	Proteomic profile	IL-7, MCP-1, MIP-1β, VEGF
Schori [61], 2018	Switzerland	NV-AMD	Identifying characteristics	Bioinformatics: Functional annotation, enrichment analysis, protein–protein interaction network	Not reported	Vitreous humor	Proteomic profile	Cholinesterase, ribonuclease, serine carboxypeptidase
Segheiri [156], 1986	Italy	DR	Diagnosis or prognosis	Supervised: Stepwise DA	Not reported	Plasma	Proteins	Fibronectin, HbA1c
Sembler-Møller [50], 2020	Denmark	Sjögren's syndrome	Diagnosis or prognosis	Unsupervised: PCA, hierarchal clustering Bioinformatics: Enrichment analysis, KEGG	Not reported	Saliva, plasma, salivary gland tissue	Proteomic profile	Neutrophil elastase, calreticulin, tripartite motif-containing protein 29, immunoin- flammatory pathway, slivary secretion pathway proteins
Semerero [157], 2011	Italy	DR	Diagnosis or prognosis	Supervised: Decision tree, random forest	ROC: 0.825	Serum, urine	Proteins	HbA1c, albumin
Sharma [11], 2018	USA	POAG	Identifying characteristics	Bioinformatics: Functional annotation, protein–protein interaction network, path analysis	Not reported	Aqueous humor	Proteomic profile	IGKC, ITIH4, APOC3, IDH3A, LOC105369216. SERPINF2, NPC2, SUCLG2, KIAA0100, CNOT4, AQP4, COL18A1, NWD1, TMEM120B
Shi [158], 2017	China	Uveal melanoma	Diagnosis or prognosis	Supervised: KNN	Accuracy: 95.0%	Serum	Proteomic profile	Biomarkers identified at 2024 Da, 3194 Da, 4396 Da, 4645 Da
Shimizu [159], 2020	Japan	Uveitis	Identifying characteristics	Unsupervised: Hierarchal clustering Bioinformatics: Functional annotation	Not reported	Serum	Metabolomic profile	Arginine, proline, glycine, serine, threonine, alanine, aspartate, glutamate, valine, leucine, isoleucine
Shimizu [41], 2021	Japan	IgG4-Related Ophthalmic Disease	Diagnosis or prognosis	Supervised: Random forest Unsupervised: PCA Bioinformatics: Path analysis	AUC: 0.863	Orbital adipose tissue biopsy	Metabolomic and lipidomic profiles	N1,N12- diacetylspermine, spermine, malate, glycolate
Sivagurunathan [160], 2021	India	AMD	Identifying characteristics	Bioinformatics: Functional annotation, path analysis	Not reported	Serum, urine	Proteomic profile	Cell adhesion molecules, complement, SERPINA-1, TIMP-1, APOA-1
Skeie [161], 2015	USA	Exploratory	Exploratory	Unsupervised: Unbiased clustering Bioinformatics: Functional annotation, protein–protein interaction network, path analysis	Not reported	Vitreous humor	Proteomic profile	Rhodopsin, PDE6, GFAP, Serum coagulation pathway, extracellular matrix turnover, oxidative stress regulation and energy metabolism proteins, immunoglobulin, complement pathway, damage-associated molecular patterns, evolutionarily conserved antimicrobial proteins
Sommer [162], 2019	Germany	GCA	Diagnosis or prognosis	Supervised: DA	Accuracy: 97.3%	Serum	Protein	CRP

Table 4 (continued)

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Soria [42], 2015	Spain	Keratoconus	Identifying characteristics	Unsupervised: PCA, hierarchal clustering Bioinformatics: Protein–protein interaction network, enrichment analysis, path analysis	Not reported	Aqueous humor	Proteomic profile	Proteolytic, hypoxic, hydrogen peroxide response pathways
Srinivasan [163], 2012	USA	DE	Diagnosis or prognosis	Bioinformatics: Functional annotation	Not reported	Tears	Proteomic profile	Aldehyde dehydrogenase, haptoglobin
Sudha [164], 2017	India	X-linked retinoschisis	Exploratory	Bioinformatics: Functional annotation	Not reported	Intraschisis fluid	Proteomic profile	Retinol dehydrogenase, signal transduction, LXR/RXR activation, complement system, acute phase response signalling
