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Label-free, *in vivo* virtual histology of skin using reflectance confocal microscopy and deep learning

Jingxi Li[#,1,2,3], Jason Garfinkel[#,4], Xiaoran Zhang[1], Di Wu[5], Yijie Zhang[1,2,3], Kevin de Haan[1,2,3], Hongda Wang[1,2,3], Tairan Liu[1,2,3], Bijie Bai[1,2,3], Yair Rivenson[1,2,3], Gennady Rubinstein[4], Philip O. Scumpia[6,7], Aydogan Ozcan[*,1,2,3,8]

[1]Electrical and Computer Engineering Department, University of California, Los Angeles, CA, 90095, USA.

[2]Bioengineering Department, University of California, Los Angeles, CA, 90095, USA.

[3]California NanoSystems Institute (CNSI), University of California, Los Angeles, CA, 90095, USA.

[4]Dermatology and Laser Centre, Studio City, CA, 91604, USA.

[5]Computer Science Department, University of California, Los Angeles, CA, 90095, USA.

[6]Division of Dermatology, University of California, Los Angeles, CA, 90095, USA.

[7]Department of Dermatology, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, 90073, USA.

[8]Department of Surgery, University of California, Los Angeles, CA, 90095, USA.

[#]These authors contributed equally to the work

*Address correspondence to:

Aydogan Ozcan, PhD, email; ozcan@ucla.edu

250-word abstract

An invasive biopsy followed by histological staining forms the standard process for pathological diagnosis of skin malignancies. However, this approach is not desirable since it often results in unnecessary biopsies and scarring and is time-consuming, costly and laborious. As a non-invasive alternative solution, skin imaging using reflectance confocal microscopy (RCM) can offer cellular-level resolution of skin structure. Nevertheless, the evaluation of these label-free RCM images requires specific expertise because these grayscale images lack explicit association with conventional histology. Here, we report label-free, in vivo virtual histology of skin using RCM and deep learning. Using RCM images of excised unstained skin tissue samples as inputs and RCM images of the same tissue stained with acetic acid as ground truth, we trained a deep neural network that can transform *in vivo* RCM images of unstained skin into virtually stained H&E-like

microscopic images with nuclear contrast revealed. Our results showed that this framework could successfully generalize to diverse skin conditions, including normal skin, basal cell carcinoma, and melanocytic nevi with pigmented melanocytes, as well as distinct skin layers, including the epidermis, dermal-epidermal junction, and superficial dermis layers. This label-free *in vivo* skin virtual histology framework can be transformative for faster and more accurate diagnosis of malignant skin neoplasms, and has the potential to significantly reduce unnecessary skin biopsies.

100-word summary

We report label-free, in vivo virtual histology of skin using reflectance confocal microscopy (RCM). We trained a deep neural network to transform in vivo RCM images of unstained skin into virtually stained H&E-like microscopic images with nuclear contrast. This framework successfully generalized to diverse skin conditions, e.g., normal skin, basal cell carcinoma, and melanocytic nevi, as well as distinct skin layers, including the epidermis, dermal-epidermal junction, and superficial dermis layers. This label-free in vivo skin virtual histology framework can be transformative for faster and more accurate diagnosis of malignant skin neoplasms, with the potential to significantly reduce unnecessary skin biopsies.

Keywords:

Optical biopsy, Confocal microscopy, Virtual staining, Skin cancer, Neural networks, Deep learning