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Investigation of teledermatology and multispectral imaging as novel skin cancer screening modalities

PhD thesis

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List of abbreviations

AD	Aggregated diagnostic
AF	Autofluorescence
AK	Actinic keratosis
AUC	Area under the curve
BCC	Basal cell carcinoma
CI	Confidence interval
COVID-19	Coronavirus disease-19
EESZT	National eHealth Infrastructure system of Hungary
FN	False negative
FP	False positive
FTF	Face-to-face
G	Green
HIS	Hospital information system
LED	Light-emitting diode
MM	Malignant melanoma
MSI	Multispectral imaging
NMSC	Non-melanoma skin cancer
No.	Number
NPV	Negative predictive value
PD	Primary diagnostic
PPV	Positive predictive value
R	Red
ROC	Receiver operating characteristic
ROI	Region of interest
SCC	Squamous cell carcinoma
SD	Standard deviation
SK	Seborrheic keratosis
TD	Teledermatology
TN	True negative
TP	True positive
USA	United States of America
κ	Cohen’s kappa coefficient

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1. Introduction

1.1. Skin cancers

Skin cancer is the most common malignancy worldwide (1, 2). In the previous decades, incidence rates of skin cancers have dramatically increased in all age groups, especially among people over 60 (3, 4). Furthermore, incidence curves suggest that the incidence will continue to increase in the upcoming years (5, 6). Skin cancers are classified as non-melanoma skin cancer (NMSC) or malignant melanoma (MM) (7). Globally, it is estimated that 325.000 new cases of MM are diagnosed each year (8). The American Cancer Society predicts that by 2023, the number of new MM cases is projected to be 97.610 in the country, while mortality will reach 7.990 cases, as MM accounts for the most skin cancer deaths (9, 10). Early detection is considered effective in reducing mortality as localized MM has a significantly lower risk of metastasis and a better prognosis with a relatively high survival rate of 98% in 5 years (11). However, the survival rate decreases significantly if the patient is diagnosed with advanced (64%) or metastatic MM (23%) (12). As for NMSCs, basal cell carcinoma (BCC) is the most common skin cancer in the Caucasian population (13). Although BCCs are often not properly registered, the incidence in the United States of America (USA) is estimated at 3.6 million new cases per year (14-16). Despite the fact that metastasis from a BCC is extremely rare, locally advanced BCC's can result in significant morbidity through local destruction (17, 18). Besides BCC, cutan squamous cell carcinoma (SCC) is the second most common skin cancer with an estimated incidence of 1.8 million new cases annually in the USA (19). SCC also accounts for most NMSC-related metastatic diseases and deaths (20). Early detection is pivotal in skin cancer management if we consider increasing incidence, high mortality rates and costs of medical treatment (21). Consequently, a wide variety of imaging technologies are evolving to reform skin cancer screening (22)

1.2. Teledermatology

1.2.1. Definition of telemedicine and teledermatology

The term telemedicine was used the first time by Thomas Bird in the 1970s (23, 24). It comes from the Greek word "tele" and the Latin word "medicus", which means "healing at a distance" (24, 25). Nowadays, telemedicine can be defined as the use of telecommunication

technologies to improve access to patient care and medical information (26, 27). In recent years, many subspecialty fields within medicine have already started to implement telemedicine services, such as teleradiology, telecardiology, telepathology, teleophthalmology, telepediatrics or telestroke (28-30). Dermatology is particularly suitable for telemedicine-based patient care as skin disorders are almost always visible (31). Teledermatology (TD) is a subspecialty of dermatology that has the potential to diagnose skin conditions and offer treatment from a distance (32).

1.2.2. Teledermatology before the outbreak of the COVID-19 pandemic

With the advancement of telecommunication technologies, there has been a rapid development and increased use of various imaging technologies, which has made TD an emerging process in patient care (33). TD has been routinely used since the mid-2000s in Western European countries' public health care systems (34). The Netherlands individually integrated online care for dermatology patients into its health care system uniformly, while online care varies among regions in other European countries (35). In the United Kingdom, the proportion of dermatologists actively practicing TD was 17% in 2006, rising to 48% in 2016 (36). In the USA, the number of dermatology specialists varies considerably between regions. In metropolitan areas, there is an average of 4.03 dermatologists per 100 000 inhabitants, compared to 3.06 in rural areas (37). This has led to significant investment to develop TD platforms across the country in recent years, as 102 different platforms were registered in 2016, three times more than in 2011 (38).

1.2.3. Teledermatology after the outbreak of the COVID-19 pandemic

After the outbreak of the COVID-19 pandemic, the role of telemedicine has undergone explosive growth all around the world in every field of medicine (39, 40). Reports suggest that some health care facilities have increased the rate of telemedicine visits from 10% before the pandemic to more than 90% during the first wave in the USA (41). Changes in outpatient care contributed to the increased use of different TD modalities, significantly minimizing the spread of COVID-19 (42). Temiz et al. (2020) were the first to publish that telemedicine could provide appropriate patient care to reduce face-to-face (FTF) consultations in dermatology at the time of the COVID-19 era (43). Most health care facilities that had not

developed their own TD system before restrictions, started to use electronic mail and various communication applications (WhatsApp, Facebook, Zoom, Skype) (44-46). A global survey was filled out by 733 dermatologists and indicated an immediate effect of the pandemic on conventional dermatology practice. The number of specialists who used TD during the first wave of the COVID-19 epidemic increased three-fold compared to the period before the outbreak of the pandemic. There was a 53% decrease in the number of specialists who provided FTF consultations, while 15.6% of respondents stopped seeing patients (47). Following the introduction of restrictions, Skayem et al. (2020) estimated that the mean number of TD consultations per day increased from 9.28 to 36.4 at their department in France, primarily for cutaneous lesions of suspected COVID-19 infections (48). In addition, the pandemic had a significant impact on dermatology residency programs. Due to the limited patient flow, various learning strategies and activities were implemented into TD care (49, 50). As for oncodermatology, TD had been already used for skin cancer screening before the pandemic yet it gained unprecedented importance after restrictions were introduced in public health care systems (51, 52).

1.2.4. Implementation of teledermatology

There are two forms of TD based on how the patient is involved in the communication process. During direct consultation session, the patients refer themselves to online care and also communicate with the dermatologist. In contrast, indirect consultation includes the communication between the referring physician (for example general practitioner) and dermatologist about the patient's condition (53, 54). In terms of technical implementation, the most widely used TD modality is asynchronous, where communication between the parties is separated by space and time (55). The asynchronous form is called "store-and-forward" TD in the literature (56). Clinical history and digital images of skin lesions are obtained by patients or the requesting clinician and then referred to a dermatologist (31). Nowadays, high-resolution digital images taken by digital cameras, mobile phones or tablets could ensure simplified use and advanced visualization of the lesions (57). In addition, a growing number of mobile phone applications are available that can provide TD care directly to patients (58-60). Therefore, store-and-forward TD may have the potential to integrate

artificial intelligence and automate the diagnostic process (61). However, the most common problem encountered in asynchronous care is the lack of relevant information, such as incomplete medical history, failure to answer relevant questions, low quality of photographs or problematic use of technology by patients (32, 62). The synchronous form is called "real-time" TD and provides limitless interaction between the parties via live video (63). Responding immediately to patients can make diagnosis faster and more efficient but also increase the amount of irrelevant information. The main limitation of the synchronous form could be the slow internet connection of the patients (56, 64). An additional problem may occur that live video is less informative than pre-submitted photographs because of its lower quality (31, 62). The hybrid form is a combination of synchronous and asynchronous TD (65). Medical history and digital images are sent to the dermatologist, followed by telephone or videoconference (66).

1.2.5. Application of teledermatology

The use of TD can facilitate the flow of medical information and help patient care in many ways. TD can reduce the number of FTF consultations for easily diagnosed and less urgent conditions as the online prescription of certain medicines is allowed (67, 68). Moreover, skin diseases can be followed up, when an already diagnosed condition or the effectiveness of the therapy is monitored (69). Therefore, TD has the potential to simplify patient care in case of autoimmune (atopic dermatitis, psoriasis) or any other chronic diseases (acne, rosacea) (70-72). Triage is one of the most common application forms, as it could improve access to dermatological care and reduce waiting time to treat urgent cases (53, 73). Therefore, TD services could allow for the early detection of skin cancers (74). The use of TD can also offer the possibility of screening elderly and disabled patients and in areas with a shortage of dermatological care (75). In addition, the combination of TD and conventional imaging techniques can ensure more reliable skin cancer screening (52).

1.3. Dermoscopy

Handheld dermoscopy has become the most commonly used noninvasive, in-vivo imaging technique in dermatology (76, 77). It allows 10x power magnification, thus provides additional details of the skin that are invisible to the naked eye (78-80). Moreover,

dermoscopy is a cost-effective and fast tool to screen patients for different skin cancers (81, 82). When one considers the pitfalls of dermoscopy, the possibility of misidentification is not to be neglected, thus its use requires extensive training (83). Accordingly, dermoscopy is not a substitute for histopathological evaluation (84). Nevertheless, certain countries encourage the dissemination of dermoscopy among general practitioners to screen patients for skin cancer or send suspected lesions for TD consultation (85, 86). Additionally, dermoscopy devices that can be attached to mobile phone cameras have also been developed. The process of referring magnified images for TD consultation is called teledermoscopy (87). Videodermoscopy is another emerging method performed by a high-resolution color video camera that offers magnification from 10 to 1000 times (88). The electronic storage allows the comparison of different images during later examinations of suspicious lesions (80). Digital dermoscopy is another method that offers a high-magnification view of extensive skin lesions (89). This technique could be an effective imaging method in preoperative mapping of skin lesions and follow-up of atypical dysplastic nevus syndrome or congenital melanocytic nevus (77, 79). First, multiple consecutive dermoscopic images are taken containing different parts of the lesion, then all records are combined (77, 90). Despite advances in dermoscopic imaging, there is a great need to develop other screening techniques that are easy to use and accessible to other health care professionals (91, 92).

