

***Look DEEP into the cornea to diagnose peripheral neuropathy***

**Aim:** The development of an artificial intelligence (AI)-based deep learning algorithm (DLA), without the use of image annotation and applying attribution methods, to corneal confocal microscopy (CCM) images, to be used to diagnose and classify peripheral neuropathy.

**Methods:** The study population was composed by 90 healthy volunteers (HV) and 279 patients (88 with type 1 diabetes, 141 with type 2 diabetes and 50 with prediabetes), among which 149 without (PN-) and 130 with peripheral neuropathy (PN+), according to the Toronto Consensus criteria for confirmed diabetic neuropathy. Each patient underwent CCM. A modified residual neural network (ResNet-50) was developed and trained for 300 epochs on 329 corneal nerve images from CCM to extract features images and perform classification. Then, it was tested on 40 participants (15 HV, 13 PN-, 12 PN+) using 1 image from each participant. The used attribution methods were the Gradient-weighted Class Activation Mapping (Grad-CAM), Guided Grad-CAM and occlusion sensitivity, which highlighted the image areas providing the greatest impact on the algorithm decision. Moreover, ResNet-50 was compared to two other different models (MobileNet and MobileNetV2) to demonstrate the effectiveness of the chosen algorithm.

**Results:** The trained AI-based DLA correctly classified all HV images. Out of the PN- images, eleven were correctly detected and two misclassified as HV images. Of the PN+ images, ten were correctly detected, with one misclassified as PN- and one as HV. The features focused by the attribution methods effectively demonstrated more corneal nerves in HV, a reduction in corneal nerves for PN- and an absence of corneal nerves for PN+ images. Furthermore, the ResNet-50 showed the lowest number of misclassifications and a better performance compared with MobileNet and MobileNetV2.

**Conclusions:** The AI-based DLA demonstrated promising results in the rapid classification of peripheral neuropathy using a single corneal image.

**Comments.** CCM is a rapid, non-invasive and reproducible imaging technique able to quantify small nerve fiber damage in the cornea and to identify corneal nerve loss in subclinical diabetic peripheral neuropathy and during the progression of the neuropathy severity. Automated AI-based DLAs, using convolutional neural networks, have been already applied to CCM analysis and quantification and have shown high diagnostic performance for diabetic peripheral neuropathy (Williams BM et al *Diabetologia* 2020; 63:419–430; Scarpa F et al *Cornea* 2020; 39:342–347). This study shows, for the first time, that an AI-based DLA can correctly classify peripheral neuropathy in diabetes and prediabetes without image segmentation and by using a single CCM image. The no need for image annotation allows the utilization of larger image datasets to get more robust model. Moreover, this is the first study that applies the attribution methods to favor transparency in decision making process corroborating its acceptance in clinical practice. If validated in large-scale multicentre study, the developed algorithm could be adopted as potential and rapid screening method for diabetic neuropathy.

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**Reference.** Preston FG, Meng Y, Burgess J, Ferdousi M, Azmi S, Petropoulos IN, Kaye S, Malik RA, Zheng Y, Alam U. Artificial intelligence utilising corneal confocal microscopy for the diagnosis of peripheral neuropathy in diabetes mellitus and prediabetes. *Diabetologia*. 2022 Mar;65(3):457-466. doi: 10.1007/s00125-021-05617-x. Epub 2021 Nov 21.

<https://link.springer.com/content/pdf/10.1007/s00125-021-05617-x.pdf>