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30 Abstract

Background and Objectives: Pathological myopia (PM) is the seventh leading cause of blindness, with a reported global prevalence up to 3%. Early and automated PM detection from fundus images could aid to prevent blindness in a world population that is characterized by a rising myopia prevalence. We aim to assess the use of convolutional neural networks (CNNs) for the detection of PM and semantic segmentation of myopia-induced lesions from fundus images on a recently introduced reference data set.

37 Methods: This investigation reports on the results of CNNs developed for the recently introduced Pathological Myopia (PALM) dataset, which consists of 1200 images. Our CNN bundles lesion 38 segmentation and PM classification, as the two tasks are heavily intertwined. Domain knowledge is 39 40 also inserted through the introduction of a new Optic Nerve Head (ONH)-based prediction 41 enhancement for the segmentation of atrophy and fovea localization. Finally, we are the first to 42 approach fovea localization using segmentation instead of detection or regression models. Evaluation 43 metrics include area under the receiver operating characteristic curve (AUC) for PM detection, Euclidean distance for fovea localization, and Dice and F1 metrics for the semantic segmentation tasks 44 45 (optic disc, retinal atrophy and retinal detachment).

46 Results: Models trained with 400 available training images achieved an AUC of 0.9867 for PM 47 detection, and a Euclidean distance of 58.27 pixels on the fovea localization task, evaluated on a test 48 set of 400 images. Dice and F1 metrics for semantic segmentation of lesions scored 0.9303 and 49 0.9869 on optic disc, 0.8001 and 0.9135 on retinal atrophy, and 0.8073 and 0.7059 on retinal 450 detachment, respectively.

51 Conclusions: We report a successful approach for a simultaneous classification of pathological myopia 52 and segmentation of associated lesions. Our work was acknowledged with an award in the context of 53 the "Pathological Myopia detection from retinal images" challenge held during the IEEE International 54 Symposium on Biomedical Imaging (April 2019). Considering that (pathological) myopia cases are 55 often identified as false positives and negatives in glaucoma deep learning models, we envisage that 56 the current work could aid in future research to discriminate between glaucomatous and highly-myopic eyes, complemented by the localization and segmentation of landmarks such as fovea, optic disc andatrophy.

Key words: pathological myopia, fovea localization, peripapillary atrophy, retinal detachment,
convolutional neural network, fundus image, glaucoma

61 Introduction

62 Myopia or nearsightedness currently affects approximately 34% of the world population.¹ High myopia, often defined as a spherical equivalent that exceeds -6.00 diopter or an axial length of 26.5mm or 63 more, has a prevalence ranging from 1% in African Americans² and up to 5.5% in the Japanese Tajimi 64 65 study³. Approximately 1-3% of the world population develops vision-impairing macular lesions (lacquer cracks, choroidal neovascularization, and Fuchs spots) as a result of high myopia, referred to as 66 myopic maculopathy.^{4,5} Both the presence of myopic maculopathy and posterior staphyloma are used 67 68 to define pathological myopia (PM), which causes uncorrected and irreversible visual impairment.⁶ 69 Other retinal changes due to myopia include: fundus tessellation, (peripapillary) atrophy, optic disc 70 tilting, retinal tear and retinal detachment. Additionally, myopia increases the risk of developing open-71 angle glaucoma⁷, presumably because myopic eyes have thinner and weaker lamina cribrosa tissue⁸. 72 Optic nerve head (ONH) changes such as temporal disc flattening and tilting⁹, as a consequence of 73 myopia, hampers glaucoma detection through ONH assessment during fundoscopy or fundus image analysis¹⁰. Peripapillary atrophy (PPA), being attenuation of retinal pigment epithelium (RPE) 74 75 neighboring the ONH, is associated with both myopia and glaucoma, and is one of the causes for a 76 high number of myopic patients being diagnosed as glaucoma suspects.

Previous work on automated pathological myopia detection from retinal images is limited. Liu et al described a methodology dubbed PAMELA (Pathological Myopia Detection Through Peripapillary Atrophy), in which a support vector machine (SVM) is trained using exclusively PPA texture features from fundus images.¹¹ They reported sensitivity and specificity of 0.85 and 0.90, respectively, on 40 test images. As mentioned above, PPA is not unique to pathological myopia, and not the only retinal change induced by the disease. Zhang et al also employed an SVM, but expanded on the feature set by incorporating additional retinal information such as ONH-related parameters and socio-demographic variables including age and race.¹² 10-fold cross validation led to accuracies ranging from 84.9% to 89.3% on a private data set encompassing imaged eyes of 800 primary school students.

87 Deep learning-based classification of pathological myopia has not been previously explored, although 88 convolutional neural networks (CNNs) are showing great potential in ophthalmic research for disease 89 identification and staging¹³. Relevant for this manuscript is refraction estimation from fundus images 90 using deep learning by Varadarajan et al., who developed a regression model that estimates refractive error with high accuracy (<1 diopter mean absolute error).¹⁴ Their approach could be useful in 91 92 stratifying fundus images into emmetropia (normal refraction), hyperopia (farsightedness), myopia 93 (nearsightedness), and high myopia (exceeding -6.0 diopters). The last group could then be further analyzed to detect myopia-induced lesions. 94

95 Semantic segmentation or pixel-wise classification has experienced major advances through the introduction of fully convolutional networks (FCN) in 2015.¹⁵ For fundus images, ample FCN-based 96 segmentation networks have been described in popular tasks like vessel extraction¹⁶, artery/vein 97 discrimination¹⁷, and optic cup/disc estimation¹⁸. Recent work on retinal lesion segmentation in fundus 98 99 images is dominated by microaneurysms, hard exudates and cotton wool spots induced by diabetic retinopathy.¹⁹ Segmentation of myopia-related lesions (e.g. PPA) from fundus images has been 100 101 obtained using classic computer vision methods. Lu et al. employed a modified Chan-Vese 102 segmentation tool with shape constraints to delineate both optic disc and PPA, reporting 92.5% accuracy in PPA size estimation on 40 test images.²⁰ 103

Here, we report our CNN-based methods and results developed for the classification of (non-)pathological myopia, fovea localization, and semantic segmentation of optic disc, retinal atrophy and detachment on a novel reference data set. The multitude of tasks encouraged us to fuse classification and segmentation tasks when proven to be beneficial on the validation set. Joint disease classification and lesion segmentation systems have been described in deep learning literature, leading to improved 109 classification performance.²¹ We also introduce a novel ONH-based prediction enhancement that 110 results in improved performance for the tasks of lesion segmentation and fovea localization. The latter 111 task is being obtained through a segmentation approach for the first time, improving vastly on 112 coordinate regression. Our results are benchmarked against a holdout validation set, other state-of-113 the-art methods, and evaluated on external labeled data sets where possible.

