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Artificial Intelligence and Corneal Diseases

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Abstract

Purpose of review: Artificial intelligence has advanced rapidly in recent years and has provided powerful tools to aid with the diagnosis, management, and treatment of ophthalmic diseases. This article aims to review the most current clinical artificial intelligence applications in anterior segment diseases, with an emphasis on microbial keratitis (MK), keratoconus, dry eye syndrome (DES), and Fuchs endothelial dystrophy.

Recent findings: Most current artificial intelligence approaches have focused on developing deep learning algorithms based on various imaging modalities. Algorithms have been developed to detect and differentiate MK classes and quantify MK features. Artificial intelligence may aid with early detection and staging of keratoconus. Many advances have been made to detect, segment, and quantify features of DES and Fuchs. There is significant variability in the reporting of methodology, patient population, and outcome metrics.

Summary: Artificial intelligence shows great promise in detecting, diagnosing, grading, and measuring diseases. There is a need for standardization of reporting to improve the transparency, validity, and comparability of algorithms.

Keywords

Artificial Intelligence; microbial keratitis; keratoconus; dry eye syndrome; Fuchs endothelial dystrophy

INTRODUCTION

Advances in artificial intelligence (AI) have generated novel insights and are transforming screening, diagnosis, and treatment in various medical fields. AI in ophthalmology has expanded significantly in the last decade. The eye community is well-positioned to create AI strategies given the broad use of imaging tools in clinical practice and hence the availability of codified data from imaging to numeric clinical parameters (e.g., visual acuity, intraocular pressure, etc.). Image-based ophthalmic AI began by focusing on eye diseases involving the posterior segment, such as macular degeneration, diabetic retinopathy, and glaucoma, due to

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the population prevalence and use of ophthalmic imaging in routine clinical practice [1–4]. This led to advances in medicine - the first autonomous AI-based diagnostic tool approved by the Food and Drug Administration was for detecting diabetic retinopathy [5].

These advances have inspired AI development to address diagnostic and management concerns for diseases of the anterior segment. AI algorithms for anterior segment conditions have been reviewed in the past [6–14,13**]. This review article focuses on advancements in the past eighteen months for the use of AI for corneal diseases.

METHODS

A literature search was conducted using PubMed and Scopus databases. The search focused on studies involving the use of AI in screening, diagnosis, staging, or management of corneal diseases, with special emphasis on microbial keratitis, keratoconus, dry eye syndrome including meibomian gland dysfunction, and Fuchs endothelial dystrophy. Full methods, inclusion, and exclusion criteria are found in Supplemental Material 1. Articles are summarized into tabular format (Table 1).

Microbial Keratitis

Microbial keratitis (MK) is a leading cause worldwide of corneal opacification and resulting vision impairment. Management of MK is complex due to delayed patient presentation, unclear differentiation of the organism, lack of a staging system linked to outcomes, and lack of quantified methods to evaluate healing (or non-healing) of MK to tailor management appropriately. In addition, clinicians managing MK are rarely experts in this condition. As a result, clinicians could benefit from AI software and tools that could help alleviate some of the underlying uncertainties with detection, diagnosis, and management of MK.

Detection of MK—Primary detection of MK and differentiation of MK from other conditions and normal eyes has been the focus of recent research. Li et al. optimized pre-existing convolutional neural network (CNN) software to detect keratitis using slit lamp photography (SLP) and smartphone photography [15*]. The best model detected MK with an area under the curve (AUC) of 0.998 from normal eyes and other corneal conditions. Tiwari et al. trained a CNN to differentiate MK ulceration from healed scars from external photographs. The model was tested on internal (India) and external (United States) data sets and achieved high performance (AUCs>0.94) [16**]. Xu et al. gathered SLP data from 89 corneal conditions including patients with MK subtypes to train a CNN model [17*]. Final overall accuracy was 80%, outperforming ophthalmologists reviewing imaging data, but was variable when differentiating organism subtypes. Wang et al. also detected MK and differentiated between organism types on a larger SLP dataset with reported AUC of 0.959 and improved accuracy when compared to clinicians [18].

