INTRODUCTION AND OBJECTIVES

Skin malignancies are the most common type of cancer diagnosed in the United States, and Australia and New Zealand lead the world in the number of diagnosed skin malignancies per capita [1, 2]. Incidence rates of skin cancer, including malignant melanoma and non-melanoma skin cancer (NMSC), have increased by 44% and 77%, respectively, in recent decades [3]. However, if detected early, skin cancer has proven to be highly curable.

The standard skin cancer diagnosis method is visual inspection with diagnostic aids, but the accuracy is dependent on the clinician's experience [4]. Recently, technology-based methods have been developed that significantly improve the non-invasive diagnosis accuracy, but they require but they require significant training (e.g. dermoscopy) and/or have high implementation cost (e.g. total body photography, confocal microscopy)"

Elastic-scattering spectroscopy (ESS) is a specialized form of spectroscopy that shows great promise for skin cancer detection [6] —

particularly when used with interpretative systems based on machine learning (ML) models, such as convolutional neural networks (CNN). This study evaluates the effectiveness and performance of a hand-held ESS-based device, which uses a spectral classification algorithm, as an objective, non-invasive tool for evaluating patients with skin lesions suggestive of melanoma, basal cell carcinoma, and squamous cell carcinoma [7].

MATERIALS AND METHODS

The Handheld ESS device, measures spectra of skin lesions and uses CNN to classify the lesion's scanned properties against those of known malignant and benign lesions. The output of the ESS classifier is "Investigate Further" or "Monitor". Additionally, for "Investigate Further" classified lesions, a score from 1 to 10 is provided which corresponds to the amount of spectral similarity a lesion demonstrates to malignant lesions in studies with 10 representing the highest amount.

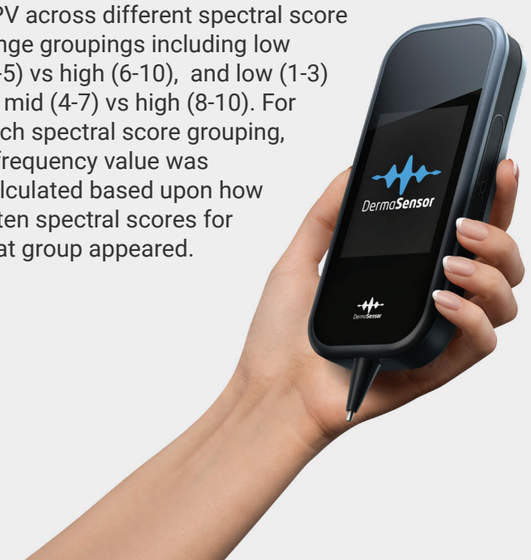
The algorithm implemented in the Handheld ESS device was trained and validated using over 11,000 spectral recordings from nearly 2,300 skin lesions, including histologically confirmed melanoma and NMSC; as well as biopsied and unbiopsied benign lesions, as identified or diagnosed by board-certified dermatologists [6].

A prospective, single-arm, blinded, Investigator-Initiated study was conducted in New Zealand at a single site from 2020-2021 by a board-certified dermatologist. The study included benign lesions deemed to be suggestive of skin cancer to less dermatologically trained clinicians (e.g. primary care physicians) and assessed anatomical, clinical and patient risk factors to diagnose whether a lesion was benign or malignant and recorded how confident the investigator was in his assessment (high vs low).

The Investigator then scanned the lesion with the Handheld ESS device and took a digital photo of the lesion. Lesions considered to be malignant were biopsied per the investigator's standard of care and pathology reports were used to determine final diagnosis.

The clinical endpoints included diagnostic sensitivity and specificity of the Handheld ESS device using dermatologist assessment and pathology results for diagnosis of malignant and benign lesions. Sensitivity is the probability of a malignant lesion being correctly categorized as "Investigate Further". Specificity is the probability of a benign lesion being correctly categorized as "Monitor". Confidence intervals were calculated using the Wilson method, as outlined in Saha et al. (2016) [8] to account for potential within-subject correlation. Positive predictive values (PPV) and negative predictive values (NPV) were calculated from these results based upon the trial population.

Further analysis was conducted for "Investigate Further" categorized lesions to examine the PPV across different spectral score range groupings including low (1-5) vs high (6-10), and low (1-3) vs mid (4-7) vs high (8-10). For each spectral score grouping, a frequency value was calculated based upon how often spectral scores for that group appeared.