114 Methodology

115 Dataset and evaluation

116 Retinal images were made available in the context of the "Pathological Myopia detection from retinal images" challenge held on the occasion of the IEEE International Symposium on Biomedical Imaging 117 organized in April 2019.²² The PALM dataset consists of 1200 anonymized color fundus images that 118 were captured with a Zeiss VISUCAM device at a 45° angle with a 2124 x 2156 resolution or 30° with 119 120 a 1444 x 1444. The images are macula- or optic disc-centered of left eyes with no disclosure of the 121 number of different eyes or patients that were included in the dataset. The 1200 images are split into 122 equally sized train, validation, and test sets sharing the same characteristics. Publicly available labels 123 for the training set of 400 images encompass (1) the binary label for (non-)pathological myopia classification, (2) cartesian coordinates corresponding to the location of the fovea, and (3) semantic 124 125 segmentation ground truth on pixel level for optic disc, peripapillary/retinal atrophy and retinal detachment. The myopia labels were extracted from the health records of the Zhongshan Ophthalmic 126 127 Center, Sun Yat-sen University (China) and were determined during an ophthalmic examination, including optical coherence tomography (OCT) and visual field (VF) testing. The fovea coordinates 128 and segmentation masks were generated by seven independent ophthalmologists from the same 129 130 clinic. The PM detection training labels are balanced (53% PM images), but do not match the 131 prevalence encountered in screening context (up to 3%). Ground truth of optic discs is available for 132 most images, with an empty ground truth mask in case of an absent or partially visible disc. An overview of official training set characteristics is provided in Table 1. Differences in PM and non-PM 133 134 characteristics were analyzed using a two-tailed t-test.

PM detection was quantified using area under the receiver operating characteristic (AUC), while the fovea localization was evaluated using the average Euclidean distance between the predicted cartesian coordinates and ground truth. The three predicted segmentation masks (optic disc, atrophy, detachment) were evaluated using a weighted combination of Dice²³ similarity coefficient (segmentation) and test's accuracy using the F1 score (detection). See supplementary information for full details on evaluation framework as defined by PALM organizers.

Additional data to evaluate the generalization ability of trained models was included where possible. For PM detection, we evaluated on the recently-introduced Ocular Disease Intelligent Recognition (ODIR) data set aimed at multi-disease classification.²⁴ The original competition did not include PM detection as task, but structured labels are available in the file with diagnostic keywords. We selected the subset of images having either 'normal fundus' or 'pathological myopia' in the diagnostic keywords (3350 out of 7000 fundus images). Fovea localization was evaluated on Messidor²⁵, for which 1136 out of 1200 fundus images have official fovea coordinates.

148 Network architectures and loss functions

UNet++²⁶, a nested variant of the widely used U-Net²⁷, was selected for the segmentation tasks 149 because of its reported improved performance. The widely used ResNet²⁸ encoders were tested as 150 151 feature extractors to enable transfer learning with pretrained ImageNet²⁹ weights. We selected a 152 pretrained ResNet-18 encoder as feature extractor as it satisfies our preset conditions of minimizing 153 the amount of trainable weights (there is a limited amount of labeled training images), while maximizing 154 the input size that fits on GPU memory (larger size yields the best performance for segmentation). At 155 the end of the contracting path (ResNet-18), where the input image is converted to a representation in latent space (shape 9x9x512), we added a second output branch for PM classification in light of co-156 regularization.³⁰ Figure 1 displays the full architecture, with the contracting path extracting and refining 157 158 feature maps through convolutional, batch normalization and pooling layers (ResNet-18). In UNet++, 159 these feature maps are connected to a number of dense convolution blocks, before being inserted in 160 the expanding path (decoder). The principle of dense convolution blocks as extended skip connections is illustrated in Figure 1 as well (highlighted in dark green). The UNet++ with ResNet-18 encoder
amounts to a total of 16 million trainable weights, with the detection branch adding 513 trainable
weights because of the additional 1x1 convolutional layer.

The employed loss function for PM classification is standard binary cross-entropy. Fovea localization labels are cartesian coordinates, but were converted to filled circles with varying radii to allow for segmentation, as an alternative approach to standard coordinate regression. All segmentation models employed standard binary/categorical cross-entropy as loss function, complemented by Dice similarity coefficient. Finally, we experimented with the Lovàsz-Softmax³¹ as third loss component. The latter serves as a tractable surrogate for the optimization of intersection over union (IoU), and has proven itself as finetuning loss in recent semantic segmentation challenges.³²

171 Preprocessing, Data augmentation, Training details

172 Color fundus images are unevenly illuminated due to the curvature of the retina. Local contrast 173 enhancement through background subtraction estimated by a large Gaussian kernel was used to 174 correct this³³. Data augmentation techniques used throughout all experiments include random cropping, mild elastic deformation, and horizontal flips. Random cropping was performed selecting 175 176 patches of 288 x 288 within resized images of a random size between half and original image size to 177 teach the model features at multiple resolutions. Data augmentation was not applied to the 40 holdout 178 images used to select the best model weights. The model input of 288 x 288 was selected based on 179 a balance between the merits of pretrained weights (224 x 224) and segmentation output (higher resolution leads to better results). 180

Due to the severe class imbalance of the retinal detachment segmentation, we adopted a sampling strategy that oversamples images with retinal detachment at earlier stages of the training process to an equal mini-batch distribution, only to gradually slim down to the original data distribution (x 0.75 per five epochs). As such, the model is less likely to treat the detachment label as noise at training start. Model development was done in Keras v2.2.4 with TensorFlow v1.4.1 backend. All models used Adam³⁴ optimizer with a default starting learning rate at 0.001. A plateau callback decreased the learning rate by 25% after ten successive epochs of stagnation in validation metric (Dice). To obtain a wider optimum, model weights were averaged over the last twenty epochs when the learning rate reached a value of 1e^{-5.35} Internal validation was performed on a holdout set of 40 images, representing 10% of available training data.