Distinguishing Between MK Types—Eye clinicians recognize the complexity of differentiating organism types causing MK. Organisms cause different, but often overlapping, morphologic characteristics. The combination of organisms, patient inflammatory responses, and circumstances of the infection, lead to clinical presentations that make determination of the underlying organism difficult, even for cornea specialists

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[19]. AI algorithms have the potential to guide clinicians to aid point-of-care diagnosis. Three recent studies expanded upon previous work [11] by testing CNN algorithms to distinguish MK organisms. Koyama et al. trained models based on SLP images to differentiate between bacterial, fungal, herpes simplex, and *Acanthamoeba* keratitis (BK, FK, HSK, and AK, respectively) [20*]. The overall accuracy of multiclass diagnosis was 88% and >90% for differentiation of each organism subtype. However, another study, using binary classification on external photography images, had lower accuracy for BK and FK [21**]. The best performing CNN had an AUC of 0.81, 75% sensitivity to detect BK from FK, and 81% sensitivity to detect FK from BK. Another study trained an ensemble CNN to discriminate between BK and FK using SLP images with a sensitivity of 77% and F1 score of 83% [22]. Other studies have reported performance below the recommended threshold of 80% sensitivity and/or 80% specificity [23–25].

It is known that interpretation of confocal images requires expertise and time. Optimizing CNN algorithms for confocal interpretation could aid clinicians. Lv et al. and Liu et al. trained CNNs on confocal images with and without FK [26*,27]. Both models showed high performance with accuracies of 96% and 99.9%, respectively. The former research team [26*] then used gradient-weighted class activation mapping to enhance evaluation helping to identify fungal hyphae [28].

Quantifying MK Features—Evaluating MK severity and healing has been explored less extensively. A recent publication for MK severity staging was performed with classical [29] but not with machine learning (ML) methods. Our group has focused on quantifying morphologic features of MK to aid MK staging and monitoring of features over time. We used a de novo CNN architecture to quantify MK features on SLP imaging with promising results [30]. That architecture was refined, and feature sizes were found to be correlated with the patient's visual acuity [31*].

Keratoconus

Keratoconus (KCN) is a prevalent corneal condition causing ectatic changes to the cornea. The disease is progressive, and is often detected by and monitored with imaging, particularly the early form of KCN called forme fruste KCN (ffKCN). The presence of imaging on many patients with various stages of KCN makes it a primary target for AI algorithm development.

Detection of KCN—Several studies have aimed to detect KCN, ffKCN, and normal eyes. Most studies trained models using corneal tomography images with promising results. Al-Timemy et al. trained a hybrid-CNN deep learning (DL) model to identify features then used to train a support vector machine to detect KCN [32]. The final model had a 92% accuracy in differentiating normal from KCN eyes and 69% accuracy in differentiating normal, suspected KCN, and KCN. Two studies used CNN models to differentiate normal, ffKCN, and KCN eyes with high accuracy (99% [33], 95% [34]), while another successfully detected KCN from normal and post-refractive eyes with 99% accuracy [35]. Finally, a study used both tomography and optical coherence tomography (OCT) images to detect disease with resulting high discrimination between normal and ffKCN (AUC=0.93) [36]. However, implementing multimodality imaging in a clinical setting may prove difficult.

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Several studies focused specifically on detecting ffKCN, given the clinical need to detect progression early so surgical interventions can be offered. Kuo et al. trained three CNN models with topography images of normal, ffKCN, and KCN eyes with high performance (AUC>0.95) [37]. Additionally, feature recognition was performed; the models identified patterns of ffKCN including asymmetric bowtie, inferior steepening, and presence of a central cone. Other studies have compared ML algorithms to detect ffKCN. Castro-Luna et al. found that the random forest (RF) outperformed decision tree model (89% accuracy vs 71%, respectively) based on tomographic and biomechanical variables [38]. Cao et al. also found the RF model outperformed other ML algorithms using tomographic and demographic data [39], while Aatila et al. found the RF model to have the highest accuracy compared to other ML models trained on anterior segment (AS)-OCT images in detecting all classes of KCN including ffKCN [40].

Staging of KCN—Some studies have focused on staging KCN severity. Malyugin et al. trained a ML model using tomography images and visual acuity to classify KCN stage based on the Amsler-Krumeich classification system [41]. The model's overall classification accuracy was 97%, highest for stage 4 KCN and lowest for ffKCN. Another study trained an ensemble CNN on tomography measurements to differentiate between normal eyes and early, moderate, and advanced KCN with a staging accuracy of 98% [42]. Two studies used only topography images to detect and stage KCN [43*,44]. Both studies had high overall accuracies (79% [43*] 93% [44]), with better performance on color-coded maps than the raw topographic indices.

