Cell Reports Medicine, Volume *4*

Supplemental information

Artificial intelligence in ophthalmology:

The path to the real-world clinic

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Supplementary Table 1. Summary of different imaging types for different purposes in ophthalmology.

Imaging types	Purposes	Target eye disorders	Examples of current and future AI applications in ophthalmology
Color Fundus Photography	Color fundus photography is the process of taking serial photographs of the retina, to show the optic disc, macula, and retinal vasculature. It can also show drusen, abnormal bleeding, scar tissue, and areas of atrophy. In sum, the purpose of this exam is to provide the ophthalmologist with a visual picture of any abnormalities that may be present in the back of the eye.	• Retinal vascular disease: diabetic retinopathy, central/branch retinal artery occlusion, central/branch retinal vein occlusion, and Coats disease • Glaucoma • Retinal detachment • Optic atrophy • Papilledema • Hypertensive retinopathy • Macular disease: age-related macular degeneration, central serous chorioretinopathy, and cystoid macular edema • Retinal vasculitis • Posterior uveitis • Oncology: retinal pigment epithelium adenoma, melanomas, and retinoblastoma • Other fundus diseases	• Current AI application Detecting multiple retinal diseases such as diabetic retinopathy, glaucoma, retinal vein occlusion, and age-related macular degeneration based on fundus images[1,2]. • Future AI application Assisting in progression prediction and treatment decision-making for retinal vascular disease, macular disease, glaucoma, etc.
Ultra-widefield Fundus Imaging	Optos ultra-widefield fundus imaging can provide a 200-degree panoramic image of the retina for the identification of both posterior and peripheral retinal lesions. More	• Retinal periphlebitis • Retinopathy of prematurity • Lattice degeneration • Retinal breaks • Retinitis pigmentosa	• Current AI application Screening for retinal diseases, especially for lesions in the peripheral retina, such as lattice

	important, the peripheral retina can be observed through this imaging with a single capture without requiring a dark setting, contact lens, or pupillary dilation.	• Intermediate uveitis • Subclinical retinal detachment • Other retinal diseases that can be detected from color fundus photography	degeneration, retinal breaks, and subclinical retinal detachment[3,4]. • Future AI application Detecting retinal diseases in both posterior pole and peripheral regions of the retina and predicting systemic diseases.
Optical Coherence Tomography	Optical coherence tomography is a noninvasive imaging technique, which generates images from interferometry patterns of low coherence near-infrared light when it interacts with ocular tissues. Utilizing a wavelength of light that is on the order of a micron or less, it can perform a real-time, cross-sectional, high-resolution imaging of biological tissues, with direct visualization of the histological structure of the ocular tissue with micrometer resolution, including the retina layers, optic nerve head, macular, cornea, and anterior chamber.	• Macular edema • Age-related macular degeneration • Macular hole • Vitreomacular traction • Glaucoma • Retinal hemorrhage • Retinal detachment • Retinal pigment epithelium detachment • Epiretinal membrane • Retinoschisis • Central serous chorioretinopathy • Optic disc edema • Optic nerve head drusen • Neovascularization • Various corneal and ocular surface disorders • Other fundus diseases located in the posterior pole of the retina	• Current AI application Automated diagnosis of optic neuropathies and macular diseases, such as papilledema and central serous chorioretinopathy, and visual prognosis prediction for AMD patients[5-7]. • Future AI application Expanding to discern the disease progression in patients with various neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.