191 ONH-based prediction enhancement

Theoretically, there should be no overlap between atrophy and optic nerve head (ONH). Peripapillary atrophy represents loss of RPE and choriocapillaris, which ends/starts in Bruch's membrane opening (BMO), and simultaneously delineates the optic disc boundary. Leveraging this domain knowledge, the optic disc and peripapillary/retinal atrophy segmentation tasks were bundled by fusing the two ground masks. Retinal detachment ground truth does overlap with atrophy in certain cases, hence this ground truth was left unprocessed.

In addition to standard coordinate regression, we rebranded the fovea localization task as a segmentation problem. The ground truth masks were generated by drawing filled circles (varying radii between 25 and 75 pixels) based on the official cartesian coordinates as centroids. The optic disc is located on the nasal side of the fovea. Hence, the optic disc segmentation ground truth was added to the fovea ground truth, to implicitly insert this domain knowledge. We also experimented with the implementation of cutout³⁶, a common regularization technique, to improve the learning of the ONH – fovea relation.

The predicted fovea segmentations required post-processing in case of missing or unlikely predictions. Two sanity checks were performed prior to reconversion to coordinates: (1) whether there is a fovea prediction made, and (2) whether it falls within normal range compared to optic disc location. Normal range was defined as mean $\pm 2 x$ standard deviation, with population mean and deviation estimated from the training labels (grouped by image resolution). If the assertions failed, the predicted fovea coordinates were determined based on optic disc centroid and mean distance between optic disc and fovea. For benchmarking purposes, we also report on experiments without joint optic disc segmentation. Here, the postprocessing was limited to the use of image center coordinates in case of missing fovea prediction.

214 Ensembling on image and model level

215 Ensembling on image and model level tend to lead to small performance gains due to its decrease in prediction variance. Hence, final predictions of (non-)pathological myopia classification on the test 216 217 images were obtained through commonly-used test-time augmentation (TTA) techniques (elastic 218 deformation and horizontal flips). We further enhanced TTA predictions by ensembling on model level 219 through the averaging of predictions obtained on seven separately trained models with different 220 random seed on train/holdout split. Segmentation results were generated using averaged predictions 221 on overlapping 288 x 288 patches from resized images (288 x 288, 294 x 294, and 302 x 302). 222 Overlapping patches were only possible in the last two resolutions.

223 Results

Table 1 reveals that the largest group of available training images are 45° macula-centered images, whereas its disc-centered variant contains only 3 images. Complete optic discs are missing in all 30° macula-centered images, and in some PM cases imaged at 45° as well. Optic disc area ranged between 1-4%, and was significantly larger in 30° disc-centered PM images. Retinal atrophy was present in almost all PM cases, and in roughly half of non-PM images. The area covered by atrophy was larger in PM images for all modalities. The fovea is visible in nearly all images.

The Dice score on ONH segmentation was found to be the highest in the vanilla setup with a single model (0.9481 Dice). For retinal atrophy however, multi-class segmentation with Lovász as loss component did lead to better performance (0.6948 Dice) when compared to two individual models (0.6210 Dice). The balanced data generator did lead to better performance in segmentation of retinal detachment (0.9998 Dice).

Table 2 summarizes our quantitative results on a holdout validation set, the official test set, obtained 235 236 through the online competition evaluation server hosted at 237 http://ai.baidu.com/broad/subordinate?dataset=pm, and external data if available. We also provide the official test results obtained by other onsite PALM participants. All PM cases were correctly classified 238 239 in both experiments on the holdout validation set (n=40), but the validation loss was significantly lower 240 in the setup with combined ONH and atrophy segmentation (0.0824 versus 0.1146). Our trained 241 models for detection of pathological myopia achieve a final AUC value of 0.986 on the test set. There is no statistical significant difference observed between AUC values among PALM participants (range 242 243 0.987-0.997). Without having to retrain the model for PM classification with ONH/atrophy 244 segmentation, a high AUC of 0.924 is recorded on fundus images of the ODIR data set, which is significantly higher compared to using a classification-only model (AUC = 0.858). The ROC curves of 245 both PM models on ODIR are plotted in Figure 2. An overview of all PM experiments and results are 246 247 given in the first section of Table 2.

The move from regression to segmentation for fovea localization seems to be beneficial, with average 248 249 Euclidean distance at 229 and 129 pixels, respectively recorded on the internal holdout validation set 250 (n=40). The result using a segmentation approach also improved when employing a larger fovea 251 radius of 75 pixels (110 pixels Euclidean distance). Our proprietary ONH-based prediction enhancement led to a major performance gain (87 pixels Euclidean distance). Finally, the post-252 253 processing that deals with missing and unrealistic predictions resulted in the best observed performance (62 pixels Euclidean distance). The result on the official PALM set (n=400) is equivalent, 254 255 with a Euclidean distance of 58.3 pixels. Euclidean distances reported by other PALM participants 256 differed considerably, ranging from 55.7-172.9. Furthermore, our findings are confirmed on the Messidor data set for which the best performance (lowest Euclidean distance) is also obtained using 257 a segmentation approach complemented with our ONH-based prediction enhancement. A complete 258 259 results overview for fovea localization can be found in section 2 of Table 2.

Table 2 also shows that the Dice score on ONH segmentation was found to be the highest in the 260 261 vanilla setup with a single model (0.9481 Dice on holdout validation set). For retinal atrophy however (4th section of Table 2), multi-class segmentation with Lovász as loss component did lead to better 262 performance (0.6948 Dice) when compared to two individual models (0.6210 Dice). ONH 263 264 segmentation on PALM test data achieved a Dice of 0.93. Other participants reported results ranging 265 from 0.91-0.95. The atrophy segmentation Dice result on the PALM test set (0.8001) is considerably higher than the best Dice recorded on the holdout validation set, which is likely caused by the low 266 number of validation images. Again, there existed a small variability in atrophy segmentation Dice 267 268 results among participants (0.77-0.82).