Progression of KCN—Other studies have focused on detecting KCN progression, though each study had varying definitions of disease progression. The first study trained a CNN model on AS-OCT images, which achieved a 79% accuracy in discriminating KCN with and without progression [45*]. Analysis of the posterior elevation map had the highest accuracy and pachymetry map had the lowest in detecting progression. Another study trained a model to predict KCN progression and the need for corneal crosslinking using tomography maps and patient age with an AUC of 0.814 [46]. Another group trained an unsupervised ML model to predict need for keratoplasty using baseline OCT data and reported the normalized likelihoods of receiving certain kinds of transplants; however, algorithm performance was not reported [47]. AI may be able to aid clinicians in determining timing of interventions for KCN.

Dry Eye Syndrome

Dry eye syndrome (DES) is a multifactorial disease of the ocular surface characterized by the loss of homeostasis of the tear film. DES can be caused by many factors including reduced tear production, increased evaporation of the tear film, or abnormalities of the ocular surface. Diagnosing DES can be challenging due to a variety of signs and symptoms and the low standardization of interpreting clinical tests. Diagnostic tests employed do not always link to clinical symptom findings. As a result, development of AI algorithms for DES is complicated by the difficulty in "ground truth" diagnosis of DES.

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Detection of DES—Some recent AI studies have focused on detecting DES. Chase et al. developed a CNN algorithm to detect DES using AS-OCT images with good performance (accuracy=85%, sensitivity=86%, specificity=82%) [48**]. The model had a significantly higher accuracy at detecting DES than corneal staining, conjunctival staining, and Schirmer's testing, but not Ocular Surface Disease Index or tear breakup time. Maruoka et al. focused specifically on detecting meibomian gland dysfunction (MGD) from confocal images by training CNN models [49*]. The highest performing single and ensemble model achieved an AUC of 0.966 and 0.981, respectively.

Quantifying DES Features—Authors of two recent publications report CNN models based on SLP to detect and quantify surface keratopathy. A model by Su et al. that automatically quantified and staged keratopathy in DES patients achieved a 97% accuracy in detecting keratopathy [50]. Keratopathy quantification was correlated with clinical grade, but the model's sensitivity and specificity of determining clinical grade from quantification did not achieve 80% for every grade. A model developed by Qu et al. achieved an AUC of 0.940 and accuracy of 77% in grading keratopathy. The model's automated grading scores had strong correlation with clinical grades of the images [51].

Other imaging modalities have been employed to quantify specific features of DES, for example the lower tear meniscus height (LTMH). A custom built AS-OCT was used by Stegmann et al. to train a CNN that quantified the LTMH [52]. Two approaches were tested: direct segmentation of the tear meniscus and segmentation localized to the region of interest. Both models had an accuracy, sensitivity, and specificity >93%. However, since images were obtained from a custom-built system, clinical translatability may be difficult. Another group trained a CNN on topography images to quantify the LTMH, which achieved a sensitivity and F1 score of 90% [53*]. Sub-basal corneal nerve fibers have also been quantified on confocal images [54]. The CNN model achieved an AUC of 0.96. Though this algorithm was not built specifically for DES, the authors propose that it could be applied to this population because nerve fiber length has been shown to be reduced in DES patients [55].

Many recent AI approaches have focused on quantifying MGD features by training models based on meibography images using both machine [56] and deep [57–60] learning methods with promising results.

Fuchs Endothelial Dystrophy

Fuchs endothelial dystrophy (FED) is the most prevalent form of corneal endothelial dystrophies. Hence, many advances in AI algorithms have focused on FED. The diagnosis of FED is typically performed by clinicians using slit lamp examination. However, many diagnostic tools are used for clinical staging including specular microscopy, OCT, and tomography to evaluate endothelial cell count, corneal thickness, corneal haze, and other features.

Detection of FED—Eleiwa et al. trained a CNN model to detect cases without clinically evident corneal edema (termed early-FED) using AS-OCT images and achieved high performance in differentiating early-FED, late-FED, and normal corneas (AUCs >0.97, sensitivities and specificities >91%) [61**]. Zéboulon et al. developed a CNN model to

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differentiate corneal edema from normal eyes and eyes with other corneal conditions from AS-OCT images with high performance (AUROC=0.994, accuracy=99%) [62].