1.4. Multispectral imaging

Multi-modal spectroscopy or multispectral imaging (MSI) is an emerging non-invasive technique that combines spectroscopic and other digital imaging methods (93). MSI is based on the fact that illumination of the skin with different wavelength bands of visible and infrared lights results in different pictures. When the reflected light is collected, it shows the spectral properties of the skin (94). The analysis of reflected light helps to determine the pathological and morphological features of various skin lesions (2, 95). Spectral properties of the skin are defined by organic molecules (melanin, hemoglobin, water, beta-carotene, collagen, bilirubin) called chromophores. These molecules are shown to be diverse among skin lesions of different etiologies (94, 96). In the field of dermatology, most studies have investigated the use of MSI to discriminate malignant from benign lesions (97). Others have

already reported that MSI has the potential to identify malignant lesions at a high success rate (98, 99). In addition, MSI systems that incorporate artificial intelligence-based image recognition algorithms have already been tested as a prebiopsy tool to rule out the possibility of malignancy and decrease the number of unnecessary excisions (95). This technique can be easily integrated into mobile phone cameras or serve as a standalone handheld device (100). Consequently, MSI could become a fast and cheap decision support device for the early diagnosis and management of skin cancers (101).

1.5. Differentiation of malignant melanoma from seborrheic keratosis

Diagnosis of MM is among the most challenging processes in dermatology practice as it requires high levels of expertise (102). MM is caused by the malignancy of melanocytes, the risk of which is greatly increased by intermittent sun exposure (103). Besides rare forms, different main types of invasive melanoma are known, such as superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma (104-107). Similarly to NMSCs, the gold standard for the diagnosis of MM is histological examination, but visual criteria are required to perform effective screening (108). Diagnostic criteria (ABCDEs) of visual inspection to identify MM are asymmetry, border irregularity, coloration, diameter and evolution (109, 110). Most MMs contain any of the following dermoscopic criteria: atypical pigmented network, blue whitish veil, atypical vascular pattern, regression structures, irregular dots, globules, streaks or blotches (Figure 1) (111). Because of the great variety of clinical morphology, MM has the potential to contain unusual features and mimic other skin lesions (112, 113). One of the most challenging presentations of MM is the ones that clinically resemble seborrheic keratosis (SK) (114, 115).

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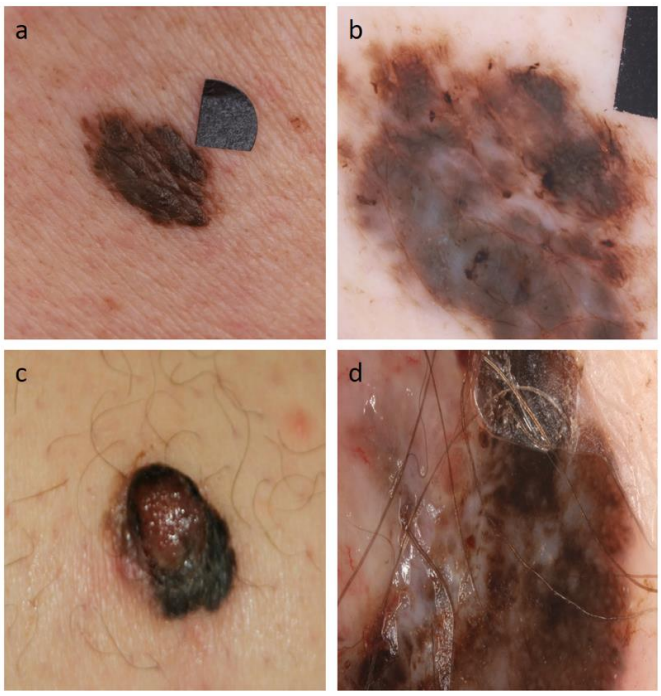

Figure 1. Superficial spreading melanoma (a, b) and nodular melanoma (c, d). Dermoscopic images (b, d) show usual features of malignant melanoma: atypical pigmented network, blue whitish veil, atypical vascular pattern, irregular globules and blotches (109, 111). Clinical (a, c) and dermoscopic images were taken at the Department of Dermatology, Venereology and Dermatooncology.

SK is among the most common benign skin lesions arising from epidermal keratinocytes (116). The incidence increases with age, yet it can also occur in young individuals (117). Generally, SKs are diagnosed clinically and removed for aesthetic reason, tactile discomfort, irritation or itchiness (118, 119). SKs can appear as papules or plaques (118). Most SKs are well-demarcated with a verrucous appearance and range from light brown to black in color. The surface is most commonly keratotic, but it can be waxy, scaly, or greasy (120). SKs can also exhibit exophytic, hyperplastic or hyperpigmented variants (121). The diagnostic algorithm of SK with dermoscopy is based on the detection of sharp demarcation, moth-eaten borders, milia-like cysts and comedo-like openings. The presence of fissures and ridges, hairpin vessels, crypts, exophytic papillary structures and brown fingerprint-like structures are also among the diagnostic criteria (Figure 2) (118, 122).

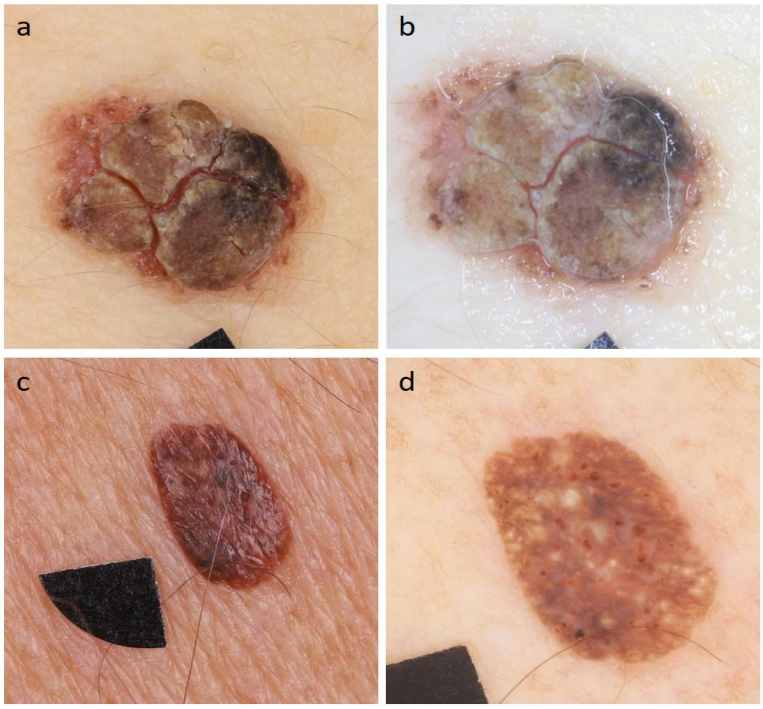

Figure 2. Macroscopic (a, c) and dermoscopic (b, d) features of seborrheic keratosis. Macroscopic (a) and dermoscopic images (b) of verrucous seborrheic keratosis contain fissures and ridges. Seborrheic keratosis (c, d) shows hyperpigmented areas and sharp demarcation from the skin. The dermoscopic image (d) shows milia-like cysts and comedo-like openings (120, 121). Clinical and dermoscopic images were taken at the Department of Dermatology, Venereology and Dermatooncology.

Dermoscopic features could improve diagnostic accuracy to differentiate SK from MM resembling SK (SK-like MM) (123, 124). Carrera et al. estimated that diagnostic accuracy to clinically identify SK-like MMs was 60.1% by dermatologists, while it increased to 68.1% with the involvement of dermoscopy (125). Therefore, the clinical identification of MMs from SKs with uncommon morphology can be complicated even for board-certified dermatologists (119). Misdiagnosed or delayed diagnosis of MM has a serious impact on the prognosis of the disease (126). Inappropriate management could significantly decrease the five-year survival rate of the patients (127, 128). On the top of that SKs can also resemble MMs (MM-like SK) (118, 129). In these clinically doubtful cases, histological examination is the most reliable process that can determine the correct diagnosis. However, misclassified SKs could result in unwanted psychological stress and needless excision (130).

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2. Objectives

2.1. Project I.

The primary outcome measure was to investigate the efficacy of store-and-forward TD system for skin cancer screening during the first wave of the COVID-19 pandemic. We reviewed the outcome of TD consultations based on macroscopic images sent by the patients and matched them with the result of subsequent FTF or histopathological examinations. We aimed to assess the overall diagnostic agreement of TD care among patients referred for dermoscopic examination. We also evaluated the diagnostic parameters of different malignant and non-malignant lesions and compared them with the result of other studies before the pandemic. Another goal was to investigate the effectiveness of TD as a triage tool to refer patients with potential skin cancer for FTF examination.

2.2. Project II.

Our objective was to set the most suitable threshold of a light-emitting diode (LED)-based MSI device to optimize the identification of MM from SK and SK-like MM from MM-like SK. Receiver operating characteristic (ROC) curves were performed to determine the appropriate value of the SK index as a threshold for screening.

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3. Methods

3.1. Project I.

3.1.1. Patient data

This retrospective and single-center study focused on patients who submitted their cases via an asynchronous TD system (developed by MedInnoScan, Research and Development Ltd., Budapest, Hungary) for consultation between 25 March 2020 and 13 July 2020 at the Department of Dermatology, Venereology and Dermatooncology, Semmelweis University (Budapest, Hungary). Our study was approved by the Ethics Committee of the National Institute of Pharmacy and Nutrition (OGYÉI/20793/2020). First, medical records of TD consultations were reviewed in the local hospital information system (HIS) (e-Medsolution, T-Systems Hungary Ltd., Budapest, Hungary) to obtain information on patients who were invited for a personal examination with a dermoscope during TD care. These documents included demographic data of the patients, one or more possible differential diagnoses of the lesion(s) and the urgency of the case determined by teledermatologists. If the dermatologists considered that the quality of the images sent by the patients were inadequate and could make it challenging to establish the correct diagnosis, it was noted as well. Digital images taken by patients in JPEG format could be uploaded with a resolution of at least 8 megapixels. Later, follow-up of patients was performed between 1 March and 30 April 2021 to collect the results of FTF or potential histopathological examinations. Data were collected from the HIS and the National eHealth Infrastructure system of Hungary (EESZT, see http://www.eeszt.gov.hu (accessed on 5 March 2023)). If it was necessary, patients were contacted by phone.