Finally, the F1 metric for retinal detachment segmentation reveals that the test set contain 11 cases of retinal detachment. The trained deep learning model identified six correct cases. For this subtask, we obtained the highest Dice score (0.8073) among all participants (0.0030-0.7449), as can be retrieved from the last section of Table 2.

273 Ground truth for validation and test sets on image level will be made publicly available at a later date 274 by the organizers of the PALM challenge. Hence, the gualitative results of four test images displayed 275 in Figure 3 cannot be visually compared to the official ground truth. The optic disc – outlined in green 276 - is detected in both non-pathological (A) and pathological (B,C) fundus images (not present in D), 277 and does not overlap with peripapillary atrophy (B,C). The fovea – indicated by a cross – is localized 278 well in cases of a clear (A) and covered (C,D) macula, or added during postprocessing (B). Atrophy -279 outlined in white – is segmented at both peripapillary (A,B,C,D) and macular (B) regions. In images 280 where 30% of the image is predicted to be retinal detachment, the prediction is replaced with the size 281 of the image mask (yellow outline of image C).

Figure 4 showcases two examples of bad segmentations for both atrophy and optic disc tasks. These cases were quantitatively selected on the 40 holdout validation images for which the ground truth is publicly available at this time. For atrophy segmentation, we observe the lowest scores in images that feature a small amount of peripapillary atrophy (often healthy eyes). The highest Dice scores are obtained on images with a lot of retinal atrophy present (eyes with pathological myopia). For optic disc
segmentation, the roles are reversed. Lower performance is recorded in challenging cases with
atrophy surrounding the disc; while the highest performance is obtained in healthy eyes.

289 Discussion

290 This deep learning study on fundus images describes (1) the detection of pathological myopia (PM), 291 (2) the localization of the fovea, and (3) the segmentation of optic disc, retinal atrophy and retinal 292 detachment. The results are obtained after training on 400 labeled fundus images and relies on 293 transfer learning and co-regularization through weight sharing. The methodology described in the 294 manuscript led to a third place in PALM challenge hosted at ISBI 2019. The PALM dataset provides 295 novel challenges to existing research topics, as myopic optic discs are often tilted (optic disc 296 segmentation), and the fovea obscured due to tessellation and macular atrophy in some cases of 297 pathological myopia (fovea localization).

298 The PM detection task scored an AUC of 0.9867 on the official test set of 400 images. PM detection 299 from fundus images has not been covered in deep learning literature prior to the launch of PALM. The 300 work of Varadajaran et al (2018) comes closest, but employs a whole different setup. Their goal was to develop a data-driven regression model that estimates refractive error (including cases of 301 302 pathological myopia), using the spherical equivalent as target. In our investigation, the task of PM 303 detection was approached in a different manner, given the different nature of the task and materials. 304 The definition of PM states that a highly myopic case is converting to pathological once a posterior 305 myopia-specific pathology from axial elongation is developing, such as vision-impairing myopiainduced lesions. This is corroborated by the explorative analysis of the training set, given in Table 1. 306 307 Retinal atrophy, being progressive RPE thinning and attenuation, is present in 98.3% cases of PM, versus 52.6% in non-PM images (restricted to the modality of 45° macula-centered images). By 308 309 combining atrophy segmentation and PM classification, one forces the model to focus on lesions as 310 main features that contribute to PM classification. This implies a step towards explainable AI or sufficient transparency to gain clinicians' trust in the future use of deep learning detection systems inophthalmology.

All valid PM detection results at the onsite PALM challenge scored above 0.98 AUC. Although an official rank is maintained, there exists no statistical significant difference in results between teams, due to the low amount of test images (at 95% confidence interval). Other participants also relied on transfer learning, but not in combination with segmentation. For example, team Vistalab employed a ResNet-50 pretrained on ImageNet, reporting an AUC of 0.998.³⁷ Their data augmentation strategy included Gaussian noise addition and random rotations.

Our PM detection model trained on PALM also generalizes well to images captured with multiple fundus cameras (Figure 2). On data from the recent ODIR challenge, we obtain AUC values of 0.858 and 0.924 using a standard classification model and using a combined lesion segmentation branch, respectively. This further illustrates that segmentation on related tasks (myopia-induced lesions) can augment classification performance.

324 For fovea localization, we obtained the 2nd place among all PALM participants. We initially considered adding a regression branch to the segmentation model for optic disc and retinal atrophy. However, 325 326 due to subpar performance (229 pixels Euclidean distance), this idea was discarded and replaced by 327 a standalone segmentation model. One potential explanation for poor regression performance could 328 be the combination of scarcity in available regression labels (1 per image) when compared to segmentation labels (1 per pixel), and low variance in coordinate values (the fovea is centrally located 329 in macula-centered images). However, the winning submission by Vistalab did follow a regression 330 approach, using a modified pretrained VGG19³⁸ model. The main disadvantage of a segmentation 331 approach is the loss of direct optimization on the competition metric. Thoughtful post-processing that 332 333 relies on domain knowledge further enhanced our final predictions. Fovea localization in fundus images has been investigated with deep learning prior to PALM, but primarily in clean datasets with 334 clear macular depression.³⁹ To illustrate this, we evaluated on diabetic retinopathy cases from the 335 Messidor data, without retraining. The significantly lower Euclidean distance obtained on this data 336

emphasizes the difficulty aspect introduced by the novel PALM data. Our domain knowledge insertion
– combined optic disc and fovea localization – is considered useful in the move towards general deep
learning models that can process large amounts of fundus images with unclear macular regions. Such
fovea localizing models can assist future big data research. One application would be the automated
image cropping of the macula area to facilitate diabetic retinopathy screening.

