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Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multi-centre, prospective and blinded clinical trial on efficacy and safety

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Abstract

Aim: To assess the effectiveness and safety of the Nevisense system in the distinction of benign lesions of the skin from melanoma with electrical impedance spectroscopy.

Method: This multi-center, prospective, and blinded clinical study was conducted at 5 US and 17 European investigational sites. All eligible skin lesions in the study were examined with the Nevisense electrical impedance spectroscopy system, photographed, removed by excisional biopsy and subjected to histopathological evaluation. A post-procedure clinical follow up was conducted at 7 +/- 3 days from the initial measurement.

A total of 1,951 subjects with 2,416 lesions were enrolled into the study; 1,943 lesions were eligible and evaluable for the primary efficacy endpoint (including 265 melanomas - 112 in situ and 153 invasive melanomas with a median Breslow thickness of 0.57 mm, 48 BCC and 7 SCC).

Results: The observed sensitivity of Nevisense was 96.6% (256 of 265 melanomas) with an exact one-sided 95% lower confidence bound estimated at 94.2% and an observed specificity of 34.4% with an exact two-sided 95% confidence bounds estimated at 32.0% to 36.9%. The positive and negative predictive value of Nevisense was 21.1% and 98.2%, respectively. The observed sensitivity for non-melanoma skin cancer was 100% (55 of 48 BCC and 7 SCC) with an exact two-sided 95 confidence bound estimated at 93.5% to 100%.

Conclusion: Nevisense is an accurate and safe device to support clinicians in the detection of cutaneous melanoma.

Key Words: safety and efficacy – electric impedance – melanoma –skin cancer – dermoscopy – early detection

Introduction

Early detection of melanoma is vital for treatment outcome and survival. Treatment of early stage melanoma is mostly curative, whereas thicker melanomas are associated with a poor 5-year survival rate due to increased metastatic potential[1-2]. In most instances physicians feel fairly confident when distinguishing non-suspicious from suspicious lesions by relying on unaided eye examination, dermoscopy assessment, and patient history. However, cutaneous melanomas can be misdiagnosed as benign while a significant proportion of benign lesions are unnecessarily excised. The sensitivity of

the clinical diagnosis of cutaneous melanoma with unaided eye examination is around 60% and can improve significantly with the use of dermoscopy[3-37]. Although progress has been made in the detection of melanoma it still poses a challenge, especially in its earlier stages. Therefore, a number of technologies utilizing either visual or non-visual techniques, such as total body photography[38-39], confocal microscopy[40-41], Raman spectroscopy[42-43], multispectral imaging[44], automated dermoscopy image analysis[45], genomic detection of melanoma by stratum corneum stripping[46], and electrical impedance spectroscopy (EIS)[47-48] have been developed to support physicians to detect melanomas at an earlier stage. In a previous study, the EIS-based Nevisense system was shown to have the potential to be used as an adjunct diagnostic tool, although it was concluded that more clinical data was necessary to ensure safety and effectiveness of the system[48].

The aim of this clinical investigation was to assess safety and effectiveness of the Nevisense system designed to aid in the discrimination between benign lesions and primary cutaneous melanoma. In this paper, results are presented and discussed in the context of clinical utility.

Materials and Methods

Ethical Conduct

The Guidelines of the World Medical Association Declaration of Helsinki in its revised edition, the Guidelines of Good Clinical Practice (GCP), ISO-14155 as well as the demands of national and data protection laws and other applicable regulatory requirements were followed. Registration number in ClinicalTrials.gov NCT01077050.

Study Design and Data Acquisition

Recruitment into this blinded multi-center prospective study was conducted at 5 US and 17 European investigational sites (Sweden, Germany, Austria, Hungary, United Kingdom, and Spain). Potential study subjects were screened according to the inclusion and exclusion criteria. Subsequent to written informed consent subjects were asked about their medical history and a clinical evaluation was performed. A photograph and dermoscopic image of each included lesion was taken before and after Nevisense measurements to document evaluation according to the protocol. In accordance with standard clinical practice, eligible and evaluable lesions were excised and subjected to the investigational site's histopathology evaluation and managed accordingly.

A further histopathological evaluation was completed by a panel of three experienced histopathologists who evaluated each lesion independently and blinded from the investigational site's original histopathology diagnosis. In the case of agreement among the experts, the diagnosis was considered as the study's histopathological gold standard (HGS). If there was significant disagreement among the pathology reviewers on whether the lesion represented a malignancy, the respective slides were submitted to two additional experts whose diagnosis was then chosen as the HGS if they reached

an agreement. In case of disagreement by the two additional reviewers, the corresponding lesion was excluded from the efficacy analysis.