3.1.2. Diagnostic groups

All types of MM were categorized into one diagnostic group. Similarly, all forms of BCC and SCC were divided into two separate groups. Actinic keratoses (AKs) were also listed as malignant lesions, while the diagnostic group called “other malignancies” included skin cancers that could be classified other than the previous ones. As for non-malignant pigmented lesions, dysplastic naevi were represented as a separate group, while all other naevi were grouped together as “naevi”. SK’s, haemangiomas and warts were also defined

as different groups. All additional diagnoses with a lower number of cases were grouped into the “other lesions” group.

3.1.3. Triage groups

All cases were classified into three triage groups by the immediacy of the findings during TD consultations: high-urgency, moderate-urgency and low-urgency group (Figure 3). If more than one lesion was referred to TD consultation by a patient, the same triage status was assigned to both lesions, equally.

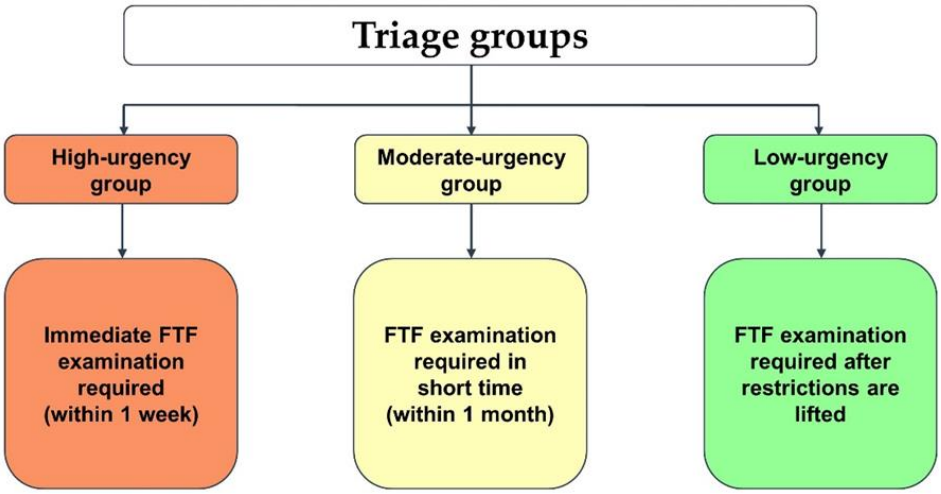

Figure 3. Definition of the triage groups. Abbreviations: FTF, face-to-face. The high-urgency group included cases where FTF examination was considered by teledermatologists to be warranted within a week at the latest. The medium-urgency group included cases referred for FTF examination within one month but at least one week. The low-urgency group included cases sent for dermoscopic examination after restrictions had been lifted (131).

3.1.4. Statistical analyses

Descriptive statistics were reported for patient demographics and lesion localizations. In this study two reference standards were defined. Histopathology was the reference standard in cases when lesions were excised. Where no histology was performed, the reference meant the result of the FTF examination. In all cases, the result of the TD examination was compared with the reference standard. Confusion matrix was used to report the number of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) cases

(Table 1). Based on confusion matrix, diagnostic parameters (sensitivity, specificity, predictive values) were calculated within each diagnostic group. Cohen's kappa coefficient (κ) was assessed for each diagnostic group, separately. The concordance quantified by κ may indicate different strengths of agreement: $\kappa \leq 0.2$ indicates slight agreement, κ of 0.21–0.40 indicates fair agreement, κ of 0.41–0.60 indicates moderate agreement, κ of 0.61–0.80 indicates substantial agreement and κ of 0.81–0.10 almost perfect agreement (132, 133). Overall diagnostic accuracy and κ value of the system were also calculated. Diagnostic agreement of all malignant and non-malignant lesions was measured, separately. All diagnostic performances were calculated based on primary and aggregated diagnoses, as well. Primary diagnostic agreement is defined as the agreement of the most possible diagnosis considered during TD consultation with the result of FTF or histological examination (134). The aggregated diagnostic agreement is the concordance of any differential diagnosis of the lesion considered during TD consultation with the reference standard (57).

Table 1. Definition of true positive, true negative, false positive and false negative cases (135, 136)

True Positive	Result of a TD consultation that correctly indicates the presence of a particular condition
True Negative	Result of a TD consultation that correctly indicates the absence of a particular condition
False Positive	Result of a TD consultation that wrongly indicates the presence of a particular condition
False Negative	Result of a TD consultation that wrongly indicates the absence of a particular condition

Abbreviations: TD: teledermatology

Pearson's chi-square test (two-tailed) was used for categorical variables. The proportion of TP and FN diagnoses was compared among different triage groups. The distribution of confirmed malignancies and non-malignant lesions was also compared among various triage groups. Confidence intervals (95% CI) were calculated whenever appropriate. The *p* value below 0.0001 was considered statistically significant in all calculations. Statistical analyses were performed using Statistica v13.5.0.17 software (TIBCO Software Inc., Palo Alto, CA, USA). κ values were assessed using GraphPad QuickCalcs calculator (GraphPad Software Inc., San Diego, CA, USA).

3.1.5. Inclusion Criteria

Later, all patients whose photographs were deemed of sufficient quality by teledermatologists and later attended personal examination with dermoscopy. Diagnostic verification of all MMs, SCCs, BCCs and other malignancies was established by histological examination. The availability of at least results from the FTF examination was an additional criterion in case of confirmed AKs and benign lesions.

3.1.6. Exclusion Criteria

If teledermatologists could not determine the diagnosis due to lack of adequate photographs or absence of medical history. Patients were also excluded from the study if no follow-up information could be obtained.

3.2. Project II.

3.2.1. General data

Measurements were carried out at the Department of Dermatology, Venereology and Dermatooncology, Semmelweis University (Budapest, Hungary) and at the Oncology Centre of Latvia (Riga, Latvia). Our study was approved by the Institutional Ethics Committee of Semmelweis University (SE RKEB no. 228/2018) and by the Research Ethics Committee of the Institute of Cardiology and Regenerative Medicine, University of Latvia (approved on: 26 February 2019). Patients with lesions such as MM, SK, SK-like MM and MM-like SK were measured with a MSI device. Lesions were first evaluated by clinical examination and the use of handheld Heine Delta 20 (HEINE Optotechnik GmbH & Co KG, Gilching, Germany) dermoscopy by dermatologists. In cases where it was deemed necessary to remove the lesion, a histological examination was also performed.

3.2.2. LED-based multispectral imaging device

We used a prototype of a handheld MSI device developed by the Biophotonics Laboratory, Institute of Atomic Physics and Spectroscopy, University of Latvia and Faculty of Computer Science and Information Technology, Riga Technical University. This device employs an illumination source with four types of LEDs (SML-LXL8047UVC, Lumex, Inc., Ronkonkoma, NY, USA) with wavelengths of 405 nm to induce skin autofluorescence (AF)

and 525 nm green (G), 660 nm red (R) and 940 nm infrared for diffuse reflectance imaging (137, 138). The lights penetrate different layers of the skin with irradiating power density of 20 mW/cm². Images were collected with a color CMOS 5 megapixel IDS camera (MT9P006STC, IDS uEye UI3581LE-C-HQ, Obersulm, Germany). The camera was fixed from the skin at 6 cm distance with a field of view of 2 x 2 cm². If the surface of the skin was not flat the image focus was slightly adapted by the adjustment of the region of interest (ROI). At the end of the process, all images were automatically transferred to a cloud server (139, 140). In many cases, more than one image sets were taken because of the lesions' number and size. A black marker was applied next to the captured lesions to improve the alignment of the images (area: 0.125 cm²).

3.2.3. Intensity and Particle Analysis

The images were analyzed using ImageJ v1.46 software (NIH, Bethesda, MD, USA). ROI of the skin lesions were selected manually to investigate spectral reflectance and autofluorescence properties. Quantitative parameters such as mean intensity and standard deviation (SD) were analyzed in different channels (AF, G, and R). The ratio of pixels with the lowest and highest intensity values (Min/Max) of all lesions was measured within the AF channel. The intensity values of the lesions were compared with those of the adjacent control skin for normalization. AF images were converted into 8-bit form to analyze the fluorescence values of particles. Automated default thresholding process (Overlay Masks) of the ImageJ software was used to visualize the particles. The size of the particles was determined between the range of 10 and 100.000 pixels. Circularity was set between 0.4 and 1.0, while the edges were excluded. If more than one SK was in one field of view or hair affected the measurement, ROI was manually selected to specify the lesion for particle analysis. The area percentage (%) was calculated from the ratio of the area of the particles with fluorescence values above the threshold and the area of the lesion.

3.2.4. SK Index

Quantitative parameters and the result of particle analysis were combined to calculate the SK index of each lesion (Figure 4).

$$\text{SK index} = \frac{2 \cdot \text{AF} \cdot \text{SD} \cdot \left(\frac{\text{Min}}{\text{Max}}\right)}{\text{G} \cdot \text{R}} + \left(\text{Particle number} \cdot \text{Area \%}\right)$$

Figure 4. Calculation of the SK index. The mean intensity values of different channels (AF, G, and R) were included in the algorithm. In case of the AF channel, standard deviation, minimum/maximum ratio, particle number, area percentage of the particles were also added (141).