Optical Coherence Tomography Angiography	Optical coherence tomography angiography is a non-invasive imaging modality that provides three-dimensional delineation of retinal vasculatures at the capillary level resolution, without the need to intravenously administer fluorescent dyes. It can also detect subtle vascular distortions associated with the progression of retinal pathologies, such as vessel dropout, foveal abnormalities, and increased vessel tortuosity. At the same time, it has the ability to perform depth-resolved analysis, in which the flow within a specific axial location of the retinal or choroid can be analyzed.	• Diabetic retinopathy • Diabetic macular edema • Age-related macular degeneration • Glaucoma • Choroidal neovascularization • Polypoidal choroidal vasculopathy • Central serous chorioretinopathy • Retinal vein occlusion • Retinal arterial occlusion • Macular telangiectasia type 2 • Choroidal nevus • Choroidal melanoma • Choroidal hemangiomas • Retinal toxicity • Other fundus diseases located in the posterior pole of the retina	• Current AI application Grading the diabetic retinopathy severity, detecting macular ischemia, distinguishing between healthy eyes and glaucoma, etc[8]. • Future AI application Identifying the primary angle open glaucoma at the preclinical detectable phases and differentiating between the primary angle open glaucoma and ocular hypertension.
Slit Lamp Imaging	The slit lamp is a stereoscopic biomicroscope that emits a focused beam of light that can be adjusted from a very broad pattern to a very narrow slit and utilizes a variety of magnifications and angles of view to highlight the areas of interest. Slit-lamp imaging is the photography of the	• Conjunctivitis • Pterygium • Keratitis • Leukoma • Corneal dermoid tumor • Corneal degeneration • Corneal dystrophy • Cataract	• Current AI application Screening for keratitis, pterygium, corneal degeneration, cataract, etc[9,10]. • Future AI application

	structures of the anterior segment and surrounding areas of the eye, such as cornea, conjunctiva, sclera, anterior chamber, aqueous humor, pupil, lens, iris, etc.	• Lens dislocation or subluxation • Iris cysts • Anterior uveitis • Other anterior segment ocular diseases	Further classifying keratitis into bacterial, fungal, viral, amebic, and noninfectious keratitis.
Fundus Fluorescein Angiography	Fundus fluorescein angiography is an important clinical examination used to investigate and document the status of the retinal and choroidal vascular systems. Fluorescein dye is administered intravenously and followed by rapid-sequence serial photographs through a dedicated fundus camera equipped with excitation and barrier filters, which produces an angiographic display that is used to visualize and document retinal blood flow dynamics while recording the integrity of the inner blood-retinal barriers and the fine details of the retinal pigment epithelium, simultaneously revealing abnormal blood vessels. Pathologic changes are recognized by the identification of areas that exhibit	• Vogt-Koyanagi-Harada disease • Age-related macular degeneration • Macular edema • Retinal vascular disease: diabetic retinopathy, central/branch retinal artery occlusion, and central/branch retinal vein occlusion • Anterior ischemic optic neuropathy • Macular pucker • Ocular melanoma • Other retinal and choroidal vascular diseases	• Current AI application Grading the severity of diabetic retinopathy and detecting leakage points in central serous chorioretinopathy[11,12]. • Future AI application In combination with time information to enhance classification results, such as differentiating between neuromyelitis optica and optic neuritis.

	hypofluorescence (darkness) and/or hyperfluorescence (brightness).		
Indocyanine Green Angiography	Indocyanine Green Angiography is an important invasive dynamic imaging modality that uses ICG dye which glows or fluoresces in the infrared spectrum and can be imaged through the pigmented layer using special filters, to image the choroidal circulation and its abnormalities. In particular, it plays an important role in detecting, classifying, and guiding the treatment of choroidal neovascularization.	• Idiopathic polypoidal choroidal vasculopathy • Retinal angiomatous proliferation • Central serous chorioretinopathy • Bruch's Membrane Breaks • Birdshot chorioretinopathy • Choroidal tumors：malignant melanoma, choroidal hemangioma, and choroidal osteomas • Other choroidal disorders	• Current AI application Classification of pachychoroid disease and diagnosis of polypoidal choroidal vasculopathy[13,14]. • Future AI application Identification of other retinal/choroidal abnormalities, such as retinal angiomatous proliferation and choroidal tumors.
Gonioscopic Angle Imaging	Gonioscopic angle Imaging is a technique that uses a gonioscope in conjunction with a slit lamp or operating microscope to gain a view of the anterior chamber angle structures and their configuration.	• Narrowness or closure of the anterior chamber angle • Classification of glaucoma • Anterior chamber neovascularization • Iris cysts • Pseudoexfoliative material • Angle recession • Foreign bodies in the anterior chamber angle • Other abnormalities located in the anterior chamber angle	• Current AI application Detecting anterior chamber angle closure[15]. • Future AI application Providing individualized treatment strategies for patients with primary angle closure glaucoma.