The optic disc segmentation model obtained a Dice similarity coefficient of 0.9303, scoring in line with 342 343 relevant work.⁴⁰ Due to axial elongation, myopia induces anatomical changes to the optic nerve head, 344 resulting in tilted and oval-shaped optic discs, often surrounded by peripapillary atrophy. These 345 alterations are significant, as a pretrained optic disc segmentation model on non-myopic fundus 346 images failed to properly delineate the discs in the PALM dataset. Another factor could be the larger optic disc size observed in myopic eyes^{41,42}. From Table 1, there is a moderate significance (P < 0.01) 347 found between PM and non-PM (which also includes high myopia) in the 30° disc-centered images. 348 Hence, optic disc size is unlikely to be an informative predictor in PM detection. 349

350 This original investigation also introduces a pioneering result of 0.8001 Dice on the segmentation of retinal atrophy (PPA, lacquer cracks and Fuch's spots) in fundus images. This type of segmentation 351 352 can support future research in discriminating between myopia- and glaucoma-induced peripapillary atrophic changes. This is relevant because in previous work it has been observed that false positive 353 354 and negative predictions in glaucoma classification models are often due to cases of high/degenerative 355 myopia. For example, Liu et al (2019) observed that the most common reason for both false-negative 356 and false-positive grading by their DL model (46.3% and 32.3%) and manual grading (44.2% and 34.0%) was pathological or high myopia.¹⁰ Several studies investigated the discriminatory properties 357 358 of beta- (area with intact Bruch's membrane) and gamma-PPA (lacking Bruch's membrane) for myopia and glaucoma using OCT, but report contradictory findings and low discriminatory power.^{43,44} Another 359 recent study discovered a relationship between PPA shape and glaucoma progression, stating that 360 progression is more correlated with eccentric PPA than concentric PPA.⁴⁵ DL may assist in analyzing 361 362 PPA in a larger set of patients than previous investigations.

The fusion of optic disc and atrophy segmentation tasks ensured no overlap in final predictions. This form of joint prediction increases the odds of generalization to unseen samples (in this case, 800 images split in validation and test set of equal size). Ground truth fusion did lead to better performance for atrophy segmentation, but not for ONH segmentation. Another important motivation for joint training is explainable artificial intelligence, as previously discussed.

Finally, this study reports a top-ranked Dice score of 0.8073 on the task of retinal detachment segmentation. The high performance is mainly due to the correct predictions of empty masks in the high number of cases (~97% of images) without retinal detachment. The actual performance would be much lower when the images with retinal detachment would be isolated. In most cases, retinal detachment covers more than half of the field of view (FOV) in the fundus. Hence, one could question the added value of segmentation over a classification approach.

374 Other participating teams also heavily relied on the combination of FCN architectures and existing 375 feature extractors pretrained on ImageNet for the segmentation tasks. For optic disc segmentation, Vistalab (2nd place) combined ResNet-34 followed by an Atrous Spatial Pyramid Pooling (ASPP)^{46(p)} 376 operator in a U-Net architecture. The winning submission in all segmentation tasks is obtained using 377 a lesion-aware segmentation network described by team PingAn Smart Health.⁴⁷ They introduce three 378 innovations: an additional classification branch to aid the network in becoming better aware of lesion 379 380 presence in images; a custom feature fusion module, and lastly a loss function dubbed edge overlap 381 rate that boosts the accuracy of lesion edge segmentation.

The strengths of our work are significant. We describe a CNN architecture that bundles classification and segmentation tasks when deemed relevant (domain knowledge) and when empirically proven on the validation set. Next, we introduce a new approach to obtain fovea localization in fundus images through the reformulation as a segmentation problem. Further domain knowledge is inserted through a custom ONH-based post-processing scheme that leverages anatomical properties of the retina. We describe and compare our state-of-the-art results on a novel reference data set that is expected to be widely used. Finally, our models on PM detection and fovea localization generalize well to unseen
heterogeneous data sets without recalibration to the target domain.

This study also suffers from several limitations. The ground truth on image level for PALM validation and test sets are currently unavailable, hampering the qualitative comparison of semantic segmentation results, and the calculation of specificity and sensitivity. On the other hand, the introduction of medical labeled datasets and robust online evaluation server should be encouraged, as they allow the objective comparison of innovations in deep learning for medical imaging.

395 Conclusions

396 We report a successful approach for a simultaneous classification of pathological myopia and 397 segmentation of associated lesions. These award-winning results were obtained in the context of the 398 "Pathological Myopia detection from retinal images" challenge held on the occasion of the IEEE 399 International Symposium on Biomedical Imaging organized in April 2019. Considering that 400 (pathological) myopia cases are often found as false positives in glaucoma deep learning models, we 401 envision that the current work could aid in future research to discriminate between glaucomatous and 402 highly-myopic eyes, complemented by the localization and segmentation of landmarks such as fovea, optic disc and atrophy. 403

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411 References

- Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036-1042. doi:10.1016/j.ophtha.2016.01.006
- 415 2. Katz J, Tielsch JM, Sommer A. Prevalence and risk factors for refractive errors in an adult inner city
 416 population. *Invest Ophthalmol Vis Sci.* 1997;38(2):334-340.
- Sawada A, Tomidokoro A, Araie M, Iwase A, Yamamoto T. Refractive Errors in an Elderly Japanese
 Population: The Tajimi Study. *Ophthalmology*. 2008;115(2):363-370.e3.
 doi:10.1016/j.ophtha.2007.03.075
- 420 4. Vongphanit J, Mitchell P, Wang JJ. Prevalence and progression of myopic retinopathy in an older 421 population. *Ophthalmology*. 2002;109(4):704-711. doi:10.1016/S0161-6420(01)01024-7
- Liu HH, Xu L, Wang YX, Wang S, You QS, Jonas JB. Prevalence and Progression of Myopic
 Retinopathy in Chinese Adults: The Beijing Eye Study. *Ophthalmology*. 2010;117(9):1763-1768.
 doi:10.1016/j.ophtha.2010.01.020
- 6. Ohno-Matsui K. WHAT IS THE FUNDAMENTAL NATURE OF PATHOLOGIC MYOPIA?: *Retina*.
 2017;37(6):1043-1048. doi:10.1097/IAE.00000000001348
- 427 7. Marcus MW, de Vries MM, Montolio FGJ, Jansonius NM. Myopia as a Risk Factor for Open-Angle
 428 Glaucoma: A Systematic Review and Meta-Analysis. *Ophthalmology*. 2011;118(10):1989-1994.e2.
 429 doi:10.1016/j.ophtha.2011.03.012
- Yun S-C, Hahn IK, Sung KR, Yoon JY, Jeong D, Chung HS. Lamina cribrosa depth according to the level of axial length in normal and glaucomatous eyes. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(12):2247-2253. doi:10.1007/s00417-015-3131-y
- 433 9. Mitchell P, Hourihan F, Sandbach J, Jin Wang J. The relationship between glaucoma and myopia:
 434 The blue mountains eye study. *Ophthalmology*. 1999;106(10):2010-2015. doi:10.1016/S0161435 6420(99)90416-5
- Liu H, Li L, Wormstone IM, et al. Development and Validation of a Deep Learning System to Detect
 Glaucomatous Optic Neuropathy Using Fundus Photographs. *JAMA Ophthalmol.* Published online
 September 12, 2019. doi:10.1001/jamaophthalmol.2019.3501
- 439 11. Liu J, Wong DWK, Lim JH, et al. Detection of Pathological Myopia by PAMELA with Texture-Based
 440 Features through an SVM Approach. Journal of Healthcare Engineering.
 441 doi:https://doi.org/10.1260/2040-2295.1.1.1
- I2. Zhang Z, Jun Cheng, Liu J, Yeo Cher May Sheri, Chui Chee Kong, Saw Seang Mei. Pathological
 Myopia detection from selective fundus image features. In: 2012 7th IEEE Conference on Industrial
 Electronics and Applications (ICIEA).; 2012:1742-1745. doi:10.1109/ICIEA.2012.6361007
- Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. *Br J Ophthalmol.* 2019;103(2):167-175. doi:10.1136/bjophthalmol-2018-313173
- 447 14. Varadarajan AV, Poplin R, Blumer K, et al. Deep Learning for Predicting Refractive Error From
 448 Retinal Fundus Images. *Invest Ophthalmol Vis Sci.* 2018;59(7):2861-2868. doi:10.1167/iovs.18449 23887
- Long J, Shelhamer E, Darrell T. Fully convolutional networks for semantic segmentation. In: 2015
 IEEE Conference on Computer Vision and Pattern Recognition (CVPR). ; 2015:3431-3440.
 doi:10.1109/CVPR.2015.7298965