3.2.5. Statistical analysis

Rare forms with morphological overlaps of both MM (SK-like MM) and SK (MM-like SK) were separated from typical forms. Therefore, diagnostic parameters could be measured separately in clinically undefined cases. SK index value of all lesions was calculated, then logarithmic transformation was performed. Welch's t-test was used to compare the SK index value of MMs with SKs and SK-like MMs with MM-like SKs. ROC curves were used based on the SK index values of different lesion groups to count the area under the curves (AUC) and characterize the diagnostic performance of the LED-based MSI device. The *p* value below 0.05 was considered statistically significant in all calculations. Finally, sensitivity and specificity pairs of different cut-off points were spotted to determine the equivalent threshold, which could be uniformly suitable for the identification of both MM from SK and SK-like MM from MM-like SK. Statistical analysis was performed with the use of GraphPad Prism v8.0.1. software (GraphPad Software Inc., La Jolla, CA, USA).

3.2.6. Inclusion criteria

Lesions on body parts accessible to the MSI device were involved in the study. Only histologically confirmed MMs were included in the study. All SKs had to be confirmed by at least clinical and dermoscopic examination by a board-certified dermatologist.

3.2.7. Exclusion criteria

Clinically diagnosed MM were excluded without histological validation. Furthermore, ulcerated lesions were also excluded from the study.

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4. Results

4.1. Project I.

4.1.1. Inclusion and patient data

A total of 10.287 cases were submitted for TD consultation, while 749 patients with 779 lesions were included (Figure 5) as they underwent FTF dermoscopic examination.

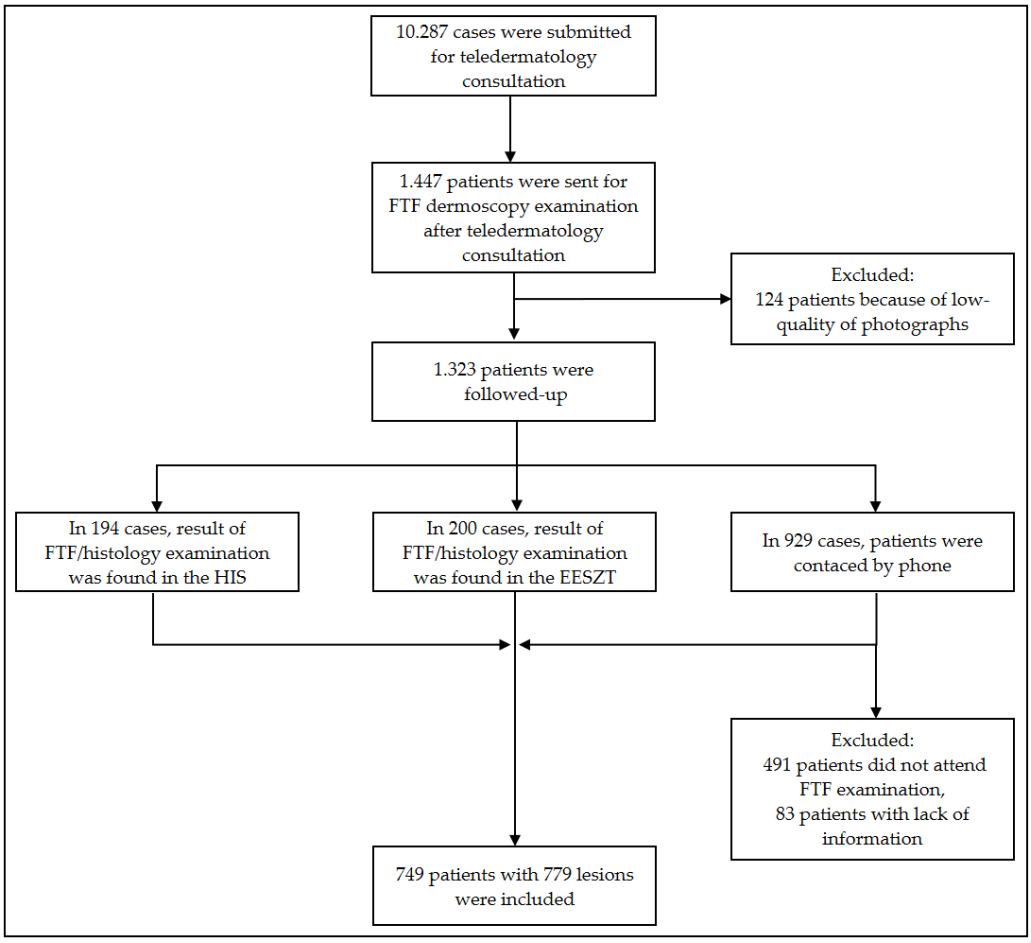

Figure 5. Patient selection. 10.287 consultations were performed via store-and-forward TD. In total, 1447 patients with 1495 lesions were sent for dermoscopic examination. Before follow-up, lesions were excluded if teledermatologists deemed low quality of the photographs (124 patients with 124 lesions). After that HIS and EESZT were viewed and patients were called if any information could not be found about FTF examinations. After the follow-up, patients were also ruled out if they did not attend to FTF examination (491 patients with 509 lesions) or did not answer the call (83 patients with 83 lesions) (131).

Patient characteristics are shown in Table 2. The mean age of the included patients was 43.54 ± 21.03 years. The median number of lesions per patient was one (interquartile range: 1–2). 45 patients (6%) had skin cancer in their personal history, 18 patients (2.4%) had it in their family history, while two patients (0.3%) had it in both. The remaining 684 patients (91.3%) had no skin cancer in their medical history.

Table 2. **Characteristics of the included patients (131)**

Variables	Number of patients
Age composition	
0-19	87 (11.6%)
20-39	225 (30.0%)
40-59	245 (32.7%)
60-79	164 (21.9%)
80≤	28 (3.7%)
Sex	
Female	474 (63.3%)
Male	275 (36.7%)
Ethnicity	
Caucasian	744 (99.3%)
Others	5 (0.7%)
Lesion location	
Head/neck	193 (24.8%)
Hand/arm	117 (15.0%)
Trunk	350 (44.9%)
Leg/foot	103 (13.2%)
Buttock/groin	16 (2.1%)

During TD consultation sessions, 639 (82%), 132 (17%) and eight lesions (1%) received a single, two and three diagnoses, respectively. Consultations were carried out by 29 dermatologist specialists and specialist registrars. The average number of completed cases per dermatologist was 25.8 ± 17.8. Dermatology residents cared for 565 patients with 586 lesions (75.2%) under the supervision of a specialist. The remaining 184 patients with 193 lesions (24.8%) were managed exclusively by a specialist.

4.1.2. Triage Groups

Figure 6 reveals the distribution of triage groups among TP and FN diagnoses. 206 lesions (26.5%) were triaged as high-urgency, 227 lesions (29.1%) as moderate-urgency, and 346

lesions (44.4%) as low-urgency by teledermatologists, respectively. In 30 cases, two separate lesions were referred to TD consultation by the same patient. The same triage status was assigned equally to both lesions.

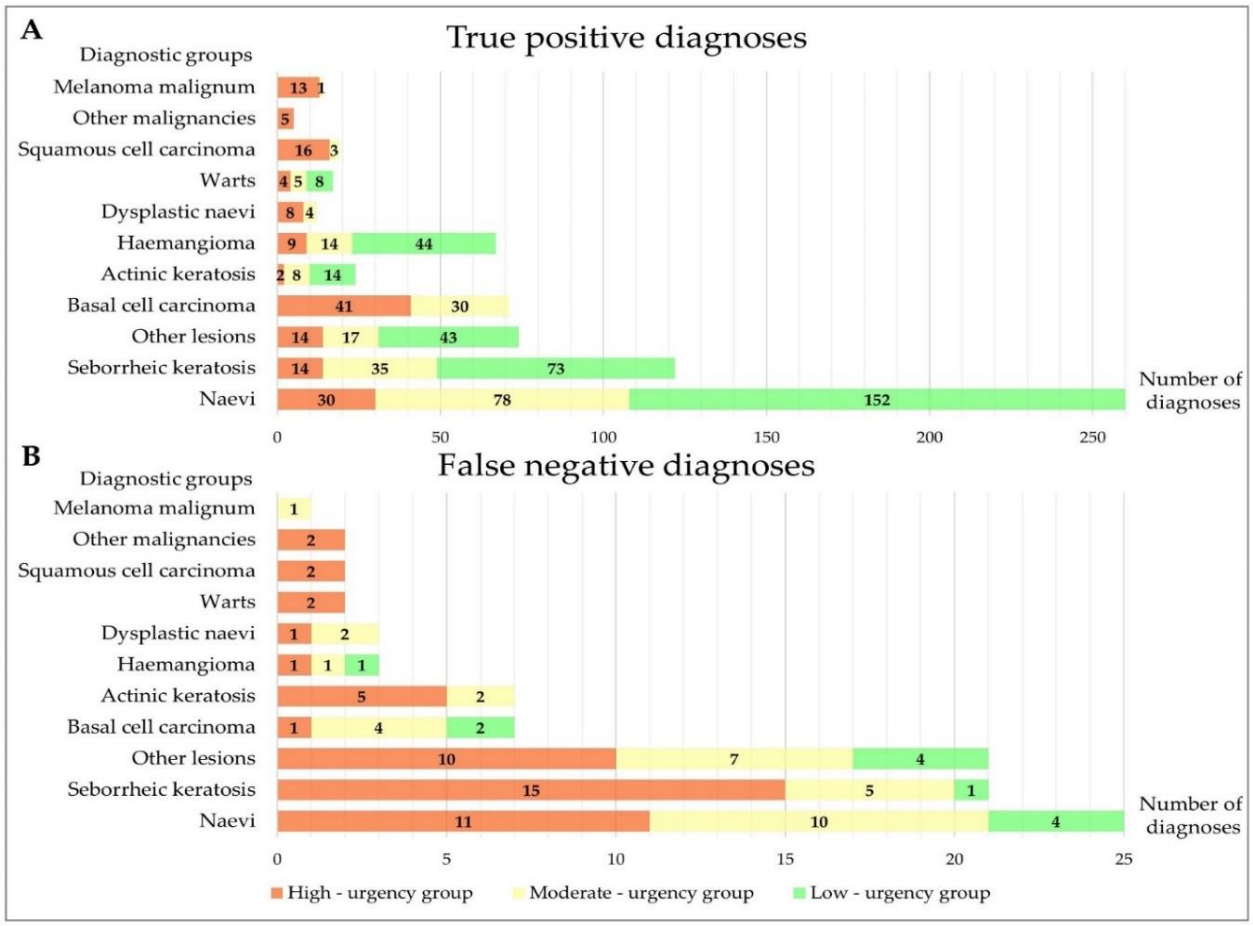

Figure 6. Distribution of different triage groups among true positive (Panel A) and false negative diagnoses (Panel B), considering aggregated diagnoses of the lesions during teledermatology consultations. 156 lesions (75.7%) were diagnosed correctly in the high-urgency group, 195 (85.9%) lesions in the moderate-urgency group and 334 lesions (96.5%) in the low-urgency group, respectively. Considering misdiagnosed cases, 50 lesions (24.3%) were categorized in the high-urgency group, 32 lesions (14.1%) in the moderate-urgency group and 12 (3.5%) lesions in the low-urgency group, respectively ($p < 0.0001$). After the follow-up, 87 malignancies (42.2%) and 119 benign lesions (57.7%) were confirmed in the high-urgency group, 49 malignant (21.6%) and 178 benign lesions (78.4%) in the moderate-urgency group, while 16 malignant (4.6%) and 330 benign lesions (95.4%) in the low-urgency group, respectively ($p < 0.0001$) (131).