A post-procedure follow up either by a telephone call or a subject´s visit at the investigational site was conducted at 7 +/- 3 days after the Nevisense evaluation, at which time the subject was evaluated for any adverse events.

Inclusion and Exclusion Criteria

Subjects with skin lesions selected for total excision to rule out melanoma were asked to participate in the study. To minimize selection bias, all lesions from a subject destined for excision were eligible for the study. To ensure a broad spectrum of excised lesions, dermatologists were encouraged to enrol a mix of lesions with an even distribution of low, medium, and high risk lesions. The exclusion criteria were derived from previous studies conducted with the investigational device[47-48] and are listed in Table 1.

Review of images

The photographs and dermoscopic images were taken with a Sony DSC-W290 and a hand-held dermoscope (DermLite II PRO HR®; 3Gen). The images were reviewed by three dermatologists with 2-5 years of experience in dermoscopy assessment. The option to reach out to additional experienced dermoscopist in difficult cases was allowed. Lesions were classified according to, the clinical ABCD rule[49-50], dermoscopic ABCD rule[51], 7-point checklist[52], and the overall suspicion of malignancy classified by the visual classification board from 0 (benign) to 10 (malignant). This was conducted to ascertain a standardized clinical and dermoscopic classification of the degree of suspicion of malignancy of each study lesion.

Blinding

The case report forms, the Nevisense measurements, and the histopathological reports were kept blinded from the sponsor by a Contract Research Organization (CRO) until classification of all lesions in the pivotal study had been made.

The investigators were blinded to the entire diagnostic information of the device to ensure that the investigational device could not bias the clinical judgment nor affect the patient clinical management in any way.

Electrical Impedance Spectroscopy (EIS) Measurements

Electrical impedance was measured with the Nevisense system (SciBase AB, Stockholm, Sweden) equipped with a spring-loaded probe and a disposable electrode having an active area of approximately 5x5 mm^2. Prior to measurement, the skin was moistened for 30 seconds with physiological saline solution after which a reference measurement of healthy skin close to the lesion was performed. The procedure was then repeated on the lesion under study. The system measures the

overall electrical resistance and reactance at 35 different frequencies logarithmically distributed between 1.0 kHz and 2.5 MHz at four depth settings with a total of 10 permutations. The applied voltage and resulting current is limited to 150mV and 75μA respectively and is not sensed by the patient. Measurements take approximately 8 seconds and within seconds the system computes both a score (0 - 10) and a dichotomous output (EIS negative/positive) at a fixed cut-off. The fixed threshold is set at 4, i.e., scores less than 4 are EIS negative and scores 4 or greater are EIS positive. The dichotomous output was used in the study to demonstrate the sensitivity and specificity endpoints.

Study Objective and End-point

The objective of this clinical investigation was to determine the safety and effectiveness of the Nevisense device designed to help distinguish between cutaneous melanoma and benign lesions of the skin, using EIS relative to the HGS.

This study had two co-primary analyses, aiming to demonstrate the accuracy of the Nevisense device: (1) One-sided exact 95% confidence bound of the sensitivity to detect cutaneous melanoma above 90% (sensitivity ≥ 0.90 to detect melanoma) and (2) non-random at the given sensitivity, i.e. sensitivity + specificity > 1.0.

The safety of the Nevisense analysis was measured by the occurrence and incidence of all adverse events reported for study subjects throughout their participation in the study. The primary safety endpoint was achieved if no serious adverse events related to the device had occurred.

Additional Analysis

Clinical histopathological gold standard

To estimate the sensitivity and specificity of the clinical histopathological gold standard used for treatment, i.e. investigational site's histopathological diagnoses were compared with the study HGS. The analysis was conducted on the eligible and evaluable lesions.

Unaided lesion evaluation and dermoscopy assessment

The observed sensitivity and specificity of the visual reference standard was calculated using the cut-offs pre-specified from literature and the outcome of the different visual classification algorithms.