- 453 16. Liskowski P, Krawiec K. Segmenting Retinal Blood Vessels With Deep Neural Networks. *IEEE Trans* 454 *Med Imaging*. 2016;35(11):2369-2380. doi:10.1109/TMI.2016.2546227
- Hemelings R, Elen B, Stalmans I, Van Keer K, De Boever P, Blaschko MB. Artery–vein segmentation
 in fundus images using a fully convolutional network. *Comput Med Imaging Graph*. 2019;76:101636.
 doi:10.1016/j.compmedimag.2019.05.004
- 458 18. Fu H, Cheng J, Xu Y, Wong DWK, Liu J, Cao X. Joint Optic Disc and Cup Segmentation Based on
 459 Multi-Label Deep Network and Polar Transformation. *IEEE Trans Med Imaging*. 2018;37(7):1597460 1605. doi:10.1109/TMI.2018.2791488
- 461 19. Orlando JI, Prokofyeva E, Del Fresno M, Blaschko MB. An ensemble deep learning based approach
 462 for red lesion detection in fundus images. *Comput Methods Programs Biomed*. 2018;153:115-127.
 463 doi:10.1016/j.cmpb.2017.10.017
- 464 20. Lu C-K, Tang TB, Laude A, Deary IJ, Dhillon B, Murray AF. Quantification of Parapapillary Atrophy 465 and Optic Disc. *Investig Opthalmology Vis Sci*. 2011;52(7):4671. doi:10.1167/iovs.10-6572
- 466 21. Xie Y, Zhang J, Xia Y, Shen C. A Mutual Bootstrapping Model for Automated Skin Lesion
 467 Segmentation and Classification. *IEEE Trans Med Imaging*. 2020;39(7):2482-2493.
 468 doi:10.1109/TMI.2020.2972964
- 469 22. Huazhu Fu FL José Ignacio Orlando, Hrvoje Bogunović, Xu Sun, Jingan Liao, Yanwu Xu, Shaochong
 470 Zhang, Xiulan Zhang. PALM: PAthoLogic Myopia Challenge. Published online 2019. 10.21227/55pk471 8z03
- 472 23. Dice LR. Measures of the Amount of Ecologic Association Between Species. *Ecology*.
 473 1945;26(3):297-302. doi:10.2307/1932409
- 474 24. introduction Grand Challenge. grand-challenge.org. Accessed November 23, 2020.
 475 https://odir2019.grand-challenge.org/
- 476 25. Decencière E, Zhang X, Cazuguel G, et al. FEEDBACK ON A PUBLICLY DISTRIBUTED IMAGE
 477 DATABASE: THE MESSIDOR DATABASE. *Image Anal Stereol*. 2014;33(3):231-234.
 478 doi:10.5566/ias.1155
- 26. Zhou Z, Rahman Siddiquee MM, Tajbakhsh N, Liang J. UNet++: A Nested U-Net Architecture for
 Medical Image Segmentation. In: Stoyanov D, Taylor Z, Carneiro G, et al., eds. *Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support*. Lecture Notes in
 Computer Science. Springer International Publishing; 2018:3-11. doi:10.1007/978-3-030-00889-5_1
- 27. Ronneberger O, Fischer P, Brox T. U-Net: Convolutional Networks for Biomedical Image
 Segmentation. In: Navab N, Hornegger J, Wells WM, Frangi AF, eds. *Medical Image Computing and Computer-Assisted Intervention MICCAI 2015*. Lecture Notes in Computer Science. Springer
 International Publishing; 2015:234-241. doi:10.1007/978-3-319-24574-4_28
- 487 28. He K, Zhang X, Ren S, Sun J. Deep Residual Learning for Image Recognition. *ArXivorg Ithaca*.
 488 Published online December 10, 2015. Accessed November 20, 2019.
 489 http://search.proquest.com/docview/2083823373?rfr_id=info%3Axri%2Fsid%3Aprimo
- 29. Deng J, Dong W, Socher R, Li L-J, Kai Li, Li Fei-Fei. ImageNet: A large-scale hierarchical image
 database. In: 2009 IEEE Conference on Computer Vision and Pattern Recognition. ; 2009:248-255.
 doi:10.1109/CVPR.2009.5206848