RESULTS

For this interim analysis, a total of 509 lesions from a private practice serving a heavily sun-damaged population in an area of New Zealand having one of the world's highest incidences of Melanoma[9] were scanned with the Handheld ESS device from February 2020 to July 2021. Final analysis revealed that 89% of the enrolled lesions were benign and 11% were categorized as malignant. There were a variety of lesion types enrolled including Seborrheic keratoses (SK, 43%), Actinic keratoses (AK, 22%), Benign melanocytic nevi (21%), Basal cell carcinomas (BCC, 7%), Squamous cell carcinomas (SCC, 3%), Melanomas (1.2%) among others. There were no adverse events reported related to device usage.

The overall sensitivity of the Handheld ESS device in detecting malignant skin lesions was 98.2% (CI: 90.2-99.9%).

Table 1: Concordance Between Device Output and Pathology Results

Device Reading	Pathology Results		Total
	Benign	Malignant	
Benign	211 (46.5%)	1 (1.8%)	212
Malignant	243 (53.5%)	54 (98.2%)	297

Overall specificity for detecting benign skin lesions was 46.5% (CI:41.8-51.2%) (Table 2).

The NPV of a Monitor output from the Handheld ESS device was 99.5% (CI: 97.4-99.9%), the associated PPV for all spectral scores in the Investigate Further category was calculated at 18.1% (CI: 14.0-23.1%) and the PPV for the Investigate Further category spectral score range grouping 8-10 was 58.6% (CI: 38.9-76.5%). (Table 2b, Table 3b).

Table 2a: Device Sensitivity and Specificity for Detecting Malignant Lesions

	Result	Exact 95% CI
Specificity	46.5% (211/454)	41.8% to 51.2%
Specificity Excluding AKs	52.6% (181/344)	47.2% to 58.0%
Sensitivity	98.2% (54/55)	90.3% to 100.0%

Table 2b: Device NPV and PPV with and without AKs for Detecting Malignant Lesions

	Result	Exact 95% CI
NPV	99.5% (211/212)	97.4% to 100.0%
NPV Excluding AKs	99.5% (181/182)	97.0% to 100.0%
PPV	18.2% (54/297)	14.0% to 23.0%
PPV Excluding AKs	24.9% (54/217)	19.3% to 31.2%

Tables on the next flap present PPV and frequency distributions for different spectral score groupings (Table 3 a and b) of "Investigate Further" categorized lesions in the trial.

RESULTS, CONT.

Across all groupings, a higher spectral score was directly correlated with an increased positive predictive value.

Table 3a Spectral Score Groupings 1-5 and 6-10		
Spectral Scores Groupings	PPV	Frequency of 'Investigate Further' Lesions
1-5	*8.5%*	*76.8%*
6-10	*42.4%*	*23.2%*

Table 3b Spectral Score Groupings 1-4, 5-7 and 8-10		
Spectral Scores Groupings	PPV	Frequency of 'Investigate Further' Lesions
1-4	*71.%*	*64.2%*
5-7	*27.9%*	*28.7%*
8-10	*58.6%*	*7.1%*

DISCUSSION AND CONCLUSION

The Handheld ESS device's technology has a high sensitivity at 98.2% for detecting malignant skin lesions as demonstrated in this study and a specificity of 46.5%. The negative predictive value of 99% highlights the accuracy of the Handheld ESS device in detecting malignant disease and reassures dermatologists and other clinicians when a "Monitor" output is in concordance with their ongoing clinical evaluation.

The addition of spectral scores to the "Investigate Further" output expands the objective applicability of the Handheld ESS technology and helps inform providers as they conduct their medical decision-making process on appropriate management of a skin lesion found to be suggestive of melanoma, basal cell carcinoma, and/or squamous cell carcinoma.

The study's inclusion of lesions suggestive of skin cancer to those less trained than a dermatologist suggests a potential beneficial role of the device in helping reduce unnecessary biopsies based upon the specificity rate outcomes. Additionally, as a portable, affordable device, the tool's spectral score has the potential to inform prioritization of care for patients with large numbers of pigmented lesions particularly in rural areas where mole mapping may not be available.

The relationship between primary care and specialty care is a critical part of the patient journey particularly for dermatology where accessibility and waiting times pose a general problem.[10] As levels of skin cancer continue to rise in many countries around the world, **the use of such a device may contribute to early identification and management of patients presenting with malignant skin lesions and increase efficiency and efficacy of referrals.**

Further studies should include a comparison of the device with Dermoscopy on the impact on management accuracy and an evaluation of outcomes when combining Dermoscopy with the device.

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DISCLOSURES

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Use of **Elastic-Scattering Spectroscopy** and **Machine Learning** when **Assessing Skin Lesions** Suggestive of **Skin Cancer**

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