Tang [24], 2021	China	POAG	Identifying characteristics	Supervised: PLS-DA, random forest Bioinformatics: KEGG Statistical method: Regression	1) AUC = 0.89 for PLS regression* 2) AUC = 0.79 for logistic regression 3) AUC = 0.89 for random forest* 4) AUC for each individual metabolite ranged from 0.58–0.87, with the most accurate being cyclic AMP	Aqueous humor, serum	Metabolic profile	Cyclic AMP, 2-methylbenzoic acid, 3'-sialyllactose, lysopc 18:0, dulcitol, lysopc 15:0, hypoxanthine Uric Acid, phenyllactate, xanthosine, lysopc 16:0, Lysopc 18:3, hydroxyphenyllactic acid, lysopa 16:0, lysopc 16:1, barbituric acid, L-3-phenyllactic acid, PAF C-16, N6-succinyl adenosine, hexadecanamide, lysopc 18:1, 3-(4-hydroxyphenyl)-propionic acid, N-lactoyl-phenylalanine, 9-hpode, D-mannitol, inosine, guanidinoethyl sulfonate, P-aminobenzoate, hydroxyacetone, 2-aminoadipic acid
Tebani [165], 2020	France	Fabry disease	Identifying characteristics	Unsupervised: Hierarchical cluster analysis, PCA	Not reported	Serum	Targeted proteomic profile for Fabry disease (40 proteins, involved in inflammation and angiogenesis)	Fibroblast growth factor 2, vascular endothelial growth factor A, vascular endothelial growth factor C, interleukin 7
Testa [28], 1985	USA	DR	Diagnosis or prognosis	Supervised: LDA (multivariate discriminant function analysis) Statistical method: Stepwise multiple regression	Accuracy = 71%, Sn = 0.9–0.92, Sp = 0.45 for DR progression using regression	Serum	Diabetic profile (cholesterol, triglycerides, glucose, HbA1c, creatinine, demographic and clinical)	Cholesterol, triglycerides, glucose, HbA1c, creatinine
Ting [166], 2019	Singapore	DR	Identifying characteristics	Supervised: Deep learning, forest plot	AUC = 0.863 (95% CI 0.854–0.871) for DR, AUC = 0.963 (95% CI 0.956–0.969) for referable DR, AUC = 0.950 (95% CI 0.940–0.959) for vision threatening DR	Serum	Diabetic profile (HbA1c, total cholesterol, triglycerides)	HbA1c

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Tokuda [72], 2012	Japan	POAG	Diagnosis or prognosis	Supervised: LDA, SVM, NBC, DT	1) LDA: accuracy = 0.688, Sn = 0.712, Sp = 0.654 using genotype data, accuracy = 0.592, Sn = 0.466, Sp = 0.769 using cytokine data, accuracy = 0.632, Sn = 0.616, Sp = 0.654 using integrated 2) SVM linear: accuracy = 0.664, Sn = 0.699, Sp = 0.615 using genotype data, accuracy = 0.568, Sn = 0.452, Sp = 0.731 using cytokine data, accuracy = 0.659, Sn = 0.648, Sp = 0.673 using integrated 3) SVM polynomial: accuracy = 0.648, Sn = 0.589, Sp = 0.731 using genotype data, accuracy = 0.512, Sn = 0.658, Sp = 0.308 using cytokine data, accuracy = 0.656, Sn = 0.521, Sp = 0.846 using integrated 4) SVM RBF*: accuracy = 0.688, Sn = 0.712, Sp = 0.654 using genotype data, accuracy = 0.648, Sn = 0.712, Sp = 0.558 using cytokine data, accuracy = 0.744, Sn = 0.767, Sp = 0.712 using integrated 5) NBC: accuracy = 0.640, Sn = 0.671, Sp = 0.596 using genotype data, accuracy = 0.624, Sn = 0.479, Sp = 0.827 using cytokine data, accuracy = 0.744, Sn = 0.767, Sp = 0.712 using integrated 6) Decision tree: accuracy = 0.536, Sn = 0.342, Sp = 0.808 using genotype data, accuracy = 0.624, Sn = 0.904, Sp = 0.231 using cytokine data, accuracy = 0.600, Sn = 0.959, Sp = 0.0.096 using integrated	Serum	Cytokine profile	3 cytokines, Fas Ligand, Eotaxin, MIG
Tong [167], 2017	Singapore	DE	Treatment decisions	Unsupervised: Hierarchical cluster analysis Statistical method: Logistic regression	Not reported	Tears	Proteomic profile, demographic and clinical	Biomarkers: Glutathione synthetase, interleukin-1 receptor antagonist gene, alcohol dehydrogenase 1C, angiotensinogen, cholinergic receptor alpha-7, histone cluster 1 H4E, lymphocyte cytosolic protein-1, H3 histone family member 3A Pathways: Inflammation, lacrimal proteins