Ocular Ultrasound	Ocular ultrasound is an imaging technique that uses high-frequency sound waves that travel through the eye to create an image of the retina and the surrounding structures. It is a safe, non-invasive tool with real-time feedback, which can evaluate the structure and pathology of the eye. It can also assess the surrounding tissues and measure the size of the eye. In addition, it can provide information that is not readily obtained by direct visualization of ocular tissues.	• Retrobulbar hematoma • Foreign body • Lens dislocation (ectopia lentis) • Retinal detachment • Posterior vitreous detachment • Vitreous hemorrhage • Vitreous traction • Intraocular tumor • Blood beneath the retina • Other vitreous and retinal diseases	• Current AI application Detection of vitreoretinal abnormalities and mathematical analysis of retinal detachment area[16,17]. • Future AI application Identification of referable vitreoretinal abnormalities.
Computed Tomography	Computed tomography (CT) is a technology using X-ray radiation beams and an array of radiation detectors that surround the part being examined. A CT of the orbits takes very thin slice images of the eyes and orbits at three different angles (coronal, sagittal, horizontal) to create detailed pictures of the orbits, eyes, surrounding bones, and underlying soft tissue. Three-dimensional reconstructions and enhanced scanning are done as needed. CT can provide useful information	• Eye injury: foreign body, eyeball rupture, orbital fracture, soft tissue hematoma • Orbital adjacent structural lesions • Optic pathologic lesions • Thyroid associated ophthalmopathy • Dacryocystitis • Dacryagogatresia • Retinoblastoma • Other orbital and ocular diseases	• Current AI application Screening for thyroid-associated ophthalmopathy and diagnosing benign and malignant orbital tumors[18,19]. • Future AI application Providing decision-making recommendations and prognosis judgment for patients with orbit diseases, such as malignant orbital

	when ocular trauma is clinically suspected. For example, it can be used to detect intraorbital and intraocular hemorrhage and emphysema, globe rupture, optic nerve injury, and extraocular muscle injury.		tumors and thyroid-associated ophthalmopathy.
Magnetic Resonance Imaging	Magnetic Resonance Imaging (MRI) is a non-invasive imaging technology that uses a magnetic field and radio waves to produce proton-density images without the use of ionizing radiation. It can create three-dimensional detailed anatomical images of the eye and its surrounding tissue in the orbit, especially in providing excellent spatial and contrast resolution of the orbital soft tissues.	• Orbital pathologies： • Capillary and cavernous hemangioma • Optic pathway glioma • Optic nerve sheath meningioma • Optic nerve neuritis • Benign mixed tumor • Dacryoadenitis • Dacryocystitis • Eyelid tumors • Cellulitis • Subperiosteal abscess • Mucocele & Pyocele • Myasthenia Gravis • Dermoid cyst • Lymphoma • Lymphangioma • Schwannoma • Orbital metastasis • Idiopathic inflammatory orbital disease (Orbital pseudotumor)	• Current AI application Detecting orbit and periorbital lesions, such as orbital multiple myelomas, cavernous venous malformations, cysts, and basal or squamous cell carcinomas around the eye[20], and differentiating cavernous hemangioma from schwannoma[21]. • Future AI application Providing individualized treatment strategies for patients with orbit and periorbital lesions.

		• Thyroid associated orbitopathy • Ocular pathologies： • Hemangioma • Leiomyoma • Persistent hyperplastic primary vitreous • Uveal melanoma • Choroidal metastasis • Coloboma/staphyloma • Other orbital and ocular diseases	
Ultrasound Biomicroscopy	Ultrasound biomicroscopy is a high-resolution, in vivo imaging tool, which uses high-frequency sound waves rather than coherent light to obtain two-dimensional gray-scale images. It is primarily used for imaging much of the anatomy of the anterior segment, as well as associated pathologies. It also plays a particular role in imaging the intricate iridociliary complex, and for anterior segment imaging with corneal haze or opacity.	• Iris and ciliary cysts • Angle closure • Angle recession • Lens dislocation • Cyclodialysis • Iridodialysis • Plateau iris • Other anterior segment abnormalities	• Current AI application Detecting angle closure and quantitatively measuring angle parameters in an automated fashion, such as trabecular-iris angle, angle-opening distance, angle recess area, and angle width[22,23]. • Future AI application Offering individualized treatment recommendations for patients with anterior chamber angle closure.
Corneal Topography	Corneal topography is a computer-assisted diagnostic tool for mapping a detailed three-dimensional map of	• Keratoconus • Corneal abrasions • Corneal deformities	• Current AI application

