Guest Editorial
Ophthalmic Image Analysis and Informatics

EYE diseases, e.g., diabetic retinopathy (DR), glaucoma, and age-related macular degeneration (AMD), are leading causes of vision impairment and blindness worldwide. These diseases lead to reduced quality of life for individuals and their careers, and to substantial economic loss for the society and healthcare systems. In a WHO report [1], it estimates that at least 2.2 billion people have vision impairment, globally, of whom at least 1 billion have vision impairment that could have been prevented or has yet to be addressed. This burden can be avoided or reduced by early and reliable diagnosis and effective treatment strategies. Diagnostic and interventional eye imaging is key technology transforming eye care and treatment. Many automatic and semi-automatic image analysis methods and computer aided diagnosis and image-guided eye surgery systems have been proposed in the context of eye research and, increasingly, some have percolated into clinical ophthalmology [2]. Increasing interest has been developed in understanding retinal vasculature and neuro-retinal architecture as a source of biomarkers for several high-prevalence conditions like dementia, cardiovascular disease, and complications of diabetes. More recently, AI system, especially the deep learning technique, and increasing availability of ever-larger scale databases have led to actively exploring new approaches to ocular image analysis and commercial systems, which have shown impressive performances. Deep learning-based AI system has shown its abilities across multiple medical domains [2]. However, considerable challenges remain in terms of new imaging methods and systems for ophthalmology, reliability and validation of ophthalmic imaging biomarkers, cross-modal image analysis (e.g., fundus, optical coherence tomography (OCT), fluorescein angiography, and scanning laser ophthalmoscopy), cross-organ image analysis (e.g., eye-brain, eye-heart, etc.) methods for more interpretable and explainable machine learning in ophthalmic image analysis and informatics.

This special issue invited contributions reporting on methodological breakthroughs in artificial intelligence in ophthalmology, and systems and insights that make use of large-scale datasets linking across multiple imaging modalities, image phenotyping, and imaging omics. This Special Issues aims to (1) encourage the novel ophthalmic imaging modalities; (2) develop AI system and tool for ophthalmic image analysis and informatics; (3) build the computer-aided detection and diagnosis of eye disease on single and multi-modal ophthalmic image; (4) evaluate and review the new benchmark datasets related to multiple eye diseases. In the Call-For-Papers, researchers were encouraged to submit high quality data and unpublished work. A total of 60 submissions have been received covering a variety of topics in these areas with the papers in the area of ophthalmic image analysis and informatics. After several rounds of review, 17 papers were accepted finally. These papers propose novel solutions on major eye diseases, including glaucoma, AMD, DR, dry eye, and also vessel detections that might be useful for eye-brain and eye-heart association studies.

The special issues begin with a review paper by Sarhan *et al.* [4], which reviews machine learning approaches for diagnosing ophthalmic diseases during the last four years. This review covers over 60 publications and 25 public datasets and challenges related to the detection, grading, and lesion segmentation of the three considered diseases (i.e., DR, AMD, and glaucoma).

After the review paper, five papers of color fundus image are presented. Meng *et al.* [5] proposes a framework that generates heatmaps reflecting lesion regions precisely in fundus image. Then, they utilize the gradient-based classification activation map to reveal the lesion regions for disease classification. Hernandez-Matas *et al.* [6] proposes a registration framework to simultaneously estimate eye pose and shape in fundus image. Luo *et al.* [7] addresses challenges of degraded image quality due to cataracts by two designed two neural networks. The first network was intended for the synthesis of cataract-like images through unpaired clear retinal images and cataract images. The second one was trained using pairs of synthesized cataract-like images and the corresponding clear images through supervised learning. Wang *et al.* [8] addresses the challenges of detecting vessels from hard regions. An algorithm with three decoder networks is proposed: the first of which dynamically locates which image regions are "hard" or "easy" to analyze, while the other two aim to segment retinal vessels in these "hard" and "easy" regions independently. Wang *et al.* [9] proposes an approach for simultaneous diagnosis of DR severity and DR related features in fundus images.

OCT imaging is another important ocular imaging technique. In this special issue, we collect five works on OCT data. Zhang *et al.* [10] incorporate medical and imaging prior knowledge with deep learning to address the challenging issue of the segmentation and visualization of choroid in OCT. A biomarker infused global-to-local network is designed to regularize the segmentation via predicted choroid thickness, simultaneously, leverage a global-to-local segmentation strategy to provide global structure information and suppress overfitting. George *et al.* [11] proposes an end-to-end attention guided 3D deep learning model for glaucoma detection and estimating visual function from retinal structures. The model is trained directly

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on 3D OCT volumes using three inputs, original 3D-OCT cube and the other two are computed during training guided by 3D grad-CAM heatmaps. Wang *et al.* [12] proposes a weakly deep supervised learning framework with uncertainty estimation to address the macula-related disease classification problem from OCT images with the only volume level label. It eliminates the need to obtain fine-grained expert annotations, which is usually quite difficult and expensive. Ma *et al.* [13] proposes a novel weakly supervised model for geographic atrophy segmentation in spectral-domain OCT. A scaling and upsampling module and an attentional fully connected model are adopted. Romo-Bucheli *et al.* [14] proposes deep learning model for prediction from longitudinal retinal OCT applied to predicting treatment requirements for the management of neovascular AMD. The model comprises of a densely connected neural network and a recurrent neural network, trainable end-to-end.

Optical Coherence Tomography Angiography (OCTA) as an innovative imaging technology has received more attention. In this special issue, two OCTA based methods are proposed. Sarabi *et al.* [15] considers the vessel density mapping in Optical Coherence Tomography Angiography (OCTA). They provide a novel multimodal 3D framework by utilizing information from OCT and OCTA to detect localized capillary changes at voxel-level between longitudinal scans and across populations. Wu *et al.* [16] addresses the issue of removing strip noise in OCT angiogram. Two novel image decomposition modules including cooperative uniformity destriping module and cooperative similarity destriping module are proposed.

Beside above ocular imaging, this special issue also considers more other ophthalmic modalities. Da Cruz *et al.* [17] present a method for classification of the tear film lipid layer without using deep learning approaches. The method employs phylogenetic diversity indexes and Ripley's K function. Chesley and Barbour [18] evaluates the utility of a novel general estimator applied to visual field testing using a multidimensional psychometric function estimation tool built on semiparametric probabilistic classification. It combines the flexibility of nonparametric estimators and the efficiency of parametric estimators. Rodrigues *et al.* [19] proposes a coupled region growing and machine learning approach for multi-modal vessel segmentation. The proposed method captures complementary evidence based on grey level and vessel connectivity properties, which is seamlessly propagated through the pixels at the classification phase. Liu *et al.* [20] proposes a spatially-aware, Dense-LinkNet based regression approach to improve the detection of in vivo fluorescent cell patterns, demonstrating the utility of incorporating spatial inputs into a deep learning-based regression framework for cell detection.

These papers presented in this special issue introduce the latest advances in the field of ophthalmic image analysis and informatics, which enable and drive the research, development, and application of key technologies into ocular healthcare.

The guest editors thank all those who helped to make the special issue possible, especially the Editor-in-Chief, editorial staff and the reviewers. We hope that the latest work published in this special issue could bring new cutting-edge visions, models, algorithms, methods and perspectives that push forward the research on Ophthalmic Image Analysis and Informatics.

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