4.1.3. Overall primary and aggregated diagnostic agreement

Considering overall primary and aggregated diagnostic concordance of malignant lesions, substantial agreement was seen between the diagnosis of TD consultations and reference standards. In contrast, non-malignant lesions showed almost perfect agreement considering primary diagnosis, while aggregated diagnostic concordance indicated substantial agreement. The overall concordance between all TD consultations and the reference standard showed substantial agreement. Primary diagnosis of 633 lesions during TD consultations matched with the reference standard, while 146 lesions were misdiagnosed. When all differential diagnoses were included, 685 lesions matched with the reference standard, while 94 lesions failed to do so. In total, a significant difference was assessed between overall aggregated and primary diagnostic accuracy ($p < 0.0001$) (Table 3).

Table 3. Overall diagnostic agreement (131)

PD / AD	Accuracy	Cohen's kappa
	Malignant lesions	
PD	86.3% (84.1% - 88.7%)	0.647 (0.574 - 0.720)
AD	85.3% (82.9% - 87.9%)	0.644 (0.572 – 0.716)
	Non-malignant lesions	
PD	81.3% (78.6% - 84.0%)	0.811 (0.790 -0.830)
AD	86.5% (84.1% – 88.9%)	0.790 (0.769 – 0.810)
	All lesions	
PD	81.2% (78.4% - 83.8%)	0.769 (0.747 – 0.792)
AD	87.9% (85.5% - 90.0%)	0.754 (0.722 – 0.776)

Abbreviations: PD: primary diagnostic, AD: aggregated diagnostic, CI: Confidence Interval.

4.1.4. Diagnostic parameters of malignant diagnostic groups

According to the primary diagnoses, the possibility of malignancy was raised in 198 lesions, while it increased to 228 lesions by involving another differential (aggregated) diagnoses. The chance of two different malignancies was considered in 12 cases during TD consultations. Later, 152 patients (female-male ratio: 48.7%-51.3%; mean age: 62.26 years ± 16.13) were diagnosed with malignancy. Histological examination confirmed the diagnosis of MM in 15 cases, BCC in 78 cases, SCC in 21 cases, other malignancies in seven cases and AK in three cases. In case of the other 28 AKs, result of the FTF examination was considered the reference standard. In the other malignancies group, all diagnoses were confirmed by histological examination: primary cutaneous follicle center lymphoma (3 lesions), invasive mammary carcinoma (1 lesion), dermatofibrosarcoma protuberans (1 lesion), metastasis of Merkel cell carcinoma (1 lesion), metastasis of adenocarcinoma (1 lesion). Considering all patients with confirmed malignancies, history of previous skin cancer was mentioned during TD consultation in 24 cases (15.8%), In comparison, at least one close relative was diagnosed with skin cancer in 6 cases (3.9%). The remaining 122 patients (80.3%) did not mention any related information during TD consultation. Sensitivity values of different malignancies ranged from 64.5% to 89.7% (κ=0.410 - 0.770) according to the primary diagnoses, while sensitivity values improved to 71.4% - 93.3% (κ=0.485 - 0.714) with the involvement of other differential diagnoses of the lesions (Table 4).

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Table 4. Diagnostic parameters and concordance of malignant diagnostic groups (131)

PD / AD	No. of diagnoses during TD consultations	TP	FN	Cohen's kappa (95% CI)	Sensitivity (95% Cl)	Specificity (95% Cl)	PPV (95% CI)	NPV (95% CI)
Malignant melanoma								
PD	32	10	5	0.410 (0.231 - 0.589)	66.7% (41.7% - 84.8%)	97.1% (95.7% - 98.1%)	31.3% (18.0% - 48.6%)	99.3% (98.44% - 99.7%)
AD	42	14	1	0.476 (0.317 - 0.636)	93.3% (70.2% - 99.7%)	96.3% (94.8% - 97.5%)	33.3% (21.0% - 48.5%)	99.9% (99.2% -100.0%)
Squamous cell carcinoma								
PD	36	13	8	0.437 (0.273 - 0.600)	61.9% (40.9% - 79.3%)	97.0% (95.5% - 98.0%)	36.1% (22.5% - 52.4%)	98.9% (97.9% - 0,99.5%)
AD	45	19	2	0.560 (0.415-0.704)	90.5% (71.1% - 98.3%)	96.6% (95.0% - 97.7%)	42.2% (29.0% - 56.7%)	99.7% (99.0% - 100.0%)
Basal cell carcinoma								
PD	98	70	8	0.770 (0.698 - 0.842)	89.7% (81.1% - 94.7%)	96.0% (94.3% - 97.2%)	71.4% (61.8% - 79.4%)	98.8% (97.7% - 99.4%)
AD	112	71	7	0.714 (0.638 - 0.789)	91,00% (82.6% - 95.6%)	94.2% (92.2% - 95.7%)	63,4% (54.2% - 71.7%)	99,00% (97.9% - 99.5%)
Other malignancies								
PD	8	5	2	0.663 (0.386 - 0.941)	71.4% (35.9% - 94.9%)	99.6% (98.9% - 99.9%)	62.5% (30.6% - 86.3%)	99.7% (99.1% - 99.9%)
AD	8	5	2	0.663 (0.386 - 0.941)	71.4% (35.9% - 94.9%)	99.6% (98.9 – 99.9%)	62.5% (30.6% - 86.3%)	99.7% (99.1 - 100.0%)
Actinic keratosis								
PD	25	20	11	0.704 (0.566 - 0.842)	64.5% (47.0% - 78.9%)	99.3% (98.4% - 99.7%)	80.0% (60.9% - 91.1%)	98.5% (97.4% - 99.2%)
AD	33	24	7	0.739 (0.617 - 0.862)	77.4% (60.2% - 88.6%)	98.8% (97.7% - 99.4%)	72.7% (55.8% - 84.9%)	99.1% (98.1% - 99.5%)

Abbreviations: PD: primary diagnostic, AD: aggregated diagnostic, No.: number, TDC: teledermatology consultations, TP: true positive, FN: false negative, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

4.1.5. Diagnostic parameters of pigmented non-malignant diagnostic groups

The result of the FTF examination was the gold standard in 481 cases, while histological evaluation confirmed the diagnosis in the remaining 146 cases of non-malignant lesions. In our study, the naevi diagnostic group represented itself with the highest number. Concordance of naevi indicated almost perfect agreement, while fair and moderate agreements were assessed for dysplastic naevi. In terms of all non-malignant pigmented lesions, sensitivity values ranged from 80% to 91.2% (Table 5).

Table 5. Diagnostic parameters and concordance of dysplastic naevi and naevi groups (131)

PD / AD	No. of diagnoses during TD consultations	TP	FN	Cohen's kappa (95% CI)	Sensitivity (95% Cl)	Specificity (95% Cl)	PPV (95% CI)	NPV (95% CI)
					Dysplastic naevi			
PD	38	12	3	0.437 (0.270 - 0.605)	80.0% (54.8% - 93.0%)	96.6% (95.1% - 97.7%)	31.6% (19.1% - 47.5%)	99.6% (98.8% - 99.9%)
AD	46	12	3	0.375 (0.220 - 0.530)	80.0% (54.8% - 93.0%)	95.50% (93.9% - 96.8%)	26.10% (15.6% - 40.3%)	99.6% (98.8% - 99.9%)
					Naevi			
PD	265	248	37	0.848 (0.809 - 0.887)	87.0% (82.6% - 90.4%)	96.6% (94.6% - 97.8%)	93.6% (90.0% - 96.0%)	92.8% (90.2% - 94.7%)
AD	290	260	25	0.848 (0.810 - 0.887)	91.2% (87.4% - 94.0%)	93.9% (91.5% - 95.7%)	89.7% (85.6% - 92.7%)	94.9% (92.6% - 96.5%)

Abbreviations: PD: primary diagnostic, AD: aggregated diagnostic, No.: number, TDC: teledermatology consultations, TP: true positive, FN: false negative, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

4.1.6. Diagnostic parameters of non-malignant diagnostic groups

Aggregated diagnostic concordance of other lesions (κ=0.676) and SK (κ=0.780) diagnostic groups indicated substantial agreement. Considering non-malignant diagnostic groups, other lesions had the lowest sensitivity (77.9%) as 15 out of 21 FN cases were diagnosed as malignant lesions during TD consultations. SKs were misdiagnosed as

malignant lesions in 14 out of 21 FN cases. In case of haemangiomas (κ=0.961) and warts (κ=0.943), almost perfect agreement was indicated (Table 6).