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Torok [62], 2013	Hungary	DR	Diagnosis or prognosis	Supervised: SVM, random forest, NBC, KNN Statistical method: Recursive partitioning, logistic regression	1) NBC: Sn = 0.6691, Sp = 0.4186 using full data, Sn = 0.8000, Sp = 0.3874 using markers only 2) KNN: Sn = 0.6711, Sp = 0.5000 using full data, Sn = 0.6614, Sp = 0.5000 using markers only 3) Regression: Sn = 0.6923, Sp = 0.3846 using full data, Sn = 0.6615, Sp = 0.3077 using markers only 4) Random forest: Sn = 0.6929, Sp = 0.4483 using full data, Sn = 0.6923, Sp = 0.4103 using markers only 5) Recursive partitioning*: Sn = 0.7083, Sp = 0.4722 using full data, Sn = 0.7404, Sp = 0.4375 using markers only 6) SVM: Sn = 0.6645, Sp = 0 using full data, Sn = 0.6623, Sp = 0 using markers only	Tears	Proteomic profile	34 proteins identified for model development, of which six were classified as marker proteins
Torok [168], 2015	Hungary	DR	Diagnosis or prognosis	Supervised: GBM	1) Sn = 0.84, Sp = 0.86 for microaneurysm count GBM model 2) Sn = 0.87, Sp = 0.68 for proteomic profile GBM model 3) Sn = 0.93, Sp = 0.78 using combined retinal photograph and proteomic GBM model*	Tears	Proteomic profile, retinal photographs	Not reported
Tsubota [169], 2020	Japan	Primary vitreoretinal lymphoma	Diagnosis or prognosis	Unsupervised: Hierarchical cluster analysis	1) ROC = 0.60–0.71 for prognosis using IgG, IgA (serum)*, IL-10, Il-6	Serum, vitreous humor	Complete Serum count, sIL-2, soluble IL-2, β2MG, IgG, IgA, IL-10, IL-6, demographic and clinical	IgA (serum)

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Tsubota [170], 2020	Japan	Immunoglobulin G4-related ophthalmic disease	Identifying characteristics	Supervised: Random forest Unsupervised: Hierarchical cluster analysis	1) ROC = 0.67–0.71 for extraocular muscle enlargement using WBC, Eo count, CRP, IgE* and unreported model 2) ROC = 0.67–0.80 for worsening BCVA using IgG3*, WBC, TP, CRP, IgG, IgA, IgE, β2MG and unreported model 3) ROC = 0.63 for lesion above the neck using WBC count and unreported model 4) 0.78 (95% CI 0.668–0.904) for extraocular muscle enlargement using random forest with IgE, Eo count, and T-Bil 5) 0.86 (95% CI 0.781–0.942) using random forest with WBC, T-BIL, serum IgG, serum IgA, β2-MG, serum IgG4	Serum	Complete Serum count, liver enzymes, renal panel, cute phase proteins IgG, IgA, IgE, β2MG, sIL-2R, IgG4, demographic and clinical	Serum IgE, Eo count, and T-Bil as predictors of extraocular muscle enlargement, and serum IgG4, serum IgG, T-Bil, serum IgA, β2MG, and WBC is the best predictor of worsening BCVA
Varghese [171], 2021	USA	DR	Identifying characteristics	Unsupervised: Non-negative matrix factorization Statistical method: Multinomial logistic regressions	Not reported	Serum	HbA1c, Serum glucose, demographic and clinical	HbA1c, Serum glucose, demographic and clinical data
Velez [172], 2016	USA	Posterior uveitis	Identifying characteristics	Unsupervised: Unbiased cluster analysis	Not reported	Vitreous humor	Cytokine profile	Interleukin 23, IL-1 receptor I, IL-17R, tissue inhibitors of metalloproteinase 1 and 2, insulin like growth factor–binding protein 2, nerve growth factor, platelet-derived growth factor receptor β polypeptide, bone morphogenic protein 4, stem cell factor
Velez [55], 2017	USA	Neovascular inflammatory vitreoretinopathy	Treatment decisions	Unsupervised: Hierarchical cluster analysis Bioinformatics: Pathway analysis (Pathway Commons and WikiPathways)	Not reported	Vitreous humor	Cytokine profile	Biomarkers: 64 proteins, three downregulated and 61 upregulated, including TNF-a, VEGF, VEGFR3, PDGFRβ, FGF-4, FGF-7, IL-6 Pathways: mTOR signalling, class I P13K signalling