Quantifying FED features—Recent advances to measure FED features have focused on training models to quantify cell counting and morphologic characteristics from specular microscopy images. Shilpashree et al. trained a CNN model to segment endothelial cell density, coefficient of variation, and percentage of guttae with high performance (AUROC=0.967, accuracy=88%) [63*]. Analysis of specular microscopy images has also been performed to analyze cell counts after keratoplasty [64].

Multiple Cornea Conditions

AI algorithms have also been explored to detect and screen for multiple corneal conditions simultaneously. Elsawy et al. developed a DL algorithm using AS-OCT images to detect FED and KCN from normal eyes, which achieved an image classification accuracy of 94% [65**]. The model had the highest performance for FED patients, followed by KCN, then healthy controls. The algorithm was expanded to include DES patients and achieved AUROCs >0.99 for diagnosing each corneal condition [66]. Two other studies used DL algorithms trained on SLP images to detect different corneal pathologies. Gu et al. trained a hierarchical DL framework to detect infectious keratitis, noninfectious keratitis, and other corneal conditions [67**]. The AUC for detecting each disease was >0.91 and performed on par or better than clinical diagnoses made by ophthalmologists. The other study combines a semantic segmentation annotation technique to improve the performance of a DL algorithm for detection of anterior segment pathologies [68**]. The model had an accuracy of differentiating normal from abnormal eyes of 100% and accuracy of 79–99% in diagnosing 10 different pathological features.

CONCLUSION

There are limitations to the field of AI algorithm development. Trust will be critical for clinicians to use AI tools as there is a clear lack of standardization of reporting. Changing from “black box” to “clear box” AI methodologies are meant to build that trust. Methodology should be honed to prevent cross-contamination of groups (e.g., datasets split by patients, not by images) and variability in reporting results. Importantly, representation of all persons equitably in the datasets is needed to ameliorate inherent biases. Thought leaders have highlighted these limitations and are working on improving this burgeoning field to the benefit of science, medicine, and patient care [69].

Overall, this review shows the great promise to aid clinicians with algorithms developed to detect a specific corneal condition, to differentiate between types or stages of a condition, and to quantify features. However, most studies and datasets have been limited to single institutions or single healthcare systems. High performance of these algorithms should spur research teams to expand external datasets for training and testing in other patient populations. Another next logical step would be to pilot test algorithms for anterior segment diseases in clinical settings to learn implementation issues and to begin randomized controlled trials to test algorithm performance. Another key advance will be when datasets and algorithms and methods are made available open source. Ultimately, the reported AI

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algorithms and tools in development for corneal conditions are helping us to understand disease pathogenesis, identify disease biomarkers, and develop novel treatments for corneal diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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65 **. Elsawy A, Abdel-Mottaleb M. A Novel Network With Parallel Resolution Encoders for the Diagnosis of Corneal Diseases. IEEE Trans Biomed Eng. 2021 Dec;68(12):3671–80. [PubMed: 34014818] This study uses an AS-OCT based deep learning model to diagnose dry eye disease, Fuchs endothelial dystrophy, and keratoconus from healthy eyes. On the eye level, the model achieved AUROCs >0.99 for each of the corneal conditions and healthy eye diagnosis.

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67 **. Gu H, Guo Y, Gu L, et al. Deep learning for identifying corneal diseases from ocular surface slit-lamp photographs. Sci Rep. 2020 Oct 20;10(1):17851. [PubMed: 33082530] This study used a hierarchical DL algorithm trained on SLP images to diagnose five anterior segment conditions: infectious keratitis, noninfectious keratitis, corneal degeneration/dystrophy, corneal/limbal neoplasm, and cataract. The AUCs for each disease were >0.90. The model was then tested prospectively on 510 cases and achieved a sensitivity and specificity similar to or better than the average values of all ophthalmologists who reviewed the images.

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Key points:

- AI algorithms had high performance across corneal diseases.
- There was variable reporting of methodology, patient populations, and outcome metrics.
- As most algorithms were developed and tested within one institution, testing with other population data sets are needed to improve generalizability.

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Table 1.

Summary of reviewed articles.