Table 6. Diagnostic parameters and concordance of SK, haemangiomas, warts and other lesions groups (131)

PD / AD	No. of diagnoses during TD consultations	TP	FN	Cohen's kappa (95% CI)	Sensitivity (95% Cl)	Specificity (95% Cl)	PPV (95% CI)	NPV (95% CI)
Seborrheic keratosis								
PD	123	112	31	0.810 (0.754 - 0.865)	78.3% (70.9% - 84.3%)	98.3% (96.9% - 99.0%)	91.10% (84.7% - 94.9%)	95.30% (93.4% - 96.7%)
AD	154	122	21	0.780 (0.723 - 0.836)	85.3% (78.6% - 90.2%)	95.0% (93.0% - 96.4%)	79.2% (72.1% - 84.9%)	96.6% (94.9% - 97.8%)
Haemangiomas								
PD	67	65	5	0.944 (0.903 - 0.985)	92.9% (84.3% - 96.9%)	99.7% (99.0% - 100.0%)	97.0% (89.8% - 99.5%)	99.3% (98.4% - 99.7%)
AD	69	67	3	0.961 (0.926 - 0.995)	95.7% (88.1% - 98.8%)	99.7% (99.0% - 100.0%)	97.1% (90.0% - 99.5%)	99.6% (98.8% - 99.9%)
Warts								
PD	15	15	4	0.880 (0.763 - 0.996)	78.9% (56.7% - 91.5%)	100% 0,9950 to 1,000	100% (79.6% - 100.0%)	99.5% (98.7% - 99.8%)
AD	17	17	2	0.943 (0.865 - 1.000)	89.5% (68.6% – 98.1%)	100% (99.5% to 100.0%)	100% (81.6% - 100.0%)	99.7% (99.1% - 100.0%)
Other lesions								
PD	72	63	32	0.731 (0.652 - 0.810)	66.3% (56.3% - 75.0%)	98.7% (97.5% - 99.3%)	87.5% (77.9% - 93.3%)	95.5% (93.7% - 96.8%)
AD	111	74	21	0.676 (0.598 - 0.753)	77.9% (68.6% - 85.1%)	94.6% (92.6% - 96.1%)	66.7% (57.5% - 74.8%)	96.9% (95.2% - 97.9%)

Abbreviations: PD: primary diagnostic, AD: aggregated diagnostic, No.: number, TDC: teledermatology consultations, TP: true positive, FN: false negative, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

4.2. Project II.

4.2.1. Patient data

A total of 266 patients were included in our study. The diagnosis of MM was proven in 127 cases (161 image sets) by histological examination. 66 out of all were diagnosed with superficial spreading melanoma (52 %), 18 with nodular melanoma (14.1%), 21 with in situ melanoma (16.6%), 3 with acral lentiginous melanoma (2.4%), 1 with lentigo maligna melanoma (0.8%), while 18 was unclassified (14.1%). Six patients had SK-like MM (6 image sets). The mean age of all patients with melanoma was 64.09 ±13.55 years (female-male ratio: 45.6%-54.3%). 139 patients (319 lesions with 319 image sets) were involved in the study with the diagnosis of SK. 30 patients had MM-like SK (52 image sets). The mean age of patients with all types of SK was 70.19 ±11.147 years (female-male ratio: 44.6%-55.4%). Representative images of MM, SK, SK-like MM and MM-like SK are shown in Figure 7.

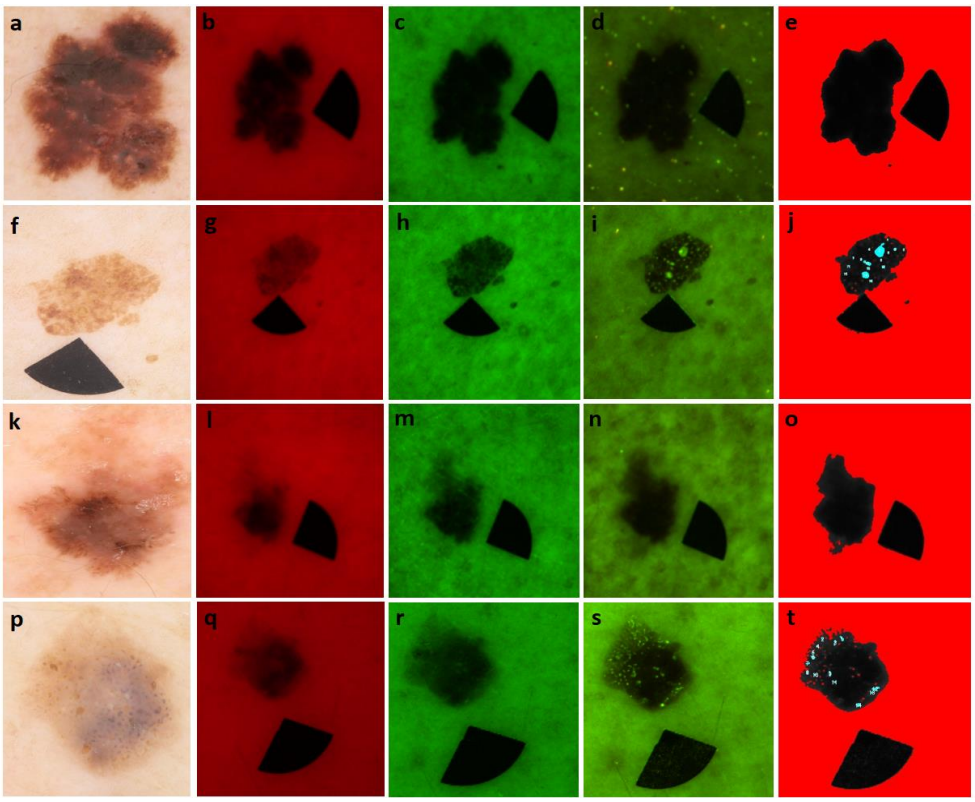

Figure 7. Representative dermoscopic and multispectral LED images of MM (a-e), SK (f-j), SK-like MM (k-o) and MM-like SK (p-t). Dermoscopic images (a, f, k, p), red channel (b, g, l, q),

green channel (c, h, m, r), autofluorescence channel (d, i, n, s). Milia-like cysts and comedo-like openings are visualized in the autofluorescence channel as bright particles in SK (i) and MM-like SK (s) lesions. Particles are visualized in blue (j, t) with the Overlay Masks option of the ImageJ software after threshold processing (141). MSI and dermoscopic images were taken at the Department of Dermatology, Venereology and Dermatooncology.

4.2.2. SK index

After logarithmic transformation, SK index values of SKs were proved to be significantly higher compared to MMs. There was no significant difference between SK-like MM and MM-like SK (Figure 8).

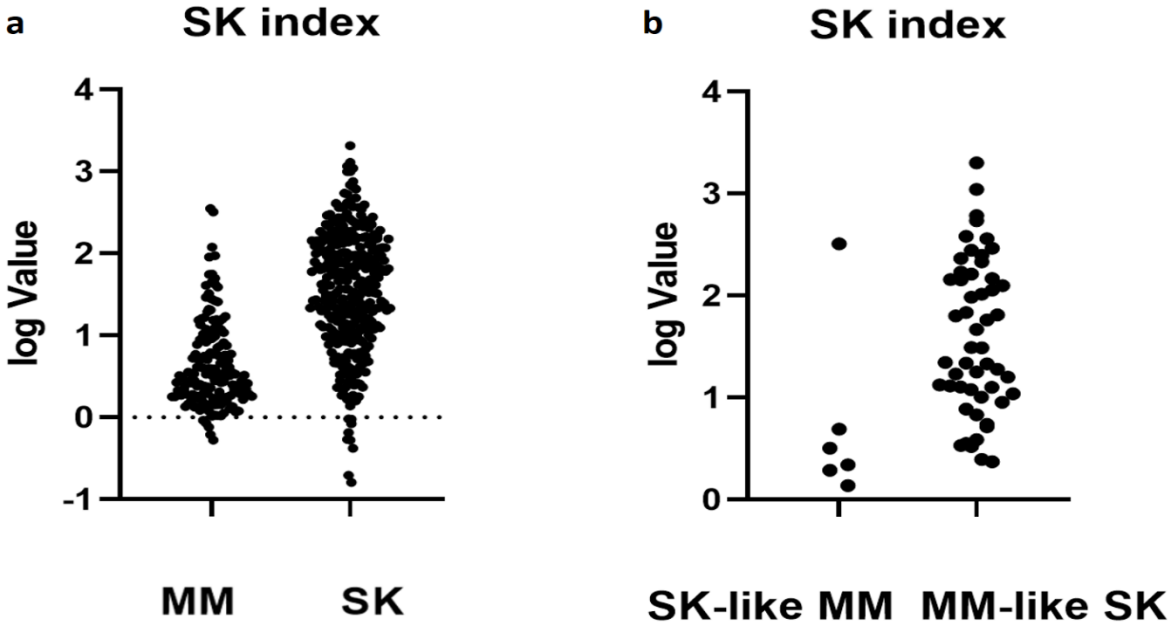

Figure 8. Comparison of log SK index values - MM with SK (a) and SK-like MM with MM-like SK (b). Logarithmic transformation of the SK index values was performed. Welch's t-tests were used for statistical analysis to compare SK index values between lesion groups after logarithmic transformation. Means ± SD: 0.649 ± 0.528 (MM) vs. 1.565 ± 0.729 (SK), $p < 0.0001$ (**a**); 0.745 ± 0.747 (SK-like MM) vs. 1.607 ± 0.884 (MM-like SK), $p = 0.06$ (**b**) (Unpublished results).

4.2.3. Threshold optimization

Threshold determination was based on the results of ROC analyses. The selection method of the equivalent threshold was chosen to equally identify both MM from SK and SK-like MM from MM-like SK, as shown in Figure 9. The 30 value of the SK index was selected as

the optimal threshold. Lesions below this value were identified as MM or SK-like MM, while lesions above 30 were identified as SK or MM-like SK.