Velez [173], 2017	USA	Elevated IOP with RD	Identifying characteristics	Unsupervised: Unbiased cluster analysis	Not reported	Aqueous humor	Proteomic profile	18 upregulated proteins, 63 downregulated proteins, including elevated levels of hepcidin and Cystatin C
Velez [174], 2019	USA	CAPN5 Neovascular Inflammatory Vitreoretinopathy	Identifying characteristics	Supervised: KNN Unsupervised: PCA, hierarchical cluster analysis Bioinformatics: GO, pathway analysis, PANTHER	Not reported	Vitreous humor	Proteomic profile	Biomarkers: 261 proteins Pathways: Decreased synaptic signaling proteins, inflammatory mediators of the acute phase response, complement cascade

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Verhagen [43], 2019	Netherlands	HLA-B27-positive acute anterior uveitis	Identifying characteristics	Supervised: PLS-DA Unsupervised: PCA, hierarchical cluster analysis Bioinformatics: Pathway analysis	Accuracy = 0.7–1.0 (most accurate utilized ketoleucine, leucine, L-valine, ascorbic acid, xylose 5-P, threonic acid, succinic acid, L-cystine, L-aspartate 4-semialdehyde, and pyruvic acid)	Aqueous humor	Metabolic profile	Biomarkers: 19, including ascorbic acid and ketoleucine Pathways: Branched-chain amino acid biosynthesis, ascorbate and aldarate metabolism, the tricarboxylic acid cycle, and glycolysis-diverting pathways
Wang [175], 2019	China	Posner–Schlossman Syndrome	Identifying characteristics	Supervised: OPLS-DA Unsupervised: PCA Bioinformatics: KEGG Statistical method: Logistic regression	AUC = 0.70833–0.88889 (with glycine demonstrating the highest AUC)	Aqueous humor	Metabolic profile	Biomarkers: 3-Hydroxybutyric acid, allose, alpha-ketoisovaleric acid, aminoadipic acid, fumaric acid, glycine, homogentisic acid, ketoleucine, L-arabinose, L-glutamine, mannitol, phenylpyruvic acid, sorbitol, succinic acid Pathways: Alanine, aspartate, and glutamate metabolism, butanoate metabolism, citrate cycle, fructose and mannose metabolism, lysine degradation, nitrogen metabolism, phenylalanine metabolism, synthesis and degradation of ketone bodies, tyrosine metabolism, valine, leucine, and isoleucine biosynthesis and degradation
Wang [176], 2020	China	DR	Identifying characteristics	Supervised: OPLS-DA Unsupervised: PCA Bioinformatics: KEGG Statistical method: Forward stepwise logistic regression	1) AUC = 0.95, Sn = 0.88, Sp = 0.957 for logistic regression using d-2,3-Dihydroxypropanoic acid, isocitric acid, fructose 6-phosphate, and l-Lactic acid in the aqueous humor 2) AUC = 0.951, Sn = 0.955, Sp = 0.857 for logistic regression using pyroglutamic acid and pyruvic acid in the vitreous humor	Aqueous humor, vitreous humor	Metabolic profile	Biomarkers: 15 vitreous proteins, eight aqueous proteins Pathways: 9 identified, including gluconeogenesis, ascorbate–aldarate metabolism, valine–leucine–isoleucine biosynthesis, and arginine–proline metabolism
Wang [177], 2021	China	DR	Identifying characteristics	Unsupervised: k-means cluster analysis	Not reported	Serum	Diabetic profile	Used in cluster analysis model: glutamic acid decarboxylase antibodies, glycosylated haemoglobin, homeostasis model-assessed beta cell function, demographic and clinical (body mass index, insulin resistance index, and age at diagnosis of diabetes)
Wei [178], 2019	China	High myopia choroid neovascularization	Treatment decisions	Bioinformatics: GO, DAVID, QARIP tool	Not reported	Vitreous humor	Proteomic profile	Biomarkers: 310 proteins were differentially expressed in eyes with choroidal neovascularisation. 28 proteins were down-regulated in IVC-treated eyes, including a-smooth muscle actin, aA-crystallin and fibrillin-1 Pathways: Cellular adhesion, protease inhibitors, proangiogenic factors, and antiangiogenic factors