	the cornea, examining characteristics of the cornea such as shape, curvature, power, and thickness. It enables the detection of irregular corneal conditions, even which are invisible in most conventional testing. It also helps identify corneal diseases, such as swelling, scarring, abrasions, and deformities.	• Irregular astigmatism • Other corneal abnormalities	Detecting corneal ectasia and screening candidates for refractive surgery[24,25]. • Future AI application In combination with a biomechanical index to enhance the ability to screen for subclinical keratoconus.
In Vivo Confocal Microscopy	In vivo confocal microscopy is a novel noninvasive clinical technique, which enables morphological and quantitative analysis of ocular surface microstructure, including corneal epithelium, Bowman's layer, stroma, Descemet's membrane, and the corneal endothelium.	• Corneal dystrophies • Corneal ectatic disorders • Corneal degenerations • Corneal deposits (e.g., pseudoexfoliation syndrome） • Limbal stem cell deficiency • Iridocorneal endothelial syndrome • Dry eye disease • Keratitis (microbial, fungal, parasitic, viral) • Endothelial abnormalities • Other ocular surface disorders	• Current AI application Diagnosis of fungal keratitis and obstructive meibomian gland dysfunction[26,27]. • Future AI application In combination with the height of the tear meniscus, tear film break-up time, and tear secretion to enhance the ability to detect dry eye diseases.
Corneal Endothelial Photography	Corneal endothelial photography is a tool by which endothelial cells lining the posterior surface of the cornea in the living eye are photographed by a	• Fuchs' endothelial dystrophy • Iridocorneal Endothelial Syndrome • Corneal guttata • Age-related endotheliopathy	• Current AI application Analyzing the size, shape, and density of endothelial cells and

	camera attached to a specialized specular microscope. It can measure the morphology of corneal endothelial cells and the endothelial cell density in cells per square millimeter.	• Contact lens-induced endotheliopathy • Other corneal endothelial abnormalities	detecting Fuchs' endothelial dystrophy[28,29]. • Future AI application In combination with the guttae area ratio parameter to classify Fuchs' dystrophy into different stages.
Automated Perimetry	Automated perimetry is a tool that uses a computer program to test an individual's visual field.	• Glaucoma • Retinitis pigmentosa • Retrobulbar neuritis • Papilledema • Ischemic optic neuropathy • Visual pathway diseases • Other optic nerve and retinal disorders	• Current AI application Diagnosing glaucoma and distinguishing pre-perimetric glaucoma from healthy eyes[30,31]. • Future AI application Distinguishing glaucoma from other optic nerve diseases in an automated fashion.