Results

Study Subjects and Skin Lesions

A total of 1951 subjects with 2416 lesions were recruited between March 2010 and November 2011. The demographic characteristics of the study population are presented in Table 2. The subjects' median age was 48 years ranging from 18 to 91 years; the female proportion was 51.9%; most of the subjects (97.1%) were white; the majority of subjects were either of Fitzpatrick skin type 2 or 3. No

significant differences in the demographic characteristics between the enrolled and the eligible lesions were observed.

Table 3 presents the distribution of reasons for exclusion from the effectiveness analysis. Out of the 2416 registered lesions a total of 473 were excluded, mainly due to investigator oversight or the inability to render a final histopathological diagnosis. Approximately one-fourth of the excluded lesions were device related (inadequate reference measurement quality or general device failures).

Performance of Nevisense

The dichotomous outcome of the Nevisense system was compared with the HGS. Of the 1943 eligible and evaluable lesions (Table 4), 265 (13.2%) were cutaneous melanoma, 55 (2.8%) were non-melanoma skin cancer including basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) of which Nevisense correctly identified 256 melanomas and all 55 non-melanoma skin cancers, yielding an observed sensitivity of 96.6% and 100%, respectively. A total of 157 nevi with severe dysplasia were included of which Nevisense gave a positive reading for malignancy in 132 cases. Seven out of eight actinic keratoses gave a positive reading. One Merkel cell carcinoma was included, which was correctly identified as malignant. Out of the remaining 1457 lesions, 501 were diagnosed as negative, yielding an observed specificity of 34.4%. No significant difference in the presented sensitivity and specificity was encountered, when the possible dependency in outcome between the lesions of the same subject was accounted for through a generalized linear mixed model. The positive predictive value (PPV) of Nevisense was 21.1% and the negative predictive value (NPV) was 98.2%. The Nevisense score was compared with lesion severity and, as can be discerned from Fig. 1, a clear step function is evident for the score outcome with increasing lesion severity.

Nevisense False Negatives (FN)

Of the nine melanoma classified by Nevisense as FN, seven had sufficient image quality to render an outcome for the ABCD dermoscopy rule and 7-point checklist by the reviewing dermatologists. The overall visual malignancy grading scored two of this subset of seven melanomas as positive with a score of 4, and five as negative with a score of 0 to 2.

Three of the nine FN lesions were identified on patients <30 years. The median diameter of these 9 lesions was 4 mm (range 2-8 mm) of which five had a diameter less than 6 mm. Seven were in situ and 2 were early invasive melanoma (T1a) with a Breslow thickness of 0.4 mm and 0.6 mm, respectively. The lesions were located on the following anatomical locations: lower extremities (4), upper extremities (1), upper back (2), buttocks (1), and facial area (1).

Performance of the unaided examination and dermoscopy assessment

To determine the diagnostic uncertainty of the study lesions, a post-excisional performance study of unaided examination and dermoscopy was completed. Of the 1943 eligible and evaluable lesions,

1701 (238 melanomas) had sufficient image quality to enable a classification according to the ABCD rule, ABCD dermoscopy rule and the 7-point checklist.

The result of the dermoscopic and investigational site's histopathological evaluations in conjunction with the Nevisense are presented in Table 5, and grouped according to the study's HGS.

The observed sensitivity with the ABCD dermoscopy rules for melanoma detection with a cut-off of 4.75 and 5.45 was 54.2% and 47.1% with an observed specificity of 90.1% and 94%, respectively.

The original and weighted 7-point checklists' observed sensitivity for melanoma detection was 49.2% and 60.9% with an observed specificity of 94.2% and 89.2%, respectively.

The observed sensitivity for the reviewing dermatologist, when considering the combined features for malignancy (overall visual board malignancy grading), was 70.6% with an observed specificity of 81.4%.

Performance Investigational Site's Histopathology

The observed sensitivity and specificity for melanoma of the investigational site's histopathologists was 85.0% (225/265) and 98.1% (1429/1457), respectively. The observed sensitivity increased with melanoma thickness, from 73.2% for Tis to 100% for T2b-T4.

Safety

A total of 36 adverse events (AEs) were observed in 28 subjects (1.5%), out of which only 3 AEs that occurred on three subjects (0.2%) were defined as definitely related to the device; All AEs related to the device were of mild severity. No serious adverse event, serious adverse device effect or unanticipated adverse device effect was observed throughout the entire study.