Wei [179], 2020	China	CRVO	Identifying characteristics	Supervised: OPLS-DA, PLS-DA Bioinformatics: KEGG	$R^2Y = 0.998$, $Q^2 = 0.834$	Aqueous humor	Metabolic profile	Biomarkers: 37 metabolites, of which 12 were amino acids Pathways: Valine, leucine and isoleucine biosynthesis, starch and sucrose metabolism, protein digestion and absorption, prolactin signalling, mineral absorption, biosynthesis of amino acids, arginine and proline metabolism, amino-acyl-tRNA biosynthesis, ABC transporters, 2-oxocarboxylic acid metabolism

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Wen [180], 2021	China	High myopia	Identifying characteristics	Bioinformatics: GO, KEGG, STRING	AUC = 0.8750 (95% CI 0.7280–1.022;) with plasminogen protein only	Aqueous humor	Proteomic profile	Biomarkers: 58 proteins, including plasminogen, P0C0L5 (complement), P00747 (plasminogen), Q86YA3 (protein ZGRF1), Q14515 (high endothelial venule protein), A0A075B6K5 (immunoglobulin lambda variable 3–9), P01780 (immunoglobulin heavy variable 3–7), P23142 (fbulin-1), A0A0A0MS15 (immunoglobulin heavy variable 3–49), P31025 (lipocalin-1), P02750 (rho-GTPase-activating protein LRG1) Pathways: Complement and coagulation cascades and cholesterol metabolism, glycolysis/gluconeogenesis, biosynthesis of amino acids, HIF-1 signaling
Wojakowska [44], 2020	Poland	Keratoconus	Identifying characteristics	Unsupervised: PCA, hierarchical cluster analysis Bioinformatics: Pathway analysis (Metabolite Set Enrichment Analysis, Gene Set Enrichment Analysis)	Not reported	Tissue biopsy (cornea)	Metabolic profile	Biomarkers: 46 metabolites, with 13 metabolites whose levels differentiated between groups, including lower levels of carboxylic acids, fatty acids, and steroids in the keratoconus group Pathways: Energy production, lipid metabolism, amino acid metabolism, oxidative stress, inflammation
Wu [181], 2016	China	RD with choroidal detachment	Identifying characteristics	Unsupervised: Hierarchical cluster analysis Bioinformatics: GO, KEGG	Not reported	Vitreous humor	Proteomic profile	Biomarkers: 103 proteins, mostly extracellular Pathways: Complement and coagulation cascades, inflammation
Wu [182], 2017	China	Cataract	Identifying characteristics	Bioinformatics: GO, KEGG, STRING	Not reported	Tissue biopsy (lens)	Proteomic profile	Biomarkers: 1251 proteins, with 16 candidate causal molecules identified Pathways: Cellular metabolic processes, immune responses and protein folding disturbances. In regenerative lens with secondary cataract the intracellular immunological signal transduction pathways were overexpressed, in congenital cataract pathways related to biological processes relating to gene expression and VEGF signaling transduction were altered, and in age-related cataract molecular functions corresponding to external stress were identified
Xiao [183], 2021	China	PDR	Identifying characteristics	Bioinformatics: GO, DAVID, pathway analysis	Not reported	Aqueous humor	Proteomic profile	Biomarkers: 191 proteins Pathways: Complement and coagulation cascades, platelet activation, extracellular matrix–receptor interaction, focal adhesion, protein digestion and absorption, human papillomavirus infection, PI3K-Akt signaling pathway, cholesterol metabolism, peroxisome proliferator-activated receptor signaling pathways, fat digestion and absorption, and vitamin digestion and absorption pathways
Xiong [184], 2021	China	DR	Identifying characteristics	Unsupervised: Cluster analysis Statistical method: Cox regression	Not reported	Serum	Diabetic profile	HbA1c, hemoglobin, total cholesterol, high density lipoprotein, low density lipoprotein, albumen, HOMA2-B, HOMAs-IR, Cr, uric acid, Vitamin D