Authors, Year	AI Method	Study Population	Outcome Measure	Imaging Modality	Number of Images	Number of Patients	Demographics Reported	Algorithm Results
Microbial Keratitis								
Li et al., 2021 [15]	CNN	MK, controls	MK detection	SLP, External Photography	13,557	7,988	Complete	AUC 0.998, Sens 98%, Spec 98%*
Tiwari et al., 2022 [16]	CNN	MK, controls	MK detection	External Photography	1,445	1,445	Partial	Internal set (India): AUC 0.973, Sens 94%, Spec 84% External set (US): AUC 0.947, Sens 78%, Spec 91%
Lv et al., 2020 [26]	CNN	FK, controls	FK detection	Confocal	2,623	NR	NR	AUC 0.988, Acc 96%, Sens 92%, Spec 98%
Xu et al., 2021 [28]	CNN	BK, FK	FK detection	Confocal	1,089	35	NR	AUROC 0.983, Acc 97%, Sens 94%, Spec 98%
Liu et al., 2020 [27]	CNN	FK, controls	FK detection	Confocal	1,213	NR	NR	Acc 99.9%
Xu et al., 2021 [17]	CNN	MK, controls	MK detection Differentiate MK subtypes	SLP	2,284	867	NR	Acc 80%, 53%, 83%, and 93% for overall, BK, FK, and HSK
Wang et al., 2021 [18]	CNN	MK, controls	MK detection Differentiate MK subtypes	SLP	5,673	3,320	Complete	AUC 0.959
Koyama et al., 2021 [20]	CNN	MK	Differentiate MK subtypes	SLP	4,306	362	Complete	Acc 88%
Hung et al., 2021 [25]	CNN	BK, FK	Differentiate MK subtypes	SLP	1,330	580	Complete	AUC 0.85, Sens range 26 – 66%, Spec range 80 – 96%, BK Acc range 80 – 96%, FK Acc range 26 – 66%
Redd et al., 2022 [21]	CNN	BK, FK	Differentiate MK subtypes	External Photography	980	980	Complete	AUC 0.83
Ghosh et al., 2021 [22]	CNN	BK, FK	Differentiate MK subtypes	SLP	2,167	194	NR	Sens 77%, F1 score 83%
Kuo et al., 2020 [24]	CNN	MK	Differentiate FK from other MK	SLP	288	288	NR	AUC 0.65
Kuo et al., 2021 [23]	CNN	MK	Differentiate BK from other MK	External Photography	1,512	1,512	NR	Sens 74%, Spec 64%
Loo et al., 2021 [30]	CNN	MK	MK feature quantification	SLP	266	133	NR	DSC range 0.62 – 0.95
Loo et al., 2021 [31]	CNN	MK	Visual Acuity	SLP	152	76	Complete	r = 0.84