Discussion

Melanoma detection often poses a challenge in equivocal lesions or in patients with many atypical nevi. Therefore, a component of the clinical work up and interpretation incorporates not only lesion-specific information, but also patient derived melanoma risk factors, which includes a comparative analysis of all lesions present on a patient[53-56]. Even if the clinical decision is based on a collective interpretation of all the presently available clinical risk factors, melanomas can still be misdiagnosed as benign lesions[37]. Since early detection of melanoma is vital for treatment outcome and survival[1-2], additional objective information that could assist in the early detection of melanoma could significantly reduce the morbidity related to the unnecessary removal of benign lesions and has the potential to improve mortality through early diagnosis.

In the present study, a post-excision evaluation of the isolated performance of dermoscopy was conducted according to three dermoscopic classification algorithms in which the evaluator was presented with the clinical and dermoscopic images of all excised lesions from a patient. The results show that a considerable amount of the included melanomas were equivocal lesions with insufficient dermoscopic criteria to be classified as malignant.

There are several plausible explanations to the relatively low sensitivity, 47.1%-70.6%, observed on the post-excisional dermoscopic evaluation with limited clinical data. Firstly, the evaluation was conducted on a cohort of 85% in situ and early invasive melanomas. In addition, the evaluations were completed by dermatologists with 2-5 years' of experience in dermoscopy with additional support in difficult cases. Most importantly, the evaluators did not have the added benefit of comparative analysis of all lesions present on the patients – i.e. they could base their judgment only on the excised lesions.

While the outcome of the dermoscopy assessment might have been different if the lesions would have been evaluated by more experienced dermoscopists, the results of the study likely reflects the dermoscopic acumen of an average dermatologist. It has to be stressed that almost all lesions were removed due to some clinical concern for melanoma, as it would not be ethical to excise lesions deemed benign clinically, except for functional or cosmetic reasons. Since mostly pre-selected equivocal lesions destined for excision were included in the study, the dermoscopic diagnostic performance is not a true reflection of the performance in normal clinical practice. However, it gives an insight to the isolated performance of dermoscopy on equivocal lesions submitted for biopsy, which is the intended use population of Nevisense.

Nevisense Performance

Nevisense was able to achieve a high sensitivity (96.6%) in a melanoma cohort consisting mostly of in situ and early invasive melanoma without fully compromising the specificity (34.4%). The observed sensitivity of the device increases with Breslow thickness, and no invasive melanoma in stage T1b to T4 were missed by the device. Cases where the investigational device gave a false negative reading occurred mostly in small lesions with few or no dermoscopic features and with low cellularity.

Two early-stage invasive melanomas were inaccurately classified as negative, but in both cases compliance with the measurement procedure could not be fully verified. In fact, for one lesion the verification data were missing, and the other lesion had not been fully covered with measurements. Since the system only detects changes that occur directly underneath the electrode it is important that the lesions are measured completely and/or that the most suspicious malignant part of the lesion is measured to ensure as accurate a reading as possible. A review of the 98 lesions excluded due to coverage issues included a total of 22 melanomas, of which the device still accurately classified 20 as positive. These are good results as for some cases only 25% of the surface had been measured with the device, suggesting that even though coverage is important, it is not vital in most cases.

The overall observed specificity was 34.4%. Approximately 1/3 of the equivocal lesions submitted

for biopsy in the study were accurately identified as negative by the device and thus would not have needed a biopsy. Furthermore, the high observed NPV of 98.2% — equal to that of the observed NPV of histology in the study — ensures that few melanomas will be inaccurately left untreated when given a low score by the device.

There are two additional results which are important to highlight. First, a high proportion of seborrhoeic keratoses were inaccurately classified as positive. The high ratio of positive readings was anticipated as this has been observed in previous studies, mainly due to its typical high degree of structural changes compared to normal skin. However, the system is intended to be used by dermatologists or clinicians trained in the diagnosis of skin cancer who will almost always recognize seborrhoeic keratoses clinically and would therefore seldom apply Nevisense to these lesions. Secondly, the observed sensitivity of 100% in non-melanoma skin cancer is extremely valuable as these malignancies should not be left untreated. Few other non-invasive technologies are able to accurately identify non-melanoma skin cancers as well as melanoma.

Clinical Utility

The observed sensitivity and specificity presented do not take into account the clinical information regarding the full extent of the patient's history as well as the comparative analysis with other lesions which has been shown to be very critical in the clinical decision whether to excise a lesion or not. However, in reality clinicians often end up performing single lesion examinations, due to factors such as time constraints, and as such the isolated performance of the dermoscopy evaluation would reflect their diagnostic accuracy[57]. As can be discerned from Table 5, a large part of melanomas included in the study are equivocal lesions and are hard to differentiate from nonmalignant equivocal lesions.