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Xu [34], 2021	China	Vogt-Koyanagi-Harada, BD	Identifying characteristics	Supervised: PLS-DA Unsupervised: PCA, hierarchical cluster analysis Bioinformatics: Pathway analysis Statistical method: Univariate logistic regression	Not reported	Aqueous humor	Metabolic profile	Biomarkers: 28 differential metabolites in Vogt-Koyanagi-Harada, 29 differential metabolites in BD, including many amino acids, palmitic acid, and oleic acid Pathways in Vogt-Koyanagi-Harada: pantothenate, CoA biosynthesis, Aminoacyl-tRNA biosynthesis Pathways in BD: D-arginine and D-ornithine metabolism, phenylalanine metabolism, Aminoacyl-tRNA biosynthesis
Xuan [185], 2020	China	DR	Identifying characteristics	Supervised: PLS-DA Unsupervised: Hierarchical cluster analysis	Predictive model developed, accuracy not reported	Serum	Lipid profile	481 lipids in 20 sub-classes
Yam [186], 2019	Singapore	Keratoconus	Identifying characteristics	Bioinformatics: GO, IPA	Not reported	Tissue biopsy (cornea)	Proteomic profile	Biomarkers: 20 epithelial and 14 stromal proteins Pathways: Altered epithelial proteome, mitochondrion, cellular assembly, altered stromal proteome, tissue organization, connective tissue disorder, endoplasmic reticulum protein folding
Yamamoto [187], 2020	Japan	DR	Identifying characteristics	Supervised: Bayesian network	Not reported	Serum	Diabetic profile	HbA1c
Yang [188], 2020	China	HSV keratitis	Identifying characteristics	Unsupervised: Hierarchical cluster analysis Bioinformatics: GO	Not reported	Tears	Proteomic profile	Biomarkers: 326 proteins, including IL1A, IL12B, DEFB4A, and CAMP Pathways: Metabolic processes, antigen presentation, inflammatory response, TNF-mediated and T cell receptor pathways, inhibition of viral infection, cell damage
Yao [189], 2013	China	BRVO	Identifying characteristics	Bioinformatics: GO	Not reported	Aqueous humor	Proteomic profile	Biomarkers: 56 proteins, of which 49 were identified, including fibroblast growth factor-4, hepatoma-derived growth factor and Crystallins Pathways: inflammation, apoptosis, angiogenesis, oxidative stress
Yao [190], 2013	China	wAMD	Identifying characteristics	Bioinformatics: GO	Not reported	Aqueous humor	Proteomic profile	Biomarkers: 78 proteins, of which 68 were identified, including fibroblast growth factor-4, hepatoma-derived growth factor Pathways: Crystallins, chemokine ligand 24, complement factor I, and isoform 1 of serum albumin precursor
Yao [57], 2019	China	DR	Diagnosis or prognosis	Supervised: ANN (back propagating) Statistical methods: Univariate and multivariate logistic regression	1) AUROC = 0.84 (95% CI 0.78–0.91) with ANN 2) AUROC = 0.77 (95% CI 0.69–0.85) with multivariate logistic regression	Serum	Diabetic profile including fasting plasma glucose, HbA1c, total cholesterol, triglycerides	HbA1c, demographic and clinical (duration of diabetes, waist to hip ratio, family history)
Ya$_{w}$ata [191], 2019	Singapore	Corneal haze following corneal transplant	Treatment decisions	Unsupervised: PCA	Not reported	Tears	Cytokine profile	51 cytokines clustered into five groups, with TGF-b2, SCF, FGF, MIG, MCP-1, IL-9, IL-4, IL-6, VEGF, IL-7, and IFN-g predicting slow recovery and MCP-1, IL-16, and CTAK at baseline, and IL-1b, MIP-1b, and SCGF-b at one week post-transplant predicting poor visual acuity