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Authors, Year	AI Method	Study Population	Outcome Measure	Imaging Modality	Number of Images	Number of Patients	Demographics Reported	Algorithm Results
Keratoconus								
Kuo et al., 2020 [37]	CNN	KCN, ffKCN, controls	KCN detection	Corneal Topography	354	206	NR	AUROC 0.995, Acc 96%, Sens 94%, Spec 97%
Cao et al., 2020 [39]	ML	ffKCN, controls	KCN detection	Corneal Tomography	NR	88	Partial	AUC 0.96, Acc 87%, Sens 88%, Spec 85%
Castro-Luna et al., 2021 [38]	ML	ffKCN, controls	KCN detection	Corneal Tomography, Tonometry	NR	81	Partial	Acc 89%, Sens 86%, Spec 93%
Al-Timemy et al., 2021. [32]	Hybrid DL - CNN	KCN, controls	KCN detection	Corneal Tomography	4,844	365	Partial	Normal vs KCN: AUC 0.99, Acc 92% Normal vs KCN vs suspected KCN: AUC 0.81, Acc 69%
Zéboulon et al., 2020 [35]	Hybrid ML - CNN	KCN, controls	KCN detection	Corneal Topography	3,000	3,000	Complete	Overall Acc: 99.3% Detection of KCN: Sens 100%, Spec 100%
Aatila et al., 2021 [40]	ML	KCN, ffKCN, controls	KCN detection, staging	AS-OCT	12,242	NR	NR	Diagnostic Acc 98% Staging Acc 95%
Ghaderi et al., 2021 [42]	CNN	KCN, controls	KCN detection, staging	Corneal Tomography	NR	450 eyes	Partial	Detection: Acc 98%, Sens 99%, Spec 96% Staging: Acc 98%, Sens 99%, Spec 99%
Feng et al., 2021 [34]	CNN	KCN, ffKCN, controls	KCN detection, staging	Corneal Tomography	854	854	Complete	Acc 95%
Abdelmotaal et al., 2020 [33]	CNN	KCN, ffKCN, controls	KCN detection, staging	Corneal Tomography	3,218	1,619	Partial	Normal: Acc 99%, Sens 99%, Spec 99% Subclinical KCN: Acc 99%, Sens 99%, Spec 99% KCN: Acc 100%, Sens 100%, Spec 100%
Shi et al., 2020 [36]	ML	KCN, ffKCN, controls	KCN detection, staging	Corneal Tomography, OCT	NR	121 eyes	NR	Normal vs ffKCN: AUC 0.93, Sens 99%, Spec 95% Normal vs KCN: AUC 1.0, Sens 100%, Spec 100%
Kamiya et al., 2021 [43]	CNN	KCN, controls	KCN detection, staging	Corneal Topography	519	519 eyes	Partial	Detection: Acc 97%, Sens 99%, Spec 94% Classification: AUC 0.888 – 0.997, Acc 79%
Chen et al., 2021 [44]	CNN	KCN, controls	KCN detection, staging	Corneal Tomography	1,926	1,836	NR	AUC range 0.82 – 0.91, Acc rage 85 – 99%, Sens range 69 – 99%, Spec range 80 – 94%
Malyugin et al., 2021 [41]	ML	KCN, controls	KCN detection, staging	Corneal Tomography	NR	852 eyes	NR	Overall AUC: 0.97 AUC by KCN stage: Normal 0.98, preclinical KCN 0.95, Stage 1 0.96,

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Authors, Year	AI Method	Study Population	Outcome Measure	Imaging Modality	Number of Images	Number of Patients	Demographics Reported	Algorithm Results
								Stage 2 0.97, Stage 3 0.97, Stage 4 1.0
Kamiya et al., 2021 [45]	DL	KCN	KCN progression	AS-OCT	NR	218	NR	Acc 79%
Kato et al., 2021 [46]	CNN	KCN	KCN progression	Corneal Tomography	274	158	Complete	AUC 0.81, Sens 78%, Spec 70%
Yousefi et al., 2020 [47]	ML	KCN, controls	KCN progression	AS-OCT	12,242	3,162	Complete	Normalized likelihood of need for keratoplasty for clusters 1–5: 2%, 1%, 33%, 33%, 31%
Dry Eye Syndrome								
Chase et al., 2021 [48]	CNN	DES, control	DES detection	AS-OCT	27,180	91	Partial	Acc 85%, Sens 86%, Spec 82%
Su et al., 2020 [50]	CNN	SPK, control	SPK detection, grading	SLP	10,468 **	101	NR	SPK detection: Acc 97% Grading threshold: Sens 97%, Spec 79%
Qu et al., 2021 [51]	CNN	SPK, control	SPK detection, grading	SLP	763	NR	NR	AUROC 0.940, Acc 77%
Stegmann et al., 2020 [52]	CNN	control	Tear meniscus segmentation	Custom OCT	6,658	10	Complete	Sens 96%, Spec 99.9%
Deng et al., 2021 [53]	CNN	NR	Tear meniscus segmentation, quantification	Corneal Topography	485	217	Complete	Segmentation: Sens 90%, F1 score 90% Quantification: r = 0.97 ($p < 0.001$)
Wei et al., 2021 [54]	CNN	NR	Corneal nerve fiber segmentation	Confocal	691	104	NR	AUC 0.96, Sens 96%, Spec 75%
Maruoka et al., 2020 [49]	CNN	MGD, control	MGD detection	Confocal	221	221	Complete	Single model: AUC 0.966, Sens 94%, Spec 82% Ensemble model: AUC 0.981, Sens 92%, Spec 99%
Yeh et al., 2021 [56]	ML	MGD, control	MGD quantification, grading	Corneal Topography	706	576	Complete	Acc 81%
Wang et al., 2021 [57]	DL	NR	MGD segmentation	Corneal Topography	1,443	475	Complete	Segmenting MG (upper, lower): Sens 54%, Sens 74% Identifying ghost glands: Sens 84%, Spec 72%
Setu et al., 2021 [58]	CNN	NR	MGD segmentation	Corneal Topography	728	NR	NR	AUROC 0.96, Sens 81%, F1 score 84%
Khan et al., 2021 [60]	CGAN	MGD	MGD segmentation	Corneal Topography	112	112	Partial	MG segmentation: F1 score 83% MG dropout grading: r = 0.962, $p < 0.001$