References

1. Lin, D., Xiong, J., Liu, C., Zhao, L., Li, Z., Yu, S., Wu, X., Ge, Z., Hu, X. and Wang, B., et al. (2021). Application of Comprehensive Artificial intelligence Retinal Expert (CARE) system: A national real-world evidence study. Lancet Digit Health *3*, e486-e495.
2. Cen, L.P., Ji, J., Lin, J.W., Ju, S.T., Lin, H.J., Li, T.P., Wang, Y., Yang, J.F., Liu, Y.F. and Tan, S., et al. (2021). Automatic detection of 39 fundus diseases and conditions in retinal photographs using deep neural networks. Nat. Commun. *12*, 4828.
3. Li, Z., Guo, C., Nie, D., Lin, D., Zhu, Y., Chen, C., Zhang, L., Xu, F., Jin, C. and Zhang, X., et al. (2019). A deep learning system for identifying lattice degeneration and retinal breaks using ultra-widefield fundus images. Annals of Translational Medicine *7*, 618.
4. Li, Z., Guo, C., Nie, D., Lin, D., Zhu, Y., Chen, C., Wu, X., Xu, F., Jin, C. and Zhang, X., et al. (2020). Deep learning for detecting retinal detachment and discerning macular status using ultra-widefield fundus images. Communications Biology *3*, 15.
5. Han, J., Choi, S., Park, J.I., Hwang, J.S., Han, J.M., Ko, J., Yoon, J., and Hwang, D.D. (2023). Detecting macular disease based on optical coherence tomography using a deep convolutional network. J Clin Med *12*.
6. Biousse, V., Danesh-Meyer, H.V., Saindane, A.M., Lamirel, C. and Newman, N.J. (2022). Imaging of the optic nerve: Technological advances and future prospects. Lancet Neurol. *21*, 1135-1150.
7. Chandra, R.S. and Ying, G.S. (2023). Evaluation of multiple machine learning models for predicting a number of Anti-VEGF injections in the comparison of AMD treatment trials (CATT). Transl Vis Sci Technol *12*, 18.
8. Yang, D., Ran, A.R., Nguyen, T.X., Lin, T., Chen, H., Lai, T., Tham, C.C. and Cheung, C.Y. (2023). Deep learning in optical coherence tomography angiography: Current progress, challenges, and future directions. Diagnostics (Basel) *13*.
9. Li, Z., Jiang, J., Chen, K., Chen, Q., Zheng, Q., Liu, X., Weng, H., Wu, S. and Chen, W. (2021). Preventing corneal blindness caused by keratitis using artificial intelligence. Nat. Commun. *12*, 3738.
10. Keenan, T., Chen, Q., Agron, E., Tham, Y.C., Goh, J., Lei, X., Ng, Y.P., Liu, Y., Xu, X. and Cheng, C.Y., et al. (2022). DeepLensNet: Deep learning automated diagnosis and quantitative classification of cataract type and severity. Ophthalmology.
11. Gao, Z., Jin, K., Yan, Y., Liu, X., Shi, Y., Ge, Y., Pan, X., Lu, Y., Wu, J. and Wang, Y., et al. (2022). End-to-end diabetic retinopathy grading based on fundus fluorescein angiography images using deep learning. Graefes Arch Clin Exp Ophthalmol *260*, 1663-1673.
12. Chen, M., Jin, K., You, K., Xu, Y., Wang, Y., Yip, C.C., Wu, J. and Ye, J. (2021). Automatic detection of leakage point in central serous chorioretinopathy of fundus fluorescein angiography based on time sequence deep learning. Graefes Arch Clin Exp Ophthalmol *259*, 2401-2411.
13. Kim, I.K., Lee, K., Park, J.H., Baek, J. and Lee, W.K. (2021). Classification of pachychoroid disease on ultrawide-field indocyanine green angiography using auto-machine learning platform. Br J Ophthalmol *105*, 856-861.
14. Yang, J., Zhang, C., Wang, E., Chen, Y. and Yu, W. (2020). Utility of a public-available artificial intelligence in diagnosis of polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol *258*, 17-21.
15. Chiang, M., Guth, D., Pardeshi, A.A., Randhawa, J., Shen, A., Shan, M., Dredge, J., Nguyen, A., Gokoffski, K. and Wong, B.J., et al. (2021). Glaucoma Expert-Level detection of angle closure in

goniophotographs with convolutional neural networks: The Chinese American Eye Study. Am. J. Ophthalmol. *226*, 100-107.