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Young [192], 2009	UK	Uveitis	Diagnosis or prognosis	Supervised: PLS-DA, KNN Unsupervised: PCA Bioinformatics: Multivariate variable selection	1) Sn = 78%, Sp = 85% for PLS-DA 2) Sn/Sp = 0.926–0.984 for multivariate classification coupled with genetic algorithm	Vitreous humor	Metabolic profile	Not fully detailed. Oxaloacetate, acetate, and lactate are noted
Yu [193], 2014	China	Epiretinal membrane	Identifying characteristics	Bioinformatics: GO, KEGG	Not reported	Vitreous humor	Proteomic profile	Biomarkers: 226 proteins, including higher levels of complement components, inflammation-related proteins, and matrix metalloproteinase, lower levels of cytoskeletal proteins Pathways: Immune response, inflammatory, coagulation cascade
Yu [194], 2015	China	RD with choroidal detachment	Identifying characteristics	Supervised: PLS-DA Unsupervised: PCA	Not reported	Vitreous humor	Metabolic profile	Biomarkers: 265 metabolites, of which 24 were identified Pathways: Lysine degradation, urea cycle, purine metabolism, citrate cycle, glycerophospholipid metabolism, phenylalanine metabolism, tyrosine metabolism, arachidonic acid metabolism, and ascorbate and aldarate metabolism involved in proliferation, inflammatory reactions, and hemodynamic changes
Zhang [195], 2018	UK	Grave's ophthalmopathy	Diagnosis or prognosis	Supervised: LASSO Unsupervised: Cluster analysis Bioinformatics: In-house model (Bioinformatics Unit of PTP Science Park), KEGG Statistical methods: Multinomial logistical regression	Accuracy: 0.86 ± 0.18, range of 0.712 − 0.863 for used LASSO and regression model. Protein + microRNA models were the most accurate, followed by protein only models, then microRNA models	Serum	Proteomic profile, microRNA	Biomarkers: 178 proteins, 27 micro RNAs, including haptoglobin-related protein, haptoglobin–zonulin–and zinc-alpha-2-glycoprotein, coiled-coil domain-containing protein 25 Pathways: Arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, hippo signaling pathway, regulation of actin cytoskeleton
Zhang [196], 2020	China	DE	Treatment decisions	Bioinformatics: GO, KEGG	Not reported	Tissue biopsy (conjunctiva)	Cytokine profile	Biomarkers: 17 conjunctival cytokines, including monocyte chemoattractant protein 1, macrophage colony-stimulating factor, regulated on activation in normal T-cell expressed and secreted, and tissue inhibitor of metalloproteinases 1 Pathways: Jak-STAT signaling, chemokine signaling, tumor necrosis factor signaling
Zhang [197], 2021	China	Cataract	Identifying characteristics	Bioinformatics: GO, KEGG	Not reported	Tissue biopsy (cataract)	Phosphoproteomes	Biomarkers: 164 phosphoproteins, including phosphorylated phosphoglycerate kinase 1 Pathways: Glutathione metabolism, structural integrity, glycolysis
Zhavoronkov [198], 2016	USA	POAG	Identifying characteristics	Unsupervised: Hierarchical cluster analysis Bioinformatics: Pathway analysis (Pathway Activation Strength)	Not reported	Serum, tissue biopsy	Proteomic profile	Biomarkers: TGFb, 50 differentially activated signaling pathways

Table 4 (continued)

First Author, Publication Year	Country of Publication	Disease(s) of Interest	Study Objective	Statistical, AI, bioinformatics methods (*most accurate)	Model Accuracy (if reported)	Biofluid	Biomarker(s) Analyzed	Significant biomarkers and key pathways, or biomarkers used in model
Zhou [199], 2012	Singapore	Exploratory	Exploratory	Bioinformatics: GO, DAVID	Not reported	Tears	Proteomic profile	Biomarkers: 1543 proteins, including cytoplasmic (25%), nuclear (14%), extracellular (10%), cytoskeletal (10%) and lysosomal (10%) proteins Pathways: Cellular carbohydrate catabolic process (15%), proteolysis (13%), protein transport or localization (12%), cofactor metabolic process (9%), cellular component organization and biogenesis (8%), inorganic substance response (8%), immunity (7%), protein oligomerization (7%), cytoskeleton organization (7%), regulation of apoptosis (7%), protein complex assembly and biogenesis (7%)