The Nevisense system is intended for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma. The system is designed to be used when a clinician chooses to obtain additional information when considering excision and is not meant to be used to confirm a clinical diagnosis of melanoma. It should be used by physicians trained in the clinical diagnosis of skin cancer to ensure the system result is one element of the overall clinical assessment. Not only should the negative or positive EIS outcome be incorporated into the assessment, but also the EIS score as it is coupled with a lesion's stage and severity.

In summary, Nevisense has been shown to be an accurate and safe device that should be used in conjunction with the clinical risk assessment for patients with suspicion of melanoma in the intended use population. A negative or positive EIS reading in combination with the score outcome should be used as guidance for whether a lesion should be excised or not.

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Author Contribution

Study concept and design: Ulrik Birgersson, Joseph Malvehy, Allan Halpern and SciBase AB. *Acquisition of data:* All authors together with all the principal investigators mentioned in the acknowledgement, except Ulrik Birgersson. *Analysis and interpretation of data:* All authors. *Drafting of the manuscript:* Joseph Malvehy and Ulrik Birgersson *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Efficacy and safety analysis conducted by independent statistical consulting firm. Additional analysis conducted by Ulrik Birgersson. *Funding/Support*: This study was funded by SciBase AB. *Study supervision:* Independet Contract Research Organisation. *Financial Disclosure*: Ulrik Birgersson is employed by SciBase AB. Axel Hauschild, Peter Mohr and Uwe Rheinhold serve as consultants to SciBase AB.

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Tables and figures

Table 1. Exclusion criteria.

#	Exclusion Criteria
1	Men or women of any ethnic group aged < 18 years
2	Subject not willing or able to read, understand and sign the study specific informed consent form
3	Metastases or recurrent lesions
4	Lesion smaller than 2 mm or larger than 20 mm in diameter
5	Lesion located on acral skin, e.g. sole or palm
6	Lesion located on areas of scars, crusts, psoriasis, eczema or similar skin conditions
7	Lesion on hair-covered areas, e.g. scalp, beards, moustaches or whiskers
8	Lesion located on genitalia
9	Lesion located in an area that has been previously biopsied or subjected to any kind of surgical intervention or traumatized
10	Lesion located on mucosal surfaces
11	Lesion with foreign matter, e.g. tattoo or splinter
12	Lesion and/or reference located on acute sunburn
13	Skin surface not measurable, e.g. lesion on a stalk
14	Skin surface not accessible, e.g. inside ears, under nails
15	Skin not intact (measurement area) e.g. bleeding or with clinical noticeable ulceration

Table 2. Demographic characteristics of the enrolled and eligible subjects.

Characteristics	Subjects Enrolled* (n=1950)	Subjects with eligible lesions* (n=1611)
Gender		
Male	929 (47.6)	765 (47.5)
Female	1013 (51.9)	846 (52.5)
Missing	8 (0.4)	0 (0)
Age, median (range), year	48 (18-91)	48 (18-91)
Race and Ethnicity		
Asian	5 (0.3)	5 (0.3)
White	1893 (97.1)	1571 (97.5)
Black or African American	2 (0.1)	2 (0.1)
Hispanic or Latino	29 (1.5)	25 (1.6)
Other	12 (0.6)	8 (0.5)
Missing	9 (0.5)	0 (0)
Fitzpatrick Skin Type		
1. Always burns easily; never tans	136 (7)	117 (7.3)
2. Always burns easily; tans minimally	945 (48.5)	783 (48.6)
3. Burns moderately; tans gradually	635 (32.6)	526 (32.7)
4. Burns minimally; always tans well	192 (9.8)	158 (9.8)
5. Rarely burns; tans profusely	29 (1.5)	23 (1.4)
6. Never burns; deeply pigmented	1 (0.1)	1 (0.1)
Missing	12 (0.6)	3 (0.2)

* All data presented as number (percentage) of subjects, except for age. For one subject, the signed informed consent form could not be located at the site and the data was thus deleted.

Table 3. Reasons for exclusion of lesions from the analysis.