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Authors, Year	AI Method	Study Population	Outcome Measure	Imaging Modality	Number of Images	Number of Patients	Demographics Reported	Algorithm Results
Prabhu et al., 2020 [59]	CNN	MGD, control	MGD segmentation, quantification	Corneal Topography, Prototype handheld camera	800	NR	NR	p - values > 0.005 for all metrics between CNN and manual
Fuchs Endothelial Dystrophy								
Eleiwa et al., 2020 [61]	CNN	FED, control	FED detection	AS-OCT	18,720	81	Complete	Early-stage FED: AUC 0.997, Sens 91%, Spec 97% Late-stage FED: AUC 0.974, Sens up to 100%, Spec 92% Healthy vs. all FED: AUC 0.998, Sens 99%, Spec 98%
Zéboulon et al., 2021 [62]	CNN	Edema, control	Edema detection	AS-OCT	806	110	Partial	AUROC 0.994, Acc 99%, Sens 96%, Spec 100%
Shilpashree et al., 2021 [63]	CNN	FED, control	FED segmentation, quantification	Specular Microscopy	2,246	130	Complete	AUROC 0.967, Acc of 88%, F1 score 82%
Vigueras-Guillén et al., 2020 [64]	CNN	FED, control	FED segmentation, quantification	Specular Microscopy	783	141	Partial	CNN: able to estimate parameters in 98% of images; percentage error 2.5% - 5.7% Specular Microscopy: able to estimate parameters in in 31 – 72% of images; percentage error 7.5% - 18.3%
Multiple Cornea Conditions								
Elsawy et al., 2021 [65]	DL	FED, KCN, controls	Multi-disease diagnosis	AS-OCT	16,721	258	NR	FED: AUC 1.0, Sens 94%, Spec 100% KCN: AUC 0.95, Sens 94%, Spec 94% Healthy: AUC 0.93, Sens 91%, Spec 95%
Elsawy et al., 2021 [66]	CNN	FED, KCN, DES, controls	Multi-disease diagnosis	AS-OCT	158,220	478	Complete	FED: AUC 1.0, F1 score 100% KCN: AUC 0.99, F1 score 98% DES: AUC 0.99, F1 score 90% Healthy: AUC 0.98, F1 score 93%
Gu et al., 2020 [67]	DL	MK, noninfectious keratitis, corneal dystrophy, surface neoplasm, cataract, controls	Multi-disease diagnosis	SLP	5,835	≥ 510 ***	NR	Retrospective data set: AUC range 0.903 – 0.951 Prospective data set: AUC > 0.91
Li et al., 2020 [68]	DL	Keratitis; pterygium; conjunctival hyperemia, hemorrhage, edema; cataract	Multi-disease diagnosis	SLP	1,772	NR	Partial	Acc range 79 – 99%, Sens range 53 – 99%, Spec range 85 – 99%

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Acc, accuracy; AK, acanthamoeba keratitis; ANN, artificial neural network; AS-OCT, Anterior segment optical coherence tomography; AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; BK, bacterial keratitis; CGAN, conditional generative adversarial network; CNN, convolutional neural network; DES, dry eye syndrome; DL, deep learning; DSC, Dice similarity coefficient; ffKCN, forme fruste keratoconus; FK, fungal keratitis; HSV, herpes simplex virus keratitis; KCN, keratoconus; MGD meibomian glad dysfunction; MK, microbial keratitis; ML, machine learning; NR, not reported; Sens, sensitivity; SLP, slit lamp photography; Spec, specificity; SPK, superficial punctate keratitis; r, Pearson correlation coefficient, UHR-OCT, Ultra-high-resolution optical coherence tomography; VK, Viral keratitis.

*Multiple algorithms testing different outcome measures and in different datasets.

**Number of original images, study augmented images to increase number for final data set.

***Number of patients partially reported.