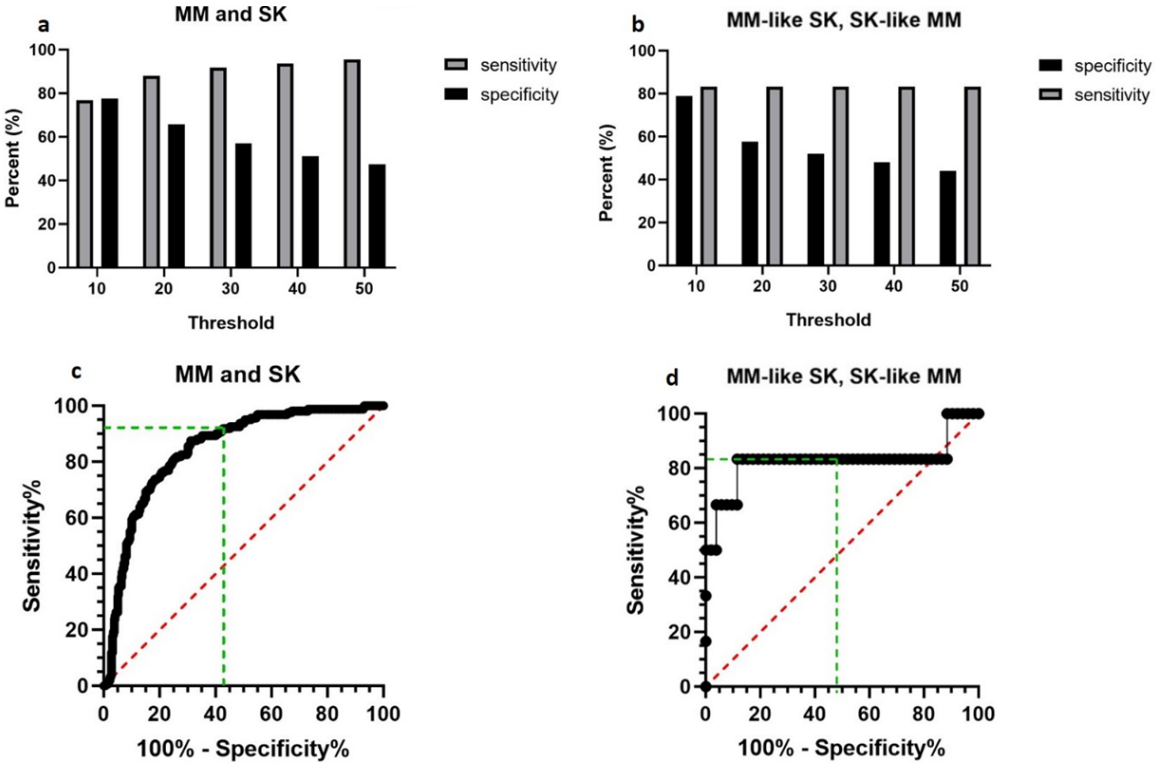

Figure 9. Setting the equivalent threshold for the differentiation of both MM from SK and SK-like MM from MM-like SK. The Area Under the Curve (AUC) was 0.844 (patients: MM, control: SK, 95% CI: 0.8085 – 0.8811, $p < 0.0001$) on the MM and SK ROC curve. AUC was 0.826 (patients: SK-like MM, control: MM-like SK, 95% CI: 0.5681 – 1.000, $p = 0.0092$) on ROC curve of the MM-like SK and SK-like MM comparison. Different SK index values were used to determine the optimal threshold, which could provide appropriate diagnostic parameters for the differentiation of MM from SK and MM-like SK from SK-like MM group **(a, b).** The 30 value of SK index proved to be the most suitable threshold for screening, as the sensitivity reached 91.88% (95% CI: 86.60% - 95.19%), while specificity was 57.05% (95% CI: 51.57% - 62.37%) (**a, c**). PPV was 51.76% (95% CI: 45.96% - 57.51%), while NPV reached 93.33% (95% CI: 88.93% - 96.06%). The 30 threshold was also suitable with a sensitivity of 83.3% (95% CI:43.65% - 99.15%) and specificity of 51.9% (38.69% - 64.90%) to identify MM-like SK from SK-like MM (**b, d**). The PPV reached 16.67% (95% CI: 7.34% - 33.56%), while NPV was 96.43% (95% CI: 82.29% to 99.82%). The red diagonal dotted line represents a non-discriminatory test, the green dotted line represents appropriate diagnostic parameters with the application of the 30 values of the SK index as threshold (**c**, **d**) (141).

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5. Discussion

The COVID-19 pandemic presented the world with unprecedented challenges and highlighted the importance of novel skin cancer screening technologies in early 2020 (22). Health care systems were under tremendous pressure, thus providing primary care and various skin cancer screening opportunities appeared to be challenging (142). Emergency conditions were the only exceptions (143). This situation has led to a sudden demand for the implementation of telemedicine all around the world (144). Although others have published their experiences with TD and skin cancer screening, most of these findings represented the service of teledermoscopy before the pandemic era (51, 52, 145). In our first project, the aim was to evaluate the effectiveness of a store-and-forward TD system for skin cancer screening during the first wave of the COVID-19 pandemic. Our findings characterized the use of TD in a real crisis situation, when dermatologists could rely on macroscopic images sent by the patients via a mobile phone application.

In the literature, few studies have been carried out using macroscopic images, which were most commonly taken by health care professionals. (52, 146). Moreno-Ramirez et al. (2007) investigated the efficacy of TD in a large population (890 patients), in a study similar to ours. They estimated perfect agreement (κ=0.81) with the use of macroscopic images taken by digital cameras (134). Our results were close to their calculation as the overall concordance indicated substantial agreement according to both primary (81.2%, κ=0.769) and aggregated diagnoses (87.9%, κ=0.754). Lamel et al. (2012) was the first to evaluate the efficacy of TD based on digital images taken directly by mobile phone camera in 87 patients with 137 lesions. They measured the primary diagnostic concordance as 0.60, while the aggregated diagnostic concordance was 0.62 (147). Markun et al. (2017) reached slight agreement (77.5%, κ=0.20) with the application of a mobile phone camera in 195 lesions (148). Clarke et al. (2021) took digital images of the lesions when patients applied for FTF examination in outpatient care. Later the records were sent for TD evaluation and reported moderate agreement (66.6%, κ=0.60) for the primary diagnosis of 308 lesions (132). Considering these studies, the strength of agreement differs from our result, as we measured higher values. This

could be due to the lower number of participants and the different proportion of easily diagnosed and uncertain lesions in other reports.

In previous studies, overall diagnostic concordance of malignancies varied between moderate and substantial agreement (κ=0.41-0.63), while accuracy ranged from 51% to 87.3% (149-151). We observed a diagnostic accuracy at the higher end compared to the literature by reaching 85.3% with substantial agreement (κ=0.644). We assessed moderate agreement for MMs (κ=0.475) and SCCs (κ=0.560), while substantial agreement was assessed for BCCs (κ=0.714) and AKs (κ=0.739). This could be related to low positive predictive values as a higher number of FP than TP cases were found in the MM and SCC diagnostic groups (Table 4). Before the outbreak of the COVID-19 pandemic, Giavina-Bianchi et al. (2020) investigated the use of asynchronous TD to screen for skin cancer in Sao Paulo, Brazil (149). In this work a mobile application was designed for health care workers to send macroscopic photographs of individuals for online consultation. Our findings showed similarities with their results as substantial agreement was found in cases with BCCs (κ=0.680) and AKs (κ=0.724). In contrast with our results, they evaluated substantial agreement in cases of SCCs (κ=0.627), while only fair agreement was estimated for MMs (κ=0.209). It could be concluded that store-and-forward TD could display similar concordances of skin cancers when the image acquisition is made by patients instead of pretrained professionals.

Considering potential clinical outcomes, proper diagnosis of MM is the most essential compared to SCC and BCC (151). In case of MM (93.3%), SCC (90.5%) and BCC (91%) diagnostic groups, higher sensitivity values were estimated with the involvement of all differential diagnoses and were equivalent with other studies in the literature (52). In comparison with our findings, malignant lesions other than MMs, SCCs, BCCs or AKs have been rarely observed in studies focusing on TD (134, 151). Beer et al. (2020) emphasized during the pandemic era that widespread implementation of TD would serve as an adequate alternative for the diagnosis and follow-up of patients with rare skin cancers such as cutaneous lymphomas (152). The diagnosis of other malignancies was correctly established during TD evaluation in five patients at our department. The availability of medical history

aided the diagnosis correctly in four of these cases. All of these malignancies were eventually found to be recurring tumors. Similarly to us, others have estimated the importance of various telemedicine modalities in the follow-up of oncology patients at the time of the restrictions (153, 154).

Other studies have already highlighted that cases with suspected skin cancer can be referred to FTF examination more quickly with TD compared to conventional outpatient care system (155). This could be particularly true during the first wave of the COVID-19 pandemic, when outpatient care was limited in health care systems (156). From another point of view, the priority could not be to make the correct diagnosis in urgent cases during TD consultations, but to send patients for immediate FTF examination (157). Consequently, reduced time to attend FTF examination is associated with decreased mortality rate and lower cost of the treatment (148, 158, 159). Although the highest number of misdiagnosed cases were found in the high-urgency group, the vast majority of later confirmed MMs, SCCs and other malignancies were categorized to attend immediate FTF examination (Figure 6). In the low-urgency group, 14 of 16 cases of AK were correctly diagnosed. These patients were informed during TD consultation that they should attend FTF examination if restrictions have been lifted. After the first wave of the pandemic, the remaining two misdiagnosed superficial BCCs in the low-urgency group were removed with adequate safety margin, and no further treatment was needed. Therefore, it can be concluded that TD served as an effective triage tool in the pandemic era to send patients with skin cancer for personal examination within a short time.