Exclusion Reason	No. Lesions		Source
	No	%	
Lesions included	2416		
Signed Informed Consent Form Missing	1	0,04%	Investigator 11.0%
Withdrawal	17	0,7%	
Not eligible (i.e. inclusion/exclusion)	61	2,5%	
Major Protocol Violation	29	1,2%	
Measurement not acquired	60	2,5%	
Coverage***	98	4,1%	
Not eligible histopathology (preparation quality)	8	0,3%	Pathology 4.1%
Missing histopathology*	39	1,6%	
Inaccurate mapping of histopathology†	7	0,3%	
No Consensus‡	44	1,8%	
Poor Reference Quality**	95	3,9%	Device related 4.5%
Device failure	14	0,6%	
Eligible Lesions	1943		

* No histology slides were/could be provided by the site.

† Provided histology slides were not mapped accurately to the lesion measured.

‡ The consensus board could not reach an agreement on a final diagnosis.

** Inability to obtain a reference measurement with adequate quality after 4 consecutive attempts.

*** Less than 75% of the lesion was covered with measurements, for example a 10x10 mm^2 lesion only measured once was excluded.

Table 4. Observed Sensitivity (Sens) and Specificity (Spec) for Nevisense combined with lower and upper 95% confidence bounds (LCB/UCB), true and false positives/negatives (TP/TN/FP/FN) in the efficacy analysis population differentiated by histopathological lesion type and melanoma thickness.

Type	**Sensitivity**	**TP**[*]	**FN**[*]	**Total**	**LCB**[†]	**UCB**[†]
Melanoma**[¶]	***96,6***	***256***	***9***	***265***	***93,7***	***98,4***
pTis	93,8	105	7	112	87,6	97,5
pT1a	97,9	92	2	94	92,5	99,7
pT1b	100	19	0	19	82,4	100
pT2a	100	24	0	24	85,8	100
pT2b	100	11	0	11	71,5	100
pT3a	100	1	0	1	2,50	100
pT3b	100	3	0	3	29,2	100
pT4a	100	1	0	1	2,50	100
pT4b	N/A	0	0	0	NA	NA
Severe Dysplasia[‡]	***84,1***	***132***	***25***	***157***	***77,4***	***89,4***
Type	**Specificity**	**TN**[*]	**FP**[*]	**Total**	**LCB**[†]	**UCB**[†]
Mild/Moderate Dysplasia	***36,1***	***357***	***631***	***988***	***33,1***	***39,2***
Moderate dysplasia	24,1	80	252	332	19,6	29,1
Mild dysplasia	41,3	212	301	513	37,0	45,7
Dysplastic Lentigo	40,0	2	3	5	5,27	85,3
Structural disorder only	73,3	11	4	15	44,9	92,2
Undecided[#]	42,3	52	71	123	33,4	51,5
Melanocytic Nevus	***36,7***	***131***	***226***	***357***	***31,7***	***41,9***
Blue nevus	24,0	6	19	25	9,36	45,1
Compound nevus	34,0	33	64	97	24,7	44,3
Dermal nevus	38,5	37	59	96	28,8	49,0
Halo nevus	42,9	3	4	7	9,90	81,6
Junction nevus	85,7	6	1	7	42,1	99,6
Lentigo	55,0	11	9	20	31,5	76,9
Other	33,3	9	18	27	16,5	54,0
Reed's nevus	31,3	5	11	16	11,0	58,7
Spitz nevus	0,0	0	5	5	0,00	52,2
Undecided	36,8	21	36	57	24,5	50,7
Other	***11,6***	***13***	***99***	***112***	***6,33***	***19,0***
Lichenoid keratosis	0,00	0	4	4	0,00	60,2
Seborrhoeic keratosis	7,84	4	47	51	2,18	18,9
Other	15,8	9	48	57	7,50	27,9
Overall Spec	***34,4***	***501***	***956***	***1457***	***32,0***	***36,9***
Type	**Sensitivity**	**TP**[*]	**FN**[*]	**Total**	**LCB**[†]	**UCB**[†]
Non-Melanoma Skin Cancer	***100***	***55***	***0***	***55***	***93,5***	***100***
BCC	100	48	0	48	92,6	100
SCC	100	7	0	7	59,0	100
SCC in situ	100	6	0	6	54,1	100
SCC invasive	100	1	0	1	2,50	100

Actinic keratosis	***87,5***	***7***	***1***	***8***	***47,4***	***99,7***
Merkel Cell Carinoma.	***100***	***1***	***0***	***1***	***2,50***	***100***

* TP correctly identified as positive, FN incorrectly identified as negative, TN correctly identified as negative, FP incorrectly identified as positive, by the investigational device.