16. Gupta, R., Gupta, V., Kumar, B., Singh, P.K. and Singh, A.K. (2020). A novel method for automatic retinal detachment detection and estimation using ocular ultrasound image. Multimed. Tools Appl. *79*, 11143-11161.
17. Adithya, V.K., Baskaran, P., Aruna, S., Mohankumar, A., Hubschman, J.P., Shukla, A.G. and Venkatesh, R. (2022). Development and validation of an offline deep learning algorithm to detect vitreoretinal abnormalities on ocular ultrasound. Indian J. Ophthalmol. *70*, 1145-1149.
18. Song, X., Liu, Z., Li, L., Gao, Z., Fan, X., Zhai, G. and Zhou, H. (2021). Artificial intelligence CT screening model for thyroid-associated ophthalmopathy and tests under clinical conditions. Int J Comput Assist Radiol Surg *16*, 323-330.
19. Shao, J., Zhu, J., Jin, K., Guan, X., Jian, T., Xue, Y., Wang, C., Xu, X., Sun, F. and Si, K., et al. (2023). End-to-End Deep-Learning-Based diagnosis of benign and malignant orbital tumors on computed tomography images. J Pers Med *13*.
20. Aydin, N., Saylisoy, S., Celik, O., Aslan, A.F. and Odabas, A. (2022). Segmentation of orbital and periorbital lesions detected in orbital magnetic resonance imaging by deep learning method. Pol J Radiol *87*, e516-e520.
21. Bi, S., Chen, R., Zhang, K., Xiang, Y., Wang, R., Lin, H. and Yang, H. (2020). Differentiate cavernous hemangioma from schwannoma with artificial intelligence (AI). Ann Transl Med *8*, 710.
22. Wang, W., Wang, L., Wang, X., Zhou, S., Lin, S. and Yang, J. (2021). A deep learning system for automatic assessment of anterior chamber angle in ultrasound biomicroscopy images. Transl Vis Sci Technol *10*, 21.
23. Wang, W., Wang, L., Wang, T., Wang, X., Zhou, S., Yang, J. and Lin, S. (2021). Automatic localization of the scleral spur using deep learning and ultrasound biomicroscopy. Transl Vis Sci Technol *10*, 28.
24. Shanthi, S., Aruljyothi, L., Balasundaram, M.B., Janakiraman, A., Nirmaladevi, K. and Pyingkodi, M. (2022). Artificial intelligence applications in different imaging modalities for corneal topography. Surv. Ophthalmol. *67*, 801-816.
25. Xie, Y., Zhao, L., Yang, X., Wu, X., Yang, Y., Huang, X., Liu, F., Xu, J., Lin, L. and Lin, H., et al. (2020). Screening candidates for refractive surgery with corneal Tomographic-Based deep learning. JAMA Ophthalmol. *138*, 519-526.
26. Lv, J., Zhang, K., Chen, Q., Chen, Q., Huang, W., Cui, L., Li, M., Li, J., Chen, L. and Shen, C., et al. (2020). Deep learning-based automated diagnosis of fungal keratitis with in vivo confocal microscopy images. Ann Transl Med *8*, 706.
27. Maruoka, S., Tabuchi, H., Nagasato, D., Masumoto, H., Chikama, T., Kawai, A., Oishi, N., Maruyama, T., Kato, Y. and Hayashi, T., et al. (2020). Deep neural Network-Based method for detecting obstructive meibomian gland dysfunction with in vivo laser confocal microscopy. Cornea *39*, 720-725.
28. Fabijanska, A. (2018). Segmentation of corneal endothelium images using a U-Net-based convolutional neural network. Artif. Intell. Med. *88*, 1-13.
29. Sierra, J.S., Pineda, J., Rueda, D., Tello, A., Prada, A.M., Galvis, V., Volpe, G., Millan, M.S., Romero, L.A. and Marrugo, A.G. (2023). Corneal endothelium assessment in specular microscopy images with Fuchs' dystrophy via deep regression of signed distance maps. Biomed. Opt. Express *14*, 335-351.

30. Lee, S.D., Lee, J.H., Choi, Y.G., You, H.C., Kang, J.H. and Jun, C.H. (2019). Machine learning models based on the dimensionality reduction of standard automated perimetry data for glaucoma diagnosis. Artif. Intell. Med. *94*, 110-116.
31. Asaoka, R., Murata, H., Iwase, A. and Araie, M. (2016). Detecting preperimetric glaucoma with standard automated perimetry using a deep learning classifier. Ophthalmology *123*, 1974-1980.