Among non-malignant pigmented lesions, naevi diagnostic group reached the highest concordance (κ=0.848) with a sensitivity of 91.2%. In case of dysplastic naevi, immediate FTF examination was preferred to reduce the chance of unrecognized MM. For this reason, concordance (κ=0.375) for dysplastic naevi indicated only fair agreement. In contrast, most SKs were diagnosed correctly and indicated substantial agreement (κ=0.780), which was better compared to the results (κ=0.513) of Giavina-Bianchi et al. (2020) (149). Otherwise, similarly to other studies, we concluded that most misdiagnosed SKs were evaluated as FP diagnosis of MM or NMSC (160, 161). Taking into account all diagnostic groups,

haemangiomas showed the highest sensitivity (95.7%) and concordance (κ=0.961) values. All infants were referred to FTF examination with large haemangiomas in a short term to rule out internal vascular malformations and to start the adequate therapy (Figure 6). In line with our findings, Betlloch-Mas et al. estimated very high concordance for haemangiomas (κ=0.924) in pediatric TD care (162). In total, significant proportion of non-malignant lesions was correctly recognized by teledermatologists.

To the best of our knowledge, we were the first to investigate the utilization of TD for the detection of skin cancers in Central Europe. Our store-and-forward type TD provided effective skin cancer care and served as an accurate triage system during the first wave of the COVID-19 pandemic. In contrast with other studies, our findings represented a unique situation when dermatologists could only use macroscopic images taken by patients. After the pandemic, the role of TD could be essential due to the rising incidence of skin cancers and lack of dermatologists (51). From another point of view, combination of macroscopic and dermoscopic images could significantly increase diagnostic performance and reduce unnecessary FTF consultations (52, 163). High-resolution images captured by mobile phones could contribute to the integration of artificial intelligence into TD platforms, which would operate as a decision support system for dermatologists (164, 165). Furthermore, TD could increase access to dermatology care, which would provide population-based screening and alleviate the burden of health care systems (166).

In the second project, the equivalent threshold of an imaging algorithm was determined to optimize the identification of MM from SK with a LED-based MSI device. MM and SK could resemble each other in some cases, thus correct differentiation of these lesions can be complicated even for experienced dermatologists (167). Nowadays, MSI is an emerging technique, which could identify a wide variety of skin diseases (2). Besides rare skin disorders, MSI modalities are developed to serve as a potential adjunct tool to detect skin cancers (168). Setting the appropriate threshold is crucial for the effectiveness of the screening device (169). The screening method for life-threatening diseases should minimize the number of FN test results to provide high sensitivity, even if specificity is lower (170). This was a design feature of our research, as serious consequences of misdiagnosed MMs

are disproportionate to the increased number of FP cases (171, 172). The ROC analysis proved that the MSI device combined with the SK index could significantly discriminate MM from SK as AUC reached 0.844. Bratchenko et al. (2022) utilized convolutional neural network for Raman spectra analysis and obtained an AUC of 0.92 (95% CI: 0.87 - 0.97) for the classification of MM from SK. They reached sensitivity of 90 (95% CI: 0.80 – 0.97) and specificity of 83% (95% CI: 17% - 97%) (173). Although we experienced lower AUC values, direct comparison is limited, as diagnostic performance varies with different diagnostic techniques and the proportion of different lesions (174). In line with our SK index, Christensen et al. (2021) created the discrimination index to characterize lesions with a numerical variable based on the measurements of a hyperspectral imaging device. They estimated significant differences (AUC of 0.800) between MM and benign pigmented lesions, while an appropriate cut-off point was established similarly to us. Besides nevi, some SKs were also included in the benign lesion group, but a high proportion was incorrectly classified with the use of the discrimination index (175). In general, a large number of inaccurately diagnosed SKs have been already observed with different imaging modalities as lesions can manifest wide variety of morphological characteristics (176).

The clinical diagnosis is subjective, so while one dermatologist may classify a lesion as SK-like MM, another may recognize it as MM (119). Consequently, a collective threshold was chosen to ensure adequate diagnostic performance to differentiate both MMs from SKs and SK-like MMs from MM-like SKs. Despite the fact that the SK index values of SK lesions were significantly higher, determination of the threshold was challenging. This could be attributed to the large variation of the SK index values within each lesion group. Therefore, the 30 value of the SK index was chosen as the equivalent threshold, which resulted in a sensitivity of 91.88% and specificity of 57.05% for the identification of MMs from SKs. Spyridonos et al. (2021) used artificial intelligence to analyze dermoscopic images and reached a sensitivity of 78.6% and a specificity of 84.5% to differentiate directly MM from SK (119). Despite they observed lower number of FP cases, we managed to reach higher sensitivity. Other studies combined artificial intelligence with MSI and found an average sensitivity of 92.9% and specificity of 43.6%. Although the main focus of these

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projects was to identify MM from naevi (177). In the future, our LED-based MSI device could be a preferable adjunct tool to decrease inter-physician variability and standardize the differentiation of MM from SK. In addition, early detection of MM with atypical morphology could reduce mortality rates and the number of unnecessary diagnostic examinations (178, 179).

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6. Conclusion

6.1. Project I.

During the first wave of the COVID-19 pandemic, a mobile phone-based store-and-forward teledermatology system was set up at the Department of Dermatology, Venereology and Dermatooncology of Semmelweis University in Budapest, Hungary. Based on our findings the following statements can be said:

1. Teledermatology serves as an effective triage tool to refer patients with skin cancer for personal examination when outpatient care is restricted for any reason.
2. Teledermatology can ensure effective detection of MM in real crisis situations when macroscopic images are not taken by health care professionals.
3. Teledermatology enables reliable BCC and SCC screening, when access to personal visits is limited.
4. Teledermatology may be considered as an appropriate alternative of personal examination to detect benign skin lesions, such as SKs, haemangiomas and warts.

6.2. Project II.

The handheld LED-based MSI device has the potential to serve as an accurate screening tool. We have come to a conclusion:

1. Determination of the appropriate threshold of the SK index algorithm is needed to optimize the differentiation of both MM from SK and SK-like MM from MM-like SK.

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7. Summary

Skin cancers are known to be the most common malignancies in the Caucasian population (180). Furthermore, the incidence of both MM and NMSC are on the rise globally (181). Early detection of skin cancers is pivotal to decrease mortality rates and minimize health care costs (182). In the past decades, dermoscopy has become the most established non-invasive imaging method for screening (85). However, skills to use dermoscopy properly requires extensive training that makes specialists rare and may lead to limited accessibility in remote areas (183). Nowadays, various non-invasive technologies have been investigated to supplement or replace conventional methods (168). Widespread use of digital cameras and mobile phones are suitable for patients to refer suspicious skin lesions to TD consultation (184). Besides high-resolution macroscopic images, parallel assessment of dermoscopic images improves diagnostic accuracy as well (52). To sum up, several studies have already established that TD could represent a fast and cost-effective way to screen skin cancers (2). After the outbreak of the COVID-19 pandemic, an unprecedented need occurred for the implementation of TD services all around the world (185). As a result, a store-and-forward type TD service was established for the first time in the Hungarian health care when outpatient care was restricted. In our four month experience TD proved to be suitable for dermatologists to diagnose MM and NMSC with high diagnostic accuracy. From another point of view, every suspected life-threatening condition (MM, SCC and other malignancies) were sent for personal examination in a short time to confirm the diagnosis and initiate the adequate treatment. MSI is another noninvasive imaging modality that has the potential to revolutionize early recognition of skin cancers (97). MSI can be implemented into mobile phones and used as a single handheld device (186). We optimized the algorithm of a LED-based MSI device to provide high diagnostic performance for the identification of MM from SK and SK-like MM from MM-like SK. In the future, our device may serve as potential screening tool in the hands of non-expert health care professionals with the appropriate accuracy. Further investigations are also required to integrate artificial intelligence into both TD and MSI to improve efficacy and decrease the burden of the health care systems.

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9. Bibliography of the candidate's publications

9.1. Publications directly related to this thesis

1. **Jobbágy A**, Kiss N, Meznerics F A, Farkas K, Plázár D, Bozsányi S, Fésűs L, Bartha Á, Szabó E, Lőrincz K, Sárdy M, Wikonkál NM, Szoldán P, Bánvölgyi A. (2022) Emergency Use and Efficacy of an Asynchronous Teledermatology System as a Novel Tool for Early Diagnosis of Skin Cancer during the First Wave of COVID-19 Pandemic. *Int J Environ Res Public Health*, 19(5):2699. **IF: 3.390**

2. Bozsányi S, Farkas K, Bánvölgyi A, Lőrincz K, Fésűs L, Anker P, Zakariás S, **Jobbágy A**, Lihacova I, Lihachev A, Lange M, Bliznuks D, Medvecz M, Kiss N, Wikonkál NM. (2021) Quantitative Multispectral Imaging Differentiates Melanoma from Seborrheic Keratosis. *Diagnostics*, 11(8):1315. **IF: 3.706**

3. **Jobbágy A**, Meznerics F A, Farkas K, Plázár D, Bozsányi Sz, Fésűs L, Róbert L, Schveibert Á, Kuzmanovszki D, Szoldán P, Lőrincz K, Kiss N, Wikonkál N, Sárdy M, Bánvölgyi A. (2022) Teledermatology: the new era of digitalization in dermatology care. *Bőrgyógyászati és Venerológiai Szemle,* 98(3):100-107. **IF:-**

9.2. Publications not related to this thesis

1. Polak K, **Jobbágy A**, Muszyński T, Wojciechowska K, Frątczak A, Bánvölgyi A, Bergler-Czop B, Kiss N. (2021) Microbiome Modulation as a Therapeutic Approach in Chronic Skin Diseases. *Biomedicines*, 9(10):1436. **IF: 6.081**

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6. **Jobbágy A**, Fésűs L, Kiss N, Lőrincz K, Sárdy M, Wikonkál N, Bánvölgyi A. (2020) Hyperhidrosis: clinical classification and treatment options. *Bőrgyógyászati és Venerológiai Szemle,* 96(1):36-43. **IF: -**

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