- 493 30. Cai Z, Fan Q, Feris RS, Vasconcelos N. A Unified Multi-scale Deep Convolutional Neural Network for
 494 Fast Object Detection. In: Leibe B, Matas J, Sebe N, Welling M, eds. *Computer Vision ECCV 2016*.
 495 Lecture Notes in Computer Science. Springer International Publishing; 2016:354-370.
 496 doi:10.1007/978-3-319-46493-0_22
- 497 31. Berman M, Triki AR, Blaschko MB. The Lovász-Softmax loss: A tractable surrogate for the
 498 optimization of the intersection-over-union measure in neural networks. *ArXivorg Ithaca*. Published
 499 online April 9, 2018. Accessed November 20, 2019.
- 500 http://search.proquest.com/docview/2071981122?rfr_id=info%3Axri%2Fsid%3Aprimo
- 32. Babakhin Y, Sanakoyeu A, Kitamura H. Semi-Supervised Segmentation of Salt Bodies in Seismic
 Images using an Ensemble of Convolutional Neural Networks. *CoRR*. 2019;abs/1904.04445.
 http://arxiv.org/abs/1904.04445
- 33. Hemelings R, Elen B, Barbosa-Breda J, et al. Accurate prediction of glaucoma from colour fundus
 images with a convolutional neural network that relies on active and transfer learning. *Acta Ophthalmol (Copenh)*. n/a(n/a). doi:10.1111/aos.14193
- 507 34. Kingma DP, Ba J. Adam: A Method for Stochastic Optimization. *ArXivorg Ithaca*. Published online
 508 January 30, 2017. Accessed November 20, 2019.
 509 http://search.proguest.com/docview/2075396516?rfr id=info%3Axri%2Fsid%3Aprimo
- 510 35. Izmailov P, Podoprikhin D, Garipov T, Vetrov D, Wilson AG. *Averaging Weights Leads to Wider* 511 *Optima and Better Generalization.*; 2018.
- 512 36. Devries T, Taylor GW. Improved Regularization of Convolutional Neural Networks with Cutout.
 513 CoRR. 2017;abs/1708.04552. http://arxiv.org/abs/1708.04552
- 37. Xie R, Liu L, Liu J, Qiu CS. Pathological Myopic Image Analysis with Transfer Learning. In: ; 2019.
 Accessed October 3, 2020. https://openreview.net/forum?id=BkeLp6mTFE
- Simonyan K, Zisserman A. Very Deep Convolutional Networks for Large-Scale Image Recognition.
 ArXiv14091556 Cs. Published online April 10, 2015. Accessed May 15, 2020.
 http://arxiv.org/abs/1409.1556
- 39. Babu SC, Maiya SR, Elango S. *Relation Networks for Optic Disc and Fovea Localization in Retinal Images.*; 2018.
- 40. Orlando JI, Fu H, Barbossa Breda J, et al. REFUGE Challenge: A unified framework for evaluating
 automated methods for glaucoma assessment from fundus photographs. *Med Image Anal.*2020;59:101570. doi:10.1016/j.media.2019.101570
- 41. Wu R-Y, Wong T-Y, Zheng Y-F, et al. Influence of Refractive Error on Optic Disc Topographic
 Parameters: The Singapore Malay Eye Study. *Am J Ophthalmol.* 2011;152(1):81-86.
 doi:10.1016/j.ajo.2011.01.018
- 42. Ramrattan RS, Wolfs RCW, Jonas JB, Hofman A, Jong PTVM de. Determinants of optic disc
 characteristics in a general population: The Rotterdam study1. *Ophthalmology*. 1999;106(8):15881596. doi:10.1016/S0161-6420(99)90457-8
- 43. Dai Y, Jonas JB, Huang H, Wang M, Sun X. Microstructure of Parapapillary Atrophy: Beta Zone and
 Gamma Zone. *Invest Ophthalmol Vis Sci*. 2013;54(3):2013-2018. doi:10.1167/iovs.12-11255

- 44. Vianna JR, Malik R, Danthurebandara VM, et al. Beta and Gamma Peripapillary Atrophy in Myopic
 Eyes With and Without Glaucoma. *Invest Ophthalmol Vis Sci*. 2016;57(7):3103-3111.
 doi:10.1167/iovs.16-19646
- 45. Song MK, Sung KR, Shin JW, Kwon J, Lee JY, Park JM. Progressive change in peripapillary atrophy
 in myopic glaucomatous eyes. *Br J Ophthalmol*. 2018;102(11):1527-1532. doi:10.1136/bjophthalmol 2017-311152
- 46. Chen L-C, Zhu Y, Papandreou G, Schroff F, Adam H. Encoder-Decoder with Atrous Separable
 Convolution for Semantic Image Segmentation. In: Ferrari V, Hebert M, Sminchisescu C, Weiss Y,
 eds. *Computer Vision ECCV 2018*. Vol 11211. Lecture Notes in Computer Science. Springer
 International Publishing; 2018:833-851. doi:10.1007/978-3-030-01234-2
- 47. Guo Y, Wang R, Zhou X, et al. Lesion-Aware Segmentation Network for Atrophy and Detachment of
 Pathological Myopia on Fundus Images. In: 2020 IEEE 17th International Symposium on Biomedical
 Imaging (ISBI). ; 2020:1242-1245. doi:10.1109/ISBI45749.2020.9098669



Figure 1: Overview of the final model architecture used for inference on the PALM official validation and test set. Our model is aimed at PM classification with simultaneous segmentation of ONH and retinal atrophy. The ResNet encoder accepts resized fundus images of (288 x 288) and outputs (9 x 9 x 512) at the latent space. The decoder upscales this output back to the original image size, using a plethora of skip connections (principle given in bottom center). The graphic on the upper right represents the generated segmentation map of the ONH (grey) and retinal atrophy (olive). The output of the encoder is also separately transformed to a single prediction for PM classification (through average pooling and a convolution operation). The model for fovea localization employs a similar architecture as for ONH/atrophy segmentation, but generates a circle. This circle is then transformed to coordinates using its centroid (visualized by the orange cross on the right bottom segmentation map). Finally, the UNet++ model for segmentation of retinal detachment is identical to the other models, but outputs detachment.



Figure 2: ROC curves of models trained on PALM data, evaluated on 3350 images of ODIR. The model with combined lesion segmentation significantly outperforms the classification-only model.

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Figure 3: Qualitative results giving four cases of the official test set. The optic nerve head (outlined in green) is
detected and segmented in A, B and C. Retinal atrophy is detected and segmented (outlined in white) in B and C.
Retinal detachment was detected in C, for which the whole fundus is outlined in yellow. Finally, the fovea is localized
in all cases, indicated by a purple cross. Image D does not feature an optic disc, but clear retinal atrophy on the left.



