INNODERM

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D5.6: REPORT ON A VALIDATED PORTFOLIO OF IMAGING FEATURES (PIF)

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1. Purpose of this Document

During INNODERM, we have performed pilot studies in which the RSOM was used to image a wide range of skin diseases (Table 2.1). For each disease, we found imaging features that could serve as biomarkers in order to perform diagnosis, severity assessment, therapy monitoring, clinical decision making, etc. From these biomarkers, we have constructed a Portfolio of Imaging Features (PIF), which serves as the basis for disseminating and exploiting the Raster-Scanning Optoacoustic Mesoscopy (RSOM) system that was developed during the INNODERM project.

The most promising biomarkers detected during the study were ones related to inflammatory skin diseases (psoriasis, eczema). For psoriasis, RSOM images show a great deal of coherence when distinguishing between healthy and diseased skin, with diseased skin always exhibiting the same easily identifiable and measureable structures and biomarkers. Subsequently, we studied psoriasis biomarkers in depth, performing quantitative validation, which is presented in this document and in more detail the final technical report.

2. Clinical Justification

Affecting around 2% of the general population in Europe and North America, psoriasis is a widespread chronic inflammatory skin disease that severely impairs quality of life and financially burdens the healthcare system and society.

There is no known cure for psoriasis. There is, however, strong interest in developing new treatments for managing the disease and suppressing the symptoms, and several treatment alternatives exist already. Treatment is often required for a lifetime, but responses to therapies differ for each patient. Novel treatment with biologics is about 10 times more expensive than conventional treatments (around 20 000-30 000 € per year), their role remains largely restricted to second-line therapy.

Research into novel therapeutics and optimization of treatment requires accurate and longitudinal assessment of disease severity on an individualized basis. Ineffective therapies must be recognized and adapted or changed as early as possible in order to avoid risking disease progression and potentially generating high costs. Adapting, for example, the frequency of biologics administration to the patient's response could make these therapies more cost efficient.

Grading of disease severity over time is mainly based on clinical scores, in particular the psoriasis severity index (PASI), which is calculated from the percentage of affected body surface, as well as redness (erythema), thickness (induration) and scaling of the psoriatic plaque as graded by visual and palpation assessment. The local PASI (plaque PASI) is equal to the standard PASI, but does not take into account the percentage of the body affected. The plaque PASI can be used when small changes in severity are being tracked.

Despite the acceptance of PASI as a disease severity metric, visual inspection is inherently subjective, offers only a two-dimensional surface view of the skin condition, has low sensitivity to capturing subtle changes in mild disease, and cannot assess critical pathological features within the skin, in particular vascular abnormalities and inflammation. Moreover, microvascular changes are increasingly being

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identified as important pathophysiological hallmarks of the underlying inflammation driving progression of the disease, but are not accurately capture by PASI. Resolving and monitoring pathological vascular features is expected to be critical in characterizing inflammation and disease severity.

We investigated how RSOM features relate to treatment response and whether we can identify quantitative image parameters that can serve as biomarkers for disease monitoring.

3. Imaging Features

For psoriasis, the RSOM images show a great deal of coherence when distinguishing healthy skin from diseased skin. The diseased skin always show the same structures and biomarkers can be easily identified and measured. As a result, RSOM can nicely show the progress of therapy on the disease (fin).

Importantly, the biomarkers "width of capillary loops" (MCLL) and "width of sub-epidermal plexus" (MPW) correlate with corresponding treatment and show therapeutic effects, whereas the same therapeutic effects cannot be identified with the standard severity assessment made using the naked eye (PASI index). The biomarker "axial loop diameter" (MCLD) initially decreased with treatment and stabilized afterwards. These results encouraged us to make a precision and accuracy study of the biomarkers in order to validate them.

4. Precision and Accuracy of the Biomarkers

In the context of this study, the precision of a measurement is a function of errors introduced by the operator, patient and the system, which challenge the repeatability of measurements obtained by a single operator. These errors can derive from difficulties in positioning the scan head in the same location, motion, or the variable pressure exerted on the skin layers, which may compress the vascular structure. We estimated the precision by conducting a repeatability study in which nine plaques of different patients were imaged at one time point (t=0) and then 10 minutes after (t=10) by the same operator, who also derived the biomarkers from the reconstructed images. The repeatability coefficient was then calculated using an ANOVA model and represents the value below which the absolute difference between two repeated results may be expected to lie with a probability of 95%. The differences in the t=0 and t=10 images revealed that the scan-head placement method can lead to small discrepancies in positioning of a few hundred microns. We also observed in a few cases that the image quality varied between both images. However, such errors barely affected the MCLL and MPW values, which showed a repeatability coefficient of 36.7 and 38.4 μm, respectively. We found that blurring due to motion highly affected the measurement of MCLD, preventing us from obtaining sensible values or a repeatability coefficient for this parameter.

The accuracy of a measurement is related to its discrepancy with respect to its actual value. For all the measured biomarkers, the accuracy is given by the axial resolution of the system, which is 7 μm. The precision and accuracy values of the biomarkers are below the subtle differences in value observed in the biomarkers in the cases where the PASI index did not vary. In the case corresponding to the difference between days 8 and 10, the MPW decreased by 56 μm and the MCLL decreased by 49 μm, while PASI remained constant. Therefore, such differences can be attributed to actual effects of the therapy on the microvascular structure.

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Table 2.1. Imaged diseases and their corresponding biomarkers, and associated publications.

Disease	Imaging features/biomarkers	Article status
Melanoma	Depth of melanocytic cells	https://doi.org/10.1101/2021.05.25.21257525 (medRxiv, paper under-review in nature communications)
	Vessel density	
	Average vessel length	
	Total blood volume	
	Tortuosity	
	Lacunarity	
	Fractal number	
Inflammatory diseases (psoriasis, eczema)	Total blood volume	https://doi.org/10.1038/s41551-017-0068
	Epidermal thickness	
	Capillary density	
	Capillary diameter	
	Plexus width	In preparation (eczema)
	Capillary thickness	
Scleroderma	Capillary density	https://doi.org/10.1016/j.pacs.2018.02.002
	Capillary thickness	
Allergy	Blood volume per surface	https://doi.org/10.1111/cod.13563
	Width of vascularized dermis	
	Ratio low/high frequency content	
	Vessel fragmentation	
Phototesting	Change of blood fraction	https://doi.org/10.1111/bjd.19463
	Microvessel diameter	

5. CONCLUSIONS

During INNODERM, we have objectively and with high accuracy and precision demonstrated that RSOM is capable of monitoring and quantifying internal changes in microvascular morphology in psoriatic skin during psoriasis treatment. Moreover, we have shown that RSOM outperforms the sensitivity of traditional visual inspection methods by revealing subtle sub-surface therapeutic effects. These results demonstrate for the first time that RSOM is capable of providing objective, precise and sensitive metrics during psoriasis treatment, which are needed for effective and cost-efficient personalized medicine, as well as for comparative studies in drug development. Future plans consist of performing similar studies for other diseases for which RSOM showed initial promising results.

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