Zhu [200], 2020	China	High myopia	Identifying characteristics	Bioinformatics: STRING, GO	Not reported	Aqueous humor	Growth factor profile	Biomarkers: 26 proteins, including growth differentiation factor 15, hepatocyte growth factor, plate-derived growth factor-AA, VEGF Pathways: Cell migration, cellular component movement, cell motility
Zou [201], 2018	China	PDR	Treatment decisions	Bioinformatics: GO, pathway analysis (REACTOME), STRING, DAVID	Not reported	Vitreous humor	Proteomic profile	Biomarkers: 307 proteins Pathways: Innate immune response, platelet degradation, extra-cellular matrix organization, protein binding, regulation of complement cascade, integrin cell surface interactions, amyloid fiber formation
Zou [202], 2020	China	DE	Identifying characteristic	Bioinformatics: WGCNA, GO, KEGG	Not reported	Tears	Proteomic profile	Biomarkers: 1089 proteins, most from extracellular exosomes, vesicles, and organelles Pathways: Retinal homeostasis, myeloid leukocyte activation, cell secretion, immune activation, inflammation, lipid metabolism
Zou [203], 2021	China	DR	Diagnosis or prognosis	Supervised: OPLS-DA Unsupervised: PCA Statistical methods: Linear regression	Validation set: AUC = 0.92 (range 0.84–1.0), Sn = 96%, Sp = 76% (other models also reported)	Serum	Metabolic profile	Biomarkers: 63 metabolites, especially linoleic acid, nicotinuric acid, ornithine, phenylacetylglutamine

Acronyms: *AMD* = age-related macular degeneration; *ANN* = artificial neural network; *BCVA* = best corrected visual acuity; *BD* = Behcet's disease; *BRVO* = branched retinal vein occlusion; *CRP* = C reactive protein; *CRVO* = central retinal vein occlusion; *DA* = discriminant analysis; *DAVID* = database for annotation, visualization and integrated discovery; *DE* = dry eye; *DME* = diabetic macular edema; *DR* = diabetic retinopathy; *GA* = geographic atrophy; *GBM* = Gradient Boosting Machine; *GCA* = giant cell arteritis; *GO* = gene ontology; *HSV* = herpes simplex virus; *IOP* = intraocular pressure; *IPA* = Ingenuity Pathway Analysis; *IVC* = intravitreal conbercept; *KEGG* = Kyoto Encyclopedia of Genes and Genomes; *KNN* = k-nearest neighbors algorithm; *LASSO* = least absolute shrinkage and selection operator; *LDA* = linear discriminant analysis; *LHON* = Leber's hereditary optic neuropathy; *nAMD* = neovascular age-related macular degeneration; *NBC* = Naive Bayes classifier; *NMO* = neuromyelitis optica; *NMOSD* = neuromyelitis optica spectrum disorder; *NPDR* = proliferative diabetic retinopathy; *NTG* = normal tension glaucoma; *OPLS-DA* = orthogonal partial least squares discriminant analysis; *OSD* = ocular surface disease; *PACG* = primary angle closure glaucoma; *PANTHER* = Protein Analysis Through Evolutionary Relationships; *PCA* = principal component analysis; PDR = proliferative diabetic retinopathy; *PLS-DA* = partial least squares discriminant analysis; *POAG* = primary open angle glaucoma; *PXG* = pseudoexfoliation glaucoma; *RD* = retinal detachment; *RP* = retinitis pigmentosa; *RVO* = retinal vein occlusion; Sn = sensitivity; *SOAG* = secondary open angle glaucoma; Sp = specificity; *STRING* = Search Tool for the Retrieval of Interacting Genes/Proteins; *SVM* = support vector machine; *VEGF* = vascular endothelial growth factor; *wAMD* = wet age-related macular degeneration; *WGCNA* = weighted correlation network analysis

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Declarations

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