Figure 4: Selected samples of atrophy (top row) and optic disc (bottom row) segmentations. Per row, the images with lowest Dice scores on the holdout set of 40 images are visualized (left and middle column), complemented with the image for which the best prediction was obtained (far right).

Tables

674 Table 1: Overview of characteristics of labeled training set of 400 images. Significance level between PM and Non-PM on same camera settings provided with asterisks (where applicable, * <0.05, ** <0.01, *** <0.001, **** <0.0001).

		N	lacula			Disc	;	
Angle	3	30°	4	l5°	3	30°	4	5°
	PM	Non-PM	PM	Non-Pm	PM	Non-PM	PM	Non-PM
Number of images	6	4	174	173	31	9	2	1
Images with full optic disc	0%	0%	94.8%	100%	100%	100%	100%	100%
Images with atrophy	100%	75%	98.3%	52.6%	100%	77.8%	100%	0%
Images with fovea	100%	100%	99.4%	100%	96.8%	88.9%	100%	100%
Optic disc area	-	-	1.66%	1.72%	3.38%	2.61%**	1.69%	1.15%
Atrophy area	5.93%	0.41%*	11.77%	0.25%****	13.97%	0.70%****	42.37%	-
Fovea x mean	768	758	1236	1102****	1261	1387*	1748	1792
Fovea y mean	713	741	1026	1081****	754	715	1144	1049

691 692 Table 2: Results for five tasks, obtained on holdout validation set (PALM holdout), the official PALM test set, and external data sets when available (ODIR and Messidor). PM detection is measured in AUC, fovea localization in Euclidean distance. Dice and F1 are given for the three segmentation tasks (ONH, atrophy, detachment).

PM detection (AUC)	PALM holdout (n=40)	PALM test set (n=400)	ODIR (n=3350)
Classification	1 (loss: 0.1446)	-	0.8584
Classification combined with	1 (loss: 0.0824)	0.9867	0.9245
ONH/atrophy segmentation			
Fovea localization (Euclidean dist)	PALM holdout (n=40)	PALM test set (n=400)	Messidor (n=1136)
Regression	229.428	-	53.488
Segmentation, radius 25 pixels	129.182	-	25.765
Segmentation, radius 75 pixels	109.770	-	20.220
Segmentation, combined with ONH	86.675	-	18.296
Segmentation, combined with ONH,	61.924	58.3	-
postprocessing			
ONH segmentation	PALM holdout (n=40)	PALM test	set (n=400)
Metric	Dice	Dice	F1
Segmentation	0.9481	0.9303	0.9869
Segmentation combined with	0.9462	-	-
atrophy			
Segmentation combined with	0.9414	-	-
atrophy, Lovász loss			
Atrophy segmentation	PALM holdout (n=40)	PALM test	set (n=400)
Metric	Dice	Dice	F1
Segmentation	0.6210	-	-
Segmentation combined with	0.6810	-	-
atrophy			
Segmentation combined with	0.6948	0.8001	0.9135
atrophy, Lovász loss			
Detachment segmentation	PALM holdout (n=40)	PALM test	set (n=400)
Metric	Dice	Dice	F1
Segmentation	0.9500	-	-
Segmentation with a balanced data	0.9998	0.8073	0.7059
generator			

Supplementary material

707 708 Tables 3-7: Results for five tasks, obtained on holdout validation set (PALM holdout), the official PALM test set, and external data sets when available (ODIR and Messidor). Team A-F correspond to Vistalab, Masker, LAIS, PingAn Smart Heatlh, CUHK, and RYE-NUS, respectively.

PM detection	PALM holdout (n=40)	PALM test set (n=400)	ODIR (n=3350)
Classification	1 (loss: 0.1446)	-	0.8584
Classification combined with ONH/atrophy segmentation	1 (loss: 0.0824)	0.9867	0.9245
Team A	-	0.9974	-
Team B	-	0.9960	-
Team C	-	0.9957	-
Team D	-	0.9934	-
Team E	-	-	-
Team F	-	-	-

Fovea localization	PALM holdout (n=40)	PALM test set (n=400)	Messidor (n=1136)
Regression	229.428	-	53.488
Segmentation, radius 25 pixels	129.182	-	25.765
Segmentation, radius 75 pixels	109.770	-	20.220
Segmentation, combined with ONH	86.675	-	18.296
Segmentation, combined with ONH, postprocessing	61.924	58.3	-
Team A	-	55.7	-
Team B	-	172.9	-
Team C	-	71.3	-
Team D	-	66.6	-
Team E	-	-	-
Team F	-	-	-

ONH segmentation	PALM holdout (n=40)	P	ALM test set (n=400)
Metric	Dice	Dice	F1
Segmentation	0.9481	0.9303	0.9869
Segmentation combined with atrophy	0.9462	-	-
Segmentation combined with atrophy, Lovász loss	0.9414	-	-
Team A	-	0.9362	0.9909
Team B	-	0.9367	0.9806
Team C	-	0.9093	0.9855
Team D	-	0.9508	0.9974
Team E	-	-	-
Team F	-	0.9288	0.9871

Atrophy segmentation	PALM holdout (n=40)	P/	ALM test set (n=400)	
Metric	Dice	Dice	F1	
Segmentation	0.6210	-	-	
Segmentation combined with atrophy	0.6810	-	-	
Segmentation combined with atrophy, Lovász loss	0.6948	0.8001	0.9135	
Team A	-	0.7879	0.8972	
Team B	-	0.7702	0.8372	
Team C	-	0.7798	0.9091	
Team D	-	0.8220	0.9303	
Team E	-	0.8183	0.9199	
Team F	-	-	-	

	Detachment segmentation	PALM holdout (n=40)	PALM test set (n=400)	
	Metric	Dice	Dice	F1
	Segmentation	0.9500	-	-
	Segmentation with a balanced data	0.9998	0.8073	0.7059
	generator			
	Team A	-	0.1584	0.1667
	Team B	-	0.0030	0.0541
	Team C	-	0.5546	0.7273
	Team D	-	0.6617	0.9091
	Team E	-	0.7449	0.8571
	Team F	-	-	-
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