** AJCC 6th edition from 2002 was used [58] with ad hoc adoption to the 7th edition [2] during the course of the study when pronounced mitosis was present

♯ No majority board agreement on degree of dysplasia.

† Exact Lower and Upper Confidence bounds (LCB/UCB) calculated using Clopper-Pearson

¶ Exact Clopper Pearson and mid-p one-sided 95% lower confidence bound estimated at 94.2% and 94.4% respectively

‡ Severe cytologic atypia or architectural disorder where diagnosed as severe dysplasia.

Table 5. Observed sensitivity and specificity for the dermoscopic, investigational site's histopathology evaluations as well as the Nevisense result grouped according to the study's histopathological gold standard (HGS). **NB:** the results are derived from the cohort of eligible and evaluable lesions that had sufficient image quality to render a dermoscopic evaluation.

Type	7 point	7 point weighted	ABCD Derm < 5,45	ABCD Derm <4.75	Malignancy Grading	Investigational site's Histopathology*	Nevisense
Melanoma Sensitivity	***49,2%***	***60,9%***	***47,1%***	***54,2%***	***70,6%***	***84,5%***	***97,1%***
pTis	28,7%	43,6%	28,7%	37,6%	55,4%	73,3%	94,1%
pT1a	57,1%	65,5%	51,2%	57,1%	75,0%	89,3%	98,8%
pT1b	76,5%	76,5%	76,5%	82,4%	88,2%	100,0%	100,0%
pT2a	63,6%	86,4%	72,7%	72,7%	90,9%	95,5%	100,0%
pT2b	88,9%	100,0%	88,9%	88,9%	100,0%	100,0%	100,0%
pT3a	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
pT3b	100,0%	100,0%	66,7%	100,0%	100,0%	100,0%	100,0%
pT4a	100,0%	100,0%	0,0%	100,0%	100,0%	100,0%	100,0%
Severe Dysplasia** Sensitivity	***12,1%***	***24,8%***	***12,8%***	***20,8%***	***38,3%***	***NA***	***83,9%***
Overall Specificity	***94,2%***	***89,2%***	***94,0%***	***90,1%***	***81,4%***	***98,0%***	***35,8%***

* Overall malignancy grading as determined by the visual classification board with a fixed cut-off at 4.

** Severe cytologic atypia or architectural disorder where diagnosed as severe dysplasia.

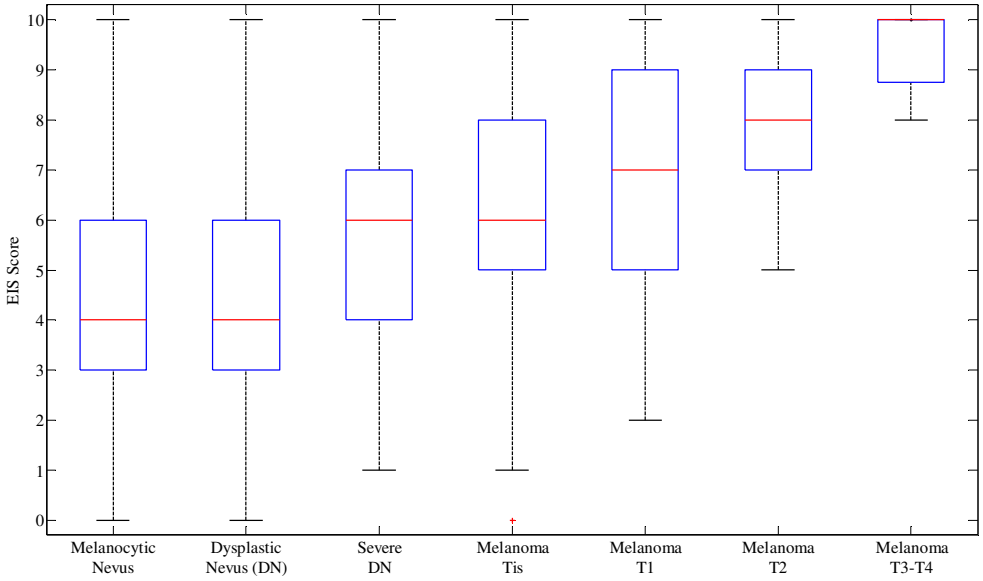

Figure 1. Study's histopathological gold standard (HGS) plotted against Nevisense score outcome (EIS).